ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 January 26; 11(1): 1-46

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 1 January 26, 2019

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Contents

World Journal of Cardiology

Volume 11 Number 1 January 26, 2019

ABOUT COVER

Editor-in-Chief of *World Journal of Cardiology*, Dimitrios Tousoulis, FACC, MD, PhD, Full Professor, 1st Department of Cardiology, Hippokration Hospital, Medical School of National and Kapodistrian University of Athens, Athens 115 27, Greece

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Cardiology (*WJC*) is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Han Song* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
January 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 January 26; 11(1): 1-12

DOI: 10.4330/wjc.v11.i1.1

ISSN 1949-8462 (online)

MINIREVIEWS

Heart disease in Friedreich's ataxia

Emily Hanson, Mark Sheldon, Brenda Pacheco, Mohammed Alkubeysi, Veena Raizada

ORCID number: Mohammed Alkubeysi (0000-0002-4095-9828); Veena Raizada (0000-0002-2511-6443).

Author contributions: Hanson E wrote the manuscript; Sheldon M, Pacheco B and Alkubeysi M contributed to the aim of the manuscript and the diagnostic process of the case study used in the manuscript; Raizada V contributed to writing and editing of the manuscript and is the corresponding author.

Conflict-of-interest statement: There are no conflicts of interest to report.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: November 14, 2018
Peer-review started: November 14, 2018
First decision: November 29, 2018
Revised: December 11, 2018
Accepted: January 5, 2019
Article in press: January 6, 2019
Published online: January 26, 2019

Emily Hanson, Mark Sheldon, Brenda Pacheco, Mohammed Alkubeysi, Veena Raizada, Department of Internal Medicine, Cardiology Section, University of New Mexico, Albuquerque, NM 87106, United States

Corresponding author: Veena Raizada, MD, Doctor, Professor, Department of Internal Medicine, Cardiology Section, University of New Mexico, 2211 Lomas Blvd NE, Albuquerque, NM 87131, United States. vraizada@salud.unm.edu
Telephone: +1-404-8230602

Abstract

Friedreich's ataxia (FRDA), which occurs in 1/50000 live births, is the most prevalent inherited neuromuscular disorder. Nearly all FRDA patients develop cardiomyopathy at some point in their lives. The clinical manifestations of FRDA include ataxia of the limbs and trunk, dysarthria, diabetes mellitus, and cardiac diseases. However, the broad clinical spectrum makes FRDA difficult to identify. The diagnosis of FRDA is based on the presence of suspicious clinical factors, the use of the Harding criteria and, more recently, the use of genetic testing for identifying the expansion of a triplet nucleotide sequence. FRDA is linked to a defect in the mitochondrial protein frataxin; an epigenetic alteration interferes with the folding of this protein, causing a relative deficiency of frataxin in affected patients. Frataxins are small essential proteins whose deficiency causes a range of metabolic disturbances, including oxidative stress, iron-sulfur cluster deficits, and defects in heme synthesis, sulfur amino acid metabolism, energy metabolism, stress responses, and mitochondrial function. The cardiac involvement seen in FRDA is a consequence of mitochondrial proliferation as well as the loss of contractile proteins and the subsequent development of myocardial fibrosis. The walls of the left ventricle become thickened, and different phenotypic manifestations are seen, including concentric or asymmetric hypertrophy and (less commonly) dilated cardiomyopathy. Dilated cardiomyopathy and arrhythmia are associated with mortality in patients with FRDA, whereas hypertrophic cardiomyopathy is not. Systolic function tends to be low-normal in FRDA patients, with an acute decline at the end of life. However, the literature includes only a few long-term prospective studies of cardiac progression in FRDA, and the cause of death is often attributed to heart failure and arrhythmia postmortem. Cardiomyopathy tends to be correlated with the clinical neurologic age of onset and the nucleotide triplet repeat length (*i.e.*, markers of phenotypic disease severity) rather than the duration of disease or the severity of neurologic symptoms. As most patients are wheelchair-bound within 15 years of diagnosis, the clinical determination of cardiac involvement is often complicated by comorbidities. Researchers are currently testing targeted therapies for FRDA, and a centralized database, patient registry, and natural

history study have been launched to support these clinical trials. The present review discusses the pathogenesis, clinical manifestations, and spectrum of cardiac disease in FRDA patients and then introduces gene-targeted and pathology-specific therapies as well as screening guidelines that should be used to monitor cardiac disease in this mitochondrial disorder.

Key words: Friedreich's ataxia; Mitochondrial disorder; Nonischemic cardiomyopathy; Cardiac disease

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The present review discusses the pathogenesis, clinical manifestations, and spectrum of cardiac disease in Friedreich's Ataxia, and introduces gene-targeted and pathology-specific therapies, in addition to the screening guidelines that should be used to monitor cardiac disease in this mitochondrial disorder.

Citation: Hanson E, Sheldon M, Pacheco B, Alkubeysi M, Raizada V. Heart disease in Friedreich's ataxia. *World J Cardiol* 2019; 11(1): 1-12
URL: https://www.wjgnet.com/1949-8462/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i1.1

INTRODUCTION

Friedreich's ataxia (FRDA) is the most common autosomal recessive spinocerebellar ataxia. FRDA was first reported in the 1860s but remained difficult to distinguish from other spinocerebellar ataxias until the causative gene was determined in 1996. Since then, evidence has accumulated regarding the pathogenesis, specialized treatment and prognosis of this disease. We now know that FRDA is a mitochondrial disorder that primarily affects neural pathways and cardiac muscle. While FRDA is most clinically renowned for its progressive, unremitting ataxia and neuromuscular decline, significant mortality occurs as a result of cardiomyopathy.

HISTORY AND EPIDEMIOLOGY

In the 1860s, Nikolaus Friedreich, a professor of medicine at the University of Heidelberg, first identified the disease when he described two symptomatic siblings with asymptomatic parents[1]. Diagnostic criteria based on clinical features were first published in 1976. The modified criteria published by Harding[2] in 1981 were the diagnostic tool of choice until 1996, when Campuzano *et al*[3] identified the causative alteration of the *frataxin* gene. This outcome paved the way for genetic testing. Even with the availability of genetic testing, the diagnosis of FRDA often relies on the exclusion of acute neurologic abnormalities and the presence of a slowly progressive clinical course. Thus, diagnosis is often delayed.

FRDA exhibits variable phenotypes, and distinct early-onset and late-onset groups may be classified based on the symptom onset before or after age 25, respectively[4]. Late-onset FRDA is characterized by less severe cardiomyopathy and neurologic symptoms, while early-onset typically exhibits more rapid progression with higher morbidity and mortality. For early-onset FRDA, the typical age of onset is approximately 10 years; most patients are wheelchair-bound between 19 and 26 years of age, with mortality by a mean age of 39 years[5]. In comparison, late-onset FRDA is much less decapacitating with nearly average mortality.

FRDA occurs in 1/50000 live births, is most prevalent in Caucasians and is nearly absent in Sub-Saharan Africans, Asians and Native Americans. This factor reflects a single founder event that is responsible for 90% of the large normal alleles that constitute the primary reservoir of this triplet repeat disease. Heterozygous carriers constitute approximately 1% of the population, and homozygous point mutations in one or the other allele account for 5% of FRDA manifestations[6,7].

PATHOLOGY

The characteristic clinical picture of FRDA reflects malfunction of the central sensory pathways found in the posterior columns of the spinal cord, the spinocerebellar tracts, the cerebellar efferent pathway, and the distal portion of the corticospinal motor tracts. Other abnormalities include atrophy of cerebellar regions, including the dentate nuclei. Peripheral nerves show a loss of large myelinated sensory fibers, resulting in the loss of large primary sensory neurons in the dorsal root ganglia. These neurologic abnormalities cause the progressive and unremitting mixed cerebellar and sensory ataxia that characterizes the disease.

CLINICAL MANIFESTATIONS

The clinical manifestations of FRDA include ataxia of the limbs and trunk, dysarthria, diabetes mellitus, and cardiac diseases. The diagnosis is first made on the presence of suspicious clinical factors. Harding *et al*[2] initially described the primary criteria of progressive gait and limb ataxia, absent patellar and ankle reflexes, dysarthria, muscle weakness, loss of vibration or position and onset before the age of 25 years; the secondary criteria were a positive Babinski reflex, pes cavus, scoliosis, and cardiomyopathy. If secondary criteria were not present, then the patient must have an affected sibling. Most often, FRDA patients first present at a young age with increasing clumsiness but normal findings on an magnetic resonance imaging (MRI). The onset is typically before the age of 18 years, and electromyogram studies can help confirm the diagnosis. Genetic testing is now available but is only given when the clinical suspicion is high. Thus, diagnosis is often delayed. As nearly all patients develop cardiomyopathy at some point in their lives, and this aspect of the disease can be the most severe in the youngest cohort, FRDA patients must be referred to a cardiologist upon diagnosis. Indeed, 5% of FRDA patients may present with severe cardiomyopathy in the absence of neurologic symptoms. Cerebellar atrophy on an MRI and the absence of cardiomyopathy are both negative predictors of an FRDA diagnosis[8].

FRDA is the most frequent hereditary ataxia, with an estimated prevalence of 3-4 cases per 50000 individuals. This autosomal-recessive neurodegenerative disease is characterized by progressive gait and limb ataxia, dysarthria, lower-limb areflexia, decreased vibration sense, muscular weakness in the legs, and a positive extensor plantar response. Nonneurological signs include hypertrophic cardiomyopathy and diabetes mellitus. The symptom onset typically occurs around puberty, and the life expectancy of FRDA patients is 40-50 years. The disease is usually caused by a large GAA triplet repeat expansion within the first intron of the *frataxin* gene. *Frataxin* mutations cause deficiencies of the iron-sulfur cluster-containing subunits of mitochondrial electron transport complexes I, II, and III and of the iron-sulfur protein, aconitase. The mitochondrial dysfunction in FRDA patients has been addressed in several open-label, nonplacebo-controlled trials, whose results indicate that treatment with idebenone might ameliorate hypertrophic cardiomyopathy. Indeed, a well-designed phase II clinical trial suggested that idebenone may yield concentration-dependent functional improvements in nonwheelchair-bound children and adolescents. Other current experimental approaches seek to address the iron-mediated toxicity or to increase the *frataxin* protein level.

BIOGENETICS AND THE ROLE OF FRATAXIN

FRDA is linked to a defect in the mitochondrial protein, frataxin, through epigenetic alterations that interfere with protein folding to cause a relative deficiency of frataxin in affected patients (Figure 1). The *frataxin* gene, which is located at chromosome 9q21.11, harbors an intronic trinucleotide repeat sequence (guanine-adenine-adenine; GAA). Most FRDA patients are homozygous for an expansion of this GAA repeat, whereas a typical gene contains 6-36 trinucleotide repeats; those associated with FRDA typically have between 66 and 1700 trinucleotide repeats[9]. This repeat expansion and other mutations in the *frataxin* gene impact the ability of the encoded protein to participate in mitochondrial oxidative phosphorylation, and the cell suffers in terms of energy production. More specifically, FRDA-associated mutations impair mitochondrial function, increase reactive oxygen species, and trigger redistribution of iron in the mitochondria and the cytosol. Mitochondria proliferate but remain dysfunctional. Physiologically, these changes reduce the myocardial reserve as evidenced by the enhancement of the late gadolinium signal on cardiac MRI (cMRI)[10]

(Figure 2).

Frataxin also participates in iron metabolism; its deficiency interferes with iron hemostasis, leading to the deposition of iron in cells. Such deposition in cardiomyocytes often accompanies myocardial hypertrophy in FRDA patients, suggesting that iron toxicity-mediated oxidative tissue damage may play a role in this disease[10]. Indeed, autopsies of FRDA patients suggested that iron-induced myocarditis may be involved in the pathology of this unique cardiomyopathy[11]. Iron deposition, myocardial hypertrophy and oxidative tissue damage are also associated with an impaired lipid metabolism and a lower threshold for oxidative stress, which may contribute to cardiac disease progression. FRDA is known to most strongly affect tissues that are primarily involved in oxidative phosphorylation and are rich with mitochondria (*e.g.*, dorsal root ganglion, cardiomyocytes and B-islet cells of the pancreas). However, we still do not know why some spinal and brainstem motor neurons are affected, while others remain normal.

Structural studies carried out on different orthologs have shown that eukaryotic frataxin proteins take on a folded conformation (called the frataxin fold) that involves a flexible N-terminal region present only in eukaryotes, whereas all frataxins have a highly conserved C-terminal globular domain. Frataxins bind iron directly but show very unusual properties in this regard, as iron coordination is achieved solely by glutamates and aspartates exposed on the protein surface. It has been suggested that frataxin functions as a ferritin-like protein, as an iron chaperone of the iron-sulfur cluster machinery and heme metabolism and/or as a controller of cellular oxidative stress. If we hope to fully understand the pathology of FRDA and to design novel therapeutic strategies, we must first precisely identify the cellular role of frataxin[9].

Histologically, frataxin deficiency causes failure of iron clearance from myocytes as well as myocardial necrosis, myocardial apoptosis, chronic inflammation and scarring or fibrosis. However, iron deposits are not thought to be the initial direct cause of this disease; in the frataxin knockout model, mice die in utero but do not have manifestations of iron deposition. Although animal models have been used to describe the pathogenesis of FRDA and test targeted treatments, the causes of necrosis or cardiomyocyte apoptosis have not yet been determined in human FRDA patients, and it is not clear whether frataxin is a protective factor or a pathogenic contributor in cardiomyopathy. The protein stores of frataxin in FRDA patients are 20%-25% of those seen in normal individuals, but we do not yet know how much protein is required for a normal phenotype. The embryonic lethality of frataxin knockout mice indicates that a complete lack of *frataxin* is incompatible with life, whereas the conditional mouse models with a post developmental knockout of *frataxin* demonstrate mitochondrial pathologies[12].

Centralized database, patient registry, and natural history studies have been launched to support clinical trials in FRDA. The 2011 Neurobiology of Disease in Children symposium, which is held in conjunction with the 40th annual Child Neurology Society meeting, aimed to: (1) describe the clinical features surrounding FRDA, including the cardiomyopathy and the genetics of the disorder; (2) discuss recent advances in our understanding of FRDA pathogenesis and the development of clinical trials; (3) review new investigations of characteristic symptoms; and (4) establish clinical and biochemical overlaps in neurodegenerative diseases and possible directions for future basic, translational and clinical studies.

SPECTRUM OF HEART DISEASE IN FRDA

The cardiac involvement in this mitochondrial disorder is a consequence of mitochondrial proliferation, the loss of contractile proteins, and the subsequent development of myocardial fibrosis. The left ventricular walls become thickened and show a range of phenotypic manifestations, including concentric/asymmetric hypertrophy or dilated cardiomyopathy. Concentric/asymmetric hypertrophy is less common, but dilated cardiomyopathy with arrhythmia is more often associated with mortality compared to hypertrophic cardiomyopathy. The systolic function of FRDA patients tends to be low-normal and show an acute decline at the end of life. However, there is little data from long-term prospective studies of cardiac progression in these patients, and the cause of death is often attributed to heart failure and arrhythmia postmortem. As a marker of phenotypic disease severity, cardiomyopathy tends to be correlated with the clinical neurologic age of onset and the GAA triplet repeat length but not the duration of disease or the severity of neurologic symptoms[13]. However, the clinical determination of cardiac involvement is difficult, as most patients are wheelchair-bound within 15 years of diagnosis due to comorbidities associated with the systemic disease process.

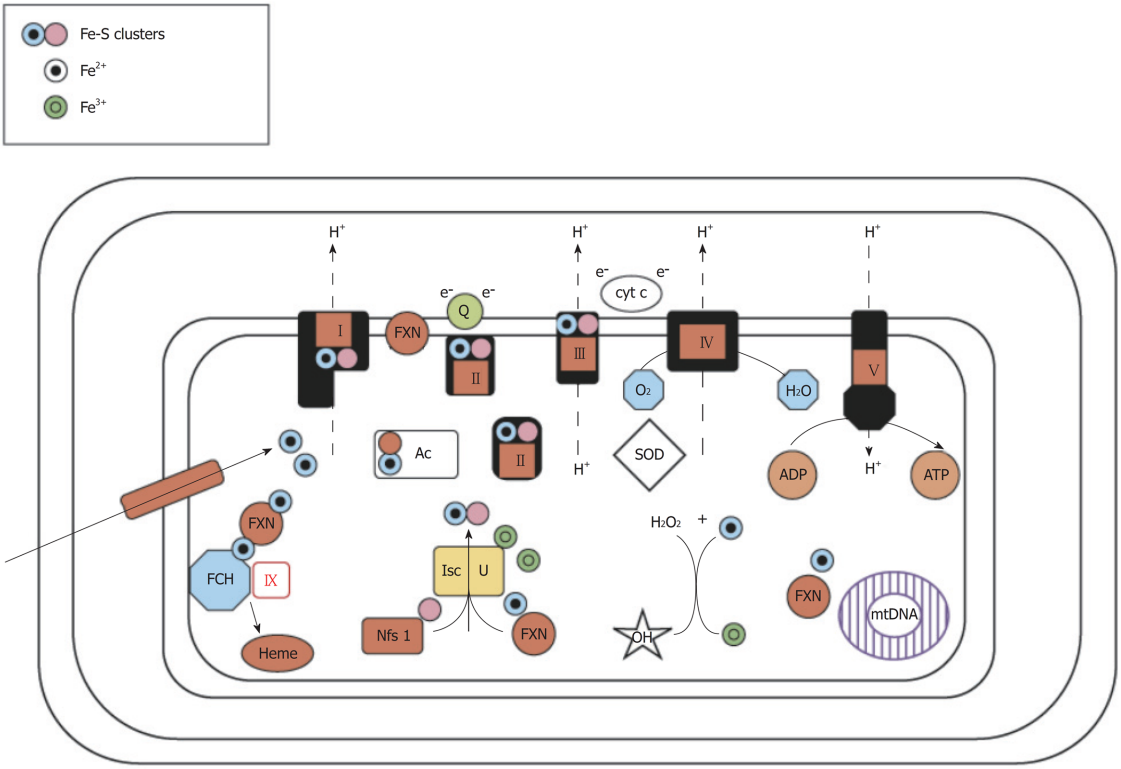


Figure 1 Postulated functions of frataxin. (1) Frataxin is a general iron chaperone that provides Fe^{2+} to ferrochelatase (FCH) for heme biosynthesis, mitochondrial iron-sulfur (Fe-S) cluster biogenesis, and maintenance of the mitochondrial aconitase (Ac) Fe-S cluster; (2) Frataxin may directly interact with respiratory chain complexes (I-V); (3) Frataxin prevents oxidative stress, protects mitochondrial proteins and mitochondrial DNA (mtDNA) from free Fe^{2+}, and prevents the Fenton reaction by converting Fe^{2+} to Fe^{3+}, thereby blocking hydroxyl radical formation. ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; cyt c: Cytochrome c; e^-: Electron; SOD: Superoxide dismutase; FXN: Frataxin.

The cardiac diseases of FRDA patients include concentric LV hypertrophy, which leads to the most common causes of death, arrhythmia and heart failure, among these patients. Heart disease can be asymptomatic, and shortness of breath or palpitations are the most common clues. Early age of FRDA onset and GAA repeat length predict cardiac severity and worse LV hypertrophy, LV function, LV mass and eventual mortality, with most cardiac-related deaths occurring prior to age 40[13]. FRDA patients with cardiac-related death usually have a disease duration of 10 years or less, and a disease duration of greater than 20 years significantly reduces the predisposition to cardiac-related death[14] (Figure 3).

Asymmetric septal hypertrophy with an LV outflow gradient is uncommon in FRDA patients, and only a handful of reported cases have undergone septal myomectomy. In fact, the typical beta-blockade-based treatment for hypertrophic cardiomyopathy may be harmful in FRDA patients, given their loss of contractile fibers in the myocardium[15]. Dilated cardiomyopathy is also rare in FRDA; however, when present, it is accompanied by a more severe systolic dysfunction. It has been postulated that ventricular hypertrophy progresses to dilation with fibrotic replacement of myocardium in FRDA, but these observations may also represent different cardiac phenotypes[16,17].

Other cardiac abnormalities of FRDA include echocardiographic findings of a granular speckle-like appearance similar to that seen in amyloidosis, though without pericardial effusion or biatrial enlargement[18]. cMRI studies have detected subclinical LV fibrosis and concentric remodeling even prior to hypertrophy, along with a late gadolinium enhancement indicative of a decreased myocardial perfusion reserve[18]. As systolic dysfunction may indicate certain severe phenotypes late in the course of disease, longitudinal LV strain has been identified as a potential early marker of cardiomyopathy and systolic dysfunction. Although, once again, longitudinal studies of progression from longitudinal LV strain to systolic dysfunction are lacking[19]. These findings of early disease progression may have importance for identifying future therapeutic targets or developing methods to screen for cardiac disease that may otherwise progress undetected in asymptomatic patients who lack exertional symptoms of heart failure because they are non-ambulatory[20] (Figure 4).

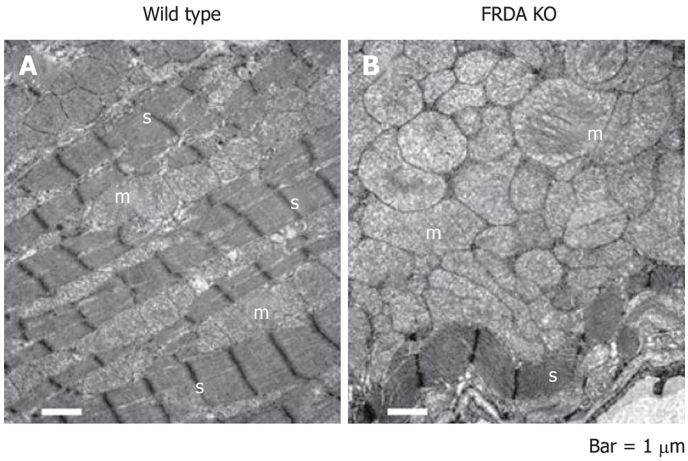


Figure 2 Electron microscopy of Friedreich's ataxia-knockout and wild-type control mouse heart tissues from 28-d-old littermates. A: Wild type mouse showing normal mitochondria ("m") in rows between abundant, well-ordered sarcomeres ("s"); B: Conditional Friedreich's ataxia-knockout (FRDA KO) mouse with ablation of the FRDA locus in the heart and brain (NSE-Cre promoter). Note the extreme proliferation of enlarged mitochondria in B. There is a severe loss of sarcomeres ("s"). Bars = 1000 nm.

CONDUCTION DISEASE

The conduction disease seen in FRDA patients is thought to be a result of fibrotic myocardial replacement and scarring, which predispose the patient to atrioventricular conduction blocks and atrial or ventricular tachy- and bradyarrhythmias. Atrial arrhythmias, atrial flutter and atrial fibrillation occur in FRDA patients, but they are not frequent; ventricular arrhythmias are seen even less frequently. A cardiac pacemaker or defibrillator may benefit affected FRDA patients and should be implanted when indicated according to the American Heart Association and American College of Cardiology Guidelines for the general population.

ECG CHARACTERISTICS

In many cohort studies, T-wave repolarization abnormalities, especially in the inferior and lateral leads, were the most common abnormalities seen on the electrocardiogram (ECG) of FRDA patients (approximately 85%). Bundle branch blocks were found in 15% of FRDA patients. The QT interval tended to be normal, as did the QRS, indicating that there was a relatively low risk for ventricular tachyarrhythmias[10,13,15,18].

CORONARY ARTERY DISEASE

It is generally thought that the only increased risk factor for FRDA patients is a predisposition to diabetes mellitus due to beta islet cell disease of the pancreas. However, some histopathologic studies suggest that there is also an increased risk for coronary artery disease. Although one study found no occlusive coronary disease in postmortem patients[21], another study of three postmortem patients identified potential occlusive coronary disease in the microvasculature of the coronary arteries[20]. Fibrotic replacement of the coronary intima has also been identified, and it has been proposed that the coronary arteries of FRDA patients are susceptible to fibromuscular dysplasia. Inducible subendocardial defects detected by late enhancement gadolinium on cMRI indicate a reduced myocardial perfusion reserve as a source of ischemia that may warrant further study as a potential clinical correlate of microvascular coronary disease[20].

CLINICAL COURSE OF CARDIAC DISEASE

There has been debate regarding the progression of cardiac disease and the presence of variable phenotypes in FRDA. A small study of 28 FRDA patients over 5 years examined the TTE of these patients in childhood. Though LV systolic function was diminished in at least one examination, all were normal on subsequent examinations,

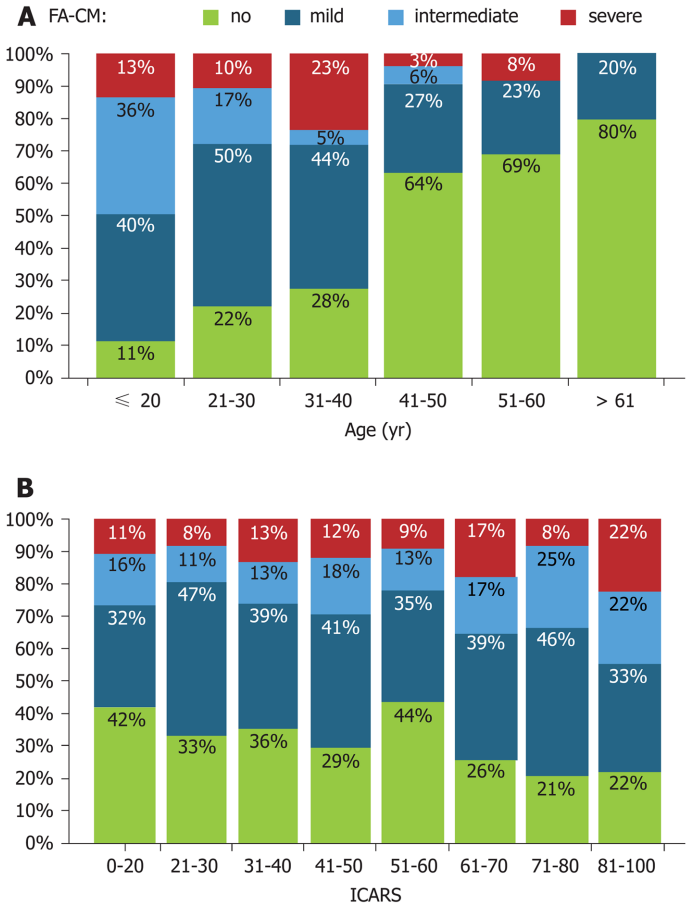


Figure 3 The more severe Friedreich's ataxia cardiomyopathy groups were found at younger ages (A), in contrast, the severity of the Friedreich's ataxia cardiomyopathy was independent of neurological involvement measured by the International Cooperative Ataxia Rating Scale score (B).

leading the investigators to assume that the cardiac disease of these patients was stable until at least the age of 22 years[22]. The authors proposed that this cardiac disease progressed from hypertrophic to dilated cardiomyopathy and was not correlated with the GAA repeat length. A prospective open-label trial of 105 patients identified their baseline characteristics as hypertrophic cardiomyopathy with either septal or posterior wall asymmetric hypertrophy of the left ventricle. After treatment with high-dose idebenone, these patients experienced reductions in left ventricular mass with only small declines in their systolic function. Dilated cardiomyopathy was present in only one patient[23].

Notably, cross-sectional and retrospective data support the contention that there are clear differences in the clinical course and presence of systolic cardiomyopathy across FRDA patients. Investigators have proposed that various phenotypes reflect the GAA repeat length, although additional factors likely contribute to the differences seen in cardiac left ventricular hypertrophy, mass and dilatation. One study of 103 patients over a mean of 10 years found that the majority of patients (78%) were distributed in the low-risk group with normal LVEF at baseline and stable (ejection fraction) EF over time. In contrast, the LVEF of patients in the high-risk group (22%) declined an average of 21% over the 10-year period. Such phenotypes have already been observed and described as early- and late-onset FRDA[13].

Late-onset FRDA, which may be diagnosed beyond the criterion age of 25 years, includes a phenotypically variable group of patients who show later disease onset and slower progression compared to patients with early-onset FRDA. This finding emphasizes the need for a dynamic definition of the genetic and clinical criteria used to diagnose FRDA and suggests that the variable phenotypes may represent more than the simple expansion of the specific trinucleotide repeat sequence.

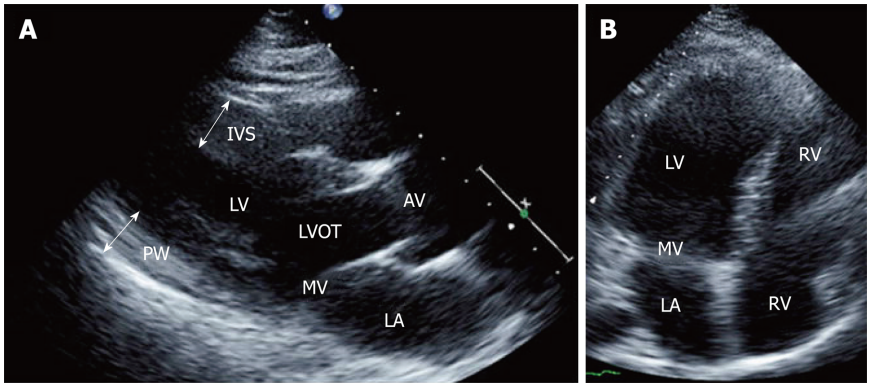


Figure 4 Two-dimensional echocardiographic still frames from a patient with Friedreich's ataxia. A: Parasternal long-axis view showing thickening of the interventricular septum and posterior wall; B: Apical four-chamber view showing dilatation of left ventricular cavity. IVS: Interventricular septum; PW: Posterior wall; LV: Left ventricle; LA: Left atrium; MV: Mitral valve; AV: Aortic valve; LVOT: Left ventricular outflow tract.

CLINICAL CASE

The cardiac abnormalities seen in one of our patients are illustrated in Figure 3. A 25-year-old female recently diagnosed with FRDA presented to the cardiology clinic with 6 months of dyspnea on exertion, chest pressure radiating to her neck and paroxysmal nocturnal dyspnea. An ECG showed T wave inversions in the precordial leads, which in the context of chest pain, were suggestive of coronary artery disease. A TTE showed a normal ejection fraction and left ventricular wall thickness, though diastolic dysfunction was present and showed a restrictive pattern (Figure 5).

Cardiac catheterization revealed normal coronary arteries but showed that the left ventricular end-diastolic pressure was severely elevated to 28 mmHg. The patient was diagnosed with left ventricular diastolic heart failure with a preserved ejection fraction.

CLINICAL CARDIAC MONITORING

Heart failure and sudden cardiac death are the most commonly reported causes of death among FRDA patients (Table 1)[24].

Cardiomyopathy is thus important, especially in early-onset patients, who exhibit more severe cardiac disease. In addition, the progression to heart failure and deterioration of LVEF may be difficult to detect, as decreased systolic function usually occurs shortly before death, and this is difficult to correlate clinically given the lack of ambulation in most patients without correlation of neurologic severity to cardiac severity. Sudden progression of cardiac disease may not be detectable due to these comorbidities. Given the above issues, routine screening of the structural indicators of cardiomyopathy may be more valuable than the symptom review in FRDA patients, and the use of current imaging modalities may be indicated. A consensus statement proposed in 2014 for the multidisciplinary treatment of patients with FRDA recommended that ECG and echocardiography should be performed at the initial presentation and that patients should be referred to a cardiologist only for cardiac symptoms or abnormal cardiac testing[25]. However, we feel that patients should be screened at least annually with an ECG and a TTE. Moreover, cMRI (which can detect remodeling and decreased myocardial perfusion reserve) may prove useful in the future for the early detection of disease and/or monitoring the therapeutic response. The arrhythmias of FRDA patients are normally atrial in origin and may indicate the severity of left ventricular involvement rather than acting as a risk factor for sudden cardiac death due to arrhythmia. Although cMRI is not currently used to detect structural abnormalities in classifying heart failure, it may prove useful in this role, especially in situations (such as FRDA) where structural disease may be the best indicator of cardiac mortality risk.

PHARMACOLOGIC TREATMENT RESEARCH AND ADVANCES

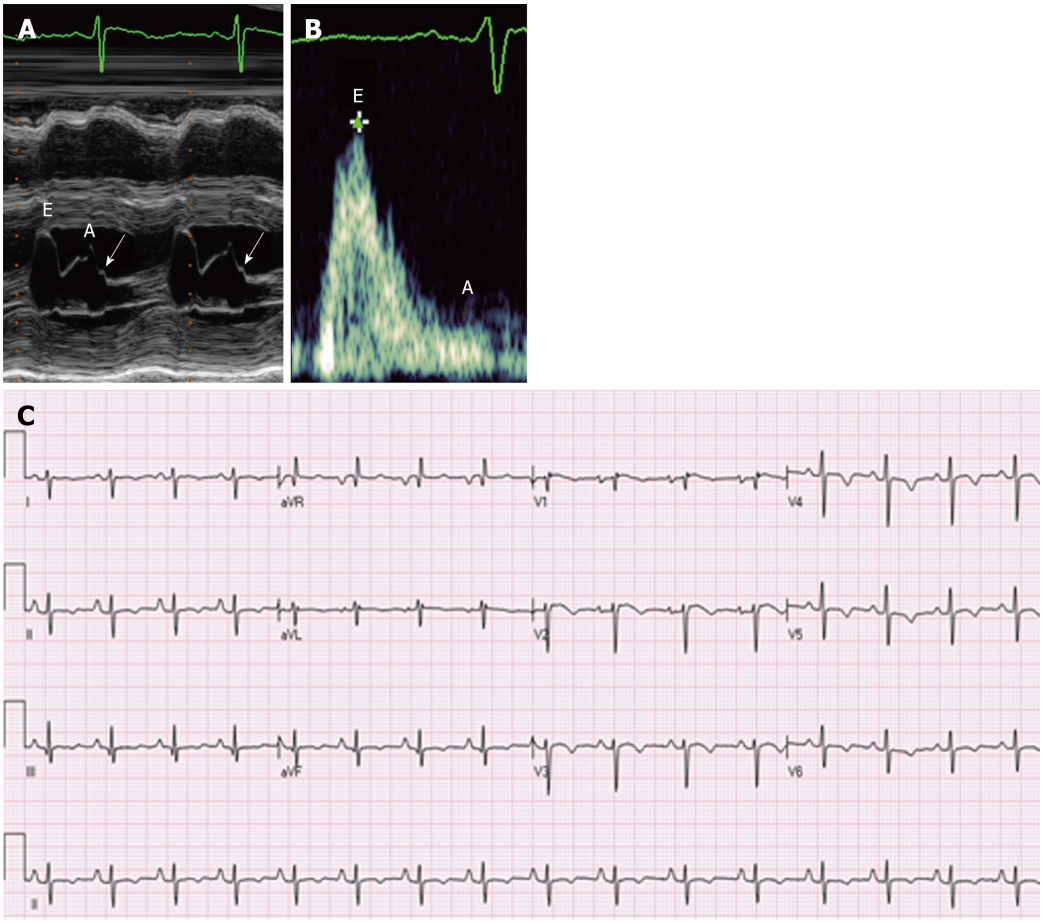


Figure 5 M-Mode image of the mitral valve, Transmitral Doppler flow showing diastolic flow and Twelve-lead electrocardiogram. A: M-Mode image of the mitral valve in the parasternal long-axis view. Mitral valve excursion in early diastole can be seen, as can excursion due to atrial contraction in late diastole. A: "B-bump" (arrow) may be seen on the downslope of the A wave; this suggests that the end-diastolic atrial pressure is greater than the end-diastolic ventricular pressure, which is a marker of diastolic dysfunction; B: Transmitral Doppler flow showing diastolic flow. Note the large E wave in early diastole and the diminutive A wave in late diastole. The ratio of peak E wave velocity to peak A wave velocity is > 1.5, which is consistent with a "restrictive" pattern, particularly when paired with other indicators of diastolic dysfunction; C: Twelve-lead electrocardiogram demonstrating normal sinus rhythm, significant right axis deviation, poor R wave progression, and nonspecific T wave inversions in the lateral leads.

The cardiomyopathy of FRDA has a unique pathogenesis, and specific targeted pharmaceuticals have yielded mixed results. Idebenone is a coenzyme Q10 analog that has been shown to have antioxidant activity and to facilitate mitochondrial phosphorylation as an electron carrier, which is important in mitochondrial function and energy production. Idebenone has improved cardiomyopathy in a very limited number of patients, as assessed by cMRI, but the clinical impact of this treatment has not yet been fully assessed[26]. Studies of shorter duration (*e.g.*, 6 wk) failed to observe any benefit[26], and a review of the only two studies that were 12 mo or longer showed no change in baseline systolic function on an echocardiogram, although cMRI was not included as a measure in these randomized controlled trials[27]. MICONOS published an interim report in 2010 (the full study has not yet been reported) stating that, in their study, idebenone had not reached its primary endpoint of change with respect to the International Cooperative Ataxia Rating Scale (ICARS) score or cardiologic secondary endpoint. Idebenone has shown the potential to benefit hypertrophy in terms of septal wall thickness, posterior wall thickness and left ventricular mass (LVM) in open-label studies, but randomized controlled trials have not yet shown any clear benefit[26]. A study by Mariotti *et al*[27] showed that LVM was reduced over 12 mo in patients receiving idebenone compared to placebo, but the cohort was limited to 28 patients. Thus, idebenone has yielded mixed results with respect to cardiac function, and the clinical implication and timing of this pharmaceutical intervention have not yet been determined in detail.

One drawback of antioxidant or iron chelation therapy, in which plasma-bound iron is removed from the body, is the lack of evidence for cardiomyopathy reversal and convincing proof of clinical impact. Alternatively, gene therapy showed potential for reversing the biochemical, cellular and physiologic changes of FRDA cardiomyopathy in a mouse model, offering proof of concept[28]. Mice with a

Table 1 Causes of death

Causes of death	Frequency	Percentage
Cardiac	36	59.0
CHF/cardiac failure	18	28.5
CHF complicated significant arrhythmia	5	8.2
Arrhythmia	5	8.2
Ischemic disease	3	4.9
Stroke (associated with atrial fibrillation or mural thrombus)	4	6.6
Other	1	1.6
Probable cardiac	2	3.3
Severe cardiomyopathy	1	1.6
Arrhythmia	1	1.6
Non-cardiac	17	27.9
Pneumonia	6	9.8
Sepsis	1	1.6
Renal failure	1	1.6
Breast cancer	1	1.6
Accidental drowning	1	1.6
Suicide	1	1.6
Other	6	9.8
Unknown	6	9.8

conditional knockout of frataxin in cardiac muscle show progressive and severe cardiomyopathy characterized by systolic dysfunction and increased left ventricular mass. Treatment of these mice with a vector that restored the capacity to transcribe frataxin rapidly normalized systolic cardiac function, halted histologic fibrosis and restored mitochondrial function in terms of iron accumulation, iron hemostatic protein levels and mitochondrial proliferation. When the mice of the asymptomatic mouse model were pretreated with this therapeutic vector, their cardiac function was indistinguishable from that of wild-type mice[28]. These findings suggest that such treatment might prevent cardiomyopathy in early-onset patients and reverse cardiomyopathy in the progressive cardiac disease associated with FRDA of any phenotype.

CARDIAC TRANSPLANT IN FRDA

Cardiac transplantation was offered in approximately five FRDA patients between 2001 and 2011[29]. Some of these patients had both classic hypertrophy and dilated cardiomyopathy. In one case, the transplant occurred in a pediatric patient with cardiomyopathy who later developed FRDA. This is not surprising, as cardiomyopathy may present, even in a severe form, prior to the onset of neurologic disease[29]. The transplanted patients appeared to experience an arrest in the progression of neurologic disease and had some recovery of motor skills and strength. In this population, transplant decisions must be made with considerations of life span and comorbidities.

CONCLUSION

The cardiac disease of FRDA is variable in its clinical phenotype and severity, complicating its timely and appropriate diagnosis and treatment. The research has progressed since frataxin was first shown to play a role in cardiomyopathy, and new treatments using antioxidants and gene therapy have been trialed, most successfully in animal models. To prevent cardiac mortality in FRDA patients, we may need targeted treatments and management guidelines tailored to this unique mitochondrial pathology. Clinicians are urged to provide genetic testing for patients with highly suggestive clinical pictures, as well as yearly cardiac monitoring and counseling on treatment decisions for this patient population.

INNOVATION

FRDA is the most prevalent inherited neuromuscular disorder associated with cardiomyopathy. It is caused by a genetic defect in a mitochondrial protein, frataxin, involving skeletal as well as cardiac muscle leading to physical incapacitation later in life. Interventricular posterior wall thickness was found to be the most sensitive echocardiographic criteria to determine the actual LV mass when compared to Cardiac MRI[30]. Cardiac function tends to be low normal initially in these patients, with an acute decline at the end of life. However neurological status cannot be determined by cardiomyopathy status as correlation was negative[30]. Several investigators have proposed criteria to stage cardiomyopathy based on several markers which were positive in up to two thirds of patients: (1) ECG abnormalities including supraventricular tachycardia and T wave inversion[30]; (2) fibrosis on Cardiac MRI and Hs TNT > 14 ng/mL[31]; and (3) reduction in both S′ and E′ by Tissue Doppler (Mott), which, however, did not demonstrate a consistent correlation with GAA repeats[32]. Furthermore, gene targeted therapies based on these studies have not been successful in reversing the progression of FRDA.

REFERENCES

1 **Hewer R**. The heart in Friedreich's ataxia. *Br Heart J* 1969; **31**: 5-14 [PMID: 5774037 DOI: 10.1136/hrt.31.1.5]
2 **Harding AE**. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain* 1981; **104**: 589-620 [PMID: 7272714 DOI: 10.1093/brain/104.3.589]
3 **Campuzano V**, Montermini L, Lutz Y, Cova L, Hindelang C, Jiralerspong S, Trottier Y, Kish SJ, Faucheux B, Trouillas P, Authier FJ, Dürr A, Mandel JL, Vescovi A, Pandolfo M, Koenig M. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum Mol Genet* 1997; **6**: 1771-1780 [PMID: 9302253 DOI: 10.1093/hmg/6.11.1771]
4 **Pandolfo M**. Friedreich ataxia. *Arch Neurol* 2008; **65**: 1296-1303 [PMID: 18852343 DOI: 10.1001/archneur.65.10.1296]
5 **Reetz K**, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, Parkinson MH, Sweeney MG, Mariotti C, Panzeri M, Nanetti L, Arpa J, Sanz-Gallego I, Durr A, Charles P, Boesch S, Nachbauer W, Klopstock T, Karin I, Depondt C, vom Hagen JM, Schöls L, Giordano IA, Klockgether T, Bürk K, Pandolfo M, Schulz JB. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol* 2015; **14**: 174-182 [PMID: 25566998 DOI: 10.1016/S1474-4422(14)70321-7]
6 **Dürr A**, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, Mandel JL, Brice A, Koenig M. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996; **335**: 1169-1175 [PMID: 8815938 DOI: 10.1056/NEJM199610173351601]
7 **Labuda M**, Labuda D, Miranda C, Poirier J, Soong BW, Barucha NE, Pandolfo M. Unique origin and specific ethnic distribution of the Friedreich ataxia GAA expansion. *Neurology* 2000; **54**: 2322-2324 [PMID: 10881262 DOI: 10.1016/S0090-3019(00)00309-8]
8 **Schulz JB**, Boesch S, Bürk K, Dürr A, Giunti P, Mariotti C, Pousset F, Schöls L, Vankan P, Pandolfo M. Diagnosis and treatment of Friedreich ataxia: a European perspective. *Nat Rev Neurol* 2009; **5**: 222-234 [PMID: 19347027 DOI: 10.1038/nrneurol.2009.26]
9 **Ashley CN**, Hoang KD, Lynch DR, Perlman SL, Maria BL. Childhood ataxia: clinical features, pathogenesis, key unanswered questions, and future directions. *J Child Neurol* 2012; **27**: 1095-1120 [PMID: 22859693 DOI: 10.1177/0883073812448840]
10 **Payne RM**, Wagner GR. Cardiomyopathy in Friedreich ataxia: clinical findings and research. *J Child Neurol* 2012; **27**: 1179-1186 [PMID: 22764179 DOI: 10.1177/0883073812448535]
11 **Koeppen AH**, Ramirez RL, Becker AB, Bjork ST, Levi S, Santambrogio P, Parsons PJ, Kruger PC, Yang KX, Feustel PJ, Mazurkiewicz JE. The pathogenesis of cardiomyopathy in Friedreich ataxia. *PLoS One* 2015; **10**: e0116396 [PMID: 25738292 DOI: 10.1371/journal.pone.0116396]
12 **Pandolfo M**, Pastore A. The pathogenesis of Friedreich ataxia and the structure and function of frataxin. *J Neurol* 2009; **256** Suppl 1: 9-17 [PMID: 19283345 DOI: 10.1007/s00415-009-1003-2]
13 **Pousset F**, Legrand L, Monin ML, Ewenczyk C, Charles P, Komajda M, Brice A, Pandolfo M, Isnard R, Tezenas du Montcel S, Durr A. A 22-Year Follow-up Study of Long-term Cardiac Outcome and Predictors of Survival in Friedreich Ataxia. *JAMA Neurol* 2015; **72**: 1334-1341 [PMID: 26414159 DOI: 10.1001/jamaneurol.2015.1855]
14 **Weidemann F**, Scholz F, Florescu C, Liu D, Hu K, Herrmann S, Ertl G, Störk S. [Heart involvement in Friedreich's ataxia]. *Herz* 2015; **40** Suppl 1: 85-90 [PMID: 24848865 DOI: 10.1007/s00059-014-4097-y]
15 **Payne RM**, Peverill RE. Cardiomyopathy of Friedreich's ataxia (FRDA). *Ir J Med Sci* 2012; **181**: 569-570 [PMID: 22373590 DOI: 10.1007/s11845-012-0808-7]
16 **Casazza F**, Morpurgo M. The varying evolution of Friedreich's ataxia cardiomyopathy. *Am J Cardiol* 1996; **77**: 895-898 [PMID: 8623752 DOI: 10.1016/S0002-9149(97)89194-1]
17 **Regner SR**, Lagedrost SJ, Plappert T, Paulsen EK, Friedman LS, Snyder ML, Perlman SL, Mathews KD, Wilmot GR, Schadt KA, Sutton MS, Lynch DR. Analysis of echocardiograms in a large heterogeneous cohort of patients with friedreich ataxia. *Am J Cardiol* 2012; **109**: 401-405 [PMID: 22078220 DOI: 10.1016/j.amjcard.2011.09.025]
18 **Weidemann F**, Störk S, Liu D, Hu K, Herrmann S, Ertl G, Niemann M. Cardiomyopathy of Friedreich ataxia. *J Neurochem* 2013; **126** Suppl 1: 88-93 [PMID: 23859344 DOI: 10.1111/jnc.12217]
19 **St John Sutton M**, Ky B, Regner SR, Schadt K, Plappert T, He J, D'Souza B, Lynch DR. Longitudinal strain in Friedreich Ataxia: a potential marker for early left ventricular dysfunction. *Echocardiography* 2014; **31**: 50-57 [PMID: 23834395 DOI: 10.1111/echo.12287]
Raman SV, Phatak K, Hoyle JC, Pennell ML, McCarthy B, Tran T, Prior TW, Olesik JW, Lutton A,

20 Rankin C, Kissel JT, Al-Dahhak R. Impaired myocardial perfusion reserve and fibrosis in Friedreich ataxia: a mitochondrial cardiomyopathy with metabolic syndrome. *Eur Heart J* 2011; **32**: 561-567 [PMID: 21156720 DOI: 10.1093/eurheartj/ehq443]

21 **Raman SV**, Dickerson JA, Al-Dahhak R. Myocardial ischemia in the absence of epicardial coronary artery disease in Friedreich's ataxia. *J Cardiovasc Magn Reson* 2008; **10**: 15 [PMID: 18397518 DOI: 10.1186/1532-429X-10-15]

22 **Kipps A**, Alexander M, Colan SD, Gauvreau K, Smoot L, Crawford L, Darras BT, Blume ED. The longitudinal course of cardiomyopathy in Friedreich's ataxia during childhood. *Pediatr Cardiol* 2009; **30**: 306-310 [PMID: 18716706 DOI: 10.1007/s00246-008-9305-1]

23 **Rustin P**, Bonnet D, Rötig A, Munnich A, Sidi D. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2004; **62**: 524-525; author reply 525; discussion 525 [PMID: 14872056 DOI: 10.1212/wnl.62.3.524]

24 **Tsou AY**, Paulsen EK, Lagedrost SJ, Perlman SL, Mathews KD, Wilmot GR, Ravina B, Koeppen AH, Lynch DR. Mortality in Friedreich ataxia. *J Neurol Sci* 2011; **307**: 46-49 [PMID: 21652007 DOI: 10.1016/j.jns.2011.05.023]

25 **Corben LA**, Lynch D, Pandolfo M, Schulz JB, Delatycki MB; Clinical Management Guidelines Writing Group. Consensus clinical management guidelines for Friedreich ataxia. *Orphanet J Rare Dis* 2014; **9**: 184 [PMID: 25928624 DOI: 10.1186/s13023-014-0184-7]

26 **Meier T**, Buyse G. Idebenone: an emerging therapy for Friedreich ataxia. *J Neurol* 2009; **256** Suppl 1: 25-30 [PMID: 19283347 DOI: 10.1007/s00415-009-1005-0]

27 **Mariotti C**, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 2003; **60**: 1676-1679 [PMID: 12771264]

28 **Perdomini M**, Belbellaa B, Monassier L, Reutenauer L, Messaddeq N, Cartier N, Crystal RG, Aubourg P, Puccio H. Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia. *Nat Med* 2014; **20**: 542-547 [PMID: 24705334 DOI: 10.1038/nm.3510]

29 **Leonard H**, Forsyth R. Friedreich's ataxia presenting after cardiac transplantation. *Arch Dis Child* 2001; **84**: 167-168 [PMID: 11159298 DOI: 10.1136/adc.84.2.167]

30 **Weidemann F**, Rummey C, Bijnens B, Störk S, Jasaityte R, Dhooge J, Baltabaeva A, Sutherland G, Schulz JB, Meier T; Mitochondrial Protection with Idebenone in Cardiac or Neurological Outcome (MICONOS) study group. The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. *Circulation* 2012; **125**: 1626-1634 [PMID: 22379112 DOI: 10.1161/CIRCULATIONAHA.111.059477]

31 **Weidemann F**, Liu D, Hu K, Florescu C, Niemann M, Herrmann S, Kramer B, Klebe S, Doppler K, Üçeyler N, Ritter CO, Ertl G, Störk S. The cardiomyopathy in Friedreich's ataxia - New biomarker for staging cardiac involvement. *Int J Cardiol* 2015; **194**: 50-57 [PMID: 26005806 DOI: 10.1016/j.ijcard.2015.05.074]

32 **Mottram PM**, Delatycki MB, Donelan L, Gelman JS, Corben L, Peverill RE. Early changes in left ventricular long-axis function in Friedreich ataxia: relation with the FXN gene mutation and cardiac structural change. *J Am Soc Echocardiogr* 2011; **24**: 782-789 [PMID: 21570254 DOI: 10.1016/j.echo.2011.04.004]

P- Reviewer: Anan R, Falconi M, Kharlamov AN, Pastromas S
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Song H

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 January 26; 11(1): 13-23

DOI: 10.4330/wjc.v11.i1.13

ISSN 1949-8462 (online)

MINIREVIEWS

Current evidence of drug-elution therapy for infrapopliteal arterial disease

Stavros Spiliopoulos, Nikiforos Vasiniotis Kamarinos, Elias Brountzos

ORCID number: Stavros Spiliopoulos (0000-0003-1860-0568); Nikiforos Vasiniotis Kamarinos (0000-0002-1162-1270); Elias Brountzos (0000-0002-7504-2016).

Author contributions: Spiliopoulos S conceived the review and made critical revisions to its content; Vasiniotis Kamarinos N drafted the manuscript and made critical revisions to its content; Brountzos E drafted the manuscript and made critical revisions to its content; all authors approved the final version of the article.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: July 27, 2018
Peer-review started: July 30, 2018
First decision: October 5, 2018
Revised: October 23, 2018
Accepted: January 1, 2019

Stavros Spiliopoulos, Nikiforos Vasiniotis Kamarinos, Elias Brountzos, 2nd Radiology Department, Interventional Radiology Unit, University of Athens, Attikon University General Hospital, Athens 12461, Greece

Corresponding author: Stavros Spiliopoulos, MD, PhD, Assistant Professor, 2nd Radiology Department, Interventional Radiology Unit, Attikon University Hospital, University of Athens, Attikon University General Hospital, Athens 12461, Greece, Athens 12461, Greece.
stavspiliop@med.uoa.gr
Telephone: +30-210-5831832

Abstract

New and sophisticated endovascular devices, such as drug-eluting stents (DES) and drug-coated balloons (DCB), provide targeted drug delivery to affected vessels. The invention of these devices has made it possible to address the reparative cascade of arterial wall injury following balloon angioplasty that results in restenosis. DESs were first used for the treatment of infrapopliteal lesions almost 20 years ago. More recently, however, DCB technology is being investigated to improve outcomes of endovascular below-the-knee arterial procedures, avoiding the need for a metallic scaffold. Today, level IA evidence supports the use of infrapopliteal DES for short to medium length lesions, although robust evidence that justifies the use of DCBs in this anatomical area is missing. This review summarizes and discusses all available data on infrapopliteal drug-elution devices and highlights the most promising future perspectives.

Key words: Drug-elution therapy; Infrapopliteal arterial disease; Current evidence; Drug-coated balloons; Drug-eluting stents

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Currently available level IA evidence justifies the use of infrapopliteal drug-eluting stents for short to medium length lesions in selected patients with specific anatomical criteria. The role of infrapopliteal drug-coated balloons remains to be determined.

Citation: Spiliopoulos S, Vasiniotis Kamarinos N, Brountzos E. Current evidence of drug-elution therapy for infrapopliteal arterial disease. *World J Cardiol* 2019; 11(1): 13-23
URL: https://www.wjgnet.com/1949-8462/full/v11/i1/13.htm

Article in press: January 1, 2019
Published online: January 26, 2019

DOI: https://dx.doi.org/10.4330/wjc.v11.i1.13

INTRODUCTION

Infrapopliteal atherosclerotic arterial disease, either alone or combined with aortoiliac and femoropopliteal vascular disease, is the leading cause of critical limb ischemia (CLI) and severe, lifestyle-limiting, intermittent claudication (IC)[1]. In the western population, the incidence of infrapopliteal disease is strongly correlated with the prevalence of diabetes mellitus, and is continuously rising due to increased life expectancy in developed countries[2]. Foot ulceration with tissue loss and gangrene are some of the manifestations of CLI, which may lead to major amputation if the affected arteries are not promptly revascularized[3]. CLI is considered to be responsible for approximately 90% of the major amputations performed worldwide, and is a significant cause of morbidity and mortality[2,3]. In diabetic patients, CLI represents a medical emergency, as the concomitant foot architectural changes and potential infections can rapidly compromise limb salvage[4]. Besides, the long vessel occlusions combined with poor distal runoff, prevalent in diabetic CLI patients, represent a considerable challenge for healthcare specialists[5].

Patients with ischemic rest pain, diabetic or non-healing foot ulcers, or gangrene involving any portion of the lower limbs should be evaluated with the WIFI classification system that assesses the three primary factors contributing to limb threat risk: wound (W), ischemia (I) and foot infection (FI)[6,7]. After considering these components and staging each patient, revascularization should be attempted[7]. The WIFI classification system is depicted in Table 1. Femorodistal below-the-knee (BTK) bypass surgery with autologous vein grafts has been established in the past as the gold standard treatment for CLI[2]. However, the presence of various underlying comorbidities, as well as the scarcity of non-diseased donor and run-off vessels, render a significant number of CLI patients unsuitable for surgery. Direct comparison data between bypass surgery and percutaneous BTK procedures are limited, with only one randomized multi-center trial available in the literature. Nevertheless, the evolution of interventional techniques, along with the development of novel devices, contributed to a paradigm shift in CLI treatment; nowadays endovascular methods can be used for multiple vessel recanalization and are related to comparable clinical outcomes for open surgery[3,8-10]. Endovascular revascularization, by virtue of its minimally-invasive nature, is characterized by decreased perioperative complications and cardiovascular stress that result in both shorter hospital stays as well as low morbidity and mortality[11,12].

Plain balloon angioplasty was the primary endovascular therapy utilized in the infrapopliteal territory. Although it appeared to be effective in the short-term, post-angioplasty elastic vessel recoil and flow-limiting dissection contributed to reocclusion and relapse of ischemic symptoms[13]. Despite the fact that balloon angioplasty may be repeated, each procedure involves an inherent risk of technical failure and yields additional cost[4]. Attempting to address this issue, Dorros *et al*[14] pioneered the placement of the first infrapopliteal bare metal stent (BMS) 25 years ago. However, BMS application has been associated with poor outcomes in the mid-term due to the phenomenon of in-stent restenosis[15]. Constant irritation of the vessel wall by the metal stent mesh results in inflammation, intimal hyperplasia, negative vessel remodeling and ultimate reocclusion[16,17]. Occlusion rates are high; half of the BMS become occluded within the first year and can lead to major amputation[18,19]. As a result, stenting in the infrapopliteal region has been reserved as a bail-out procedure in order to maximize acute lumen gain and avoid early vessel reocclusion.

New and sophisticated endovascular devices, such as drug-eluting stents (DES) and drug-coated balloons (DCB), provide targeted drug delivery to affected vessels. The invention of these devices has made it possible to address the reparative cascade of arterial wall injury following balloon angioplasty that results in restenosis. BTK arteries share many characteristics with coronary arteries; this fact has motivated several investigators to apply this drug-eluting technology, widely used in percutaneous coronary interventions, in the infrapopliteal territory in order to improve clinical outcomes.

DES

Table 1 Assessment of amputation risk: wound (W), ischemia (I) and foot infection classification[6,7]

Component	Score	Description		
W	0	No ulcer (ischemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I		ABI	Ankle pressure (mmHg)	Toe pressure or TcPO2
	0	≥ 0.80	> 100	≥ 60
	1	0.6-0.79	70-100	40-59
	2	0.4-0.59	50-70	30-39
	3	< 0.40	< 50	< 30
FI	0	No symptoms or signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

DESs were introduced into clinical practice by interventional cardiologists, and demonstrated favorable outcomes regarding late lumen loss (LLL) and rate-of-repeat revascularization procedures[20]. The comparable size of tibial to coronary arteries, and the superior efficacy of these stents compared to BMSs, led to the first clinical application of DES in the infrapopliteal arteries, with the goal of inhibiting restenosis and prolong uninterrupted blood supply to the foot[4]. The concept of DES technology is based on covering the stent's strut with a polymer matrix, such as silicone, polyethylene vinyl alcohol or cellulose ester, that is saturated with a specific drug. Some DESs are polymer-free, and the drug is applied directly onto the metallic strut[21]. DESs inhibit neointimal hyperplasia and smooth muscle cell proliferation by releasing the incorporated drug into the vessel wall over a standard period of time. The pharmaceutical agents that are most commonly used are immunosuppressants of the "-olimus family," *i.e.*, sirolimus, everolimus and tacrolimus, or the anti-mitotic agent paclitaxel. Sirolimus (rapamycin) is a natural lipophilic macrolide compound with both immunosuppressive and antiproliferative properties. Paclitaxel is a cytotoxic and antineoplastic drug that promotes microtubule stabilization, blocking M phase of the cell cycle, thus leading to cellular death[18]. The first clinical applications of DES in infrapopliteal arteries for the treatment of CLI demonstrated encouraging mid-term results[18,22-25].

Following these initial promising single-center studies, multicenter randomized controlled trials (RCT) (YUKON-BTX, DESTINY and ACHILLES trials), reported low infrapopliteal vessel restenosis rate, higher event-free survival and improved quality of life. These provided level IA evidence for DES use in short focal infrapopliteal lesions (< 120 mm)[26-28].

In the ACHILLES trial, precisely 200 patients suffering from either CLI (> 60%) or Rutherford class 3 IC were enrolled in 17 European centers and were randomized to undergo primary DES with the CYPHER SELECT© PLUS sirolimus-eluting stent (Cordis, United States) or plain balloon angioplasty of the infrapopliteal arteries. Mean lesion length was 27 ± 21 mm. The device success rate was significantly higher for DES (95.5% *vs* 58.2%, $P = 0.001$), while DES at 12 mo achieved significantly lower restenosis rates (22.4% *vs* 41.9%, $P = 0.019$), superior patency (75.0% *vs* 57.1%, $P = 0.025$) and improved Rutherford class. Revascularization procedures and amputation rates were similar for both treatment options[28]. In a post hoc analysis of this trial, Katsanos *et al*[29] reported that DES use was found to accelerate wound healing compared with balloon angioplasty, a substantial outcome especially for patients with diabetes, to whom rapid wound healing is imperative to avoid superinfection and subsequent limb loss[29]. In the DESTINY multicenter RCT, 140 patients with CLI were randomized to receive either the XIENCE V Everolimus-eluting balloon-expandable stent or the Multilink vision bare balloon-expandable stent (ABBOTT, United States). The maximum lesion length allowed was 40mm, and primary patency was defined as the absence of > 50% restenosis assessed by quantitative analysis of contrast angiography. At 12 mo, both primary patency (85% *vs* 54%, $P = 0.0001$) and re-intervention (85% *vs* 54%, $P = 0.0001$) rates were significantly improved with DES use. Moreover, the Xience V DES significantly reduced both mean in-stent stenosis (21% ± 21% *vs* 47% ± 27%, $P < 0.0001$) and mean in-stent LLL (0.78 ± 0.63 mm *vs* 1.41 ± 0.89 mm, $P = 0.001$)[27]. Finally, the YUKON-BTK

multicenter, double-blind RCT randomized 161 suffering patients (CLI or IC) to receive endovascular treatment with either the YUKON-BTX polymer-free sirolimus-eluting stent (Translumina, Germany) or a placebo-coated bare-metal stent. Again, the 12 mo primary (80.6% *vs* 55.6%, $P = 0.004$) and secondary (91.9% *vs* 71.4%, $P = 0.005$) patency rates were significantly higher for the DES group, while changes in Rutherford-Becker classification were also significantly superior in the DES group[26].

Meta-analysis of the above three multicenter RCTs confirmed these findings and demonstrated the superiority of DES over plain balloon angioplasty and BMSs[30]. Specifically, DESs were proven to be significantly superior in terms of 1 year primary patency [80.0% *vs* 58.5%; number needed-to-treat (NNT) = 4.8], improvement of Rutherford-Becker class (79.0% *vs* 69.6%; NNT = 11.1), target lesion revascularization (TLR) events (9.9% *vs* 22.0%; NNT = 8.3), wound healing (76.8% *vs* 59.7%; 2; NNT = 5.9), and event-free survival (72.2% *vs* 57.3%; pooled; NNT = 6.7).

Recently, data about long-term outcomes of DES application in infrapopliteal arterial disease were published in the PADI study; the only multicenter RCT study with the long-awaited 5-year follow up data[31]. In three vascular centers in the Netherlands, Paclitaxel-eluting stents (PES) (TAXUS Liberte; Boston Scientific, United States) were randomized *vs* both PTA and bail-out bare metal stenting. A total of 137 patients with CLI were included in the study. At 5 years follow-up, amputation-free survival and event-free survival rates were significantly superior in the PES group (26.2% *vs* 15.3%, $P = 0.041$ and 31.8% *vs* 20.4%, $P = 0.043$, respectively), while amputation rate was also lower for PES (19.3% *vs* 34.0%, $P = 0.091$). Survival rates were similar between the two groups, while the duplex-assessed patency rate was still significantly higher in the PES group after four years follow-up (13.5% *vs* 32.6%, $P = 0.031$). All randomized controlled trials for infrapopliteal drug-eluting technologies are analytically reported in Table 2.

Long-term outcomes of DES placement in diabetic patients with CLI were evaluated in a clinical study that reported a 90.4% amputation-free interval at 5 and 10 years after the procedure, while survival rate was 55.5% and 36.2% at 5 and 10 years follow-up, respectively[5]. Half of the patients (50.3%) underwent a repeat revascularization procedure due to clinical relapse at 10 years follow-up. Nevertheless, long-term data beyond a 1 year follow-up of infrapopliteal DES remain scarce, and further multicenter RCTs are required to prove whether the use of this technology can improve long-term clinical outcomes. Specifically, in a recent meta-analysis of ten studies (eight RCTs and two cohort studies), which included 927 patients assigned to either DES (484) or control treatment (443), primary patency was significantly in favor of DES at one year. However, this advantage was not evident at 3 years follow-up. The authors concluded that more high-level, long-term data are needed[32].

The safety and superiority of DES in short to medium length lesions has been demonstrated by level IA evidence. Nevertheless, the polymorphic nature of BTK disease, which usually presents with very long lesions (> 20 cm) and requires treatment of bifurcations and flexion points, such as the distal anterior tibial artery and the pedal arch, still has several controversies and thus requires further investigation. Specifically, the YUKON-BTX, DESTINY, and ACHILLES trials excluded patients with infrapopliteal trifurcation lesions, lesions in juxta-articular regions or lesions subject to external compression. In an attempt to address these issues, Spiliopoulos e*t al*[33] reported the treatment outcomes of 39 patients with infrapopliteal bifurcation disease using techniques of coronary DES placement. The mean clinical follow-up period was 47.56 ± 14.8 mo, while the mean angiographic follow-up period was 17.56 ± 12.5 mo. The application of DES across the origin of tibial vessels was proven as a safe and effective method, and was associated with satisfactory long-term angiographic and clinical outcomes. Specifically, the overall amputation-free survival and TLR-free survival at 5 years were 84.3% and 58.0%, respectively. Two-vessel primary patency (no revascularization and no > 50% angiographic restenosis of either vessel forming the target bifurcation) was 77.2%, 47.5% and 33.9%, at 12, 24 and 36 mo follow-up, while primary patency of at least one of the treated vessels was 84.0%, 65.5% and 54.5%, at 12, 24 and 36 mo. In a study that was published the following year, similar results were reported of 54.5% two-vessel primary patency and 81.8% one-vessel primary patency at 6 mo[34].

Another challenging issue commonly faced by medical providers is the deployment of DES in anatomic flexion points. Severe compression resulting in DES fracture at the distal third of the anterior tibial artery has been related to in-stent restenosis/reocclusion, as well as the inability to recanalize the lesion with either endovascular or surgical means. Therefore, stent placement in this area, as well as the pedal arteries, must be avoided[35]. The concern of treating infrapopliteal DES in-stent restenosis/reocclusion has also been addressed. In a retrospective analysis of 367 patients treated with infrapopliteal DES, 54 cases of DES occlusion were noted (re-

Table 2 Summary of randomized controlled trials investigating infrapopliteal drug-eluting technologies

	Trial	Study design	Patients	Follow-up	CLI	Lesion length (cm)	Primary endpoints
DES	Falkowski *et al*[25], 2009	Single-centre BMS *vs* SES	50 patients (25 *vs* 25)	6 mo	32%	1.8 ± 2.4	LLL: SES 0.46 ± 0.72 *vs* BMS 1.70 ± 0.94 mm; $P < 0.001$ 6-mo restenosis: SES 16% *vs* BMS 76%; $P < 0.001$ 6-mo TLR: SES 12% *vs* BMS 14.56%; $P < 0.05$
	ACHILLES Scheinert *et al*[28], 2012	Multicentre PTA *vs* SES	200 patients (101 *vs* 99)	1 yr	39%	both 2.7 ± 2.1	1-yr in-segment binary restenosis by quantitative angiography: SES 22.4% *vs* PTA 41.9%, $P = 0.019$
	Below Tepe *et al*[39], 2010	Single-centre SES BMS *vs* PTA	63 limbs (4-arm trial; PTA pooled)	6 mo	100%	3.4 ± 0.3	6-mo restenosis: SES 9%, BMS 67% and PTA 75%
	YUKON-BTX Rastan *et al*[26], 2012	Multicentre BMS *vs* non-polymer SES	161 patients (79 *vs* 82)	3 yr	46.60%	3.1 ± 0.9	Event-free survival: 65.8% SES *vs* 44.6% BMS; $P = 0.02$
	DESTINY Bosiers *et al*[27], 2012	Multicentre BMS *vs* Everolimus stent	140 patients (66 *vs* 74)	1 yr	100%	1.7 ± 1.0	Angiographic primary patency: 85% DES *vs* 54% BMS; $P = 0.0001$
	PADI van Overhagen *et al*[31], 2017	Multicentre PTA *vs* PES	137 patients (64 *vs* 73)	5 yr	100%	2.2 ± 2.0	Major amputation: DES 19.3% *vs* 34.0% PTA; $P = 0.091$ Amputation-free survival: DES 26.2% *vs* PTA 15.3%, $P = 0.041$ Event-free survival: 31.8% DES *vs* 20.4% PTA, $P = 0.043$
PCB	DEBATE-BTK Liistro *et al*[45], 2013	Single-centre PTA *vs* PCB	132 patients (67 *vs* 65)	1 yr	100%	13.0 ± 8.0	
	IN.PACT DEEP Zeller *et al*[46], 2014	Multicentre PTA *vs* PCB	358 patients (119 *vs* 239)	1 yr	99.70%	11.1 ± 9.0	TLR: 9.2% PCB *vs* 13.1% PTA; $P = 0.291$ LLL: 0.61 ± 0.78 mm DCB *vs* 0.62 ± 0.78 mm PTA; $P = 0.950$
	BIOLUX P-II Zeller *et al*[47], 2015	Multicentre PTA *vs* PCB	72 patients (36 *vs* 36)	1 yr	77.80%	11.4 ± 8.7	6 mo patency loss: 17.1% PCB *vs* 26.1% PTA; $P = 0.298$
	IDEAS Siablis *et al*[52], 2014	Single-centre PCB *vs* DES	50 patients (25 *vs* 25)	6 mo	100%	DES 12.7 ± 4.6 PCB 14.8 ± 5.6	Angiographic binary restenosis: DES 28% *vs* 57.9% in PCB; $P = 0.0457$

PTA: Percutaneous transluminal angioplasty; CLI: Critical limb ischemia; BMS: Bare metal stent; PCB: Paclitaxel-coated balloon; DES: Drug-eluting stent; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TLR: Target lesion revascularization; CLI: Critical leg ischemia; LLL: Late lumen loss.

occlusion rate 11.4% within a 7 year study period), and the technical success of uneventful endovascular recanalization of DES occlusions was 90.7%. The authors concluded that intraluminal recanalization of infrapopliteal DES occlusions is safe and not technically demanding in the majority of cases[36].

DES occlusions have been studied using optical coherence tomography (OCT), which reveals in-stent neoatherosclerosis. The concept that antiproliferative properties of DES alter endothelial formation and function has been discussed but never proven. However, it's thought that these properties result in increased lipid insudation and macrophage activation, which precipitate both atherosclerosis of the neointima and vascular lumen loss[37,38]. Furthermore, the stent's durable polymer matrix acts as a source of continuous vessel irritation that triggers a local inflammatory reaction and can precipitate in-stent thrombosis. In the field of coronary disease, the phenomenon of neoatherosclerosis following both bare metal or DES has been correlated with very late acute stent thrombosis, and many authors advocate the prescription of long-term dual antiplatelet therapy to avoid late thrombotic events. Nevertheless, late stent thrombosis has never been investigated following infrapopliteal BMS placement and, therefore, whether this phenomenon is as frequent as in cases of DES placement remains to be addressed[38]. However, according to current knowledge, the need for long-term antiplatelet coverage to reduce the risk of acute or late thrombosis after DES placement might pose some restrictions on the use of these devices[20]. Tepe *et al*[39] have investigated the administration of GP IIb/IIIa blockade with sirolimus-eluting stents (SES), bare-metal stents and PTA. SES were correlated with significantly reduced restenosis, as the 6 mo restenosis rate was 9%, 67%, and 75%, respectively[39].

The development of novel DES with biodegradable polymer technology aims to improve vessel re-endothelialization and further decrease complications[40]. Initial outcomes of the application of bioabsorbable DES in 33 patients suffering from either CLI (68.4%) or claudication due to infrapopliteal vessel disease were excellent. The primary patency rates were 96% and 84.6%, and freedom from clinically-driven target lesion revascularization rates were 96% at 12 and 24 mo, respectively. Although mean lesion length was only 19.2 ± 11.6 mm, most likely due to the current availability of very short bioabsorbable DES, these results may soon lead to the implementation of this technology for CLI management[41].

Furthermore, a new generation of polymer-free, dedicated BTK DES is presently under investigation. Specifically, the Alvimedica Cre8™ BTK is a polymer-free, balloon-expandable platform-loaded stent with the Amphilimus™ antirestenotic agent (Sirolimus + Fatty Acid). Futhermore, the Angiolite BTK sirolimus-eluting peripheral stent (iVascular, Spain) is another balloon-expandable device consisting of a cobalt chromium alloy coated with a mix of sirolimus and last generation biostable fluorinated acrylate polymer. Clinical results from these devices are pending.

The cost-effectiveness of DES should indeed be placed under scrutiny; the direct cost of DES is higher than that of a plain balloon, while most CLI patients suffer from long multilevel tibial vessel lesions that cannot be treated with the short DES presently available. However, despite the increased direct cost, DESs appear cost-effective for the management of long infrapopliteal lesions due to the significantly reduced number of re-interventions that are required[42]. It is generally accepted that the direct cost-reduction resulting from deeper market penetration, combined with the development of longer devices, would further improve DES cost-effectiveness.

DCB

DCBs were first introduced in coronary artery procedures, and the applications of this technology have subsequently been expanded with the goal of confronting the endovascular treatment obstacles of femoropopliteal artery atherosclerotic disease. Today, there is strong level IA evidence derived from multiple multicenter RCTs and their meta-analysis demonstrating that femoropopliteal angioplasty using DCB significantly reduces restenosis rates[43]. This new technology to inhibit neointimal hyperplasia by administering a single dose of an antiproliferative agent within the vessel wall without the use of a permanent metallic scaffold ("leave nothing behind" concept) is rather appealing for the infrapopliteal vascular bed. As previously discussed, the distal third of the anterior tibial artery is not readily amenable to stent placement due to the compressive forces of the osseous and musculotendinous tissues in this area that can lead to stent deformations and fractures, and ultimately decreased patency rates[35]. DCB could provide a valid solution to such limitations presented by the utilization of DES in this territory. Furthermore, long lesions can be easily treated with DCBs as the available lengths reach up to 150 mm. DCB combines balloon angioplasty with local, high-dose, cytotoxic drug delivery. The drug is coated on the balloon using special excipients, and is delivered within the arterial layers during balloon inflation to both achieve a uniform application to the vessel wall and promote the death of smooth muscle cells in the media. This allows for early intimal re-endothelialization and vessel healing[4]. The pharmaceutical agent that is most

commonly used in DCB is paclitaxel, owing to its lipophilic properties that can generate high local tissue concentrations. Although the application of DCB is less likely to compromise any future surgical revascularization procedures and can achieve a drug distribution to the target lesion that is not affected by malapposition, as in the case of DES, available evidence about the efficacy of DCB in the BTK territory has been conflicting[44-47]. Despite the initial promising results deriving from single-center studies, two industry-driven, large-scale, multicenter RCT studies failed to prove any clinical or angiographic superiority of DCB over plain PTA. Precisely, the IN.PACT DEEP study was a prospective, multicenter, RCT designed to undergo independent clinical event adjudication as well as angiographic and wound core laboratory analysis. The trial included 358 CLI patients that were randomized 2:1 to receive IN.PACT Amphirion™ paclitaxel-coated balloon (Medtronic, USA) or PTA. Despite randomization of a considerably large population, significant baseline differences were noted between the two arms in important parameters, such mean lesion length (10.2 cm for DCB *vs* 12.9 cm for control, $P = 0.002$), impaired inflow (40.7% for DCB *vs* 28.8% for control, $P = 0.035$), and previous target limb revascularization (32.2% for *vs* 21.8% for control, $P = 0.047$). No statistically significant differences were detected in the primary efficacy outcomes of clinically-driven target lesion revascularization (CD-TLR: 9.2% PCB *vs* 13.1% control, $P = 0.291$) and late lumen loss (LLL: 0.61 ± 0.78 mm for PCB *vs* 0.62 ± 0.78 mm for control, $P = 0.950$) at 1 year follow-up. The composite primary safety endpoint (6 mo all-cause mortality, major amputation, and CD-TLR) was similar between PCB (17.7%) and control (15.8%), and the non-inferiority hypothesis was met ($P = 0.021$). However, major amputations at 12 mo were more than double in the PCB arm and on the verge of statistical significance (8.8% *vs* 3.6%, $P = 0.080$)[46]. After safety issues were raised, the study was interrupted, and the AmphirionTM paclitaxel-coated balloon was withdrawn from the market. It has been suggested that distal embolization due to loss of balloon coating during insertion may have contributed to these poor outcomes[48]. The company is currently recruiting patients in an RCT to investigate a novel PCB for BTK use[49]. In the BIOLUX P-II multicenter RCT study, 72 patients were randomized in a 1:1 ratio to undergo treatment with either the Passeo-18 Lux DCB (Biotronik AG, Switzerland) or Passeo-18 PTA. In this trial, the primary endpoint of 6 mo patency loss was not significantly inferior in the DCB group *vs* plain balloon angioplasty (17.1% *vs* 26.1%, respectively, $P = 0.298$), while major amputations were also similar (3.3% *vs* 5.6% at 12 mo, respectively). The 30 d composite primary safety endpoint (all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularization) was marginally superior in the DCB group (0% PCB *vs* 8.3% PTA, $P = 0.239$)[47]. The authors would like to comment that the patency rates of plain balloon angioplasty in both studies were unexpectedly high, taking into consideration reported data from previous infrapopliteal plain balloon angioplasty studies, a fact that potentially contributed to the inability to prove the anti-restenotic effect of PCB. The reason for this discrepancy remains to be clarified. Outcomes from a new generation of DCB are also pending. Lutonix® 014 DCB (paclitaxel dose 2 μg/mm^2) has been tested in a large-scale multicenter, single-arm registry, which included 314 patients from 26 sites and 12 countries. Patients suffered from either CLI or claudication due to infrapopliteal disease. Interim 6 mo results demonstrated an excellent safety profile, as freedom from major adverse limb events and perioperative death was 98.6% at 30 d and 96.0% at 6 mo, while freedom from TLR was 87.9% at 6 mo[50]. The final 24 mo results are expected in late 2019. The RangerTM (Boston Scientific Corporation, United States), a new-generation 2 μg/mm^2 DCB, is also under investigation. The single-center, open-label prospective trial sponsored by Boston Scientific has enrolled 30 CLI patients with infrapopliteal disease treated with the Ranger DCB. The study's efficacy primary outcome measures will be primary patency at 6 mo follow-up (no stenosis > 50% of the target lesion measured by quantitative vascular angiography). The safety outcome measurement will be the number of deaths and major amputations at 6 mo follow-up. The estimated study completion date is November 2018[51].

DES *VS* DCB FOR INFRAPOPLITEAL ARTERIAL DISEASE

In 2014, Siablis *et al*[52] sought to compare the efficacy of the two emerging drug-eluting technologies for long infrapopliteal lesions. The authors randomized 50 CLI patients to receive DES or DCB infrapopliteal treatment[52]. Among the inclusion criteria was a minimum lesion length of 70 mm. The primary endpoint of 6 mo angiographic > 50% restenosis, adjudicated by quantitative vessel analysis, was significantly less in the DES group (28% *vs* 57.9%, $P = 0.0457$). Nonetheless, LLL, TLR

and major amputation rates at 6 mo follow-up were similar between the two study groups. This is the only study directly comparing infrapopliteal DES *vs* DCB that reported that DCBs are associated with increased vessel restenosis at 6 mo, even though LLL was similar between the two groups. The authors can assume that reduced binary restenosis following DES deployment was due to a significantly superior initial luminal gain compared to DCB angioplasty. In addition, they can also assume that for small-vessel disease, maximizing the initial luminal gain could lead to less short-term binary restenosis. Nevertheless, better vessel preparation using atherectomy devices or less traumatic semi-compliant balloon catheters could also improve infrapopliteal DCB angioplasty outcomes. Indeed, the combination of DCB use with debulking atherectomy devices for the management of long, heavily calcified femoropopliteal de novo or restenotic lesions is supported by an increasing level of evidence. Orbital and directional atherectomy have been employed to remove occlusive intimal or neointimal tissue, allowing DCB to act directly on the vessel wall[53]. Moreover, in a recent Bayesian network meta-analysis by Katsanos *et al*[54], data from RCTs investigating all endovascular treatment options for BTK arterial disease were elaborated. In total, 16 RCTs with 1,805 patients were analyzed. Median follow-up was 1 year. The authors created a network of comparisons between infrapopliteal DES, DCB, plain balloon angioplasty and BMS, and calculated the cumulative rank probabilities to provide hierarchies of these treatments. Outcomes were found to be stable upon sensitivity and meta-regression analyses. No significant publication bias or inconsistency was detected. DESs were found to significantly reduce restenosis, amputations and revascularization procedures compared to BMSs and plain balloon angioplasty. Specifically, DES reduced restenosis compared with BMS [OR 0.26, 95%Credible Interval (CrI): 0.12 to 0.51] and plain balloon angioplasty (Odds Ratio (OR) 0.22, 95%CrI: 0.11 to 0.45), and also reduced TLR compared with plain balloon angioplasty (OR 0.41, 95%CrI: 0.22 to 0.75) and BMS (OR 0.26, 95%CrI: 0.15 to 0.45) (quality of evidence high). DCBs reduced TLR compared with plain balloon angioplasty (OR 0.55, 95%CrI: 0.34 to 0.90) and BMS (OR 0.35, 95%CrI: 0.18 to 0.67) (quality of evidence low to moderate), while plain balloon angioplasty resulted in significantly less TLR than BMS (OR 0.63, 95%CrI: 0.40 to 0.99) (level of evidence high). Furthermore, DES significantly reduced limb amputations compared with plain balloon angioplasty (OR 0.58, 95%CrI: 0.35 to 0.96), DCB (OR 0.51, 95%CrI: 0.26 to 0.98), or BMS (OR 0.38, 95%CrI: 0.19 to 0.72) (quality of evidence moderate to high), and improved wound healing compared with plain balloon angioplasty (OR 2.02, 95%CrI: 1.01 to 4.07) or BMS (OR 3.45, 95%CrI: 1.41 to 8.73) (quality of evidence high). The abovementioned high level of evidence establishes DES as the dominant endovascular treatment modality for BTK disease, although these outcomes mainly relate to short-to-medium length lesions and short-to-midterm follow-up.

DRUG INFUSION CATHETERS

New elution technologies for BTK treatment include catheters that can deliver therapeutic agents directly to the vessel wall, eliminating drug loss in the circulation. The Occlusion Perfusion Catheter (Advanced Catheter Therapies, Chattanooga, TN) is a universal delivery catheter capable of delivering paclitaxel to the media by forming a treatment chamber between two occlusion balloons. Results from a small multi-center study are promising[55]. Moreover, the infusion of dexamethasone in the adventitia of infrapopliteal arteries is also being studied. The LIMBO-PTA prospective, multicenter RCT is currently recruiting CLI patients (up to 120 participants) in up to 30 sites throughout Europe and the US in order to document the effects of adventitial delivery of dexamethasone via the Bullfrog Micro-Infusion Device (Mercator MedSystems, Inc., United States) after balloon angioplasty of infrapopliteal lesions[56]. Patients will be randomized 1:1 to receive either the active treatment or control therapy. The study is currently recruiting patients, and the estimated study completion date is February 2020.

CONCLUSION

Level IA evidence supports the use of infrapopliteal DES for short-to-medium length lesions. New developments in DES, such as bioabsorbable, polymer-free or even longer self-expanding DES, could maximize outcomes. Large trials to prove their superiority over other endovascular technologies in longer lesions are required. DCBs are a very appealing endovascular solution for infrapopliteal artery disease due to their inherent features, which enable metal-free inhibition of vessel restenosis.

However, data to prove the superiority of DCBs over plain balloon angioplasty are scarce. In a single-institution randomized comparison with DES in long infrapopliteal lesions, DES resulted in significantly less 6 mo binary restenosis. Multicenter RCTs and long-term results from large-scale registries are awaited in order to justify the use of DCBs in BTK disease. New-generation drug elution and drug infusion devices are also under investigation.

REFERENCES

1 **Graziani L**, Silvestro A, Bertone V, Manara E, Andreini R, Sigala A, Mingardi R, De Giglio R. Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. *Eur J Vasc Endovasc Surg* 2007; **33**: 453-460 [PMID: 17196848 DOI: 10.1016/j.ejvs.2006.11.022]

2 **Norgren L**, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; **45** Suppl S: S5-67 [PMID: 17223489 DOI: 10.1016/j.jvs.2006.12.037]

3 **Rooke TW**, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, Golzarian J, Gornik HL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE; American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61**: 1555-1570 [PMID: 23473760 DOI: 10.1016/j.jacc.2013.01.004]

4 **Karnabatidis D**, Spiliopoulos S, Katsanos K, Siablis D. Below-the-knee drug-eluting stents and drug-coated balloons. *Expert Rev Med Devices* 2012; **9**: 85-94 [PMID: 22145843 DOI: 10.1586/erd.11.67]

5 **Spiliopoulos S**, Theodosiadou V, Katsanos K, Kitrou P, Kagadis GC, Siablis D, Karnabatidis D. Long-Term Clinical Outcomes of Infrapopliteal Drug-Eluting Stent Placement for Critical Limb Ischemia in Diabetic Patients. *J Vasc Interv Radiol* 2015; **26**: 1423-1430 [PMID: 26250856 DOI: 10.1016/j.jvir.2015.06.034]

6 **Mills JL Sr**, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, Andros G; Society for Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg* 2014; **59**: 220-34.e1-2 [PMID: 24126108 DOI: 10.1016/j.jvs.2013.08.003]

7 **Aboyans V**, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JT, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; **39**: 763-816 [PMID: 28886620 DOI: 10.1093/eurheartj/ehx095]

8 **Adam DJ**, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H; BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 2005; **366**: 1925-1934 [PMID: 16325694 DOI: 10.1016/S0140-6736(05)67704-5]

9 **Verzini F**, De Rango P, Isernia G, Simonte G, Farchioni L, Cao P. Results of the "endovascular treatment first" policy for infrapopliteal disease. *J Cardiovasc Surg (Torino)* 2012; **53**: 179-188 [PMID: 22433737]

10 **Hicks CW**, Najafian A, Farber A, Menard MT, Malas MB, Black JH 3rd, Abularrage CJ. Below-knee endovascular interventions have better outcomes compared to open bypass for patients with critical limb ischemia. *Vasc Med* 2017; **22**: 28-34 [PMID: 27928034 DOI: 10.1177/1358863X16676901]

11 **Söder HK**, Manninen HI, Jaakkola P, Matsi PJ, Räsänen HT, Kaukanen E, Loponen P, Soimakallio S. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. *J Vasc Interv Radiol* 2000; **11**: 1021-1031 [PMID: 10997465 DOI: 10.1016/S1051-0443(07)61332-3]

12 **Nasr MK**, McCarthy RJ, Hardman J, Chalmers A, Horrocks M. The increasing role of percutaneous transluminal angioplasty in the primary management of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2002; **23**: 398-403 [PMID: 12027466 DOI: 10.1053/ejvs.2002.1615]

13 **Katsanos K**, Spiliopoulos S, Krokidis M, Karnabatidis D, Siablis D. Does below-the-knee placement of drug-eluting stents improve clinical outcomes? *J Cardiovasc Surg (Torino)* 2012; **53**: 195-203 [PMID: 22456642 DOI: 10.1532/HSF98.20111083]

14 **Dorros G**, Hall P, Prince C. Successful limb salvage after recanalization of an occluded infrapopliteal artery utilizing a balloon expandable (Palmaz-Schatz) stent. *Cathet Cardiovasc Diagn* 1993; **28**: 83-88 [PMID: 8416340 DOI: 10.1002/ccd.1810280117]

15 **Bosiers M**, Hart JP, Deloose K, Verbist J, Peeters P. Endovascular therapy as the primary approach for limb salvage in patients with critical limb ischemia: experience with 443 infrapopliteal procedures. *Vascular* 2006; **14**: 63-69 [PMID: 16956473 DOI: 10.2310/6670.2006.00014]

16 **Epstein SE**, Speir E, Unger EF, Guzman RJ, Finkel T. The basis of molecular strategies for treating coronary restenosis after angioplasty. *J Am Coll Cardiol* 1994; **23**: 1278-1288 [PMID: 8176084 DOI: 10.1016/0735-1097(94)90368-9]

17 **Herrman JP**, Hermans WR, Vos J, Serruys PW. Pharmacological approaches to the prevention of restenosis following angioplasty. The search for the Holy Grail? (Part I). *Drugs* 1993; **46**: 18-52 [PMID: 7691506 DOI: 10.2165/00003495-199346010-00003]

18 **Siablis D**, Kraniotis P, Karnabatidis D, Kagadis GC, Katsanos K, Tsolakis J. Sirolimus-eluting versus bare stents for bailout after suboptimal infrapopliteal angioplasty for critical limb ischemia: 6-month angiographic results from a nonrandomized prospective single-center study. *J Endovasc Ther* 2005; **12**: 685-695 [PMID: 16363898 DOI: 10.1583/05-1620MR.1]

19 **Siablis D**, Karnabatidis D, Katsanos K, Kagadis GC, Kraniotis P, Diamantopoulos A, Tsolakis J. Sirolimus-eluting versus bare stents after suboptimal infrapopliteal angioplasty for critical limb ischemia:

enduring 1-year angiographic and clinical benefit. *J Endovasc Ther* 2007; **14**: 241-250 [PMID: 17484536 DOI: 10.1177/152660280701400217]
20 **Karnabatidis D**, Spiliopoulos S, Diamantopoulos A, Katsanos K, Kagadis GC, Kakkos S, Siablis D. Primary everolimus-eluting stenting versus balloon angioplasty with bailout bare metal stenting of long infrapopliteal lesions for treatment of critical limb ischemia. *J Endovasc Ther* 2011; **18**: 1-12 [PMID: 21314342 DOI: 10.1583/10-3242.1]
21 **Duda SH**, Poerner TC, Wiesinger B, Rundback JH, Tepe G, Wiskirchen J, Haase KK. Drug-eluting stents: potential applications for peripheral arterial occlusive disease. *J Vasc Interv Radiol* 2003; **14**: 291-301 [PMID: 12631633 DOI: 10.1097/01.RVI.0000058423.01661.57]
22 **Marx SO**, Jayaraman T, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. *Circ Res* 1995; **76**: 412-417 [PMID: 7532117 DOI: 10.1161/01.RES.76.3.412]
23 **Commeau P**, Barragan P, Roquebert PO. Sirolimus for below the knee lesions: mid-term results of SiroBTK study. *Catheter Cardiovasc Interv* 2006; **68**: 793-798 [PMID: 17039538 DOI: 10.1002/ccd.20893]
24 **Bosiers M**, Deloose K, Verbist J, Peeters P. Percutaneous transluminal angioplasty for treatment of "below-the-knee" critical limb ischemia: early outcomes following the use of sirolimus-eluting stents. *J Cardiovasc Surg (Torino)* 2006; **47**: 171-176 [PMID: 16572091]
25 **Falkowski A**, Poncyljusz W, Wilk G, Szczerbo-Trojanowska M. The evaluation of primary stenting of sirolimus-eluting versus bare-metal stents in the treatment of atherosclerotic lesions of crural arteries. *Eur Radiol* 2009; **19**: 966-974 [PMID: 19034460 DOI: 10.1007/s00330-008-1225-1]
26 **Rastan A**, Tepe G, Krankenberg H, Zahorsky R, Beschorner U, Noory E, Sixt S, Schwarz T, Brechtel K, Böhme C, Neumann FJ, Zeller T. Sirolimus-eluting stents vs. bare-metal stents for treatment of focal lesions in infrapopliteal arteries: a double-blind, multi-centre, randomized clinical trial. *Eur Heart J* 2011; **32**: 2274-2281 [PMID: 21622669 DOI: 10.1093/eurheartj/ehr144]
27 **Bosiers M**, Scheinert D, Peeters P, Torsello G, Zeller T, Deloose K, Schmidt A, Tessarek J, Vinck E, Schwartz LB. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg* 2012; **55**: 390-398 [PMID: 22169682 DOI: 10.1016/j.jvs.2011.07.099]
28 **Scheinert D**, Katsanos K, Zeller T, Koppensteiner R, Commeau P, Bosiers M, Krankenberg H, Baumgartner I, Siablis D, Lammer J, Van Ransbeeck M, Qureshi AC, Stoll HP; ACHILLES Investigators. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. *J Am Coll Cardiol* 2012; **60**: 2290-2295 [PMID: 23194941 DOI: 10.1016/j.jacc.2012.08.989]
29 **Katsanos K**, Spiliopoulos S, Diamantopoulos A, Siablis D, Karnabatidis D, Scheinert D. Wound Healing Outcomes and Health-Related Quality-of-Life Changes in the ACHILLES Trial: 1-Year Results From a Prospective Randomized Controlled Trial of Infrapopliteal Balloon Angioplasty Versus Sirolimus-Eluting Stenting in Patients With Ischemic Peripheral Arterial Disease. *JACC Cardiovasc Interv* 2016; **9**: 259-267 [PMID: 26777329 DOI: 10.1016/j.jcin.2015.10.038]
30 **Katsanos K**, Spiliopoulos S, Diamantopoulos A, Karnabatidis D, Sabharwal T, Siablis D. Systematic review of infrapopliteal drug-eluting stents: a meta-analysis of randomized controlled trials. *Cardiovasc Intervent Radiol* 2013; **36**: 645-658 [PMID: 23435741 DOI: 10.1007/s00270-013-0578-2]
31 **Spreen MI**, Martens JM, Knippenberg B, van Dijk LC, de Vries JPM, Vos JA, de Borst GJ, Vonken EPA, Bijlstra OD, Wever JJ, Statius van Eps RG, Mali WPTM, van Overhagen H. Long-Term Follow-up of the PADI Trial: Percutaneous Transluminal Angioplasty Versus Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. *J Am Heart Assoc* 2017; **6**: pii: e004877 [PMID: 28411244 DOI: 10.1161/JAHA.116.004877]
32 **Liu X**, Zheng G, Wen S. Drug-eluting stents versus control therapy in the infrapopliteal disease: A meta-analysis of eight randomized controlled trials and two cohort studies. *Int J Surg* 2017; **44**: 166-175 [PMID: 28648791 DOI: 10.1016/j.ijsu.2017.06.075]
33 **Spiliopoulos S**, Fragkos G, Katsanos K, Diamantopoulos A, Karnabatidis D, Siablis D. Long-term outcomes following primary drug-eluting stenting of infrapopliteal bifurcations. *J Endovasc Ther* 2012; **19**: 788-796 [PMID: 23210878 DOI: 10.1583/JEVT-12-3993R.1]
34 **Werner M**, Scheinert S, Bausback Y, Bräunlich S, Ulrich M, Piorkowski M, Scheinert D, Schmidt A. Bifurcation stenting after failed angioplasty of infrapopliteal arteries in critical limb ischemia: techniques and short-term follow-up. *Catheter Cardiovasc Interv* 2013; **82**: E522-E528 [PMID: 23404942 DOI: 10.1002/ccd.24828]
35 **Karnabatidis D**, Katsanos K, Spiliopoulos S, Diamantopoulos A, Kagadis GC, Siablis D. Incidence, anatomical location, and clinical significance of compressions and fractures in infrapopliteal balloon-expandable metal stents. *J Endovasc Ther* 2009; **16**: 15-22 [PMID: 19281287 DOI: 10.1583/08-2530.1]
36 **Spiliopoulos S**, Theodosiadou V, Fragkos G, Diamantopoulos A, Katsanos K, Siablis D, Karnabatidis D. Feasibility of endovascular recanalization of occluded infrapopliteal drug-eluting stents. *J Endovasc Ther* 2014; **21**: 392-399 [PMID: 24915587 DOI: 10.1583/13-4593MR.1]
37 **Nakazawa G**, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol* 2011; **57**: 1314-1322 [PMID: 21376502 DOI: 10.1016/j.jacc.2011.01.011]
38 **Paraskevopoulos I**, Spiliopoulos S, Davlouros P, Karnabatidis D, Katsanos K, Alexopoulos D, Siablis D. Evaluation of below-the-knee drug-eluting stents with frequency-domain optical coherence tomography: neointimal hyperplasia and neoatherosclerosis. *J Endovasc Ther* 2013; **20**: 80-93 [PMID: 23391087 DOI: 10.1583/12-4091.1]
39 **Tepe G**, Schmehl J, Heller S, Brechtel K, Heuschmid M, Fenchel M, Kramer U, Miller S, Claussen CD. Drug eluting stents versus PTA with GP IIb/IIIa blockade below the knee in patients with current ulcers--The BELOW Study. *J Cardiovasc Surg (Torino)* 2010; **51**: 203-212 [PMID: 20354490 DOI: 10.1097/FJC.0b013e3181d4ca66]
40 **Kassimis G**, Spiliopoulos S, Katsanos K, Tsetis D, Krokidis ME. Bioresorbable scaffolds in peripheral arterial disease. *Expert Rev Cardiovasc Ther* 2014; **12**: 443-450 [PMID: 24650312 DOI: 10.1586/14779072.2014.897226]
41 **Varcoe RL**, Schouten O, Thomas SD, Lennox AF. Experience With the Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold in Arteries Below the Knee: 12-Month Clinical and Imaging Outcomes. *JACC Cardiovasc Interv* 2016; **9**: 1721-1728 [PMID: 27539693 DOI: 10.1016/j.jcin.2016.06.005]

42 **Katsanos K**, Karnabatidis D, Diamantopoulos A, Spiliopoulos S, Siablis D. Cost-effectiveness analysis of infrapopliteal drug-eluting stents. *Cardiovasc Intervent Radiol* 2013; **36**: 90-97 [PMID: 22414987 DOI: 10.1007/s00270-012-0370-8]

43 **Katsanos K**, Spiliopoulos S, Paraskevopoulos I, Diamantopoulos A, Karnabatidis D. Systematic Review and Meta-analysis of Randomized Controlled Trials of Paclitaxel-Coated Balloon Angioplasty in the Femoropopliteal Arteries: Role of Paclitaxel Dose and Bioavailability. *J Endovasc Ther* 2016; **23**: 356-370 [PMID: 26823485 DOI: 10.1177/1526602815626557]

44 **Schmidt A**, Piorkowski M, Werner M, Ulrich M, Bausback Y, Bräunlich S, Ick H, Schuster J, Botsios S, Kruse HJ, Varcoe RL, Scheinert D. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol* 2011; **58**: 1105-1109 [PMID: 21884945 DOI: 10.1016/j.jacc.2011.05.034]

45 **Liistro F**, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, Falsini G, Ventoruzzo G, Turini F, Bellandi G, Bolognese L. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation* 2013; **128**: 615-621 [PMID: 23797811 DOI: 10.1161/CIRCULATIONAHA.113.001811]

46 **Zeller T**, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, Peeters P, Vermassen F, Landini M, Snead DB, Kent KC, Rocha-Singh KJ; IN. PACT DEEP Trial Investigators. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol* 2014; **64**: 1568-1576 [PMID: 25301459 DOI: 10.1016/j.jacc.2014.06.1198]

47 **Zeller T**, Beschorner U, Pilger E, Bosiers M, Deloose K, Peeters P, Scheinert D, Schulte KL, Rastan A, Brodmann M. Paclitaxel-Coated Balloon in Infrapopliteal Arteries: 12-Month Results From the BIOLUX P-II Randomized Trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). *JACC Cardiovasc Interv* 2015; **8**: 1614-1622 [PMID: 26493253 DOI: 10.1016/j.jcin.2015.07.011]

48 **Herten M**, Stahlhoff S, Imm B, Schönefeld E, Schwindt A, Torsello GB. [Drug-coated balloons in the treatment of peripheral artery disease (PAD). History and current level of evidence]. *Radiologe* 2016; **56**: 240-253 [PMID: 26885653 DOI: 10.1007/s00117-015-0073-7]

49 Randomized Study of IN. PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter vs Standard Percutaneous Transluminal Angioplasty for the Treatment of Chronic Total Occlusions in the Infrapopliteal Arteries. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02963649 ClinicalTrials.gov Identifier: NCT02963649

50 **Thieme M**, Lichtenberg M, Brodmann M, Cioppa A, Scheinert D. Lutonix® 014 DCB global Below the Knee Registry Study: interim 6-month outcomes. *J Cardiovasc Surg (Torino)* 2018; **59**: 232-236 [PMID: 29363894 DOI: 10.23736/S0021-9509.18.10269-2]

51 An Efficacy and Safety Study to Evaluate Ranger Drug-eluting Balloon for Below the Knee Angioplasty in Patients With Critical Limb Ischemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: URL: https://clinicaltrials.gov/ct2/show/record/NCT02856230 ClinicalTrials.gov Identifier: NCT02856230

52 **Siablis D**, Kitrou PM, Spiliopoulos S, Katsanos K, Karnabatidis D. Paclitaxel-coated balloon angioplasty versus drug-eluting stenting for the treatment of infrapopliteal long-segment arterial occlusive disease: the IDEAS randomized controlled trial. *JACC Cardiovasc Interv* 2014; **7**: 1048-1056 [PMID: 25234679 DOI: 10.1016/j.jcin.2014.04.015]

53 **Korosoglou G**, Lichtenberg M, Celik S, Andrassy J, Brodmann M, Andrassy M. The evolving role of drug-coated balloons for the treatment of complex femoropopliteal lesions. *J Cardiovasc Surg (Torino)* 2018; **59**: 51-59 [PMID: 28975777 DOI: 10.23736/S0021-9509.17.10245-4]

54 **Katsanos K**, Kitrou P, Spiliopoulos S, Diamantopoulos A, Karnabatidis D. Comparative Effectiveness of Plain Balloon Angioplasty, Bare Metal Stents, Drug-Coated Balloons, and Drug-Eluting Stents for the Treatment of Infrapopliteal Artery Disease: Systematic Review and Bayesian Network Meta-analysis of Randomized Controlled Trials. *J Endovasc Ther* 2016; **23**: 851-863 [PMID: 27708143 DOI: 10.1177/1526602816671740]

55 **Bunch F**, Walker C, Kassab E, Carr J. A universal drug delivery catheter for the treatment of infrapopliteal arterial disease: Results from the multi-center first-in-human study. *Catheter Cardiovasc Interv* 2018; **91**: 296-301 [PMID: 28707423 DOI: 10.1002/ccd.27176]

56 LIMBO-PTA: Lower-Limb Adventitial Infusion of DexaMethasone Via Bullfrog to Reduce Occurrence of Restenosis After Percutaneous Transluminal Angioplasty Revascularization In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: URL: https://clinicaltrials.gov/ct2/show/record/NCT02479555 ClinicalTrials.gov Identifier: NCT02479555

P- Reviewer: Korosoglou G, Iacoviello M, Okutucu S
S- Editor: Ji FF **L- Editor:** Filipodia **E- Editor:** Song H

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 January 26; 11(1): 24-37

DOI: 10.4330/wjc.v11.i1.24

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Subclinical carotid atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography

Rafael Vidal-Perez, Raúl Franco-Gutiérrez, Alberto J Pérez-Pérez, Virginia Franco-Gutiérrez, Alberto Gascón-Vázquez, Andrea López-López, Ana María Testa-Fernández, Carlos González-Juanatey

ORCID number: Rafael Vidal-Perez (0000-0001-9944-8363); Raúl Franco-Gutiérrez (0000-0002-6272-2717); Alberto J Pérez-Pérez (0000-0002-7347-7024); Virginia Franco-Gutiérrez (0000-0002-9642-0848); Alberto Gascón-Vázquez (0000-0002-9601-2414); Ana María Testa-Fernández (0000-0002-9643-5847); Carlos González-Juanatey (0000-0002-4483-9778).

Author contributions: All authors helped to perform the research; Vidal-Perez R contributed to manuscript writing, performing procedures, and data analysis; Franco-Gutiérrez R contributed to manuscript writing, drafting of the document, conception and design of the study, and data analysis; Pérez-Pérez AJ, Franco-Gutierrez V, Gascón-Vázquez A and López-López A contributed to manuscript writing; Testa-Fernández AM and González-Juanatey C contributed to performing procedures, drafting of the document, and conception and design of the study.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to

Rafael Vidal-Perez, Raúl Franco-Gutiérrez, Alberto J Pérez-Pérez, Alberto Gascón-Vázquez, Andrea López-López, Ana María Testa-Fernández, Carlos González-Juanatey, Department of Cardiology, Hospital Universitario Lucus Augusti, Lugo 27003, Spain

Virginia Franco-Gutiérrez, Department of Otolaryngology, Hospital Carmen y Severo Ochoa, Cangas del Narcea 33800, Spain

Alberto Gascón-Vázquez, Faculty of Medicine, University of Santiago de Compostela, Santiago de Compostela 15782, Spain

Corresponding author: Raúl Franco-Gutiérrez, MD, Staff Physician, Department of Cardiology, Hospital Universitario Lucus Augusti, Av/Doctor Ulises Romero nº1, Lugo 27003, Spain.
raul.franco.gutierrez@sergas.es
Telephone: +34-982296738
Fax: +34-982295390

Abstract

BACKGROUND

Obesity is a major health problem due to its high prevalence. The relationship between obesity and cardiovascular disease is unclear. Some studies agree that certain conditions associated with obesity, such as physical inactivity or cardiovascular risk factors, are responsible for cardiovascular risk excess among obese people. Carotid intima-media thickness and carotid plaques (CP) have been associated with cardiovascular adverse events in healthy populations, and recent data suggest a higher prevalence of subclinical carotid atherosclerosis in obese and metabolically unhealthy patients. However, there are no studies correlating subclinical atherosclerosis and adverse events (AE) in obese subjects.

AIM

To determine the association between carotid disease and AE in obese patients with negative exercise echocardiography (EE).

METHODS

From January 1, 2006 to December 31, 2010, 2000 consecutive patients with a suspicion of coronary artery disease were submitted for EE and carotid ultrasonography. Exclusion criteria included previous vascular disease, left ventricular ejection fraction < 50%, positive EE, significant valvular heart disease

and inferior to submaximal EE. An AE was defined as all-cause mortality, myocardial infarction and cerebrovascular accident. Subclinical atherosclerosis was defined as CP presence according to Manheim and the American Society of Echocardiography Consensus.

RESULTS

Of the 652 patients who fulfilled the inclusion criteria, 226 (34.7%) had body mass indexes ≥ 30 kg/m^2, and 76 of them (33.6%) had CP. During a mean follow-up time of 8.2 (2.1) years, 27 AE were found (11.9%). Mean event-free survival at 1, 5 and 10 years was 99.1% (0.6), 95.1% (1.4) and 86.5% (2.7), respectively. In univariate analysis, CP predicted AE [hazard ratio (HR) 2.52, 95% confidence interval (CI) 1.17-5.46; P = 0.019]. In multivariable analysis, the presence of CP remained a predictor of AE (HR 2.26, 95%CI 1.04-4.95, P = 0.041). Other predictors identified were glomerular filtration rate (HR 0.98, 95%CI 0.96-0.99; P = 0.023), peak metabolic equivalents (HR 0.83, 95%CI 0.70–0.99, P = 0.034) and moderate mitral regurgitation (HR 5.02, 95%CI 1.42–17.75, P = 0.012).

CONCLUSION

Subclinical atherosclerosis defined by CP predicts AE in obese patients with negative EE. These patients could benefit from aggressive prevention measures.

Key words: Carotid intima media thickness; Carotid plaque; Carotid disease; Myocardial infarction; Mortality; Stroke; Exercise stress echocardiography

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There is a controversy about obesity and coronary artery disease prognosis. Several studies suggest a greater influence of physical inactivity than that of body mass index on mortality, but there are no data addressing the influence of subclinical atherosclerosis in patients with suspected coronary artery disease submitted to a non-invasive treadmill test. Our study shows that clinical atherosclerosis in other vascular beds, such as carotid plaque presence, is a greater predictor than functional capacity. These patients could benefit from aggressive prevention measures.

Citation: Vidal-Perez R, Franco-Gutiérrez R, Pérez-Pérez AJ, Franco-Gutiérrez V, Gascón-Vázquez A, López-López A, Testa-Fernández AM, González-Juanatey C. Subclinical carotid atherosclerosis predicts all-cause mortality and cardiovascular events in obese patients with negative exercise echocardiography. *World J Cardiol* 2019; 11(1): 24-37
URL: https://www.wjgnet.com/1949-8462/full/v11/i1/24.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i1.24

study enrolment.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript.

STROBE statement: The authors declare that the STROBE statement was followed in the article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: September 19, 2018
Peer-review started: September 19, 2018
First decision: October 26, 2018
Revised: December 16, 2018
Accepted: December 24, 2018
Article in press: December 24, 2018
Published online: January 26, 2019

INTRODUCTION

Obesity and body mass index (BMI) have increased in every nation in the last years, associating with a concomitant augmentation in the prevalence of traditional cardiovascular risk factors[1]. Obesity is independently associated with mortality and cardiovascular disease[2,3], likely through adverse remodelling of the arteries and a higher prevalence of subclinical vascular disease[4,5]. However, once cardiovascular disease (CVD) is established, the studies published so far show contradictory results. Some investigations suggest a protective effect of obesity[6,7]. Other researchers suggest that it is not the obesity itself, but certain associated characteristics, such as physical inactivity or metabolic risk factors, that explain the increased risk attributed to obese people. This suggestion gives rise to concepts such as metabolically healthy obesity[8,9] or fit obese patients[10,11].

Several epidemiological studies have demonstrated an independent association of carotid disease, defined as carotid plaques (CP) or carotid intima media thickness (CIMT), with overall mortality and cardiovascular events[12-16]. Although a negative treadmill exercise stress echocardiography is associated with good prognosis, according to European guidelines on stable coronary artery disease (CAD)[17], the annualized event rates defined as overall mortality and adverse cardiac events are nearly 1% in contemporary series[18]. It therefore seems necessary to define other tools

to decrease adverse events (AE) in these patients. As we previously described, carotid disease has been associated with adverse cardiovascular events[12-15], and one advantage of carotid ultrasonography is that it is not invasive and can be performed immediately after the exercise echocardiography (EE) using the same equipment. Moreover, ultrasound assessment of carotid arteries in patients with suspected CAD without known atherosclerotic disease is a class IIa C recommendation in the aforementioned European guidelines[17].

There are no studies addressing the value of subclinical atherosclerosis, defined as carotid disease, and AE in obese patients with or without CVD. The Multi-Ethnic Study of Atherosclerosis found significantly higher CIMT values in obese patients after adjustment for traditional CVD risk factors[4] or high-sensitivity C-reactive protein values[5]. Recent publications have found a higher percentage of subclinical carotid disease among metabolically unhealthy subjects compared to those with metabolic disease absence in obese people either with[19] or without CAD[20]. These studies emphasize the concept of obesity and associated phenotypes as predictors of AE. The aim of the current study is to determine if carotid disease is a predictor of AE in obese patients with CAD suspicion and negative treadmill stress echocardiography.

MATERIALS AND METHODS

We performed a retrospective cohort study of patients without significant heart or vascular disease, with a BMI ≥ 30 kg/m^2 and coronary artery disease suspicion with negative EE who were submitted for carotid ultrasonography.

Study population

Between January 2006 and December 2010, 2000 patients were submitted for stress echocardiography and carotid ultrasonography in our centre. Of them, 226 (11.3%) were included. Exclusion criteria included previous CAD [*n* = 702 (35.1%)], failure to achieve submaximal predicted heart rate [*n* = 159 (8.0%)], positive EE [*n* = 173 (8.7%)], hereditary cardiac disease (*e.g.*, Brugada syndrome, hypertrophic cardiomyopathy) [*n* = 25 (1.3%)], pharmacological stress test [*n* = 31 (1.6%)], previous stroke or transient ischaemic attack [*n* = 52 (2.6%)], peripheral artery disease [*n* = 31 (1.6%)], valvular heart disease, defined as aortic stenosis of any aetiology, mitral rheumatic stenosis or more than moderate valve regurgitation [*n* = 67 (3.4%)], planned revascularization [*n* = 4 (0.2%)], left ventricular ejection fraction less than 50% [*n* = 9 (0.5%)], loss during follow-up [*n* = 21 (1.1%)], technical problems accessing the stored images [*n* = 73 (3.7%)] and BMI < 30 kg/m^2 [*n* = 426 (21.3%)]. All patients signed the informed consent before performing the test. The study was approved by the Regional Ethics Committee. Figure 1 summarizes the selection criteria.

Demographic and clinical characteristics as well as CAD pre-test probabilities (PTP) were collected from available medical records at the time of the first clinical visit when EE was requested. Baseline echocardiography, carotid ultrasonography and stress testing data were collected from digitally stored images and medical records at the time of EE performance. CAD PTP and Systematic Coronary Risk Evaluation (SCORE) were assessed according to current European Society of Cardiology guidelines[1,17]. Treatment data were collected from medical records obtained at the first visit after EE performance. Of the 226 patients, 172 (76.1%) were evaluated the same day after EE performance. For the 54 patients that were not evaluated the same day, the median time between EE and first medical was 13.5 d (interquartile range 47.3).

Exercise stress echocardiography

Physiological parameters such as blood pressure, heart rate, and a 12-lead ECG were registered at baseline and at each stage of the treadmill stress protocol. The Bruce treadmill protocol was the preferred method of exercise, but Naughton was employed in a minority of subjects. A submaximal test was defined as an achievement of 85% of the age-predicted heart rate. EE was prematurely stopped in case of physical exhaustion, significant arrhythmia, severe hypertension or hypotensive response. Electrocardiographic changes suggestive of myocardial ischaemia during testing were defined as a new ST-segment deviation of 1 mm or more, measured at 80 ms after the J point.

Echocardiographic views were attained at rest, peak and immediately after exercise, and digitally stored for later comparisons. Assessment of regional wall motion was done in a 17-segment model of the left ventricle by using a motility score that ranged from 1 to 4, depending on its motion. Baseline and exercise wall motion score index were calculated as average scores of the 17 segments at rest and peak exercise, respectively. With the exception of isolated hypokinesia of the inferobasal

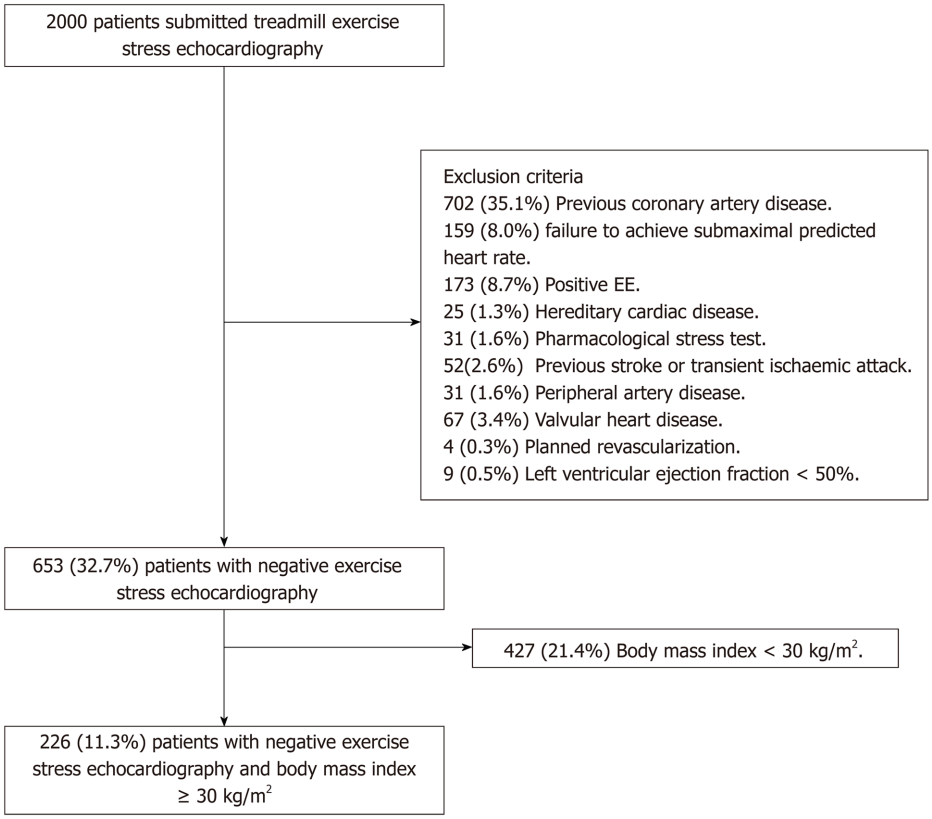


Figure 1 Flowchart of the 2000 patients submitted for exercise echocardiography. EE: Exercise echocardiography.

segment and worsening from akinesia to dyskinesia, exercise-induced echocardiography ischaemia was defined as new or worsening wall motion abnormalities developed during the stress test. When ischaemic changes affected three or more myocardial segments, the exercise test was considered as extensive ischemia, while multivessel ischaemia was defined when wall motion abnormalities were detected in two or more different coronary territories[21].

Carotid ultrasonography

The patients were submitted to carotid ultrasonography immediately after the EE performance using the same ultrasound equipment (Philips iE33; Philips Medical Systems, Best, Holland). The ARIC protocol study[12] and expert consensus[22-24] were followed for the CIMT measurement. CP was defined as focal structures invading 0.5 mm or more into the arterial lumen, presenting an increase of at least 50% in its thickness compared to the neighbouring CIMT value, or a CIMT greater than 1.5 mm as measured from the intima-lumen limit to the media adventitia limit[22-24]. Semi-automated edge recognition software was used (QLAB; Philips 110 Medical Systems, Andover, MA, United States).

Subclinical atherosclerosis was defined as a binary variable as CP presence/absence. Both carotid ultrasonography and EE stored images were examined by two cardiologists with broad experience in cardiac and carotid imaging who were blinded to the AE. A third expert reviewed the images in case of any doubt or disagreement.

End points

Follow-up data were obtained from the hospital database, medical records and death certificates. In the case of doubt, the Regional Mortality Registry was consulted. AE was defined as a combined endpoint of all-cause mortality, myocardial infarction and cerebrovascular accident. Myocardial infarction was defined as specified by the third universal definition of the myocardial infarction expert consensus document[25]. Stroke was defined as a loss of neurological function caused by an ischaemic event that lasted for more than 24 h and left residual signs.

Statistical analysis

No statistical sample-size calculation was done in our study. On the one hand, this was an innovative unicentric study in terms of using carotid ultrasonography in obese

patients with an EE with good prognosis. On the other hand, no previously published studies were found for statistical determination of sample size calculations.

Continuous variables were reported as the mean (standard deviation) or median (interquartile range) depending on Shapiro-Wilk normality test results, whereas categorical variables were reported as percentages. Cumulative death, myocardial infarction and cerebrovascular accident curves were calculated by the Kaplan-Meier method and compared using the log rank-test. Cox proportional-hazards regression was used for both univariate and multivariate analyses. All variables with *P* values less or equal to 0.2 were included in the multivariable analysis, and a retention set of 0.1 was applied. A *P* value of 0.05 or less was considered to be statistically significant.

RESULTS

Of the 226 patients, 76 (33.6%) had subclinical atherosclerosis defined by CP presence. Patients with CP were older ($P < 0.01$), with a higher prevalence of hypertension ($P = 0.002$) and dyslipidaemia ($P = 0.027$), higher SCORE ($P < 0.001$), lower glomerular filtration rate ($P < 0.001$), lower high-density lipoprotein cholesterol ($P = 0.043$) and higher triglycerides ($P = 0.011$). This group also showed a higher percentage of patients with intermediate-to-high PTP for CAD and lower percentage of cardiovascular risk factor–free subjects ($P < 0.001$). Regarding basal echocardiography, there were no differences in basal ejection fraction, but CP subjects had more mitral regurgitation ($P = 0.001$). Heart rate ($P < 0.001$), exercise time ($P = 0.011$) and metabolic equivalents (METs) ($P = 0.015$) were lower in the CP group, whereas mean CIMT ($P < 0.001$) and CIMT > 0.9 mm ($P < 0.001$) were higher. Patients with CP were more frequently on angiotensin II receptor blockers ($P = 0.001$), calcium channel blockers ($P = 0.011$), statins ($P = 0.043$) and oral antidiabetic ($P = 0.030$) treatment. The baseline characteristics are summarized in Tables 1 and 2.

Adverse events

During a mean follow-up of 8.0 (2.2) years, six (2.7%) non-ST elevation myocardial infarctions, two (0.9%) ST elevation myocardial infarctions, nine (4.0%) strokes and 15 (6.6%) deaths were recorded, for a total of 27 (11.9%) AE.

Kaplan–Meier adverse event-free survival at 1, 2, 3, 5 and 10 years was 99.1% (0.6), 98.7% (0.8), 96.9% (1.2), 95.1 (1.4%) and 86.5% (2.7%), respectively. Kaplan-Meier event-free survival was significantly higher in the non-CP group, with 99.3% (0.7) event-free survival at 1 and 2 years, 98.7% (0.9) at 2 and 3 years, 97.3% (1.3) at 5 years and 89.3% (3.5) at 10 years *vs* 98.7% (1.3) at 1 year, 97.4 (1.8%) at 2 and 3 years, 93.4 (2.8) at 5 years and 80.7% (5.0) at 10 years in the CP group ($P = 0.015$) (Figure 2).

Univariate analysis

Age ($P < 0.001$), glomerular filtration rate ($P = 0.002$), moderate mitral regurgitation ($P = 0.007$), cardiorespiratory fitness expressed in METs ($P = 0.001$) and CP presence ($P = 0.019$) were associated in univariate analysis with AE.

Multivariate analysis

Multivariable analysis showed that glomerular filtration rate ($P = 0.023$), moderate mitral regurgitation ($P = 0.012$), peak METs during the EE ($P = 0.034$) and CP ($P = 0.041$) were independent predictors of AE. Tables 3 and 4 show the univariate and multivariate analysis results.

DISCUSSION

To the best of our knowledge, this is the first article that correlates subclinical atherosclerosis with AE in obese patients, and specifically in obese patients with suspicion of ischaemic heart disease and good prognoses from EE.

Recent data from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation show that mortality in stable CAD is not negligible, with nearly 25% of patients dying during a mean follow-up of 10.5 years[26]. Moreover, the composite outcome of death, nonfatal myocardial infarction and stroke at a median follow-up period of 4.6 years has been approximately 20%[27]. For that reason, it is important to find predictors of evolution beyond the classic clinical, echocardiography, non-invasive and invasive CAD risk factors[17].

Our study shows that CP increased the probability of an AE in obese patients with CAD suspicion and negative EE by 2.26. Similar findings were obtained in other studies performed in ischaemic patients[28-34]. In the Angina Prognosis Study in

Table 1 Baseline characteristics

	n = 226	No plaque, *n* = 150	Plaque, *n* = 76	*P* value
Age	63.2 (11.4)	60.6 (12.1)	68.2 (7.3)	< 0.001[a]
Male sex	106 (46.9%)	64 (42.7%)	42 (55.3%)	0.099
Hypertension	166 (73.5%)	100 (66.7%)	66 (86.8%)	0.002[a]
Diabetes mellitus	45 (19.9%)	24 (16.0%)	21 (27.6%)	0.058
Dyslipidaemia	124 (54.9%)	74 (49.3%)	50 (65.8%)	0.027[a]
Current smoker	55 (24.3%)	36 (24.0%)	19 (25.0%)	0.999
Family history of premature CAD	17 (7.5%)	13 (8.7%)	4 (5.3%)	0.516
BMI, kg/m^2	33.3 (4.1)	33.2 (4.5)	33.4 (3.0)	0.694
Obesity				0.033[a]
Grade 1	179 (79.2%)	126 (84.0%)	53 (69.7%)	
Grade 2	39 (17.3%)	19 (12.7%)	20 (26.3%)	
Grade 3	8 (3.5%)	5 (3.3%)	3 (3.9%)	
No cardiovascular risk factors	29 (12.8%)	28 (18.7%)	1 (1.3%)	< 0.001[a]
SCORE				< 0.001[a]
Low-risk, < 1%	29 (12.8%)	28 (18.7%)	1 (1.3%)	
Moderate-risk, 1%-5%	113 (50.0%)	78 (52.0%)	35 (46.1%)	
High risk, 5%-10%	33 (14.6%)	20 (13.3%)	13 (17.1%)	
Very high-risk, ≥ 10%	49 (21.7%)	24 (16.0%)	25 (32.9%)	
Not classifiable	2 (0.9%)	0	2 (2.6%)	
CAD PTP				0.017[a]
< 15%	10 (4.4%)	10 (6.7%)	0	
15-65%	180 (79.6%)	121 (80.7%)	59 (77.6%)	
65-85%	36 (15.9%)	19 (12.7%)	17 (22.4%)	
> 85%	0 (0%)	0 (0%)	0 (0%)	
Fasting plasma glucose, mg/dL	113.8 (32.2)	112.5 (33.4)	116.6 (29.5)	0.369
Glomerular filtration rate, mL/min/1.73 m^2	87.6 (25.4)	91.4 (27.1)	79.7 (20.3)	< 0.001[a]
Total cholesterol, mg/dL	199.6 (40.5)	196.9 (38.5)	205.0 (43.9)	0.159
HDL cholesterol, mg/dL	48.6 (12.3)	49.6 (13.4)	46.5 (9.1)	0.043[a]
Triglycerides, mg/dL	143.6 (75.9)	133.0 (60.0)	164.8 (97.6)	0.011[a]
LDL cholesterol, mg/dL	122.1 (34.6)	120.2 (34.1)	125.9 (35.8)	0.257
Atrial fibrillation	26 (11.5%)	14 (9.3%)	12 (15.8%)	0.224
Treatment after EE				
Angiotensin-converting enzyme inhibitor	29 (12.8%)	16 (10.7%)	13 (17.1%)	0.247
Angiotensin II receptor blockers	99 (43.8%)	54 (36.0%)	45 (59.2%)	0.001[a]
Beta-blockers	72 (31.9%)	44 (29.3%)	28 (36.8%)	0.32
Calcium channel blockers	53 (23.5%)	27 (18.0%)	26 (34.2%)	0.011[a]
Nitrates	21 (9.3%)	13 (8.7%)	8 (10.5%)	0.832
Statins	111 (49.1%)	66 (44.0%)	45 (59.2%)	0.043[a]
Ezetimibe	6 (2.7%)	3 (2.0%)	3 (3.9%)	0.673
Fibrates	10 (4.4%)	5 (3.3%)	5 (6.6%)	0.476
Omega−3 fatty acids	4 (1.8%)	3 (2.0%)	1 (1.3%)	1
Antiplatelet drugs	109 (48.2%)	67 (44.7%)	42 (55.3%)	0.172
Anticoagulants drugs	17 (7.5%)	8 (5.3%)	9 (11.8%)	0.137
Oral antidiabetic drugs	28 (12.4%)	13 (8.7%)	15 (19.7%)	0.030[a]
Insulin treatment	5 (2.2%)	2 (1.3%)	3 (3.9%)	0.338

[a]$P < 0.05$. BMI: Body mass index; CAD: Coronary artery disease; EE: Exercise echocardiography; HDL cholesterol: High density lipoprotein cholesterol; LDL cholesterol: Low density lipoprotein cholesterol; PTP: Pre-test probability; SCORE: Systematic COronary Risk Evaluation.

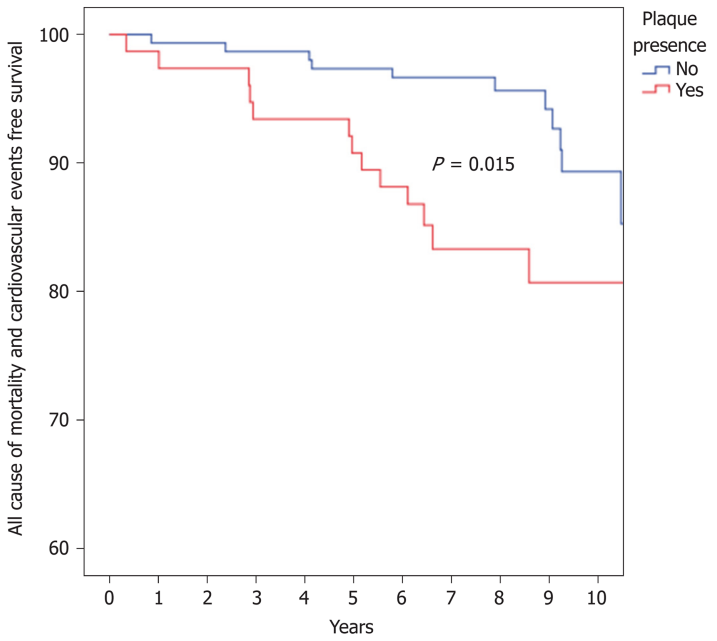
Stockholm[28], CIMT could not predict AE defined as cardiovascular death or cardiovascular events, while CP had a tendency (P = 0.056) to predict them in 809 patients younger than 70 years with clinical suspicion of CAD. Compared to our study, their patients were younger, more frequently male, with a lower percentage of

Table 2 Baseline echocardiography, treadmill exercise stress echocardiography and carotid ultrasonography characteristics

	n = 226	No plaque, *n* = 150	Plaque, *n* = 76	*P* value
Baseline echocardiography				
Baseline ejection fraction, %	64.6 (5.2)	64.5 (5.2)	64.7 (5.3)	0.823
Mitral regurgitation	82 (36.3%)	43 (28.7%)	39 (51.3%)	0.001[a]
Aortic regurgitation	57 (25.2%)	33 (22.0%)	24 (31.6%)	0.16
Tricuspid regurgitation	116 (51.3%)	73 (48.7%)	43 (56.6%)	0.325
Pulmonary regurgitation	3 (1.3%)	3 (2.0%)	0 (0%)	0.553
Pulmonary artery systolic pressure, mmHg	32.6 (7.3)	30.5 (5.8)	35.1 (6.2)	0.013[a]
Treadmill exercise stress echocardiography				
Stress protocol				0.778
Naughton	14 (6.2%)	10 (6.7%)	4 (5.3%)	
Bruce	212 (93.8%)	140 (93.3%)	72 (94.7%)	
Systolic blood pressure				
Baseline	141.8 (18.8)	140.7 (18.7)	143.9 (18.9)	0.222
Peak	197.6 (23.8)	196.6 (23.0)	199.7 (25.4)	0.361
Heart rate				
Baseline	73.6 (12.4)	74.0 (11.9)	72.8 (13.5)	0.409
Peak	146.0 (13.1)	148.2 (13.4)	141.7 (11.5)	< 0.001[a]
Percentage	93.1 (5.6)	93.0 (5.5)	93.3 (5.8)	0.718
Maximal stress test	26 (11.5%)	17 (11.3%)	9 (11.8%)	1
Rate-pressure, × 103 mmHg beats/min				
Basal	10.5 (2.4)	10.4 (2.3)	10.5 (2.6)	0.831
Peak	28.9 (4.4)	29.1 (4.4)	28.3 (4.3)	0.174
Exercise time, min	8.6 (2.9)	8.1 (2.9)	7.1 (2.4)	0.011[a]
METs	8.5 (2.9)	8.8 (3.1)	7.9 (2.3)	0.015[a]
Carotid ultrasonography				
CIMT, mm	0.80 (0.20)	0.74 (0.18)	0.91 (0.18)	< 0.001[a]
CIMT > 0.9 mm	62 (27.4%)	27 (18.0%)	35 (46.1%)	< 0.001[a]

[a]$P < 0.05$. CIMT: Carotid intima media thickness; METs: Metabolic equivalents.

traditional cardiovascular risk factors. More importantly, 14% of subjects had previous myocardial infarction, BMI was not reported, there was no prognosis assessment by non-invasive stress tests, and the CP definition was different from ours. Petersen *et al*[29] reported CP presence, especially heterogeneous plaques, as a predictor of all-cause deaths in 541 hospitalized cardiological patients, 25% of them with a BMI > 30 kg/m^2, after a median follow-up of 34 mo. Recently, Sirimarco *et al*[30] detected CP presence as a predictor of a composite of first occurrence of cardiovascular death, myocardial infarction, or coronary hospitalization during a follow-up period of 4 years in 45,227 middle-aged patients (45 years or more). In addition, CP in this study also predicted three or more cardiovascular risk factors or established CAD, cerebrovascular disease or peripheral artery disease in these patients, 28.1% of whom had BMI ≥ 30 kg/m^2. Both studies had heterogeneous populations, with 64% of patients diagnosed with ischaemic heart disease in the Petersen study and 55.6% with CAD (defined as stable angina, prior acute coronary event, history of percutaneous coronary intervention or coronary artery bypass grafting) in the Reduction of Atherothrombosis for Continued Health Registry. A non-invasive stress test was not performed in the CAD patients. Like ours, their patients with CP were older and had a higher prevalence of cardiovascular risk factors. Studies involving patients with CAD assessed by angiography have also been published. Komorovsky *et al*[31] identified echogenic or calcified CP as a predictor of cardiac death, non-fatal myocardial infarction, and rehospitalization for unstable angina in 337 consecutive patients with acute coronary syndrome submitted to coronary angiography. Along the same lines, Zielinski *et al*[32] found a significant association between CIMT and death from all causes, stroke, or myocardial infarction ($P = 0.010$) in hypertensive patients with CAD, defined as ≥ 50% stenosis by coronary angiography and a mean BMI of 28.6 (3.8) kg/m^2. Park *et al*[33] found CP as a predictor of cardiac death and hard major AE (death, stroke or myocardial infarction) in a



Years	0	2	4	6	8	10
CP abscence						
Events	0	1	2	5	6	10
Subjects at risk	150	149	148	144	92	31
CP presence						
Events	0	2	5	9	12	13
Subjects at risk	76	74	71	67	40	15

Figure 2 Time-to-event curves for the adverse events (all-cause mortality, myocardial infarction and stroke). CP: Carotid plaque.

cohort of 1,390 consecutive patients with angiographically-proven CAD and a mean BMI of 24.7 (3.4) kg/m^2 followed up during a mean of 54.2 mo. However, they did not find a significant relationship with CIMT. Although their inclusion criteria differed from ours, their findings were similar to other studies and ours in that the CP patients were older and had a greater prevalence of cardiovascular risk factors. One important issue is that 33.9% of patients had previous CAD, > 60% had left ventricular ejection fraction < 50%, 41.2% were treated with percutaneous coronary angioplasty or coronary artery bypass grafting, and they included stent restenosis and target vessel revascularization in the end point. Notably, these events were not only due to atherosclerosis progression. Finally, Steinvil *et al*[34] found significant associations between carotid stenosis and all-cause mortality, myocardial infarction, stroke, and any coronary revascularization procedure in 1,015 patients with significant CAD (defined as stenosis > 70% determined by angiography). However, they did not indicate which treatment was performed (medical, percutaneous intervention or surgical) or which medication was administered, and they did not specify other important prognostic factors, such as left ventricular ejection fraction.

Although CIMT was associated in classic[12-14] and contemporary studies[16] with overall mortality and cardiovascular events, we were not able to make this association in this research. CIMT as a surrogate marker of atherosclerosis and predictor of AE is penalized by the highly variability association in the different studies published so far[12-14,16,28,35]. Possible explanations for this discrepancy are differences in measurement methods, definitions of abnormal CIMT, atherosclerosis development between the vascular beds and in the adaptive response[16,35]. Recent studies have shown CP as a better predictor of cardiovascular events than CIMT[15]. It is possible that CP represents a more advanced atherogenesis stage than CIMT[15,36,37]. This issue explains why CP groups have a consistently higher prevalence of cardiovascular risk factors and are older[29,33], and why there was a lower percentage of patients with "healthy metabolic obesity" in our CP group. Our findings are in consonance with current European Guidelines on Cardiovascular Disease Prevention in Clinical Practice, where CIMT screening for cardiovascular risk assessment is not recommended (Class III level A indication), whereas CP assessment is a IIb B recommendation for the same purpose[1]. In this sense, patients with CP might benefit from aggressive preventive

Table 3 Univariate analysis of adverse events (all-cause mortality, myocardial infarction and cerebrovascular accident)

	Hazard ratio	95% Confidence interval	*P* value
Age	1.1	1.05-1.15	< 0.001[a]
Male sex	0.68	0.31-1.50	0.338
Hypertension	2.52	0.75-8.44	0.134
Diabetes mellitus	1.42	0.60-3.38	0.427
Dyslipidaemia	1.89	0.82-4.36	0.134
Current smoker	1.23	0.52-2.95	0.635
Family history of premature CAD	2.17	0.65-7.26	0.21
No cardiovascular risk factors	0.3	0.04-2.24	0.242
High/very high SCORE	2.15	0.98-4.71	0.055
Atrial fibrillation	2.45	0.98-6.10	0.055
CAD PTP ≥ 65%	1.44	0.57-3.60	0.441
BMI, kg/m^2	0.93	0.80-1.09	0.381
Fasting plasma glucose	1	0.99-1.01	0.863
Glomerular filtration rate, mL/min/1.73 m^2	0.98	0.96-0.99	0.002[a]
Total cholesterol, mg/dL	1	0.99-1.00	0.333
HDL cholesterol, mg/dL	1	0.95-1.02	0.409
Triglycerides, mg/dL	1	0.99-1.01	0.189
LDL cholesterol, mg/dL	0.99	0.98-1.01	0.294
Left ventricular ejection fraction, %	0.98	0.91-1.06	0.563
Moderate mitral regurgitation	5.29	1.57-17.84	0.007[a]
Moderate aortic regurgitation	4.24	0.57-31.55	0.158
Moderate tricuspid regurgitation	2.03	0.27-15.19	0.492
METs	0.77	0.66-0.90	0.001[a]
CIMT	0.91	0.14-6.19	0.926
CIMT > 0.9 mm	0.79	0.33-1.91	0.603
CP presence	2.52	1.17-5.46	0.019[a]

[a]*P* < 0.05. BMI: Body mass index; CAD: Coronary artery disease; CIMT: Carotid intima media thickness; CP: Carotid plaque; HDL cholesterol: High density lipoprotein cholesterol; LDL cholesterol: Low density lipoprotein cholesterol; METs: Metabolic equivalents; PTP: Pre-test probability; SCORE: Systematic Coronary Risk Evaluation.

measures, and it is important to highlight that in our study not all patients with subclinical atherosclerosis were treated after EE, such as very high-risk patients, with only 59.2% of the CP group receiving statins.

In addition to carotid disease, functional capacity was associated with AE. As previously mentioned, functional capacity has been associated with mortality in obese patients. Barry *et al*[10] meta-analysis showed that overweight and obese fit people presented similar mortality risks to normal weight fit subjects (odds ratio 1.21; 95% confidence interval (CI) 0.95 to 1.52), whereas obese unfit patients had higher overall mortality compared to normal weight fit individuals (odds ratio 2.46; 95%CI 1.92 to 3.14). Focusing on obese patients with CAD, Goel *et al*[38] found a statistical association between low fitness and mortality in patients with central obesity and a tendency towards such an association in obese and overweight patients. This was assessed by measuring the BMI of 855 patients who were enrolled in the Mayo Clinic cardiac rehabilitation programme, ultimately revealing that the association of BMI with mortality is complex and altered by fitness level.

It was not surprising to find glomerular filtration rate and mitral valve regurgitation as AE predictors. Several articles have found a significant relationship between CP and/or CIMT and CAD presence and extension in dialysis or end-stage renal disease patients[39,40]. Moreover, renal disease has been associated with a worse prognosis after acute coronary syndrome[41]. Focusing in obese patients with angiographic CAD, chronic kidney disease, defined as glomerular filtration rate < 60 mL/min/1.73 m^2, was a strong predictor of cardiac events [hazard ratio (HR) 1.63, 95%CI 1.05-2.53] and overall mortality (HR 2.17, 95%CI 1.54-3.07) in Asiatic subjects with BMI > 25 kg/m^2[42]. On the other hand, mitral valve regurgitation has been identified as an important long-term predictor of adverse outcomes in patients with

Table 4 Multivariate adverse event analysis (all-cause mortality, myocardial infarction and cerebrovascular accident)

	Hazard ratio	95% Confidence interval	*P* value
Glomerular filtration rate	0.98	0.96-0.99	0.023[a]
Moderate mitral regurgitation	5.02	1.42-17.75	0.012[a]
METs	0.83	0.70-0.99	0.034[a]
CP presence	2.26	1.04-4.95	0.041[a]

[a]$P < 0.05$. CP: Carotid plaque; METs: Metabolic equivalents.

ischaemic heart disease in different clinical scenarios, such as after acute myocardial infarction[43], coronary artery bypass graft surgery[44], percutaneous coronary intervention[45] and even stable CAD[46]. Recently, it has also been associated with a worse prognosis in patients referred for non-invasive stress testing (dobutamine stress echocardiography)[47].

The main strength of our study is the restrictive inclusion criteria, including obese patients with a good prognosis from EE, and the exclusion of potential confounding factors such as decreased left ventricular ejection fraction, previous CAD (and a subsequent different treatment approach), valvular heart disease that can evolve and produce AE (like aortic stenosis) and hereditary cardiac disease. Moreover, and in contrast to the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation study where patients were included after coronary angiography[26,27], our study is in consonance with European guidelines where PTP is first determined and then non-invasive testing is performed to establish CAD diagnosis and prognosis[17]. The main limitation of our study is that it is a retrospective and single centre study. For that reason, circulating or urinary biomarkers that might be helpful for guiding therapy in certain situations (*e.g.*, albuminuria in hypertension or DM) were not analysed. Nevertheless, this strategy is in consonance with 2016 European guidelines on CVD prevention in clinical practice, which advise against the routine assessment of circulating or urinary biomarkers as a method to reclassify cardiovascular risk[1]. Another limitation is the number of patients studied. However, even with a small sample size, this study was big enough to reveal significant differences in several issues traditionally related to AE in obese and non-obese patients, such as carotid disease, cardiorespiratory fitness, moderate mitral regurgitation and glomerular filtration rate. It is possible, however, that other clinical conditions like traditional cardiovascular risk factors may not be represented in the multivariate analysis due to insufficient statistical power. Finally, treatments were not included in the AE analysis. The main reason for this is because baseline medications are difficult to maintain throughout the study (mean follow-up time 8.2 ± 2.1 years) and can skew the results, since they can be easily added or removed by different professionals who are in charge of the patient throughout this extended period of time.

In conclusion, subclinical atherosclerosis defined by CP presence predicts AE in obese patients with negative EE. These patients could benefit from aggressive prevention measures.

ARTICLE HIGHLIGHTS

Research background

Obesity is independently associated with mortality and cardiovascular disease. However, once cardiovascular disease is established, the studies published so far show contradictory results. On the other hand, several epidemiological studies have demonstrated an independent association of carotid disease, defined as carotid plaques or carotid intima media thickness, with overall mortality and cardiovascular events.

Research motivation

There are no studies addressing the value of subclinical atherosclerosis, defined as carotid disease, and adverse events in obese patients with or without cardiovascular disease.

Research objectives

This study aimed to determine if carotid disease is a predictor of adverse events in obese patients with coronary artery disease suspicion and negative treadmill stress echocardiography.

Research methods

A retrospective cohort study of patients without significant heart or vascular disease, body mass

index ≥ 30 kg/m^2 and coronary artery disease suspicion with negative exercise echocardiography (EE) submitted to carotid ultrasonography. Between January 2006 and December 2010, 2000 patients were submitted for stress echocardiography and carotid ultrasonography in our centre. Of them, 226 (11.3%) were included. Adverse events were defined as all-cause mortality, myocardial infarction and cerebrovascular accident.

Research results

We found that 226 patients had body mass indexes ≥ 30 kg/m^2, and 76 of them (33.6%) had carotid plaques. During a mean follow-up time of 8.2 (2.1) years, 27 adverse events were found (11.9%). Mean event-free survival at 1, 5 and 10 years was 99.1% (0.6), 95.1% (1.4) and 86.5% (2.7), respectively. In univariate analysis, carotid plaques predicted adverse events (hazard ratio (HR) 2.52, 95% confidence interval (CI) 1.17-5.46; P = 0.019). In multivariable analysis, the presence of carotid plaques remained a predictor of adverse events (HR 2.26, 95%CI 1.04-4.95, P = 0.041). Other predictors identified were glomerular filtration rate, metabolic equivalents and moderate mitral regurgitation.

Research conclusions

This study demonstrates that subclinical atherosclerosis defined by carotid plaques predicts adverse events in obese patients with negative EE.

Research perspectives

To the best of our knowledge, this is the first article that correlates subclinical atherosclerosis and adverse events in obese patients, and specifically in obese patients with suspicion of ischaemic heart disease and a good prognosis from EE. One lesson from this study is that these good prognosis patients could be further stratified with carotid imaging and, in the case of plaque presence, benefit from more aggressive prevention measures.

REFERENCES

1 **Piepoli MF**, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention and amp; Rehabilitation (EACPR). *Eur Heart J* 2016; **37**: 2315-2381 [PMID: 27222591 DOI: 10.1093/eurheartj/ehw106]

2 **McGee DL**; Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol* 2005; **15**: 87-97 [PMID: 15652713 DOI: 10.1016/j.annepidem.2004.05.012]

3 **Emerging Risk Factors Collaboration**; Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; **377**: 1085-1095 [PMID: 21397319 DOI: 10.1016/S0140-6736(11)60105-0]

4 **Burke GL**, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, Chung H, Carnethon MR. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: The Multi-Ethnic Study of Atherosclerosis. *Arch Intern Med* 2008; **168**: 928-935 [PMID: 18474756 DOI: 10.1001/archinte.168.9.928]

5 **Blaha MJ**, Rivera JJ, Budoff MJ, Blankstein R, Agatston A, O'Leary DH, Cushman M, Lakoski S, Criqui MH, Szklo M, Blumenthal RS, Nasir K. Association between obesity, high-sensitivity C-reactive protein ≥2 mg/L, and subclinical atherosclerosis: implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2011; **31**: 1430-1438 [PMID: 21474823 DOI: 10.1161/ATVBAHA.111.223768]

6 **Oreopoulos A**, Padwal R, Norris CM, Mullen JC, Pretorius V, Kalantar-Zadeh K. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)* 2008; **16**: 442-450 [PMID: 18239657 DOI: 10.1038/oby.2007.36]

7 **Romero-Corral A**, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systematic review of cohort studies. *Lancet* 2006; **368**: 666-678 [PMID: 16920472 DOI: 10.1016/s0140-6736(06)69251-9]

8 **Kramer CK**, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. *Ann Intern Med* 2013; **159**: 758-769 [PMID: 24297192 DOI: 10.7326/0003-4819-159-11-201312030-00008]

9 **van der A DL**, Nooyens AC, van Duijnhoven FJ, Verschuren MM, Boer JM. All-cause mortality risk of metabolically healthy abdominal obese individuals: the EPIC-MORGEN study. *Obesity (Silver Spring)* 2014; **22**: 557-564 [PMID: 23595997 DOI: 10.1002/oby.20480]

10 **Barry VW**, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness *vs* fatness on all-cause mortality: A meta-analysis. *Prog Cardiovasc Dis* 2014; **56**: 382-390 [PMID: 24438729 DOI: 10.1016/j.pcad.2013.09.002]

11 **Ekelund U**, Ward HA, Norat T, Luan J, May AM, Weiderpass E, Sharp SJ, Overvad K, Østergaard JN, Tjønneland A, Johnsen NF, Mesrine S, Fournier A, Fagherazzi G, Trichopoulou A, Lagiou P, Trichopoulos D, Li K, Kaaks R, Ferrari P, Licaj I, Jenab M, Bergmann M, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Peeters PH, Monnikhof E, Bueno-de-Mesquita HB, Quirós JR, Agudo A,

Sánchez MJ, Huerta JM, Ardanaz E, Arriola L, Hedblad B, Wirfält E, Sund M, Johansson M, Key TJ, Travis RC, Khaw KT, Brage S, Wareham NJ, Riboli E. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: The European Prospective Investigation into Cancer and Nutrition Study (EPIC). *Am J Clin Nutr* 2015; **101**: 613-621 [PMID: 25733647 DOI: 10.3945/ajcn.114.100065]

12 **Chambless LE**, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol* 1997; **146**: 483-494 [PMID: 9290509 DOI: 10.1093/oxfordjournals.aje.a009302]

13 **Lorenz MW**, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation* 2007; **115**: 459-467 [PMID: 17242284 DOI: 10.1161/CIRCULATIONAHA.106.628875]

14 **Lorenz MW**, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke* 2006; **37**: 87-92 [PMID: 16339465 DOI: 10.1161/01.STR.0000196964.24024.ea]

15 **Inaba Y**, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis* 2012; **220**: 128-133 [PMID: 21764060 DOI: 10.1016/j.atherosclerosis.2011.06.044]

16 **Lorenz MW**, Gao L, Ziegelbauer K, Norata GD, Empana JP, Schmidtmann I, Lin HJ, McLachlan S, Bokemark L, Ronkainen K, Amato M, Schminke U, Srinivasan SR, Lind L, Okazaki S, Stehouwer CDA, Willeit P, Polak JF, Steinmetz H, Sander D, Poppert H, Desvarieux M, Ikram MA, Johnsen SH, Staub D, Sirtori CR, Iglseder B, Beloqui O, Engström G, Friera A, Rozza F, Xie W, Parraga G, Grigore L, Plichart M, Blankenberg S, Su TC, Schmidt C, Tuomainen TP, Veglia F, Völzke H, Nijpels G, Willeit J, Sacco RL, Franco OH, Uthoff H, Hedblad B, Suarez C, Izzo R, Zhao D, Wannarong T, Catapano A, Ducimetiere P, Espinola-Klein C, Chien KL, Price JF, Bergström G, Kauhanen J, Tremoli E, Dörr M, Berenson G, Kitagawa K, Dekker JM, Kiechl S, Sitzer M, Bickel H, Rundek T, Hofman A, Mathiesen EB, Castelnuovo S, Landecho MF, Rosvall M, Gabriel R, de Luca N, Liu J, Baldassarre D, Kavousi M, de Groot E, Bots ML, Yanez DN, Thompson SG; PROG-IMT study group. Predictive value for cardiovascular events of common carotid intima media thickness and its rate of change in individuals at high cardiovascular risk - Results from the PROG-IMT collaboration. *PLoS One* 2018; **13**: e0191172 [PMID: 29649236 DOI: 10.1371/journal.pone.0191172]

17 **Montalescot G**, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL; Task Force Members; ESC Committee for Practice Guidelines; Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; **34**: 2949-3003 [PMID: 23996286 DOI: 10.1093/eurheartj/eht296]

18 **Bouzas-Mosquera A**, Peteiro J, Alvarez-García N, Broullón FJ, Mosquera VX, García-Bueno L, Ferro L, Castro-Beiras A. Prediction of mortality and major cardiac events by exercise echocardiography in patients with normal exercise electrocardiographic testing. *J Am Coll Cardiol* 2009; **53**: 1981-1990 [PMID: 19460612 DOI: 10.1016/j.jacc.2009.01.067]

19 **Talavera-Garcia E**, Delgado-Lista J, Garcia-Rios A, Delgado-Casado N, Gomez-Luna P, Gomez-Garduño A, Gomez-Delgado F, Alcala-Diaz JF, Yubero-Serrano E, Marin C, Perez-Caballero AI, Fuentes-Jimenez FJ, Camargo A, Rodriguez-Cantalejo F, Tinahones FJ, Ordovas JM, Perez-Jimenez F, Perez-Martinez P, Lopez-Miranda J. Influence of Obesity and Metabolic Disease on Carotid Atherosclerosis in Patients with Coronary Artery Disease (CordioPrev Study). *PLoS One* 2016; **11**: e0153096 [PMID: 27064675 DOI: 10.1371/journal.pone.0153096]

20 **Laing ST**, Smulevitz B, Vatcheva KP, Rahbar MH, Reininger B, McPherson DD, McCormick JB, Fisher-Hoch SP. Subclinical atherosclerosis and obesity phenotypes among Mexican Americans. *J Am Heart Assoc* 2015; **4**: e001540 [PMID: 25787312 DOI: 10.1161/JAHA.114.001540]

21 **Pellikka PA**, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG; American Society of Echocardiography. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr* 2007; **20**: 1021-1041 [PMID: 17765820 DOI: 10.1016/j.echo.2007.07.003]

22 **Touboul PJ**, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Jaff M, Kownator S, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS, Zannad F, Zureik M. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007; **23**: 75-80 [PMID: 17108679 DOI: 10.1159/000097034]

23 **Touboul PJ**, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 2012; **34**: 290-296 [PMID: 23128470 DOI: 10.1159/000343145]

24 **Touboul PJ**, Hennerici MG, Meairs S, Adams H, Amarenco P, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Kownator S, Prati P, Rundek T, Taylor A, Bornstein N, Csiba L, Vicaut E, Woo KS, Zannad F; Advisory Board of the 3rd Watching the Risk Symposium 2004, 13th European Stroke Conference. Mannheim intima-media thickness consensus. *Cerebrovasc Dis* 2004; **18**: 346-349 [PMID: 15523176 DOI: 10.1159/000081812]

25 **Thygesen K**, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow

DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation* 2012; **126**: 2020-2035 [PMID: 22923432 DOI: 10.1161/CIR.0b013e31826e1058]

26 **Sedlis SP**, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GB, Kostuk W, Chaitman BR, Berman D, Lorin JD, Dada M, Weintraub WS, Boden WE; COURAGE Trial Investigators. Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease. *N Engl J Med* 2015; **373**: 1937-1946 [PMID: 26559572 DOI: 10.1056/NEJMoa1505532]

27 **Boden WE**, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**: 1503-1516 [PMID: 17387127 DOI: 10.1056/NEJMoa070829]

28 **Held C**, Hjemdahl P, Eriksson SV, Björkander I, Forslund L, Rehnqvist N. Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris. *Eur Heart J* 2001; **22**: 62-72 [PMID: 11133211 DOI: 10.1053/euhj.1999.2006]

29 **Petersen C**, Peçanha PB, Venneri L, Pasanisi E, Pratali L, Picano E. The impact of carotid plaque presence and morphology on mortality outcome in cardiological patients. *Cardiovasc Ultrasound* 2006; **4**: 16 [PMID: 16563156 DOI: 10.1186/1476-7120-4-16]

30 **Sirimarco G**, Amarenco P, Labreuche J, Touboul PJ, Alberts M, Goto S, Rother J, Mas JL, Bhatt DL, Steg PG; REACH Registry Investigators. Carotid atherosclerosis and risk of subsequent coronary event in outpatients with atherothrombosis. *Stroke* 2013; **44**: 373-379 [PMID: 23306325 DOI: 10.1161/STROKEAHA.112.673129]

31 **Komorovsky R**, Desideri A, Coscarelli S, Cortigiani L, Tonello D, Visonà A, Celegon L. Predictive value of associations between carotid and coronary artery disease in patients with acute coronary syndromes. *Am J Cardiol* 2005; **95**: 116-119 [PMID: 15619407 DOI: 10.1016/j.amjcard.2004.08.075]

32 **Zielinski T**, Dzielinska Z, Januszewicz A, Rynkun D, Makowiecka Ciesla M, Tyczynski P, Prejbisz A, Demkow M, Kadziela J, Naruszewicz M, Januszewicz M, Juraszynski Z, Korewicki J, Ruzyllo W. Carotid intima-media thickness as a marker of cardiovascular risk in hypertensive patients with coronary artery disease. *Am J Hypertens* 2007; **20**: 1058-1064 [PMID: 17903688 DOI: 10.1016/j.amjhyper.2007.05.011]

33 **Park HW**, Kim WH, Kim KH, Yang DJ, Kim JH, Song IG, Kwon TG, Bae JH. Carotid plaque is associated with increased cardiac mortality in patients with coronary artery disease. *Int J Cardiol* 2013; **166**: 658-663 [PMID: 22192294 DOI: 10.1016/j.ijcard.2011.11.084]

34 **Steinvil A**, Sadeh B, Bornstein NM, Havakuk O, Greenberg S, Arbel Y, Konigstein M, Finkelstein A, Banai S, Halkin A. Impact of carotid atherosclerosis on the risk of adverse cardiac events in patients with and without coronary disease. *Stroke* 2014; **45**: 2311-2317 [PMID: 24938841 DOI: 10.1161/STROKEAHA.114.005663]

35 **Naqvi TZ**, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging* 2014; **7**: 1025-1038 [PMID: 25051948 DOI: 10.1016/j.jcmg.2013.11.014]

36 **Spence JD**. Technology Insight: ultrasound measurement of carotid plaque--patient management, genetic research, and therapy evaluation. *Nat Clin Pract Neurol* 2006; **2**: 611-619 [PMID: 17057748 DOI: 10.1038/ncpneuro0324]

37 **Spence JD**, Hegele RA. Noninvasive phenotypes of atherosclerosis: similar windows but different views. *Stroke* 2004; **35**: 649-653 [PMID: 14963285 DOI: 10.1161/01.str.0000116103.19029.db]

38 **Goel K**, Thomas RJ, Squires RW, Coutinho T, Trejo-Gutierrez JF, Somers VK, Miles JM, Lopez-Jimenez F. Combined effect of cardiorespiratory fitness and adiposity on mortality in patients with coronary artery disease. *Am Heart J* 2011; **161**: 590-597 [PMID: 21392616 DOI: 10.1016/j.ahj.2010.12.012]

39 **Fabbian F**, Cacici G, Franceschini L, Russo G, Vassanelli C, Catizone L, Lupo A. The relationship between carotid and coronary atherosclerotic damage in dialysis patients. *Int J Artif Organs* 2007; **30**: 315-320 [PMID: 17520568 DOI: 10.1177/039139880703000406]

40 **Modi N**, Kapoor A, Kumar S, Tewari S, Garg N, Sinha N. Utility of carotid intimal medial thickness as a screening tool for evaluation of coronary artery disease in pre-transplant end stage renal disease. *J Postgrad Med* 2006; **52**: 266-270 [PMID: 17102544 DOI: 10.1016/j.jpainsymman.2006.05.014]

41 **Keough-Ryan TM**, Kiberd BA, Dipchand CS, Cox JL, Rose CL, Thompson KJ, Clase CM. Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia. *Am J Kidney Dis* 2005; **46**: 845-855 [PMID: 16253724 DOI: 10.1053/j.ajkd.2005.07.043]

42 **Li YH**, Lin GM, Lin CL, Wang JH, Han CL. Relation of estimated glomerular filtration rate and body mass index to mortality in non-dialysis patients with coronary artery disease: a report from the ET-CHD registry, 1997-2003. *J Cardiol* 2013; **62**: 144-150 [PMID: 23731921 DOI: 10.1016/j.jjcc.2013.03.016]

43 **Barzilai B**, Gessler C, Pérez JE, Schaab C, Jaffe AS. Significance of Doppler-detected mitral regurgitation in acute myocardial infarction. *Am J Cardiol* 1988; **61**: 220-223 [PMID: 3341197 DOI: 10.1016/0002-9149(88)90919-8]

44 **Fattouch K**, Sampognaro R, Speziale G, Salardino M, Novo G, Caruso M, Novo S, Ruvolo G. Impact of moderate ischemic mitral regurgitation after isolated coronary artery bypass grafting. *Ann Thorac Surg* 2010; **90**: 1187-1194 [PMID: 20868812 DOI: 10.1016/j.athoracsur.2010.03.103]

45 **Ellis SG**, Whitlow PL, Raymond RE, Schneider JP. Impact of mitral regurgitation on long-term survival after percutaneous coronary intervention. *Am J Cardiol* 2002; **89**: 315-318 [PMID: 11809433 DOI: 10.1016/S0002-9149(01)02231-7]

46 **Gahl K**, Sutton R, Pearson M, Caspari P, Lairet A, McDonald L. Mitral regurgitation in coronary heart disease. *Br Heart J* 1977; **39**: 13-18 [PMID: 137731 DOI: 10.1136/hrt.39.1.13]

47 **O'Driscoll JM**, Gargallo-Fernandez P, Araco M, Perez-Lopez M, Sharma R. Baseline mitral regurgitation predicts outcome in patients referred for dobutamine stress echocardiography. *Int J Cardiovasc Imaging* 2017; **33**: 1711-1721 [PMID: 28685313 DOI: 10.1007/s10554-017-1163-6]

P- Reviewer: Avtanski D, Fabbian F, Karatza AA, Kharlamov AN
S- Editor: Yan JP **L- Editor:** Filipodia **E- Editor:** Song H

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 January 26; 11(1): 38-46

DOI: 10.4330/wjc.v11.i1.38

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Contemporary characteristics and outcomes of adults with familial dilated cardiomyopathy listed for heart transplantation

Mohamed Khayata, Sadeer G Al-Kindi, Guilherme H Oliveira

ORCID number: Mohamed Khayata (0000-0001-8116-4311); Sadeer G Al-Kindi (0000-0002-1122-7695); Guilherme H Oliveira (0000-0003-0054-3438).

Author contributions: All authors helped to perform the research; Khayata M and Al-Kindi SG contributed equally to the manuscript, and are co-first authors; Khayata M manuscript writing, drafting conception and design, data analysis; Al-Kindi SG manuscript writing, data analysis; Oliveira GH manuscript writing, drafting conception and design.

Institutional review board statement: Institutional review board approval was not required because only deidentified data sets were used for this analysis.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

Mohamed Khayata, Sadeer G Al-Kindi, Guilherme H Oliveira, Cardiology Section, Department of Internal Medicine, University Hospitals Cleveland Medical Center, Harrington Heart and Vascular Institute, Cleveland, OH 44106, United States

Corresponding author: Guilherme H Oliveira, MD, FACC, Associate Professor, Section of Heart Failure and Transplant, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106, United States. guilherme.oliveira@uhhospitals.org
Telephone: +1-216-844-8242
Fax: +1-216-844-8954

Abstract

BACKGROUND

Familial dilated cardiomyopathy (FDCM) account for 20%-30% of non-ischemic cardiomyopathies (NICM). Previous published data showed that some patients with FDCM tend to have rapidly progressive disease; however, five-year mortality was not significantly different in the familial and non-familial forms of NICM with optimal medical therapy.

AIM

To better define the characteristics and clinical outcomes of FDCM patients listed for heart transplantation (HT).

METHODS

We queried the United Network for Organ Sharing Registry to identify FDCM patients listed for HT between January 2008 and September 2015 and compared them to NICM and ischemic cardiomyopathy (ICM) patients. We included all patients ≥ 18 years old and we separated patients to three groups: FDCM, NICM and ICM. Chi-square test was used to compare between categorical variables, the t-test was used to compare between continues variables, and Cox-proportional hazards model was used to perform time-dependent survival analyses.

RESULTS

Of the 24809 adults listed for HT, we identified 677 patients (2.7%) with the diagnosis of FDCM. Compared to patients with NICM and ICM, FDCM patients were younger (FDCM 43.9 ± 13.5 *vs* NICM 50.9 ± 12.3, $P < 0.001$, *vs* ICM 58.5 ± 8.1, $P < 0.001$), more frequently listed as status 2 (FDCM 35.2% *vs* NICM 26.5%, $P < 0.001$), with significantly lower left ventricular assist device (LVAD) utilization (FDCM 18.4% *vs* NICM 25.1%, $P < 0.001$; *vs* ICM 25.6%, $P < 0.001$), but higher use of total artificial heart (FDCM 1.3% *vs* NICM 0.6%, $P = 0.039$; *vs* ICM 0.4%, $P =$

the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: August 23, 2018
Peer-review started: August 23, 2018
First decision: October 4, 2018
Revised: November 1, 2018
Accepted: January 3, 2019
Article in press: January 4, 2019
Published online: January 26, 2019

0.002). Additionally, patients with FDCM were less frequently delisted for clinical deterioration or death and more likely to be transplanted compared to those with NICM [hazard ratio (HR): 0.617, 95% confidence interval (CI): 0.47-0.81; HR: 1.25, 95%CI: 1.14-1.37, respectively], and ICM (HR: 0.5, 95%CI: 0.38-0.66; HR: 1.18, 95%CI: 1.08-1.3, respectively). There was more frequent rejection among patients with FDCM (FDCM 11.4% *vs* NICM 9.8%, $P = 0.28$; *vs* ICM 8.4%, $P = 0.034$). One, three, and five post-transplant survival of patients with FDCM (91%, 88% and 80%) was similar to those with NICM (91%, 84%, 79%, $P = 0.225$), but superior to those with ICM (89%, 82%, 75%, $P = 0.008$), respectively.

CONCLUSION
End-stage FDCM patients are more likely to be transplanted, more likely to have early rejection, and have similar or higher survival than patients with other cardiomyopathies.

Key words: Familial dilated cardiomyopathy; End-stage heart failure; Wait list; Transplant; Outcomes

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Familial dilated cardiomyopathy (FDCM) can lead to end-stage heart failure requiring heart transplantation (HT). There is little contemporary information on progression, circulatory mechanical support use, and HT outcomes of these patients. We aimed to define the characteristics and outcomes of FDCM patients and to compare FDCM to non-ischemic cardiomyopathy (NICM) and ischemic cardiomyopathy (ICM) patients listed for HT. FDCM patients were younger, more frequently listed as status 2, and more likely to be transplanted. There was more frequent rejection among patients with FDCM compared to ICM. Post-transplant survival of FDCM patients was similar to NICM, but superior to ICM patients.

Citation: Khayata M, Al-Kindi SG, Oliveira GH. Contemporary characteristics and outcomes of adults with familial dilated cardiomyopathy listed for heart transplantation. *World J Cardiol* 2019; 11(1): 38-46
URL: https://www.wjgnet.com/1949-8462/full/v11/i1/38.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i1.38

INTRODUCTION

Familial dilated cardiomyopathy (FDCM) account for 20%-30% of non-ischemic cardiomyopathies (NICM)[1-3]. They are most often inherited in a Mendelian autosomal dominant fashion, although autosomal recessive or X-linked transmission exists[4]. Therefore, first-degree relatives have a higher risk of developing the disease[5]. In the United States, around 26% of patients listed for heart transplantation (HT) in the United Network for Organ Sharing (UNOS) Registry are diagnosed with FDCM[6]. Most previous outcome studies of NICM have not studied FDCM as a separate entity[2,7], perhaps because of the challenge in identifying these patients[2]. To make the diagnosis of FDCM, patients should have two or more affected relatives with NICM or a relative of a NICM patient with unexplained sudden death before the age of 35 years[8,9]. Previous published data showed that some patients with FDCM tend to have rapidly progressive disease[1,2], however, five-year mortality was not significantly different in the familial and non-familial forms of NICM with optimal medical therapy[2,3]. Similarly, mechanical circulatory support (MCS) utilization and HT outcomes have not well studied in FDCM patients and most available data are derived from relatively small cohorts and case reports. In this study, we used a large, contemporary, nationwide database to investigate the clinical characteristics, natural history, MCS use, and HT outcomes of patients with end-stage heart failure due to FDCM.

MATERIALS AND METHODS

Data source

We used the thoracic transplantation files from the UNOS Registry contracted with the Health Resources and Services Administration. UNOS includes transplantation information on listed patients in all centers across the United States. Data are collected at different time points: at listing, before transplantation, and continually after transplantation. The listing center is responsible for providing the data. Data is used to match patients with donors, for administrative purposes, and for research reporting. The UNOS registry includes data on patient demographics, cause of cardiomyopathy, implanted devices, causes of removal from wait list, hemodynamics, comorbid conditions, listing status, laboratory tests, donor demographics, laboratory and other testing, post-transplantation complications [rejection, infection, kidney failure, length of stay (LOS)], vital status, and cause of death. The registry is continuously audited with strict quality control[10]. Data included in the UNOS are extracted from the transplant candidate registration form, which is filled at time of transplantation; and transplant recipient follow-up form, which is filled at follow-up. At the time of analysis, the database included 99177 patients listed for HT (1985-2015).

Patient population

We included adults (≥ 18 years old), listed for HT with a diagnosis of idiopathic dilated cardiomyopathy "Dilated myopathy: idiopathic", FDCM "Dilated Myopathy: Familial" and ischemic cardiomyopathy (ICM) "Dilated Myopathy: Ischemic", between January 1st, 2008 to September 30th, 2015. We separated patients to three groups: FDCM, NICM and ICM and compared them. Additional cases were identified in the diagnosis free text variable. We compared their baseline characteristics, MCS utilization, and post-transplant outcomes to patients with the diagnosis of ICM and NICM.

Statistical analyses

All analyses were performed using Statistical Package for Social Sciences (SPSS, version 19.0; SPSS Inc, Chicago, IL). The primary outcomes of this study were waitlist mortality/delisting for clinical deterioration, and post-transplantation mortality among patients who undergo transplantation. Secondary outcomes were as follows: delisting due to improvement, transplant, post-transplantation stroke, post-transplantation permanent pacemaker implantation, post-transplantation acute rejection, post-transplantation dialysis, and LOS for index transplant hospitalization.

Categorical variables were presented as numbers and percentages and were compared using Pearson χ^2 test. Continuous variables were presented as means and standard deviations and were compared with Student *t*-test and. Survival analyses were done using Kaplan-Meier method with log-rank test and adjusted survival using Cox-proportional-hazard model. Variables that were significant in univariable models ($P < 0.05$) were included in the multivariable model. All tests were two sided. $P < 0.05$ was considered statistically significant. No assumptions were used for missing data. Institutional review board approval was not required because only deidentified data sets were used for this analysis. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Demographic characteristics

Of the 24809 adults listed for HT between January 2008 and September 2015, we identified 677 patients (2.7%) with the diagnosis of FDCM, and compared them with 8416 patients (33.9%) with NICM, and 8301 (33.5%) patients with ICM patients (Table 1).

Patients with FDCM were younger (mean age: 43.9 ± 13.5 *vs* NICM 50.9 ± 12.3, $P < 0.001$; *vs* ICM 58.5 ± 8.1; $P < 0.001$) and less predominantly men (FDCM 65.6% *vs* NICM 72.6%, $P < 0.001$; *vs* ICM 86.9%, $P < 0.001$). FDCM patients were more often listed as a status 2 (FDCM 35.2% *vs* NICM 26.5%, $P < 0.001$ *vs*, ICM 34.1%, $P = 0.956$), had significantly less left ventricular assist device (LVAD) use (FDCM 18.4% *vs* NICM 25.1%, $P < 0.001$; *vs* ICM 25.6%, $P < 0.001$) but more use of total artificial heart (TAH) (FDCM 1.3% *vs* NICM 0.6%, $P = 0.039$; *vs* ICM 0.4%, $P = 0.002$), had lower creatinine (FDCM 1.3 ± 0.7 *vs* NICM 1.4 ± 1.0, $P = 0.008$; *vs* ICM 1.4 ± 0.9, $P < 0.001$), had higher albumin (FDCM 3.8 ± 0.6 *vs* NICM 3.7 ± 0.7, $P = 0.001$; *vs* ICM 3.7 ± 0.7, $P = 0.001$), had lower pulmonary artery systolic pressure (FDCM 42.7 ± 13.2 *vs* NICM 44.73 ± 13.9, $P = 0.004$; *vs* ICM 44.8 ± 15.2; $P = 0.001$) , and lower cardiac output (FDCM 4.1 ± 1.3 *vs* NICM 4.3 ± 1.4, $P = 0.011$; *vs* ICM 4.5 ± 1.3, $P < 0.001$) (Table 1).

Table 1 Baseline characteristics by etiology *n* (%)

	NICM (*n* = 8416)	FDCM (*n* = 677)	*P* value	ICM (*n* = 8301)	*P* value
Age at listing	50.9 ± 12.3	43.9 ± 13.5	< 0.001	58.5 ± 8.1	< 0.001
Male gender	6113 (72.6)	444 (65.6)	< 0.001	7212 (86.9)	< 0.001
Ethnicity			< 0.001		< 0.001
White	4609 (54.8)	444 (65.6)		6411 (77.2)	
Black	2776 (33.0)	159 (23.5)		976 (11.8)	
Hispanic	705 (8.4)	54 (8.0)		575 (6.9)	
Asian	223 (2.6)	14 (2.1)		269 (3.2)	
Other or unknown	103 (1.2)	6 (0.9)		70 (0.8)	
Initial status			< 0.001		0.956
1A	1918 (22.8)	147 (21.7)		1823 (22.0)	
1B	4023 (47.8)	273 (40.3)		3415 (41.1)	
2	2227 (26.5)	238 (35.2)		2831 (34.1)	
7	248 (2.9)	19 (2.8)		232 (2.8)	
Therapies					
Inotropes	2947 (35)	233 (34.4)	0.769	2386 (28.7)	0.002
ECMO	52 (0.6)	4 (0.6)	1.0	87 (1.0)	0.320
IABP	395 (4.7)	21 (3.1)	0.056	403 (4.9)	0.038
Mechanical ventilation	141 (1.7)	10 (1.5)	0.875	209 (2.5)	0.118
LVAD	2104 (25.1)	124 (18.4)	< 0.001	2116 (25.6)	< 0.001
BiVAD	153 (1.8)	8 (1.2)	0.288	157 (1.9)	0.233
TAH	50 (0.6)	9 (1.3)	0.039	31 (0.4)	0.002
ICD	6985 (83.5)	562 (83.8)	0.914	6652 (80.9)	0.073
Laboratory values					
Creatinine	1.4 ± 1.0	1.3 ± 0.7	0.008	1.4 ± 0.9	< 0.001
Albumin	3.7 ± 0.7	3.8 ± 0.6	0.001	3.7 ± 0.7	0.001
Bilirubin	1.1 ± 1.8	1.1 ± 1.0	0.578	1.0 ± 2.0	0.540
PRA class I	7.1 ± 18.6	7.2 ± 18.5	0.892	5.7 ± 16.2	0.084
PRA class II	4.8 ± 15.7	5.2 ± 16.2	0.645	3.4 ± 12.6	0.012
Hemodynamics					
PA systolic pressure (mmHg)	44.3 ± 13.9	42.7 ± 13.2	0.004	44.8 ± 15.2	0.001
PA diastolic pressure (mmHg)	22.1 ± 8.9	21.7 ± 8.7	0.266	20.8 ± 8.6	0.013
PA mean pressure (mmHg)	30.5 ± 10.2	29.7 ± 9.8	0.052	29.8 ± 10.5	0.821
PCWP (mmHg)	20.5 ± 9.0	20.4 ± 8.5	0.735	19.7 ± 8.9	0.081
CO (L/min)	4.3 ± 1.4	4.1 ± 1.3	0.011	4.5 ± 1.3	< 0.001

NICM: Non-ischemic cardiomyopathy; FDCM: Familial dilated cardiomyopathy; ICM: Ischemic cardiomyopathy; UNOS: United network for organ sharing; ECMO: Extracoroporeal membrane oxygenation; IABP: Intraaortic balloon pump; VAD: Ventricular assist device; LVAD: Left ventricular assist device; BiVAD: Biventricular assist device; TAH: Total artificial heart; ICD: Implantable cardioverter-defibrillator; PA: Pulmonary artery; PCWP: Pulmonary capillary wedge pressure; CO: Cardiac output.

Wait list outcome

Of 677 FDCM patients, 33 patients (4.8%) died while waiting HT, 7 patients (1%) were delisted for improvement, 20 patients (2.9%) were delisted for deterioration, 470 patients (69%) were transplanted, 3 patients (0.4%) refused transplantation, and 13 patients (1.9%) transferred to another center. Causes of Death in FDCM patients were: multiple organ failure [11 patients (2%)], cardiovascular [6 patients (1%)], cerebrovascular [6 patients (1%)], infections [3 patients (< 1%)], respiratory [2 patients (< 1%)], hemorrhage [1 patient (< 1%)], and other [4 patients (< 1%)].

Patients with FDCM were less likely to die compared to NICM [hazard ratio (HR): 0.720, 95% confidence interval (CI): 0.507-1.023] and ICM (HR: 0.61, 95%CI: 0.43-0.86), less likely to be delisted due to deterioration compared to NICM (HR: 0.49, 95%CI: 0.32-0.78) and ICM (HR: 0.39, 95%CI: 0.25-0.6), less likely to die or to be delisted due to deterioration compared to NICM (HR: 0.62, 95%CI: 0.47-0.81) and ICM (HR: 0.5, 95%CI: 0.38-0.66), less likely to be delisted due to improvement compared to NICM (HR: 0.28, 95%CI: 0.13-0.59) and ICM (HR: 0.35, 95%CI: 0.16-0.74), and more likely to be transplanted compared to NICM (HR: 1.25, 95%CI: 1.14-1.37) and ICM (HR: 1.83,

95%CI: 1.08-1.3) while waiting HT (Table 2).

Factors associated with waitlist mortality or delisting for FDCM on multivariate analysis patients were: mechanical ventilation (HR: 3.69, 95%CI: 1.02-13.36), creatinine (HR: 1.38, 95%CI: 1.21-1.57), and UNOS status 1A (Table 3).

Post-transplant outcomes

There was no significant difference between FDCM and other types of cardiomyopathies in stroke rates (FDCM 1.4% *vs* NICM 2.3%, *P*=0.239; *vs* ICM 3.0%; *P* = 0.051), permanent pacemaker placement (FDCM 3.6% *vs* NICM 3.4%, *P* = 0.785, *vs* ICM 3.3%, *P* = 0.681), rejection rates (FDCM 11.4% *vs* NICM 9.8%, *P* = 0.283), dialysis need (FDCM 9.7% *vs* NICM 9.5%, *P* = 0.866; *vs* ICM 10.2%, *P* = 0.806), and LOS (FDCM 17.3 ± 13.1 *vs* NICM 19 ± 22, *P* = 0.105) after HT. When compared to ICM, FDCM patients had significantly higher early rejection rates (FDCM 11.4% *vs* ICM 8.4%, *P* < 0.034), and lower LOS (FDCM 17.3 ± 13.1 *vs* ICM 20.7 ± 25.4, *P* < 0.006) (Table 4).

One, three, and five-year post-transplant survival were as follows: FDCM (91%, 88%, and 80%), NICM (91%, 84%, 79%), and ICM (89%, 82%, 75%), respectively, with no statistically significant differences between FDCM and NICM (*P* = 0.225) but higher survival compared to ICM (*P* = 0.008)(Figure 1).

DISCUSSION

Herein we describe the largest contemporary cohort of patients with end-stage heart failure from FDCM listed for HT and report on their clinical characteristics and outcomes.

Our data showed that around 2.7% of patients listed for HT have FDCM, considerably lower than the overall prevalence of FDCM. The low prevalence of the disease among patients listed for HT in our cohort might be explained by the fact that FDCM is often underdiagnosed[6].

We found that patients with FDCM who are listed for HT tended to be younger and less predominantly males compared to ICM and NICM patients, which is consistent with previous literature[7]. In addition, we found that the diagnosis of FDCM is associated with less acuity at listing, as FDCM patients were more likely to be listed as a status 2, less likely to need LVAD, and more likely to be transplanted. When FDCM patients do need MCS, they more often need biventricular support, as is illustrated by their higher usage of TAHs.

We also presented the clinical course of FDCM patients in the transplant waitlist and we showed that FDCM patients were less likely to deteriorate or die, but also less likely to improve compared to other heart failure patients. As a result, FDCM patients were more likely to be transplanted. This suggests that listed FDCM patients can be safely followed until a suitable donor is available, obviating the need for MCS as a bridge to transplant.

We also investigated transplantation outcomes in FDCM patients, which might be a concern on these patients given the fear of early rejection, as they tend to be younger with active immune system[11,12]. Previously published data compared between FDCM and non-FDCM patients who are listed for HT and showed that rejection incidence is similar in both groups[1], however, immunosuppression therapies have significantly changed since that study. We found that FDCM patients were more likely to be treated for post transplantation rejection (11.4%) compared to ICM (8.4%). That maybe explained, in part, by the fact that FDCM patients were younger and likely to have more active immune system compared to older patients[11-14].

To the best of our knowledge, our study is the largest contemporary study that compared FDCM to NICM and ICM, and followed patients after HT. We found that FDCM patients had higher survival at one, three, and five years after HT compared to ICM patients, with no significant difference compared to NICM patients. As FDCM patients were less likely to have hepatic or renal dysfunction, that may explain the higher rates of survival after HT in this group[15]. Besides that, ICM patients tend to have more comorbidities compared to patients with NICM, which may explain the higher mortality rate in ICM group[16]. Valentine *et al*. compared between FDCM and NICM and found that FDCM patients had higher survival compared to NICM patients 5 years after HT, however, the large discrepancy in sample size between the 2 groups in that study makes statistical comparison invalid[1].

Our study presents the clinical outcomes of patients with end-stage heart failure from FDCM listed for HT. The outcomes of our study may help providers in making clinical decisions while following these patients before and after HT.

Limitations of our study are mainly associated with registry-based analysis with a

Table 2 Wait-list outcomes by etiology

Outcome	FDCM *vs* NICM HR (95%CI), *P* value	FDCM *vs* ICM HR (95%CI), *P* value
Waitlist mortality	0.720 [0.507-1.023], $P = 0.067$	0.609 [0.429-0.864], $P = 0.005$
Delisting due to deterioration	0.499 [0.319-0.781], $P = 0.002$	0.387 [0.248-0.604], $P < 0.001$
Waitlist mortality or delisting due to deterioration	0.617 [0.468-0.813], $P = 0.001$	0.501 [0.381-0.659], $P = 0.001$
Delisting due to improvement	0.277 [0.131-0.588], $P = 0.001$	0.347 [0.163-0.735], $P = 0.006$
Transplant	1.248 [1.135-1.373], $P < 0.001$	1.183 [1.076-1.302], $P = 0.001$

NICM: Non-ischemic cardiomyopathy; FDCM: Familial dilated cardiomyopathy.

limited sample size of patients with FDCM, due to underestimation of the disease[6]. Therefore, our results should be interpreted in this context. Although regularly onsite audits are performed for the UNOS registry, the actual quality of the patient data has not been subject to a comprehensive audit[10]. Second, this database did not address how the diagnosis of FDCM was made and whether relatives of patients with FDCM had echocardiography to confirm the diagnosis of FDCM. Third, this registry did not mention the type of inotrope, doses, and other treatments such as: inhaled nitric oxide, or prostacyclins that were used while awaiting transplantation. Fourth, the database is missing the reason of mechanical ventilation. Although the difference of its incidence was not significant, we did not know if patients were intubated due to a cardiac etiology or any other reason. Fifth, graft failure rates might be underestimated across the groups, as its occurrence requires inotropes or mechanical ventilation support after transplantation, which is not captured by the UNOS database. Finally, as listing practices and peri-transplant care may be different in different countries, our results may not be applicable to transplant centers in other countries because UNOS is a US-based registry.

In conclusion, patients with end-stage FDCM are listed at a younger age, most often as status 2, and more frequently transplanted than patients with other cardiomyopathies. Although FDCM is associated with more frequent early rejection, survival of these patients is similar or better than other heart transplant recipients.

Table 3 Determinants of wait-list mortality or delisting

	Univariable HR (95%CI)	*P* value	Multivariable HR (95%CI)	*P* value
Age at listing		0.082		
Gender		0.413		
Ethnicity		0.712		
UNOS listing status		< 0.001		0.001
1b *vs* 1a	0.431 [0.231-0.805]		0.606 [0.305-1.204]	
2 *vs* 1a	0.160 [0.073-0.350]		0.176 [0.073-0.424]	
7 *vs* 1a	0.852 [0.252-2.886]		1.326 [0.373-4.707]	
Inotropes		0.110		
ECMO		0.229		
IABP	3.987 [1.575-10.090]	0.004		0.124
Mechanical Ventilation	4.294 [1.333-13.831]	0.015	3.694 [1.022-13.360]	0.046
VAD		0.009		0.519
LVAD *vs* no VAD	1.084 [0.540-2.179]			
BiVAD *vs* no VAD	7.636 [2.342-24.900]			
TAH *vs* no VAD	1.724 [0.236-12.600]			
ICD		0.392		
Creatinine	1.275 [1.142-1.422]	< 0.001	1.377 [1.211-1.566]	< 0.001
PASP	1.022 [1.002-1.043]	0.033		0.169
PADP		0.067		
PAMP		0.097		
PCWP		0.387		
CO		0.093		
List year		0.282		

UNOS: United network for organ sharing; ECMO: Extracoroporeal membrane oxygenation; IABP: Intraaortic balloon pump; VAD: Ventricular assist device; LVAD: Left ventricular assist device; BiVAD: Biventricular assist device; ICD: Implantable cardioverter-defibrillator; PCWP: Pulmonary capillary wedge pressure; CO: Cardiac output.

Table 4 Post-transplantation outcomes *n* (%)

	NICM	FDCM	*P*-value	ICM	*P* value
Stroke	114 (2.3)	6 (1.4)	0.239	147 (3.0)	0.051
Permanent pacemaker	171 (3.4)	16 (3.6)	0.785	164 (3.3)	0.681
Treated for rejection	496 (9.8)	51 (11.4)	0.283	416 (8.4)	0.034
Dialysis	476 (9.5)	43 (9.7)	0.866	507 (10.2)	0.806
LOS (d)	19 ± 22	17.3 ± 13.1	0.105	20.7 ± 25.4	0.006

NICM: Non-ischemic cardiomyopathy; FDCM: Familial dilated cardiomyopathy; ICM: Ischemic cardiomyopathy; LOS: Length of stay.

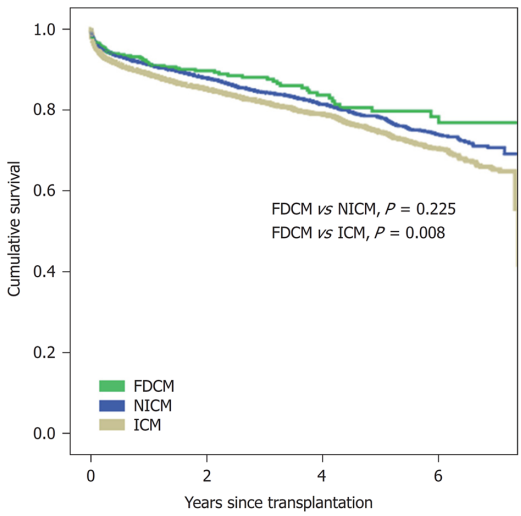


Figure 1 Kaplan-Meir graph showing post-transplant survival in familial dilated cardiomyopathy, non-ischemic cardiomyopathy, and ischemic cardiomyopathy patients. One, three, and five years post-transplant survival of patients with FDCM (91%, 88%, and 80%) was similar to those with NICM (91%, 84%, 79%, *P* = 0.225), but superior to those with ICM (89%, 82%, 75%, *P* = 0.008), respectively. NICM: Non-ischemic cardiomyopathy; FDCM: Familial dilated cardiomyopathy; ICM: Ischemic cardiomyopathy.

ARTICLE HIGHLIGHTS

Research background

Familial dilated cardiomyopathy (FDCM) is a sub-type of non-ischemic cardiomyopathy (NICM) that may lead to end-stage heart failure requiring heart transplantation (HT). This group of patients tends to develop heart failure at earlier age and they are more likely to have less comorbidity, which suggest they may have better outcomes after HT. Although characteristics of FDCM patients with end-stage heart failure have been reported, the outcomes of FDCM patients listed for HT were not described.

Research motivation

As the outcomes of FDCM listed for HT patients were not studied, we used a large database to compare FDCM to ischemic cardiomyopathy (ICM) and NICM patients who are listed for HT. Our results may help to better understand the clinical course of FDCM patients while they are awaiting HT and their outcomes after being transplanted.

Research objectives

The objective of this study was to compare FDCM to ICM and NICM patients who are listed for HT and describe their clinical course while awaiting HT and their post-HT outcomes.

Research methods

We identified patients who are listed for HT using the United Network for Organ Sharing Registry. We divided patients to three groups: ICM, NICM, and FDCM, and compared clinical outcomes of FDCM to ICM and NICM patients who are listed for HT.

Research results

FDCM patients were younger, less likely to be males, more likely to be listed as status 2, less likely to require mechanical support, but more likely to need total artificial heart. While awaiting HT, FDCM patients were less likely to die compared to ICM [HR 0.609 (0.429-0.864)], less likely to be delisted due to deterioration compared to ICM [0.387 (0.248-0.604)] and NICM [0.499 (0.319-0.781)], less likely to die or to be delisted due to deterioration compared ICM [0.501 (0.381-0.659)] and NICM [0.617 (0.468-0.813)], less likely to be delisted due to improvement compared to ICM [0.347 (0.163-0.735)] and NICM [0.277 (0.131-0.588)], and more likely to be transplanted compared to ICM [1.183 (1.076-1.302)] and NICM [1.248 (1.135-1.373)]. After HT, FDCM patients were more likely to have early rejection compared to ICM (FDCM 11.4% *vs* ICM 8.4%; $P < 0.034$), but more likely to survive (91%, 88%, and 80%) compared to ICM (89%, 82%, and 75%) at 1, 3, and 5 years, respectively.

Research conclusions

Patients with end-stage heart failure due to FDCM are more likely to be transplanted compared to NICM and ICM. After HT, they are more likely to develop early rejection, but more likely to survive compared to ICM patients.

Research perspectives

This study may help providers in making clinical decisions for patients with end-stage heart failure due to FDCM while waiting and after HT.

REFERENCES

1 **Valantine HA**, Hunt SA, Fowler MB, Billingham ME, Schroeder JS. Frequency of familial nature of dilated cardiomyopathy and usefulness of cardiac transplantation in this subset. *Am J Cardiol* 1989; **63**: 959-963 [PMID: 2648793 DOI: 10.1016/0002-9149(89)90148-3]

2 **Michels VV**, Driscoll DJ, Miller FA, Olson TM, Atkinson EJ, Olswold CL, Schaid DJ. Progression of familial and non-familial dilated cardiomyopathy: long term follow up. *Heart* 2003; **89**: 757-761 [PMID: 12807850 DOI: 10.1136/heart.89.7.757]

3 **Martins E**, Cardoso JS, Campelo M, Amorim S, Moura B, Maciel MJ, Gonçalves FR. Survival of patients with familial dilated cardiomyopathy on optimal heart failure therapy. *Rev Port Cardiol* 2009; **28**: 263-268 [PMID: 19480309]

4 **Monserrat L**, Hermida M, Bouzas B, Mosquera I, Mahon N, Peteiro J, Alvarez N, Penas-Lado M, Crespo M, Castro-Beiras A. Familial dilated cardiomyopathy in patients transplanted for idiopathic dilated cardiomyopathy. *Rev Esp Cardiol* 2002; **55**: 725-732 [PMID: 12113700 DOI: 10.1016/S0300-8932(02)76691-8]

5 **Baig MK**, Goldman JH, Caforio AL, Coonar AS, Keeling PJ, McKenna WJ. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. *J Am Coll Cardiol* 1998; **31**: 195-201 [PMID: 9426040 DOI: 10.1016/S0735-1097(97)00433-6]

6 **Seidelmann SB**, Laur O, Hwa J, Depasquale E, Bellumkonda L, Sugeng L, Pomianowski P, Testani J, Chen M, McKenna W, Jacoby D. Familial dilated cardiomyopathy diagnosis is commonly overlooked at the time of transplant listing. *J Heart Lung Transplant* 2016; **35**: 474-480 [PMID: 26852066 DOI: 10.1016/j.healun.2015.12.002]

7 **Bahler RC**. Assessment of prognosis in idiopathic dilated cardiomyopathy. *Chest* 2002; **121**: 1016-1019 [PMID: 11948024 DOI: 10.1378/chest.121.4.1016]

8 **Taylor MR**, Carniel E, Mestroni L. Cardiomyopathy, familial dilated. *Orphanet J Rare Dis* 2006; **1**: 27 [PMID: 16839424 DOI: 10.1186/1750-1172-1-27]

9 **Mestroni L**, Maisch B, McKenna WJ, Schwartz K, Charron P, Rocco C, Tesson F, Richter A, Wilke A, Komajda M. Guidelines for the study of familial dilated cardiomyopathies. Collaborative Research Group of the European Human and Capital Mobility Project on Familial Dilated Cardiomyopathy. *Eur Heart J* 1999; **20**: 93-102 [PMID: 10099905 DOI: 10.1053/euhj.1998.1145]

10 **Daily OP**, Kauffman HM. Quality control of the OPTN/UNOS Transplant Registry. *Transplantation* 2004; **77**: 1309; author reply 1309-1309; author reply 1310 [PMID: 15114106 DOI: 10.1097/01.TP.0000120943.94789.E4]

11 **Tjang YS**, van der Heijden GJ, Tenderich G, Körfer R, Grobbee DE. Impact of recipient's age on heart transplantation outcome. *Ann Thorac Surg* 2008; **85**: 2051-2055 [PMID: 18498818 DOI: 10.1016/j.athoracsur.2008.02.015]

12 **Sharma G**, Hanania NA, Shim YM. The aging immune system and its relationship to the development of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2009; **6**: 573-580 [PMID: 19934352 DOI: 10.1513/pats.200904-022RM]

13 **Kilic A**, Weiss ES, Allen JG, Conte JV, Shah AS, Baumgartner WA, Yuh DD. Simple score to assess the risk of rejection after orthotopic heart transplantation. *Circulation* 2012; **125**: 3013-3021 [PMID: 22634267 DOI: 10.1161/CIRCULATIONAHA.111.066431]

14 **Marelli D**, Laks H, Kobashigawa JA, Bresson J, Ardehali A, Esmailian F, Plunkett MD, Kubak B. Seventeen-year experience with 1,083 heart transplants at a single institution. *Ann Thorac Surg* 2002; **74**: 1558-1566; discussion 1567 [PMID: 12440609 DOI: 10.1016/S0003-4975(02)03933-4]

15 **Grimm JC**, Shah AS, Magruder JT, Kilic A, Valero V, Dungan SP, Tedford RJ, Russell SD, Whitman GJ, Sciortino CM. MELD-XI Score Predicts Early Mortality in Patients After Heart Transplantation. *Ann Thorac Surg* 2015; **100**: 1737-1743 [PMID: 26387720 DOI: 10.1016/j.athoracsur.2015.07.026]

16 **Shore S**, Grau-Sepulveda MV, Bhatt DL, Heidenreich PA, Eapen ZJ, Hernandez AF, Yancy CW, Fonarow GC. Characteristics, Treatments, and Outcomes of Hospitalized Heart Failure Patients Stratified by Etiologies of Cardiomyopathy. *JACC Heart Fail* 2015; **3**: 906-916 [PMID: 26454848 DOI: 10.1016/j.jchf.2015.06.012]

P- Reviewer: Kharlamov AN, Vermeersch P, Traykov V, Amrousy DE
S- Editor: Dou Y **L- Editor:** A **E- Editor:** Song H

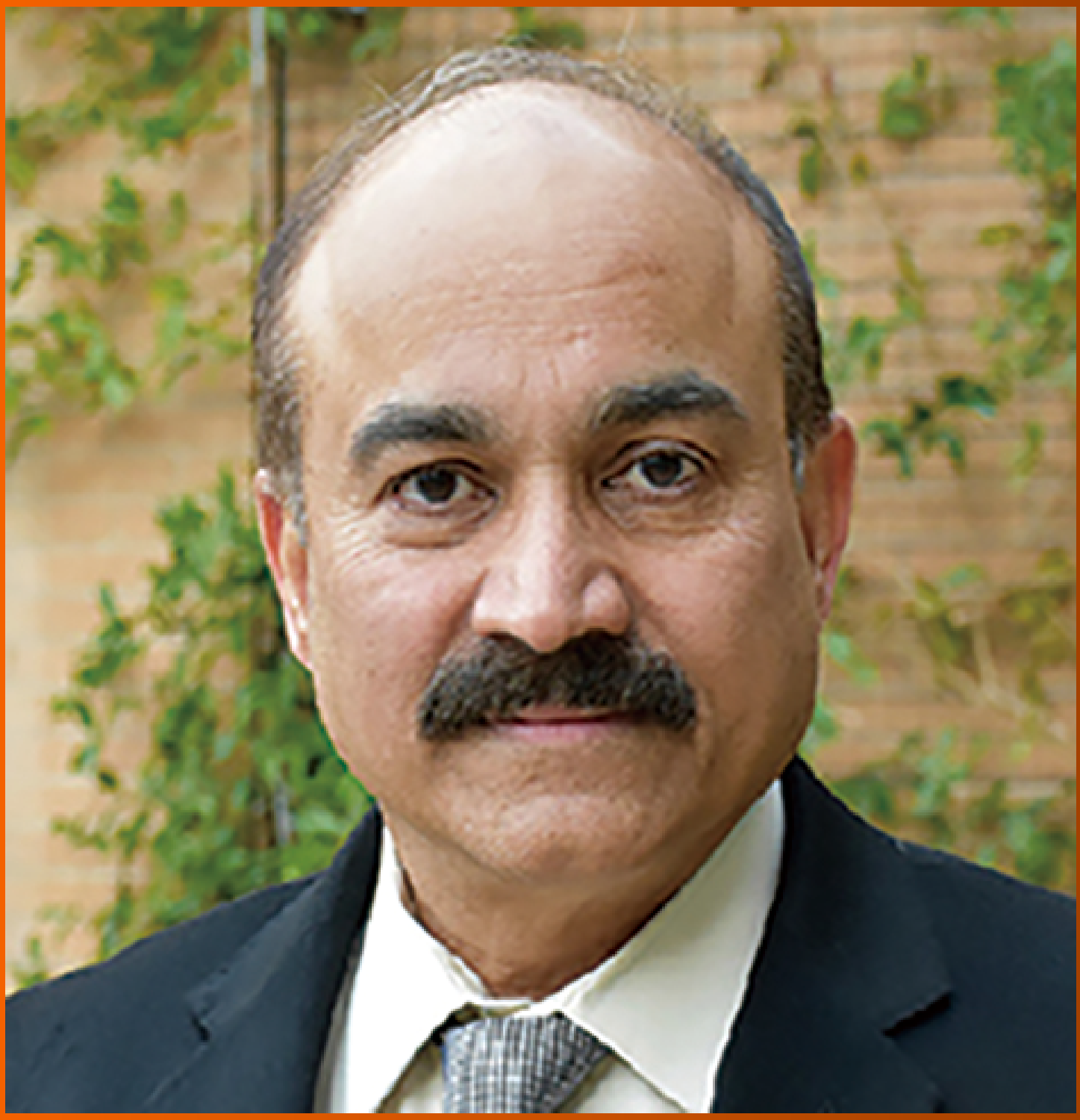
Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 February 26; 11(2): 47-93



Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 2 February 26, 2019

Contents

World Journal of Cardiology

Volume 11 Number 2 February 26, 2019

ABOUT COVER

Editor-in-Chief of *World Journal of Cardiology*, Ramdas G Pai, FACC, FRCP (Hon), MD, Doctor, Professor, Director Cardiovascular Fellowship Program, Chair of Clinical Sciences, University of California Riverside School of Medicine, Riverside, CA 92507, United States

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yun-Xiaojian Wu* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
February 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 February 26; 11(2): 47-56

DOI: 10.4330/wjc.v11.i2.47

ISSN 1949-8462 (online)

EDITORIAL

Not all arrestins are created equal: Therapeutic implications of the functional diversity of the β-arrestins in the heart

Anastasios Lymperopoulos, Shelby L Wertz, Celina M Pollard, Victoria L Desimine, Jennifer Maning, Katie A McCrink

ORCID number: Anastasios Lymperopoulos (0000-0001-9817-6319); Shelby L Wertz (0000-0003-2201-0341); Celina M Pollard (0000-0002-3105-7291); Victoria L Desimine (0000-0003-4093-4580); Jennifer Maning (0000-0001-5405-669X); Katie A McCrink (0000-0002-2170-343X).

Author contributions: All authors performed literature research and contributed to the writing of the manuscript; Lymperopoulos A supervised the project and wrote the paper.

Supported by a NSU's President's Faculty Research and Development Grant (PFRDG).

Conflict-of-interest statement: The authors declare no conflict of interest related to this publication.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Anastasios Lymperopoulos, Shelby L Wertz, Celina M Pollard, Victoria L Desimine, Jennifer Maning, Katie A McCrink, Laboratory for the Study of Neurohormonal Control of the Circulation, Department of Pharmaceutical Sciences (Pharmacology), College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL 33328, United States

Jennifer Maning, Jackson Memorial Hospital, Miami, FL 33136, United States

Katie A McCrink, Massachusetts General Hospital, Boston, MA 02114, United States

Corresponding author: Anastasios Lymperopoulos, BPharm, MSc, PhD, FAHA, FESC, Associate Professor, Laboratory for the Study of Neurohormonal Control of the Circulation, Department of Pharmaceutical Sciences (Pharmacology), College of Pharmacy, Nova Southeastern University, 3200 S. University Dr., HPD (Terry) Bldg/Room 1338, Fort Lauderdale, FL33328, United States. al806@nova.edu
Telephone: +1-954-262-1338
Fax: +1-954-262-2278

Abstract

The two ubiquitous, outside the retina, G protein-coupled receptor (GPCR) adapter proteins, β-arrestin-1 and -2 (also known as arrestin-2 and -3, respectively), have three major functions in cells: GPCR desensitization, *i.e.*, receptor decoupling from G-proteins; GPCR internalization *via* clathrin-coated pits; and signal transduction independently of or in parallel to G-proteins. Both β-arrestins are expressed in the heart and regulate a large number of cardiac GPCRs. The latter constitute the single most commonly targeted receptor class by Food and Drug Administration-approved cardiovascular drugs, with about one-third of all currently used in the clinic medications affecting GPCR function. Since β-arrestin-1 and -2 play important roles in signaling and function of several GPCRs, in particular of adrenergic receptors and angiotensin II type 1 receptors, in cardiac myocytes, they have been a major focus of cardiac biology research in recent years. Perhaps the most significant realization coming out of their studies is that these two GPCR adapter proteins, initially thought of as functionally interchangeable, actually exert diametrically opposite effects in the mammalian myocardium. Specifically, the most abundant of the two β-arrestin-1 exerts overall detrimental effects on the heart, such as negative inotropy and promotion of adverse remodeling post-myocardial infarction (MI). In contrast, β-arrestin-2 is overall beneficial for the myocardium, as it has anti-apoptotic and anti-inflammatory effects that result in attenuation of post-MI adverse remodeling, while promoting cardiac contractile function. Thus, design of novel cardiac GPCR

Received: October 16, 2018
Peer-review started: October 16, 2018
First decision: November 15, 2018
Revised: November 28, 2018
Accepted: January 10, 2019
Article in press: January 10, 2019
Published online: February 26, 2019

ligands that preferentially activate β-arrestin-2 over β-arrestin-1 has the potential of generating novel cardiovascular therapeutics for heart failure and other heart diseases.

Key words: Adverse remodeling; β-arrestin; Biased signaling; Cardiac myocyte; Cardiac fibroblast; contractility; Functional divergence; G protein-coupled receptor; Heart failure; Hormone; Myocardial infarction; Signal transducer

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Presumed functionally similar for a long time, we now know that the two β-arrestins display significant functional diversity in several organs and tissues, including in the cardiovascular system. Their functional distinction also in the mammalian heart has been clearly documented over the past few years. β-arrestin-1, which is far more abundant than β-arrestin-2 in almost every tissue including the myocardium, opposes the cyclic adenosine monophosphate (cAMP)-dependent pro-contractile signaling of the β_1 adrenergic receptor (β_1AR), and promotes cardiac apoptosis, inflammation, and other adverse remodeling-associated processes post-myocardial infarction. Conversely, β-arrestin-2 promotes catecholamine-dependent cardiac contractility directly, *via* SERCA2a potentiation, and indirectly, by leaving β_1AR's cAMP-dependent pro-contractile signaling unaffected.

Citation: Lymperopoulos A, Wertz SL, Pollard CM, Desimine VL, Maning J, McCrink KA. Not all arrestins are created equal: Therapeutic implications of the functional diversity of the β-arrestins in the heart. *World J Cardiol* 2019; 11(2): 47-56
URL: https://www.wjgnet.com/1949-8462/full/v11/i2/47.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i2.47

INTRODUCTION

Out of the four mammalian arrestins, only the two ubiquitous (outside the retina) arrestin-2 and -3, also known as β-arrestin-1 and -2 respectively, are expressed in the mammalian cardiovascular system. Like in almost every tissue, β-arrestin-1 protein is approximately 10-15-fold more abundant than β-arrestin-2 in the circulatory system, as well[1]. Both β-arrestins regulate all non-opsin G protein-coupled receptors (GPCRs), also known as seven transmembrane-spanning receptors (7TMRs), including those responsible for neurohormonal regulation of cardiovascular physiology[2,3]. For instance, cardiac function (contractility) is tightly controlled by the activity of β-adrenergic receptors (βARs) located in the membranes of cardiac myocytes[4-8]. Cardiac structure and morphology are regulated by angiotensin II (AngII) type 1 receptors (AT_1Rs) present (mainly) in cardiac fibroblast and endothelial cell membranes[4,7]. Even the production and release of the regulatory hormones per se, whether it be catecholamine and corticosteroid release by the adrenal glands or activation of the renin-angiotensin-aldosterone system by the juxtagomerular apparatus of the kidneys or release of neurotransmitters by central and peripheral neurons innervating cardiovascular organs, is under tight regulation by various GPCRs[1,4,7].

Cardiovascular GPCRs can signal either through G-proteins or β-arrestins with the natural, endogenous agonist hormones activating both signal transducers at each receptor fully and equally[1,9]. Several "biased" GPCR ligands have been discovered that (relatively) selectively activate either G proteins or β-arrestins[1,9]. This "bias" in terms of the activated signal transducer is always relative but the concept of "biased" signaling and its attainability for therapeutic purposes has been challenged recently. Specifically, recent studies have shown that receptors can activate both G-proteins and β-arrestins at the same time[10] or that β-arrestins do not even need to bind the agonist-activated receptor to get ("catalytically") activated[11]. Additionally, it was very recently clearly demonstrated that G-protein activation is absolutely necessary, at least initially upon agonist activation, for β-arrestin activation and signaling to follow[12,13]. This sequence of activation of the two signal transducers, *i.e.*, G-proteins being activated first followed by activation of β-arrestins, is also corroborated well by the majority of structural studies on mechanisms of GPCR activation done to date.

Specifically, the receptor seems to require the interaction with the heterotrimeric G-protein in order to become fully activated by the agonist. In other words, in the absence of a G-protein, agonist binding per se is simply insufficient for the receptor to break the huge energy barrier that prevents it from reaching the active state[2,14]. Taken together, G-protein activation and signaling appears to be a prerequisite for β-arrestin signaling by GPCRs and thus, discrimination between these two families of signal transducers for any given GPCR ligand, which represents the foundation of the "biased signaling" concept for GPCRs, is essentially unfeasible. However, whereas the selective stimulation of G-protein vs. β-arrestin signaling for therapeutic purposes is most likely impossible, selective stimulation of β-arrestin-1 *vs* β-arrestin-2 might be feasible, similarly to the selective stimulation (or inhibition) of various Gα, which is pharmacologically achievable and currently exploited therapeutically. The first hint at signaling and functional differences between the two β-arrestins came over a decade ago with the realization that β-arrestin-1, but not β-arrestin-2 which has a nuclear export signal sequence (NES), can translocate to the nucleus where it regulates gene transcription[15]. Since then, the experimental evidence supporting functional divergence between the signaling properties of the two β-arrestins both *in vitro* and in several tissues and organs *in vivo*, including in the heart, has been mounting at an accelerating pace. Thus, β-arrestin isoform-selective targeting may have a place in the design and development of novel drugs. Below, we review this evidence known so far for the cardiac β-arrestins and discuss what it could signify for heart failure drug development. Given that almost all of the *in vivo* studies on cardiac β-arrestins done so far are in relation to the effects of these two proteins on βAR and AT_1R signaling in the heart, the evidence for cardiac β-arrestins' functional diversity reviewed below pertains exclusively to cardiac βARs and AT_1Rs.

FUNCTIONAL DIFFERENCES BETWEEN THE TWO BETA ARRESTINS IN CARDIAC BETA-AR SIGNALING

The β_1AR is by far the predominant βAR subtype in human adult cardiac myocytes, representing 75%-80% of total βAR density, followed by the β_2AR, which comprises about 15-18% of total cardiomyocyte βARs and the remaining 2%-3% is β_3ARs[4,7,16]. β_1AR stimulation by catecholamines results in the dissociation of the stimulatory G protein alpha subunit ($G\alpha_s$) from $G_{\beta\gamma}$. $G_{\alpha s}$ stimulates adenylyl cyclase (AC) to produce cyclic adenosine monophosphate (cAMP), which, in turn, activates protein kinase A (PKA) and regulates different intracellular, sarcolemmal and myofibrillar substrates[4,5,7]. Thus, cAMP-dependent signaling in cardiomyocytes mediates the cellular effects of β_1AR activation on stimulation of cardiac chronotropy, inotropy, dromotropy, and lusitropy (Figure 1)[4,5,7]. As co-factors of GPCR-kinases (GRKs) in βAR desensitization/downregulation, β-arrestins normally diminish the inotropic and β-adrenergic reserves of the failing heart and their inhibition should theoretically be beneficial in acute decompensated heart failure (ADHF)[4,7]. Indeed, genetic deletion of β-arrestin-1 in the heart results in several desirable therapeutic effects in heart failure, such as dramatic improvements in both cardiac β-adrenergic and inotropic reserves, amelioration of adverse remodeling and increased survival post-myocardial infarction (MI) (Figure 1)[17,18]. In contrast however, cardiac β-arrestin-2 has been shown to be cardio-protective, as it inhibits cardiac apoptosis, inflammation, and significantly attenuates overall adverse remodeling post-MI (Figure 1)[19]. One of the underlying mechanisms for the anti-inflammatory effects of cardiac β-arrestin-2 is nuclear factor-kappaB (NFκB) inhibition in cardiac myocytes, which, again, appears to be mediated only by β-arrestin-2 and not by β-arrestin-1 in the heart (Figure 1)[19,20]. Importantly, β_1AR-stimulated β-arrestin-2 was also recently documented to increase cardiac contractility both directly and indirectly (Figure 1)[20]. Directly, by interacting with Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase (SERCA)-2a leading to enhanced Small Ubiquitin-related MOdifier (SUMO)-ylation of the latter[20]. This process, deficient in human heart failure, is known to directly stimulate SERCA2a activity, thereby increasing cardiac contractility[21]. β-arrestin-2 also increases cardiac function indirectly by leaving the β_1AR-stimulated cAMP-dependent pro-contractile signaling intact (*i.e.*, not desensitizing it) in cardiac myocytes *in vitro* and in post-MI heart failure mice *in vivo* (Figure 1)[20]. Importantly, these effects are not shared by the vastly more abundant in the human heart β-arrestin-1[22].

One of the salient mechanisms for the anti-apoptotic effects of cardiac β-arrestin-2 is transactivation of the epidermal growth factor receptor (EGFR) by the cardiac β_1AR (Figure 1)[18,23]. β-arrestin-1 seems again unable to stimulate this and instead, promotes cardiac apoptosis post-MI (Figure 1)[18]. Older studies had reported that mice expressing a mutant β_1AR that cannot undergo GRK-dependent desensitization or

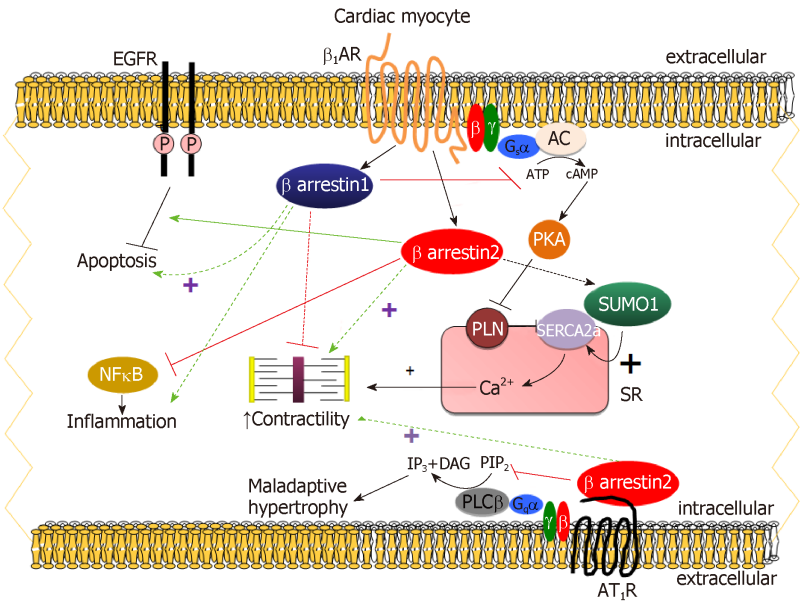


Figure 1 The functional distinction between β-arrestin-1 and β-arrestin-2 in cardiac myocytes. ATP: Adenosine triphosphate; P: Phosphorylation; SR: Sarcoplasmic reticulum; SUMO1: Small ubiquitin-like modifier protein-1; PLN: Phospholamban; PIP_2: Phosphatidyl-inositol 4,5-bisphosphate; IP_3: Inositol 1,4,5-trisphosphate; DAG: 1,2-Diacylglycerol; EGFR: Epidermal growth factor receptor; AR: Adrenergic receptor.

activate β-arrestins in their hearts lack cardiac EGFR transactivation and suffer from massive cardiac apoptosis and left ventricular dilatation compared to wild type controls[23]. Interestingly, the β-blocker drug carvedilol, an inverse agonist towards G-protein activation[16], is a weak β-arrestin-biased agonist that activates ERKs (Extracellular signal-Regulated Kinases) *via* EGFR transactivation also[24,25]. It should be pointed out though that carvedilol`s "biased" β-arrestin agonism has been demonstrated only in heterologous recombinant cell systems without cardiovascular (or any other physiological) relevance (mostly, transfected HEK293 cells). However, if this holds true in actual cardiomyocytes *in vivo*, it might be part of the mechanism for this β-blocker`s cardio-protective effects. However, several studies do not lend support to this notion; sustained β_1AR activation by catecholamines, markedly more potent activators of β-arrestin-dependent ERKs in the heart than carvedilol, increases cardiac adverse remodeling even in the absence of cardiac injury[26]. Moreover, carvedilol is also a β_2- and α_1AR antagonist, which may interfere with its β-arrestin-activating properties in the heart[27]. On the other hand, carvedilol`s effects in the heart are virtually exclusively mediated by the β_1AR, due to its relative selectivity for the human β_1AR over the other human AR subtypes (β_2AR and α_1AR) and to the vast preponderance of the β_1AR over the rest of AR subtypes in the human adult myocardium[16]. Last but not least, recent studies have been unable to directly detect β-arrestin interactions with either β_1AR or β_2AR bound to carvedilol, including a study reporting the intriguing finding that carvedilol requires $G_{\alpha i}$ protein recruitment to the β_1AR in order to induce EGFR transactivation *via* β-arrestins[28-31]. Nevertheless, carvedilol has been shown to selectively recruit β-arrestin-2 to the hyperfunctional human polymorphic Arg389 β_1AR in cardiomyocytes *in vitro*[32]. Therefore, the more robust, compared to its Gly389 counterpart, pro-contractile signaling of this β_1AR variant[33] might be, at least partly, due to its unique β-arrestin-2-interacting tropism. In this vein, very recent data from our lab indicate that carvedilol-bound β_1AR uniquely stimulates β-arrestin-2-dependent SERCA2a activity and fractional shortening of cardiomyocytes *in vitro*[34].

FUNCTIONAL DIFFERENCES BETWEEN THE TWO BETA-ARRESTINS IN CARDIAC AT_1R SIGNALING

Despite its very low abundance in adult human myocardium (density ratio of AT_1R/β_1AR in the non-failing human heart: approximately 1:15)[16], the AT_1R plays important regulatory roles in the heart, but mainly *via* actions in cardiac fibroblasts and endothelial cells, rather than in cardiac myocytes[4,7,35-37]. The AngII peptide analog SII ([Sar^1-Ile^4-Ile^8]-AngII) does not elicit G_q protein signaling when bound to the

AT_1R[9,38]. When it was discovered to induce β-arrestin signaling from the AT_1R, the concept of biased signaling was introduced and ushered in a completely new field in cardiovascular drug development with companies designing novel "biased" AT_1R ligands that only activate β-arrestins while retaining G-protein-blocking properties. SII has now been documented to not be completely β-arrestin-"biased", as it can activate some G-protein types (*e.g.*, G_s, G_i) from the AT_1R[9]. Nevertheless, studies have shown that AT_1R-elicited β-arrestin-dependent signaling in cardiac myocytes leads to cardiomyocyte proliferation without hypertrophy, which is $G_{q/11}$ protein signaling-dependent, and may even result in positive inotropy and lusitropy depending on which GRK isoform is involved (the so-called receptor "bar-coding" by GRKs). Interestingly, which β-arrestin is engaged is also crucial[39,40]. Specifically, GRK2-dependent phosphorylation followed by β-arrestin-1 binding seems to reduce, whereas GRK6-dependent phosphorylation followed by β-arrestin-2 interaction seems to promote AT_1R-induced contractility in primary murine adult cardiomyocytes (Figure 1)[39]. However, AT_1R-activated β-arrestins have no effect on contractility in isolated Langendorff-perfused cardiac preparations[41]. Furthermore, a recombinant $AT_{1A}R$ capable of only signaling through β-arrestins inhibits myocardial apoptosis and fibrosis, and enhances cardiomyocyte hypertrophy, upon transgenic overexpression in mouse hearts[42]. Interestingly, a β-arrestin-2-"biased" ligand at the AT_1R is very beneficial in mice suffering from dilated cardiomyopathy as it prevents maladaptive signaling and improves myofilament Ca^{2+} sensitivity[43]. Thus, cardiac AT_1R promotes hypertrophy and cardiomyocyte proliferation *via* the classic G_q protein/phospholipase C-β-signaling pathway, which is inhibited by the β-arrestins (classic AT_1R desensitization), and, at the same time, β-arrestin-2 (but not β-arrestin-1) can increase cardiac function *via* its cardiac AT_1R-dependent signaling (Figure 1).

Based on the above studies, several SII-derivative peptides have been synthesized and tested in animal models of ADHF with promising initial results[44,45]. Unfortunately, these compounds failed in large phase III clinical trials (BLAST-AHF, ClinicalTrials.gov number, NCT01966601). There are probably several reasons for this. First, findings in animal models do not always translate into humans. Second, the compounds might have not been completely β-arrestin-"biased" (*i.e.*, maybe they had some weak, residual activity towards certain G-proteins). One intriguing possibility is that, due to the significantly lower abundance of the cardioprotective β-arrestin-2, compared to the cardio-toxic β-arrestin-1, in human cardiomyocytes[22], these β-arrestin-"biased" compounds stimulated, in reality, β-arrestin-1 instead of β-arrestin-2 in the patients` hearts and that's why their clinical outcomes were not the desired ones. Finally, it is very likely that these compounds stimulated the AT_1R only in cardiac fibroblasts, which would preclude any clinical benefit for ADHF patients. In fact, both β-arrestins have been shown to regulate human cardiac fibroblast differentiation and to mediate collagen synthesis in human failing left ventricle-derived fibroblasts, thereby promoting the adverse remodeling process of cardiac fibrosis[46].

Notably, β-arrestins have been reported to mediate signaling by the mechanical stretch-activated (unliganded) cardiac AT_1R[47], which has been suggested to underlie one of the fundamental laws of cardiac physiology, the Frank-Starling mechanism of cardiac contractility[48]. Although intriguing, this finding is very difficult to interpret, given that the Frank-Starling mechanism is hemodynamically/biomechanically governed rather than dependent on hormonal receptors/effects. Besides, if it was mediated by a cardiac GPCR, then that receptor would definitely be the β_1AR, the by far most abundant GPCR (and at least 15-fold more abundant than the AT_1R) in cardiomyocytes[16].

Finally, β-arrestin-mediated signaling by the AT_1R that can regulate cardiac function occurs in the adrenal cortex, as well. Specifically, the AT_1R promotes the adrenocortical production of aldosterone, a cardio-toxic hormone elevated in chronic human heart failure, *via* both $G_{q/11}$-proteins and β-arrestin-1[35,49-51]. In fact, adrenal β-arrestin-1 is essential for aldosterone production, since, in mice lacking the *β-arrestin-1* gene, circulating aldosterone levels do not increase even in the presence of MI[18]. Interestingly, the prototypic AT_1R antagonist (ARB, angiotensin receptor blocker) losartan is a relatively G protein-"biased" antagonist, which means it cannot suppress β-arrestin-1-dependent aldosterone production[51-54]. In contrast, candesartan and valsartan are potent β-arrestin-inverse agonists at the adrenal AT_1R and very effective at suppressing aldosterone *in vitro* and *in vivo*[52,53]. These differences among ARBs, which are all orthosteric antagonists, in their potency at blocking AT_1R-activated β-arrestin signaling may reflect their differential abilities to suppress β-arrestin signaling by the unliganded (*i.e.*, constitutively active) AT_1R[47,55]. In other words, the ARBs seem to be inverse agonists not only for G-proteins but also for β-arrestins at the AT_1R.

THERAPEUTIC IMPLICATIONS IN HEART FAILURE

It becomes clear from the above that the signaling effects of the two β-arrestins in the heart are not just different but actually diametrically opposite. This is true for several other mammalian organ systems and tissue types[56-58] and is completely corroborated by molecular, biophysical, crystallographic, and proteomic studies[59-62]. It also makes sense from the evolutionary point of view, as functional redundancy of proteins is usually not favored by natural selection. Only during embryonic development might the two β-arrestins be able to compensate for each other, since single β-arrestin-knockout mice (either β-arrestin-1- or β-arrestin-2-knockouts) are viable and breed normally but the double β-arrestin-knockout mouse is embryonic-lethal[63].

Regarding the myocardium, all the functional studies on β-arrestins done so far are in relation to either βARs or the AT_1R. Studies on β-arrestin signaling from other cardiac GPCRs in cardiac cells are lacking. Based on the available data for β_1AR, β_2AR, or AT_1R signaling through β-arrestins in cardiac cells, it can be safely concluded that β-arrestin-1 is the arrestin responsible for the classic desensitization of the cAMP-dependent pro-contractile signaling of the β_1AR. This quite simply means that β-arrestin-1 exerts overall negative inotropy and is responsible (together with the elevated in human heart failure cardiac GRK2) for the diminished inotropic and adrenergic reserves of the failing human heart. In addition, β-arrestin-1 promotes cardiac apoptosis, inflammation, and accelerates cardiac adverse remodeling post-MI. In direct contrast, β-arrestin-2 promotes β_1AR-mediated cardiac contractility both directly and indirectly. Directly, *via* augmentation of SERCA2a activity, and indirectly, by leaving the β_1AR's cAMP-dependent pro-contractile signaling intact (*i.e.*, no desensitization). On the other hand, it inhibits apoptosis and inflammation, and overall attenuates cardiac adverse remodeling post-MI, *via* stimulation of a variety of molecular pathways, such as EGFR transactivation and NFκB inhibition, which β-arrestin-1 does not activate. Induction of ERK and of other mitogenic/proliferative molecular signaling pathways in cardiomyocytes play auxiliary roles in β-arrestin-2's reverse remodeling effects, as well. Of note, the same functional distinction between the two cardiac β-arrestins (*i.e.*, β-arrestin-1 being detrimental, β-arrestin-2 being beneficial) applies to cardiac AT_1R signaling, too. Regardless of how small the contribution of this GPCR to the overall contractile function of the cardiac myocyte is, β-arrestin-2 again appears to promote contractility and cardiomyocyte survival in response to AT_1R activation. Conversely, β-arrestin-1 (again in conjunction with GRK2) opposes the AT_1R-dependent pro-contractile signaling in cardiac myocytes. However, β-arrestin-1 might exert an indirect beneficial effect in the hypertrophic heart by desensitizing (reducing) the pro-hypertrophic signaling of the cardiac AT_1R through $G_{q/11}$-proteins. In conclusion, based on their observed effects on the signaling of both β_1ARs and AT_1Rs in cardiac myocytes, documented either directly (in β-arrestin-knockout mice) or indirectly (with the use of "biased" receptor ligands), cardiac β-arrestin-2 stimulation and/or β-arrestin-1 inhibition might be valid therapeutic strategies in human heart failure. By the way, it is interesting to note here that probably the exact opposite is the case in the systemic vasculature. In vascular smooth muscle cells, β-arrestin-1 appears beneficial in terms of vasodilation and attenuation of hyperplasia and β-arrestin-2 seems to promote hypertrophy /hyperplasia[58]. This should not come as a surprise at all, given the different cellular machineries and GPCR types involved in β-arrestin signaling between cardiomyocytes (mainly β_1AR) and vascular smooth muscle cells (mainly AT_1R and, to a lesser extent, β_2AR). Besides, this is exactly what happens with the major second messenger cAMP: stimulated by the β_1AR, it is pro-contractile in cardiomyocytes, but stimulated by the β_2AR, it is pro-dilatory in vascular smooth muscle.

CONCLUSION

In the adult myocardium, the actions of β-arrestin-1 are detrimental, since they result in depletion of the functional and adrenergic reserves of the heart. In contrast, β-arrestin-2 is beneficial, since it can increase both of these cardiac reserves or at least preserve them in the face of a cardiac insult/damage, such as an MI. Thus, from the therapeutic standpoint, cardiac β-arrestin-1 blockade or β-arrestin-2 stimulation should be pursued for heart disease treatment. Of course, there are at least three very important questions awaiting answer in future studies in order to fully validate these strategies as therapeutic options for human heart failure. First, the effects of the two β-arrestins on the signaling of other important cardiac GPCRs in the heart, *i.e.*, beyond the βARs and the AT_1R, need to be elucidated. The second issue to resolve is what the effects of the two β-arrestins in other tissues/components of the cardiovascular

system are, *e.g.*, vasculature, platelets, adrenals, *etc*. This is particularly important if the pharmacological targeting of the β-arrestins with systemically administered agents is being explored. For instance, β-arrestin-2 is beneficial in the heart, in platelets, and in vascular endothelium but might be detrimental in vascular smooth muscle[58]. Its exact effects in all of these tissues need to be thoroughly investigated and determined, if a drug that stimulates this β-arrestin isoform is to be designed and developed. Finally, the third and therapeutically salient unanswered question pertains to the expression levels of the cardiac β-arrestins in the failing human heart. Although β-arrestin-2 protein is significantly under-expressed, compared to β-arrestin-1, in the non-failing human adult myocardium[22,64], which makes cardiac-specific β-arrestin-2 gene transfer an enticing approach for heart failure treatment, its protein levels (and if they change) in human heart failure remain unknown. However, given that it is significantly expressed at the mRNA level, and in fact at levels comparable to those of β-arrestin-1 mRNA, in the failing human heart[64], it is quite plausible that it might be upregulated at the protein level, similarly to GRK2, as a homeostatic mechanism of the failing human myocardium to confer cardioprotection. The only study done to date investigating β-arrestin expression in failing human hearts is quite old (was published almost 25 years ago) and could not detect any changes in the protein levels of either β-arrestin[64]. Nevertheless, although β-arrestin-1 protein probably does not change in human heart failure, because it is already highly expressed in normal, healthy human hearts, that study failed to detect any β-arrestin-2 protein at all, even in normal healthy human hearts, probably due to technical deficiencies of the antibody it used[64]. Therefore, it is rather inconclusive with regard to cardiac β-arrestin-2 protein expression in humans and whether cardiac β-arrestin-2 protein changes in human heart failure remains an open question. In fact, a much more recent study done in human cardiac fibroblasts isolated from left ventricles of heart failure patients hinted at β-arrestin-2 protein being upregulated in human failing hearts[46]. In any case, more studies are certainly warranted, especially in human cardiac specimens, to unravel the full spectrum of physiological (and pathophysiological) actions of the two cardiac β-arrestins, beginning with the answering of the three outstanding questions mentioned above. Only then will the true potential of individual cardiac β-arrestin isoform targeting for heart failure therapy be revealed, so that the pharmaceutical industry can begin its realization.

REFERENCES

1 **Desimine VL**, McCrink KA, Parker BM, Wertz SL, Maning J, Lymperopoulos A. Biased Agonism/Antagonism of Cardiovascular GPCRs for Heart Failure Therapy. *Int Rev Cell Mol Biol* 2018; **339**: 41-61 [PMID: 29776604 DOI: 10.1016/bs.ircmb.2018.02.007]

2 **Hilger D**, Masureel M, Kobilka BK. Structure and dynamics of GPCR signaling complexes. *Nat Struct Mol Biol* 2018; **25**: 4-12 [PMID: 29323277 DOI: 10.1038/s41594-017-0011-7]

3 **Peterson YK**, Luttrell LM. The Diverse Roles of Arrestin Scaffolds in G Protein-Coupled Receptor Signaling. *Pharmacol Rev* 2017; **69**: 256-297 [PMID: 28626043 DOI: 10.1124/pr.116.013367]

4 **Lymperopoulos A**, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. *Circ Res* 2013; **113**: 739-753 [PMID: 23989716 DOI: 10.1161/CIRCRESAHA.113.300308]

5 **Lymperopoulos A**, Garcia D, Walklett K. Pharmacogenetics of cardiac inotropy. *Pharmacogenomics* 2014; **15**: 1807-1821 [PMID: 25493572 DOI: 10.2217/pgs.14.120]

6 **Siryk-Bathgate A**, Dabul S, Lymperopoulos A. Current and future G protein-coupled receptor signaling targets for heart failure therapy. *Drug Des Devel Ther* 2013; **7**: 1209-1222 [PMID: 24143078 DOI: 10.2147/DDDT.S35905]

7 **Capote LA**, Mendez Perez R, Lymperopoulos A. GPCR signaling and cardiac function. *Eur J Pharmacol* 2015; **763**: 143-148 [PMID: 25981298 DOI: 10.1016/j.ejphar.2015.05.019]

8 **Lymperopoulos A**, Bathgate A. Arrestins in the cardiovascular system. *Prog Mol Biol Transl Sci* 2013; **118**: 297-334 [PMID: 23764059 DOI: 10.1016/B978-0-12-394440-5.00012-7]

9 **Whalen EJ**, Rajagopal S, Lefkowitz RJ. Therapeutic potential of β-arrestin- and G protein-biased agonists. *Trends Mol Med* 2011; **17**: 126-139 [PMID: 21183406 DOI: 10.1016/j.molmed.2010.11.004]

10 **Ranjan R**, Dwivedi H, Baidya M, Kumar M, Shukla AK. Novel Structural Insights into GPCR-β-Arrestin Interaction and Signaling. *Trends Cell Biol* 2017; **27**: 851-862 [PMID: 28651823 DOI: 10.1016/j.tcb.2017.05.008]

11 **Eichel K**, Jullié D, Barsi-Rhyne B, Latorraca NR, Masureel M, Sibarita JB, Dror RO, von Zastrow M. Catalytic activation of β-arrestin by GPCRs. *Nature* 2018; **557**: 381-386 [PMID: 29720660 DOI: 10.1038/s41586-018-0079-1]

12 **Grundmann M**, Merten N, Malfacini D, Inoue A, Preis P, Simon K, Rüttiger N, Ziegler N, Benkel T, Schmitt NK, Ishida S, Müller I, Reher R, Kawakami K, Inoue A, Rick U, Kühl T, Imhof D, Aoki J, König GM, Hoffmann C, Gomeza J, Wess J, Kostenis E. Lack of beta-arrestin signaling in the absence of active G proteins. *Nat Commun* 2018; **9**: 341 [PMID: 29362459 DOI: 10.1038/s41467-017-02661-3]

13 **Luttrell LM**, Wang J, Plouffe B, Smith JS, Yamani L, Kaur S, Jean-Charles PY, Gauthier C, Lee MH, Pani B, Kim J, Ahn S, Rajagopal S, Reiter E, Bouvier M, Shenoy SK, Laporte SA, Rockman HA, Lefkowitz RJ. Manifold roles of β-arrestins in GPCR signaling elucidated with siRNA and CRISPR/Cas9. *Sci Signal* 2018; **11**: pii: eaat7650 [PMID: 30254056 DOI: 10.1126/scisignal.aat7650]

14 **Weis WI**, Kobilka BK. The Molecular Basis of G Protein-Coupled Receptor Activation. *Annu Rev Biochem* 2018; **87**: 897-919 [PMID: 29925258 DOI: 10.1146/annurev-biochem-060614-033910]

15 **Ma L**, Pei G. Beta-arrestin signaling and regulation of transcription. *J Cell Sci* 2007; **120**: 213-218 [PMID: 17215450 DOI: 10.1242/jcs.03338]
16 **Yoshikawa T**, Port JD, Asano K, Chidiak P, Bouvier M, Dutcher D, Roden RL, Minobe W, Tremmel KD, Bristow MR. Cardiac adrenergic receptor effects of carvedilol. *Eur Heart J* 1996; **17** Suppl B: 8-16 [PMID: 8733065 DOI: 10.1093/eurheartj/17.suppl_B.8]
17 **Conner DA**, Mathier MA, Mortensen RM, Christe M, Vatner SF, Seidman CE, Seidman JG. beta-Arrestin1 knockout mice appear normal but demonstrate altered cardiac responses to beta-adrenergic stimulation. *Circ Res* 1997; **81**: 1021-1026 [PMID: 9400383 DOI: 10.1161/01.RES.81.6.1021]
18 **Bathgate-Siryk A**, Dabul S, Pandya K, Walklett K, Rengo G, Cannavo A, De Lucia C, Liccardo D, Gao E, Leosco D, Koch WJ, Lymperopoulos A. Negative impact of β-arrestin-1 on post-myocardial infarction heart failure via cardiac and adrenal-dependent neurohormonal mechanisms. *Hypertension* 2014; **63**: 404-412 [PMID: 24218435 DOI: 10.1161/HYPERTENSIONAHA.113.02043]
19 **Watari K**, Nakaya M, Nishida M, Kim KM, Kurose H. β-arrestin2 in infiltrated macrophages inhibits excessive inflammation after myocardial infarction. *PLoS One* 2013; **8**: e68351 [PMID: 23861891 DOI: 10.1371/journal.pone.0068351]
20 **McCrink KA**, Maning J, Vu A, Jafferjee M, Marrero C, Brill A, Bathgate-Siryk A, Dabul S, Koch WJ, Lymperopoulos A. β-Arrestin2 Improves Post-Myocardial Infarction Heart Failure via Sarco(endo)plasmic Reticulum Ca2+-ATPase-Dependent Positive Inotropy in Cardiomyocytes. *Hypertension* 2017; **70**: 972-981 [PMID: 28874462 DOI: 10.1161/HYPERTENSIONAHA.117.09817]
21 **Kho C**, Lee A, Jeong D, Oh JG, Chaanine AH, Kizana E, Park WJ, Hajjar RJ. SUMO1-dependent modulation of SERCA2a in heart failure. *Nature* 2011; **477**: 601-605 [PMID: 21900893 DOI: 10.1038/nature10407]
22 **McCrink KA**, Maning J, Vu A, Jafferjee M, Marrero C, Brill A, Bathgate-Siryk A, Dabul S, Koch WJ, Lymperopoulos A. Cardiac βarrestin2 Improves Contractility and Adverse Remodeling in Heart Failure, But Is Underexpressed in Humans. *J Am Coll Cardiol* 2017; **70**: 2948-2949 [PMID: 29216991 DOI: 10.1016/j.jacc.2017.10.008]
23 **Noma T**, Lemaire A, Naga Prasad SV, Barki-Harrington L, Tilley DG, Chen J, Le Corvoisier P, Violin JD, Wei H, Lefkowitz RJ, Rockman HA. Beta-arrestin-mediated beta1-adrenergic receptor transactivation of the EGFR confers cardioprotection. *J Clin Invest* 2007; **117**: 2445-2458 [PMID: 17786238 DOI: 10.1172/JCI31901]
24 **Kim IM**, Tilley DG, Chen J, Salazar NC, Whalen EJ, Violin JD, Rockman HA. Beta-blockers alprenolol and carvedilol stimulate beta-arrestin-mediated EGFR transactivation. *Proc Natl Acad Sci USA* 2008; **105**: 14555-14560 [PMID: 18787115 DOI: 10.1073/pnas.0804745105]
25 **Wisler JW**, DeWire SM, Whalen EJ, Violin JD, Drake MT, Ahn S, Shenoy SK, Lefkowitz RJ. A unique mechanism of beta-blocker action: carvedilol stimulates beta-arrestin signaling. *Proc Natl Acad Sci USA* 2007; **104**: 16657-16662 [PMID: 17925438 DOI: 10.1073/pnas.0707936104]
26 **Kaur K**, Parra S, Chen R, Charbeneau RA, Wade SM, Jay PY, Neubig RR. Gαi2 signaling: friend or foe in cardiac injury and heart failure? *Naunyn Schmiedebergs Arch Pharmacol* 2012; **385**: 443-453 [PMID: 22411356 DOI: 10.1007/s00210-011-0705-z]
27 **Carr R**, Schilling J, Song J, Carter RL, Du Y, Yoo SM, Traynham CJ, Koch WJ, Cheung JY, Tilley DG, Benovic JL. β-arrestin-biased signaling through the β2-adrenergic receptor promotes cardiomyocyte contraction. *Proc Natl Acad Sci USA* 2016; **113**: E4107-E4116 [PMID: 27354517 DOI: 10.1073/pnas.1606267113]
28 **Littmann T**, Göttle M, Reinartz MT, Kälble S, Wainer IW, Ozawa T, Seifert R. Recruitment of β-arrestin 1 and 2 to the β2-adrenoceptor: analysis of 65 ligands. *J Pharmacol Exp Ther* 2015; **355**: 183-190 [PMID: 26306764 DOI: 10.1124/jpet.115.227959]
29 **Shukla AK**, Westfield GH, Xiao K, Reis RI, Huang LY, Tripathi-Shukla P, Qian J, Li S, Blanc A, Oleskie AN, Dosey AM, Su M, Liang CR, Gu LL, Shan JM, Chen X, Hanna R, Choi M, Yao XJ, Klink BU, Kahsai AW, Sidhu SS, Koide S, Penczek PA, Kossiakoff AA, Woods VL, Kobilka BK, Skiniotis G, Lefkowitz RJ. Visualization of arrestin recruitment by a G-protein-coupled receptor. *Nature* 2014; **512**: 218-222 [PMID: 25043026 DOI: 10.1038/nature13430]
30 **O'Hayre M**, Eichel K, Avino S, Zhao X, Steffen DJ, Feng X, Kawakami K, Aoki J, Messer K, Sunahara R, Inoue A, von Zastrow M, Gutkind JS. Genetic evidence that β-arrestins are dispensable for the initiation of β2-adrenergic receptor signaling to ERK. *Sci Signal* 2017; **10**: pii: eaal3395 [PMID: 28634209 DOI: 10.1126/scisignal.aal3395]
31 **Wang J**, Hanada K, Staus DP, Makara MA, Dahal GR, Chen Q, Ahles A, Engelhardt S, Rockman HA. Gαi is required for carvedilol-induced β1 adrenergic receptor β-arrestin biased signaling. *Nat Commun* 2017; **8**: 1706 [PMID: 29167435 DOI: 10.1038/s41467-017-01855-z]
32 **McCrink KA**, Brill A, Jafferjee M, Valero TR, Marrero C, Rodriguez MM, Hale GM, Lymperopoulos A. β1-adrenoceptor Arg389Gly polymorphism confers differential β-arrestin-binding tropism in cardiac myocytes. *Pharmacogenomics* 2016; **17**: 1611-1620 [PMID: 27643874 DOI: 10.2217/pgs-2016-0094]
33 **Liggett SB**, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT, Anderson JL, Carlquist JF, Krause-Steinrauf HJ, Lazzeroni LC, Port JD, Lavori PW, Bristow MR. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc Natl Acad Sci USA* 2006; **103**: 11288-11293 [PMID: 16844790 DOI: 10.1073/pnas.0509937103]
34 **Lymperopoulos A**, Desimine VL, McCrink KA, Maning J, Wertz SL, Markan U, Pasupuleti S, Brill A, Parker BM. Positive cardiac inotropy by carvedilol via unique beta-arrestin2-dependent SERCA2a stimulation. *Eur Heart J* 2018; **39**: Suppl_1, 1 [DOI: 10.1093/eurheartj/ehy563.3144]
35 **Maning J**, Negussie S, Clark MA, Lymperopoulos A. Biased agonism/antagonism at the AngII-AT1 receptor: Implications for adrenal aldosterone production and cardiovascular therapy. *Pharmacol Res* 2017; **125**: 14-20 [PMID: 28511989 DOI: 10.1016/j.phrs.2017.05.009]
36 **Lymperopoulos A**. Beta-arrestin biased agonism/antagonism at cardiovascular seven transmembrane-spanning receptors. *Curr Pharm Des* 2012; **18**: 192-198 [PMID: 22229558 DOI: 10.2174/138161212799040475]
37 **Thomas WG**, Thekkumkara TJ, Baker KM. Cardiac effects of AII. AT1A receptor signaling, desensitization, and internalization. *Adv Exp Med Biol* 1996; **396**: 59-69 [PMID: 8726686 DOI: 10.1007/978-1-4899-1376-0_7]
38 **Saulière A**, Bellot M, Paris H, Denis C, Finana F, Hansen JT, Altié MF, Seguelas MH, Pathak A, Hansen JL, Sénard JM, Galés C. Deciphering biased-agonism complexity reveals a new active AT1 receptor entity. *Nat Chem Biol* 2012; **8**: 622-630 [PMID: 22634635 DOI: 10.1038/nchembio.961]

39 **Rajagopal K**, Whalen EJ, Violin JD, Stiber JA, Rosenberg PB, Premont RT, Coffman TM, Rockman HA, Lefkowitz RJ. Beta-arrestin2-mediated inotropic effects of the angiotensin II type 1A receptor in isolated cardiac myocytes. *Proc Natl Acad Sci USA* 2006; **103**: 16284-16289 [PMID: 17060617 DOI: 10.1073/pnas.0607583103]

40 **Zidar DA**, Violin JD, Whalen EJ, Lefkowitz RJ. Selective engagement of G protein coupled receptor kinases (GRKs) encodes distinct functions of biased ligands. *Proc Natl Acad Sci USA* 2009; **106**: 9649-9654 [PMID: 19497875 DOI: 10.1073/pnas.0904361106]

41 **Aplin M**, Christensen GL, Schneider M, Heydorn A, Gammeltoft S, Kjølbye AL, Sheikh SP, Hansen JL. Differential extracellular signal-regulated kinases 1 and 2 activation by the angiotensin type 1 receptor supports distinct phenotypes of cardiac myocytes. *Basic Clin Pharmacol Toxicol* 2007; **100**: 296-301 [PMID: 17448114 DOI: 10.1111/j.1742-7843.2007.00064.x]

42 **Zhai P**, Yamamoto M, Galeotti J, Liu J, Masurekar M, Thaisz J, Irie K, Holle E, Yu X, Kupershmidt S, Roden DM, Wagner T, Yatani A, Vatner DE, Vatner SF, Sadoshima J. Cardiac-specific overexpression of AT1 receptor mutant lacking G alpha q/G alpha i coupling causes hypertrophy and bradycardia in transgenic mice. *J Clin Invest* 2005; **115**: 3045-3056 [PMID: 16276415 DOI: 10.1172/JCI25330]

43 **Ryba DM**, Li J, Cowan CL, Russell B, Wolska BM, Solaro RJ. Long-Term Biased β-Arrestin Signaling Improves Cardiac Structure and Function in Dilated Cardiomyopathy. *Circulation* 2017; **135**: 1056-1070 [PMID: 28104714 DOI: 10.1161/CIRCULATIONAHA.116.024482]

44 **Violin JD**, DeWire SM, Yamashita D, Rominger DH, Nguyen L, Schiller K, Whalen EJ, Gowen M, Lark MW. Selectively engaging β-arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. *J Pharmacol Exp Ther* 2010; **335**: 572-579 [PMID: 20801892 DOI: 10.1124/jpet.110.173005]

45 **Boerrigter G**, Soergel DG, Violin JD, Lark MW, Burnett JC. TRV120027, a novel β-arrestin biased ligand at the angiotensin II type I receptor, unloads the heart and maintains renal function when added to furosemide in experimental heart failure. *Circ Heart Fail* 2012; **5**: 627-634 [PMID: 22891045 DOI: 10.1161/CIRCHEARTFAILURE.112.969220]

46 **Li J**, Philip JL, Xu X, Theccanat T, Abdur Razzaque M, Akhter SA. β-Arrestins regulate human cardiac fibroblast transformation and collagen synthesis in adverse ventricular remodeling. *J Mol Cell Cardiol* 2014; **76**: 73-83 [PMID: 25134464 DOI: 10.1016/j.yjmcc.2014.08.006]

47 **Rakesh K**, Yoo B, Kim IM, Salazar N, Kim KS, Rockman HA. beta-Arrestin-biased agonism of the angiotensin receptor induced by mechanical stress. *Sci Signal* 2010; **3**: ra46 [PMID: 20530803 DOI: 10.1126/scisignal.2000769]

48 **Abraham DM**, Davis RT, Warren CM, Mao L, Wolska BM, Solaro RJ, Rockman HA. β-Arrestin mediates the Frank-Starling mechanism of cardiac contractility. *Proc Natl Acad Sci USA* 2016; **113**: 14426-14431 [PMID: 27911784 DOI: 10.1073/pnas.1609308113]

49 **Lymperopoulos A**, Aukszi B. Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy. *World J Cardiol* 2017; **9**: 200-206 [PMID: 28400916 DOI: 10.4330/wjc.v9.i3.200]

50 **Lymperopoulos A**, Rengo G, Zincarelli C, Kim J, Soltys S, Koch WJ. An adrenal beta-arrestin 1-mediated signaling pathway underlies angiotensin II-induced aldosterone production in vitro and in vivo. *Proc Natl Acad Sci USA* 2009; **106**: 5825-5830 [PMID: 19289825 DOI: 10.1073/pnas.0811706106]

51 **Lymperopoulos A**, Rengo G, Zincarelli C, Kim J, Koch WJ. Adrenal beta-arrestin 1 inhibition in vivo attenuates post-myocardial infarction progression to heart failure and adverse remodeling via reduction of circulating aldosterone levels. *J Am Coll Cardiol* 2011; **57**: 356-365 [PMID: 21232674 DOI: 10.1016/j.jacc.2010.08.635]

52 **Lymperopoulos A**, Sturchler E, Bathgate-Siryk A, Dabul S, Garcia D, Walklett K, Rengo G, McDonald P, Koch WJ. Different potencies of angiotensin receptor blockers at suppressing adrenal β-Arrestin1-dependent post-myocardial infarction hyperaldosteronism. *J Am Coll Cardiol* 2014; **64**: 2805-2806 [PMID: 25541135 DOI: 10.1016/j.jacc.2014.09.070]

53 **Dabul S**, Bathgate-Siryk A, Valero TR, Jafferjee M, Sturchler E, McDonald P, Koch WJ, Lymperopoulos A. Suppression of adrenal βarrestin1-dependent aldosterone production by ARBs: head-to-head comparison. *Sci Rep* 2015; **5**: 8116 [PMID: 25631300 DOI: 10.1038/srep08116]

54 **Valero TR**, Sturchler E, Jafferjee M, Rengo G, Magafa V, Cordopatis P, McDonald P, Koch WJ, Lymperopoulos A. Structure-activity relationship study of angiotensin II analogs in terms of β-arrestin-dependent signaling to aldosterone production. *Pharmacol Res Perspect* 2016; **4**: e00226 [PMID: 27069636 DOI: 10.1002/prp2.226]

55 **Tóth AD**, Prokop S, Gyombolai P, Várnai P, Balla A, Gurevich VV, Hunyady L, Turu G. Heterologous phosphorylation-induced formation of a stability lock permits regulation of inactive receptors by β-arrestins. *J Biol Chem* 2018; **293**: 876-892 [PMID: 29146594 DOI: 10.1074/jbc.M117.813139]

56 **Srivastava A**, Gupta B, Gupta C, Shukla AK. Emerging Functional Divergence of β-Arrestin Isoforms in GPCR Function. *Trends Endocrinol Metab* 2015; **26**: 628-642 [PMID: 26471844 DOI: 10.1016/j.tem.2015.09.001]

57 **Lymperopoulos A**, Negussie S. βArrestins in cardiac G protein-coupled receptor signaling and function: partners in crime or "good cop, bad cop"? *Int J Mol Sci* 2013; **14**: 24726-24741 [PMID: 24351844 DOI: 10.3390/ijms141224726]

58 **Lymperopoulos A**. Arrestins in the Cardiovascular System:. *An Update Prog Mol Biol Transl Sci* 2018; In press [DOI: 10.1016/bs.pmbts.2018.07.003]

59 **Zhan X**, Gimenez LE, Gurevich VV, Spiller BW. Crystal structure of arrestin-3 reveals the basis of the difference in receptor binding between two non-visual subtypes. *J Mol Biol* 2011; **406**: 467-478 [PMID: 21215759 DOI: 10.1016/j.jmb.2010.12.034]

60 **Zhuo Y**, Vishnivetskiy SA, Zhan X, Gurevich VV, Klug CS. Identification of receptor binding-induced conformational changes in non-visual arrestins. *J Biol Chem* 2014; **289**: 20991-21002 [PMID: 24867953 DOI: 10.1074/jbc.M114.560680]

61 **Gurevich VV**, Gurevich EV. Extensive shape shifting underlies functional versatility of arrestins. *Curr Opin Cell Biol* 2014; **27**: 1-9 [PMID: 24680424 DOI: 10.1016/j.ceb.2013.10.007]

62 **Xiao K**, McClatchy DB, Shukla AK, Zhao Y, Chen M, Shenoy SK, Yates JR, Lefkowitz RJ. Functional specialization of beta-arrestin interactions revealed by proteomic analysis. *Proc Natl Acad Sci USA* 2007; **104**: 12011-12016 [PMID: 17620599 DOI: 10.1073/pnas.0704849104]

63 **Luttrell LM**, Gesty-Palmer D. Beyond desensitization: physiological relevance of arrestin-dependent signaling. *Pharmacol Rev* 2010; **62**: 305-330 [PMID: 20427692 DOI: 10.1124/pr.109.002436]

64 **Ungerer M**, Parruti G, Böhm M, Puzicha M, DeBlasi A, Erdmann E, Lohse MJ. Expression of beta-

arrestins and beta-adrenergic receptor kinases in the failing human heart. *Circ Res* 1994; **74**: 206-213 [PMID: 8293560 DOI: 10.1161/01.RES.74.2.206]

P- Reviewer: Aksu T, Liberale L, Pastromas S
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu YXJ

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 February 26; 11(2): 57-70

DOI: 10.4330/wjc.v11.i2.57

ISSN 1949-8462 (online)

REVIEW

Percutaneous devices for left atrial appendage occlusion: A contemporary review

Homam Moussa Pacha, Yasser Al-khadra, Mohamad Soud, Fahed Darmoch, Abdulghani Moussa Pacha, M Chadi Alraies

ORCID number: Homam Moussa Pacha (https://orcid.org/0000-0003-4403-0941); Yasser Al-khadra (https://orcid.org/0000-0002-6618-1401); Mohamad Soud (https://orcid.org/0000-0003-2265-0875); Fahed Darmoch (https://orcid.org/0000-0003-2094-7368); Abdulghani Moussa Pacha (0000-0001-9159-2811); M Chadi Alraies (0000-0002-7874-4566).

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: October 16, 2018

Homam Moussa Pacha, Mohamad Soud, MedStar Washington Hospital Center, Washington, DC 20010, United States

Yasser Al-khadra, Cleveland Clinic, Medicine Institute, Cleveland, OH 44195, United States

Fahed Darmoch, Beth Israel Deaconess Medical center/Harvard Medical School, Boston, MA 02215, United States

Abdulghani Moussa Pacha, University Hospital of Mainz, Mainz 55122, Germany

M Chadi Alraies, Wayne State University, Detroit Medical Center, Detroit Heart Hospital, Detroit, MI 48201, United States

Corresponding author: M Chadi Alraies, MD, Wayne State University, Detroit Medical Center, Detroit Heart Hospital, 311 Mack Ave, Detroit, MI 48201, United States. makraies@dmc.org
Telephone: +1-216-2550008
Fax: +1-313-7453500

Abstract

Patient with atrial fibrillation (AF) are at risk of developing stroke with the left atrial appendage (LAA) being the most common site for thrombus formation. If left untreated, AF is associated with 4 to 5 folds increase in the risk of ischemic stroke in all age groups. About 5% to 15% of AF patients have atrial thrombi on transesophageal echocardiography, and 91% of those thrombi are located in the LAA in patient with nonrheumatic AF. Although oral anticoagulants are the gold-standard treatment for stroke prevention in patients with non-valvular AF, some patients are at high risk of bleeding and deemed not candidates for anticoagulation. Therefore, LAA occlusion (LAAO) has emerged as alternative approach for stroke prevention in those patients. Surgical LAAO is associated with high rate of unsuccessful closure and recommended only in patients with AF and undergoing cardiac surgery. Percutaneous LAAO uses transvenous access with trans-septal puncture and was first tested using the PLAATO device. Watchman is the most common and only Food and Drug Administration (FDA) approved device for LAAO. LAAO using Watchman device is non-inferior to warfarin therapy in preventing ischemic stroke/systemic thromboembolism. However, it is associated with lower rates of hemorrhagic stroke, bleeding and death. Amplatzer is another successful LAAO device that has CE mark and is waiting for FDA approval. Optimal antithrombotic therapy post LAAO is still under debate and highly patient-specific. The aim of this paper is to systematically review the current literature to evaluate the efficacy and safety of

Peer-review started: October 16, 2018
First decision: October 26, 2018
Revised: December 12, 2018
Accepted: December 17, 2018
Article in press: December 17, 2018
Published online: February 26, 2019

different LAAO devices.

Key words: Left atrial appendage; Atrial fibrillation; Anticoagulation; Stroke; Mortality

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Left atrial appendage occlusion (LAAO) is a reasonable alternative approach that is used in patients with atrial fibrillation who are not candidates for anticoagulation. A number of key trials have shown that Watchman device is non-inferior to warfarin therapy in preventing ischemic stroke/systemic thromboembolism. However, it is associated with lower rates of hemorrhagic stroke, bleeding and death. Multiple retrospective and prospective studies of Amplatzer device (ACP and Amulet) reported high success rates in device implantation and stroke prevention. Our objective is to consolidate the current literature to better delineate the safety, efficacy and indication of LAAO for stroke prevention.

Citation: Moussa Pacha H, Al-khadra Y, Soud M, Darmoch F, Moussa Pacha A, Alraies MC. Percutaneous devices for left atrial appendage occlusion: A contemporary review. *World J Cardiol* 2019; 11(2): 57-70
URL: https://www.wjgnet.com/1949-8462/full/v11/i2/57.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i2.57

INTRODUCTION

Atrial fibrillation (AF) affects 2.7 to 6.1 million in the United States and 33.5 million worldwide[1-3]. The projected prevalence of AF in the United States is expected to be 12.1 million by 2030[4]. AF-associated stroke is the most feared complication and the leading cause of disability in the United States[5]. If left untreated, AF is associated with 4 to 5 folds increase in the risk of ischemic stroke in all age groups[5,6]. Furthermore, AF is associated with increased risk of extracranial thromboembolic events to the aorta; and renal, mesenteric, and peripheral arteries[7]. The proportion of strokes attributed solely to AF increases with age and may reach up to 23.5%[6,8]. Oral anticoagulants (OACs) remain to be the gold standard treatment for stroke prevention, and their role in preventing AF-related strokes is well established[9,10]. Yet, OACs are contraindicated in a subset of patients who are at high risk of bleeding. As a result, left atrial appendage occlusion (LAAO) has emerged as an alternative approach in this group. In the current article, we present the most updated studies describing safety, efficacy and outcome of different LAAO devices.

LITERATURE SEARCH

A systematic literature search was conducted using PubMed, EMBASE, and Cochrane Library to identify relevant articles from 1990 to 2018. The following search terms were used: "atrial fibrillation", "stroke", "left atrial appendage", "occlusion" or "closure", and "percutaneous" or "surgical." A total of 78 studies were included for review. Of the included studies on LAAO, 3 studies contained surgical LAAO, two contained Atriclip device, two contained Tiger Paw system, 6 contained Lariat device, 4 contained PLAATO device, 19 contained Watchman device, and 12 contained Amplatzer (ACP/Amulet) device.

LEFT ATRIAL APPENDAGE AND THROMBUS FORMATION

Left atrial appendage (LAA) is trabeculated long tubular structure that has narrow junction with the venous component of left atrium. it varies greatly in sizes and shapes and has bent or spiral axis in 70% of patients[11]. Anatomically, LAA is best divided into the ostium, neck, and lobar region[12]. In patients with chronic AF, remodeling of LAA leads to dilation, stretching and reduction in pectinate muscle volume[13].

Approximately, 5% to 15% of AF patients have atrial thrombi on Transesophageal

echocardiography (TEE)[14-17], and 91% of those thrombi are located in LAA in patients with nonrheumatic AF[18]. The reason for LAA predilection for thrombus formation in AF is still not well known. One theory suggests that the extent of LAA filling and emptying is influenced more by changes in the left ventricular (which is impaired in AF) than LAA function[19]. Ventricular filling creates intracavitary suction effect which influences the emptying and filling of left atrium and LAA.

IMAGING ASSESSMENT OF LAA

Accurate assessment of anatomic LAA characteristics is crucial prior to LAAO due to substantial variations in LAA anatomy that impact device selection and efficacy. TEE is the most widely used imaging tool for periprocedural LAA assessment. It is used for the detection of thrombi in the LA and LAA as well other cardiac masses and thrombi prior to LAAO[12,20]. Features on TEE associated with increased risk of thrombus formation include: reduced LAA flow velocity, spontaneous left atrial contrast, and aortic atheroma[16]. TEE is very important imaging to support fluoroscopy during device implantation. 3D TEE has shown to be more accurate than 2D TEE in LAA assessment and thrombi detection[21,22]; and therefore, it is recommended for the guidance of LAAO[23]. It is used to guide trans-septal puncture, verify catheter and sheath position in the LAA, aid device delivery and positioning, confirm adequate LAA sealing, and detect complications[12]. Follow-up TEE is also recommended after LAAO to reassess the implanted device, confirm complete LAA closure, and rule out complications. Intracardiac echocardiography (ICE) is comparable imaging to TEE for guiding LAAO and performing the tasks typically provided by TEE during implantation. In one study LAA measurements by ICE during LAAO were significantly correlated to angiography and TEE (Pearson correlation coefficient r = 0.94, $P < 0.0001$ for both)[24].

Multidetector computed tomography is another imaging modality that is used for the assessment of thrombus formation, LAA anatomy and function, device assessment and detection of complications post procedure[12]. It provides 3D images of the heart by using numerous planes at different points in time during the cardiac cycle and has 100% sensitivity for excluding LAA thrombus[25]. However, its use is limited due to ionizing radiation, lower temporal resolution than TEE and inability to perform during device deployment. angiography has been used for in LAA thrombi detection[26]. However, it is expensive and invasive procedure, and rarely used nowadays due to presence of TEE and other less invasive imaging modalities.

GUIDELINE THERAPY FOR STROKE PREVENTION

The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for management of AF recommends the use of anticoagulation for prevention of thromboembolism when CHA_2DS_2-VAS_C score is ≥ 2 [class I (A)][16]. The 2016 European Society of Cardiology (ESC) guidelines differentiate between males and females regarding anticoagulation recommendations[27]. While anticoagulation is class I (A) indication for males with a score ≥ 2 and females with a score ≥ 3, it's considered class IIa (B) indication for males with a score of 1 and females with a score of 2. Both American and European guidelines recommend considering surgical excision of LAA in patients who have AF and undergoing cardiac surgery [class IIb (level of evidence is "C" in AHA/ACC and "B" in the ESC guidelines)][16,27]. While AHA/ACC guidelines have no recommendations for LAAO, the ESC guidelines have class IIb (B) recommendation for LAAO in patients with AF and contra-indications for long-term anticoagulation[27]. Similarly, National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand state that LAAO may be considered for stroke prevention in patients with non-valvular AF at moderate to high risk of stroke and with contraindications to OAC (GRADE quality of evidence: Low; GRADE strength of recommendation: Strong)[28].

LAA SURGICAL CLOSURES/EXCISION

Surgical exclusion of LAA is recommended for patients with AF and undergoing concomitant cardiac surgeries. Different surgical methods to isolate LAA include: suture ligation, excision and suture closure, and stapling exclusion with or without excision[29,30]. Surgical isolation of LAA is associated with high rate of unsuccessful closure. For instance, a previous study reported only 40% (55 out of 137) complete

LAA closure noted on TEE following surgical closure[30]. Despite that, Friedman *et al*[31] reported a lower risk of readmission for thromboembolism (4.2% *vs* 6.2%, HR = 0.67; 95%CI: 0.56-0.81) and all-cause mortality (17.3% *vs* 23.9%, HR = 0.88; 95%CI: 0.79-0.97) among Medicare patients (age > 65) with AF undergoing concomitant cardiac surgery and surgical LAAO, compared with no surgical LAAO. This the largest study to date supporting the role of surgical LAAO during cardiac surgery as a mean of preventing thromboembolism in patients over the age of 65 with AF.

The Atriclip Device System (Atricure, Inc., West Chester, OH, United States) is a surgical LAA exclusion device composed of self-closing, sterile, implantable clip with a reusable deployment tool (Figure 1). It is applied epicardially by either an open surgical or a minimally-invasive technique and placed at the base of the appendage. The clip is made of 2 parallel rigid titanium tubes with elastic nitinol springs covered with a knit-braided polyester sheath (Table 1)[32,33]. The EXCLUDE study (Exclusion of LAA with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery) is a nonrandomized multicenter trial that included 70 patients to evaluate the efficacy of Atriclip device[33]. They enrolled adult patients undergoing elective primary cardiac operations via median sternotomy (coronary artery bypass grafting, valve re- pair or replacement, surgical Maze procedures, or atrial septal defect repair) and have $CHADS_2$ > 2. 67 out of 70 patients (95.7%) had successful intraoperative LAA exclusion, and 60 out of 61 patients (98.4%) had successful LAA exclusion seen on computed tomography angiography or TEE imaging after 3 mo[33]. Tiger Paw System (Terumo Cardiovascular Systems, Ann Arbor, MI, United States) is another LAA exclusion device that is used as a concomitant procedure during open cardiac surgical procedures (Figure 1). The device contains implantable fastener of titanium connectors that staples the LAA tissue and is embedded in two rims of silicone that adapts to the LAA morphology and seals the puncture sites (Table 1)[34]. Despite its efficacy in achieving complete LAA closure on prior study[34], a class 1 recall from the market by FDA was made in 2015 due to device malfunction[35].

LARIATE DEVICE CLOSURE SYSTEM

Lariat device (SentreHEART, Inc., Redwood City, California) is LAA closure system that is approved by the United States Food and Drug Administration (FDA) for soft tissue closure, but not LAAO (Figure 1). It is composed of 15-mm compliant occlusion balloon catheter (EndoCATH), 0.025-inch and 0.035-inch magnet-tipped guidewires (FindrWIRZ), and a 12-F suture delivery device (LARIAT) (Table 1). During the procedure, magnet-tipped guidewires are advanced through epicardial and transvenous accesses and connected in the LAA. Then, a suture fashioned as a Lariate or lasso is advanced over the epicardial access guidewire and tightened to occlude LAA base[29,36]. The largest prospective study of Lariate device included patients who: were ≥ 18-year-old; had nonvalvular AF; had CHADS2 ≥ 1; were poor candidate for or failed warfarin therapy; and had a life expectancy of at least 1 year[36]. They reported 95% (81 of 85 patients) complete LAA closure documented on TEE one month after the procedure. 98% of those who underwent TEE (n = 65) had complete LAA closure after 1 year, including cases of incomplete closure at earlier time. Complications in the same study were limited to only two cases of severe pericarditis, two cases of strokes, and one case with pericardial effusion[36]. Another study demonstrated similar efficacy of the Lariate device for stroke prevention[37]. Dar *et al*[38] demonstrated that LAAO using Lariate device might improve the mechanical function of the left atrium (LA) and reverse LA remodeling based on 2-dimensional speckle tracking echocardiography (a novel method for functional assessment of the LA). However, due to steep learning curve for device deployment (especially epicardial access), LAA leak and lack of direct efficacy comparison with oral anticoagulation, the device was not widely used in the United States[39-42].

PERCUTANEOUS LAA CLOSURE

The most commonly used percutaneous LAAO devices are shown in figure 1 and described in Table 1. Percutaneous LAAO uses transvenous access with trans-septal puncture and was first tested using the Percutaneous LAA Transcatheter Occlusion (PLAATO) device (Appriva Medical Inc., Sunnyvale, CA) in 2001.

PLAATO device

This device consists of self-expanding nitinol cage that is covered with polymeric membrane in order to close off blood flow into the LAA (Table 1)[43,44]. It was first

Table 1 Comparison of left atrial appendage occlusion devices

Device	Study	Year of Introduction	Description	Approach	Approval
Atriclip Device System (Atricure)	EXCLUDE study[33]	2008	Self-closing, sterile, implantable clip, with a reusable deployment tool applied pericardially.	Epicardial	CE Mark
Tiger Paw System (Terumo Cardiovascular Systems)	Slater *et al*[34]	Introduced in 2009 and recalled in 2015	Implantable fastener of titanium connectors that staples the LAA tissue plus rims of silicone that seal the puncture sites.	Epicardial	Recalled
Lariat device (SentreHEART)	Bartus *et al*[36]; Massumi *et al*[37]; Dar *et al*[38]	2009	Multicomponent system including: transvenous and epicardial balloon catheters, magnet tipped guidewires, and suture delivery system	Epicardial and transvenous	FDA approval for soft tissue closure not LAAO CE mark
PLAATO (Appriva Medical)	Sievert *et al*[43]; Ostermaye *et al*[44]; Bayard *et al*[45]; Park *et al*[46]	Introduced in 2001and discontinued in 2007	Self-expanding nitinol cage covered with polymeric membrane (ePTFE) designed to be placed in the orifice of the LAA	Transvenous, trans-septal	Discontinued
Watchman (Boston Scientific)	Pilot study[47]; PROTECT AF study[48-50]; PREVAIL study[51,52]; CAP 1 registry[53]; CAP 2 registry[54]; EWOLUTION registry[55-57]; RELEXAO Registry[72]; ASAP study[58]; ASAP TOO study[59]	2005	Self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial facing surface of the device	Transvenous, trans-septal	FDA approved and CE Mark
ACP (St. Jude Medical)	Urena *et al*[67]; Gloekler *et al*[60]; Abualsaud *et al*[61]; Korsholm *et al*[64]; Berti *et al*[65]; RELEXAO; Registry[72]	2008	Self-expanding distal lobe (6.5mm in length) and proximal disc (4-6mm larger than distal lobe) nitinol mesh with articulating waist	Transvenous, trans-septal	CE Mark
Amplatzer Amulet (St. Jude Medical)	Gloekler *et al*[60]; Abualsaud *et al*[61]; Landmesser *et al*[62]; Tzikas *et al*[63]; Korsholm *et al*[64]; Berti *et al*[65]; Kleinecke *et al*[66]; RELEXAO; Registry[72];	2013	Self-expanding distal lobe and proximal disc nitinol mesh with articulating waist, and more anchors	Transvenous, trans-septal	CE Mark

LAAO: Left atrial appendage occlusion; FDA: Food and drug administration; ACP: Amplatzer cardiac plug.

tested on 15 patients with non-valvular AF and contraindication to warfarin therapy and are at high risk of thromboembolism based on $CHADS_2$ score[43]. Successful occlusion of LAA was observed in all cases and no device related complications were reported. A larger prospective study enrolled patients using similar inclusion criteria to undergo LAAO using PLAATO device[44]. Similarly, they reported high successful device Implantation in 108 out of 111 patients (97.3%) with only 2 patients developed stroke on follow up (2.2% annual risk of stroke). Subsequently, the European PLAATO2 trial reported successful LAAO in 90% (126 out of 140) of patients with reduction of stroke rate from 6.6% (based on $CHADS_2$ score) to 2.3% per year[45]. Besides, a single center prospective study on 73 cases who had PLAATO device reported death due to device embolization in one patient and implant instability requiring open heart surgery in another one[46]. Interestingly, there was no incidence of stroke for 24 mo of follow-up in the same study. Despite this success, the device was discontinued for unspecified reasons and replaced by Watchman device.

Watchman device

The Watchman device (Boston Scientific, Marlborough, MA), is the only FDA-approved percutaneous device for LAAO. The device is composed of self-expanding

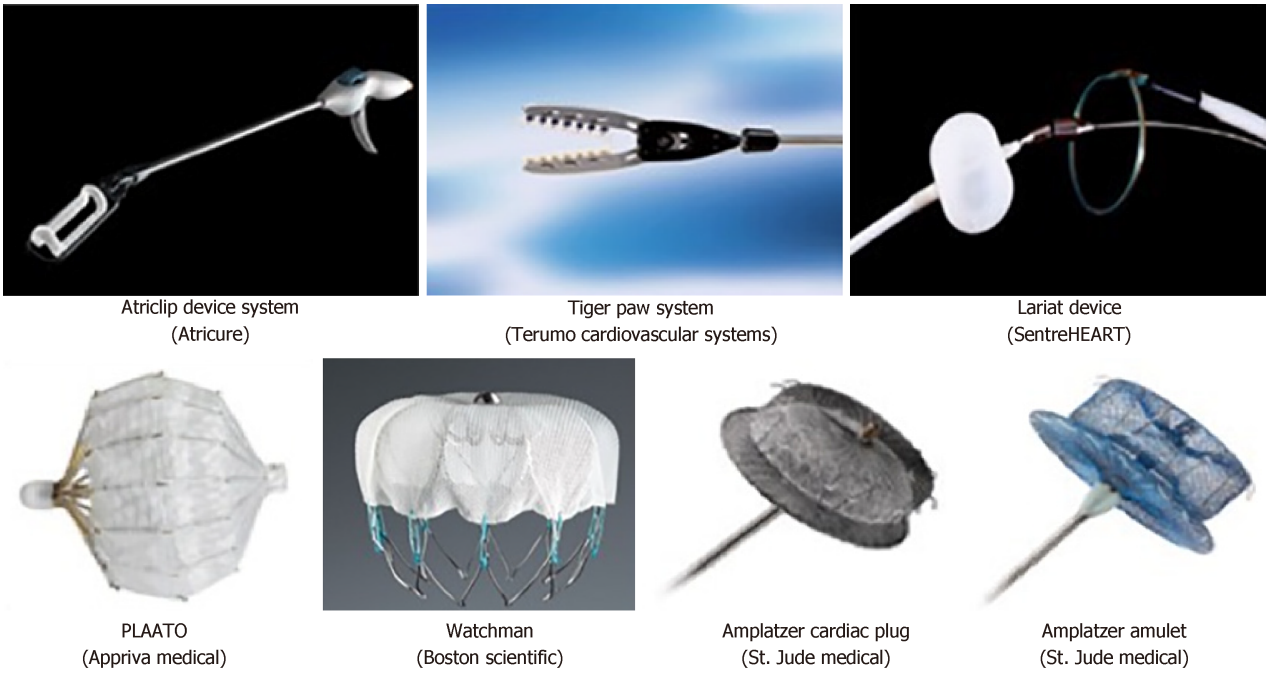


Figure 1 Surgical and percutaneous devices that are used for left atrial appendage occlusion.

nitinol frame structure with fixation barbs and a permeable polyester fabric that covers the atrial facing surface of the device (Table 1)[47]. Multiple trials were done to evaluate the safety, efficacy and outcomes of watchmen device.

Pilot study was a non-randomized trial that included 75 patients and was done to assess the feasibility and safety of watchman device[47]. They enrolled adult patients who: had non-valvular AF for 2 years, were eligible for warfarin therapy, and had $CHADS_2$ of at least 1. Although this was the first human trial to evaluate the efficacy and safety of Watchman device, the success rate of LAAO was very high and complications were relatively low. 88% of patients had successful device implantation and 93% of them had complete LAAO. Reported complications included; device embolization in 2 patients, device-related thrombus formation in 4 patients, and transient ischemic attack in 2 patients. There was no reported major strokes or procedure-related mortality.

PROTECT AF study (WATCHMAN LAA System for Embolic Protection in Patients with Atrial Fibrillation) was the first randomized trial to compare the efficacy and safety of LAAO using Watchman device with chronic warfarin therapy in patients with non-valvular AF and had $CHADS_2$ of 1 or more[48]. Exclusion criteria included contraindications to warfarin, chronic warfarin use, LAA thrombus, a patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease. This trial enrolled 707 patients from 59 centers worldwide and assigned them randomly to LAAO with Watchman device (n = 463) or warfarin therapy (n = 244) with INR goal of 2 to 3. Watchman group was treated with warfarin for 45 d after device deployment to allow proper endothelialization. Warfarin was discontinued if TEE showed complete closure or significantly decreased flow around the device. Afterward, patients were given aspirin and clopidogrel for 6 mo followed by lifelong aspirin. At 1065 patient-years (PY) of follow-up (mean follow up 18 mo), Watchman device was non-inferior to warfarin for primary efficacy endpoint of stroke (either ischemic or hemorrhagic), cardiovascular death, or systemic thromboembolism. The Event rates of primary efficacy endpoint were 3% and 4.9% for Watchman and warfarin groups, respectively. Since then, two studies were published with two different follow up period[49,50]. At 2.3 ± 1.1 years (2621 PY), Watchman device continued to be non-inferior to warfarin therapy with 3% and 4.3% event rates of primary efficacy endpoint for Watchman and warfarin groups, respectively[49]. The second trial with 3.8 ± 1.7 years of follow up (2621 PY) showed event rate of 2.3% in the watchman group and 3.8% in the warfarin group (P = 0.0348), leading to 40% risk reduction in primary efficacy endpoint with Watchman device[50].

PREVAIL study (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation *vs* Long Term Warfarin Therapy) was another randomized trial that assessed the safety and efficacy of Watchman device in patients non-valvular AF[51]. Investigators included a higher risk patients than PROTECT AF (CHADS2 score

of 1 plus any of the following higher-risk characteristics: female age ≥ 75 years, baseline ejection fraction ≥ 30% but < 35%, age 65 to 74 years and either diabetes or coronary disease, and age ≥ 65 years with congestive heart failure). Patients were assigned randomly to receive LAAO using Watchman (n = 269) or warfarin therapy (n = 138) in 2:l ratio. Warfarin and antiplatelet therapy post device implantion was in a similar fashion to PROTECT AF trial. Although non-inferiority criteria was not achieved for overall efficacy endpoint (stroke, systemic embolization or cardiovascualr death), the rate of second efficacy endpoint (stroke or systemic embolization) was 2.5% in the Watchman group and 2% in the warfarin group at 18 mo follow-up, achieving criteria for non-inferiority. Compared to PROTECT AF study, procedural success increased from 90.9% to 95.1% (P = 0.04), while all 7-d procedure-related complications (composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications) decreased from 8.7% to 4.2% in PREVAIL (P = 0.004).

PROTECT AF and PREVAIL results were pooled for patient level meta-analysis and with combined follow-up of 5 years (4343 PY)[52]. The primary efficacy endpoint (stroke, systemic embolization or cardiovascualr death) was similar between LAAO and warfarin groups (2.8 *vs* 3.4 events/100 PY; P = 0.27). In subgroup analysis of the same meta-analysis, the rate of all stroke or systemic embolism was similar between both groups (1.7 *vs* 1.8 events/100 PY; P = 0.87). However, there was statistically significant decrease in the rates of hemorrhagic stroke (0.17% *vs* 0.87%, P = 0.002), disabling / fatal stroke (0.37% *vs* 0.94%, P = 0.027), cardiovascular/unexplained death (1.3% *vs* 2.2%, P = 0.027), all-cause death (3.6% *vs* 4.9%, P = 0.035), and post-procedure bleeding (1.7% *vs* 3.6%, P = 0.0003) in LAAO arm when compared with warfarin arm. This meta-analysis underscores the mortality reduction and stroke prevention, patrticularly hemorrhagic stroke, associated with LAAO using Wathcman device.

Continued Access to PROTECT AF (CAP)[53] and Continued Access to PREVAIL (CAP2)[54] Registries were designed to treat patients with similar baseline characteristics and according to same protocols after PROTECT AF and PREVAIL trials enrollment had been completed. Procedural performance and associated medications were identical in each registry. However, registries did not mandate 1-year neurological assessment. A Meta-analysis of 2406 patients from the PROTECT AF and PREVAIL trials and their respective registries (CAP and CAP2) with 5,931 PY of follow-up (mean of 2.69 years) reported: similar rate of all-cause stroke between both arms (1.75 *vs* 1.87 events/100 PY, P = 0.94): higher rate of ischemic stroke in Watchman group (1.6 *vs* 0.9 events/100 PY, P = 0.05); and lower rates of hemorrhagic stroke, cardiovascular death (1.1 *vs* 2.3 events/100 PY, P = 0.006), and non-procedural bleeding (6.0% *vs* 11.3%, P = 0.02) in Watchman group[54]. Although the rate of all-cause stroke was similar between both arms, the reduction in hemorrhagic stroke with Watchman device was balanced by a relative increase in ischemic stroke rates. This may relate to possible technical failures of the device: failure to completely obliterate LAA flow, anatomical remodeling of the LAA ostium over time resulting in more leaks, or the development of thrombus on the device[54]. Compared with the pooled results of PROTECT AF and PREVAIL trials mentioned above, the difference in ischemic stroke rate was not observed between LAAO and warfarin groups at longer and combined follow-up of 5 years[52].

EWOLUTION study (Registry on Watchman Outcomes in Real-Life Utilization) is a multicenter, prospective, non-randomized cohort that aimed to collect peri-procedural and long-term outcome data for patients implanted with Watchman device for LAAO[55]. This world-wide registry enrolled 1025 patients at 47 centers from the United States, Europe, Middle east and Russia who are more than 18-year-old and require LAAO based on ESC guidelines[55-57]. The device was successfully implanted in 98.5% and complete LAAO was achieved in 99.3% noted on TEE[56,57]. the rates of procedure-related serious adverse events (defined as; perforation, tamponade, embolism, neurological events, thrombosis, and bleeding) were 2.8% at 7 d and 3.6% at 30 d with bleeding being the most common adverse event[57]. This is lower than the 7-d procedure-related serious adverse events observed in PROTECT AF (8.7%) and PREVAIL (4.2%) trials. At 1 year follow up; mortality was 9.8%, device-related thrombus was seen in 3.7% of patients, and 1.1% of patients suffered from ischemic stroke, leading to 84% risk reduction of stroke. There was no hemorrhagic stroke observed during follow-up[56].

The ASAP study (ASA Plavix Feasibility Study with Watchman LAA Closure Technology Trial to assess) was a European multicenter, prospective, non-randomized study of Watchman device in patients with non-valvular AF who had $CHADS_2$ score ≥1 and were not eligible for OACs[58]. After the device implantation, participants were given thienopyridine antiplatelet agent (clopidogrel or ticlopidine) for 6 mo and aspirin indefinitely. Out of 150 patients, 142 (94.7%) had successful implantation and 13 (8.7%) developed device-related adverse event. During mean follow up of 14.4 ±

8.6 mo, 4 patients developed stokes (2.3% per year) and 3 of them were ischemic (1.7% per year). There was 77% risk reduction in stroke compared to expected stroke risk based on $CHADS_2$ score (7.3% per year). Till this moment, there is no published randomized data on the safety and efficacy of LAAO in patients with contraindications to anticoagulation. The ASAP TOO study (The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation) is ongoing multi-center prospective randomized trial plan is to enroll up to 888 patients with non-valvular AF who are not candidate for OAC and have CHA_2DS_2-$VAS_C \geq 2$[59]. The study will randomize patients to Watchman *vs* control. Control patients will be prescribed single antiplatelet therapy, or no therapy based on physician discretion.

Amplatzer cardiac plug and amulet

Amplatzer cardiac plug (ACP) (AGA, St. Jude Medical, Minneapolis, MN, United States) is another LAAO device that consists of a lobe and disc made of nitinol mesh and polyester patch, connected by central waist. Amulet® is a second-generation device of the Amplatzer with several incremental design improvements. It is larger in size and has higher number of stabilizing wires, which allows successful closure of more LAA anatomies (Table 1). Comparative studies have shown similar results with ACP and Amulet AMPLATZER devices in terms of safety, implantation success and appropriate LAAO[60,61]. Multiple retrospective and prospective studies for ACP and Amulet reported successful device implantation in 95% to 100% patients, with major periprocedural adverse events (death, stroke/TIA, device embolization, MI /perforation/tamponade/effusion, and major bleeding) ranging from 3.2% to 8%[62-67]. An FDA approval trial is currently ongoing, with the aim of collecting randomized controlled data from the Amulet and Watchman devices from 1,600 patients worldwide. PRAGUE 17 is another ongoing prospective, multicenter, randomized trial That plan to enroll 396 patients with non-valvular AF and assign them to LAAO using Amulet or Watchman *vs* non-vitamin K oral anticoagulants (NOACs). The aim at 24 mo of follow-up is to determine whether LAAO is non-inferior to NOACs in terms of primary efficacy endpoint and peri-procedural complications[68].

COMPARISON OF MULTIPLE LAA OCCLUSION DEVICES

A meta-analysis on 2779 patients who had percutaneous LAAO with multiple devices [PLAATO (18%), Watchman (57%), and ACP (24%)] showed successful implantation in in 2611 patients (94%). The adjusted pooled incidence of stroke was 1.2 per 100 PY (95%CI: 0.9-1.6/100) and the combined efficacy outcome (stroke, systemic embolism, or cardiovascular death) rate was 2.7 per 100 PY (95%CI: 1.9-3.4/100). For combined adverse events, the random effect pooled rate was 6.5% (95%CI: 4.9%-8.2%)[69]. One single-center retrospective study in Italy compared the use ACP *vs* Watchman in 156 patients (ACP in 99 and watchman in 66 patients) and demonstrated procedural success in 99.4%. During follow-up, only 1 patient suffered from transient ischemic attack and 2 from cardiac death. Furthermore, the data showed excellent safety and efficacy with similar clinical outcomes in both devices[70]. Another multicenter retrospective registry for LAAO using various devices showed an overall success of 92.5%. The combined adverse event rate was 3.5%, leading to annual relative risk reduction for ischemic stroke, thromboembolic events, and major bleeding of 90.1%, 87.2%, and 92.9%, respectively[71]. RELEXAO (Registry on Real-Life Experience With LAA Occlusion) registry is a French retrospective cohort of patients with AF who were treated with LAAO[72]. In the study cohort from RELEXAO, Fauchier *et al*[72] reported no differences in death, ischemic stroke, major bleeding, or device related thrombus between Watchman and Amplatzer devices. Those studies underscore the high success rate in placing various LAAO devices, and their safety and efficacy in preventing strokes and adverse events.

ANTITHROMBOTIC THERAPY AFTER DEVICE IMPLANTATION

Optimal anticoagulation/antiplatelet protocol post LAAO is highly patient-specific and recommended for a limited period post LAAO to prevent device associated thrombus[72]. Different anticoagulation strategies have been described in multiple studies including: warfarin, NOACs, DAPT, single antiplatelet (SAPT), or no therapy at all (Table 2). The anticoagulation protocol described In PROTECT AF and PREVAIL trials consists of warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely[48-51]. In EWOLUTION registry for example, anticoagulation

regimens post LAAO were variable and included: warfarin in 16%, NOAC in 11%, DAPT in 60%, single antiplatelet (SAPT) in 7%, and no therapy in 6%[56]. A study on post LAAO anticoagulation in patients from EWOLUTION registry demonstrated that NOAC and DAPT were similar to warfarin in terms of device thrombus, stroke or bleeding risks[73]. Compared with EWOLUTION registry, antithrombotic regimen post LAAO In RELEXAO registry was different and included: OACs 28.8%, SAPT in 36.2%, DAPT in 23.2%, OACs plus DAPT in 4.3%, and no therapy in 7.5%. In ASAP study, patients were given DAPT for 6 mo followed by aspirin indefinitely as they were ineligible for OACs[58]. A Questionnaire sent by European Heart Rhythm Association Electrophysiology to the participating centers to assess the indications and anticoagulation regimen post LAAO, showed that DAPT for 6 wk to 6 mo followed by aspirin monotherapy as the most common regimen[74]. Interestingly, 41% of centers would prescribe no therapy and less than 10% followed PROTECT AF and PREVAIL protocol. The European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions (EHRA/EAPCI) expert consensus statement recommends treatment with DAPT for 1 to 6 mo followed by aspirin indefinitely in patients with high bleeding risk[75].

COMPLICATIONS

Complications related to LAAO are either acute or delayed and most of them can be detect by peri-procedural imaging. Table 3 summarizes LAAO related complications, their incidence and treatment options.

CONCLUSION

LAAO is a reasonable alternative approach that is used for preventing embolic events in patients with AF who are deemed not eligible for anticoagulation. While AHA/ACC guidelines have no recommendations for LAAO, the ESC guidelines have class IIb (B) recommendation for LAAO in patients with AF and contra-indications for long-term anticoagulation. Similarly, Australian guidelines recommend considering LAAO in patients with non-valvular AF at moderate to high risk of stroke and with contraindications to OAC. Watchman is the only FDA approved device for LAAO and indicated to reduce the risk of thromboembolism from the LAA in patients with non-valvular AF who: are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores; are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin. Amplatzer is another successful LAAO device that has CE mark and is waiting for FDA approval. Optimal antithrombotic regimen post LAAO is highly patient-specific and recommended to prevent device associated thrombus. Due to wide variety of shapes, sizes, indications, and implantation techniques in different LAAO devices, there is a need for further research to identify the best type of LAAO device that suites each patient profile. We believe that the development of established clinical guidelines and expert consensus supporting the use of LAAO in the foreseeable future will ultimately improve patient outcomes.

Table 2 Antithrombotic therapy regimens following left atrial appendage occlusion

Study/reference	Regimen
PROTECT AF trial[48-50]	Warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely
PREVAIL trial[51]	Warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely
EWOLUTION registry[56]	warfarin in 16%, NOAC in 11%, DAPT in 60%, SAPT in 7%, and no therapy in 6%
RELEXAO registry[72]	OACs in 28.8%, SAPT in 36.2%, DAPT in 23.2%, OACs plus DAPT in 4.3%, and no therapy in 7.5%.
ASAP trial[58]	DAPT for 6 mo followed by aspirin indefinitely
EHRA/EAPCI expert consensus[75]	DAPT for 1 to 6 mo followed by aspirin indefinitely

OAC: Oral anticoagulant; NOAC: Non-vitamin K oral anticoagulant; SAPT: Single antiplatelet; DAPT: Dual antiplatelet; EHRA/EAPCI: European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions.

Table 3 Complications related to left atrial appendage occlusion

Complication	Incidence	Treatment
Pericardial effusion/tamponade that require intervention[47,48,50,51,53,56-58,63,76]	1.2% to 5%	Pericardiocentesis
Device embolization[47,48,50,51,56-58,63,76]	0% to 3.7%	Transcatheter removal or surgery
Device related thrombus[47,56-58,63]	Up to 14%	Anticoagulation
Persistent ASD[77]	11% at 6 mo and 7% at 12 mo	Usually small no need for treatment
Cardiac perforation[51]	0% to 0.4%	surgery
Procedure related stroke[47,48,51,53,56-58,76]	0% to 1.1%	Stroke management

ASD: Atrial septal defect.

REFERENCES

1 **Go AS**, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370-2375 [PMID: 11343485 DOI: 10.1001/jama.285.18.2370]

2 **Miyasaka Y**, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; **114**: 119-125 [PMID: 16818816 DOI: 10.1161/CIRCULATIONAHA.105.595140]

3 **Chugh SS**, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; **129**: 837-847 [PMID: 24345399 DOI: 10.1161/CIRCULATIONAHA.113.005119]

4 **Colilla S**, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013; **112**: 1142-1147 [PMID: 23831166 DOI: 10.1016/j.amjcard.2013.05.063]

5 **Benjamin EJ**, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**: e146-e603 [PMID: 28122885 DOI: 10.1161/CIR.0000000000000485]

6 **Wolf PA**, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983-988 [PMID: 1866765 DOI: 10.1161/01.STR.22.8.983]

7 **Frost L**, Engholm G, Johnsen S, Møller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Intern Med* 2001; **161**: 272-276 [PMID: 11176743 DOI: 10.1001/archinte.161.2.272]

8 **Wang TJ**, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003; **290**: 1049-1056 [PMID: 12941677 DOI: 10.1001/jama.290.8.1049]

9 **Hart RG**, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131**: 492-501 [PMID: 10507957 DOI: 10.7326/0003-4819-131-7-199910050-00003]

10 **Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation**. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449-1457 [PMID: 8018000 DOI: 10.1001/archinte.1994.00420130036007]

11 **Al-Saady NM**, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999; **82**: 547-554 [PMID: 10525506]
12 **Wunderlich NC**, Beigel R, Swaans MJ, Ho SY, Siegel RJ. Percutaneous interventions for left atrial appendage exclusion: options, assessment, and imaging using 2D and 3D echocardiography. *JACC Cardiovasc Imaging* 2015; **8**: 472-488 [PMID: 25882576 DOI: 10.1016/j.jcmg.2015.02.002]
13 **Shirani J**, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. *Cardiovasc Pathol* 2000; **9**: 95-101 [PMID: 10867359 DOI: 10.1016/S1054-8807(00)00030-2]
14 **Manning WJ**, Silverman DI, Keighley CS, Oettgen P, Douglas PS. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. *J Am Coll Cardiol* 1995; **25**: 1354-1361 [PMID: 7722133 DOI: 10.1016/0735-1097(94)00560-D]
15 **Leung DY**, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J Am Coll Cardiol* 1994; **24**: 755-762 [PMID: 8077549 DOI: 10.1016/0735-1097(94)90025-6]
16 **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64**: e1-76 [PMID: 24685669 DOI: 10.1016/j.jacc.2014.03.022]
17 **Klein AL**, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001; **344**: 1411-1420 [PMID: 11346805 DOI: 10.1056/NEJM200105103441901]
18 **Blackshear JL**, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; **61**: 755-759 [PMID: 8572814 DOI: 10.1016/0003-4975(95)00887-X]
19 **Predictors of thromboembolism in atrial fibrillation: II**. Echocardiographic features of patients at risk. The Stroke Prevention in Atrial Fibrillation Investigators. *Ann Intern Med* 1992; **116**: 6-12 [PMID: 1727097 DOI: 10.1016/0736-4679(92)90169-T]
20 **Manning WJ**, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, Johnson RG, Douglas PS. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995; **123**: 817-822 [PMID: 7486462 DOI: 10.7326/0003-4819-123-11-199512010-00001]
21 **Müller S**, Feuchtner G, Bonatti J, Müller L, Laufer G, Hiemetzberger R, Pachinger O, Barbieri V, Bartel T. Value of transesophageal 3D echocardiography as an adjunct to conventional 2D imaging in preoperative evaluation of cardiac masses. *Echocardiography* 2008; **25**: 624-631 [PMID: 18652008 DOI: 10.1111/j.1540-8175.2008.00664.x]
22 **Asch FM**, Bieganski SP, Panza JA, Weissman NJ. Real-time 3-dimensional echocardiography evaluation of intracardiac masses. *Echocardiography* 2006; **23**: 218-224 [PMID: 16524392 DOI: 10.1111/j.1540-8175.2006.00196.x]
23 **Perk G**, Lang RM, Garcia-Fernandez MA, Lodato J, Sugeng L, Lopez J, Knight BP, Messika-Zeitoun D, Shah S, Slater J, Brochet E, Varkey M, Hijazi Z, Marino N, Ruiz C, Kronzon I. Use of real time three-dimensional transesophageal echocardiography in intracardiac catheter based interventions. *J Am Soc Echocardiogr* 2009; **22**: 865-882 [PMID: 19647156 DOI: 10.1016/j.echo.2009.04.031]
24 **Berti S**, Paradossi U, Meucci F, Trianni G, Tzikas A, Rezzaghi M, Stolkova M, Palmieri C, Mori F, Santoro G. Periprocedural intracardiac echocardiography for left atrial appendage closure: a dual-center experience. *JACC Cardiovasc Interv* 2014; **7**: 1036-1044 [PMID: 25234677 DOI: 10.1016/j.jcin.2014.04.014]
25 **Martinez MW**, Kirsch J, Williamson EE, Syed IS, Feng D, Ommen S, Packer DL, Brady PA. Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing catheter ablation of atrial fibrillation. *JACC Cardiovasc Imaging* 2009; **2**: 69-76 [PMID: 19356536 DOI: 10.1016/j.jcmg.2008.09.011]
26 **Sakamoto I**, Hayashi K, Matsunaga N, Ogawa Y, Matsuoka Y, Okimoto T, Takagi M, Yano K, Toda G, Miyahara Y. Coronary angiographic finding of thrombus in the left atrial appendage. *Acta Radiol* 1996; **37**: 749-753 [PMID: 8915287 DOI: 10.1177/02841851960373P264]
27 **Kirchhof P**, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893-2962 [PMID: 27567408 DOI: 10.1093/eurheartj/ehw210]
28 **NHFA CSANZ Atrial Fibrillation Guideline Working Group**. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani H, Hendriks J, Hespe C, Hung J, Kalman JM, Sanders P, Worthington J, Yan TD, Zwar N. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. *Heart Lung Circ* 2018; **27**: 1209-1266 [PMID: 30077228 DOI: 10.1016/j.hlc.2018.06.1043]
29 **Holmes DR**, Lakkireddy DR, Whitlock RP, Waksman R, Mack MJ. Left atrial appendage occlusion: opportunities and challenges. *J Am Coll Cardiol* 2014; **63**: 291-298 [PMID: 24076495 DOI: 10.1016/j.jacc.2013.08.1631]
30 **Kanderian AS**, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol* 2008; **52**: 924-929 [PMID: 18772063 DOI: 10.1016/j.jacc.2008.03.067]
31 **Friedman DJ**, Piccini JP, Wang T, Zheng J, Malaisrie SC, Holmes DR, Suri RM, Mack MJ, Badhwar V, Jacobs JP, Gaca JG, Chow SC, Peterson ED, Brennan JM. Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery. *JAMA* 2018; **319**: 365-374 [PMID: 29362794 DOI: 10.1001/jama.2017.20125]
32 **Salzberg SP**, Plass A, Emmert MY, Desbiolles L, Alkadhi H, Grünenfelder J, Genoni M. Left atrial

appendage clip occlusion: early clinical results. *J Thorac Cardiovasc Surg* 2010; **139**: 1269-1274 [PMID: 19880144 DOI: 10.1016/j.jtcvs.2009.06.033]
33 **Ailawadi G**, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ, Salamon T, Mack MJ. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg* 2011; **142**: 1002-1009, 1009.e1 [PMID: 21906756 DOI: 10.1016/j.jtcvs.2011.07.052]
34 **Slater AD**, Tatooles AJ, Coffey A, Pappas PS, Bresticker M, Greason K, Slaughter MS. Prospective clinical study of a novel left atrial appendage occlusion device. *Ann Thorac Surg* 2012; **93**: 2035-8; discussion 2038-40 [PMID: 22632497 DOI: 10.1016/j.athoracsur.2011.12.077]
35 **Ventosa-Fernandez G**, Quintana E, Castellá M, Pereda D. Exclusion of the left atrial appendage with the TigerPaw II system: a word of caution. *Interact Cardiovasc Thorac Surg* 2015; **21**: 803-804 [PMID: 26395944 DOI: 10.1093/icvts/ivv256]
36 **Bartus K**, Han FT, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, Bartus S, Yakubov SJ, Lee RJ. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol* 2013; **62**: 108-118 [PMID: 23062528 DOI: 10.1016/j.jacc.2012.06.046]
37 **Massumi A**, Chelu MG, Nazeri A, May SA, Afshar-Kharaghan H, Saeed M, Razavi M, Rasekh A. Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *Am J Cardiol* 2013; **111**: 869-873 [PMID: 23312129 DOI: 10.1016/j.amjcard.2012.11.061]
38 **Dar T**, Afzal MR, Yarlagadda B, Kutty S, Shang Q, Gunda S, Samanta A, Thummaluru J, Arukala KS, Kanmanthareddy A, Reddy M, Atkins D, Bommana S, Dawn B, Lakkireddy D. Mechanical function of the left atrium is improved with epicardial ligation of the left atrial appendage: Insights from the LAFIT-LARIAT Registry. *Heart Rhythm* 2018; **15**: 955-959 [PMID: 29477973 DOI: 10.1016/j.hrthm.2018.02.022]
39 **Giedrimas E**, Lin AC, Knight BP. Left atrial thrombus after appendage closure using LARIAT. *Circ Arrhythm Electrophysiol* 2013; **6**: e52-e53 [PMID: 23962862 DOI: 10.1161/CIRCEP.113.000532]
40 **Briceno DF**, Fernando RR, Laing ST. Left atrial appendage thrombus post LARIAT closure device. *Heart Rhythm* 2014; **11**: 1600-1601 [PMID: 24184785 DOI: 10.1016/j.hrthm.2013.10.053]
41 **Truesdell AG**, Patel CP, Maini BS. Late-occurring left atrial appendage thrombus after ligation using LARIAT. *J Interv Card Electrophysiol* 2014; **41**: 101 [PMID: 24928486 DOI: 10.1007/s10840-014-9916-9]
42 **Pillai AM**, Kanmanthareddy A, Earnest M, Reddy M, Ferrell R, Nath J, Pillarisetti J, Vallakati A, Lakkireddy D. Initial experience with post Lariat left atrial appendage leak closure with Amplatzer septal occluder device and repeat Lariat application. *Heart Rhythm* 2014; **11**: 1877-1883 [PMID: 24993460 DOI: 10.1016/j.hrthm.2014.06.035]
43 **Sievert H**, Lesh MD, Trepels T, Omran H, Bartorelli A, Della Bella P, Nakai T, Reisman M, DiMario C, Block P, Kramer P, Fleschenberg D, Krumsdorf U, Scherer D. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation* 2002; **105**: 1887-1889 [PMID: 11997272 DOI: 10.1161/01.CIR.0000015698.54752.6D]
44 **Ostermayer SH**, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, Omran H, Bartorelli AL, Della Bella P, Di Mario C, Pappone C, Casale PN, Moses JW, Poppas A, Williams DO, Meier B, Skanes A, Teirstein PS, Lesh MD, Nakai T, Bayard Y, Billinger K, Trepels T, Krumsdorf U, Sievert H. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol* 2005; **46**: 9-14 [PMID: 15992628 DOI: 10.1016/j.jacc.2005.03.042]
45 **Bayard YL**, Omran H, Neuzil P, Thuesen L, Pichler M, Rowland E, Ramondo A, Ruzyllo W, Budts W, Montalescot G, Brugada P, Serruys PW, Vahanian A, Piéchaud JF, Bartorelli A, Marco J, Probst P, Kuck KH, Ostermayer SH, Büscheck F, Fischer E, Leetz M, Sievert H. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. *EuroIntervention* 2010; **6**: 220-226 [PMID: 20562072]
46 **Park JW**, Leithäuser B, Gerk U, Vrsansky M, Jung F. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in atrial fibrillation: 2-year outcomes. *J Invasive Cardiol* 2009; **21**: 446-450 [PMID: 19726815]
47 **Sick PB**, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, Mishkel G, Almany S, Holmes DR. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007; **49**: 1490-1495 [PMID: 17397680 DOI: 10.1016/j.jacc.2007.02.035]
48 **Holmes DR**, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374**: 534-542 [PMID: 19683639 DOI: 10.1016/S0140-6736(09)61343-X]
49 **Reddy VY**, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D; PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013; **127**: 720-729 [PMID: 23325525 DOI: 10.1161/CIRCULATIONAHA.112.114389]
50 **Reddy VY**, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B, Kar S, Swarup V, Gordon N, Holmes D; PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014; **312**: 1988-1998 [PMID: 25399274 DOI: 10.1001/jama.2014.15192]
51 **Holmes DR**, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014; **64**: 1-12 [PMID: 24998121 DOI: 10.1016/j.jacc.2014.04.029]
52 **Reddy VY**, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR; PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol* 2017; **70**: 2964-2975 [PMID: 29103847 DOI: 10.1016/j.jacc.2017.10.021]
53 **Reddy VY**, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure:

results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011; **123**: 417-424 [PMID: 21242484 DOI: 10.1161/CIRCULATIONAHA.110.976449]

54 **Holmes DR**, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. *J Am Coll Cardiol* 2015; **65**: 2614-2623 [PMID: 26088300 DOI: 10.1016/j.jacc.2015.04.025]

55 **Boersma LV**, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Stein KM, Bergmann MW. EWOLUTION: Design of a registry to evaluate real-world clinical outcomes in patients with AF and high stroke risk-treated with the WATCHMAN left atrial appendage closure technology. *Catheter Cardiovasc Interv* 2016; **88**: 460-465 [PMID: 26719158 DOI: 10.1002/ccd.26358]

56 **Boersma LV**, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Foley D, Sievert H, Mazzone P, De Potter T, Vireca E, Stein K, Bergmann MW; EWOLUTION Investigators. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017; **14**: 1302-1308 [PMID: 28577840 DOI: 10.1016/j.hrthm.2017.05.038]

57 **Boersma LV**, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW; EWOLUTION investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016; **37**: 2465-2474 [PMID: 26822918 DOI: 10.1093/eurheartj/ehv730]

58 **Reddy VY**, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013; **61**: 2551-2556 [PMID: 23583249 DOI: 10.1016/j.jacc.2013.03.035]

59 **Holmes DR**, Reddy VY, Buchbinder M, Stein K, Elletson M, Bergmann MW, Schmidt B, Saw J. The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial. *Am Heart J* 2017; **189**: 68-74 [PMID: 28625383 DOI: 10.1016/j.ahj.2017.03.007]

60 **Gloekler S**, Shakir S, Doblies J, Khattab AA, Praz F, Guerios Ê, Koermendy D, Stortecky S, Pilgrim T, Buellesfeld L, Wenaweser P, Windecker S, Moschovitis A, Landmesser U, Nietlispach F, Meier B. Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation. *Clin Res Cardiol* 2015; **104**: 656-665 [PMID: 25736061 DOI: 10.1007/s00392-015-0828-1]

61 **Abualsaud A**, Freixa X, Tzikas A, Chan J, Garceau P, Basmadjian A, Ibrahim R. Side-by-Side Comparison of LAA Occlusion Performance With the Amplatzer Cardiac Plug and Amplatzer Amulet. *J Invasive Cardiol* 2016; **28**: 34-38 [PMID: 26716593]

62 **Landmesser U**, Schmidt B, Nielsen-Kudsk JE, Lam SCC, Park JW, Tarantini G, Cruz-Gonzalez I, Geist V, Della Bella P, Colombo A, Zeus T, Omran H, Piorkowski C, Lund J, Tondo C, Hildick-Smith D. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention* 2017; **13**: 867-876 [PMID: 28649053 DOI: 10.4244/EIJ-D-17-00493]

63 **Tzikas A**, Gafoor S, Meerkin D, Freixa X, Cruz-Gonzalez I, Lewalter T, Saw J, Berti S, Nielsen-Kudsk JE, Ibrahim R, Lakkireddy D, Paul V, Arzamendi D, Nietlispach F, Worthley SG, Hildick-Smith D, Thambo JB, Tondo C, Aminian A, Kalarus Z, Schmidt B, Sondergaard L, Kefer J, Meier B, Park JW, Sievert H, Omran H. Left atrial appendage occlusion with the AMPLATZER Amulet device: an expert consensus step-by-step approach. *EuroIntervention* 2016; **11**: 1512-1521 [PMID: 27107315 DOI: 10.4244/EIJV11I13A292]

64 **Korsholm K**, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *EuroIntervention* 2017; **12**: 2075-2082 [PMID: 27973336 DOI: 10.4244/EIJ-D-16-00726]

65 **Berti S**, Pastormerlo LE, Rezzaghi M, Trianni G, Paradossi U, Cerone E, Ravani M, De Caterina AR, Rizza A, Palmieri C. Left atrial appendage occlusion in high-risk patients with non-valvular atrial fibrillation. *Heart* 2016; **102**: 1969-1973 [PMID: 27492943 DOI: 10.1136/heartjnl-2015-309150]

66 **Kleinecke C**, Park JW, Gödde M, Zintl K, Schnupp S, Brachmann J. Twelve-month follow-up of left atrial appendage occlusion with Amplatzer Amulet. *Cardiol J* 2017; **24**: 131-138 [PMID: 28198520 DOI: 10.5603/CJ.a2017.0017]

67 **Urena M**, Rodés-Cabau J, Freixa X, Saw J, Webb JG, Freeman M, Horlick E, Osten M, Chan A, Marquis JF, Champagne J, Ibrahim R. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *J Am Coll Cardiol* 2013; **62**: 96-102 [PMID: 23665098 DOI: 10.1016/j.jacc.2013.02.089]

68 **Osmancik P**, Tousek P, Herman D, Neuzil P, Hala P, Stasek J, Haman L, Kala P, Poloczek M, Branny M, Chovancik J, Cervinka P, Holy J, Vancura V, Rokyta R, Taborsky M, Kovarnik T, Zemanek D, Peichl P, Haskova S, Jarkovsky J, Widimsky P; PRAGUE-17 Investigators. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). *Am Heart J* 2017; **183**: 108-114 [PMID: 27979034 DOI: 10.1016/j.ahj.2016.10.003]

69 **Xu H**, Xie X, Wang B, Ma S, Wang F. Efficacy and Safety of Percutaneous Left Atrial Appendage Occlusion for Stroke Prevention in Nonvalvular Atrial Fibrillation: A Meta-analysis of Contemporary Studies. *Heart Lung Circ* 2016; **25**: 1107-1117 [PMID: 27199213 DOI: 10.1016/j.hlc.2016.03.016]

70 **Figini F**, Mazzone P, Regazzoli D, Porata G, Ruparelia N, Giannini F, Stella S, Ancona F, Agricola E, Sora N, Marzi A, Aurelio A, Trevisi N, Della Bella P, Colombo A, Montorfano M. Left atrial appendage closure: A single center experience and comparison of two contemporary devices. *Catheter Cardiovasc Interv* 2017; **89**: 763-772 [PMID: 27567013 DOI: 10.1002/ccd.26678]

71 **Betts TR**, Leo M, Panikker S, Kanagaratnam P, Koa-Wing M, Davies DW, Hildick-Smith D, Wynne DG, Ormerod O, Segal OR, Chow AW, Todd D, Cabrera Gomez S, Kirkwood GJ, Fox D, Pepper C, Foran J, Wong T. Percutaneous left atrial appendage occlusion using different technologies in the United Kingdom: A multicenter registry. *Catheter Cardiovasc Interv* 2017; **89**: 484-492 [PMID: 27651124 DOI: 10.1002/ccd.26782]

72 **Fauchier L**, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S, Fatemi M, Franceschi F, Guedeney P,

Jacon P, Paziaud O, Venier S, Deharo JC, Gras D, Klug D, Mansourati J, Montalescot G, Piot O, Defaye P. Device-Related Thrombosis After Percutaneous Left Atrial Appendage Occlusion for Atrial Fibrillation. *J Am Coll Cardiol* 2018; **71**: 1528-1536 [PMID: 29622159 DOI: 10.1016/j.jacc.2018.01.076]

73 **Bergmann MW**, Betts TR, Sievert H, Schmidt B, Pokushalov E, Kische S, Schmitz T, Meincke F, Stein KM, Boersma LVA, Ince H. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention* 2017; **13**: 877-884 [PMID: 28606886 DOI: 10.4244/EIJ-D-17-00042]

74 **Tilz RR**, Potpara T, Chen J, Dobreanu D, Larsen TB, Haugaa KH, Dagres N. Left atrial appendage occluder implantation in Europe: indications and anticoagulation post-implantation. Results of the European Heart Rhythm Association Survey. *Europace* 2017; **19**: 1737-1742 [PMID: 29016910 DOI: 10.1093/europace/eux254]

75 **Meier B**, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *EuroIntervention* 2015; **10**: 1109-1125 [PMID: 25169595]

76 **Reddy VY**, Gibson DN, Kar S, O'Neill W, Doshi SK, Horton RP, Buchbinder M, Gordon NT, Holmes DR. Post-Approval U.S. Experience With Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol* 2017; **69**: 253-261 [PMID: 27816552 DOI: 10.1016/j.jacc.2016.10.010]

77 **Singh SM**, Douglas PS, Reddy VY. The incidence and long-term clinical outcome of iatrogenic atrial septal defects secondary to transseptal catheterization with a 12F transseptal sheath. *Circ Arrhythm Electrophysiol* 2011; **4**: 166-171 [PMID: 21248245 DOI: 10.1161/CIRCEP.110.959015]

P- Reviewer: Barik R, Dai X, Kharlamov AN, Korosoglou G, Ueda H
S- Editor: Ma YJ **L- Editor:** A **E- Editor:** Wu YXJ

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 February 26; 11(2): 71-83

DOI: 10.4330/wjc.v11.i2.71

ISSN 1949-8462 (online)

MINIREVIEWS

Heart valve disease in elderly

Carlo Rostagno

ORCID number: Carlo Rostagno (0000-0002-7764-8919).

Author contributions: Rostagno C solely contributed to this paper.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: December 18, 2018
Peer-review started: December 20, 2018
First decision: December 30, 2018
Revised: January 13, 2019
Accepted: January 26, 2019
Article in press: January 26, 2019
Published online: February 26, 2019

Carlo Rostagno, Department of Internal Medicine, University of Florence, Florence 50134, Italy

Corresponding author: Carlo Rostagno, MD, PhD, Associate Professor, Department of Internal Medicine, University of Florence, Viale Morgagni 85, Firenze 50134, Italy.
carlo.rostagno@unifi.it
Telephone: +39-55-7948063
Fax: +39-55-7947587

Abstract

The incidence of heart valve disease increases significantly with age. Degenerative abnormalities associated with severe aortic stenosis and mitral and tricuspid regurgitation are found in not less than 10% of the population aged ≥ 75 years. Surgical treatment has been considered for years to be the treatment of choice. However, it was not uncommonly associated with high perioperative morbidity and mortality due to frequent comorbidities and overall frailty conditions of these patients. Conventional risk scores such as Society of Thoracic Surgeons and European System for Cardiac Operative Risk Evaluation may underestimate the risk of surgery in elderly patients, leading to inappropriate surgical indication. On the other hand, at least 30% of patients with severe conditions are left untreated due to prohibitive surgical risk. Interventional procedures, which are in continuous development, may be actually considered for high risk patients and, as recent results suggest, also for intermediate risk patients.

Key words: Valve diseases; Elderly; Surgery; Interventional cardiology

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Severe heart valve diseases are not uncommon in the elderly and often treatment may be challenging due to high risks related both to relevant comorbidities and the frailty condition of elderly patients. Although surgery is still the first choice for most conditions, interventional strategies are emerging as a valid alternative both in high and intermediate risk patients. Careful evaluation is needed for each individual patient in order to establish a more appropriate strategy considering that the impact on the quality of life may be more relevant in this population than the effects on survival, which is already limited by decreased life expectancy related to ageing.

Citation: Rostagno C. Heart valve disease in elderly. *World J Cardiol* 2019; 11(2): 71-83
URL: https://www.wjgnet.com/1949-8462/full/v11/i2/71.htm

DOI: https://dx.doi.org/10.4330/wjc.v11.i2.71

INTRODUCTION

Progressive ageing of a population is associated with an increased prevalence of chronic degenerative diseases. Among these, heart valve abnormalities represent an important public-health problem leading to high morbidity and mortality. The Euro Heart Survey on valve heart disease (VHD) published in 2003 included 5001 adults from 25 countries suffering from moderate to severe heart valve disease[1]. Native VHD was found in about 4000 patients. The remaining had had previous valve surgery. Degenerative process was the main cause of aortic involvement and mitral regurgitation (MR). Mitral stenosis (MS) was mainly due to rheumatic disease. Incidence of valvular disease increased with age. Incidence of VHD was 6% for both mitral and aortic disease in patients aged ≥ 75 years, while in younger patients (aged < 64 years), the incidence was less than 1%. Importantly, according to the Survey, more than 30% of subjects with severe, symptomatic, single VHD, usually elderly with relevant comorbidities, did not undergo surgery.

More recently, Nkomo *et al*[2] reported the results of echocardiographic examinations in 11911 randomly selected adults who had been prospectively assessed in three large population-based epidemiological studies[3-5]. Moreover, included in the study were 16501 adults who were assessed in community by clinically indicated echocardiography. In the first group, 615 patients (5.1%) had moderate or severe valve disease. There were no gender related differences. Prevalence of valve disease increased significantly with age from 0.7% in the group comprised of 18-year-olds to 44-year-olds to 13.3% in the group of those 75 years and older (P < 0.0001). A significant increase of VHD was reported for each increment of 10 years of ageing. This was particularly evident for aortic stenosis (AS) (hazard ratio (HR) = 2.51; 95% confidence interval (CI): 2.02 to 3.12; P < 0.0001). MR was the most frequent VHD in elderly patients (9.3%) followed by AS (2.8%), aortic regurgitation (AR) (2.0%), and finally MS (0.2%).

In the community group, valve disease was diagnosed in 1505 patients. Prevalence of valve diseases increased considerably with age also in this group (0.3% in 18-44 years old, 11.7% in those aged ≥ 75 years). There was a trend that showed a lower rate of diagnosis in women than in men. Both in in the population and in the community study, valve disease was associated with an increased mortality risk ratio (RR) (1.36, 95%CI: 1.15–1.62; P = 0.0005 and respectively 1.75, 95%CI: 1.61–1.90; P < 0.0001). Incidence of heart valve disease in 500 consecutive patients aged > 8 years referred to our Center for hip fracture is reported in Figure 1.

Due to increased life expectancy in the elderly population, AS prevalence is expected to increase further. according to recent projections from The OxVALVE population cohort study in the United Kingdom, the number of elderly people with moderate or severe valvular heart disease will more than double by 2056[6].

A retrospective study from Scotland showed that among all patients hospitalized from 1 January 1997 to 31 December 2005, a final diagnosis of non-congenital aortic valve disease was made in a total of 19733 adults[7]. Discharge diagnosis was AS in 13220 (67.0%) and AR in 2807 (14.2%). Mixed aortic valve disease, or unspecified aortic valve disease, occurred respectively in 699 (3.5%) and 3007 (15.2%). Elderly patients, aged 80 and older, accounted for most of the patients included in the study. More than half had died by 31 December 2006. The risk of death (and heart failure) was 20% higher in AS in comparison to aortic insufficiency or mixed aortic valve disease. Only 19.4% of patients included in the study had aortic valve replacement during follow-up, three out four for AS. Age, female gender, and co-morbidity influenced replacement rate.

Despite the relevance of VHD as a cause of heart failure and death, the first European Heart Valve Disease survey demonstrated that the awareness and knowledge of heart valve disease in the general population was alarmingly low, and only 3.8% really knew what AS was[8]. Two years later, the second European Heart Valve Disease survey showed a mild improvement in general knowledge of heart valve disease in comparison to 2015. Despite this finding, the correct understanding of AS decreased significantly (2015: 7.2% *vs* 2017: 3.8%; P < 0.001)[9].

Treatment of VHD in the elderly requires careful evaluation since other than the effects on survival, already limited by decreased life expectancy related to ageing, the impact on the quality of life should be considered a relevant aspect. In elderly people, clinical outcome after surgical treatment is significantly influenced by concomitant

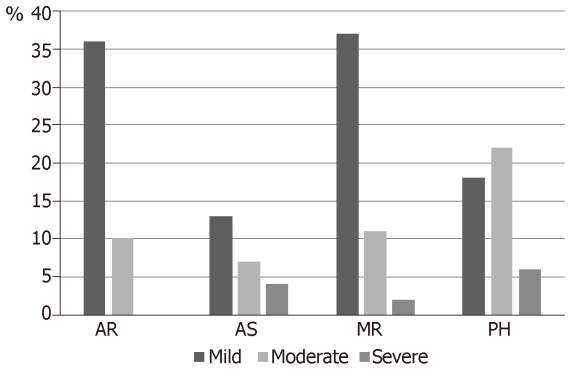


Figure 1 Incidence of valve heart disease in 500 consecutive patients aged > 80 years referred for hip fracture.

severe comorbidities [diabetes mellitus, chronic kidney disease, cerebrovascular disease, and atrial fibrillation (AF), *etc*] that may impair postoperative recovery, leading to worse outcomes[10]. A multidisciplinary approach involving cardiologists, interventional cardiologists, surgeons, anesthesiologists, and geriatricians may improve the decisional process.

AORTIC VALVE

AS

Epidemiology and pathophysiology: In the elderly, degenerative AS is one of the most common types of valvular heart disease. The prevalence of AS has been reported to be between 12% and 26% depending on the diagnostic criteria employed[1,11]. In the study by Lindroos *et al*[12], critical AS was defined as a valve area < 0.8 cm^2 or velocity ratio of < 0.35. In the 75- to 86-year-old group, the reported prevalence of disease was 2.9% (95%CI: 1.4% to 5.1%). Overall, 40% of patients with severe AS were considered to be at high surgical risk. It must be emphasized that although AS is clearly associated with adverse outcomes, even aortic sclerosis can create an increased risk of cardiovascular morbidity and mortality mainly by its being a significant risk factor for progression to AS. Degenerative calcific disease accounts for most cases of severe AS; however, a large study reported that 22% percent of octogenarians presenting for surgery for isolated AS had bicuspid valve disease[13-15].

Calcific aortic valve disease evolves over the years at a different rate in every subject. The development and progression of AS is at least in part related to active processes that have pathophysiological mechanisms in common with atherosclerotic disease[14]. First, several studies suggested that calcific degenerative AS and atherosclerosis have common risk factors such as age, smoking, hypertension, hypercholesterolemia, diabetes mellitus, and metabolic syndrome[15-18]. Since valve leaflets may have anatomic heterogeneity, different shear stresses may lead to endothelial dysfunction at the ventricular surface of the valve. Second, the loss of endothelial integrity allows lipid accumulation and cellular migration (inflammatory cells, macrophages, and T cells) in the subendothelial matrix[19] with neurohormonal activation[20]. Plaque-like subendothelial deposits may lead to downward displacement and fragmentation of the subjacent elastic lamina. The osteoblast-like activity of interstitial cells may be responsible for valvular calcification over time with a decrease in leaflet mobility[21].

AR

Epidemiology and pathophysiology: Isolated AR is significantly less common than pure AS. Degenerative and bicuspid aortic valve disease shows a different degree of both regurgitation and left ventricular obstruction; however, stenosis is usually pre-eminent. More frequently, AR is a consequence of aortic dilation and the deformation of the annulus valve. Overall prevalence of significant native AR has been reported in between 2.0% and 2.5% of patients 70 years to 83 years of age, without gender differences[22,23] although smaller studies reported a higher incidence of up to 13%. Age, aortic valve fibrocalcification, and female sex were considered independent factors related to AR, while several studies failed to find a relationship with arterial hypertension[24].

Treatment of aortic valve diseases: Surgical aortic valve replacement (SAVR) has been, for a long time, the treatment of choice for severe aortic valve disease. Improved survival and quality of life have been clearly demonstrated even in elderly patients[25-27]. Nevertheless, a non-negligible number of elderly patients are considered at very high or prohibitive risk for conventional surgical procedures, and about 30% of symptomatic subjects will never undergo surgery[1].

Non-surgical options, in particular transcatheter aortic valve replacement (TAVR), have developed as a suitable alternative to SAVR. In humans, the first transcatheter aortic stent valve was implanted in 2002, using femoral vein access and a transeptal approach[28]. In 2005, technical developments allowed for changing the approach to the transfemoral artery[29]. Transapical TAVR (TA-TAVR) has been proposed in patients with unsuitable vascular access. Several studies compared safety and efficacy between the transfemoral TAVR (TF-TAVR) and TA-TAVR. The transfemoral approach, whenever feasible, should be considered the preferable access route[30].

Initially, the indication for TAVR was limited to severely symptomatic AS with high surgical risk according to validated risk scores [Society of Thoracic Surgeons (STS) or European System for Cardiac Operative Risk Evaluation (EuroSCORE)]. At present, indications for percutaneous treatment may be extended to intermediate risk subjects. Nevertheless the use of STS-risk score (or EuroSCORE) may be misleading in very old people (aged > 80 years) since a high risk of perioperative complications may exist due to overall age and frailty *per se*[31-33]. Frailty, limited functional capacity according to Barthel scale, inadequate nutrition, and the need for non-cardiac surgery (most frequently oncologic or orthopedic surgery) are good indicators for TAVR, which allows a faster recovery and improved quality of life.

The randomized PARTNER 1B study first showed a decrease in death from any cause and death from cardiovascular causes in patients who underwent TAVR *vs* a conservative treatment[34]. The PARTNER 1A trial randomized 699 high-risk patients with severe AS to TAVR (using transfemoral or the transapical approach) or SAVR[35]. Death from any cause at 1 year was similar in the two groups, while major vascular complications (11.0% *vs* 3.2%, $P < 0.001$) and stroke (8.3% *vs* 4.3%, $P < 0.05$) were more frequent in TAVR than in SAVR. At 2 years follow-up, TAVR was associated with an increased late mortality mainly related to mechanical complications of the valve such as paravalvular leak. With first generation devices, residual AR due to para-valvular leaks was found postoperatively in about 20% of patients. Minimally invasive aortic valve replacement was proposed to manage carefully selected patients with the aim of decreasing permanent pacemaker implantation and other vascular complications that would be critical to changing patient prognosis.

In the study by Hirji *et al*[36], 1028 octogenarians underwent isolated aortic valve replacement between 2002 and 2015. Three hundred and six were treated by TAVR and 722 by SAVR (344 conventional and 378 minimally invasive valve replacement). Median follow-up was 35 mo. TAVR patients were relatively older (86.2 years *vs* 84.2 years) and in more cases had several co-morbidities. Operative mortality and mid-term survival were similar for TAVR (regardless of approach), SAVR, and minimally invasive aortic valve replacement after adjustment for confounding factors. The median in-hospital length of stay was statistically higher for the SAVR group ($P < 0.05$). Independent predictors of mortality were age, class III/IV New York Heart Association (NYHA), preoperative creatinine, severe chronic lung disease, and prior cardiac surgery (all $P < 0.05$). The authors concluded that treatment decisions should be addressed by a multi-disciplinary heart team, taking into account patient comorbidities, frailty, and quality of life.

Recently were reported the results of the FRench Aortic National CoreValve and Edwards (FRANCE-2) registry. In the study were included 2254 patients > 80 years of age who underwent TAVR. Thirty-day and 1-year mortality were not significantly different among patients aged 80 to 84 years, 85 to 89 years, and finally > 90 years (10.3% *vs* 9.5% *vs* 11.2%; $P = 0.53$ and respectively 19.8% *vs* 26.1% *vs* 27.7%; $P = 0.16$)[37].

A recent study compared carefully selected patients > 90 years old, without many comorbidities, *vs* younger patients who underwent TAVR. Major complications were similar, and all-cause mortality at 30 days and 1 year was not statistically different (2.9% and 12.5% in patients aged ≥ 90 *vs* 2.8% and 12.3% in patients aged < 90, respectively)[38].

The effects of TAVR were evaluated more recently in low-intermediate risk populations. An Italian observational, multicenter, "real-world" study included 1300 patients in a propensity-matched population. The authors did not find significant differences in mortality or major adverse cardiac and cardiovascular events between SAVR and TAVR[39].

In the PARTNER 2A randomized trial, TAVR was compared with SAVR in 2032 intermediate-risk patients. The primary endpoints were all-cause mortality or disabling stroke at 2 years. The authors did not find differences between groups.

Although major vascular complications and paravalvular regurgitation were more frequent in TAVR, surgical replacement was associated with higher rates of acute kidney injury, severe bleeding, and new-onset AF[40].

The multicenter Surgical Replacement and Transcatheter Aortic Valve Implantation trial was a randomized, clinical trial that included 1746 patients at intermediate surgical risk, of whom 1660 underwent TAVR or surgical operation[41]. The primary endpoint, a composite of death from any cause or disabling stroke at 24 mo, was 12.6% in TVAR and 14% in SAVR respectively. On the basis of these results, 2017 American Heart Association/America College of Cardiology gave a IIa indication for the TAVR procedure in intermediate surgical risk[42].

Data from studies of a low-risk group for surgery, showed that SAVR is still more advantageous than TAVR. Rosato *et al*[43] reported that survival at 3 years was 72.0% after TAVR and 83.4% after SAVR (P = 0.0015). Further studies with new generation valve prostheses are necessary before expanding indications of TAVR in lower-risk patients.

Effects of coronary artery disease: Coronary artery disease (CAD) is frequently associated with AS, in particular in elderly patients[44]. The coexistence of CAD leads to a worse prognosis for AS of comparable severity. Surgical treatment allows correction of valve disease and at the same time coronary revascularization. Data regarding elderly subjects are limited. Less is known about the effects of CAD in elderly patients undergoing TAVR.

To evaluate the effect of age on combined AVR and concomitant coronary artery bypass graft (CABG), 452 consecutive patients (mean age 64 years) were divided into three groups: Young (n = 114), middle-aged (n = 225), and elderly (n = 113). CAD was more extensive in the elderly group. Only 62.8% of elderly patients had complete myocardial revascularization in comparison to 94.1% and 76.2%, respectively, of the other two groups (P < 0.05). In-hospital mortality was 6.4% in the elderly in comparison to 2.0% and 5.3%, respectively in the other groups. Freedom from cardiac-related death at 12 mo and 60 mo was higher in young and middle-aged patients than in elderly patients[45].

How CAD impacts patient survival following TAVR has been investigated by a recent meta-analysis. Fifteen studies including 8013 patients were examined. The median age of patients was 81.3 years, 46.6% were men, and 3899 (48.7%) had CAD. All-cause mortality at 30 days post TAVR was not significantly different between patients with and without CAD. All-cause mortality however was significantly higher at 1 year in patients with CAD in comparison with patients without CAD (OR = 1.21; 95%CI: 1.07–1.36; P = 0.002). These results suggest the need to revisit the revascularization strategies for concomitant CAD in patients with TAVR[46].

AS and MR

In the elderly, AS is frequently associated with concomitant MR (22%-48%). In severe cases affecting both valves, surgical valve replacement has usually been considered the treatment of choice. Data regarding elderly subjects is limited. In the study by Yu *et al*[47], 43 high-risk patients with severe AS, aged 80 ± 6 years, underwent concomitant SAVR and mitral valve (MV) surgery. Nineteen (44%) had prior cardiac surgery, and 39 (91%) were in congestive heart failure. Five patients (11.6%) died during hospitalization or at 30 days. Mortality was 25% at 6 mo, 35% at 1 year, and 45% at 2 years. Patients often needed prolonged ventilation, and 10% developed new renal failure requiring dialysis. When AS in patients at high or prohibitive surgical risk is treated by percutaneous TAVR, concomitant significant MR usually is not corrected[48,49]. Untreated MR is associated with a significant increase in mortality and morbidity[50].

The recent availability of percutaneous devices for treating MV disease may offer an alternative for the management of MR after TAVR[51]. Few limited case series reported a procedural success (decrease of degree of MR < 2+) comprised between 92% and 100% for edge to edge MV repair with MitraClip™ (Abbott Vascular, Menlo Park, CA, United States)[52]. Recurrent 3+ MR at 1 year however occurred in 21.4%. One year survival rate was 66.5%.

In conclusion, concomitant MV surgery in patients with MV disease undergoing aortic valve replacement did not give better results on long term survival than TAVR without correction of MV regurgitation. Therefore, individual assessment should guide procedural strategy in treating MR associated with severe AS.

MV

Epidemiology and pathophysiology

Several conditions may damage the MV in older patients, such as degeneration of valve leaflets, calcification of the mitral annulus commonly involving the posterior leaflet, ischemia, and rheumatic heart disease.

Anatomo-functional abnormalities of the MV apparatus may result in valve stenosis or, more frequently, regurgitation. The most common etiology of MS is rheumatic heart disease; however, it is not common that the disease remains undiagnosed up until an advanced age[53]. Degenerative MV annulus calcification is more frequent in the elderly, but it is unclear how frequent a significant hemodynamic impact might be. Functional MS related to massive annular calcification and reduced leaflet excursion has been reported in 2.5% to 18.0% of elderly patients[54]. Degenerative MS accounted for 12.5% of MS cases according to data of the Euro Heart Survey[1]. The severity of calcification has significant implications for surgery. Debridement of the posterior annulus may be challenging, and residual calcium may not allow adequate suturing of the MV prosthesis with the risk of post-operative paravalvular regurgitation due to suture dehiscence. Moreover, there is the non-negligible risk of extensive damage and posterior disruption of the left ventricle and that of death.

In industrialized countries, MR is the most frequent valvular heart disease in patients over the age of 65 years[1,2]. Elderly patients account for about 40% of all patients with MR and 4.5% are over 80 years of age. Heart failure, arrhythmia, and death may occur in patients with severe disease. Prevalence of moderate MR in the Framingham study was 11.1% in men 70 years to 83 years of age[23]. In the study, no information was reported regarding valve morphology. Secondary MR has been reported in about 25% of patients after myocardial infarction and in more than 50% in heart failure with depressed ejection fraction.

Treatment

Etiology of MV regurgitation plays a relevant role in the decision-making process, particularly in elderly patients. MV surgery is indicated only if the balance between expected clinical improvement exceeds increased operative risk related to ageing and comorbidities. Surgical treatment is clearly suggested by American guidelines for patients with primary valve disease, while no indications are provided by ESC guidelines[42,55]. A high operative mortality (15%) was reported by a recent meta-analysis including 5572 octogenarian patients[56]. Therefore, a careful multidimensional preoperative evaluation is needed for risk stratification since STS and EuroSCORE may effectively underestimate effective surgery related risks in elderly, frail patients. Left ventricular dysfunction is more frequent with concomitant CAD. Surgical revascularization increases the risk of both early and late mortality after surgery.

Secondary MR in those aged > 75 years is likely to be more frequent than primary valve disease. In this case, no clear indication for surgery exists as the clinical benefit is uncertain. When concomitant coronary artery bypass grafting is not planned, surgical intervention may be recommended only in patients with refractory symptoms after optimization of medical therapy and eventual cardiac resynchronization therapy[57,58].

MV-repair at present is the generally accepted "gold standard" treatment for degenerative MV disease. Several studies demonstrated the superiority of repair over MV replacement (MVR)[59,60]. Patients with extensive bi-leaflet or anterior leaflet prolapse and myxomatous degeneration without extensive calcification are considered good candidates for MV repair. Nevertheless, in elderly patients MV-repair as suggested by administrative American databases was performed in less than 50%. Advanced age was as an independent predictor of valve replacement[61].

The lower technical complexity of valve replacement with shorter cardio pulmonary bypass times and decreased risk of failure with need of reintervention may explain the lower rate of MV repair than expected in elderly patients. These aspects are particularly relevant due the limited life expectancy of aged patients. Nevertheless, MVR has a high short-term mortality of 25% to 30%, frequently due to congestive heart failure possibly related to alteration of the left ventricular dimensions and geometry.

Differences in long-term clinical outcomes between surgery and conservative management were evaluated by Kang *et al*[62] in 157 patients with severe MR aged ≥ 70 years. Median follow-up was 5.4 years. Surgery was associated with a lower mortality (HR 0.31; 95%CI: 0.13 to 0.73; $P = 0.007$) other than with a decrease in overall cardiac event (HR 0.26; 95%CI: 0.13 to 0.53; $P < 0.001$).

In a single center retrospective study in 2015, consecutive patients with moderate to severe MR were divided into two groups[63]. Patients aged > 60 years (mean age 66.98 ± 5.94 years) were considered as the elderly group ($n = 680$) and compared to patients < 60 years (control group, $n = 1061$). In total, 308/680 elderly MR were denied

surgery, which was much higher than the rate of denial observed in the control group (45.29% *vs* 36.10%, $P < 0.001$). The factors associated with decreased probability of undergoing surgery were increased age, diabetes, and high risk stratification according to EuroSCORE-II. Of the 275 elderly patients with severe MR included in this study, 75 (27.27%) did not undergo surgery.

A database from the University Centre of Liepzig, Germany was examined and assessed to identify all patients aged > 70 years who underwent MV surgical procedures between 1999 and 2009. In 97% of the 2503 patients, MR was the primary indication for operation[64]. MV repair was performed in 64%. Mortality rate at 30 days was 3.1%, and survival at 5 years was 55.2%. Coronary revascularization was associated with an early and long-term poorer outcome. Several factors, such as diabetes, chronic obstructive lung disease, left ventricular function < 30%, preoperative hemodialysis, presence of endocarditis, MVR, concomitant TV procedures, urgent or emergent procedures, aortic procedures, aortic valve replacement, and CABG, were independently related younger late death[64].

A recent retrospective study by Silashi *et al*[65] reviewed the results after MV surgery in elderly patients treated over the past 20 years. Excluded from the study were patients with repeat cardiac surgery, endocarditis, and concomitant aortic valve replacement. Of 1776 patients with MV disease, 341 were aged ≥ 75 years. Two hundred and twenty-one underwent MV-repair and 120 MVR. One hundred thirty-five patients had concomitant coronary artery bypass grafting (39.6%). Fifty had tricuspid valve (TV) surgery (14.7%). Thirty-day mortality associated with MV repair was 5.4% *vs* 9.2% for MVR ($P = 0.26$). Concomitant CABG was more frequently performed in patients undergoing MV-repair (43.9% *vs* 31.7%, $P = 0.03$). In 27 patients, planned MV-repair was converted to MVR, mainly after invasive inspection of the MV. Moderate/severe MR was observed at follow-up in 15 cases after MV-repair (6.8%), of which four needed reintervention. After MVR, significant MR was observed in only 3 cases (2.5%). Overall 1- and 5-year survival was 90.7% and 74.2% *vs* 81.3% and 61.0%, respectively ($P < 0.01$).

In a propensity adjusted analysis of outcomes after MV surgery in patients aged > 80 years (mean age 83 years), overall operative mortality was 11% after MV-repair in comparison to 18.9% for MVR[66]. It must be underlined that this study also included patients with endocarditis (1.8% in MV-repair and 13.7% in MVR) and ischemic MV disease (32.2% in MV-repair).

Included in a meta-analysis by Shang *et al*[67] were seven observational clinical studies published after 2000 comparing MVP and MVR in the elderly (aged 70 years or older). Overall, 1809 patients were considered. Thirty-day mortality was significantly lower after MV repair (RR: 0.40, 95%CI: 0.25–0.64). Moreover, repair was associated with length of postoperative hospital stay and less postoperative complications in comparison to MVR. Finally long-term (1- and 5-year survival) were higher in MV-repair.

Patients at high-prohibitive risk for surgery may benefit, when technically feasible, by percutaneous interventional treatment. MitraClip™ therapy is at present the most widely used technique. The device allows for building a bridge between the anterior and posterior mitral leaflet thus mimicking the surgical technique of the Alfieri stitch. In patients treated for degenerative MR, despite good periprocedural results, the rate of recurrent severe MR after MitraClip™ therapy has been reported close to 55% at 12 mo[68]. The need for re-operations may exceed 20% at 4 years of follow-up[69].

Failure of MitraClip™ procedures may be related to the absence of concomitant annuloplasty. Failed MitraClip™ procedures may complicate eventual future MV-repair. In particular when treatment included more than one clip valves, which are often not repairable. Further techniques, such as transcatheter MV-in-ring implantation, may be considered in selected cases after failure on MV repair.

Surgery must be considered the initial "gold standard" treatment for elderly patients with degenerative MR and acceptable surgical risk should be considered. A multidisciplinary "Heart Team" should discuss the patient's condition and various treatment opportunities. New interventional treatment options may be considered for symptomatic high risk patients.

TV

Tricuspid regurgitation (TR) is the second most common VHD after MR with an incidence of 1.2% to 1.5% in the general population[1,2]. The prevalence increases with age and in particular in females. In the group of 70 to 83 year-olds, incidence is 5.6% in women as compared to 1.5% in men[23]. Severe TR is associated with higher 1-year mortality and poorer outcomes independent of age and other comorbid conditions[70].

Primary valve disease accounts for 25% of TR. This is more common in younger patients suffering from anatomic valve abnormalities (congenital, rheumatic, neoplastic, traumatic, infective endocarditis, and endomyocardial fibrosis). Other causes of TR are lead implantation for pacing or leaflet damage due to RV biopsy[71]. In elderly subjects, functional or secondary TR due to left heart disease, often MR or AS, is by far the more common etiology of TR[70]. TR secondary to left heart valve disease is often associated with poor prognosis and difficult therapeutic choices. Pulmonary hypertension, right ventricular infarction, chronic right ventricular pacing, and history of AF are other common causes of secondary TR. The term ''functional'' may be misleading for TV disease. As with the MV, annular dilatation of the tricuspid annulus and/or dislocation of papillary muscles plays just as important of a role in causing valve malfunction[72]. Annular dilatation occurs along the anterior and posterior TV leaflet implantation; therefore, the annulus becomes more circular and planar. Geometrical abnormalities may be different between secondary TR and the so-called "idiopathic TR," commonly attributed to ageing and AF[73,74]. In idiopathic TR, basal RV dilatation with relatively normal RV length and marked annular dilatation but with normal tenting height of leaflets is commonly observed. Where there is functional TR in patients with pulmonary hypertension, there is a spherical RV deformation, with less evident annular dilation but significantly greater tenting height. These morpho-functional differences have significant implications for treatment.

Treatment

A conservative (no touch) approach to TR was proposed in the 1960s. It was conceivable that the hemodynamic improvement related to the correction of the left-sided valve disease would result in a decrease of secondary TR. The experiences that followed, however, demonstrated that regression of TR is not the rule, and regurgitation may further increase in particular when the mitral and/or aortic valve diseases are not completely or adequately resolved during surgery. Moreover, it must be stressed that an isolated severe TR is now increasingly recognized even in patients with normal left heart valve function after either MV annuloplasty or replacement. The degree of right ventricular dysfunction indicated by annular dilatation may be related to impaired regression of further increased degree of valve regurgitation. Preoperative evaluation may give information whether TR will resolve after successful mitral surgery. Four hundred and thirteen patients with rheumatic heart disease, who did not have preoperative severe TR, underwent MVR without concomitant TV repair and were then followed for a median period of 13 years[75]. Forty-six patients (11.1%) had new severe TR. Independent predictors for new severe TR were preoperative moderate TR (HR 2.401; $P = 0.008$) and AF (HR 2.119; $P = 0.018$). Patients with new severe TR had larger right ventricles and higher pulmonary artery pressures on echocardiography.

Right ventricular failure is associated with a higher surgical mortality (from 5% to 11% and from 8% to 22% during follow-up)[76]. Preoperative right ventricular dysfunction and persisting TR are associated with a minor relief of symptoms and an impaired cardiac output response to exercise after correction of valve diseases.

Although it has been suggested that functional TR may be untreated in patients with a significant predictable decrease in the pulmonary resistance, at present we have no reliable methods to predict reversibility of the TR after correction of the left heart valve dysfunction. Moreover, methods of measuring and quantifying the degree of TR are still not reliable and repeatable. The clinical assessment may add information to echocardiography. Finally, there is no satisfactory method to assess true right ventricular function.

Often, in elderly patients with long standing disease, TR frequently poses a challenging treatment dilemma[77]. Severe TR may be tolerated for many years and sometimes managed conservatively until severe right heart failure and ascites develop. It is then often too late for correction since any therapy comes with extremely high risk, with unacceptable operative mortality. Moreover, the likelihood of functional recovery is poor. American College of Cardiology/American Heart Association guidelines do not give any Class I indications for isolated TV surgery[42]. Operative risk is high in these patients with a mortality rate of 7.9% at 30 days. Age is an independent predictor according to multivariable analysis. Reduction of right ventricle afterload after treatment of a left-sided valve lesion may lead to an improvement, even if often unpredictable, of severe TR. TV repair during left sided surgery does not appreciably increase the risks of surgery. TR repair is currently recommended in patients undergoing left-sided valve surgery. Effects of depressed right ventricular function on results of TV repair were examined by Subbotina *et al*[78]. Eighty-two out of 191 patients (43%) had decreased tricuspid annular plane systolic excursion (TAPSE) (13.3 ± 3.3 mm *vs* 20.2 ± 4.9 mm; $P<0.001$). In both groups, 91%

underwent ring annuloplasty. Patients with depressed right ventricular function had a higher incidence of low cardiac output syndrome after surgery (10% *vs* 27%, *P*= 0.005) and a higher early mortality. Functional improvement, expressed as change in NYHA class, was more evident in patients with preserved right ventricular function. Of 173 patients who underwent MV surgery and radiofrequency ablation of AF, only age and concomitant TV repair were independently associated with mortality according to multivariate analysis[79].

In the last years, numerous percutaneous transcatheter repair and replacement devices were developed to treat this large group of high surgical risk patients. To improve prognosis in severe TR, an earlier diagnosis and referral for treatment are essential, as are a better understanding of the different stages of disease and potential treatment options, proven safe and efficacious percutaneous options, and an evidence base for earlier surgical or percutaneous intervention of significant TR, irrespective of symptoms. The use of MitraClip™ in the tricuspid position is associated with unpredictable results. Date reported from a recent registry showed a > 50% reduction in effective regurgitant orifice area after treatment with MitraClip™. The procedure was associated with significant clinical improvement with decrease in the NYHA functional class and longer 6 minute walking distance[80]. Other transcatheter therapies are being tested in feasibility trials. Among these the Trialign system (Mitralign, Tewksbury, Massachusetts, United States) that mimics the surgical Kay annuloplasty *via* a pair of pledgeted sutures delivered percutaneously through the right internal jugular vein.

ACKNOWLEDGEMENTS

The author thanks Dr. Katharine Johnson for language editing

REFERENCES

1 **Iung B**, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003; **24**: 1231-1243 [PMID: 12831818 DOI: 10.1016/S0195-668X(03)00201-X]

2 **Nkomo VT**, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; **368**: 1005-1011 [PMID: 16980116 DOI: 10.1016/S0140-6736(06)69208-8]

3 **Hughes GH**, Cutter G, Donahue R, Friedman GD, Hulley S, Hunkeler E, Jacobs DR, Liu K, Orden S, Pirie P. Recruitment in the Coronary Artery Disease Risk Development in Young Adults (Cardia) Study. *Control Clin Trials* 1987; **8**: 68S-73S [PMID: 3440391 DOI: 10.1016/0197-2456(87)90008-0]

4 **The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives**. The ARIC investigators. *Am J Epidemiol* 1989; **129**: 687-702 [PMID: 2646917 DOI: 10.1093/oxfordjournals.aje.a115184]

5 **Fried LP**, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991; **1**: 263-276 [PMID: 1669507 DOI: 10.1016/1047-2797(91)90005-W]

6 **Berry C**, Lloyd SM, Wang Y, Macdonald A, Ford I. The changing course of aortic valve disease in Scotland: temporal trends in hospitalizations and mortality and prognostic importance of aortic stenosis. *Eur Heart J* 2013; **34**: 1538-1547 [PMID: 23111418 DOI: 10.1093/eurheartj/ehs339]

7 **Coffey S**, d'Arcy JL, Loudon MA, Mant D, Farmer AJ, Prendergast BD; OxVALVE-PCS group. The OxVALVE population cohort study (OxVALVE-PCS)-population screening for undiagnosed valvular heart disease in the elderly: study design and objectives. *Open Heart* 2014; **1**: e000043 [PMID: 25332795 DOI: 10.1136/openhrt-2014-000043]

8 **Gaede L**, Di Bartolomeo R, van der Kley F, Elsässer A, Iung B, Möllmann H. Aortic valve stenosis: what do people know? A heart valve disease awareness survey of over 8,800 people aged 60 or over. *EuroIntervention* 2016; **12**: 883-889 [PMID: 27283409 DOI: 10.4244/EIJY16M06_02]

9 **Gaede L**, Aarberge L, Brandon Bravo Bruinsma G, Macarthy P, Musumeci F, Zamorano P, Möllmann H. Heart Valve Disease Awareness Survey 2017: what did we achieve since 2015? *Clin Res Cardiol* 2019; **108**: 61-67 [PMID: 29943272 DOI: 10.1007/s00392-018-1312-5]

10 **Osnabrugge RL**, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013; **62**: 1002-1012 [PMID: 23727214 DOI: 10.1016/j.jacc.2013.05.015]

11 **Stewart BF**, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997; **29**: 630-634 [PMID: 9060903 DOI: 10.1016/S0735-1097(96)00563-3]

12 **Lindroos M**, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993; **21**: 1220-1225 [PMID: 8459080 DOI: 10.1016/0735-1097(93)90249-Z]

13 **Roberts WC**, Janning KG, Ko JM, Filardo G, Matter GJ. Frequency of congenitally bicuspid aortic valves in patients ≥80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. *Am J Cardiol* 2012; **109**: 1632-1636 [PMID: 22459301 DOI: 10.1016/j.amjcard.2012.01.390]

14 **Otto CM**, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* 1994; **90**: 844-853 [PMID: 7519131 DOI: 10.1161/01.CIR.90.2.844]

15 **Pahkala K**, Hietalampi H, Laitinen TT, Viikari JS, Rönnemaa T, Niinikoski H, Lagström H, Talvia S, Jula A, Heinonen OJ, Juonala M, Simell O, Raitakari OT. Ideal cardiovascular health in adolescence: effect of lifestyle intervention and association with vascular intima-media thickness and elasticity (the Special Turku Coronary Risk Factor Intervention Project for Children [STRIP] study). *Circulation* 2013; **127**: 2088-2096 [PMID: 23613255 DOI: 10.1161/CIRCULATIONAHA.112.000761]

16 **Spring B**, Moller AC, Colangelo LA, Siddique J, Roehrig M, Daviglus ML, Polak JF, Reis JP, Sidney S, Liu K. Healthy lifestyle change and subclinical atherosclerosis in young adults: Coronary Artery Risk Development in Young Adults (CARDIA) study. *Circulation* 2014; **130**: 10-17 [PMID: 24982115 DOI: 10.1161/CIRCULATIONAHA.113.005445]

17 **Xanthakis V**, Enserro DM, Murabito JM, Polak JF, Wollert KC, Januzzi JL, Wang TJ, Tofler G, Vasan RS. Ideal cardiovascular health: associations with biomarkers and subclinical disease and impact on incidence of cardiovascular disease in the Framingham Offspring Study. *Circulation* 2014; **130**: 1676-1683 [PMID: 25274000 DOI: 10.1161/CIRCULATIONAHA.114.009273]

18 **Loprinzi PD**, Branscum A, Hanks J, Smit E. Healthy Lifestyle Characteristics and Their Joint Association With Cardiovascular Disease Biomarkers in US Adults. *Mayo Clin Proc* 2016; **91**: 432-442 [PMID: 26906650 DOI: 10.1016/j.mayocp.2016.01.009]

19 **Bossé Y**, Mathieu P, Pibarot P. Genomics: the next step to elucidate the etiology of calcific aortic valve stenosis. *J Am Coll Cardiol* 2008; **51**: 1327-1336 [PMID: 18387432 DOI: 10.1016/j.jacc.2007.12.031]

20 **New SE**, Aikawa E. Molecular imaging insights into early inflammatory stages of arterial and aortic valve calcification. *Circ Res* 2011; **108**: 1381-1391 [PMID: 21617135 DOI: 10.1161/CIRCRESAHA.110.234146]

21 **O'Brien KD**, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb Vasc Biol* 1996; **16**: 523-532 [PMID: 8624774 DOI: 10.1161/01.ATV.16.4.523]

22 **Dweck MR**, Jones C, Joshi NV, Fletcher AM, Richardson H, White A, Marsden M, Pessotto R, Clark JC, Wallace WA, Salter DM, McKillop G, van Beek EJ, Boon NA, Rudd JH, Newby DE. Assessment of valvular calcification and inflammation by positron emission tomography in patients with aortic stenosis. *Circulation* 2012; **125**: 76-86 [PMID: 22090163 DOI: 10.1161/CIRCULATIONAHA.111.051052]

23 **Singh JP**, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999; **83**: 897-902 [PMID: 10190406 DOI: 10.1016/S0002-9149(98)01064-9]

24 **Palmieri V**, Bella JN, Arnett DK, Roman MJ, Oberman A, Kitzman DW, Hopkins PN, Paranicas M, Rao DC, Devereux RB. Aortic root dilatation at sinuses of valsalva and aortic regurgitation in hypertensive and normotensive subjects: The Hypertension Genetic Epidemiology Network Study. *Hypertension* 2001; **37**: 1229-1235 [PMID: 11358933 DOI: 10.1161/01.HYP.37.5.1229]

25 **Shapira OM**, Kelleher RM, Zelingher J, Whalen D, Fitzgerald C, Aldea GS, Shemin RJ. Prognosis and quality of life after valve surgery in patients older than 75 years. *Chest* 1997; **112**: 885-894 [PMID: 9377949 DOI: 10.1378/chest.112.4.885]

26 **Brennan JM**, Edwards FH, Zhao Y, O'Brien S, Booth ME, Dokholyan RS, Douglas PS, Peterson ED; DEcIDE AVR (Developing Evidence to Inform Decisions about Effectiveness–Aortic Valve Replacement) Research Team. Long-term safety and effectiveness of mechanical versus biologic aortic valve prostheses in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. *Circulation* 2013; **127**: 1647-1655 [PMID: 23538379 DOI: 10.1161/CIRCULATIONAHA.113.002003]

27 **Brennan JM**, Edwards FH, Zhao Y, O'Brien SM, Douglas PS, Peterson ED; Developing Evidence to Inform Decisions About Effectiveness–Aortic Valve Replacement (DEcIDE AVR) Research Team. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. *Circulation* 2012; **126**: 1621-1629 [PMID: 22907936 DOI: 10.1161/CIRCULATIONAHA.112.091371]

28 **Cribier AG**. The Odyssey of TAVR from concept to clinical reality. *Tex Heart Inst J* 2014; **41**: 125-130 [PMID: 24808769 DOI: 10.14503/THIJ-14-4137]

29 **Webb JG**, Binder RK. Transcatheter aortic valve implantation: the evolution of prostheses, delivery systems and approaches. *Arch Cardiovasc Dis* 2012; **105**: 153-159 [PMID: 22520798 DOI: 10.1016/j.acvd.2012.02.001]

30 **Biancari F**, Rosato S, D'Errigo P, Ranucci M, Onorati F, Barbanti M, Santini F, Tamburino C, Santoro G, Grossi C, Covello RD, Ventura M, Fusco D, Seccareccia F; OBSERVANT Research Group. Immediate and Intermediate Outcome After Transapical Versus Transfemoral Transcatheter Aortic Valve Replacement. *Am J Cardiol* 2016; **117**: 245-251 [PMID: 26639038 DOI: 10.1016/j.amjcard.2015.10.036]

31 **Fried LP**, Hadley EC, Walston JD, Newman AB, Guralnik JM, Studenski S, Harris TB, Ershler WB, Ferrucci L. From bedside to bench: research agenda for frailty. *Sci Aging Knowledge Environ* 2005; **2005**: pe24 [PMID: 16079413 DOI: 10.1126/sageke.2005.31.pe24]

32 **Prêtre R**, Turina MI. Cardiac valve surgery in the octogenarian. *Heart* 2000; **83**: 116-121 [PMID: 10618352 DOI: 10.1136/heart.83.1.116]

33 **Cheitlin MD**, Gerstenblith G, Hazzard WR, Pasternak R, Fried LP, Rich MW, Krumholz HM, Peterson E, Reves JG, McKay C, Saksena S, Shen WK, Akhtar M, Brass LM, Biller J. Database Conference January 27-30, 2000, Washington D.C.--Do existing databases answer clinical questions about geriatric cardiovascular disease and stroke? *Am J Geriatr Cardiol* 2001; **10**: 207-223 [PMID: 11455241 DOI: 10.1111/j.1076-7460.2003.00696.x]

34 **Smith CR**, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364**: 2187-2198 [PMID: 21639811 DOI: 10.1056/NEJMoa1103510]

35 **Kodali SK**, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012; **366**: 1686-1695 [PMID: 22443479 DOI: 10.1056/NEJMoa1200384]

36 **Hirji SA**, Ramirez-Del Val F, Kolkailah AA, Ejiofor JI, McGurk S, Chowdhury R, Lee J, Shah PB,

Sobieszczyk PS, Aranki SF, Pelletier MP, Shekar PS, Kaneko T. Outcomes of surgical and transcatheter aortic valve replacement in the octogenarians-surgery still the gold standard? *Ann Cardiothorac Surg* 2017; **6**: 453-462 [PMID: 29062740 DOI: 10.21037/acs.2017.08.01]

37 **Yamamoto M**, Mouillet G, Meguro K, Gilard M, Laskar M, Eltchaninoff H, Fajadet J, Iung B, Donzeau-Gouge P, Leprince P, Leuguerrier A, Prat A, Lievre M, Chevreul K, Dubois-Rande JL, Teiger E; FRANCE-2 Registry Investigators. Clinical results of transcatheter aortic valve implantation in octogenarians and nonagenarians: insights from the FRANCE-2 registry. *Ann Thorac Surg* 2014; **97**: 29-36 [PMID: 24140210 DOI: 10.1016/j.athoracsur.2013.07.100]

38 **Tamburino C**, Barbanti M, D'Errigo P, Ranucci M, Onorati F, Covello RD, Santini F, Rosato S, Santoro G, Fusco D, Grossi C, Seccareccia F; OBSERVANT Research Group. 1-Year Outcomes After Transfemoral Transcatheter or Surgical Aortic Valve Replacement: Results From the Italian OBSERVANT Study. *J Am Coll Cardiol* 2015; **66**: 804-812 [PMID: 26271063 DOI: 10.1016/j.jacc.2015.06.013]

39 **Abramowitz Y**, Chakravarty T, Jilaihawi H, Kashif M, Zadikany R, Lee C, Matar G, Cheng W, Makkar RR. Comparison of Outcomes of Transcatheter Aortic Valve Implantation in Patients ≥90 Years Versus <90 Years. *Am J Cardiol* 2015; **116**: 1110-1115 [PMID: 26235927 DOI: 10.1016/j.amjcard.2015.06.033]

40 **Leon MB**, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016; **374**: 1609-1620 [PMID: 27040324 DOI: 10.1056/NEJMoa1514616]

41 **Reardon MJ**, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP; SURTAVI Investigators. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2017; **376**: 1321-1331 [PMID: 28304219 DOI: 10.1056/NEJMoa1700456]

42 **Nishimura RA**, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017; **135**: e1159-e1195 [PMID: 28298458 DOI: 10.1161/CIR.0000000000000503]

43 **Rosato S**, Santini F, Barbanti M, Biancari F, D'Errigo P, Onorati F, Tamburino C, Ranucci M, Covello RD, Santoro G, Grossi C, Ventura M, Fusco D, Seccareccia F; OBSERVANT Research Group. Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients. *Circ Cardiovasc Interv* 2016; **9**: e003326 [PMID: 27154298 DOI: 10.1161/CIRCINTERVENTIONS.115.003326]

44 **Enriquez-Sarano M**, Klodas E, Garratt KN, Bailey KR, Tajik AJ, Holmes DR. Secular trends in coronary atherosclerosis--analysis in patients with valvular regurgitation. *N Engl J Med* 1996; **335**: 316-322 [PMID: 8663854 DOI: 10.1056/NEJM199608013350504]

45 **Perek B**, Casadei V, Puślecki M, Stefaniak S, Maison D, Gwizdała A, Perek A, Szarpak Ł, Jemielity M. Clinical presentation, surgical management, and outcomes of patients treated for aortic stenosis and coronary artery disease. Does age matter? *Kardiol Pol* 2018; **76**: 655-661 [PMID: 29313564 DOI: 10.5603/KP.2018.0005]

46 **Sankaramangalam K**, Banerjee K, Kandregula K, Mohananey D, Parashar A, Jones BM, Jobanputra Y, Mick S, Krishnaswamy A, Svensson LG, Kapadia SR. Impact of Coronary Artery Disease on 30-Day and 1-Year Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement: A Meta-Analysis. *J Am Heart Assoc* 2017; **6**: pii: e006092 [PMID: 29021275 DOI: 10.1161/JAHA.117.006092]

47 **Yu PJ**, Mattia A, Cassiere HA, Esposito R, Manetta F, Kohn N, Hartman AR. Should high risk patients with concomitant severe aortic stenosis and mitral valve disease undergo double valve surgery in the TAVR era? *J Cardiothorac Surg* 2017; **12**: 123 [PMID: 29284509 DOI: 10.1186/s13019-017-0688-z]

48 **Nombela-Franco L**, Ribeiro HB, Urena M, Allende R, Amat-Santos I, DeLarochellière R, Dumont E, Doyle D, DeLarochellière H, Laflamme J, Laflamme L, García E, Macaya C, Jiménez-Quevedo P, Côté M, Bergeron S, Beaudoin J, Pibarot P, Rodés-Cabau J. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. *J Am Coll Cardiol* 2014; **63**: 2643-2658 [PMID: 24681140 DOI: 10.1016/j.jacc.2014.02.573]

49 **Cortés C**, Amat-Santos IJ, Nombela-Franco L, Muñoz-Garcia AJ, Gutiérrez-Ibanes E, De La Torre Hernandez JM, Córdoba-Soriano JG, Jimenez-Quevedo P, Hernández-García JM, Gonzalez-Mansilla A, Ruano J, Jimenez-Mazuecos J, Castrodeza J, Tobar J, Islas F, Revilla A, Puri R, Puerto A, Gómez I, Rodés-Cabau J, San Román JA. Mitral Regurgitation After Transcatheter Aortic Valve Replacement: Prognosis, Imaging Predictors, and Potential Management. *JACC Cardiovasc Interv* 2016; **9**: 1603-1614 [PMID: 27491611 DOI: 10.1016/j.jcin.2016.05.025]

50 **Khawaja MZ**, Williams R, Hung J, Arri S, Asrress KN, Bolter K, Wilson K, Young CP, Bapat V, Hancock J, Thomas M, Redwood S. Impact of preprocedural mitral regurgitation upon mortality after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. *Heart* 2014; **100**: 1799-1803 [PMID: 25155800 DOI: 10.1136/heartjnl-2014-305775]

51 **Schofer J**, Siminiak T, Haude M, Herrman JP, Vainer J, Wu JC, Levy WC, Mauri L, Feldman T, Kwong RY, Kaye DM, Duffy SJ, Tübler T, Degen H, Brandt MC, Van Bibber R, Goldberg S, Reuter DG, Hoppe UC. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 2009; **120**: 326-333 [PMID: 19597051 DOI: 10.1161/CIRCULATIONAHA.109.849885]

52 **David TE**, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. *J Thorac Cardiovasc Surg* 2005; **130**: 1242-1249 [PMID: 16256774 DOI: 10.1016/j.jtcvs.2005.06.046]

53 **Kodali SK**, Velagapudi P, Hahn RT, Abbott D, Leon MB. Valvular Heart Disease in Patients ≥80 Years of Age. *J Am Coll Cardiol* 2018; **71**: 2058-2072 [PMID: 29724358 DOI: 10.1016/j.jacc.2018.03.459]

54 **Ukita Y**, Yuda S, Sugio H, Yonezawa A, Takayanagi Y, Masuda-Yamamoto H, Tanaka-Saito N, Ohnishi H, Miura T. Prevalence and clinical characteristics of degenerative mitral stenosis. *J Cardiol* 2016; **68**:

248-252 [PMID: 26546498 DOI: 10.1016/j.jjcc.2015.09.021]
55 **Kristensen SD**, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C; Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014; **35**: 2383-2431 [PMID: 25086026 DOI: 10.1093/eurheartj/ehu282]
56 **Biancari F**, Schifano P, Pighi M, Vasques F, Juvonen T, Vinco G. Pooled estimates of immediate and late outcome of mitral valve surgery in octogenarians: a meta-analysis and meta-regression. *J Cardiothorac Vasc Anesth* 2013; **27**: 213-219 [PMID: 23507013 DOI: 10.1053/j.jvca.2012.11.007]
57 **Acker MA**, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo YJ, D'Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O'Gara PT, Michler RE, Kron IL; CTSN. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med* 2014; **370**: 23-32 [PMID: 24245543 DOI: 10.1056/NEJMoa1312808]
58 **Dayan V**, Soca G, Cura L, Mestres CA. Similar survival after mitral valve replacement or repair for ischemic mitral regurgitation: a meta-analysis. *Ann Thorac Surg* 2014; **97**: 758-765 [PMID: 24370200 DOI: 10.1016/j.athoracsur.2013.10.044]
59 **Mick SL**, Keshavamurthy S, Gillinov AM. Mitral valve repair versus replacement. *Ann Cardiothorac Surg* 2015; **4**: 230-237 [PMID: 26309824 DOI: 10.3978/j.issn.2225-319X.2015.03.01]
60 **Vassileva CM**, Mishkel G, McNeely C, Boley T, Markwell S, Scaife S, Hazelrigg S. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation* 2013; **127**: 1870-1876 [PMID: 23569153 DOI: 10.1161/CIRCULATIONAHA.113.002200]
61 **Badhwar V**, Peterson ED, Jacobs JP, He X, Brennan JM, O'Brien SM, Dokholyan RS, George KM, Bolling SF, Shahian DM, Grover FL, Edwards FH, Gammie JS. Longitudinal outcome of isolated mitral repair in older patients: results from 14,604 procedures performed from 1991 to 2007. *Ann Thorac Surg* 2012; **94**: 1870-7; discussion 1877-9 [PMID: 22858278 DOI: 10.1016/j.athoracsur.2012.05.105]
62 **Kang DH**, Heo R, Lee S, Baek S, Kim DH, Song JM, Song JK, Lee JW. Initial surgery versus conservative management of symptomatic severe mitral regurgitation in the elderly. *Heart* 2018; **104**: 849-854 [PMID: 28982717 DOI: 10.1136/heartjnl-2017-311759]
63 **Zhuge RQ**, Hou XP, Qi XL, Wu YJ, Zhang MZ. Clinical features and treatment options for mitral regurgitation in elderly inpatients. *J Geriatr Cardiol* 2018; **15**: 428-433 [PMID: 30108615 DOI: 10.11909/j.issn.1671-5411.2018.06.005]
64 **Seeburger J**, Falk V, Garbade J, Noack T, Kiefer P, Vollroth M, Mohr FW, Misfeld M. Mitral valve surgical procedures in the elderly. *Ann Thorac Surg* 2012; **94**: 1999-2003 [PMID: 22835550 DOI: 10.1016/j.athoracsur.2012.05.069]
65 **Silaschi M**, Chaubey S, Aldalati O, Khan H, Uzzaman MM, Singh M, Baghai M, Deshpande R, Wendler O. Is Mitral Valve Repair Superior to Mitral Valve Replacement in Elderly Patients? Comparison of Short- and Long-Term Outcomes in a Propensity-Matched Cohort. *J Am Heart Assoc* 2016; **5**: pii: e003605 [PMID: 27468927 DOI: 10.1161/JAHA.116.003605]
66 **Chikwe J**, Goldstone AB, Passage J, Anyanwu AC, Seeburger J, Castillo JG, Filsoufi F, Mohr FW, Adams DH. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. *Eur Heart J* 2011; **32**: 618-626 [PMID: 20846993 DOI: 10.1093/eurheartj/ehq331]
67 **Shang X**, Lu R, Liu M, Xiao S, Dong N. Mitral valve repair versus replacement in elderly patients: a systematic review and meta-analysis. *J Thorac Dis* 2017; **9**: 3045-3051 [PMID: 29221278 DOI: 10.21037/jtd.2017.08.43]
68 **Feldman T**, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; **364**: 1395-1406 [PMID: 21463154 DOI: 10.1056/NEJMoa1009355]
69 **Dal-Bianco JP**, Inglessis I, Melnitchouk S, Daher M, Palacios IF. Percutaneous Mitral Valve Edge-to-Edge Repair for Degenerative Mitral Regurgitation. *Curr Treat Options Cardiovasc Med* 2015; **17**: 389 [PMID: 26070587 DOI: 10.1007/s11936-015-0389-7]
70 **Taramasso M**, Vanermen H, Maisano F, Guidotti A, La Canna G, Alfieri O. The growing clinical importance of secondary tricuspid regurgitation. *J Am Coll Cardiol* 2012; **59**: 703-710 [PMID: 22340261 DOI: 10.1016/j.jacc.2011.09.069]
71 **Cohen SR**, Sell JE, McIntosh CL, Clark RE. Tricuspid regurgitation in patients with acquired, chronic, pure mitral regurgitation. II. Nonoperative management, tricuspid valve annuloplasty, and tricuspid valve replacement. *J Thorac Cardiovasc Surg* 1987; **94**: 488-497 [PMID: 3657251]
72 **Girard SE**, Nishimura RA, Warnes CA, Dearani JA, Puga FJ. Idiopathic annular dilation: a rare cause of isolated severe tricuspid regurgitation. *J Heart Valve Dis* 2000; **9**: 283-287 [PMID: 10772049 DOI: 10.1016/S1053-2498(99)00135-7]
73 **Topilsky Y**, Khanna A, Le Tourneau T, Park S, Michelena H, Suri R, Mahoney DW, Enriquez-Sarano M. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. *Circ Cardiovasc Imaging* 2012; **5**: 314-323 [PMID: 22447806 DOI: 10.1161/CIRCIMAGING.111.967919]
74 **Mahmood F**, Kim H, Chaudary B, Bergman R, Matyal R, Gerstle J, Gorman JH, Gorman RC, Khabbaz KR. Tricuspid annular geometry: a three-dimensional transesophageal echocardiographic study. *J Cardiothorac Vasc Anesth* 2013; **27**: 639-646 [PMID: 23725682 DOI: 10.1053/j.jvca.2012.12.014]
75 **Q Tri HH**, Vinh PN. Progression of Tricuspid Regurgitation after Mitral Valve Replacement for Rheumatic Heart Disease. *J Heart Valve Dis* 2017; **26**: 290-294 [PMID: 29092113]
76 **Zack CJ**, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National Trends and Outcomes in Isolated Tricuspid Valve Surgery. *J Am Coll Cardiol* 2017; **70**: 2953-2960 [PMID: 29241483 DOI: 10.1016/j.jacc.2017.10.039]
77 **Nath J**, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004; **43**: 405-409 [PMID: 15013122 DOI: 10.1016/j.jacc.2003.09.036]
78 **Subbotina I**, Girdauskas E, Bernhardt AM, Sinning C, Reichenspurner H, Sill B. Comparison of

Outcomes of Tricuspid Valve Surgery in Patients with Reduced and Normal Right Ventricular Function. *Thorac Cardiovasc Surg* 2017; **65**: 617-625 [PMID: 28841733 DOI: 10.1055/s-0037-1604450]

79 **Rostagno C**, Gelsomino S, Stefàno PL, Padeletti L. Rhythmic and haemodynamic determinants of long-term survival after radiofrequency ablation of atrial fibrillation in mitral valve surgery. *Eur Heart J Qual Care Clin Outcomes* 2016; **2**: 285-290 [PMID: 29474714 DOI: 10.1093/ehjqcco/qcw021]

80 **Nickenig G**, Kowalski M, Hausleiter J, Braun D, Schofer J, Yzeiraj E, Rudolph V, Friedrichs K, Maisano F, Taramasso M, Fam N, Bianchi G, Bedogni F, Denti P, Alfieri O, Latib A, Colombo A, Hammerstingl C, Schueler R. Transcatheter Treatment of Severe Tricuspid Regurgitation With the Edge-to-Edge MitraClip Technique. *Circulation* 2017; **135**: 1802-1814 [PMID: 28336788 DOI: 10.1161/CIRCULATIONAHA.116.024848]

P- Reviewer: Akin I, Chang ST, Li D

S- Editor: Ji FF **L- Editor:** Filipodia **E- Editor:** Wu YXJ

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 February 26; 11(2): 84-93

DOI: 10.4330/wjc.v11.i2.84

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Prevalence and clinical characteristics associated with left atrial thrombus detection: Apixaban

Hoyle L Whiteside, Arun Nagabandi, Kristen Brown, Deepak N Ayyala, Gyanendra K Sharma

ORCID number: Hoyle L Whiteside (0000-0002-7181-2482); Arun Nagabandi (https://orcid.org/0000-0002-1668-6970); Kristen Brown (https://orcid.org/0000-0002-5589-7172); Deepak N Ayyala (https://orcid.org/0000-0002-7251-580X); Gyanendra K Sharma (https://orcid.org/0000-0001-9027-4440).

Author contributions: Whiteside HL wrote the manuscript; Whiteside HL, Nagabandi A and Sharma GK reviewed and revised the final version of the manuscript; Whiteside HL, Nagabandi A and Sharma GK designed the study; Whiteside HL, Nagabandi A and Brown K coordinated and provided the data collection; Ayyala DN provided statistical consultation and analysis.

Institutional review board statement: The Institutional Review Board of Augusta University reviewed and approved this study on February 8, 2017.

Informed consent statement: This study was a retrospective analysis utilizing data readily available within the electronic medical record system. The study received a waiver of the consent process upon review by the Institutional Review Board and the dataset was stored electronically on an institutional research drive.

Conflict-of-interest statement: The authors report no financial relationships or conflicts of interest regarding the content.

Open-Access: This article is an

Hoyle L Whiteside, Kristen Brown, Division of Internal Medicine, Medical College of Georgia at Augusta University, Augusta, GA 30912, United States

Arun Nagabandi, Gyanendra K Sharma, Division of Cardiology, Medical College of Georgia at Augusta University, Augusta, GA 30912, United States

Deepak N Ayyala, Division of Biostatistics and Data Science, Department of Population Health Sciences, Medical College of Georgia at Augusta University, Augusta, GA 30912, United States

Corresponding author: Hoyle L Whiteside, MD, Doctor, Division of Internal Medicine, Medical College of Georgia at Augusta University, 1120 15th St., Augusta, GA30909, United States. hwhiteside@augusta.edu
Telephone: +1-706-7212423
Fax: +1-706-7211059

Abstract

BACKGROUND

The prevalence of left atrial appendage (LAA) thrombus detection by transesophageal echocardiogram (TEE) in patients with non-valvular atrial fibrillation (AF) anticoagulated with apixaban is not well defined and identification of additional risk factors may help guide the selection process for pre-procedural TEE. The purpose of our study was to retrospectively analyze the prevalence of LAA thrombus detection by TEE in patients continuously anticoagulated with apixaban for ≥ 4 wk and evaluate for any cardiac risk factors or echocardiographic characteristics which may serve as predictors of thrombus formation.

AIM

To retrospectively analyze the prevalence of LAA thrombus detection by TEE in patients continuously anticoagulated with apixaban.

METHODS

Clinical and echocardiographic data for 820 consecutive patients with AF undergoing TEE at Augusta University Medical Center over a four-year period were retrospectively analyzed. All patients (apixaban: 226) with non-valvular AF and documented compliance with apixaban for ≥ 4 wk prior to index TEE were included.

RESULTS

Following ≥ 4 wk of continuous anticoagulation with apixaban, the prevalence of

open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: October 24, 2018
Peer-review started: October 24, 2018
First decision: December 10, 2018
Revised: December 18, 2018
Accepted: January 8, 2019
Article in press: January 9, 2019
Published online: February 26, 2019

LAA thrombus and LAA thrombus/dense spontaneous echocardiographic contrast was 3.1% and 6.6%, respectively. Persistent AF, left ventricular ejection fraction < 30%, severe LA dilation, and reduced LAA velocity were associated with thrombus formation. Following multivariate logistic regression, persistent AF (OR: 7.427; 95%CI: 1.02 to 53.92; P = 0.0474), and reduced LAA velocity (OR: 1.086; 95%CI: 1.010 to 1.187; P = 0.0489) were identified as independent predictors of LAA thrombus. No Thrombi were detected in patients with a CHA_2DS_2-VASc score ≤ 1.

CONCLUSION

Among patients with non-valvular AF and ≥ 4 wk of anticoagulation with apixaban, the prevalence of LAA thrombus detected by TEE was 3.1%. This suggests that continuous therapy with apixaban does not completely eliminate the risk of LAA thrombus and that TEE prior to cardioversion or catheter ablation may be of benefit in patients with multiple risk factors.

Key words: Atrial fibrillation; Anticoagulation; Left atrial appendage thrombus; Transesophageal echocardiography

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The prevalence of left atrial appendage (LAA) thrombus detection by transesophageal echocardiogram (TEE) in patients with non-valvular atrial fibrillation (AF) anticoagulated with apixaban is not well defined and identification of additional risk factors may help guide the selection process for pre-procedural TEE. At our institution, the prevalence of thrombus detection in patients compliant with apixaban was 3.1%. Persistent AF, left ventricular ejection fraction < 30%, severe LA dilation, and reduced LAA velocity were associated with thrombus formation. Following multivariate logistic regression, persistent AF and reduced LAA velocity were identified as independent predictors of thrombus detection.

Citation: Whiteside HL, Nagabandi A, Brown K, Ayyala DN, Sharma GK. Prevalence and clinical characteristics associated with left atrial thrombus detection: Apixaban. *World J Cardiol* 2019; 11(2): 84-93
URL: https://www.wjgnet.com/1949-8462/full/v11/i2/84.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i2.84

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risk of systemic thromboembolism due to the development of left atrial (LA) and LA appendage (LAA) thrombi[1,2]. Among patients with non-valvular AF, 90% of atrial thrombi are seen within the LAA[3]. Transesophageal echocardiography (TEE) is the most sensitive and specific imaging modality for the detection LA thrombi and is routinely utilized in patients undergoing elective cardioversion or catheter ablation to reduce the risk of thromboembolic events[1,2,4-7]. Risk factors such as structural heart disease, left atrial size, reduced left ventricular ejection fraction (LVEF), persistent AF, an CHA_2DS_2-VASc score have been reported as independent predictors of LAA thrombus detection by TEE[8-13].

Several randomized trials have demonstrated the efficacy of non-vitamin K dependent oral anticoagulants (NOACs) to reduce rates of stroke and systemic thromboembolism compared to warfarin, however, their impact on the detection of LA thrombi by TEE is less well established[14,15]. In patients receiving ≥ 3 wk of continuous anticoagulation with warfarin, the prevalence of LA thrombus detection is reported to be between 1.55% and 7.7%[8,12,13,16-20]. Recent data has helped to elucidate the prevalence of LA thrombi in patients anticoagulated with NOACs, particularly in patients prescribed dabigatran or rivaroxaban prior to catheter ablation[18-20]. With regards to apixaban, data remains limited[18-22]. With at least one study reporting a decline in utilization of TEE prior to catheter ablation and prescription rates for NOACs increasing on a yearly basis, further analysis of patients prescribed apixaban could have clinically meaningful implications[22,23]. Identification of additional risk

factors which may predict LAA thrombus detection in patients prescribed apixaban is of particular interest as it could help identify a population which would be at increased risk of adverse outcomes should intervention be performed without TEE.

MATERIALS AND METHODS

Study population

Following institutional review board approval, we retrospectively identified 820 consecutive patients with a diagnosis of AF undergoing TEE at Augusta University Medical Center between January 1, 2014 and September 30, 2017 (Figure 1). We excluded 146 patients who were not on any anticoagulation, 183 patients anticoagulated with other NOACs (Rivaroxaban: 122, Dabigatran: 60, Edoxaban: 1), 221 patients anticoagulated with Warfarin, and 15 patients who were determined to be incorrectly coded as AF and in whom TEE was performed for an alternative indication. Two hundred fifty-five patients were anticoagulated with apixaban. Within this cohort, 13 patients were excluded due to documented non-compliance with continuous oral anticoagulation in the 4 wk preceding index TEE, 8 for LAA ligation, 2 for valvular AF, and 6 patients with incomplete echocardiographic data. The final study population included 226 patients anticoagulated with apixaban.

Data extraction and baseline assessment

A detailed chart review was conducted in accordance with the study protocol targeting cardiac risk factors, anticoagulant therapy, and echocardiographic data. A CHA_2DS_2-VASc score was calculated for each patient in accordance with Lip *et al*[24] AF lasting ≤ 7 d or > 7 d was defined as paroxysmal and persistent, respectively[1,2]. All physician notes in the four weeks preceding TEE were reviewed. Any patient with documented medication noncompliance was excluded from the study.

Cardiac imaging

TEE Imaging was performed using Phillips EPIQ 7 ultrasound machine and Phillips IE33 ultrasound transducer (Andover, Massachusetts). Standard TEE images were acquired including focused imaging of the LA and LAA. Technique routinely used at our institution involves acquisition of at least two orthogonal views of the LAA. All TEEs were reviewed by at least one of two echocardiographers with strong agreement between observers (Cohen's kappa: 0.89). A thrombus was reported if a well-circumscribed, echo-reflective mass distinct from the LA endocardium or pectinate muscles was present in the appendage or body of the LA[4]. Spontaneous echo contrast (SEC) was classified as dense, clearing, or absent correlating with 3-4+, 1-2+, or 0 as graded by Fatkin *et al*[25] SEC was classified as dense if a dense swirling pattern was observed in the LAA and was detectable throughout the cardiac cycle (with variable intensity). SEC was classified as clearing if minimal echodensity was observed in the LAA and was detectable transiently during the cardiac cycle. LAA velocities were determined based on peak velocities averaged over a minimum of two full cardiac cycles in the view which was most parallel to the LAA ostium. LA size was assessed semi-quantitatively and documented as normal, mildly, moderately, or severely dilated.

Follow up

For any patient with LA or LAA thrombi identified on TEE, data was collected for 180 d following index study. If a subsequent TEE was performed between 30 and 180 d following diagnosis of LA or LAA thrombi, then follow up data was collected including changes in oral anticoagulation, antiplatelet therapy, and resolution of thrombus.

Statistical analysis

All statistical computations and hypothesis tests were performed using R 3.4.3 (https://www.r-project.org/). To compare demographics and echocardiographic variables between groups, Fisher's exact test was used for categorical variables and Welch's *t*-test was used for the continuous variables. All hypothesis tests were performed at 5% significance level. Univariate logistic regression model was used to associate the odds of occurrence of an event (LAA thrombus formation, dense SEC) to demographic and echocardiographic factors. For scenarios where the odds of the event are zero, pseudo-data points were added to obtain valid estimates and test statistics. Significance of the factors was determined using a two-sided *z*-test. For each univariate model, a two-sided 95% confidence interval (CI) is reported. Using the variables deemed as significant, a multivariate logistic regression was fit to study independence of the variables.

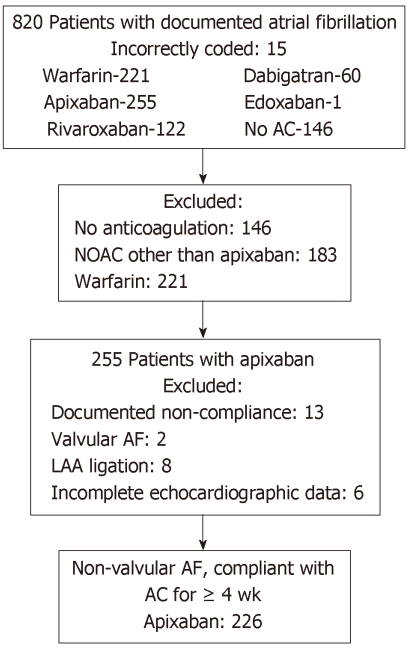


Figure 1 Study population. AC: Anticoagulation; AF: Atrial fibrillation; LAA: Left atrial appendage; NOAC: Non-vitamin K oral anticoagulant.

RESULTS

Population demographics and echocardiographic characteristics

Patient demographics, cardiac risk factors and echocardiographic characteristics for patients with and without thrombus detection are reported in Table 1. The presence of end-stage renal disease, persistent AF, reduced LAA velocities, severe LA dilation, and dense SEC were more common in patients found to have LAA thrombus. Overall, the study population was at meaningful risk of thromboembolic events as 181 (80.1%) patients had CHA_2DS_2-VASc score ≥ 2.

Prevalence of LAA thrombus and SEC

In patients compliant with apixaban, the prevalence of LAA thrombus and LAA thrombus/Dense SEC was 3.1% and 6.6%, respectively. Full data for the study population based on prevalence of thrombus is provided in Table 1. A similar table, based on the prevalence of thrombus/dense SEC, is available in the online materials (Supplementary Table 1). Among patients with LVEF < 30% and ≥ 50%, thrombus was detected in 9.1% and 2.0% (P = 0.074), respectively. The prevalence of LAA thrombus based on CHA_2DS_2-VASc score is summarized in Supplementary Table 2. Notably, no thrombi were identified in the 45 (19.9%) patients with a CHA_2DS_2-VASc score ≤ 1.

Univariate and multivariate predictors of LAA thrombus

In patients anticoagulated with apixaban, persistent AF, LVEF < 30%, severe LA dilation, and reduced LAA velocity were identified as univariate predictors of LAA thrombus detection (Table 2). On multivariate logistic regression, persistent AF (OR: 7.427; 95%CI: 1.02 to 53.92; P = 0.0474), and reduced LAA velocity (OR: 1.086; 95%CI: 1.010 to 1.187; P = 0.0489) remained independent predictors of LAA thrombus detection. On further analysis, the OR for each 10% decrease in LVEF was 1.517 (95%CI: 0.971 to 2.369; P = 0.067). For the combined endpoint of LAA thrombus detection/dense SEC, reduced LAA velocity (OR: 1.131; 95% CI: 1.031 to 1.235; p = 0.0061), was a significant independent predictor on multivariate logistic regression with persistent AF (OR: 4.665; 95%CI: 0.81 to 27.0; P = 0.0856) and severe LA dilation (OR: 5.915; 95%CI: 0.74 to 46.98; P = 0.0927) approaching significance (Supplementary Table 3).

Subsequent cardiac imaging and thrombus resolution

Six patients had a subsequent TEE performed 30-180 d following the diagnosis of LAA thrombus and documented compliance with continuous anticoagulation. Anticoagulation and echocardiographic data, as well as, CHA_2DS_2-VASc score for each patient is provided in Table 3. These patients were anticoagulated for a mean of

Table 1 Cardiac risk factors and echocardiographic characteristics by presence of thrombus

	Study population (*n* = 226)	Apixaban-thrombus (*n* = 7)	Apixaban - no thrombus (*n* = 219)	*P*-value[1]
Age	65.8 ± 11.9	68.1 ± 8.0	65.7 ± 11.9	0.458
Race				
White	190 (84.1)	4 (57.1)	186 (84.9)	0.0825
Black	34 (15.0)	3 (42.9)	31 (14.2)	0.0712
Hispanic	0 (0)	0 (0)	0 (0)	-
Asian	2 (0.9)	0 (0)	2 (0.9)	1
Most recent Cr	1.01 ± 0.33	1.18 ± 0.82	1.01 ± 0.32	0.662
ESRD	6 (2.7)	2 (28.5)	4 (1.8)	0.012
Clopidogrel	7 (3.1)	0 (0)	7 (3.2)	1
Aspirin	83 (36.7)	2 (28.5)	81 (37.0)	1
CHA_2DS_2-VASc	2.83 ± 1.62	3.43 ± 1.40	2.81 ± 1.62	0.354
CHF	88 (34.5)	3 (42.9)	75 (34.2)	0.695
Hypertension	184 (81.4)	7 (100)	177 (80.8)	0.353
Age > 75	50 (22.1)	1 (14.3)	49 (22.4)	1
Diabetes	50 (22.1)	2 (28.5)	48 (21.9)	0.652
Stroke	11 (4.9)	0 (0)	11 (5.0)	1
Vascular disease	26 (11.5)	1 (14.3)	25 (11.4)	0.580
Age > 65	145 (64.2)	6 (85.7)	139 (63.5)	0.426
Female	87 (38.5)	2 (28.5)	85 (38.8)	0.710
Persistent AF	59 (26.1)	5 (71.4)	54 (24.7)	0.014
Echocardiographic data				
LVEF	47.8 ± 14.3	38.6 ± 19.3	48.1 ± 14.1	0.241
LVEF < 30	33 (14.6)	3 (42.9)	30 (13.7)	0.066
LVEF 30-49	44 (19.5)	1 (14.3)	43 (19.6)	1
LVEF ≥ 50	149 (65.9)	3 (42.9)	146 (66.7)	0.233
LAA velocity	48.4 ± 18.1	27.8 ± 10.5	49.0 ± 18.0	0.001
LAA velocity < 40 cm/s	71 (31.4)	6 (85.7)	65 (29.7)	0.004
SEC classification				
None	206 (91.2)	1 (14.3)	205 (93.6)	<0.001
Clearing	7 (3.1)	1 (14.3)	6 (2.7)	0.200
Dense	13 (5.8)	5 (71.4)	8 (3.7)	<0.001
LA dilation				
Moderate	66 (29.2)	1 (14.3)	65 (29.7)	0.677
Severe	59 (26.1)	6 (85.7)	53 (24.2)	0.001
Mitral Regurgitation				
Moderate	53 (23.5)	1 (14.3)	52 (23.7)	1
Severe	5 (2.2)	1 (14.3)	4 (1.8)	0.147

[1]*P*-values denote differences between cohorts with and without thrombus. AF: Atrial fibrillation; CHF: Congestive heart failure; Cr: Creatinine; ESRD: End-stage renal disease; LA: Left atria; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; SEC: Spontaneous echo contrast.

94.0 d and thrombus resolution occurred in 83.3%.

DISCUSSION

The purpose of our study was to retrospectively analyze the prevalence of LAA thrombus in patients continuously anticoagulated with apixaban for ≥ 4 wk and evaluate for any cardiac risk factors or echocardiographic characteristics which may serve as predictors of thrombus formation.

Prevalence of LAA thrombus detection

To date, there remains limited data on the prevalence of LAA thrombus detection by TEE amongst patients with non-valvular AF on apixaban therapy. Multiple recent retrospective analyses have helped to elucidate the prevalence of LAA thrombus in

Table 2 Univariate and multivariate predictors of left atrial appendage thrombus

Apixaban						
Variable	Unadjusted (univariate analysis)			Adjusted (multivariate analysis)		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
CHF	1.440	0.31-6.60	0.6388			
Hypertension	1.933	0.24-15.87	0.5396			
Age > 65	3.453	0.41-29.20	0.2552			
Age > 75	0.578	0.07-4.92	0.6160			
Diabetes	1.425	0.27-7.58	0.6778			
Stroke	2.177	0.25-18.85	0.4800			
Vascular disease	1.293	0.15-11.19	0.8152			
CHA_2DS_2-VASc	1.261	0.80-2.00	0.3240			
Gender (female)	0.631	0.12-3.32	0.5866			
Persistent AF	7.639	1.44-40.51	0.0169[1]	7.427	1.02-53.92	0.0474
LVEF < 30%	4.725	1.01-22.17	0.0489[1]	0.726	0.10-5.12	0.7480
LVEF < 50%[2]	2.667	0.58-12.23	0.2069			
Severe left atrial dilation[1]	8.877	1.27-61.85	0.0275[1]	5.901	0.69-50.62	0.1054
LAA velocity (decrease)[1]	1.110	1.031-1.19	0.0032[1]	1.086	1.010-1.187	0.0489
LAA velocity < 40 cm/s[2]	14.215	1.68-120.40	0.0149[2]			

[1]Significant factor in the univariate model which is used in the multivariate model;
[2]Significant factor in the univariate model but not considered in the multivariate model. AF: Atrial fibrillation; CHF: Congestive heart failure; CI: Confidence interval; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; OR: Odds ratio.

patients treated with NOACs, in particular, patients undergoing catheter ablation[18-20,22]. However, apixaban is often the least represented oral anticoagulant in these studies with a reported prevalence of 0% to 2.9%[21]. In our study population, the prevalence of LAA thrombus was 3.1% despite ≥ 4 wk of continuous anticoagulation which is consistent with previously published data from smaller cohorts when risk factors are considered. The cohort was at considerable risk given mean CHA_2DS_2-VASc 2.83 ± 1.62 and 80.1% of patients with CHA_2DS_2-VASc ≥ 2.

Predictors of LAA thrombus detection

The presence of persistent AF, reduced LVEF, severe LA dilation, and reduced LAA velocity were identified as univariate predictors of LA thrombus detection in the apixaban cohort. Following evaluation with multivariate logistic regression, persistent AF and reduced LAA velocity were identified as independent predictors of LA thrombus detection. Commonly identified independent predictors of thrombus formation in recent studies include CHF, persistent AF, reduced LVEF, and elevated CHA_2DS_2-VASc score[18-20]. Of note, apixaban was often the least represented NOAC in these studies and made minimal contribution to the population with thrombus. Finally, these analyses pooled vitamin K antagonist and NOAC data in order perform multivariate analysis with one exception, in which the authors describe only 1 independent predictor and report small sample size as a limitation[18-20]. CHA_2DS_2-VASc score was not identified as a univariate predictor which is likely a result of the relatively small number of low-risk patients in our study population as only 19.9% of patients had CHA_2DS_2-VASc score < 2. Of note, reduced LVEF < 30% was identified as a significant univariate predictor in both analyses, however was not determined to be a significant independent predictor. We believe that reduced LVEF is a significant predictor of thrombus formation as identified in similar studies with variable anticoagulation strategies and rates of compliance[9,13,19,20]. However, our result likely reflects a limitation of sample size as well as an inherent relationship between advanced cardiomyopathy and clinical/echocardiographic findings most prevalent in high-risk patients with AF.

Rate of LAA thrombus resolution

Data regarding thrombus resolution in patients prescribed apixaban has thus far been limited to case reports and small cohorts[19,20,26,27]. While data regarding thrombus resolution in patients prescribed warfarin is more prevalent, rates of resolution range

Table 3 Clinical characteristics and thrombus resolution

Study ID	AC after thrombus identification	Thrombus resolution	Duration of AC (d)	P2Y12 inhibitor	Aspirin	LVEF (%)	LA dilation	Spontaneous contrast	LAA velocity (cm/s)	Duration of A-fib	CHADS-VASc score
Apixaban following index TEE (n = 6)											
LA-011	Apixaban	Yes	143	No	No	55	Moderate	None	30.4	Paroxysmal	3
LA-016	Apixaban	Yes	38	Yes	Yes	15	Severe	Severe	14.4	Paroxysmal	2
LA-017	Apixaban	Yes	175	No	Yes	15	Severe	Mild	34.0	Paroxysmal	4
LA-019	Apixaban	Yes	40	No	No	30	Severe	None	26.5	Paroxysmal	2
LA-020	Apixaban	Yes	56	No	Yes	25	Severe	Moderate	28.0	Persistent	3
LA-005	Apixaban	No	112	No	No	65	Moderate	Moderate	49.2	Persistent	4
		5/6 (83.3%)	Mean 94.0 Median 84.0								

AC: Anticoagulation; A-fib: Atrial fibrillation; LA: Left atrium; LAA: Left atrial appendage; LVEF: Left ventricular ejection fraction; TEE: Transesophageal echocardiogram.

from 55% to 82%[16,17,28]. In our limited cohort, we identified thrombus resolution in 83.3% of patients anticoagulated with apixaban (n = 6). Although all patients were confirmed to be compliant with continuous anticoagulation throughout the follow up period, there was significant heterogeneity in the duration of therapy prior to repeat cardiac imaging which limits our ability to draw conclusions regarding the optimal duration of anticoagulation. Regardless, apixaban appears to be a reasonable anticoagulation strategy in this population and warrants further investigation in prospective trial.

Application of study findings

A recent expert consensus statement recommends that current anticoagulation guidelines as they pertain to cardioversion of AF should be observed for patients presenting with AF prior to catheter ablation and that TEE is reasonable despite ≥ 3 wk of continuous anticoagulation[1,2,7]. Two recent surveys, one including 16 Canadian centers and the other including 521 ablation centers in 24 countries, report that > 70% of ablation centers routinely utilized pre-procedure TEE in all patients[29,30]. One cost-effectiveness analysis reports an incremental cost-effectiveness ratio of $226608 per quality-adjusted life year for routine use of TEE in an unselected population prior to pulmonary vein isolation modeled with a 4% prevalence of thrombus. While the prevalence is likely overestimated, this analysis highlights the need to better identify patients with a high pretest probability of LAA thrombus despite continuous anticoagulation in order to improve the cost-benefit ratio of the procedure[31]. A trend toward more conservative use of pre-procedural TEE appears to be underway as one large ablation center reports a significant decline in the routine utilization of TEE from 86% to 42% over a 5 year period[22]. While another recent study completely eliminated pre-procedural TEE in favor of intracardiac echocardiography prior to AF ablation. Despite adequate imaging of the LAA in only 71% of patients, the authors report excellent outcomes[32]. This study is retrospective and meant to explore variables which could be predictors of thrombus formation in patients treated with apixaban. A prospective randomized trial would be needed to conclusively determine and validate a scoring system and/or various cutoffs. However, this may not be practical given the low event rate in this population. Nonetheless, we hope that our work can provide evidence to help guide the selection of patients for pre-procedural TEE.

Study limitations

Our study is limited by the retrospective nature of the data collected. In addition, we cannot objectively confirm 100% compliance with apixaban therapy as quantitative assays are not routinely used in clinical practice. Although we took great effort to exclude any patients with documented non-compliance, our ability to do so would be limited by the history provided and documentation of health care professionals.

In patients with non-valvular AF and a minimum of 4 wk continuous oral

anticoagulation with apixaban, the prevalence of LAA thrombus and LAA thrombus/dense SEC detected by TEE was 3.1% and 6.6%, respectively. Both persistent AF and reduced LAA velocity were identified as independent predictors of LA thrombus detection in patients anticoagulated with apixaban. In addition, LVEF < 30% and severe LA dilation were identified as univariate predictors. We hope that the presence or absence of these clinical findings in addition to established risk factors can help guide the selection process for utilization of pre-procedural TEE in future patients with non-valvular AF anticoagulated with apixaban.

ARTICLE HIGHLIGHTS

Research background

The prevalence of left atrial appendage (LAA) thrombus detection by transesophageal echocardiogram (TEE) in patients anticoagulated for ≥ 4 wk with apixaban is not well defined and predictors of LAA thrombus detection are not completely understood. Furthermore, the efficacy of apixaban to resolve pre-existing LAA thrombi is not well documented.

Research motivation

Prescriptions rates for non-vitamin K dependent oral anticoagulants are increasing on a yearly basis and further analysis of patients prescribed apixaban could have clinically meaningful implications. We aimed to identify significant predictors of LAA thrombus detection on TEE to aid in the selection process for screening in future patients undergoing direct current cardioversion or catheter ablation.

Research objectives

The purpose of our study was to retrospectively analyze the prevalence of LAA thrombus detection by TEE in patients continuously anticoagulated with apixaban for ≥ 4 wk and evaluate for any cardiac risk factors or echocardiographic characteristics which may serve as predictors of thrombus formation.

Research methods

Clinical and echocardiographic data for 820 consecutive patients with atrial fibrillation (AF) undergoing TEE at Augusta University Medical Center over a four-year period were retrospectively analyzed. All patients (apixaban: 226) with non-valvular AF and documented compliance with apixaban for ≥ 4 wk prior to index TEE were included.

Research results

Following ≥ 4 wk of continuous anticoagulation with apixaban, the prevalence of LAA thrombus and LAA thrombus/dense spontaneous echocardiographic contrast was 3.1% and 6.6%, respectively. Persistent AF, left ventricular ejection fraction < 30%, severe LA dilation, and reduced LAA velocity were associated with thrombus formation. Following multivariate logistic regression, persistent AF (OR: 7.427; 95%CI: 1.02 to 53.92; P = 0.0474), and reduced LAA velocity (OR: 1.086; 95%CI: 1.010 to 1.187; P = 0.0489) were identified as independent predictors of LAA thrombus. No Thrombi were detected in patients with a CHA_2DS_2-VASc score ≤ 1.

Research conclusions

Among patients with non-valvular AF and ≥ 4 wk of anticoagulation with apixaban, the prevalence of LAA thrombus detected by TEE was 3.1%. This suggests that continuous therapy with apixaban does not completely eliminate the risk of LAA thrombus and that TEE prior to cardioversion or catheter ablation may be of benefit in patients with multiple risk factors.

Research perspectives

Compliance with non-vitamin K oral anticoagulants reduces but does not eliminate the prevalence of thrombus detection by TEE. However, available cost-effectiveness analysis reports that pre-procedural TEE is unlikely to be cost-effective in an unselected population. Therefore, there is a need to better identify patients with increased pretest probability of LAA thrombus in order to improve the cost-benefit ratio of the procedure. It is our hope that identification of additional clinical and echocardiographic characteristics; in addition to established risk factors, can help guide the selection process for utilization of pre-procedural TEE

REFERENCES

1 **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; **130**: e199-e267 [PMID: 24682347 DOI: 10.1161/CIR.0000000000000041]

2 **Kirchhof P**, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in

collaboration with EACTS. *Eur Heart J* 2016; **37**: 2893-2962 [PMID: 27567408 DOI: 10.1093/eurheartj/ehw210]

3 **Al-Saady NM**, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999; **82**: 547-554 [PMID: 10525506 DOI: 10.1136/hrt.82.5.547]

4 **Manning WJ**, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, Johnson RG, Douglas PS. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995; **123**: 817-822 [PMID: 7486462 DOI: 10.7326/0003-4819-123-11-199512010-00001]

5 **Manning WJ**, Silverman DI, Gordon SP, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. *N Engl J Med* 1993; **328**: 750-755 [PMID: 8437595 DOI: 10.1056/NEJM199303183281102]

6 **Klein AL**, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001; **344**: 1411-1420 [PMID: 11346805 DOI: 10.1056/NEJM200105103441901]

7 **Calkins H**, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017; **14**: e275-e444 [PMID: 28506916 DOI: 10.1016/j.hrthm.2017.05.012]

8 **Wallace TW**, Atwater BD, Daubert JP, Voora D, Crowley AL, Bahnson TD, Hranitzky PM. Prevalence and clinical characteristics associated with left atrial appendage thrombus in fully anticoagulated patients undergoing catheter-directed atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2010; **21**: 849-852 [PMID: 20158561 DOI: 10.1111/j.1540-8167.2010.01729.x]

9 **Puwanant S**, Varr BC, Shrestha K, Hussain SK, Tang WH, Gabriel RS, Wazni OM, Bhargava M, Saliba WI, Thomas JD, Lindsay BD, Klein AL. Role of the CHADS2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. *J Am Coll Cardiol* 2009; **54**: 2032-2039 [PMID: 19926009 DOI: 10.1016/j.jacc.2009.07.037]

10 **Yamamoto M**, Seo Y, Kawamatsu N, Sato K, Sugano A, Machino-Ohtsuka T, Kawamura R, Nakajima H, Igarashi M, Sekiguchi Y, Ishizu T, Aonuma K. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circ Cardiovasc Imaging* 2014; **7**: 337-343 [PMID: 24523417 DOI: 10.1161/CIRCIMAGING.113.001317]

11 **Calvo N**, Mont L, Vidal B, Nadal M, Montserrat S, Andreu D, Tamborero D, Pare C, Azqueta M, Berruezo A, Brugada J, Sitges M. Usefulness of transoesophageal echocardiography before circumferential pulmonary vein ablation in patients with atrial fibrillation: is it really mandatory? *Europace* 2011; **13**: 486-491 [PMID: 21186230 DOI: 10.1093/europace/euq456]

12 **Scherr D**, Dalal D, Chilukuri K, Dong J, Spragg D, Henrikson CA, Nazarian S, Cheng A, Berger RD, Abraham TP, Calkins H, Marine JE. Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2009; **20**: 379-384 [PMID: 19017348 DOI: 10.1111/j.1540-8167.2008.01336.x]

13 **McCready JW**, Nunn L, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow AW. Incidence of left atrial thrombus prior to atrial fibrillation ablation: is pre-procedural transoesophageal echocardiography mandatory? *Europace* 2010; **12**: 927-932 [PMID: 20304842 DOI: 10.1093/europace/euq074]

14 **Savarese G**, Giugliano RP, Rosano GM, McMurray J, Magnani G, Filippatos G, Dellegrottaglie S, Lund LH, Trimarco B, Perrone-Filardi P. Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure: A Meta-Analysis. *JACC Heart Fail* 2016; **4**: 870-880 [PMID: 27614940 DOI: 10.1016/j.jchf.2016.07.012]

15 **Ruff CT**, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**: 955-962 [PMID: 24315724 DOI: 10.1016/S0140-6736(13)62343-0]

16 **Jaber WA**, Prior DL, Thamilarasan M, Grimm RA, Thomas JD, Klein AL, Asher CR. Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: A transesophageal echocardiographic study. *Am Heart J* 2000; **140**: 150-156 [PMID: 10874278 DOI: 10.1067/mhj.2000.106648]

17 **Seidl K**, Rameken M, Drögemüller A, Vater M, Brandt A, Schwacke H, Bergmeier C, Zahn R, Senges J. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. *J Am Coll Cardiol* 2002; **39**: 1436-1442 [PMID: 11985904 DOI: 10.1016/S0735-1097(02)01785-0]

18 **Wyrembak J**, Campbell KB, Steinberg BA, Bahnson TD, Daubert JP, Velazquez EJ, Samad Z, Atwater BD. Incidence and Predictors of Left Atrial Appendage Thrombus in Patients Treated With Nonvitamin K Oral Anticoagulants Versus Warfarin Before Catheter Ablation for Atrial Fibrillation. *Am J Cardiol* 2017; **119**: 1017-1022 [PMID: 28153350 DOI: 10.1016/j.amjcard.2016.12.008]

19 **Frenkel D**, D'Amato SA, Al-Kazaz M, Markowitz SM, Liu CF, Thomas G, Ip JE, Sharma SK, Yang H, Singh P, Lerman BB, Cheung JW. Prevalence of Left Atrial Thrombus Detection by Transesophageal Echocardiography: A Comparison of Continuous Non-Vitamin K Antagonist Oral Anticoagulant Versus Warfarin Therapy in Patients Undergoing Catheter Ablation for Atrial Fibrillation. *JACC Clin Electrophysiol* 2016; **2**: 295-303 [PMID: 29766887 DOI: 10.1016/j.jacep.2016.01.004]

20 **Da Costa A**, Delolme C, Guichard JB, Gerbay A, Pierrard R, Romeyer-Bouchard C, Isaaz K. Comparison of prevalence and management of left atrial appendage thrombi under old and new anticoagulants prior to left atrial catheter ablation. *Am Heart J* 2017; **193**: 8-15 [PMID: 29129259 DOI: 10.1016/j.ahj.2017.07.016]

21 **Flaker G**, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, Zhu J, Mohan P, Garcia D, Bartunek J, Vinereanu D, Husted S, Harjola VP, Rosenqvist M, Alexander JH, Granger CB; ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol* 2014; **63**: 1082-1087 [PMID: 24211508 DOI: 10.1016/j.jacc.2013.09.062]

22 **Balouch M**, Gucuk Ipek E, Chrispin J, Bajwa RJ, Zghaib T, Berger RD, Ashikaga H, Calkins H, Nazarian S, Marine JE, Spragg DD. Trends in Transesophageal Echocardiography Use, Findings, and Clinical Outcomes in the Era of Minimally Interrupted Anticoagulation for Atrial Fibrillation Ablation. *JACC Clin Electrophysiol* 2017; **3**: 329-336 [PMID: 29759444 DOI: 10.1016/j.jacep.2016.09.011]

23 **Marzec LN**, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation. *J Am Coll Cardiol* 2017; **69**: 2475-2484 [PMID: 28521884 DOI: 10.1016/j.jacc.2017.03.540]

24 **Lip GY**, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137**: 263-272 [PMID: 19762550 DOI: 10.1378/chest.09-1584]

25 **Fatkin D**, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994; **23**: 961-969 [PMID: 8106703 DOI: 10.1016/0735-1097(94)90644-0]

26 **Dobashi S**, Fujino T, Ikeda T. Use of apixaban for an elderly patient with left atrial thrombus. *BMJ Case Rep* 2014; **2014**: pii: bcr2014203870 [PMID: 24962484 DOI: 10.1136/bcr-2014-203870]

27 **Miwa Y**, Minamishima T, Sato T, Sakata K, Yoshino H, Soejima K. Resolution of a warfarin and dabigatran-resistant left atrial appendage thrombus with apixaban. *J Arrhythm* 2016; **32**: 233-235 [PMID: 27354873 DOI: 10.1016/j.joa.2016.01.009]

28 **Corrado G**, Tadeo G, Beretta S, Tagliagambe LM, Manzillo GF, Spata M, Santarone M. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. *Chest* 1999; **115**: 140-143 [PMID: 9925075 DOI: 10.1378/chest.115.1.140]

29 **Cappato R**, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; **3**: 32-38 [PMID: 19995881 DOI: 10.1161/CIRCEP.109.859116]

30 **Awad S**, Mohajer K, Baranchuk A, Pal RS. Current clinical practice of transesophageal echocardiography and cardiac computed tomography prior to atrial fibrillation ablation in Canada. *Int J Cardiol* 2015; **189**: 300-301 [PMID: 25967570 DOI: 10.1016/j.ijcard.2015.03.318]

31 **Gula LJ**, Massel D, Redfearn DP, Krahn AD, Yee R, Klein GJ, Skanes AC. Impact of routine transoesophageal echocardiography on safety, outcomes, and cost of pulmonary vein ablation: inferences drawn from a decision analysis model. *Europace* 2010; **12**: 1550-1557 [PMID: 20716548 DOI: 10.1093/europace/euq306]

32 **Di Biase L**, Briceno DF, Trivedi C, Mohanty S, Gianni C, Burkhardt JD, Mohanty P, Bai R, Gunda S, Horton R, Bailey S, Sanchez JE, Al-Ahmad A, Hranitzky P, Gallinghouse GJ, Reddy YM, Zagrodzky J, Hongo R, Beheiry S, Lakkireddy D, Natale A. Is transesophageal echocardiogram mandatory in patients undergoing ablation of atrial fibrillation with uninterrupted novel oral anticoagulants? Results from a prospective multicenter registry. *Heart Rhythm* 2016; **13**: 1197-1202 [PMID: 26994940 DOI: 10.1016/j.hrthm.2016.03.024]

P- Reviewer: Hochholzer W, Kharlamov AN
S- Editor: Ji FF **L- Editor:** A **E- Editor:** Wu YXJ

Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 March 26; 11(3): 94-125

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 3 March 26, 2019

Contents

World Journal of Cardiology

Volume 11 Number 3 March 26, 2019

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
March 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 March 26; 11(3): 94-102

DOI: 10.4330/wjc.v11.i3.94

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Improved scoring system for the electrocardiographic diagnosis of left ventricular hypertrophy

Eric D Braunstein, Lori B Croft, Jonathan L Halperin, Steve L Liao

ORCID number: Eric D Braunstein (0000-0001-5290-9089); Lori B Croft (0000-0003-3962-8922); Jonathan L Halperin (0000-0002-8318-5471); Steve L Liao (0000-0002-8161-0294).

Author contributions: Braunstein ED designed the project, performed data collection and statistical analysis, and drafted the manuscript; Croft LB assisted with data collection and provided critical review of the manuscript; Halperin JL provided critical review of the manuscript; Liao SL designed the project, provided study oversight, and provided critical review of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Human Research Protection Program at the Icahn School of Medicine at Mount Sinai in October 2015.

Informed consent statement: A waiver of informed consent was granted by the institutional review board due to the retrospective nature of the study, minimal risk to study subjects, and impracticality of obtaining consent from all subjects.

Conflict-of-interest statement: The authors have no relevant sources of funding or conflicts of interest to disclose.

STROBE statement: The guidelines of the STROBE Statement have been adopted for this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and

Eric D Braunstein, Division of Cardiology, Department of Medicine, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York, NY 10467, United States

Lori B Croft, Jonathan L Halperin, Steve L Liao, Division of Cardiology, Icahn School of Medicine at Mount Sinai, Mount Sinai Medical Center, New York, NY 10029, United States

Corresponding author: Steve L. Liao, MD, Assistant Professor, Division of Cardiology, Mount Sinai Medical Center, 1176 5th Avenue, New York, NY 10029, United States.
steve.liao@mountsinai.org
Telephone: +1-212-4271540
Fax: +1-212-4107196

Abstract

BACKGROUND

Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease and a risk factor for cardiovascular morbidity and mortality, but available methods for its electrocardiographic (ECG) diagnosis have limited accuracy.

AIM

To investigate findings associated with LVH on ECG and developed an improved system for the diagnosis of LVH.

METHODS

A cohort study comparing ECG data acquired within 30 days of transthoracic echocardiography (TTE) was performed. Multivariate regression analysis identified ECG findings associated with increased LV mass and mass index. A scoring system was derived and performance compared to established criteria for LVH.

RESULTS

Data from 5486 outpatients with TTEs and corresponding ECGs were included in the derivation cohort, 333 (6.1%) of whom had LVH by TTE. In the primary regression analysis, findings associated with LVH were amplitudes of Q in V3, R in V6, S in V3, T in V6, P' in V1, P in V6, as well as R and T-axis discordance, R peak time in V6, QRS duration, weight, height, sex, and age. From this we derived a score consisting of 5 criteria, and validated it in an independent cohort of 910 patients. With a threshold of 1.5 points, sensitivity and specificity were 67.9% and 81.4%, and 62.5% and 83.2% in the derivation and validation cohorts, respectively. With a threshold of 2 points, sensitivity and specificity were 42.3% and 93.0%, and 37.5% and 93.4% in these cohorts.

fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: November 19, 2018
Peer-review started: November 19, 2018
First decision: December 10, 2018
Revised: December 12, 2018
Accepted: December 24, 2018
Article in press: December 24, 2018
Published online: March 26, 2019

P-Reviewer: Gulel O, Hatipoglu S
S-Editor: Yan JP
L-Editor: A
E-Editor: Zhang YL

CONCLUSIONS
This score had superior sensitivity for detection of LVH by ECG while making a modest sacrifice in specificity compared to conventional criteria.

Key words: Left ventricular hypertrophy; Electrocardiogram; Echocardiogram; Diagnostic criteria; Scoring system

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In this study we performed analysis of a large number of echocardiograms with corresponding electrocardiographic (ECG), and though multivariate regression analysis identified ECG findings associated with left ventricular hypertrophy (LVH). Using these findings, a five-item scoring system was developed to diagnose LVH on ECG. The performance characteristics of the system were compared to several conventional criteria, and it was seen to have superior sensitivity, including in an independent validation cohort. Using this scoring system, we believe that the diagnosis of LVH on ECG will be more clinically applicable in certain patient populations given the enhanced sensitivity of this test.

Citation: Braunstein ED, Croft LB, Halperin JL, Liao SL. Improved scoring system for the electrocardiographic diagnosis of left ventricular hypertrophy. *World J Cardiol* 2019; 11(3): 94-102
URL: https://www.wjgnet.com/1949-8462/full/v11/i3/94.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i3.94

INTRODUCTION

Left ventricular hypertrophy (LVH) is a common consequence of various cardiovascular diseases, and has been associated with increased risks of morbidity and mortality. Specifically, LVH has been associated with several adverse cardiac outcomes including heart failure, angina pectoris, myocardial infarction, and sudden cardiac death[1-5]. Upwards of 30 electrocardiographic (ECG) criteria have been proposed for diagnosis of LVH[6], but most have low sensitivity in the general population. Transthoracic echocardiography (TTE) is often required to confirm the diagnosis[7,8]. Antihypertensive treatment can promote regression of LVH and prevent adverse cardiovascular events in patients with hypertension[9,10], and TTE is preferred over ECG to assess myocardial mass in this setting[8,11], although detection of left ventricular electrical remodeling may have prognostic implications independent of mass[12-16]. Despite the availability of multiple criteria for ECG diagnosis of LVH, relatively few are widely implemented in clinical practice. Several models have been correlated with echocardiographic, cardiac magnetic response imaging, and autopsy measurements of LV mass, but these have not been integrated into commonly used ECG analysis software, while others are too complex for practical use. The aim of this study was to identify ECG findings associated with increased LV mass and develop an improved and easy to use scoring system to facilitate the diagnosis of and screening for LVH.

MATERIALS AND METHODS

Data collection and processing

The Institutional Review Board approved the protocol in October 2015. Clinical data available in the information systems of the Mount Sinai Medical Center, a large urban academic medical center, were derived from two sources, one for ECGs, and another for echocardiographic data. Data from all standard 12-lead ECGs recorded between December 1, 2013 and January 31, 2015 was exported from the MUSE v8.0 SP2 system (GE Healthcare, Chicago, IL, United States). Computer performed measurements including ventricular rate, PR interval, QRS duration, R-axis, T-axis, P-, P′- (second phase of P-wave), Q-, R-, S-, R′- and T-wave maximum amplitude, duration, area and peak time, maximum and minimum ST-segment level, and ST-segment deviation at J-point, mid-ST-segment and end-ST-segment. Measurements in each standard lead

were averaged across the ECG by the MUSE software. ECGs were not manually verified or measured and all ECGs except for those noted below were included in analyses.

Data from all outpatient TTEs acquired from patients ≥ 18 yr of age between January 1, 2014 and December 31, 2014 were exported from a proprietary echocardiography reporting system. Two-dimensional echocardiograms were performed using Siemens SC-2000, Siemens Acuson Sequoia, Phillips IE-33 or GE Vivid 7 cardiac ultrasound equipment. Measurements of the left ventricle were made in the parasternal long-axis view perpendicular to the axis at or immediately below the level of the mitral valve leaflet tips. Internal ventricular dimensions were measured linearly from two dimensional (2D) echocardiographic images to avoid oblique sections, or from 2D-guided M-mode echocardiography. Posterior and septal wall thickness and left ventricular end-diastolic and end-systolic diameters were measured according to the recommendations of the American Society of Echocardiography[17]. Measurements were made during routine clinical interpretation of the echocardiogram and were not repeated or verified for the purposes of this study. Demographic data including age, sex, height, and weight (patient reported at the time of the study) were also collected.

Left ventricular mass was calculated using the method of Devereux *et al*[18]. Body mass index, body surface area, and LV mass index were calculated using the standard methods. LVH was defined by LV mass index one standard deviation above the mean, stratified by sex (145 g/m^2 for males, 125 g/m^2 for females). Data from the first 10 mo of the study period comprised the derivation set, while those from the final 2 mo were used to validate the derived model.

TTEs and ECGs were matched by selecting the ECG obtained most proximate to each TTE. When patients had more than one TTE during the study period, only the first was included for analyses. Echocardiograms with incomplete demographic or measurement data and those without a corresponding ECG within 30 d were excluded. Also excluded were ECGs showing complete (but not incomplete) left bundle branch block or a paced rhythm, as identified by the MUSE software and confirmed by a board-certified cardiologist.

Statistical analysis

A multivariate linear regression model was constructed using LV mass as the endpoint and covariates including P-, P'- (second phase of P-wave), Q-, R-, S-, R'- and T-wave amplitudes in each lead, R-wave peak time in each lead (intrinsicoid deflection), maximum and minimum ST levels in each lead, ST-segment deviation at the J-point and mid-ST-segment in each lead, QRS duration, PR interval, difference between R-axis and T-axis, and patient weight, height, sex and age (152 degrees of freedom). A similar model using LV mass index as the endpoint yielded similar output with reduced fit parameters. Another model constructed using wave-complex areas (as opposed to maximum amplitudes) was less strongly associated with the endpoint. Covariates most strongly correlated with LV mass (based on regression *P*- and *t*-values, and a *P*-value threshold set at $P \leq 0.005$ in the linear regression model) were retained for multivariate logistic regression analysis. Additional logistic regression models were constructed stratifying the data set by sex in order to assess differences in ECG findings between sexes.

As several of the amplitudes and durations included in the model are correlated, we minimized effects of multicollinearity by calculating variance inflation factors (VIF) for covariates likely to be correlated and manually removing colinear covariates (VIF > 5) in a stepwise fashion while maximizing fit parameters of the overall model. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States).

Scoring system development

A scoring system was derived using scaled and rounded regression Wald chi-square and beta-coefficients similar to the method of Sullivan *et al*[19]. Thresholds for the prediction model were developed based on standard deviations of the covariates, established LVH criteria, and iteration. The derived diagnostic criteria as well as several accepted criteria for LVH (Cornell[20], Sokolow-Lyon[21], Cornell product[22], Sokolow-Lyon product[23], Gubner-Ungerleider[24], Sum-of-12-lead[25], Romhilt-Estes[26], Framingham-adjusted Cornell[27], R-wave amplitude in aVL, Peguero-Lo Presti[28]) were evaluated. Sensitivity and specificity were calculated for each criterion in both cohorts, along with 95% confidence intervals using binomial proportions in the derivation cohort. Positive and negative predictive values were also calculated.

RESULTS

Patient characteristics

During the 1-yr inclusion period, 11087 outpatient TTEs were obtained, while 202706 ECGs were recorded during the bracketed 14-mo period for the study. After matching each TTE with available ECGs and excluding those with incomplete data (n = 570), subsequent TTE examinations in the same patients (695), those with left bundle-branch block (128) or paced rhythm (235), and those without corresponding ECGs within 30 days (1396), a total of 5486 cases were entered into the derivation cohort. Applying the same criteria, 910 cases comprised the validation cohort. Patients characteristics were similar between both cohorts, and patients included in analyses in the cohorts had mean age around 60, were on average overweight but not obese, and were about half male (Table 1).

Regression results

In the derivation cohort, 333 patients (6.1%) had LVH as defined by the foregoing TTE criteria. Utilizing the full set of 152 covariates available, multivariate logistic analysis for the endpoint of LV mass yielded a regression coefficient of 0.502. The most highly associated variables ($P \leq 0.005$) included Q-wave amplitude in V3, R-wave amplitude in V6, S-wave amplitude in V3, QRS duration, difference between R and T-wave axis, R-wave peak time in V6, T-wave peak amplitude in V6 (inversely associated with the outcome), P′-wave amplitude in V1 (inversely associated), P-wave amplitude in V6, weight, height, sex, and age. Using these covariates, a logistic regression model was constructed for LVH (Table 2) with area under the ROC curve estimated by the c-statistic at 0.867.

Scoring system development and evaluation

To derive a scoring system (Table 3), we summed the amplitude predictors and set a threshold of two standard deviations above the mean in the derivation cohort data, distinguished by sex. The QRS duration threshold was set arbitrarily at 100 ms, the upper limit of normal. The absence of a positive T-wave component in V6 was set based on the negative association of maximum T-wave amplitude in the regression model. Definition of R- and T-wave precordial axis discordance was set at ± 75°, although similar results were seen at ± 45° and ± 90°. P-wave negative deflection greater than positive deflection in V1 was used due to the negative association of P′-wave amplitude in V1 in the model. Despite its association with LVH in the regression model, patient height was omitted from the scoring system to enhance clinical convenience.

Additional logistic regression models were constructed stratifying the data set by sex in order to assess differences in ECG findings between sexes (Table 4). Findings in these cohorts were similar to those in the overall analysis; however, notably discordance between R and T-wave axis was only found to be associated with LVH in men but not in women.

The derived prediction model and other criteria for ECG diagnosis of LVH were evaluated in the derivation and validation cohorts, calculating sensitivity and specificity as well as positive and negative predictive values (Table 5). Using a threshold of 2 points, the score exhibited sensitivity superior to previous methods while sacrificing little to no specificity; using a cutoff of 1.5 points, the score improved sensitivity while maintaining specificity > 80%. Looked at another way, the score was also seen to have superior positive predictive values utilizing a cutoff of 2 points than established criteria while maintaining a high negative predictive value; all positive predictive values in this study for the derived and established criteria were relatively low because of the low overall prevalence of LVH in the studied population.

DISCUSSION

In this study of 5486 patients undergoing TTE within 30 d of a 12-lead ECG, several ECG findings were associated with increased LV mass from a set of 147 ECG variables, many of which are included in established criteria for LVH, along with several others heretofore unrecognized. In our model, QRS duration was independently associated with LVH, even when the voltage QRS duration products were tested as the other covariates. For this reason, we included QRS duration rather than a voltage duration product as an independent predictor. This independent association suggests that voltage duration products may not be optimal for identification of LVH. In contrast to established schema, R-wave amplitude in lead aVL was not independently associated with echocardiographic LVH in this analysis,

Table 1 Patient characteristics

Characteristic - no. (%) unless noted	Derivation cohort (*n* = 5486)	Validation cohort (*n* = 910)
Age (mean ± SD)	59.1 ± 15.8	58.6 ± 15.2
18-29	265 (4.8)	30 (3.3)
30-39	408 (7.4)	91 (10.0)
40-49	708 (12.9)	105 (11.5)
50-59	1295 (23.6)	224 (24.6)
60-69	1358 (24.8)	242 (26.6)
70 +	1452 (26.5)	218 (24.0)
Male sex	2869 (52.3)	448 (49.2)
Body mass index		
Mean ± SD	28.0 ± 6.6	28.5 ± 6.5
Median (range)	26.9 (12.9-75.2)	27.5 (15.8-66.1)
Left ventricular mass by echocardiogram		
Mean ± SD	167.2 ± 62.1	173.3 ± 64.8
Median (intraquartile range)	155.4 (123.3-200.4)	163.0 (124.1-205.0)
Left ventricular hypertrophy present by echocardiogram	333 (6.1)	80 (8.6)
Time between echocardiogram and electrocardiogram in days (mean, intraquartile range)	6.7 (0-13)	5.9 (0-11)

possibly due to interactions with precordial lead amplitude.

P-wave amplitude in V6 and negative P-terminal force in V1 were associated with LVH, likely reflecting left atrial pathology. P-wave duration (encompassing both positive and negative components), however, was not associated with LVH. These variations suggest the need for further study of the ECG manifestations of left atrial conduction delay. Unlike previous systems for identification of LVH, which typically include only R and S-wave amplitudes, we found an association of Q-wave in addition to S-wave amplitude in V3 with LVH. This could indicate an association of the total negative QRS vector in this lead, rather than the S-wave alone, with LVH. Lead V3 was found to be more highly associated with LVH than lead V1 or V2 as is seen in many other LVH criteria; this may be due to the location of lead V3 being more in line with the LV septum and therefore a better representation of its thickness.

An additional analysis looking at differences in ECG findings associated with LVH between sexes found that although most factors remained similar, R- and T-axis discordance was found to be associated with LVH in men but not in women. This may highlight differences in electrical remodeling as it relates to repolarization between sexes, and could be the subject of further study.

Conventional ECG criteria have low sensitivity for diagnosis of LVH. Several regression equations have been developed to estimate LV mass directly, but are impractical except for implementation in computerized ECG software, and correlate poorly with measurements of LV mass made by echocardiography, cardiac magnetic resonance imaging (MRI), or autopsy. The scheme we derived was evaluated using two thresholds based on distinct objectives. A threshold of 2 points yielded high specificity (approximately 93%) with improved sensitivity (approximately 40%), while a cutoff of 1.5 points markedly improved sensitivity (approximately 65%) while maintaining sensitivity at > 80%. The higher limit may be preferred for general use, while the lower value may be more applicable to patients with hypertension or clinical conditions associated with LVH. Further studies are needed to assess the utility of either cut-point for serial assessments in the same individual, or to identify those who may benefit from echocardiography or other imaging studies to assess LV mass or its response to therapeutic interventions.

The derived scoring system was compared to conventional criterial for the ECG diagnosis of LVH and our system was found to have increased sensitivity with a modest sacrifice in sensitivity. Most conventional LVH criteria have high specificity but low sensitivity which limits use as a screening test in a general population. The enhanced sensitivity of the presented scoring system may introduce improvement to clinical practice by aiding with patient risk stratification and preventing unnecessary additional testing.

An important limitation of this study was inclusion of only ambulatory outpatients. This was because fluctuating clinical circumstances in acute ill hospital inpatient could influence echocardiographic measurements of wall thickness or produce

Table 2 Multivariate logistic regression analysis for left ventricular hypertrophy

Characteristic	Wald Chi-Square	*P* value
Q-wave amplitude in V3	19.3	$P < 0.0001$
R-wave amplitude in V6	39.7	$P < 0.0001$
S-wave amplitude in V3	135	$P < 0.0001$
QRS Duration	115.4	$P < 0.0001$
Discordant R-axis and T-axis (difference ≤ 75 or > 75)	14.6	$P = 0.0001$
Maximum (positive deflection) T-wave amplitude in V6	38.5	$P < 0.0001$
Maximum P'-wave amplitude in V1	18.5	$P < 0.0001$
P-wave peak amplitude in V6	0.19	$P = 0.659$
Weight	0.008	$P = 0.927$
Height	25.2	$P < 0.0001$
Sex	6.3	$P = 0.012$
Age	0.03	$P = 0.864$

discordance with ECG's recorded within the requisite 30-d window. It is also worth noting that the ECG data we used was measured automatically, while the echocardiographic measurements were obtained manually. Echocardiographic measurement, while regarding as being relatively accurate, are not the gold standard for LV mass measurement; more accurate measurements of LV mass such as cardiac MRI were not able to be used in this study. We also were not able to collect data on patient race, cardiovascular risk factors, or comorbidities (*e.g.*, hypertension, diabetes), all of which are factors that may influence ECG estimations of LVH. Finally, while the Working Group on ECG diagnosis of LVH suggested that research on LVH focus on the potential relationship of electrical remodeling to clinical outcomes[13], we lack long-term clinical follow-up of patients to correlate the LVH score with such outcomes.

In conclusion, we identified several ECG findings that are associated with LVH and incorporated them into a score to improve the ECG diagnosis of this common condition. The scoring system may help improve clinical utility by enhancing sensitivity whilst displaying a modest sacrifice in specificity compared to conventional criteria. Further studies are needed to determine whether this scheme optimally reflects changes in the electrical characteristics of the myocardium over time, and whether it may have value for predicting cardiovascular events that are not exposed by measurement of ventricular mass alone.

ACKNOWLEDGMENTS

The authors thank Ejaz Siddiqui for assistance with obtaining ECG data.

Table 3 Components of the electrocardiographic diagnostic score for left ventricular hypertrophy

Criteria	Number of points
Sum of R-wave amplitude in V6 + S-wave amplitude in V3 + Q-wave amplitude in V3 > 4.0 mV in males and 3.2 mV in females	1
QRS duration > 100 ms	1
Absence of positive component of T-wave in V6 (maximum T-wave amplitude < 0) when overall QRS vector in V6 positive (i.e., R-wave larger than S-wave)	1
Discordant limb lead R- and T-wave axis (R- minus T-wave axis ≤ 75 or > 75 degrees)	0.5
Amplitude of negative terminal p-wave deflection in V1 greater than amplitude of positive deflection	0.5

Table 4 Multivariate logistic regression analysis for left ventricular hypertrophy stratified by sex

	Male (*n* = 2869)		Female (*n* = 2617)	
Characteristic	**Wald Chi-Square**	***P* value**	**Wald Chi-Square**	***P* value**
Q-wave amplitude in V3	14.7	*P* = 0.0001	5.0	*P* = 0.025
R-wave amplitude in V6	25.5	*P* < 0.0001	10.0	*P* = 0.001
S-wave amplitude in V3	77.0	p < 0.0001	53.6	*P* < 0.0001
QRS Duration	62.2	*P* < 0.0001	51.2	*P* < 0.0001
Discordant R-axis and T-axis (difference ≤ 75 or > 75)	17.8	p < 0.0001	0.63	*P* = 0.426
Maximum (positive deflection) T-wave amplitude in V6	16.0	*P* < 0.0001	26.1	*P* < 0.0001
Maximum P'-wave amplitude in V1	9.4	*P* = 0.002	4.6	*P* = 0.031
P-wave peak amplitude in V6	1.0	*P* = 0.314	3.5	*P* = 0.061
Weight	0.50	*P* = 0.477	0.9	*P* = 0.340
Height	6.8	*P* = 0.009	21.8	*P* < 0.0001
Age	1.4	*P* = 0.245	1.06	*P* = 0.303

Table 5 Sensitivity, specificity, and positive and negative predictive values of selected electrocardiographic criteria for left ventricular hypertrophy

		Derivation cohort				Validation cohort	
Criteria	**Cutoff**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV**	**NPV**	**Sensitivity**	**Specificity**
Derived Criteria	1.5 points	67.9 (62.6-72.9)	81.4 (80.3-82.4)	19.0	97.5	62.5	83.2
""	2 points	42.3 (37.0-47.7)	93.0 (92.3-93.7)	28.2	96.2	37.5	93.4
""	2.5 points	30.0 (25.2-35.3)	96.6 (96.1-97.1)	37.6	95.6	30.0	96.8
Cornell	-	37.8 (32.6-43.1)	92.3 (91.6-93.0)	24.1	95.8	36.2	90.3
Sokolow-Lyon	-	16.5 (12.5-20.5)	95.9 (95.4-96.5)	20.7	94.7	20.0	96.3
Cornell Product		55.0 (49.6-60.3)	88.3 (87.5-89.2)	23.3	96.8	53.8	88.1
Sokolow-Lyon Product		22.5 (18.0-27.0)	95.9 (95.3-96.4)	26.0	95.0	23.8	95.6
Gubner-Ungerleider		27.0 (22.3-31.8)	88.9 (88.0-89.8)	13.6	95.0	27.5	87.7
Sum-of-12-Lead		57.4 (51.9-62.7)	76.1 (74.9-77.3)	13.4	96.5	57.5	77.1
Romhilt-Estes	5 points	35.4 (30.3-40.8)	94.4 (93.7-95.0)	26.2	95.8	35.0	95.0
""	4 points	51.1 (45.5-56.5)	88.2 (87.3-89.0)	21.8	96.5	57.5	90.0
Framingham-adjusted Cornell		42.3 (37.0-47.7)	90.1 (89.3-90.9)	21.7	96.0	51.3	87.6
R-wave amplitude in aVL	1.1 mV	20.1 (16.0-24.8)	92.6 (91.8-93.3)	14.9	94.7	21.3	92.1
Peguero-Lo Presti		24.9 (20.3-29.6)	94.7 (94.1-95.3)	23.3	95.1	26.3	93.5

CI: Confidence interval; PPV: Positive predictive values; NPV: Negative predictive values.

ARTICLE HIGHLIGHTS

Research background

Left ventricular hypertrophy (LVH) is a common manifestation of cardiovascular disease and a risk factor for cardiovascular morbidity and mortality, but available methods for its electrocardiographic (ECG) diagnosis have limited accuracy.

Research motivation

Improvement in the ability of clinicians to diagnose LVH on ECG could aid with patient risk stratification and prevent unnecessary additional testing.

Research objectives

The aim of this study was to investigate findings associated with LVH on ECG and develop an improved system for the diagnosis of LVH.

Research methods

A cohort study comparing ECG data acquired within 30 days of transthoracic echocardiography was performed. Multivariate regression analysis identified ECG findings associated with increased LV mass and mass index. A scoring system was derived and performance compared to established criteria for LVH.

Research results

In regression analysis, findings associated with LVH were amplitudes of Q in V3, R in V6, S in V3, T in V6, P′ in V1, P in V6, as well as R and T-axis discordance, R peak time in V6, QRS duration, weight, height, sex, and age. A score consisting of 5 criteria was derived and validated it in an independent cohort. This score had superior sensitivity for detection of LVH by ECG compared to conventional criteria whilst making a modest sacrifice in specificity compared to conventional criteria.

Research conclusions

We identified several ECG findings that are associated with LVH and incorporated them into a score to improve the ECG diagnosis of this common condition. The scoring system may help improve clinical utility by enhancing sensitivity whilst displaying a modest sacrifice in specificity compared to conventional criteria.

Research perspectives

Further studies are needed to determine whether this scheme optimally reflects changes in the electrical characteristics of the myocardium over time, and whether it may have value for predicting cardiovascular events that are not exposed by measurement of ventricular mass alone.

REFERENCES

1 **Casale PN**, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 1986; **105**: 173-178 [PMID: 2942070 DOI: 10.7326/0003-4819-105-2-173]

2 **Levy D**, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. *Ann Intern Med* 1989; **110**: 101-107 [PMID: 2521199 DOI: 10.7326/0003-4819-110-2-101]

3 **Levy D**, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561-1566 [PMID: 2139921 DOI: 10.1056/NEJM199005313222203]

4 **Koren MJ**, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; **114**: 345-352 [PMID: 1825164 DOI: 10.7326/0003-4819-114-5-345]

5 **Kannel WB**, Cobb J. Left ventricular hypertrophy and mortality--results from the Framingham Study. *Cardiology* 1992; **81**: 291-298 [PMID: 1301257 DOI: 10.1159/000175819]

6 **Hancock EW**, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS, Bailey JJ, Childers R, Gorgels A, Josephson M, Kors JA, Macfarlane P, Mason JW, Pahlm O, Rautaharju PM, Surawicz B, van Herpen G, Wagner GS, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part V: electrocardiogram changes associated with cardiac chamber hypertrophy: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009; **53**: 992-1002 [PMID: 19281932 DOI: 10.1016/j.jacc.2008.12.015]

7 **Ang D**, Lang C. The prognostic value of the ECG in hypertension: Where are we now? *J Hum Hypertens* 2008; **22**: 460-467 [PMID: 18432258 DOI: 10.1038/jhh.2008.24]

8 **Bauml MA**, Underwood DA. Left ventricular hypertrophy: An overlooked cardiovascular risk factor. *Cleve Clin J Med* 2010; **77**: 381-387 [PMID: 20516249 DOI: 10.3949/ccjm.77a.09158]

9 **Schiattarella GG**, Hill JA. Inhibition of hypertrophy is a good therapeutic strategy in ventricular pressure overload. *Circulation* 2015; **131**: 1435-1447 [PMID: 25901069 DOI: 10.1161/CIRCULATIONAHA.115.013894]

10 **Okin PM**, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P,

Edelman JM, Wedel H, Lindholm LH, Dahlöf B; LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343-2349 [PMID: 15547161 DOI: 10.1001/jama.292.19.2343]

11 **Pewsner D**, Jüni P, Egger M, Battaglia M, Sundström J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. *BMJ* 2007; **335**: 711 [PMID: 17726091 DOI: 10.1136/bmj.39276.636354.AE]

12 **Bacharova L**, Schocken D, Estes EH, Strauss D. The role of ECG in the diagnosis of left ventricular hypertrophy. *Curr Cardiol Rev* 2014; **10**: 257-261 [PMID: 24827796 DOI: 10.2174/1573403X10666140514103220]

13 **Bacharova L**, Estes HE, Schocken DD, Ugander M, Soliman EZ, Hill JA, Bang LE, Schlegel TT. The 4th Report of the Working Group on ECG diagnosis of Left Ventricular Hypertrophy. *J Electrocardiol* 2017; **50**: 11-15 [PMID: 27890283 DOI: 10.1016/j.jelectrocard.2016.11.003]

14 **Rautaharju PM**, Soliman EZ. Electrocardiographic left ventricular hypertrophy and the risk of adverse cardiovascular events: a critical appraisal. *J Electrocardiol* 2014; **47**: 649-654 [PMID: 25012077 DOI: 10.1016/j.jelectrocard.2014.06.002]

15 **Estes EH**, Zhang ZM, Li Y, Tereschenko LG, Soliman EZ. The Romhilt-Estes left ventricular hypertrophy score and its components predict all-cause mortality in the general population. *Am Heart J* 2015; **170**: 104-109 [PMID: 26093870 DOI: 10.1016/j.ahj.2015.04.004]

16 **Leigh JA**, O'Neal WT, Soliman EZ. Electrocardiographic Left Ventricular Hypertrophy as a Predictor of Cardiovascular Disease Independent of Left Ventricular Anatomy in Subjects Aged ≥ 65 Years. *Am J Cardiol* 2016; **117**: 1831-1835 [PMID: 27067620 DOI: 10.1016/j.amjcard.2016.03.020]

17 **Lang RM**, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440-1463 [PMID: 16376782 DOI: 10.1016/j.echo.2005.10.005]

18 **Devereux RB**, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450-458 [PMID: 2936235 DOI: 10.1016/0002-9149(86)90771-X]

19 **Sullivan LM, Massaro JM, D'Agostino RB Sr**. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004; **23**: 1631-1660 [PMID: 15122742 DOI: 10.1002/sim.1742]

20 **Casale PN**, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: Validation with autopsy findings. *Circulation* 1987; **75**: 565-572 [PMID: 2949887 DOI: 10.1161/01.cir.75.3.565]

21 **SOKOLOW M**, LYON TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949; **37**: 161-186 [PMID: 18107386 DOI: 10.1016/0002-8703(49)90562-1]

22 **Molloy TJ**, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. *J Am Coll Cardiol* 1992; **20**: 1180-1186 [PMID: 1401620 DOI: 10.1016/0735-1097(92)90376-X]

23 **Okin PM**, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. *J Am Coll Cardiol* 1995; **25**: 417-423 [PMID: 7829796 DOI: 10.1016/0735-1097(94)00371-V]

24 **Ungerleider HE**, Gubner R. The Q3 and QS3 deflections in the electrocardiogram; criteria and significance. *Am Heart J* 1947; **33**: 807-818 [PMID: 20242367 DOI: 10.1016/0002-8703(47)90026-4]

25 **Dollar AL**, Roberts WC. Usefulness of total 12-lead QRS voltage compared with other criteria for determining left ventricular hypertrophy in hypertrophic cardiomyopathy: analysis of 57 patients studied at necropsy. *Am J Med* 1989; **87**: 377-381 [PMID: 2529761 DOI: 10.1016/S0002-9343(89)80817-4]

26 **Romhilt DW**, Estes EH. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J* 1968; **75**: 752-758 [PMID: 4231231 DOI: 10.1016/0002-8703(68)90035-5]

27 **Norman JE**, Levy D, Campbell G, Bailey JJ. Improved detection of echocardiographic left ventricular hypertrophy using a new electrocardiographic algorithm. *J Am Coll Cardiol* 1993; **21**: 1680-1686 [PMID: 8496537 DOI: 10.1016/0735-1097(93)90387-G]

28 **Peguero JG**, Lo Presti S, Perez J, Issa O, Brenes JC, Tolentino A. Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy. *J Am Coll Cardiol* 2017; **69**: 1694-1703 [PMID: 28359515 DOI: 10.1016/j.jacc.2017.01.037]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 March 26; 11(3): 103-119

DOI: 10.4330/wjc.v11.i3.103

ISSN 1949-8462 (online)

SYSTEMATIC REVIEWS

Risk factors for sudden cardiac death to determine high risk patients in specific patient populations that may benefit from a wearable defibrillator

Hilal Mohammed Khan, Stephen J Leslie

ORCID number: Hilal Mohammed Khan (0000-0003-0412-2227); Stephen J Leslie (0000-0002-1403-4733).

Author contributions: Khan HM and Leslie SJ contributed equally to this work; designed research; performed research; and wrote the paper.

Conflict-of-interest statement: The authors have no conflicts of interest to declare in relation to this manuscript.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: January 6, 2019
Peer-review started: January 8, 2019
First decision: January 21, 2019
Revised: January 27, 2019
Accepted: March 16, 2019
Article in press: March 16, 2019
Published online: March 26, 2019

Hilal Mohammed Khan, Stephen J Leslie, Cardiac Unit, Raigmore Hospital, Inverness IV2 3UJ, United Kingdom

Stephen J Leslie, Department of Diabetes and Cardiovascular Science, University of the Highlands and Islands, The Centre for Health Science, Old Perth Road, Inverness IV2 3JH, United Kingdom

Corresponding author: Stephen J Leslie, FRCP (C), MBBS, MRCP, PhD, Professor, Cardiac Unit, Raigmore Hospital, Inverness IV2 3UJ, United Kingdom. stephen.leslie@nhs.net
Telephone: +44-1463-705459

Abstract

BACKGROUND

There is a high risk for sudden cardiac death (SCD) in certain patient groups that would not meet criteria for implantable cardioverter defibrillator (ICD) therapy. In conditions such as hypertrophic cardiomyopathy (HCM) there are clear risk scores that help define patients who are high risk for SCD and would benefit from ICD therapy. There are however many areas of uncertainty such as certain patients post myocardial infarction (MI). These patients are high risk for SCD but there is no clear tool for risk stratifying such patients.

AIM

To assess risk factors for sudden cardiac death in major cardiac disorders and to help select patients who might benefit from Wearable cardiac defibrillators (WCD).

METHODS

A literature search was performed looking for risk factors for SCD in patients post-MI, patients with left ventricular systolic dysfunction (LVSD), HCM, long QT syndrome (LQTS). There were 41 studies included and risk factors and the relative risks for SCD were compiled in table form.

RESULTS

We extracted data on relative risk for SCD of specific variables such as age, gender, ejection fraction. The greatest risk factors for SCD in post MI patients was the presence of diabetes [Hazard ratio (HR) 1.90-3.80], in patient with LVSD was ventricular tachycardia (Relative risk 3.50), in LQTS was a prolonged QTc (HR 36.53) and in patients with HCM was LVH greater than 20 mm (HR 3.10). A proportion of patients currently not suitable for ICD might benefit from a WCD

P-Reviewer: Barik R, Petix NR, Ueda H
S-Editor: Wang JL
L-Editor: A
E-Editor: Zhang YL

CONCLUSION
There is a very high risk of SCD post MI, in patients with LVSD, HCM and LQTS even in those who do not meet criteria for ICD implantation. These patients may be candidates for a WCD. The development of more sensitive risk calculators to predict SCD is necessary in these patients to help guide treatment.

Key words: Sudden cardiac death; Wearable cardiac defibrillators; Myocardial infarction; Hypertrophic cardiomyopathy; Left ventricular systolic dysfunction

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This article looks at the risk factors for sudden cardiac death (SCD) in patients post myocardial infarction, patients with left ventricular systolic dysfunction, patients with hypertrophic cardiomyopathy, patients with long QT syndrome and the relative risk for sudden cardiac death of these risk factors. This is compared to the absolute risk of SCD for these conditions. We reviewed the recommendations from current guidelines and we outline where patients are at high risk for SCD but are not eligible for implantable cardioverter defibrillator implantation. The risk factors identified in this study can be used to select patients who may benefit from Wearable cardiac defibrillators therapy.

Citation: Khan HM, Leslie SJ. Risk factors for sudden cardiac death to determine high risk patients in specific patient populations that may benefit from a wearable defibrillator. *World J Cardiol* 2019; 11(3): 103-119
URL: https://www.wjgnet.com/1949-8462/full/v11/i3/103.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i3.103

INTRODUCTION

Sudden cardiac death (SCD) is a major global health problem estimated to account for 15%-20% of death[1]. The mechanism of SCD has changed substantially over the last decade with ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) accounting for between 23%-36% of out-of-hospital cardiac arrests[2,3]. This compares to 75% of cases of SCD in the 1980's and early 1990's[4,5]. The decline in SCD due to VT/VF is partly due to improved medical care such as the use of beta blockers and implantable cardioverter defibrillators (ICD)[6,7]. Thus VF and pulseless VT are potentially treatable heart rhythms particularly if patients are given an early DC shock with return of an organised rhythm in up to 70% of cases after a single biphasic shock[8]. This has led to the development of multiple measures such as automated external defibrillators in public places, ICD therapy and wearable cardioverter defibrillators (WCD) to reduce the rate of preventable death from VF/VT.

History of defibrillation

The first successful closed chest direct current cardioversion of ventricular fibrillation was performed by Paul Zoll in the 1950's[9]. This was initially a monophasic shock but more recently biphasic shocks are used. Biphasic waveforms have superior efficacy to monophasic pulses[8] and the European resuscitation council recommend a first shock at 150-200 J with subsequent shocks at a higher energy level if the device allows and the arrhythmia remains uncorrected[10]. Return of sinus rhythm and spontaneous circulation after administration of biphasic shocks occurs in up to 70% in patients with VF or VT[8]. This highlights the high efficacy of this relatively simple treatment.

The first ICD was implanted in a patient in 1980 by Mirowski *et al*[11]. There have since been multiple studies proving the benefit of ICDs in preventing SCD and reducing all-cause mortality. These include primary prevention studies which show a reduction in mortality from SCD of between 23%-54%[12-16](Table 1) and secondary prevention studies which show a reduction in mortality from SCD of between 20%-28%[17-19](Table 2). Current guidelines based on the results of these and other studies recommend the insertion of ICD in patients more than 40 d post myocardial infarction (MI) with severe LVSD (ejection fraction less than 35%), patients with severe LVSD and in several other situations such as high risk hypertrophic cardiomyopathy (HCM) patients, patients with long QT syndrome (LQTS) with a history of cardiac arrest.

These guidelines advise against inserting an ICD for patients who survive sustained VT or VF within the first 48 h of an MI unless they have pre-existing LV impairment and are on optimal medical therapy already or they have incomplete revascularisation, as it is felt that tachyarrhythmia within this period is most likely due to the acute coronary obstruction and cardiac injury[20].

In other patients an ICD may not be possible due to infection or lack of vascular access or patient preference. Thus, some high risk patients who would warrant an ICD do not have one. In order to address this, the WCD was developed. The WCD has been in development since 1986 and had been tested for 17 years prior to it receiving the Food and Drug Administration approval in 2002[21]. The WCD is a device contained within a vest worn under a patient's clothes which records a patient's rhythm and delivers a shock if a shockable rhythm occurs[22]. This has provided a much lower risk solution to ICD implantation in selected patients. Current guidelines recommend considering a WCD or ICD post MI within 40 d of their MI in patients with incomplete revascularisation, VT or VF > 48 h post MI or pre-existing LVSD[23]. Additional groups of patients that could benefit from a WCD include patients with channelopathies such as LQTS who have not suffered a VT or VF event but have high risk features, patients with HCM who have intermediate risk features but not yet achieving criteria for ICD implantation, and also patients with infected ICDs could be offered a WCD once their ICD has been removed and they are awaiting ICD re-implantation. WCD do however come with a risk of inappropriate shocks and their efficacy can be reduced due to a lack of patient compliance.

The aim of this review is to use existing literature to identify risk factors for SCD that may help identify patients who may benefit from a WCD and to discuss the potential role that WCDs could play in reducing the risk of SCD in selected patient groups who do not currently meet guidelines for ICD implantation.

MATERIALS AND METHODS

Study design

This review included available data on risk factors for SCD in predefined patient groups. All odds ratio (OR), relative risk (RR), Exp(b) and hazard ratio (HR) were rounded to 2 decimal places for consistency. OR is a statistic defined as the ratio of the odds of variable A in the presence of variable B and the odds of variable A without the presence of variable B. RR is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. The HR is an expression of the hazard or chance of events occurring in the treatment arm as a ratio of the hazard of the events occurring in the control arm

Inclusion and exclusion criteria

All studies that reported risk factors for SCD in patients with LVSD, LQTS, HCM or post MI. There was no restriction on age, gender, geographical area or date of publication. Studies reported in English. Any studies where the risk of SCD was not quantified by either a HR, OR or RR were excluded.

Search strategy

A literature search was performed in 4 main groups of patients: Search terms included: (risk of SCD* or risk factors for SCD* or SCD* or female gender and outcome* or mortality in patients* or mortality in women* or risk stratification for SCD* or risk of cardiac arrest* or atrial fibrillation and mortality* or echocardiographic predictors of outcome* or risk of death* or COPD and mortality* or prognosis of heart failure* or risk of death in patients*) and (post myocardial infarction* or after myocardial infarction* or after acute st elevation myocardial infarction* or after ST elevation myocardial infarction* or with inferior myocardial infarction* or following myocardial infarction* or after myocardial infarction* or myocardial scarring* or electrocardiographic abnormalities* or patients with hypertrophic cardiomyopathy* or heart failure* or patients with heart failure* or left ventricular dysfunction* or after hospitalization for heart failure* or in the community* or new diagnosis of heart failure* or LQTS*).

The risk factor in each group that was associated with SCD, was then tabulated along with the relevant studies that supported this finding.

RESULTS

Results of literature search

Table 1 Primary prevention implantable cardioverter defibrillator studies

Study	Intervention/control group	Inclusion criteria	Risk reduction of SCD with ICD
Multicenter Automatic Defibrillator Implantation Trial[12]	ICD *vs* antiarrhythmic drug	Previous MI; EF≤35%; nsVT; positive findings on EPS	54% (P = 0.001)
Multicenter Unsustained Tachycardia Trial[13]	EP-guided therapy *vs* placebo	Coronary disease; EF≤40%; Non-sustained VT; inducible VT at EPS	51% (P = 0.001)
Multicenter Automatic Defibrillator Implantation Trial 2[14]	ICD *vs* optimal pharmacological treatment	Prior MI EF≤30%	31% (P = 0.02)
Sudden Cardiac Death in Heart Failure Trial[15]	ICD *vs* optimal pharmacological therapy *vs* optimal pharmacological therapy + amiodarone	Ischaemic and non-ischaemic cardiomyopathy; EF≤35%	23% (P = 0.007)
Defibrillator implantation in patients with nonischemic systolic heart failure[16]	ICD *vs* optimal pharmacological therapy	Non-ischaemic cardiomyopathy; EF≤ 35%	50% (P = 0.005)

SCD: Sudden cardiac death; ICD: Implantable cardioverter defibrillator; EF: Ejection fraction; EP: Electrophysiology; MI: Myocardial infarction; EPS: Electrophysiology studies; VT: Ventricular tachycardia.

The initial search strategy produced 21620 articles. Removal of duplicates and screening of the papers reduced the number to 480 articles. A further 435 papers were removed after reading of the full text. During data extraction an additional 4 papers were removed as a result of not having the prerequisite data available in the correct form. Forty one papers were included in the final data analysis (Figure 1)

Risk of sudden cardiac death post myocardial infarction

In patients post MI, 16 studies were identified involving a total of 250766 patients[24-39](Table 3). The absolute risk of SCD in these studies varied from around 4.9%-8%[24,26,30,33]. The absolute risk of SCD was 4.9% in the first month post-MI and decreased thereafter[24]. Another study showed a cumulative risk of SCD at 1 year to be 5.3%[26]. One study showed a risk of SCD of 7% at 30 d and 11% at 2 years[30]. Another study showed a risk of SCD at 4% in those with EF > 35% and 8% in those with EF < 35% at one year[33].

Several risk factors for SCD were identified post MI in order of decreasing magnitude: diabetes (HR 1.90-3.80), LVSD (HR 1.21 to 3.64), NSVT (HR 3.30), right ventricular involvement (OR 3.20), premature ventricular complexes occurring at a frequency of 10 or more per hour (HR 2.40), female gender (OR 1.09-1.76), older age (OR 1.03-1.56), LBBB (HR 1.49), non-specific intraventricular conduction delay (HR 1.44) and LVH (OR 1.40)[24-39].

Risk factors for sudden cardiac death in heart failure

In patients with heart failure, 15 studies were identified involving a total of 65182 patients[40-54](Table 4). The absolute risk of SCD in these studies varied from 8.8%-23.7%[49,50]. Doval *et al*[49] showed that in patients with NSVT the risk of SCD at 2 year was 23.7% compared to 8.8% in those who do not have NSVT at 2 years. Teerlink *et al*[50] showed that the risk of SCD was 13% at 2 years.

Several features increasing the risk of SCD were identified in order of decreasing magnitude: VT (RR 3.50), NSVT (RR 2.77-3.89), couplets (RR 3.37), cirrhosis (OR 3.22), 1-SD difference in LV Mass (RR 2.75), a 1-SD difference in LV end systolic dimension (RR 2.73), deranged kidney function (HR 2.02-2.64), dementia (OR 2.54), cancer (OR 1.86), the degree of left ventricular impairment(less than 40%) (HR 1.29-1.80), older age (OR 1.70), COPD (OR 1.66), atrial fibrillation (HR 0.89-1.55), male gender (HR 1.21-1.50) and cerebrovascular disease (OR 1.43)[40-54].

Risk of sudden cardiac death in the long QT syndrome

In patients with LQTS, 5 studies were identified with a total of 9758 patients[55-59](Table 5). The absolute risk of SCD in these studies varied from 4.9%-13%[55,57]. Sauer *et al*[55] showed that the risk of SCD from the age of 18 until follow-up at the age of 40 was 4.9% in LQTS1, 8.0% in LQTS2 and 4.9% in LQTS3. Priori *et al*[57] showed that the risk of SCD was 13% over 28 years of follow-up before the age of 40.

Several risk factors for SCD were identified in order of decreasing magnitude including: LQTS with a prolonged QTc interval (HR 36.53), LQTS with a normal range QTc interval (HR 10.25), LQTS 1 (HR 9.88), length of QTc interval (RR 5.34-8.36), consistent QTc interval prolongation (HR 2.23-6.67), previous history of cardiac events (syncope or aborted SCA) (HR 3.10-5.10), LQTS 3 (RR 1.80-2.76), female gender (HR 2.68), LQTS 2 (RR 1.61) and bradycardia (HR 1.02)[55-59].

Table 2 Secondary prevention implantable cardioverter defibrillator studies

Study	Intervention/control group	Inclusion criteria	Risk reduction with ICD
Antiarrhythmics Versus Implantable Defibrillators study[17]	ICD *vs* antiarrhythmic drugs	Resuscitated from near-fatal VF or post-cardioversion from sustained VT	28% (P = 0.02)
Canadian Implantable Defibrillator Study[18]	ICD *vs* amiodarone	Resuscitated VF or VT or with unmonitored syncope	20% (P = 0.14)
Cardiac Arrest Study Hamburg[19]	ICD *vs* amiodarone *vs* metoprolol	Survivors of cardiac arrest secondary to documented ventricular arrhythmias	23% (P = 0.08)

ICD: Implantable cardioverter defibrillator; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

Risk of sudden cardiac death in patients with HCM

In HCM there were 5 studies involving a total of 25823 patients[60-64](Table 6). The risk of SCD in HCM was about 5% over 5 years[60].

The following risk factors for SCD in order of decreasing magnitude were identified including: LVH (highest risk when greater than 20 mm) (HR 1.05-3.17), NSVT (HR 2.53-2.92), syncope (HR 2.31-2.68), left ventricular outflow tract obstruction (HR 1.01-2.41), family history of SCD (HR 1.27-2.34), abnormal blood pressure response during exercise (HR 1.30-1.38) and an enlarged left atrial diameter (HR 1.04)[60-64].

Wearable cardioverter defibrillator studies

There are currently only a few published outcome studies of WCDs. The WCD use in patients perceived to be at high risk, early post-MI study showed that 1.6% of patients received an appropriate shock for VT/VF and up to 67% of patients with VT/VF survived because of an appropriate shock[65]. Inappropriate shocks occurred in 1.1% of patients; none of the inappropriate shocks induced an arrhythmia.

"The aggregate national experience with the WCD vest: event rates, compliance and survival study" showed that 1.7% of patients received an appropriate shock for VT/VF. It also showed that 90% of patients survived because of an appropriate shock for VT/VF[66]. Inappropriate shocks occurred in 1.9% of patients[66].

The Vest Prevention of Early Sudden Death Trial compared WCD therapy to optimal medical therapy that was the control group. This trial showed that 0.6% of patients received an inappropriate shock. 1.4% of patients received an appropriate shock. The number of hours per day, the WCD was worn was 14.1 h. The risk of SCD was 1.6% in the WCD group compared to 2.4% in the control group (P = 0.18). All-cause mortality in the WCD group was 3.1% compared to 4.9% in the control group (P = 0.04)[67](Table 7).

DISCUSSION

The risk of SCD in various groups of patients has been well studied. This has led to the development of clear criteria for ICD implantation[23]. There is data on various subgroups of patients that quantifies the magnitude of known risk factors for SCD (post MI, LQTS, HCM and LVSD). There are clear guidelines on the use of ICD in these groups of patients but a lack of clear guidelines for WCD therapy. This study has identified risk factors for several groups of patients who may not qualify for an ICD (due to the risk associated with implantation) but could benefit from WCD. These risk factors may help select patient for WCD therapy.

In patients who have recently had an MI with severe LVSD, guidelines recommend primary prevention with an ICD should be delayed for 40 d as the degree of myocardial recovery is uncertain in the acute period. This leaves certain patients without the best possible treatment if they were to have a further episode of VT/VF or patients who develop VT/VF later as a result of left ventricular dysfunction resulting from an MI. Patients post-MI are at increased risk of SCD. Several factors are associated with this increased risk of SCD. These risk factors could be used to select patient who may benefit from WCD post MI and if there risk remains high, they could be offered an ICD at 40 d. In addition, the DINAMIT study looked at early ICD implantation within 6-40 d *vs* optimal medical therapy. The DINAMIT study showed a reduction in arrhythmic death with early ICD implantation but no effect on overall mortality[68]. These results do raise the question of whether there are device related

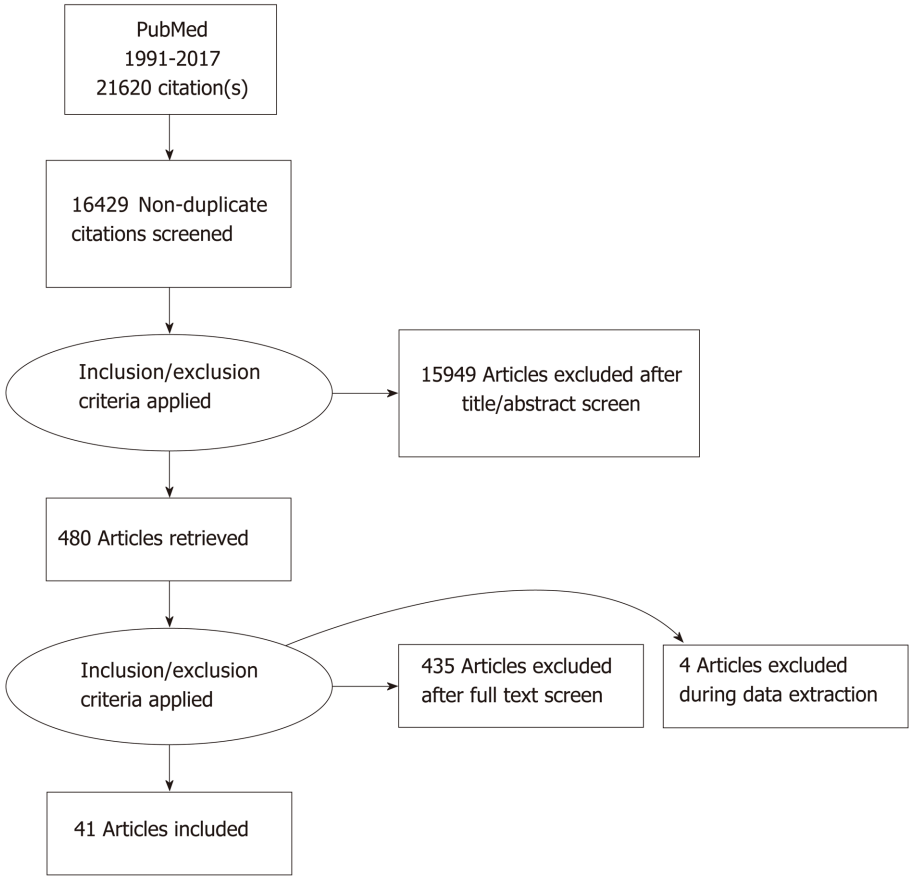


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

deaths that may reduce the overall mortality benefit such as device infections, procedural complications *etc*. These risks would not be present with WCD as there are no procedural risks associated with these devices. Some studies have advocated differentiating ICD implantation in the setting of acute MI based on whether the VT/VF occurred within 48 h in which case it could be attributed to acute MI and the treatment was revascularisation or if it occurred after 48 h in the absence of recurrent ischemia then these patients needed ICD implantation on the basis of secondary prevention and the 40 d rule in guidelines shouldn't apply[69]. These patients could also potentially be covered by using a WCD until the 40 d window has elapsed. In addition, the highest risk of SCD is within the first 30 d of an MI and so high-risk patients who have not yet suffered VT/VF may benefit from a WCD during this period[30]. The risk factors identified in this study could be used to help select such patients.

In patients with LVSD, guidelines only recommend an ICD if EF is less than 35 percent. This is the group of patients who are at the highest risk of SCD from LVSD. Studies of heart failure patients with an EF between 30% and 35% have shown that these patients also benefit from ICD therapy and have a lower mortality than the same group of patients without an ICD[70]. This would also lead one to believe that patients at higher EF with more high risk features may also benefit from having a defibrillator such patients could be offered a WCD as a lower risk option than ICD implantation. Similarly patients post-MI who develop severe LVSD are not offered a ICD and are sent home for a clinic review in 40 d to assess the degree of myocardial recovery during this period. This is potentially dangerous as the absolute risk of SCD during this period is about 4.9% which is similar to the risk of SCD in patients with HCM at which an ICD would be implanted these patients should probably all be offered a WCD during this time period[24,60]. It is important to note, however, the results of the recent VEST trial looking at the risk of SCD in WCD patient *vs* controls in the first 90 d post MI. It did not show a statistically significant reduction in SCD (1.6% *vs* 2.4%, P = 0.18) but there was a trend to lower risk of SCD in the WCD group. It did show a reduction in overall mortality (3.1% *vs* 4.9%, P = 0.04). These results are the opposite

Table 3 Risk factors for sudden cardiac death post myocardial infarction

Risk factor studied	Relative risk of SCD	*P* value	Absolute SCD risk in cohort	Study size	Year	Country
Age						
Rao *et al*[24]	OR 1.03 (1.00-1.05) (Increasing age)	0.0163	4.9% in the 1st month post MI	929	2012	India
Mehta *et al*[25]	OR 0.12; Standard error = 0.02 (Age per 1 year increase)	0.0001		2948	2001	North America
Abildstrom *et al*[26]	OR 1.56 (1.43–1.70) (Age per 10 years)	< 0.0001	5.3% at 1 year	5983	2002	Denmark
Female gender						
Rao *et al*[24]	OR 1.78 (1.02-2.85)	0.0042	4.9% in the 1st month post MI	929	2012	India
Greenland *et al*[27]	OR 1.72 (1.45-2.04)	< 0.0005		5839	1991	Israel
Greenland *et al*[27]	OR 1.32 (1.05-1.66) (Death at 1 year)	< 0.03		5839	1991	Israel
Ghaffari *et al*[28]	OR 1.76 (1.22–2.54) (univariate analysis)	0.002		1017	2017	Iran
Ghaffari *et al*[28]	OR 1.19 (0.77–1.8) (multivariate analysis)	0.407		1017	2017	Iran
Macintyre *et al*[29]	OR 1.09 (1.06 to 1.13) (Death at 1 year)	< 0.00001		201114	2001	UK
Male gender						
Abildstrom *et al*[26]	OR 1.34 (1.11–1.63)	< 0.005	5.3% at 1 year	5983	2002	Denmark
LV dysfunction						
Rao *et al*[24]	OR 2.35 (1.09-5.03) (Severe LV dysfunction ≤ 30%)	0.0292	4.9% in the 1st month post MI	929	2012	India
Solomon *et al*[30]	HR 1.21 (1.10 to 1.30) (LV depression by each 5 percentage points)		7% at 1 month post MI; 11% at 2 years post MI	14609	2005	North America, Europe and New Zealand
Klem *et al*[31]	HR 6.30 (1.40-28.00) (LVEF > 30% and significant scarring > 5% on CMRI compared to no scarring)	0.02		137	2012	USA
Klem *et al*[31]	HR 3.90 (1.20-13.10) (LVEF ≤ 30% and those with scar > 5% on CMRI compared to those with scarring)	0.03		137	2012	USA
Yeung *et al*[32]	HR 3.60 (1.46–8.75) (LVEF ≤ 30%)	< 0.01		610	2012	China
Chitnis *et al*[33]	OR 4.51 (2.20–9.24) (LVEF ≤ 35%)	< 0.0001	4% in those with EF > 35% at 1 year post MI; 8% in those with EF≤ 35% at 1 year post MI	929	2014	India
Adabag *et al*[34]	HR 3.64 (1.71-7.75) (presence of heart failure based on the framingham criteria)	< 0.001		693	2008	USA
Right ventricular involvement						
Mehta *et al*[25]	OR 3.20 (2.40-4.10)	< 0.00001		2948	2001	Canada
Diabetes						
Yeung *et al*[32]	HR 1.90 (1.04–3.40)	0.04		610	2012	China
Junttila *et al*[35]	HR 3.80 (2.40–5.80)	< 0.001		3276	2010	Finland
Ventricular arrythmia						

Maggioni *et al*[36]	RR 2.24 (1.22-4.08) (more than 10 premature ventricular beats per hour)	0.002	8676	1993	Italy
Maggioni *et al*[36]	RR 1.20 (0.80-1.79) (NSVT)		8676	1993	Italy
Mäkikallio *et al*[37]	HR 2.40 (1.30–4.40) (Ventricular premature complexes 10/h)	0.0049	2130	2005	Finland
Mäkikallio *et al*[37]	HR 3.30 (1.70–6.50) (NSVT)	< 0.0005	2130	2005	Finland
ECG features					
Mäkikallio *et al*[37]	HR 3.30 (1.70–6.50) (QRS ≥ 120 ms)	0.0004	2130	2005	Finland
Zimetbaum *et al*[38]	HR 1.44 (1.11-1.88) (Non-specific intraventricular conduction delay)	0.0069	1638	2004	USA
Zimetbaum *et al*[38]	HR 1.49 (1.02-2.17) (LBBB)	0.0400	1638	2004	USA
Zimetbaum *et al*[38]	HR 1.35 (1.08-1.69) (LVH)	0.0082	1638	2004	USA
Siscovick *et al*[39]	OR 1.40 (1.00-2.00) (LVH)	0.02	688	1996	USA

SCD: Sudden cardiac death; MI: Myocardial infarction; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

of the DINAMIT study this may be due to poor patient compliance with compliance decreasing with time during the study, which may have contributed to the lack of a significant reduction in SCD. It is important to note that at the time of SCD only 8 of 25 patients in the treatment group were wearing their WCD[67]. Another group of patient who may benefit from a WCD are those who are awaiting heart transplantation. These patients should be offered an ICD based on current guidelines pre-transplantation; however, a WCD could be used as an alternative in these patients while they await their heart transplant.

In patients with non-ischaemic cardiomyopathy, the risk for SCD appears to be lower than those with ischaemic cardiomyopathy. They also do not appear to benefit from ICD therapy in the same way as patients with ischaemic cardiomyopathy as was shown by the recent defibrillator implantation in patients with nonischemic systolic heart failure (DANISH) study. The DANISH study showed no significant reduction in all-cause mortality between the ICD therapy and standard care group (21.6% *vs* 23.4%, $P = 0.28$). It did show a reduction in sudden cardiac death in the ICD group when compared to the standard care group ((4.3% *vs* 8.2%, $P = 0.005$)[16]. This reinforces the need for a risk stratification tool to help determine individual risk factors that would make patients at higher risk for SCD. This study does help provide data that could be used to select not only patients for WCD but also patients who might benefit from an ICD in this patient group.

In patients with LQTS guidelines only recommend an ICD in these patients if they have survived an episode of VT/VF. This may be an unacceptable risk for some patients and a WCD could afford these patients with some protection until they meet criteria for a permanent ICD. One large study used 4 variables which included age, length of QTc, symptoms and the presence of cardiac arrest to determine the decision on whether patients were likely to benefit from therapy with an ICD in LQTS[71]. Such a risk score could also be used to offer patients a choice between an ICD or a WCD.

Patients with HCM who have 5 year risk of death of less than 6% could be offered a WCD if they find the risk of SCD unacceptable. The ESC HCM risk-SCD calculator has a cut off of > 6% at which an ICD should be implanted. There may be patients who do not want an ICD and these patients could also be offered a WCD as an alternative.

A large WCD registry showed that WCD usage in patients with HCM and LQTS was safe, effective and associated with a high rate of compliance[72]. A further large meta-analysis of WCD showed that WCD have a 95% success rate at terminating arrhythmias[73].The HCM risk-SCD calculator provides a very helpful measure of assessing a patient's risk of SCD and making treatment decisions in patients with HCM. It would be useful to develop risk calculators for SCD in other conditions,

Table 4 Risk factors for sudden cardiac death in heart failure

Risk factor studies	Relative risk of SCD	*P* value	Absolute SCD risk in cohort	Study size	Year	Country
Age						
Lee *et al*[40]	OR 1.70 (1.45-1.99) (Age per 10 unit increase)	< 0.001		4031	2003	Canada
Cowie *et al*[41]	HR 1.26 (1.01 to 1.57) (Age per 10 year increase)	0.04		220	2000	UK
Taylor *et al*[42]	HR 1.10 CI 1.09–1.10 (Increasing age)			6162	2012	UK
Male gender						
Taylor *et al*[42]	HR 1.50 (1.36–1.66)			6162	2012	UK
Vaartjes *et al*[43]	HR 1.21 (1.14-1.28) at 28 d; HR 1.26 (1.21-1.31) at 1 year; HR 1.28 (1.24-1.31) at year 5			29053	2010	Netherlands
Comorbidities						
Lee *et al*[40]	OR 1.43 (1.03-1.98) 30-day mortality (Cerebrovascular disease)	0.03		4031	2003	Canada
Lee *et al*[40]	OR 1.66 (1.22-2.27) (COPD)	0.002		4031	2003	Canada
Lee *et al*[40]	OR, 3.22 (1.08-9.65) (Cirrhosis)	0.04		4031	2003	Canada
Lee *et al*[40]	OR 2.54 (1.77-3.65) (Dementia)	< 0.001		4031	2003	Canada
Lee *et al*[40]	OR 1.86 (1.28-2.70) (Cancer)	0.001		4031	2003	Canada
Yoshihisa *et al*[44]	HR 3.01 (1.11–8.63) (COPD)	0.038		378	2014	Japan
Fisher *et al*[45]	RR 1.10 (1.06-1.14) Death at 1 year; RR 1.40 (1.28-1.52) death at 5 years (COPD)			9748	2015	USA
Atrial fibrillation						
Taylor *et al*[44]	HR 1.55 (1.26–1.92)			6162	2012	UK
Ahmed *et al*[46]	HR 1.41 (1.08-1.83)			944	2005	USA
Corell *et al*[47]	HR 1.38 (1.07-1.78)	0.01		1019	2007	Denmark
Middlekauff *et al*[48]	HR 0.89 (0.55-1.23)	0.013		390	1991	USA
Ventricular arrythmia						
Doval *et al*[49]	RR 2.77 (1.78-4.44) (NSVT)	< 0.001	23.7% at 2 years in those with NSVT; 8.8% at 2 years in those without NSVT	516	1996	Argentina
Doval *et al*[49]	RR 3.37 (1.57-7.25) (Couplets)	< 0.0005	23.7% at 2 years in those with NSVT; 8.8% at 2 years in those without NSVT	516	1996	Argentina
Teerlink *et al*[50]	RR 1.16 (1.09–1.24) (NSVT)	0.001	13% at 2 years	1080	2000	USA
Szabó *et al*[51]	RR 3.50 (1.54-7.98) (VT)	0.003		211	1994	Netherlands
Szabó *et al*[51]	RR 2.68 (1.11-6.48) (Freq. VT > 144 beats/min)	0.029		211	1994	Netherlands
Szabó *et al*[51]	RR 3.89 (1.61-9.43) (Length VT > 2s)	0.003		211	1994	Netherlands
Echocardiographic variables						
Taylor *et al*[42]	HR 1.80 (1.55–2.10) (EF < 40% *vs* > 50%)			6162	2012	UK

Taylor *et al*[42]	HR 1.29 (1.11–1.50) (EF 40%–50% *vs* > 50%)		6162	2012	UK
Shadman *et al*[52]	OR 1.15 (EF per 10% decrease)	0.005	9885	2015	USA
Quiñones *et al*[53]	RR 2.75 (1.62-4.66) (1-SD difference in LV Mass)	0.0002	1209	2000	USA
Quiñones *et al*[53]	RR 1.84 (1.08-3.15) (1-SD difference in LA Diameter)	0.03	1209	2000	USA
Quiñones *et al*[53]	RR 2.73 (1.43-5.20) (1-SD difference in lv end systolic dimension)	0.003	1209	2000	USA
Grayburn *et al*[54]	HR 1.01 (1.00–1.01) (LV end-diastolic volume index)	0.0012	336	2005	USA
Deranged kidney function					
Grayburn *et al*[54]	HR 2.023 (1.24–3.32)	0.0052	336	2005	USA
Cowie *et al*[41]	HR 2.64 (1.87-3.74)	< 0.001	220	2000	UK

SCD: Sudden cardiac death; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

which are more common and have a much larger impact on global mortality. This would provide patients and doctors with more information to make the best decision regarding their care.

The following groups of patients could also benefit from WCD therapy; patients who have an explanted ICD for infective endocarditis and must wait a certain time period before reinsertion, patients who have a risk of SCD but have a lower absolute risk such that the cost and risk of ICD insertion can't be justified, patients in remote areas where there is no expertise for ICD insertion, patients with myocarditis, patients with takotsubo cardiomyopathy, patients with peripartum cardiomyopathy, patients with advanced stage chronic kidney disease and children and young adults with channelopathies. The risk factors compiled in this review article could be used to help risk stratify many of these patients. The risk factors for patients post MI could be extrapolated to patients with takotsubo cardiomyopathy and myocarditis as all these processes involve an acute myocardial injury and so could be expected to have similar risk factors for SCD. In addition, the risk factors for LVSD could be extrapolated to patients with peripartum cardiomyopathy and those awaiting heart transplantation to determine high risk patients who may benefit from a WCD. There is potentially large scope for the use of WCD in carefully selected patient populations. One of the key disadvantages to WCD is the dependence on patient compliance for successful therapy as patients may decide to not wear the WCD, which can be a key limiting factor in its success.

In conclusion, we have identified multiple risk factors for sudden cardiac death in various conditions that could be used to help select patients for WCD therapy. The WCD is a landmark development that provides patients and physicians an additional therapy for the treatment of SCD; however, it is underutilized due to a lack of clear guidelines governing its usage[74]. SCD remains a common cause of death and continued effort must be made to try and develop more targeted approaches to treatment for SCD.

Table 5 Risk factors for sudden cardiac death in the long QT syndrome

Risk factor studied	Relative risk of SCD	*P* value	Absolute SCD risk in cohort	Study size	Year	Country
Female gender						
Sauer *et al*[55]	HR 2.68 (1.10–6.50)	< 0.05	Risk between ages of 18-40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
QTc interval						
Sauer *et al*[55]	HR 3.34 (1.49–7.49) (QTc 500–549 ms *vs* ≤ 499 ms)	< 0.01	Risk between ages of 18-40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
Sauer *et al*[55]	HR 6.35 (2.82–14.32) (QTc ≥ 550 ms *vs* ≤ 499 ms)	< 0.01	Risk between ages of 18-40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
Moss *et al*[56]	HR 1.05 (1.02-1.09) (QTc per 0.01 units)	< 0.01		1496	1991	USA
Priori *et al*[57]	RR 5.34 (2.82-10.13) [QTc in the third quartile (469 to 498 ms)]		Risk between ages 12-40 was 13% over 28 years	580	2003	Italy
Priori *et al*[57]	RR 8.36 (2.53-27.21) [QTc in the highest quartile (more than 498 ms)]		Risk between ages 12-40 was 13% over 28 years	580	2003	Italy
Goldenberg *et al*[58]	HR 36.53 (13.35–99.95) (LQTS with prolonged QTc interval *vs* unaffected family members)	< 0.001		3386	2012	USA, Europe, Japan and Israel
Goldenberg *et al*[58]	HR 10.25 (3.34–31.46) (LQTS with normal-range QTc interval *vs* unaffected family members)	< 0.001		3386	2012	USA, Europe, Japan and Israel
Previous history of cardiac events						
Sauer *et al*[55]	HR 5.10 (2.50–10.39) (Interim time dependant syncope *vs* no interim syncope)	< 0.01	Risk between ages of 18-40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
Moss *et al*[56]	HR 3.10 (1.30-7.20) (History of cardiac event)	< 0.01		1496	1991	USA
Genotype						
LQTS 3						
Priori *et al*[57]	RR 2.76 (1.01-7.51) (Male sex)		Risk between ages 12-40 was 13% over 28 years	580	2003	Italy
Priori *et al*[57]	RR of 1.80 (1.07-3.04) (mutation at the LQT3 locus)		Risk between ages 12-40 was 13% over 28 years	580	2003	Italy
LQTS 2						
Priori *et al*[57]	RR 1.61 (1.16-2.25) (LQT2 locus)		Risk between ages 12-40 was 13% over 28 years	580	2003	Italy
LQTS 1						
Goldenberg *et al*[58]	HR 9.88 (1.26–37.63) (LQTS 1 mutation and normal QTc)	0.03		3386	2012	USA, Europe, Japan and Israel
Heart rate						

Moss *et al*[56]	HR 1.02 (1.00-1.03) (Resting heart rate less than 60 beats/min)	0.01		1496	1991	USA
Niemeijer *et al*[59]	Bazett: HR 2.23 (1.17-4.24) Fridericia: HR 6.67 (2.96-15.06) (Consistent Qtc interval prolongation)			3484	2015	Netherlands

SCD: Sudden cardiac death; LQTS: Long QT syndrome; QTc: QT corrected interval; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

Table 6 Risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy

Risk factor studied	Relative risk of SCD	*P* value	Absolute SCD risk in cohort	Study size	Year	Country
Age						
O'Mahony *et al*[60]	HR 0.99 (0.98-1.00) (Age 42 ± 15)	0.007	5% at 5 years	3675	2014	Europe
Syncope						
Liu *et al*[61]	HR 2.31 (1.22-4.38)			12146	2017	USA, China
O'Mahony *et al*[60]	HR 2.33 (1.69-3.19)	< 0.001	5% at 5 years	3675	2014	Europe
Christiaans *et al*[62]	HR 2.68 (0.97–4.38)			9357	2010	Netherlands, UK
Family history of SCD						
Christiaans *et al*[62]	HR 1.27 (1.16–1.38)			9357	2010	Netherlands, UK
O'Mahony *et al*[60]	HR 1.76 (1.32-2.24)	<0.001	5% at 5 years	3675	2014	Europe
Liu *et al*[61]	HR 2.34 (1.46- 3.75)			12146	2017	USA, China
Abnormal blood pressure response during exercise						
Liu *et al*[61]	HR 1.38 (0.65-2.89) (BP dropping on excersice)			12146	2017	USA, China
Christiaans *et al*[62]	HR 1.30 (0.64–1.96) (BP dropping on excersice)			9357	2010	Netherlands, UK
Non sustained ventricular tachycardia						
Liu *et al*[61]	HR 2.92 (1.97-4.33)			12146	2017	USA, China
Sugrue *et al*[63]	HR 3.36 (1.00-11.35)	0.05		52	2017	USA
O'Mahony *et al*[60]	HR 2.53 (1.85-3.47)	< 0.001	5% at 5 years	3675	2014	Europe
Christiaans *et al*[62]	HR 2.89 (2.21–3.58)			9357	2010	Netherlands, UK
Left ventricular wall thickness/hypertrophy						
Liu *et al*[61]	HR3.17 (1.64-6.12) (Maximum LV wall thickness ≥ 30 mm)			12146	2017	USA, China
Maeda *et al*[64]	HR 1.21 (1.04–1.39) (Maximum left ventricular wall thickness per 1-mm increase)	0.011		593	2016	Japan
O'Mahony *et al*[60]	HR 1.05 (1.03-1.07) (Maximal LV wall thickness in mm 21.5 ± 6)	< 0.001	5% at 5 years	3675	2014	Europe
Christiaans *et al*[62]	HR 3.10 (1.81–4.40) (LVH ≥ 20 mm)			9357	2010	Netherlands, UK
Left ventricular outflow tract obstruction						
Liu *et al*[61]	HR 2.41 (1.55-3.73)			12146	2017	USA, China
O'Mahony *et al*[60]	HR 1.01 (1.00-1.01) [LVOT Gradient mmHG 18 (6-58)]	0.005	5% at 5 years	3675	2014	Europe
Left atrial diameter						

O'Mahony *et al*[60]	HR 1.04 (1.02-1.05) (LA diameter in mm 46.2 ± 9)	< 0.001	5% at 5 years	3675	2014	Europe

SCD: Sudden cardiac death; LVOT: Left ventricular outflow tract; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

Table 7 Summary of wearable cardioverter defibrillator studies

Study	General findings	Survival post shock
Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post-myocardial infarction[65]	99 out of 8453 patients received 114 inappropriate shocks. None of the inappropriate shocks induced arrhythmias. The inappropriate shock rate was 0.006 shocks per patient month of use.	67% for those with VT/VF; 62% for those treated for PMVT/VF
Aggregate national experience with the wearable cardioverter defibrillator vest: event rates, compliance and survival[66]	Inappropriate shocks occurred in 67/3569 (1.9%) patients	90% for VT/VF events; 73.6% for all events
Vest Prevention of Early Sudden Death Trial[67]	Inappropriate shocks: 0.6%; Appropriate shocks: 1.4%; Hours/day WCD worn: 14.1	Risk of SCD (WCD *vs* Control): 1.6% *vs* 2.4%, P = 0.18. All-cause mortality (WCD *vs* Control): 3.1% *vs* 4.9%, P = 0.04

VT: Ventricular tachycardia; VF: Ventricular fibrillation; WCD: Wearable cardioverter defibrillator; SCD: Sudden cardiac death.

ARTICLE HIGHLIGHTS

Research background

There are many groups of patients including those post myocardial infarction (MI), patients with hypertrophic cardiomyopathy (HCM), patients with left ventricular systolic dysfunction (LVSD) and patients with long QT syndrome (LQTS) who are at high risk of sudden cardiac death (SCD) that do not meet criteria for implantable cardioverter defibrillator (ICD) implantation. This study looked at risk factors for SCD in these patient groups, which could be used as a method for identifying patients at high risk for SCD. Patients at high risk for SCD but not meeting conventional indications for ICD therapy could be offered a WCD until an ICD was indicated.

Research motivation

There is a need for more refined risk calculators to determine the risk of SCD in various conditions as is already present for patients with HCM. There is a requisite for more refined risk calculators to determine the risk of SCD in various conditions such as patients post MI, patients with LVSD, patients with LQTS and other channelopathies, patients with post-partum cardiomyopathy, patients with takotsubo cardiomyopathy, patients with myocarditis and patients with advanced chronic renal failure. This would allow better selection of patients at high risk of SCD and allow physicians to offer their patients the best treatment for each specific patient based on their individual risk.

Research objectives

The main objectives of our study were to collate the risk factors for SCD in specific patient groups as mentioned previously. These risk factors were to be used as a guide to help in determining high-risk patients that may benefit from WCD therapy. This to the best of our knowledge is the first attempt made at collating risk factors for SCD for various conditions in one place. This should help future studies to build on this data and hopefully give rise to risk calculators for SCD in these and many more conditions.

Research methods

We performed a literature search on PubMed. The studies were then selected according to whether they met the inclusion criteria for our review article. The inclusion criteria were any study that reported risk factors for SCD in patients with LVSD, LQTS, HCM or post MI. There was no restriction on age, gender, geographical area or date of publication. Studies had to be reported in English. Any studies where the risk of SCD was not quantified by either a hazard ratio, odds ratio or relative risk were excluded. The relevant risk factors for SCD in the 4 main conditions were then collected and tabulated in table format.

Research results

We collected a large number of risk factors for SCD in all 4 patients groups. These risk factors provide a robust method of assessing a patients risk for SCD. The study also looked at several WCD studies which showed that WCD were effective at terminating VT/VF but were limited in their effectiveness by patient compliance.

Research conclusions

This review shows that there are many risk factors for SCD that to the best of our knowledge

have never been compiled together in one place such as this study has done. We also show that WCD are effective therapies for ventricular tachycardia/ventricular fibrillation, but are limited by patient compliance.

This should help in the development of more precise risk calculators for sudden cardiac death such as the existing risk calculator for HCM. This should also help select patients who may benefit from WCD.

Research perspectives

This study demonstrates the wealth of data present that could be used to create precise risk calculators for SCD. These risk calculators could be used to determine patients at high risk for SCD. It could be used to select which patients need an ICD and which could benefit from a WCD. Further study should be in the form of a meta-analysis to allow this area of research to move forward.

REFERENCES

1 **Myerburg RJ**, Castellanos A. Sudden cardiac death, Cardiac electrophysiology: From cell to bedside. Philadelphia: Saunders Elsevier 2009; 797–808

2 **Nadkarni VM**, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, Nichol G, Lane-Truitt T, Potts J, Ornato JP, Berg RA; National Registry of Cardiopulmonary Resuscitation Investigators. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006; **295**: 50-57 [PMID: 16391216 DOI: 10.1001/jama.295.1.50]

3 **Meaney PA**, Nadkarni VM, Kern KB, Indik JH, Halperin HR, Berg RA. Rhythms and outcomes of adult in-hospital cardiac arrest. *Crit Care Med* 2010; **38**: 101-108 [PMID: 19770741 DOI: 10.1097/CCM.0b013e3181b43282]

4 **Bayés de Luna A**, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; **117**: 151-159 [PMID: 2911968 DOI: 10.1016/0002-8703(89)90670-4]

5 **Myerburg RJ**, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992; **85**: I2-10 [PMID: 1728501]

6 **Chadda K**, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986; **73**: 503-510 [PMID: 3948357 DOI: 10.1161/01.CIR.73.3.503]

7 **Hulleman M**, Berdowski J, de Groot JR, van Dessel PF, Borleffs CJ, Blom MT, Bardai A, de Cock CC, Tan HL, Tijssen JG, Koster RW. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. *Circulation* 2012; **126**: 815-821 [PMID: 22869841 DOI: 10.1161/CIRCULATIONAHA.111.089425]

8 **van Alem AP**, Chapman FW, Lank P, Hart AA, Koster RW. A prospective, randomised and blinded comparison of first shock success of monophasic and biphasic waveforms in out-of-hospital cardiac arrest. *Resuscitation* 2003; **58**: 17-24 [PMID: 12867305 DOI: 10.1016/S0300-9572(03)00106-0]

9 **Zoll PM**, Linenthal AJ, Gibson W, Paul MH, Norman LR. Termination of ventricular fibrillation in man by externally applied electric countershock. *N Engl J Med* 1956; **254**: 727-732 [PMID: 13309666 DOI: 10.1056/NEJM195604192541601]

10 **Soar J**, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, Pellis T, Sandroni C, Skrifvars MB, Smith GB, Sunde K, Deakin CD; Adult advanced life support section Collaborators. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015; **95**: 100-147 [PMID: 26477701 DOI: 10.1016/j.resuscitation.2015.07.016]

11 **Mirowski M**, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980; **303**: 322-324 [PMID: 6991948 DOI: 10.1056/NEJM198008073030607]

12 **Moss AJ**, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; **335**: 1933-1940 [PMID: 8960472 DOI: 10.1056/NEJM199612263352601]

13 **Buxton AE**, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; **341**: 1882-1890 [PMID: 10601507 DOI: 10.1056/NEJM199912163412503]

14 **Moss AJ**, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877-883 [PMID: 11907286 DOI: 10.1056/NEJMoa013474]

15 **Bardy GH**, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352**: 225-237 [PMID: 15659722 DOI: 10.1056/NEJMoa043399]

16 **Køber L**, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med* 2016; **375**: 1221-1230 [PMID: 27571011 DOI: 10.1056/NEJMoa1608029]

17 **Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators**. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; **337**: 1576-1583 [PMID: 9411221 DOI: 10.1056/NEJM199711273372202]

18 **Connolly SJ**, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; **101**: 1297-1302 [PMID: 10725290 DOI: 10.1161/01.CIR.101.11.1297]

19 **Kuck KH**, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102**: 748-754 [PMID: 10942742 DOI: 10.1161/01.CIR.102.7.748]

20 **Kusumoto FM**, Calkins H, Boehmer J, Buxton AE, Chung MK, Gold MR, Hohnloser SH, Indik J, Lee R, Mehra MR, Menon V, Page RL, Shen WK, Slotwiner DJ, Stevenson LW, Varosy PD, Welikovitch L. HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. *Circulation* 2014; **130**: 94-125 [PMID: 24815500 DOI: 10.1161/CIR.0000000000000056]

21 **Food and Drug Administration**. FDA Approves First Wearable Defibrillator. Available from: http://permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/departs/2002/202_upd.html#defib

22 **Francis J**, Reek S. Wearable cardioverter defibrillator: a life vest till the life boat (ICD) arrives. *Indian Heart J* 2014; **66**: 68-72 [PMID: 24581099 DOI: 10.1016/j.ihj.2013.12.050]

23 **Priori SG**, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793-2867 [PMID: 26320108 DOI: 10.1093/eurheartj/ehv316]

24 **Rao HB**, Sastry BK, Korabathina R, Raju KP. Sudden cardiac death after acute ST elevation myocardial infarction: insight from a developing country. *Heart Asia* 2012; **4**: 83-89 [PMID: 27326036 DOI: 10.1136/heartasia-2012-010114]

25 **Mehta SR**, Eikelboom JW, Natarajan MK, Diaz R, Yi C, Gibbons RJ, Yusuf S. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol* 2001; **37**: 37-43 [PMID: 11153770 DOI: 10.1016/S0735-1097(00)01089-5]

26 **Abildstrom SZ**, Rask-Madsen C, Ottesen MM, Andersen PK, Rosthøj S, Torp-Pedersen C, Køber L; TRACE Study Group. Trandolapril cardiac evaluation. Impact of age and sex on sudden cardiovascular death following myocardial infarction. *Heart* 2002; **88**: 573-578 [PMID: 12433881 DOI: 10.1136/heart.88.6.573]

27 **Greenland P**, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. *Circulation* 1991; **83**: 484-491 [PMID: 1991367 DOI: 10.1161/01.CIR.83.2.484]

28 **Ghaffari S**, Pourafkari L, Tajlil A, Bahmani-Oskoui R, Nader ND. Is female gender associated with worse outcome after ST elevation myocardial infarction? *Indian Heart J* 2017; **69** Suppl 1: S28-S33 [PMID: 28400036 DOI: 10.1016/j.ihj.2016.12.003]

29 **MacIntyre K**, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, Finlayson A, Redpath A, Gilmour H, McMurray JJ. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol* 2001; **38**: 729-735 [PMID: 11527625 DOI: 10.1016/S0735-1097(01)01465-6]

30 **Solomon SD**, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, Harsanyi A, Rouleau JL, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf RM, Pfeffer MA; Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005; **352**: 2581-2588 [PMID: 15972864 DOI: 10.1056/NEJMoa043938]

31 **Klem I**, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, Parker MA, Judd RM, Kim RJ. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. *J Am Coll Cardiol* 2012; **60**: 408-420 [PMID: 22835669 DOI: 10.1016/j.jacc.2012.02.070]

32 **Yeung CY**, Lam KS, Li SW, Lam KF, Tse HF, Siu CW. Sudden cardiac death after myocardial infarction in type 2 diabetic patients with no residual myocardial ischemia. *Diabetes Care* 2012; **35**: 2564-2569 [PMID: 22875229 DOI: 10.2337/dc12-0118]

33 **Chitnis N**, Vooturi S, Hygriv Rao B. Sudden cardiac death early after ST elevation myocardial infarction with and without severe left ventricular dysfunction. *Indian Heart J* 2014; **66**: 569-573 [PMID: 25634386 DOI: 10.1016/j.ihj.2014.10.416]

34 **Adabag AS**, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. *JAMA* 2008; **300**: 2022-2029 [PMID: 18984889 DOI: 10.1001/jama.2008.553]

35 **Junttila MJ**, Barthel P, Myerburg RJ, Mäkikallio TH, Bauer A, Ulm K, Kiviniemi A, Tulppo M, Perkiömäki JS, Schmidt G, Huikuri HV. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. *Heart Rhythm* 2010; **7**: 1396-1403 [PMID: 20682359 DOI: 10.1016/j.hrthm.2010.07.031]

36 **Maggioni AP**, Zuanetti G, Franzosi MG, Rovelli F, Santoro E, Staszewsky L, Tavazzi L, Tognoni G. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. *Circulation* 1993; **87**: 312-322 [PMID: 8093865 DOI: 10.1161/01.CIR.87.2.312]

37 **Mäkikallio TH**, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP, Schmidt G, Huikuri HV. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J* 2005; **26**: 762-769 [PMID: 15778204 DOI: 10.1093/eurheartj/ehi188]

38 **Zimetbaum PJ**, Buxton AE, Batsford W, Fisher JD, Hafley GE, Lee KL, O'Toole MF, Page RL, Reynolds M, Josephson ME. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. *Circulation* 2004; **110**: 766-769 [PMID: 15289365 DOI: 10.1161/01.CIR.0000139311.32278.32]

39 **Siscovick DS**, Raghunathan TE, Rautaharju P, Psaty BM, Cobb LA, Wagner EH. Clinically silent electrocardiographic abnormalities and risk of primary cardiac arrest among hypertensive patients. *Circulation* 1996; **94**: 1329-1333 [PMID: 8822988 DOI: 10.1161/01.CIR.94.6.1329]

40 **Lee DS**, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003; **290**: 2581-2587 [PMID: 14625335 DOI: 10.1001/jama.290.19.2581]

41 **Cowie MR**, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000; **83**: 505-510 [PMID: 10768897 DOI: 10.1136/heart.83.5.505]

42 **Taylor CJ**, Roalfe AK, Iles R, Hobbs FD. Ten-year prognosis of heart failure in the community: follow-up data from the Echocardiographic Heart of England Screening (ECHOES) study. *Eur J Heart Fail* 2012; **14**: 176-184 [PMID: 22253455 DOI: 10.1093/eurjhf/hfr170]

43 **Vaartjes I**, Hoes AW, Reitsma JB, de Bruin A, Grobbee DE, Mosterd A, Bots MI. Age- and gender-specific risk of death after first hospitalization for heart failure. *BMC Public Health* 2010; **10**: 637 [PMID: 20969758 DOI: 10.1186/1471-2458-10-637]

44 **Yoshihisa A**, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, Iwaya S, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S, Takeishi Y. Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease. *J Cardiol* 2014; **64**: 256-264 [PMID: 24674751 DOI: 10.1016/j.jjcc.2014.02.003]

45 **Fisher KA**, Stefan MS, Darling C, Lessard D, Goldberg RJ. Impact of COPD on the mortality and treatment of patients hospitalized with acute decompensated heart failure: the Worcester Heart Failure Study. *Chest* 2015; **147**: 637-645 [PMID: 25188234 DOI: 10.1378/chest.14-0607]

46 **Ahmed A**, Perry GJ. Incident atrial fibrillation and mortality in older adults with heart failure. *Eur J Heart Fail* 2005; **7**: 1118-1121 [PMID: 16326363 DOI: 10.1016/j.ejheart.2004.12.004]

47 **Corell P**, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2007; **9**: 258-265 [PMID: 17027330 DOI: 10.1016/j.ejheart.2006.08.004]

48 **Middlekauff HR**, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation* 1991; **84**: 40-48 [PMID: 2060110 DOI: 10.1161/01.CIR.84.1.40]

49 **Doval HC**, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, Dubner S, Scapin O, Perrone SV. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators. *Circulation* 1996; **94**: 3198-3203 [PMID: 8989129 DOI: 10.1161/01.CIR.94.12.3198]

50 **Teerlink JR**, Jalaluddin M, Anderson S, Kukin ML, Eichhorn EJ, Francis G, Packer M, Massie BM. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. *Circulation* 2000; **101**: 40-46 [PMID: 10618302 DOI: 10.1161/01.CIR.101.1.40]

51 **Szabó BM**, van Veldhuisen DJ, Crijns HJ, Wiesfeld AC, Hillege HL, Lie KI. Value of ambulatory electrocardiographic monitoring to identify increased risk of sudden death in patients with left ventricular dysfunction and heart failure. *Eur Heart J* 1994; **15**: 928-933 [PMID: 7925514 DOI: 10.1093/oxfordjournals.eurheartj.a060612]

52 **Shadman R**, Poole JE, Dardas TF, Mozaffarian D, Cleland JG, Swedberg K, Maggioni AP, Anand IS, Carson PE, Miller AB, Levy WC. A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the Seattle Proportional Risk Model. *Heart Rhythm* 2015; **12**: 2069-2077 [PMID: 26142301 DOI: 10.1016/j.hrthm.2015.06.039]

53 **Quiñones MA**, Greenberg BH, Kopelen HA, Koilpillai C, Limacher MC, Shindler DM, Shelton BJ, Weiner DH. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 2000; **35**: 1237-1244 [PMID: 10758966 DOI: 10.1016/S0735-1097(00)00511-8]

54 **Grayburn PA**, Appleton CP, DeMaria AN, Greenberg B, Lowes B, Oh J, Plehn JF, Rahko P, St John Sutton M, Eichhorn EJ; BEST Trial Echocardiographic Substudy Investigators. Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (BEST). *J Am Coll Cardiol* 2005; **45**: 1064-1071 [PMID: 15808765 DOI: 10.1016/j.jacc.2004.12.069]

55 **Sauer AJ**, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, Qi M, Goldenberg I, Hobbs JB, Ackerman MJ, Benhorin J, Hall WJ, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Long QT syndrome in adults. *J Am Coll Cardiol* 2007; **49**: 329-337 [PMID: 17239714 DOI: 10.1016/j.jacc.2006.08.057]

56 **Moss AJ**, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson A. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* 1991; **84**: 1136-1144 [PMID: 1884444 DOI: 10.1161/01.CIR.84.3.1136]

57 **Priori SG**, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003; **348**: 1866-1874 [PMID: 12736279 DOI: 10.1056/NEJMoa022147]

58 **Goldenberg I**, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Platonov PG, Priori SG, Qi M, Schwartz PJ, Shimizu W, Towbin JA, Vincent GM, Wilde AA, Zhang L. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol* 2011; **57**: 51-59 [PMID: 21185501 DOI: 10.1016/j.jacc.2010.07.038]

59 **Niemeijer MN**, van den Berg ME, Deckers JW, Franco OH, Hofman A, Kors JA, Stricker BH, Rijnbeek PR, Eijgelsheim M. Consistency of heart rate-QTc prolongation consistency and sudden cardiac death: The Rotterdam Study. *Heart Rhythm* 2015; **12**: 2078-2085 [PMID: 26165945 DOI: 10.1016/j.hrthm.2015.07.011]

60 **O'Mahony C**, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014; **35**: 2010-2020 [PMID: 24126876 DOI: 10.1093/eurheartj/eht439]

61 **Liu Q**, Li D, Berger AE, Johns RA, Gao L. Survival and prognostic factors in hypertrophic cardiomyopathy: a meta-analysis. *Sci Rep* 2017; **7**: 11957 [PMID: 28931939 DOI: 10.1038/s41598-017-12289-4]

62 **Christiaans I**, van Engelen K, van Langen IM, Birnie E, Bonsel GJ, Elliott PM, Wilde AA. Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. *Europace* 2010; **12**: 313-321 [PMID: 20118111 DOI: 10.1093/europace/eup431]

63 **Sugrue A**, Killu AM, DeSimone CV, Chahal AA, Vogt JC, Kremen V, Hai J, Hodge DO, Acker NG, Geske JB, Ackerman MJ, Ommen SR, Lin G, Noseworthy PA, Brady PA. Utility of T-wave amplitude as a non-invasive risk marker of sudden cardiac death in hypertrophic cardiomyopathy. *Open Heart* 2017; **4**: e000561 [PMID: 28409011 DOI: 10.1136/openhrt-2016-000561]

64 **Maeda R**, Minami Y, Haruki S, Kanbayashi K, Itani R, Suzuki A, Ejima K, Shiga T, Shoda M, Hagiwara N. Implantable cardioverter defibrillator therapy and sudden death risk stratification in hypertrophic cardiomyopathy patients with midventricular obstruction: A single-center experience. *Int J Cardiol* 2016; **214**: 419-422 [PMID: 27088403 DOI: 10.1016/j.ijcard.2016.03.231]

65 **Epstein AE**, Abraham WT, Bianco NR, Kern KB, Mirro M, Rao SV, Rhee EK, Solomon SD, Szymkiewicz SJ. Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post-myocardial infarction. *J Am Coll Cardiol* 2013; **62**: 2000-2007 [PMID: 23916930 DOI: 10.1016/j.jacc.2013.05.086]

66 **Chung MK**, Szymkiewicz SJ, Shao M, Zishiri E, Niebauer MJ, Lindsay BD, Tchou PJ. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. *J Am Coll Cardiol* 2010; **56**: 194-203 [PMID: 20620738 DOI: 10.1016/j.jacc.2010.04.016]

67 **Olgin JE**, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, Zweibel S, Buxton AE, Elayi CS, Chung EH, Rashba E, Borggrefe M, Hue TF, Maguire C, Lin F, Simon JA, Hulley S, Lee BK; VEST Investigators. Wearable Cardioverter-Defibrillator after Myocardial Infarction. *N Engl J Med* 2018; **379**: 1205-1215 [PMID: 30280654 DOI: 10.1056/NEJMoa1800781]

68 **Hohnloser SH**, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ; DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004; **351**: 2481-2488 [PMID: 15590950 DOI: 10.1056/NEJMoa041489]

69 **Lim HS**, Lip GY, Tse HF. Implantable cardioverter defibrillator following acute myocardial infarction: the '48-hour' and '40-day' rule. *Europace* 2008; **10**: 536-539 [PMID: 18367548 DOI: 10.1093/europace/eun070]

70 **Al-Khatib SM**, Hellkamp AS, Fonarow GC, Mark DB, Curtis LH, Hernandez AF, Anstrom KJ, Peterson ED, Sanders GD, Al-Khalidi HR, Hammill BG, Heidenreich PA, Hammill SC. Association between prophylactic implantable cardioverter-defibrillators and survival in patients with left ventricular ejection fraction between 30% and 35%. *JAMA* 2014; **311**: 2209-2215 [PMID: 24893088 DOI: 10.1001/jama.2014.5310]

71 **Schwartz PJ**, Spazzolini C, Priori SG, Crotti L, Vicentini A, Landolina M, Gasparini M, Wilde AA, Knops RE, Denjoy I, Toivonen L, Mönnig G, Al-Fayyadh M, Jordaens L, Borggrefe M, Holmgren C, Brugada P, De Roy L, Hohnloser SH, Brink PA. Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them?: data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry. *Circulation* 2010; **122**: 1272-1282 [PMID: 20837891 DOI: 10.1161/CIRCULATIONAHA.110.950147]

72 **Kutyifa V**, Moss AJ, Klein H, Biton Y, McNitt S, MacKecknie B, Zareba W, Goldenberg I. Use of the wearable cardioverter defibrillator in high-risk cardiac patients: data from the Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry). *Circulation* 2015; **132**: 1613-1619 [PMID: 26316618 DOI: 10.1161/CIRCULATIONAHA.115.015677]

73 **Nguyen E**. Wearable Cardioverter-defibrillators for the Prevention of Sudden Cardiac Death: A Meta-analysis. *J Innov Card Rhythm Manag* 2018 [DOI: 10.19102/icrm.2018.090506]

74 **Pillarisetti J**, Emert M, Biria M, Chotia R, Guda R, Bommana S, Pimentel R, Vacek J, Dendi R, Berenbom L, Dawn B, Lakkireddy D. Under-Utilization of Implantable Cardioverter Defibrillators in Patients with Heart Failure - The Current State of Sudden Cardiac Death Prophylaxis. *Indian Pacing Electrophysiol J* 2016; **15**: 20-29 [PMID: 27186055 DOI: 10.1016/S0972-6292(16)30838-5]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 March 26; 11(3): 120-125

DOI: 10.4330/wjc.v11.i3.120

ISSN 1949-8462 (online)

CASE REPORT

Utility of recognizing early electrocardiogram changes in bronchogenic Takotsubo cardiomyopathy: A case report

Maria Khan, Husam Watti, Khagendra Dahal, Paari Dominic

ORCID number: Maria Khan (0000-0002-4949-1221); Husam Watti (0000-0002-4234-1431); Khagendra Dahal (0000-0001-5335-0846); Paari Dominic (0000-0002-7843-375X).

Author contributions: Khan M designed the report, collected the patient's clinical data, analyzed the data and wrote the paper; Watti H reviewed and revised the paper, collected and analyzed images and imaging related information; Dahal K revised and reviewed the paper, and analyzed images; Dominic P reviewed and revised the paper.

Informed consent statement: Consent was obtained the patient's next of kin by the primary author for publication of this report and any accompanying images.

Conflict-of-interest statement: All of the authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The guidelines of the CARE Checklist (2016) were implemented in the production of this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See:

Maria Khan, Department of Internal Medicine, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA 71130, United States

Husam Watti, Khagendra Dahal, Paari Dominic, Department of Cardiology, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA 71130, United States

Corresponding author: Maria Khan, MD, Doctor, Department of Internal Medicine, Louisiana State University Health Sciences Center Shreveport, 1501 Kings Highway, Shreveport, LA 71130, United States. mkhan9@lsuhsc.edu
Telephone: +1-816-8638730

Abstract

BACKGROUND

Takotsubo cardiomyopathy (TCM) is a transient reversible systolic dysfunction, estimated to be the culprit in 1%-2% of patients presenting with clinical symptoms of acute coronary syndrome (ACS). TCM was previously thought to be indistinguishable from ACS on the basis of electrocardiogram (EKG) findings; many authors now describe specific EKG changes that distinguish TCM from ACS as well as aid in early recognition of TCM.

CASE SUMMARY

This unique case presentation illustrates an uncommon subtype of TCM, and very clearly exemplifies the specific EKG changes meant to aid in distinguishing TCM from ACS. A bronchogenic subtype of TCM has been proposed, given its prevalence and distinguishing features from TCM without pulmonary pathology; this case exemplifies that notion. The specific EKG changes of low QRS voltage and attenuation of the amplitude of the QRS complex are now being noted in the EKGs of TCM patients. This patient presented for worsening shortness of breath and increased productive cough; her EKG revealed ST elevations in leads V3-V6, and low voltage QRS complexes when compared to previous EKG from 12 wk ago; troponin peaked at 5.16 ng/mL. Left heart catheterization did not reveal significant lesions and left ventriculogram findings were consistent with TCM. Patient was treated for COPD exacerbation, her symptoms improved significantly; she was sent home on the appropriate medications.

CONCLUSION

This case exemplifies EKG changes noted in TCM patients who may aid in early detection and appropriate treatment of TCM.

Key words: Takotsubo cardiomyopathy; Apical ballooning; Case report; Early

http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: January 11, 2019
Peer-review started: January 11, 2019
First decision: January 26, 2019
Revised: March 1, 2019
Accepted: March 16, 2019
Article in press: March 16, 2019
Published online: March 26, 2019

P-Reviewer: Fabbian F, Rostagno C
S-Editor: Ji FF
L-Editor: A
E-Editor: Wu YXJ

electrocardiogram changes; Chronic obstructive pulmonary disease exacerbation; Broken heart syndrome

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This case report presents a unique opportunity to exemplify specific electrocardiogram (EKG) changes noted in patients with Takotsubo cardiomyopathy (TCM). Low QRS voltage and attenuation of the amplitude of the QRS complex have been noted in the EKGs of TCM patients. This case report presents a patient who had an EKG performed 12 wk prior to developing TCM and thus provides a recent EKG to compare the EKG changes noted during TCM.

Citation: Khan M, Watti H, Dahal K, Dominic P. Utility of recognizing early electrocardiogram changes in bronchogenic Takotsubo cardiomyopathy: A case report. *World J Cardiol* 2019; 11(3): 120-125
URL: https://www.wjgnet.com/1949-8462/full/v11/i3/120.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i3.120

INTRODUCTION

Takotsubo cardiomyopathy (TCM) is characterized by reversible systolic dysfunction of the left ventricle in the absence of any significant obstructive coronary artery disease[1]. Most commonly, the apical and the middle segments of the left ventricle are seen to be akinetic[1]. Its clinical presentation is said to be indistinguishable from myocardial infarct[2]. The gold standard used to differentiate acute coronary syndrome (ACS) from TCM is coronary angiography as it clearly shows if a significant obstructive lesion is present[1]. Although some authors believe that it is not possible to differentiate ACS form TCM based of electrocardiogram (EKG)alone, may new case reports have been published that support the existence of unique EKG changes present only in TCM. This is a unique case presentation as it not only illustrates an uncommon subtype of TCM, but also very clearly exemplifies specific EKG changes meant to aid in distinguishing TCM from ACS. This was previously thought to be indistinguishable on the basis of electrocardiogram (EKG).

CASE PRESENTATION

Chief complaints

A 63 year-old Caucasian female presented to the emergency department for acute exacerbation of her chronic obstructive pulmonary disease (COPD). The patient had been experiencing 2 wk of worsening shortness of breath, productive cough and increased sputum production.

History of present illness

She had been using her inhalers more frequently at home and had increased her home oxygen to 3 liters, still with only minimal relief. On the day of presentation to the emergency department, the patient called an ambulance as she was concerned about her breathing.

History of past illness

She was noted to have a past medical history of COPD (on 2 liters home oxygen), coronary artery disease [status post right coronary artery (RCA) stent in 2000's], subarachnoid hemorrhage and tobacco abuse.

Personal and family history

No other family history or personal history was reported.

Physical examination upon admission

When the patient arrived in the emergency department, her physical exam revealed a blood pressure of 98/74 mmHg, pulse 101, temperature 97.5 °F (36.4 °C), temperature source Oral, respiratory rate of 27, and oxygen saturation of 95% on 3-4 liters of

oxygen. Scoliosis of spine was also noted. Patient was noted to be in respiratory distress.

Laboratory examinations

Initial troponin on presentation was 2.74 ng/mL and peaked at 5.16 ng/mL. Her renal function and hemoglobin were within normal limits. Her EKG showed sinus tachycardia with ST elevations in leads V3-V6 as well as low voltage QRS complexes when compared to previous EKG from 12 wk prior (Figures 1 and 2).

Cardiology was consulted for evaluation. The patient was advised to have an emergent left heart catheterization (LHC). However, the patient refused initially and wanted only medical management. She was not a candidate for thrombolysis due to history of subarachnoid hemorrhage.

Imaging examinations

A 2-D echocardiogram was done which showed mid and distal septal, anterior, lateral and apical wall akinesis concerning for ischemia in the left anterior descending (LAD) territory (Figure 3). The patient was then agreeable to have the cardiac angiogram 3 days after the initial presentation. Cardiac angiogram showed patent RCA stent with only mild luminal irregularities noted in the RCA. Left main was angiographically normal, as was the left circumflex. Mild to moderate stenotic lesions were noted in LAD, Diagonal 1 and Ramus Intermedius (Figure 4). A Left ventriculogram revealed hyperkinetic basal segments and akinesis of the apex and periapical segments consistent with TCM (Figure 5).

FINAL DIAGNOSIS

Based on the findings of the left ventriculogram, the LHC, and the EKG findings the patient was diagnosed with TCM.

TREATMENT

The patient was treated for COPD exacerbation. Her breathing improved, and she was back to her baseline 2 liters oxygen use. She was discharged to a long term acute care facility with medications ASA 81mg, Atorvastatin 80 mg, carvedilol 12.5 mg BID and losartan 25 mg. Her inhalers included tiotropium, fluticasone-salmeterol and ipratropium-albuterol. The patient was also started on sertraline 50 mg and instructed to continue her home medication of lorazepam 0.5 mg every 6 h as needed for anxiety.

OUTCOME AND FOLLOW-UP

Follow up Echo and EKG were planned; however, patient had passed away due to worsening of the pulmonary disease.

DISCUSSION

The Mayo Clinic diagnostic criteria, proposes that 4 criteria must be met in order to diagnose TCM: These criteria are, transient hypokinesis, akinesis or dyskinesis of the left ventricular mid segments, new ECG changes mimicking acute MI, absence of angiographic evidence of obstructive coronary disease, and absence of pheochromocytoma and myocarditis[2].

It has been widely suggested that a bronchogenic sub type of TCM exists[3]. Although not as common, there have been some reported cases of TCM in the setting of COPD or asthma[4,5]. Some authors even estimate that pulmonary pathologies are suspected to be found in as high as 44% of TCM cases[6], thus justifying the creation of a separate classification as a bronchogenic subtype. The disproportionate predominance of sympathetic activity during a COPD exacerbation has been noted as a possible trigger for TCM[4]. Rajwani *et al*[3] described 5 specific cases of bronchogenic TCM and noted some distinguishing features. The absence of chest pain, as with our patient, is noted as a main distinguishing feature of the bronchogenic subgroup of TCM. Progressive dyspnea was also a commonality noted in all 5 cases; this was also present in our patient.

TCM is commonly seen in postmenopausal women, as with our patient[2]. Also in the setting of TCM, wall motion abnormalities are seen to extend beyond the

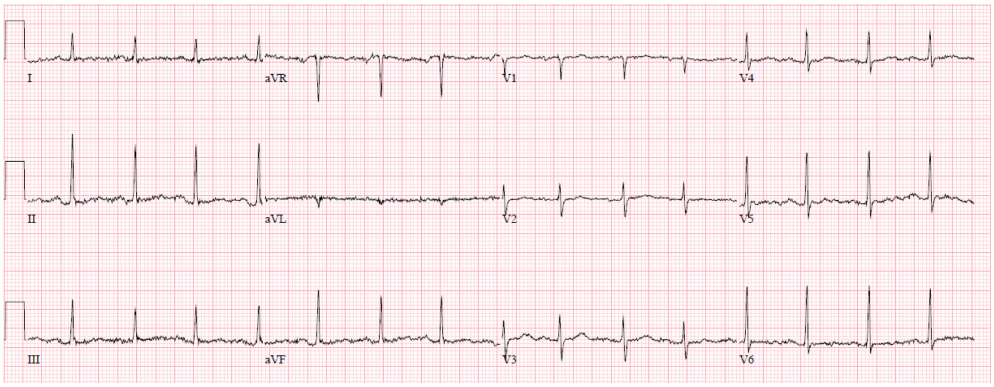


Figure 1 Electrocardiogram 12 wk before initial presentation.

distribution pattern of any single epicardial coronary artery, as seen in our case report[2]. Though TCM is thought to be indistinguishable from ACS on the basis of EKG findings, Madias *et al*[7] described a noticeably low voltage and attenuated QRS complexes in association with TCM seen in over 90% of the EKGs reviewed for published literature of TCM cases. Since then, many other cases have been reported showing marked QRS complex attenuation in the setting of TCM. In our case, a previous EKG from 12 wk before the patient presentation was available for comparison (Figures 1 and 2). Low QRS voltage (LQRSV), which is defined as ≤ 5 mm in limb leads and/or ≤ 10 mm in precordial leads, and significant attenuation of QRS complexes was appreciated. The likely mechanisms of this phenomenon was explained by author Madias who explored myocardial edema versus counterbalancing of depolarization vectors as the likely mechanisms and concluded that myocardial edema is the most likely cause of the LQRSV appreciated in EKGs of TCM patients[7]. This was supported by review of multiple TCM cases where patients had cardiac MRI performed that revealed myocardial edema[7]. Madias used Ohm's law (Voltage = Current x Resistance) to explain how changes in the resistance of the electric conductor caused by myocardial edema can account for this phenomenon of LQRSV and attenuation of the amplitude of the QRS complex (AAQRS) since anything that alters resistance or current will result in changes in voltage[7]. Extracardiac pathologies such as pulmonary congestion and pleural effusion, would also influence these changes[7].

TCM is a transient reversible systolic dysfunction and is estimated to be the culprit in 1%-2% of patient presenting with clinical symptoms of a ACS[2]. These patients do not require treatment with heparin drip and antiplatelet therapy thus it is important for clinicians to have a high level of suspicion to identify the correct etiology. As suggested by author Madias, utilizing EKG changes can aid in early identification of TCM and differentiation of TCM from ACS.

CONCLUSION

Though traditionally TCM was thought to be indistinguishable from ACS, many new case reports and papers have discussed using novel EKG criteria to aid in early recognition of TCM; this case exemplifies the characteristic EKG changes seen in TCM.

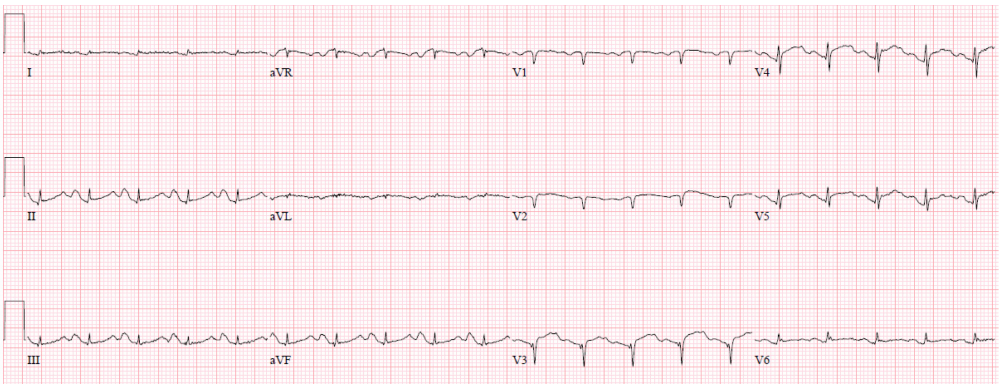


Figure 2 Electrocardiogram with acute changes on initial presentation. Significant attenuation of amplitude of QRS complexes noted diffusely.

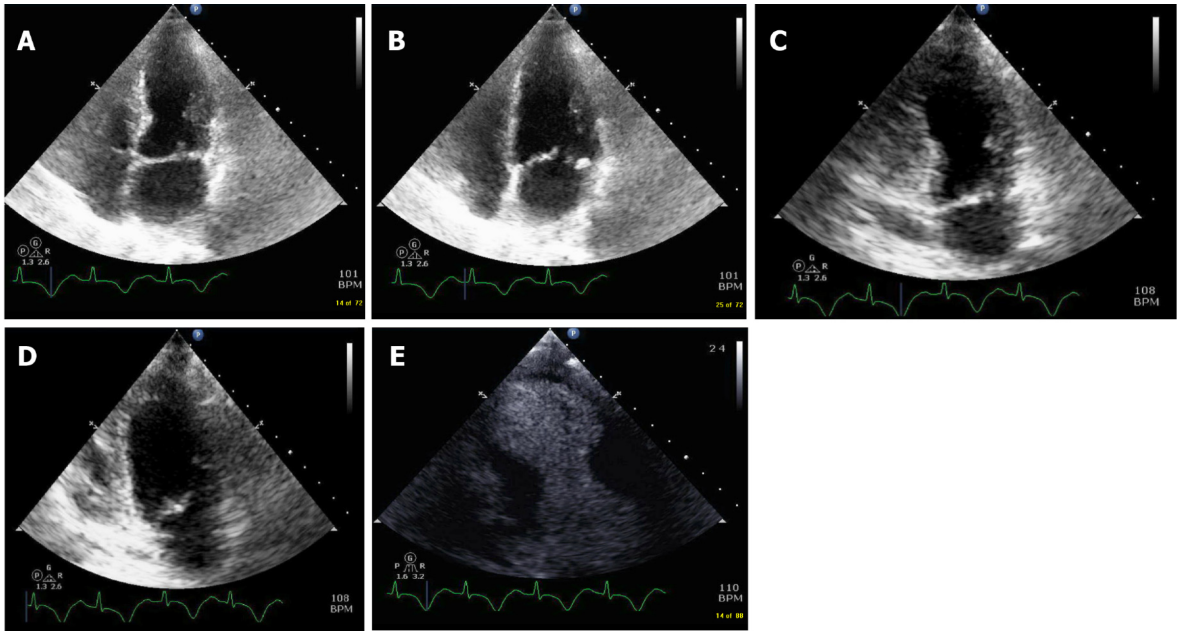


Figure 3 Four and 2 chamber view. A: 4 chamber view demonstrating akinesis of the septal and lateral apical segments; B: 4 chamber view demonstrating akinesis of the septal and lateral apical segments; C: 2-chamber view showing akinesis of anterior-inferior apical segments during systole; D: 2-chamber view showing akinesis of anterior and inferior apical segments during diastole; E: Contrast echocardiography showing akinesis of anterior and inferior apical segments.

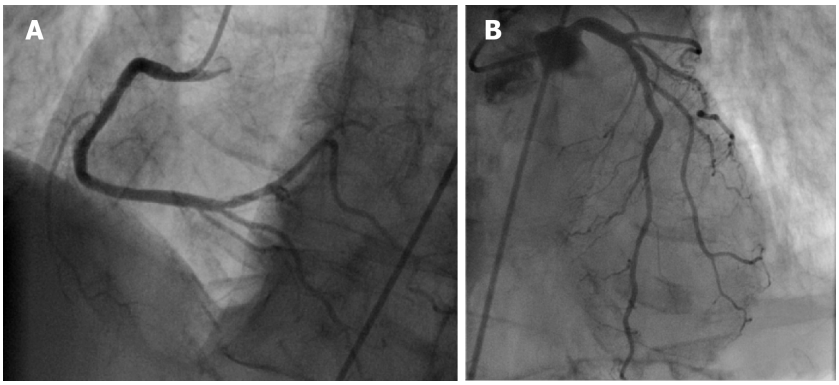


Figure 4 Coronary angiography of right coronary artery and left system demonstrating non obstructive coronary artery disease. A: Coronary angiography of right coronary artery demonstrating non obstructive coronary artery disease; B: Coronary angiography of the left system demonstrating non obstructive coronary artery disease.

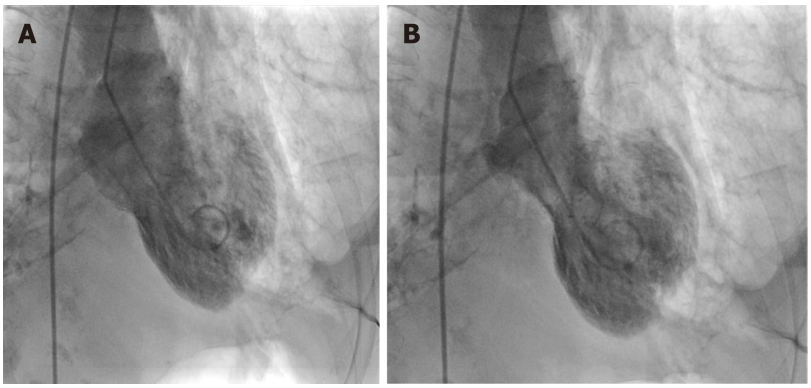


Figure 5 Left ventriculography demonstrating hyperkinetic basal segments and akinetic apex during diastole and systole. A: Left ventriculography demonstrating hyperkinetic basal segments and akinetic apex during diastole; B: Left ventriculogram demonstrating hyperkinetic basal segments and akinetic apex during systole.

REFERENCES

1 **Demirelli S**, Ermis E, Hatem E, Uslu A, Askin L. Focal mid-ventricular anterior ballooning: An unusual pattern of Takotsubo cardiomyopathy. *Intractable Rare Dis Res* 2015; **4**: 108-110 [PMID: 25984431 DOI: 10.5582/irdr.2015.01012]

2 **Madhavan M**, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. *Herz* 2010; **35**: 240-243 [PMID: 20582391 DOI: 10.1007/s00059-010-3339-x]

3 **Rajwani A**, Adam Z, Hall JA. Bronchogenic stress cardiomyopathy: a case series. *Cardiology* 2015; **130**: 106-111 [PMID: 25612607 DOI: 10.1159/000369296]

4 **Katsa I**, Christia P, Massera D, Faillace R. Recurrent Stress Cardiomyopathy During COPD Exacerbation: Are Beta-adrenergic Agonists Only to Blame? *Cureus* 2017; **9**: e1166 [PMID: 28507838 DOI: 10.7759/cureus.1166]

5 **Manfredini R**, Fabbian F, Giorgi AD, Pala M, Menegatti AM, Parisi C, Misurati E, Tiseo R, Gallerani M, Salmi R, Bossone E. Heart and lung, a dangerous liaison-Tako-tsubo cardiomyopathy and respiratory diseases: A systematic review. *World J Cardiol* 2014; **6**: 338-344 [PMID: 24944763 DOI: 10.4330/wjc.v6.i5.338]

6 **Hertting K**, Krause K, Härle T, Boczor S, Reimers J, Kuck KH. Transient left ventricular apical ballooning in a community hospital in Germany. *Int J Cardiol* 2006; **112**: 282-288 [PMID: 16325287 DOI: 10.1016/j.ijcard.2005.09.006]

7 **Madias JE**. Transient attenuation of the amplitude of the QRS complexes in the diagnosis of Takotsubo syndrome. *Eur Heart J Acute Cardiovasc Care* 2014; **3**: 28-36 [PMID: 24562801 DOI: 10.1177/2048872613504311]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 April 26; 11(4): 126-136

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 4 April 26, 2019

META-ANALYSIS

Contents

World Journal of Cardiology

Volume 11 Number 4 April 26, 2019

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Mahesh Anantha-Narayanan, MD, Academic Fellow, Doctor, Division of Cardiovascular Sciences, University of Minnesota, Minneapolis, MN 55455, United States

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yun-Xiaojian Wu* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
April 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 April 26; 11(4): 126-136

DOI: 10.4330/wjc.v11.i4.126

ISSN 1949-8462 (online)

META-ANALYSIS

Who benefits from percutaneous closure of patent foramen ovale *vs* medical therapy for stroke prevention? In-depth and updated meta-analysis of randomized trials

Khagendra Dahal, Adil Yousuf, Hussam Watti, Brannen Liang, Sharan Sharma, Jharendra Rijal, Pavan Katikaneni, Kalgi Modi, Neeraj Tandon, Michael Azrin, Juyong Lee

ORCID number: Khagendra Dahal (0000-0001-53350846); Adil Yousuf (0000-0002-9849-0938); Hussam Watti (0000-0002-4243-1431); Brannen Liang (0000-0002-6384-5938); Sharan Sharma (0000-0003-1475-6004); Jharendra Rijal (0000-0002-6964-8513); Kalgi Modi (0000-0001-8651-0826); Neeraj Tandon (0000-0002-8108-698X); Michael Azrin (0000-0002-2669-0703); Juyong Lee (0000-0001-5412-5472).

Author contributions: Dahal K, Watti H and Lee J contributed to study concept and design; Dahal K, Yousuf A, Watti H, Liang B, Sharma, Rijal J, Katikaneni P, Modi K, Tandon N, Azrin M and Lee J contributed to acquisition, analysis, or interpretation of data; Dahal K, Yousuf A, Watti H and Liang B contributed to drafting of the manuscript; Dahal K, Yousuf A, Watti H, Liang B, Sharma S, Rijal J, Katikaneni P, Modi K, Tandon N, Azrin M and Lee J contributed to critical revision of the manuscript for important intellectual content; Dahal K contributed to statistical analysis; Modi K, Tandon N, Azrin M and Lee J contributed to study supervision.

Conflict-of-interest statement: None declared.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009

Khagendra Dahal, Adil Yousuf, Hussam Watti, Pavan Katikaneni, Kalgi Modi, Division of Cardiology, Department of Medicine, Louisiana State University Health Sciences Center, Shreveport, LA 71103, United States

Brannen Liang, Department of Medicine, University of Connecticut Health Center, Farmington, CT 06030, United States

Sharan Sharma, Kansas City Heart Rhythm Institute, Overland Park, KS 66215, United States

Jharendra Rijal, Division of Cardiology, Hartford Medical Center, Hartford, CT 06102, United States

Neeraj Tandon, Cardiology Section, Overton Brooks VA Medical Center, Shreveport, LA 71101, United States

Michael Azrin, Juyong Lee, Division of Cardiology, University of Connecticut Health Center, Farmington, CT 06030, United States

Corresponding author: Juyong Lee, MD, PhD, Division of Cardiology, University of Connecticut Health Center, Farmington, CT 06030, United States. jlee@uchc.edu
Telephone: +1-860-6793343

Abstract

BACKGROUND

A few randomized clinical trials (RCT) and their meta-analyses have found patent foramen ovale closure (PFOC) to be beneficial in prevention of stroke compared to medical therapy. Whether the benefit is extended across all groups of patients remains unclear.

AIM

To evaluate the efficacy and safety of PFOC *vs* medical therapy in different groups of patients presenting with stroke, we performed this meta-analysis of RCTs.

METHODS

Electronic search of PubMed, EMBASE, Cochrane Central, CINAHL and ProQuest Central and manual search were performed from inception through September 2018 for RCTs. Ischemic stroke (IS), transient ischemic attack (TIA), a composite of IS, TIA and systemic embolism (SE), mortality, major bleeding,

atrial fibrillation (AF) and procedural complications were the major outcomes. Random-effects model was used to perform analyses.

RESULTS

Meta-analysis of 6 RCTs including 3560 patients showed that the PFOC, compared to medical therapy reduced the risk of IS [odds ratio: 0.34; 95% confidence interval: 0.15-0.78; $P = 0.01$] and the composite of IS, TIA and SE [0.55 (0.32-0.93); $P = 0.02$] and increased the AF risk [4.79 (2.35-9.77); $P < 0.0001$]. No statistical difference was observed in the risk of TIA [0.86 (0.54-1.38); $P = 0.54$], mortality [0.74 (0.28-1.93); $P = 0.53$] and major bleeding [0.81 (0.42-1.56); $P = 0.53$] between two strategies. Subgroup analyses showed that compared to medical therapy, PFOC reduced the risk of stroke in persons who were males, ≤ 45 years of age and had large shunt or atrial septal aneurysm.

CONCLUSION

In certain groups of patients presenting with stroke, PFOC is beneficial in preventing future stroke compared to medical therapy.

Key words: Patent foramen ovale; Stroke; Antiplatelet therapy; Anticoagulation; Meta-analysis

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Closure of patent foramen ovale closure (PFOC) is a treatment modality for patients with stroke. To evaluate the efficacy and safety of PFOC *vs* medical therapy in different groups of patients presenting with stroke, we performed this meta-analysis of randomized trials following standard techniques. It showed that PFOC, compared to medical therapy reduced the risk of ischemic stroke and the composite outcome of stroke, transient ischemic attack (TIA) and systemic thromboembolism but no difference was observed in the risk of TIA, mortality and major bleeding. PFOC increased the risk of atrial fibrillation. Subgroup analyses showed that PFOC reduced the risk of stroke in males.

Citation: Dahal K, Yousuf A, Watti H, Liang B, Sharma S, Rijal J, Katikaneni P, Modi K, Tandon N, Azrin M, Lee J. Who benefits from percutaneous closure of patent foramen ovale *vs* medical therapy for stroke prevention? In-depth and updated meta-analysis of randomized trials. *World J Cardiol* 2019; 11(4): 126-136
URL: https://www.wjgnet.com/1949-8462/full/v11/i4/126.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i4.126

Checklist.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: January 8, 2019
Peer-review started: January 8, 2019
First decision: January 21, 2019
Revised: February 11, 2019
Accepted: March 27, 2019
Article in press: March 28, 2019
Published online: April 26, 2019

P-Reviewer: Greenway SC, Vermeersch P
S-Editor: Ji FF
L-Editor: A
E-Editor: Wu YXJ

INTRODUCTION

Every year more than 10 million people suffer from stroke in the world, two thirds of which are ischemic in etiology[1]. Up to 32% of patients with ischemic stroke (IS) are cryptogenic in origin[2] and 43% of cryptogenic stroke patients have patent foramen ovale (PFO)[3]. Many people who are living with a PFO are asymptomatic, until they experience the symptoms of a cryptogenic stroke. While the current guidelines recommend medical therapy to prevent future strokes in such patients, percutaneous closure of PFO is an alternative that has been shown to reduce future strokes in several randomized trials and their meta-analyses[4-8].

While previously published randomized clinical trials (RCTs) were inconclusive[9-11] to show a benefit, their meta-analyses did show a statistically clear benefit of PFO closure over medical therapy[12,13]. Recently three additional trials, and a prolonged follow-up results of a previously published RCT have been published and reported more evidence of a reduction in recurrent stroke after PFO closure[6-8,14]. Nevertheless, it is unclear which group of patients benefit from PFO closure compared to medical therapy and how PFO closure compares with anticoagulation therapy. In that regard, to perform an updated meta-analysis on this evolving topic of interest and to evaluate the different patient groups who will benefit from PFO closure compared to medical therapy, we performed a meta-analysis.

MATERIALS AND METHODS

Data sources and search strategy

We performed and reported this meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15]. We searched electronic databases of MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials and CINAHL with no language restriction from inception through September 2018 using the search terms: "patent foramen ovale" OR "PFO" AND "closure" AND "stroke" OR "transient ischemic attack" OR "TIA" with restriction to randomized design. Two investigators (KD and AY) independently performed the database search and agreed on final study selection. In addition, a manual search was performed by reviewing the references of randomized trials and meta-analyses.

Study inclusion and exclusion criteria

Randomized trials comparing patent foramen ovale closure and medical therapy in adult patients (≥ 18 years) with stroke were selected for meta-analysis. Studies were excluded if they were meeting abstracts, single arm or non-randomized studies and were performed for different disease states.

Data extraction

Two investigators (BL and AY) extracted data from the selected studies in duplicate using standardized data-extraction form and obtained data on study characteristics (study design, patient selection, inclusion and exclusion criteria, follow-up duration, number of patients, type of PFO device and medical therapy and outcomes), patient characteristics (age, sex, race, co-morbidities including diabetes mellitus, hypertension, hyperlipidemia and body mass index, and medication use), and crude events on mortality, recurrent stroke, transient ischemic attack (TIA), systemic embolism (SE), major bleeding and procedural complications at follow-up.

Outcomes

Recurrent IS, TIA, SE, a composite of IS, TIA and SE, major bleeding, mortality and procedural complications including atrial fibrillation (AF) risk were the major outcomes.

Statistical analysis

We calculated odds ratio (OR) with 95% confidence interval (CI) using random-effects model from the individual studies using the total number of events and patients. The quality of studies was assessed with Cochrane Collaboration's Bias Assessment Tools[16]. Study heterogeneity was evaluated with Cochran's Q and I^2 index and significant heterogeneity ($I^2 > 50\%$) was further explored with sensitivity analyses. We planned pre-specified subgroup analyses based on age, gender, presence of atrial septal aneurysm (ASA) and PFO size (as defined the individual papers). We performed statistical analyses with Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark).

RESULTS

Description of included studies

The flow diagram of study selection is shown in Figure 1. Electronic search of five databases (PubMed, EMBASE, CENTRAL, CINAHL and ProQuest Central) retrieved a total of 564 publications. After removal of 136 duplicates, we screened 428 citations for eligibility and extracted 33 publications for full text review. Finally, we had a total of seven publications from six randomized trials for qualitative and quantitative analysis. One study resulted in two publications reporting findings at different duration of follow-up.

The individual study characteristics, patient characteristics, and procedural outcomes and complications of the included studies are shown respectively in Tables 1, 2 and 3. There were 3560 total patients (1889 in patent foramen ovale closure (PFOC) arm and 1671 in medical therapy arm). Studies included only patients under 60 years of age. Follow-up duration was between 2 and 5.9 years. The medical therapy arm in two of these trials (REDUCE and CLOSE) consisted of anti-platelet therapy only[6,8], whereas the other four trials (RESPECT, CLOSURE I, PC and DEFENSE PFO) permitted the use of anti-platelet therapy, anticoagulation or both in the medical-therapy group at the discretion of the investigating physicians[7,9,10,14].

Outcomes

PFO closure, compared to medical therapy reduced the risk of IS (OR: 0.34; 95%CI:

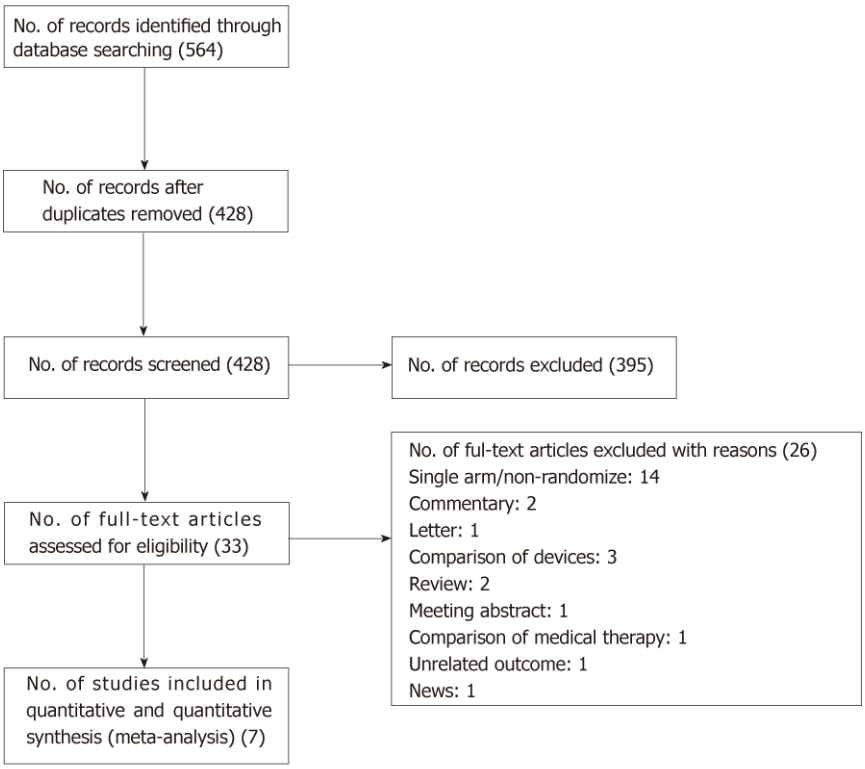


Figure 1 PRISMA flow diagram of the study search.

0.15-0.78, P = 0.01; I^2 = 54%) and the composite outcome of IS, TIA and systemic thromboembolism [0.44 (0.22-0.90); P = 0.02; I^2 = 76%] (Figure 2). With PFO closure, no difference was observed in the risk of TIA [0.55 (0.32-0.93); P = 0.02], mortality [0.74 (0.28-1.93); P = 0.53; I^2 = 0%] and major bleeding [0.81 (0.42-1.56); P = 0.53; I^2 = 19%] (Figure 3). PFO closure increased the risk of AF [4.79 (2.35-9.77); P < 0.0001; I^2 = 12%] compared to medical therapy (Figure 4). The risk of procedural complications was [18.08 (5.58-58.55); P <0.00001; I^2 = 0%].

Procedural success, complications and risk of AF

Procedural success ranged from 88.3%-99.6%, and PFO closure was successful in 88.6%-100% patients (Table 3). The risk of AF ranged from 1.4%-6.6% across different devices. The risk of AF seemed to numerically lower in patients who received Amplatzer PFO Occluder (1.4%-3.3%) compared to other devices (4.6%-6.6%).

Sensitivity and subgroup analyses

Several sensitivity analyses were planned a-priori. Since CLOSURE I Trial used Starflex closure device, which the manufacturer has stopped producing, we performed analysis after excluding that study. The overall results did not change. An analysis restricted to the studies with at least 3 years or more follow-up (after exclusion of CLOSURE I and DEFENCE PFO Trials) did not change the overall results.

Several subgroup analyses were planned a-priori. PFO closure, compared to medical therapy resulted in a reduction in the risk of stroke (Figure 5) in patients who were male [0.25; 0.07-0.96; P = 0.04; I^2 = 61%], ≤ 45 years of age [0.37; 0.17-0.82; P = 0.01; I^2 = 0%] and had large shunt [0.22; 0.11-0.47; P < 0.0001; I^2 = 0%] or ASA [0.16; 0.05-0.51; P = 0.002; I^2 = 0%]. Compared to medical therapy, PFO closure showed a reduction in stroke risk in females [0.50; 0.23-1.08; P = 0.08; I^2 = 0%] and patients > 45 years of age [0.32; 0.10-1.06; P = 0.06; I^2 = 52%]; however, it did not reach statistical significance. In patients with small shunt, there was no statistical difference in the stroke outcomes [0.88; 0.34-2.27; P = 0.8; I^2 = 11%].

Study quality and publication bias

All the randomized studies showed bias for non-blinding of the participants and the outcomes per Cochrane collaboration's bias tools. Publication bias was not tested due to small number of studies for meaningful assessment of publication bias.

Table 1 Study characteristics

Study name,year	Country of origin	Study design	Indication of PFOC	Total Patients (PFOC + medical therapy), *n*	Medical therapy	Type of device	Follow-up, in years (mean)
CLOSE[6], 2017	France and Germany	Multicenter, randomized, open-label, superiority trial	Recent stroke due to PFO with atrial septal aneurysm or substantial right-to-left intra-atrial shunt	663[1] (238 + 235)	Antiplatelet therapy (aspirin + clopidogrel)[1]	11 different devices	5.4 PFOC, 5.2 AC-AP
CLOSURE I[11], 2012	United States and Canada	Multicenter, randomized, open-label trial	Stroke or TIA within 6 mo	909 (447 + 462)	Warfarin, aspirin or both	STARFlex device	2
PC Trial[9], 2013	Europe, Canada, Brazil, and Australia	Multicenter, randomized, superiority trial	Stroke, TIA or systemic thromboembolism	414 (204 + 210)	Aspirin+ ticlopidine/clopidogrel	Amplatzer PFO occluder	4.1 PFOC, 4.0 AC/AP
REDUCE[8], 2017	Europe and United States	Multinational, prospective, randomized, controlled, open-label trial	Stroke within 180 d	664 (441 + 223)	Aspirin, aspirin + dipyridamole, or clopidogrel	Helex or Cardioform Septal Occluder	3.2
RESPECT[7], 2017	United States and Canada	Multicenter, randomized, open-label, controlled clinical trial	Stroke within 270 d	980 (499 + 481)	Aspirin + clopidogrel	Amplatzer PFO occluder	5.9
DEFENCE PFO[14], 2018	South Korea	Multicenter, randomized, open-label, superiority	Ischemic stroke in past 6 mos	120 (60 + 60)	Aspirin, aspirin + clopidogrel, aspirin + cilostazol, or warfarin	Amplatzer PFO occluder	2.8

[1]There were patients who received anticoagulation alone but the comparator for that arm was antiplatelet therapy not PFOC. AC: Anticoagulation; AP: Anti-platelet; PFOC: Patent foramen ovale closure.

DISCUSSION

The major findings of our meta-analysis were the reduced risk of recurrent IS and the composite outcome of stroke, TIA, and systemic thromboembolism with PFO closure compared with the medical therapy in patients who presented with stroke. Interestingly, subgroup analyses showed such benefits in persons who were males, ≤ 45 years of age and had large shunt or ASA. In females and persons > 45 years of age, there was a strong trend towards reduction in stroke risk, but it did not reach statistical significance.

Despite all three former PFO trials showing a lack of benefit from PFO closure in reducing the risk of recurrent stroke, meta-analyses and pooled analysis of individual participant data from these three trials showed a significant risk reduction of recurrent IS with PFO closure compared with medical therapy[12,17]. The reported risk of recurrent stroke in these studies was small and less than anticipated, which indicated the need for a larger sample and longer follow-ups to increase the possibility of detecting a significant difference in reducing the risk of recurrent stroke. Three recently published trials and a long-term follow-up of a previously published trial demonstrated that among patients with PFO and cryptogenic IS, PFO closure combined with medical therapy was associated with significantly lower risk of recurrent stroke compared with medical therapy alone. Subsequently, a few meta-analyses have been published comparing PFOC with medical therapy, that have consistently shown a reduction in stroke with PFOC[4,5]. Our meta-analysis adds substantially by performing subgroup analyses in an attempt to define which groups of patients clearly benefit from PFO closure. In addition, we performed an in-depth analysis on the increased risk of AF and the role of anticoagulation as medical therapy. It is interesting to note that our meta-analysis clearly showed benefit in males who are 45 years of age or younger with large shunt or ASA. These are the patient groups who are at increased risk of stroke. In females and patients > 45 years of age, it did not show statistical significance, which could largely be an issue of sample size.

Medical therapy arm across the studies were not the same, which made it hard to

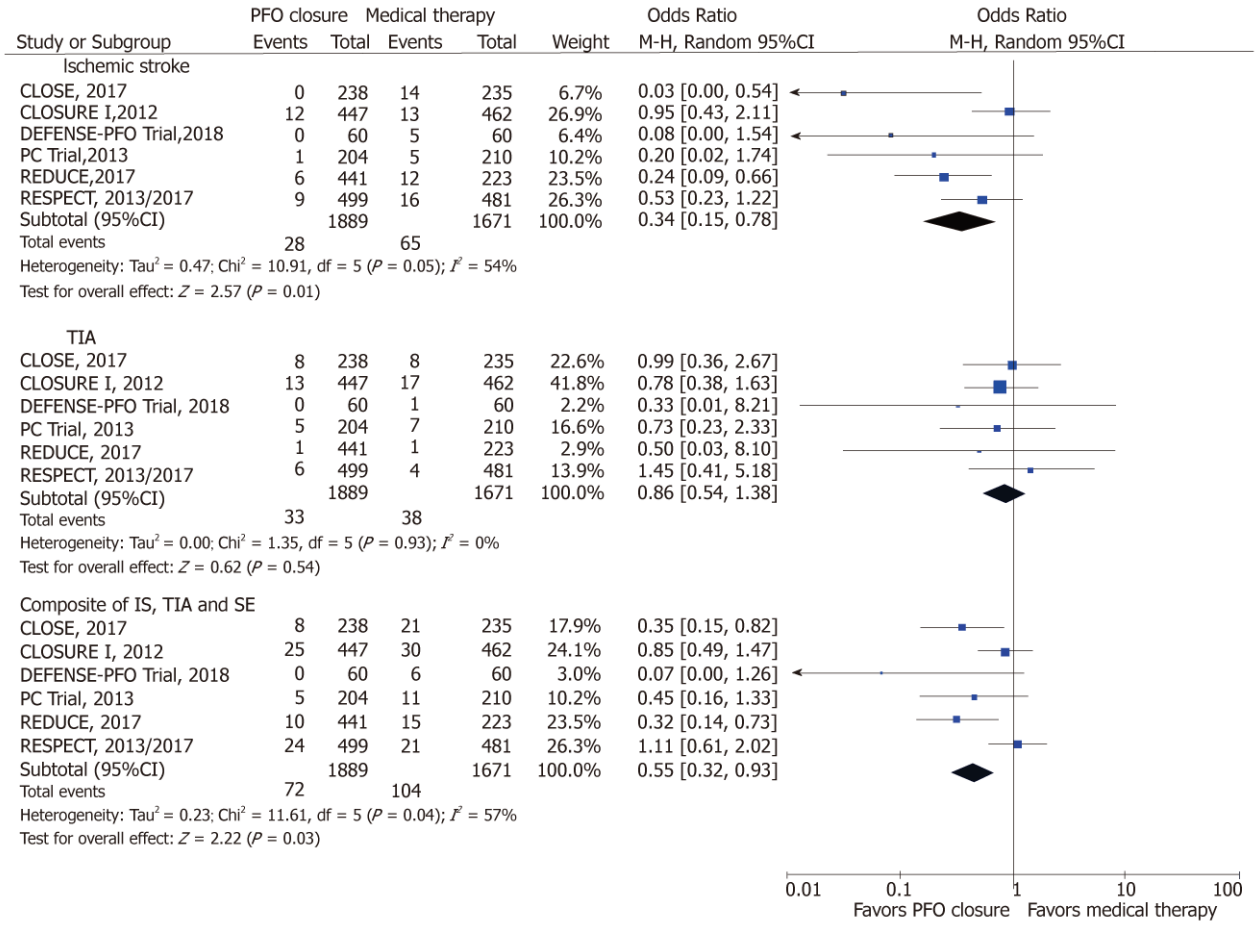


Figure 2 Forest plot for stroke, transient ischemic attack and composite of ischemic stroke, transient ischemic attack and systemic embolism. PFO: Patent foramen ovale.

make a definite statement regarding a medical therapy regimen when compared to PFOC. In the RESPECT trial, anti-platelet agents constituted 74.8% of the medical therapy arm but in the CLOSURE and PC trials, the percentage of patients prescribed antiplatelet *vs* oral anticoagulation was not reported. The subgroup analyses comparing PFO closure *vs* oral anticoagulation in the RESPECT trial did not show advantage in reduction of stroke, whereas similar analysis in CLOSURE Trial did not show advantage of PFOC *vs* medical therapy in reduction of primary end-point, which was a composite of death, stroke, TIA or SE. No such outcomes were reported in the PC trial. In the CLOSE trial, the only trial to compare the anti-platelet agents to oral anticoagulants, the patients in the anti-platelet arm could receive aspirin or aspirin with clopidogrel or with extended release dipyridamole and patients in the oral anticoagulants arm could take either vitamin K antagonists (93%) or direct oral anticoagulants (7%). There were numerically fewer recurrent strokes in the anticoagulation group compared to the antiplatelet group in the intention-to-treat cohort; however, the trial was not powered to detect a difference in such a comparison. Therefore, there is a need for randomized trials with large study population powered to compare the PFO closure to anticoagulation therapy, and anticoagulation to anti-platelet therapy to address the efficacy and safety of anticoagulation therapy compared to antiplatelet therapy and PFO closure.

There was a significant increase in the risk of AF in the PFO closure group compared to the medical therapy group in our meta-analysis, a finding that was reported in several individual trials (CLOSE, REDUCE, CLOSURE-I) and observational studies that used different devices[18,19]. Most of the cases occurred within 30-45 d of the procedure and the majority were transient without recurrence at long-term follow-up (Table 1). This finding suggests that the PFO closure itself could increase the risk for developing AF. However, the significance and clinical relevance of AF associated with PFO closure and the subsequent risk of stroke remains unclear and warrants additional investigations.

Study limitations

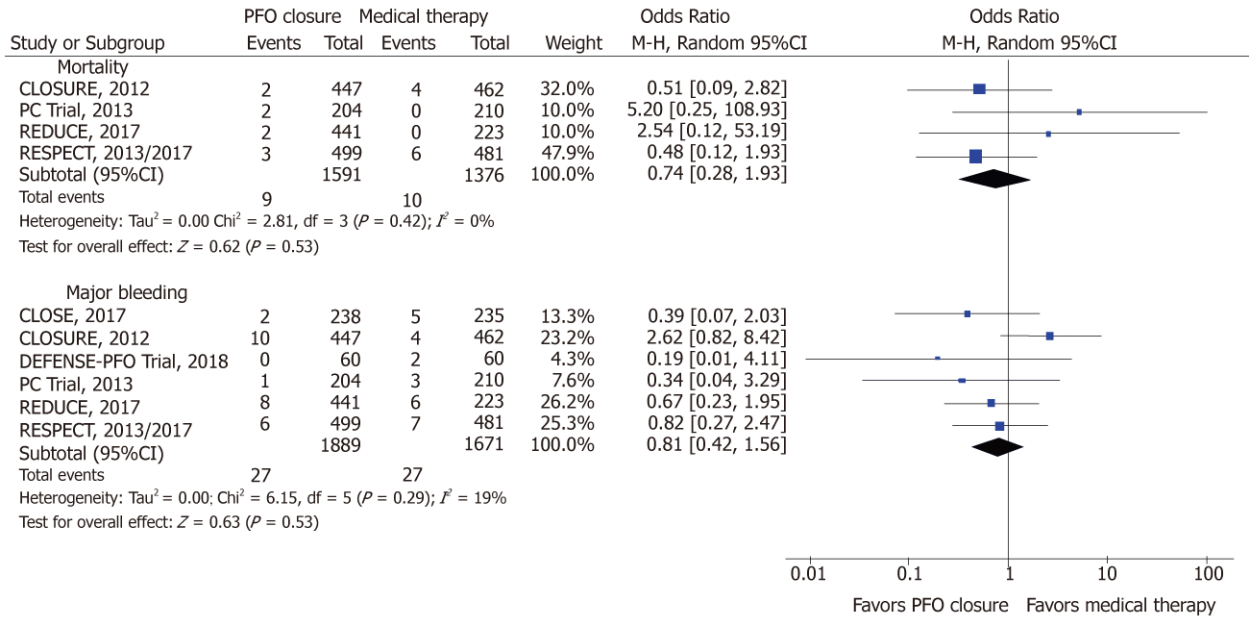


Figure 3 Forest Plot for mortality and major bleeding. PFO: Patent foramen ovale.

The studies were not blinded, which is always a problem in the procedural trials. The medical therapy arms were heterogenous, which limits our ability to make a definite statement regarding specific medical treatment. The subgroup analyses should be interpreted with caution as not all studies reported those outcomes, which reduced the number of individual patients for analysis. However, this meta-analysis is strengthened by in-depth analysis on the type of patients who may benefit from PFO closure compared to medical therapy.

In conclusion, patients with PFO and cryptogenic stroke benefit from percutaneous closure more so in certain population. Further research is needed to assess how the increased periprocedural AF from PFO closure impacts these patients and how does PFO closure compare with anticoagulation in head-to-head trials.

Table 3 Procedural success and complications

Study name, year	Total patients PFOC	Type of Device	Success of device implantation	Success of PFO closure	Procedural complications	Atrial fibrillation/ flutter in PFOC, *n* (%)	Timing of Afib/flutter	Recurrence of Afib/flutter at f/u
CLOSE[6], 2017	238	11 different devices	234/235 (99.6)	202/228 (88.6)	14/238 (5.9)	11 (4.6)	10/11 within a month	None
CLOSURE I[11], 2012	447	STARFlex device	362/405 (89.4)	315/366 (86.1)	13/402 (3.2)	23 (5.7)	14/23 within a month	6 persistent
PC Trial[9], 2013	204	Amplatzer PFO occluder	188/196 (95.9)	142/148 (95.9)	3/204 (1.5)	6 (2.9)	Timing not defined	1 persistent
REDUCE[8], 2017	441	Helex or Cardioform Septal Occluder	408/413 (98.8)	408/413 (98.8)	11/441 (2.5)	29 (6.6)	24 within 45 d	Not defined
RESPECT[7], 2017	499	Amplatzer PFO occluder	462/464 (99.1)	NR	25/499 (5.0)	7 (1.4)	Periprocedural period	NR
Defense Trial PFO[14], 2018	60	Amplatzer PFO occluder	53/60 (88.3)	53/53 (100)	2/60 (3.3)	2 (3.3)	1 periprocedural	NR

Afib: Atrial fibrillation; f/u: follow-up; NR: Not reported; PFOC: Patent foramen ovale closure.

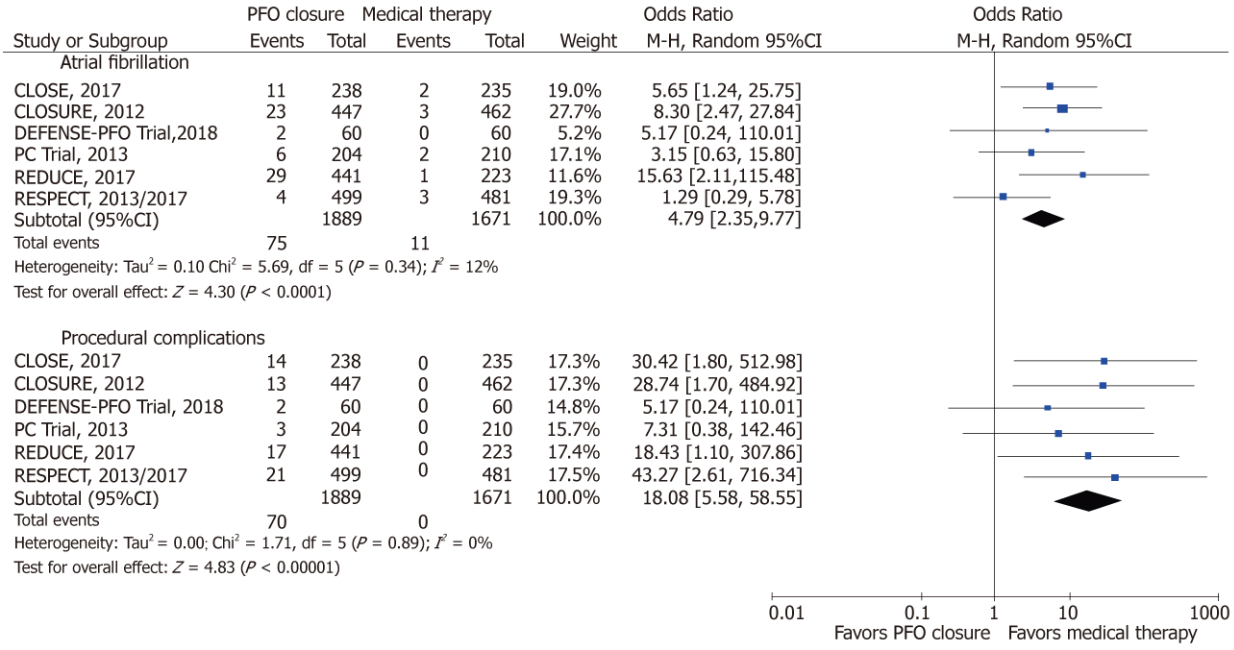


Figure 4 Forest plot for atrial fibrillation and procedural complications. PFO: Patent foramen ovale.

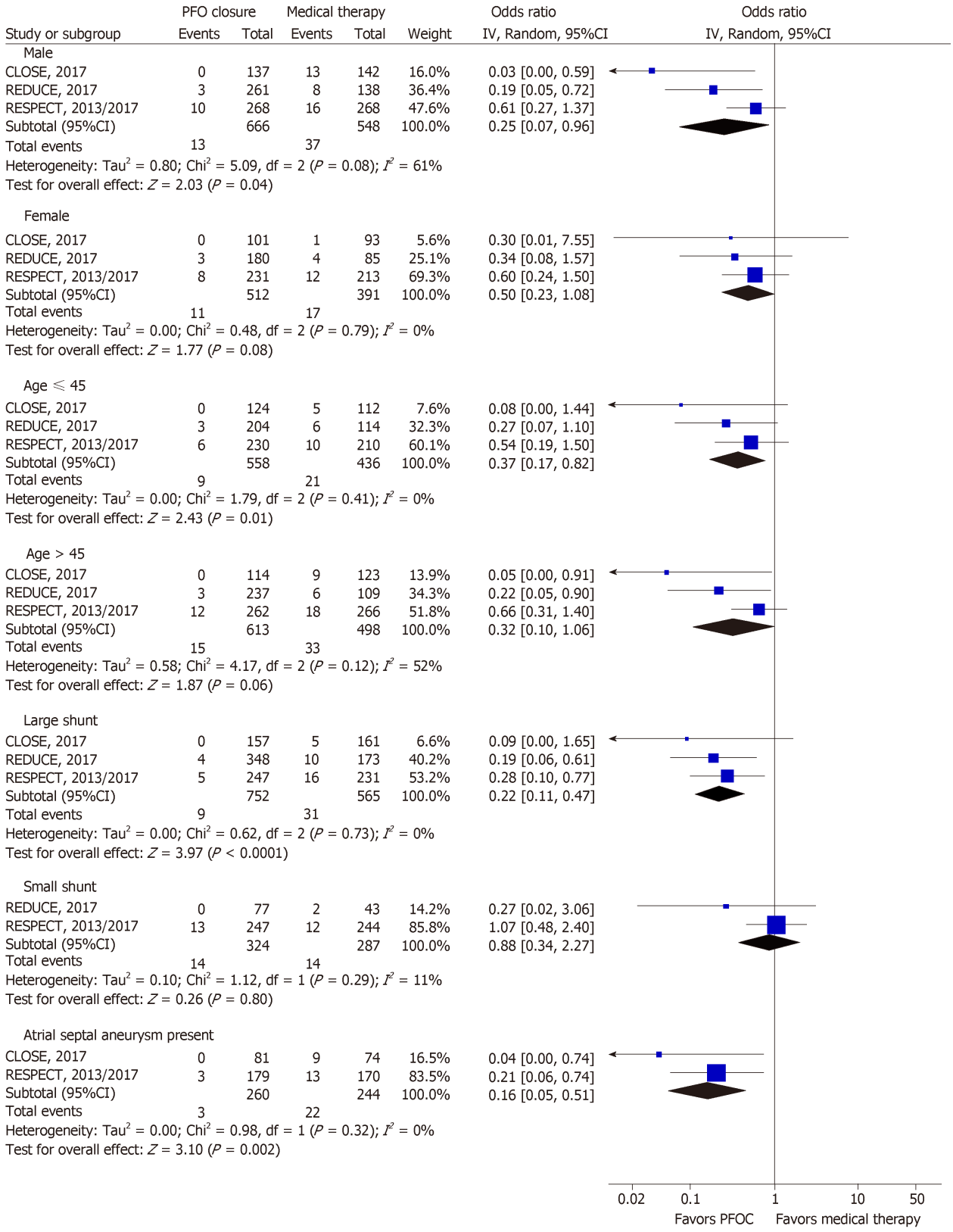


Figure 5 Subgroup analysis of stroke recurrence. PFOC: Patent foramen ovale closure.

ARTICLE HIGHLIGHTS

Research background

A few randomized clinical trials (RCT) and their meta-analyses have found patent foramen ovale closure (PFOC) to be beneficial in prevention of stroke compared to medical therapy.

Research motivation
Whether the benefit is extended across all groups of patients remains unclear.

Research objectives
To evaluate the efficacy and safety of PFOC *vs* medical therapy in different groups of patients presenting with stroke, we performed this meta-analysis of RCTs.

Research methods
Following standard technique, a meta-analysis of randomized clinical trials was performed. Random-effects model was used to analyze summary results.

Research results
PFO closure is beneficial in preventing stroke in patients with stroke and a PFO. In certain population, the benefits are clear.

Research conclusions
This study showed that PFO closure is beneficial in patients with PFO and stroke. It was beneficial in patients who were male, younger than 45, had atrial septal aneurysm and had a large shunt.

Research perspectives
Future research should compare anticoagulation *vs* PFO closure and establish whether PFO closure can be useful in all group of patients.

REFERENCES

1 **Kernan WN**, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**: 2160-2236 [PMID: 24788967 DOI: 10.1161/STR.0000000000000024]

2 **Yaghi S**, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic Stroke: Research and Practice. *Circ Res* 2017; **120**: 527-540 [PMID: 28154102 DOI: 10.1161/CIRCRESAHA.116.308447]

3 **Handke M**, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007; **357**: 2262-2268 [PMID: 18046029 DOI: 10.1056/NEJMoa071422]

4 **Smer A**, Salih M, Mahfood Haddad T, Guddeti R, Saadi A, Saurav A, Belbase R, Ayan M, Traina M, Alla V, Del Core M. Meta-analysis of Randomized Controlled Trials on Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Prevention of Cryptogenic Stroke. *Am J Cardiol* 2018; **121**: 1393-1399 [PMID: 29680170 DOI: 10.1016/j.amjcard.2018.02.021]

5 **De Rosa S**, Sievert H, Sabatino J, Polimeni A, Sorrentino S, Indolfi C. Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale: A Systematic Review and Meta-analysis. *Ann Intern Med* 2018; **168**: 343-350 [PMID: 29310133 DOI: 10.7326/M17-3033]

6 **Mas JL**, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Béjot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guérin P, Piot C, Rossi R, Dubois-Randé JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard JM, Chatellier G; CLOSE Investigators. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. *N Engl J Med* 2017; **377**: 1011-1021 [PMID: 28902593 DOI: 10.1056/NEJMoa1705915]

7 **Saver JL**, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. *N Engl J Med* 2017; **377**: 1022-1032 [PMID: 28902590 DOI: 10.1056/NEJMoa1610057]

8 **Søndergaard L**, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, Spence JD, Thomassen L; Gore REDUCE Clinical Study Investigators. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med* 2017; **377**: 1033-1042 [PMID: 28902580 DOI: 10.1056/NEJMoa1707404]

9 **Meier B**, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, Wahl A, Windecker S, Jüni P; PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013; **368**: 1083-1091 [PMID: 23514285 DOI: 10.1056/NEJMoa1211716]

10 **Carroll JD**, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013; **368**: 1092-1100 [PMID: 23514286 DOI: 10.1056/NEJMoa1301440]

11 **Furlan AJ**, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L; CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012; **366**: 991-999 [PMID: 22417252 DOI: 10.1056/NEJMoa1009639]

12 **Rengifo-Moreno P**, Palacios IF, Junpaparp P, Witzke CF, Morris DL, Romero-Corral A. Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2013; **34**: 3342-3352 [PMID: 23847132 DOI: 10.1093/eurheartj/eht285]

13 **Pandit A**, Aryal MR, Pandit AA, Jalota L, Kantharajpur S, Hakim FA, Lee HR. Amplatzer PFO occluder device may prevent recurrent stroke in patients with patent foramen ovale and cryptogenic stroke: a meta-

analysis of randomised trials. *Heart Lung Circ* 2014; **23**: 303-308 [PMID: 24495944 DOI: 10.1016/j.hlc.2013.12.003]

14 **Lee PH**, Song JK, Kim JS, Heo R, Lee S, Kim DH, Song JM, Kang DH, Kwon SU, Kang DW, Lee D, Kwon HS, Yun SC, Sun BJ, Park JH, Lee JH, Jeong HS, Song HJ, Kim J, Park SJ. Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. *J Am Coll Cardiol* 2018; **71**: 2335-2342 [PMID: 29544871 DOI: 10.1016/j.jacc.2018.02.046]

15 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

16 **Higgins JPT**, Green S. *Cochrane handbook for systematic reviews of interventions* 2011; Available from: http://www.njrcentre.org.uk/

17 **Kent DM**, Dahabreh IJ, Ruthazer R, Furlan AJ, Reisman M, Carroll JD, Saver JL, Smalling RW, Jüni P, Mattle HP, Meier B, Thaler DE. Device Closure of Patent Foramen Ovale After Stroke: Pooled Analysis of Completed Randomized Trials. *J Am Coll Cardiol* 2016; **67**: 907-917 [PMID: 26916479 DOI: 10.1016/j.jacc.2015.12.023]

18 **Sievert H**, Wunderlich N, Reiffenstein I, Ruygrok P, Grube E, Buellesfeld L, Meier B, Schofer J, Muller D, Jones RK, Gillam L. Initial clinical experience with the Coherex FlatStent™ and FlatStent™ EF PFO closure system for in-tunnel PFO closure: results of the Coherex-EU study. *Catheter Cardiovasc Interv* 2014; **83**: 1135-1143 [PMID: 22815250 DOI: 10.1002/ccd.24565]

19 **Burow A**, Schwerzmann M, Wallmann D, Tanner H, Sakata T, Windecker S, Meier B, Delacrétaz E. Atrial fibrillation following device closure of patent foramen ovale. *Cardiology* 2008; **111**: 47-50 [PMID: 18239392 DOI: 10.1159/000113427]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 May 26; 11(5): 137-158

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 5 May 26, 2019

ORIGINAL ARTICLE

Retrospective Study

Observational Study

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Xuming Dai, FACC, MD, PhD, Assistant Professor, Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Jie Wang* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
May 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 May 26; 11(5): 137-148

DOI: 10.4330/wjc.v11.i5.137

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Impact of gout on in-hospital outcomes of acute coronary syndrome-related hospitalizations and revascularizations: Insights from the national inpatient sample

Rupak Desai, Tarang Parekh, Hemant Goyal, Hee Kong Fong, Dipen Zalavadia, Nanush Damarlapally, Rajkumar Doshi, Sejal Savani, Gautam Kumar, Rajesh Sachdeva

ORCID number: Rupak Desai (0000-0002-5315-6426); Tarang Parekh (0000-0002-3494-0020); Hemant Goyal (0000-0002-9433-9042); Hee Kong Fong (0000-0001-5499-2533); Dipen Zalavadia (0000-0001-7913-5191); Nanush Damarlapally (0000-0002-0688-659X); Rajkumar Doshi (0000-0002-5618-2750); Sejal Savani (0000-0002-3677-2251); Gautam Kumar (0000-0002-4284-846X); Rajesh Sachdeva (0000-0002-7729-6247).

Author contributions: Desai R and Parekh T equal contribution to the manuscript; Desai R, Sachdeva R and Kumar G contributed to conception and design; Desai R and Doshi R contributed to provision of study material or patients; all authors contributed to collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Institutional review board statement: This study was exempt from an IRB review.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data from a publically accessible dataset.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Open-Access: This article is an

Rupak Desai, Gautam Kumar, Rajesh Sachdeva, Division of Cardiology, Atlanta VA Medical Center, Decatur, GA 30033, United States

Tarang Parekh, Department of Health Administration and Policy, George Mason University, Fairfax, VA 22030, United States

Hemant Goyal, Department of Internal Medicine, Macon University School of Medicine, Macon, GA 31207, United States

Hee Kong Fong, Department of Internal Medicine, University of Missouri-Columbia, Columbia, MO 65212, United States

Dipen Zalavadia, Department of Internal Medicine, The Wright Center for Graduate Medical Education, Scranton, PA 18503, United States

Nanush Damarlapally, Department of Health Sciences, Coleman College of Health Sciences, Houston, TX 77030, United States

Rajkumar Doshi, Department of Internal Medicine, University of Nevada School of Medicine, Reno, NV 89557, United States

Sejal Savani, Public Health, New York University, New York, NY 10010, United States

Gautam Kumar, Rajesh Sachdeva, Division of Cardiology, Emory University School of Medicine, Atlanta, GA 30322, United States

Rajesh Sachdeva, Division of Cardiology, Morehouse School of Medicine, Atlanta, GA 30310, United States

Corresponding author: Hemant Goyal, FACP, MBBS, MD, Assistant Professor, Department of Internal Medicine, Macon University School of Medicine, 707 Pine St., Macon, GA31207, United States. doc.hemant@yahoo.com
Telephone: +1-478-3015862

Abstract

BACKGROUND

Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations

open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: February 20, 2019
Peer-review started: February 22, 2019
First decision: March 15, 2019
Revised: April 2, 2019
Accepted: May 22, 2019
Article in press: May 22, 2019
Published online: May 26, 2019

P-Reviewer: Altarabsheh SE, Ciccone MM, Karatza AA, Vidal-Perez R
S-Editor: Ji FF
L-Editor:E-Editor: Wang J

and post-revascularization is inadequate.

AIM
To evaluate the impact of gout on in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality.

METHODS
We used the national inpatient sample (2010-2014) to identify the ACS and gout-related hospitalizations, relevant comorbidities, revascularization and post-revascularization outcomes using the ICD-9 CM codes. A multivariable analysis was performed to evaluate the predictors of post-revascularization in-hospital mortality.

RESULTS
We identified 3144744 ACS-related hospitalizations, of which 105198 (3.35%) also had gout. The ACS-gout cohort were more often older white males with a higher prevalence of comorbidities. Coronary artery bypass grafting was required more often in the ACS-gout cohort. Post-revascularization complications including cardiac (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort ($P < 0.001$). An older age (OR 15.63, CI: 5.51-44.39), non-elective admissions (OR 2.00, CI: 1.44-2.79), lower household income (OR 1.44, CI: 1.17-1.78), and comorbid conditions predicted higher mortality in ACS-gout cohort undergoing revascularization ($P < 0.001$). Odds of post-revascularization in-hospital mortality were lower in Hispanics (OR 0.45, CI: 0.31-0.67) and Asians (OR 0.65, CI: 0.45-0.94) as compared to white ($P < 0.001$). However, post-operative complications significantly raised mortality odds. Mean length of stay, transfer to other facilities, and hospital charges were higher in the ACS-gout cohort.

CONCLUSION
Although gout was not independently associated with an increased risk of post-revascularization in-hospital mortality in ACS, it did increase post-revascularization complications.

Key words: Gout; Serum uric acid; Acute coronary syndrome; Unstable angina; Myocardial infarction; Revascularization; Percutaneous coronary intervention; Coronary artery bypass grafting; In-hospital outcomes

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations and post-revascularization is inadequate. In this largest nationwide cohort, we identified 3144744 ACS-related hospitalizations, of which 105198 (3.35%) also had gout. Coronary artery bypass grafting was required more often in the ACS-gout cohort. Post-revascularization (percutaneous coronary intervention/coronary artery bypass grafting) complications including cardiovascular (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher and raised the mortality odds whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort. Mean length of stay, transfers and hospital charges were higher in the ACS-gout cohort.

Citation: Desai R, Parekh T, Goyal H, Fong HK, Zalavadia D, Damarlapally N, Doshi R, Savani S, Kumar G, Sachdeva R. Impact of gout on in-hospital outcomes of acute coronary syndrome-related hospitalizations and revascularizations: Insights from the national inpatient sample. *World J Cardiol* 2019; 11(5): 137-148
URL: https://www.wjgnet.com/1949-8462/full/v11/i5/137.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i5.137

INTRODUCTION

Acute coronary syndrome (ACS) comprises a range of diseases including unstable angina (UA), non-ST segment elevation myocardial infarction, and acute ST-elevation myocardial infarction (STEMI)[1]. It is one of the major causes of mortality around the world. Several independent predictors including advanced age, gender, history of diabetes or hypertension, obesity, and socioeconomic status have been determined for the unfavorable outcomes and rise in the overall mortality in ACS patients[2,3]. Gout is a common inflammatory disease associated with hyperuricemia and has shown to be associated with almost 410% increase in the hospitalizations in the last two decades in the United States[4]. The clinical evidence has shown that uric acid (UA) may have a pro-inflammatory effect on the vascular cells contributing to the negative effects of hyperuricemia in cardiovascular diseases (CVD) including ACS[5,6]. Previous studies have also suggested that gout patients have two to five-fold higher mortality risk in patients with CVD[7,8]. Recent studies have also established the crucial role of high UA levels in predicting the higher odds of MI and subsequent in-hospital mortality in ACS and STEMI hospitalizations[9,10]. Furthermore, microvasculature is becoming a key prognostic factor in patients undergoing percutaneous coronary intervention (PCI) since UA has been found to induce microvascular lesions, accounting for vascular dementia and allograft vasculopathy post-cardiac transplantation[11]. While quick restoration of blood flow through an infarct-related artery is important, the presence of distal microvascular disease can result in impaired myocardial flow leading to an increased risk of major adverse cardiac events after acute MI[12,13]. Nevertheless, the relationship between gout and healthcare resource utilization and post-revascularization outcomes in ACS hospitalizations has not been previously studied on a large scale in the United States. Therefore, in this retrospective population-based study, we aim to evaluate the impact of gout on the in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality using the largest nationwide cohort from January 2010 through December 2014.

MATERIALS AND METHODS

Source of data

The study cohort was derived from the national inpatient sample (NIS) database from January 2010 through December 2014, which is a part of the Healthcare Cost and Utilization Project held by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest publicly accessible all-payer inpatient database in the United States and incorporates diverse identifiers for the hospitalization and clinical data for each visit including up to 25 discharge diagnoses and 15 procedures[14]. It includes discharge statistics from 20% inpatient discharges of all non-federal United States hospital facilities (not including rehabilitation and long-term acute care hospitals), disclosing up to 95% of hospital releases across the country. Nationwide assessments were generated utilizing discharge weights provided by AHRQ.

Study population

All ACS-related adult hospitalizations were recognized by applying International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM) codes 410.1x and 411.1 for the primary discharge diagnosis. These codes have been successfully utilized in earlier studies[15]. We then divided ACS population into the two cohorts: one who had baseline gout and another without gout by using ICD-9 CM codes 274.x or 274.xx in any of the secondary discharge diagnoses.

Study variables

Patient and hospital-level variables including age, gender, race, median household income, primary payer, hospital location/teaching status, bed size, and regions were studied and compared between ACS hospitalizations with *vs* without gout. Underlying comorbid illnesses were also compared between the ACS population with *vs* without gout. Revascularization comprised of thrombolysis (ICD-9 CM diagnosis code V45.88 or procedure code 99.10), PCI (ICD-9 CM procedure codes 00.66, 36.01, 36.02, 36.05, 36.06, and 36.07, 17.55) OR CABG (ICD-9 CM procedure codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, 36.3, 36.31, 36.32, 36.33, 36.34, 36.39). Since the NIS is an openly available database with de-identified data, our study was exempt from an Institutional Review Board authorization.

Study outcomes

The primary outcomes of interest were all-cause in-hospital mortality, revascula-

rization (thrombolysis, PCI or CABG) rates, discharge disposition, length of hospital stay (LOS), and total hospital charges (denotes the total amount payable for service rather than the actual payment received). The secondary outcomes were post-revascularization complications in ACS-hospitalizations including all-cause in-hospital mortality, hemorrhage, blood transfusion, hypotension/shock, cardiac complications, postoperative myocardial infarction, stroke, respiratory complications, gastrointestinal complications including gastrointestinal hemorrhage, acute kidney injury (AKI) requiring dialysis, urinary complications, postoperative infections, and predictors of in-hospital mortality. Comorbidities and postoperative complications were identifying from the secondary discharge diagnoses. The codes used in the study to identify comorbidities and post-revascularization complications are mentioned in Supplementary Table 1.

Statistical analyses

We integrated the discharge weights to unweighted records, to generate the national estimates. The missing data (< 10% for any variable) were omitted from the analysis. The baseline characteristics were compared amongst ACS patients with gout and without gout by applying Pearson's Chi-square test for categorical and Student's t-test for the continuous variable where appropriate. We developed a two-step hierarchical multivariate logistic regression model to evaluate for the patient and hospital level components, and in-hospital outcomes such as in-hospital mortality and procedural complications related to the ACS. This model permitted us to represent the possible relationship of insights into each hospital visit. Both patient and hospital level components along with all relevant comorbidities were incorporated into the multivariable model to control confounders. In addition to unadjusted analysis, post-revascularization outcomes were also analyzed using a propensity score-matched analysis with a caliper width of 0.01 without replacement and adjusting for demographics and all relevant comorbid conditions (Supplementary Tables 2 and 3). A two-tailed *P*-value of < 0.5 was considered statistically significant. All statistical analyses were completed utilizing SPSS Statistics 24 (IBM Corp., Armonk, NY).

RESULTS

Population demographics and comorbidities

We identified 3144744 ACS-related hospitalizations during the study period, of whom 3.34% (n = 105198) also had gout as comorbidity (Table 1). Patients with gout were older with more than two-thirds being > 65 years old (mean age 71.3 years), white (71.8%), mostly males (74%), and Medicare enrollees (69.1%). Interestingly, the ACS-gout cohort consisted of comparatively higher median household income population (76-100th percentile: 21.9% *vs* 19.1%, P < 0.001), and were more likely to be admitted to urban-teaching (54.3% *vs* 50.5%, P < 0.001) and Southern region hospitals (20.6% *vs* 17.7%, P < 0.001) as compared to those without gout. The majority (94.1%) of admissions was non-elective, and 74.4% of admissions occurred on the weekdays. As compared to ACS patients without gout, those with gout had a higher prevalence of baseline comorbidities, except CHF and previous history of cardiac arrest (Table 2). The ACS-gout patients had higher frequency of traditional comorbid risk factors such as: hypertension (83.3% *vs* 71.4%, P < 0.001), dyslipidemia (71.0% *vs* 61.8%, P < 0.001), diabetes (46.7% *vs* 36.6%, P < 0.001), and obesity (21.9% *vs* 14.6%, P < 0.001). They also had the higher prevalence of chronic kidney disease (45.5% *vs* 19.0%, P < 0.001), AKI (45% *vs* 18.7%, P < 0.001), and deficiency anemias (26.7% *vs* 16.0%, P < 0.001).

Revascularization rates and in-hospital outcomes in ACS-related hospitalizations with vs. without gout

As shown in Table 2, the ACS patients with gout had a higher rate of undergoing CABG (9.2% *vs* 8.1%, P < 0.001) as compared to those without gout. All-cause in-hospital mortality associated with revascularization was lower in the ACS patients with gout compared to those without gout (4.3% *vs* 5.0%, P < 0.001). Gout patients were more likely to be discharged to skilled nursing facilities, intermediate care facility or similar facilities (14.8% *vs* 12.1%, P < 0.001) and were less likely to be discharged routinely (56.7% *vs* 61.8%, P < 0.001). The average LOS was higher (5.1 d *vs* 4.5 d, P < 0.001) and mean total hospital charges were higher ($72328 *vs* $71312, P < 0.001) for ACS patients with gout compared to those without gout (Table 3).

Post-revascularization outcomes in ACS hospitalizations with gout

The ACS-gout cohort undergoing PCI or CABG demonstrated a higher number of postoperative complications including cardiovascular, respiratory, stroke,

Table 1 Baseline characteristics of acute coronary syndrome hospitalizations without *vs* with gout (*n* = 3144744)

Variables	Without gout(*n* = 3039546)	With gout(*n* = 105198)	*P* value
Age (yr) at hospitalization			**< 0.001**[a]
mean (± SD)	66.9 (± 14.2)	71.3 (± 12.5)	
18-44	171857 (5.7)	2337 (2.2)	
45-64	1178621 (38.8)	28567 (27.2)	
65-84	1288783 (42.4)	57054 (54.2)	
≥ 85	400285 (13.2)	17240 (16.4)	
Sex			**< 0.001**[a]
Male	1830228 (60.2)	77834 (74.0)	
Female	1209120 (39.8)	27355 (26.0)	
Race			**< 0.001**[a]
White	2102509 (75.4)	69431 (71.8)	
African American	302121 (10.8)	14798 (15.3)	
Hispanic	218605 (7.8)	4833 (5.0)	
Asian and Pacific Islander	61156 (2.2)	4799 (5.0)	
Native American	16624 (0.6)	394 (0.4)	
Others	88091 (3.2)	2477 (2.6)	
Admission type			**< 0.001**
Non-elective	2847182 (93.9)	98886 (94.1)	
Elective	185903 (6.1)	6149 (5.9)	
Median household income percentile for patient's zip code[1]			**< 0.001**[a]
0-25th	894564 (30.1)	29758 (28.8)	
26-50th	807784 (27.2)	26606 (25.8)	
51-75th	701363 (23.6)	24152 (23.4)	
76-100th	566069 (19.1)	22637 (21.9)	
Primary expected payer			**< 0.001**[a]
Medicare	1709250 (56.4)	72559 (69.1)	
Medicaid	218428 (7.20)	4232 (4.0)	
Private including HMO	803459 (26.5)	22757 (21.7)	
Self-pay/no charge/others	301827 (10.0)	5433 (5.2)	
Control/ownership of hospital			**< 0.001**[a]
Government, nonfederal	305519 (10.1)	9697 (9.3)	
Private, non-profit	2258936 (74.7)	81175 (77.4)	
Private, invest-own	459942 (15.2)	13962 (13.3)	
Bed size of hospital			0.157
Small	351544 (11.6)	12101 (11.5)	
Medium	767625 (25.4)	26387 (25.2)	
Large	1905229 (63.0)	66346 (63.3)	
Location/teaching status			**< 0.001**[a]
Rural	312292 (10.3)	10030 (9.6)	
Urban non-teaching	1183544 (39.1)	37858 (36.1)	
Urban teaching	1528562 (50.5)	56946 (54.3)	
Region of hospital			**< 0.001**[a]
Northeast	575864 (18.9)	19077 (18.1)	
Midwest	705042 (23.2)	24946 (23.7)	
South	1219352 (40.1)	39502 (37.5)	
West	539288 (17.7)	21672 (20.6)	

[a]*P* < 0.05 indicates clinical significance. The bed size cutoff points are derived from https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nisnote.jsp. [1]Represents a quartile classification of the estimated median household income of residents in the patient's ZIP Code, derived from https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp. HMO: Health maintenance organization; SNF: Skilled nursing facility; ICF: Intermediate care facility.

hemorrhage, hypotension/shock, need of blood transfusion, AKI requiring dialysis,

Table 2 Comorbidities in acute coronary syndrome without *vs* with gout

Comorbidities	ACS + no gout	ACS + gout	*P* value
Alcohol abuse	95449 (3.1)	3768 (3.6)	**< 0.001**[a]
Deficiency anemias	487126 (16.0)	28065 (26.7)	**< 0.001**[a]
Rheumatoid arthritis/collagen vascular diseases	72214 (2.4)	3343 (3.2)	**< 0.001**[a]
Congestive heart failure	24213 (0.8)	811 (0.8)	0.357
Chronic pulmonary disease	634046 (20.9)	22789 (21.7)	**< 0.001**[a]
Coagulopathy	152932 (5.0)	7283 (6.9)	**< 0.001**[a]
Diabetes, uncomplicated	911629 (30.0)	36556 (34.7)	**< 0.001**[a]
Diabetes with chronic complications	200881 (6.6)	12597 (12.0)	**< 0.001**[a]
Drug abuse	95449 (3.1)	1519 (1.4)	**< 0.001**[a]
Hypertension	75189 (2.5)	87598 (83.3)	**< 0.001**[a]
Hypothyroidism	2170519 (71.4)	15366 (14.6)	**< 0.001**[a]
Liver disease	334044 (11.0)	2013 (1.9)	**< 0.001**[a]
Fluid and electrolyte disorders	43749 (1.4)	26081 (24.8)	**< 0.001**[a]
Other neurological disorders	636496 (20.9)	6138 (5.8)	**< 0.001**[a]
Obesity	186097 (6.1)	23082 (21.9)	**< 0.001**[a]
Peripheral vascular disorders	443723 (14.6)	16964 (16.1)	**< 0.001**[a]
Renal failure	355484 (11.7)	47359 (45.0)	**< 0.001**[a]
Valvular disease	568903 (18.7)	327 (0.3)	**< 0.001**[a]
Dyslipidemia	7101 (0.2)	74674 (71.0)	**< 0.001**[a]
Coronary atherosclerosis	1879620 (61.8)	89777 (85.3)	**< 0.001**[a]
Previous history of MI	2500606 (82.3)	16972 (16.1)	**< 0.001**[a]
Family history of CAD	359298 (11.8)	8442 (8.0)	**< 0.001**[a]
Previous PCI	298852 (9.8)	18591 (17.7)	**< 0.001**[a]
Previous CABG	439722 (14.5)	13165 (12.5)	**< 0.001**[a]
Previous history of cardiac arrest	247161 (8.1)	405 (0.4)	0.786
Smoking	11543 (0.4)	34019 (32.3)	**< 0.001**[a]
History of venous thromboembolism	1210142 (39.8)	3146 (3.0)	**< 0.001**[a]
Chronic kidney disease	66017 (2.2)	47909 (45.5)	**< 0.001**[a]
Dialysis status	576268 (19.0)	4388 (4.2)	**< 0.001**[a]

[a]$P < 0.05$ (bold value) indicates clinical significance. ACS: Acute coronary syndrome; MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting.

and gastrointestinal and urinary complications as compared to those without gout (Table 3). However, overall in-hospital mortality was lower (2.2% *vs* 3.0%, $P < 0.001$) in patients with gout and there were no significant differences in the post-revascularization myocardial infarction and infection rates between both the cohorts. We also confirmed the comparable results with a comprehensive propensity-score matched analysis (Supplementary Tables 2 and 3).

Predictors of in-hospital mortality

On multivariable analysis, advanced age (> 85 years *vs* 18-44 years: OR 15.63, 95%CI: 5.51-44.39; $P < 0.001$), non-elective admissions (OR 2.00, 95%CI: 1.44-2.79; $P < 0.001$), and lower household income (OR 1.44; 95%CI: 1.17-1.78; $P < 0.001$) had significantly higher odds of in-hospital mortality in ACS patients with gout undergoing PCI or CABG (Table 4). Among ACS-gout cohort, Hispanics (OR 0.45, CI: 0.31-0.67; $P < 0.001$) and Asians (OR 0.65, CI: 0.45-0.94; $P < 0.001$) undergoing PCI or CABG demonstrated significantly lower odds of in-hospital mortality as compared to whites (Table 5). Rheumatoid arthritis/collagen vascular diseases, valvular heart diseases, CHF, fluid and electrolyte disorders, coagulopathy, drug abuse, neurological disorders, peripheral vascular disorders, and renal failure independently predicted a greater risk of in-hospital mortality. Additionally, ACS-gout cohort undergoing PCI or CABG revealed highest odds of in-hospital mortality due to postoperative infections followed by hypotension/shock, postoperative myocardial infarction, and postoperative stroke, respiratory, AKI, and cardiac complications.

Table 3 Revascularization rates and outcomes in acute coronary syndrome with *vs* without gout

Outcomes	ACS + no gout(*n* = 3039546)	ACS + gout(*n* = 105198)	*P* value
Revascularization			
Thrombolysis	56694 (1.9)	1408 (1.3)	**< 0.001**[a]
PCI	1369759 (45.1)	38301 (36.4)	**< 0.001**[a]
CABG	245983 (8.1)	9657 (9.2)	**< 0.001**[a]
All-cause in-hospital mortality	151213 (5.0)	4539 (4.3)	**< 0.001**[a]
Disposition			**< 0.001**[a]
Routine	1878724 (61.8)	59605 (56.7)	
Transfer to short-term hospital	290145 (9.6)	10506 (10.0)	
Other transfers (SNF, ICF, other)	367183 (12.1)	15586 (14.8)	
Home Health Care	318501 (10.5)	14208 (13.5)	
Against Medical Advice	30531 (1.0)	681 (0.6)	
Length of stay (d) mean (± SD)	4.5 (± 5.2)	5.1 (± 5.0)	**< 0.001**[a]
Hospital charges ($) mean (± SD)	71312.73 (± 85186.10)	72328.21 (± 86223.92)	**< 0.001**[a]

[a]$P < 0.05$ indicates clinical significance. ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SNF: Skilled nursing facility; ICF: Intermediate care facility.

DISCUSSION

This is the first large scale study that evaluates the impact of gout on in-patient mortality in ACS patients and post-revascularization outcomes, predictors of in-hospital mortality during the post-revascularization period and healthcare resource utilization using the largest nationally representative cohort of ACS hospitalizations.

We found that ACS hospitalizations with gout comprised of older white men with a higher median household income, mostly Medicare beneficiaries, and were likely to be admitted to urban-teaching and Southern region hospitals more frequently. These patients also had a higher prevalence of comorbidities. Furthermore, the average LOS and total hospitalization charges were significantly higher. ACS patients with gout underwent CABG more often whereas the PCI revascularizations were comparable between both the cohorts. Those who underwent revascularizations (PCI or CABG) had shown higher overall complications; however lower all-cause in-hospital mortality compared to those without gout. A multivariate analysis demonstrated that older age, Hispanic and Asian race, lower household income, non-elective admissions, a previous history of CHF, valvular diseases, septicemia, shock, and cardiovascular complications were independent predictors of in-hospital mortality in ACS hospitalizations with gout post-revascularization.

In the study, the prevalence of gout among ACS patients was about 3.35% similar to the prevalence of gout among healthy United States population to be 3%-5%, with the age-standardized prevalence of hyperuricemia being 12%-15%[16]. In this study, gout has been prevalent in ACS patients with lower all-cause mortality compared to without gout. More recently, Latif *et al*[17] indicated that higher UA levels are associated with lower all-cause and cardiovascular mortality, however, they included only hemodialysis patients. Similarly, another study using the NIS suggested that co-occurring gout is associated with reduced in-hospital mortality among postmenopausal women admitted for AMI[18]. The paradoxical association with mortality could be due to focus on the short-term post-revascularization in-hospital outcomes, residual confounding factors in administrative data, or missed diagnosis in patients without gout. As shown with previous studies, our findings also showed that ACS hospitalizations with gout consisted of older white men, with higher co-existing comorbid conditions, mostly Medicare enrollees, and a lower median income quartile[19-21]. Surprisingly, Harrold *et al*[22] found that older women with gout more often had coronary heart disease. The results of our study suggest that ACS patients with gout had prolonged hospital stays post-revascularizations and management costs. A few other studies have also confirmed similar findings[23,24]. These studies have given a possible explanation for a prolonged stay and increased hospital cost due to increased risk of recurrent events and complications; however, the results were limited to the economic impact of ACS in general. This would be one of the few studies to describe the impact of gout on outcomes of ACS hospitalizations in terms of healthcare resource utilization including revascularization, the ensuing economic impact and the predictors of post-revascularization inpatient mortality.

Table 4 Post-revascularization (percutaneous coronary intervention or coronary artery bypass grafting) complications in acute coronary syndrome patients with *vs* without gout

Complications	No gout(*n* = 1592156)	Gout(*n* = 47307)	*P* value
All-cause in-hospital mortality	47466 (3.0)	1038 (2.2)	**< 0.001**[a]
Hemorrhage	43541 (2.7)	1470 (3.1)	**< 0.001**[a]
Blood transfusion	12272 (0.8)	524 (1.1)	**< 0.001**[a]
Hypotension/shock	7319 (0.5)	261 (0.6)	**0.004**[a]
Cardiac complications	46511 (2.9)	1523 (3.2)	**< 0.001**[a]
Postoperative myocardial infarction	27176 (1.7)	798 (1.7)	0.74
Stroke	3926 (0.2)	140 (0.3)	**0.033**[a]
Respiratory complications	46531 (2.9)	1642 (3.5)	**< 0.001**[a]
Gastrointestinal complications	25573 (1.6)	980 (2.1)	**< 0.001**[a]
AKI requiring dialysis	7843 (0.5)	628 (1.3)	**< 0.001**[a]
Urinary complications	4641 (0.3)	307 (0.6)	**< 0.001**[a]
Post procedural infections	24473 (1.5)	687 (1.5)	0.139

[a]$P < 0.05$ indicates clinical significance. ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; AKI: Acute kidney injury.

We found that age, race, median income, relevant comorbidities, and post-revascularization outcomes/postoperative complications in ACS patients undergoing PCI or CABG were independently predictive of in-hospital mortality in ACS patients with gout. Conversely, no association was observed in gender, which is consistent with a previous meta-analysis[25]. The gender-specific relative risk for congestive heart diseases (CHD) in that metanalysis for each increase of 1 mg/dL in serum UA was similar, but not statistically significant. However, subgroup analysis showed a significant association between hyperuricemia and CHD incidence in men, but increased risk of CHD mortality in women. The result differs from the previous studies that showed both men and women with gout have increased the risk of cardiovascular mortality compared with those without gout[26-28]. A retrospective study of STEMI patients who underwent PCI reported that one in every five patients had higher UA levels and it was independently associated with increased risk of in-hospital mortality[10]. Ndrepepa *et al*[29] reported that every 1 mg/dL rise in UA increased by 12% in the adjusted risk for 1-year mortality in an unselected cohort. Alcohol consumption and dyslipidemia have been associated with significantly increase the risk of hyperuricemia[30,31], which could further precipitate or increase the severity of gout. Interestingly, we observed the lower odds of in-hospital mortality with alcohol abuse, dyslipidemia, and obesity in ACS patients with gout undergoing revascularization. The implication of our findings is important for targeted preventive intervention in a certain population at the risk of gout and ACS.

Several potential mechanisms including causal role of UA in hypertension and atherosclerosis development, vasoconstriction, role of UA as pro-oxidant or gout per se promoting atherosclerosis, explain the increased risk of cardiovascular mortality in patients with gout[32,33]. However, whether gout is an independent factor with a pathogenic role in ACS or only attributing for associated risk factors of ACS, such as obesity, renal diseases, and diabetes, remains debatable[26,34]. In several large sample studies, gout was linked to increased all-cause and CV mortality rates[28,35,36], nonetheless, data on the impact of gout on post-revascularization remains limited in the literature.

Our study extends on the impact of gout on ACS patients with other comorbid conditions and revascularization complications. The study showed that cardiac, renal, pulmonary and vascular comorbidities are the risk factors for post-revascularization complications as well. Previous studies have shown an association of gout and hyperuricemia with many comorbid conditions. Demir *et al*[37] showed increased serum UA levels in calcific aortic valve stenosis (AS), with a positive correlation in the severity of the disease. Raised serum UA level may initiate calcification in the aortic valve and accelerate the progression by causing endothelial dysfunction[32]. Similarly, a prospective longitudinal study with a large cohort of 11681 men also concluded that CHF decompensation is independently associated with increased risk of hyperuricemia and likely gout, by increased urate production and decreased renal urate excretion[38]. Our study also shows an increased risk of in-hospital mortality in ACS patients with gout who are drug abusers that have never been evaluated in the

Table 5 Predictors of in-hospital mortality in acute coronary syndrome patients with gout undergoing revascularization

Predictor	Adjusted odds ratio	95%CI (LL-UL)	*P* value
Age in years at admission			**< 0.001**[a]
45-64 *vs* 18-44	2.99	1.08-8.30	**0.036**[a]
65-84 *vs* 18-44	5.72	2.04-16.01	**0.001**[a]
≥ 85 *vs* 18-44	15.63	5.51-44.39	**< 0.001**[a]
Male *vs* female	0.89	0.75-1.05	0.155
Race			**< 0.001**[a]
African American *vs* white	1.09	0.88-1.35	0.413
Hispanic *vs* white	0.45	0.31-0.67	**< 0.001**[a]
Asian *vs* white	0.65	0.45-0.94	**0.022**[a]
Non-elective *vs* elective admission	2.00	1.44-2.79	**< 0.001**[a]
Median household income quartile 0-25th *vs* 76-100$^{th\#}$	1.44	1.17-1.78	**0.001**[a]
Comorbidities			
Alcohol abuse	0.49	0.31-0.79	**0.003**[a]
Rheumatoid arthritis/collagen vascular diseases	1.57	1.09-2.25	**0.016**[a]
Congestive heart failure	5.91	3.54-9.86	**0.000**[a]
Coagulopathy	1.29	1.05-1.58	**0.014**[a]
Drug abuse	2.33	1.34-4.05	**0.003**[a]
Fluid and electrolyte disorders	2.88	2.49-3.35	**< 0.001**[a]
Other neurological disorders	1.72	1.33-2.23	**< 0.001**[a]
Obesity	0.79	0.66-0.95	**0.012**[a]
Peripheral vascular disorders	1.60	1.36-1.88	**< 0.001**[a]
Renal failure	2.04	1.13-3.70	**0.019**[a]
Valvular disease	8.15	3.87-17.15	**< 0.001**[a]
Dyslipidemia	0.63	0.54-0.72	**< 0.001**[a]
Outcomes/postoperative complications			
Hypotension/shock	2.97	1.93-4.56	**< 0.001**[a]
Cardiac complications	1.59	1.19-2.11	**0.002**[a]
Postoperative myocardial infarction	2.53	1.74-3.68	**< 0.001**[a]
Perioperative stroke	2.48	1.20-5.10	**0.014**[a]
Respiratory complications	1.80	1.41-2.30	**< 0.001**[a]
Postoperative acute kidney injury	1.48	1.26-1.74	**< 0.001**[a]
Infections/septicemia	3.94	3.01-5.16	**< 0.001**[a]

[a]$P < 0.05$ indicates clinical significance. CI: Confidence interval; LL: Lower level; UL: Upper level, Multivariate regression model was adjusted for age, gender, race, admission type, median household income, payer status, hospital characteristics and all relevant comorbidities and prior medical history.

past.

Systemic (kidney, respiratory and vascular) complications of revascularization in ACS patients with gout were likely to increase in-hospital mortality compared to patients without gout. This could also be the reason for prolonged hospitalization and increased treatment cost. Ejaz *et al*[39] showed that the UA is associated with a five to eight-fold increase in the post-cardiac surgery AKI. A study from the United Kingdom found 1.71 times higher risk of stroke in patients with gout than in the general population[40]. A nationwide population-based cohort study showed that gout was associated with an increased risk of pulmonary embolism by almost 53%[41]. Several studies have shown an association between gout and collagen vascular diseases, such as systemic sclerosis and rheumatoid arthritis[42,43]. Our findings would be prospective to initiate the discussion of screening and appropriate treatment of gout in ACS patients, and other dynamics responsible for gout should be considered when targeting new therapeutic strategies to prevent postoperative complications. In addition, appropriate screening for CVD in patients with gout is suggested as these patients have worse cardiovascular outcomes.

Our retrospective database study has few limitations which need to be mentioned. Due to the administrative nature of this database, some baseline patient's data might be missing, and follow up data was not available. There is a possibility of a misclassification bias from the use of diagnostic codes to define gout based on the clinical

findings by physicians or to diagnose ACS, with a possible change in terminology and use of generalized diagnostic codes by the clinicians. The NIS database does not contain information on serum uric acid level in gout patients so the severity and the extent of worse outcomes in ACS and post-revascularization outcomes with a unit increase in uric acid levels are not possible to be evaluated. In addition, each hospitalization is considered separately in the NIS, which could result in overestimation of the number of admissions for the same patient. Furthermore, the study emphasizes the short-term in-hospital impact of gout, lacking long-term follow-up outcomes. Nevertheless, the current study showed several important strengths, including nationwide large sample size, standardized methods, and absence of selection bias.

In conclusion, although gout did not increase the in-hospital mortality in ACS-related hospitalizations, the findings from this nationwide cohort highlight the significant impact of gout on in-hospital outcomes in ACS patients in terms of higher cardiovascular comorbidities, CABG frequency, post-revascularization complications, hospital stay, and total hospital charges.

ARTICLE HIGHLIGHTS

Research background

Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations and post-revascularization is inadequate.

Research motivation

Limited data exist on impact of gout on in-hospital outcome of ACS in terms of healthcare utilization and post-revascularization outcomes.

Research objective

The study aimed to evaluate the impact of gout on in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality.

Research methods

We used the national inpatient sample (2010-2014) to identify the ACS and gout-related hospitalizations, relevant comorbidities, revascularization and post-revascularization outcomes using the ICD-9 CM codes. A multivariable analysis was performed to evaluate the predictors of post-revascularization in-hospital mortality.

Research results

Out of 3144744 ACS-related hospitalizations, 105198 (3.35%) patients had gout. The ACS-gout cohort were more often older white males with a higher prevalence of comorbidities. ACS-gout cohort showed comparativly higher prevalence of Coronary artery bypass grafting. Post-revascularization complications including cardiac (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort ($P < 0.001$). An older age (OR 15.63, CI: 5.51-44.39), non-elective admissions (OR 2.00, CI: 1.44-2.79), lower household income (OR 1.44; CI: 1.17-1.78), and comorbid conditions predicted higher mortality in ACS-gout cohort undergoing revascularization ($P < 0.001$). Odds of post-revascularization in-hospital mortality were lower in Hispanics (OR 0.45, CI: 0.31-0.67) and Asians (OR 0.65, CI: 0.45-0.94) as compared to white ($P < 0.001$). However, post-operative complications significantly raised mortality odds. Mean length of stay, transfer to other facilities, and hospital charges were higher in the ACS-gout cohort.

Research conclusions

Gout was not independently associated with an increased risk of post-revascularization in-hospital mortality in ACS. However, gout did increase post-revascularization complications.

Research perspectives

This study may help clinicians making evidence-based decision in patients with history of gout who are admitted with primary diagnosis of ACS and have undergone re-vascularization.

REFERENCES

1 **Kumar A**, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clin Proc* 2009; **84**: 917-938 [PMID: 19797781 DOI: 10.1016/S0025-6196(11)60509-0]

2 **Granger CB**, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003; **163**: 2345-2353 [PMID: 14581255 DOI: 10.1001/archinte.163.19.2345]

3 **Fox KA**, Goodman SG, Anderson FA, Granger CB, Moscucci M, Flather MD, Spencer F, Budaj A,

Dabbous OH, Gore JM; GRACE Investigators. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003; **24**: 1414-1424 [PMID: 12909070 DOI: 10.1016/S0195-668X(03)00315-4]

4 **Singh G**, Mithal A, Mithal A. THU0409 Not just a swollen big toe: increasing all-cause hospitalizations in patients with gout in the United States: 1993-2014. *Ann Rheum Dis* 2017; **76**: 362 [DOI: 10.1136/annrheumdis-2017-eular.5458]

5 **Chapman PT**, Yarwood H, Harrison AA, Stocker CJ, Jamar F, Gundel RH, Peters AM, Haskard DO. Endothelial activation in monosodium urate monohydrate crystal-induced inflammation: in vitro and in vivo studies on the roles of tumor necrosis factor alpha and interleukin-1. *Arthritis Rheum* 1997; **40**: 955-965 [PMID: 9153559 DOI: 10.1002/1529-0131(199705)40:5<955::AID-ART24>3.0.CO;2-F]

6 **Borghi C**, Cicero AFG. Serum uric acid and acute coronary syndrome: Is there a role for functional markers of residual cardiovascular risk? *Int J Cardiol* 2018; **250**: 62-63 [PMID: 29169763 DOI: 10.1016/j.ijcard.2017.06.053]

7 **Lottmann K**, Chen X, Schädlich PK. Association between gout and all-cause as well as cardiovascular mortality: a systematic review. *Curr Rheumatol Rep* 2012; **14**: 195-203 [PMID: 22350606 DOI: 10.1007/s11926-011-0234-2]

8 **Bickel C**, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, Hofmann KP, Meyer J. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; **89**: 12-17 [PMID: 11779515 DOI: 10.1016/S0002-9149(01)02155-5]

9 **Magnoni M**, Berteotti M, Ceriotti F, Mallia V, Vergani V, Peretto G, Angeloni G, Cristell N, Maseri A, Cianflone D. Serum uric acid on admission predicts in-hospital mortality in patients with acute coronary syndrome. *Int J Cardiol* 2017; **240**: 25-29 [PMID: 28476518 DOI: 10.1016/j.ijcard.2017.04.027]

10 **Lazzeri C**, Valente S, Chiostri M, Sori A, Bernardo P, Gensini GF. Uric acid in the acute phase of ST elevation myocardial infarction submitted to primary PCI: its prognostic role and relation with inflammatory markers: a single center experience. *Int J Cardiol* 2010; **138**: 206-209 [PMID: 18684529 DOI: 10.1016/j.ijcard.2008.06.024]

11 **Kittleson MM**, Bead V, Fradley M, St John ME, Champion HC, Kasper EK, Russell SD, Wittstein IS, Hare JM. Elevated uric acid levels predict allograft vasculopathy in cardiac transplant recipients. *J Heart Lung Transplant* 2007; **26**: 498-503 [PMID: 17449420 DOI: 10.1016/j.healun.2007.01.039]

12 **Morishima I**, Sone T, Mokuno S, Taga S, Shimauchi A, Oki Y, Kondo J, Tsuboi H, Sassa H. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. *Am Heart J* 1995; **130**: 239-243 [PMID: 7631601 DOI: 10.1016/0002-8703(95)90434-4]

13 **Morishima I**, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H, Matsui H, Toki Y, Ito T, Hayakawa T. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. *J Am Coll Cardiol* 2000; **36**: 1202-1209 [PMID: 11028471 DOI: 10.1016/S0735-1097(00)00865-2]

14 **Healthcare Cost and Utilization Project**. Overview of the National (Nationwide) Inpatient Sample (NIS). Available from: https://www.hcup-us.ahrq.gov/nisoverview.jsp

15 **Elgendy IY**, Mahmoud AN, Mansoor H, Bavry AA. Early Invasive Versus Initial Conservative Strategies for Women with Non-ST-Elevation Acute Coronary Syndromes: A Nationwide Analysis. *Am J Med* 2017; **130**: 1059-1067 [PMID: 28238691 DOI: 10.1016/j.amjmed.2017.01.049]

16 **Chen-Xu M**, Yokose C, Choi HK. SAT0703 Racial disparities in gout and hyperuricemia - a united states general population study. *Ann Rheum Dis* 2018; **77**: 1199-200 [DOI: 10.1136/annrheumdis-2018-eular.6059]

17 **Latif W**, Karaboyas A, Tong L, Winchester JF, Arrington CJ, Pisoni RL, Marshall MR, Kleophas W, Levin NW, Sen A, Robinson BM, Saran R. Uric acid levels and all-cause and cardiovascular mortality in the hemodialysis population. *Clin J Am Soc Nephrol* 2011; **6**: 2470-2477 [PMID: 21868616 DOI: 10.2215/CJN.00670111]

18 **Adegbala O**, Adejumo AC, Olakanmi O, Akinjero A, Akintoye E, Alliu S, Edo-Osagie E, Chatterjee A. Relation of Cannabis Use and Atrial Fibrillation Among Patients Hospitalized for Heart Failure. *Am J Cardiol* 2018; **122**: 129-134 [PMID: 29685570 DOI: 10.1016/j.amjcard.2018.03.015]

19 **Pagidipati NJ**, Hess CN, Clare RM, Akerblom A, Tricoci P, Wojdyla D, Keenan RT, James S, Held C, Mahaffey KW, Klein AB, Wallentin L, Roe MT. An examination of the relationship between serum uric acid level, a clinical history of gout, and cardiovascular outcomes among patients with acute coronary syndrome. *Am Heart J* 2017; **187**: 53-61 [PMID: 28454808 DOI: 10.1016/j.ahj.2017.02.023]

20 **Pillinger MH**, Bangalore S, Klein AB, Baumgartner S, Morlock R. Cardiovascular Disease and Gout: Real-World Experience Evaluating Patient Characteristics, Treatment Patterns, and Health Care Utilization. *J Manag Care Spec Pharm* 2017; **23**: 677-683 [PMID: 28530520 DOI: 10.18553/jmcp.2017.23.6.677]

21 **Singh JA**, Yu S. Gout-related inpatient utilization: a study of predictors of outcomes and time trends. *Arthritis Res Ther* 2016; **18**: 57 [PMID: 26935737 DOI: 10.1186/s13075-016-0936-y]

22 **Harrold LR**, Yood RA, Mikuls TR, Andrade SE, Davis J, Fuller J, Chan KA, Roblin D, Raebel MA, Von Worley A, Platt R, Saag KG. Sex differences in gout epidemiology: evaluation and treatment. *Ann Rheum Dis* 2006; **65**: 1368-1372 [PMID: 16644784 DOI: 10.1136/ard.2006.051649]

23 **Roger VL**, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012; **125**: e2-e220 [PMID: 22179539 DOI: 10.1161/CIR.0b013e31823ac046]

24 **LaMori JC**, Shoheiber O, Dudash K, Crivera C, Mody SH. The economic impact of acute coronary syndrome on length of stay: an analysis using the Healthcare Cost and Utilization Project (HCUP) databases. *J Med Econ* 2014; **17**: 191-197 [PMID: 24451040 DOI: 10.3111/13696998.2014.885907]

25 **Kim SY**, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2010; **62**: 170-180 [PMID: 20191515 DOI: 10.1002/acr.20065]

26 **Choi HK**, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; **116**: 894-900 [PMID: 17698728 DOI: 10.1161/CIRCULATIONAHA.107.703389]

27 **Krishnan E**, Svendsen K, Neaton JD, Grandits G, Kuller LH; MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008; **168**: 1104-1110 [PMID: 18504339 DOI: 10.1001/archinte.168.10.1104]

28 **De Vera MA**, Rahman MM, Bhole V, Kopec JA, Choi HK. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study. *Ann Rheum Dis* 2010; **69**: 1162-1164 [PMID: 20124358 DOI: 10.1136/ard.2009.122770]

29 **Ndrepepa G**, Braun S, Haase HU, Schulz S, Ranftl S, Hadamitzky M, Mehilli J, Schömig A, Kastrati A. Prognostic value of uric acid in patients with acute coronary syndromes. *Am J Cardiol* 2012; **109**: 1260-1265 [PMID: 22325088 DOI: 10.1016/j.amjcard.2011.12.018]

30 **Li Z**, Guo X, Liu Y, Chang Y, Sun Y, Zhu G, Abraham MR. The Relation of Moderate Alcohol Consumption to Hyperuricemia in a Rural General Population. *Int J Environ Res Public Health* 2016; **13**: pii: E732 [PMID: 27447659 DOI: 10.3390/ijerph13070732]

31 **Peng TC**, Wang CC, Kao TW, Chan JY, Yang YH, Chang YW, Chen WL. Relationship between hyperuricemia and lipid profiles in US adults. *Biomed Res Int* 2015; **2015**: 127596 [PMID: 25629033 DOI: 10.1155/2015/127596]

32 **Kanellis J**, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005; **25**: 39-42 [PMID: 15660333 DOI: 10.1016/j.semnephrol.2004.09.007]

33 **Feig DI**, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008; **359**: 1811-1821 [PMID: 18946066 DOI: 10.1056/NEJMra0800885]

34 **Johnson RJ**, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; **41**: 1183-1190 [PMID: 12707287 DOI: 10.1161/01.HYP.0000069700.62727.C5]

35 **Kuo CF**, See LC, Luo SF, Ko YS, Lin YS, Hwang JS, Lin CM, Chen HW, Yu KH. Gout: an independent risk factor for all-cause and cardiovascular mortality. *Rheumatology (Oxford)* 2010; **49**: 141-146 [PMID: 19933595 DOI: 10.1093/rheumatology/kep364]

36 **Stack AG**, Hanley A, Casserly LF, Cronin CJ, Abdalla AA, Kiernan TJ, Murthy BV, Hegarty A, Hannigan A, Nguyen HT. Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. *QJM* 2013; **106**: 647-658 [PMID: 23564632 DOI: 10.1093/qjmed/hct083]

37 **Demir B**, Caglar IM, Ugurlucan M, Ozde C, Tureli HO, Cifci S, Vural A, Karakaya O. The relationship between severity of calcific aortic stenosis and serum uric acid levels. *Angiology* 2012; **63**: 603-608 [PMID: 22261436 DOI: 10.1177/0003319711433198]

38 **Misra D**, Zhu Y, Zhang Y, Choi HK. The independent impact of congestive heart failure status and diuretic use on serum uric acid among men with a high cardiovascular risk profile: a prospective longitudinal study. *Semin Arthritis Rheum* 2011; **41**: 471-476 [PMID: 21435695 DOI: 10.1016/j.semarthrit.2011.02.002]

39 **Ejaz AA**, Kambhampati G, Ejaz NI, Dass B, Lapsia V, Arif AA, Asmar A, Shimada M, Alsabbagh MM, Aiyer R, Johnson RJ. Post-operative serum uric acid and acute kidney injury. *J Nephrol* 2012; **25**: 497-505 [PMID: 22684655 DOI: 10.5301/jn.5000173]

40 **Seminog OO**, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. *Rheumatology (Oxford)* 2013; **52**: 2251-2259 [PMID: 24046469 DOI: 10.1093/rheumatology/ket293]

41 **Huang CC**, Huang PH, Chen JH, Lan JL, Tsay GJ, Lin HY, Tseng CH, Lin CL, Hsu CY. An Independent Risk of Gout on the Development of Deep Vein Thrombosis and Pulmonary Embolism: A Nationwide, Population-Based Cohort Study. *Medicine (Baltimore)* 2015; **94**: e2140 [PMID: 26705202 DOI: 10.1097/MD.0000000000002140]

42 **Gigante A**, Barbano B, Barilaro G, Quarta S, Gasperini ML, Di Mario F, Romaniello A, Amoroso A, Cianci R, Rosato E. Serum uric acid as a marker of microvascular damage in systemic sclerosis patients. *Microvasc Res* 2016; **106**: 39-43 [PMID: 27003713 DOI: 10.1016/j.mvr.2016.03.007]

43 **Jebakumar AJ**, Udayakumar PD, Crowson CS, Matteson EL. Occurrence of gout in rheumatoid arthritis: it does happen! A population-based study. *Int J Clin Rheumtol* 2013; **8**: 433-437 [PMID: 24443656 DOI: 10.2217/ijr.13.45]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 May 26; 11(5): 149-158

DOI: 10.4330/wjc.v11.i5.149

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Observational Study

Feasibility and safety of cryoballoon ablation for atrial fibrillation in patients with congenital heart disease

Sylvia Abadir, Victor Waldmann, Katia Dyrda, Mikael Laredo, Blandine Mondésert, Marc Dubuc, Paul Khairy

ORCID number: Sylvia Abadir (0000-0001-8948-1418); Victor Waldmann (0000-0001-8057-1900); Katia Dyrda (0000-0002-0171-9311); Mikael Laredo (0000-0002-7326-2656); Blandine Mondésert (0000-0001-7777-5689); Marc Dubuc (0000-0002-5996-298X); Paul Khairy (0000-0003-4059-3800).

Author contributions: Abadir S and Waldmann V contributed equally to the manuscript as co-first authors; Abadir S, Waldmann V and Khairy P contributed to concept/design, drafting article, statistics, data collection, data analysis and interpretation; Dyrda K, Laredo M, Mondésert B and Dubuc M contributed to critical revision of article; Abadir S, Waldmann V, Dyrda K, Laredo M, Mondésert B, Dubuc M and Khairy P approval of article; Khairy P contributed to funding.

Institutional review board statement: The study was approved by the local institutional review board.

Conflict-of-interest statement: Dr. Dubuc is a consultant for Medtronic CryoCath LP. The authors have no other relevant conflicts of interest to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

Sylvia Abadir, Victor Waldmann, Katia Dyrda, Mikael Laredo, Blandine Mondésert, Marc Dubuc, Paul Khairy, Electrophysiology Service and Adult Congenital Heart Center, Montreal Heart Institute, Université de Montréal, Montreal QC H1T 1C8, Canada

Corresponding author: Paul Khairy, FRCPC, MD, PhD, Full Professor, Electrophysiology Service and Adult Congenital Heart Center, Montreal Heart Institute, Université de Montréal, 5000 Belanger St E, Montreal QC H1T 1C8, Canada. paul.khairy@umontreal.ca
Telephone: +1-514-3763330-3800
Fax: +1-514-5932581

Abstract

BACKGROUND

The prevalence of atrial fibrillation (AF) is on the rise in the aging population with congenital heart disease (CHD). A few case series have described the feasibility and early outcomes associated with radiofrequency catheter ablation of AF centered on electrically isolating pulmonary veins (PV) in patients with CHD. In contrast, cryoballoon ablation has not previously been studied in this patient population despite its theoretical advantages, which include a favorable safety profile and shorter procedural time.

AIM

To assess the safety and feasibility of cryoballoon ablation for AF in an initial cohort of patients with CHD.

METHODS

The study population consisted of consecutive patients with CHD and cryoballoon ablation for AF at the Montreal Heart Institute between December 2012 and June 2017. Procedural complications, acute success, and 1-year freedom from recurrent AF after a single procedure with or without antiarrhythmic drugs were assessed. Procedures were performed under conscious sedation. Left atrial access was obtained via a single transseptal puncture or through an existing atrial septal defect (ASD). Cryoballoon occlusion was assessed by distal injection of 50% diluted contrast into the pulmonary vein. At least one 240-second cryothermal application was performed upon obtaining complete pulmonary vein occlusion. Following ablation, patients were routinely followed at outpatient visits at 1, 3, 6, and 12 mo, and then annually.

RESULTS

Ten patients, median age 57.9 (interquartile range 48.2-61.7) years, 60% female, met inclusion criteria and were followed for 2.8 (interquartile range 1.4-4.5) years.

and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: February 3, 2019
Peer-review started: February 11, 2019
First decision: April 16, 2019
Revised: April 19, 2019
Accepted: May 14, 2019
Article in press: May 14, 2019
Published online: May 26, 2019

P-Reviewer: Pastromas S, Vermeersch P
S-Editor: Ji FF
L-Editor: A
E-Editor: Wang J

Two had moderately complex CHD (sinus venosus ASD with partial anomalous pulmonary venous return; aortic coarctation with a persistent left superior vena cava), with the remainder having simple defects. AF was paroxysmal in 8 (80.0%) and persistent in 2 (20.0%) patients. The pulmonary vein anatomy was normal in 6 (60.0%) patients. Four had left common PV (n = 3) and/or 3 right PV (n = 2). Electrical pulmonary vein isolation (PVI) was acutely successful in all. One patient had transient phrenic nerve palsy that recovered during the intervention. No major complication occurred. One year after a single ablation procedure, 6 (60%) patients remained free from AF. One patient with recurrent AF had recovered pulmonary vein conduction and underwent a second PVI procedure. A second patient had ablation of an extra-pulmonary vein trigger for AF.

CONCLUSION
Cryoballoon ablation for AF is feasible and safe in patients with simple and moderate forms of CHD, with an excellent acute success rate and modest 1-year freedom from recurrent AF.

Key words: Congenital heart disease; Atrial fibrillation; Cryoballoon ablation; Pulmonary vein isolation; Catheter ablation

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Whereas, a few studies have described radiofrequency ablation for atrial fibrillation (AF) in patients with congenital heart disease (CHD), herein we report the first case series of cryoballoon ablation. Ten patients with CHD, median age 57.9 years, underwent cryoballoon ablation and were followed for a median of 2.8 years. Pulmonary vein isolation was acutely successful in all. No major complication occurred. One year after a single procedure, 6 (60%) patients remained free from AF. In conclusion, cryoballoon ablation is feasible and appears to be safe, with an excellent acute success rate and modest 1-year freedom from recurrent AF.

Citation: Abadir S, Waldmann V, Dyrda K, Laredo M, Mondésert B, Dubuc M, Khairy P. Feasibility and safety of cryoballoon ablation for atrial fibrillation in patients with congenital heart disease. *World J Cardiol* 2019; 11(5): 149-158
URL: https://www.wjgnet.com/1949-8462/full/v11/i5/149.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i5.149

INTRODUCTION

As patients with congenital heart disease (CHD) live longer, they are subject to numerous late complications of which arrhythmias figure prominently[1]. Atrial arrhythmias are the leading cause of morbidity and hospitalizations, with an estimated prevalence of 50% by the age of 65 years[2,3]. Whereas intra-atrial reentrant tachycardia (IART) is the most pervasive arrhythmia in patients with CHD, the prevalence of atrial fibrillation (AF) is on the rise in the aging population. Indeed, AF has already surpassed IART as the most common presenting arrhythmia in patients with CHD over 50 years of age[4].

A few case series have described the feasibility and early outcomes associated with radiofrequency catheter ablation of AF centered on electrically isolating pulmonary veins (PV) in patients with CHD. In the largest series of 57 patients, single procedure arrhythmia-free survival rates on or off antiarrhythmic drugs were 63% at 1 year and 22% at 5 years[5]. Cryoballoon ablation for paroxysmal AF is generally considered non-inferior to radiofrequency ablation in patients with normal hearts or acquired heart disease[6]. However, cryoballoon ablation has not previously been assessed in patients with CHD. Theoretical advantages include the favorable safety profile and shorter procedural time, which could be of value when targeting multiple substrates, as is often the case in patients with CHD[6,7]. We, therefore, assessed our early experience with cryoballoon ablation in patients with CHD.

MATERIALS AND METHODS

Study population

The study population consisted of all consecutive patients with CHD and cryoballoon ablation for AF at the Montreal Heart Institute between December 2012 and June 2017. Eligible patients were identified through the institutional adult CHD catheter ablation database and the tailored informatics system, CONGENERATE, which contains comprehensive diagnostic and procedural codes for patients followed at the Montreal Heart Institute Adult Congenital Center. All patients had symptomatic and drug refractory paroxysmal or early persistent AF (< 1 year in duration), documented by a surface electrocardiogram (ECG). Written informed consent for procedures was obtained in all patients. The study was approved by the local institutional review board.

Pulmonary vein isolation procedure

Patients were anticoagulated a minimum of 4 wk prior to the intervention. For those on vitamin K antagonists, the anticoagulant was continued throughout with a targeted international normalized ratio of 2 to 3. Direct oral anticoagulants were interrupted 24 h prior to the procedure. All patients underwent pre-procedural transesophageal echocardiography to rule-out thrombus, in addition to an imaging study by cardiac computed tomography (CT) or magnetic resonance imaging (MRI) to assess PV anatomy and exclude PV stenosis.

Procedures were performed under conscious sedation, with boluses of remifentanil for analgesia and a continuous infusion of propofol. A diagnostic 6-French deflectable decapolar catheter was positioned in the coronary sinus and a 9-French 9-MHz intracardiac echocardiography (ICE) catheter placed in the right atrium. Left atrial access was obtained via a single transseptal puncture or through an existing atrial septal defect (ASD) under ICE and fluoroscopic guidance. In the setting of an ASD closure device, ICE was used to identify areas of the native septum considered suitable for the transseptal puncture. Intravenous heparin was administered as a combination of boluses and an infusion to achieve and maintain an activated clotting time (ACT) > 300 s after transseptal access. The standard transseptal sheath was exchanged for a 15-French FlexCath (Medtronic CryoCath LP, Montreal, Canada) steerable sheath, through which a first- or second-generation 23- or 28-mm cryoballoon was advanced to the left atrium.

The size of the cryoballoon was selected according to PV diameters determined by CT, MRI, or PV angiography, with a preference for the larger 28-mm size (Figure 1A). PV potentials were recorded by a circular mapping catheter (Achieve, Medtronic, Minneapolis, MN) introduced in the central lumen of the cryoballoon catheter. The Achieve catheter was advanced distally into the PV to optimize support during cryoballoon positioning. The cryoballoon was inflated within the left atrium under fluoroscopic guidance and advanced to the PV ostium. The Achieve catheter was then withdrawn proximally to record PV potentials. Cryoballoon occlusion was assessed by distal injection of 50% diluted contrast into the PV. At least one standard 240-scryothermal application was delivered upon obtaining complete PV occlusion. Additional lesions were not systematically applied in the absence of a clinical reason to do so, such as delayed pulmonary vein isolation (PVI) or relatively warm ablation temperatures[8,9].

During cryoballoon ablation of right-sided PVs, diaphragmatic excursion was monitored by abdominal palpation while pacing the right phrenic nerve by the decapolar catheter positioned at the superior vena cava cranial to the right superior PV. In addition, diaphragmatic electromyographic monitoring of the compound motor action potential was systematically performed using a technique we previously described[10,11]. The procedural endpoint was PVI, as assessed by entrance and exit block. No extra-PV substrate was systematically targeted, although additional arrhythmias were also treated.

Post-ablation management and follow-up

Oral anticoagulation was restarted the evening following the intervention, typically 6 h post-procedure, and continued for a minimum of 6 mo. Patients were discharged home within 24 h. All patients were treated with proton-pump inhibitors for 4 wk. The decision to pursue antiarrhythmic therapy post procedure was at the physician's discretion based on clinical elements. Patients were routinely followed at outpatient visits with ECG recordings at 1, 3, 6, and 12 mo, and then annually. Regular telephone interviews were also performed and medical consultations were promptly scheduled in the event of symptoms suggestive of arrhythmia. For patients with recurrent symptoms not captured by ECGs, 24-h Holter and/or event recorder monitoring was performed. Recurrence was defined as any episode of AF lasting more than 30 s after

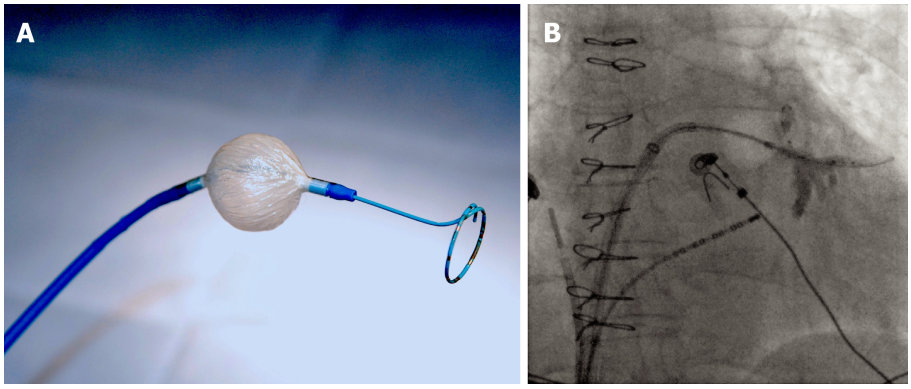


Figure 1 Cryoballoon ablation for atrial fibrillation in a patient with a sinus venosus atrial septal defect and partial anomalous pulmonary venous return. A: A 28-mm cryoballoon catheter (Arctic Front Advance, Medtronic, Minneapolis, MN) along with a circular mapping catheter (Achieve, Medtronic, Minneapolis, MN) introduced in its central lumen; B: The cryoballon is positioned at the ostium of the left inferior pulmonary vein (LIPV) in a patient with a sinus venous atrial septal defect and partial anomalous pulmonary venous return. The circular mapping catheter is placed inside the proximal LIPV. Contrast injection reveals complete cryoballoon occlusion of the LIPV.

a 3-mo blanking period. The primary endpoint was 1-year freedom from recurrent AF after a single procedure, with or without antiarrhythmic drugs.

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR; 25th-75th percentile) and categorical variables as frequencies and percentages. Recurrence-free survival was plotted using the Kaplan-Meier product limit method. Complete data were available in all patients. Considering the descriptive nature of the study, inferential statistics were not performed. Statistical analysis was conducted using R software, version 3.3.2 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics

Ten patients, median age 57.9 (IQR 48.2-61.7) years, 60% female, met inclusion criteria and underwent cryoballoon ablation for AF. Baseline clinical characteristics are summarized in Table 1. Eight patients had simple forms of CHD [*i.e.*, ASD (n = 6), ASD associated with ventricular septal defect (VSD; n = 1), and quadricuspid aortic valve with aortic stenosis (n = 1)]. Two had moderately complex CHD [*i.e.*, sinus venosus ASD with partial anomalous pulmonary venous return (n = 1; Figure 1B), and aortic coarctation with a persistent left superior vena cava (n = 1)]. Three patients with ASDs had percutaneous device closure 3 to 6 months following the AF ablation procedure. In the remaining 7 patients, cryoballoon ablation was performed a median of 15.5 (IQR 8.2-30.3) years after repair of CHD (Table 2).

All patients experienced palpitations during AF episodes. In addition, 8 (80.0%) reported dyspnea, with 2 (20.0%) having associated congestive heart failure. Seven (70.0%) had unplanned hospitalizations for AF, and 6 (60.0%) had electrical cardioversions. The AF pattern was paroxysmal in 8 (80.0%) and early persistent in 2 (20.0%). Patients were referred for AF ablation a median of 4.6 (IQR 0.9-10.3) years after the initial diagnosis of AF and had received a median of 2 (IQR 2-3) antiarrhythmic drugs. All patients had preserved left ventricular ejection fractions (when in sinus rhythm), with a median indexed left atrial volume of 34.5 (IQR 27.3-44.0) mL/m^2 by echocardiography. IART and/or focal atrial tachycardia (FAT) were also documented in 5 (50.0%) patients, with one having had a prior catheter ablation procedure (for a cavotricuspid isthmus-dependent IART, lateral right atrial IART, and inferoseptal non-automatic FAT).

Pulmonary vein anatomy and procedural characteristics

The PV anatomy was normal in 6 (60.0%) patients. Two had a left common PV (LCPV), 1 had a LCPV with 3 right PVs, and 1 had 3 right PVs. In all patients, left atrial access was obtained through a portion of the native or surgically repaired atrial septum. A single 28-mm cryoballoon was used in 6 (60.0%) and a single 23-mm cryoballoon in 3 (30.0%) patients. In one patient, both 28- and 23-mm cryoballoons were used. Main procedural characteristics are summarized in Table 3. PVI was

Table 1 Baseline characteristics

	n = 10
Age, yr	57.9 (48.2-61.7)
Female gender, *n* (%)	6 (60.0)
Type of congenital heart disease, *n* (%)	
Simple	8 (80.0)
Atrial septal defect	6 (60.0)
Atrial and ventricular septal defects	1 (10.0)
Quadricuspid aortic valve with aortic stenosis	1 (10.0)
Moderate	2 (20.0)
Sinus venosus atrial septal defect with PAPVR	1 (10.0)
Aortic coarctation with persistent left superior vena cava	1 (10.0)
Age at repair, yr	44.3 (12.9-54.7)
Hypertension, *n* (%)	5 (50.0)
Dyslipidemia, *n* (%)	3 (30.0)
Diabetes mellitus, *n* (%)	1 (10.0)
Body mass index > 30 kg/m^2, *n* (%)	2 (20.0)
Current smoker, *n* (%)	1 (10.0)
Coronary artery disease, *n* (%)	3 (30.0)
Symptoms/signs associated with atrial fibrillation, *n* (%)	
Palpitations	10 (100.0)
Dyspnea	8 (80.0)
Congestive heart failure	2 (20.0)
Prior hospitalization for atrial fibrillation, *n* (%)	7 (70.0)
Left ventricular ejection fraction, %	60 (55-60)
Left atrial volume, mL/m^2	34.5 (27.3-44.0)
Pattern of atrial fibrillation, *n* (%)	
Paroxysmal	8 (80.0)
Persistent	2 (20.0)
Time from diagnosis of atrial fibrillation to procedure, years	4.6 (0.9-10.3)
Number of antiarrhythmic drugs tried	2 (2-3)
Pharmacological therapy, *n* (%)	
Antiarrhythmic drug	10 (100.0)
Beta-blockers	7 (70.0)
Amiodarone	3 (30.0)
Sotalol	2 (20.0)
Flecainide	2 (20.0)
Propafenone	1 (10.0)
Dofetilide	1 (10.0)
Dronedarone	1 (10.0)
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	4 (40.0)
Anticoagulant	8 (80.0)
Diuretic	2 (20.0)

Continuous variables are expressed as median and interquartile range (25th-75th percentile). PAPVR: Partial anomalous pulmonary venous return.

achieved in all patients. Transient phrenic nerve palsy occurred in one patient, requiring prompt termination of the cryoballoon application. Diaphragmatic excursion fully recovered during the intervention. No major complication occurred.

Recurrence of AF during follow-up

Patients were followed for a median of 2.8 (IQR 1.4 to 4.5) years after ablation. One year after a single procedure, 6 (60%) patients remained free from AF, including 4 (66.7%) without antiarrhythmic agents. Propafenone was continued in 2 patients. Freedom from AF is plotted in Figure 2. Two of the four patients with recurrent AF

Table 2 Individual patient characteristics

Patient #	Age(yr)	Sex	CHD	Type of repair	Age at repair(yr)	Age at first AF(yr)	AF pattern	Number AADs	LA volume (mL/m²)
1	46.4	F	ASD + VSD	Surgical patch	1.5	38.5	Paroxysmal	5	27
2	55.8	F	ASD	Percutaneous device	55.7	55.3	Paroxysmal	5	52
3	60.0	F	SVASD + PAPVR	Surgical patch	44.3	46.3	Paroxysmal	2	26
4	69.2	F	ASD	Percutaneous device	53.7	67.8	Paroxysmal	2	45
5	69.5	F	ASD	Surgical patch	24.3	68.6	Paroxysmal	2	39
6	62.3	F	ASD	None	N/A	61.4	Paroxysmal	2	23
7	15.4	M	AoCo + LSVC	Surgical AoCo repair	0.0	14.4	Paroxysmal	3	30
8	59.9	M	Quadricuspid AS	Aortic valvuloplasty	59.0	37.9	Persistent	3	45
9	38.8	M	ASD	None	N/A	28.5	Paroxysmal	2	28
10	53.4	M	ASD	None	N/A	53.0	Persistent	2	41

CHD: Congenital heart disease; AF: Atrial fibrillation; AAD: Antiarrhythmic drug; LA: Left atrial; F: Female; M: Male; ASD: Atrial septal defect; SVASD: Sinus venosus ASD; PAPVR: Partial anomalous pulmonary venous return; AoCo: Aortic coarctation; LSVC: Left superior vena cava; AS: Aortic stenosis; N/A: Not applicable

had a subsequent catheter ablation procedure. One had recovered PV conduction and underwent antral PVI with radiofrequency energy. In the other patient, AF was triggered by a scar-based IART circuit that was ablated with radiofrequency energy, along with the cavotricuspid isthmus.

DISCUSSION

This study is the first to report on the feasibility and safety of cryoballoon ablation for AF in patients with CHD. Main findings were as follows: The procedures were acutely successful in all, no major complication occurred, and the 1-year single-procedure success rate was modest and within the range reported for radiofrequency catheter ablation.

With AF poised to become the next arrhythmic epidemic after IART in patients with CHD, a better understanding of mechanisms and management are key challenges for the coming years. Atrial arrhythmias are notoriously difficult to control with antiarrhythmic drugs in patients with CHD. Moreover, in those with fragile physiologies, these arrhythmias can result in rapid hemodynamic deterioration, heart failure, and sudden death. The disappointing experience with long-term medical therapy has contributed to the growing preference for non-pharmacological options[12,13]. Yet, while numerous studies have focused on IART or FAT in CHD, few have reported acute and long-term outcomes for AF ablation and none have used the cryoballoon.

The largest report on radiofrequency catheter ablation of AF included 57 patients of whom 35 (61.4%) had mild, 10 (17.5%) moderate, and 12 (21.1%) severe forms of CHD[5]. If PVI failed to restore sinus rhythm, additional linear lesions were performed and complex fractionated atrial electrograms were targeted. Consistent with our results, the one-year arrhythmia-free survival rate after a single procedure was 63%. It then declined to 22% at 5 years. In another series of 36 patients with CHD and AF, the majority of whom had atrial (61%) or ventricular (17%) septal defects, antral PVI was performed[14]. Additional ablation sites in some patients included the superior vena cava junction, left atrial septum and posterior wall, coronary sinus ostium, and crista terminalis. After a single procedure, freedom from recurrent AF in the absence of antiarrhythmic drugs was 42% at 300 d and 27% at 4 years. These rates were not significantly different from age-matched controls without CHD. Two series of 39 and 45 patients with AF and ASD closure devices reported successful transseptal access in 90%-98%, with 76-77% freedom from recurrent arrhythmias with or without antiarrhythmic drugs at 12 to 14 mo[15]. For more complex forms of CHD, the literature is largely limited to case reports of AF ablation[16,17].

The small sample size in our early case series precludes definitive conclusions as to

Table 3 Procedural characteristics

	n = 10
Access to the left atrium, *n* (%)	
Across an atrial septal defect	3 (30.0)
Trans-septal puncture across the native septum	5 (50.0)
Trans-septal puncture across a surgical patch	2 (20.0)
Trans-septal puncture across a percutaneous closure device	0 (0.0)
Cryoballoon size, *n* (%)	
23 mm	4 (40.0)
28 mm	7 (70.0)
Total cryoablation time, seconds	
Left superior pulmonary vein	374 (252-475)
Left inferior pulmonary vein	480 (240-480)
Left common pulmonary vein	480 (480-700)
Right superior pulmonary vein	360 (261-453)
Right inferior pulmonary vein	315 (247-450)
Number of applications	
Left superior pulmonary vein	2 (1.5-2.0)
Left inferior pulmonary vein	1 (1.0-2.0)
Left common pulmonary vein	2 (2.0-3.5)
Right superior pulmonary vein	2 (1.25-2.75)
Right inferior pulmonary vein	2 (1.0-2.0)
Minimal temperature reached, °C	
Left superior pulmonary vein	-49 (-49, -51)
Left inferior pulmonary vein	-45 (-41, -52)
Left common pulmonary vein	-48 (-46, -54)
Right superior pulmonary vein	-45 (-40, -51)
Right inferior pulmonary vein	-45 (-39, -54)
Total procedural time, min	183.0 (152.5, 224.0)
Total fluoroscopy time, min	33.5 (27.5-43.0)

Continuous variables are expressed as median and interquartile range (25^{th}-75^{th} percentile).

whether the observed 1-year arrhythmia free survival rate of 60% is significantly lower than the 75%-80% rate reported with cryoballoon ablation in patients without CHD[6,18-20]. However, anatomical, mechanistic, and technical aspects can potentially contribute to lower success rates in patients with CHD. First, access to the left atrium can lead to an unusual course of the ablation catheter by virtue of abnormal septal anatomy, traversing an existing ASD, or puncturing at an unconventional site. The resulting lack of support can render it more difficult to achieve complete cryoballoon PV occlusion. The high number of applications in each PV and relatively lengthy fluoroscopy times reflect these technical challenges. Second, although it is well documented that most triggers for paroxysmal AF arise from PVs in patients with structurally normal hearts, this is not necessarily the case for those with CHD[21]. Anatomical differences, surgical scarring, hemodynamic sequelae, and/or hypoxic stress can contribute to a higher prevalence of extra-PV triggers, as observed in one of our patients[22]. Focal non-PV drivers for AF have been described in a few patients with CHD[23]. These drivers were characterized by circumscribed areas exhibiting continuous electrical activity coexisting with parts of the atrium activated in a regular manner. Application of radiofrequency energy at these sites terminated AF. These extra-PV substrates cannot be targeted by the cryoballoon. Third, AF ablation outcomes are more favorable in patients with a short-lasting history of AF and no extensive atrial remodeling[24]. In contrast, considering the challenges discussed, CHD patients are typically referred later in their disease course, often after failing several antiarrhythmic drugs[14]. A higher perceived level of difficulty combined with uncertain outcomes may discourage operators from considering AF ablation at an earlier stage. Delayed referral can theoretically impact results owing to a higher degree of atrial structural and electrical remodeling changes. Lastly, chronic volume and pressure loads in patients with CHD result in thickening of atrial walls that can

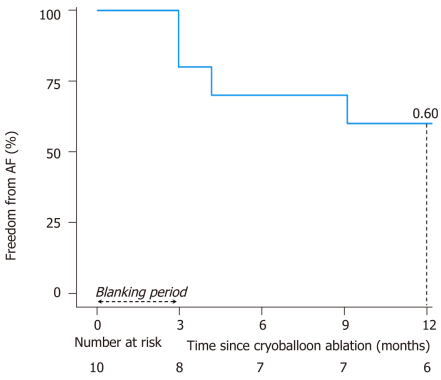


Figure 2 Kaplan–Meier survival curve for freedom from atrial fibrillation after a single cryoballoon ablation procedure.

hinder the creation of durable circumferential PV ablation lesions[25].

In our study, a substantial proportion of patients had factors classically associated with AF in the general population. Hypertension, dyslipidemia, smoking, higher body mass index, and coronary artery disease have also recently been associated with AF in a multicenter study of patients with heterogeneous forms of CHDs[4]. This observation paves the way for future studies as to whether education and preventive risk factor management can significantly impact the AF burden in patients with CHD. Furthermore, it highlights the epidemiological changes associated with the aging CHD population and the potential interplay between CHD and acquired comorbidities.

In addition to AF, half the patients in our study had coexisting atrial arrhythmias, mainly IART, and benefitted from catheter ablation of these other substrates. The co-occurrence of AF and other atrial arrhythmias is well described in patients with CHD[4]. Considering the propensity to develop various forms of arrhythmias, catheter ablation procedures in adults with CHD should generally be considered palliative[12]. Some evidence suggests that even if arrhythmias are not entirely eliminated, clinical outcomes improve[26].

Limitations

This single-center retrospective study represents the first foray into cryoballoon ablation for AF in CHD and demonstrates feasibility and safety. The study is underpowered to explore factors associated with recurrent arrhythmias. Although ECGs were systematically performed at regular follow-up intervals, continuous monitoring was symptom-based such that asymptomatic self-terminating episodes of AF may have escaped detection. The population is limited to patients with simple or moderate forms of CHD such that results should not be extrapolated to those with complex CHD. No direct comparisons were made to AF ablation using radiofrequency energy in patients with CHD, or to cryoballoon ablation in controls without CHD.

In conclusion, cryoballoon ablation for AF is feasible and appears to have an acceptable safety profile in patients with simple and moderate forms of CHD. In this initial experience, the acute success rate for PVI was high, with a modest 1-year event-free survival rate after a single procedure. Recurrences may be due to non-PV triggers. Further studies are required to provide mechanistic insights regarding triggers and substrates for AF in the various forms of CHD, and to compare cryoballoon to radiofrequency catheter ablation.

ARTICLE HIGHLIGHTS

Research background

The prevalence of atrial fibrillation (AF) is on the rise in the growing and aging population with congenital heart disease (CHD). Whereas a few case series have described the feasibility and early outcomes associated with radiofrequency catheter ablation of AF, cryoballoon ablation has not previously been studied in this patient population.

Research motivation

Theoretical advantages of cryoballoon ablation include its favorable safety profile and shorter procedural time, which could be valuable when targeting multiple arrhythmias during a single

intervention, as is often the case in patients with CHD.

Research objectives
We sought to assess feasibility, safety, and recurrence-free survival in our initial experience with cryoballoon ablation for AF in patients with CHD.

Research methods
A single-center cohort study was conducted on consecutive patients with CHD and cryoballoon ablation for AF at the Montreal Heart Institute between December 2012 and June 2017. Procedural complications, acute success, and 1-year freedom from recurrent AF after a single procedure with or without antiarrhythmic drugs were assessed.

Research results
Ten patients with CHD, median age 57.9 years, underwent cryoballoon ablation and were followed for a median of 2.8 years. Pulmonary vein isolation was acutely successful in all. No major complication occurred. One year after a single procedure, 6 (60%) patients remained free from AF.

Research conclusions
Cryoballoon ablation for AF is feasible and appears to have an acceptable safety profile in patients with CHD. In our initial experience, the acute success rate for PVI was high, with a modest 1-year event-free survival rate after a single procedure.

Research perspectives
Further studies are required to provide mechanistic insights regarding triggers and substrates for AF in the various forms of CHD, and to compare cryoballoon to radio-frequency catheter ablation.

REFERENCES

1 **Khairy P**, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol* 2010; **56**: 1149-1157 [PMID: 20863956 DOI: 10.1016/j.jacc.2010.03.085]

2 **Bouchardy J**, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. *Circulation* 2009; **120**: 1679-1686 [PMID: 19822808 DOI: 10.1161/CIRCULATIONAHA.109.866319]

3 **Yang H**, Kuijpers JM, de Groot JR, Konings TC, van Dijk A, Sieswerda GT, Post MC, Mulder BJM, Bouma BJ. Impact of atrial arrhythmias on outcome in adults with congenital heart disease. *Int J Cardiol* 2017; **248**: 152-154 [PMID: 28942870 DOI: 10.1016/j.ijcard.2017.06.073]

4 **Labombarda F**, Hamilton R, Shohoudi A, Aboulhosn J, Broberg CS, Chaix MA, Cohen S, Cook S, Dore A, Fernandes SM, Fournier A, Kay J, Macle L, Mondésert B, Mongeon FP, Opotowsky AR, Proietti A, Rivard L, Ting J, Thibault B, Zaidi A, Khairy P; AARCC. Increasing Prevalence of Atrial Fibrillation and Permanent Atrial Arrhythmias in Congenital Heart Disease. *J Am Coll Cardiol* 2017; **70**: 857-865 [PMID: 28797355 DOI: 10.1016/j.jacc.2017.06.034]

5 **Sohns C**, Nürnberg JH, Hebe J, Duckeck W, Ventura R, Konietschke F, Cao C, Siebels J, Volkmer M. Catheter Ablation for Atrial Fibrillation in Adults With Congenital Heart Disease: Lessons Learned From More Than 10 Years Following a Sequential Ablation Approach. *JACC Clin Electrophysiol* 2018; **4**: 733-743 [PMID: 29929666 DOI: 10.1016/j.jacep.2018.01.015]

6 **Kuck KH**, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016; **374**: 2235-2245 [PMID: 27042964 DOI: 10.1056/NEJMoa1602014]

7 **Andrade JG**, Khairy P, Dubuc M. Catheter cryoablation: biology and clinical uses. *Circ Arrhythm Electrophysiol* 2013; **6**: 218-227 [PMID: 23424224 DOI: 10.1161/CIRCEP.112.973651]

8 **Dorwarth U**, Schmidt M, Wankerl M, Krieg J, Straube F, Hoffmann E. Pulmonary vein electrophysiology during cryoballoon ablation as a predictor for procedural success. *J Interv Card Electrophysiol* 2011; **32**: 205-211 [PMID: 21594628 DOI: 10.1007/s10840-011-9585-x]

9 **Fürnkranz A**, Köster I, Chun KR, Metzner A, Mathew S, Konstantinidou M, Ouyang F, Kuck KH. Cryoballoon temperature predicts acute pulmonary vein isolation. *Heart Rhythm* 2011; **8**: 821-825 [PMID: 21315836 DOI: 10.1016/j.hrthm.2011.01.044]

10 **Franceschi F**, Dubuc M, Guerra PG, Delisle S, Romeo P, Landry E, Koutbi L, Rivard L, Macle L, Thibault B, Talajic M, Roy D, Khairy P. Diaphragmatic electromyography during cryoballoon ablation: a novel concept in the prevention of phrenic nerve palsy. *Heart Rhythm* 2011; **8**: 885-891 [PMID: 21256978 DOI: 10.1016/j.hrthm.2011.01.031]

11 **Franceschi F**, Dubuc M, Guerra PG, Khairy P. Phrenic nerve monitoring with diaphragmatic electromyography during cryoballoon ablation for atrial fibrillation: the first human application. *Heart Rhythm* 2011; **8**: 1068-1071 [PMID: 21315843 DOI: 10.1016/j.hrthm.2011.01.047]

12 **Khairy P**, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot Nd, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm* 2014; **11**: e102-e165 [PMID: 24814377 DOI: 10.1016/j.hrthm.2014.05.009]

13 **Hernández-Madrid A**, Paul T, Abrams D, Aziz PF, Blom NA, Chen J, Chessa M, Combes N, Dagres N, Diller G, Ernst S, Giamberti A, Hebe J, Janousek J, Kriebel T, Moltedo J, Moreno J, Peinado R, Pison L, Rosenthal E, Skinner JR, Zeppenfeld K; ESC Scientific Document Group. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAECE. *Europace* 2018; **20**: 1719-1753 [PMID: 29579186 DOI: 10.1093/europace/eux380]

14 **Philip F**, Muhammad KI, Agarwal S, Natale A, Krasuski RA. Pulmonary vein isolation for the treatment of drug-refractory atrial fibrillation in adults with congenital heart disease. *Congenit Heart Dis* 2012; **7**: 392-399 [PMID: 22469422 DOI: 10.1111/j.1747-0803.2012.00649.x]

15 **Santangeli P**, Di Biase L, Burkhardt JD, Horton R, Sanchez J, Bailey S, Zagrodzky JD, Lakkireddy D, Bai R, Mohanty P, Beheiry S, Hongo R, Natale A. Transseptal access and atrial fibrillation ablation guided by intracardiac echocardiography in patients with atrial septal closure devices. *Heart Rhythm* 2011; **8**: 1669-1675 [PMID: 21703215 DOI: 10.1016/j.hrthm.2011.06.023]

16 **Frankel DS**, Shah MJ, Aziz PF, Hutchinson MD. Catheter ablation of atrial fibrillation in transposition of the great arteries treated with mustard atrial baffle. *Circ Arrhythm Electrophysiol* 2012; **5**: e41-e43 [PMID: 22511665 DOI: 10.1161/CIRCEP.111.969857]

17 **Kirubakaran S**, Rajani R, Linton N, Kiesewetter C, Anderson D, O'Neill M. Catheter ablation for persistent atrial fibrillation in a patient with previous repair of total anomalous pulmonary venous connection. *Circ Arrhythm Electrophysiol* 2013; **6**: e54-e55 [PMID: 23962863 DOI: 10.1161/CIRCEP.113.000483]

18 **Packer DL**, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN; STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013; **61**: 1713-1723 [PMID: 23500312 DOI: 10.1016/j.jacc.2012.11.064]

19 **Luik A**, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M, Schmitt C. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation* 2015; **132**: 1311-1319 [PMID: 26283655 DOI: 10.1161/CIRCULATIONAHA.115.016871]

20 **Aryana A**, Singh SM, Kowalski M, Pujara DK, Cohen AI, Singh SK, Aleong RG, Banker RS, Fuenzalida CE, Prager NA, Bowers MR, D'Avila A, O'Neill PG. Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. *J Cardiovasc Electrophysiol* 2015; **26**: 832-839 [PMID: 25917655 DOI: 10.1111/jce.12695]

21 **Haïssaguerre M**, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; **339**: 659-666 [PMID: 9725923 DOI: 10.1056/NEJM199809033391003]

22 **Chang HY**, Lo LW, Lin YJ, Chang SL, Hu YF, Li CH, Chao TF, Chung FP, Ha TL, Singhal R, Chong E, Yin WH, Tsao HM, Hsieh MH, Chen SA. Long-term outcome of catheter ablation in patients with atrial fibrillation originating from nonpulmonary vein ectopy. *J Cardiovasc Electrophysiol* 2013; **24**: 250-258 [PMID: 23210627 DOI: 10.1111/jce.12036]

23 **de Groot NM**, Zeppenfeld K, Wijffels MC, Chan WK, Blom NA, Van der Wall EE, Schalij MJ. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. *Heart Rhythm* 2006; **3**: 526-535 [PMID: 16648056 DOI: 10.1016/j.hrthm.2006.01.011]

24 **Cappato R**, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; **3**: 32-38 [PMID: 19995881 DOI: 10.1161/CIRCEP.109.859116]

25 **Sherwin ED**, Triedman JK, Walsh EP. Update on interventional electrophysiology in congenital heart disease: evolving solutions for complex hearts. *Circ Arrhythm Electrophysiol* 2013; **6**: 1032-1040 [PMID: 24129205 DOI: 10.1161/CIRCEP.113.000313]

26 **Triedman JK**, Alexander ME, Love BA, Collins KK, Berul CI, Bevilacqua LM, Walsh EP. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol* 2002; **39**: 1827-1835 [PMID: 12039499 DOI: 10.1016/S0735-1097(02)01858-2]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 June 26; 11(6): 159-170

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 6 June 26, 2019

REVIEW

Contents

World Journal of Cardiology

Volume 11 Number 6 June 26, 2019

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
June 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 June 26; 11(6): 159-170

DOI: 10.4330/wjc.v11.i6.159

ISSN 1949-8462 (online)

REVIEW

Broken heart: A matter of the endoplasmic reticulum stress bad management?

Souad Belmadani, Khalid Matrougui

ORCID number: Souad Belmadani (0000-0002-7355-9142); Khalid Matrougui (0000-0001-9269-2937).

Author contributions: Belmadani S and Matrougui K contributed equally to this work.

Conflict-of-interest statement: None

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: February 23, 2019
Peer-review started: February 26, 2019
First decision: April 15, 2019
Revised: April 29, 2019
Accepted: June 12, 2019
Article in press: June 13, 2019
Published online: June 26, 2019

P-Reviewer: Petix NR, Ueda H
S-Editor: Ji FF
L-Editor: A
E-Editor: Xing YX

Souad Belmadani, Khalid Matrougui, Department of Physiological Science, Eastern Virginia Medical School, Norfolk, VA 23501, United States

Corresponding author: Souad Belmadani, PhD, Assistant Professor, Department of Physiological Science, Eastern Virginia Medical School, 700 W Olney Rd, Norfolk, VA23501, United States. belmads@evms.edu
Telephone: +1-757-4465880

Abstract

Cardiovascular diseases are the number one cause of morbidity and mortality in the United States and worldwide. The induction of the endoplasmic reticulum (ER) stress, a result of a disruption in the ER homeostasis, was found to be highly associated with cardiovascular diseases such as hypertension, diabetes, ischemic heart diseases and heart failure. This review will discuss the latest literature on the different aspects of the involvement of the ER stress in cardiovascular complications and the potential of targeting the ER stress pathways as a new therapeutic approach for cardiovascular complications.

Key words: Heart complications; Endoplasmic reticulum stress; Inflammation; Apoptosis; Autophagy

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The central mechanisms involved in heart failure, a public health crisis, remain unknown. Current therapies, in addition to their strong side effects, neither halt nor reverse heart complications. The endoplasmic reticulum (ER) stress has been shown to be involved in cardiovascular diseases. Here we analyzed the role and mechanism of the ER stress in heart failure.

Citation: Belmadani S, Matrougui K. Broken heart: A matter of the endoplasmic reticulum stress bad management? *World J Cardiol* 2019; 11(6): 159-170
URL: https://www.wjgnet.com/1949-8462/full/v11/i6/159.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i6.159

INTRODUCTION

The endoplasmic reticulum (ER), one of the largest organelles in the eukaryotic cells was described for the first time in 1945 by Porter *et al*[1]. The ER is responsible for protein synthesis, and folding of most secreted and membrane protein, which represent approximately 35% of all protein[2].The ER is also the site of protein translocation, calcium homeostasis, lipid, and steroid biosynthesis[3]. Effective ER function relies on various quality control factors such as molecular chaperones, protein oxidoreductases, and enzymes involved in glycosylation, sulfation and proteolysis[4]. This highly organized machinery requires an optimal ER environment. Various factors such as myocardial ischemia, diabetes, hypertension, and heart failure can disrupt this environment provoking the accumulation of misfolded proteins[4]. When the ER homeostasis is altered by the accumulation of unfolded/misfolded protein; signaling pathways are activated triggering an adaptive response known as the unfolded protein response (UPR). The primary goal of the UPR is to restore the protein balance by suppressing protein translation, increased clearance of unfolded or misfolded proteins and promoting cell survival. Unfortunately, if the ER homeostasis is not restored, the cell dysfunction and death signaling pathways is launched. The UPR re-establishes homeostasis through three distinct branches that are initiated by the ER-resident protein folding sensors, inositol-requiring protein-1 (IRE1α), activating transcription factor-6 (ATF6) or protein kinase RNA-like ER kinase (PERK). Each branch uses a unique mechanism to activate transcription factors and up-regulate UPR target genes. These three ER-transmembrane proteins serve both as sensors for the ER stress and effectors for the response to the ER stress induction. Under basal conditions, the ER-resident transmembrane proteins ATF6, IRE1, and PERK are maintained in an inactive state *via* their binding to the ER chaperone glucose-regulated protein (GRP78)[5]. Under stress conditions where misfolded proteins are increased in the ER, GRP78 binds misfolded protein and releases from the ER stress sensors, leading to their activation.

IRE1 is the most ancient ER transmembrane protein containing an ER-luminal sensor domain recognizing unfolded peptides, kinase and endoribonuclease (RNase) domain on its cytosolic portion[6]. IRE1 has two isoforms, IRE1α and IRE1β[6]. IRE1α is ubiquitously expressed whereas IRE1β is only expressed in the gut[6]. In the absence of the ER stress, GRP78 binds to the luminal domain of IRE1α. Under stress situations, IRE1 is activated by homodimerization after release from GRP78 and auto-phosphorylation leading to the activation of the kinase and the endoribonuclease activity of IRE1. Active IRE1α splices a transcription factor X-box-binding-protein-1 (XBP1) mRNA to spliced XBP1 (XBP1s). XBP1s is a potent transcription factor for a variety of genes involved in retrograde transport of proteins from the ER to cytosol and in ER-induced protein degradation[7]. Moreover, IRE1 degrades mRNAs *via* regulated IRE1-dependent mRNA decay (RIDD) mechanism to reinstate homeostasis in the ER.

ATF6, a 670 amino acids type II transmembrane protein with a bZIP transcription factor motif. At resting conditions ATF6 is localized at the ER through its interaction with GRP78. Following the stress, unfolded/misfolded proteins accumulation enhance the release of the ATF6 and its translocation to the Golgi apparatus where the luminal and transmembrane domains are cleaved by site-1 and site-2 proteases (S1P and S2P) *via* regulated intra-membrane proteolysis. This results in an active ATF6 capable of interacting with regulatory sequences called ER stress response elements and regulating the expression of chaperones, X box-binding protein 1 (XBP1) toward restoring protein folding and cellular homeostasis[8,9].

Like IRE1, PERK has a protein kinase activity, and after its dissociation from GRP78, PERK dimerizes and autophosphorylates. Active PERK phosphorylates the eukaryotic initiation factor 2α (eIF2α), which blocks unfolded protein translation promoting cell survival and also activates the transcription of the ATF4 to decrease Unfolded protein level in the ER *via* the activation of various UPR genes[10]. If the adaptive mechanisms do not sufficiently recover the ER homeostasis, the UPR can switch from a pro-adaptive to a pro-apoptotic role[11].

ER STRESS AND HEART

Numerous studies have linked the disruption of the ER homeostasis to the pathophysi-ology of many diseases including heart diseases. However, the specific role of the ER stress signaling in the heart is yet to be defined and whether ER stress signaling is detrimental or protective in the heart is still a challenging question that needs to be answered[4,12]. In cardiomyocyte, Bcl2 proteins family was shown to induce

apoptosis *via* calcium signaling during ER stress induction[13]. In line with this study, prolonged ER stress triggered cardiomyocyte apoptosis and oxidation of CaMKII, a redox-sensitive enzyme, which was rescued by antioxidant or CamKII inhibitors treatments[14]. Furthermore, it has been shown that the oxidation of CaMKII may lead to cardiac dysfunction and apoptosis[15]. In this context, Roe *et al*[14] showed that CaMKII oxidation mediates ER stress-induced cardiac dysfunction and apoptosis and could be used as a potential target in cardiac diseases triggered by the ER stress. GRP78 has been found to increase in patients with heart failure suggesting the implication of the UPR activation in heart failure[16]. Patients with heart failure display a structural and architecture alteration of the ER as well as dys-regulation of the ER proteins involved in the UPR response[17]. In fact, spliced XBP1s, GRP78, ATF4, and CHOP were all induced in failing human heart[16-20]. Using the transverse aortic constriction (TAC) mouse model to induce heart failure, Okada *et al*[20] showed that the ER stress was induced in both hypertrophic and failing heart. Remarkably, the ER stress-CHOP and apoptosis were only seen in failing heart but not in hypertrophic heart indicating the differential effect of the ER stress pathology-dependent. Moreover, the ER stress-CHOP deficient mice develop less cardiac hypertrophy, fibrosis, and cardiac dysfunction compared to wild mice. Our recent study showed that the inhibition of the ER stress protected the heart against myocardial infarction induced by ischemia-reperfusion injury[21]. Together these studies suggest that the ER stress could be involved in the development of myocardial infarction, cardiac hypertrophy, and the transition from hypertrophy to heart failure[22,23].

Recently, PERK was shown to protect the heart from pressure overload-induced heart failure[24]. Cardiomyocyte-specific disruption of PERK did not affect the cardiac structure or function under normal conditions but exacerbates the development of heart failure in response to TAC[25]. The hearts of PERK knockout mice showed a dramatic reduction in Serca2α expression and an increase in apoptosis and UPR genes expression (GRP78, GRP94, CHOP) in response to TAC. These results suggest the importance of PERK in the maintenance of intracellular calcium homeostasis, control of the ER stress level and cell survival[25].

The activation of the UPR has been shown in ischemic heart diseases[26,27]. PERK activation was also observed in ischemic hearts, and its overexpression seems to promote cell survival while its down regulation is detrimental to cells[28,29].

XBP1s and GRP78 were increased in the ischemic heart of patients and animal models[27,30]. XBP1s seem to be cardio-protective in mice after ischemia-reperfusion injury[31,32]. Moreover, the ER stress-CHOP, PUMA and Tribbles3 downstream effectors of PERK play a significant role in cell death induced by the ER stress after myocardial ischemia-reperfusion injury[33].

ATF6, the third ER stress member that is activated during myocardial I/R injury. Using genetic and pharmacological approaches, Glembotski's group and others showed that ATF6 protects the heart against myocardial I/R injury probably through the induction of the ERAD machinery leading to the degradation of misfolded proteins in the ER[34-37]. Recently, it has been found that thrombospondin-4 protects the heart by promoting the adaptive response of the ER stress through the activation of the ER stress ATF6[38,39]. The authors showed that ATF6 location and activity could be determined *via* its interaction with thrombospondin-4. These results suggest the benefit of enhancing the adaptive response mediated by ATF6 as a potential therapy to target ischemic heart diseases.

INFLAMMATION AND ER STRESS

In recent years, various studies found links between the ER stress pathways and inflammation[40]. Ischemic heart disease, a significant cause of death is recognized as an inflammatory disease involving infiltration of monocytes and macrophages. Recently, cardiac-specific expression of monocyte chemoattractant protein-1 (MCP-1) in mice causes heart failure, which was correlated with the activation of a cluster of the ER stress-related genes[41]. It has been shown that the production of the pro-inflammatory cytokine such IFNγ, TNF-α, MCP-1, and IL-8 required the activation of the IRE1 and XBP1[42,43]. IRE1 has also been linked to inflammation mediated by NFκB cascade *via* its binding to TRAF2[44,45]. Moreover, ATF 6 can also trigger NFκB mediated inflammation through AKT phosphorylation[46].

ER STRESS AND APOPTOSIS

When the UPR fails to reestablish the ER homeostasis, the detrimental apoptotic

signaling pathway is activated. Up to date, it is still a mystery how cells chose between the adaptive/survival pathway *vs* the detrimental /death once the UPR machinery is triggered. Under sustained ER stress induction, IRE1α triggers apoptosis *via* the activation of JNK and p38 through TRAF2 and ASK1 mechanism[47,48].

Cardiac myocyte lacking ASK1 were resistant to apoptosis induced by the hydrogen peroxide[49]. Cardiac overexpression of ASK1 showed an increase in cardiac apoptosis in a mice model of TAC while ASK1 deficient mice were protected from heart failure[50]. In a rat model of I/R injury, the inhibition of ASK1 was able to reduce apoptosis and myocardial infarct size[51]. The p38 activates the ER stress CHOP and both p38 and JNK can activate Bax to initiate apoptosis. IRE1 is also known to activate caspase12 leading to apoptosis[52,53]. Moreover, the RNase activity of IRE1 known as RIDD may promote cell death *via* the degradation of mRNAs involved in protein survival[54]. It is worth noting that IRE1 exerts two opposing functions: death and survival depending on the conformational of the protein and the intensity of the stress mild *vs* high. Under mild conditions of the ER stress, IRE1 helps to relieve the stress by splicing XBP-1. Under high-prolonged ER stress, IRE1 triggers apoptosis *via* the interaction with TRAF2 and ASK1[54]. Erhardt's group recently described that the ER stress requires the proapoptotic Bcl-2 family protein (Puma) to promote apoptosis in cardiac myocytes[55]. Puma is critical for cell death related to I/R[56]. Thus, the overexpression of PUMA in cardiac myocytes contributes to apoptosis induced by the ER stress while deletion protects the heart from I/R injury[57]. These results suggest inhibition of Puma activity may be used to treat cardiac infarcts or prevent heart failure by blocking ER stress-induced apoptosis[56,58]. Additionally, evidence suggests that the ER stress-CHOP plays a pivotal role in mitochondria-dependent apoptosis in the heart with pressure overload[22]. It is clear that the ER stress induction is a mechanism that leads to apoptosis and therefore tissue damage.

ER STRESS AND AUTOPHAGY

Autophagy or "self-eating" is a highly conserved cell-recycling program for the clearance of damaged proteins and organelles. Autophagy has been reported in many cells type of the cardiovascular system and been classified into microautophagy, macroautophagy, and chaperone-mediated autophagy. Autophagy is necessary for the preservation of normal cardiac function. However, deficient or excessive cardiac autophagy is considered as a maladaptive response. Moreover, autophagy is regarded as "double edge sword" for its different role in the cardiovascular system.

Recently, the ER stress emerges as an important inducer of autophagy and a link between the ER stress, autophagy and cardiac function have been proposed[59,60]. Although, abundant data showed that cross talks exist between the ER stress and autophagy, the molecular mechanism is yet to be determined[61]. Zhang *et al*[62] recently showed that mitochondrial aldehyde dehydrogenase (ALDH2) was able to alleviate ER stress-induced cardiomyopathy *via* autophagy reduction. Reticulon, a membrane-associated protein localized at the ER has been shown to be involved in the induction of autophagy leading to the ER stress induction demonstrating the relationship between autophagy, reticulum and the ER stress[63]. Furthermore, the activation of the IRE1 induces autophagy *via* its interaction with TRAF2 and the activation of JNK leading to the regulation of Beclin-1 expression. Moreover, advance glycation products (AGEs) were able to trigger autophagy in cardiac myocytes probably *via* the ER stress signaling. In fact, crosstalk between advanced AGEs and ER stress signaling could mediate the induction of autophagy by AGES[64,65]. In a mouse model of sepsis, Cardiac-specific overexpression of the antioxidant metallothionein (MT) was able to rescue cardiac contractility dysfunction probably *via* ER stress and oxidative stress modulation[66]. In a swine model of hypertension, the progression of LVH has been shown to involve an early activation of the ER stress followed by an increase in autophagy leading to apoptosis[67]. SIRT1, a member of the sirtuins family, histone/protein deacetylases known to be crucially involved in signaling related to cell death/survival and has been found to be activated in the heart to promote cell adaptation and survival under stress[68]. Recently Lemaire's group reported that in cardiac cells, Sirt1 was able to modulate the induction of autophagy in response to the ER stress induction suggesting the possibility of tuning the adaptive autophagy in cardiac pathologies related to ER stress[69].

In summary, the ER stress and autophagy play an important role in the pathogenesis of cardiac complications. Although, ample studies established the interplay and the interaction between the ER stress and autophagy, and their role in the progression of heart diseases, the molecular mechanism remained unknown. Who are the players, how can we better tune the ER stress and autophagy? It is evident now

that the ER stress and autophagy are influencing each other. Therefore, a good understanding of the interconnection between these two important physiological processes, especially under pathological conditions will be of great importance and may shed light on developing new therapeutic strategies to rescue the cardiovascular system.

ER STRESS AND MICRORNAS

MicroRNAs (miRNAs or miRs) are a class of conserved small, 20-23 nucleotide, single-stranded, non-coding RNAs that post-transcriptionally regulate gene expression[70]. They were first described in the 1993 and had been linked to various cellular stress such oxidative stress, inflammation, and the ER stress in the setting of cardiovascular complications[71]. The miRNAs are increasingly recognized as a master regulator of the ER stress and an important player in the UPR response, which manage the UPR balance between survival and cell death during the ER stress-induction. In fact, several miRNAs have been demonstrated to be regulated by the ER stress and to regulate the ER stress by optimizing the levels of key proteins involved in the UPR. For instance PERK pathway induces the expression of miR-30c-2*, which represses XBP1s synthesis at the translational level[72]. Although miR-30c-2* level increases after the ER stress induction along with the XBP1s level, miR-30c-2* was still capable of affecting the XBP1 level in the course of the UPR[72]. In cardiac myocytes and using a Tamoxifen-inducible ATF6 in the heart of transgenic mice, activated ATF6 regulates the expression of 13 miRNAs[73]. The miRNA-455, one of the miRNAs down regulated by ATF6, negatively regulates calreticulin (a calcium chaperone protein) involved in the folding of nascent polypeptides[73]. Therefore, the ER stress ATF6 down regulates miRNA-455, which up-regulates calreticulin, a cardio-protective gene. While the ER stress ATF6 regulates the expression of miRNAs, it was also a target of miR-702[74]. Together, the two studies showed the existence of interplay between miRNAs and the pro-adaptive activity of the UPR in the heart. Another class of miRNAs linked to the ER stress includes member of miRNA-30 family. The miRNA30 is one of the most abundant miRNAs expressed in the myocardium and has been shown to be down-regulated in heart failure and hypertension in both vascular smooth muscle cells and cardiac neonate cells. Under ER stress conditions, miRNA-30 was down-regulated while GRP78 was up-regulated. Moreover, GRP78 up-regulation seems to modulate miRNA-30 expression through the inhibition of the C/EBP trans-activity by CHOP in the myocardium[75]. Interestingly, Knockdown of miRNA-30 in cardiac cells triggered ER stress and identified the ER stress ATF6/CHOP and caspase-12 as indirect targets of this miRNAs. While the transfection of miR-30 was able to abolish the ER stress suggesting that miRNA30 plays a role in the regulation of cell death and miRNA30 replacement could be considered as an approach for targeting the ER stress and the related pathological diseases[76]. Recent studies indicated that miRNA214 is a negative regulator of angiogenesis in the retina and heart[19,77]. XBP1 was found to be a direct target of miR214 in endothelial cells. The blockade of the endogenous miRNA214 expression regulated cardiac function and cardiac angiogenesis. Interestingly, cardiac overexpression of miRNA-214 in mice had no morphological changes suggesting that miRNA214 regulates cardiac and vascular angiogenesis only when XBP-1 is dys-regulated[78]. This study highlighted another scenario of ''cross talk'' between miRNAs and the ER stress components in the cardiovascular system. Independently of XBP-1, a recent study proposed a new role of the ER stress sensor IRE1α in the modulation of miRNA-200 and miRNA-466 and the improvement of bone marrow derived progenitor cells (BMPC) function *via* its endonuclease activity in diabetes[79]. This study outlined the importance of the ER stress IRE1α as a crucial modulator of the fate/function of BMPCs during angio-genesis and tissue repair *via* the modulation of miRNA expression levels and may be therefore involved in another ischemic setting such ischemic heart diseases and heart failure. Further studies are needed to determine the mechanism that inhibits IRE1α activity in diabetic BMPCs and the potential of expanding these findings to other cardiovascular complications, such as the heart failure[80]. The ER stress ATF4, a downstream effector of the ER stress PERK, has been linked to miR-663 in endothelial cells[81]. The inhibition of miRNA663 during the ER stress induction leads to a decrease in the ER stress ATF4 expression as well as its target gene, the VEGF. Moreover, miRNA708 was the first ER stress-induced miRNA discovered[82].

MicroRNAs and the ER stress interaction is a very young research area. More work is required to unravel the array of microRNA targets and determine their function in the ER stress-induced death/survival. Moreover, it is essential to recognize that the results obtained so far showing the interaction/link/correlation/regulation of the ER

stress by miRNAs or vice versa represent a promising avenue for cardiovascular diseases. As mentioned above, one of the significant challenges of the ER stress response in pathological situations is the fact that it is difficult to distinguish between the protective pathways and the detrimental pathways once the UPR response is triggered. Differentiating between the detrimental pathways and the adaptive pathways of the ER stress players *via* its miRNAs target will advance the field tremendously and opens new opportunities for novel therapeutic strategies targeting ER stress *via* miRNAs in cardiovascular diseases.

ER STRESS AS A TARGET THERAPY

ER stress has been involved in numerous cardiovascular diseases such as diabetes, hypertension, myocardial infarction and heart failure. Therefore, targeting the ER stress in cardiovascular disease *via* the activation of the adaptive pathway of the UPR or the inhibition of the detrimental pro-apoptotic pathways of the UPR will be a beneficial therapy for cardiovascular diseases.

Chemical chaperones, small molecules that work similarly to the endogenous molecular chaperone machinery to stabilize misfolded proteins, facilitate their proper folding and reduce the ER stress. Among the chemical chaperones that have been extensively used in various diseases related to the ER stress, Tauroursodeoxycholic (TUDCA) and 4-phenylbutyric acid (PBA).

TUDCA is a non-toxic hydrophilic bile acid that functions as a chemical chaperone and has been extensively used in colitis, pulmonary fibrosis, biliary cirrhosis, and recently in patients with obesity and insulin resistant[83-85]. In animal models, TUDCA has been shown to protect the heart against myocardial dysfunction in obesity, and reduce apoptosis in a mouse model of myocardial infarction[86]. Under pressure overload, TUDCA was shown to attenuate cardiac remodeling through down-regulation of the GRP78 and GRP94 and the regulation of the ER stress PERK phosphorylation and eIF2α[87]. Moreover, in a mouse model of heart failure induced by calreticulin overexpression, the inhibition of the UPR using TUDCA decreased cardiac fibrosis, which was mediated through the inhibition of the ER stress IRE1 activation and XBP1 splicing[88]. Together, these results highlight the cardioprotective effect of TUDCA treatment and the therapeutic potential of using TUDCA in the management of cardiac complications[66].

PBA, a low-molecular-weight aromatic fatty acid, has a chaperone-like activity and has been shown to attenuate cardiac hypertrophy, fibrosis, and apoptosis in a pressure overload animal model[89]. In isolated rat hearts subjected to I/R injury, 4-PBA was revealed to be a potent cardioprotective agent *via*: (1) The reduction in the I/R injury-induced myocardial dysfunction and cell apoptosis; (2) The delay of the onset of the ER stress *via* the regulation of Grp78 expression, PERK phosphorylation; and (3) The inhibition of oxidative stress[90]. In a cell and a clinically relevant dog model for atrial fibrillation, the blockade of the ER stress by PBA inhibits the induction of the autophagy and suppresses cardiomyocytes remodeling suggesting the potential of using PBA to protect the heart against clinical atrial fibrillation[91]. Furthermore, PBA and TUDCA were also able to reduce the cardio-toxicity effect of doxorubicin (a chemotherapeutic agent commonly used in cancer). Moreover, PBA and TUDCA reduced cardiomyocyte apoptosis and alleviated cardiac dysfunction in a mouse model of cardiomyopathy induced by doxorubicin[92]. Considering that TUDCA and PBA are FDA-approved chemical chaperones and already used clinically for the treatment of some diseases, it will be exciting and safer to test TUDCA and PBA in patients with cardiovascular complications related to the ER disturbance. Future basic and clinical studies are critically needed to determine: (1) The right doses required to obtain the cardioprotective effect; and (2) To delineate the mechanism of how chemical chaperones promote the protein folding.

Statin therapy has been shown to be beneficial for heart failure treatment[93]. Interestingly, a recent study showed that in a mouse model of pressure overload and this effect was associated with a reduction in the ER stress[94-97]. The results suggest that the reduction in the ER stress might be a novel mechanism for the beneficial effect of statin for heart failure[98]. Moreover, in a rat model of heart failure, the modulation of the ER stress markers such as Caspase12, the ER stress-CHOP, and GRP78 was proposed as a mechanism by which Atorvastatin (another statin drug) protects the heart against heart failure[99]. Interestingly, the administration of Atorvastatin improved left ventricular ejection fraction and attenuated left ventricular remodeling in patients with heart failure[100]. These results could be clinically relevant for the treatment and the prevention of heart failure.

Apelin recently discovered as an endogenous ligand for the G protein-coupled

receptor APJ and has been shown to be a beneficial therapy for patients with heart failure[101-103]. Apelin seems to have a positive effect on peripheral and coronary vasodila-tation, cardiac output, and cardiac function[104,105]. The cardioprotective effect of apelin could be mediated through the inhibition of the ER stress dependent apoptosis[106]. Furthermore, in a mouse model of obesity-induced cardiac complications, exogenous administration of apelin attenuates myocardial contractile dysfunctions and cardiac hypertrophy through the inhibition of the ER stress and the restoration of autophagy[107]. On the other hand, apelin 13 (the main subtype of apelin in the human heart) induced cardiomyocytes hypertrophy through autophagy and the ER stress mechanisms[108]. From these studies, the benefits *vs* the detrimental role of apelin in cardiac complication seem to depend on the conditions basic *vs* stress and could be explained by the UPR status of the ER stress adaptive *vs* detrimental UPR response.

Adenosine monophosphate-activated kinase (AMPK) recognized as an intracellular energy and stress sensor that function to maintain intracellular homeostasis during stress conditions. Dysregulation of AMPK has been reported in humans and animal models of metabolic syndrome[109-111]. The 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR) and metformin, antidiabetic drugs activate AMPK, reduce the ER stress and slow the progression of heart failure[112]. Additionally, AICAR activates nuclear factor-E2-related factor (Nrf2) through AMPK independent pathways, which helps combat oxidative damage. Increased expression of Nrf2 reduces cardiac hypertrophy, myocardial infarct, and the progression of heart failure. However, AMPK and Nrf2 pathways show convergence as well[113]. Therapies that activate AMPK and Nrf2, as well as the UPR and apoptotic pathways, hold promise in the treatment cardiac complications. Moreover, therapeutic efforts aimed at oxidative stress also reduce the ER stress. Thus, the ER stress appears to be, a key player in cardiovascular complications and a large number of drugs seemed to protect the heart against failure involved the ER stress modulation. Targeting the ER stress pathways hold a great feature for patients with cardiac complications. As the prevalence of heart diseases raises yearly worldwide, it becomes significant to understand the relationship between heart failure and the ER stress. There is still much to understand about the contribution of the ER stress in heart complications (Figure 1).

CONCLUSION

Significant attention was given to the ER stress in the recent years from "bench to bed" due to its involvement in numerous cardiovascular diseases such as diabetes, hypertension, myocardial infarction, and heart failure. Although many studies have characterized signaling pathways of the ER stress and the UPR in general and particularly in the cardiac field, many questions remained to be addressed. How can we tame the ER stress and what is the best way to control it? How can we balance "too much or too little" of the ER stress to promote survival and inhibit apoptosis in cardiac pathology? How can we integrate conventional therapies (AMP kinase drugs, ACE inhibitors, autophagy (activators/inhibitors) with the UPR target against cardiovascular diseases? How can we use MicroRNAs and gene therapy to regulate the ER stress toward a better and safe future therapy? Can the chemical chaperone be "the ER stress therapy" by excellence against cardiac complications? Only the future will tell us.

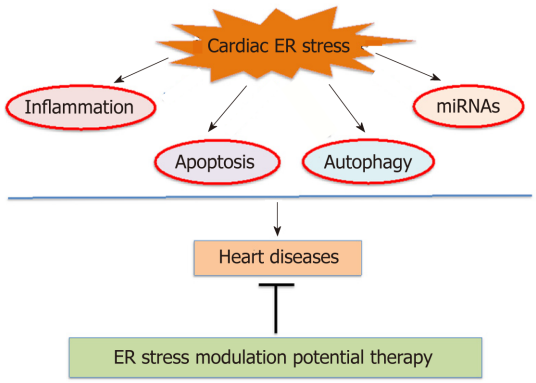


Figure 1 Schema recapitulating the involvement of the endoplasmic reticulum stress in heart diseases. ER: Endoplasmic reticulum.

REFERENCES

1 **Porter KR**, Claude A, Fullam EF. A study of tissue culture cells by electron microscopy: Methods and preliminary observations. *J Exp Med* 1945; **81**: 233-246 [PMID: 19871454 DOI: 10.1084/jem.81.3.233]
2 **Palade GE**. The endoplasmic reticulum. *J Biophys Biochem Cytol* 1956; **2**: 85-98 [PMID: 13357527 DOI: 10.1083/jcb.2.4.85]
3 **van der Kant R**, Neefjes J. Small regulators, major consequences - Ca² and cholesterol at the endosome-ER interface. *J Cell Sci* 2014; **127**: 929-938 [PMID: 24554437 DOI: 10.1242/jcs.137539]
4 **Glembotski CC**. Endoplasmic reticulum stress in the heart. *Circ Res* 2007; **101**: 975-984 [PMID: 17991891 DOI: 10.1161/CIRCRESAHA.107.161273]
5 **Pfaffenbach KT**, Lee AS. The critical role of GRP78 in physiologic and pathologic stress. *Curr Opin Cell Biol* 2011; **23**: 150-156 [PMID: 20970977 DOI: 10.1016/j.ceb.2010.09.007]
6 **Wang XZ**, Harding HP, Zhang Y, Jolicoeur EM, Kuroda M, Ron D. Cloning of mammalian Ire1 reveals diversity in the ER stress responses. *EMBO J* 1998; **17**: 5708-5717 [PMID: 9755171 DOI: 10.1093/emboj/17.19.5708]
7 **Rao RV**, Bredesen DE. Misfolded proteins, endoplasmic reticulum stress and neurodegeneration. *Curr Opin Cell Biol* 2004; **16**: 653-662 [PMID: 15530777 DOI: 10.1016/j.ceb.2004.09.012]
8 **Schröder M**, Kaufman RJ. The mammalian unfolded protein response. *Annu Rev Biochem* 2005; **74**: 739-789 [PMID: 15952902 DOI: 10.1146/annurev.biochem.73.011303.074134]
9 **Jin JK**, Blackwood EA, Azizi K, Thuerauf DJ, Fahem AG, Hofmann C, Kaufman RJ, Doroudgar S, Glembotski CC. ATF6 Decreases Myocardial Ischemia/Reperfusion Damage and Links ER Stress and Oxidative Stress Signaling Pathways in the Heart. *Circ Res* 2017; **120**: 862-875 [PMID: 27932512 DOI: 10.1161/CIRCRESAHA.116.310266]
10 **Harding HP**, Zhang Y, Ron D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* 1999; **397**: 271-274 [PMID: 9930704 DOI: 10.1038/16729]
11 **Tabas I**, Ron D. Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nat Cell Biol* 2011; **13**: 184-190 [PMID: 21364565 DOI: 10.1038/ncb0311-184]
12 **Xu C**, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. *J Clin Invest* 2005; **115**: 2656-2664 [PMID: 16200199 DOI: 10.1172/JCI26373]
13 **Diwan A**, Matkovich SJ, Yuan Q, Zhao W, Yatani A, Brown JH, Molkentin JD, Kranias EG, Dorn GW 2nd. Endoplasmic reticulum-mitochondria crosstalk in NIX-mediated murine cell death. *J Clin Invest* 2009; **119**: 203-212 [PMID: 19065046 DOI: 10.1172/JCI36445]
14 **Roe ND**, Ren J. Oxidative activation of Ca(2+)/calmodulin-activated kinase II mediates ER stress-induced cardiac dysfunction and apoptosis. *Am J Physiol Heart Circ Physiol* 2013; **304**: H828-H839 [PMID: 23316062 DOI: 10.1152/ajpheart.00752.2012]
15 **Erickson JR**, Joiner ML, Guan X, Kutschke W, Yang J, Oddis CV, Bartlett RK, Lowe JS, O'Donnell SE, Aykin-Burns N, Zimmerman MC, Zimmerman K, Ham AJ, Weiss RM, Spitz DR, Shea MA, Colbran RJ, Mohler PJ, Anderson ME. A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. *Cell* 2008; **133**: 462-474 [PMID: 18455987 DOI: 10.1016/j.cell.2008.02.048]
16 **Dally S**, Monceau V, Corvazier E, Bredoux R, Raies A, Bobe R, del Monte F, Enouf J. Compartmentalized expression of three novel sarco/endoplasmic reticulum Ca2+ATPase 3 isoforms including the switch to ER stress, SERCA3f, in non-failing and failing human heart. *Cell Calcium* 2009; **45**: 144-154 [PMID: 18947868 DOI: 10.1016/j.ceca.2008.08.002]
17 **Ortega A**, Roselló-Lletí E, Tarazón E, Molina-Navarro MM, Martínez-Dolz L, González-Juanatey JR, Lago F, Montoro-Mateos JD, Salvador A, Rivera M, Portolés M. Endoplasmic reticulum stress induces different molecular structural alterations in human dilated and ischemic cardiomyopathy. *PLoS One* 2014; **9**: e107635 [PMID: 25226522 DOI: 10.1371/journal.pone.0107635]
18 **Duan Q**, Ni L, Wang P, Chen C, Yang L, Ma B, Gong W, Cai Z, Zou MH, Wang DW. Deregulation of XBP1 expression contributes to myocardial vascular endothelial growth factor-A expression and angiogenesis during cardiac hypertrophy in vivo. *Aging Cell* 2016; **15**: 625-633 [PMID: 27133203 DOI: 10.1111/acel.12460]
19 **Duan Q**, Yang L, Gong W, Chaugai S, Wang F, Chen C, Wang P, Zou MH, Wang DW. MicroRNA-214 Is Upregulated in Heart Failure Patients and Suppresses XBP1-Mediated Endothelial Cells Angiogenesis. *J Cell Physiol* 2015; **230**: 1964-1973 [PMID: 25656649 DOI: 10.1002/jcp.24942]
20 **Okada K**, Minamino T, Tsukamoto Y, Liao Y, Tsukamoto O, Takashima S, Hirata A, Fujita M, Nagamachi Y, Nakatani T, Yutani C, Ozawa K, Ogawa S, Tomoike H, Hori M, Kitakaze M. Prolonged endoplasmic reticulum stress in hypertrophic and failing heart after aortic constriction: possible contribution of endoplasmic reticulum stress to cardiac myocyte apoptosis. *Circulation* 2004; **110**: 705-712

[PMID: 15289376 DOI: 10.1161/01.CIR.0000137836.95625.D4]
21 **Mali V**, Haddox S, Hornersmith C, Matrougui K, Belmadani S. Essential role for EGFR tyrosine kinase and ER stress in myocardial infarction in type 2 diabetes. *Pflugers Arch* 2018; **470**: 471-480 [PMID: 29288332 DOI: 10.1007/s00424-017-2097-5]
22 **Fu HY**, Okada K, Liao Y, Tsukamoto O, Isomura T, Asai M, Sawada T, Okuda K, Asano Y, Sanada S, Asanuma H, Asakura M, Takashima S, Komuro I, Kitakaze M, Minamino T. Ablation of C/EBP homologous protein attenuates endoplasmic reticulum-mediated apoptosis and cardiac dysfunction induced by pressure overload. *Circulation* 2010; **122**: 361-369 [PMID: 20625112 DOI: 10.1161/CIRCULATIONAHA.109.917914]
23 **Ohoka N**, Yoshii S, Hattori T, Onozaki K, Hayashi H. TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death. *EMBO J* 2005; **24**: 1243-1255 [PMID: 15775988 DOI: 10.1038/sj.emboj.7600596]
24 **Liu X**, Kwak D, Lu Z, Xu X, Fassett J, Wang H, Wei Y, Cavener DR, Hu X, Hall J, Bache RJ, Chen Y. Endoplasmic reticulum stress sensor protein kinase R-like endoplasmic reticulum kinase (PERK) protects against pressure overload-induced heart failure and lung remodeling. *Hypertension* 2014; **64**: 738-744 [PMID: 24958502 DOI: 10.1161/HYPERTENSIONAHA.114.03811]
25 **Lu Z**, Xu X, Fassett J, Kwak D, Liu X, Hu X, Wang H, Guo H, Xu D, Yan S, McFalls EO, Lu F, Bache RJ, Chen Y. Loss of the eukaryotic initiation factor 2α kinase general control nonderepressible 2 protects mice from pressure overload-induced congestive heart failure without affecting ventricular hypertrophy. *Hypertension* 2014; **63**: 128-135 [PMID: 24166753 DOI: 10.1161/HYPERTENSIONAHA.113.02313]
26 **Glembotski CC**. The role of the unfolded protein response in the heart. *J Mol Cell Cardiol* 2008; **44**: 453-459 [PMID: 18054039 DOI: 10.1016/j.yjmcc.2007.10.017]
27 **Sawada T**, Minamino T, Fu HY, Asai M, Okuda K, Isomura T, Yamazaki S, Asano Y, Okada K, Tsukamoto O, Sanada S, Asanuma H, Asakura M, Takashima S, Kitakaze M, Komuro I. X-box binding protein 1 regulates brain natriuretic peptide through a novel AP1/CRE-like element in cardiomyocytes. *J Mol Cell Cardiol* 2010; **48**: 1280-1289 [PMID: 20170659 DOI: 10.1016/j.yjmcc.2010.02.004]
28 **Szegezdi E**, Duffy A, O'Mahoney ME, Logue SE, Mylotte LA, O'brien T, Samali A. ER stress contributes to ischemia-induced cardiomyocyte apoptosis. *Biochem Biophys Res Commun* 2006; **349**: 1406-1411 [PMID: 16979584 DOI: 10.1016/j.bbrc.2006.09.009]
29 **Lu PD**, Jousse C, Marciniak SJ, Zhang Y, Novoa I, Scheuner D, Kaufman RJ, Ron D, Harding HP. Cytoprotection by pre-emptive conditional phosphorylation of translation initiation factor 2. *EMBO J* 2004; **23**: 169-179 [PMID: 14713949 DOI: 10.1038/sj.emboj.7600030]
30 **Thuerauf DJ**, Marcinko M, Gude N, Rubio M, Sussman MA, Glembotski CC. Activation of the unfolded protein response in infarcted mouse heart and hypoxic cultured cardiac myocytes. *Circ Res* 2006; **99**: 275-282 [PMID: 16794188 DOI: 10.1161/01.RES.0000233317.70421.03]
31 **Wang ZV**, Deng Y, Gao N, Pedrozo Z, Li DL, Morales CR, Criollo A, Luo X, Tan W, Jiang N, Lehrman MA, Rothermel BA, Lee AH, Lavandero S, Mammen PPA, Ferdous A, Gillette TG, Scherer PE, Hill JA. Spliced X-box binding protein 1 couples the unfolded protein response to hexosamine biosynthetic pathway. *Cell* 2014; **156**: 1179-1192 [PMID: 24630721 DOI: 10.1016/j.cell.2014.01.014]
32 **Vitadello M**, Penzo D, Petronilli V, Michieli G, Gomirato S, Menabò R, Di Lisa F, Gorza L. Overexpression of the stress protein Grp94 reduces cardiomyocyte necrosis due to calcium overload and simulated ischemia. *FASEB J* 2003; **17**: 923-925 [PMID: 12670879 DOI: 10.1096/fj.02-0644fje]
33 **Wang S**, Binder P, Fang Q, Wang Z, Xiao W, Liu W, Wang X. Endoplasmic reticulum stress in the heart: insights into mechanisms and drug targets. *Br J Pharmacol* 2018; **175**: 1293-1304 [PMID: 28548229 DOI: 10.1111/bph.13888]
34 **Martindale JJ**. Protecting the Myocardium from Ischemia and Reperfusion Injury Via Inducible Activation of ATF6 Or Constitutive Expression of MKK62006: ProQuest. Available from: URL: https://www.proquest.com/APAC-CN/
35 **Doroudgar S**, Thuerauf DJ, Marcinko MC, Belmont PJ, Glembotski CC. Ischemia activates the ATF6 branch of the endoplasmic reticulum stress response. *J Biol Chem* 2009; **284**: 29735-29745 [PMID: 19622751 DOI: 10.1074/jbc.M109.018036]
36 **Belmont PJ**, Chen WJ, San Pedro MN, Thuerauf DJ, Gellings Lowe N, Gude N, Hilton B, Wolkowicz R, Sussman MA, Glembotski CC. Roles for endoplasmic reticulum-associated degradation and the novel endoplasmic reticulum stress response gene Derlin-3 in the ischemic heart. *Circ Res* 2010; **106**: 307-316 [PMID: 19940266 DOI: 10.1161/CIRCRESAHA.109.203901]
37 **Toko H**, Takahashi H, Kayama Y, Okada S, Minamino T, Terasaki F, Kitaura Y, Komuro I. ATF6 is important under both pathological and physiological states in the heart. *J Mol Cell Cardiol* 2010; **49**: 113-120 [PMID: 20380836 DOI: 10.1016/j.yjmcc.2010.03.020]
38 **Lynch JM**, Maillet M, Vanhoutte D, Schloemer A, Sargent MA, Blair NS, Lynch KA, Okada T, Aronow BJ, Osinska H, Prywes R, Lorenz JN, Mori K, Lawler J, Robbins J, Molkentin JD. A thrombospondin-dependent pathway for a protective ER stress response. *Cell* 2012; **149**: 1257-1268 [PMID: 22682248 DOI: 10.1016/j.cell.2012.03.050]
39 **Doroudgar S**, Glembotski CC. ATF6 [corrected] and thrombospondin 4: the dynamic duo of the adaptive endoplasmic reticulum stress response. *Circ Res* 2013; **112**: 9-12 [PMID: 23287452 DOI: 10.1161/CIRCRESAHA.112.280560]
40 **Zhang K**. Integration of ER stress, oxidative stress and the inflammatory response in health and disease. *Int J Clin Exp Med* 2010; **3**: 33-40 [PMID: 20369038 DOI: doi:10.1007/978-1-4419-5635-4_11]
41 **Azfer A**, Niu J, Rogers LM, Adamski FM, Kolattukudy PE. Activation of endoplasmic reticulum stress response during the development of ischemic heart disease. *Am J Physiol Heart Circ Physiol* 2006; **291**: H1411-H1420 [PMID: 16617122 DOI: 10.1152/ajpheart.01378.2005]
42 **Zeng L**, Liu YP, Sha H, Chen H, Qi L, Smith JA. XBP-1 couples endoplasmic reticulum stress to augmented IFN-beta induction via a cis-acting enhancer in macrophages. *J Immunol* 2010; **185**: 2324-2330 [PMID: 20660350 DOI: 10.4049/jimmunol.0903052]
43 **Gargalovic PS**, Gharavi NM, Clark MJ, Pagnon J, Yang WP, He A, Truong A, Baruch-Oren T, Berliner JA, Kirchgessner TG, Lusis AJ. The unfolded protein response is an important regulator of inflammatory genes in endothelial cells. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2490-2496 [PMID: 16931790 DOI: 10.1161/01.ATV.0000242903.41158.a1]
44 **Hu P**, Han Z, Couvillon AD, Kaufman RJ, Exton JH. Autocrine tumor necrosis factor alpha links endoplasmic reticulum stress to the membrane death receptor pathway through IRE1alpha-mediated NF-kappaB activation and down-regulation of TRAF2 expression. *Mol Cell Biol* 2006; **26**: 3071-3084 [PMID: 16581782 DOI: 10.1128/MCB.26.8.3071-3084.2006]

45 **Kaneko M**, Niinuma Y, Nomura Y. Activation signal of nuclear factor-kappa B in response to endoplasmic reticulum stress is transduced via IRE1 and tumor necrosis factor receptor-associated factor 2. *Biol Pharm Bull* 2003; **26**: 931-935 [PMID: 12843613 DOI: 10.1248/bpb.26.931]

46 **Yamazaki H**, Hiramatsu N, Hayakawa K, Tagawa Y, Okamura M, Ogata R, Huang T, Nakajima S, Yao J, Paton AW, Paton JC, Kitamura M. Activation of the Akt-NF-kappaB pathway by subtilase cytotoxin through the ATF6 branch of the unfolded protein response. *J Immunol* 2009; **183**: 1480-1487 [PMID: 19561103 DOI: 10.4049/jimmunol.0900017]

47 **Nishitoh H**, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, Inoue K, Hori S, Kakizuka A, Ichijo H. ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. *Genes Dev* 2002; **16**: 1345-1355 [PMID: 12050113 DOI: 10.1101/gad.992302]

48 **Urano F**, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP, Ron D. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science* 2000; **287**: 664-666 [PMID: 10650002 DOI: 10.1126/science.287.5453.664]

49 **He X**, Liu Y, Sharma V, Dirksen RT, Waugh R, Sheu SS, Min W. ASK1 associates with troponin T and induces troponin T phosphorylation and contractile dysfunction in cardiomyocytes. *Am J Pathol* 2003; **163**: 243-251 [PMID: 12819028 DOI: 10.1016/S0002-9440(10)63647-4]

50 **Yamaguchi O**, Higuchi Y, Hirotani S, Kashiwase K, Nakayama H, Hikoso S, Takeda T, Watanabe T, Asahi M, Taniike M, Matsumura Y, Tsujimoto I, Hongo K, Kusakari Y, Kurihara S, Nishida K, Ichijo H, Hori M, Otsu K. Targeted deletion of apoptosis signal-regulating kinase 1 attenuates left ventricular remodeling. *Proc Natl Acad Sci U S A* 2003; **100**: 15883-15888 [PMID: 14665690 DOI: 10.1073/pnas.2136717100]

51 **Gerczuk PZ**, Breckenridge DG, Liles JT, Budas GR, Shryock JC, Belardinelli L, Kloner RA, Dai W. An apoptosis signal-regulating kinase 1 inhibitor reduces cardiomyocyte apoptosis and infarct size in a rat ischemia-reperfusion model. *J Cardiovasc Pharmacol* 2012; **60**: 276-282 [PMID: 22635076 DOI: 10.1097/FJC.0b013e31825ea0fa]

52 **Nakagawa T**, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature* 2000; **403**: 98-103 [PMID: 10638761 DOI: 10.1038/47513]

53 **Saleh M**, Mathison JC, Wolinski MK, Bensinger SJ, Fitzgerald P, Droin N, Ulevitch RJ, Green DR, Nicholson DW. Enhanced bacterial clearance and sepsis resistance in caspase-12-deficient mice. *Nature* 2006; **440**: 1064-1068 [PMID: 16625199 DOI: 10.1038/nature04656]

54 **Logue SE**, Cleary P, Saveljeva S, Samali A. New directions in ER stress-induced cell death. *Apoptosis* 2013; **18**: 537-546 [PMID: 23430059 DOI: 10.1007/s10495-013-0818-6]

55 **Toth A**, Jeffers JR, Nickson P, Min JY, Morgan JP, Zambetti GP, Erhardt P. Targeted deletion of Puma attenuates cardiomyocyte death and improves cardiac function during ischemia-reperfusion. *Am J Physiol Heart Circ Physiol* 2006; **291**: H52-H60 [PMID: 16399862 DOI: 10.1152/ajpheart.01046.2005]

56 **Nickson P**, Toth A, Erhardt P. PUMA is critical for neonatal cardiomyocyte apoptosis induced by endoplasmic reticulum stress. *Cardiovasc Res* 2007; **73**: 48-56 [PMID: 17107669 DOI: 10.1016/j.cardiores.2006.10.001]

57 **Mandl A**, Huong Pham L, Toth K, Zambetti G, Erhardt P. Puma deletion delays cardiac dysfunction in murine heart failure models through attenuation of apoptosis. *Circulation* 2011; **124**: 31-39 [PMID: 21670227 DOI: 10.1161/CIRCULATIONAHA.110.988303]

58 **Mandl A**. Puma Deletion Delays Cardiac Dysfunction in Mouse Heart Failure Models Through Attenuation of Apoptosis. 2014; Available from: URL: http://aok.pte.hu/hu/egyseg/almenu/1670/docs/phd/file/dolgozatok/2014/Mandl_Adel_PhD_dolgozat.pdf

59 **Fouillet A**, Levet C, Virgone A, Robin M, Dourlen P, Rieusset J, Belaidi E, Ovize M, Touret M, Nataf S, Mollereau B. ER stress inhibits neuronal death by promoting autophagy. *Autophagy* 2012; **8**: 915-926 [PMID: 22660271 DOI: 10.4161/auto.19716]

60 **Wang S**, Chen X, Nair S, Sun D, Wang X, Ren J. Deletion of protein tyrosine phosphatase 1B obliterates endoplasmic reticulum stress-induced myocardial dysfunction through regulation of autophagy. *Biochim Biophys Acta Mol Basis Dis* 2017; **1863**: 3060-3074 [PMID: 28941626 DOI: 10.1016/j.bbadis.2017.09.015]

61 **Razani B**, Feng C, Coleman T, Emanuel R, Wen H, Hwang S, Ting JP, Virgin HW, Kastan MB, Semenkovich CF. Autophagy links inflammasomes to atherosclerotic progression. *Cell Metab* 2012; **15**: 534-544 [PMID: 22440612 DOI: 10.1016/j.cmet.2012.02.011]

62 **Zhang Y**, Wang C, Zhou J, Sun A, Hueckstaedt LK, Ge J, Ren J. Complex inhibition of autophagy by mitochondrial aldehyde dehydrogenase shortens lifespan and exacerbates cardiac aging. *Biochim Biophys Acta Mol Basis Dis* 2017; **1863**: 1919-1932 [PMID: 28347844 DOI: 10.1016/j.bbadis.2017.03.016]

63 **Zhang C**, Syed TW, Liu R, Yu J. Role of Endoplasmic Reticulum Stress, Autophagy, and Inflammation in Cardiovascular Disease. *Front Cardiovasc Med* 2017; **4**: 29 [PMID: 28553639 DOI: 10.3389/fcvm.2017.00029]

64 **Hou X**, Hu Z, Xu H, Xu J, Zhang S, Zhong Y, He X, Wang N. Advanced glycation endproducts trigger autophagy in cadiomyocyte via RAGE/PI3K/AKT/mTOR pathway. *Cardiovasc Diabetol* 2014; **13**: 78 [PMID: 24725502 DOI: 10.1186/1475-2840-13-78]

65 **Piperi C**, Adamopoulos C, Dalagiorgou G, Diamanti-Kandarakis E, Papavassiliou AG. Crosstalk between advanced glycation and endoplasmic reticulum stress: emerging therapeutic targeting for metabolic diseases. *J Clin Endocrinol Metab* 2012; **97**: 2231-2242 [PMID: 22508704 DOI: 10.1210/jc.2011-3408]

66 **Ceylan-Isik AF**, Sreejayan N, Ren J. Endoplasmic reticulum chaperon tauroursodeoxycholic acid alleviates obesity-induced myocardial contractile dysfunction. *J Mol Cell Cardiol* 2011; **50**: 107-116 [PMID: 21035453 DOI: 10.1016/j.yjmcc.2010.10.023]

67 **Zhang X**, Gibson ME, Li ZL, Zhu XY, Jordan KL, Lerman A, Lerman LO. Autophagy Portends the Level of Cardiac Hypertrophy in Experimental Hypertensive Swine Model. *Am J Hypertens* 2016; **29**: 81-89 [PMID: 25904651 DOI: 10.1093/ajh/hpv057]

68 **Tanno M**, Kuno A, Horio Y, Miura T. Emerging beneficial roles of sirtuins in heart failure. *Basic Res Cardiol* 2012; **107**: 273 [PMID: 22622703 DOI: 10.1007/s00395-012-0273-5]

69 **Guilbert A**, Prola A, Ventura-Clapier V, Lemaire C. P79 Sirt1 modulates endoplasmic reticulum stress-induced autophagy in heart. *Cardiovasc Res* 2014; **103**: S13 [DOI: 10.1093/cvr/cvu082.22]

70 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

71 **Lee RC**, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993; **75**: 843-854 [PMID: 8252621 DOI:

10.1016/0092-8674(93)90529-Y]
72 **Byrd AE**, Aragon IV, Brewer JW. MicroRNA-30c-2* limits expression of proadaptive factor XBP1 in the unfolded protein response. *J Cell Biol* 2012; **196**: 689-698 [PMID: 22431749 DOI: 10.1083/jcb.201201077]
73 **Belmont PJ**, Chen WJ, Thuerauf DJ, Glembotski CC. Regulation of microRNA expression in the heart by the ATF6 branch of the ER stress response. *J Mol Cell Cardiol* 2012; **52**: 1176-1182 [PMID: 22326432 DOI: 10.1016/j.yjmcc.2012.01.017]
74 **Zhang WG**, Chen L, Dong Q, He J, Zhao HD, Li FL, Li H. Mmu-miR-702 functions as an anti-apoptotic mirtron by mediating ATF6 inhibition in mice. *Gene* 2013; **531**: 235-242 [PMID: 24035931 DOI: 10.1016/j.gene.2013.09.005]
75 **Tang Q**, Len Q, Liu Z, Wang W. Overexpression of miR-22 attenuates oxidative stress injury in diabetic cardiomyopathy via Sirt 1. *Cardiovasc Ther* 2018; 36 [PMID: 29288528 DOI: 10.1111/1755-5922.12318]
76 **Chen M**, Ma G, Yue Y, Wei Y, Li Q, Tong Z, Zhang L, Miao G, Zhang J. Downregulation of the miR-30 family microRNAs contributes to endoplasmic reticulum stress in cardiac muscle and vascular smooth muscle cells. *Int J Cardiol* 2014; **173**: 65-73 [PMID: 24612558 DOI: 10.1016/j.ijcard.2014.02.007]
77 **van Mil A**, Grundmann S, Goumans MJ, Lei Z, Oerlemans MI, Jaksani S, Doevendans PA, Sluijter JP. MicroRNA-214 inhibits angiogenesis by targeting Quaking and reducing angiogenic growth factor release. *Cardiovasc Res* 2012; **93**: 655-665 [PMID: 22227154 DOI: 10.1093/cvr/cvs003]
78 **van Rooij E**, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, Richardson JA, Olson EN. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proc Natl Acad Sci U S A* 2006; **103**: 18255-18260 [PMID: 17108080 DOI: 10.1073/pnas.0608791103]
79 **Wang JM**, Qiu Y, Yang ZQ, Li L, Zhang K. Inositol-Requiring Enzyme 1 Facilitates Diabetic Wound Healing Through Modulating MicroRNAs. *Diabetes* 2017; **66**: 177-192 [PMID: 27634225 DOI: 10.2337/db16-0052]
80 **Belmadani S**, Matrougui K. The Unraveling Truth About IRE1 and MicroRNAs in Diabetes. *Diabetes* 2017; **66**: 23-24 [PMID: 27999104 DOI: 10.2337/dbi16-0058]
81 **Afonyushkin T**, Oskolkova OV, Bochkov VN. Permissive role of miR-663 in induction of VEGF and activation of the ATF4 branch of unfolded protein response in endothelial cells by oxidized phospholipids. *Atherosclerosis* 2012; **225**: 50-55 [PMID: 22776647 DOI: 10.1016/j.atherosclerosis.2012.06.016]
82 **Behrman S**, Acosta-Alvear D, Walter P. A CHOP-regulated microRNA controls rhodopsin expression. *J Cell Biol* 2011; **192**: 919-927 [PMID: 21402790 DOI: 10.1083/jcb.201010055]
83 **Ozcan L**, Ergin AS, Lu A, Chung J, Sarkar S, Nie D, Myers MG, Ozcan U. Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab* 2009; **9**: 35-51 [PMID: 19117545 DOI: 10.1016/j.cmet.2008.12.004]
84 **Ozcan U**, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Görgün CZ, Hotamisligil GS. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* 2006; **313**: 1137-1140 [PMID: 16931765 DOI: 10.1126/science.1128294]
85 **Engin F**, Hotamisligil GS. Restoring endoplasmic reticulum function by chemical chaperones: an emerging therapeutic approach for metabolic diseases. *Diabetes Obes Metab* 2010; **12** Suppl 2: 108-115 [PMID: 21029307 DOI: 10.1111/j.1463-1326.2010.01282.x]
86 **Rivard AL**, Steer CJ, Kren BT, Rodrigues CM, Castro RE, Bianco RW, Low WC. Administration of tauroursodeoxycholic acid (TUDCA) reduces apoptosis following myocardial infarction in rat. *Am J Chin Med* 2007; **35**: 279-295 [PMID: 17436368 DOI: 10.1142/S0192415X07004813]
87 **Rani S**, Sreenivasaiah PK, Kim JO, Lee MY, Kang WS, Kim YS, Ahn Y, Park WJ, Cho C, Kim DH. Tauroursodeoxycholic acid (TUDCA) attenuates pressure overload-induced cardiac remodeling by reducing endoplasmic reticulum stress. *PLoS One* 2017; **12**: e0176071 [PMID: 28426781 DOI: 10.1371/journal.pone.0176071]
88 **Groenendyk J**, Lee D, Jung J, Dyck JR, Lopaschuk GD, Agellon LB, Michalak M. Inhibition of the Unfolded Protein Response Mechanism Prevents Cardiac Fibrosis. *PLoS One* 2016; **11**: e0159682 [PMID: 27441395 DOI: 10.1371/journal.pone.0159682]
89 **Park CS**, Cha H, Kwon EJ, Sreenivasaiah PK, Kim DH. The chemical chaperone 4-phenylbutyric acid attenuates pressure-overload cardiac hypertrophy by alleviating endoplasmic reticulum stress. *Biochem Biophys Res Commun* 2012; **421**: 578-584 [PMID: 22525677 DOI: 10.1016/j.bbrc.2012.04.048]
90 **Jian L**, Lu Y, Lu S, Lu C. Chemical Chaperone 4-Phenylbutyric Acid Reduces Cardiac Ischemia/Reperfusion Injury by Alleviating Endoplasmic Reticulum Stress and Oxidative Stress. *Med Sci Monit* 2016; **22**: 5218-5227 [PMID: 28036323 DOI: 10.12659/MSM.898623]
91 **Wiersma M**, Meijering RAM, Qi XY, Zhang D, Liu T, Hoogstra-Berends F, Sibon OCM, Henning RH, Nattel S, Brundel BJJM. Endoplasmic Reticulum Stress Is Associated With Autophagy and Cardiomyocyte Remodeling in Experimental and Human Atrial Fibrillation. *J Am Heart Assoc* 2017; **6**: pii: e006458 [PMID: 29066441 DOI: 10.1161/JAHA.117.006458]
92 **Fu HY**, Sanada S, Matsuzaki T, Liao Y, Okuda K, Yamato M, Tsuchida S, Araki R, Asano Y, Asanuma H, Asakura M, French BA, Sakata Y, Kitakaze M, Minamino T. Chemical Endoplasmic Reticulum Chaperone Alleviates Doxorubicin-Induced Cardiac Dysfunction. *Circ Res* 2016; **118**: 798-809 [PMID: 26838784 DOI: 10.1161/CIRCRESAHA.115.307604]
93 **Boklage SH**, Malangone-Monaco E, Lopez-Gonzalez L, Ding Y, Henriques C, Elassal J. Statin Utilization Patterns and Outcomes for Patients with Acute Coronary Syndrome During and Following Inpatient Admissions. *Cardiovasc Drugs Ther* 2018; **32**: 273-280 [PMID: 29855748 DOI: 10.1007/s10557-018-6800-3]
94 **Zhao H**, Liao Y, Minamino T, Asano Y, Asakura M, Kim J, Asanuma H, Takashima S, Hori M, Kitakaze M. Inhibition of cardiac remodeling by pravastatin is associated with amelioration of endoplasmic reticulum stress. *Hypertens Res* 2008; **31**: 1977-1987 [PMID: 19015605 DOI: 10.1291/hypres.31.1977]
95 **Xu Z**, Okamoto H, Akino M, Onozuka H, Matsui Y, Tsutsui H. Pravastatin attenuates left ventricular remodeling and diastolic dysfunction in angiotensin II-induced hypertensive mice. *J Cardiovasc Pharmacol* 2008; **51**: 62-70 [PMID: 18209570 DOI: 10.1097/FJC.0b013e31815bb629]
96 **Han ZH**, Wu XS, Zhang XX, Hu R, Zhao H, Wang CM, Ren XJ, Jiang TY, Zhang WD, Chen F. [The primary observation on the effect of pravastatin to non-ischemic heart failure]. *Zhonghua Xinxueguanbing Zazhi* 2007; **35**: 603-606 [PMID: 17961422]
97 **Nakaya R**, Uzui H, Shimizu H, Nakano A, Mitsuke Y, Yamazaki T, Ueda T, Lee JD. Pravastatin suppresses the increase in matrix metalloproteinase-2 levels after acute myocardial infarction. *Int J Cardiol* 2005; **105**: 67-73 [PMID: 16207547 DOI: 10.1016/j.ijcard.2004.12.024]
98 **Liao Y**, Takashima S, Zhao H, Asano Y, Shintani Y, Minamino T, Kim J, Fujita M, Hori M, Kitakaze M.

Control of plasma glucose with alpha-glucosidase inhibitor attenuates oxidative stress and slows the progression of heart failure in mice. *Cardiovasc Res* 2006; **70**: 107-116 [PMID: 16510136 DOI: 10.1016/j.cardiores.2006.01.021]

99 **Song XJ**, Yang CY, Liu B, Wei Q, Korkor MT, Liu JY, Yang P. Atorvastatin inhibits myocardial cell apoptosis in a rat model with post-myocardial infarction heart failure by downregulating ER stress response. *Int J Med Sci* 2011; **8**: 564-572 [PMID: 21960749 DOI: 10.7150/ijms.8.564]

100 **Sola S**, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. *J Am Coll Cardiol* 2006; **47**: 332-337 [PMID: 16412856 DOI: 10.1016/j.jacc.2005.06.088]

101 **Xu J**, Chen L, Jiang Z, Li L. Biological functions of Elabela, a novel endogenous ligand of APJ receptor. *J Cell Physiol* 2018; **233**: 6472-6482 [PMID: 29350399 DOI: 10.1002/jcp.26492]

102 **Luo X**, Liu J, Zhou H, Chen L. Apelin/APJ system: A critical regulator of vascular smooth muscle cell. *J Cell Physiol* 2018; **233**: 5180-5188 [PMID: 29215755 DOI: 10.1002/jcp.26339]

103 **Huang Z**, Wu L, Chen L. Apelin/APJ system: A novel potential therapy target for kidney disease. *J Cell Physiol* 2018; **233**: 3892-3900 [PMID: 28796300 DOI: 10.1002/jcp.26144]

104 **Gao LR**, Xu RY, Zhang NK, Chen Y, Wang ZG, Zhu ZM, Fei YX, Cao Y, Xu HT, Yang Y. Increased apelin following bone marrow mononuclear cell transplantation contributes to the improvement of cardiac function in patients with severe heart failure. *Cell Transplant* 2009; **18**: 1311-1318 [PMID: 19785937 DOI: 10.3727/096368909X474843]

105 **Japp AG**, Cruden NL, Barnes G, van Gemeren N, Mathews J, Adamson J, Johnston NR, Denvir MA, Megson IL, Flapan AD, Newby DE. Acute cardiovascular effects of apelin in humans: potential role in patients with chronic heart failure. *Circulation* 2010; **121**: 1818-1827 [PMID: 20385929 DOI: 10.1161/CIRCULATIONAHA.109.911339]

106 **Zhang Z**, Yu B, Tao GZ. Apelin protects against cardiomyocyte apoptosis induced by glucose deprivation. *Chin Med J (Engl)* 2009; **122**: 2360-2365 [PMID: 20079140 DOI: 10.3760/cma.j.issn.0366-6999.2009.19.031]

107 **Ceylan-Isik AF**, Kandadi MR, Xu X, Hua Y, Chicco AJ, Ren J, Nair S. Apelin administration ameliorates high fat diet-induced cardiac hypertrophy and contractile dysfunction. *J Mol Cell Cardiol* 2013; **63**: 4-13 [PMID: 23859766 DOI: 10.1016/j.yjmcc.2013.07.002]

108 **Xie F**, Wu D, Huang SF, Cao JG, Li HN, He L, Liu MQ, Li LF, Chen LX. The endoplasmic reticulum stress-autophagy pathway is involved in apelin-13-induced cardiomyocyte hypertrophy in vitro. *Acta Pharmacol Sin* 2017; **38**: 1589-1600 [PMID: 28748915 DOI: 10.1038/aps.2017.97]

109 **Hall DT**, Griss T, Ma JF, Sanchez BJ, Sadek J, Tremblay AMK, Mubaid S, Omer A, Ford RJ, Bedard N, Pause A, Wing SS, Di Marco S, Steinberg GR, Jones RG, Gallouzi IE. The AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), but not metformin, prevents inflammation-associated cachectic muscle wasting. *EMBO Mol Med* 2018; **10**: pii: e8307 [PMID: 29844217 DOI: 10.15252/emmm.201708307]

110 **Valero T**. Mitochondrial biogenesis: pharmacological approaches. *Curr Pharm Des* 2014; **20**: 5507-5509 [PMID: 24606795 DOI: 10.2174/1381612820351409111421118]

111 **Viollet B**, Guigas B, Leclerc J, Hébrard S, Lantier L, Mounier R, Andreelli F, Foretz M. AMP-activated protein kinase in the regulation of hepatic energy metabolism: from physiology to therapeutic perspectives. *Acta Physiol (Oxf)* 2009; **196**: 81-98 [PMID: 19245656 DOI: 10.1111/j.1748-1716.2009.01970.x]

112 **Malick R**, Belmadani S. Endoplasmic Reticulum Stress and Heart Complication in Diabetes. *J Diabetes Metab* 2015; **6**: 12 [DOI: 10.4172/2155-6156.1000630]

113 **Xie W**, Zhou P, Sun Y, Meng X, Dai Z, Sun G, Sun X. Protective Effects and Target Network Analysis of Ginsenoside Rg1 in Cerebral Ischemia and Reperfusion Injury: A Comprehensive Overview of Experimental Studies. *Cells* 2018; **7** [PMID: 30545139 DOI: 10.3390/cells7120270]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 July 26; 11(7): 171-194

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 7 July 26, 2019

REVIEW

CASE REPORT

Contents

World Journal of Cardiology

Volume 11 Number 7 July 26, 2019

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Alberto Cuocolo, MD, Full Professor, Department of Advanced Biomedical Sciences, University of Naples Federico II, Napoli 80131, Italy

AIMS AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, *etc*. We encourage authors to submit their manuscripts to *WJC*.

We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
July 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 July 26; 11(7): 171-188

DOI: 10.4330/wjc.v11.i7.171

ISSN 1949-8462 (online)

REVIEW

High-intensity interval training for health benefits and care of cardiac diseases - The key to an efficient exercise protocol

Shigenori Ito

ORCID number: Shigenori Ito (0000-0002-3319-1697).

Author contributions: Ito S performed all of the followings by himself: experimental design, research, data analysis, and writing and revision the paper.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: February 10, 2019
Peer-review started: February 12, 2019
First decision: March 15, 2019
Revised: April 18, 2019
Accepted: July 16, 2019
Article in press: July 17, 2019
Published online: July 26, 2019

P-Reviewer: Kaypaklı O, Tousoulis D
S-Editor: Dou Y
L-Editor: A

Shigenori Ito, Division of Cardiology, Sankuro Hospital, Aichi-ken, Toyota 4710035, Japan

Corresponding author: Shigenori Ito, MD, PhD, Doctor, Division of Cardiology, Sankuro Hospital, 7-80 Kosaka-cho, Aichi-ken, Toyota 4710035, Japan. shigeito918@gmail.com
Telephone: +81-565-320282
Fax: +81-565-352570

Abstract

Aerobic capacity, which is expressed as peak oxygen consumption (VO_{2peak}), is well-known to be an independent predictor of all-cause mortality and cardiovascular prognosis. This is true even for people with various coronary risk factors and cardiovascular diseases. Although exercise training is the best method to improve VO_{2peak}, the guidelines of most academic societies recommend 150 or 75 min of moderate- or vigorous- intensity physical activities, respectively, every week to gain health benefits. For general health and primary and secondary cardiovascular prevention, high-intensity interval training (HIIT) has been recognized as an efficient exercise protocol with short exercise sessions. Given the availability of the numerous HIIT protocols, which can be classified into aerobic HIIT and anaerobic HIIT [usually called sprint interval training (SIT)], professionals in health-related fields, including primary physicians and cardiologists, may find it confusing when trying to select an appropriate protocol for their patients. This review describes the classifications of aerobic HIIT and SIT, and their differences in terms of effects, target subjects, adaptability, working mechanisms, and safety. Understanding the HIIT protocols and adopting the correct type for each subject would lead to better improvements in VO_{2peak} with higher adherence and less risk.

Key words: High-intensity interval training; Exercise; Training; Coronary artery disease; Chronic heart failure; Prevention; Lifestyle; Health; Peak O_2 consumption; Aerobic capacity

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There are numerous of high-intensity interval training (HIIT) protocols, which can be classified into aerobic HIIT and anaerobic HIIT [usually called sprint interval training (SIT)]. Professionals in health-related fields, including primary physicians and cardiologists, may find it confusing when selecting an appropriate protocol for their patients. This review describes the classifications of aerobic HIIT and SIT, and their differences in terms of effects, target subjects, adaptability, working mechanisms, and

E-Editor: Xing YX

safety. Understanding the HIIT protocols and adopting the correct type for each patient would lead to better improvements in VO_{2peak} with higher adherence and less risk.

Citation: Ito S. High-intensity interval training for health benefits and care of cardiac diseases - The key to an efficient exercise protocol. *World J Cardiol* 2019; 11(7): 171-188
URL: https://www.wjgnet.com/1949-8462/full/v11/i7/171.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i7.171

INTRODUCTION

Accumulated evidence suggests that aerobic capacity (VO_{2peak}) is the strongest predictor of future health, all-cause mortality[1-3], and cardiovascular risks[4,5]. Moreover, several studies have suggested that people with established coronary vascular disease (CVD) risk factors (such as high body mass index, hypertension, or diabetes) and high cardiorespiratory fitness have a highly attenuated risk of CVD and premature mortality[4,5]. Thus, it has become a major goal in the medical field to improve VO_{2peak} in patients with lifestyle-related diseases with (as a secondary prevention strategy) or without (as a primary prevention strategy) cardiac disorders. For improvement in public health, performing regular physical exercise is indispensable together with a nutritional approach. Healthy young and middle-aged people can select from the many choices of exercise training methods, including recreational sports, in daily life. In contrast, people with lifestyle-related disease and/or elderly people are often sedentary and physically unfit. Thus, some useful techniques and limitations exist when encouraging exercise training with adequate safety and high adherence in these people. High-intensity interval training (HIIT) has been recognized as an alternative and more efficient protocol than moderate-intensity continuous training (MCT), which is the gold standard recommended in several guidelines[6-8]. HIIT and sprint interval training (SIT) for 6-8 wk increase VO_{2peak} more than or at least comparable to MCT. In this comprehensive review, many protocols of HIIT and SIT for improving aerobic and metabolic capacity were evaluated for their effects in patients with sedentary lifestyle-related diseases with or without cardiac disease to determine appropriate protocol recommendations for different patient populations. General practitioners and cardiologists should pay more attention to exercise and physical activity rather than to the prescription of drugs.

EXERCISE IS MEDICINE (EIM) ENCOURAGES PEOPLE TO FORM EXERCISE HABITS

To improve primary and secondary prevention methods in cardiovascular medicine, physical activity should be promoted as a first-line strategy despite new drug developments in the medical treatment field.

Although the value of exercise for improving health is well recognized worldwide[9], widespread adoption of exercise habits has not been adequately achieved, especially in highly developed countries where the use of automobiles is highly prevalent. In a recent study from the World Health Organization[10], about 27.5% of the population in 2016 was recognized as sedentary (*i.e.*, with insufficient physical activity). In this context, EIM is a global health initiative promoted worldwide by the American College of Sports Medicine[11]. EIM encourages primary care physicians and other health-care providers to include physical activity when designing treatment plans, and to offer evidenced-based exercise programs to their patients or refer their patients to qualified exercise professionals. EIM is committed to the belief that physical activity promotes optimal health, is integral in the prevention and treatment of many medical conditions, and should be regularly assessed and included as part of health care. Irrespective of disease severity, exercise can bring improvements in aerobic and metabolic capacity as well as cardiac function if performed with an optimal dose, frequency, and intensity. Despite the continuous recommendations by the American College of Sports Medicine and related pro-fessional societies worldwide, the effects of such recommendations on public awareness have been very limited. Many kinds of wearable heart rate monitors and accelerometers are commercially available. Although these state-of-the art products could motivate sedentary people and increase their frequency of exercise training or participation in

sports events, more efficient and effective exercise training strategies are still required.

For the success of EIM, professionals who can encourage target people to exercise in a planned way according to detailed exercise protocols, functioning as an intermediary between physicians and patients, would be very important.

GUIDELINE RECOMMENDATION: MCT AS A CLASSIC AND SIMPLE PROTOCOL

The current guidelines on physical activity for health recommend that adults should engage in at least 150 min of moderate-intensity activity or 75 min of vigorous-intensity activity per week, or any combination of activities that amount to the same total energy expenditure[6,12]. Similarly, in the field of cardiac rehabilitation, MCT has been the gold standard for many years for patients with cardiac diseases[13]. The current guidelines on cardiac rehabilitation/exercise training recommend endurance exercises with a moderate intensity at 50%-85% (mostly 70%-85%) of the peak heart rate or anaerobic threshold level for patients with CVD or chronic heart failure (CHF)[7,8,14]. The latest guidelines suggest HIIT as an alternative protocol to improve aerobic capacity and cardiac function. However, the adoption of HIIT in the cardiac rehabilitation setting is still controversial among researchers. In Japan, only a few studies describing the effects of HIIT have been published[15-17]. On the other hand, MCT has been used as a control strategy in randomized controlled trials (RCTs) that evaluated HIIT or SIT. Thus, evidence for the same amount of MCT has been accumulated. In representative MCTs such as walking or jogging, each workout is time consuming and usually monotonous and boring. Therefore, although MCT has become a classic protocol based on evidence from RCTs, it remains difficult for most people, with lack of time being cited as a common hindrance[18].

HIGH INTENSITY IS THE KEY ELEMENT OF EFFICIENT EXERCISE PROTOCOLS: HIIT AND SIT

HIIT

The inclusion of "adapted" high intensity (relative to a subject's current physical ability) in the exercise protocol is a key component for exercise to be more efficient as a "medicine." The clinical and physiological benefits of HIIT compared with those of MCT are shown in Table 1. In multiple RCTs, a wide range of targets, including skeletal muscles[19-22], risk factors[21], vasculature[19-22], respiration[22,23], autonomic function[24], cardiac function[20,22,25-27], exercise capacity[26], inflammation[27], quality of life[27], physiological markers such as VO_{2peak}, and endothelial function, showed better improvements with HIIT than with MCT.

High-intensity exercise consists of aerobic HIIT and anaerobic SIT.

Figure 1 illustrates the representative protocols of aerobic HIIT and 2 anaerobic SITs, as well as a comparison of their intensities, duration, and frequencies. These exercise protocols require a shorter exercise duration to obtain the same benefit as that provided by moderate-intensity exercises. Although maintaining a high intensity exercise workout for a longer duration could be preferred, high-intensity exercise can be realistically tolerated by people with sedentary lifestyle, obesity, old age, or cardiac disease only in the form of interval training. In this regard, HIIT consists of brief, intermittent bursts of vigorous activity (less than VO_{2peak} but usually involves < 100% [70%-90%] of VO_{2peak} or 85%-95% of the peak heart rate) interspersed with active rest periods[22,28,29], whereas SIT is classically a Wingate-type protocol (all-out, vigorous-intensity exercise involving approximately 350% of VO_{2peak}[30]) interspersed with longer complete rest periods. These high-intensity protocols are demanding for the subjects even though the intensity is adapted to the individual's aerobic capacity and the rest period. Although the most popular and evidence-rich protocols are the Wingate test[31] for SIT, and the 4 × 4 min[28,32] or 10 × 1 min protocol for HIIT, many other protocols can be applied by modifying the workout duration, rest interval (work/rest ratio[33]), workout intensity, and workout frequency. The difference between HIIT and SIT is that SIT refers to anaerobic supramaximal VO_{2max} (all-out) intensity and HIIT refers to aerobic submaximal VO_{2max} intensity. The peak power output (PPO) of SIT is about 350% of the power output at VO_{2max}[30]. Meanwhile, the common elements between the two protocols are the high work intensity adapted to the current aerobic capacity of the individual, and the aim of improving both aerobic capacity (VO_{2peak}) and metabolic capacity. However, the risk of these protocols has also been a concern, and more studies are warranted before these protocols are

Table 1 Variables improved by high-intensity interval training

Variables	Target
Skeletal muscle biopsy	
PGC-1α	
Mitochondrial function in lateral vastus	O_2 consumption
Fatty acid transporter in the vastus lateralis and FAS (a key lipogenic enzyme)	
IR β subunit in skeletal muscle (peripheral insulin sensitivity)	Metabolic
Re-uptake of Ca2+ into the salcoplasmic reticulum	
Physiological test	
Exercise test	
Improvement of ventilatory efficiency (increased value of PETCO2)	Respiratory function
Oxygen consumption at the first ventilator threshold	Cardiac function
Oxygen pulse	Cardiac function
Parasympathetic activity (HR recovery)	Autonomic function
Duration of exercise time	Autonomic function
Distance walked during the 6-min walk	Work capacity
Ultrasonography	
Cardiac function	
Reversed LV re-modelling (LV end diastolic and systolic volumes)	Cardiac function
Ea	
Diastolic function (e′, E, E/ e′, E/A ratio, higher proportion of e′ > 8 cm/s, E improvement during exercise),	
Systolic function after 12 wk at rest and during exercise)	
E reduction	
Deceleration time increase	
Left atrial volume	
Reduced-plasma BNP	
Vascular	
Endothelial dysfunction (FMD)	Vascular function
Coronary plaque necrotic core reduction in defined coronary segments	Vascular function
Laboratory test	
Myeloperoxidase	Anti-oxidant
High sensitivity CRP	Inflammation
Interleukin-6	
insulin sensitivity (HOMA index)	Metabolic
HbA_1C	
Clinico-social data	
Increased Short Form-36 physical/mental component scores and decreased Minnesota Living with Heart Failure questionnaire score	Quality of life
Frequency of metabolic syndrome	Risk factor

HOMA: Homoestasis model assessment; IR: Insulin receptor; PGC: Peroxisome-proliferator activated receptor γcoactivator; FMD: Flow mediated dilation; FAS: Fatty acid synthase; $PETCO_2$: End-tidal carbon dioxide; HR: Heart rate; LV: Left ventricular; BNP: Brain natriuretic peptide.

adopted to more common use. A supervised workout is mandatory to maintain high-intensity adherence until the participants become accustomed to the intensity and to heart rate measurements during physical activity by using a wearable heart rate monitoring device. Home-based HIIT is also possible if experienced management programs are provided by renowned centers[34].

Definitions of HIIT and SIT

Unfortunately, the definition of "HIIT" varies across different studies. This review uses the recently suggested definition, which describes HIIT as high-intensity exercise with aerobic intervals, with the target intensity existing in submaximal VO_{2max} between 85% and 95% of the peak heart rate[35]. This definition is distinct from that of SIT, which involves low-volume supramaximal (*i.e.*, all-out) performance[36]. Often, the term "aerobic HIIT" is used for HIIT with sub-VO_{2max} intensity. In this regard, in this review, SIT was evaluated separately from HIIT because its intensity is about 3.5-fold

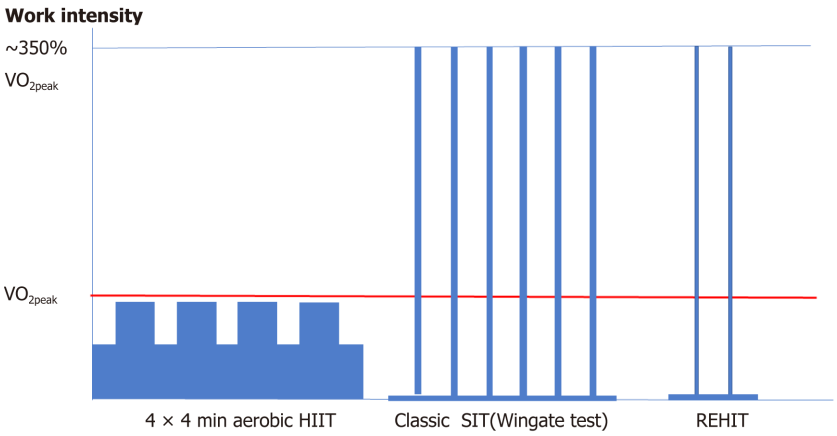


Figure 1 Schema of high-intensity interval training (HIIT) protocols. Adapted from Ito S. EC Cardiology 6.3 (2019): 196-200. HIIT is classified into two types: submaximal aerobic HIIT and all-out anaerobic HIIT [sprint interval training (SIT)]. Reduced-exertion HIIT (REHIT) is a low-dose and shorter SIT that is modified from SIT but is still an all-out anaerobic exercise. 4 × 4 min HIIT: four 4-min intervals at 90%-95% of maximal heart rate separated by 3-min active recovery periods of moderate intensity at 60%-70% of the maximal heart rate. Classic SIT: repeated (6-8) all-out bouts at vigorous intensity ~350% of VO_{2peak} of short duration (30 s) followed by a long complete rest (2-5 min). REHIT: 10-min cycling session at 25 W interspersed with 1 (first session) or 2 (all remaining sessions) Wingate-type cycle-sprints against a constant torque of 0.65 Nmkg lean mass^{-1}. Sprints last 10 s in sessions 1-4, 15 s in sessions 5-12, and 20 s in the remaining 12 sessions.

(350% VO_{2max}) the intensity of HIIT; thus, SIT is a very demanding exercise protocol and has been deemed adaptable only to young healthy people in previous studies[36,37]. Elderly people, those with lifestyle-related diseases other than diabetes mellitus, and patients with CVDs have been excluded from the target subjects of SIT.

Representative HIIT protocols

The exercise duration of HIIT has been defined as 30 s to several minutes. This type of HIIT has been adapted for people with lifestyle-related diseases with or without cardiac diseases. There have been RCTs comparing HIIT and MCT for patients with coronary artery diseases (Table 2, showing positive[28,38-41] and negative[19,23,42,43] results) and CHF (Table 3, showing positive[22,25,26,44] and negative[24,45-47] results), with the aim of improving aerobic capacity[48]. The protocols of HIIT and the number of studies showing the superiority of HIIT over MCT in each protocol are shown in Table 4. In both groups, the 4 × 4 min protocol was the most frequently used, showing positive rate of 70.2% in the coronary artery disease group and 75% in the CHF group. The other protocols with exercise durations of 30 s, 2 min, and 3 min were also effective in a limited number of studies.

The 4 × 4 min protocol is popularly used in patients with lifestyle-related plus cardiac disease, and was initially adapted for cardiac disease by Wisløff and Rognmo *et al*[22,28]. In the first RCT on HIIT in a clinical setting, Rognmo *et al*[28] evaluated the effects of HIIT compared with those of MCT, with the same total training load, and found that HIIT produced a higher increase of VO_{2peak} in patients with stable coronary artery disease than MCT. This trial adapted the 4 × 4 min method for patients with cardiac disease for the first time, using the same protocol as that used by the same group for young football players[32]. Leading researchers have reported the positive effects of HIIT on aerobic and metabolic capacity in single-center RCTs and meta-analyses. According to several RCTs, HIIT was superior in improving VO_{2peak} in 60% (6/10) of patients with coronary artery disease and in 45.6% of those with CHF (Table 4). The effect of HIIT depends on the workout duration/rest ratio. In contrast, the latest multicenter RCT [Study of Myocardial Recovery After Exercise Training in Heart Failure: (SMARTEX)] showed a negative result using the 4 × 4 min method for patients with CHF with reduced left ventricular dysfunction[45] despite many other studies reporting positive results[22,25,26,44]. Furthermore, this study clarified a problem in this protocol: A low adherence to the exercise intensity. There was a large overlap in the intensity between the HIIT and MCT groups, and this could be a key factor explaining the lack of a difference in the increase of VO_{2peak} between groups[45,49].

Although the 4 × 4 min aerobic HIIT protocol has been used in many studies, it did not consistently yield good results. Some researchers do not recommend this protocol because they believe that the load is excessive and the workout duration is too long for patients with sedentary/cardiac diseases, suggesting that it is a clinically unrealistic training method.

Table 2 Mode, intensity, and VO_{2peak} increment in high-intensity interval training versus moderate-intensity continuous training in randomized controlled trials (coronary artery disease)

Study	Published yr	Sample	*n*	HIIT	MCT	Duration	Mode	VO_{2peak} pre		VO_{2peak} %increase	
								HIIT	MCT	HIIT (%)	MCT (%)
1 Rognmo *et al*[28]	2004	CAD	17 (HIIT = 8)	3 d/wk 4 × 4 min@80%-90% VO_{2peak} total 33min	3 d/wk 41 min@50%-60% VO_{2peak} isoload to HIIT	10 wk	TM	31.8	32.1	17.9[a]	7.9
2 Warburton *et al*[41]	2005	CAD (previous CABG or AP)	14 (HIIT = 7)	2 d/wk, 2 min@90%VO_2R, 2 min recovery, 30 min total	2 d/wk 30 min @65%VO2R, average training volume similar to HIIT	16 wk	TM *etc*[1]	22	21	31.8[a]	9.5
3 Tjønna *et al*[21]	2008	Metabolic syndrome	28 (HIIT = 9)	3 d/wk 4 × 4 min@90%$HR_{max,}$ 3 min active recovery @70% HR_{max} 40 min total	3 d/wk 47 min @70% $HR_{max,}$ equalized training volume	16 wk	TM	33.6	36	35[a]	16
4 Moholdt *et al*[43]	2009	post CABG	59 (HIIT = 28)	5 d/wk 4 × 4 min@90%$HR_{peak,}$ 3 min recovery	5 d/wk 46 min + Aerobic group exercise, iso energic to HIIT	4 wk	TM	27.1	26.2	12.1	8.8
5 Moholdt *et al*[40]	2011	post MI	89 (HIIT = 30)	2 d/wk 4 × 4 min@85%-95%$HR_{peak,}$ 3 min recovery	2 d/wk 60 min@58% PPO	12 wk	TM[1]	31.6	32.2	14.6[a]	7.8
6 Rocco *et al*[23]	2012	CAD	37 (HIIT = 17)	3 d/wk 7 × 3 min@RCP, 7×3 min recovery@ VAT total 42 min	3 d/wk 50 min@VAT	3 mo	TM	18	17.9	23.3	24.6
7 Currie *et al*[51]	2013	recent event CAD post PCI, CABG, *etc*	22 (HIIT = 11)	2 d/wk 10 × 1 min@89% (80%-104%) PPO, 1 min recovery@10%PPO, 1 d/wk home-based @similar intensity	2 d/wk 30-50 min @58% PPO, 1d/wk home-based @similar intensity not isocaloric	12 wk	bike	19.8	18.7	24	19
8 Keteyian *et al*[38]	2014	Stable CAD (post MI CABG and/or PCI)	28 (HIIT = 15)	3 d/wk 4 × 4 min@80%-90%HHR	3 d/wk 30 min@60%-70%HRR	10 wk	TM	22.4	21.8	16[a]	8
9 Madssen *et al*[39]	2014	CAD with stents	36 (HIIT = 16)	3 d/wk 4 × 4 min@85%-95%$HR_{peak,}$ 3 min active recovery@70%HR_{peak}	3 d/wk 46 min@ 70%$HR_{max,}$ isocaloric	12 wk	TM	31.2	29.8	10.6[a]	6.7

10 Conraads *et al*[19]	2015	CAD	173 (HIIT = 85)	3 d/wk 4 × 4 min@90%-95%HR_{peak}, 3 min active recovery	3 d/wk 37 min@ 70%-75% %HR_{max}	12 wk	bike	23.5	22.2	22.7	20.3

Adapted from Ito S *et al*. Internal Medicine. 2016; 55: 2329-2336.
[a] in VO_{2peak} % increase raw: There is significant difference in % increase of VO_{2peak} between HIIT and MCT. 4 × 4 min means 4 × 4 min intervals per one HIIT training session. Study 2: [a] data shown is VO_2 at anaerobic threshold. Data is shown in figure without exact value at VO_{2peak} (30+ in HIIT 30 in MCT)., and %increase at peak exercise is similar. TM etc[1] means TM or stair climber,or, upper leg ergometer. Study 4: There was no difference at 4 wk: Increase of VO_{2peak} between 4 wk and 6 mo was significant within HIIT and between HIIT and MCT. The participant attended additional sessions with various intensity at the center with their choice. Exercise was performed at center for 4 wk and at home for 6 mo. Study 5: TM[1] means TM or aerobic exercise. AP: Angina pectoris; bike: Cycle ergometer; Cont: Continuous; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; TM: Treadmill; HIIT: High-intensity interval training; HR_{peak}: Peak heart rate; HRR: Heart rate reserve; MCT: Moderate-intensity continuous training; PPO: Peak power output; RCP: Respiratory compensation point; VAT: Ventilator anaerobic threshold; VO2R: VO_2 reserve; WRp: Peak work rate.

The aerobic 10 × 1 min HIIT protocol has also been developed by Gibala's group for broader targets including people with obesity and a sedentary lifestyle by decreasing the intensity from all-out performance to approximately VO_{2max} and by increasing each workout duration from 30 s to 60 s[29,50]. The number of repetitions was increased from 4-6 to 8-12 during the training course. This led to concomitant doubling of the total external energy expenditure. This protocol was utilized for patients with coronary artery disease by Currie *et al*[42,51] and in patients with CHF by Smart and Steele[47]. In an RCT comparing the 10 × 1 min HIIT and MCT, HIIT was not found to be superior in improving VO_{2peak}. The intensity of exercise was similar to that of the 4 × 4 min aerobic HIIT protocol. Each workout duration was as short as 1 min, but the frequency was higher than that of the 4 × 4 min. There are fewer studies about the 10 × 1 min HIIT protocol than those on the 4 × 4 min protocol. The duration of 1 min at 89% (80%-104%) PPO[51] might be rather short because the target heart rate cannot be attained within that time.

RCTs that compare the superiority of multiple different HIIT protocols in improving aerobic and metabolic parameters are limited[52,53]. Thus, researchers tend to select the protocol based on their experience, or they modify the exercise parameters (work and rest time). The effects of varying interval training intensities on the 40-km time-trial performance of trained cyclists were evaluated in a single study by Stepto *et al*[53], in which well-trained male cyclists were randomly assigned to 1 of 5 groups with different HIIT protocols (12 × 30 s at 175% PPO, 12 × 1 min at 100% PPO, 12 × 2 min at 90% PPO, 8 × 4 min at 85% PPO, and 4 × 8 min at 80% PPO). The cyclists completed 6 HIIT sessions over a 3-week period in addition to their habitual aerobic base training. The groups that followed the 12 × 30 s and 4 × 8 min protocols showed better improvement with respect to speed.

Unique HIIT protocols

The aim of recent exercise trends is to obtain benefits with the lowest and shortest workload.

Several groups have tried to establish shorter protocols in HIIT and SIT. These seem to be beneficial to the physical structure and fitness even in targets with lifestyle-related diseases, old age, or cardiac disorders. To overcome the criticisms of the 4 × 4 min protocol, a couple of finely tuned HIIT protocols, in which the frequency, workload, and work duration are initially set at low levels and altered during the training course, have been reported by several researchers[15,54-57].

Matsuo *et al*[15]: The Japanese high-intensity interval aerobic training (J-HIAT) program: 3 sets of 2–3-min cycling at vigorous intensity (first and second sets: 3 min at 85%-90% VO_{2peak}, third set: 3 min at 80%-85% VO_{2max}) with 2-min active rest at 50%VO_{2peak} between each set (healthy, sedentary young 20–30-year-old adults)[15]. This protocol was developed to control energy expenditure for astronauts participating in long-term space missions.

Osuka *et al*[58]: The elderly Japanese male version of high-intensity interval aerobic training (EJ-HIAT): 3 sets of 2–3 min cycling at 75%-85% VO_{2peak} (first set: 3 min at 85% VO_{2peak}, second set: 2 min at 80% VO_{2peak}, and third set: 2 min at 75% VO_{2peak}) with 1–2-min active rest at 50% VO_{2peak} (first set: 2 min, second set: 1 min) (60–69-year-old sedentary elderly men; mean age, 67.6 ± 1.8 years). A gradually decreasing load was planned for 2-3 wk, aiming at the protocol described above. A significant aerobic and metabolic response was attained by the shorter protocol than the 4 × 4 min protocol with a completion rate of 100%.

Table 3 Mode, intensity, and VO_{2peak} increment in high-intensity interval training versus moderate-intensity continuous training (congestive heart failure or diastolic dysfunction) in randomized

Study	Published yr	Sample	*n*	HIIT	MCT	Duration	Mode	VO_{2peak} pre		VO_{2peak} %increase	
								HIIT	MCT	HIIT (%)	MCT (%)
1 Dimopoulos *et al*[24]	2006	CHF	24 (HIIT = 10)	3 d/wk, 30 seconds@100% WRp, 30 s rest	3 d/wk, 40 mins@50% WRp	36 sessions	bike	15.4	15.5	7.8	5.8
2 Wisloff *et al*[22]	2007	CHF, Post MI	27 (HIIT = 9)	3 d (2 d supervised) /wk 4 × 4 min @90%-95%HR_{peak}, 3 min active recovery 50%-70% HR_{peak}, total 38 min	3 d (2 d supervised) /wk, 47 min@70%-75% HR_{peak}, isoload to HIIT	12 wk	TM	13	13	46[a]	14
3 Roditis *et al*[46]	2007	CHF	21 (HIIT = 11)	3 d/wk 30 secc @WR_{peak} 30 s rest, total of 40 min	3 d/wk 40 min@50% WR_{peak}, equal to total work of HIIT	36 sessions	bike	14.2	15.3	8.5	8.5
4 Smart *et al*[47]	2012	CHF (LVEF< 35%)	20 (HIIT = 10)	3 d/wk 30 × 1 min @70% VO_{2peak}, 1 min recovery	3 d/wk 30 min@70%VO_{2peak}, same absolute volume of work	16 wk	bike	12.2	12.4	21	13
5 Freyssin *et al*[26]	2012	CHF (LVEF< 40%)	26 (HIIT = 12)	5 d/wk 12 × 30 sec@50% (4 wk) + 80% (4 wk) of maximum power[b] 1 min @ complete rest	5 d/wk 45 min@HRVT1[c]	8 wk	Bike (HIIT), bike + TM (MCT)	10.7	10.8	27.1[a]	1.9
6 Fu *et al*[44]	2013	CHF (LVEF40%) NYHA II, III	45 (HIIT = 15)	3 d/wk 5 × 3 min@80%VO_{2peak} 3 min recovery@40% VO_{2peak}	3 d/wk 60 min @60% VO_{2peak}, isoload to Int	12 wk	bike	16	15.9	22.5[b]	0.6
7 Iellamo *et al*	2013	CHF with OMI (LVEF< 40%)	20 (HIIT = 10)	2-5 d/wk 2-4 × 4 min@75%-80%HRR, 3 min active pause walk@45%-50%HRR	2-5 d/wk 30-45 min @45%-60%HRR, equated training load ($TRIMP_i$)	12 wk	TM	18.7	18.4	8 22	4 22
8 Hollekim-Strand *et al*[20]	2014	diastolic dysfunction with Diabetes mellitus	37 (HIIT = 20)	3 d/wk 4 × 4 min @90%-95%HR_{peak}, total 40 min	Current guideline 10 min/bout 210 min/wk)	12 wk, Home-based thereafter	unknown	31.5	33.2	13.0[a]	3.6
9 Angadi *et al*[25]	2015	CHF with preserved EF	15 (HIIT = 9)	3 d/wk 4 × 4 min @85%-90%HR_{peak}, 3 min active recovery	3 d/wk 30 min@70%HR_{peak}	4 wk		19.2	16.9	9.4[a]	0

10 Ellingsen *et al*[45]	SMARTex-HF, 2017	Stable CHF (NYHA2-3) EF35%	200 (3 arms) (HIIT=77)	25 sessions 4 × 4 min@90%-95% $HR_{peak,}$ 3 min active recovery 50%-70% HR_{peak} total 38 min	25 sessions, 47 min@60-70%HR_{peak}	12 wk	bike or TM	0.9	1.1	5.4	6.8
11 Suchy C *et al*	OptimEX-CLIN, Ongoing	HFpEF	180 (HIIT 60)	3 d/wk 4 × 4 min@ 90%-95% $HR_{peak,}$ 3 min active recovery 50%-70% $HR_{peak,}$ total 38 min	5 d/wk 40 min@60%-70%HR_{peak}	3, 12 mo, home-based after 3 mo	bike	?	?	?	?

Controlled Trials Adapted from Ito S *et al*. Internal Medicine. 2016; 55: 2329-2336.
[a] in pre VO_{2peak} % increase raw: There is significant difference in % increase of VO_{2peak} between HIIT and MCT. Study 5: [b] each training session consisted of 3 series (12 repetitions of 30 s of exercises, separated by 5 minutes of rest); [c] half of the MCT was on a treadmill and half on a bike. Study 6: [b] pre versus post (not between groups). Study 7: Study hypothesis is similar adaptation in HIIT and MCT. Study 9: [a] evaluated by standardized effect size (d = 0.94) Bike: Cycle ergometer; CAD: Coronary artery disease; CHF: Congestive heart failure; EF: Ejection fraction; HR_{peak}: Peak heart rate; HIIT: High intensity interval training; HRVT1: Heart rate at the first ventilator threshold; HRR: Heart rate reserve; LVEF: Left ventricular ejection fraction; MCT: Moderate-intensity continuous training; MI: Myocardial infarction; min, minute; NYHA: New York Heart Association; RCP: Respiratory compensation point; VAT: Ventilator anaerobic threshold; PPO: Peak power output; TM: Treadmill; VO2R: VO2 reserve; VT1: First ventilator threshold; WRp: Peak work rate.

Alvarez *et al*[54,55]: During all training sessions, patients were instructed by the exercise specialists to jog/run and walk at a steady pace, which should be controlled by maintaining a score of 15–17 (jogging/running) and < 9 (walking) in the 15-point rating of perceived exertion scale. The goal was to reach 90%-100% and 70% of their predicted reserve heart rate at the end of the jogging/running and walking intervals, respectively. The progressive HIIT protocol started (1–2 wk) with 8 jogging/running intervals of approximately 30 s interspersed with approximately 120 s of low-intensity walking. To promote sufficient workloads for eliciting improvements throughout the 12-wk follow-up, there was a 7%-10% increase in the high-intensity interval duration and a 4% decrease in the recovery interval duration every 2 wk. There was also an increase of 2 exercise intervals every 4 wk of follow-up. The total workout duration increased from 4 to 13.5 min (weeks 1–16). The total recovery duration ranged from 18 to 24 min (weeks 1–16). The number of intervals ranged from 8 to 14 (weeks 1–16). The exercise duration ranged from 30 to 58 s. The target subjects were overweight/obese adult women aged 35–55 years with type 2 diabetes (T2D).

SIT

Classic SIT (Wingate test)

Because SIT is the highest-intensity workout program that needs an intensity more than the VO_{2peak}, the protocol is characterized by a short duration (30 s workout), followed by a long complete rest (2-5 min). This causes acute hemodynamic changes, such as abrupt blood pressure and heart rate increases, which may lead to a disruption of plaque and visceral organ ischemia by blood flow redistribution. Thus, SIT should be adapted only for young sedentary/recreationally active subjects but not for patients with hypertension, chronic kidney disease, and CVDs under the classic SIT protocol. Allemeier *et al*[59] demonstrated that VO_{2max} can be improved by approximately 14% by as little as three repeated Wingate sprints per training session. The classic SIT protocol incorporating up to six repeated 30-s Wingate sprints was first used in a study by Barnett *et al*[60], who reported an 8% increase in VO_{2max} and a 42% increase in maximal citrate synthase activity after 8 wk of SIT. This protocol was subsequently used by Gibala's group with minor modification, to investigate the aerobic adaptation associated with classic SIT[36,37]. Although classic Wingate protocols[31] use "4-6" repeated 30-s sprints, none of the studies provided a specific justification for the use of this method. Thus far, no studies have attempted to justify the 4-6 × 30 s Wingate sprints as an optimal SIT protocol[61].

The effects of 8-10 × 30-s Wingate sprints in the 1980s and 1990s included the following wide-ranging parameters: Maximal glycolytic and mitochondrial enzyme

Table 4 High-intensity interval training (HIIT) protocol and superiority of HIIT to moderate-intensity continuous training in VO_{2peak} improvement

	Protocol	No. of study	More improvement of VO_{2peak} in HIIT than in MCT
Coronary artery disease	10 × 1 min	1	0/1
	8 × 2 min	1	1/1
	7 × 3 min	1	0/1
	4 × 4 min	7	5/7 (70.2%)
Chronic heart failure	40 × 30 s	3	1/3
	30 × 1 min	1	0/1
	5 × 3 min	1	1/1
	4 × 4 min	6	3/4 (75%)
			56% (5/9) 2 studies ongoing

Randomized controlled trials comparing improvement of VO_{2peak} after exercise between HIIT and MCT in patients with CAD or CHF are shown. The protocols of HIIT and incidence of superiority of HIIT to MCT in each protocol are shown. In both groups 4×4 min was most frequently used showing positive rate 70.2% in the coronary artery disease group and 75% in the chronic heart failure group. The other protocols with 30 s, 2 min, and 3 min exercise duration are also effective in the limited number of studies. HIIT: High-intensity interval training; MCT: Moderate-intensity continuous training; CAD: Coronary artery disease; CHF: Chronic heart failure.

activity[62,63], purine metabolism[64], pulmonary and muscle gas exchange[65], muscle metabolism and ion regulation[66], muscle buffering capacity[67], erythrocyte characteristics[68], and improvement of VO_{2max}[63,65,66,68].

Concept of "low-volume/shorter" SIT for adaptation to a wide range of sedentary/recreationally active people

It has been consistently shown that a single 30-s Wingate sprint can reduce muscle glycogen stores in the vastus lateralis by 20%-30%[61,69-72]. What is intriguing, however, is that glycogenolysis is only activated during the first 15 s of the sprint and is then strongly attenuated during the final 15 s[72]. Moreover, activation of glycogenolysis is inhibited in subsequent repeated sprints[72]. This suggests that the classic SIT (4-6 repeated 30-s Wingate sprints) may be unnecessarily strenuous, as similar glycogen depletion may be achieved with 1–2 sprints of a shorter duration (15-20 s)[61,73,74]. In turn, this would make the training sessions more time efficient, less strenuous, and more applicable to the sedentary general population. Hazell *et al*[75] directly compared the impact of reducing the sprint duration in the classic SIT protocol from 30 s to 10 s, and reported similar increases in VO_{2max} with the 10-s protocol. Similarly, Zelt *et al*[76] reported no significant difference in the VO_{2max} response to the classic SIT protocol with 30-s sprints (4%) and a modified protocol with 15-s sprints (8%). Similar to a reduction in the sprint duration, a reduction in the number of sprint repetitions was evaluated in two studies. Allemeier *et al*[59] and Ijichi *et al*[16] demonstrated robust improvements in VO_{2max} after a protocol involving three repeated 30-s Wingate sprints. The protocol in these two studies had longer passing interval durations of 20 and 10 min, respectively.

One possible alternative strategy could be to define the minimum volume of exercise required to improve health indices with the aim of increasing exercise adherence. Vollaard *et al*[77] reviewed SIT protocols with the shortest duration and least amount of work. They also constructed a modified SIT aiming for the most time-efficient and effective protocol with high adherence for sedentary subjects and diabetic patients[61,74,78]. To date, this training protocol, named reduced-exertion HIIT (REHIT) (10-min SIT sessions, 3 sessions a week for 6 wk, involving only two 20-s Wingate sprints), represents the smallest volume of exercise (when considered per session) that has been shown to induce positive effects on health. This protocol was sufficient to improve VO_{2max} by 10%-13%[61,74]. Vollaard *et al*[77]also found that after performing only two maximal sprint intervals, each additional sprint in a training session reduced the overall improvement in fitness by around 5%. It is important to remember that these findings are only applicable to supramaximal exercise, which requires specialized exercise bikes that enable extremely high intensity exercise. This result might raise questions about the previously held "common sense" idea that performing more repetitions of high-intensity exercise would produce greater improvements in cardiorespiratory fitness. Ruffino *et al*[78] compared the effects of REHIT and moderate-intensity walking on health markers in patients with T2D in a counterbalanced crossover study. Sixteen men with T2D (mean age: 55 ± 5 years) completed 8 wk of REHIT and 8 wk of moderate-intensity walking (five 30-min

sessions/wk at an intensity corresponding to 40%-55% of the heart rate reserve), with a 2-mo washout period between interventions. They concluded that REHIT was superior to a 5-fold larger volume of moderate-intensity walking in improving aerobic fitness but had a similar result in terms of improving insulin sensitivity or glycemic control in patients with T2D in the short term. In studies evaluating REHIT, subjects with age > 60 years, uncontrolled hypertension, liver dysfunction, and renal dysfunction were excluded. Although evidence for patients with these comorbidities are lacking, the REHIT protocol might have a potential application for patients with some lifestyle-related diseases if careful attention is paid to hemodynamic changes, especially blood pressure spikes.

FEASIBILITY OF AND LIMITATIONS IN ADOPTING HIIT AND SIT FOR SEDENTARY/OBESE/ELDERLY/DISEASED SUBJECTS

HIIT

Even in exercise training with submaximal aerobic HIIT, adequate adherence to the target intensity and frequency was not achieved in multicenter RCTs[8,45,49]. Another clear limitation is the large dropout rate during follow-up after the supervised exercise period[79]. HIIT has been accepted for patients with cardiac diseases, as shown in the protocols in Table 4. Although the target heart rate was as high as 90%-95% of the peak heart rate, the intensity was calculated from an individual's peak heart rate, and these aerobic HIIT protocols could be utilized for a wide range of targets subjects including the elderly and patients with diseases.

SIT

The tolerability and adherence of SIT for non-athletes and sedentary people is low.

The target subjects in previous studies on SIT include young people who are healthy and/or recreationally active. The number of subjects in each study was very small, and there might be bias in the selection of study subjects. It was possible that subjects who have no or little experience in sports/exercise training, irrespective of age, may have had difficulties in performing the all-out exercises. In this regard, REHIT may widen the target subjects owing to its smallest volume of exercise among the available protocols. Furthermore, it can be adapted for all age groups of sedentary, recreationally active, and of course highly trained people, but not in those who are sedentary, aged > 60 years, and with CVD (personal communication with Dr. Vollaard).

POTENTIAL RISKS OF THE HIIT AND SIT PROTOCOLS

HIIT

Previously reported studies on HIIT had small numbers of subjects and contained limited reference about the safety and injury risk of this training protocol in the general population. A Norwegian group observed only two knee injuries in extremely overweight patients[21]. Levinger *et al*[80] published a systematic review about adverse events during or immediately after HIIT. They found that the incidence of adverse responses during or 24 h after HIIT, as acute responses to a single session of HIIT, in patients with cardiometabolic diseases was around 8%, which was somewhat higher than the previously reported risk during MCT[80]. Rognmo *et al*[81] examined the risk of cardiovascular events during organized HIIT and MCT among 4846 patients with coronary heart disease in 3 Norwegian cardiac rehabilitation centers. In a total of 175820 exercise training hours, during which all patients performed both types of training, 1 fatal cardiac arrest during moderate-intensity exercise (129456 exercise hours) and 2 nonfatal cardiac arrests during HIIT (46364 exercise hours) were reported. No myocardial infarctions were reported. They concluded that the risk of a cardiovascular event was low after both HIIT and MCT in a cardiovascular rehabilitation setting[81].

SIT and low-dose/shorter SIT

Systematic reviews on the safety and injury risk of SIT are very limited. Supramaximal sprints used in protocols such as the Wingate protocol are associated with a short but sharp increase in blood pressure as well as an increase in blood flow, which could pose a risk of dislodging unstable plaques. Redistribution of blood flow (increased flow in muscle followed by decreased flow in visceral organs) might pose a

risk to patients with CVD and chronic kidney disease. However, SIT or shorter/low-dose SIT has been adopted only in healthy, sedentary, and usually young people. For these subjects, the cardiovascular risk could be very low because the incidence of hypertension and/or atheroscrelotic disease is low. For individuals with lifestyle-related diseases and/or CVD, the potential risk of the SIT/REHIT protocol has not been evaluated. Thus, currently, it should not be adopted for these individuals. Ruffino *et al*[78] investigated REHIT for patients with T2D, and neither risk nor cardiovascular event was reported.

INTRODUCTION OF THE OPTIMAL INTENSITY/DOSE OF ACTIVITY IN DAILY LIFE: PERSONAL ACTIVITY INDEX

Other than supervised exercise training using sophisticated exercise protocols, non-supervised daily training and activity could also be useful to improve aerobic capacity. For activity counseling and promotion of physical activity, providing some feedback to individuals with personalized and meaningful information would be beneficial to motivate them to increase or maintain their physical activity[73,82]. Goals such as "10000 steps per day" or "30 min of activity per day," which are the same for all people, are easily understandable but do not reflect the body's response to each activity. The goal "10000 steps" has a different meaning for each individual [*e.g.*, what speed, where (uphill or downhill)]. The most personalized, accurate way to track and measure the body's response to activity is by monitoring the heart rate. Changes in heart rate reflect the body's response to physical activity regardless of the activity type. Because there has never been a simple way to convert heart rate to a metric, Nes *et al*[83] developed a new single metric called the Personalized Activity Index (PAI). PAI can be integrated in self-assessment heart rate devices and defines a weekly beneficial heart rate pattern during physical activity. Furthermore, PAI could translate into reduced long-term risk of premature CVD and all-cause mortality, according to the epidemiologic study (HUNT)[83-85] performed in Nord-Trøndelag county in Norway, which analyzed a large, apparently healthy, general population cohort (n = 29950, aged ≥ 20 years). Obtaining a score of ≥ 100 weekly PAI has been shown to reduce the risk of premature CVD death in healthy subjects as well as in individuals with known CVD risk factors, regardless of whether or not the current physical activity recommendations were met[86]. PAI could inform potential users of how much physical activity is needed to reduce the risk of premature CVD death[83]. PAI users could also identify know the exercise intensity and time of exercise that are effective and efficient for appropriate exercise/physical activity according to their own daily experience followed by feedback. For example, exercising at very vigorous intensities may yield high PAI scores and higher $VO_{2peak,}$ even with considerably lower total exercise time than expressed in the current recommendations[84]. As a simple pattern, exercise once a week is also effective[85] if the exercise intensity is enough to improve VO_{2peak}.

WORKING MECHANISMS OF HIIT AND SIT

The mechanisms involved in the superiority of HIIT to MCT have not been clearly elucidated. However, there are several potential mechanisms[48] (Figure 2). The first reason for the improvement in the aerobic capacity with HIIT can be explained by the following intracellular signaling sequence[87]: Muscular stimulus by HIIT → increase in 5′-AMP-activated protein kinase (AMPK) activity in muscle cells → increase in peroxisome proliferator activated receptor-γcoactivator-1α (PGC-1α) mRNA and protein → increase in the mRNA and protein expression of the mitochondrial oxygenation enzyme → improvement in physical fitness (aerobic capacity)[88]. Secondly, it is reasonable to speculate that the higher shear stress in HIIT during exercise bouts may trigger greater responses at the cellular and molecular levels, leading to a partial recovery from endothelial dysfunction. Thirdly, Hanssen *et al*[89]recently reported another potential reason for the benefits of HIIT; they reported the acute effects of interval versus continuous-endurance training on pulse wave reflection in healthy young men. Although initially higher after HIIT, the augmentation index at a set heart rate declined in the 24-h follow-up period, indicating favorable effects on pulse-wave reflection compared with that after MCT. The possible mechanism of the REHIT protocol using two (but not three or more) repeated bouts of supramaximal 20-s workout was proposed by Vollaard *et al*[77,90]. The adaptations to SIT for VO_{2max} may be peripheral in origin owing to improved skeletal muscle oxygen extraction because of mitochondrial density[77]. Vollaard *et*

al[77]proposed that both increased blood volume and increased mitochondrial density could plausibly be explained by the rapid glycogen depletion associated with supramaximal exercise[73]. Glycogen breakdown during repeated supramaximal sprints has been shown to be completely attenuated by the time of the third sprint. Thus, it is plausible, according to the two speculated mechanisms[77,90] below, that performing only two repeated supramaximal sprints is sufficient to saturate the adaptive response.

The first mechanism is as follows: maximal rates of glycogenolysis in the initial 15s of a supramaximal sprint → accumulation of metabolic derivatives → hypertonic intramyocellular environment → influx of water to the myocardium → transient approximately 15%-20% drop in plasma volume within a time span of only a few minutes. This severe disturbance of circulatory homeostasis could be a stimulus for the body to increase blood volume in response to repeated SIT sessions.

The second mechanism is as follows: Glycogenolysis → release and activation of glycogen-bound AMPK[91] → downstream signaling pathway involving PGC-1α → increased mitochondrial density.

FUTURE PERSPECTIVES

More studies are warranted to establish the most efficient protocol for each target subject according to clinical characteristics and fitness level, to improve aerobic capacity and to establish higher adherence. Thus far, aerobic HIIT (submaximal intensity) could be feasible and has a low risk for people with lifestyle-related diseases, obesity, sedentary lifestyle, old age, or cardiac disorders when performed, at their own individual intensity. In contrast, classic SIT (supramaximal) is applicable only for healthy young people. A smaller-dose and shorter SIT such as the 2 × 20 s protocol (REHIT) could be utilized for sedentary young/middle-aged targets. The feasibility and safety of REHIT for elderly and sedentary people, patients with stable ischemic heart disease and CHF, and patients with chronic kidney disease have not been evaluated. Figure 3 shows a personal proposal of HIIT protocols for target people stratified by age, exercise habits, and cardiovascular disease. Although the increased application of HIIT in the health and medical fields is expected, its feasibility and safety should be further evaluated in the near future.

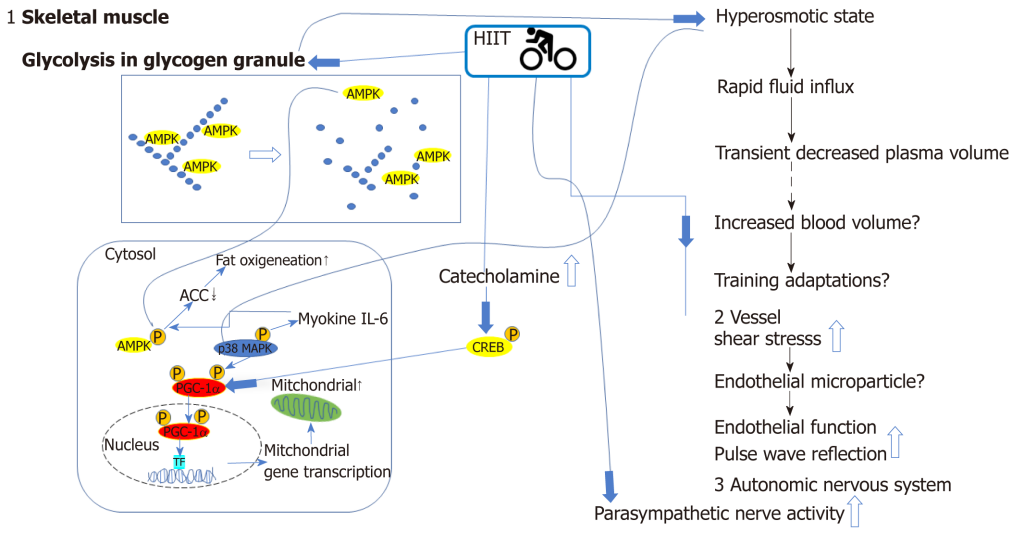


Figure 2 Graphic representation of beneficial cardiovascular and metabolic effects and relevant mechanisms activated by high-intensity interval training. Glycolysis of glycogen granules in the skeletal muscle, catecholamine release, increased shear stress in the vessels, and increased autonomic nerve activity by HIIT are related to increased aerobic and metabolic capacities. Activity in skeletal muscle cells and arteries are increased during HIIT. The decrease in glycogen content by glycolysis results in the release of the AMP-activated protein kinase (AMPK) from the glycogen particle, resulting in greater activity and altered localization. In addition, exercise in a low-glycogen state after glycolysis leads to the phosphorylation and activation of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α). Finally, the osmotic stress associated with a rapid change in glycogen content and increased glucose concentration can activate mitogen-activated protein kinases (MAPKs) such as p38, which can phosphorylate and activate PGC-1. Another target of p38 is interleukin 6 (IL-6), which targets AMPK as one of the potential targets. These alterations in muscle signaling also result in improved circulating fatty acid (FA) utilization. The increased catecholamine level promotes an increase in fat metabolism by activating heat shock protein through protein kinase A. An additional cellular target of catecholamine is the cAMP response element-binding protein (CREB). HIIT can increase the phosphorylation and activation of CREB in both exercised muscle and muscles that were not recruited during the exercise due to the central effects of elevated central nervous system activity. One of the targets of CREB is PGC-1α. An increase in PGC-1α mRNA and protein with co-activation of the transcription factor results in the increase in the mRNA and protein of the mitochondrial oxygenation enzyme, and finally, improvements in physical fitness (aerobic capacity). HIIT increases cardiac output, leading to shear stress in arteries and resulting in improvements in endothelial function and pulse wave reflection potentially through endothelial microparticles.ACC: Acetyl CoA carboxylase; AMPK: AMP-activated protein kinase; CREB: cAMP response element-binding protein; HIIT: High-intensity interval training; IL-6: Interleukin 6; MAPK: Mitogen-activated protein kinases; PGC1α: Peroxisome proliferator-activated receptor γ coactivator 1-α; TF: Transcription factor.

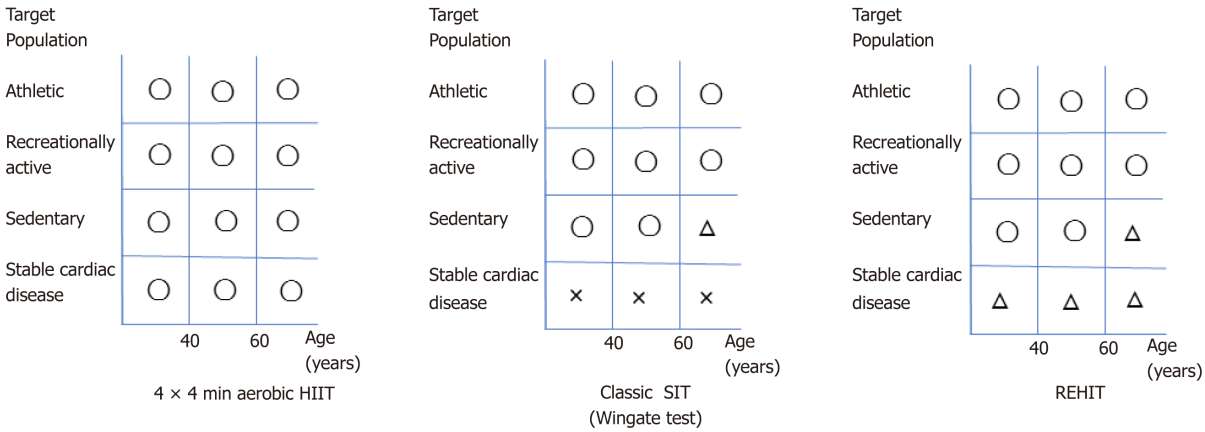


Figure 3 Personal proposal of high-intensity interval training (HIIT) protocols for target people stratified by age, exercise habits, and cardiovascular disease. 4 × 4 min HIIT: Can be adopted for all subjects, with the intensity maintained at 85%-95% of an individual 's peak heart rate. Classic sprint interval training (SIT): The feasibility and safety of this protocol for patients complicated with cardiovascular disease have not been evaluated. Reduced-exertion HIIT (REHIT): Its feasibility and safety for patients complicated with cardiovascular disease have not been evaluated. Because REHIT is much less strenuous than classic SIT, future research on this protocol is expected for patients with stable cardiovascular diseases besides high-risk patients, such as those with refractory hypertension and coronary heart disease with atherosclerotic plaque. O: adaptable for all target subjects; Δ: potentially adaptable for target subjects without risk; ×: should be prohibited for all target subjects.

REFERENCES

1 **Blair SN**, Kohl HW, Barlow CE, Paffenbarger RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA* 1995; **273**: 1093-1098 [PMID: 7707596 DOI: 10.1001/jama.273.14.1093]

2 **Lee DC**, Sui X, Ortega FB, Kim YS, Church TS, Winett RA, Ekelund U, Katzmarzyk PT, Blair SN. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med* 2011; **45**: 504-510 [PMID: 20418526 DOI: 10.1136/bjsm.2009.066209]

3 **Myers J**, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; **346**: 793-801 [PMID: 11893790 DOI: 10.1056/NEJMoa011858]

4 **DeFina LF**, Haskell WL, Willis BL, Barlow CE, Finley CE, Levine BD, Cooper KH. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? *Prog Cardiovasc Dis* 2015; **57**: 324-329 [PMID: 25269066 DOI: 10.1016/j.pcad.2014.09.008]

5 **Myers J**, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis* 2015; **57**: 306-314 [PMID: 25269064 DOI: 10.1016/j.pcad.2014.09.011]

6 **Garber CE**, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; **43**: 1334-1359 [PMID: 21694556 DOI: 10.1249/MSS.0b013e318213fefb]

7 **Piepoli MF**, Corrà U, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, Dendale P, Doherty P, Gaita D, Höfer S, McGee H, Mendes M, Niebauer J, Pogosova N, Garcia-Porrero E, Rauch B, Schmid JP, Giannuzzi P. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol* 2014; **21**: 664-681 [PMID: 22718797 DOI: 10.1177/2047487312449597]

8 **JCS Joint Working Group**. Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). *Circ J* 2014; **78**: 2022-2093 [PMID: 25047729 DOI: 10.1253/circj.CJ-66-0083]

9 **Pedersen BK**, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports* 2006; **16** Suppl 1: 3-63 [PMID: 16451303 DOI: 10.1111/j.1600-0838.2006.00520.x]

10 **Guthold R**, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. *Lancet Glob Health* 2018; **6**: e1077-e1086 [PMID: 30193830 DOI: 10.1016/S2214-109X(18)30357-7]

11 **Lobelo F**, Stoutenberg M, Hutber A. The Exercise is Medicine Global Health Initiative: a 2014 update. *Br J Sports Med* 2014; **48**: 1627-1633 [PMID: 24759911 DOI: 10.1136/bjsports-2013-093080]

12 **Haskell WL**, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007; **39**: 1423-1434 [PMID: 17762377 DOI: 10.1249/mss.0b013e3180616b27]

13 **Hambrecht R**, Niebauer J, Fiehn E, Kälberer B, Offner B, Hauer K, Riede U, Schlierf G, Kübler W, Schuler G. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol* 1995; **25**: 1239-1249 [PMID: 7722116 DOI: 10.1016/0735-1097(94)00568-b]

14 **Balady GJ**, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, Franklin B, Sanderson B, Southard D; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Association of Cardiovascular and Pulmonary Rehabilitation. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007; **115**: 2675-2682 [PMID: 17513578 DOI: 10.1161/CIRCULATIONAHA.106.180945]

15 **Matsuo T**, Saotome K, Seino S, Shimojo N, Matsushita A, Iemitsu M, Ohshima H, Tanaka K, Mukai C. Effects of a low-volume aerobic-type interval exercise on VO2max and cardiac mass. *Med Sci Sports Exerc* 2014; **46**: 42-50 [PMID: 23846165 DOI: 10.1249/MSS.0b013e3182a38da8]

16 **Ijichi T**, Hasegawa Y, Morishima T, Kurihara T, Hamaoka T, Goto K. Effect of sprint training: training once daily versus twice every second day. *Eur J Sport Sci* 2015; **15**: 143-150 [PMID: 24993562 DOI: 10.1080/17461391.2014.932849]

17 **Nakahara H**, Ueda SY, Miyamoto T. Low-frequency severe-intensity interval training improves cardiorespiratory functions. *Med Sci Sports Exerc* 2015; **47**: 789-798 [PMID: 25137370 DOI: 10.1249/MSS.0000000000000477]

18 **Trost SG**, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: review and update. *Med Sci Sports Exerc* 2002; **34**: 1996-2001 [PMID: 12471307 DOI: 10.1097/00005768-200212000-00020]

19 **Conraads VM**, Pattyn N, De Maeyer C, Beckers PJ, Coeckelberghs E, Cornelissen VA, Denollet J, Frederix G, Goetschalckx K, Hoymans VY, Possemiers N, Schepers D, Shivalkar B, Voigt JU, Van Craenenbroeck EM, Vanhees L. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *Int J Cardiol* 2015; **179**: 203-210 [PMID: 25464446 DOI: 10.1016/j.ijcard.2014.10.155]

20 **Hollekim-Strand SM**, Bjørgaas MR, Albrektsen G, Tjønna AE, Wisløff U, Ingul CB. High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. *J Am Coll Cardiol* 2014; **64**: 1758-1760 [PMID: 25323267 DOI: 10.1016/j.jacc.2014.07.971]

21 **Tjønna AE**, Lee SJ, Rognmo Ø, Stølen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E, Slørdahl SA, Kemi OJ, Najjar SM, Wisløff U. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 2008; **118**: 346-354 [PMID: 18606913 DOI: 10.1161/CIRCULATIONAHA.108.772822]

22 **Wisløff U**, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, Tjønna AE, Helgerud J, Slørdahl SA, Lee SJ, Videm V, Bye A, Smith GL. Najjar SM, Ellingsen Ø, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 2007; **115**: 3086-3094 [PMID: 17548726 DOI: 10.1161/circulationaha.106.675041]

23 **Rocco EA**, Prado DM, Silva AG, Lazzari JM, Bortz PC, Rocco DF, Rosa CG, Furlan V. Effect of continuous and interval exercise training on the PETCO2 response during a graded exercise test in patients with coronary artery disease. *Clinics (Sao Paulo)* 2012; **67**: 623-628 [PMID: 22760902 DOI: 10.6061/clinics/2012(06)13]

24 **Dimopoulos S**, Anastasiou-Nana M, Sakellariou D, Drakos S, Kapsimalakou S, Maroulidis G, Roditis P, Papazachou O, Vogiatzis I, Roussos C, Nanas S. Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 67-73 [PMID: 16449866 DOI: 10.1097/01.hjr.0000198449.20775.7c]

25 **Angadi SS**, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985)* 2015; **119**: 753-758 [PMID: 25190739 DOI: 10.1152/japplphysiol.00518.2014]

26 **Freyssin C**, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. *Arch Phys Med Rehabil* 2012; **93**: 1359-1364 [PMID: 22446291 DOI: 10.1016/j.apmr.2012.03.007]

27 **Buchheit M**, Laursen PB. High-intensity interval training, solutions to the programming puzzle: Part I: cardiopulmonary emphasis. *Sports Med* 2013; **43**: 313-338 [PMID: 23539308 DOI: 10.1007/s40279-013-0029-x]

28 **Rognmo Ø**. Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004; **11**: 216-222 [PMID: 15179103 DOI: 10.1097/01.hjr.0000131677.96762.0c]

29 **Gibala MJ**, Little JP, Macdonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol* 2012; **590**: 1077-1084 [PMID: 22289907 DOI: 10.1113/jphysiol.2011.224725]

30 **Burgomaster KA**, Hughes SC, Heigenhauser GJ, Bradwell SN, Gibala MJ. Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *J Appl Physiol (1985)* 2005; **98**: 1985-1990 [PMID: 15705728 DOI: 10.1152/japplphysiol.01095.2004]

31 **Sands WA**, McNeal JR, Ochi MT, Urbanek TL, Jemni M, Stone MH. Comparison of the Wingate and Bosco anaerobic tests. *J Strength Cond Res* 2004; **18**: 810-815 [PMID: 15574087 DOI: 10.1519/13923.1]

32 **Helgerud J**, Engen LC, Wisloff U, Hoff J. Aerobic endurance training improves soccer performance. *Med Sci Sports Exerc* 2001; **33**: 1925-1931 [PMID: 11689745 DOI: 10.1097/00005768-200111000-00019]

33 **Kavaliauskas M**, Aspe RR, Babraj J. High-Intensity Cycling Training: The Effect of Work-to-Rest Intervals on Running Performance Measures. *J Strength Cond Res* 2015; **29**: 2229-2236 [PMID: 26203737 DOI: 10.1519/JSC.0000000000000868]

34 **Aamot IL**, Karlsen T, Dalen H, Støylen A. Long-term Exercise Adherence After High-intensity Interval Training in Cardiac Rehabilitation: A Randomized Study. *Physiother Res Int* 2016; **21**: 54-64 [PMID: 25689059 DOI: 10.1002/pri.1619]

35 **Weston KS**, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med* 2014; **48**: 1227-1234 [PMID: 24144531 DOI: 10.1136/bjsports-2013-092576]

36 **Gibala MJ**, Little JP, van Essen M, Wilkin GP, Burgomaster KA, Safdar A, Raha S, Tarnopolsky MA. Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J Physiol* 2006; **575**: 901-911 [PMID: 16825308 DOI: 10.1113/jphysiol.2006.112094]

37 **Burgomaster KA**, Howarth KR, Phillips SM, Rakobowchuk M, Macdonald MJ, McGee SL, Gibala MJ. Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J Physiol* 2008; **586**: 151-160 [PMID: 17991697 DOI: 10.1113/jphysiol.2007.142109]

38 **Keteyian SJ**, Hibner BA, Bronsteen K, Kerrigan D, Aldred HA, Reasons LM, Saval MA, Brawner CA, Schairer JR, Thompson TM, Hill J, McCulloch D, Ehrman JK. Greater improvement in cardiorespiratory fitness using higher-intensity interval training in the standard cardiac rehabilitation setting. *J Cardiopulm Rehabil Prev* 2014; **34**: 98-105 [PMID: 24531203 DOI: 10.1097/HCR.0000000000000049]

39 **Madssen E**, Moholdt T, Videm V, Wisløff U, Hegbom K, Wiseth R. Coronary atheroma regression and plaque characteristics assessed by grayscale and radiofrequency intravascular ultrasound after aerobic exercise. *Am J Cardiol* 2014; **114**: 1504-1511 [PMID: 25248813 DOI: 10.1016/j.amjcard.2014.08.012]

40 **Moholdt T**, Aamot IL, Granøien I, Gjerde L, Myklebust G, Walderhaug L, Hole T, Graven T, Stølen T, Mølmen-Hansen HE, Støylen A, Skogvoll E, Slørdahl SA, Wisløff U. Long-term follow-up after cardiac rehabilitation: a randomized study of usual care exercise training versus aerobic interval training after myocardial infarction. *Int J Cardiol* 2011; **152**: 388-390 [PMID: 21907424 DOI: 10.1016/j.ijcard.2011.08.025]

41 **Warburton DE**, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, Chan SY. Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol* 2005; **95**: 1080-1084 [PMID: 15842976 DOI: 10.1016/j.amjcard.2004.12.063]

42 **Currie KD**, Bailey KJ, Jung ME, McKelvie RS, MacDonald MJ. Effects of resistance training combined with moderate-intensity endurance or low-volume high-intensity interval exercise on cardiovascular risk factors in patients with coronary artery disease. *J Sci Med Sport* 2015; **18**: 637-642 [PMID: 25308628 DOI: 10.1016/j.jsams.2014.09.013]

43 **Moholdt TT**, Amundsen BH, Rustad LA, Wahba A, Løvø KT, Gullikstad LR, Bye A, Skogvoll E, Wisløff U, Slørdahl SA. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J* 2009; **158**: 1031-1037 [PMID: 19958872 DOI: 10.1016/j.ahj.2009.10.003]

44 **Fu TC**, Wang CH, Lin PS, Hsu CC, Cherng WJ, Huang SC, Liu MH, Chiang CL, Wang JS. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *Int J Cardiol* 2013; **167**: 41-50 [PMID: 22197120 DOI: 10.1016/j.ijcard.2011.11.086]

45 **Ellingsen Ø**. Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, Larsen AI, Hole T, Mezzani A,

Van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Höllriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A; SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation* 2017; **135**: 839-849 [PMID: 28082387 DOI: 10.1161/CIRCULATIONAHA.116.022924]

46 **Roditis P**, Dimopoulos S, Sakellariou D, Sarafoglou S, Kaldara E, Venetsanakos J, Vogiatzis J, Anastasiou-Nana M, Roussos C, Nanas S. The effects of exercise training on the kinetics of oxygen uptake in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2007; **14**: 304-311 [PMID: 17446812 DOI: 10.1097/HJR.0b013e32808621a3]

47 **Smart NA**, Steele M. A comparison of 16 weeks of continuous vs intermittent exercise training in chronic heart failure patients. *Congest Heart Fail* 2012; **18**: 205-211 [PMID: 22809258 DOI: 10.1111/j.1751-7133.2011.00274.x]

48 **Ito S**, Mizoguchi T, Saeki T. Review of High-intensity Interval Training in Cardiac Rehabilitation. *Intern Med* 2016; **55**: 2329-2336 [PMID: 27580530 DOI: 10.2169/internalmedicine.55.6068]

49 **Karlsen T**. Aamot IL, Haykowsky M, Rognmo Ø, High Intensity Interval Training for Maximizing Health Outcomes. *Prog Cardiovasc Dis* 2017; **60**: 67-77 [PMID: 28385556 DOI: 10.1016/j.pcad.2017.03.006]

50 **Little JP**, Safdar A, Wilkin GP, Tarnopolsky MA, Gibala MJ. A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. *J Physiol* 2010; **588**: 1011-1022 [PMID: 20100740 DOI: 10.1113/jphysiol.2009.181743]

51 **Currie KD**, Dubberley JB, McKelvie RS, MacDonald MJ. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc* 2013; **45**: 1436-1442 [PMID: 23470301 DOI: 10.1249/MSS.0b013e31828bbbd4]

52 **Bækkerud FH**. Solberg F, Leinan IM, Wisløff U, Karlsen T, Rognmo Ø. Comparison of Three Popular Exercise Modalities on V˙O2max in Overweight and Obese. *Med Sci Sports Exerc* 2016; **48**: 491-498 [PMID: 26440134 DOI: 10.1249/MSS.0000000000000777]

53 **Stepto NK**, Hawley JA, Dennis SC, Hopkins WG. Effects of different interval-training programs on cycling time-trial performance. *Med Sci Sports Exerc* 1999; **31**: 736-741 [PMID: 10331896 DOI: 10.1097/00005768-199905000-00018]

54 **Alvarez C**, Ramírez R, Flores M, Zúñiga C, Celis-Morales CA. [Effect of sprint interval training and resistance exercise on metabolic markers in overweight women]. *Rev Med Chil* 2012; **140**: 1289-1296 [PMID: 23559286 DOI: 10.4067/S0034-98872012001000008]

55 **Alvarez C**, Ramirez-Campillo R, Martinez-Salazar C, Mancilla R, Flores-Opazo M, Cano-Montoya J, Ciolac EG. Low-Volume High-Intensity Interval Training as a Therapy for Type 2 Diabetes. *Int J Sports Med* 2016; **37**: 723-729 [PMID: 27259099 DOI: 10.1055/s-0042-104935]

56 **Matsuo T**, Ohkawara K, Seino S, Shimojo N, Yamada S, Ohshima H, Tanaka K, Mukai C. An exercise protocol designed to control energy expenditure for long-term space missions. *Aviat Space Environ Med* 2012; **83**: 783-789 [PMID: 22872993 DOI: 10.3357/ASEM.3298.2012]

57 **Matsuo T**, Saotome K, Seino S, Eto M, Shimojo N, Matsushita A, Iemitsu M, Ohshima H, Tanaka K, Mukai C. Low-volume, high-intensity, aerobic interval exercise for sedentary adults: VOmax, cardiac mass, and heart rate recovery. *Eur J Appl Physiol* 2014; **114**: 1963-1972 [PMID: 24917354 DOI: 10.1007/s00421-014-2917-7]

58 **Osuka Y**, Matsubara M, Hamasaki A, Hiramatsu Y, Ohshima H, Tanaka K. Development of low-volume, high-intensity, aerobic-type interval training for elderly Japanese men: a feasibility study. *Eur Rev Aging Phys Act* 2017; **14**: 14 [PMID: 28855969 DOI: 10.1186/s11556-017-0184-4]

59 **Allemeier CA**, Fry AC, Johnson P, Hikida RS, Hagerman FC, Staron RS. Effects of sprint cycle training on human skeletal muscle. *J Appl Physiol (1985)* 1994; **77**: 2385-2390 [PMID: 7868459 DOI: 10.1152/jappl.1994.77.5.2385]

60 **Barnett C**, Carey M, Proietto J, Cerin E, Febbraio MA, Jenkins D. Muscle metabolism during sprint exercise in man: influence of sprint training. *J Sci Med Sport* 2004; **7**: 314-322 [PMID: 15518296 DOI: 10.1016/S1440-2440(04)80026-4]

61 **Metcalfe RS**, Babraj JA, Fawkner SG, Vollaard NB. Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. *Eur J Appl Physiol* 2012; **112**: 2767-2775 [PMID: 22124524 DOI: 10.1007/s00421-011-2254-z]

62 **Jacobs I**, Esbjörnsson M, Sylvén C, Holm I, Jansson E. Sprint training effects on muscle myoglobin, enzymes, fiber types, and blood lactate. *Med Sci Sports Exerc* 1987; **19**: 368-374 [PMID: 2958671 DOI: 10.1249/00005768-198708000-00008]

63 **MacDougall JD**, Hicks AL, MacDonald JR, McKelvie RS, Green HJ, Smith KM. Muscle performance and enzymatic adaptations to sprint interval training. *J Appl Physiol (1985)* 1998; **84**: 2138-2142 [PMID: 9609810 DOI: 10.1152/jappl.1998.84.6.2138]

64 **Stathis CG**, Febbraio MA, Carey MF, Snow RJ. Influence of sprint training on human skeletal muscle purine nucleotide metabolism. *J Appl Physiol (1985)* 1994; **76**: 1802-1809 [PMID: 8045862 DOI: 10.1152]

65 **McKenna MJ**, Heigenhauser GJ, McKelvie RS, Obminski G, MacDougall JD, Jones NL. Enhanced pulmonary and active skeletal muscle gas exchange during intense exercise after sprint training in men. *J Physiol* 1997; **501**: 703-716 [PMID: 9218229 DOI: 10.1111/j.1469-7793.1997.703bm.x]

66 **Harmer AR**, McKenna MJ, Sutton JR, Snow RJ, Ruell PA, Booth J, Thompson MW, Mackay NA, Stathis CG, Crameri RM, Carey MF, Eager DM. Skeletal muscle metabolic and ionic adaptations during intense exercise following sprint training in humans. *J Appl Physiol (1985)* 2000; **89**: 1793-1803 [PMID: 11053328 DOI: 10.1152/jappl.2000.89.5.1793]

67 **Sharp RL**, Costill DL, Fink WJ, King DS. Effects of eight weeks of bicycle ergometer sprint training on human muscle buffer capacity. *Int J Sports Med* 1986; **7**: 13-17 [PMID: 3957514 DOI: 10.1055/s-2008-1025727]

68 **Katz A**, Sharp RL, King DS, Costill DL, Fink WJ. Effect of high intensity interval training on 2,3-diphosphoglycerate at rest and after maximal exercise. *Eur J Appl Physiol Occup Physiol* 1984; **52**: 331-335 [PMID: 6539689 DOI: 10.1007/BF01015222]

69 **Esbjörnsson-Liljedahl M**, Bodin K, Jansson E. Smaller muscle ATP reduction in women than in men by repeated bouts of sprint exercise. *J Appl Physiol (1985)* 2002; **93**: 1075-1083 [PMID: 12183505 DOI: 10.1152/japplphysiol.00732.1999]

70 **Esbjörnsson-Liljedahl M**, Sundberg CJ, Norman B, Jansson E. Metabolic response in type I and type II muscle fibers during a 30-s cycle sprint in men and women. *J Appl Physiol (1985)* 1999; **87**: 1326-1332

[PMID: 10517759 DOI: 10.1152/jappl.1999.87.4.1326]
71 **Gibala MJ**, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1alpha in human skeletal muscle. *J Appl Physiol (1985)* 2009; **106**: 929-934 [PMID: 19112161 DOI: 10.1152/japplphysiol.90880.2008]
72 **Parolin ML**, Chesley A, Matsos MP, Spriet LL, Jones NL, Heigenhauser GJ. Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. *Am J Physiol* 1999; **277**: E890-E900 [PMID: 10567017 DOI: 10.1152/ajpendo.1999.277.5.E890]
73 **Metcalfe RS**, Koumanov F, Ruffino JS, Stokes KA, Holman GD, Thompson D, Vollaard NB. Physiological and molecular responses to an acute bout of reduced-exertion high-intensity interval training (REHIT). *Eur J Appl Physiol* 2015; **115**: 2321-2334 [PMID: 26156806 DOI: 10.1007/s00421-015-3217-6]
74 **Metcalfe RS**, Tardif N, Thompson D, Vollaard NB. Changes in aerobic capacity and glycaemic control in response to reduced-exertion high-intensity interval training (REHIT) are not different between sedentary men and women. *Appl Physiol Nutr Metab* 2016; **41**: 1117-1123 [PMID: 27753506 DOI: 10.1139/apnm-2016-0253]
75 **Hazell TJ**, Macpherson RE, Gravelle BM, Lemon PW. 10 or 30-s sprint interval training bouts enhance both aerobic and anaerobic performance. *Eur J Appl Physiol* 2010; **110**: 153-160 [PMID: 20424855 DOI: 10.1007/s00421-010-1474-y]
76 **Zelt JG**, Hankinson PB, Foster WS, Williams CB, Reynolds J, Garneys E, Tschakovsky ME, Gurd BJ. Reducing the volume of sprint interval training does not diminish maximal and submaximal performance gains in healthy men. *Eur J Appl Physiol* 2014; **114**: 2427-2436 [PMID: 25091854 DOI: 10.1007/s00421-014-2960-4]
77 **Vollaard NBJ**, Metcalfe RS, Williams S. Effect of Number of Sprints in an SIT Session on Change in V˙O2max: A Meta-analysis. *Med Sci Sports Exerc* 2017; **49**: 1147-1156 [PMID: 28079707 DOI: 10.1249/MSS.0000000000001204]
78 **Ruffino JS**, Songsorn P, Haggett M, Edmonds D, Robinson AM, Thompson D, Vollaard NB. A comparison of the health benefits of reduced-exertion high-intensity interval training (REHIT) and moderate-intensity walking in type 2 diabetes patients. *Appl Physiol Nutr Metab* 2017; **42**: 202-208 [PMID: 28121184 DOI: 10.1139/apnm-2016-0497]
79 **Tjønna AE**, Stølen TO, Bye A, Volden M, Slørdahl SA, Odegård R, Skogvoll E, Wisløff U. Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents. *Clin Sci (Lond)* 2009; **116**: 317-326 [PMID: 18673303 DOI: 10.1042/CS20080249]
80 **Levinger I**, Shaw CS, Stepto NK, Cassar S, McAinch AJ, Cheetham C, Maiorana AJ. What Doesn't Kill You Makes You Fitter: A Systematic Review of High-Intensity Interval Exercise for Patients with Cardiovascular and Metabolic Diseases. *Clin Med Insights Cardiol* 2015; **9**: 53-63 [PMID: 26157337 DOI: 10.4137/CMC.S26230]
81 **Rognmo Ø**. Moholdt T, Bakken H, Hole T, Mølstad P, Myhr NE, Grimsmo J, Wisløff U. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation* 2012; **126**: 1436-1440 [PMID: 22879367 DOI: 10.1161/CIRCULATIONAHA.112.123117]
82 **Peacock OJ**, Western MJ, Batterham AM, Stathi A, Standage M, Tapp A, Bennett P, Thompson D. Multidimensional individualised Physical ACTivity (Mi-PACT)--a technology-enabled intervention to promote physical activity in primary care: study protocol for a randomised controlled trial. *Trials* 2015; **16**: 381 [PMID: 26314577 DOI: 10.1186/s13063-015-0892-x]
83 **Nes BM**, Gutvik CR, Lavie CJ, Nauman J, Wisløff U. Personalized Activity Intelligence (PAI) for Prevention of Cardiovascular Disease and Promotion of Physical Activity. *Am J Med* 2017; **130**: 328-336 [PMID: 27984009 DOI: 10.1016/j.amjmed.2016.09.031]
84 **Nes BM**, Janszky I, Aspenes ST, Bertheussen GF, Vatten LJ, Wisløff U. Exercise patterns and peak oxygen uptake in a healthy population: the HUNT study. *Med Sci Sports Exerc* 2012; **44**: 1881-1889 [PMID: 22525768 DOI: 10.1249/MSS.0b013e318258b443]
85 **Wisløff U**, Nilsen TI, Drøyvold WB, Mørkved S, Slørdahl SA, Vatten LJ. A single weekly bout of exercise may reduce cardiovascular mortality: how little pain for cardiac gain? 'The HUNT study, Norway'. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 798-804 [PMID: 17001221 DOI: 10.1097/01.hjr.0000216548.84560.ac]
86 **Zisko N**, Skjerve KN, Tari AR, Sandbakk SB, Wisløff U, Nes BM, Nauman J. Personal Activity Intelligence (PAI), Sedentary Behavior and Cardiovascular Risk Factor Clustering - the HUNT Study. *Prog Cardiovasc Dis* 2017; **60**: 89-95 [PMID: 28274818 DOI: 10.1016/j.pcad.2017.02.007]
87 **Terada S**, Kawanaka K, Goto M, Shimokawa T, Tabata I. Effects of high-intensity intermittent swimming on PGC-1alpha protein expression in rat skeletal muscle. *Acta Physiol Scand* 2005; **184**: 59-65 [PMID: 15847644 DOI: 10.1111/j.1365-201X.2005.01423.x]
88 **Terada S**, Tabata I. Effects of acute bouts of running and swimming exercise on PGC-1alpha protein expression in rat epitrochlearis and soleus muscle. *Am J Physiol Endocrinol Metab* 2004; **286**: E208-E216 [PMID: 14570700 DOI: 10.1152/ajpendo.00051.2003]
89 **Hanssen H**, Nussbaumer M, Moor C, Cordes M, Schindler C, Schmidt-Trucksäss A. Acute effects of interval versus continuous endurance training on pulse wave reflection in healthy young men. *Atherosclerosis* 2015; **238**: 399-406 [PMID: 25558034 DOI: 10.1016/j.atherosclerosis.2014.12.038]
90 **Vollaard NBJ**, Metcalfe RS. Research into the Health Benefits of Sprint Interval Training Should Focus on Protocols with Fewer and Shorter Sprints. *Sports Med* 2017; **47**: 2443-2451 [PMID: 28391489 DOI: 10.1007/s40279-017-0727-x]
91 **Philp A**, Hargreaves M, Baar K. More than a store: regulatory roles for glycogen in skeletal muscle adaptation to exercise. *Am J Physiol Endocrinol Metab* 2012; **302**: E1343-E1351 [PMID: 22395109 DOI: 10.1152/ajpendo.00004.2012]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 July 26; 11(7): 189-194

DOI: 10.4330/wjc.v11.i7.189

ISSN 1949-8462 (online)

CASE REPORT

Use of rotablation to rescue a "fractured" micro catheter tip: A case report

Mohammad Alkhalil, Conor McQuillan, Michael Moore, Mark S. Spence, Colum Owens

ORCID number: Mohammad Alkhalil (0000-0002-3088-8878); Conor McQuillan (0000-0001-7217-362X); Colum G. Owens (0000-0002-5386-2208).

Author contributions: Alkhalil M conceptualised, collected and analysed data, drafted the manuscript; McQuillan C collected and analysed data, reviewed the manuscript; Moore M provided resources, reviewed and edited the manuscript; Spence M supervised, reviewed and edited the manuscript; Owens C supervised, reviewed and edited the manuscript.

Informed consent statement: The patient has provided consent for publication.

Conflict-of-interest statement: None.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See:

Mohammad Alkhalil, Conor McQuillan, Mark S. Spence, Colum Owens, Cardiology Department, Royal Victoria Hospital, Belfast BT12 6BA, United Kingdom

Michael Moore, Cardiology Department, Craigavon Area Hospital, Portadown BT63 5QQ, United Kingdom

Corresponding author: Mohammad Alkhalil, DPhil, MRCP, Doctor, Cardiology Department, Royal Victoria Hospital, 274 Grosvenor Road, Belfast BT12 6BA, United Kingdom.
mak-83@hotmail.com
Telephone: +44-2890-240503

Abstract

BACKGROUND

High-speed rotational atherectomy (HSRA) is most commonly used to modify calcified coronary artery lesions to facilitate stent deployment and expansion. The use of HSRA as an emergency rescue technique to release a fractured micro-catheter has not been described. We report the use of HSRA in a case of a fracture trapped corsair tip that was impeding coronary flow causing a ST elevation myocardial infarct.

CASE SUMMARY

A 79 years old male was scheduled for elective percutaneous coronary intervention (PCI) to his left anterior descending artery (LAD). Given its calcific nature, a decision was made for upfront rotablation. During procedural preparations, the tip of an employed micro-catheter was separated from the shaft resulting in obstructing coronary flow and ST-segment elevation. The consensus was for an attempt bail out PCI strategy. A rotafloppy wire was advanced to the distal LAD using a corsair micro-catheter which was placed proximal to the occlusion site. Modification of the mid LAD segment was performed, resulting in mobilising the corsair tip, and deflecting it to a small diagonal branch. Following serial predilation, the procedure was completed using two overlapping drug eluting stents, jailing the corsair tip in the diagonal branch. The patient made uneventful recovery and was clinically stable at one year follow up.

CONCLUSION

HSRA may be offered as a bailed-out strategy to rescue fractured and jailed micro-catheter tip in high risk surgical cases.

Key words: Micro-catheter; Rotational atherectomy; Calcification; Case report

http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: January 30, 2019
Peer-review started: January 31, 2019
First decision: April 15, 2019
Revised: April 22, 2019
Accepted: June 20, 2019
Article in press: June 21, 2019
Published online: July 26, 2019

P-Reviewer: Altarabsheh SE, Kharlamov AN, Pastromas S, Ueda H
S-Editor: Ji FF
L-Editor: A
E-Editor: Xing YX

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Fractured micro-catheter tip impeding flow has not been previously described. With aging population and increasing calcification, this phenomenon is likely to face interventional cardiologists in the future. Non-surgical bailed-out strategy to rescue the trapped tip is described in the current case.

Citation: Alkhalil M, McQuillan C, Moore M, Spence MS, Owens C. Use of rotablation to rescue a "fractured" micro catheter tip: A case report. *World J Cardiol* 2019; 11(7): 189-194
URL: https://www.wjgnet.com/1949-8462/full/v11/i7/189.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i7.189

INTRODUCTION

Calcification remains a challenging feature of coronary atherosclerosis. The ageing population coupled with increased co-morbidities, such as renal failure and diabetes, make coronary calcification more commonly seen in daily practice[1]. In calcific lesions, high-speed rotational atherectomy (HSRA) is often necessary for lesion modification to permit optimal stent deployment and expansion[1]. HSRA has been demonstrated to be more successful than modified balloon (scoring or cutting balloon) prior to drug eluting stent implantation in severely calcified lesions[2]. The use of micro-catheter exchange to allow distal passage of the rota wire to facilitate HSRA is well described and is a useful technique in complex anatomy[1].

Here we report a complication of rotablation where the micro-catheter tip (Corasir, Asahi) was fractured and jailed in complex anatomy resulting in ST elevation myocardial infarction (STEMI) and the use of rescue HSRA to address this unique problem.

CASE PRESENTATION

Chief complaints

A 79 years old male was electively admitted for complex percutaneous coronary intervention (PCI) to left anterior descending artery (LAD) in a district general hospital without cardiac surgical support.

History of present illness

He initially presented with a lateral STEMI whereby successful primary PCI was performed to his left circumflex artery.

History of past illness

His medical history was significant for chronic obstructive pulmonary disease, hypertension and chronic kidney disease (stage III).

Physical examination upon admission

Cardiovascular examination was unremarkable.

Imaging examination

The LAD had calcific diffuse disease extending beyond the mid segment of the LAD with severe ostial disease in a diseased small calibre diagonal branch (Figure 1). Given the calcific nature of the LAD, a decision was made for upfront rotablation. A Sion blue wire (Asahi) was placed in the distal LAD to facilitate micro-catheter exchange for a rotafloppy wire (RotaLink, Boston Scientific). Despite combination of rotation and forward tension, the corsair was unsuccessful in traversing the mid LAD. Upon attempted retraction of the Corsair (Asahi) micro-catheter, it was evident that the tip of the Corsair was separated from the shaft and was trapped in the LAD (Figure 2A) resulting in obstruction of coronary flow and ST-segment elevation (Figure 2B). In an attempt to establish flow, a 1.5 mm MINI TREK (Abbott Vascular) was advanced over a second angioplasty wire beside the trapped corsair tip but would not advance past the fractured corsair tip despite Guidezilla (Boston Scientific) support. A wire-wrap technique was unsuccessfully used to try and retrieve the fractured tip but this resulted in loss of wire position. An intra-aortic balloon pump was inserted via the

right femoral artery to stabilise the patient for transfer to our tertiary centre for rescue coronary artery bypass graft (CABG).

FINAL DIAGNOSIS

STEMI secondary to fractured and trapped micro-catheter tip.

TREATMENT

On arrival, CABG was deemed high risk due his STEMI presentation and comorbidities. The consensus from the heart team was made for bail out PCI. Right radial access was used and a 7 French VL 3.5 guide catheter was chosen for support. Repeat imaging confirmed a heavily calcified LAD with a fractured corsair tip impeding coronary flow. A Sion blue wire was advanced beyond the occlusion site and a Corsair micro-catheter was advanced proximal to the occlusion site. A rotafloppy wire was exchanged and advanced to the distal LAD (Supplementary video 1). A 1.25 mm then 1.5 mm rota burr were used to modify the LAD past the corsair tip to free the trapped segment (Figure 3A) (Supplementary video 2). This has resulted in mobilising the corsair tip, deflecting to the small diagonal branch during the forward movement of the rota burr and restoration of flow in the LAD (Figure 3B) (Supplementary video 3). The LAD was pre-dilated with a 2.5 mm × 30 mm non-compliant balloon and stented distally to proximally with two overlapping Synergy drug eluting stents (3.0 mm × 38 mm and 3.5 mm × 38 mm) (Boston Scientific) back to the ostium of the LAD thus jailing the corsair tip in the diagonal branch (Figure 4). This did not result in any significant hemodynamic or ECG compromise with resolution of ST elevation.

OUTCOME AND FOLLOW-UP

The patient made uneventful recovery without need for rescue CABG and was clinically stable at one year follow up.

DISCUSSION

The presence of severe coronary calcification is a well-established predictor of procedural success and worse clinical outcomes[3]. This remained unchanged despite improvements in contemporary PCI, including the advent of drug eluting stents[4]. In patient-level pooled analysis from seven contemporary trials, coronary calcification was associated with 33% increase in mortality rate irrespective of the Syntax score[4]. While this could be attributed to the residual and untreated coronary artery disease, coronary calcification is also considered as marker of more advanced and atherosclerotic disease making those patients at higher risk prior to any coronary intervention[5,6]. Regardless of the mechanism, heavily calcified segments may render coronary stenoses undilatable with conventional balloon angioplasty thus compromising optimal stent deployment. Optimal lesion preparation by differential cutting using HSRA has been reported more than 3 decades ago and debulking coronary atheroma with HSRA ensures less resistant plaque surface allowing balloon and subsequently stent crossing[2,6]. The use of HSRA is not without complications and includes slow flow, coronary dissection or perforation, burr lodging within the stenotic segment and thermal injury from heating to the adjacent tissue[1,7]. Here we describe, an unreported complication associated with wire exchange to facilitate HSRA. The micro-catheter was used in this case to facilitate rotafloppy wire exchange and although a useful and often necessary technique, over torqueing the micro-catheter coupled with heavy coronary calcification can result in micro-catheter tip "fracture" as in this case.

Broken and retained interventional instruments continue to be reported and may be attributed to the increasing complexity of percutaneous interventional procedures[8]. The combination of tortuosity and calcification of coronary arteries pose difficulties in navigating and delivering devices across lesions. In our case, the coronary anatomy, in addition to micro-catheter over torqueing have led the tip to "snap" and to separate from the main shaft obstructing flow. Extensive literature exist reporting fractured and retained wires that go back to the early days of coronary angioplasty[9,10]. Similarly stent loss has also been reported in a large scale study of more than 11000 PCI procedures with an incidence of < 0.5%[11]. Overall, the incidence

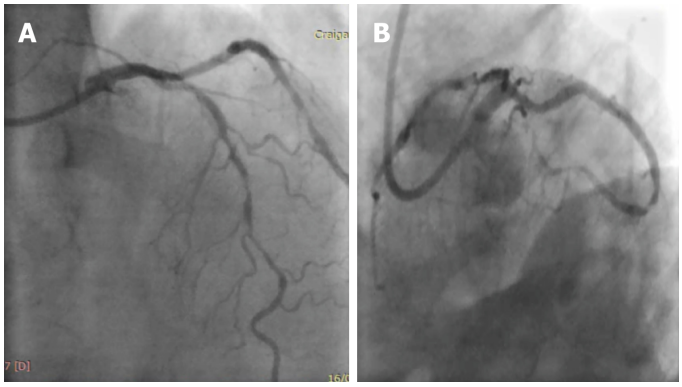


Figure 1 Left coronary angiography demonstrating heavily calcified left anterior descending artery. A: Cranial projection; B: Caudal projection. Excellent results from previous percutaneous coronary intervention to LCx.

of retained angioplasty tools did not change over time despite undergoing extensive refinements and this could be attributed to the increased complexity of PCI procedures in current daily practices. More recently, other angioplasty devices such as fragments of balloons or thrombectomy catheter have been reported to be trapped within the coronary artery[8,12]. To the best of our knowledge, this is the first report of fractured corsair catheter impeding flow and leading to STEMI. While any broken fragment could serve as a nidus for thrombus formation, vessel occlusion in our case was more related to the actual presence of the micro-catheter tip blocking the flow in a heavily calcified artery. In order to establish flow, an attempt to deliver a small balloon beyond the occlusion site was made. However, the balloon was deemed impassable and, therefore, precluded any attempt to use balloon-assisted retrieval technique to recover the retained corsair tip.

Numerous techniques have been previously reported to facilitate retrieval of entrapped coronary equipment and interventional cardiologists should familiarise themselves with different retrieval techniques[13]. In this case, use of HSRA permitted lesion modification and mobilisation of the fractured trapped corsair tip to the diagonal side branch were it was subsequently jailed by LAD stenting. Importantly, there was a risk of thermal injury to the hydrophilic tip while using HSRA. In order to prevent any excessive rise in temperature, the speed of the rotablator was set up at 180000 rpm with focus attention not to drop more than 5000-7000 rpm and a total duration of less than 20 s for each rotablation run[1,7].

We elected not to retrieve the deflected corsair tip in the diagonal branch given its relative small size with a potential risk of jeopardising the LAD. While this could be considered as a limitation, losing a side branch is not infrequent during coronary bifurcation stenting. Decision to rescue the side branch depends on numerous factors, including the size of myocardium at jeopardy[14]. The benign long term outcome of the patient supports our pragmatic decision in approaching this case.

CONCLUSION

Use of HSRA in an emergency bail out setting for a fractured and jailed corsair tip re-established coronary flow and permitted rescue of an otherwise high risk surgical bail out.

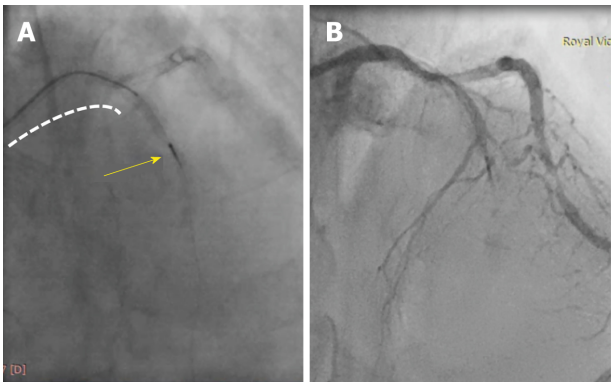


Figure 2 Fractured micro-catheter tip. A: The yellow arrow points at the trapped corsair tip in mid left anterior descending artery (LAD) with the remaining micro-catheter in the proximal LAD segment (dotted white line); B: No flow in the LAD as a result of the jailed tip.

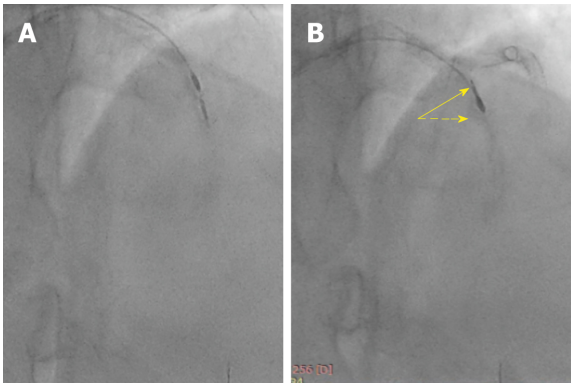


Figure 3 Rotational atherectomy was performed to modify calcification adjacent to the trapped tip. A: Calcium modifications using rota burr; B: Corsair tip was freed up and directed towards small diagonal branch.

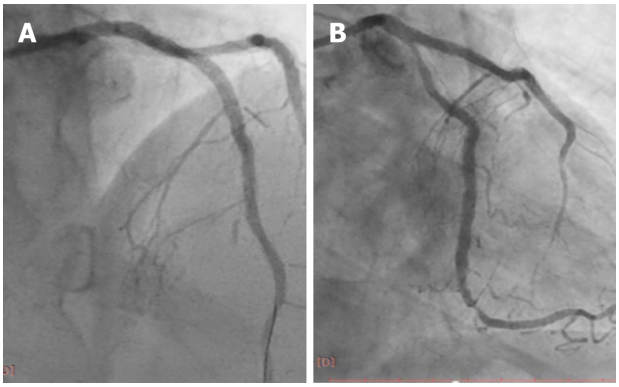


Figure 4 Final angiographic results. A: Good flow in the left anterior descending artery with occluded diagonal branch by the corsair tip in the cranial projection; B: Caudal projection demonstrating final angiographic results.

REFERENCES

1 **Barbato E**, Carrié D, Dardas P, Fajadet J, Gaul G, Haude M, Khashaba A, Koch K, Meyer-Gessner M, Palazuelos J, Reczuch K, Ribichini FL, Sharma S, Sipötz J, Sjögren I, Suetsch G, Szabó G, Valdés-Chávarri M, Vaquerizo B, Wijns W, Windecker S, de Belder A, Valgimigli M, Byrne RA, Colombo A, Di Mario C, Latib A, Hamm C; European Association of Percutaneous Cardiovascular Interventions. European expert consensus on rotational atherectomy. *EuroIntervention* 2015; **11**: 30-36 [PMID: 25982648 DOI: 10.4244/EIJV11I1A6]

2 **Abdel-Wahab M**, Toelg R, Byrne RA, Geist V, El-Mawardy M, Allali A, Rheude T, Robinson DR, Abdelghani M, Sulimov DS, Kastrati A, Richardt G. High-Speed Rotational Atherectomy Versus Modified Balloons Prior to Drug-Eluting Stent Implantation in Severely Calcified Coronary Lesions. *Circ Cardiovasc Interv* 2018; **11**: e007415 [PMID: 30354632 DOI:

10.1161/CIRCINTERVENTIONS.118.007415]
3 **Savage MP**, Goldberg S, Hirshfeld JW, Bass TA, MacDonald RG, Margolis JR, Taussig AS, Vetrovec G, Whitworth HB, Zalewski A. Clinical and angiographic determinants of primary coronary angioplasty success. M-HEART Investigators. *J Am Coll Cardiol* 1991; **17**: 22-28 [PMID: 1987229 DOI: 10.1016/0735-1097(91)90700-j]
4 **Bourantas CV**, Zhang YJ, Garg S, Iqbal J, Valgimigli M, Windecker S, Mohr FW, Silber S, Vries Td, Onuma Y, Garcia-Garcia HM, Morel MA, Serruys PW. Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials. *Heart* 2014; **100**: 1158-1164 [PMID: 24846971 DOI: 10.1136/heartjnl-2013-305180]
5 **Sotomi Y**, Shlofmitz RA, Colombo A, Serruys PW, Onuma Y. Patient Selection and Procedural Considerations for Coronary Orbital Atherectomy System. *Interv Cardiol* 2016; **11**: 33-38 [PMID: 29588702 DOI: 10.15420/icr.2015:19:2]
6 **Valdes PJ**, Diaz MA. *Rotational Atherectomy. StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2019; [PMID: 29763091]
7 **Reisman M**, Shuman BJ, Harms V. Analysis of heat generation during rotational atherectomy using different operational techniques. *Cathet Cardiovasc Diagn* 1998; **44**: 453-455 [PMID: 9716217 DOI: 10.1002/(SICI)1097-0304(199808)44:43.0.CO;2-I]
8 **Mehta V**, Pandit BN, Trehan V. Retrieval of Broken Export Catheter during Primary Angioplasty. *Int J Angiol* 2013; **22**: 185-188 [PMID: 24436609 DOI: 10.1055/s-0033-1347897]
9 **Iturbe JM**, Abdel-Karim AR, Papayannis A, Mahmood A, Rangan BV, Banerjee S, Brilakis ES. Frequency, treatment, and consequences of device loss and entrapment in contemporary percutaneous coronary interventions. *J Invasive Cardiol* 2012; **24**: 215-221 [PMID: 22562915]
10 **Hartzler GO**, Rutherford BD, McConahay DR. Retained percutaneous transluminal coronary angioplasty equipment components and their management. *Am J Cardiol* 1987; **60**: 1260-1264 [PMID: 2961239]
11 **Brilakis ES**, Best PJ, Elesber AA, Barsness GW, Lennon RJ, Holmes DR, Rihal CS, Garratt KN. Incidence, retrieval methods, and outcomes of stent loss during percutaneous coronary intervention: a large single-center experience. *Catheter Cardiovasc Interv* 2005; **66**: 333-340 [PMID: 16142808 DOI: 10.1002/ccd.20449]
12 **Kunwar BK**, Jain P, Ghogare M. Catheter-Assisted Balloon-Supported Retrieval of a Broken Semi-Compliant Balloon from a Coronary Artery. *J Clin Diagn Res* 2017; **11**: OD06-OD07 [PMID: 28511441 DOI: 10.7860/JCDR/2017/24775.9580]
13 **Paulus BM**, Fischell TA. Retrieval devices and techniques for the extraction of intravascular foreign bodies in the coronary arteries. *J Interv Cardiol* 2010; **23**: 271-276 [PMID: 20636848 DOI: 10.1111/j.1540-8183.2010.00560.x]
14 **Lassen JF**, Burzotta F, Banning AP, Lefèvre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y, Stankovic G. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. *EuroIntervention* 2018; **13**: 1540-1553 [PMID: 29061550 DOI: 10.4244/EIJ-D-17-00622]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 August 26; 11(8): 195-212

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 8 August 26, 2019

Contents

World Journal of Cardiology

Volume 11 Number 8 August 26, 2019

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
August 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 August 26; 11(8): 195-199

DOI: 10.4330/wjc.v11.i8.195

ISSN 1949-8462 (online)

EDITORIAL

Cardiovascular magnetic resonance: Stressing the future

Ioannis Merinopoulos, Tharusha Gunawardena, Simon C Eccleshall, Vassilios S Vassiliou

ORCID number: Ioannis Merinopoulos (0000-0002-2059-0357); Tharusha Guanwardena (0000-0003-4456-2649); Simon C Eccleshall (0000-0002-6395-2389); Vassilios S Vassiliou (0000-0002-4005-7752).

Author contributions: Merinopoulos I and Vassiliou VS conceived the plan for this editorial; Merinopoulos I drafted the manuscript; Gunawardena T, Eccleshall SC and Vassiliou VS critically revised and approved the manuscript.

Conflict-of-interest statement: All authors have no conflict of interest related to the manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: March 14, 2019
Peer-review started: March 15, 2019
First decision: June 6, 2019
Revised: July 8, 2019
Accepted: July 30, 2019
Article in press: July 30,2019
Published online: August 26, 2019

Ioannis Merinopoulos, Tharusha Gunawardena, Vassilios S Vassiliou, Norwich Medical School, University of East Anglia, Norfolk and Norwich University Hospital, Norwich NR4 7UY, United Kingdom

Ioannis Merinopoulos, Tharusha Gunawardena, Simon C Eccleshall, Vassilios S Vassiliou, Department of Cardiology, Norfolk and Norwich University Hospital, Norwich NR4 7UQ, United Kingdom

Corresponding author: Vassilios S Vassiliou, Norwich Medical School, University of East Anglia, Norfolk and Norwich University Hospital, Floor 2, Bob Champion Research and Education Building, James Watson Road, Norwich Research Park, Norwich NR4 7UQ, United Kingdom. v.vassiliou@uea.ac.uk
Telephone: +44-160-3592534
Fax: +44-160-3592534

Abstract

Non-invasive cardiac stress imaging plays a central role in the assessment of patients with known or suspected coronary artery disease. The current guidelines suggest estimation of the myocardial ischaemic burden as a criterion for revascularisation on prognostic grounds despite the lack of standardised reporting of the magnitude of ischaemia on various non-invasive imaging methods. Future studies should aim to accurately describe the relationship between myocardial ischaemic burden as assessed by cardiovascular magnetic resonance imaging and mortality.

Key words: Coronary artery disease; Myocardial ischaemic burden; Non-invasive imaging; Cardiac stress; Magnetic resonance imaging

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Further studies should aim to accurately describe the relationship between myocardial ischaemic burden as assessed by stress cardiovascular magnetic resonance and mortality.

Citation: Merinopoulos I, Gunawardena T, Eccleshall SC, Vassiliou VS. Cardiovascular magnetic resonance: Stressing the future. *World J Cardiol* 2019; 11(8): 195-199
URL: https://www.wjgnet.com/1949-8462/full/v11/i8/195.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i8.195

P-Reviewer: Gao BL, Versaci F
S-Editor: Ma YJ
L-Editor: A
E-Editor: Zhou BX

INTRODUCTION

Non-invasive cardiac stress imaging plays a central role in guiding the treatment of patients with known or suspected coronary artery disease (CAD). Stress testing techniques performed include stress echocardiography, single photon emission computed tomography (SPECT) myocardial perfusion imaging and more recently cardiovascular magnetic resonance imaging (CMR). All functional tests support diagnosis, risk stratification and subsequent management decisions[1] and thus allow myocardial ischaemia to play a crucial role in the management of patients with CAD[2]. As the availability and use of CMR increases, it is increasingly emerging as the gold standard method of safe, radiation-free perfusion imaging providing functional assessment and tissue characterisation.

In this editorial, we focus on a recent article by Heitner *et al*[3] published in JAMA Cardiology as we feel it is an important study adding credence to the growing role of pharmacological stress CMR in the assessment of patients with known or suspected CAD . We will also provide our perspective for the future direction of stress CMR.

STUDY ANALYSIS

Heitner *et al*[3] provided real-world data for 9151 patients referred for evaluation of myocardial ischaemia with stress CMR across 7 participating centres followed for a total of 48000 patient-years. Their analysis demonstrated a strong association of abnormal CMR results with all-cause mortality over long-term follow-up up to 10 years with a hazard ratio of 1.8 between the patients who had abnormal scans and those that did not. This hazard ratio remained significant in all 8 patient subpopulations (presence/absence of history of CAD, normal/abnormal left ventricular ejection fraction (LVEF), presence/absence of typical chest pain, presence/absence of Late Gadolinium Enhancement). The multivariate analysis also showed that addition of stress CMR in two different models significantly increased the χ^2 from 581.8 to 687.4 ($P < 0.001$) and from 620.7 to 721.1 ($P < 0.001$) respectively, indicating that the addition of stress CMR in the model significantly predicts mortality over and above the other variables (including age, sex, diabetes, hypertension, hyperlipidaemia, smoking status, history of CAD or Myocardial Infarction, body mass index, family history of CAD and LVEF).

Whilst this was not a randomised control trial, it crucially provides real-world data and demonstrated for the first time that stress CMR is significantly associated with mortality. The major strengths of the study lie in the large number of patients included and the high number of outcomes over long-term follow up. It is important to consider however, that there were certain limitations. The cause of death is not known in the study and future studies will have to investigate if stress CMR is able to predict specific cardiovascular events rather than all-cause mortality. Nevertheless, as discussed by the authors, all-cause mortality is an objective, unbiased and clinically relevant hard end point. The authors also acknowledged that they had not been able to determine if patients were revascularised after the stress CMR. They reasonably anticipated that revascularisation would occur more commonly in patients with abnormal stress CMR and that revascularisation would improve prognosis and not increase mortality. Another important limitation is that the study CMRs did not assess the extent of ischaemic burden but instead categorised ischaemia into "negative" or "positive" even if just one segment showed abnormal perfusion. Although full quantified perfusion[4] is not yet part of routine practice, visual semi-quantitative methods have been described[5] and might have further improved the association with mortality. Furthermore, information about patient revascularisation in combination with myocardial ischaemic burden (MIB) might had allowed estimation of a threshold for MIB, similarly to the way it was estimated in the SPECT studies originally [6], providing valuable information regarding the threshold of ischaemic burden as assessed with stress CMR .

Hachamovitch *et al*[6] for the first time in 2003 successfully estimated the 10% MIB threshold with SPECT above which revascularisation offers a survival benefit over medical therapy, using propensity match scoring of observational data. In 2011, the same group used SPECT to demonstrate in a slightly larger observational series that patients with significant ischaemia but without extensive scar were likely to benefit from revascularisation in contrast to patients with minimal ischaemia[7]. The 10% threshold for myocardial ischaemia based on SPECT has correlated with perfusion defect in 2/16 segments on CMR[8] and has been incorporated in the ESC 2018 guidelines as a criterion for revascularisation on prognostic grounds and in the ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 guidelines as a high-risk

indicator[1,9]. Despite the significance of ischaemia in decision making, there is a lack of standardized reporting of the magnitude of ischaemia on non-invasive testing, which contributes to the variability in translating the severity of ischaemia across stress imaging modalities[8]. Given the high diagnostic and prognostic yield of pharmacological stress CMR with regards to CAD, it will be valuable for future studies to attempt to delineate the relationship between MIB and prognosis. Nonetheless, Heitner *et al*[3] should be highly commended for contributing to the medical literature; a very well undertaken and described study including a significant number of patients and an extended follow up, supporting the prognostically beneficial use of CMR perfusion in the routine evaluation of patients with suspected coronary artery disease.

FUTURE DIRECTIONS

Over the last few years, adenosine stress CMR has been established as a highly accurate non-invasive and radiation-free method for the diagnosis and prognosis of CAD. The initial CE-MARC study demonstrated that stress CMR was superior to SPECT regarding the diagnostic accuracy for CAD[10]. It has also been shown that compared with stress echocardiography, stress CMR was the strongest independent predictor of significant CAD among patients with intermediate probability of CAD presenting to emergency department[11]. The 5-year follow up data from CE-MARC study demonstrated that stress CMR was the only significant predictor of MACE in addition to major cardiovascular risk factors, angiographic findings or the effect of initial treatment[12]. Even though stress CMR is not universally, easily available currently, the increasing number of studies demonstrating its cost effectiveness over other non-invasive imaging modalities indicate that it will become more widely available in the near future[13-15]. In addition to accurate assessment of ischaemia, stress CMR offers accurate localisation of ischaemic segments and the extent of myocardial scar, which have prognostic implications[16]. It has been shown that ischaemia in ≥ 1.5 myocardial segments (in a 16 segment model) is significantly associated with poor prognosis as is the presence of myocardial scar, albeit to a lesser degree[17]. Two potential drawbacks of stress CMR perfusion include the visual assessment of perfusion defects as well as the incomplete myocardial coverage. The continuous development of quantified myocardial perfusion reserve aims to reduce the inherent interpreter-bias of visual assessment and to increase the diagnostic ability in the presence of triple-vessel disease. Comparison of quantitative myocardial perfusion reserve with qualitative assessment of stress CMR has demonstrated that quantitative assessment differentiates significantly better the MIB particularly in the context of triple-vessel disease[18]. More recently, it was also shown that quantitative assessment of MIB was superior to visual assessment with respect to prognosis[4]. The ongoing development of whole-heart perfusion aims to address the limited, non-contiguous coverage of 2D stress CMR and ultimately provide a non-invasive, non-ionizing radiation method for accurate measurement of MIB. It has been demonstrated that whole-heart perfusion CMR has high diagnostic accuracy for the detection of significant CAD as defined by Fractional Flow Reserve, while estimation of MIB by whole-heart perfusion has very good correlation with SPECT[19,20]. Comparison of whole-heart perfusion with high-resolution 2D perfusion has shown that there is strong correlation between the two techniques for the estimation of MIB however, there is still uncertainty around the clinically relevant threshold of 10%[21].

In summary, non-invasive accurate assessment of myocardial ischaemic burden is a clinical necessity with significant implications for prognosis and clinical decision making. In the near future, further development of stress CMR perfusion techniques may reveal that quantified, whole-heart perfusion is the most accurate non-invasive method for the diagnosis and prognosis of CAD.

CONCLUSION

Heitner *et al*[3] showed for the first time that stress CMR is significantly associated with worse mortality in a large study of real-world data. This is an important study that confirms the prognostic significance of stress CMR in terms of mortality in the real world. The study is a valuable addition to the growing volume of data that supports the central role of CMR in the diagnosis and stratification of CAD in routine clinical practice. However, as information about MIB as assessed by stress CMR was not available, future studies could aim to describe accurately the relationship between MIB, revascularisation and mortality.

REFERENCES

1 **Neumann FJ**, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2018; 1-96 [PMID: 30165632 DOI: 10.1093/eurheartj/ehy394]

2 **Iwasaki K**. Myocardial ischemia is a key factor in the management of stable coronary artery disease. *World J Cardiol* 2014; **6**: 130-139 [PMID: 24772253 DOI: 10.4330/wjc.v6.i4.130]

3 **Heitner JF**, Kim RJ, Kim HW, Klem I, Shah DJ, Debs D, Farzaneh-Far A, Polsani V, Kim J, Weinsaft J, Shenoy C, Hughes A, Cargile P, Ho J, Bonow RO, Jenista E, Parker M, Judd RM. Prognostic Value of Vasodilator Stress Cardiac Magnetic Resonance Imaging: A Multicenter Study With 48 000 Patient-Years of Follow-up. *JAMA Cardiol* 2019; [Epub ahead of print] [PMID: 30735566 DOI: 10.1001/jamacardio.2019.0035]

4 **Sammut EC**, Villa ADM, Di Giovine G, Dancy L, Bosio F, Gibbs T, Jeyabraba S, Schwenke S, Williams SE, Marber M, Alfakih K, Ismail TF, Razavi R, Chiribiri A. Prognostic Value of Quantitative Stress Perfusion Cardiac Magnetic Resonance. *JACC Cardiovasc Imaging* 2018; **11**: 686-694 [PMID: 29153572 DOI: 10.1016/j.jcmg.2017.07.022]

5 **Gómez-Revelles S**, Rossello X, Díaz-Villanueva J, López-Lima I, Sciarresi E, Estofán M, Carreras F, Pujadas S, Pons-Lladó G. Prognostic value of a new semiquantitative score system for adenosine stress myocardial perfusion by CMR. *Eur Radiol* 2019; **29**: 2263-2271 [PMID: 30406310 DOI: 10.1007/s00330-018-5774-7]

6 **Hachamovitch R**, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107**: 2900-2907 [PMID: 12771008 DOI: 10.1161/01.CIR.0000072790.23090.41]

7 **Hachamovitch R**, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; **32**: 1012-1024 [PMID: 21258084 DOI: 10.1093/eurheartj/ehq500]

8 **Shaw LJ**, Berman DS, Picard MH, Friedrich MG, Kwong RY, Stone GW, Senior R, Min JK, Hachamovitch R, Scherrer-Crosbie M, Mieres JH, Marwick TH, Phillips LM, Chaudhry FA, Pellikka PA, Slomka P, Arai AE, Iskandrian AE, Bateman TM, Heller GV, Miller TD, Nagel E, Goyal A, Borges-Neto S, Boden WE, Reynolds HR, Hochman JS, Maron DJ, Douglas PS; National Institutes of Health/National Heart, Lung, and Blood Institute-Sponsored ISCHEMIA Trial Investigators. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. *JACC Cardiovasc Imaging* 2014; **7**: 593-604 [PMID: 24925328 DOI: 10.1016/j.jcmg.2013.10.021]

9 **Patel MR**, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, Smith PK. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017; **69**: 2212-2241 [PMID: 28291663 DOI: 10.1016/j.jacc.2017.02.001]

10 **Greenwood JP**, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, Bijsterveld P, Ridgway JP, Radjenovic A, Dickinson CJ, Ball SG, Plein S. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012; **379**: 453-460 [PMID: 22196944 DOI: 10.1016/S0140-6736(11)61335-4]

11 **Heitner JF**, Klem I, Rasheed D, Chandra A, Kim HW, Van Assche LM, Parker M, Judd RM, Jollis JG, Kim RJ. Stress cardiac MR imaging compared with stress echocardiography in the early evaluation of patients who present to the emergency department with intermediate-risk chest pain. *Radiology* 2014; **271**: 56-64 [PMID: 24475814 DOI: 10.1148/radiol.13130557]

12 **Greenwood JP**, Herzog BA, Brown JM, Everett CC, Nixon J, Bijsterveld P, Maredia N, Motwani M, Dickinson CJ, Ball SG, Plein S. Prognostic Value of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Suspected Coronary Heart Disease: Long-Term Follow-up of a Prospective, Diagnostic Accuracy Cohort Study. *Ann Intern Med* 2016; [Epub ahead of print] [PMID: 27158921 DOI: 10.7326/M15-1801]

13 **Pletscher M**, Walker S, Moschetti K, Pinget C, Wasserfallen JB, Greenwood JP, Schwitter J, Girardin FR. Cost-effectiveness of functional cardiac imaging in the diagnostic work-up of coronary heart disease. *Eur Heart J Qual Care Clin Outcomes* 2016; **2**: 201-207 [PMID: 29474611 DOI: 10.1093/ehjqcco/qcw008]

14 **Boldt J**, Leber AW, Bonaventura K, Sohns C, Stula M, Huppertz A, Haverkamp W, Dorenkamp M. Cost-effectiveness of cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary artery disease in Germany. *J Cardiovasc Magn Reson* 2013; **15**: 30 [PMID: 23574690 DOI: 10.1186/1532-429X-15-30]

15 **Francis S**, Cohen J, Olchanski N, Coelho-Filho OR, Heydari B, Shah R, Leavitt MB, Gewirtz H, Kwong R. Stress CMR myocardial perfusion imaging (CMR-MPI) is cost-effective compared to nuclear SPECT: a retrospective cost-effectiveness analysis. *J Cardiovasc Magn Reson* 2012; **14**: O3 [DOI: 10.1186/1532-429X-14-S1-O3]

16 **Catalano O**, Moro G, Perotti M, Frascaroli M, Ceresa M, Antonaci S, Baiardi P, Napolitano C, Baldi M, Priori SG. Late gadolinium enhancement by cardiovascular magnetic resonance is complementary to left ventricle ejection fraction in predicting prognosis of patients with stable coronary artery disease. *J Cardiovasc Magn Reson* 2012; **14**: 29 [PMID: 22607320 DOI: 10.1186/1532-429X-14-29]

17 **Vincenti G**, Masci PG, Monney P, Rutz T, Hugelshofer S, Gaxherri M, Muller O, Iglesias JF, Eeckhout E, Lorenzoni V, Pellaton C, Sierro C, Schwitter J. Stress Perfusion CMR in Patients With Known and Suspected CAD: Prognostic Value and Optimal Ischemic Threshold for Revascularization. *JACC Cardiovasc Imaging* 2017; **10**: 526-537 [PMID: 28412420 DOI: 10.1016/j.jcmg.2017.02.006]

18 **Patel AR**, Antkowiak PF, Nandalur KR, West AM, Salerno M, Arora V, Christopher J, Epstein FH, Kramer CM. Assessment of advanced coronary artery disease: advantages of quantitative cardiac magnetic resonance perfusion analysis. *J Am Coll Cardiol* 2010; **56**: 561-569 [PMID: 20688211 DOI: 10.1016/j.jacc.2010.02.061]

19 **Manka R**, Wissmann L, Gebker R, Jogiya R, Motwani M, Frick M, Reinartz S, Schnackenburg B, Niemann M, Gotschy A, Kuhl C, Nagel E, Fleck E, Marx N, Luescher TF, Plein S, Kozerke S. Multicenter evaluation of dynamic three-dimensional magnetic resonance myocardial perfusion imaging for the detection of coronary artery disease defined by fractional flow reserve. *Circ Cardiovasc Imaging* 2015; **8**: e003061 [PMID: 25901043 DOI: 10.1161/CIRCIMAGING.114.003061]

20 **Jogiya R**, Morton G, De Silva K, Reyes E, Hachamovitch R, Kozerke S, Nagel E, Underwood SR, Plein S. Ischemic burden by 3-dimensional myocardial perfusion cardiovascular magnetic resonance: comparison with myocardial perfusion scintigraphy. *Circ Cardiovasc Imaging* 2014; **7**: 647-654 [PMID: 24867884 DOI: 10.1161/CIRCIMAGING.113.001620]

21 **McDiarmid AK**, Ripley DP, Mohee K, Kozerke S, Greenwood JP, Plein S, Motwani M. Three-dimensional whole-heart vs. two-dimensional high-resolution perfusion-CMR: a pilot study comparing myocardial ischaemic burden. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 900-908 [PMID: 26450417 DOI: 10.1093/ehjci/jev231]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 August 26; 11(8): 200-208

DOI: 10.4330/wjc.v11.i8.200

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

One-year outcomes of a NeoHexa sirolimus-eluting coronary stent system with a biodegradable polymer in all-comers coronary artery disease patients: Results from NeoRegistry in India

Rajagopal Jambunathan, Dinesh Basavanna, Preeti Vani, Malte Neuss, Prashant Janbandhu

ORCID number: Rajagopal Jambunathan (0000-0001-7969-3564); Dinesh Basavanna (0000-0003-0361-5441); Preeti Vani (0000-0001-5665-1062); Malte Neuss (0000-0003-3046-4140); Prashant Jandandhu (0000-0001-5816-4006).

Author contributions: Jambunathan R, Basavanna D, Vani P, Neuss M and Janbandhu P were equally involved in designing the report, collecting and analysis of patient's clinical data, and preparing the manuscript.

Supported by the Sahajanand Laser Technology Ltd,India.

Institutional review board statement: This study was approved by the Ethics Committee of Mysore Medical College and Research Institute (EC REG: ECR/134/Inst/KA/2013/RR-16).

Informed consent statement: As per IEC, in case of prospective studies, there is a need to take informed consent from subjects. However, in our case (a retrospective trial) permission should be taken from the Head of Institution.

Conflict-of-interest statement: Mr. Prashant, Dr. Malte, and Ms. Preeti are employees of Sahajanand Laser Technology Ltd. India. All other authors have nothing to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external

Rajagopal Jambunathan, Dinesh Basavanna, Cauvery Heart and Multispecialty Hospital, Mysore, Karnataka 570011, India

Dinesh Basavanna, Department of Cardiology Mysore Medical College and Research Institute, Mysore, Karnataka 570001, India

Preeti Vani, Malte Neuss, Prashant Janbandhu, Medical Division, Sahajanand Laser Technology Ltd., Gandhinagar, Gujarat 382027, India

Malte Neuss, Manemed Research and Development, Roeckumstr, Bonn 53123, Germany

Corresponding author: Prashant Janbandhu, MSc, Medical Division, Sahajanand Laser Technology Ltd., Gandhinagar, Gujarat 382027, India. clinical@sltl.com
Telephone: +91-72-27039377
Fax: +91-79-23287470

Abstract

BACKGROUND

Biodegradable polymer drug-eluting stents (BP-DES) have shown to reduce restenosis rates and have low rates of stent thrombosis. The present postmarketing surveillance assessed 1-year clinical outcomes of patients who had received NeoHexa DES in real practice.

AIM

To investigate 1-year clinical outcomes of Neohexa DES in real practice.

METHODS

Data obtained from a single-center cohort of patients who had received NeoHexa stents as part of routine treatment of coronary artery disease (CAD) were retrospectively investigated. The primary study endpoint was the rate of major adverse cardiac events (MACEs) defined as the composite of death, myocardial infarction (MI), and target lesion revascularization (TLR) during the follow-up at 1 mo, 6 mo, and 1 year after the index procedure.

RESULTS

A total of 129 patients with 172 lesions were enrolled. The most common comorbid conditions were hypertension (49.61%) and diabetes mellitus (39.53%). Procedural success was achieved in all patients, and no in-hospital MACE was reported. The incidence of composite MACE at 30 d, 6 mo, and 1 year was 0.78%,

reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: April 4, 2019
Peer-review started: April 4, 2019
First decision: June 7, 2019
Revised: June 18, 2019
Accepted: July 17, 2019
Article in press: July 17,2019
Published online: August 26, 2019

P-Reviewer: Exbrayat JM
S-Editor: Ma YJ
L-Editor: Wang TQ
E-Editor: Zhou BX

3.94%, and 4.87%, respectively. The rate of possible and probable late stent thrombosis was 0.78%. The cumulative incidences of death, MI, and TLR at 1 year were 2.44%, 0.81%, and 1.63%, respectively.

CONCLUSION
The relatively low rates of MACE and stent thrombosis in this study support safety and performance of NeoHexa stents, suggesting it to be an effective alternative to other contemporary stents for the treatment of de novo lesions in native coronary arteries.

Key words: Sirolimus; Drug-eluting stent; Myocardial infarction; Thrombosis; Coronary artery disease

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Reports have indicated the use of stents in patients with coronary artery disease has reduced the rates of restenosis. Biodegradable polymer drug eluting stents, have shown to reduce restenosis rates and lower the stent thrombosis rate. Our study assessed 1-year, single-center cohort for clinical outcomes of patients who had received NeoHexa sirolimus drug-eluting stents in real practice. It showed relatively low rates of major adverse cardiac event and stent thrombosis supporting safety and performance of NeoHexa stent and supporting its use as an effective alternative to other existing stents.

Citation: Jambunathan R, Basavanna D, Vani P, Neuss M, Janbandhu P. One-year outcomes of a NeoHexa sirolimus-eluting coronary stent system with a biodegradable polymer in all-comers coronary artery disease patients: Results from NeoRegistry in India. *World J Cardiol* 2019; 11(8): 200-208
URL: https://www.wjgnet.com/1949-8462/full/v11/i8/200.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i8.200

INTRODUCTION

The prevalence of cardiovascular diseases, particularly coronary artery disease (CAD), is ever-increasing in India and has reached epidemic proportions[1]. Approximately 17% of total deaths were attributed to coronary heart disease in 2001–2003, which increased to 23% in 2010–2013 in India[1,2]. Percutaneous coronary intervention (PCI) is one of the most commonly performed cardiac procedures aimed at improving symptoms and quality of life of patients with CAD[3-5].

The unceasing research over decades in the field of PCI has led to improved devices and treatment strategies. Bare-metal stents (BMS) are able to reduce the rates of restenosis and acute occlusion compared with balloon angioplasty. Subsequently, the advent of drug-eluting stents (DES) has further decreased the rates of restenosis. Of note, first-generation DES were durable polymer DES, and delayed re-endothelialization due to the polymer raised concerns regarding late and very-late stent thrombosis (ST). Despite several efforts to reduce the ST rates of durable polymer DES such as alteration of stent platforms to increase tissue compatibility, modification of the outer layer of the stent surface, and using effective antiproliferative drugs and appropriate polymer carriers, the issue of inflammatory response still persists. Therefore, biodegradable polymer drug-eluting stents (BP-DES) were introduced with anticipation to reduce ST[6-8]. As expected, long-term clinical evidence has demonstrated superiority of BP-DES in reducing very-late ST events compared with durable polymer DES[9-11].

NeoHexa is one of such BP-DES designed with the aim to reduce rates of late ST and was launched in July 2015. The present study investigated the 1-year clinical outcomes of patients who had received this new DES in real clinical practice.

MATERIALS AND METHODS

Study design and patient selection

Data obtained from a single-center cohort of patients who had received NeoHexa stents as part of routine treatment for CAD between July 2015 and July 2016 at the

Cauvery Heart and Multispecialty Hospital, Mysore, were retrospectively investigated in January 2017. The study was conducted in accordance with the Helsinki Declaration and was approved by an independent ethics committee. Verbal informed consent was obtained before collecting data from patients who were contacted to participate in this study. This investigator initiated trial was registered with Clinical Trial Registry of India (CTRI/2018/03/012522)

Description of device

NeoHexa is a cobalt-chromium sirolimus-eluting coronary stent system. It is a premounted, balloon expandable DES with a persistent coating of BP carrier, loaded with 1.0 μg/mm^2 sirolimus in a slow-release formulation. It is mounted on a rapid exchange percutaneous transluminal coronary angioplasty balloon catheter. It has two radiopaque markers beside the mounted stent for accurate placement. It is available in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, and 4.5 mm and in stent lengths of 7, 10, 13, 15, 17, 20, 24, 28, 33, 38, 42, and 45 mm.

Study procedure and data collection

This was an all-comer study, and the indications for the angioplasty procedure and technique of stent implantation were as per the discretion of the treating physician. All patients were advised to receive dual antiplatelet therapy with clopidogrel and aspirin. Patients who were not pretreated received a bolus dose of 300-600 mg of clopidogrel or 60 mg of prosugrel and ≥ 100 mg of soluble aspirin just before the procedure.

Data were sourced from clinical notes, including inpatient progress notes and outpatient notes and letters, angiogram reports, and procedural angiographic images. Case report forms were completed for all patients, and data were stored in a secure, off-site database. Follow-up data were collected using either clinical visits or telephonic interactions by using structured questionnaires developed for this study to determine endpoint status at 1 mo, 6 mo, and 1 year after the index procedure. Supporting clinical documents were sought when necessary. Patients with incomplete clinical notes or who were noncontactable *via* telephone were excluded from the analysis.

Endpoint definitions

The primary endpoint of the study was the rate of major adverse cardiac events (MACEs) defined as the composite of death, myocardial infarction (MI), and target lesion revascularization (TLR) during the follow-up period after the index procedure. Deaths were categorized as cardiac or noncardiac. Stent thrombosis was evaluated according to the Academic Research Consortium criteria[12]. Procedural success was defined as successful stent placement at the desired position with < 30% residual stenosis.

Sample size and statistical analysis

A random sample size of 129 patients was calculated based on the primary endpoint of the study. Categorical data are presented as numbers and percentages. Continuous variables are presented as the mean ± SD. All data were processed using the statistical analysis software SPSS, version 21 or higher (SPSS Inc., Chicago, IL, United States).

RESULTS

Baseline demographic and clinical characteristics

In total, 129 patients with 172 lesions were enrolled in the study. Baseline demographics and clinical characteristics are summarized in Table 1. Mean age of patients was 56.57 ± 11.73 years, and the majority were men (76.74%). The most common comorbid conditions were hypertension (49.61%), followed by diabetes mellitus (39.53%). Over 70% of patients presented with angina class II and above.

Lesion and procedural characteristics

Most lesions were located in LAD (42.44%), RCA (32.56%), and LCx (21.51%), and a majority of them were positioned proximal (48.26%), mid (31.39%), or distal (12.79%) (Table 2). Approximately 72% of patients had a lesion length ranging 20–40 cm. The average stenosis rate was 88.12%. Bifurcation and thrombotic lesions comprised approximately 11% of all lesions. Approximately 95% lesions were moderate- to high-risk lesions as per ACC/AHA criteria, and most (96.51%) lesions had a TIMI flow grade below 3. The average length and diameter of the stent was 27.30 ± 9.20 and 2.98 ± 0.69, respectively. Average stent per patient was 1.34 ± 0.53, and pre- and post-dilation was performed in 97.67% and 26.16% of patients, respectively. Procedural success was achieved in all patients, and no in-hospital MACE was reported.

Table 1 Demographic and baseline clinical characteristics

Characteristics	*n* = 129 patients
Patient demographics	
Age, yr	56.57 ± 11.73
Male	99 (76.74)
Baseline medical history	
Diabetes mellitus	51 (39.53)
Hypertension	64 (49.61)
Smoking	11 (8.53)
Family history of coronary artery disease	04 (3.10)
History of alcohol consumption	05 (3.88)
Renal disease	01 (0.77)
Atrial fibrillation	01 (0.77)
Cardiac status - Angina class	
I	08 (6.20)
II	26 (20.15)
III	71 (55.04)
IV	23 (17.83)
Unknown	01 (0.77)

Data presented as mean ± SD or *n* (%).

Clinical outcomes during follow-up

The incidence of composite of MACE at 30 d was 0.78% with one cardiac death. MACE rates during the follow-up duration are depicted in Table 3. In brief, MACEs were reported in 6 (4.87%) patients at 1 year, consisting of 2 cardiac deaths, one noncardiac death, one (0.81%) MI, and 2 (1.63%) TLR events. Both TLR events were PCI, and the patients recovered after treatment. As shown in Table 4, the cumulative rate of ST was 1.55% (2/129) at 1 year and late ST was ARC-possible ST.

DISCUSSION

The present postmarketing surveillance study was conducted to support the safety of NeoHexa stents for treatment of coronary artery lesions in real-world clinical practice. One-year follow-up results demonstrated the favorable safety and performance of the stent with low rates of MACE and ST of 4.87% and 1.55%, respectively.

We evaluated real-world data of NeoHexa in an unselected clinical practice population with diverse clinical profiles, which included diabetes (39.53%), hypertension (49.61%), bifurcation and thrombotic lesions (11.04%), and ACC/AHA type B and C lesions (94.77%). The presentation of patients was similar to that reported in studies of other similar stents[13,14]. The NeoHexa stent is designed to have thin struts (60 μm) on a cobalt-chromium platform with a unique and innovative "s" link and an alternate "C" link, which provides high radial strength and no foreshortening, making it ideal for all lesion locations including ostial lesions.

The first-generation DES were built on bulky stent platforms, making deliverability quite challenging[15]; however, the thin struts and growth of 8% from nominal pressure to rated burst pressure of this new-generation NeoHexa DES offer good deliverability and conformability, thereby allowing complete deployment and good wall apposition. The design leads to a minimal balloon overhang, minimizing the risk of edge dissection/injury, which is a common procedural complication of PCIs. The finding that procedural success was achieved in 100% of patients in this study supports these claims.

Compared with BMS, first-generation DES with a durable polymer have reduced the rate of restenosis but are associated with higher late ST[11]. Delayed endothelial healing secondary to a hypersensitivity reaction to the durable polymer could be responsible for the observed high rate of ST with such DES[16-18]. BP-DES were developed to address this potential limitation of durable polymer DES. The drug encapsulated in polymer is completely released within 3–9 mo, and the polymer also gradually degrades into carbon dioxide and water molecules. Therefore, BP-DES

Table 2 Lesion and procedural characteristics (*n* = 129 patients and 172 lesions)

Characteristics	*n* = 172 lesions
Target vessel location	
LAD	73 (42.44)
LCx	37 (21.51)
RCA	56 (32.56)
Ramus	03 (1.74)
Other	03 (1.74)
Target lesion location	
Ostial	05 (2.91)
Proximal	83 (48.26)
Mid	54 (31.39)
Distal	22 (12.79)
Unknown	08 (4.65%)
Lesion length	
< 20 mm	39 (22.67)
20–40 mm	124 (72.09)
> 40 mm	08 (4.65)
Stenosis	88.12
Bifurcation	3 (1.74)
Thrombotic lesions	16 (9.30)
ACC/AHA lesion type	
A	09 (5.23)
B	92 (53.49)
C	71 (41.28)
TIMI flow grade at baseline	
0	45 (26.16)
1	49 (28.49)
2	72 (41.86)
3	05 (2.91)
Unknown	01 (0.58)
Average stent length	27.30 ± 9.20
Average stent diameter	2.98 ± 0.69
Average stent per patient	1.34 ± 0.53
Predilation	168 (97.67)
Postdilation	45 (26.16)

Data presented as mean ± SD or *n* (%). ACC: American College of Cardiology; AHA: American Heart Association; LAD: Left anterior descending; LCx: Left circumflex; RCA: Right coronary artery; TIMI: Thrombolysis in myocardial infarction.

initially provide antiproliferative benefits similar to durable polymer DES and later behave like BMS once drug delivery and polymer biodegradation are complete[19]. Given the importance of ST in evaluating the overall performance of DES, we estimated the ST rate in our study. The rates of both possible and probable late ST was 0.78% in the present study, which are comparable to those of other standard BP-DES such as sirolimus-eluting Orsiro stents (0.4%), biolimus-eluting Nobori stents (1.2%), and Biolimus A9 stents (0.2%) at 1-year follow-up[14,20]. The low rate of ST observed in our study could be attributed to complete wall apposition of the NeoHexa stent and appropriate endothelial healing over the 1-year period.

Although there is no scientific difference between indigenously developed DES *vs* those developed and marketed by global manufacturers, cost effectiveness remains a key factor in the decision-making process for patients and health care providers in India[21]. The most promising results of this retrospective study are 100% procedural success rate and low rates of MACE (4.87%). MACE rates in our study are comparable to previously reported incidence rates for other BP-DES: Endeavor stent (12.9%), NOBORI stent (11%), and Metafor SES (1.6%)[13,22,23]. Moreover, our results are comparable to the rate observed in the SPIRIT II trial (7.2%)[7].

Table 3 Mortality, morbidity, and major adverse cardiac event, *n* (%)

Events	In-hospital	1 mo	6 mo	1 yr
MACE	0	01 (0.78)	05 (3.94)	06 (4.87)
Death	0	01 (0.78)	03 (2.36)	03 (2.44)
Myocardial infarction	0	0	01 (0.79)	01 (0.81)
Clinically driven TLR	0	0	01 (0.79)	02 (1.63)

MACE: Major adverse cardiac event; TLR: Target lesion revascularization.

A major limitation of the present study is the observational design and retrospective analysis of data. However, observational data allow true representation of all-comer population unlike randomized trials with restricted enrollment criteria. In addition, a 1-year follow-up period might not be adequate to evaluate the safety and performance of NeoHexa DES. Therefore, our results must be further substantiated in well-designed studies with longer follow-up duration.

In conclusion, the relatively low rates of MACE and ST in this cohort of patients after 1 year of follow-up support the favorable safety and performance of NeoHexa stents. Product characteristics such as advanced sent design with the use of biodegradable polymer that provides high radial strength, minimal balloon overhang, low recoil, and uniform scaffolding could be responsible for these results. NeoHexa could be suggested as an effective alternative to other contemporary stents available in the market for the treatment of *de novo* lesions in native coronary arteries.

Table 4 Stent thrombosis, *n* (%)

Timing of stent thrombosis	Incidence	Type of stent thrombosis	Incidence
Early	0	Definite	0
Late	01 (0.78)	Probable	02 (1.55)
	01 (0.78)	Possible	

ARTICLE HIGHLIGHTS

Research background

Biodegradable polymer drug-eluting stents have been shown to reduce restenosis rates and have low rates of stent thrombosis. Thus, this post-marketing surveillance assessing outcomes after 1 year of treatment shows the real implications of biodegradable drug eluting stents.

Research motivation

Proving the real-life reduced restenosis rates of biodegradable stents was the motivation behind this study. Key problems were the rates of major adverse cardiac events (MACEs) myocardial infarction, and target lesion revascularization. Solving this would increase patient survival rate.

Research objectives

The main objective was to identify the rate of MACE during the follow-up period at 1 mo, 6 mo, and 1 year after the procedure completion.

Research methods

This was a retrospective analysis of a single-centre cohort of patients who had received NeoHexa stents as part of routine treatment for CAD.

Research results

Procedural success was achieved in all patients, and no in-hospital MACE was reported. The incidence of composite MACE at 30 d, 6 mo, and 1 year was 0.78%, 3.94%, and 4.87%, respectively.

Research conclusions

Relatively low rates of MACE and stent thrombosis in this study support the safety and performance of NeoHexa stents, suggesting that it is an effective alternative for treatment of *de novo* lesions.

Research perspectives

Our results must be further substantiated in well-designed studies with longer follow-up duration.

ACKNOWLEDGEMENTS

Authors would like to thank CBCC Global Research for providing medical writing assistance in the preparation of this manuscript which was funded by Sahajanand Laser Technology Ltd., India.

REFERENCES

1 **Gupta R**, Mohan I, Narula J. Trends in Coronary Heart Disease Epidemiology in India. *Ann Glob Health* 2016; **82**: 307-315 [PMID: 27372534 DOI: 10.1016/j.aogh.2016.04.002]
2 **Registrar General of India**. Sample Registration System Report Office of the Registrar General, New Delhi, India, 2011. Available URL: http://www.censusindia.gov.in/vital_statistics/causesofdeath.html
3 **Boden WE**, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356**: 1503-1516 [PMID: 17387127 DOI: 10.1056/NEJMoa070829]
4 **Sedlis SP**, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GB, Kostuk W, Chaitman BR, Berman D, Lorin JD, Dada M, Weintraub WS, Boden WE; COURAGE Trial Investigators. Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease. *N Engl J Med* 2015; **373**: 1937-1946 [PMID: 26559572 DOI: 10.1056/NEJMoa1505532]
5 **Fihn SD**, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR, Smith SC, Spertus JA, Williams SV; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline

for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2012; **126**: 3097-3137 [PMID: 23166210 DOI: 10.1016/j.jacc.2012.07.013]

6 **Hamon M**, Niculescu R, Deleanu D, Dorobantu M, Weissman NJ, Waksman R. Clinical and angiographic experience with a third-generation drug-eluting Orsiro stent in the treatment of single de novo coronary artery lesions (BIOFLOW-I): a prospective, first-in-man study. *EuroIntervention* 2013; **8**: 1006-1011 [PMID: 23339805 DOI: 10.4244/EIJV8I9A155]

7 **Garg S**, Serruys P, Onuma Y, Dorange C, Veldhof S, Miquel-Hébert K, Sudhir K, Boland J, Huber K, Garcia E, te Riele JA; SPIRIT II Investigators. 3-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2009; **2**: 1190-1198 [PMID: 20129545 DOI: 10.1016/j.jcin.2009.10.002]

8 **Finn AV**, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol* 2007; **27**: 1500-1510 [PMID: 17510464 DOI: 10.1161/ATVBAHA.107.144220]

9 **Parsa E**, Saroukhani S, Majlessi F, Poorhosseini H, Lofti-Tokaldany M, Jalali A, Salarifar M, Nematipour E, Alidoosti M, Aghajani H, Amirzadegan A, Kassaian SE. Biodegradable-Polymer Biolimus-Eluting Stents versus Durable-Polymer Everolimus-Eluting Stents at One-Year Follow-Up: A Registry-Based Cohort Study. *Tex Heart Inst J* 2016; **43**: 126-130 [PMID: 27127426 DOI: 10.14503/THIJ-14-4997]

10 **Goyal BK**, Kalmath BC, Kawar R, Sharma A, Khemnar B, Rangnekar H. Experience with BioMatrix BES and other DES in all-comers setting: a retrospective overview. *Indian Heart J* 2013; **65**: 678-682 [PMID: 24407537 DOI: 10.1016/j.ihj.2013.10.014]

11 **Stefanini GG**, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J* 2012; **33**: 1214-1222 [PMID: 22447805 DOI: 10.1093/eurheartj/ehs086]

12 **Cutlip DE**, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**: 2344-2351 [PMID: 17470709 DOI: 10.1161/CIRCULATIONAHA.106.685313]

13 **Prakasa Rao VS**, Narayana Rao ASV, Kapardhi PLN, Shah PK, Viswanath R, Mehetre SG, Srivastava AK. Safety and Performance of Sirolimus-Eluting Coronary Stent System with Biodegradable Polymer: A Retrospective Analysis in Real-World Patient Population. *World J Cardiovasc Dis* 2017; **7**: 163 [DOI: 10.4236/wjcd.2017.75015]

14 **Mehta AB**, Chandra P, Dalal J, Shetty P, Desai D, Chocklingam K, Prajapati J, Kumar P, Magarkar V, Vasawada A, Goyal BK, Kumar V, Rao VS, Babu R, Parikh P, Kaul U, Patil A, Mhetre T, Rangnekar H. One-year clinical outcomes of BioMatrix™-Biolimus A9™ eluting stent: the e-BioMatrix multicenter post marketing surveillance registry in India. *Indian Heart J* 2013; **65**: 593-599 [PMID: 24206883 DOI: 10.1016/j.ihj.2013.08.031]

15 **Navarese EP**, Kowalewski M, Kandzari D, Lansky A, Górny B, Kołtowski L, Waksman R, Berti S, Musumeci G, Limbruno U, van der Schaaf RJ, Kelm M, Kubica J, Suryapranata H. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. *Open Heart* 2014; **1**: e000064 [PMID: 25332803 DOI: 10.1136/openhrt-2014-000064]

16 **Finn AV**, Nakazawa G, Kolodgie FD, Virmani R. Temporal course of neointimal formation after drug-eluting stent placement: is our understanding of restenosis changing? *JACC Cardiovasc Interv* 2009; **2**: 300-302 [PMID: 19463440 DOI: 10.1016/j.jcin.2009.01.004]

17 **Nebeker JR**, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, Davidson CJ, McKoy JM, Raisch DW, Whisenant BK, Yarnold PR, Belknap SM, West DP, Gage JE, Morse RE, Gligoric G, Davidson L, Feldman MD. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006; **47**: 175-181 [PMID: 16386683 DOI: 10.1016/j.jacc.2005.07.071]

18 **Joner M**, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; **48**: 193-202 [PMID: 16814667 DOI: 10.1016/j.jacc.2006.03.042]

19 **Vorpahl M**, Finn AV, Nakano M, Virmani R. The bioabsorption process: tissue and cellular mechanisms and outcomes. *EuroIntervention* 2009; **5** Suppl F: F28-F35 [PMID: 22100673 DOI: 10.4244/EIJV5IFA5]

20 **Jensen LO**, Thayssen P, Maeng M, Ravkilde J, Krusell LR, Raungaard B, Junker A, Terkelsen CJ, Veien KT, Villadsen AB, Kaltoft A, Tilsted HH, Hansen KN, Aaroe J, Kristensen SD, Hansen HS, Jensen SE, Madsen M, Bøtker HE, Berencsi K, Lassen JF, Christiansen EH. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent With a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated With Percutaneous Coronary Intervention: The SORT OUT VII Trial. *Circ Cardiovasc Interv* 2016; **9**: e003610 [PMID: 27412869 DOI: 10.1161/CIRCINTERVENTIONS.115.003610.]

21 **Sastry BKS**, Nallamalla KR, Kumar N, Kodati D, Menon R. One-year clinical outcomes of different coronary drug eluting stents-Data from a prospective registry. *Indian Heart J* 2018; **70**: 580-583 [PMID: 30170658 DOI: 10.1016/j.ihj.2018.05.012]

22 **Maeng M**, Tilsted HH, Jensen LO, Kaltoft A, Kelbæk H, Abildgaard U, Villadsen AB, Krusell LR, Ravkilde J, Hansen KN, Christiansen EH, Aarøe J, Jensen JS, Kristensen SD, Bøtker HE, Madsen M, Thayssen P, Sørensen HT, Thuesen L, Lassen JF. 3-Year clinical outcomes in the randomized SORT OUT III superiority trial comparing zotarolimus- and sirolimus-eluting coronary stents. *JACC Cardiovasc Interv* 2012; **5**: 812-818 [PMID: 22917452 DOI: 10.1016/j.jcin.2012.04.008]

23 **Natsuaki M**, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T. Final 3-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Either Biodegradable Polymer or Durable Polymer:

NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial. *Circ Cardiovasc Interv* 2015; **8**: e002817 [PMID: 26446596 DOI: 10.1161/CIRCINTERVENTIONS.115.002817]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 August 26; 11(8): 209-212

DOI: 10.4330/wjc.v11.i8.209

ISSN 1949-8462 (online)

CASE REPORT

Successful minimal approach transcatheter aortic valve replacement in an allograft heart recipient 19 years post transplantation for severe aortic stenosis: A case report

Sravani Avula, Sudhir Mungee, Marco A Barzallo

ORCID number: Sravani Avula (0000-0001-9371-2426); Sudhir Mungee (0000-0003-3753-7701); Marco A Barzallo (0000-0003-4149-357X).

Author contributions: Avula S, Mungee S and Barzallo MA contributed equally to this work.

Informed consent statement: Informed consent to publish was obtained from the patient.

Conflict-of-interest statement: All the authors of this article declare that there is no conflict of interest regarding the publication of this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited

Sravani Avula, Sudhir Mungee, Department of Cardiovascular Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL 61637, United States

Marco A Barzallo, Key Clinal Faculty, Department of Cardiovascular Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL 61637, United States

Corresponding author: Sravani Avula, MD, Cardiology Fellow, Division of Cardiology, Department of Internal Medicine, University of Illinois College of Medicine at Peoria, 530 NE Glen Oak Ave, Peoria, IL 61637, United States. sravani.avula@osfhealthcare.org
Telephone: +1-309-6557257

Abstract

BACKGROUND

Aortic stenosis is one of the rare valvular complications in a transplanted heart. Over the past 8 years, transcatheter approach for aortic valve replacement (TAVR) has been slowly evolving to be the preferred approach in these patient population when compared to the surgical approach. We report a second case in the United States with successful transfemoral minimal approach with minimal sedation for TAVR in a heart transplant recipient 19 years post transplantation for severe symptomatic calcified aortic stenosis.

CASE SUMMARY

We present a case of 73-year-old male who has undergone successful minimal approach transcatheter aortic valve replacement in an allograft heart. Patient had received orthotopic heart transplantation 19 years ago for non-ischemic cardiomyopathy. Follow up transthoracic echocardiograms as per routine protocol did not show any aortic valve disease until 15 years post transplantation. Aortic valve was noted to be mildly sclerotic at that time and gradually progressed to severe symptomatic aortic stenosis over the next 4 years. Patient had complaints of worsening shortness of breath that limited his functional capacity. Overall his post heart transplantation period has been mostly uneventful except for allograft non occlusive vasculopathy and aortic stenosis. His Society of Thoracic Surgery risk score was 12.205% and he was considered to be a high-risk surgical candidate by surgeon. Decision was made to undergo transcatheter aortic valve replacement.

CONCLUSION

With the improved survival of these patients, we think it is time to look into

manuscript

Received: January 18, 2019
Peer-review started: January 18, 2019
First decision: January 26, 2019
Revised: August 2, 2019
Accepted: August 6, 2019
Article in press: August 7, 2019
Published online: August 26, 2019

P-Reviewer: Kaypakli O, Erkut B
S-Editor: Dou Y
L-Editor: A
E-Editor: Zhou BX

pathophysiology of valvular disease in transplant heart recipients. Some other unanswered questions include, underlying donor and recipient risk factors for valvular diseases in heart transplant recipients.

Key words: Transcatheter aortic valve replacement; Heart transplant; Minimal approach valve replacement; Severe aortic stenosis; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We report a second case in the United States with successful transfemoral minimal approach with minimal sedation for transcatheter approach for aortic valve replacement in a heart transplant recipient. We believe, with the increase of number of reported cases with valvular diseases in heart transplant patients, it is time for further research in valvular disease in allograft heart recipients.

Citation: Avula S, Mungee S, Barzallo MA. Successful minimal approach transcatheter aortic valve replacement in an allograft heart recipient 19 years post transplantation for severe aortic stenosis: A case report. *World J Cardiol* 2019; 11(8): 209-212
URL: https://www.wjgnet.com/1949-8462/full/v11/i8/209.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i8.209

INTRODUCTION

The survival of heart transplant recipients has significantly improved over the past few decades with advanced surgical techniques and immunosuppressive therapies. Valvular diseases like aortic stenosis is seen as one of the late complications in cardiac allograft recipients given improved long-term survival in these patient population[1-3]. Aortic valve replacement through median or partial sternotomy has been considered to be the standard treatment of choice[4-6]. Over the past decade transcatheter aortic valve replacement has been evolving given that it is less invasive in these high risk transplant recipients[6-10]. On review of literature, only 6 case reports have been reported thus far, of which one has been reported in the United States[2,7]. Most of the case reports comment only on immediate post-operative outcomes.

CASE PRESENTATION

Chief complaints

Progressive shortness of breath.

History of present illness

A 73-year-old male with history of hypertension, orthotopic heart transplantation 19 years ago has been followed closely for symptoms of worsening shortness of breath in the setting of severe aortic stenosis. His functional capacity has been gradually declined to NYHA Class IV (New York Heart Association).

History of past illness

Hypertension, status post heart transplantation, allograft non occlusive vasculopathy and aortic stenosis.

Personal and family history

Included above.

Physical examination

Physical examination upon admission: He was noted to have elevated jugular venous pulse, bibasilar lung crackles and bilateral pedal edema.

Laboratory examination

None.

Imaging examinations

Follow up transthoracic echocardiograms as per routine protocol did not show any aortic valve disease until 15 years post transplantation when the aortic valve was noted to be mildly sclerotic at that time and gradually progressed to symptomatic severe aortic stenosis over the next 4 years.

FINAL DIAGNOSIS

Symptomatic severe aortic stenosis.

TREATMENT

Transcatheter aortic valve replacement.

OUTCOME AND FOLLOW-UP

Patient had tolerated the procedure well and was discharged home on post procedure day 2. His symptoms of shortness of breath and functional capacity were noted to be significantly improved during post procedure follow up in the clinic.

DISCUSSION

Patient was minimally sedated with subcutaneous lidocaine in bilateral groin sites along with small dose of versed and fentanyl pushes per anesthesia protocol.

The left groin was accessed with a 6 French sheath. A pigtail was advanced for aortoiliac angiography and contralateral access guidance. Aortic root angiography was performed for guidance of valve deployment. A 6 French venous sheath was obtained in the left common femoral vein and a temporary pacemaker was advanced into the right ventricle. With contralateral guidance, a 6 French sheath was placed into the right common femoral artery. Two Preclose devices were deployed and a 16 French sheath was placed. An Amplatz catheter and a Newton wire was advanced, across the aortic valve into the left ventricle followed by advancing a preshaped stiff amplatz wire. Later, the prosthetic aortic valve was advanced across the aortic valve. Once the valve was noted to be in proper position, a 29-mm Sapien 3 valve was deployed in the usual sequence of rapid pacing, balloon inflation and balloon deflation. Once the valve was deployed, transthoracic echocardiography was done that confirmed adequate valve function. No aortic regurgitation was noted. The delivery system and the 16 French sheath and hemostasis was achieved successfully. The left common femoral access sheath was removed and a 6 French Mynx device was placed. No immediate complications were seen. Patient did tolerate the procedure well and was discharged on post op day 2 (Figure 1).

CONCLUSION

Minimal approach transcatheter aortic valve replacement has proven to have good outcomes in high risk patients. Its use in allograft heart is also showing to have good immediate post-operative outcomes. All the case reports thus far have commented on immediate post-operative outcomes, but more data is needed in regard to long-term prognosis. There is inadequate data in regard to valvular diseases in heart transplant recipients. Vasculopathy is a well-known complication in this patient population. With the improved survival of these patients, we think it is time to look into pathophysiology of valvular disease in transplant heart recipients. Some other unanswered questions include, underlying donor and recipient risk factors for valvular diseases in heart transplant recipients.

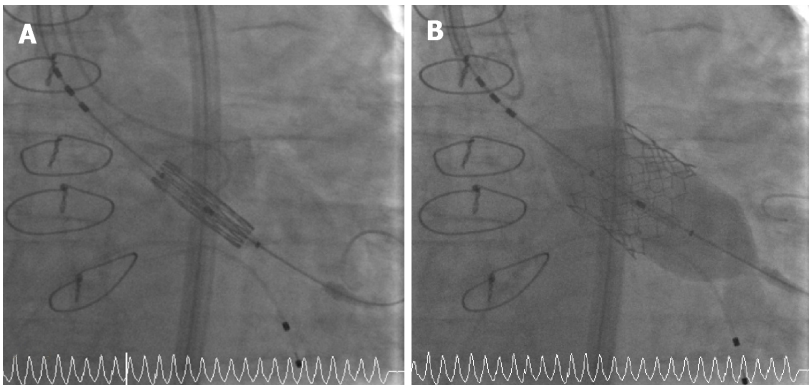


Figure 1 Fluoroscopic pictures. A: The fluoroscopic pictures of pre deployment of the Transcatheter Aortic Aortic Valve B: The fluoroscopic pictures of post deployment of the TAVR valve.

REFERENCES

1 **Bruschi G**, De Marco F, Oreglia J, Colombo P, Moreo A, De Chiara B, Paino R, Frigerio M, Martinelli L, Klugmann S. Transcatheter aortic valve implantation after heart transplantation. *Ann Thorac Surg* 2010; **90**: e66-e68 [PMID: 20971222 DOI: 10.1016/j.athoracsur.2010.08.021]

2 **De Praetere H**, Ciarka A, Dubois C, Herijgers P. Transapical transcatheter aortic valve implantation in a heart transplant recipient with severely depressed left ventricular function. *Interact Cardiovasc Thorac Surg* 2013; **16**: 906-908 [PMID: 23460597 DOI: 10.1093/icvts/ivt048]

3 **Vistarini N**, D'Armini AM, Pellegrini C, Aiello M, Toscano M, Minzioni G, Viganò M. Minimally invasive aortic valve replacement in a transplanted heart. *Ann Thorac Surg* 2010; **90**: 1688-1690 [PMID: 20971292 DOI: 10.1016/j.athoracsur.2010.08.013]

4 **Ross J**, Braunwald E. Aortic stenosis. *Circulation* 1968; **38**: 61-67 [PMID: 4894151 DOI: 10.1161/01.CIR.38.1S5.V-61]

5 **Schwarz F**, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, Schmitz W, Kübler W. The effect of aortic valve replacement on survival. *Circulation* 1982; **66**: 1105-1110 [PMID: 7127696 DOI: 10.1161/01.CIR.66.5.1105]

6 **Seiffert M**, Meyer S, Franzen O, Conradi L, Baldus S, Schirmer J, Deuse T, Costard-Jaeckle A, Reichenspurner H, Treede H. Transcatheter aortic valve implantation in a heart transplant recipient: a case report. *Transplant Proc* 2010; **42**: 4661-4663 [PMID: 21168756 DOI: 10.1016/j.transproceed.2010.09.148]

7 **Zanuttini D**, Armellini I, Bisceglia T, Spedicato L, Bernardi G, Muzzi R, Proclemer A, Livi U. Transcatheter aortic valve implantation for degenerative aortic valve regurgitation long after heart transplantation. *Ann Thorac Surg* 2013; **96**: 1864-1866 [PMID: 24182478 DOI: 10.1016/j.athoracsur.2013.03.040]

8 **Margale S**, Natani S. Anesthetic Management of Transfemoral Transcatheter Aortic Valve Replacement (TAVR) in a Heart Transplant Recipient With Severely Depressed Left Ventricular Function and Renal Failure. *J Cardiothorac Vasc Anesth* 2017; **31**: 1032-1036 [PMID: 27693207 DOI: 10.1053/j.jvca.2016.07.026]

9 **Leon MB**, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; **363**: 1597-1607 [PMID: 20961243 DOI: 10.1056/NEJMoa1008232]

10 **Smith CR**, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; **364**: 2187-2198 [PMID: 21639811 DOI: 10.1056/NEJMoa1103510]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 September 26; 11(9): 213-216

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 9 September 26, 2019

EDITORIAL

Contents

World Journal of Cardiology

Volume 11 Number 9 September 26, 2019

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Steven C Greenway, FRCP (C), MD, MSc, Assistant Professor, Paediatrics, Cardiac Sciences, Biochemistry and Molecular Biology, Alberta Children's Hospital and University of Calgary, Calgary T3B 6A8, Alberta, Canada

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Lu-Lu Qi*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Marco Matteo Ciccone, Ramdas G Pai, Dimitrios Tousoulis

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE
Ruo-Yu Ma, Director

PUBLICATION DATE
September 26, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 September 26; 11(9): 213-216

DOI: 10.4330/wjc.v11.i9.213

ISSN 1949-8462 (online)

EDITORIAL

Takotsubo syndrome: The past, the present and the future

Nauman Khalid, Pooja Sareen, Sarah Aftab Ahmad, Lovely Chhabra

ORCID number: Nauman Khalid (000-0003-4159-555X); Pooja Sareen (0000-0002-3625-2061); Sarah Aftab Ahmad (0000-0002-8648-9948); Lovely Chhabra (0000-0002-9193-5981).

Author contributions: All authors conceived the study and drafted the manuscript; Khalid N and Chhabra L approved the final version of the article.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: March 27, 2019
Peer-review started: March 28, 2019
First decision: August 2, 2019
Revised: August 14, 2019
Accepted: August 21, 2019
Article in press: August 21, 2019
Published online: September 26, 2019

P-Reviewer: Kharlamov AN, Petix NR, Teragawa H, Ueda H
S-Editor: Ma RY

Nauman Khalid, Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC 20010, United States

Pooja Sareen, Department of Medicine, Harrisburg Medical Center, Harrisburg, IL 62946, United States

Sarah Aftab Ahmad, Department of Cardiovascular Surgery, Saint Francis Medical Center, Monroe, LA 71201, United States

Lovely Chhabra, Department of Cardiology, Heartland Regional Medical Center, Marion, IL 62959, United States

Corresponding author: Lovely Chhabra, FACC, MD, Assistant Professor, Department of Cardiology, Heartland Regional Medical Center, 3331 W Deyoung, Marion, IL 62959, United States. lovids@hotmail.com
Telephone: +1-508-6675052
Fax: +1-888-5986647

Abstract

Takotsubo syndrome is a wide spectrum disease with a dramatic clinical presentation mimicking acute coronary syndrome albeit without obstructive coronary disease and typically manifests in the backdrop of intense emotional or physical trigger. Pathophysiology is incompletely understood with multifactorial mechanistic pathways circling around a heart-brain-endocrine axis. Several anatomic and phenotypic variants exist with varied clinical manifestations. The aftermath of Takotsubo syndrome is not always benign and both short- and long-term complications can occur which may impact its prognosis. Several gaps in knowledge exist providing an impetus for tremendous future research opportunities.

Key words: Takotsubo syndrome; Triggers; Pathophysiology; Anatomic variants; Prognosis

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Further research is necessary in order to better understand the underlying triggers and pathophysiologic principles of Takotsubo syndrome which will help optimize both in-hospital acute and long-term management pathways.

Citation: Khalid N, Sareen P, Ahmad SA, Chhabra L. Takotsubo syndrome: The past, the present and the future. *World J Cardiol* 2019; 11(9): 213-216

L-Editor: A
E-Editor: Qi LL

URL: https://www.wjgnet.com/1949-8462/full/v11/i9/213.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i9.213

INTRODUCTION

Chest pain and dyspnea are ubiquitous and common clinical symptoms for patients presenting to the Emergency Department and majority of these patients are initially labelled with the diagnosis of coronary artery disease, heart failure or pulmonary disease. Hitherto less well known clinical entity - Takotsubo syndrome (TTS), first described in Japan, is becoming increasingly recognized in the Western world and shares many clinical features indistinguishable from acute coronary syndrome (ACS) or acute heart failure. TTS is a heterogenous entity characterized by transient wall motion abnormalities (WMA) of the left ventricle typically without angiographically significant epicardial coronary artery disease or acute plaque rupture, manifesting with chest pain, dynamic reversible ST segment and T wave abnormalities, and modest elevation of cardiac biomarkers disproportionate to the extent of WMA[1-4] - thus mimicking ACS in many ways (Figure 1). It has also been described as an acute heart failure syndrome characterized by left ventricular systolic and diastolic function, myocardial strain abnormalities, and significant elevation of beta natriuretic peptide. Over the past three decades, our understanding of the pathophysiologic mechanisms of this disease has improved; thanks to the widespread availability of urgent coronary angiography and technological advances in the imaging arena such as modern echocardiography, speckle strain imaging, cardiac magnetic resonance imaging, single-photon emission computed tomography and positron emission tomography, however, several knowledge gaps still remain. What has become clear now is that TTS is much more common than previously anticipated. It predominantly affects post-menopausal women[5] and portends significant morbidity and mortality approaching that of ACS, although still underappreciated. A hallmark feature of TTS is its association with a preceding negative stressful trigger (emotional or physical) - the so-called "broken heart syndrome" or "stress-induced cardiomyopathy". However, in some cases no stressors may be identified and in few the trigger could even be a positive emotion - the soi-disant "happy heart syndrome".

Electrocardiographic manifestations of TC patients progress through similar evolutionary pattern as the ECG staging in pericarditis[6]. Stage 1 demonstrates ST segment elevation, followed by normalization of ST segment in stage 2. T-wave inversions develop in stage 3, with subsequent normalization of T waves or rarely persistence of T-wave inversions noted in stage 4[6]. Certainly, an overlap between these changes may exist, whereas some patients may not demonstrate all evolutionary stage changes. Several anatomic and phenotypic variants of TTS have been described with varied clinical manifestations. The most common form is the typical apical ballooning which occurs in 75%-80% of patients; it's easily recognized and is associated with typical complications including thrombus formation due to apical akinesis and left ventricular outflow tract obstruction due to basal hyperkinesis[7]. Other less common types include midventricular, basal or inverted, biventricular, right ventricular, or focal dysfunction[7]. Numerous putative mechanisms have been proposed for development of TTS - these include coronary vasospasm, microvascular spasm or dysfunction [as demonstrated by abnormal Thrombolysis in Myocardial Infarction (TIMI) Frame Count or TIMI perfusion grade], neurogenic stunned myocardium with underlying enhanced sympathetic activity, elevated levels of circulating plasma catecholamines and its metabolites, inflammation, estrogen deficiency, and spontaneously aborted myocardial infarction[8-12]. A possible autoimmune and/or autoinflammatory component has also been hypothesized for TTS, akin to myocardial infarction, thereby providing an impetus to explore long-term immunological effects of TTS[13]. Associated comorbidities and risk factor profile is similar to coronary artery disease although some reports suggest that diabetes mellitus is noted less frequently in patients with TTS suggesting a possible protective mechanism[14,15].

The most commonly applied diagnostic criteria include the Revised Mayo Clinic Criteria[16], International Takotsubo Diagnostic Criteria (InterTAK)[17], and the Heart Failure Association-European Society of Cardiology Criteria[18]. Transthoracic echocardiography with color and tissue Doppler is the preferred noninvasive imaging modality for patients suspected of TTS but most of these patients undergo emergent coronary angiography to rule out ACS. Correct diagnosis is critical since TTS is not a benign condition and is associated with potentially serious short- and long-term

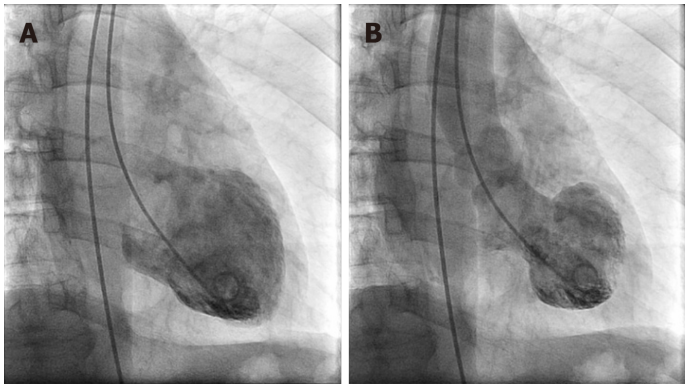


Figure 1 Ventriculogram of the left ventricle in diastole (A) and systole (B) demonstrating typical apical ballooning with apical akinesis and basal hyperkinesis.

complications such as ventricular arrhythmias, dynamic left ventricular outflow tract obstruction, pump failure with cardiogenic shock, thromboembolic sequelae, intramyocardial hemorrhage and rupture, pulmonary edema and others[7]. In-hospital mortality remains high (about 5%) and acute management focuses on the specific complications[7]. Physical triggers, acute neurologic or psychiatric illnesses, elevated cardiac biomarkers (troponin), and a low left ventricular ejection fraction on admission were independent predictors for in-hospital complications[19]. Currently no evidence exists for long-term management of TTS. Nonetheless, beta-blockers are advocated especially in patients with increased sympathetic tone[7]. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers have demonstrated a marginal benefit at 1-year[19]. Recurrence rate is reported at 1.8% where the trigger is typically different, and the recurrence can occur at any time[19].

CONCLUSION

TTS presents with symptoms similar to ACS characterized by transient left ventricular dysfunction typically manifesting in the setting of stressful triggers. Dynamic reversible ST segment and T wave abnormalities, modest elevation of troponin, significant elevation of beta natriuretic peptide, several anatomic variants, potentially serious short- and long-term complications, prognosis similar to ACS are some important features of this entity. Our current understanding of the pathophysiologic underpinnings has improved compared to its first description in 1990 yet there are several knowledge gaps that need to be addressed. Future potential research opportunities include exploring reasons for gender predilection, triggering factors and their role in the development and prognosis of TTS, different phenotypes of TTS, intracellular and intercellular mechanisms involved, genetic predisposition, exact pathophysiologic mechanism, specific acute- and long-term management and the role of animal models. Future larger randomized controlled studies will help resolve these queries.

REFERENCES

1 **Mejía-Rentería HD**, Núñez-Gil IJ. Takotsubo syndrome: Advances in the understanding and management of an enigmatic stress cardiomyopathy. *World J Cardiol* 2016; **8**: 413-424 [PMID: 27468334 DOI: 10.4330/wjc.v8.i7.413]
2 **Komamura K**, Fukui M, Iwasaku T, Hirotani S, Masuyama T. Takotsubo cardiomyopathy: Pathophysiology, diagnosis and treatment. *World J Cardiol* 2014; **6**: 602-609 [PMID: 25068020 DOI: 10.4330/wjc.v6.i7.602]
3 **Khalid N**, Iqbal I, Coram R, Raza T, Fahsah I, Ikram S. Thrombolysis In Myocardial Infarction Frame Count in Takotsubo Cardiomyopathy. *Int J Cardiol* 2015; **191**: 107-108 [PMID: 25965614 DOI: 10.1016/j.ijcard.2015.04.192]
4 **Khalid N**, Chhabra L. Takotsubo cardiomyopathy and microcirculatory dysfunction. *Nat Rev Cardiol* 2015; **12**: 497 [PMID: 26076951 DOI: 10.1038/nrcardio.2015.88]
5 **Khalid N**, Ahmad SA, Shlofmitz E, Chhabra L. Racial and gender disparities among patients with Takotsubo syndrome. *Clin Cardiol* 2019; **42**: 19 [PMID: 30525217 DOI: 10.1002/clc.23130]
6 **Chhabra L**, Khalid N, Sareen P. Extremely Low Prevalence of Takotsubo Cardiomyopathy and Transient Cardiac Dysfunction in Stroke Patients With T-wave Abnormalities. *Am J Cardiol* 2019; **123**: 1009 [PMID: 30661722 DOI: 10.1016/j.amjcard.2019.01.001]
7 **Medina de Chazal H**, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, Abbate A.

Stress Cardiomyopathy Diagnosis and Treatment: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018; **72**: 1955-1971 [PMID: 30309474 DOI: 10.1016/j.jacc.2018.07.072]

8 **Gopalakrishnan P**, Zaidi R, Sardar MR. Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis. *World J Cardiol* 2017; **9**: 723-730 [PMID: 29081904 DOI: 10.4330/wjc.v9.i9.723]

9 **Khalid N**, Ahmad SA, Umer A. Mechanisms of Takotsubo cardiomyopathy; role of microcirculatory dysfunction. *Int Cardiovas Forum J* 2016; **5**: 30-32 [DOI: 10.17987/icfj.v5i0.237]

10 **Chhabra L**, Khalid N, Kluger J, Spodick DH. Lupus myopericarditis as a preceding stressor for takotsubo cardiomyopathy. *Proc (Bayl Univ Med Cent)* 2014; **27**: 327-330 [PMID: 25484500 DOI: 10.1080/08998280.2014.11929147]

11 **Khalid N**, Ahmad SA, Umer A, Chhabra L. Takotsubo cardiomyopathy and myopericarditis: Unraveling the inflammatory hypothesis. *Int J Cardiol* 2015; **196**: 168-169 [PMID: 26114444 DOI: 10.1016/j.ijcard.2015.05.175]

12 **Khalid N**, Chhabra L. Takotsubo Cardiomyopathy and Viral Myopericarditis: An Association Which Should be Considered in the Differential Diagnosis. *Angiology* 2016; **67**: 398 [PMID: 25969569 DOI: 10.1177/0003319715585665]

13 **Sattler S**, Couch LS, Harding SE. Takotsubo Syndrome: Latest Addition to the Expanding Family of Immune-Mediated Diseases? *JACC Basic Transl Sci* 2018; **3**: 779-781 [PMID: 30623137 DOI: 10.1016/j.jacbts.2018.11.003]

14 **Khalid N**, Ahmad SA, Umer A, Chhabra L. Role of Microcirculatory Disturbances and Diabetic Autonomic Neuropathy in Takotsubo Cardiomyopathy. *Crit Care Med* 2015; **43**: e527 [PMID: 26468716 DOI: 10.1097/CCM.0000000000001183]

15 **Khalid N**, Chhabra L, Ahmad SA, Sareen P, Spodick DH. Autonomic Dysfunction and Takotsubo Cardiomyopathy. *Am J Med* 2015; **128**: e45-e46 [PMID: 26500214 DOI: 10.1016/j.amjmed.2015.06.013]

16 **Bybee KA**, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004; **141**: 858-865 [PMID: 15583228 DOI: 10.7326/0003-4819-141-11-200412070-00010]

17 **Ghadri JR**, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J* 2018; **39**: 2032-2046 [PMID: 29850871 DOI: 10.1093/eurheartj/ehy076]

18 **Lyon AR**, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016; **18**: 8-27 [PMID: 26548803 DOI: 10.1002/ejhf.424]

19 **Templin C**, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med* 2015; **373**: 929-938 [PMID: 26332547 DOI: 10.1056/NEJMoa1406761]

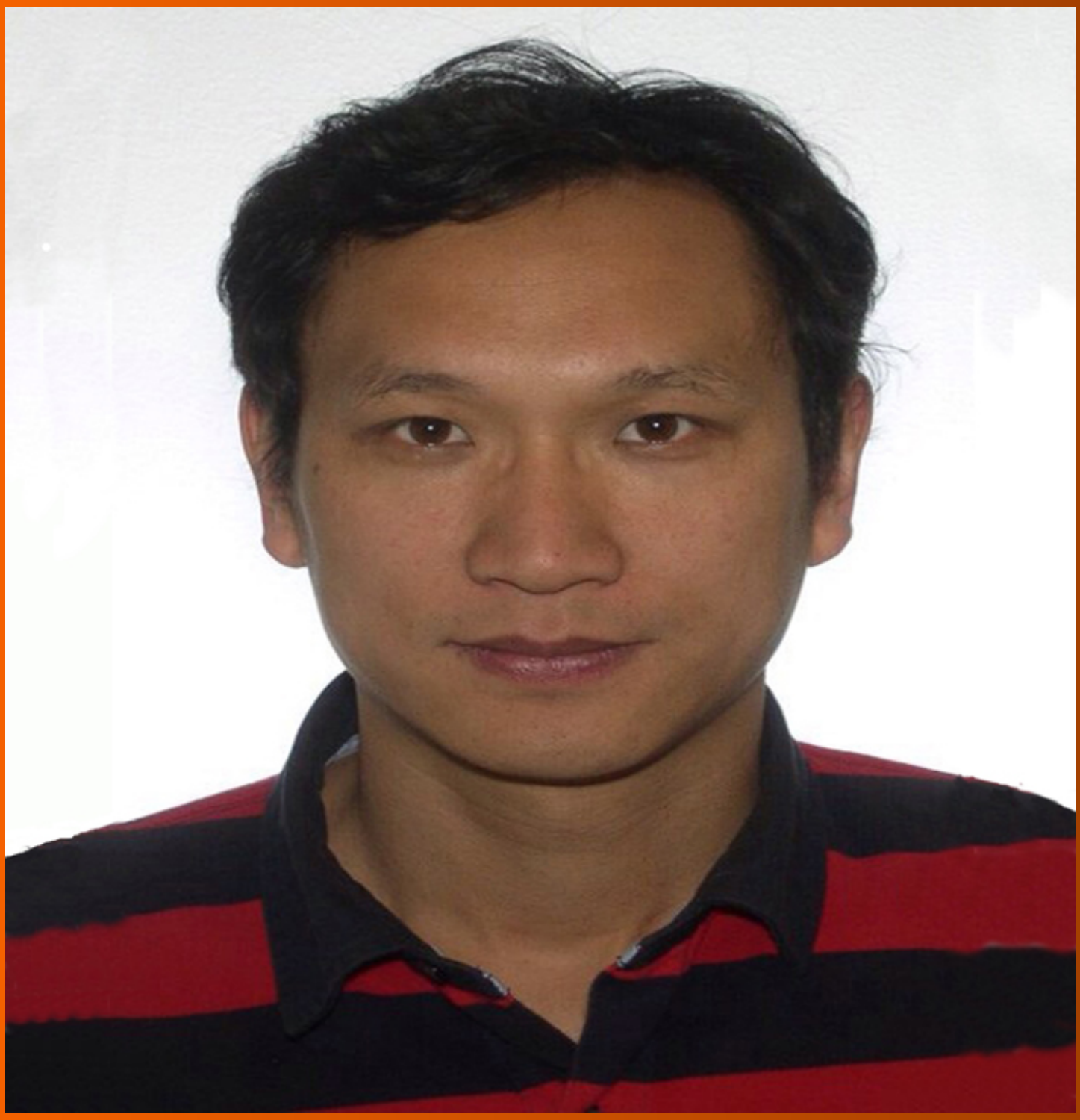
Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 October 26; 11(10): 217-255



Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 10 October 26, 2019

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Basic Study

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Jianguang Ji, MD, PhD, Associate Professor, Center for Primary Health Care Research, Lund University/Region Skane, Malmo SE-20502, Sweden

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ramdas G. Pai MD, FACC, FRCP (Edin), Marco Matteo Ciccone, Dimitris Tousoulis

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE

Ruo-Yu Ma, Director

PUBLICATION DATE

October 26, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 October 26; 11(10): 217-220

DOI: 10.4330/wjc.v11.i10.217

ISSN 1949-8462 (online)

EDITORIAL

Social media in cardiology: Reasons to learn how to use it

Rafael Vidal-Perez, José Juan Gómez de Diego, Julia Grapsa, Ricardo Fontes-Carvalho, Jose Ramon Gonzalez-Juanatey

ORCID number: Rafael Vidal-Perez (0000-0001-9944-8363); José Juan Gómez de Diego (0000-0003-2397-3481); Julia Grapsa (0000-0003-4620-6234); Ricardo Fontes-Carvalho (0000-0003-2306-8393); Jose Ramon Gonzalez-Juanatey (0000-0001-9681-3388).

Author contributions: All authors similarly contributed to this paper regarding design, analysis, critical revision and editing.

Conflict-of-interest statement: No potential conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: May 15, 2019
Peer-review started: May 20, 2019
First decision: June 6, 2019
Revised: June 18, 2019
Accepted: September 25, 2019
Article in press: September 25, 2019
Published online: October 26, 2019

P-Reviewer: Kharlamov AN, Najafi

Rafael Vidal-Perez, Jose Ramon Gonzalez-Juanatey, Heart Failure Unit, Cardiology Department, Hospital Clinico Universitario de Santiago, Santiago de Compostela 15706, A Coruña, Spain

Rafael Vidal-Perez, Jose Ramon Gonzalez-Juanatey, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Spain, Santiago de Compostela 15706, A Coruña, Spain

José Juan Gómez de Diego, Cardiovascular Institute, Hospital Universitario San Carlos, Madrid 28040, Spain

Julia Grapsa, Cardiology Department, St Bartholomew Hospital, Barts Health Trust, London EC1A 7BE, United Kingdom

Ricardo Fontes-Carvalho, Cardiology Department, Centro Hospitalar Gaia, University of Porto, Porto 4434-502, Portugal

Corresponding author: Rafael Vidal-Perez, MD, PhD, Doctor, Reader (Associate Professor), Staff Physician, Heart Failure Unit, Cardiology Department, Hospital Clinico Universitario de Santiago, Travesía da Choupana s/n, Santiago de Compostela 15706, A Coruña, Spain.
rafavidal@hotmail.com
Telephone: +34-981-950757

Abstract

Social media has changed the way we learn, educate, and interact with our peers. The dynamic nature of social media and their immediate availability through our portable devices (smartphones, tablets, smartwatches, *etc.*) is quickly transforming the way we participate in society. The scope of these digital tools is broad as they deal with many different aspects: Teaching and learning, case discussion, congresses coverage, peer to peer interaction, research are examples worth mentioning. The scientific societies considered more innovative, are promoting these tools between their members. These new concepts need to be known by the cardiologists to stay updated, as countless information is moving rapidly through these channels. We summarize the main reasons why learning how to use these tools to be part of the conversation is essential for the cardiologist in training or fully stablished.

Key words: Social media; Cardiology; Congress; Learning; Teaching; Interaction; Cardiovascular diseases; Impact Factor; Portable devices; Smartphone; Tablet

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Social media has changed the way we learn, educate, and interact with our

M, Teragawa H, Ueda H
S-Editor: Ma RY
L-Editor: A
E-Editor: Xing YX

peers. The scientific societies considered more innovative are promoting these tools between their members. These new concepts need to be known by the cardiologists to stay updated, as countless information is moving rapidly through these channels. We summarize the main reasons why learning how to use these tools to be part of the conversation is essential for the cardiologist.

Citation: Vidal-Perez R, Gómez de Diego JJ, Grapsa J, Fontes-Carvalho R, Gonzalez-Juanatey JR. Social media in cardiology: Reasons to learn how to use it. *World J Cardiol* 2019; 11(10): 217-220
URL: https://www.wjgnet.com/1949-8462/full/v11/i10/217.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i10.217

INTRODUCTION

Social media could be considered as interactive computer-mediated communication tools which have important penetration rates in the general population in middle and high-income countries. Though, in health sciences, many stakeholders (*e.g.*, clinicians, academic institutions, professional colleges, administrators, ministries of health, between others) are unconscious of social media's relevance[1].

Social media has changed the way we learn, educate, and interact with our peers. The dynamic nature of social media and their immediate availability through our portable devices (smartphones, tablets, smartwatches, *etc.*) is quickly transforming the way we participate in society[2].

The scope of these digital tools is broad as they deal with many different aspects: Teaching and learning, case discussion, congresses coverage, peer to peer interaction, research are examples worth mentioning. A good summary was shown by Snipelisky[3] about the 4 main reasons to be involved with social media tools: Personal use, networking, education and public health. There are many others, but these 4 aspects are probably the main points. As other authors have highlighted literacy in the "Digital Age" it is a necessity. The two unquestioned realities of the digital times are that you can produce your online digital story, or someone else will make it for you[4].

REASONS TO LEARN HOW TO USE SOCIAL MEDIA

Social media tools like Twitter could be considered as a new core competency for cardiologists[5]. Why is so important? Twitter can be used to learn, educate, network, and advocate; and these four reasons together give to the social media experts access to great opportunities.

Many authors underline the potential for engagement between peers, there are no boundaries and the communications are near to be immediate[6,7]; even some people believe that mentoring could be possible through social media[8]. Also contact with patients could be done through Social media but we must be cautious with these approach[9].

Another reason to pay attention to these tools is the impact in the cardiology congresses, probably it is the best way to follow minute to minute a congress at home, previously you needed to wait for your partners coming from the Congress or read web chronicles or article publications, now is at the same time all over the world. You only need to search or follow a congress hashtag (like #ACC18 or #ESCCongress or #AHA17), after that you will reach all the content like you were in the congress arena[10,11]. The impact of social media could be measured through the hashtags and is really high as we show in Table 1.

Another motive to be involved in social media is to reach a good knowledge about the current scientific research and discuss it with peers, maybe the discussion in social media could increment the citations of the papers or even to increase the impact of the author in the community when they discuss directly their research[12,13]. In the last years, many journals are adopting a strategy to spread the journal content through social media[14]. New ways to measuring the impact metrics of the research publications through social media are used now, one of the best examples Altmetrics[15], that maybe could compete with the classic impact factor in the future.

Another interesting social media tool that needs to be mentioned is Youtube, as the

Table 1 Impact of Cardiology Social Media by conference hashtag measurement

Conference hashtag	Hashtag registration date[1]	Total tweets[2] (thousands)	Total retweets (thousands)	Total participants (thousands)	Digital impressions[3] (millions)	Visuals[4] (thousands)	Papers[5] (thousands)
#AHA17	06/29/17	62.0	42.4	17.4	339.1	44.5	17.7
#ACC18	12/11/17	51.4	35.6	10.1	372.5	42.2	14.8
#ESC18	12/29/17	54.5	20.0	23.8	137.5	17.9	4.6

[1]Registration date reflects the date the hashtag was registered with symplur.com. Individual hashtag data is from the registration date to access on September 22, 2018;
[2]The total number of unique tweets since the hashtag was registered on symplur.com;
[3]Impressions are computed by taking the number of times an account has tweeted multiplied by the account's number of followers repeated for all accounts, then finally summed up;
[4]The total number of times each photo, GIF, or video was shared;
[5]The total number of papers or links/URLs shared. Data from Symplur signals[23].

second common search engine after Google. Many journals or scientific societies are using it for the dissemination of content and interaction with their potential audience[16].

If you are an academic leader probably you need to embrace the social media tools as there is a need for leadership on the social media discussions; the classic leaders are reluctant to abandon the typical forums of debate and the discussion it will be not there again, the audience is worldwide and the way to discuss is quickly changing[17,18].

For sure the future research will be about social media use, and it will focus on the impact on public health and the education of patients without any doubt. It is not noise it is a great opportunity[19-21].

CONCLUSION

The scientific societies considered more innovative are promoting these tools between their members. These new concepts need to be known by the cardiologists in training or fully stablished to stay updated, as countless information is moving rapidly through these channels. Do as the cardiology leadership is doing and don´t stay away from social media, there are more benefits than threats there[22].

REFERENCES

1 **Grajales FJ**, Sheps S, Ho K, Novak-Lauscher H, Eysenbach G. Social media: a review and tutorial of applications in medicine and health care. *J Med Internet Res* 2014; **16**: e13 [PMID: 24518354 DOI: 10.2196/jmir.2912]
2 **Parwani P**, Choi AD, Lopez-Mattei J, Raza S, Chen T, Narang A, Michos ED, Erwin JP, Mamas MA, Gulati M. Understanding Social Media: Opportunities for Cardiovascular Medicine. *J Am Coll Cardiol* 2019; **73**: 1089-1093 [PMID: 30846102 DOI: 10.1016/j.jacc.2018.12.044]
3 **Snipelisky D**. Social Media in Medicine: A Podium Without Boundaries. *J Am Coll Cardiol* 2015; **65**: 2459-2461 [PMID: 26046741 DOI: 10.1016/j.jacc.2015.04.019]
4 **Mandrola J**. RESPONSE: The Necessity of Social Media Literacy. *J Am Coll Cardiol* 2015; **65**: 2461 [PMID: 26244189]
5 **Alraies MC**, Raza S, Ryan J. Twitter as a New Core Competency for Cardiologists. *Circulation* 2018; **138**: 1287-1289 [PMID: 30354418 DOI: 10.1161/CIRCULATIONAHA.118.032999]
6 **Alraies MC**, Sahni S. Why cardiologists should be on social media - the value of online engagement. *Expert Rev Cardiovasc Ther* 2017; **15**: 889-890 [PMID: 29164942 DOI: 10.1080/14779072.2017.1408408]
7 **Widmer RJ**, Larsen CM. Call for FITs/ECs to Become Engaged With Social Media. *J Am Coll Cardiol* 2016; **68**: 422-425 [PMID: 27443439 DOI: 10.1016/j.jacc.2016.06.003]
8 **Wong K**, Swamy L, Jardine LDA. #TipsForNewDocs: Mentoring From Miles Away. *J Grad Med Educ* 2017; **9**: 674-675 [PMID: 29075404 DOI: 10.4300/JGME-D-17-00723]
9 **Barreto JE**, Whitehair CL. Social Media and Web Presence for Patients and Professionals: Evolving Trends and Implications for Practice. *PM R* 2017; **9**: S98-S105 [PMID: 28527508 DOI: 10.1016/j.pmrj.2017.02.012]
10 **Hudson S**, Mackenzie G. 'Not your daughter's Facebook': Twitter use at the European Society of Cardiology Conference 2018. *Heart* 2019; **105**: 169-170 [PMID: 30327394 DOI: 10.1136/heartjnl-2018-314163]
11 **Tanoue MT**, Chatterjee D, Nguyen HL, Sekimura T, West BH, Elashoff D, Suh WH, Han JK. Tweeting the Meeting. *Circ Cardiovasc Qual Outcomes* 2018; **11**: e005018 [PMID: 30571329 DOI: 10.1161/CIRCOUTCOMES.118.005018]
12 **Capodanno D**. Twitterature. *EuroIntervention* 2018; **14**: e959-e961 [PMID: 30307394 DOI:

10.4244/EIJV14I9A170]
13 **Serruys PW**, Onuma Y. Twitterature: will social media have an impact on scientific journals? *EuroIntervention* 2018; **14**: e962-e964 [PMID: 30307395 DOI: 10.4244/EIJV14I9A171]
14 **Ladeiras-Lopes R**. New from ESC: ESC Journals Twitter. *Eur Heart J* 2017; **38**: 3340 [PMID: 29206968 DOI: 10.1093/eurheartj/ehx676]
15 **Crotty D**. Altmetrics. *Eur Heart J* 2017; **38**: 2647-2648 [PMID: 28934843 DOI: 10.1093/eurheartj/ehx447]
16 **Smith AA**. YouTube your science. *Nature* 2018; **556**: 397-398 [PMID: 29666498 DOI: 10.1038/d41586-018-04606-2]
17 **Pawar S**, Siddiqui G, Desai NR, Ahmad T. The Twittersphere Needs Academic Cardiologists!: #heartdisease #No1Killer #beyondjournals. *JACC Heart Fail* 2018; **6**: 172-173 [PMID: 29226817 DOI: 10.1016/j.jchf.2017.10.008]
18 **Yeh RW**. Academic Cardiology and Social Media: Navigating the Wisdom and Madness of the Crowd. *Circ Cardiovasc Qual Outcomes* 2018; **11**: e004736 [PMID: 29650720 DOI: 10.1161/CIRCOUTCOMES.118.004736]
19 **Redfern J**, Ingles J, Neubeck L, Johnston S, Semsarian C. Tweeting our way to cardiovascular health. *J Am Coll Cardiol* 2013; **61**: 1657-1658 [PMID: 23500293 DOI: 10.1016/j.jacc.2013.01.041]
20 **Turakhia MP**, Harrington RA. Twitter and Cardiovascular Disease: Useful Chirps or Noisy Chatter? *JAMA Cardiol* 2016; **1**: 1036-1037 [PMID: 27680424 DOI: 10.1001/jamacardio.2016.3150]
21 **Gouda P**, Das D, Clark A, Ezekowitz JA. The Impact and Implications of Twitter for Cardiovascular Medicine. *J Card Fail* 2017; **23**: 266-267 [PMID: 28010999 DOI: 10.1016/j.cardfail.2016.12.005]
22 **Walsh MN**. Social Media and Cardiology. *J Am Coll Cardiol* 2018; **71**: 1044-1047 [PMID: 29495984 DOI: 10.1016/j.jacc.2018.01.037]
23 **Symplur Signals**. 2019; [accessed 2019 May]. Available from: https://www.symplur.com/signals/

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 October 26; 11(10): 221-235

DOI: 10.4330/wjc.v11.i10.221

ISSN 1949-8462 (online)

REVIEW

Cellular models for human cardiomyopathy: What is the best option?

Nerea Jimenez-Tellez, Steven C Greenway

ORCID number: Nerea Jimenez-Tellez (0000-0001-8898-2165); Steven Clive Greenway (0000-0002-6981-1720).

Author contributions: Both authors contributed to the writing of this paper.

Supported by Children's Cardiomyopathy Foundation.

Conflict-of-interest statement: No potential conflicts of interest.

Open-Access: This is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: March 11, 2019
Peer-review started: March 12, 2019
First decision: June 13, 2019
Revised: June 17, 2019
Accepted: September 22, 2019
Article in press: September 22, 2019
Published online: October 26, 2019

P-Reviewer: Nurzynska D, Vidal-Perez R
S-Editor: Gong ZM
L-Editor: A

Nerea Jimenez-Tellez, Department of Biochemistry & Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary, AB T2N 4N1, Canada

Steven C Greenway, Departments of Pediatrics, Cardiac Sciences, Biochemistry & Molecular Biology, Cumming School of Medicine, Libin Cardiovascular Institute of Alberta, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB T2N 4N1, Canada

Corresponding author: Steven C Greenway, MD, Assistant Professor, Staff Physician, Departments of Pediatrics, Cardiac Sciences, Biochemistry & Molecular Biology, Cumming School of Medicine, Libin Cardiovascular Institute of Alberta, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB T2N 4N1, Canada. scgreenw@ucalgary.ca
Telephone: +1-403-9555049
Fax: +1-403-9557621

Abstract

The genetic cardiomyopathies are a group of disorders related by abnormal myocardial structure and function. Although individually rare, these diseases collectively represent a significant health burden since they usually develop early in life and are a major cause of morbidity and mortality amongst affected children. The heterogeneity and rarity of these disorders requires the use of an appropriate model system in order to characterize the mechanism of disease and develop useful therapeutics since standard drug trials are infeasible. A common approach to study human disease involves the use of animal models, especially rodents, but due to important biological and physiological differences, this model system may not recapitulate human disease. An alternative approach for studying the metabolic cardiomyopathies relies on the use of cellular models which have most frequently been immortalized cell lines or patient-derived fibroblasts. However, the recent introduction of induced pluripotent stem cells (iPSCs), which have the ability to differentiate into any cell type in the body, is of great interest and has the potential to revolutionize the study of rare diseases. In this paper we review the advantages and disadvantages of each model system by comparing their utility for the study of mitochondrial cardiomyopathy with a particular focus on the use of iPSCs in cardiovascular biology for the modeling of rare genetic or metabolic diseases.

Key words: Cardiomyopathy; Mitochondria; Induced pluripotent stem cells; Fibroblasts; Cellular models

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

E-Editor: Xing YX

Core tip: Several experimental model systems exist for the modeling of cardiomyopathies, including those caused by rare metabolic or mitochondrial diseases. We compare and contrast the cellular models that have been used to date to model several different mitochondrial disorders with a particular focus on the advantages and disadvantages of induced pluripotent stem cells.

Citation: Jimenez-Tellez N, Greenway SC. Cellular models for human cardiomyopathy: What is the best option? *World J Cardiol* 2019; 11(10): 221-235
URL: https://www.wjgnet.com/1949-8462/full/v11/i10/221.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i10.221

INTRODUCTION

The cardiomyopathies are defined as a group of diseases of the heart characterized by abnormal structure and function of the myocardium[1]. The cardiomyopathies have been classically grouped according to cardiac morphology with the major categories being: hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy and left ventricular non-compaction cardiomyopathy (LVNC)[2]. These groups can be further subdivided into genetic and acquired forms based on disease mechanism[2]. The genetic cardiomyopathies generally arise in childhood or early adulthood and include metabolic and monogenic diseases.

The inborn errors of metabolism (IEM) are a heterogeneous group of rare genetic diseases caused by defects in energy production or intermediary metabolism[3,4]. Within the pediatric cardiomyopathies, IEM affect between 5% and 26% of infants and children[5]. There are more than 40 different IEM that are associated with the development of cardiomyopathy[3]. The mitochondrial cardiomyopathies represent the largest subset and result from pathologic mutations in either mitochondrial or nuclear genes[6] that ultimately lead to dysfunction of the electron transport chain[7], the main supplier of cellular energy under aerobic conditions[8]. Since the heart is one of the most energy-demanding organ in the body[9], cardiomyopathies are found in 20%-40% of children with mitochondrial disease[10]. Given the early onset of these devastating multisystem diseases, research into disease mechanism and the identification of potential therapeutics is essential. However, the heterogeneity and rarity of the IEM and the mitochondrial cardiomyopathies preclude randomized clinical drug trials with standardized end-points. This makes disease modelling using animals or cells an essential component in the study of these diseases.

ANIMAL MODELS

The use of animal models for research, with rodents in particular, continues to represent the most commonly used and successful approach in reductionist biology. However, despite its many successes, this methodology is still questioned because of ethical implications, the frequent inability to totally recapitulate human genetic variability[11] and the fact that important species-specific differences exist for many aspects of biology which complicate both the study of disease and the translation of therapies into human subjects[12]. For example, in cardiac research specifically, the use of rodent models may be limited due to substantial biological differences in the cardiovascular system between rodents and humans. Rodent hearts beat at considerably higher heart rates (200-300 beats per minute) than humans (60-100 beats per minute)[13] and the duration of the ventricular action potential is significantly shorter in rodents[14] compared to humans[15]. Additionally, cardiomyocytes differ in the proteins expressed in the myofilaments, which affects repolarization and calcium sensitivity[13]. One potential strategy to improve the utility of animal models is to create "humanized models" using genetic engineering[11] or engrafting animals with human cells or tissues and immune suppressing them to prevent rejection of the foreign material[16]. Although this type of model is useful for studying many conditions including cancer[17], infectious diseases[18] and liver disease[19], they have important limitations, especially in terms of time, cost and difficulties in creation and maintenance. Furthermore, these hybrid animal models are often not feasible for studying the heart and cardiovascular system.

CELLULAR MODELS FOR CARDIOVASCULAR DISEASE

The adult mammalian heart is composed of multiple cell types, including cardiomyocytes, fibroblasts, endothelial cells, vascular and perivascular cells. The composition of the heart varies greatly between species[20] but, in humans, cardiomyocytes are the dominant cell type by volume, encompassing 70%-85% of the total heart. Cardiomyocytes give rise to specialized cells such as atrial myocytes, ventricular myocytes and Purkinje cells[21] and are responsible for the generation of contractile force[22]. However, although the other cell types only account for a small portion of the overall total myocardial mass, they are essential for maintaining homeostasis by providing the extracellular matrix and intercellular communication networks necessary to ensure proper cardiac function[23]. Although cardiomyocytes may be dominant by volume, they are not the most abundant cells. Fibroblasts are actually the most common cell type in the heart and are vital for maintaining the structure, mechanical and electrical functions of the heart[24]. Cardiomyocytes and fibroblasts are the best-studied cardiac cells and, since both cell types have important functions in the heart, we would suggest that both need to be examined to fully comprehend the cardiomyopathies.

Cell culture, using cardiomyocytes, fibroblasts and other cardiac-related cells, represents another well-established system to study human biology, understand disease and assess response to therapeutics. Primary cells and immortalized cell lines derived from human tissues represent two commonly-used experimental models. Primary cells reflect disease biology most faithfully since they are directly isolated from the tissue of interest and they maintain the morphology, function and protein markers in the dish as they possessed *in vivo*, but they are relatively delicate cells that can be difficult to maintain in culture and have a finite lifespan with limited potential for expansion[25]. Immortalized cells are derived by altering cell-cycle check points or modifying telomerase activity and, although these cells don't have a limited lifespan and are capable of sustained active proliferation, they frequently contain genetic aberrations that can accumulate over time and lead to cellular behaviours that are distinct from those demonstrated *in vivo*[26].

Another approach to model disease involves the use of patient-derived cells. These cells are obtained from an individual patient and therefore allow for the study of human disease in its original genetic context and also have important advantages over primary or immortalized cells. The two most commonly used patient-derived cell types used for research today are induced pluripotent stem cells (iPSCs) and fibroblasts. Given that the genetic background for an individual is preserved, the use of these patient-specific cells represents perhaps the best tool to realize personalized medicine[27]. Personalized medicine refers to a health care approach which recognizes each person's distinct genetic, clinical and environmental history[28]. Personalized medicine ideally adapts therapeutics in order to ensure the best response and safety for the treatment of specific diseases with an individualized approach[29]. Using patient-specific cells can help realize this vision by helping researchers identify and understand individual differences.

In conclusion, there are important differences between model systems (Table 1), with advantages and disadvantages that are often dependent on the condition being studied. In reality, a combination of models enabling both *in vivo* and *in vitro* studies is often required. In this paper, our main focus will be to discuss and compare the different cell types which could be useful for studying genetic cardiomyopathies as an alternative to primary cardiac cells. We will illustrate our discussion with examples of mitochondrial cardiomyopathies that have been studied using different cellular models.

IMMORTALIZED CELL LINES

Immortalized cells are defined as cells whose proliferative capacity has been enhanced using different methods[30]. There are a variety of established approaches to immortalize cell lines including the introduction of oncogenes[31-33], viral transformation[34,35], the inactivation of tumor suppressor genes[36,37] or the inactivation of telomere-controlled senescence[38]. The establishment of immortalized cell lines has helped the scientific community to study different biological and molecular events[26], although, this approach has been questioned since these immortalized cells differ significantly from cells with an intact cell cycle control and they are more similar to malignant cells in many respects. Therefore, the results obtained with these cells can potentially be misleading if these differences are not considered[39]. However, the use of immortalized cells still remains one of the most popular models for the study of

Table 1 Comparison between animal and cell models

Properties	Animal	Cellular
Maintain genetic background	No	Yes
Cost of maintenance	Expensive	Less Expensive
Ease of maintenance	Simple	Difficult
Time required	+++	+
Drug effects	Potentially not translatable	Translatable
Study of paracrine effects	Yes	No
Study of circulatory effects	Yes	No

disease.

Immortalized cells have been used to study two inherited diseases caused by point mutations in mitochondrial DNA (mtDNA), mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), and myoclonic epilepsy and ragged-red fibres (MERRF). In both diseases, an alteration in the post-transcriptional modification of a uridine located in an essential position of specific mitochondrial tRNAs, causes oxidative phosphorylation impairment that leads to the inability to generate sufficient ATP to meet the energy demands of the cell[40]. These mitochondrial disorders can be caused by mutations in several genes but, in this example, the immortalized cells were used to model the effect of an A>G transition at nucleotide 3243 in the $tRNA^{Leu}$ gene causing MELAS[41] and a A>G change in the $tRNA^{Lys}$ gene at position 8344 causing MERRF[42]. Two different studies recapitulated these diseases using cybrid cells[43,44]. Cytoplasmic hybrid cells (cybrid) are created using a recipient cell line called rho-zero cells, whose mtDNA has been depleted but the nuclear DNA remains intact and a donor cell which provides mtDNA to the union[45]. This approach has the advantage of being able to isolate mtDNA from a donor patient with a specific mtDNA mutation, allowing for the study of the pathology in an immortalized cell line.

Another rare human disorder, Barth syndrome (BTHS) was studied using immortalized cell lines. BTHS is an X-linked recessive disorder characterized by early-onset cardiomyopathy (usually LVNC or DCM), skeletal muscle weakness and neutropenia related to abnormal mitochondrial structure[46]. Disease severity is highly variable, with patients ranging from being asymptomatic to having severe cardiomyopathy and end-stage heart failure[47]. Studies have shown that BTHS is caused by loss-of-function mutations in the tafazzin (*TAZ*) gene[48]. *TAZ* is a phospholipid transacylase located in the inner mitochondrial membrane and is responsible for remodeling of the phospholipid cardiolipin[49] which is an essential component of the mitochondrial membrane[50,51]. The *TAZ* gene consists of 11 different exons[52] and mutations have been identified in each exon, primarily missense mutations, although small insertions and deletions have also been found[53].

To study BTHS, the authors used a myoblast cell line (C2C12) derived from mouse skeletal myoblast cells, which is commonly used as a model of disease in mammals for skeletal muscle disorders and myopathies[54,55]. The authors designed a stable TAZ knockout (KO) using clustered regularly interspaced short palindromic repeats (CRISPR) technology to target exon 3 in mouse TAZ and cloned it into a plasmid together with the Cas9 nuclease and co-transfected into the cells with a plasmid that allowed for selection with puromycin[56]. With the introduction of the plasmids into the cell, the guide RNA binds to exogenous exon 3, and this binding is recognized by the nuclease, which performs the cutting of the gene, disrupting it. The clone whose genomic TAZ DNA band was fragmented into three pieces was the chosen one to be the model of the disease. According to the authors, this model served to recapitulate BTHS, being consistent with other previous models, showing mitochondrial defects such as accumulation of monolyso-cardiolipin, impaired mitochondrial respiration and increased mitochondrial ROS species[56].

Although these studies have used different immortalized cell models, these might not be the best tool to recapitulate the diseases with accuracy. First of all, these cells are derived either from tumors or from the immortalization of other cell times where the cell cycle or the telomerase activity is compromised, therefore, these cells do not resemble normal cell lines in terms of replication and lifespan and, consequently, this can cause genetic and phenotypic variation over time leading to create heterogeneity in the same cell line[57]. Secondly, these cell lines, like all cell lines are vulnerable to contamination (*e.g.*, Mycoplasma) which can remain undetected and modify cell behaviour and gene expression[58]. Finally, the use of cellular models generated by

using techniques that knockout a gene in particular in a cell line, might not be sufficient to recapitulate the entire spectrum of disease since additional genetic modifiers are not reproduced.

FIBROBLASTS

Fibroblasts are the major stromal cell-type present in connective tissue and are characterized by a flattened and elongated shape with a central nucleus[59] (Figure 1). They are derived from mesenchymal precursors and are part of a heterogenous collection of cells widely distributed over the body. Fibroblasts play an important role in connective tissue by producing extracellular matrix compounds, principally collagen type I and III. Fibroblasts not only have a structural role but they are able to repair damaged tissue by migrating to the site of injury and rapidly proliferating to restore the wounded area[60]. This proliferation potential explains why fibroblasts are so widely used and why they grow *in vitro* very easily[61]. In addition to their growth-related properties, fibroblasts are also increasingly recognized as an important contributor to cardiac biology through cell-cell signalling and physical interactions[62,63]. Unfortunately, fibroblasts have distinct electrophysiological properties and these cells are not electrically excitable despite the presence of multiple ion channels, including potassium and sodium channels[64]. Fibroblasts also lack a specific cell surface marker that distinguishes them from other cell types[65]. However, they can be isolated from a skin biopsy and grown in culture[66] but they do have a limited lifespan[67], so their use to study function, structure and disease mechanism is limited to cells that have not undergone an excessive (< 20) number or cell divisions or passages[66].

Fibroblasts have also been used to study MELAS and MERRF. This study demonstrated that the tRNA point mutations did not modify the number of normal mitochondria but there were important differences found regarding the number of secondary lysosomes and residual bodies in both diseases compared to the control cells[68]. Furthermore, in both diseases, there was impaired respiratory enzyme activity which decreased mitochondrial respiration rate and membrane potential and impacted cell viability due to the inability to synthesize enough ATP to meet the energy requirements of the cell[68]. Even though the cell types affected by MELAS and MERRF in humans are mainly neurons and myocytes[69,70], the easily obtainable skin fibroblasts were sufficient to provide a helpful model to understand some of the mechanisms by which these cell types are compromised. Fibroblasts were also used in BTHS to help understand the molecular basis of the disease. As previously mentioned, diverse mutations have been found in each exon of TAZ, however, there is no clear correlation between the gene mutation type and the different patient phenotypes[71]. The authors used fibroblasts from pediatric patients to correlate the severity of the disease with cellular lipid abnormalities and found that there was abnormal composition of cardiolipin, phosphatidyl-choline and phosphatidylethanolamine[72]. In this study fibroblasts allowed the distinct lipid composition for each patient to be characterized, which enabled insight into the phenotypic complexity of the disease[72].

Although all these studies successfully used fibroblasts to analyze different mitochondrial cardiomyopathies, all studies had to work within the limitation of fibroblast passage number. The passage number refers to the number of times that the cell can undergo cell division and replication. Studies have shown that, with every passage, the number of mitochondria decreases and that there are changes in the structure of these organelles[73]. If not recognized and controlled for, these changes have the potential to mislead researchers into making false conclusions regarding mitochondrial morphology and function.

IPSCS

iPSCs were first created in 2006 after Shinya Yamanaka successfully reprogrammed adult mouse fibroblasts into iPSCs by introducing the pluripotency factors Oct3/4 (Octamer binding transcription factor 3/4), Sox2 (sex determining region Y)-box 2), c-Myc and Kfl4 (Kruppel Like Factor-4) under embryonic stem cells (ESC) conditions[74]. ESCs are derived from the inner cell mass of mammalian blastocysts and possess self-renewal capacity, the ability to grow with an unlimited lifespan and the ability to maintain pluripotency and differentiate into every cell type of the three germ layers[75,76]. The iPSCs created with these "Yamanaka factors" showed the morphology (Figure 2), proliferative properties and gene expression associated with pluripotency

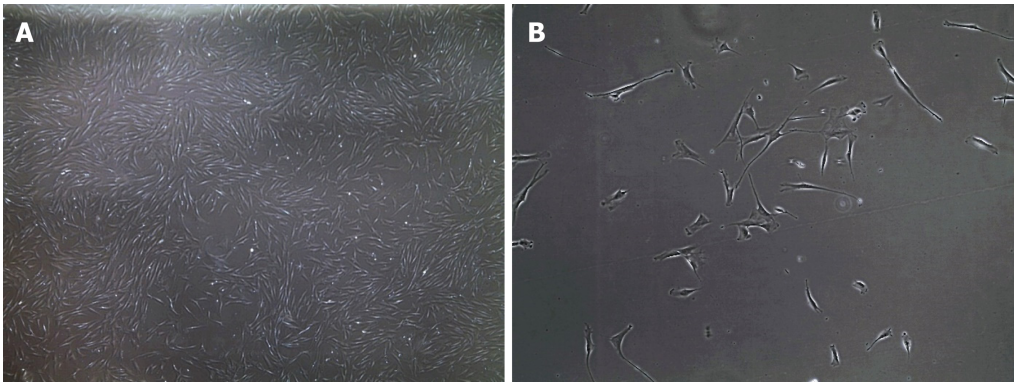


Figure 1 Bright field microscopy images of human fibroblasts. A: 4 × magnification; and B: 20 × magnification.

in ESCs[74] but, importantly, did not have to be derived from discarded human embryos. Currently, iPSCs can be created from a variety of mature, differentiated cells most commonly fibroblasts and peripheral blood mononuclear cells[77].

There are several technical approaches for the delivery of the four critical pluripotency factors necessary for cellular reprogramming to occur[78]. There are integrating methods that include retroviral transduction[74], lentiviral delivery[79] and non-integrative methods such as adenoviral transduction[80], plasmid DNA (episomal) transfer[81], lox p lentivirus delivery[82], Sendai virus delivery[83], piggyBAC transposon[84], protein-mediated (polyarginine-tagged polypeptide)[85] and modified synthetic mRNA[86] (Table 2). Each methodology has its advantages and disadvantages[87-89] and the choice of delivery vector can have important implications in downstream applications and, therefore, needs to be considered carefully.

Once created, iPSCs have significant advantages compared to other cell types as a model of disease. Since they possess the ability to self-renew, there is no concern about how many passages the cells can tolerate and these cells can be relatively easily expanded *in vitro* and be used for many experiments[90]. Furthermore, since they can be differentiated into mostly every cell type[91], researchers can generate patient-disease- and tissue-specific cells for the disease of interest.

DIFFERENTIATION of IPSCS INTO CARDIOMYOCYTES

Most applications using iPSCs to study human heart disease have differentiated them into beating cardiomyocytes[92] although one group (discussed later) took a rather unique approach and differentiated the iPSCs back into fibroblasts[93]. There are several different published and commercial methods to differentiate iPSCs into cardiomyocytes all of which are generally based on the signaling factors that are part of the developmental pathway of cardiomyocytes *in vivo*[94-96] (Figure 3).

Although the ability to generate patient- and disease-specific beating cardiomyocytes is a powerful tool for the study of individual cardiomyopathies[97], the cardiomyocytes that are generated using current methods do have some limitations. First of all, following differentiation, the final population of cardiomyocytes are not completely homogeneous. Differentiated cells contain a mixture of atrial, ventricular and Purkinje cell-types with variable functional properties[98]. If a homogeneous population is desired, it may be necessary to select for the cellular subpopulation of interest using sorting techniques based on surface marker expression[99] or genetic selection[100] which further complicates the process requiring additional time and expense and exposes the cells to additional handling and stresses which they may not survive. Furthermore, for some cell types, *e.g*. ventricular myocytes, unique cell surface markers do not exist[101]. Another issue is that the cardiomyocytes obtained using current differentiation strategies have a phenotype resembling fetal cells in terms of structure, molecular markers and metabolism[102]. This lack of maturity can require additional steps (which are not fully established or reliably reproducible at this time) or additional time in culture to obtain a more adult-like cardiomyocyte population[103] Several methods to stimulate the maturation of iPSC-derived cardiomyocytes have been published based upon electrical[104], mechanical[105], chemical stimulation[106] or matrix modification[107]. This is currently an area of active investigation and future advances and improvements are certain which will further enhance the utility of iPSC-CMs for the study of genetic cardiomyopathies. However, even with these functional limitations of derived cells, they have been helpful for

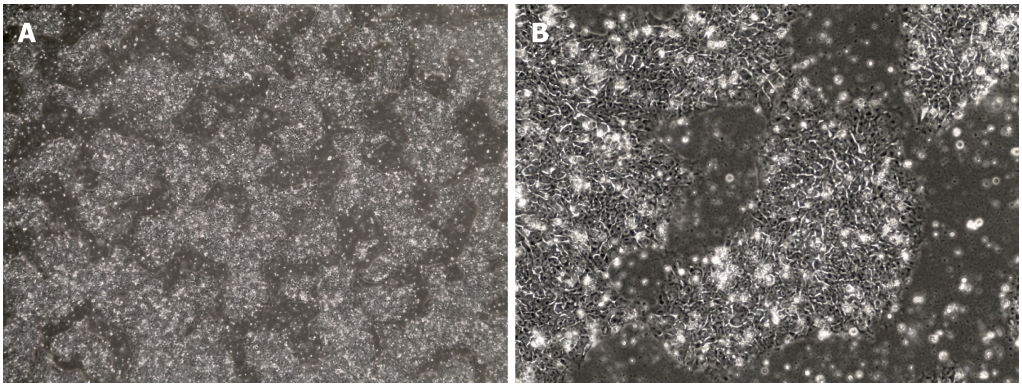


Figure 2 Bright field microscopy images of human induced pluripotent stem cells. Cells display a round morphology with a large nucleus and grow firmly packed in colonies. A: 4 × magnification. B: 20 × magnification.

scientists seeking insight into cardiac biology and disease[108,109].

STUDYING GENETIC CARDIOMYOPATHIES USING IPSCS

Primary fibroblasts from a patient with MELAS were reprogrammed into iPSCs using a retroviral approach in order to establish a novel disease model[110]. As standard practice, the differentiation capacities of the iPSCs were tested using a teratoma formation assay to demonstrate that the cells were capable of generating all germ layers and immunocytochemistry for the pluripotency markers Oct-4 and SSEA-4 was performed to confirm pluripotency. Tissues in MELAS patients can vary in the levels of abnormal mitochondria (heteroplasmy)[111] so the researchers assessed this in patient cells using quantitative real-time PCR to measure mutation ratios and mtDNA copy number. They found that different fibroblast lines had different levels of heteroplasmy ranging from < 5% to 95%. They then demonstrated that those fibroblasts with lower levels of heteroplasmy showed increased heteroplasmy after several passages while those with higher levels did not vary significantly after multiple passages. There were also variations with regards to mtDNA copy number after each passage. This data suggests that the mitochondrial abnormalities in patient fibroblasts can change over time in culture. However, because of their importance in cardiac biology, the authors still wanted to study MELAS. Therefore, the MELAS iPSCs were differentiated back into fibroblasts but, because of the unique self-renewing properties of iPSCs, the authors could overcome passage-associated changes in the mitochondria. In the fibroblasts derived from patient iPSCs, levels of heteroplasmy were found to be similar to the iPSCs from which they were differentiated. These iPSC-derived fibroblasts were then characterized with regards to the enzymatic activities of the mitochondrial respiratory complexes and compared to primary skin fibroblasts. These studies revealed that the iPSC-derived cells recapitulated the disease phenotype and did not demonstrate altered levels of heteroplasmy in culture and therefore represent a unique and novel *in vitro* model of MELAS[110].

MERRF has also been studied using retrovirus-reprogrammed iPSCs. In this study, they generated iPSCs from patient dermal fibroblasts. After reprogramming the fibroblasts using OCT4, SOX2, KLF4, and GLIS1 delivered into the cells, they differentiated the resulting iPSCs into the two different cell types most involved in the disease, cardiomyocytes (iPSC-CMs)[112] and neural progenitor cells (iPSC-NPCs). When they tested all three cell types, they found that all MERRF patient-derived cells (iPSCs, iPSC-CMs and iPSC-NPCs) had reduced oxygen consumption, elevated reactive oxygen species (ROS), reduced growth and fragmented mitochondria. The cellular phenotype correlated with the molecular mechanism of the disease, allowing iPSCs and iPSC-derived cells to serve as a model for the disease[93].

Differentiated iPSCs have also been used in the study of BTHS. The cells of two unrelated patients were reprogrammed using either retroviral[113] or modified RNA approaches[114]. These two patients had different mutations in TAZ, one having a frameshift mutation and the other a missense mutation. After the generation of the iPSCs, they differentiated them into cardiomyocytes that they then used to create tissue layers and a heart-on-chip model[115]. The iPSC-CMs showed abnormalities in cardiolipin processing, sarcomere assembly, myocardial contraction, ROS production and cardiomyocyte functioning, correlating with the abnormalities and cardiac

Table 2 Methods of delivery for reprogramming factors

Method	Advantages	Disadvantages
Retroviral transduction	Efficient, validated for multiple cell types, easy	Transgene integration
Lentiviral delivery	Very efficient	Transgene integration
Adenoviral transduction	Does not integrate	Low efficiency, only validated for fibroblasts
Plasmid DNA transfer (episomal)	Good efficiency, does not integrate, able to replicate autonomously, validated for multiple cell types	Low efficiency in fibroblast reprogramming
Lox p lentivirus delivery	High efficiency, excision of the integrated sequence, gene expression profile closer to hES cells	Genomic instability and genome rearrangements and loxP site remains integrated
Sendai virus	Efficient, does not integrate, validated for multiple cell types	Cost if purchased commercially or challenging if generated by a laboratory
PiggyBAC transposon	Efficient, precise and efficient self-excision, does not remain integrated	Published work only in fibroblasts, licensing patent issues, pBt gene may remain active post-transposition
Polyarginine tagged polypeptide	Does not integrate	Low efficiency, time-consuming, technically challenging and work only on fibroblasts
RNA modified synthetic mRNA	Very efficient, does not integrate, factor available commercially	Cost if purchased commercially or challenging if generated by a laboratory and work only on fibroblasts

dysfunction observed in patients, demonstrating again that is possible to use an *in vitro* model to provide insight into human disease and test potential therapeutics[116].

iPSC-CMs have also been used to study other cardiomyopathies. For example, iPSC-CMs have also been used to understand the pathological effects caused by the reduced expression of frataxin (FXN) in Friedreich ataxia (FA). This neurodegenerative disease is caused by the expansion of a short tandem repeat (GAA) in the *FXN* gene, which can result in transcriptional silencing[117] and therefore, the development of HCM[118] which is an important component of the disease phenotype but its development is not understood. In this study, the researchers generated iPSCs from three patients using an episomal reprogramming approach and then differentiated the resulting iPSCs into cardiomyocytes[119]. Analysis of the iPSC-CMs showed that these cells had an increased beating rate which was related to a defect in calcium handling. Therefore, these cells revealed novel biology that could potentially contribute to the future development of treatment for this disease[120]. It is important to note that this cellular phenotype could arguably not have been accomplished with any other cell type.

The DCM with ataxia syndrome (DCMA) is an autosomal recessive disorder caused by mutation in DNAJC19 and is characterized by 39% mortality[121] during early childhood due to severe heart failure[122]. DCMA has been related to BTHS due to the presence of metabolic abnormalities (*i.e.* production of 3-methylglutaconic acid) and abnormal mitochondria are thought to be responsible for heart failure[123]. Rohani *et al*[123] successfully established four patient iPSC lines that have been differentiated into CMs expressing cardiac-specific markers and this will allow for the study of four unique patient cell lines. This disease still needs to be further characterized but the use of iPSC-CMs derived from patients looks promising as a cellular model to provide a better understanding of the disease.

Finally, iPSC-CMs have also been used to study familial HCM, characterized by thickened left ventricular walls, myofiber disarrays and myocardial fibrosis that often results in arrhythmias[124]. This can be caused by different mutation in at least 11 different genes which encode sarcomeric proteins[125]. In this study, the authors generated iPSC-CMs derived from an HCM patient that had a single missense mutation in the β-myosin heavy chain (*MYH7*) gene. Whole transcriptional analysis of these iPSC-CMs provided useful insights into the disease, revealing important signaling pathways implicated in the pathogenicity of HCM[126].

FIBROBLASTS *VS* IPSCS

As we have described, both fibroblasts and iPSCs have been used to model genetic cardiomyopathies and both cell types have important advantages and disadvantages (Table 3). The characteristics of a specific cell type and the disease being studied may have an important influence on the researcher's choice of cellular model and, in some

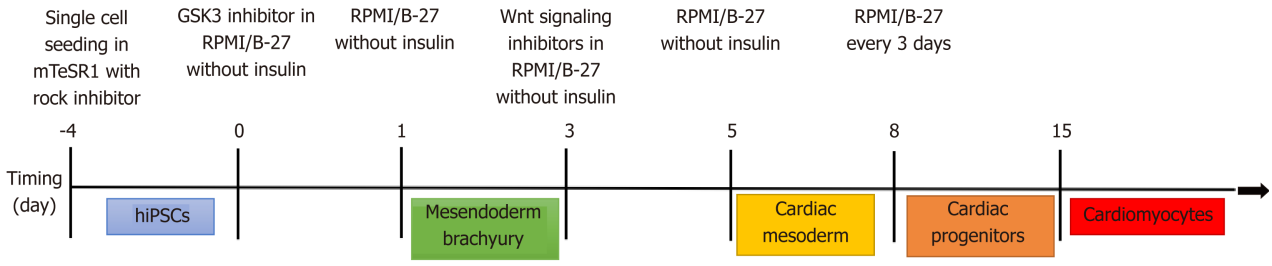


Figure 3 Cardiomyocyte differentiation protocol. Modified from Lian *et al*[135], 2012. hiPSCs: Human induced pluripotent stem cells.

situations, the study of both fibroblasts and iPSCs may be complementary. For instance, in a disease in which the interaction between cardiomyocytes and fibroblast plays a role in the development of the pathogenesis, for example in cardiac fibrosis and arrhythmias[127], the study of both cell types would likely be beneficial.

In order to solve the lifespan problem with primary cells such as fibroblasts, reversible immortalization could be performed to increase the number of passages and limit the risk for the development of aberrations in the genome[128]. In one study, this reversible immortalization was performed in primary neonatal rat cardiomyocytes using lentiviral transduction with either simian virus 40 large T antigen (TAg) or Bmi-1 together with the human telomerase reverse transcriptase (hTERT). After the cells were expanded, the introduced genes were removed using an adenoviral vector expressing Cre recombinase. The transduction of Bm1-1/hTERT into the primary cardiomyocytes successfully immortalized the cells and they maintained the expected cell morphology and presence of contact inhibition, suggesting that the cells had not become aberrant during the immortalization process[129]. This technique is an example of how genetic engineering could be used to overcome some of the limitations of cell biology which may be useful to researchers seeking to study a particular cell type.

Although patient-derived iPSCs and the differentiated cells that are created are excellent models of disease, the generation of appropriate controls is essential since they will help to define the abnormal phenotype. For some diseases that are enriched in specific populations with a unique genetic background, for example, DCMA, which is highly prevalent in the Hutterite population of southern Alberta[130], there is a need for controls who also have the same genetic background. The Hutterites are an isolated and genetically-closed population descended from a limited number of European ancestors with a communal religious lifestyle[131]. CRISPR/Cas9[132] can be used to repair the DNA mutation in patient cells to create isogenic controls[133] that are genetically identical except for a single genetic mutation background[134].

CONCLUSION

Cellular models represent an important tool for investigating rare human diseases including the genetic cardiomyopathies. Generic immortalized cells are the most commonly used cell model as they are the easiest to handle in terms of proliferation capacity, growth rate and low maintenance and can be easily genetically manipulated. Conversely, obtaining cells from individual patients allows the study of inter-individual differences and the important role of genetic modifiers in shaping disease phenotype and increases the possibility of developing personalized therapeutics. Certainly, *in vitro* models have some significant limitations but, in many cases, can provide a model that is otherwise not available. Particularly for cells differentiated from iPSCs, it is true that further research is necessary to optimize these cells but the potential for the development of an accurate and personalized cellular model is very promising for those diseases where conventional cells and animal models are limited.

Table 3 Advantages and disadvantages of different cell types for modeling disease *in vitro*

Properties	Fibroblasts	iPSCs
Proliferation capacity	+	++
Self-renewal	No	Yes
Longevity	Limited	Unlimited
Differentiation	No	Yes
Metabolism	Quiescent	Energetic
Acquisition	Easy	Difficult
Cost	+	+++
Ease of maintenance	Simple	Difficult
Necessary expertise	Low	High
Disease modeling	+	++
Structure	Single elongated cells	Round colonies/beating CM sheets
Maturation	Not applicable	Required for CM

iPSCs: Induced pluripotent stem cells; CM: Cardiomyopathy.

REFERENCES

1 **Sisakian H**. Cardiomyopathies: Evolution of pathogenesis concepts and potential for new therapies. *World J Cardiol* 2014; **6**: 478-494 [PMID: 24976920 DOI: 10.4330/wjc.v6.i6.478]
2 **Maron BJ**, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**: 1807-1816 [PMID: 16567565 DOI: 10.1161/CIRCULATIONAHA.106.174287]
3 **Cox GF**. Diagnostic Approaches to Pediatric Cardiomyopathy of Metabolic Genetic Etiologies and Their Relation to Therapy. *Prog Pediatr Cardiol* 2007; **24**: 15-25 [PMID: 19030119 DOI: 10.1016/j.ppedcard.2007.08.013]
4 **Mak CM**, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. *Crit Rev Clin Lab Sci* 2013; **50**: 142-162 [PMID: 24295058 DOI: 10.3109/10408363.2013.847896]
5 **Byers SL**, Ficicioglu C. Infant with cardiomyopathy: When to suspect inborn errors of metabolism? *World J Cardiol* 2014; **6**: 1149-1155 [PMID: 25429327 DOI: 10.4330/wjc.v6.i11.1149]
6 **Schaefer AM**, Taylor RW, Turnbull DM, Chinnery PF. The epidemiology of mitochondrial disorders--past, present and future. *Biochim Biophys Acta* 2004; **1659**: 115-120 [PMID: 15576042 DOI: 10.1016/j.bbabio.2004.09.005]
7 **El-Hattab AW**, Scaglia F. Mitochondrial Cardiomyopathies. *Front Cardiovasc Med* 2016; **3**: 25 [PMID: 27504452 DOI: 10.3389/fcvm.2016.00025]
8 **Munnich A**, Rötig A, Rio M. Defects of the Respiratory Chain. *Inborn Metabolic Diseases*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012; 223-238 [DOI: 10.1007/978-3-642-15720-2_15]
9 **Chinnery PF**, Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A. Mitochondrial Disorders Overview 2014 [PMID: 20301403]
10 **Holmgren D**, Wåhlander H, Eriksson BO, Oldfors A, Holme E, Tulinius M. Cardiomyopathy in children with mitochondrial disease; clinical course and cardiological findings. *Eur Heart J* 2003; **24**: 280-288 [PMID: 12590906]
11 **Ericsson AC**, Crim MJ, Franklin CL. A brief history of animal modeling. *Mo Med* 2013; **110**: 201-205 [PMID: 23829102]
12 **Shultz LD**, Brehm MA, Garcia-Martinez JV, Greiner DL. Humanized mice for immune system investigation: progress, promise and challenges. *Nat Rev Immunol* 2012; **12**: 786-798 [PMID: 23059428 DOI: 10.1038/nri3311]
13 **Milani-Nejad N**, Janssen PM. Small and large animal models in cardiac contraction research: advantages and disadvantages. *Pharmacol Ther* 2014; **141**: 235-249 [PMID: 24140081 DOI: 10.1016/j.pharmthera.2013.10.007]
14 **Nerbonne JM**. Studying cardiac arrhythmias in the mouse--a reasonable model for probing mechanisms? *Trends Cardiovasc Med* 2004; **14**: 83-93 [PMID: 15121155 DOI: 10.1016/j.tcm.2003.12.006]
15 **Glukhov AV**, Fedorov VV, Lou Q, Ravikumar VK, Kalish PW, Schuessler RB, Moazami N, Efimov IR. Transmural dispersion of repolarization in failing and nonfailing human ventricle. *Circ Res* 2010; **106**: 981-991 [PMID: 20093630 DOI: 10.1161/CIRCRESAHA.109.204891]
16 **Ito R**, Takahashi T, Katano I, Ito M. Current advances in humanized mouse models. *Cell Mol Immunol* 2012; **9**: 208-214 [PMID: 22327211 DOI: 10.1038/cmi.2012.2]
17 **Suemizu H**, Monnai M, Ohnishi Y, Ito M, Tamaoki N, Nakamura M. Identification of a key molecular regulator of liver metastasis in human pancreatic carcinoma using a novel quantitative model of metastasis in NOD/SCID/gammacnull (NOG) mice. *Int J Oncol* 2007; **31**: 741-751 [PMID: 17786304]
18 **Zhang L**, Meissner E, Chen J, Su L. Current humanized mouse models for studying human immunology

and HIV-1 immuno-pathogenesis. *Sci China Life Sci* 2010; **53**: 195-203 [PMID: 20596827 DOI: 10.1007/s11427-010-0059-7]
19 **Mercer DF**, Schiller DE, Elliott JF, Douglas DN, Hao C, Rinfret A, Addison WR, Fischer KP, Churchill TA, Lakey JR, Tyrrell DL, Kneteman NM. Hepatitis C virus replication in mice with chimeric human livers. *Nat Med* 2001; **7**: 927-933 [PMID: 11479625 DOI: 10.1038/90968]
20 **Pinto AR**, Ilinykh A, Ivey MJ, Kuwabara JT, D'Antoni ML, Debuque R, Chandran A, Wang L, Arora K, Rosenthal NA, Tallquist MD. Revisiting Cardiac Cellular Composition. *Circ Res* 2016; **118**: 400-409 [PMID: 26635390 DOI: 10.1161/CIRCRESAHA.115.307778]
21 **Olson EN**. A decade of discoveries in cardiac biology. *Nat Med* 2004; **10**: 467-474 [PMID: 15122248 DOI: 10.1038/nm0504-467]
22 **Woodcock EA**, Matkovich SJ. Cardiomyocytes structure, function and associated pathologies. *Int J Biochem Cell Biol* 2005; **37**: 1746-1751 [PMID: 15950518 DOI: 10.1016/J.BIOCEL.2005.04.011]
23 **Zhou P**, Pu WT. Recounting Cardiac Cellular Composition. *Circ Res* 2016; **118**: 368-370 [PMID: 26846633 DOI: 10.1161/CIRCRESAHA.116.308139]
24 **Doppler SA**, Carvalho C, Lahm H, Deutsch MA, Dreßen M, Puluca N, Lange R, Krane M. Cardiac fibroblasts: more than mechanical support. *J Thorac Dis* 2017; **9**: S36-S51 [PMID: 28446967 DOI: 10.21037/jtd.2017.03.122]
25 **Welser J**. Primary Cells Versus Cell Lines [Internet]. ScienCell Research Laboratories. 2015; [cited 2018 Jun 30] Available from: https://sciencellonline.com/blog/primary-cells-versus-cell-lines/
26 **Maqsood MI**, Matin MM, Bahrami AR, Ghasroldasht MM. Immortality of cell lines: challenges and advantages of establishment. *Cell Biol Int* 2013; **37**: 1038-1045 [PMID: 23723166 DOI: 10.1002/cbin.10137]
27 **Shaw SY**, Brettman AD. Phenotyping patient-derived cells for translational studies in cardiovascular disease. *Circulation* 2011; **124**: 2444-2455 [PMID: 22125190 DOI: 10.1161/CIRCULATIONAHA.111.043943]
28 **Chan IS**, Ginsburg GS. Personalized medicine: progress and promise. *Annu Rev Genomics Hum Genet* 2011; **12**: 217-244 [PMID: 21721939 DOI: 10.1146/annurev-genom-082410-101446]
29 **Vogenberg FR**, Isaacson Barash C, Pursel M. Personalized medicine: part 1: evolution and development into theranostics. *P T* 2010; **35**: 560-576 [PMID: 21037908]
30 **Shay JW**, Wright WE, Werbin H. Defining the molecular mechanisms of human cell immortalization. *Biochim Biophys Acta* 1991; **1072**: 1-7 [PMID: 1850299 DOI: 10.1016/0304-419X(91)90003-4]
31 **Yeh HH**, Wu CH, Giri R, Kato K, Kohno K, Izumi H, Chou CY, Su WC, Liu HS. Oncogenic Ras-induced morphologic change is through MEK/ERK signaling pathway to downregulate Stat3 at a posttranslational level in NIH3T3 cells. *Neoplasia* 2008; **10**: 52-60 [PMID: 18231638]
32 **Hurlin PJ**, Maher VM, McCormick JJ. Malignant transformation of human fibroblasts caused by expression of a transfected T24 HRAS oncogene. *Proc Natl Acad Sci U S A* 1989; **86**: 187-191 [PMID: 2643097]
33 **Kelekar A**, Cole MD. Immortalization by c-myc, H-ras, and Ela oncogenes induces differential cellular gene expression and growth factor responses. *Mol Cell Biol* 1987; **7**: 3899-3907 [PMID: 2963209]
34 **Shay JW**, Wright WE. Quantitation of the frequency of immortalization of normal human diploid fibroblasts by SV40 large T-antigen. *Exp Cell Res* 1989; **184**: 109-118 [PMID: 2551703 DOI: 10.1016/0014-4827(89)90369-8]
35 **Graham FL**, Smiley J, Russell WC, Nairn R. Characteristics of a human cell line transformed by DNA from human adenovirus type 5. *J Gen Virol* 1977; **36**: 59-74 [PMID: 886304 DOI: 10.1099/0022-1317-36-1-59]
36 **Metz T**, Harris AW, Adams JM. Absence of p53 allows direct immortalization of hematopoietic cells by the myc and raf oncogenes. *Cell* 1995; **82**: 29-36 [PMID: 7606782 DOI: 10.1016/0092-8674(95)90049-7]
37 **Yamamoto A**, Kumakura S, Uchida M, Barrett JC, Tsutsui T. Immortalization of normal human embryonic fibroblasts by introduction of either the human papillomavirus type 16 E6 or E7 gene alone. *Int J Cancer* 2003; **106**: 301-309 [PMID: 12845665 DOI: 10.1002/ijc.11219]
38 **Lee KM**, Choi KH, Ouellette MM. Use of exogenous hTERT to immortalize primary human cells. *Cytotechnology* 2004; **45**: 33-38 [PMID: 19003241 DOI: 10.1007/10.1007/s10616-004-5123-3]
39 **Kavsan VM**, Iershov AV, Balynska OV. Immortalized cells and one oncogene in malignant transformation: old insights on new explanation. *BMC Cell Biol* 2011; **12**: 23 [PMID: 21605454 DOI: 10.1186/1471-2121-12-23]
40 **DiMauro S**, Schon EA. Mitochondrial disorders in the nervous system. *Annu Rev Neurosci* 2008; **31**: 91-123 [PMID: 18333761 DOI: 10.1146/annurev.neuro.30.051606.094302]
41 **Rahman S**, Poulton J, Marchington D, Suomalainen A. Decrease of 3243 A-->G mtDNA mutation from blood in MELAS syndrome: a longitudinal study. *Am J Hum Genet* 2001; **68**: 238-240 [PMID: 11085913 DOI: 10.1086/316930]
42 **Shoffner JM**, Lott MT, Lezza AM, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. *Cell* 1990; **61**: 931-937 [PMID: 2112427 DOI: 10.1016/0092-8674(90)90059-N]
43 **Karicheva OZ**, Kolesnikova OA, Schirtz T, Vysokikh MY, Mager-Heckel AM, Lombès A, Boucheham A, Krasheninnikov IA, Martin RP, Entelis N, Tarassov I. Correction of the consequences of mitochondrial 3243A>G mutation in the MT-TL1 gene causing the MELAS syndrome by tRNA import into mitochondria. *Nucleic Acids Res* 2011; **39**: 8173-8186 [PMID: 21724600 DOI: 10.1093/nar/gkr546]
44 **Chuang YC**, Liou CW, Chen SD, Wang PW, Chuang JH, Tiao MM, Hsu TY, Lin HY, Lin TK. Mitochondrial Transfer from Wharton's Jelly Mesenchymal Stem Cell to MERRF Cybrid Reduces Oxidative Stress and Improves Mitochondrial Bioenergetics. *Oxid Med Cell Longev* 2017; **2017**: 5691215 [PMID: 28607632 DOI: 10.1155/2017/5691215]
45 **Wilkins HM**, Carl SM, Swerdlow RH. Cytoplasmic hybrid (cybrid) cell lines as a practical model for mitochondriopathies. *Redox Biol* 2014; **2**: 619-631 [PMID: 25460729 DOI: 10.1016/j.redox.2014.03.006]
46 **Barth PG**, Scholte HR, Berden JA, Van der Klei-Van Moorsel JM, Luyt-Houwen IE, Van 't Veer-Korthof ET, Van der Harten JJ, Sobotka-Plojhar MA. An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. *J Neurol Sci* 1983; **62**: 327-355 [PMID: 6142097]
47 **Ichida F**, Tsubata S, Bowles KR, Haneda N, Uese K, Miyawaki T, Dreyer WJ, Messina J, Li H, Bowles NE, Towbin JA. Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. *Circulation* 2001; **103**: 1256-1263 [PMID: 11238270]
48 **Bione S**, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D. A novel X-linked gene, G4.5. is responsible for Barth syndrome. *Nat Genet* 1996; **12**: 385-389 [PMID: 8630491 DOI:

10.1038/ng0496-385]
49 **Jefferies JL**. Barth syndrome. *Am J Med Genet C Semin Med Genet* 2013; **163C**: 198-205 [PMID: 23843353 DOI: 10.1002/ajmg.c.31372]
50 **Koshkin V**, Greenberg ML. Cardiolipin prevents rate-dependent uncoupling and provides osmotic stability in yeast mitochondria. *Biochem J* 2002; **364**: 317-322 [PMID: 11988106]
51 **Gonzalvez F**, Gottlieb E. Cardiolipin: setting the beat of apoptosis. *Apoptosis* 2007; **12**: 877-885 [PMID: 17294083 DOI: 10.1007/s10495-007-0718-8]
52 **Bolhuis PA**, Hensels GW, Hulsebos TJ, Baas F, Barth PG. Mapping of the locus for X-linked cardioskeletal myopathy with neutropenia and abnormal mitochondria (Barth syndrome) to Xq28. *Am J Hum Genet* 1991; **48**: 481-485 [PMID: 1998334]
53 **Gonzalez IL**. Barth syndrome: TAZ gene mutations, mRNAs, and evolution. *Am J Med Genet A* 2005; **134**: 409-414 [PMID: 15793838 DOI: 10.1002/ajmg.a.30661]
54 **Mullen PJ**, Lüscher B, Scharnagl H, Krähenbühl S, Brecht K. Effect of simvastatin on cholesterol metabolism in C2C12 myotubes and HepG2 cells, and consequences for statin-induced myopathy. *Biochem Pharmacol* 2010; **79**: 1200-1209 [PMID: 20018177 DOI: 10.1016/J.BCP.2009.12.007]
55 **Burattini S**, Ferri P, Battistelli M, Curci R, Luchetti F, Falcieri E. C2C12 murine myoblasts as a model of skeletal muscle development: morpho-functional characterization. *Eur J Histochem* 2004; **48**: 223-233 [PMID: 15596414]
56 **Lou W**, Reynolds CA, Li Y, Liu J, Hüttemann M, Schlame M, Stevenson D, Strathdee D, Greenberg ML. Loss of tafazzin results in decreased myoblast differentiation in C2C12 cells: A myoblast model of Barth syndrome and cardiolipin deficiency. *Biochim Biophys Acta Mol Cell Biol Lipids* 2018; **1863**: 857-865 [PMID: 29694924 DOI: 10.1016/J.BBALIP.2018.04.015]
57 **Kaur G**, Dufour JM. Cell lines: Valuable tools or useless artifacts. *Spermatogenesis* 2012; **2**: 1-5 [PMID: 22553484 DOI: 10.4161/spmg.19885]
58 **Capes-Davis A**, Theodosopoulos G, Atkin I, Drexler HG, Kohara A, MacLeod RA, Masters JR, Nakamura Y, Reid YA, Reddel RR, Freshney RI. Check your cultures! A list of cross-contaminated or misidentified cell lines. *Int J Cancer* 2010; **127**: 1-8 [PMID: 20143388 DOI: 10.1002/ijc.25242]
59 **Ravikanth M**, Soujanya P, Manjunath K, Saraswathi TR, Ramachandran CR. Heterogenecity of fibroblasts. *J Oral Maxillofac Pathol* 2011; **15**: 247-250 [PMID: 22529592 DOI: 10.4103/0973-029X.84516]
60 **Bainbridge P**. Wound healing and the role of fibroblasts. *J Wound Care* 2013; **22**: 407-408, 410-412 [PMID: 23924840 DOI: 10.12968/jowc.2013.22.8.407]
61 **Alberts B**, Johnson A, Lewis J, Raff M, Keith R, Walter P. Fibroblasts and Their Transformations: The Connective-Tissue Cell Family. In: Molecular Biology of the Cell. Garland Science; 2014; 1228-1232 [DOI: 10.1016/j.jid.2017.10.012]
62 **Ieda M**, Tsuchihashi T, Ivey KN, Ross RS, Hong TT, Shaw RM, Srivastava D. Cardiac fibroblasts regulate myocardial proliferation through beta1 integrin signaling. *Dev Cell* 2009; **16**: 233-244 [PMID: 19217425 DOI: 10.1016/j.devcel.2008.12.007]
63 **Iwamiya T**, Matsuura K, Masuda S, Shimizu T, Okano T. Cardiac fibroblast-derived VCAM-1 enhances cardiomyocyte proliferation for fabrication of bioengineered cardiac tissue. *Regen Ther* 2016; **4**: 92-102 [PMID: 31245492 DOI: 10.1016/J.RETH.2016.01.005]
64 **Baum J**, Duffy HS. Fibroblasts and myofibroblasts: what are we talking about? *J Cardiovasc Pharmacol* 2011; **57**: 376-379 [PMID: 21297493 DOI: 10.1097/FJC.0b013e3182116e39]
65 **Camelliti P**, Borg TK, Kohl P. Structural and functional characterisation of cardiac fibroblasts. *Cardiovasc Res* 2005; **65**: 40-51 [PMID: 15621032 DOI: 10.1016/j.cardiores.2004.08.020]
66 **Vangipuram M**, Ting D, Kim S, Diaz R, Schüle B. Skin punch biopsy explant culture for derivation of primary human fibroblasts. *J Vis Exp* 2013; e3779 [PMID: 23852182 DOI: 10.3791/3779]
67 **Hayflick L**. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res* 1965; **37**: 614-636 [PMID: 14315085 DOI: 10.1016/0014-4827(65)90211-9]
68 **James AM**, Wei YH, Pang CY, Murphy MP. Altered mitochondrial function in fibroblasts containing MELAS or MERRF mitochondrial DNA mutations. *Biochem J* 1996; **318**: 401-407 [PMID: 8809026]
69 **Mancuso M**. Antimyoclonic Effect of Levetiracetam in MERRF Syndrome. *J Neurol Sci* 2006; 243
70 **Finsterer J**. Central nervous system manifestations of mitochondrial disorders. *Acta Neurol Scand* 2006; **114**: 217-238 [PMID: 16942541 DOI: 10.1111/j.1600-0404.2006.00671.x]
71 **D'Adamo P**, Fassone L, Gedeon A, Janssen EA, Bione S, Bolhuis PA, Barth PG, Wilson M, Haan E, Orstavik KH, Patton MA, Green AJ, Zammarchi E, Donati MA, Toniolo D. The X-linked gene G4.5 is responsible for different infantile dilated cardiomyopathies. *Am J Hum Genet* 1997; **61**: 862-867 [PMID: 9382096 DOI: 10.1086/514886]
72 **Schlame M**, Kelley RI, Feigenbaum A, Towbin JA, Heerdt PM, Schieble T, Wanders RJ, DiMauro S, Blanck TJ. Phospholipid abnormalities in children with Barth syndrome. *J Am Coll Cardiol* 2003; **42**: 1994-1999 [PMID: 14662265 DOI: 10.1016/J.JACC.2003.06.015]
73 **Fujioka H**, Tandler B, Consolo MC, Karnik P. Division of mitochondria in cultured human fibroblasts. *Microsc Res Tech* 2013; **76**: 1213-1216 [PMID: 24009193 DOI: 10.1002/jemt.22287]
74 **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; **126**: 663-676 [PMID: 16904174 DOI: 10.1016/J.CELL.2006.07.024]
75 **Martin GR**. Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proc Natl Acad Sci U S A* 1981; **78**: 7634-7638 [PMID: 6950406]
76 **Evans MJ**, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. *Nature* 1981; **292**: 154-156 [PMID: 7242681 DOI: 10.1038/292154a0]
77 **Raab S**, Klingenstein M, Liebau S, Linta L. A Comparative View on Human Somatic Cell Sources for iPSC Generation. *Stem Cells Int* 2014; **2014**: 768391 [PMID: 25431601 DOI: 10.1155/2014/768391]
78 **Singh VK**, Kalsan M, Kumar N, Saini A, Chandra R. Induced pluripotent stem cells: applications in regenerative medicine, disease modeling, and drug discovery. *Front Cell Dev Biol* 2015; **3**: 2 [PMID: 25699255 DOI: 10.3389/fcell.2015.00002]
79 **Huangfu D**, Maehr R, Guo W, Eijkelenboom A, Snitow M, Chen AE, Melton DA. Induction of pluripotent stem cells by defined factors is greatly improved by small-molecule compounds. *Nat Biotechnol* 2008; **26**: 795-797 [PMID: 18568017 DOI: 10.1038/nbt1418]
80 **Stadtfeld M**, Maherali N, Breault DT, Hochedlinger K. Defining molecular cornerstones during fibroblast to iPS cell reprogramming in mouse. *Cell Stem Cell* 2008; **2**: 230-240 [PMID: 18371448 DOI: 10.1016/j.stem.2008.02.001]

81 **Okita K**, Nakagawa M, Hyenjong H, Ichisaka T, Yamanaka S. Generation of mouse induced pluripotent stem cells without viral vectors. *Science* 2008; **322**: 949-953 [PMID: 18845712 DOI: 10.1126/science.1164270]

82 **Somers A**, Jean JC, Sommer CA, Omari A, Ford CC, Mills JA, Ying L, Sommer AG, Jean JM, Smith BW, Lafyatis R, Demierre MF, Weiss DJ, French DL, Gadue P, Murphy GJ, Mostoslavsky G, Kotton DN. Generation of transgene-free lung disease-specific human induced pluripotent stem cells using a single excisable lentiviral stem cell cassette. *Stem Cells* 2010; **28**: 1728-1740 [PMID: 20715179 DOI: 10.1002/stem.495]

83 **Chen IP**, Fukuda K, Fusaki N, Iida A, Hasegawa M, Lichtler A, Reichenberger EJ. Induced pluripotent stem cell reprogramming by integration-free Sendai virus vectors from peripheral blood of patients with craniometaphyseal dysplasia. *Cell Reprogram* 2013; **15**: 503-513 [PMID: 24219578 DOI: 10.1089/cell.2013.0037]

84 **Woltjen K**, Michael IP, Mohseni P, Desai R, Mileikovsky M, Hämäläinen R, Cowling R, Wang W, Liu P, Gertsenstein M, Kaji K, Sung HK, Nagy A. piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells. *Nature* 2009; **458**: 766-770 [PMID: 19252478 DOI: 10.1038/nature07863]

85 **Kim D**, Kim CH, Moon JI, Chung YG, Chang MY, Han BS, Ko S, Yang E, Cha KY, Lanza R, Kim KS. Generation of human induced pluripotent stem cells by direct delivery of reprogramming proteins. *Cell Stem Cell* 2009; **4**: 472-476 [PMID: 19481515 DOI: 10.1016/j.stem.2009.05.005]

86 **Warren L**, Manos PD, Ahfeldt T, Loh YH, Li H, Lau F, Ebina W, Mandal PK, Smith ZD, Meissner A, Daley GQ, Brack AS, Collins JJ, Cowan C, Schlaeger TM, Rossi DJ. Highly efficient reprogramming to pluripotency and directed differentiation of human cells with synthetic modified mRNA. *Cell Stem Cell* 2010; **7**: 618-630 [PMID: 20888316 DOI: 10.1016/j.stem.2010.08.012]

87 **Rao MS**, Malik N. Assessing iPSC reprogramming methods for their suitability in translational medicine. *J Cell Biochem* 2012; **113**: 3061-3068 [PMID: 22573568 DOI: 10.1002/jcb.24183]

88 **Schlaeger TM**, Daheron L, Brickler TR, Entwisle S, Chan K, Cianci A, DeVine A, Ettenger A, Fitzgerald K, Godfrey M, Gupta D, McPherson J, Malwadkar P, Gupta M, Bell B, Doi A, Jung N, Li X, Lynes MS, Brookes E, Cherry AB, Demirbas D, Tsankov AM, Zon LI, Rubin LL, Feinberg AP, Meissner A, Cowan CA, Daley GQ. A comparison of non-integrating reprogramming methods. *Nat Biotechnol* 2015; **33**: 58-63 [PMID: 25437882 DOI: 10.1038/nbt.3070]

89 **Lai MI**, Wendy-Yeo WY, Ramasamy R, Nordin N, Rosli R, Veerakumarasivam A, Abdullah S. Advancements in reprogramming strategies for the generation of induced pluripotent stem cells. *J Assist Reprod Genet* 2011; **28**: 291-301 [PMID: 21384252 DOI: 10.1007/s10815-011-9552-6]

90 **He S**, Nakada D, Morrison SJ. Mechanisms of stem cell self-renewal. *Annu Rev Cell Dev Biol* 2009; **25**: 377-406 [PMID: 19575646 DOI: 10.1146/annurev.cellbio.042308.113248]

91 **Shiraki N**, Higuchi Y, Harada S, Umeda K, Isagawa T, Aburatani H, Kume K, Kume S. Differentiation and characterization of embryonic stem cells into three germ layers. *Biochem Biophys Res Commun* 2009; **381**: 694-699 [PMID: 19250925 DOI: 10.1016/j.bbrc.2009.02.120]

92 **Yang C**, Al-Aama J, Stojkovic M, Keavney B, Trafford A, Lako M, Armstrong L. Concise Review: Cardiac Disease Modeling Using Induced Pluripotent Stem Cells. *Stem Cells* 2015; **33**: 2643-2651 [PMID: 26033645 DOI: 10.1002/stem.2070]

93 **Chou SJ**, Tseng WL, Chen CT, Lai YF, Chien CS, Chang YL, Lee HC, Wei YH, Chiou SH. Impaired ROS Scavenging System in Human Induced Pluripotent Stem Cells Generated from Patients with MERRF Syndrome. *Sci Rep* 2016; **6**: 23661 [PMID: 27025901 DOI: 10.1038/srep23661]

94 **Laflamme MA**, Chen KY, Naumova AV, Muskheli V, Fugate JA, Dupras SK, Reinecke H, Xu C, Hassanipour M, Police S, O'Sullivan C, Collins L, Chen Y, Minami E, Gill EA, Ueno S, Yuan C, Gold J, Murry CE. Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts. *Nat Biotechnol* 2007; **25**: 1015-1024 [PMID: 17721512 DOI: 10.1038/nbt1327]

95 **Yang L**, Soonpaa MH, Adler ED, Roepke TK, Kattman SJ, Kennedy M, Henckaerts E, Bonham K, Abbott GW, Linden RM, Field LJ, Keller GM. Human cardiovascular progenitor cells develop from a KDR+ embryonic-stem-cell-derived population. *Nature* 2008; **453**: 524-528 [PMID: 18432194 DOI: 10.1038/nature06894]

96 **Tran TH**, Wang X, Browne C, Zhang Y, Schinke M, Izumo S, Burcin M. Wnt3a-induced mesoderm formation and cardiomyogenesis in human embryonic stem cells. *Stem Cells* 2009; **27**: 1869-1878 [PMID: 19544447 DOI: 10.1002/stem.95]

97 **Burridge PW**, Diecke S, Matsa E, Sharma A, Wu H, Wu JC. Modeling Cardiovascular Diseases with Patient-Specific Human Pluripotent Stem Cell-Derived Cardiomyocytes. *Methods Mol Biol* 2016; **1353**: 119-130 [PMID: 25690476 DOI: 10.1007/7651_2015_196]

98 **Lee JH**, Protze SI, Laksman Z, Backx PH, Keller GM. Human Pluripotent Stem Cell-Derived Atrial and Ventricular Cardiomyocytes Develop from Distinct Mesoderm Populations. *Cell Stem Cell* 2017; **21**: 179-194.e4 [PMID: 28777944 DOI: 10.1016/j.stem.2017.07.003]

99 **Rust W**, Balakrishnan T, Zweigerdt R. Cardiomyocyte enrichment from human embryonic stem cell cultures by selection of ALCAM surface expression. *Regen Med* 2009; **4**: 225-237 [PMID: 19317642 DOI: 10.2217/17460751.4.2.225]

100 **Anderson D**, Self T, Mellor IR, Goh G, Hill SJ, Denning C. Transgenic enrichment of cardiomyocytes from human embryonic stem cells. *Mol Ther* 2007; **15**: 2027-2036 [PMID: 17895862 DOI: 10.1038/sj.mt.6300303]

101 **Yechikov S**, Copaciu R, Gluck JM, Deng W, Chiamvimonvat N, Chan JW, Lieu DK. Same-Single-Cell Analysis of Pacemaker-Specific Markers in Human Induced Pluripotent Stem Cell-Derived Cardiomyocyte Subtypes Classified by Electrophysiology. *Stem Cells* 2016; **34**: 2670-2680 [PMID: 27434649 DOI: 10.1002/stem.2466]

102 **Rajala K**, Pekkanen-Mattila M, Aalto-Setälä K. Cardiac differentiation of pluripotent stem cells. *Stem Cells Int* 2011; **2011**: 383709 [PMID: 21603143 DOI: 10.4061/2011/383709]

103 **Machiraju P**, Greenway SC. Current methods for the maturation of induced pluripotent stem cell-derived cardiomyocytes. *World J Stem Cells* 2019; **11**: 33-43 [PMID: 30705713 DOI: 10.4252/wjsc.v11.i1.33]

104 **Sun X**, Nunes SS. Maturation of Human Stem Cell-derived Cardiomyocytes in Biowires Using Electrical Stimulation. *J Vis Exp* 2017; 123 [PMID: 28518082 DOI: 10.3791/55373]

105 **Ruan JL**, Tulloch NL, Razumova MV, Saiget M, Muskheli V, Pabon L, Reinecke H, Regnier M, Murry CE. Mechanical Stress Conditioning and Electrical Stimulation Promote Contractility and Force Maturation of Induced Pluripotent Stem Cell-Derived Human Cardiac Tissue. *Circulation* 2016; **134**: 1557-1567 [PMID: 27737958 DOI: 10.1161/CIRCULATIONAHA.114.014998]

106 **Correia C**, Koshkin A, Duarte P, Hu D, Teixeira A, Domian I, Serra M, Alves PM. Distinct carbon sources affect structural and functional maturation of cardiomyocytes derived from human pluripotent stem cells. *Sci Rep* 2017; **7**: 8590 [PMID: 28819274 DOI: 10.1038/s41598-017-08713-4]

107 **Herron TJ**, Rocha AM, Campbell KF, Ponce-Balbuena D, Willis BC, Guerrero-Serna G, Liu Q, Klos M, Musa H, Zarzoso M, Bizy A, Furness J, Anumonwo J, Mironov S, Jalife J. Extracellular Matrix-Mediated Maturation of Human Pluripotent Stem Cell-Derived Cardiac Monolayer Structure and Electrophysiological Function. *Circ Arrhythm Electrophysiol* 2016; **9**: e003638 [PMID: 27069088 DOI: 10.1161/CIRCEP.113.003638]

108 **Moretti A**, Laugwitz KL, Dorn T, Sinnecker D, Mummery C. Pluripotent stem cell models of human heart disease. *Cold Spring Harb Perspect Med* 2013; **3** [PMID: 24186488 DOI: 10.1101/cshperspect.a014027]

109 **Peter AK**, Bjerke MA, Leinwand LA. Biology of the cardiac myocyte in heart disease. *Mol Biol Cell* 2016; **27**: 2149-2160 [PMID: 27418636 DOI: 10.1091/mbc.E16-01-0038]

110 **Kodaira M**, Hatakeyama H, Yuasa S, Seki T, Egashira T, Tohyama S, Kuroda Y, Tanaka A, Okata S, Hashimoto H, Kusumoto D, Kunitomi A, Takei M, Kashimura S, Suzuki T, Yozu G, Shimojima M, Motoda C, Hayashiji N, Saito Y, Goto Y, Fukuda K. Impaired respiratory function in MELAS-induced pluripotent stem cells with high heteroplasmy levels. *FEBS Open Bio* 2015; **5**: 219-225 [PMID: 25853038 DOI: 10.1016/j.fob.2015.03.008]

111 **Gropman AL**. Diagnosis and treatment of childhood mitochondrial diseases. *Curr Neurol Neurosci Rep* 2001; **1**: 185-194 [PMID: 11898515 DOI: 10.1007/s11910-001-0015-9]

112 **Lian X**, Hsiao C, Wilson G, Zhu K, Hazeltine LB, Azarin SM, Raval KK, Zhang J, Kamp TJ, Palecek SP. Robust cardiomyocyte differentiation from human pluripotent stem cells via temporal modulation of canonical Wnt signaling. *Proc Natl Acad Sci U S A* 2012; **109**: E1848-E1857 [PMID: 22645348 DOI: 10.1073/pnas.1200250109]

113 **Takahashi K**, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131**: 861-872 [PMID: 18035408 DOI: 10.1016/j.cell.2007.11.019]

114 **Warren L**, Ni Y, Wang J, Guo X. Feeder-free derivation of human induced pluripotent stem cells with messenger RNA. *Sci Rep* 2012; **2**: 657 [PMID: 22984641 DOI: 10.1038/srep00657]

115 **Shiba Y**, Fernandes S, Zhu WZ, Filice D, Muskheli V, Kim J, Palpant NJ, Gantz J, Moyes KW, Reinecke H, Van Biber B, Dardas T, Mignone JL, Izawa A, Hanna R, Viswanathan M, Gold JD, Kotlikoff MI, Sarvazyan N, Kay MW, Murry CE, Laflamme MA. Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts. *Nature* 2012; **489**: 322-325 [PMID: 22864415 DOI: 10.1038/nature11317]

116 **Wang G**, McCain ML, Yang L, He A, Pasqualini FS, Agarwal A, Yuan H, Jiang D, Zhang D, Zangi L, Geva J, Roberts AE, Ma Q, Ding J, Chen J, Wang DZ, Li K, Wang J, Wanders RJ, Kulik W, Vaz FM, Laflamme MA, Murry CE, Chien KR, Kelley RI, Church GM, Parker KK, Pu WT. Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies. *Nat Med* 2014; **20**: 616-623 [PMID: 24813252 DOI: 10.1038/nm.3545]

117 **Pandolfo M**. Molecular basis of Friedreich ataxia. *Mov Disord* 2001; **16**: 815-821 [PMID: 11746610 DOI: 10.1002/mds.1162]

118 **Weidemann F**, Störk S, Liu D, Hu K, Herrmann S, Ertl G, Niemann M. Cardiomyopathy of Friedreich ataxia. *J Neurochem* 2013; **126** Suppl 1: 88-93 [PMID: 23859344 DOI: 10.1111/jnc.12217]

119 **Minami I**, Yamada K, Otsuji TG, Yamamoto T, Shen Y, Otsuka S, Kadota S, Morone N, Barve M, Asai Y, Tenkova-Heuser T, Heuser JE, Uesugi M, Aiba K, Nakatsuji N. A small molecule that promotes cardiac differentiation of human pluripotent stem cells under defined, cytokine- and xeno-free conditions. *Cell Rep* 2012; **2**: 1448-1460 [PMID: 23103164 DOI: 10.1016/j.celrep.2012.09.015]

120 **Crombie DE**, Curl CL, Raaijmakers AJ, Sivakumaran P, Kulkarni T, Wong RC, Minami I, Evans-Galea MV, Lim SY, Delbridge L, Corben LA, Dottori M, Nakatsuji N, Trounce IA, Hewitt AW, Delatycki MB, Pera MF, Pébay A. Friedreich's ataxia induced pluripotent stem cell-derived cardiomyocytes display electrophysiological abnormalities and calcium handling deficiency. *Aging (Albany NY)* 2017; **9**: 1440-1452 [PMID: 28562313 DOI: 10.18632/aging.101247]

121 **Greenway SC**, Dallaire F, Hazari H, Patel D, Khan A. Addition of Digoxin Improves Cardiac Function in Children With the Dilated Cardiomyopathy With Ataxia Syndrome: A Mitochondrial Cardiomyopathy. *Can J Cardiol* 2018; **34**: 972-977 [PMID: 29887217 DOI: 10.1016/J.CJCA.2018.02.019]

122 **Ojala T**, Polinati P, Manninen T, Hiippala A, Rajantie J, Karikoski R, Suomalainen A, Tyni T. New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. *Pediatr Res* 2012; **72**: 432-437 [PMID: 22797137 DOI: 10.1038/pr.2012.92]

123 **Rohani L**, Meng G, Machiraju P, Liu S, Wu J, Kovalchuk I, Lewis I, Shutt TE, Khan A, Rancourt DE, Greenway S. Modeling the dilated cardiomyopathy with ataxia syndrome (DCMA), a pediatric mitochondrial cardiomyopathy, using cardiomyocytes derived from induced pluripotent stem cells. *Can J Cardiol* 2017; **33**: S163–S164 [DOI: 10.1016/j.cjca.2017.07.319]

124 **Maron BJ**. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002; **287**: 1308-1320 [PMID: 11886323]

125 **Maron BJ**, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol* 2012; **60**: 705-715 [PMID: 22796258 DOI: 10.1016/j.jacc.2012.02.068]

126 **Han L**, Li Y, Tchao J, Kaplan AD, Lin B, Li Y, Mich-Basso J, Lis A, Hassan N, London B, Bett GC, Tobita K, Rasmusson RL, Yang L. Study familial hypertrophic cardiomyopathy using patient-specific induced pluripotent stem cells. *Cardiovasc Res* 2014; **104**: 258-269 [PMID: 25209314 DOI: 10.1093/cvr/cvu205]

127 **Pellman J**, Zhang J, Sheikh F. Myocyte-fibroblast communication in cardiac fibrosis and arrhythmias: Mechanisms and model systems. *J Mol Cell Cardiol* 2016; **94**: 22-31 [PMID: 26996756 DOI: 10.1016/j.yjmcc.2016.03.005]

128 **Xie F**, Gong K, Li K, Zhang M, Chang JC, Jiang S, Ye L, Wang J, Tan Y, Kan YW. Reversible Immortalization Enables Seamless Transdifferentiation of Primary Fibroblasts into Other Lineage Cells. *Stem Cells Dev* 2016; **25**: 1243-1248 [PMID: 27328768 DOI: 10.1089/scd.2016.0035]

129 **Zhang Y**, Nuglozeh E, Touré F, Schmidt AM, Vunjak-Novakovic G. Controllable expansion of primary cardiomyocytes by reversible immortalization. *Hum Gene Ther* 2009; **20**: 1687-1696 [PMID: 19708763 DOI: 10.1089/hum.2009.057]

130 **Davey KM**, Parboosingh JS, McLeod DR, Chan A, Casey R, Ferreira P, Snyder FF, Bridge PJ, Bernier FP. Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. *J Med Genet* 2006;

43: 385-393 [PMID: 16055927 DOI: 10.1136/jmg.2005.036657]
131 **Sparkes R**, Patton D, Bernier F. Cardiac features of a novel autosomal recessive dilated cardiomyopathic syndrome due to defective importation of mitochondrial protein. *Cardiol Young* 2007; **17**: 215-217 [PMID: 17244376 DOI: 10.1017/S1047951107000042]
132 **Sander JD**, Joung JK. CRISPR-Cas systems for editing, regulating and targeting genomes. *Nat Biotechnol* 2014; **32**: 347-355 [PMID: 24584096 DOI: 10.1038/nbt.2842]
133 **Kim HS**, Bernitz JM, Lee DF, Lemischka IR. Genomic editing tools to model human diseases with isogenic pluripotent stem cells. *Stem Cells Dev* 2014; **23**: 2673-2686 [PMID: 25075441 DOI: 10.1089/scd.2014.0167]
134 **Marthaler AG**, Schmid B, Tubsuwan A, Poulsen UB, Engelbrecht AF, Mau-Holzmann UA, Hyttel P, Nielsen JE, Nielsen TT, Holst B. Generation of an isogenic, gene-corrected control cell line of the spinocerebellar ataxia type 2 patient-derived iPSC line H271. *Stem Cell Res* 2016; **16**: 180-183 [PMID: 27345809 DOI: 10.1016/j.scr.2015.12.028]
135 **Lian X**, Zhang J, Azarin SM, Zhu K, Hazeltine LB, Bao X, Hsiao C, Kamp TJ, Palecek SP. Directed cardiomyocyte differentiation from human pluripotent stem cells by modulating Wnt/β-catenin signaling under fully defined conditions. *Nat Protoc* 2013; **8**: 162-175 [PMID: 23257984 DOI: 10.1038/nprot.2012.150]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 October 26; 11(10): 236-243

DOI: 10.4330/wjc.v11.i10.236

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Basic Study

Differential effects of atrial and brain natriuretic peptides on human pulmonary artery: An *in vitro* study

Azar Hussain, Robert T Bennett, Zaheer Tahir, Emmanuel Isaac, Mubarak A Chaudhry, Syed S Qadri, Mahmoud Loubani, Alyn H Morice

ORCID number: Azar Hussain (0000-0002-7073-9738); Robert T Bennett (0000-0002-3746-367X); Zaheer Tahir (0000-0001-6754-4473); Syed Qadri (0000-0001-5188-9207); Mahmoud Loubani (0000-0003-1826-6686); Alyn H Morice (0000-0002-6135-9610).

Author contributions: Hussain A was the principal investigator and was responsible for the design and conduct of the study; Hussain A was responsible for the acquisition, analysis and interpretation of the data and initial draft of the manuscript; Bennett RT, Tahir Z, Isaac E, Chaudhry MA, Qadri SS, Loubani M and Morice AH supervised the study and critically reviewed the article.

Institutional review board statement: The study was reviewed and approved by the North West – Liverpool Central Research Ethics Committee (Approval no: 15/NW/0808).

Informed consent statement: All patients were consulted and consented for resected lung tissue to be studied for our research prior to their operation at the time of their consent for surgery.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript

Azar Hussain, Robert T Bennett, Zaheer Tahir, Emmanuel Isaac, Mubarak A Chaudhry, Syed S Qadri, Mahmoud Loubani, Department of Cardiothoracic Surgery, Castle Hill Hospital, Cottingham HU16 5JQ, United Kingdom

Alyn H Morice, Centre for Cardiovascular and Metabolic Research, Hull York Medical School, Castle Hill Hospital, Cottingham HU16 5JQ, United Kingdom

Corresponding author: Azar Hussain, MBBS, MRCS (Ed), Clinical Research Fellow, Department of Cardiothoracic Surgery, Castle Hill Hospital, Castle Road, Cottingham HU16 5JQ, United Kingdom. azar.hussain@hey.nhs.uk
Telephone: +44-774-8019242

Abstract

BACKGROUND

The prevalence of cardiovascular diseases, especially heart failure, continues to rise worldwide. In heart failure, increasing levels of circulating atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are associated with a worsening of heart failure and a poor prognosis.

AIM

To test whether a high concentration of BNP would inhibit relaxation to ANP.

METHODS

Pulmonary arteries were dissected from disease-free areas of lung resection, as well as pulmonary artery rings of internal diameter 2.5–3.5 mm and 2 mm long, were prepared. Pulmonary artery rings were mounted in a multiwire myograph, and a basal tension of 1.61gf was applied. After equilibration for 60 min, rings were pre-constricted with 11.21 μmol/L $PGF_{2\alpha}$ (EC_{80}), and concentration response curves were constructed to vasodilators by cumulative addition to the myograph chambers.

RESULTS

Although both ANP and BNP were found to vasodilate the pulmonary vessels, ANP is more potent than BNP. pEC50 of ANP and BNP were 8.96 ± 0.21 and 7.54 ± 0.18, respectively, and the maximum efficacy (E_{max}) for ANP and BNP was -2.03 gf and -0.24 gf, respectively. After addition of BNP, the E_{max} of ANP reduced from -0.96gf to -0.675gf (P = 0.28).

CONCLUSION

was prepared and revised according to ARRIVE guidelines.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: February 10, 2019
Peer-review started: February 12, 2019
First decision: April 11, 2019
Revised: August 31, 2019
Accepted: September 15, 2019
Article in press: September 15, 2019
Published online: October 26, 2019

P-Reviewer: Bełtowski J
S-Editor: Ma YJ
L-Editor: Filipodia
E-Editor: Xing YX

BNP could be acting as a partial agonist in small human pulmonary arteries, and inhibits relaxation to ANP. Elevated levels of circulating BNP could be responsible for the worsening of decompensated heart failure. This finding could also explain the disappointing results seen in clinical trials of ANP and BNP analogues for the treatment of heart failure.

Key words: Heart failure; Atrial natriuretic peptide; Brain natriuretic peptide; *In-vitro*; Humans

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This study demonstrated that both atrial natriuretic peptide and brain natriuretic peptide (BNP) vasodilate isolated human pulmonary artery rings, and that BNP acts as a partial agonist and inhibits the effects of atrial natriuretic peptide. The finding that the addition of BNP inhibits the effects of atrial natriuretic peptide suggests that BNP does act as a partial agonist, and could be advancing the progression to decompensated heart failure.

Citation: Hussain A, Bennett RT, Tahir Z, Isaac E, Chaudhry MA, Qadri SS, Loubani M, Morice AH. Differential effects of atrial and brain natriuretic peptides on human pulmonary artery: An *in vitro* study. *World J Cardiol* 2019; 11(10): 236-243
URL: https://www.wjgnet.com/1949-8462/full/v11/i10/236.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i10.236

INTRODUCTION

Decompensated heart failure is a worldwide health issue that is associated with considerable morbidity and mortality[1,2]. Despite the development of several device- and medical-based therapies over the past few decades, the rate of rehospitalisation and early death has not significantly improved[3].

The natriuretic peptides (NPs) family consists of three structurally interrelated vasoactive peptides, and was initially discovered by de Bold *et al*[4] in 1981. The family includes atrial natriuretic peptide (ANP), brain natriuretic peptides (BNPs) and C-type natriuretic peptide (CNP), which are mainly secreted by cardiac myocytes in response to wall stress[5,6]. ANP and BNP act *via* guanylyl cyclase-linked natriuretic peptide receptor-A (NPR-A), whereas CNP activates the related cyclase natriuretic peptide receptor-B (NPR-B)[7]. ANP and BNP exert their beneficial effects by reducing systemic and pulmonary vascular resistance, and by increasing natriuresis and diuresis[8]. In addition to their haemodynamic effects, NPs attenuate vascular smooth muscle proliferation and cardiac hypertrophy[9,10]. They also inhibit the synthesis of growth factors, by counteracting the effects of the renin-angiotensin system, which is involved in the development of pulmonary hypertension[11].

In vitro studies on pulmonary arterial rings and isolated lung models have shown that ANP and BNP infusion induced pulmonary vasodilation by reducing pulmonary vascular resistance[12,13]. However, in heart failure, increasing levels of circulating ANP and BNP are associated with a worsening of heart failure and a poor prognosis[14]. The aim of this study is to evaluate whether BNP acts as a partial agonist, and inhibits the effects of ANP.

MATERIALS AND METHODS

Study patients

Local research ethics committee and institutional (Hull & East Yorkshire Hospitals NHS Trust) Research and Development Department approval was obtained for the use of lung specimens and surplus lung tissue from patients undergoing elective lobe or lung resection for cancer. Patients gave written consent for the use of surplus tissue for research purposes.

In accordance with the recommendations of the human tissue act (2004) 127 and the conditions of the local ethics committee approval, the donor patient was anonymous to the researcher.

Tissue collection

Excess segments of pulmonary artery were obtained from patients undergoing lobectomy, and the sample was immediately transferred to the lab in Krebs-Henseleit solution after resection. After the removal of connective tissue, the pulmonary artery (PA) sample was divided into 2 mm long rings. The small pulmonary vessels with an internal diameter of 2-4 mm were used for these experiments.

Experimental protocol

A multiwire myograph system was used for the measurement of isometric tension. Under physiological conditions (37°C, 21%O_2), PA rings were mounted in Krebs Henseleit solution. A resting tension of 1.61 gf was applied, which was calculated from earlier experiments[15], and the vessels were left to equilibrate for 60-90 min. After equilibration, vessels were pre-constricted with 11.21 μmol/L PGF2**α** ($EC_{80,}$ calculated from earlier experiments[16]), and concentration response curves were constructed to ANP and BNP by cumulative addition to the myograph chambers.

In another set of experiments, once the vessels tension reached a plateau after pre-constriction with PGF2α, 300 nmol/L of BNP was added and the vessels were left for 30 min. When a stable resting tension was achieved, concentration response curves were constructed to ANP. Vessels were then washed for 30 min, and the whole experiment was repeated again without the addition of BNP.

Active tension was calculated in gram force (gf) as maximum tension at plateau (gf) – resting tension (gf). The maximum efficacy (E_{max}) for each agent was determined in gf and expressed as gf/mm internal diameter of each vessel (to take into account the variability in PA ring diameter). The integrity of the endothelium was confirmed with 1μM Acetylcholine, and KCl was added to check viability. Vessels that did not constrict with KCl were excluded from the study. Figure 1 shows the schematic representation of myograph setup for measuring isometric tension.

Chemicals

A 5% CO_2/balance air was sourced from BOC Limited (Guilford, Surrey, United Kingdom). The agents used were (supplier in parentheses) ANP (Tocris Bioscience, part of Bio-Techne, Abingdon, United Kingdom), BNP (Tocris Bioscience) Acetylcholine (Sigma-Aldrich, St. Louis, MO, United States) and PGF2α (Tocris Bioscience). Stock solutions of drugs were prepared using the solvents recommended by the suppliers, and control responses to solvents were obtained when necessary. Fresh serial dilutions were made using the appropriate solvent for each experiment. All other reagents were obtained from Thermo Fisher Scientific unless otherwise stated.

Statistical analysis

Data are presented as mean ± SD, and n represents the number of individual PA rings used in an experiment. Agonist EC_{50} concentrations (the concentration required to elicit 50% of the maximum response) were determined using nonlinear regression to fit a standard slope model using the statistical analysis function of GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA, United States). More details can be found at http://www.graphpad.com/guides/prism/6/curve-fitting/index.htm). Agonist potency is presented as pEC_{50} (the negative logarithm of the molar EC_{50} concentration). Significance was taken as $P < 0.05$.

RESULTS

A total of 35 PA rings were obtained from 15 patients. The internal diameter of PAs ranged from 2.5–3.5 mm. Nine rings were not included, as they did not respond to KCl.

Concentration-dependent effect of ANP and BNP on human PAs

ANP and BNP caused a concentration-dependent relaxation of PAs pre-constricted to $PGF_{2α}$, with a pEC_{50} of 8.96 ± 0.21 and 7.54 ± 0.18 for ANP and BNP, respectively (Figure 2). The maximum efficacy (E_{max}) for ANP and BNP was -2.03 gf and -0.24 gf, respectively.

Another set of experiments was conducted to determine whether a high concentration of BNP would inhibit relaxation to ANP. After addition of BNP, the E_{max} of ANP was reduced by 30% from -0.96 gf to -0.675 gf ($P = 0.28$, $n = 11$) (Figure 3).

Concentration response curve of ANP-induced pulmonary vasodilation

All vessels vasodilate in response to ANP. Increasing the concentration of ANP from 3pmol/L–1 μmol/L were used on 8 PA rings. Maximal relaxation was seen at 100

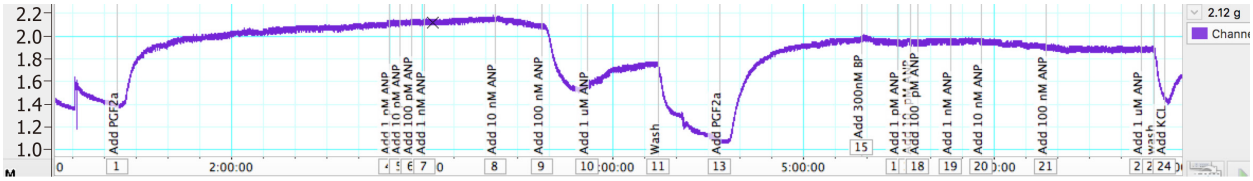


Figure 1 Schematic representation of myograph setup for measuring isometric tension.

nmol/L (log -7.0 mol/L), and the EC20, EC50 and EC80 were 0.17 nmol/L, 1.105 nmol/L and 7.01 nmol/L, respectively. The hill slope was -0.75 ± 0.5.

Concentration response curve of BNP-induced pulmonary vasodilation

In order to evaluate the effect of BNP on pulmonary vessels, 7 PA rings and a concentration of BNP from 1 nmol/L–1 μmol/L was used. As the concentration went above 10 nmol/L, vessels start to vasodilate and the maximum vasodilatory response was seen at 300 nmol/L (log -6.5 mol/L). The EC20, EC50 and EC80 were 13.3 nmol/L, 28.7 nmol/L and 61.5 nmol/L, respectively. The hill slope was -1.818 ± 2.55.

Cumulative concentration response curve of ANP and BNP-induced pulmonary vasodilation

In another set of experiments, the cumulative vasodilator effect of ANP and BNP on pulmonary vascular tone was investigated. Sixteen PA rings from seven patients, and an increasing concentration of ANP from 1 pmol/L–1 μmol/L, was used. Five rings were excluded, as they did not respond to KCl. When a stable resting tension was achieved, vessels were pre-constricted to 11.21 μmol/L $PGF_{2\alpha}$ (EC_{80}). When a stable plateau relaxation was achieved, the effect of ANP on active tension was determined by cumulative addition to the myograph chambers.

The PA rings were washed for 60 min, and were pre-constricted again with 11.21 μmol/L $PGF_{2\alpha}$ (EC_{80}). A single dose of 300 nm of BNP was added and left for 30 min. Once a plateau was achieved by cumulative addition to the myograph chambers, the concentration response curve of ANP was performed. The addition of BNP reduced the E_{max} of ANP by 30% (from -0.96 gf to -0.675 gf).

DISCUSSION

In this study, we demonstrated for the first time that (1) both ANP and BNP vasodilate isolated human PA rings; and (2) that BNP acts as a partial agonist and inhibits the effects of ANP. The finding that the addition of BNP inhibits the effects of ANP suggests that BNP does act as a partial agonist, and could be advancing the progression to decompensated heart failure.

The circulating concentration of ANP, BNP and CNP is low in healthy individuals, but it is elevated in heart failure patients, although to variable degrees (*e.g.*, CNP elevated to a lower extent than its counterparts)[17,18]. In patients with HF, circulating concentration of BNP exceeds that of ANP; this consistency of response and high dynamic range makes bioassays for plasma BNP more useful than ANP[19,20]. This might be due to the fact that BNP is also a marker of cardiac remodelling[21]. Previous studies have shown that in heart failure (HF) patients, BNP and NT-pro BNP (N-terminal pro b-type NP) are independent predictors of cardiovascular mortality, worsening HF and need for hospitalization[22-24]. Although BNP and NT-pro BNP have prognostic value, their therapeutic value is inconclusive in HF patients[25].

In the early 21st century, the United States Food and Drug Administration (FDA) approved the use of nesiritide (recombinant endogenous BNP) for heart failure patients[26]. However, several subsequent studies demonstrated that Nesiritide is associated with worsening renal function and increased risk of death[27]. A randomized, double blind, placebo-controlled, ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial concluded that nesiritide showed no substantial improvement in dyspnoea or clinical outcomes[28]. Another double-blinded, multicentre, randomized clinical trial, ROSE-AHF (Renal Optimization Strategies Evaluation - Acute Heart Failure) enrolled 360 patients. The study was designed to evaluate the use of low dose nesiritide, with the view that there would be less side effects and substantial therapeutic effects. However, the study failed to provide significant evidence in support of the routine use of nesiritide in heart failure patients[29].

Although NPs are always attractive therapeutic targets for heart failure treatment,

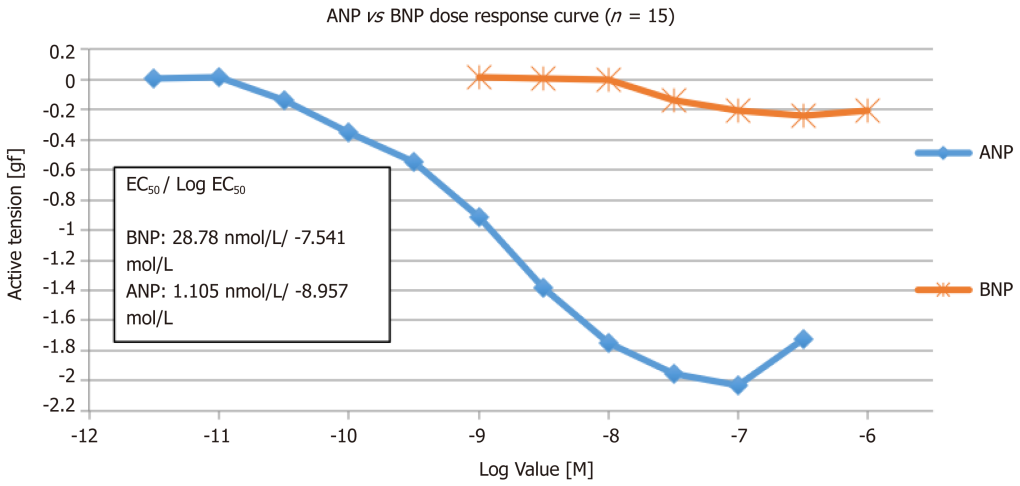


Figure 2 Cumulative concentration response curve to ANP and BNP (*n* = 15). Findings show that both ANP and BNP cause vasodilation. ANP is more potent and efficacious than BNP. pEC_{50} of ANP and BNP were 8.96 ± 0.21 and 7.54 ± 0.18, respectively. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide.

their use is limited by inadequate clinical efficacy. It is thought that the activity of neprilysin, a protease produced by the kidney that cleaves various vasoactive compounds including BNP, is increased in heart failure[30]. In heart failure, increasing levels of circulating ANP and BNP are associated with worsening heart failure and a poor prognosis. This raised the suspicion that BNP might act as a partial agonist and inhibit the effects of ANP, as shown in this study. These findings could also explain the disappointing results seen in clinical trials of ANP and BNP analogues for the treatment of heart failure. Further studies are needed to confirm the findings of this study, which raises the possibility that selective BNP antagonists could be of greater clinical benefit than BNP agonists for the treatment of heart failure.

Limitations

Our study had several limitations. It was a laboratory-based project that was carried out in a control setting, which may not truly reflect the *in vivo* environment. The therapeutic dose and the dose provided in the experiments may differ. We also used the pre-constrictor $PGF_{2\alpha,}$ and since the potency of the agent depends on the pre-constrictor, other pre-constrictors need to be analysed and compared. The full potential of the study needs to be backed by a double-blinded randomized control trial.

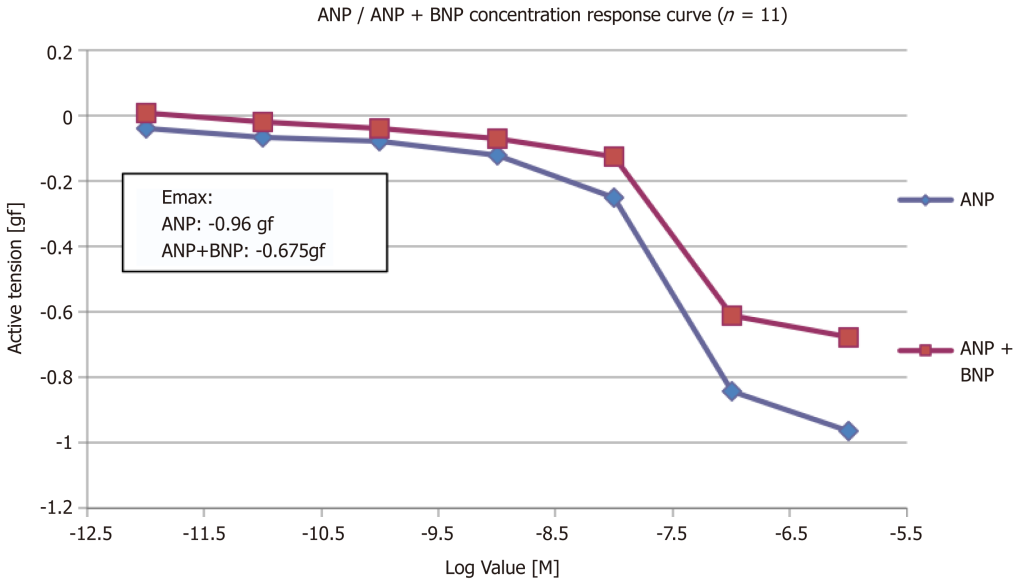


Figure 3 Concentration response curve to ANP alone and ANP + BNP (*n* = 11). The E_{max} of ANP was 0.96 gf, which reduced to -0.675 gf when BNP was added. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide.

ARTICLE HIGHLIGHTS

Research background

The prevalence of cardiovascular diseases, especially heart failure, continues to rise worldwide. In heart failure, increasing levels of circulating atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are associated with worsening heart failure and poor prognosis.

Research motivation

ANP and BNP play an important role in homeostasis, but trials with BNP and ANP infusion showed disappointing results for unknown reasons.

Research objectives

The aim of this study was to evaluate whether BNP acts as a partial agonist and inhibits the effect of ANP.

Research methods

In this study, the effect of natriuretic peptides (ANP and BNP) on human pulmonary arteries was evaluated by cumulative addition to the myograph.

Research results

Both ANP and BNP act as pulmonary vasodilators, although ANP was found to be more potent and efficacious than BNP. Also, the addition of BNP reduced the efficacy of ANP.

Research conclusions

The study confirms that BNP inhibits the effects of ANP, and acts as a partial agonist. These findings also explained the disappointing results associated with the ANP and BNP infusion trials.

Research perspectives

Further studies are needed to validate the results of this study, and to evaluate the possibility of the clinical beneficial role of BNP antagonists for heart failure treatment.

REFERENCES

1 **Lloyd-Jones D**, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; **121**: 948-954 [PMID: 20177011 DOI: 10.1161/CIRCULATIONAHA.109.192666]

2 **Nieminen MS**, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L; EuroHeart Survey Investigators; Heart Failure

Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006; **27**: 2725-2736 [PMID: 17000631 DOI: 10.1093/eurheartj/ehl193]
3 **Bueno H**, Ross JS, Wang Y, Chen J, Vidán MT, Normand SL, Curtis JP, Drye EE, Lichtman JH, Keenan PS, Kosiborod M, Krumholz HM. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. *JAMA* 2010; **303**: 2141-2147 [PMID: 20516414 DOI: 10.1001/jama.2010.748]
4 **de Bold AJ**, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981; **28**: 89-94 [PMID: 7219045 DOI: 10.1016/0024-3205(81)90370-2]
5 **Pandey KN**. Guanylyl cyclase / atrial natriuretic peptide receptor-A: role in the pathophysiology of cardiovascular regulation. *Can J Physiol Pharmacol* 2011; **89**: 557-573 [PMID: 21815745 DOI: 10.1139/y11-054]
6 **Potter LR**. Guanylyl cyclase structure, function and regulation. *Cell Signal* 2011; **23**: 1921-1926 [PMID: 21914472 DOI: 10.1016/j.cellsig.2011.09.001]
7 **Potter LR**, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *Handb Exp Pharmacol* 2009; 341-366 [PMID: 19089336 DOI: 10.1007/978-3-540-68964-5_15]
8 **Del Ry S**, Cabiati M, Clerico A. Natriuretic peptide system and the heart. *Front Horm Res* 2014; **43**: 134-143 [PMID: 24943304 DOI: 10.1159/000360597]
9 **Itoh H**, Pratt RE, Dzau VJ. Atrial natriuretic polypeptide inhibits hypertrophy of vascular smooth muscle cells. *J Clin Invest* 1990; **86**: 1690-1697 [PMID: 2173726 DOI: 10.1172/JCI114893]
10 **Hutchinson HG**, Trindade PT, Cunanan DB, Wu CF, Pratt RE. Mechanisms of natriuretic-peptide-induced growth inhibition of vascular smooth muscle cells. *Cardiovasc Res* 1997; **35**: 158-167 [PMID: 9302360 DOI: 10.1016/s0008-6363(97)00086-2]
11 **Hu RM**, Levin ER, Pedram A, Frank HJ. Atrial natriuretic peptide inhibits the production and secretion of endothelin from cultured endothelial cells. Mediation through the C receptor. *J Biol Chem* 1992; **267**: 17384-17389 [PMID: 1324935]
12 **Jin H**, Yang RH, Chen YF, Jackson RM, Oparil S. Atrial natriuretic peptide attenuates the development of pulmonary hypertension in rats adapted to chronic hypoxia. *J Clin Invest* 1990; **85**: 115-120 [PMID: 2136863 DOI: 10.1172/JCI114400]
13 **Klinger JR**, Warburton RR, Pietras L, Hill NS. Brain natriuretic peptide inhibits hypoxic pulmonary hypertension in rats. *J Appl Physiol (1985)* 1998; **84**: 1646-1652 [PMID: 9572812 DOI: 10.1152/jappl.1998.84.5.1646]
14 **Wright GA**, Struthers AD. Natriuretic peptides as a prognostic marker and therapeutic target in heart failure. *Heart* 2006; **92**: 149-151 [PMID: 16216866 DOI: 10.1136/hrt.2003.018325]
15 **Hussain A**, Bennett RT, Chaudhry MA, Qadri SS, Cowen M, Morice AH, Loubani M. Characterization of optimal resting tension in human pulmonary arteries. *World J Cardiol* 2016; **8**: 553-558 [PMID: 27721938 DOI: 10.4330/wjc.v8.i9.553]
16 **Hussain A**, Bennett R, Haqzad Y, Qadri S, Chaudhry M, Cowen M, Loubani M, Morice A. The differential effects of systemic vasoconstrictors on human pulmonary artery tension. *Eur J Cardiothorac Surg* 2017; **51**: 880-886 [PMID: 28164217 DOI: 10.1093/ejcts/ezw410]
17 **Charles CJ**, Prickett TC, Espiner EA, Rademaker MT, Richards AM, Yandle TG. Regional sampling and the effects of experimental heart failure in sheep: differential responses in A, B and C-type natriuretic peptides. *Peptides* 2006; **27**: 62-68 [PMID: 16095755 DOI: 10.1016/j.peptides.2005.06.019]
18 **Del Ry S**, Passino C, Maltinti M, Emdin M, Giannessi D. C-type natriuretic peptide plasma levels increase in patients with chronic heart failure as a function of clinical severity. *Eur J Heart Fail* 2005; **7**: 1145-1148 [PMID: 15922659 DOI: 10.1016/j.ejheart.2004.12.009]
19 **Maisel A**. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? *Circulation* 2002; **105**: 2328-2331 [PMID: 12021215 DOI: 10.1161/01.CIR.0000019121.91548.C2]
20 **de Lemos JA**, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. *Lancet* 2003; **362**: 316-322 [PMID: 12892964 DOI: 10.1016/S0140-6736(03)13976-1]
21 **Gaggin HK**, Januzzi JL. Biomarkers and diagnostics in heart failure. *Biochim Biophys Acta* 2013; **1832**: 2442-2450 [PMID: 23313577 DOI: 10.1016/j.bbadis.2012.12.014]
22 **Balion C**, Santaguida PL, Hill S, Worster A, McQueen M, Oremus M, McKelvie R, Booker L, Fagbemi J, Reichert S, Raina P. Testing for BNP and NT-proBNP in the diagnosis and prognosis of heart failure. *Evid Rep Technol Assess (Full Rep)* 2006; 1-147 [PMID: 17764210]
23 **Doust JA**, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 2005; **330**: 625 [PMID: 15774989 DOI: 10.1136/bmj.330.7492.625]
24 **Vrtovec B**, Delgado R, Zewail A, Thomas CD, Richartz BM, Radovancevic B. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. *Circulation* 2003; **107**: 1764-1769 [PMID: 12665499 DOI: 10.1161/01.CIR.0000057980.84624.95]
25 **Balion C**, Don-Wauchope A, Hill S, Santaguida PL, Booth R, Brown JA, Oremus M, Ali U, Bustamam A, Sohel N, McKelvie R, Raina P. Use of Natriuretic Peptide Measurement in the Management of Heart Failure [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013; 13(14)-EHC118-EF [PMID: 24404625]
26 **Colucci WS**, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagoner LE, Givertz MM, Liang CS, Neibaur M, Haught WH, LeJemtel TH. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med* 2000; **343**: 246-253 [PMID: 10911006 DOI: 10.1056/NEJM200007273430403]
27 **Sackner-Bernstein JD**, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293**: 1900-1905 [PMID: 15840865 DOI: 10.1001/jama.293.15.1900]
28 **van Deursen VM**, Hernandez AF, Stebbins A, Hasselblad V, Ezekowitz JA, Califf RM, Gottlieb SS, O'Connor CM, Starling RC, Tang WH, McMurray JJ, Dickstein K, Voors AA. Nesiritide, renal function, and associated outcomes during hospitalization for acute decompensated heart failure: results from the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF). *Circulation* 2014; **130**: 958-965 [PMID: 25074507 DOI: 10.1161/CIRCULATIONAHA.113.003046]
29 **Chen HH**, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC,

Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili EO, Mann DL, Dávila-Román VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013; **310**: 2533-2543 [PMID: 24247300 DOI: 10.1001/jama.2013.282190]

30 **Knecht M**, Pagel I, Langenickel T, Philipp S, Scheuermann-Freestone M, Willnow T, Bruemmer D, Graf K, Dietz R, Willenbrock R. Increased expression of renal neutral endopeptidase in severe heart failure. *Life Sci* 2002; **71**: 2701-2712 [PMID: 12383878 DOI: 10.1016/s0024-3205(02)01990-2]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 October 26; 11(10): 244-255

DOI: 10.4330/wjc.v11.i10.244

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Basic Study

Evaluating the quality of evidence for diagnosing ischemic heart disease from verbal autopsy in Indonesia

Wenrong Zhang, Yuslely Usman, Retno Widyastuti Iriawan, Merry Lusiana, Sha Sha, Matthew Kelly, Chalapati Rao

ORCID number: Wenrong Zhang (0000-0003-4744-8470); Yuslely Usman (0000-0001-9694-613X); Retno Iriawan (0000-0003-0348-113X); Merry Lusiana (0000-0001-6370-0774); Sha Sha (0000-0002-7179-611X); Matthew Kelly (0000-0001-7963-2139); Chalapati Rao (0000-0002-9554-0581).

Author contributions: Zhang W collected the data, carried out data analysis and drafted the paper; Sha S collaborated on the study design and development of analysis methods; Kelly M and Rao C conceived the design of the study and contributed to drafting the paper; Usman Y, Iriawan RW and Lusiana M provided access to the data, and guided and assisted with data collection; All authors contributed to final editing of the paper.

Supported by the Department of Foreign Affairs and Trade, Australian Government, under the Government Partnership for Development program, No. 70856.

Institutional review board statement: This research was approved by the Australian National University Human Ethics Review board with protocol number 2018/493. It was also approved by the Indonesian National Agency for Health Research and Development ethics review board.

Institutional animal care and use committee statement: All procedures involving animals were

Wenrong Zhang, Sha Sha, Matthew Kelly, Chalapati Rao, Department of Global Heath, Research School of Population Health, Australian National University, Canberra, ACT 2602, Australia

Yuslely Usman, Retno Widyastuti Iriawan, Merry Lusiana, National Agency for Health Research and Development, Ministry of Health, Jakarta 10110, Indonesia

Corresponding author: Wenrong Zhang, Doctor, Department of Global Heath, Research School of Population Health, Australian National University, 62 Mills Road, Canberra, ACT 2602, Australia. wenrong.zhang@anu.edu.au
Telephone: +61-2-61250714

Abstract

BACKGROUND

Mortality and cause of death data are fundamental to health policy development. Civil Registration and Vital Statistics systems are the ideal data source, but the system is still under development in Indonesia. A national Sample Registration System (SRS) has provided nationally representative mortality data from 128 sub-districts since 2014. Verbal autopsy (VA) is used in the SRS to obtain causes of death. The quality of VA data must be evaluated as part of the SRS data quality assessment.

AIM

To assess the strength of evidence used in the assignment of Ischaemic Heart Disease (IHD) as causes of death from VA.

METHODS

The sample frame for this study is the 4,070 deaths that had IHD assigned as the underlying cause in the SRS 2016 database. From these, 400 cases were randomly selected. A data extraction form and data entry template were designed to collect relevant data about IHD from VA questionnaires. A standardised categorisation was designed to assess the strength of evidence used to infer IHD as a cause of death. A pilot test of 50 cases was carried out. IBM SPSS software was used in this study.

RESULTS

Strong evidence of IHD as a cause of death was assigned based on surgery for coronary heart disease, chest pain and two out of: sudden death, history of heart disease, medical diagnosis of heart disease, or terminal shortness of breath. More than half (53%) of the questionnaires contained strong evidence. For deaths

reviewed and approved by the Institutional Animal Care and Use Committee of Australian National University.

Conflict-of-interest statement: The authors declare no conflicts of interest.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: June 4, 2019
Peer-review started: June 6, 2019
First decision: July 30, 2019
Revised: August 29, 2015
Accepted: September 13, 2019
Article in press: September 13, 2019
Published online: October 26, 2019

P-Reviewer: Ueda H
S-Editor: Dou Y
L-Editor: Filipodia
E-Editor: Xing YX

outside health facilities, VA questionnaires for male deaths contained acceptable evidence in significantly higher proportions as compared to those for female deaths. ($P < 0.001$). Nearly half of all IHD deaths were concentrated in the 50-69 year age group (48.40%), and a further 36.10% were aged 70 years or more. Nearly two-thirds of the deceased were male (58.40%). Smoking behaviour was found in 44.11% of IHD deaths, but this figure was 73.82% among males.

CONCLUSION
More than half of the VA questionnaires from the study sample were found to contain strong evidence to infer IHD as the cause of death. Results from medical records such as electrocardiograms, coronary angiographies, and load tests could have improved the strength of evidence and contributed to IHD cause of death diagnosis.

Key words: Verbal autopsy; Data quality evaluation; Mortality; Cause of death

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In many countries in Southeast Asia, systems for recording mortality and causes of death are under development. In such settings, due to large proportions of deaths happening outside of health facilities, verbal autopsy interviews with families of the deceased are often used to ascertain the cause of death. However, there is a need to evaluate the quality of cause of death estimation from the verbal autopsy. This study specifically addresses the assignment of ischemic heart disease as a cause of death, concluding that a significant proportion of deaths were assigned this cause using strong evidence.

Citation: Zhang W, Usman Y, Iriawan RW, Lusiana M, Sha S, Kelly M, Rao C. Evaluating the quality of evidence for diagnosing ischemic heart disease from verbal autopsy in Indonesia. *World J Cardiol* 2019; 11(10): 244-255
URL: https://www.wjgnet.com/1949-8462/full/v11/i10/244.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i10.244

INTRODUCTION

Sustained, accurate and timely data on mortality and cause of death patterns, especially the leading causes of death, is essential for local, national and global public health policy development, evaluation, and research[1,2]. The optimal method of obtaining data on mortality and causes of death is to have an attending physician complete a medical certificate of cause of death with the support of detailed clinical documents and to register these deaths in a universal Civil Registration and Vital Statistics (CRVS) system[3,4]. Efficient CRVS systems are still under development in many countries in the Asia-Pacific region, including Indonesia. As an interim step towards strengthening CRVS systems, Indonesia has established a national Sample Registration System (SRS)[5], similar to other countries in the region with large populations, such as India, China, and Bangladesh[6-8]. The aim of the Indonesian national SRS is to register deaths in a nationally representative sample of 128 sub-districts across the country and to estimate indicators of total and cause-specific mortality for health policy and program evaluation. Despite potential limitations in data availability, as well as quality since its inception in 2014, the Indonesian SRS has consistently reported ischemic heart disease (IHD) among the observed leading causes of death in the sample population from 2014-2016[9]. Therefore, it is important to evaluate the reliability of the Indonesian SRS in determining IHD as an underlying cause of death.

Since most deaths in Indonesia occur at home without medical attention, there is limited potential to implement medical certification of cause of death in the SRS. Under these circumstances, an alternative process termed verbal autopsy (VA) is used to ascertain the cause of death in the Indonesian SRS. VA involves a retrospective interview with the deceased's relatives or primary caregivers, who are familiar with the illness and circumstances preceding death[10]. The interview is carried out by trained interviewers after a certain interval following the death. The questionnaire

collects information about pre-existing disease suffered by the deceased, symptoms and clinical events during the illness preceding death, as well as details of interactions with health facilities before death, as reported by the respondent. Based on the answers from the interview, the cause of death is inferred through physician review of completed questionnaires, who then assign probable cause(s) for each death, or the cause of death is inferred using computerised algorithms[10]. The World Health Organi-zation (WHO) has recognised VA as a viable alternative for ascertaining causes of death for population health assessments, where medical certification of cause of death by attending physicians is not available, and has recommended international standards for this methodology[11]. As in Indonesia, there is now a movement in other settings with low-performing vital statistics systems to integrate VA into routine data collection[12].

The diagnoses from VA can be influenced by many factors, such as the design of questionnaires, interviewer skills, characteristics of respondents (including proximity to the deceased), recall period for the interview, and method used for ascertaining causes of death[13]. Given these potential sources of bias, the WHO has recommended the conduct of scientific studies to assess the quality of causes of death from VA[14,15]. Hence, this study was designed to evaluate the quality of evidence used to assign IHD as a cause of death from VA, in order to determine the reliability of IHD mortality estimates from the Indonesian SRS. The study also evaluated potential differences in the quality of evidence according to age group, gender, and place of death of the deceased, in order to develop recommendations to strengthen VA data quality from ongoing SRS operations.

MATERIALS AND METHODS

In general, the optimal method to validate VA methods is to compare the underlying cause of death derived from the VA to the reference diagnosis of the underlying cause for the same death, as derived from a pathological autopsy or the next best alternative, medical records for the deceased[16,17]. In view of the limited availability of pathological autopsies or medical records for community deaths in Indonesia, this study was designed to evaluate the quality of evidence that was available from VA questionnaires, to formulate the diagnosis of ischaemic heart disease as the underlying cause of death from VA. For this purpose, the study reviewed a sample of VA questionnaires for content related to IHD, in terms of medical history, symptoms, and signs of terminal illness, and details of clinical events and treatment as recorded in the questionnaire. VA data quality was analysed according to three categories of strong, acceptable, and weak evidence, a methodology that is conceptually similar to that used in studies to evaluate the quality of evidence for medical certification of causes of death[18-20].

Study design and sample

A cross-sectional study was designed to evaluate the quality of evidence recorded in a sample of VA questionnaires for which IHD was diagnosed as the underlying cause of death from the SRS in 2016. Overall, 30,633 deaths were registered in the 2016 SRS, of which 4,070 deaths had IHD assigned as the underlying cause of death, and this group forms the sampling frame for this study[9]. There was no prior information on the expected proportion of VA cases with strong evidence to support an IHD diagnosis. Hence, to maximise our sample size, we hypothesised that about 50% of VA questionnaires would have strong evidence, and it was estimated that a random sample of 384 questionnaires would be required to estimate this proportion at the 95% confidence level, within a 5% tolerable margin of error[21].

Data collection and processing

A total of 400 VA questionnaires with IHD as the underlying cause of death were randomly selected from the sampling frame. At first, the sample was tested and found to be representative of the whole sampling frame by age and sex. A data extraction form was used to collect required information of interest from the sampled VA questionnaires for the variables listed in Table 1. A brief explanation of the relevance of these variables for evaluating quality of evidence from VA will help place this study into context. In general, the variables presented in Table 1 were either used to assess the quality of evidence or to analyse the determinants or predictors of data quality. The place of death, whether at home or in the hospital, could influence the availability of specific information on the terminal illness, specifically with regard to the details of treatment and diagnosis. The relationship of the respondent could determine their proximity to the deceased, and therefore their knowledge of the terminal illness and events. The length of the recall period between the death and the

interview could also affect the quality of information. The past medical history and specific details of symptoms, signs and events during the terminal illness serve as primary data for reviewing physicians to formulate diagnoses.

The questionnaires also provide important information from three sections that record information in unstructured formats. Firstly, respondents describe their recollec-tions of the symptoms and clinical events during the terminal illness leading to death, in their own words. This section is referred to as the open narrative section. Secondly, the questionnaire also records information on the use of health services and any supporting information from other health records, such as hospital discharge state-ments, laboratory or imaging test reports, or drug prescriptions, among others. Finally, the questionnaire has a section in which the reviewing physician documents a summary of his impressions from the questionnaire review, which provides a basis for his/her assignment of causes of death. In some instances, this section could include information based on the reviewing physician's prior knowledge of the deceased and the terminal illness. Information from these three sections was trans-cribed and translated by local SRS staff, which were used in ascertaining quality of evidence.

The study team identified several key symptoms and other elements of information potentially available from VA interviews that could be used to diagnose IHD. The key symptoms include chest pain, terminal shortness of breath, and sudden death. History of heart disease in the deceased is also important evidence to support the diagnosis of IHD as the cause of death. A history of hypertension is also considered as a risk factor associated with cardiovascular disease mortality. A special variable termed "medical diagnosis" was created from the data, which was rated positive if either IHD was recorded as the cause of death reported by health staff for deaths in hospitals, or if IHD was recorded as a cause by the reviewing physician in the case summary. The study team developed three categories to assess the strength of evidence for the diagnosis of IHD, based on a combination of clinical history, symptoms and diagnostic information, as available. Each case was assigned a category of strength of evidence, the criteria for which are listed in Table 2.

Data analysis

Firstly, this study calculated the distribution of IHD deaths in the study sample by sex, age, place of death (inside or outside health facilities), previous medical history, and presence of risk factors. Data quality consistency between open narratives and structured questions in the questionnaire was measured as an indicator to assess the quality of the VA interview.

Next, this study calculated the frequency and proportion of cases assigned to each category of strength of evidence. Further, the distribution of the strength of evidence was evaluated by sex, age, place of death (hospital or home), the relationship of the respondent with the deceased, and whether the respondent resided with the deceased during the course of death. IBM SPSS statistical software was used in this study to calculate chi-square values and p-values to detect the statistical significance of variation in the strength of evidence by socio-demographic information, place of death and the relationship between respondents and the deceased.

The study data were also evaluated for consistency as an indicator of data quality. In general, the open narrative section is likely to include specific elements of information, such as the occurrence of chest pain, terminal shortness of breath, and previous history of heart disease or hypertension, all of which are also directly enquired by the structured questions. Consistency of such information across both the open-ended sections as well as the structured questions can reflect the quality of the interview, as well as justify the need for both sections in the questionnaire if the information is present only in one source. This study has examined this consistency by comparing information for key variables between the structured questions and open narratives in the same questionnaire.

Ethics consideration

Ethical approval for the overall SRS study has been obtained from the Indonesian Ministry of Health. The study proposed here also obtained ethical approval from both the Australia National University Human Research Ethics Committee (protocol number 2018/493) and the Ethics Board of NIHRD, Indonesia.

RESULTS

As mentioned in the Methods, the study sample was tested and found to be representative of the overall IHD deaths in the SRS 2016 data. Table 3 demonstrates that more than half of the deaths were among males (58.40%), and nearly half of all

Table 1 Data variables used for analysis of quality of evidence from verbal autopsy questionnaires

Data category	Data variables
General information of deceased	Age / sex
	Place of death (health facilities/home)
	Relationship with respondent
	Recall period of interview
Structured questions	Previous medical history (heart disease, stroke, hypertension, diabetes, *etc.*)
	Signs and symptoms of terminal illness
	Risk factors
	Use of health services
	Cause of death provided by health staff
Open sections	Respondent's free-flowing narrative of the course of illness and terminal events
	Information from available health records
	Physician reviewer's case summary

IHD deaths were concentrated in the 50-69 year age-group (48.40%), in approximately the same gender ratio, and a further 36.10% were aged 70 years or more. More than twice the number of deaths occurred at home than in a health facility, while male deaths were more likely to have occurred in health facilities than female deaths, which could have an influence on gender diffe-rentials in the quality of available evidence. Similarly, about half of all cases had a previous history of heart disease, again with males more likely to have such history compared to females. Among the risk factors of importance, about 40.35% of IHD deaths had a prior history of hypertension. Overall, 44.11% of the deceased had a positive history of smoking, but more importantly, almost three-fourths of the male IHD deaths had ever smoked. The average recall period for interviews was about four months, which is within the recommendations for VA.

Table 2 presents the distribution of IHD deaths according to the various categories of strength of diagnostic evidence. Only 4 cases mentioned a previous history of cardiac surgery associated with terminal cardiac symptoms, which represented the strongest possible evidence for IHD. In addition to these four cases, a substantial number of questionnaires included definitive information on terminal chest pain along with other symptoms, positive history, or a medical diagnosis of IHD, as defined in the Methods section. Together, these cases accounted for more than half the sample being assigned to the category of strong diagnostic evidence for IHD from VA.

In another 22% of cases, there was evidence that was reasonably suggestive of IHD, either in the form of terminal chest pain, or a combination of history of sudden death with previous heart disease or a medical diagnosis. While less convincing than the criteria defined for the category of strong evidence, we chose to allocate these cases to the "medium" strength of evidence category. For the remaining cases, the VA questionnaires only included minimal information either in the form of isolated clinical features such as sudden death, terminal shortness of breath, or previous history of heart disease or hypertension. In all these cases, the questionnaires did not contain any information suggestive of any other potential cause of death, but the absence of specific evidence of IHD necessitates these cases to be assigned the category of weak evidence. In two of the sampled cases, there was no symptom suggestive of any cause of death and were hence clearly incorrectly assigned to be caused by IHD.

We further analysed the data to evaluate the demographic and other factors that could be associated with the strength of evidence for the diagnosis of IHD. For this analysis, we combined the deaths from "strong" and "medium" evidence into one category termed "acceptable" evidence and compared it with those from the "weak" evidence category, as shown in Table 4. The analysis showed that while there was no association between strength of evidence and age at death, acceptable evidence to diagnose IHD was significantly associated with the occurrence of deaths in hospitals. Acceptable evidence was also positively associated with deaths in males as compared to deaths in females (Table 4), but a stratified analysis (Table 5) showed that this association was statistically significant only for male deaths that occurred at home (P = 0.005). More pertinent was the finding that there was a significant likelihood of recording better evidence if the respondent belonged to the same generation as the deceased (spouse or sibling), as compared to either a parent or offspring of the deceased being from a different generation. Paradoxically, acceptable evidence was

Table 2 Distribution of each category of strength of evidence

Category	Criteria	Cases	Proportion
Strong	(1) Surgery for coronary heart disease (1%); (2) Terminal chest pain and two of: (A) Sudden death; (B) History of heart disease; (C) Medical diagnosis of heart disease[3]; (D) Terminal shortness of breath.	213	53%
Medium	(1) Terminal chest pain alone; (2) Sudden death AND either: (A) History of heart disease OR; (B) Medical diagnosis of heart disease; (3) Only medical diagnosis of heart disease.	87	22%
Weak	(1) Only history of heart disease; (2) Only symptomatic evidence (without chest pain): (A) Sudden death; (B) Hypertension; (C) Shortness of breath.	98	24.5%
Nil	No evidence for the cause of death.	2	0.5%
TOTAL		400	100

Medical diagnosis of heart disease[3]: (A) informed by health facility staff where treatment accessed during illness; or (B) recorded by local health centre physician with prior knowledge of medical condition of deceased.

significantly associated with longer recall periods (> 90 d), a finding that was also observed in the same population for a similar study conducted to assess the quality of evidence for VA diagnoses of cerebrovascular disease.

This study also analysed the availability and consistency of information across different sections of VA questionnaires. Figure 1 displays the frequencies of positive responses to several key variables from either or both the structured questions and open text sections of the questionnaire. Overall, there was the consistency of information across the two sources within the questionnaire in only 60%-70% of deaths for all of the key variables. The symptoms of chest pain, sudden death, and previous history of heart disease and hypertension were all reported more frequently in response to structured questions. In contrast, the symptoms of shortness of breath and unconsciousness were reported more often in the open text sections. A positive response in at least one source was used in assigning the category of strength of supporting evidence for each case.

Another factor that could influence the quality of information in the VA questionnaires is whether the death took place in a health facility or at home. Figure 2 displays the proportions of deaths in these two locations for which a positive response was provided for certain key symptoms, as well as for the constructed variable "medical diagnosis of heart disease" (see Methods). As per usual expectation, respondents for deaths in health facilities provide higher levels of positive responses, indicative of increased awareness of the clinical features of the terminal illness, likely communicated by the health care staff. This is also evident in the higher proportions of cases with a medical diagnosis of heart disease, as recorded in the questionnaire. All of these observations support the general finding of significantly higher levels of acceptable evidence for deaths in hospitals, as reported in Table 4.

DISCUSSION

VA is currently being promoted as a viable option for deriving information on causes of death in countries where medical certification of cause of death is unavailable or limited[21]. Despite methodological limitations of VA in terms of its reliance on second-hand information from the deceased's relatives, which follows a considerable recall period, causes of death from VA are increasingly being used for national mortality estimation[22,23]. IHD is estimated to be among the top five leading causes of death in the world, as well as in Indonesia. To our knowledge, this study provides the first ever empirical assessment of the quality of evidence available to infer a diagnosis of ischaemic heart disease as the underlying cause of death from VA. Our study identified that more than half (53%) of sample questionnaires from the Indonesian SRS contained strong evidence about IHD. Furthermore, another 22% of cases included sufficient evidence to support a diagnosis of IHD. For the remaining one

Table 3 Sample description by socio-demographic factors and health background

Variable	Female		Male		Total		Chi-square	*P* value
	n	%	*n*	%	*n*	%	χ^2	*P*
Age								
< 30	2	1.2	3	1.3	5	1.3	-	-
30-49	27	16.3	30	12.9	57	14.3	-	1.000
50-69	70	42.2	123	52.8	193	48.4	-	1.000
70+	67	40.4	77	33.0	144	36.1	-	1.000
All ages	166	41.6	233	58.4	399	100		
Place of death								
Health facilities[1]	46	28.0	80	34.3	126	31.6	-	-
Home[2]	118	72.0	153	65.7	271	67.9	1.8	0.185
Medical history								
Hypertension	74	44.6	87	37.3	161	40.4	-	-
Heart disease	73	44.0	133	57.9	206	51.6	4.2	0.041[a]
Diabetes	20	12.0	30	12.1	50	12.5	-	0.516
Risk factors								
Smoking	4	66.7	172	93.0	176	44.1	-	-
Alcohol	2	33.3	13	7.0	15	3.8	-	0.072
Recall period in days								
Mean	110		123				-	-
Median	102		114				0	0.998

[1]Health facilities[1]: Includes deaths occurring in hospital, other health facilities and walk-in clinic; Home[2]: Includes deaths occurring at home and in transit;
[a]*P* value < 0.05.

fourth of the sample, although the evidence used to assign IHD was weak, there was no evidence in the questionnaires to indicate an alternative VA-based cause of death. Overall, our study findings indicate that VA protocols employed in the Indonesian SRS generate evidence of sufficient quality for diagnosing IHD as an underlying cause of death, but with some room for improvement.

More detailed analyses identified that there was a significant likelihood for acceptable diagnostic evidence of IHD from VA for deaths that occurred in health facilities, among male deaths at home, or for which the respondents were from the same generation as the deceased. The availability of strong evidence for hospital deaths is generally plausible and readily understood, owing to the potential for family members to receive direct medical information about the illness from medical staff, which was observed for both male and female deaths. However, for deaths at home, there was a significantly higher proportion of male deaths with acceptable evidence compared to female deaths. In general, it was also observed that the quality of evidence was uniformly better from wives as respondents, in comparison with husbands as respondents (data not shown). This could be a reason for the gender differentials in the quality of evidence. More detailed qualitative research is required to ascertain the reasons for this difference in response patterns. Also, the finding that respon-dents from the same generation (either a spouse or sibling) as the deceased are associated with better quality of VA evidence as compared to either the parents or offspring (a different generation) of the deceased is important. This finding suggests that for adult deaths, interviewers should actively seek and preferably conduct the VA with a spouse or sibling, rather than other adult relatives who may not pay the same attention to details of the terminal illness or the health care received by the deceased.

From a diagnostic perspective, IHD poses particular challenges, in that its cardinal symptom - acute chest pain - is essentially subjective in nature, as compared to the directly observable unilateral paralysis in cases of cerebrovascular stroke. The subjective nature of the occurrence, intensity, and duration of chest pain makes it challenging for VA respondents to report this symptom, as evidenced from its reporting in only about 60% of deaths. This is further compounded by the incidence of

Table 4 Associations between strength of evidence and Verbal Autopsy interview characteristics

Variable	Category	Evidence				Chi-square	*P* value
		Acceptable		Weak			
		n	%	*n*	%	X^2	*P*
Sex of deceased							
	Male	189	81.5	43	18.5	-	-
	Female	110	66.7	55	33.3	11.4	< .001[a]
Age of deceased							
	30-69	191	76.4	59	23.6	-	-
	70+	106	74.1	37	25.9	0.3	0.627
Place of death							
	Hospital	111	87.4	16	12.6	-	-
	Home	188	69.9	81	30.1	14.3	< 0.001[a]
Relationship between respondent and deceased							
	Spouse/sibling	109	86.5	17	13.5	-	-
	Parent/offspring	126	69.6	55	30.4	11.8	< 0.001[a]
Respondent living with the deceased							
	Yes	223	76.4	69	23.6	-	-
	No	69	70.4	29	29.6	0.2	0.281
Recall period							
	> 90 d	172	80.0	43	20.0	-	-
	≤ 90 d	122	70.1	52	29.9	4.4	0.036[a]

[a]*P* value < 0.05.

sudden death in IHD, which is mostly due to cardiac causes as compared to cerebrovascular stroke[24]. In the SRS VA protocol, the structured question on 'sudden death' enquires about the occurrence of death in an individual without any serious illness in the period immediately preceding 24 h. The response to this question also has a degree of subjectivity, which gets further blurred by the length of the recall period. Also, there needs to be clarity in the interviewer's understanding of the phenomenon of sudden death, and (s)he should be able to clearly convey this concept to the respondent, in order to elicit and record the correct response. In our study sample, sudden death was reported in over 70% of cases. In the absence of a medical certificate of cause of death, we considered that a verbal confirmation of chest pain and sudden death is highly suggestive of the cause being IHD. A third important element in our diagnostic criteria was the availability of a "medical diagnosis", as defined in the methods. The SRS interview protocol gives strict instruction to interviewers to not ask leading questions naming specific causes when recording the open narrative, or the structured questions on health care access, or diagnoses provided by healthcare staff. Further, a diagnosis of IHD recorded in the VA reviewing physician's summary is either based on his opinion from the questionnaire review or from prior knowledge of the deceased's clinical history. Hence, taken together, these three elements - chest pain, sudden death, and a medical diagnosis - formed the core criteria for strong evidence in support of an IHD diagnosis. Other categories of evidence included less specific features for IHD.

In terms of the availability of direct clinical information, only four cases reported a previous history of cardiac surgery. Also, there was no information from the health records section providing diagnostic evidence from previous hospital discharge documents, electrocardiograms, laboratory or imaging test reports, or drug prescriptions, which could have aided us in evaluating the strength of evidence. Such information was not available, even though a third of the study sample deaths occurred in hospitals, for which the only useful information from the health records section was from the cause of death communicated by the health staff. A recent study in Vietnam identified that clinical discharge records are valuable evidence for deaths in individuals who accessed health facilities but died within a month following discharge[25]. A likely reason for the absence of this information in Indonesia is the

Table 5 Deaths in health facilities and outside health facilities by gender

Deaths in health facilities	Acceptable evidence		Weak evidence		Chi-square	
	n	%	*n*	%	χ^2	*P* value
Male	72	90.0	8	10.0	-	-
Female	38	82.6	8	17.4	-	0.271
Deaths outside health facilities						
Male	117	77.0	35	23.0	-	-
Female	71	60.7	46	39.3	-	0.005[a]

[a]*P* value < 0.05.

cultural practice of disposing all medical documents and health care materials belonging to the deceased at the time of or soon after the funeral. Future community sensitization events about the VA program could appeal for such documentation to be preserved and made available during VA enquiries.

The findings on the availability and consistency of information from different sections of the VA questionnaire also have important implications for VA implementation. The two main questionnaire components comprising the open text sections and structured questions offer opportunities to record similar information for certain key variables potentially. This provision has been made in the questionnaires to accommodate an observed inherent variability in response patterns during VA interviews, as demonstrated both in our study (Figure 1) as well as in a similar study that only assessed such variation in the reporting of paralysis in deaths from cerebrovascular stroke in Vietnam[26]. Some respondents require prompting through structured questions to elicit all relevant information, while others are more comfortable with giving information in their own words and are non-committal or even inattentive during the structured questions. The open narrative section in questionnaires has generally been found to be very important in determining the cause of death, similar to studies conducted elsewhere[27,28]. Constructing a timeline that puts the history of disease, individual symptoms, signs, and chronology of clinical events together can help characterise the events leading to death, if the respondents were familiar with the deceased. In the Indonesian VA physician review protocol, reviewers are also trained to utilise the information from all sections of the questionnaire to construct such a summary, in order to guide their diagnostic decisions. In many instances, it is likely that physician reviewers would be able to diagnose causes of death largely from the open narratives, although they should always seek corroborating information from the structured questions. Ultimately, better consistency of information across both sources increases confidence in the veracity of information available to formulate diagnoses.

In conclusion, this study demonstrates a process for reviewing the quality of evidence in VA questionnaires, in the context of assigning ischaemic heart disease as the underlying cause of death. While acceptable evidence was available for three-fourths of the cases in our study sample, several measures could be taken to improve overall data quality. Firstly, the questionnaire could be modified to elicit more detail in regard to the designation and/or qualification of health staff (doctors, nurses, or paramedics) who provided an opinion as to the cause of death for events in health facilities. This would enable more accurate use of this information in deciding the level of evidence. Secondly, communities should be sensitised to the benefit of retaining and sharing available health care documents within the household with the local health centre staff, instead of casual disposal following the final rites. Thirdly, the SRS program could initiate activities to liaise with secondary and tertiary hospitals in cities and major towns in the proximity of SRS sites, from where some cause of death-related data may be obtained for facility deaths. Eventually, medical certification of the cause of death scheme could be introduced in these hospitals, to improve the overall quality of evidence for mortality statistics from the SRS. Also, further qualitative research could help design improved community interactions to access the most appropriate respondent, as well as improved interviewing techniques to strengthen VA data quality. These study methods for ischaemic heart disease could be used as a model to investigate the quality of evidence for other major causes of death such as cerebrovascular disease, diabetes, tuberculosis, and chronic lung disease, among others, in Indonesia as well as other settings where VA is routinely implemented. Periodic evaluation of the quality of VA evidence is essential to

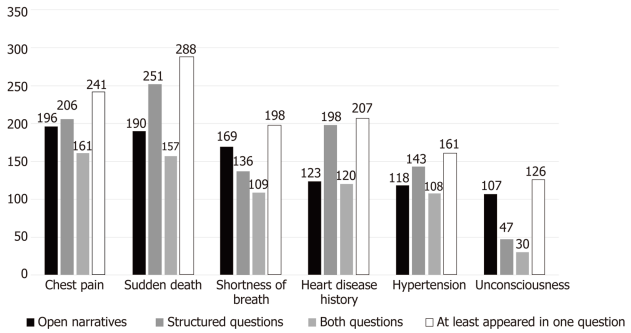


Figure 1 Quality consistency of data in different sections of questionnaire.

improve the empirical use of VA data for mortality and cause of death measurements for health policy, monitoring, and evaluation.

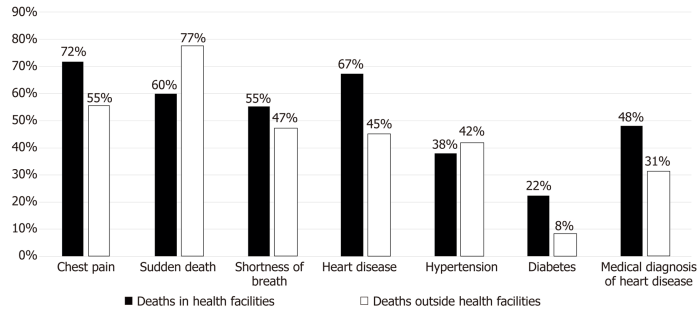


Figure 2 Symptom frequencies between deaths at health facilities and at home.

ARTICLE HIGHLIGHTS

Research background

Mortality and cause of death data are the basis for health policy and research. The Civil Registration and Vital Statistics (CRVS) system is the ideal source of data, but the CRVS in Indonesia is still under development. Since 2014, the National Sample Registration System (SRS) has provided nationally representative mortality data from 128 sub-districts. Verbal autopsy (VA) is used in SRS to obtain the cause of death.

Research motivation

The evidence available from the VA to diagnose causes of death must be assessed to establish the reliability and utility of SRS data. The diagnosis of VA may be influenced by many factors, such as questionnaire design, interviewer skills, characteristics of respondents (including proximity to the deceased), recall period for interviews, and methods for determining the cause of death. Given these potential sources of bias, the World Health Organization recommends conducting scientific research to assess the quality of VA's cause of death, hence necessitating this study.

Research objectives

This study was designed to assess the quality of evidence used to diagnose Ischaemic Heart Disease (IHD) as a cause of death from VA. The study also sought to evaluate various factors that could influence the quality of evidence, such as age and gender of the deceased, place of death, relationship of the respondent, and recall period.

Research methods

The study sample comprised a random sample of 400 deaths out of a total of 4,070 cases diagnosed from IHD in the SRS data for 2016. A data extraction form and data entry template were designed to collect relevant IHD data from VA questionnaires. A standardised classification was designed to IHD cases to categories with strong, medium and weak evidence. Strong evidence of IHD was defined to include surgery for coronary heart disease, or the history of chest pain along with two additional characteristics among sudden death; history of heart disease; the medical diagnosis of heart disease; or terminal shortness of breath. Statistical analysis was conducted to assess the frequency of cases with different levels of evidence, as well as to identify associations between case characteristics and levels of evidence.

Research results

Nearly half of all IHD deaths were concentrated in the 50-69 age group (48.40%), and another 36.10% were 70-years-old or older. Two-thirds of the deceased were male (58.40%). VA questionnaires for about three-quarters of all cases contained strong or medium evidence to diagnose IHD. Quality of evidence was significantly associated with the occurrence of deaths in hospitals, with male deaths at home, and with deaths for which the respondent belonged to the same generation as the deceased.

Research conclusions

VA diagnoses of IHD was found to be based on acceptable evidence in the majority of cases in the study sample. Attention is required to improve recording of information during VA interviews, particularly in regard to correct interpretation of responses for symptoms and signs, and more importantly, clinical details from interactions with health services. Such studies should be conducted for other leading causes of death in Indonesia, as well as across space and time.

Research perspectives

The study assessed levels and determinants of the quality of diagnostic evidence to assign Ischaemic Heart Disease as a cause of death from VA methods in Indonesia. The study results provided perspectives on VA data collection processes, evidence patterns guiding VA diagnosis, and the influence of various circumstances of the death event and household interview on the overall quality of evidence from VA.

REFERENCES

1 **Ruzicka LT**, Lopez AD. The use of cause-of-death statistics for health situation assessment: national and international experiences. *World Health Stat Q* 1990; **43**: 249-258 [PMID: 2293493]
2 **Mahapatra P**, Shibuya K, Lopez AD, Coullare F, Notzon FC, Rao C, Szreter S; Monitoring Vital Events. Civil registration systems and vital statistics: successes and missed opportunities. *Lancet* 2007; **370**: 1653-1663 [PMID: 18029006 DOI: 10.1016/S0140-6736(07)61308-7]
3 **World Health Organization**. Strengthening civil registration and vital statistics through innovative approaches in the health sector. Geneva; 2014. Report No: WHO/HIS/HSI/2014/1. Available from: https://www.unicef.org/protection/files/Strengthening_Civil_Registration_and_Vital_Statistics_Systems_through_Innovative_Approaches_in_the_Health_Sector.pdf
4 **Rao C**. Breathing life into mortality data collection. *Science* 2011; **333**: 1702 [PMID: 21940876 DOI: 10.1126/science.333.6050.1702-a]
5 **Pratiwi ED**, Kose S. Development of an Indonesian sample registration system: A longitudinal study. *The Lancet* 2013; **381**: S118 [DOI: 10.1016/S0140-6736(13)61372-0]
6 **Vital Statistics (Sample Registration System) Division**. Sample Registration System New Delhi: Vital Statistics Division, Office of the Registrar General & Census Commissioner, India; 2007. Available from: http://www.censusindia.gov.in/Vital_Statistics/SRS/Sample_Registration_System.aspx
7 **Yang G**, Hu J, Rao KQ, Ma J, Rao C, Lopez AD. Mortality registration and surveillance in China: History, current situation and challenges. *Popul Health Metr* 2005; **3**: 3 [PMID: 15769298 DOI: 10.1186/1478-7954-3-3]
8 **Bangladeh Bureau of Statistics**. Report on Bangladesh Sample Vital Registration System 2010. Dhaka: Statistics Division: Ministry of Planning; 2012; Available from: http://203.112.218.65:8008/WebTestApplication/userfiles/Image/LatestReports/SVRS-10.pdf
9 **Usman Y**, Iriawan R, Rosita T, Lusiana M, Kosen S, Kelly M, Forsyth S, Rao C, Indonesia's sample registration system in 2018: A work in progress. *JPSS* 2019; **27**: 39-52 [DOI: 10.25133/JPSSv27n1.003]
10 **Fottrell E**, Byass P. Verbal autopsy: methods in transition. *Epidemiol Rev* 2010; **32**: 38-55 [PMID: 20203105 DOI: 10.1093/epirev/mxq003]
11 **World Health Organization**. Verbal autopsy standards: ascertaining and attributing cause of death. Geneva: World Health Organization; 2007; Available from: http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index3.html
12 **de Savigny D**, Riley I, Chandramohan D, Odhiambo F, Nichols E, Notzon S, AbouZahr C, Mitra R, Cobos Muñoz D, Firth S, Maire N, Sankoh O, Bronson G, Setel P, Byass P, Jakob R, Boerma T, Lopez AD. Integrating community-based verbal autopsy into civil registration and vital statistics (CRVS): system-level considerations. *Glob Health Action* 2017; **10**: 1272882 [PMID: 28137194 DOI: 10.1080/16549716.2017.1272882]
13 **Chandramohan D**, Maude GH, Rodrigues LC, Hayes RJ. Verbal autopsies for adult deaths: issues in their development and validation. *Int J Epidemiol* 1994; **23**: 213-222 [PMID: 8082945 DOI: 10.1093/ije/23.2.213]
14 **Joshi R**, Kengne AP, Neal B. Methodological trends in studies based on verbal autopsies before and after published guidelines. *Bull World Health Organ* 2009; **87**: 678-682 [PMID: 19784447 DOI: 10.2471/BLT.07.049288]
15 **Nichols EK**, Byass P, Chandramohan D, Clark SJ, Flaxman AD, Jakob R, Leitao J, Maire N, Rao C, Riley I, Setel PW; WHO Verbal Autopsy Working Group. The WHO 2016 verbal autopsy instrument: An international standard suitable for automated analysis by InterVA, InSilicoVA, and Tariff 2.0. *PLoS Med* 2018; **15**: e1002486 [PMID: 29320495 DOI: 10.1371/journal.pmed.1002486]
16 **Misganaw A**, Mariam DH, Araya T, Aneneh A. Validity of verbal autopsy method to determine causes of death among adults in the urban setting of Ethiopia. *BMC Med Res Methodol* 2012; **12**: 130 [PMID: 22928712 DOI: 10.1186/1471-2288-12-130]
17 **Ganapathy SS**, Yi Yi K, Omar MA, Anuar MFM, Jeevananthan C, Rao C. Validation of verbal autopsy: determination of cause of deaths in Malaysia 2013. *BMC Public Health* 2017; **17**: 653 [PMID: 28800758 DOI: 10.1186/s12889-017-4668-y]
18 **Moriyama IM**, Dawber TR, Kannel WB. Evaluation of diagnostic information supporting medical certification of deaths from cardiovascular disease. *Natl Cancer Inst Monogr* 1966; **19**: 405-419 [PMID: 5905676]
19 **Moriyama IM**, Baum WS, Haenszel WM, Mattison BF. Inquiry into diagnostic evidence supporting medical certifications of death. *Am J Public Health Nations Health* 1958; **48**: 1376-1387 [PMID: 13583282 DOI: 10.2105/AJPH.48.10.1376]
20 **Rao C**, Yang G, Hu J, Ma J, Xia W, Lopez AD. Validation of cause-of-death statistics in urban China. *Int J Epidemiol* 2007; **36**: 642-651 [PMID: 17329316 DOI: 10.1093/ije/dym003]
21 **Kirkwood BR**, Sterne JA. Calculation of required sample size. Essential Medical Statistics. Massachusetts: Blackwell Science Ltd 2003; 413-428
22 **Garenne M**, Fauveau V. Potential and limits of verbal autopsies. Bulletin of the World Health Organization. Available from: http://www.who.int/bulletin/volumes/84/3/editorial30306html/en/
23 **Jha P**, Gajalakshmi V, Gupta PC, Kumar R, Mony P, Dhingra N, Peto R; RGI-CGHR Prospective Study Collaborators. Prospective study of one million deaths in India: rationale, design, and validation results. *PLoS Med* 2006; **3**: e18 [PMID: 16354108 DOI: 10.1371/journal.pmed.0030018]
24 **Hoa NP**, Rao C, Hoy DG, Hinh ND, Chuc NT, Ngo DA. Mortality measures from sample-based surveillance: evidence of the epidemiological transition in Viet Nam. *Bull World Health Organ* 2012; **90**: 764-772 [PMID: 23109744 DOI: 10.2471/BLT.11.100750]
25 **Adabag AS**, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. *Nat Rev Cardiol* 2010; **7**: 216-225 [PMID: 20142817 DOI: 10.1038/nrcardio.2010.3]
26 **Tran HT**, Nguyen HP, Walker SM, Hill PS, Rao C. Validation of verbal autopsy methods using hospital medical records: a case study in Vietnam. *BMC Med Res Methodol* 2018; **18**: 43 [PMID: 29776431 DOI: 10.1186/s12874-018-0497-7]
27 **Gupta S**, Khieu TQ, Rao C, Anh N, Hoa NP. Assessing the quality of evidence for verbal autopsy diagnosis of stroke in Vietnam. *J Neurosci Rural Pract* 2012; **3**: 267-275 [PMID: 23188975 DOI: 10.4103/0976-3147.102603]
28 **Polprasert W**, Rao C, Adair T, Pattaraarchachai J, Porapakkham Y, Lopez AD. Cause-of-death ascertainment for deaths that occur outside hospitals in Thailand: application of verbal autopsy methods. *Popul Health Metr* 2010; **8**: 13 [PMID: 20482760 DOI: 10.1186/1478-7954-8-13]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 November 26; 11(11): 256-281

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 11 November 26, 2019

EDITORIAL

REVIEW

CASE REPORT

Contents

World Journal of Cardiology

Volume 11 Number 11 November 26, 2019

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Samuel Levy, FACC, FAHA, MD, Emeritus Professor, Full Professor, Professor, School of Medicine, University of Méditerannée, Marseille 13008, France.

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ramdas G. Pai MD, FACC, FRCP (Edin), Marco Matteo Ciccone, Dimitris Tousoulis

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE

Ruo-Yu Ma, Director

PUBLICATION DATE

November 26, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 November 26; 11(11): 256-265

DOI: 10.4330/wjc.v11.i11.256

ISSN 1949-8462 (online)

EDITORIAL

Novel lipid-modifying therapies addressing unmet needs in cardiovascular disease

Constantine E Kosmas, Andreas Sourlas, Delia Silverio, Peter D Montan, Eliscer Guzman

ORCID number: Constantine E Kosmas (0000-0003-3926-0304); Andreas Sourlas (0000-0002-5737-106X); Delia Silverio (0000-0001-6333-6247); Peter D Montan (0000-0001-9204-6943); Eliscer Guzman (0000-0001-7153-7516).

Author contributions: Kosmas CE conceived the concepts and analyzed the data. Sourlas A and Kosmas CE wrote the first draft of the manuscript. Silverio D, Montan PD and Eliscer Guzman E contributed to the writing of the manuscript. All of the authors agreed with manuscript results and conclusions. Kosmas CE jointly developed the structure and arguments for the paper and made critical revisions and approved final version. All authors reviewed and approved the final manuscript.

Conflict-of-interest statement: Kosmas CE and Guzman E are members of the Dyslipidemia Speaker Bureau of Amgen, Inc. The other authors declare no potential conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licen

Constantine E Kosmas, Eliscer Guzman, Department of Medicine, Division of Cardiology, Montefiore Medical Center, Bronx, NY 10467, United States

Andreas Sourlas, School of Medicine, University of Crete, Heraklion 71003, Greece

Delia Silverio, Peter D Montan, Cardiology Clinic, Cardiology Unlimited, PC, New York, NY 10033, United States

Corresponding author: Constantine E Kosmas, FACC, FACP, MD, PhD, Attending Doctor, Department of Medicine, Division of Cardiology, Montefiore Medical Center, Bronx, 111 E 210th St, Bronx, NY 10467, United States. cekosmas1@gmail.com
Telephone: +1-646-7347969

Abstract

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide. Currently, it is well established that dyslipidemia is one of the major risk factors leading to the development of atherosclerosis and CVD. Statins remain the standard-of-care in the treatment of hypercholesterolemia and their use has significantly reduced cardiovascular morbidity and mortality. In addition, recent advances in lipid-modifying therapies, such as the development of proprotein convertase subtilisin/kexin type 9 inhibitors, have further improved cardiovascular outcomes in patients with hypercholesterolemia. However, despite significant progress in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events. Furthermore, in some cases, an effective therapy for the identified primary cause of a specific dyslipidemia has not been found up to date. Thus, a number of novel pharmacological interventions are under early human trials, targeting different molecular pathways of lipid formation, regulation and metabolism. This editorial aims to discuss the current clinical and scientific data on new promising lipid-modifying therapies addressing unmet needs in CVD, which may prove beneficial in the near future.

Key words: Lipid-modifying therapies; Cardiovascular disease; Dyslipidemia

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Despite significant progress in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events. Ongoing research has led to the discovery of several different molecules involved in lipid homeostasis, which can serve as possible targets for new lipid-modifying therapies. Novel medications that have

ses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: March 29, 2019
Peer-review started: April 3, 2019
First decision: August 2, 2019
Revised: August 22, 2019
Accepted: October 6, 2019
Article in press: October 6, 2019
Published online: November 26, 2019

P-Reviewer: Cirillo P, Teragawa H, Ueda H, Vidal-Perez R
S-Editor: Dou Y
L-Editor: A
E-Editor: Liu MY

provided promising results in early human trials include inclisiran, bempedoic acid, seladelpar, CSL-112, apabetalone, volanesorsen, APO(a)-RX, and APO(a)-LRX. Furthermore, several other lipid-lowering agents are being evaluated in ongoing trials. Thus, there is optimism that use of these lipid-lowering medications may in the future lead to a reduction of the residual cardiovascular risk.

Citation: Kosmas CE, Sourlas A, Silverio D, Montan PD, Guzman E. Novel lipid-modifying therapies addressing unmet needs in cardiovascular disease. *World J Cardiol* 2019; 11(11): 256-265
URL: https://www.wjgnet.com/1949-8462/full/v11/i11/256.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i11.256

INTRODUCTION

Cardiovascular disease (CVD) has consistently been the leading cause of death in the United States from 1950 through 2014[1]. However, a significant decline in premature mortality due to heart disease is projected through 2030 in United States, attributed mainly to sustained declines in smoking, cholesterol and hypertension, which are major risk factors for CVD, as well as to presumed future advances in medical care and treatment[2].

Undoubtedly, lipid-modifying therapies have played a crucial role in the prevention and treatment of major adverse CV events, improving the CV outcomes of patients with dyslipidemia. Statins are the standard-of-care for the treatment of hypercholesterolemia and their use is supported by extensive evidence demonstrating their effectiveness in lowering low density lipoprotein cholesterol (LDL-C) and in reducing CVD risk in both primary and secondary prevention[3]. Furthermore, statins exert a number of pleiotropic cardioprotective effects, including improved endothelial function, reduced vascular inflammation, and reduced platelet adhesion and thrombosis, which also definitely contribute in the reduction of CVD risk[4]. Another recent success story is the development of monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9), which cause a 54.0%-62.7% incremental reduction in LDL-C levels when administered on top of statins and are associated with a significant reduction of adverse CV events[5,6]. Certainly, several other lipid-modifying therapies are currently being used in everyday clinical practice, such as fibrates, ezetimibe, bile acid sequestrants and niacin.

However, despite the significant progress made in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events[7,8]. Our current pharmacological interventions are able to target a finite only number of lipid pathways. For example, up to date, no specific therapy has been found, which would specifically and significantly improve high-density lipoprotein (HDL) functionality and cholesterol efflux capacity (CEC), leading to a reduction of CVD risk. Moreover, there are many rare, yet important, genetic diseases that cause dyslipidemia and hence premature CVD, for which a specific therapy has not yet been found. In addition, intolerance to certain lipid-lowering medications, especially statins, due to side effects (mostly myalgias and weakness), as well as inability to achieve the LDL-C goal despite use of maximally tolerated dose of statins, are factors that undoubtedly contribute to the residual CVD risk[9].

Given the above, extensive research is being conducted for the development of new drugs that would reduce residual CV risk and address other unmet needs in CVD. Thus, this editorial aims to discuss the current clinical and scientific data on new promising lipid-modifying therapies addressing unmet needs in CVD, which may prove beneficial in the near future.

MEDICATIONS THAT DECREASE LDL CHOLESTEROL LEVELS

The direct association between plasma LDL-C concentration and the incidence of CVD has been unequivocally proven in many epidemiological studies. Inclisiran is a new, recently developed agent, which targets PCSK9 *via* a different route, as compared to PCSK9 monoclonal antibodies. Inclisiran, which is administered

subcutaneously, is a chemically synthesized small interfering RNA molecule, which targets the hepatic production of PCSK9, as it affects the degradation of mRNA post-transcription, thus preventing translation of PCSK9[10]. ORION-1 was a phase 2, multicenter, double-blind, placebo-controlled, multiple ascending-dose trial of inclisiran, administered in patients at high risk for CVD with elevated plasma LDL-C concentration. Administration of a single or two doses of inclisiran was associated with marked declines in LDL-C and PCSK9 levels, as compared to placebo. The greatest LDL-C reduction (52.6%) was observed in association with the two-dose 300-mg regimen of inclisiran[11]. An ongoing phase 3 clinical trial, ORION-11, is expected to provide more information about the cardioprotective properties of inclisiran and its long-term safety and efficacy. The results of this trial are expected to be available in late 2019[12].

Undoubtedly, inclisiran is a new promising agent for further reduction of the residual cardiovascular risk in patients with elevated LDL-C. Furthermore, there is optimism that inclisiran only needs to be administered once every 3-6 mo, which would significantly improve compliance and comfort for the patients.

Another novel LDL-C targeting drug, which is currently under clinical trials, is ETC-1002 or bempedoic acid, a dual modulator of hepatic adenosine triphosphate-citrate lyase (ACL) and adenosine monophosphate-activated protein kinase (AMPK). Inhibition of ACL leads to reduced acetyl coenzyme A (CoA) and hence decreased 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which is the molecular target of statins. Adding to that, activation of AMPK leads to an inhibitory phosphorylation of HMG-CoA reductase and to improved glucose regulation[9,13]. In a phase 2a clinical trial, ETC-1002 was shown to be safe and well tolerated and it significantly lowered LDL-C by up to 27% in a dose-dependent manner in patients with hypercholesterolemia[13]. In another phase 2a clinical trial, ETC-1002 not only reduced LDL-C by 43% after 4 wk, but also decreased high sensitivity CRP (hsCRP) by 41% in patients with hypercholesterolemia and type 2 diabetes mellitus without worsening glycemic control[14]. Moreover, ETC-1002 was shown to be effective, causing a significant reduction in LDL-C levels, when administered to patients with statin intolerance or when given as add-on therapy to statin- or ezetimibe-treated patients[15-17].

The results of a phase 3 trial with bempedoic acid (CLEAR Wisdom Trial) were very recently presented at the American College of Cardiology 2019 Scientific Sessions. Bempedoic acid (ETC-1002), added to maximally tolerated statin therapy in patients with hypercholesterolemia and high risk for CVD, lowered LDL-C by 17.4% at 12 wk compared to placebo and maintained significant LDL-C reductions for 52 wk. In addition, bempedoic acid decreased hsCRP by 18.7%. There was no worsening of glycemic control in patients with a history of diabetes and the side effect profile of bempedoic acid was similar to that of placebo. No difference was noted for clinical outcomes, although the trial was not powered for this endpoint[18]. Thus, further outcome studies are required to more definitely assess the role of bempedoic acid in reducing CV risk. Notwithstanding, bempedoic acid may in the future provide an additional therapeutic option to safely lower LDL-C in high CV risk patients with elevated LDL-C treated with maximally tolerated dose of statins and other lipid-modifying therapies.

Peroxisome proliferator-activated receptors (PPARs) are molecular sensors that regulate diverse aspects of lipid metabolism, thus playing a crucial role in lipid homeostasis. Three isotypes of PPARs have been described: α (NR1C1), β/δ (NR1C2) and γ (NR1C3). Fibrates are classical PPARα agonists, whereas thiazolidinediones are potent PPARγ agonists. PPARβ/δ agonists are not currently used in clinical practice; however, they have shown promising results in early clinical trials[19].

Seladelpar or MBX-8025 is a selective PPAR-δ agonist, which has emerged as a promising new agent for the treatment of mixed dyslipidemia. In a multicenter, randomized, double-blind, placebo-controlled study, MBX-8025 was administered to patients with mixed dyslipidemia, alone or in combination with atorvastatin, for 8 wk. In this study, MBX-8025 reduced LDL-C by 18%-43%, triglycerides by 26%-30% and hsCRP by 43%-72%, favorably affecting multiple metabolic parameters. The administration of MBX-8025 was safe and generally well-tolerated[20]. Moreover, MBX-8025 produced substantial reductions in small and very small LDL particles, which translated to reversal of the small dense LDL phenotype in the vast majority of participants[21]. Although these initial results with the use of MBX-8025 appear very promising, further large clinical studies are required to definitely ascertain that the use of MBX-8025 (or another PPARβ/δ agonist) will be truly associated with a reduction in CV risk.

MEDICATIONS THAT INCREASE HDL CHOLESTEROL LEVELS AND/OR FUNCTIONALITY

The inverse association of HDL cholesterol (HDL-C) with future risk of CVD has been unequivocally demonstrated in several epidemiological studies. Although the concept of developing a drug that would raise HDL-C levels and subsequently reduce CV risk exists for many years, no selective HDL-C-raising medication has proven its atheroprotective properties in previous clinical trials. In fact, our current knowledge indicates that HDL functionality plays a much more crucial role in atheroprotection than circulating HDL-C levels[22].

A reconstituted infusible human apolipoprotein A-I (ApoA-I), CSL-112, is under early human trials. In a phase 2a, randomized, double-blind, multicenter, dose-ranging trial, a single intravenous infusion of CSL-112 in patients with stable atherosclerotic disease was shown to be safe and well tolerated. It produced marked and rapid dose-dependent increases in ApoA-I levels (up to 145% increase in the 6.8-g group after 2 h from the time of administration). In addition, total CEC, a key metric of HDL functionality was increased up to 3.1-fold, as compared with placebo[23]. In another phase 2b trial, 4 consecutive weekly infusions of CSL-112, administered to patients with a recent acute myocardial infarction, induced an increase in ApoA-I levels, HDL-C levels, as well as CEC, and preferentially ATP-binding cassette transporter A1 (ABCA1)-dependent CEC, in a dose-dependent manner and with no significant side effects[24]. Given the above, CSL-112 appears to be a very promising new therapeutic intervention for patients with CVD and currently a phase 3 trial is ongoing to assess the potential benefit of CSL-112 in reducing major adverse CV events in patients with acute coronary syndrome. The results of this trial are expected to be available in 2022[25].

Apabetalone or RVX-208 is an orally active small molecule, which increases ApoA-I transcription through an epigenetic mechanism that is mediated by bromodomain and extra-terminal domain (BET) protein 4 (BRD4)[26]. In a multicenter, randomized, double-blind, placebo-controlled study, RVX-208 was administered at varying doses twice daily for 12 wk to statin-treated patients with stable coronary artery disease (CAD). In this study, administration of RVX-208 led to a significant, dose-dependent increase of ApoA-I levels by up to 5.6%. HDL-C levels were also increased by 3.2% to 8.3%, with increasing doses of RVX-208. In addition, there was an increase of the large HDL particles. Transient and reversible elevations in liver transaminases, but with no associated increase in bilirubin levels, were observed in some patients treated with RVX-208[27]. Another study, which retrospectively analyzed the clinical data from two randomized, double-blind, placebo-controlled, similarly designed phase 2b clinical trials of RVX-208 treatment over 6 mo in patients with CAD (SUSTAIN and ASSURE trials), demonstrated a statistically significant increase in HDL-C, ApoA-I, large HDL particles, and average HDL particle size of 7.69%, 10.3%, 30.7%, and 1.16%, respectively, versus placebo. Moreover, a post-hoc analysis showed lower instances of major adverse cardiac events in patients receiving RVX-208[28]. In addition, there is evidence suggesting that RVX-208 may exert some protective effects against the development of type 2 diabetes[29]. Notwithstanding, further studies will be required to better define the role of RVX-208 in the reduction of the risk for CVD.

MEDICATIONS THAT DECREASE TRIGLYCERIDE LEVELS

ApoC-III is another molecule that plays an important regulative role in lipoprotein metabolism. ApoC-III raises plasma triglycerides through inhibition of lipoprotein lipase (LPL), an enzyme essential for the hydrolysis and distribution of triglyceride-rich lipoproteins (TRLs) to extrahepatic tissues, as well as through stimulation of very low-density lipoprotein secretion and *via* prevention of the hepatic clearance of TRL-remnants by the LDL receptor[30]. Elevated plasma triglyceride levels are associated with CVD and clinical studies have clearly shown that non-fasting triglyceride levels are strongly predictive of ischemic events and all-cause mortality, even when differences in plasma HDL-C are taken into account[30]. Epidemiological evidence shows that carriers of loss-of-function mutations of the ApoC-III gene have 39% lower triglycerides, 22% higher HDL-C, and 16% lower LDL-C plasma concentrations. More importantly, their risk of coronary heart disease is reduced by 40%[31].

Given the above, reduction of ApoC-III plasma levels has emerged as a promising therapeutic strategy to decrease risk for CVD. This has led to the development of volanesorsen or ISIS 304801, which is a human antisense oligonucleotide (ASO) that binds to mRNA of the ApoC-III gene and blocks its expression. In a randomized, double-blind, placebo-controlled, dose-ranging, phase 2 study, ISIS 304801,

administered as a single agent to patients with hypertriglyceridemia, produced dose-dependent mean reductions in APOC-III levels of up 79.6% and reductions in triglycerides of up to of 70.9%. No safety concerns related to the use of ISIS 304801 were identified in this study[32]. In another study, volanesorsen (ISIS 304801), administered to patients with hypertriglyceridemia, including familial chylomicronemia syndrome, uniformly lowered ApoC-III on ApoB-100, lipoprotein (a) [Lp(a)] and ApoA-I. Thus, it was suggested that volanesorsen may be a potent agent to reduce triglycerides and CV risk mediated by ApoC-III[33]. In addition, there is evidence that volanesorsen may be an especially useful treatment option for patients with hypertriglyceridemia and type 2 diabetes mellitus, as it improves glucose disposal, insulin sensitivity and various integrative markers of diabetes after short treatment[34]. Given the above, volanesorsen appears to be a novel promising therapy for hypertriglyceridemia, which may also decrease the burden associated with certain genetic diseases causing hypertriglyceridemia, such as the familial chylomicronemia syndrome[35]. Notwithstanding, further investigation on the long-term efficacy and safety of volanesorsen is warranted.

MEDICATIONS THAT DECREASE LIPOPROTEIN (a) LEVELS

There is extensive clinical evidence demonstrating that elevated Lp(a) levels is an independent causative risk factor for CVD and aortic stenosis. Current treatments that are being used to decrease Lp(a) include nicotinic acid, aspirin and, in more severe cases, lipoprotein apheresis. Statins may raise Lp(a) by 10%-20% but are also being used in patients with elevated Lp(a) levels only to decrease LDL-C levels and reduce CVD risk. PCKS9 inhibitors have also been shown to reduce Lp(a) levels by approximately 30%, but up to date they have not been approved for the treatment of high Lp(a) levels[36]. The causality of the relation between Lp(a) and CVD is considered significant and hence the concept of developing drugs that effectively reduce Lp(a) exists for many years. However, it is difficult to target Lp(a), as it has no enzymatic activity and it cannot be feasibly targeted with small molecules or monoclonal antibodies. RNA therapeutics, and specifically ASOs, represent an elegant method to reduce circulating Lp(a). Thus, APO(a)-Rx and APO(a)-LRx were developed, which are ASOs that are administered subcutaneously, inhibiting the synthesis of the atherogenic Apo(a), which is primarily synthesized in the liver[37].

In a randomised, double-blind, placebo-controlled, phase 1 clinical study, participants were treated with a single subcutaneous injection or with six injections of APO(a)-Rx at varying doses. The single injection regimen did not provide any reduction in Lp(a) plasma levels. However, the six injections of APO(a)-Rx resulted in dose-dependent decreases in plasma Lp(a) levels with the highest administered dose of 300 mg being the most effective treatment, as it produced a 77.8%reduction in Lp(a) levels from baseline. Similar reductions were observed in the amount of oxidized phospholipids associated with ApoB-100 and Apo(a). The treatment with APO(a)-Rx was safe and generally well-tolerated, as the most common adverse events were mild injection site reactions[38]. In a phase 2 trial of APO(a)-Rx, which was administered subcutaneously once a week for 12 wk in an ascending-dose design, similar reductions in Lp(a) levels of 66.8%-71.6% were observed[39]. In a phase 1/2a trial of the other developed agent, APO(a)-LRx, the highest administered dose of 40 mg provided a decrease of 92% in Lp(a) levels after six doses in healthy human volunteers. Both agents were also safe[39]. Thus, these new agents targeting the synthesis of Apo(a) may assist clinicians to effectively diminish Lp(a)-mediated cardiovascular risk.

A summary of the mechanisms of action of the aforementioned novel lipid-modifying therapies is shown in Table 1. In addition, the molecular pathways of action and effects of the aforementioned novel lipid-modifying therapies are shown in Figure 1.

ON THE HORIZON

Liver X receptors (LXRs) are members of the nuclear receptor superfamily of DNA-binding transcription factors and act as sensors of cholesterol homeostasis. LXRs mediate physiological responses to cellular and systemic cholesterol overload, including the upregulation of the reverse cholesterol transport (RCT), thus having cardioprotective effects against atherosclerosis. The development of drugs that stimulate LXRs have emerged as a new promising therapeutic intervention[40,41]. There are two isotypes of LXRs; LXRα and LXRβ. XL-652 or BMS-779788 is a partial LXR agonist with LXRβ selectivity. When tested in nonhuman primates, XL-652 appears to

Table 1 Mechanisms of action of novel lipid-modifying therapies addressing unmet needs in cardiovascular disease

Novel pharmacological agent	Mechanism of action
Inclisiran	Small interfering RNA targeting the hepatic synthesis of PCSK9
Bempedoic Acid	Inhibition of hepatic ACL and activation of AMPK
Seladelpar	Selective PPAR-δ agonist
CSL-112	Reconstituted infusible human ApoA-I
Apabetalone	Increase of ApoA-I transcription acting on bromodomain and extra-terminal domain (BET) protein 4 (BRD4)
Volanesorsen	Human ASO inhibiting the expression of mRNA of the ApoC-III gene
APO(a)-Rx and APO(a)-LRx	ASOs inhibiting the synthesis of the apolipoprotein (a)
XL-652	Partial LXR agonist with LXRβ selectivity
Allicin	Upregulation of ABCA1 expression in macrophage-derived foam cells
ACP-501	Recombinant human LCAT

PCSK9: Proprotein convertase subtilisin/kexin type 9; ACL: Adenosine triphosphate-citrate lyase; AMPK: Adenosine monophosphate-activated protein kinase; PPAR: Peroxisome proliferator-activated receptor; ApoA-I: Apolipoprotein A-I; ASO: Antisense oligonucleotide; LXR: Liver X receptor; ABCA1: ATP-binding cassette transporter A1; LCAT: lecithin-cholesterol acyltransferase.

have decreased lipogenic potential, as compared with a full pan agonist, but with similar potency in the induction of genes known to stimulate RCT[42]. XL-652 has also been proven to be safe enough to continue with clinical trials[19].

Another important molecule involved in lipid homeostasis is ABCA1, which has a critical role in modulating efflux of tissue cholesterol and phospholipids into the RCT pathway, thus clearing excess cholesterol from macrophages and preventing atherosclerosis. There is a clinical entity, known as Tangier disease, which is caused by mutations of the ABCA1 gene leading to ABCA1 deficiency[43]. Allicin is a novel anti-atherosclerotic molecule with anti-oxidant and anti-inflammatory properties, which can be extracted from garlic. Allicin has been shown to reduce lipid accumulation through the upregulation of ABCA1 expression in macrophage-derived foam cells[44]. Furthermore, in a randomized, placebo-controlled, clinical trial, the oral administration of a garlic powder tablet, containing 1200 mg of allicin, twice daily for 3 mo, was shown to be superior to placebo in the prevention of carotid intima-media thickness progression in patients with CAD[45]. Another novel promising molecule, which has also been shown in animal studies to up-regulate ABCA1-mediated cholesterol efflux and retard atherosclerosis, is apigenin, a natural flavonoid compound[46]. Thus, given the above, allicin (and possibly apigenin) may be proven useful in the future for the management of CVD and may also potentially have a place in the treatment of patients with Tangier disease with some residual ABCA1 activity.

Lecithin-cholesterol acyltransferase (LCAT) is a key enzyme for the esterification of cholesteryl esters in plasma, promoting also the formation of HDL and enhancing RCT. Mutations in the human LCAT gene underlie either familial LCAT deficiency (FLD) or fish-eye disease (FED)[47]. In this regard, the infusion of recombinant human LCAT is a promising therapeutic option that remains to be explored. In a phase 1b, open-label, single-dose escalation study, a single intravenous infusion of a recombinant human LCAT (ACP-501) had an acceptable safety profile and led to significant dose-proportional increases of both LCAT and HDL-C, as well as to a favorable modification of HDL metabolism. The results of this study provide support for the use of recombinant human LCAT in future clinical trials in patient with CHD and/or FLD[48]. In a first-in-human treatment with enzyme replacement in FLD, ACP-501 infusion therapy improved the anemia, stabilized the renal function, transiently normalized plasma lipids, and favorably modified HDL metabolism. Moreover, ACP-501 therapy was safe and well-tolerated[49]. Hence, the results of these studies are encouraging and support continued development of the recombinant human LCAT therapy.

Last but not least, it should be noted that many other novel lipid-modifying therapies are being currently tested in ongoing trials. These therapies include medications that target protein asialoglycoprotein receptor 1, angiopoietin-related protein 4, desmocollin 1 and many other molecules playing significant roles in lipid homeostasis[50,51].

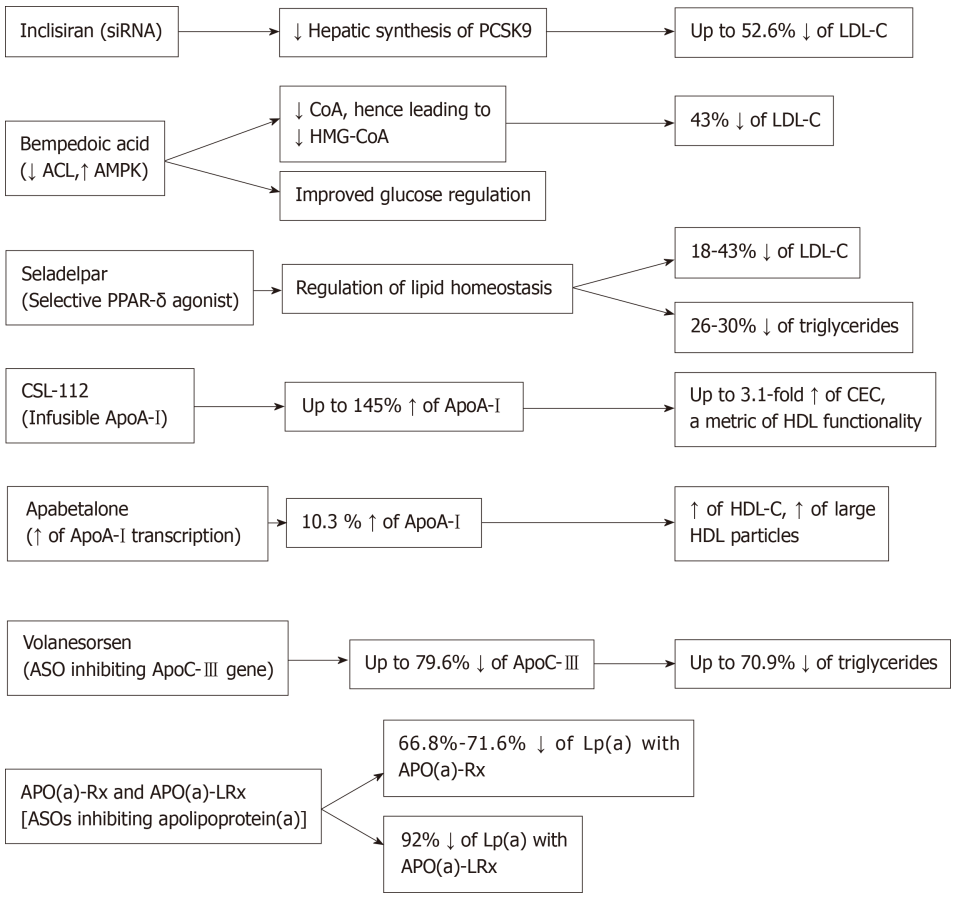


Figure 1 Molecular pathways of action and effects of novel lipid-modifying therapies addressing unmet needs in cardiovascular disease. siRNA: Small interfering RNA; ACL: Adenosine triphosphate-citrate lyase; AMPK: Adenosine monophosphate-activated protein kinase; PPARs: Peroxisome proliferator-activated receptors; Apo: Apolipoprotein; ASO: Antisense oligonucleotide; PCSK9: Proprotein convertase subtilisin/kexin type 9; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; Lp(a): Lipoprotein (a); LXRs: Liver X receptors; LDL-C: Low-density lipoprotein cholesterol; CEC: Cholesterol efflux capacity.

CONCLUSION

It has been well established that despite the significant progress made in the management of CVD, there are still several unmet needs to be addressed. Currently, various lipid-modifying therapies are being evaluated in ongoing trials, targeting a number of different molecules involved in lipid homeostasis. There is optimism that some of these lipid-modifying therapies will be proven clinically beneficial and will eventually enter everyday clinical practice, hence enhancing the armamentarium for the optimal management of CV risk in dyslipidemic patients. Even if some of these drugs do not succeed in future trials, undoubtedly, we will still be a step forward towards a better understanding of the pathogenesis of atherosclerosis and to creating a better future for our patients, decreasing the risk of CVD.

REFERENCES

1 **Heron M**, Anderson RN. Changes in the Leading Cause of Death: Recent Patterns in Heart Disease and Cancer Mortality. *NCHS Data Brief* 2016; 1-8 [PMID: 27598767]
2 **Best AF**, Haozous EA, Berrington de Gonzalez A, Chernyavskiy P, Freedman ND, Hartge P, Thomas D, Rosenberg PS, Shiels MS. Premature mortality projections in the USA through 2030: a modelling study. *Lancet Public Health* 2018; **3**: e374-e384 [PMID: 30037721 DOI: 10.1016/S2468-2667(18)30114-2]
3 **Baigent C**, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267-1278 [PMID: 16214597 DOI: 10.1016/S0140-6736(05)67394-1]
4 **Liao JK**, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol* 2005; **45**: 89-118 [PMID: 15822172 DOI: 10.1146/annurev.pharmtox.45.120403.095748]
5 **Sabatine MS**, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; **376**: 1713-1722 [PMID: 28304224 DOI: 10.1056/NEJMoa1615664]

6 **Schwartz GG**, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; **379**: 2097-2107 [PMID: 30403574 DOI: 10.1056/NEJMoa1801174]

7 **Sampson UK**, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep* 2012; **14**: 1-10 [PMID: 22102062 DOI: 10.1007/s11883-011-0219-7]

8 **Perrone V**, Sangiorgi D, Buda S, Degli Esposti L. Residual cardiovascular risk in patients who received lipid-lowering treatment in a real-life setting: retrospective study. *Clinicoecon Outcomes Res* 2016; **8**: 649-655 [PMID: 27822076 DOI: 10.2147/CEOR.S107992]

9 **Kosmas CE**, Frishman WH. New and Emerging LDL Cholesterol-Lowering Drugs. *Am J Ther* 2015; **22**: 234-241 [PMID: 25486520 DOI: 10.1097/MJT.0000000000000063]

10 **Kosmas CE**, Muñoz Estrella A, Sourlas A, Silverio D, Hilario E, Montan PD, Guzman E. Inclisiran: A New Promising Agent in the Management of Hypercholesterolemia. *Diseases* 2018; **6** [PMID: 30011788 DOI: 10.3390/diseases6030063]

11 **Ray KK**, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, Hall T, Troquay RP, Turner T, Visseren FL, Wijngaard P, Wright RS, Kastelein JJ. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *N Engl J Med* 2017; **376**: 1430-1440 [PMID: 28306389 DOI: 10.1056/NEJMoa1615758]

12 **The Medicines Company**. Inclisiran for Subjects With ACSVD or ACSVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11). [accessed 2019 Mar 23]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03400800 ClinicalTrials.gov Identifier: NCT03400800

13 **Ballantyne CM**, Davidson MH, Macdougall DE, Bays HE, Dicarlo LA, Rosenberg NL, Margulies J, Newton RS. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *J Am Coll Cardiol* 2013; **62**: 1154-1162 [PMID: 23770179 DOI: 10.1016/j.jacc.2013.05.050]

14 **Gutierrez MJ**, Rosenberg NL, Macdougall DE, Hanselman JC, Margulies JR, Strange P, Milad MA, McBride SJ, Newton RS. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2014; **34**: 676-683 [PMID: 24385236 DOI: 10.1161/ATVBAHA.113.302677]

15 **Thompson PD**, Rubino J, Janik MJ, MacDougall DE, McBride SJ, Margulies JR, Newton RS. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. *J Clin Lipidol* 2015; **9**: 295-304 [PMID: 26073387 DOI: 10.1016/j.jacl.2015.03.003]

16 **Ballantyne CM**, McKenney JM, MacDougall DE, Margulies JR, Robinson PL, Hanselman JC, Lalwani ND. Effect of ETC-1002 on Serum Low-Density Lipoprotein Cholesterol in Hypercholesterolemic Patients Receiving Statin Therapy. *Am J Cardiol* 2016; **117**: 1928-1933 [PMID: 27138185 DOI: 10.1016/j.amjcard.2016.03.043]

17 **Thompson PD**, MacDougall DE, Newton RS, Margulies JR, Hanselman JC, Orloff DG, McKenney JM, Ballantyne CM. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. *J Clin Lipidol* 2016; **10**: 556-567 [PMID: 27206943 DOI: 10.1016/j.jacl.2015.12.025]

18 **Goldberg AC**. Efficacy and safety of bempedoic acid added to maximally tolerated statins in patients with hypercholesterolemia and high cardiovascular risk: the CLEAR Wisdom trial. ACC 2019 March 18; New Orleans, LA, 2019.

19 **Xu P**, Zhai Y, Wang J. The Role of PPAR and Its Cross-Talk with CAR and LXR in Obesity and Atherosclerosis. *Int J Mol Sci* 2018; **19** [PMID: 29690611 DOI: 10.3390/ijms19041260]

20 **Bays HE**, Schwartz S, Littlejohn T, Kerzner B, Krauss RM, Karpf DB, Choi YJ, Wang X, Naim S, Roberts BK. MBX-8025, a novel peroxisome proliferator receptor-delta agonist: lipid and other metabolic effects in dyslipidemic overweight patients treated with and without atorvastatin. *J Clin Endocrinol Metab* 2011; **96**: 2889-2897 [PMID: 21752880 DOI: 10.1210/jc.2011-1061]

21 **Choi YJ**, Roberts BK, Wang X, Geaney JC, Naim S, Wojnoonski K, Karpf DB, Krauss RM. Effects of the PPAR-δ agonist MBX-8025 on atherogenic dyslipidemia. *Atherosclerosis* 2012; **220**: 470-476 [PMID: 22169113 DOI: 10.1016/j.atherosclerosis.2011.10.029]

22 **Kosmas CE**, Martinez I, Sourlas A, Bouza KV, Campos FN, Torres V, Montan PD, Guzman E. High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease. *Drugs Context* 2018; **7**: 212525 [PMID: 29623098 DOI: 10.7573/dic.212525]

23 **Tricoci P**, D'Andrea DM, Gurbel PA, Yao Z, Cuchel M, Winston B, Schott R, Weiss R, Blazing MA, Cannon L, Bailey A, Angiolillo DJ, Gille A, Shear CL, Wright SD, Alexander JH. Infusion of Reconstituted High-Density Lipoprotein, CSL112, in Patients With Atherosclerosis: Safety and Pharmacokinetic Results From a Phase 2a Randomized Clinical Trial. *J Am Heart Assoc* 2015; **4**: e002171 [PMID: 26307570 DOI: 10.1161/JAHA.115.002171]

24 **Michael Gibson C**, Korjian S, Tricoci P, Daaboul Y, Yee M, Jain P, Alexander JH, Steg PG, Lincoff AM, Kastelein JJ, Mehran R, D'Andrea DM, Deckelbaum LI, Merkely B, Zarebinski M, Ophuis TO, Harrington RA. Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Apolipoprotein A-I, After Acute Myocardial Infarction: The AEGIS-I Trial (ApoA-I Event Reducing in Ischemic Syndromes I). *Circulation* 2016; **134**: 1918-1930 [PMID: 27881559 DOI: 10.1161/CIRCULATIONAHA.116.025687]

25 **CSL Behring**. Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome (AEGIS-II). [accessed 2019 Mar 24] In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03473223 ClinicalTrials.gov Identifier: NCT03473223

26 **McLure KG**, Gesner EM, Tsujikawa L, Kharenko OA, Attwell S, Campeau E, Wasiak S, Stein A, White A, Fontano E, Suto RK, Wong NC, Wagner GS, Hansen HC, Young PR. RVX-208, an inducer of ApoA-I in humans, is a BET bromodomain antagonist. *PLoS One* 2013; **8**: e83190 [PMID: 24391744 DOI: 10.1371/journal.pone.0083190]

27 **Nicholls SJ**, Gordon A, Johansson J, Wolski K, Ballantyne CM, Kastelein JJ, Taylor A, Borgman M, Nissen SE. Efficacy and safety of a novel oral inducer of apolipoprotein a-I synthesis in statin-treated patients with stable coronary artery disease a randomized controlled trial. *J Am Coll Cardiol* 2011; **57**:

1111-1119 [PMID: 21255957 DOI: 10.1016/j.jacc.2010.11.015]
28 **Gilham D**, Wasiak S, Tsujikawa LM, Halliday C, Norek K, Patel RG, Kulikowski E, Johansson J, Sweeney M, Wong NC, Gordon A, McLure K, Young P. RVX-208, a BET-inhibitor for treating atherosclerotic cardiovascular disease, raises ApoA-I/HDL and represses pathways that contribute to cardiovascular disease. *Atherosclerosis* 2016; **247**: 48-57 [PMID: 26868508 DOI: 10.1016/j.atherosclerosis.2016.01.036]
29 **Siebel AL**, Trinh SK, Formosa MF, Mundra PA, Natoli AK, Reddy-Luthmoodoo M, Huynh K, Khan AA, Carey AL, van Hall G, Cobelli C, Dalla-Man C, Otvos JD, Rye KA, Johansson J, Gordon A, Wong NC, Sviridov D, Barter P, Duffy SJ, Meikle PJ, Kingwell BA. Effects of the BET-inhibitor, RVX-208 on the HDL lipidome and glucose metabolism in individuals with prediabetes: A randomized controlled trial. *Metabolism* 2016; **65**: 904-914 [PMID: 27173469 DOI: 10.1016/j.metabol.2016.03.002]
30 **Kohan AB**. Apolipoprotein C-III: a potent modulator of hypertriglyceridemia and cardiovascular disease. *Curr Opin Endocrinol Diabetes Obes* 2015; **22**: 119-125 [PMID: 25692924 DOI: 10.1097/MED.0000000000000136]
31 **TG and HDL**. Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin DY, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med* 2014; **371**: 22-31 [PMID: 24941081 DOI: 10.1056/NEJMoa1307095]
32 **Gaudet D**, Alexander VJ, Baker BF, Brisson D, Tremblay K, Singleton W, Geary RS, Hughes SG, Viney NJ, Graham MJ, Crooke RM, Witztum JL, Brunzell JD, Kastelein JJ. Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia. *N Engl J Med* 2015; **373**: 438-447 [PMID: 26222559 DOI: 10.1056/NEJMoa1400283]
33 **Yang X**, Lee SR, Choi YS, Alexander VJ, Digenio A, Yang Q, Miller YI, Witztum JL, Tsimikas S. Reduction in lipoprotein-associated apoC-III levels following volanesorsen therapy: phase 2 randomized trial results. *J Lipid Res* 2016; **57**: 706-713 [PMID: 26848137 DOI: 10.1194/jlr.M066399]
34 **Digenio A**, Dunbar RL, Alexander VJ, Hompesch M, Morrow L, Lee RG, Graham MJ, Hughes SG, Yu R, Singleton W, Baker BF, Bhanot S, Crooke RM. Antisense-Mediated Lowering of Plasma Apolipoprotein C-III by Volanesorsen Improves Dyslipidemia and Insulin Sensitivity in Type 2 Diabetes. *Diabetes Care* 2016; **39**: 1408-1415 [PMID: 27271183 DOI: 10.2337/dc16-0126]
35 **Arca M**, Hsieh A, Soran H, Rosenblit P, O'Dea L, Stevenson M. The effect of volanesorsen treatment on the burden associated with familial chylomicronemia syndrome: the results of the ReFOCUS study. *Expert Rev Cardiovasc Ther* 2018; **16**: 537-546 [PMID: 29889589 DOI: 10.1080/14779072.2018.1487290]
36 **Saeed A**, Virani SS. Lipoprotein(a) and cardiovascular disease: current state and future directions for an enigmatic lipoprotein. *Front Biosci (Landmark Ed)* 2018; **23**: 1099-1112 [PMID: 28930591]
37 **Hegele RA**, Tsimikas S. Lipid-Lowering Agents. *Circ Res* 2019; **124**: 386-404 [PMID: 30702996 DOI: 10.1161/CIRCRESAHA.118.313171]
38 **Tsimikas S**, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, Burkey JL, Yang Q, Marcovina SM, Geary RS, Crooke RM, Witztum JL. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet* 2015; **386**: 1472-1483 [PMID: 26210642 DOI: 10.1016/S0140-6736(15)61252-1]
39 **Viney NJ**, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witztum JL, Stroes ES, Tsimikas S. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet* 2016; **388**: 2239-2253 [PMID: 27665230 DOI: 10.1016/S0140-6736(16)31009-1]
40 **Ma Z**, Deng C, Hu W, Zhou J, Fan C, Di S, Liu D, Yang Y, Wang D. Liver X Receptors and their Agonists: Targeting for Cholesterol Homeostasis and Cardiovascular Diseases. *Curr Issues Mol Biol* 2017; **22**: 41-64 [PMID: 27669666 DOI: 10.21775/cimb.022.041]
41 **Lee SD**, Tontonoz P. Liver X receptors at the intersection of lipid metabolism and atherogenesis. *Atherosclerosis* 2015; **242**: 29-36 [PMID: 26164157 DOI: 10.1016/j.atherosclerosis.2015.06.042]
42 **Kirchgessner TG**, Martin R, Sleph P, Grimm D, Liu X, Lupisella J, Smalley J, Narayanan R, Xie Y, Ostrowski J, Cantor GH, Mohan R, Kick E. Pharmacological characterization of a novel liver X receptor agonist with partial LXRα activity and a favorable window in nonhuman primates. *J Pharmacol Exp Ther* 2015; **352**: 305-314 [PMID: 25467132 DOI: 10.1124/jpet.114.219923]
43 **Oram JF**. Tangier disease and ABCA1. *Biochim Biophys Acta* 2000; **1529**: 321-330 [PMID: 11111099 DOI: 10.1016/s1388-1981(00)00157-8]
44 **Lin XL**, Hu HJ, Liu YB, Hu XM, Fan XJ, Zou WW, Pan YQ, Zhou WQ, Peng MW, Gu CH. Allicin induces the upregulation of ABCA1 expression via PPARγ/LXRα signaling in THP-1 macrophage-derived foam cells. *Int J Mol Med* 2017; **39**: 1452-1460 [PMID: 28440421 DOI: 10.3892/ijmm.2017.2949]
45 **Mahdavi-Roshan M**, Zahedmehr A, Mohammad-Zadeh A, Sanati HR, Shakerian F, Firouzi A, Kiani R, Nasrollahzadeh J. Effect of garlic powder tablet on carotid intima-media thickness in patients with coronary artery disease: a preliminary randomized controlled trial. *Nutr Health* 2013; **22**: 143-155 [PMID: 25573347 DOI: 10.1177/0260106014563446]
46 **Ren K**, Jiang T, Zhou HF, Liang Y, Zhao GJ. Apigenin Retards Atherogenesis by Promoting ABCA1-Mediated Cholesterol Efflux and Suppressing Inflammation. *Cell Physiol Biochem* 2018; **47**: 2170-2184 [PMID: 29975943 DOI: 10.1159/000491528]
47 **Rousset X**, Vaisman B, Amar M, Sethi AA, Remaley AT. Lecithin: cholesterol acyltransferase--from biochemistry to role in cardiovascular disease. *Curr Opin Endocrinol Diabetes Obes* 2009; **16**: 163-171 [PMID: 19306528]
48 **Shamburek RD**, Bakker-Arkema R, Shamburek AM, Freeman LA, Amar MJ, Auerbach B, Krause BR, Homan R, Adelman SJ, Collins HL, Sampson M, Wolska A, Remaley AT. Safety and Tolerability of ACP-501, a Recombinant Human Lecithin:Cholesterol Acyltransferase, in a Phase 1 Single-Dose

Escalation Study. *Circ Res* 2016; **118**: 73-82 [PMID: 26628614 DOI: 10.1161/CIRCRESAHA.115.306223]

49 **Shamburek RD**, Bakker-Arkema R, Auerbach BJ, Krause BR, Homan R, Amar MJ, Freeman LA, Remaley AT. Familial lecithin:cholesterol acyltransferase deficiency: First-in-human treatment with enzyme replacement. *J Clin Lipidol* 2016; **10**: 356-367 [PMID: 27055967 DOI: 10.1016/j.jacl.2015.12.007]

50 **Tang WH**, Hazen SL. Atherosclerosis in 2016: Advances in new therapeutic targets for atherosclerosis. *Nat Rev Cardiol* 2017; **14**: 71-72 [PMID: 28094270 DOI: 10.1038/nrcardio.2016.216]

51 **Choi HY**, Ruel I, Malina A, Garrod DR, Oda MN, Pelletier J, Schwertani A, Genest J. Desmocollin 1 is abundantly expressed in atherosclerosis and impairs high-density lipoprotein biogenesis. *Eur Heart J* 2018; **39**: 1194-1202 [PMID: 29106519 DOI: 10.1093/eurheartj/ehx340]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 November 26; 11(11): 266-276

DOI: 10.4330/wjc.v11.i11.266

ISSN 1949-8462 (online)

REVIEW

Multi-modality imaging in transthyretin amyloid cardiomyopathy

Bryan Paul Traynor, Aamir Shamsi, Victor Voon

ORCID number: Bryan Paul Traynor (0000-0002-3010-8851); Aamir Shamsi (0000-0002-4142-7882); Victor Voon (0000-0002-9923-2279).

Author contributions: Voon V and Traynor BP conceived of the initial idea of the study. Traynor BP acquired the data for publication and drafted the article. All authors revised it critically for important intellectual content. All authors approved the final version of the manuscript to be submitted.

Conflict-of-interest statement: The author declare they have no potential conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: April 22, 2019
Peer-review started: April 23, 2019
First decision: August 2, 2019
Revised: September 8, 2019
Accepted: October 6, 2019
Article in press: October 6, 2019
Published online: November 26, 2019

P-Reviewer: Bamoshmoosh M,

Bryan Paul Traynor, Department of Cardiology, Connolly Hospital Blanchardstown, Abbottstown, Dublin D15X40D, Ireland

Aamir Shamsi, Victor Voon, Department of Cardiology, St George's University Hospital NHS Foundation Trust, London SW170QT, United Kingdom

Corresponding author: Victor Voon, MD, MBChB, MRCP, Doctor, Clinical Fellow in Cardiovascular Imaging, Department of Cardiology, St George's University Hospital NHS Foundation Trust, Cranmer Terrace, Tooting, London SW170QT, United Kingdom.
victor.voon@nhs.net
Telephone: +44-20-87251220
Fax: +44-20-87253178

Abstract

Transthyretin amyloid (TTR) cardiomyopathy is a disease of insidious onset, which is often accompanied by debilitating neurological and/or cardiac complications. The true prevalence is not fully known due to its elusive presentation, being often under-recognized and usually diagnosed only late in its natural history and in older patients. Because of this, effective treatment options are usually precluded by multiple comorbidities and frailty associated with such patients. Therefore, high clinical suspicion with earlier and better detection of this disease is needed. In this review, the novel applications of multimodality imaging in the diagnostic pathway of TTR cardiomyopathy are explored. These include the complimentary roles of transthoracic echocardiography, cardiac magnetic resonance, nuclear scintigraphy and positron emission tomography in quantifying cardiac dysfunction, diagnosis and risk stratification. Recent advances in novel therapeutic options for TTR have further enhanced the importance of a timely and accurate diagnosis of this disease.

Key words: Multimodality imaging; Cardiac amyloidosis; Transthyretin; Echocardiography; Cardiac magnetic resonance; Nuclear imaging

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Non-invasive diagnosis of transthyretin amyloid (TTR) cardiomyopathy is improving with significant developments in multiple imaging modalities available to date. A greater appreciation of the various strengths and limitations of these imaging modalities is vital, as is high clinical suspicion and timely investigation for the disease, which remains insidious and elusive. This is of particular relevance in light of emerging novel effective therapeutic options. This focused review aims to highlight the role of multimodality imaging in the diagnosis and risk stratification of patients with TTR

Iacoviello M
S-Editor: Dou Y
L-Editor: A
E-Editor: Liu MY

cardiomyopathy.

Citation: Traynor BP, Shamsi A, Voon V. Multi-modality imaging in transthyretin amyloid cardiomyopathy. *World J Cardiol* 2019; 11(11): 266-276
URL: https://www.wjgnet.com/1949-8462/full/v11/i11/266.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i11.266

INTRODUCTION

Transthyretin amyloid (TTR) cardiomyopathy is a disease characterized by extracellular accumulation of abnormal amyloid protein fibrils due to autosomal dominant hereditary mutation transmission or from a wild type (acquired) form, previously referred to as senile amyloidosis. Transthyretin is a protein primarily synthesized in the liver and can dissociate, subsequently aggregating to produce amyloid. Distinctively, TTR cardiomyopathy lies in one part of the spectrum of amyloid cardiomyopathy compared to primary systemic amyloidosis or light-chain amyloid (AL) cardiomyopathy, often due to plasma cell dyscrasia.

However, amyloid cardiomyopathy, particularly the TTR subtype, is often under-diagnosed, as patients are often asymptomatic or present with nonspecific symptoms early in the trajectory of the disease. Although certain electrocardiographic markers (*i.e.*, low voltage QRS) may suggest the presence of amyloid cardiomyopathy, these markers are not specific, particularly for TTR[1]. Left ventricular (LV) hypertrophy criteria on electrocardiography has only been observed in 25% of TTR cardiomyopathy[2]. While biomarkers such as natriuretic peptides and troponin may be elevated in TTR cardiomyopathy, inferring worse prognosis, their utility in diagnosis of the disease is limited[3,4]. The diagnostic yield is further challenged by the utility of the gold standard of endomyocardial biopsy, which may be limited by sampling errors in early disease and false positive/negative rates of approximately 10%[5].

Therefore, the true prevalence of TTR cardiomyopathy is not fully known as it is usually diagnosed late in its natural history when the disease is well established. Previous reports using imaging and histological evidence have estimated TTR cardiomyopathy prevalence to be between 0.36% to 25% in different cohorts of elderly patients, including those with aortic stenosis and heart failure with preserved ejection fraction. These have been associated with worse outcomes[6-12]. With that, these observations support the need for higher clinical suspicion and earlier screening and diagnosis of TTR cardiomyopathy with non-invasive imaging modalities.

Indeed, the timely detection of TTR cardiomyopathy may allow earlier implementation of disease-modifying therapy, improving survival. Conventionally, orthotopic liver and/or heart transplantation has been offered to these patients as possible curative treatments, as the misfolded TTR protein is synthesized in the liver[13]. Advanced age at liver transplantation and duration of disease have been associated with increased mortality[13]. Patients are also more likely to be suitable surgical candidates at earlier stages of the disease. Furthermore, recent studies have demonstrated beneficial outcomes in patients with TTR treated with novel medical therapies[14,15]. Published data from the ATTR-ACT trial has shown significant reductions in all-cause mortality in TTR-diagnosed patients treated with Tafamidis, a novel agent with TTR stabilizing properties, along with improvements in cardiovascular-related hospitalizations and quality of life measurements[14]. The authors of this study speculate that treatment with this agent early in the disease course will convey greater benefit, similar to its effect in TTR familial amyloid neuropathy[16]. In a subpopulation of the APOLLO study, the RNA inhibitor, Patisiran, has shown statistically significant improvements in certain exploratory endpoints measuring cardiac function, including natriuretic peptide levels, LV wall thickness and global longitudinal strain[15]. These therapeutic options offer promising solutions and support the need for a timely diagnosis. Otherwise, TTR cardiomyopathy is commonly associated with long-term debilitating neurological and cardiac complications such as arrhythmias and heart failure[17].

With that, this focused review aims to highlight the role of multimodality imaging in the diagnosis and risk stratification of patients with TTR cardiomyopathy.

TRANSTHORACIC ECHOCARDIOGRAPHY

Echocardiography is the primary initial imaging modality performed in the investigation of amyloid cardiomyopathy when clinically suspected. While it is a widely available and inexpensive imaging modality, its ability to differentiate between amyloid cardiomyopathy subtypes is limited and when amyloid cardiomyopathy is suspected based on echocardiography, further investigations are necessary to confirm TTR cardiomyopathy.

Increased LV wall thickness, particularly in the absence of high electrocardiographic voltages, and diastolic dysfunction are among the common early echocardiographic features seen which can raise suspicion of amyloid cardiomyopathy, although the differentials for such features are wide[18,19]. In the later stages of the disease, a restrictive filling pattern and biatrial dilatation may be accompanied by pleural and/or pericardial effusions[19-21]. Although not highly specific, LV wall thickness tends to increase to a greater degree in TTR compared to AL cardiomyopathy[18].

Using myocardial strain analysis, the presence of relative apical sparing of longitudinal strain is very characteristic of amyloid cardiomyopathy and has been demonstrated as a reproducible method of accurately differentiating amyloid cardiomyopathy from other causes of LV hypertrophy. In a study comparing 55 patients with amyloid cardiomyopathy to 30 patients with LV hypertrophy due to due to either hypertrophic cardiomyopathy or aortic stenosis, the presence of relative apical longitudinal strain was 93% sensitive and 82% specific in identifying amyloid cardiomyopathy[22].

This apical sparing pattern of global circumferential strain is usually observed unless severe diastolic dysfunction is present[23]. Furthermore, this imaging technique may better aid the identification of amyloid cardiomyopathy in challenging patient subgroups with mild LV wall thickening and preserved ejection fraction[24]. Despite that, there is limited data on echocardiographic features specific to TTR cardiomyopathy. In a study of biopsy-proven TTR patients using speckle-tracking echocardiography, acquired TTR was characterized by lower LV ejection fraction, as well as lower basal and mid LV radial strain compared to inherited TTR[25].

In addition, only few echocardiographic markers have demonstrated prognostic value specific to TTR cardiomyopathy. Among these, impairment of left atrial function, using conventional and strain-derived speckle-tracking parameters, has been demonstrated in amyloid cardiomyopathy and closely correlates to LV deformation. Acquired TTR was associated with worse left atrial function when compared to inherited TTR or AL[26]. In terms of strain imaging, 4-chamber longitudinal strain was significantly associated with major adverse cardiovascular events in amyloid cardiomyopathy, superior to traditional parameters[27]. Relative apical sparing pattern of global longitudinal strain may indicate worse prognosis, particularly when combined with low LV ejection fraction[28]. In assessing the right ventricle, TAPSE can independently predict major adverse events in amyloid cardiomyopathy patients[29]. Right ventricular dilatation has also been associated with more severe cases of amyloid cardiomyopathy and infers very poor prognosis[30].

BONE SCINTIGRAPHY

In 1975, ^{99m}Tc -methylene diphosphonate accumulation in amyloid cardiomyopathy was reported for the first time[31]. Since then, multiple bone scintigraphy tracers have been tested, although their cellular binding mechanisms are not fully known. Several of these tracers have been predominantly utilized and are described below. Scintigraphy tracer uptake in TTR cardiomyopathy has been suggested as possibly due to the increased number of small microcalcifications seen in the myocardium in TTR[32]. The presence of cardiac tracer uptake confirms amyloid cardiomyopathy but has not been able to exclusively differentiate TTR cardiomyopathy from other subtypes. In addition, the absence of tracer uptake does not rule out amyloid cardiomyopathy.

The authors of a large study of 1217 patients that underwent radionuclide scintigraphy, either ^{99m}Technetium-3,3-disphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), ^{99m}Technetium pyrophosphate (^{99m}Tc-PYP) or ^{99m}Tc-hydroxymehtylene diphosphonate (^{99m}Tc-HMDP) proposed a non-invasive diagnostic criteria for TTR cardiomyopathy[33]. TTR was suggested by a score of 2 or 3 with the use of the Perugini visual score of myocardial radiotracer enhancement (Table 1). Grade 2 or 3 enhancement was shown to be 90% sensitive and 97% specific for TTR cardiomyopathy using this scoring system. Furthermore, when grade 2 or 3 uptake is

combined with absence of monoclonal proteins in serum or urine testing, the diagnostic accuracy improves further. A specificity and positive predictive value of 100% has been demonstrated in this regard. This was consistent among all three of the radiotracers used in the study.

Interestingly, while absence of abnormal cardiac uptake of radionucleotide tracer confers a prognostic benefit, Perugini grade stratification at diagnosis has yet to show prognostic significance in TTR cardiomyopathy[34]. These observations are further supported by a study of a large cohort of patients undergoing scintigraphy for non-cardiac reasons. Of 12521 patients included, myocardial tracer uptake was demonstrated in 0.36%[6].

Despite the added value of nuclear scintigraphy in the diagnostic pathway of amyloid cardiomyopathy, there remains low penetrance and high variability in its utilization[35], thus indicating a greater need for standardization in technique between centres.

^{99m}Tc-DPD scintigraphy

^{99m}Tc-DPD scintigraphy is a highly sensitive technique for imaging TTR cardiomyopathy. In a study utilizing ^{99m}Tc-DPD scintigraphy, all 158 patients with TTR and clinical cardiac involvement demonstrated cardiac tracer uptake[36]. In the diagnosis of TTR cardiomyopathy, a study comparing 15 patients with TTR cardiomyopathy to 10 patients with AL-related cardiomyopathy revealed both sensitivity and specificity of 100% in identifying the TTR cohort using ^{99m}Tc-DPD scintigraphy[37]. Another more recent study comparing a larger group of 45 patients with TTR cardiomyopathy to 34 with AL cardiomyopathy and 15 controls again showed high levels of accuracy with positive and negative predictive values of 88% and 100% using a visual score of ≥ 2[38]. ^{99m}Tc -DPD use as a modality in diagnosing and differentiating TTR from AL cardiomyopathy has also been supported by a study of a small Australian cohort of 13 TTR patients, all showing diagnostic tracer uptake, while 25% of patients with AL-related cardiac involvement showed uptake[39].

^{99m}Tc-DPD has been observed to distribute predominantly in the cardiac septal and basal segments and lowest uptake is found in the apical and apico-antero-lateral segments[40].

Furthermore, reasonable intermodality agreement ^{99m}Tc-DPD has been shown with cardiac magnetic resonance (CMR) in the identification of TTR cardiomyopathy. Significantly improved estimation of cardiac involvement was seen using ^{99m}Tc –DPD scintigraphy when compared to late gadolinium enhancement (LGE) on CMR in a study of 18 patients diagnosed with TTR. These consecutively diagnosed patients had a mean age of 50 years, 56% were female and 56% were asymptomatic[41]. Interestingly, amyloid fibril composition has been shown to affect the result of ^{99m}Tc-DPD scintigraphy. Among 55 biopsy-proven TTR patients, all of those with type A fibrils, and none of those with type B, showed tracer uptake. Type B fibrils were associated with early-onset V30M mutation and in patients carrying the Y114C mutation in inherited TTR, whereas type A was noted in all other mutations currently examined as well as in acquired TTR cardiomyopathy[42].

^{99m}Tc-PYP scintigraphy

^{99m}Tc-PYP is currently the most commonly used form of nuclear scintigraphy. There is growing evidence behind its use of as a cardiac tracer in TTR. In a large multicenter study of 171 patients with CA, 121 due to TTR, ^{99m}Tc-PYP showed 91% sensitivity and 92% specificity in diagnosing TTR cardiomyopathy[43]. Another study demonstrated the ability of ^{99m}Tc -PYP cardiac imaging to distinguish AL from TTR cardiomyopathy with a sensitivity of 97% and specificity of 100% when heart-to-contralateral ratio of > 1.5 was used[44]. Furthermore, ^{99m}Tc-PYP scintigraphy showed reduced uptake in the apical segments of the LV in TTR. This correlates with apical sparing of longitudinal strain seen on echocardiography[45].

In addition, there may be potential to diagnose early TTR cardiomyopathy. An observational study of carriers of inherited TTR mutations included 12 asymptomatic carriers with normal echocardiographic and biochemical parameters. Cardiac ^{99m}Tc-PYP uptake was abnormal by visual scoring, comparing cardiac to bone tracer uptake, in 84%. Grade 2 or 3 tracer avidity, indicating TTR deposition, was seen in 58%[46]. However, serial ^{99m}Tc-PYP scanning has not been shown to track disease progression accurately, as demonstrated in a small study, which showed no significant change in tracer uptake after 18 mo despite obvious clinical progression of disease[47].

POSITRON EMISSION TOMOGRAPHY

Radiolabelled amyloid ligands have previously been developed to investigate for

Table 1 Perugini visual scoring

Score	Cardiac uptake and bone uptake
Score 0	Absent cardiac uptake and normal bone uptake
Score 1	Mild cardiac uptake
Score 2	Moderate cardiac uptake accompanied by attenuated bone uptake
Score 3	Strong cardiac uptake with mild/absent bone uptake

amyloid deposits in the brain in Alzheimer's disease. These tracers have also shown some utility in amyloid cardiomyopathy. Its concomitant use with nuclear scintigraphy aids in confirming localization of tracer uptake in heart. A systematic review of six studies involving the use of positron emission tomography (PET) in amyloid cardiomyopathy, including 98 patients, demonstrated a pooled sensitivity of 95% and specificity of 98% in differentiating amyloid cardiomyopathy from controls[48]. Although the individual studies have been small, due to high levels of accuracy, the use of PET and scintigraphy may potentially aid in screening early phases of TTR cardiomyopathy where structural disease may not be apparent on echocardiography or CMR[49]. This requires further exploration. Evidence of PET studies utilizing various cardiac tracers are described below.

^{11}C-Pittsburgh compound B, a radiotracer commonly used in the investigation of Alzheimer's disease, has the ability to identify amyloid cardiomyopathy due to both type A and type B amyloid fibrils. While this method does not distinguish between TTR and AL, it may help identify certain patients with type B amyloid fibril disease, predominantly V30M mutation-associated TTR cardiomyopathy where ^{99m}Tc-DPD scintigraphy has shown a lack of tracer uptake. However, the mechanism of this is not fully known[42,50]. In addition, the utility of this compound is limited by its very short half-life and difficult production.

^{18}F-florbetaben PET has been shown to help identify patients with amyloid cardiomyopathy, due to TTR or AL. Percentage ^{18}F-florbetaben retention was shown to predict myocardial dysfunction in amyloid cardiomyopathy[51]. In another study of 14 patients, 9 with AL or TTR cardiomyopathy and 5 controls, ^{18}F-florbetapir uptake was seen in all patients with amyloid cardiomyopathy and none of the controls[49]. An autopsy study of 20 patients with autopsy-documented amyloid cardiomyopathy, either due to AL or TTR, and 10 controls, showed binding of ^{18}F-florbetapir, a similar tracer to ^{18}F-florbetaben, in myocardial sections in all amyloid cardiomyopathy patients and in none of the controls[52].

^{18}F-fluorine sodium fluoride is a PET tracer that has been shown, in a small study, to differentiate biopsy-proven TTR from AL cardiomyopathy and controls. Tracer uptake was shown to be present in all of the TTR cardiomyopathy patients and none of either the AL-related patients or controls[53]. This radioisotope was also able to quantify the degree and regional distribution of tracer uptake. However, another report of two patients with TTR cardiomyopathy did not show any uptake of this tracer[54]. The authors hypothesized that specific TTR mutation may influence radioisotope uptake. Therefore, while ^{18}F-fluorine sodium fluoride shows promise as a TTR-specific investigative and disease-monitoring tool, it requires further investigation in larger studies.

CARDIAC COMPUTED TOMOGRAPHY

Currently, there is limited evidence regarding the utility of computed tomography (CT) in diagnosing TTR cardiomyopathy. Myocardial iodine concentration and ratio were increased in amyloid cardiomyopathy and can accurately distinguish amyloid cardiomyopathy from non-amyloid hypertrophic cardiomyopathy and healthy controls with an AUC of 0.99. At a threshold of 0.65, iodine ratio demonstrated a sensitivity of 100% and a specificity of 92% in diagnosing amyloid cardiomyopathy[55]. Myocardial extracellular volume measured using CT has been shown to accurately track laboratory and echocardiographic markers of amyloid cardiomyopathy severity and correlate with bone scintigraphy quantification of amyloid burden[56]. Furthermore, determining the myocardial extracellular volume previously required blood sampling to measure haematocrit level. However, recently, a methodology of calculating the extracellular volume, using a calculation involving the attenuation of blood, has eliminated the need for blood sampling from this process. This improves the feasibility of using CT as a potentially useful imaging modality in amyloid

cardiomyopathy[57].

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) is a useful imaging modality in the diagnosis of amyloid cardiomyopathy. Its utility in assessing abnormal myocardial interstitium was described in 2005[58]. Characteristic features seen in amyloid cardiomyopathy were described as a subendocardial tram-line pattern on LGE imaging which can progress to transmural enhancement in later stages of the disease[59] (Figure 1). Alongside LGE, conventional sequences and non-contrast techniques including native T1 mapping can help diagnose amyloid cardiomyopathy and quantify amyloid burden, although caution should be applied in the setting of ectopic beats, which is not uncommonly associated with amyloid cardiomyopathy, but may result in overlapping blood pool and subsequent false positive diffuse elevation of T1 levels. Cardiac involvement in patients with inherited TTR can be seen in patients without clinical cardiac signs or increased LV wall thickness on CMR, suggesting a potential role in detecting pre-clinical amyloid cardiomyopathy in certain at-risk patients[60].

LATE GADOLINIUM ENHANCEMENT

LGE on CMR has been shown to be of high diagnostic value in amyloid cardiomyopathy and has achieved a diagnostic sensitivity of 85% and specificity of 92% in a meta-analysis of five studies[61]. Transmural pattern of LGE has been shown to be more associated with TTR than AL, although the classically described circumferential subendocardial or transmural LGE is not seen in most patients with amyloid cardiomyopathy. Other findings which are more suggestive of TTR include greater intraventricular septal wall thickness and right ventricular LGE[62]. These investigators also proposed a scoring system, derived from CMR with LGE, which differentiates TTR from AL with 87% sensitivity and 96% specificity[62].

Furthermore, the results of a study by Fontana and colleagues suggested that phase sensitive inversion recovery should replace conventional magnitude inversion recovery for LGE determination in the setting of amyloid cardiomyopathy. Phase sensitive inversion recovery helps to remove the potential confounder of incorrect inversion recovery time selection in diffuse infiltrative disease[63]. Higher proportion of left atrial LGE has been shown to have a strong association with amyloid cardiomyopathy and may help in differentiating amyloid cardiomyopathy from other cardiomyopathies. A sensitivity of 76% and specificity of 94% has been shown where left atrial LGE is > 33%, with significant reduction in left atrial emptying function[64].

However, LGE has some limitations in the investigation of amyloid cardiomyopathy. LGE does not enable assessment of diffuse changes in interstitial space secondary to amyloid deposition or quantitative assessment of expanded interstitium. This is due to inversion time adjustment to the least-enhancing myocardial region. As a result, absence of LGE does not confirm normal myocardium in amyloid cardiomyopathy[65]. Another limitation associated with gadolinium enhancement is the risk of nephropathy. Caution is warranted due to the high prevalence of renal impairment in patients with amyloid cardiomyopathy.

T1 MAPPING

T1 native mapping using non-contrast MRI has shown high levels of diagnostic accuracy in detecting AL cardiomyopathy. In a study of 53 AL amyloidosis patients, 28 patients with confirmed AL cardiomyopathy were compared to 36 healthy controls and 17 patients with aortic stenosis. Accuracy of 92% was seen using a non-contrast T1 cut-off of 1020 ms[66]. Compared to TTR cardiomyopathy, T1 elevations are higher in AL cardiomyopathy but similar diagnostic and disease-tracking performance has been shown in TTR. In TTR, T1 also correlates with left atrial area and with PR interval and QRS duration on electrocardiogram[67]. Quantification methods of myocardial T1, such as weighted mean shortened modified look-locker inversion recovery sequence T1 values have been shown to be significantly higher in amyloid cardiomyopathy when compared to healthy controls[68]. T1 mapping allows detection of diffuse myocardial disease and quantitative assessments, which are limited in LGE imaging[65].

T1 mapping can accurately identify patients with LGE-confirmed cardiac involvement in TTR and correlates well with the degree of amyloid deposition[69]. As a

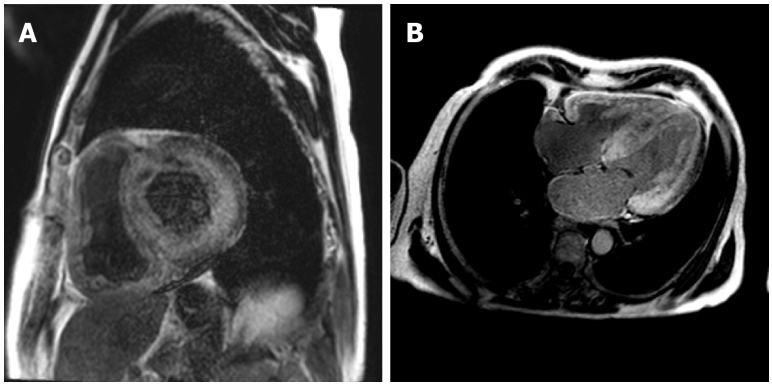


Figure 1 Cardiac magnetic resonance. A, B: Cardiac magnetic resonance demonstrating diffuse, circumferential and near transmural late gadolinium enhancement of the left ventricle in the 4-chamber (A) and short axis views (B), features which are characteristic of amyloid cardiomyopathy.

result, it can help improve detection rates of amyloid cardiomyopathy when used in combination with LGE sequences. It is also a particularly useful tool when contrast is contraindicated due to renal impairment and when LGE artefacts occur due to poor breath-holding and arrhythmias; diagnostic problems commonly seen in these patients.

MYOCARDIAL EXTRACELLULAR VOLUME

Myocardial extracellular volume is another cardiac mapping technique using CMR that is a validated indicator of myocardial fibrosis[70]. It involves T1 mapping acquisitions before and after T1-shortening contrast injection. Both T1 mapping and extracellular volume have recently been shown to perform well as diagnostic techniques in differentiating TTR from other causes of hypertrophic cardiomyopathy[71]. While not a specific feature of amyloid cardiomyopathy, it has been identified as a potential disease-marker to track therapeutic response in the reduction of hepatic amyloid burden following the use of anti-serum amyloid P component antibody in systemic amyloidosis[72].

Extracellular volume correlates with amyloid burden and has been shown to be an independent prognostic factor for survival in TTR cardiomyopathy patients[73]. Furthermore, extracellular volume has been suggested as a more robust marker in TTR cardiomyopathy when compared to T1 mapping as it has shown independent prediction of mortality, where T1 mapping has not[71]. In this regard, T1 mapping and extracellular volume are divergent when comparing TTR to AL cardiomyopathy. Extracellular volume is higher in TTR, reflecting proportionally more amyloid deposition. In contrast, native T1 levels, reflecting both interstitial and cellular changes, are lower in TTR[74]. However, these differing myocardial observations are poorly understood.

OTHER SEQUENCES

CMR-measured longitudinal strain can demonstrate the relative apical sparing and base-to-apex gradient in longitudinal strain, with significantly reduced global longitudinal strain, which is characteristic of amyloid cardiomyopathy[75]. Strain analysis using CMR can help diagnose LGE-positive amyloid cardiomyopathy patients while avoiding the need for contrast medium. Peak circumferential strain level and variability may be more sensitive when compared to LGE imaging in detecting early cardiac involvement in amyloid cardiomyopathy[76]. Basal segments strain parameters can accurately identify cardiac involvement in patients with amyloidosis[77].

Operator-independent heart deformation analysis using CMR has been shown to accurately reproduce radial and circumferential regional myocardial motion patterns, which correlate with feature-tracking indices in amyloid cardiomyopathy[78].

Reduced T2 ratio, comparing the T2 signal intensity of myocardium to skeletal muscle, has shown some utility in amyloid cardiomyopathy diagnosis and can predict mortality[79]. Myocardial oedema, as assessed by T2 mapping, is elevated in both TTR and AL cardiomyopathy, although to a higher degree in AL[80].

CONCLUSION

The use of multi-modality imaging in the diagnosis and management of suspected TTR cardiomyopathy is becoming increasingly accurate and necessary. In light of recent evidence for disease-specific therapeutic agents, high clinical suspicion coupled with earlier utilization of non-invasive imaging modalities are essential for diagnosing this insidious and elusive disease.

REFERENCES

1 **Ruberg FL**, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation* 2012; **126**: 1286-1300 [PMID: 22949539 DOI: 10.1161/CIRCULATIONAHA.111.078915]

2 **Dungu J**, Sattianayagam PT, Whelan CJ, Gibbs SD, Pinney JH, Banypersad SM, Rowczenio D, Gilbertson JA, Lachmann HJ, Wechalekar A, Gillmore JD, Hawkins PN, Anderson LJ. The electrocardiographic features associated with cardiac amyloidosis of variant transthyretin isoleucine 122 type in Afro-Caribbean patients. *Am Heart J* 2012; **164**: 72-79 [PMID: 22795285 DOI: 10.1016/j.ahj.2012.04.013]

3 **Gillmore JD**, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018; **39**: 2799-2806 [PMID: 29048471 DOI: 10.1093/eurheartj/ehx589]

4 **Kelley WE**, Januzzi JL, Christenson RH. Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. *Clin Chem* 2009; **55**: 2098-2112 [PMID: 19815610 DOI: 10.1373/clinchem.2009.130799]

5 **Ardehali H**, Qasim A, Cappola T, Howard D, Hruban R, Hare JM, Baughman KL, Kasper EK. Endomyocardial biopsy plays a role in diagnosing patients with unexplained cardiomyopathy. *Am Heart J* 2004; **147**: 919-923 [PMID: 15131552 DOI: 10.1016/j.ahj.2003.09.020]

6 **Longhi S**, Guidalotti PL, Quarta CC, Gagliardi C, Milandri A, Lorenzini M, Potena L, Leone O, Bartolomei I, Pastorelli F, Salvi F, Rapezzi C. Identification of TTR-related subclinical amyloidosis with 99mTc-DPD scintigraphy. *JACC Cardiovasc Imaging* 2014; **7**: 531-532 [PMID: 24831216 DOI: 10.1016/j.jcmg.2014.03.004]

7 **Castaño A**, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017; **38**: 2879-2887 [PMID: 29019612 DOI: 10.1093/eurheartj/ehx350]

8 **Treibel TA**, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, Roberts N, Hutt DF, Rowczenio DM, Whelan CJ, Ashworth MA, Gillmore JD, Hawkins PN, Moon JC. Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement. *Circ Cardiovasc Imaging* 2016; 9 [PMID: 27511979 DOI: 10.1161/CIRCIMAGING.116.005066]

9 **Damy T**, Costes B, Hagège AA, Donal E, Eicher JC, Slama M, Guellich A, Rappeneau S, Gueffet JP, Logeart D, Planté-Bordeneuve V, Bouvaist H, Huttin O, Mulak G, Dubois-Randé JL, Goossens M, Canoui-Poitrine F, Buxbaum JN. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J* 2016; **37**: 1826-1834 [PMID: 26537620 DOI: 10.1093/eurheartj/ehv583]

10 **González-López E**, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015; **36**: 2585-2594 [PMID: 26224076 DOI: 10.1093/eurheartj/ehv338]

11 **Bennani Smires Y**, Victor G, Ribes D, Berry M, Cognet T, Méjean S, Huart A, Roussel M, Petermann A, Roncalli J, Carrié D, Rousseau H, Berry I, Chauveau D, Galinier M, Lairez O. Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy. *Int J Cardiovasc Imaging* 2016; **32**: 1403-1413 [PMID: 27240600 DOI: 10.1007/s10554-016-0915-z]

12 **Tanskanen M**, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008; **40**: 232-239 [PMID: 18382889 DOI: 10.1080/07853890701842988]

13 **Carvalho A**, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl* 2015; **21**: 282-292 [PMID: 25482846 DOI: 10.1002/lt.24058]

14 **Maurer MS**, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018; **379**: 1007-1016 [PMID: 30145929 DOI: 10.1056/NEJMoa1805689]

15 **Adams D**, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Planté-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med* 2018; **379**: 11-21 [PMID: 29972753 DOI: 10.1056/NEJMoa1716153]

16 **Keohane D**, Schwartz J, Gundapaneni B, Stewart M, Amass L. Tafamidis delays disease progression in patients with early stage transthyretin familial amyloid polyneuropathy: additional supportive analyses from the pivotal trial. *Amyloid* 2017; **24**: 30-36 [PMID: 28393570 DOI: 10.1080/13506129.2017.1301419]

17 **Castaño A**, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev* 2015; **20**: 163-178 [PMID: 25408161 DOI: 10.1007/s10741-014-9462-7]

18 **Falk RH**, Quarta CC, Dorbala S. How to image cardiac amyloidosis. *Circ Cardiovasc Imaging* 2014; **7**: 552-562 [PMID: 24847009 DOI: 10.1161/CIRCIMAGING.113.001396]

19 **Selvanayagam JB**, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. *J Am Coll Cardiol* 2007; **50**: 2101-2110 [PMID: 18036445 DOI: 10.1016/j.jacc.2007.08.028]

20 **Klein AL**, Hatle LK, Taliercio CP, Taylor CL, Kyle RA, Bailey KR, Seward JB, Tajik AJ. Serial Doppler echocardiographic follow-up of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol* 1990; **16**: 1135-1141 [PMID: 2229760 DOI: 10.1016/0735-1097(90)90545-Z]

21 **Siqueira-Filho AG**, Cunha CL, Tajik AJ, Seward JB, Schattenberg TT, Giuliani ER. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. *Circulation* 1981; **63**: 188-196 [PMID: 7438392 DOI: 10.1161/01.CIR.63.1.188]

22 **Phelan D**, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012; **98**: 1442-1448 [PMID: 22865865 DOI: 10.1136/heartjnl-2012-302353]

23 **Lo Q**, Haluska B, Chia EM, Lin MW, Richards D, Marwick T, Thomas L. Alterations in regional myocardial deformation assessed by strain imaging in cardiac amyloidosis. *Echocardiography* 2016; **33**: 1844-1853 [PMID: 27600102 DOI: 10.1111/echo.13355]

24 **Pagourelias ED**, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, Kuznetsova T, Voigt JU. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. *Circ Cardiovasc Imaging* 2017; **10**: e005588 [PMID: 28298286 DOI: 10.1161/CIRCIMAGING.116.005588]

25 **Minamisawa M**, Koyama J, Sekijima Y, Ikeda S, Kozuka A, Ebisawa S, Miura T, Motoki H, Okada A, Izawa A, Ikeda U. Comparison of the standard and speckle tracking echocardiographic features of wild-type and mutated transthyretin cardiac amyloidoses. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 402-410 [PMID: 26873458 DOI: 10.1093/ehjci/jew003]

26 **Nochioka K**, Quarta CC, Claggett B, Roca GQ, Rapezzi C, Falk RH, Solomon SD. Left atrial structure and function in cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1128-1137 [PMID: 28637305 DOI: 10.1093/ehjci/jex097]

27 **Kado Y**, Obokata M, Nagata Y, Ishizu T, Addetia K, Aonuma K, Kurabayashi M, Lang RM, Takeuchi M, Otsuji Y. Cumulative Burden of Myocardial Dysfunction in Cardiac Amyloidosis Assessed Using Four-Chamber Cardiac Strain. *J Am Soc Echocardiogr* 2016; **29**: 1092-1099.e2 [PMID: 27614542 DOI: 10.1016/j.echo.2016.07.017]

28 **Senapati A**, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, Collier P, Hanna M, Popovic ZB, Phelan D. Prognostic implication of relative regional strain ratio in cardiac amyloidosis. *Heart* 2016; **102**: 748-754 [PMID: 26830665 DOI: 10.1136/heartjnl-2015-308657]

29 **Bodez D**, Ternacle J, Guellich A, Galat A, Lim P, Radu C, Guendouz S, Bergoend E, Couetil JP, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Deux JF, Mohty D, Damy T. Prognostic value of right ventricular systolic function in cardiac amyloidosis. *Amyloid* 2016; **23**: 158-167 [PMID: 27348696 DOI: 10.1080/13506129.2016.1194264]

30 **Patel AR**, Dubrey SW, Mendes LA, Skinner M, Cupples A, Falk RH, Davidoff R. Right ventricular dilation in primary amyloidosis: an independent predictor of survival. *Am J Cardiol* 1997; **80**: 486-492 [PMID: 9285663 DOI: 10.1016/S0002-9149(97)00400-1]

31 **VanAntwerp JD**, O'Mara RE, Pitt MJ, Walsh S. Technetium-99m-diphosphonate accumulation in amyloid. *J Nucl Med* 1975; **16**: 238-240 [PMID: 1113174]

32 **Stats MA**, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. *Cardiovasc Pathol* 2016; **25**: 413-417 [PMID: 27469499 DOI: 10.1016/j.carpath.2016.07.001]

33 **Gillmore JD**, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016; **133**: 2404-2412 [PMID: 27143678 DOI: 10.1161/CIRCULATIONAHA.116.021612]

34 **Hutt DF**, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, Page J, Martinez-Naharro A, Wechalekar AD, Lachmann HJ, Quarta CC, Rezk T, Mahmood S, Sachchithanantham S, Youngstein T, Whelan CJ, Lane T, Gilbertson JA, Rowczenio D, Hawkins PN, Gillmore JD. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1344-1350 [PMID: 28159995 DOI: 10.1093/ehjci/jew325]

35 **Harb SC**, Haq M, Flood K, Guerrieri A, Passerell W, Jaber WA, Miller EJ. National patterns in imaging utilization for diagnosis of cardiac amyloidosis: A focus on Tc99m-pyrophosphate scintigraphy. *J Nucl Cardiol* 2017; **24**: 1094-1097 [PMID: 27016106 DOI: 10.1007/s12350-016-0478-3]

36 **Hutt DF**, Quigley AM, Page J, Hall ML, Burniston M, Gopaul D, Lane T, Whelan CJ, Lachmann HJ, Gillmore JD, Hawkins PN, Wechalekar AD. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. *Eur Heart J Cardiovasc Imaging* 2014; **15**: 1289-1298 [PMID: 24939945 DOI: 10.1093/ehjci/jeu107]

37 **Perugini E**, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, Fallani F, Branzi A, Rapezzi C. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99m Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005; **46**: 1076-1084 [PMID: 16168294 DOI: 10.1016/j.jacc.2005.05.073]

38 **Rapezzi C**, Quarta CC, Guidalotti PL, Longhi S, Pettinato C, Leone O, Ferlini A, Salvi F, Gallo P, Gagliardi C, Branzi A. Usefulness and limitations of 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in the aetiological diagnosis of amyloidotic cardiomyopathy. *Eur J Nucl Med Mol Imaging* 2011; **38**: 470-478 [PMID: 21069320 DOI: 10.1007/s00259-010-1642-7]

39 **Moore PT**, Burrage MK, Mackenzie E, Law WP, Korczyk D, Mollee P. The Utility of ^{99m}Tc-DPD Scintigraphy in the Diagnosis of Cardiac Amyloidosis: An Australian Experience. *Heart Lung Circ* 2017; **26**: 1183-1190 [PMID: 28256403 DOI: 10.1016/j.hlc.2016.12.017]

40 **Abulizi M**, Cottereau AS, Guellich A, Vandeventer S, Galat A, Van Der Gucht A, Plante-Bordeneuve V, Dubois-Randé JL, Bodez D, Rosso J, Damy T, Itti E. Early-phase myocardial uptake intensity of ^{99m}Tc-HMDP vs ^{99m}Tc-DPD in patients with hereditary transthyretin-related cardiac amyloidosis. *J Nucl Cardiol*

2018; **25**: 217-222 [PMID: 27804073 DOI: 10.1007/s12350-016-0707-9]
41 **Minutoli F**, Di Bella G, Mazzeo A, Donato R, Russo M, Scribano E, Baldari S. Comparison between (99m)Tc-diphosphonate imaging and MRI with late gadolinium enhancement in evaluating cardiac involvement in patients with transthyretin familial amyloid polyneuropathy. *AJR Am J Roentgenol* 2013; **200**: W256-W265 [PMID: 23436870 DOI: 10.2214/AJR.12.8737]
42 **Pilebro B**, Suhr OB, Näslund U, Westermark P, Lindqvist P, Sundström T. (99m)Tc-DPD uptake reflects amyloid fibril composition in hereditary transthyretin amyloidosis. *Ups J Med Sci* 2016; **121**: 17-24 [PMID: 26849806 DOI: 10.3109/03009734.2015.1122687]
43 **Castano A**, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, Pozniakoff T, Ruberg FL, Miller EJ, Berk JL, Dispenzieri A, Grogan M, Johnson G, Bokhari S, Maurer MS. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. *JAMA Cardiol* 2016; **1**: 880-889 [PMID: 27557400 DOI: 10.1001/jamacardio.2016.2839]
44 **Bokhari S**, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging* 2013; **6**: 195-201 [PMID: 23400849 DOI: 10.1161/CIRCIMAGING.112.000132]
45 **Sperry BW**, Vranian MN, Tower-Rader A, Hachamovitch R, Hanna M, Brunken R, Phelan D, Cerqueira MD, Jaber WA. Regional Variation in Technetium Pyrophosphate Uptake in Transthyretin Cardiac Amyloidosis and Impact on Mortality. *JACC Cardiovasc Imaging* 2018; **11**: 234-242 [PMID: 28917675 DOI: 10.1016/j.jcmg.2017.06.020]
46 **Haq M**, Pawar S, Berk JL, Miller EJ, Ruberg FL. Can ^{99m}Tc-Pyrophosphate Aid in Early Detection of Cardiac Involvement in Asymptomatic Variant TTR Amyloidosis? *JACC Cardiovasc Imaging* 2017; **10**: 713-714 [PMID: 27568122 DOI: 10.1016/j.jcmg.2016.06.003]
47 **Castaño A**, DeLuca A, Weinberg R, Pozniakoff T, Blaner WS, Pirmohamed A, Bettencourt B, Gollob J, Karsten V, Vest JA, Chiuzan C, Maurer MS, Bokhari S. Serial scanning with technetium pyrophosphate (^{99m}Tc-PYP) in advanced ATTR cardiac amyloidosis. *J Nucl Cardiol* 2016; **23**: 1355-1363 [PMID: 26453570 DOI: 10.1007/s12350-015-0261-x]
48 **Kim YJ**, Ha S, Kim YI. Cardiac amyloidosis imaging with amyloid positron emission tomography: A systematic review and meta-analysis. *J Nucl Cardiol* 2018 [PMID: 30022405 DOI: 10.1007/s12350-018-1365-x]
49 **Dorbala S**, Vangala D, Semer J, Strader C, Bruyere JR, Di Carli MF, Moore SC, Falk RH. Imaging cardiac amyloidosis: a pilot study using ^{1}F-florbetapir positron emission tomography. *Eur J Nucl Med Mol Imaging* 2014; **41**: 1652-1662 [PMID: 24841414 DOI: 10.1007/s00259-014-2787-6]
50 **Pilebro B**, Arvidsson S, Lindqvist P, Sundström T, Westermark P, Antoni G, Suhr O, Sörensen J. Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR). *J Nucl Cardiol* 2018; **25**: 240-248 [PMID: 27645889 DOI: 10.1007/s12350-016-0638-5]
51 **Law WP**, Wang WY, Moore PT, Mollee PN, Ng AC. Cardiac Amyloid Imaging with 18F-Florbetaben PET: A Pilot Study. *J Nucl Med* 2016; **57**: 1733-1739 [PMID: 27307344 DOI: 10.2967/jnumed.115.169870]
52 **Park MA**, Padera RF, Belanger A, Dubey S, Hwang DH, Veeranna V, Falk RH, Di Carli MF, Dorbala S. 18F-Florbetapir Binds Specifically to Myocardial Light Chain and Transthyretin Amyloid Deposits: Autoradiography Study. *Circ Cardiovasc Imaging* 2015; 8 [PMID: 26259579 DOI: 10.1161/CIRCIMAGING.114.002954]
53 **Morgenstern R**, Yeh R, Castano A, Maurer MS, Bokhari S. ^{18}Fluorine sodium fluoride positron emission tomography, a potential biomarker of transthyretin cardiac amyloidosis. *J Nucl Cardiol* 2018; **25**: 1559-1567 [PMID: 28176254 DOI: 10.1007/s12350-017-0799-x]
54 **Gagliardi C**, Tabacchi E, Bonfiglioli R, Diodato S, Nanni C, Guidalotti P, Lorenzini M, Lodi F, Milandri A, Rapezzi C, Fanti S. Does the etiology of cardiac amyloidosis determine the myocardial uptake of [18F]-NaF PET/CT? *J Nucl Cardiol* 2017; **24**: 746-749 [PMID: 26976144 DOI: 10.1007/s12350-016-0457-8]
55 **Chevance V**, Damy T, Tacher V, Legou F, Ridouani F, Luciani A, Kobeiter H, Rahmouni A, Deux JF. Myocardial iodine concentration measurement using dual-energy computed tomography for the diagnosis of cardiac amyloidosis: a pilot study. *Eur Radiol* 2018; **28**: 816-823 [PMID: 28812126 DOI: 10.1007/s00330-017-4984-8]
56 **Treibel TA**, Bandula S, Fontana M, White SK, Gilbertson JA, Herrey AS, Gillmore JD, Punwani S, Hawkins PN, Taylor SA, Moon JC. Extracellular volume quantification by dynamic equilibrium cardiac computed tomography in cardiac amyloidosis. *J Cardiovasc Comput Tomogr* 2015; **9**: 585-592 [PMID: 26209459 DOI: 10.1016/j.jcct.2015.07.001]
57 **Treibel TA**, Fontana M, Steeden JA, Nasis A, Yeung J, White SK, Sivarajan S, Punwani S, Pugliese F, Taylor SA, Moon JC, Bandula S. Automatic quantification of the myocardial extracellular volume by cardiac computed tomography: Synthetic ECV by CCT. *J Cardiovasc Comput Tomogr* 2017; **11**: 221-226 [PMID: 28268091 DOI: 10.1016/j.jcct.2017.02.006]
58 **Maceira AM**, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, Sheppard MN, Poole-Wilson PA, Hawkins PN, Pennell DJ. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2005; **111**: 186-193 [PMID: 15630027 DOI: 10.1161/01.CIR.0000152819.97857.9D]
59 **Messroghli DR**, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017; **19**: 75 [PMID: 28992817 DOI: 10.1186/s12968-017-0389-8]
60 **Deux JF**, Damy T, Rahmouni A, Mayer J, Planté-Bordeneuve V. Noninvasive detection of cardiac involvement in patients with hereditary transthyretin associated amyloidosis using cardiac magnetic resonance imaging: a prospective study. *Amyloid* 2014; **21**: 246-255 [PMID: 25211144 DOI: 10.3109/13506129.2014.956924]
61 **Zhao L**, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2016; **16**: 129 [PMID: 27267362 DOI: 10.1186/s12872-016-0311-6]
62 **Dungu JN**, Valencia O, Pinney JH, Gibbs SD, Rowczenio D, Gilbertson JA, Lachmann HJ, Wechalekar A, Gillmore JD, Whelan CJ, Hawkins PN, Anderson LJ. CMR-based differentiation of AL and ATTR

cardiac amyloidosis. *JACC Cardiovasc Imaging* 2014; **7**: 133-142 [PMID: 24412186 DOI: 10.1016/j.jcmg.2013.08.015]

63 **Fontana M**, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, Maestrini V, Barcella W, Rosmini S, Bulluck H, Sayed RH, Patel K, Mamhood S, Bucciarelli-Ducci C, Whelan CJ, Herrey AS, Lachmann HJ, Wechalekar AD, Manisty CH, Schelbert EB, Kellman P, Gillmore JD, Hawkins PN, Moon JC. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation* 2015; **132**: 1570-1579 [PMID: 26362631 DOI: 10.1161/CIRCULATIONAHA.115.016567]

64 **Kwong RY**, Heydari B, Abbasi S, Steel K, Al-Mallah M, Wu H, Falk RH. Characterization of Cardiac Amyloidosis by Atrial Late Gadolinium Enhancement Using Contrast-Enhanced Cardiac Magnetic Resonance Imaging and Correlation With Left Atrial Conduit and Contractile Function. *Am J Cardiol* 2015; **116**: 622-629 [PMID: 26076990 DOI: 10.1016/j.amjcard.2015.05.021]

65 **Hashimura H**, Kimura F, Ishibashi-Ueda H, Morita Y, Higashi M, Nakano S, Iguchi A, Uotani K, Sugimura K, Naito H. Radiologic-Pathologic Correlation of Primary and Secondary Cardiomyopathies: MR Imaging and Histopathologic Findings in Hearts from Autopsy and Transplantation. *Radiographics* 2017; **37**: 719-736 [PMID: 28129067 DOI: 10.1148/rg.2017160082]

66 **Karamitsos TD**, Piechnik SK, Banypersad SM, Fontana M, Ntusi NB, Ferreira VM, Whelan CJ, Myerson SG, Robson MD, Hawkins PN, Neubauer S, Moon JC. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2013; **6**: 488-497 [PMID: 23498672 DOI: 10.1016/j.jcmg.2012.11.013]

67 **Fontana M**, Banypersad SM, Treibel TA, Maestrini V, Sado DM, White SK, Pica S, Castelletti S, Piechnik SK, Robson MD, Gilbertson JA, Rowczenio D, Hutt DF, Lachmann HJ, Wechalekar AD, Whelan CJ, Gillmore JD, Hawkins PN, Moon JC. Native T1 mapping in transthyretin amyloidosis. *JACC Cardiovasc Imaging* 2014; **7**: 157-165 [PMID: 24412190 DOI: 10.1016/j.jcmg.2013.10.008]

68 **van den Boomen M**, Slart RHJA, Hulleman EV, Dierckx RAJO, Velthuis BK, van der Harst P, Sosnovik DE, Borra RJH, Prakken NHJ. Native T^1 reference values for nonischemic cardiomyopathies and populations with increased cardiovascular risk: A systematic review and meta-analysis. *J Magn Reson Imaging* 2018; **47**: 891-912 [PMID: 29131444 DOI: 10.1002/jmri.25885]

69 **Oda S**, Utsunomiya D, Morita K, Nakaura T, Yuki H, Kidoh M, Hirata K, Taguchi N, Tsuda N, Shiraishi S, Namimoto T, Hirakawa K, Takashio S, Izumiya Y, Yamamuro M, Hokimoto S, Tsujita K, Ueda M, Yamashita T, Ando Y, Yamashita Y. Cardiovascular magnetic resonance myocardial T1 mapping to detect and quantify cardiac involvement in familial amyloid polyneuropathy. *Eur Radiol* 2017; **27**: 4631-4638 [PMID: 28477167 DOI: 10.1007/s00330-017-4845-5]

70 **Miller CA**, Naish JH, Bishop P, Coutts G, Clark D, Zhao S, Ray SG, Yonan N, Williams SG, Flett AS, Moon JC, Greiser A, Parker GJ, Schmitt M. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. *Circ Cardiovasc Imaging* 2013; **6**: 373-383 [PMID: 23553570 DOI: 10.1161/CIRCIMAGING.112.000192]

71 **Martinez-Naharro A**, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, Treibel TA, Whelan CJ, Knight DS, Kellman P, Ruberg FL, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Native T1 and Extracellular Volume in Transthyretin Amyloidosis. *JACC Cardiovasc Imaging* 2019; **12**: 810-819 [PMID: 29550324 DOI: 10.1016/j.jcmg.2018.02.006]

72 **Richards DB**, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, Fontana M, Moon JC, Pinzani M, Gillmore JD, Hawkins PN, Pepys MB. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. *N Engl J Med* 2015; **373**: 1106-1114 [PMID: 26176329 DOI: 10.1056/NEJMoa1504942]

73 **Martinez-Naharro A**, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T, Rosmini S, Quarta CC, Whelan CJ, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. *J Am Coll Cardiol* 2017; **70**: 466-477 [PMID: 28728692 DOI: 10.1016/j.jacc.2017.05.053]

74 **Fontana M**, Banypersad SM, Treibel TA, Maestrini V, Sado D, White SK, Bulluck H, Herrey AS, Hawkins PN, Moon J. AL and ATTR cardiac amyloid are different: native T1 mapping and ECV detect different biology. *J Cardiovasc Magn Reson* 2014; **16**: 341 [DOI: 10.1186/1532-429X-16-S1-P341]

75 **Williams LK**, Forero JF, Popovic ZB, Phelan D, Delgado D, Rakowski H, Wintersperger BJ, Thavendiranathan P. Patterns of CMR measured longitudinal strain and its association with late gadolinium enhancement in patients with cardiac amyloidosis and its mimics. *J Cardiovasc Magn Reson* 2017; **19**: 61 [PMID: 28784140 DOI: 10.1186/s12968-017-0376-0]

76 **Oda S**, Utsunomiya D, Nakaura T, Yuki H, Kidoh M, Morita K, Takashio S, Yamamuro M, Izumiya Y, Hirakawa K, Ishida T, Tsujita K, Ueda M, Yamashita T, Ando Y, Hata H, Yamashita Y. Identification and Assessment of Cardiac Amyloidosis by Myocardial Strain Analysis of Cardiac Magnetic Resonance Imaging. *Circ J* 2017; **81**: 1014-1021 [PMID: 28367859 DOI: 10.1253/circj.CJ-16-1259]

77 **Pandey T**, Alapati S, Wadhwa V, Edupuganti MM, Gurram P, Lensing S, Jambhekar K. Evaluation of Myocardial Strain in Patients With Amyloidosis Using Cardiac Magnetic Resonance Feature Tracking. *Curr Probl Diagn Radiol* 2017; **46**: 288-294 [PMID: 28063633 DOI: 10.1067/j.cpradiol.2016.11.008]

78 **Meng L**, Lin K, Collins J, Markl M, Carr JC. Automated Description of Regional Left Ventricular Motion in Patients With Cardiac Amyloidosis: A Quantitative Study Using Heart Deformation Analysis. *AJR Am J Roentgenol* 2017; **209**: W57-W63 [PMID: 28537770 DOI: 10.2214/AJR.16.16982]

79 **Legou F**, Tacher V, Damy T, Planté-Bordeneuve V, Rappeneau S, Benhaiem N, Rosso J, Itti E, Luciani A, Kobeiter H, Rahmouni A, Deux JF. Usefulness of T2 ratio in the diagnosis and prognosis of cardiac amyloidosis using cardiac MR imaging. *Diagn Interv Imaging* 2017; **98**: 125-132 [PMID: 27692958 DOI: 10.1016/j.diii.2016.08.007]

80 **Kotecha T**, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, Knight DS, Zumbo G, Rosmini S, Maestrini V, Bulluck H, Rakhit RD, Wechalekar AD, Gilbertson J, Sheppard MN, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Myocardial Edema and Prognosis in Amyloidosis. *J Am Coll Cardiol* 2018; **71**: 2919-2931 [PMID: 29929616 DOI: 10.1016/j.jacc.2018.03.536]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 November 26; 11(11): 277-281

DOI: 10.4330/wjc.v11.i11.277

ISSN 1949-8462 (online)

CASE REPORT

Management of atherosclerotic plaque in left internal mammary artery graft five years after angiographic patency: A case report

Savvy Nandal, Om Narayan, Peter Barlis, Francis A Ponnuthurai

ORCID number: Savvy Nandal (0000-0001-7105-5832); Om Narayan (0000-0002-4703-1256); Peter Barlis (0000-0003-2447-6815); Francis A Ponnuthurai (0000-0002-5883-8266).

Author contributions: Nandal S wrote the manuscript and reviewed the literature. Ponnuthurai F and Narayan O were patient's intervention cardiologists. Ponnuthurai F, Narayan O and Barlis P reviewed the literature and revised the final version of the manuscript. All authors issued final approval for the version to be submitted.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016). The guidelines of the CARE Checklist (2016) have been adopted.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

Savvy Nandal, Om Narayan, Peter Barlis, Francis A Ponnuthurai, Department of Cardiology, The Northern Hospital, Epping, Victoria 3076, Australia

Corresponding author: Savvy Nandal, MBBS, Research Associate, Department of Cardiology, The Northern Hospital, 185 Cooper Street, Epping, Victoria 3076, Australia.
savvy.nandal@nh.org.aa
Telephone: +61-38-4058000
Fax: +61-38-4058405

Abstract

BACKGROUND

The left internal mammary artery (LIMA) has demonstrated excellent long-term patency rates when used as a bypass conduit with complications usually occurring in the early postoperative period. The rapid development of de-novo atherosclerosis in a previously non-diseased LIMA, subsequently leading to an acute coronary syndrome (ACS) is rarely encountered.

CASE SUMMARY

A 67-year-old man with history of triple coronary artery bypass graft (8 years ago) presented to our hospital with an ACS. He had undergone angiography 5 years ago to investigate episodic chest pain and imaging of the LIMA at the time did not demonstrate the atherosclerotic process. Emergent angiography demonstrated a severe diffuse stenosis in the proximal to mid segment of the LIMA, with embolization of a moderate sized thrombus to the distal skip segment. The LIMA stenosis was characterised by overlying haziness, consistent with acute plaque rupture, associated with residual luminal thrombus. The patient was managed with antithrombotic therapy to reduce the thrombus burden until repeat angiography after 72 h. At repeat angiography, the thrombus burden was substantially reduced at the distal skip segment as well as at the proximal to mid LIMA with the demonstration of multiple plaque cavities. This lesion was predilated and a 2.75 mm × 33 mm everolimus-eluting stent was implanted to a final diameter of 3.0 mm. The patient made a good clinical recovery and was discharged after 6 d.

CONCLUSION

This case highlights the rapid and late development of atherosclerosis in a graft 5 years after documented patency and the importance for consideration of expectant thrombus management.

Key words: Left internal mammary artery graft; Atherosclerosis; Thrombus; Case report

and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: May 30, 2019
Peer-review started: June 4, 2019
First decision: August 2, 2019
Revised: August 9, 2019
Accepted: October 7, 2019
Article in press: October 7, 2019
Published online: November 26, 2019

P-Reviewer: Petix NR, Teragawa H, Traykov V
S-Editor: Dou Y
L-Editor: A
E-Editor: Liu MY

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Late complications of the left internal mammary artery (LIMA) graft occur rarely. We present the case of a 67-year-old man with an acute myocardial infarction due to the rapid progression of atherosclerotic plaque in the mid shaft of the IMA, culminating in plaque rupture and thromboembolism. This case highlights the importance of consideration of expectant thrombus management as well as the importance of considering late complication of LIMA graft as a cause of acute coronary syndrome.

Citation: Nandal S, Narayan O, Barlis P, Ponnuthurai FA. Management of atherosclerotic plaque in left internal mammary artery graft five years after angiographic patency: A case report. *World J Cardiol* 2019; 11(11): 277-281
URL: https://www.wjgnet.com/1949-8462/full/v11/i11/277.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i11.277

INTRODUCTION

The left internal mammary artery (LIMA) has demonstrated excellent long term patency rates when used as a bypass conduit[1,2]. When vessel occlusion does occur, it is typically associated with the presence of competitive flow from the native circulation leading to atresia, issues relating to surgical technique resulting in distal anastomotic failure or rarely due to dissection (either spontaneous or iatrogenic). The rapid development of de-novo atherosclerosis in a previously non-diseased LIMA, subsequently leading to an acute coronary syndrome (ACS) is rarely encountered. We present the case of a 67-year-old man presenting with an acute myocardial infarction due to the rapid progression of atherosclerotic plaque in the mid shaft of the IMA, culminating in plaque rupture and thromboembolism.

CASE PRESENTATION

Chief complaints

A 67-year-old man presented to the emergency department of our hospital complaining of worsening central chest pain for the duration of 3 h.

History of past illness

The patient had past history of coronary artery bypass graft (8 years ago) LIMA-diagonal to Left Anterior Descending (LAD) artery, free right internal mammary artery (RIMA)-ramus intermedius skip to OM and a left radial artery anastomosed to the PDA and ischaemic cardiomyopathy with moderate segmental systolic dysfunction. He also had history of treated hypertension, dyslipidaemia, rheumatoid arthritis and partial nephrectomy for clear cell carcinoma. His regular medications included aspirin 100 mg daily, atorvastatin 80 mg daily (low density lipoprotein cholesterol 1.7 mmol/L), frusemide 40 mg daily, metoprolol 50 mg twice daily and ramipril 5 mg daily.

Physical and laboratory examinations

The patient's cardiovascular examination revealed his heart sounds were dual with no added murmurs and his chest was clear. Electrocardiogram showed anterolateral ST changes of ischaemia (Figure 1) and troponin elevation to 44 ug/L (reference range < 0.05 ug/L). Full blood picture was normal and biochemistry revealed glomerular filtration rate of 63 mL/min/1.73 m^2 (reference range > 90). C-reactive protein was mildly raised at 6.7 mg/L (reference range < 3.0).

Imaging examinations

A computed tomography aortogram was performed to exclude other differentials for his presentation that revealed no aortic dissection, ulceration or aneurysm apart from scattered small areas of calcified arteriosclerotic plaque. No large central pulmonary embolus was seen either.

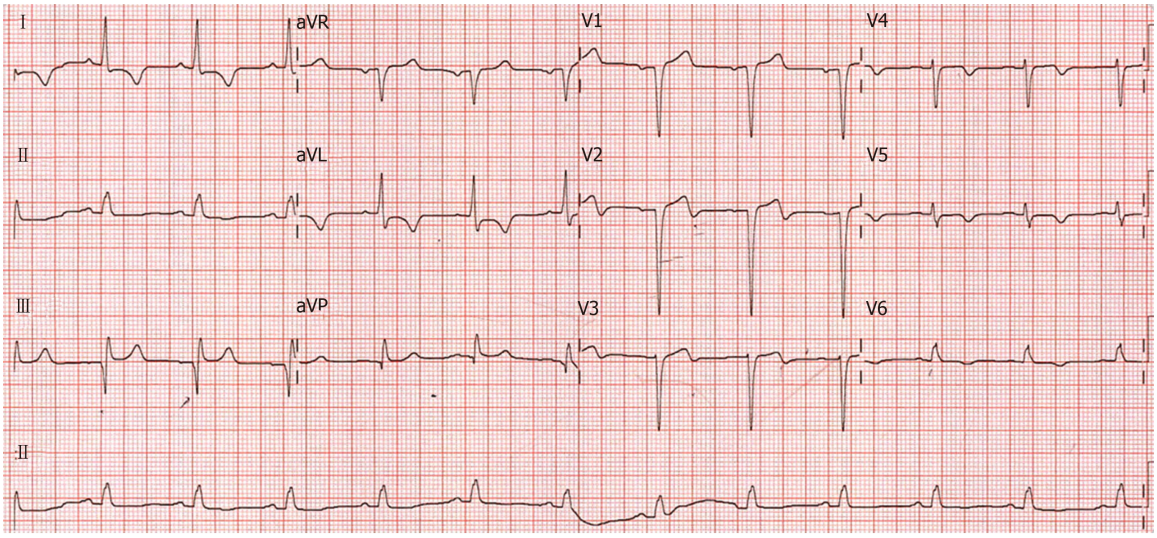


Figure 1 12-lead electrocardiograph at presentation.

Further diagnostic workup

Emergent angiography was organised for this patient due to his clinical picture and raised cardiac markers. Notably, he had undergone angiography 5 years ago to investigate episodic chest pain and imaging of the LIMA at the time did not demonstrate any evidence for atherosclerotic plaque formation (Figure 2A). Angiography demonstrated a severe diffuse stenosis in the proximal to mid segment of the LIMA, with embolization of a moderate sized thrombus to the distal skip segment and anastomosis with the first diagonal branch ("coronary saddle thrombus"). The LIMA stenosis was characterised by overlying haziness, consistent with acute plaque rupture, associated with residual luminal thrombus (Figure 2B).

FINAL DIAGNOSIS

Acute plaque rupture in the LIMA with residual luminal thrombus and distal embolization of the thrombus.

TREATMENT

The patient was managed with intensive antithrombotic therapy initially to reduce the thrombus burden with eptifibatide (10.5 mg/h for 48 h), enoxaparin (1 mg/kg at 80 mg twice daily for 72 h), ticagrelor 90 mg twice daily and aspirin until repeat angiography after 72 h.

At repeat angiography, the thrombus burden was substantially reduced at the distal anastomosis with the diagonal branch and skip graft to LAD. Similarly, the lesion within the proximal to mid LIMA demonstrated marked resolution with the demonstration of multiple plaque cavities and a reduction in overlying thrombus burden (Figure 2C).

This lesion was consequently predilated with 2.5 mm × 15 mm balloon. A 2.75 mm × 33 mm everolimus-eluting stent was implanted with post dilatation to a final diameter of 3.0 mm (Figure 2D).

OUTCOME AND FOLLOW UP

The patient made a good clinical recovery and was discharged after 6 d. On follow-up, he remained well with no further episodes of angina.

DISCUSSION

We describe a case of ACS secondary to atherosclerotic plaque rupture complicated

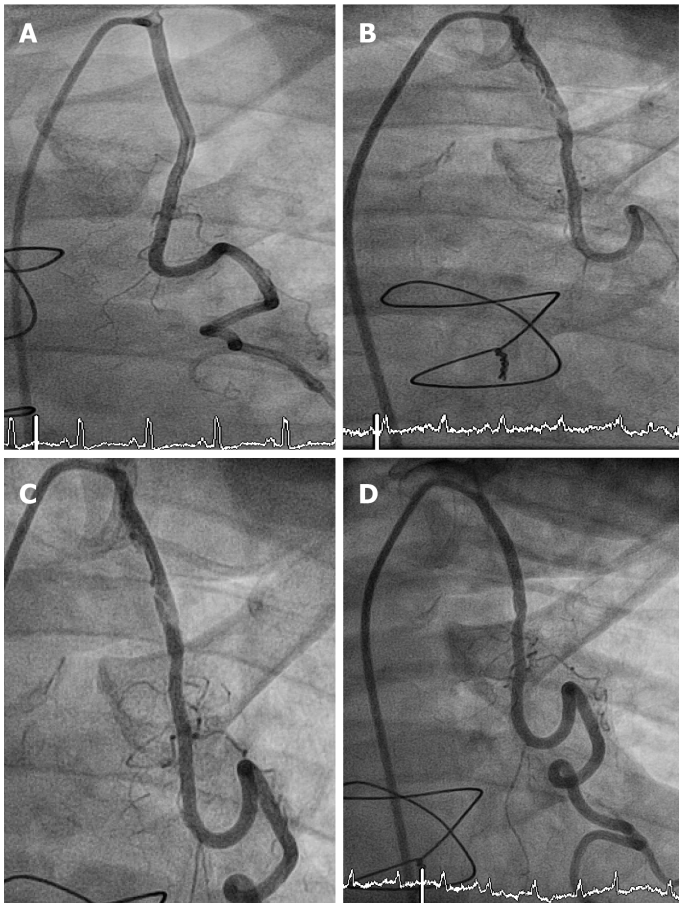


Figure 2 Result of angiography. A: LIMA graft Angiogram performed 5 years prior to the current presentation demonstrates no evidence of atherosclerotic plaque formation; B: Proximal LIMA graft lesion; C: Residual atheroma of the LIMA graft post anti-thrombotic therapy; D: Post stent insertion.

by distal embolization in a LIMA conduit 8 years after surgery and 5 years after angiography revealing a patent graft. Most LIMA occlusions occur in the early postoperative period and are associated with surgical complications such as dissection, hematoma, spasm, or anastomotic stenosis. LIMA-LAD grafts are associated with excellent long-term patency and improved outcomes compared to the saphenous vein grafts. The 10-year patency rate of LIMA grafts is approximately 90% if the graft is patent 1 wk after the procedure[1,2]. Myocardial infarction caused by *de-novo* atherothrombotic disease within the LIMA in the late postoperative period is rare. Our patient's clinical history of dyslipidaemia, hypertension and rheumatoid arthritis increases rate of atherosclerosis progression. Atherosclerotic lesions are also more prone to rupture in patients with rheumatoid arthritis[3].

Atherothrombotic graft occlusion within the IMA itself is rarely described[4,5]. Several unique structural and physiological characteristics protect the LIMA from atherogenesis, which include fewer fenestrations in the endothelial layer, lower intercellular junction permeability, enhanced endothelial expression of anti-thrombotic molecules such as heparin sulfate and tissue plasminogen activator, and higher endothelial nitric oxide production[6].

The most common late complication of LIMA-LAD graft has been dissection, either spontaneous or post intervention, even this is rarely reported in the literature[7]. Spontaneous coronary artery dissection (SCAD) type III was also considered in our case given the appearance of a long lesion with haziness and linear stenosis. However, this was considered less likely due to the appearance of the lesion with multiple plaque cavities and the overlying thrombus.

At the time of angiography, the patient was clinically stable and pain free therefore we elected to defer a percutaneous strategy at the index procedure and use an initial antithrombotic strategy for the following reasons of large thrombus burden, risk of further distal embolization and challenges with protecting both the LAD and diagonal territories. The reduction in thrombus burden would also potentially reduce lumen compression if SCAD were the underlying pathology.

Whilst thrombectomy was considered for acute management, we were dissuaded

by the significant tortuosity of the LIMA (limiting deliverability), concerns regarding the passage of a thrombectomy device into the diagonal vessel could lead to thrombus dislodgment and embolization into the LAD (or vice versa). Whilst SCAD was considered less likely, there remained a risk that wiring the vessel could inadvertently lead to sub-intimal wire passage with consequent distal propagation of the dissection.

At repeat angiography, the thrombus burden was substantially reduced suggesting that this strategy may have mitigated the risk of distal embolization and peri-procedural infarction. Similarly, whilst further imaging with Optical Coherence Tomography (OCT) or Intravascular ultrasonography (IVUS) was considered, we felt the angiographic appearances of the lesion to be sufficiently characteristic of an atherosclerotic process rather than SCAD. In particular, OCT imaging would necessitate pressurized contrast delivery to achieve clearing of the blood pool, hence raising the risk of either propagation of an underlying dissection or hydraulic dissection of the LIMA ostium that such evaluation would be rendered redundant. In addition, there is risk of further extension of SCAD with OCT due to pressurised contrast injection.

The available medical literature comparing the incidence of atheromatous plaque formation with that of SCAD within LIMA conduits is scant, perhaps due to the relative rarity of such events. However, prompt recognition and appropriate management is clearly critical, given the life-threatening nature of such occlusions and the important technical considerations needed to achieve successful reperfusion. Relevant considerations include attention to guiding catheter and coronary wire length (guide catheter shortening and the use of longer length coronary guide wires may be required). The risk of vessel occlusion due to guide wired induced straightening of a tortuous LIMA is a further consideration. This case highlights the rapid development of atherosclerotic disease in a graft 5 years after documented patency and the importance for consideration of expectant thrombus management in a patient with atheromatous plaque rupture of the LIMA graft, to our knowledge; this is the first case in literature describing this strategy.

CONCLUSION

Whilst use of IMA conduits is associated with excellent long-term patency, late atherogenesis complicated by plaque rupture is rarely encountered and the natural history of atheromatous plaque rupture in the LIMA is unknown. Prompt recognition, together with judicious use of antithrombotic and anti-platelet therapy may facilitate optimal percutaneous reperfusion. Confirmatory imaging with IVUS or OCT may provide useful additional lesion definition and help to distinguish between dissection and atheromatous aetiologies.

REFERENCES

1 **Goldman S**, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W, VA Cooperative Study Group #207/297/364. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol* 2004; **44**: 2149-2156 [PMID: 15582312 DOI: 10.1016/j.jacc.2004.08.064]

2 **Taggart DP**. Current status of arterial grafts for coronary artery bypass grafting. *Ann Cardiothorac Surg* 2013; **2**: 427-430 [PMID: 23977618 DOI: 10.3978/j.issn.2225-319X.2013.07.21]

3 **Skeoch S**, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nat Rev Rheumatol* 2015; **11**: 390-400 [PMID: 25825281 DOI: 10.1038/nrrheum.2015.40]

4 **Nakamura T**, Yamamoto S, Funayama H, Mitsuhashi T, Momomura SI. Acute occlusion of the left internal mammary artery graft in the late postoperative period. *J Cardiol Cases* 2014; **10**: 51-53 [PMID: 30546504 DOI: 10.1016/j.jccase.2014.04.007]

5 **Akyüz S**, Öz TK, Özer N. Acute thrombosis of the left internal mammary artery graft 14 years after coronary bypass surgery. *Anatol J Cardiol* 2014; **14**: 301-302 [DOI: 10.5152/akd.2014.5275]

6 **Otsuka F**, Yahagi K, Sakakura K, Virmani R. Why is the mammary artery so special and what protects it from atherosclerosis? *Ann Cardiothorac Surg* 2013; **2**: 519-526 [PMID: 23977631 DOI: 10.3978/j.issn.2225-319X.2013.07.06]

7 **Yip A**, Saw J. Spontaneous coronary artery dissection-A review. *Cardiovasc Diagn Ther* 2015; **5**: 37-48 [PMID: 25774346 DOI: 10.3978/j.issn.2223-3652.2015.01.08]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.

ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2019 December 26; 11(12): 282-321

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 12 December 26, 2019

REVIEW

MINIREVIEWS

CASE REPORT

Contents

World Journal of Cardiology

Volume 11 Number 12 December 26, 2019

ABOUT COVER

Editorial Board of *World Journal of Cardiology*, Vassil Traykov, MD, Assistant Professor, Department of Invasive Electrophysiology and Pacing, Acibadem City Clinic Tokuda Hospital, Sofia 1164, Bulgaria

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ramdas G. Pai MD, FACC, FRCP (Edin), Marco Matteo Ciccone, Dimitris Tousoulis

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1949-8462/editorialboard.htm

EDITORIAL OFFICE

Ruo-Yu Ma, Director

PUBLICATION DATE

December 26, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 December 26; 11(12): 282-291

DOI: 10.4330/wjc.v11.i12.282

ISSN 1949-8462 (online)

REVIEW

Pericardial decompression syndrome: A comprehensive review

Yougeesh Prabhakar, Amandeep Goyal, Nauman Khalid, Nitish Sharma, Raj Nayyar, David H Spodick, Lovely Chhabra

ORCID number: Yougeesh Prabhakar (000-0001-8715-4421); Amandeep Goyal (000-0001-6070-1747); Nauman Khalid (000-0003-4159-555X); Nitish Sharma (0000-0002-6221-3197); Raj Nayyar (0000-0003-0034-923X); David H Spodick (0000-0003-3968-8941); Lovely Chhabra (0000-0002-9193-5981).

Author contributions: Chhabra L and Spodick DH designed the study concept; Prabhakar Y, Goyal A, Khalid N, Spodick DH and Chhabra L reviewed the data and drafted the review article. Khalid N drafted the illustrative case; Goyal A and Chhabra L designed the schematic illustrations and figure legends; Nayyar R helped with edition of schematic illustrations and literature review; Chhabra L and Spodick DH performed major revisions and approved the final version of the article.

Conflict-of-interest statement: All authors have no any conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Yougeesh Prabhakar, Raj Nayyar, Lovely Chhabra, Department of Cardiology, Heartland Regional Medical Center, Marion, IL 62959, United States

Amandeep Goyal, Department of Medicine, Marietta Memorial Hospital, Marietta, OH45750, United States

Nitish Sharma, Department of Interventional Cardiology, Medstar Washington Hospital Center, Washington, DC 20010, United States

Nitish Sharma, David H Spodick, Department of Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Corresponding author: Lovely Chhabra, MD, FACC, Heartland Regional Medical Center, 3331 W. DeYoung St, Marion, IL 62959, United States. lovids@hotmail.com
Telephone: +1-618-9987600
Fax: +1-888-5986647

Abstract

Pericardial decompression syndrome (PDS) is an infrequent, life-threatening complication following pericardial drainage for cardiac tamponade physiology. PDS usually develops after initial clinical improvement following pericardiocentesis and is significantly underreported and may be overlooked in the clinical practice. Although the precise mechanisms resulting in PDS are not well understood, this seems to be highly associated with patients who have some underlying ventricular dysfunction. Physicians performing pericardial drainage should be mindful of the risk factors associated with the procedure including the rare potential for the development of PDS.

Key words: Pericardial decompression syndrome; Cardiac tamponade; Pericardiocentesis; Pericardiostomy; Low cardiac output syndrome

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Pericardial decompression syndrome (PDS) is an infrequent, life-threatening complication following an uncomplicated pericardial evacuation for cardiac tamponade physiology. Physicians should be familiar with the prevention strategies for PDS and offer vulnerable patients a very close clinical monitoring, especially those undergoing pericardial drainage for large malignant effusions for suspected tamponade.

Citation: Prabhakar Y, Goyal A, Khalid N, Sharma N, Nayyar R, Spodick DH, Chhabra L.

Manuscript source: Invited manuscript

Received: March 26, 2019
Peer-review started: March 28, 2019
First decision: June 6, 2019
Revised: June 25, 2019
Accepted: November 20, 2019
Article in press: November 20, 2019
Published online: December 26, 2019

P-Reviewer: Greenway SC
S-Editor: Ma YJ
L-Editor: A
E-Editor: Zhang YL

Pericardial decompression syndrome: A comprehensive review. *World J Cardiol* 2019; 11(12): 282-291
URL: https://www.wjgnet.com/1949-8462/full/v11/i12/282.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i12.282

INTRODUCTION

Cardiac tamponade is an emergent clinical condition that occurs after a rapid and/or excessive accumulation of fluid in the pericardial space. It restricts appropriate filling of the cardiac chambers and impairs normal hemodynamics which ultimately causes hypotension and cardiac arrest[1-3]. Pericardial drainage either by pericardiocentesis or pericardiotomy is required to make the patients hemodynamically stable, however, it has been associated with many complications including a rare, underreported and potentially fatal complication known as pericardial decompression syndrome (PDS).

PDS was first described in 1983 by Vandyke *et al*[4]and the terminology was first proposed by Angouras *et al*[5] in 2010 and since then, it has been recognized in multiple clinical settings[6-9]. PDS is characterized by a paradoxical hemodynamic instability and/or pulmonary edema following an otherwise non-complicated pericardial drainage. Another terminology used to describe PDS is the post-pericardial drainage low cardiac output syndrome[10-12]. Epidemiological data is limited, however, the incidence of PDS from a few studies is estimated to be around < 5%, following surgical drainage[11]. The exact etiology of PDS remains unclear, but most patients usually have an underlying pathology involving myocardial or ventricular dysfunction. There have been various suggested pathophysiological mechanisms for this phenomenon in the literature.

In this paper, we provide a comprehensive case-based review of the PDS describing the etiology, pathophysiology, clinical presentation and prevention and treatment related strategies.

LITERATURE RESEARCH

We searched MEDLINE/PubMed and google scholar literature database for original articles, reviews, editorials, abstracts and case reports published between 1983 and 2017. The search terms we used, alone or in combination, were "pericardial decompression syndrome", "cardiac tamponade", "pericardial effusion", "pericardiostomy", and "low cardiac output syndrome". All articles were independently reviewed for their appropriateness for data analysis and inclusion for drafting this review. The articles were independently screened to avoid any duplication of reported cases or reports. Also, any books or book chapters were screened for the search term of pericardial decompression syndrome and cardiac tamponade. Subsequently, the data from all studies were carefully selected for inclusion which was found most relevant to the subject of this review. All articles included in the data assessment were English-language, full-text papers and/or abstracts.

PATHOPHYSIOLOGY OF CARDIAC TAMPONADE

In cardiac tamponade, the main abnormality is rapid or slow compression of the cardiac chambers resulting from an increased intrapericardial pressure. Once the pericardial contents reach the limit of the pericardial reserve volume (volume resulting in pericardial distension), the expansion rate increases significantly thus exceeding the pericardial stretch[1-3]. While the pericardium gradually stretches over time, when at any instant it is inextensible, it impairs the cardiac contractility as the heart has to compete with the increased pericardial contents for a fixed intrapericardial volume. As the cardiac chambers become sequentially smaller in size, the myocardial diastolic compliance is reduced leading to a limited cardiac inflow; and ultimately leading to equalization of the mean diastolic pericardial and chamber pressures. The rate of fluid accumulation relative to pericardial stretch is the key element to the effectiveness of compensatory mechanisms[1-3].

Rapidly developing pericardial effusion such as acute intrapericardial hemorrhage or cardiac rupture may lead to a quick development of tamponade physiology as

there is a relatively stiff pericardium with limited stretch capacity and there is less time for adaptation before routine activation of the most of the compensatory mechanisms. On the contrary, in cases of a slow increase in pericardial effusion such as idiopathic or malignant effusions, effusion size of 2 L or even more can occur before critical tamponade physiology may ensue[1-3].

Rising pericardial pressure reduces and ultimately offsets the transmural pressure (intracardiac minus pericardial pressure), first for the right heart and ultimately for all chambers. Usually, during inspiration, the right heart filling increases at the expense of the left, so that its transmural pressure shows transient improvement which then reverses during expiration and this phenomenon is referred to as interventricular dependence in tamponade (Figure 1). When florid tamponade ensues, this mechanism cannot compensate for reduced stroke volumes, as these volumes are dependent on the elements which protect cardiac output and arterial pressures, mainly beta-adrenergic response causing increased heart rate, systemic peripheral resistance and ventricular ejection fraction. Emergent needle decompression of the pericardial fluid or pericardiocentesis is often required in tamponade as it helps in improvement of the transmural pressure, releases the interventricular dependence and thus ultimately restores normal hemodynamics (Figure 2). Rarely, there can be a paradoxical worsening of the hemodynamics after an otherwise successful and uncomplicated pericardial drainage (usually in long-standing large pericardial effusions) causing cardiac tamponade which can result in PDS and its pathophysiology has been discussed in further details below.

PATHOPHYSIOLOGY OF PDS

Various hypotheses have been reported to describe the clinical mechanism of PDS, however, its exact pathophysiology still remains unclear[12-34]. The proposed mechanism of PDS centers around three main hypotheses, namely: Hemodynamic, ischemic and autonomic hypothesis. These mechanisms provide greater insight into the possible pathophysiology of the PDS.

Hemodynamic hypothesis

The simplest explanation of PDS is hemodynamic changes related to the interventricular interdependence. The hemodynamic hypothesis was first proposed in 1983 by Vandyke *et al*[4] when they first reported pulmonary edema in a patient who underwent uncomplicated pericardiocentesis for cardiac tamponade. Vandyke *et al*[4] hypothesized that pulmonary edema was precipitated by preload/afterload mismatch.

Following the rapid removal of the pericardial fluid originally compressing the right sided chambers during tamponade, now may lead to an increased venous return causing significant right ventricular expansion at the expense of the left chamber resulting in the reduced left ventricle volume/output and thus ensuing decompensated left heart failure and/or pulmonary edema. The rapid tamponade release is also followed by a net increase in the pulmonary venous return (left ventricular preload) while adaptive systemic vascular resistance (after-load) being still high (which is usually a compensatory phenomenon in tamponade to counteract hypotension response) may result in preload/afterload mismatch thus precipitating an acute onset heart failure (Figure 3)[10,11,14-16].

Ischemic hypothesis

It is postulated that the coronary artery blood perfusion may be impaired due to compression caused by the pericardial fluid that may augment the risk of myocardial ischemia, leading to transient myocardial stunning that can persist after the removal of pericardial fluid thus causing transient left ventricular dysfunction.

Skalidis *et al*[21] demonstrated the first human-based report on how pericardial pressure can affect the coronary blood flow in humans, while previous reports had been based solely on animal studies. They studied a case of 52-years old patient with lung cancer who developed cardiac tamponade. The patient had successful pericardiocentesis, resulting in the removal of 850 mL of hemorrhagic fluid. The patient underwent a percutaneous balloon pericardiotomy 5 d later due to recurrence of pericardial effusion. During the pericardiotomy, the authors performed calculation of the amount of blood flow to the non-diseased left anterior descending coronary artery while pericardial pressure was gradually increased by infusing warmed normal saline at the rate of 30 mL/min. Coronary vasodilator reserve was computed using intracoronary adenosine. With increase in pericardial pressure, there was a gradual decline in the coronary blood flow, a gradual increase in the coronary vascular resistance, and an unaffected hyperemic response throughout. The maximal

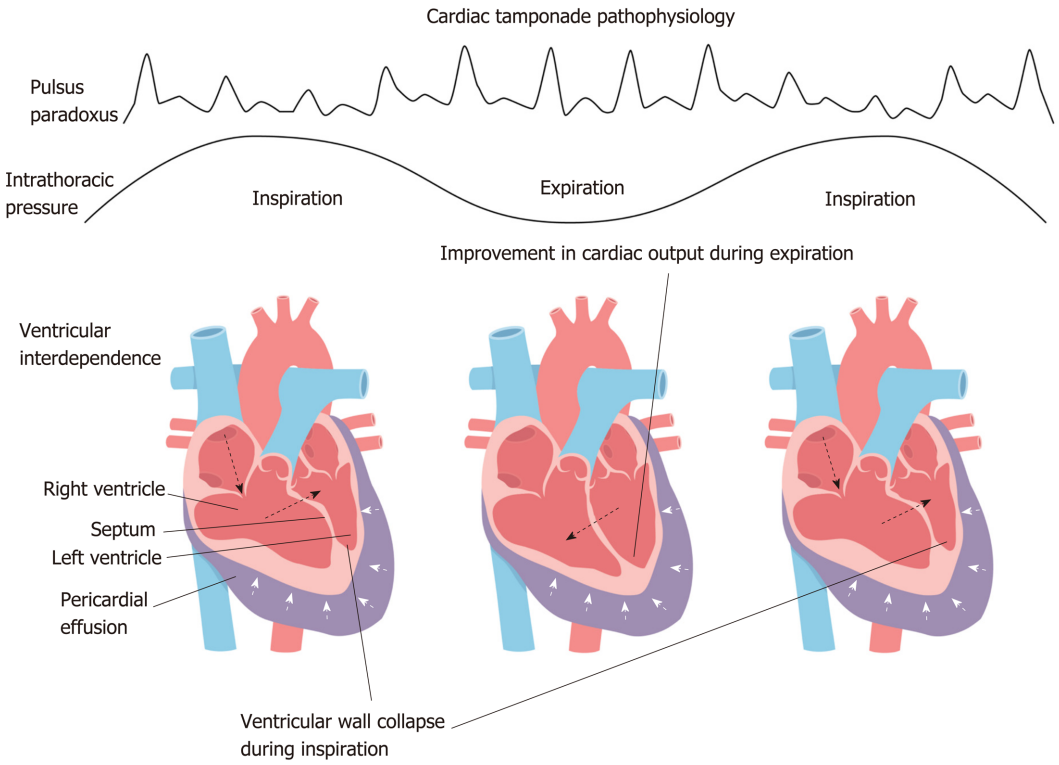


Figure 1 Cardiac tamponade physiology. There is offset of the transmural pressure (intracardiac minus pericardial pressure) in cardiac tamponade. During inspiration, the right heart filling occurs at the expense of the left, so that its transmural pressure transiently improves and then reverts during expiration and this phenomenon is referred to as interventricular dependence.

hyperemic flow was significantly less under the increased pericardial pressure than at normal pericardial pressure, which suggested an increased susceptibility to myocardial ischemia. In conclusion, the increased pericardial pressure during tamponade physiology can impair coronary perfusion leading to myocardial ischemia which can eventually cause left ventricular myocardial stunning that may persist even after pericardial drainage and can result in diastolic dysfunction thereby increasing the risk of PDS.

Autonomic/sympathetic overdrive hypothesis

The imbalance in the autonomic system, specifically acute withdrawal of sympathetic stimulus after removal of pericardial fluid, may also be a precipitating factor for myocardial dysfunction and PDS. The myocardial dysfunction may occur by two ways due to this mechanism: One being the unmasking of underlying/pre-existing myocardial dysfunction and the second being the development of new myocardial dysfunction.

Wolfe and Edelman[14] reported that removal of sympathetic stimulus after pericardiocentesis might lead to unfolding of underlying left ventricular dysfunction that was not previously revealed due to an excessive catecholamine state, producing a markedly positive chronotropic and inotropic effect. Furthermore, Martins and colleagues showed that even though exogenous catecholamine administration improved coronary blood flow in patients with tamponade, filling pressures remained unchanged and there was only a modest increase in the cardiac index[22]. They proposed that since the sympathetic nervous system activation was already present, the elevated endogenous catecholamine levels did not provide any further potential benefit. The removal of the stimulus for an increased sympathetic state (that is, the relief of tamponade by pericardiocentesis) might well lead to the unmasking of left ventricular dysfunction that was previously compensated for by high endogenous catecholamine levels[17,18]. Thus, sympathetic overdrive mechanism might play an important role in the etiology of PDS because left ventricular systolic function abnormalities may occur after pericardiocentesis intervention as described.

Secondly, the patients may develop *de novo* transient systolic dysfunction due to overwhelming autonomic functional variations as a result of the stress from the cardiac tamponade and sudden hemodynamic alterations predisposed by the rapid evacuation of the pericardial space. This hypothesis may share some similar

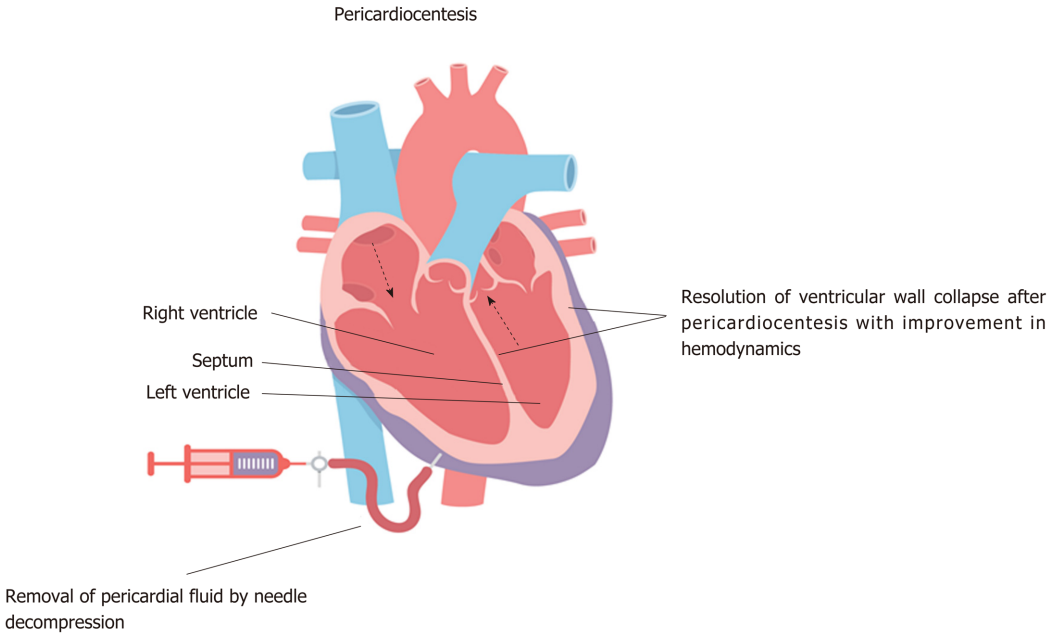


Figure 2 Pericardiocentesis. Emergent needle decompression of the pericardial fluid with pericardiocentesis is often required in tamponade as it helps in restoration of a normal transmural pressure and thus ultimately restores normal hemodynamics. Interventricular dependence has resolved with pericardial decompression.

characteristics to the pathophysiology of patients with Takotsubo syndrome or stress-related cardiomyopathy[23].

AN ILLUSTRATIVE CASE OF PDS

A 58-year-old woman with a history of Hodgkin lymphoma status post radiation therapy ten years ago, hypertension, diabetes mellitus and hypothyroidism presented to the emergency room with increasing dyspnea on exertion over 2 wk duration. Her medications included metformin 500 mg twice daily, aspirin 81 mg daily, levothyroxine 100 mcg daily, and metoprolol 25 mg twice a day. Initial vital signs demonstrated blood pressure of 96/60 mmHg, heart rate of 110 beats per minute (regular) and 96% oxygen saturation on room air. Her lung fields were clear, jugular venous pressure was elevated to the earlobe in an upright position, and the heart sounds were faint and distant. Peripheral pulses were weak bilaterally. 12-lead electrocardiogram showed low voltage and sinus tachycardia. Chest X-ray demonstrated cardiomegaly but otherwise was clear. Transthoracic echocardiogram demonstrated a left ventricular ejection fraction (LVEF) of 60%-65%, a large circumferential pericardial effusion with end diastolic right ventricular compression, and a swing sign (Figure 4A-B). Patient was taken to the cardiac catheterization laboratory for emergent pericardiocentesis. Ultrasound-guided pericardiocentesis resulted in rapid drainage of approximately 2200 mL of serous fluid with minimal improvement in hemodynamics. Patient was then taken to the cardiac catheterization laboratory holding area to be transported to the coronary care unit with the pericardial drain sutured in place. About 1 h later, the patient developed worsening dyspnea, hypotension (blood pressure of 72/40 mmHg), and labored breathing. Emergent chest radiograph showed diffuse bilateral pulmonary edema. She required intubation for hypoxic respiratory failure. Hemodynamic support was initiated with dobutamine and norepinephrine. Repeat emergent limited bedside echocardiogram demonstrated interval resolution of pericardial effusion, low-normal LVEF (50%), and mild to moderately dilated right ventricle with mild right ventricular (RV) hypokinesis and septal shift towards the left ventricle (Figure 4C). Patient was administered an intravenous saline bolus. Subsequently, the patient required hemodynamic support with intravenous vasopressors (norepinephrine) and inotropes (low-dose dopamine). Later, she was diuresed with intravenous lasix and vasopressor-inotropic support was gradually weaned off over the next 48 h. CT-chest angiography showed no evidence of pulmonary embolism with interval improvement in pulmonary edema. On day 3, patient's hemodynamics improved without requirement of vasopressors and she was extubated. A repeat echocardiogram on day

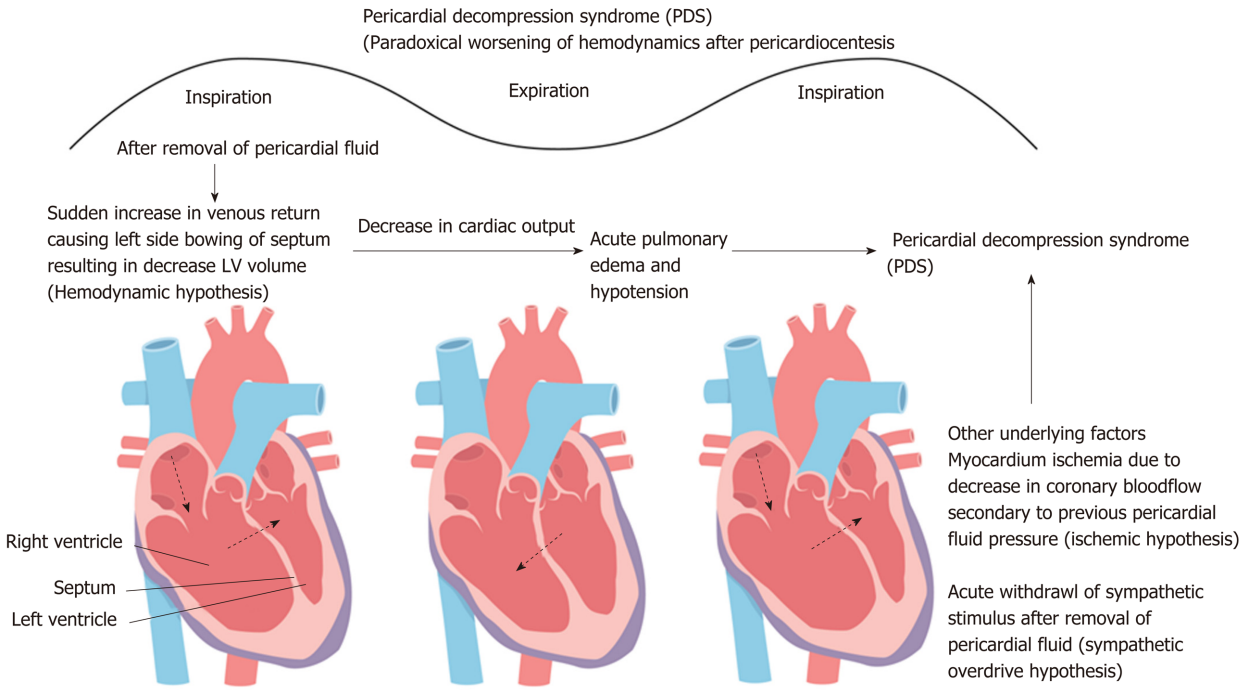


Figure 3 Pericardial decompression syndrome. Following the rapid removal of the pericardial fluid originally compressing the right sided chambers during tamponade, may lead to an increased venous return causing significant right ventricular expansion at the expense of the left chamber resulting in the reduced left ventricle volume/output and thus ensuing decompensated left heart failure and/or pulmonary edema. The rapid tamponade release is also followed by a net increase in the pulmonary venous return (left ventricular preload) while adaptive systemic vascular resistance (after-load) being still high and may result in preload/afterload mismatch thus precipitating an acute onset heart failure.

5 demonstrated normalized ventricular function and trivial/minimal pericardial effusion (Figure 4D). She was discharged to home on day 6. We suspect that this patient developed pericardial decompression syndrome shortly after the pericardial drainage. Rapid pericardial fluid decompression may have resulted in paradoxical worsening of hemodynamics likely secondary to a combination of two factors, the first being a sudden increase in the venous return with still relatively higher systemic vascular resistance posing to a preload-afterload mismatch (hemodynamic hypothesis) and secondly likely due to sympathetic overdrive (as possibly evident from transient mild RV hypokinesis). These factors may have possibly led to the development of pulmonary edema, respiratory failure, and transient ventricular dysfunction. Supportive management resulted in spontaneous gradual improvement of her cardiopulmonary function.

PRESENTATION AND TREATMENT OF PDS

Symptoms of pericardial decompression syndrome usually accompany with the paradoxical worsening of the patient's hemodynamics after a brief initial improvement in hemodynamics. The symptoms may be similar to those of acute heart failure exacerbation such as development of dyspnea, leg swelling, and increasing oxygen requirements, usually associated with rapid clinical deterioration including pulmonary edema and/or shock. Based on the papers by Pradhan *et al*[10] and Imazio[11], the onset of the syndrome ranged from immediate to usually 48 h following the pericardial fluid drainage for cardiac tamponade as an indication. According to an excellent analysis of 35 published cases from 1983 to 2013 by Pradhan *et al*[10], about 40% of patients had shock with left ventricular failure, 29% with pulmonary edema without shock, 20% with shock associated with biventricular failure and 11% with shock associated with RV failure and non-cardiogenic pulmonary edema. Diagnosis of PDS should only be established when other conditions predisposing to a shock-like state such as septic shock, cardiogenic shock resulting from MI and intraprocedural mechanical trauma (such as cardiac puncture, pneumothorax, diaphragmatic injury) have been ruled out. In relevant cases such as those presenting with isolated or significant RV dysfunction, exclusion of new-onset pulmonary embolism should probably be considered. Another important differential diagnosis is Takotsubo cardiomyopathy (TC) or stress-induced cardiomyopathy with cardiac tamponade,

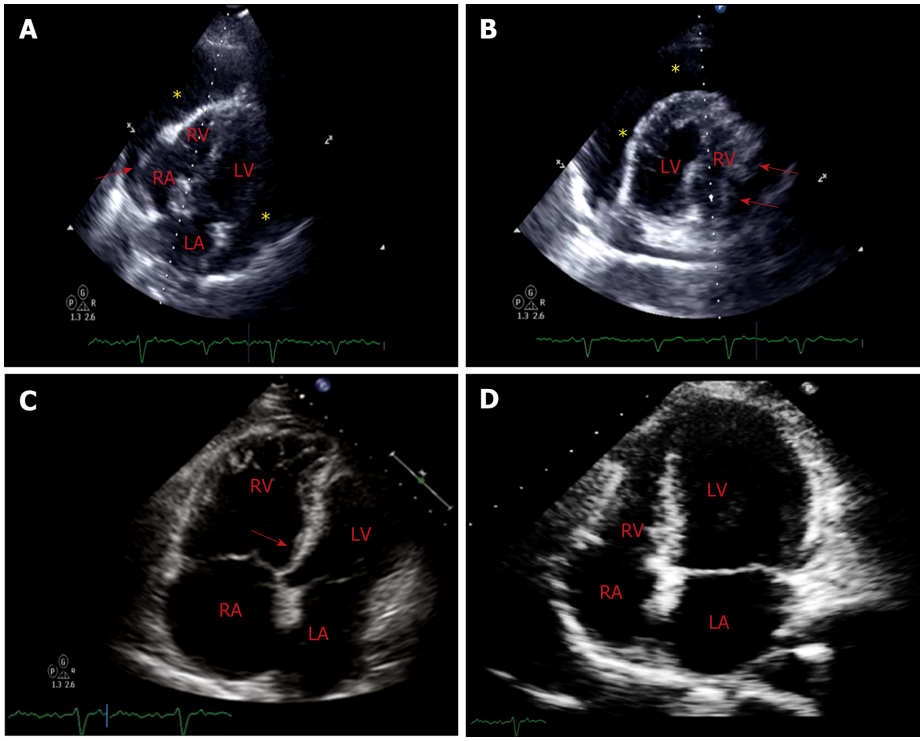


Figure 4 Computed tomography. A: Off-axis 4-chamber view of transthoracic echocardiogram demonstrates a large circumferential pericardial effusion (marked by *) with evidence of end diastolic right chamber compression (marked by red arrow) and normal left ventricular ejection fraction. Swinging heart sign was also noted which is used to describe pendular swinging of the heart inside the pericardial space and is associated with a large pericardial effusion; B: 4-chamber view (mirror-view) demonstrates RA inversion, RV diastolic compression (marked by red arrows) and the swinging heart sign; C: Limited surface echocardiogram after pericardiocentesis demonstrated interval resolution of pericardial effusion and mild to moderately dilated right ventricle with mild RV hypokinesis and septal shift towards the left ventricle(as marked by red arrow). Patient demonstrated paradoxical worsening of blood pressure. Rapid pericardial fluid decompression may have resulted in paradoxical worsening of hemodynamics likely secondary to a combination of two factors: the first being a sudden increase in the venous return with still relatively higher systemic vascular resistance posing to a preload-afterload mismatch (hemodynamic hypothesis) and secondly likely being focal RV hypokinesis, predisposed by an increased sympathetic tone; D: A repeat echocardiogram on day 5 demonstrated normalized ventricular function. RV: Right ventricular; LV: Left ventricular; RA: Right atrial; LA: Left atrial.

emotional stress and stress from significant hemodynamic derangements being the precipitating stressors for the development of TC[20,23]. In fact, transient ventricular (single or biventricular) dysfunction may be one of the driving mechanisms for the development of PDS as reported in some previous reports. The transient cardiac systolic dysfunction may be mechanistically very similar to TC. Most of the cases of primary TC are usually associated with characteristic staged ECG changes (which may include ST-elevations and T-wave inversions), rise in cardiac enzymes with most common presenting symptom being chest pain. In most of the reported cases of PDS (mimicking pathophysiology of TC) however, the patients usually have experienced dyspnea with no rise in cardiac enzymes and characteristic ECG changes only in minority[24,25].

The treatment of PDS is essentially supportive as the improvement of ventricular function is expected in survivors[7,10-12]. Patients undergoing pericardiocentesis or pericardiotomy require very close monitoring for the first 24 h, preferably in the intensive care unit[1,12,26]. In case of development of PDS, patients would require a very critical intensive monitoring, management with inotropic support, aggressive heart failure treatment with pressors and diuretics and as needed hemodynamic device support such as with an intra-aortic balloon pump.

GENERAL DISCUSSION AND PREVENTION STRATEGIES FOR PDS

Till date, there are no clear evidence-based guidelines or recommendations to specifically prevent PDS. A sensible strategy would be not drain large quantities of

pericardial fluid in a single sitting especially in case of large pericardial effusions. The most reasonable approach would be to remove the amount of pericardial fluid just enough to result in the resolution of the cardiac tamponade physiology (which can be easily achieved by hemodynamic or echo-doppler monitoring) and then place a prolonged pericardial drainage to achieve a slow and gradual removal of additional pericardial fluid. Prolonged pericardial drainage may be removed when there is a daily fluid return below 30-50 mL[1,11]. The maximum amount of safely drainable pericardial fluid and rate of drainage has been previously suggested in some studies and guideline documents[1,27,28]. European Society of Cardiology 2004 guidelines generally recommend draining pericardial fluid in steps of less than 1 L at a time to avoid PDS based on case series of 3 patients with echocardiographic evidence of volume overload after pericardiocentesis[27,28]. Although judicious pericardial drainage may be potentially preventative against PDS, PDS may rarely develop even after small amount of pericardial drainage as previously documented in an isolated case report where patient developed PDS with pericardial fluid drainage of as little as 450 mL[29]. In general, the experts recommend stopping the initial drainage following the improvement of symptoms and hemodynamics followed by a slow gradual decompression through an indwelling pericardial catheter[4,27,30]. The slow gradual drainage may potentially allow a myocardial adaptation to the hemodynamic and filling pressure changes.

Cardiac tamponade is a critical clinical condition that results from a sudden and/or excessive accumulation of pericardial fluid. The treatment of cardiac tamponade is pericardiocentesis, preferably by a needle with the use of echocardiography. However, hemodynamically unstable patients warrant the use of pericardiocentesis without imaging following ruling out type A aortic dissection. Surgical drainage is required if the heart cannot be reached by a needle such as loculated effusion or predominant posterior location, clotted hemopericardium or ongoing intrapericardial bleeding where needle drainage is either ineffective or contraindicated[1].

Pericardiocentesis and pericardiostomy has its own procedure-related mechanical complications that include cardiac puncture, arrhythmias, pneumothorax, hemothorax, pneumopericardium, hepatic and diaphragmatic injury[27,35]. PDS is a rare complication that manifests as paradoxical worsening of hemodynamics following pericardial fluid drainage. The actual incidence of PDS is unknown among the general patient population with cardiac tamponade and may be related to its under-reporting and/or low general familiarity to the Cardiologists regarding PDS. Incidence has been estimated to be between 5% to 34% following pericardial drainage from malignant pericardial effusion from a handful of case studies and series[20,24]. The clinical presentation may be variable that may include pulmonary edema, shock and/or reversible ventricular impairment (RV, LV or biventricular dysfunction). Certain clinical variables such as history of malignancy, prior radiotherapy use, pericardial calcification, low ejection fraction, and connective tissue disorders have been known to increase the risk of PDS. Among these, most of the reported cases in literature who developed pericardial effusion leading to cardiac tamponade and PDS were related to malignant effusions. Thus, patients with history of malignancy and suspected malignant pericardial effusion may require more close monitoring for possible development of PDS. Halting the initial pericardial drainage following the improvement of symptoms and hemodynamics followed by gradual slow decompression by using pericardial catheter may be a favored approach in such patients[11]. Some authors also favor pericardiocentesis over pericardiotomy as pericardiotomy was associated with a higher mortality in patients who developed PDS. Although no precise reason known for this observation, it has been argued that surgical drainage may lead to a more rapid expansion of the right ventricle due to a rapid pericardial decompression[10,36].

Supportive therapy is the key for the treatment of PDS that includes intra-aortic balloon pump, inotropic support, and aggressive heart failure treatment as previously discussed. LV dysfunction if present, may usually demonstrate improvement within a few days, accompanied with a solid mid-term prognosis[37].

CONCLUSION

PDS is an uncommon complication of pericardial drainage and has a high mortality and morbidity. Physicians should be familiar with the prevention strategies for PDS and offer vulnerable patients a very close clinical monitoring, especially those undergoing pericardial drainage for large malignant effusions for suspected tamponade.

Further studies are needed to for better understanding of the pathophysiology and

prevention strategies for PDS. Also, establishing a large multicenter registry database may provide further insights about the best choices for the drainage techniques and treatment strategies.

REFERENCES

1 **Spodick DH**. Acute cardiac tamponade. *N Engl J Med* 2003; **349**: 684-690 [PMID: 12917306 DOI: 10.1056/NEJMra022643]
2 **Spodick DH**. The normal and diseased pericardium: current concepts of pericardial physiology, diagnosis and treatment. *J Am Coll Cardiol* 1983; **1**: 240-251 [PMID: 6338077 DOI: 10.1016/S0735-1097(83)80025-4]
3 **Chhabra L**, Spodick DH, Aronow WS, Fleg JL, Rich MW. Pericardial disease in the elderly. Tresch and Aronow's Cardiovascular Disease in the Elderly. 5th ed. Aronow WS, Fleg JL, Rich MW. Boca Raton, FL: CRC Press; 2014; 644-668
4 **Vandyke WH**, Cure J, Chakko CS, Gheorghiade M. Pulmonary edema after pericardiocentesis for cardiac tamponade. *N Engl J Med* 1983; **309**: 595-596 [PMID: 6877287 DOI: 10.1056/NEJM198309083091006]
5 **Angouras DC**, Dosios T. Pericardial decompression syndrome: a term for a well-defined but rather underreported complication of pericardial drainage. *Ann Thorac Surg* 2010; **89**: 1702-3; author reply 1703 [PMID: 20417826 DOI: 10.1016/j.athoracsur.2009.11.073]
6 **Lim AS**, Paz-Pacheco E, Reyes M, Punzalan F. Pericardial decompression syndrome in a patient with hypothyroidism presenting as massive pericardial effusion: a case report and review of related literature. *BMJ Case Rep* 2011; **2011**: bcr0420114117 [PMID: 22679149 DOI: 10.1136/bcr.04.2011.4117]
7 **Fozing T**, Zouri N, Adam O, Oezbek C. Management of a patient with pericardial decompression syndrome and HOCM. *BMJ Case Rep* 2016; **2016**: bcr2015211550 [PMID: 27251601 DOI: 10.1136/bcr-2015-211550]
8 **Ligero C**, Leta R, Bayes-Genis A. Transient biventricular dysfunction following pericardiocentesis. *Eur J Heart Fail* 2006; **8**: 102-104 [PMID: 16111917 DOI: 10.1016/j.ejheart.2005.05.012]
9 **Glasser F**, Fein AM, Feinsilver SH, Cotton E, Niederman MS. Non-cardiogenic pulmonary edema after pericardial drainage for cardiac tamponade. *Chest* 1988; **94**: 869-870 [PMID: 3168582 DOI: 10.1378/chest.94.4.869]
10 **Pradhan R**, Okabe T, Yoshida K, Angouras DC, DeCaro MV, Marhefka GD. Patient characteristics and predictors of mortality associated with pericardial decompression syndrome: a comprehensive analysis of published cases. *Eur Heart J Acute Cardiovasc Care* 2015; **4**: 113-120 [PMID: 25178691 DOI: 10.1177/2048872614547975]
11 **Imazio M**. Pericardial decompression syndrome: a rare but potentially fatal complication of pericardial drainage to be recognized and prevented. *Eur Heart J Acute Cardiovasc Care* 2015; **4**: 121-123 [PMID: 25406423 DOI: 10.1177/2048872614557771]
12 **Sabzi F**, Faraji R. Predictors of post pericardiotomy low cardiac output syndrome in patients with pericardial effusion. *J Cardiovasc Thorac Res* 2015; **7**: 18-23 [PMID: 25859311 DOI: 10.15171/jcvtr.2015.04]
13 **Braverman AC**, Sundaresan S. Cardiac tamponade and severe ventricular dysfunction. *Ann Intern Med* 1994; **120**: 442 [PMID: 8304672 DOI: 10.7326/0003-4819-120-5-199403010-00030]
14 **Wolfe MW**, Edelman ER. Transient systolic dysfunction after relief of cardiac tamponade. *Ann Intern Med* 1993; **119**: 42-44 [PMID: 8498762 DOI: 10.7326/0003-4819-119-1-199307010-00007]
15 **Hamaya Y**, Dohi S, Ueda N, Akamatsu S. Severe circulatory collapse immediately after pericardiocentesis in a patient with chronic cardiac tamponade. *Anesth Analg* 1993; **77**: 1278-1281 [PMID: 8250323 DOI: 10.1213/00000539-199312000-00031]
16 **Wechsler AS**, Auerbach BJ, Graham TC, Sabiston DC. Distribution of intramyocardial blood flow during pericardial tamponade. Correlation with microscopic anatomy and intrinsic myocardial contractility. *J Thorac Cardiovasc Surg* 1974; **68**: 847-856 [PMID: 4423787 DOI: 10.1002/2015JD023697-T]
17 **Chamoun A**, Cenz R, Mager A, Rahman A, Champion C, Ahmad M, Birnbaum Y. Acute left ventricular failure after large volume pericardiocentesis. *Clin Cardiol* 2003; **26**: 588-590 [PMID: 14677814 DOI: 10.1002/clc.4960261209]
18 **Weijers RW**, Post JC. Transient left ventricular systolic dysfunction mimicking myocardial infarction after pericardiocentesis. *Neth Heart J* 2013; **21**: 364-366 [PMID: 23653292 DOI: 10.1007/s12471-013-0421-z]
19 **Palatianos GM**, Thurer RJ, Pompeo MQ, Kaiser GA. Clinical experience with subxiphoid drainage of pericardial effusions. *Ann Thorac Surg* 1989; **48**: 381-385 [PMID: 2774723 DOI: 10.1016/S0003-4975(10)62862-7]
20 **Versaci F**, Donati R, Mezzanotte R, Chiariello L, Ammirati F. An unusual complication following pericardiocentesis: reversible left ventricular dysfunction. *J Cardiovasc Med (Hagerstown)* 2015; **16** Suppl 2: S133-S135 [PMID: 20625309 DOI: 10.2459/JCM.0b013e32833cdbf1]
21 **Skalidis EI**, Kochiadakis GE, Chrysostomakis SI, Igoumenidis NE, Manios EG, Vardas PE. Effect of pericardial pressure on human coronary circulation. *Chest* 2000; **117**: 910-912 [PMID: 10713029 DOI: 10.1378/chest.117.3.910]
22 **Martins JB**, Manuel WJ, Marcus ML, Kerber RE. Comparative effects of catecholamines in cardiac tamponade: experimental and clinical studies. *Am J Cardiol* 1980; **46**: 59-66 [PMID: 7386394 DOI: 10.1016/0002-9149(80)90606-2]
23 **Ayoub C**, Chang M, Kritharides L. A case report of ventricular dysfunction post pericardiocentesis: stress cardiomyopathy or pericardial decompression syndrome? *Cardiovasc Ultrasound* 2015; **13**: 32 [PMID: 26179174 DOI: 10.1186/s12947-015-0026-3]
24 **Pilgrim TM**, Wyss TR. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. *Int J Cardiol* 2008; **124**: 283-292 [PMID: 17651841 DOI: 10.1016/j.ijcard.2007.07.002]
25 **Wagner PL**, McAleer E, Stillwell E, Bott M, Rusch VW, Schaffer W, Huang J. Pericardial effusions in the cancer population: prognostic factors after pericardial window and the impact of paradoxical hemodynamic instability. *J Thorac Cardiovasc Surg* 2011; **141**: 34-38 [PMID: 21092993 DOI: 10.1016/j.jtcvs.2010.09.015]

26 **Neelakandan B**, Jayanthi N, Kanthimathi R. Subxiphoid drainage for pericardial tamponade. *J Thorac Cardiovasc Surg* 1996; **111**: 489 [PMID: 8583827 DOI: 10.1016/S0022-5223(96)70463-4]

27 **Maisch B**, Seferović PM, Ristić AD, Erbel R, Rienmüller R, Adler Y, Tomkowski WZ, Thiene G, Yacoub MH; Task Force on the Diagnosis and Management of Pricardial Diseases of the European Society of Cardiology. Guidelines on the diagnosis and management of pericardial diseases executive summary; The Task force on the diagnosis and management of pericardial diseases of the European society of cardiology. *Eur Heart J* 2004; **25**: 587-610 [PMID: 15120056 DOI: 10.1016/j.ehj.2004.02.002]

28 **Armstrong WF**, Feigenbaum H, Dillon JC. Acute right ventricular dilation and echocardiographic volume overload following pericardiocentesis for relief of cardiac tamponade. *Am Heart J* 1984; **107**: 1266-1270 [PMID: 6720556 DOI: 10.1016/0002-8703(84)90289-8]

29 **Dosios T**, Theakos N, Angouras D, Asimacopoulos P. Risk factors affecting the survival of patients with pericardial effusion submitted to subxiphoid pericardiostomy. *Chest* 2003; **124**: 242-246 [PMID: 12853529 DOI: 10.1378/chest.124.1.242]

30 **Albeyoglu S**, Aldag M, Ciloglu U, Kutlu H, Dagsali S. Biventricular transient systolic dysfunction after mitral valve replacement: Pericardial decompression syndrome. *Int J Surg Case Rep* 2016; **28**: 145-148 [PMID: 27710875 DOI: 10.1016/j.ijscr.2016.09.045]

31 **Khalid N**, Ahmad SA, Shlofmitz E, Chhabra L. Pathophysiology of Takotsubo Syndrome. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019; [PMID: 30844187]

32 **Chhabra L**, Chaubey VK. Right Ventricle Involvement in Tako-Tsubo Cardiomyopathy. *JACC Cardiovasc Imaging* 2016; **9**: 632-633 [PMID: 26897678 DOI: 10.1016/j.jcmg.2015.02.031]

33 **Khalid N**, Chhabra L, Ahmad SA, Sareen P, Spodick DH. Autonomic Dysfunction and Takotsubo Cardiomyopathy. *Am J Med* 2015; **128**: e45-e46 [PMID: 26500214 DOI: 10.1016/j.amjmed.2015.06.013]

34 **Gowdar S**, Syal S, Chhabra L. Probable protective role of diabetes mellitus in takotsubo cardiomyopathy: a review. *Vessel Plus* 2017; **1**: 129-136 [DOI: 10.20517/2574-1209.2017.12]

35 **Charron P**, Adler Y. 'Ten Commandments' of 2015 ESC Guidelines for diagnosis and management of pericardial diseases. *Eur Heart J* 2015; **36**: 2874 [PMID: 26866075]

36 **Allen KB**, Faber LP, Warren WH, Shaar CJ. Pericardial effusion: subxiphoid pericardiostomy versus percutaneous catheter drainage. *Ann Thorac Surg* 1999; **67**: 437-440 [PMID: 10197666 DOI: 10.1016/S0003-4975(98)01192-8]

37 **Moreno Flores V**, Pascual Figal DA, Caro Martínez C, Valdés-Chávarri M. Transient left ventricular dysfunction following pericardiocentesis. An unusual complication to bear in mind. *Rev Esp Cardiol* 2009; **62**: 1071-1072 [PMID: 19712632 DOI: 10.1016/S1885-5857(09)73277-3]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 December 26; 11(12): 292-304

DOI: 10.4330/wjc.v11.i12.292

ISSN 1949-8462 (online)

REVIEW

Red blood cell distribution width: A marker of anisocytosis potentially associated with atrial fibrillation

Giuseppe Lippi, Gianfranco Cervellin, Fabian Sanchis-Gomar

ORCID number: Giuseppe Lippi (0000-0001-9523-9054); Gianfranco Cervellin (0000-0002-7723-7239); Fabian Sanchis-Gomar (0000-0003-0424-4208).

Author contributions: Lippi G and Cervellin G contributed equally to this work; Lippi G and Sanchis-Gomar F generated the tables and figures; Lippi G, Cervellin G and Sanchis-Gomar F reviewed wrote the paper contributed to editing, reviewing, and final approval of the article.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: March 14, 2019
Peer-review started: March 15, 2019
First decision: August 2, 2019
Revised: August 21, 2019
Accepted: October 18, 2019
Article in press: October 18, 2019

Giuseppe Lippi, Section of Clinical Biochemistry, University of Verona, Verona 37134, Italy

Gianfranco Cervellin, Emergency Department, University Hospital of Parma, Parma 43126, Italy

Fabian Sanchis-Gomar, Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia 46010, Spain

Corresponding author: Fabian Sanchis-Gomar, MD, Research Scientist, Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Av. Blasco Ibañez 15, Valencia 46010, Spain. fabian.sanchis@uv.es
Telephone: +34-96-5813115
Fax: +34-96-3864642

Abstract

The incorporation of biomarkers in the actually used risk scores seem to be helpful for early identifying atrial fibrillation (AF) patients at higher risk. The aim of this critical review of the scientific literature is to investigate the potential clinical significance of red blood cell distribution width (RDW) in AF. A systematic electronic search was carried out to identify all articles describing an epidemiological association between RDW and AF in adult human populations. Data abstraction was conducted on a final number of 35 articles (13 cross-sectional, 12 prospective and 10 retrospective studies). The results of these epidemiological investigations were all virtually concordant to emphasize that an enhanced RDW value is not only a predictive factor and a marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality. AF patients with RDW values exceeding the local reference range may be more aggressively investigated and managed, in order to identify and attenuate the impact of possible underlying disorders causing both anisocytosis and AF.

Key words: Atrial fibrillation; Arrhythmia; Erythrocytes; Red blood cell distribution width

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This critical review of the scientific literature aims to investigate the potential clinical significance of red blood cell distribution width (RDW) in atrial fibrillation (AF). We concluded that an enhanced RDW value is not only a predictive factor and a

Published online: December 26, 2019

P-Reviewer: Barik R, Pastromas S, Ueda H,
S-Editor: Zhang L
L-Editor: A
E-Editor: Zhang YL

marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality.

Citation: Lippi G, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width: A marker of anisocytosis potentially associated with atrial fibrillation. *World J Cardiol* 2019; 11(12): 292-304
URL: https://www.wjgnet.com/1949-8462/full/v11/i12/292.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i12.292

INTRODUCTION

Atrial fibrillation (AF) is the most common heart arrhythmia worldwide[1]. Worryingly, AF is related to higher rates of stroke and mortality[2]. Many risk scores and biological markers have been identified and developed to predict future AF events. Among the most frequently used and validated risk scores based on clinical parameters are CHADS2 [congestive heart failure, hypertension, age ≥ 75 years, diabetes, and stroke or transient ischemic attack (2 points)] and CHA2DS2-VASc [cardiac failure or dysfunction, hypertension, age 65-74 (1 point) or ≥ 75 years (2 points), diabetes mellitus, and stroke, TIA or thromboembolism (2 points) –vascular disease, and sex category (female)][3,4]. In addition, biomarkers may significantly contribute to obtain additional information regarding the risk that could influence the management of AF. Therefore, there is also an increasing interest in determining whether biomarkers themselves or in combination with clinical risk scores enhances prognostic accuracy for thromboembolism and mortality in AF patients[5,6]. A wide range of biomarkers have been evaluated as predictors and/or prognostics, such as cardiac troponin I and T, natriuretic peptides, D-dimer, CRP, galectin-3, growth differentiation factor-15, among others[1,5,7,8].

The incorporation of biomarkers in the actually used risk scores seem to be helpful for early identifying AF patients at higher risk (*i.e.*, enhanced risk for stroke, systemic embolic event or death), determining also their eligibility for anticoagulation and/or individualizing the most appropriate treatment strategy. Biomarkers are dynamic, and for that reason, they are also highly recommended to be included into management of patients with AF. Therefore, knowledge of new biomarkers related to AF may provide clinicians with more potential tools to quickly identify patients at higher risk of AF, attenuate its occurrence, improve its management, and decrease the risk of adverse events in patients with AF.

The search for hematological predictors of AF commenced in 1987 with the publication of a seminal study by Imataka *et al*[9], who demonstrated that plasma volume and erythrocyte biology may be significantly perturbed in patients with AF. Ten years later, Takahashi *et al*[10] first showed that erythrocyte size was altered both before and after the onset of chronic AF, thus leading to way to subsequent research aimed to define whether high heterogeneity of erythrocytes volumes, conventionally known as anisocytosis, may have clinical significance in AF.

Anisocytosis, defined as the presence of red blood cells (RBCs) with a broad heterogeneity of size and volume in peripheral blood, can be reliably estimated by the vast majority of modern hematological analyzers using different techniques, which provide a similar final index called RBC distribution width (RDW)[11]. The RDW, which is not directly measured by the analyzers, but can be calculated as standard deviation (SD) of the mean corpuscular volume (MCV), and is usually expressed in absolute value (*i.e.*, RDW-SD) or as the coefficient of variation [*i.e.*, RDW-CV: (RDW-SD)/(MCV) × 100]. Albeit largely instrument-dependent, the reference range of RDW-CV is usually comprised between 11.5%-14.5%[12]. Increased RDW values, thus reflecting anisocytosis, may be due to many pathological conditions including congenital erythrocyte disorders (*i.e.*, β-thalassemia, sickle cell disease, hereditary spherocytosis), anemia (*e.g.*, due to iron, folate or vitamin B deficiencies), blood transfusions, some forms of hemolytic anemias, oxidative stress, inflammation and impaired renal function[13-15]. Since the measurement of RDW has now become a useful part in diagnostic and prognostic assessment of many cardiovascular disorders such as acute coronary syndrome (ACS), heart failure and venous thromboembolism[16,17], the aim of this critical review of the scientific literature is to investigate the potential

clinical significance of measuring RDW in patients with, or at risk of, AF.

SEARCH STRATEGY

A systematic electronic search was carried out using the three well-recognized and widely accessed scientific databases (*i.e.*, Medline interface PubMed, Web of Science and Scopus/EMBASE)[18], with no date or language limits, to identify all articles which described the association between RDW and AF in epidemiological investigations involving human adult populations (cross-sectional, retrospective and prospective studies). The following keywords were used: "atrial fibrillation" AND "red blood cell distribution width" OR "RDW". The bibliographic references of selected items were also carefully checked for identifying additionally relevant documents. The title, abstract and full text of the articles were accurately reviewed by two authors (Lippi G and Cervellin G), and potential disagreement for inclusion was eventually resolved by the opinion of the third author. Although no meta-analysis was specified before the electronic search, since it was already clear that the studies could not be combined due to large heterogeneity in sample size, setting, and endpoints, it was our aim to explore whether this approach would still be possible after analyzing the data of the included studies.

SEARCH RESULTS

The search strategy retrieved a total number of 70 documents after elimination of replicates among the three scientific search platforms. Thirty five studies ought to be excluded since they did not match our search criteria (Figure 1). Data abstraction was hence conducted on a final number of 35 articles describing an epidemiological association between RDW and atrial fibrillation in adult populations, published between the years 2010 and 2019 (13 cross-sectional, 12 prospective and 10 retrospective studies) (Figure 1). It was finally decided that, as predictable, a meta-analysis was unfeasible due to large heterogeneity of the different studies (difference in nature, clinical settings, and endpoints, sample size from 49 to over 69000, no clear description of comorbidities in all studies, use of rather different RDW thresholds) (Table 1).

DESCRIPTION OF STUDIES OUTCOME

The first epidemiological investigation which could be identified in this critical literature review was published in 2010 by Horne and collaborators[19]. In this prospective investigation, based on the Intermountain Heart Collaborative Study, a total number of 3927 patients undergoing coronary angiography were evaluated after 1 year and 30 d, with the aim of defining the frequency of incident cardiovascular disorders and complications (including AF). When patients were classified according to quintiles of RDW, the frequency of incident AF steadily increased from the lowest up to the highest (*i.e.*, from 2% to 14%) RDW quintiles. A highly significant trend towards increasing frequency of AF was consistently observed across RDW quintiles ($P < 0.001$).

Providência *et al*[20] carried out a cross-sectional study including 247 patients presenting with symptomatic AF to the emergency department, who were then subjected to transesophageal echocardiography for ruling out left atrial appendage thrombus. Overall, eft atrial appendage thrombus was evidenced in 21/247 (8.5%) of all AF patients, and its presence was found to be significantly more frequent in patients with RDW ≥ 15.0% than in those with lower RDW values (14.8% *vs* 5.4%; $P = 0.013$).

Liu *et al*[21] carried out another cross-sectional study including 133 patients with paroxysmal AF and 101 healthy controls. In multivariate logistic regression analysis, a RDW value > 12.55% was associated with a 63% enhanced risk of AF (odds ratio, 1.63; 95%CI: 1.01-2.61).

Ertaş *et al*[22] retrospectively studied 132 patients undergoing nonemergency coronary artery bypass graft (CABG) surgery. A RDW > 13.45% was associated with a nearly 1.5-fold increased risk of new-onset AF (hazard ratio 1.48; 95%CI: 1.07-2.06). The same team of authors published another cross-control study, in which RDW was measured in 126 patients with non-valvular AF (39 with stroke and 87 without) and in 126 healthy controls with no AF[23]. The value of RDW was found to be significantly higher in AF patients with (14.1% ± 1.7%) or without stroke (14.3% ± 1.8%) compared

Table 1 Summary and concise description of the studies

Authors	Study design	Study population	Endpoints	Outcome
Horne *et al*[19], 2010	Prospective	3927 patients undergoing coronary angiography, endpoints collected at 30-d and 1-yr	Risk of developing cardiovascular diseases and complications	RDW positively correlated with the frequency of incident AF
Providência *et al*[20], 2013	Cross-sectional	247 patients presenting with symptomatic AF	Association with outcomes of transesophageal echocardiography	High RDW associated with left atrial appendage thrombosis
Liu *et al*[21], 2014	Cross-sectional	133 patients with paroxysmal AF and 101 healthy controls	Difference between groups	High RDW independently associated with AF
Ertaş *et al*[22], 2013	Retrospective	132 patients undergoing nonemergency CABG	Risk of new-onset AF until hospital discharge	RDW independently predicted the risk of developing AF
Ertaş *et al*[23], 2013	Cross-sectional	126 patients with AF (39 with stroke and 87 without) and 126 healthy controls	Difference among groups	RDW significantly higher in patients with AF than in controls, but non different between AF patients with or without stroke
Kurt *et al*[24], 2014	Cross-sectional	320 patients with AF	Relationship with CHA2DS2-VASc score	High RDW independently associated with higher CHA2DS2-VASc score
Güngör *et al*[25], 2014	Cross-sectional	117 patients with AF and 60 health control subjects	Difference among groups	RDW significantly higher in AF patients than in controls
Adamsson Eryd *et al*[26], 2014	Prospective	27124 subjects free from AF at enrollment, followed-up for 13.6 yr	Risk of developing AF	RDW independently predicted the risk of developing AF
Sarikaya *et al*[27], 2014	Cross-sectional	126 hypertensive patients (63 with AF and 63 without)	Difference among groups	High RDW significantly associated with AF
Gurses *et al*[28], 2015	Prospective	299 AF patients undergoing cryoballoon-based ablation, followed-up for 24 mo	Outcome of cryoballoon-based ablation	RDW independently predicted the risk of recurrence and duration of AF
Korantzopoulos *et al*[29], 2015	Prospective	109 patients undergoing elective cardiac surgery, followed-up throughout hospitalization	Risk of AF lasting > 5 min during hospitalization	RDW independently predicted the risk of postoperative AF
Wan *et al*[30], 2015	Prospective	300 patients with AF followed-up for a median up period of 3.2 yr	Risk of adverse clinical outcomes	RDW independently predicted the risk of major adverse events and death
Lee *et al*[31], 2015	Prospective	567 patients with newly diagnosed paroxysmal AF	Risk of adverse clinical outcomes	RDW independently predicted the risk of new-onset stroke, composite outcome and bleeding
Zhao *et al*[32], 2015	Cross-sectional	90 AF patients, 24 with evidence of left atrial thrombus (n = 11) or left atrial spontaneous echo contrast (n = 13)	Evidence of left atrial thrombus or left atrial spontaneous echo contrast	RDW associated with presence of left atrial thrombus or left atrial spontaneous echo contrast
Aksu *et al*[33], 2015	Prospective	49 patients with AF followed-up for 10 mo	Risk of AF recurrence	RDW predicted the risk of AF recurrence
Korantzopoulos *et al*[34], 2016	Cross-sectional	101 patients with sick sinus syndrome (32 with AF)	Difference between groups	High RDW independently associated with AF
Karataş *et al*[35], 2016	Retrospective	621 patients with myocardial infarction undergoing primary percutaneous coronary intervention	Risk of new-onset AF throughout hospitalization	RDW independently predicted the risk of new-onset AF
Yanagisawa *et al*[36], 2016	Prospective	757 AF patients undergoing radiofrequency catheter ablation followed-up for 22 mo	Risk of adverse clinical outcomes	RDW independently predicted the risk of recurrent AF and major adverse events
Vizzardi *et al*[37], 2016	Retrospective	232 patients with stable heart failure 1 yr after enrolment	Risk of adverse events 1 yr after enrolment	RDW independently predicted the risk of cardiovascular death and/or hospitalization for heart failure

Geçmen *et al*[38], 2016	Prospective	94 patients undergoing isolated on-pump CABG surgery followed-up until discharge from cardiovascular intensive care unit	Risk of postoperative AF	RDW independently predicted the risk postoperative AF
Zhang *et al*[39], 2017	Prospective	172 patients with nonvalvular AF undergoing catheter ablation, followed-up for 3 mo	Risk of bleeding	RDW predicted the risk of bleeding events
Al-Kindi *et al*[40], 2017	Retrospective	46720 patients with a diagnosis of HIV infection followed-up for development of cardiovascular complications	Risk of cardiovascular complications	RDW independently predicted the risk of AF
Liu *et al*[41], 2017	Cross-sectional	99 patients with AF, categorized according to their CHADS2 and CHA2DS2-VASc scores	Association with risk of stroke	High RDW independently associated with higher CHADS2 and CHA2DS2-VASc scores
Saliba *et al*[42], 2017	Retrospective	69412 patients with AF	Risk of death 2 yr after study entry	RDW independently predicted the risk of death; persistently increased RDW values at two time points stronger predictors of death than a single increased RDW value
Kaya *et al*[43], 2017	Cross-sectional	619 patients with AF (325 with left atrial stasis and 294 without)	Association with left atrial stasis	High RDW independently associated with left atrial stasis
Cha *et al*[44], 2017	Retrospective	5082 patients with AF	Risk of thromboembolic events during 5.2 yr	High peak RDW value during follow-up independently associated with the risk of thromboembolic events
Nam *et al*[45], 2017	Cross-sectional	103 healthy control subjects and 117 patients with AF patients, 65 of whom with paroxysmal and 52 with persistent AF	Difference among groups	RDW values non significantly different between controls and all AF cases; RDW values significantly higher in patients with persistent than in those with paroxysmal AF
Wasilewski *et al*[46], 2017	Retrospective	1734 patients with LVEF ≤ 35% and without ACS	Risk of AF after 660 d	High RDW independently predicted the risk of AF
Kilicgedik *et al*[48], 2018	Retrospective	358 patients after who underwent CABG surgery (57 with PSAF and 301 patients with non-PSAF)	Risk of AF after CABG surgery	High RDW was predictive of PSAF
Cerşit *et al*[47], 2018	Retrospective	50 patients with AF and 62 age- and sex- matched controls, who had presented with ACS	Association and predictive value of RDW with AF in patients with ACS.	High RDW was associated with AF and had long-term predictive value
Ozsin *et al*[49], 2018	Retrospective	93 patients who underwent off-pump CABG (24 patients with PSAF and 69 without PSAF)	Association and predictive value of RDW for development PSAF	Elevated RDW levels may be predictive of PSAF
Pilling *et al*[50], 2018	Prospective	240477 healthy UK Biobank study volunteers aged 40 ± 70 yr at baseline (follow-up ≤ 9 yr)	Association of RDW with AF in healthy subjects.	High RDW was associated with AF and had long-term predictive value
Han *et al*[51], 2019	Cross-sectional	303 patients with nonvalvular AF living at low altitude (3.5 m above the sea level) and high altitude (2260 m above the sea level).	Association of RDW with AF in subjects living at low and high altitude.	Elevated RDW levels were an independent risk marker for AF and is affected by type of AF and altitude
Jurin *et al*[52], 2019	Prospective	579 patients with AF (non-permanent and permanent AF), with a median follow-up time of 21 mo	Association of RDW values with progression to permanent AF	RDW was independently associated with AF progression
Li *et al*[53], 2019	Cross-sectional	106998 Chinese individuals	Relationship between RDW and AF	Elevated RDW is significantly related to higher prevalence of AF in a general Chinese population

AF: Atrial fibrillation; RDW: Red blood cell distribution width; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft; ACS: Acute

coronary syndrome; PSAF: Post-surgery atrial fibrillation.

to the control population (13.2% ± 0.9%), but its value did not differ among AF patients with or without stroke ($P > 0.05$).

Kurt *et al*[24] measured RDW in 320 patients with AF and found that those with a higher CHA2DS2-VASc score had also significantly higher RDW values than those with a lower CHA2DS2-VASc score (14.9% ± 2.7% *vs* 13.6% ± 1.7%; $P < 0.001$). A highly significant correlation could be observed between RDW and CHA2DS2-VASc score ($r = 0.383$; $P < 0.001$). In multivariate analysis, a RDW value > 14.05% was associated with a 25% higher risk (odds ratio, 1.25; 95%CI: 1.11-1.42) of having high CHA2DS2-VASc score (*i.e.*, ≥ 2).

In an ensuing investigation, Güngör *et al*[25] studied 117 patients with AF and 60 healthy control subjects, concluding that RDW values were significantly higher in AF cases than in controls (13.4% *vs* 12.6%; $P = 0.01$). In multivariate regression analysis, a RDW > 12.9% was associated with a nearly 4-fold higher risk (odds ratio, 4.18; 95%CI: 2.15-8.15) of AF.

Adamsson Eryd *et al*[26] carried out a large prospective study including 27124 subjects free from AF at enrollment, who were followed-up for a mean period of 13.6 years. Subjects in the highest quartile of RDW had a 33% enhanced risk (hazard ratio, 1.33; 95%CI: 1.16-1.53) of developing AF on follow-up compared to those in the lowest quartile. Moreover, each 1 SD increase of RDW value was associated with a 8% higher risk (hazard ratio, 1.08; 95%CI: 1.04-1.12) of incident AF.

Sarikaya *et al*[27] studied 126 patients with hypertension (63 with AF and 63 without) and reported that RDW values were significantly higher in patients with AF than in those without (15.1% ± 1.6% *vs* 14.0% ± 1.1%; $P = 0.001$). In multivariate logistic regression analysis, a RDW value > 14.2% was found to be independently associated with 1.8-fold higher risk (odds ratio, 1.85; 95%CI: 1.22-2.79) of AF.

Gurses *et al*[28] measured RDW in 299 patients with paroxysmal or persistent AF undergoing cryoballoon-based ablation, and who were then followed-up for a mean period of 24 mo. A RDW value > 13.75% was independently associated with both early (hazard ratio, 6.39; 95%CI: 3.41-11.97) and late (hazard ratio, 1.88; 95%CI: 1.41-2.50) recurrence of AF, enhanced left atrial diameter (hazard ratio, 3.09; 95%CI: 1.81-5.27), as well as with duration of AF (hazard ratio, 1.04; 95%CI: 1.01-1.07).

Korantzopoulos *et al*[29] studied 109 patients undergoing elective cardiac surgery, who were then prospectively followed-up throughout hospitalization. In multivariate logistic regression analysis, a RDW > 13.35% was independently associated with a 46% higher risk (odds ratio, 1.46; 95%CI: 1.08-1.99) of developing postoperative AF during hospital stay.

Wan *et al*[30] carried out a prospective study including 300 patients with AF who were followed-up at a median period of 3.2 years. Patients in the fourth quartile of RDW values had a 2.7-fold higher risk (hazard ratio, 2.70; 95%CI: 1.35-5.83) of major adverse events (all-cause mortality, ACS, stroke and major hemorrhage) and a 3.8-fold higher risk (hazard ratio, 3.83; 95%CI: 1.53-9.58) of death during follow-up.

Lee *et al*[31] measured RDW values in 567 patients with newly diagnosed paroxysmal AF, who were followed-up for a median period of 4.8 years. In multivariate analysis, an increased RDW value (no indications provided on the cut-off used) was independently associated with 47% higher risk (hazard ratio, 1.47; 95%CI: 1.05-2.05) of new-onset stroke, 26% higher risk (hazard ratio, 1.26; 95%CI: 1.02-1.54) of composite outcome (mortality, new-onset stroke and hospitalization for heart failure), and 74% enhanced risk of bleeding (hazard ratio, 1.74; 95%CI: 1.28-2.36) throughout follow-up.

Zhao *et al*[32] retrospectively analyzed a local echocardiology database for identifying all AF patients who underwent transesophageal echocardiography before catheter ablation or electrical cardioversion. The final study population consisted of 90 AF patients, 24 of whom had evidence of left atrial thrombus ($n = 11$) or left atrial spontaneous echo contrast ($n = 13$). The mean RDW value was found to be significantly higher in patients with these two complications than in those without (13.0% ± 0.9% *vs* 12.6% ± 0.8%; $P = 0.039$).

Aksu *et al*[33] studied 49 patients with symptomatic paroxysmal AF who underwent cryoballoon ablation and were then followed-up for a mean period of 10 mo. Patients with AF recurrence on follow-up had significantly higher RDW values than those without (16.1% ± 1.4% *vs* 14.9% ± 0.5%; $P = 0.033$). Interestingly, the post-ablation RDW value remained almost unchanged in patents without recurrence of AF, but in those with AF recurrence the RDW significantly increased from 16.1% ± 1.4% to 16.3% ± 2.4% ($P < 0.05$).

In another study, Korantzopoulos *et al*[34] measured RDW in 101 patients with sick

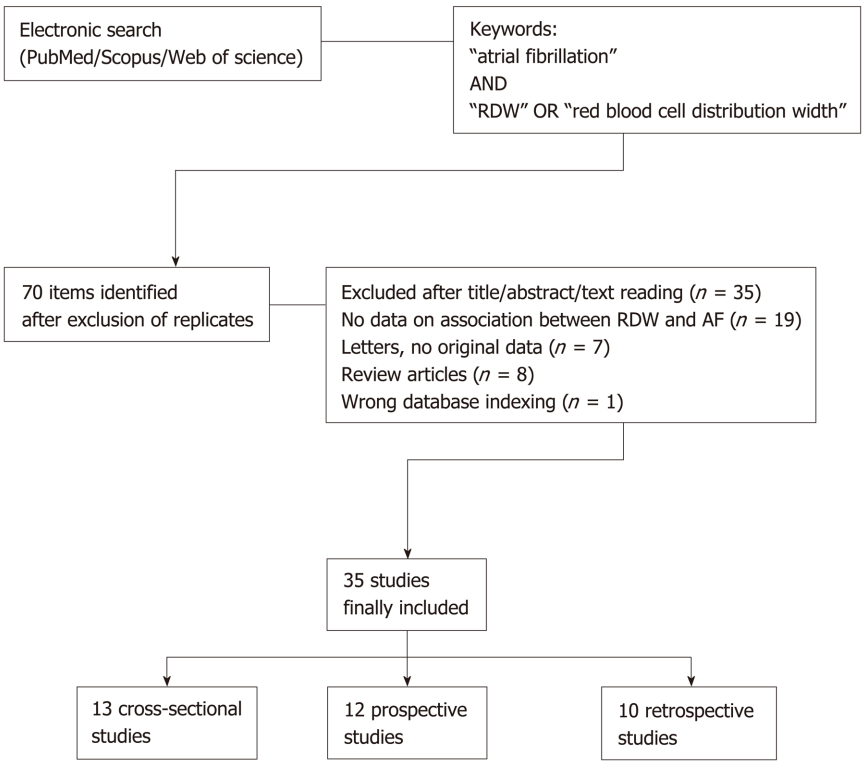


Figure 1 Search strategy and search results.

sinus syndrome (32 with AF), and found that a RDW value > 14.0% was independently associated with AF (odds ratio, 1.58; 95%CI: 1.06-2.85).

Karataş *et al*[35] studied 621 patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, and who were followed-up throughout hospitalization. Patients with RDW > 13.4% had a 55% higher risk (odds ratio, 1.55; 95%CI: 1.20-2.01) of developing new-onset AF until hospital discharge.

Yanagisawa *et al*[36] measured RDW in 757 patients undergoing radiofrequency catheter ablation for AF, who were then followed-up for a mean period of 22 mo. In multivariate linear regression analysis, a RDW value > 13.9% was associated with 20% higher risk (hazard ratio, 1.20; 95%CI: 1.01-1.40) of recurrent AF in patients with heart failure, whilst no significant association was found in those without heart failure. In patients with heart failure, a RDW value > 14.8% was also associated with 83% higher risk (hazard ratio, 1.83; 95%CI: 1.13-2.72) of developing major adverse events (all-cause mortality, hospitalization for heart failure and cerebral ischemia) during follow-up.

Vizzardi *et al*[37] carried out a retrospective study including 232 patients with stable heart failure, whose clinical outcome was assessed 1 year after enrolment. In multivariate logistic regression analysis, a RDW value > 14.45% was independently associated with 3.9-fold enhanced risk (odds ratio, 3.89; 95%CI: 1.04-14.55) of cardiovascular death and/or hospitalization for heart failure in the first year after enrolment.

Geçmen *et al*[38] carried out a prospective study including 94 patients undergoing isolated on-pump CABG surgery, who were followed-up until discharge from the cardiovascular intensive care unit. In univariate analysis, higher RDW values were associated with a 41% higher risk (odds ratio, 1.41; 95%CI: 1.01-1.96) of postoperative AF during cardiovascular intensive care unit stay. The cut-off value of RDW was unavailable in the publication and the association between RDW and postoperative AF was not tested in multivariate analysis.

Zhang *et al*[39] measured RDW in 172 patients diagnosed with nonvalvular AF, who were followed up for 3 mo after catheter ablation. The overall number of bleeding events was found to be higher in patients with RDW values > 12.8% than in those with lower RDW values (11.8% *vs* 3.4%). Interestingly, the diagnostic efficiency (*i.e.*, area under the receiver operating characteristics curve; AUC) for predicting bleeding occurrence was higher for RDW than for activated partial thromboplastin time (0.737 *vs* 0.558; $P < 0.01$).

Al-Kindi *et al*[40] used a large commercial database including electronic health

records of many participating hospitals, with the aim of identifying patients aged 18 years or older with a diagnosis of HIV and who had at least one available RDW measurement. The search allowed the extraction of a total number of 46720 records (mean or median follow-up period for development of cardiovascular complications is unavailable in the article). In these HIV patients, a RDW value > 14.5% was independently associated with a 96% higher risk (odds ratio, 1.96; 95%CI: 1.64-2.33) of incident AF.

Liu *et al*[41] studied 99 patients with AF, divided into two groups according to their CHADS2 and CHA2DS2-VASc scores. In multivariate logistic regression analysis, a RDW value > 12.55% was found to be significantly associated with higher (≥ 2) CHADS2 score (odds ratio, 2.18; 95CI%: 1.14-3.22), whilst a RDW value > 12.75% was found to be significantly associated with higher (≥ 2) CHA2DS2-VASc score (odds ratio, 5.75; 95%CI: 3.70-7.79).

Saliba *et al*[42] searched the electronic database for a large national health maintenance for identifying all patients diagnosed with AF in whom at least two RDW measurements were performed 1 year before study entry. Mortality data were retrospectively reviewed for up to 2 years after patients inclusion in the database. The electronic search identified a total of 69412 records. A RDW value > 14.5% was independently associated with a 49% increased risk (hazard ratio, 1.49; 95%CI, 1.43-1.55) of all-cause mortality during the follow-up period. More importantly, persistently increased RDW values at the two-time points were independently associated with an even higher risk of death during the same follow-up period (HR, 1.70; 95%CI: 1.61-1.79).

Kaya *et al*[43] analyzed the data of 619 AF patients undergoing transesophageal echocardiography examination before cardioversion or AF ablation. In multivariate regression analysis, a RDW value > 13.7% was associated with a 67% increased risk of left atrial stasis (odds ratio, 1.67; 95%CI: 1.44-1.94).

Cha *et al*[44] carried out a retrospective study including 5082 patients with non-valvular AF, who were followed-up for a mean period of 5.2 years. The RDW was measured several times during follow-up, allowing to identify nadir (*i.e.*, the lowest), peak (*i.e.*, the highest) and mean RDW values. Among the various RDW measures, a peak value ≥ 13.9% was independently associated with a 66% enhanced risk (odds ratio, 1.66; 95%CI: 1.41-1.96) of thromboembolic events, including ischemic stroke and systemic embolism.

Nam *et al*[45] carried out a cross-sectional study including 103 healthy control subjects and 117 patients with AF, 65 of whom with paroxysmal AF and 52 with persistent AF. Overall, no significant difference was found in mean RDW values between controls and AF cases (13.4% ± 1.6% *vs* 13.5% ± 0.8%; $P = 0.343$), whilst patients with persistent AF exhibited significantly higher mean RDW values than those with paroxysmal AF (13.9% ± 0.9% *vs* 13.3% ± 0.6%; $P < 0.05$).

Wasilewski *et al*[46] performed a sub-analysis of the COMMIT-HF (COnteMporary Modalities In Treatment of Heart Failure) registry, including 1734 patients with left ventricular ejection fraction ≤ 35% and without ACS at baseline, who were retrospectively investigated for a median period of 660 d. Patients in the highest RDW tertile had a more than double risk of developing AF on follow-up compared to those in the lowest tertile (44.1% *vs* 20.2%; $P < 0.01$).

Cerşit *et al*[47] investigated the association between RDW and AF in 50 patients with and without AF after an ACS. RDW was significantly higher in patients with AF than the control group (14.5% ± 2% *vs* 12.6% ± 1%, $P < 0.001$). A RDW of > 11.7% also predicted AF (sensitivity 56% and specificity of 64%; AUC = 0.637, $P < 0.001$).

Kılıcgedik *et al*[48] evaluated the RDW values in 358 patients who underwent CABG surgery [57 with post-surgery AF (PSAF) and 301 patients with non-PSAF]. Interestingly, RDW values were significantly higher in PSAF group. In multivariate analysis, RDW [OR:1.16 (95%CI: 1.0-1.36), $P = 0.05$] was found to be predictive for PSAF (68.4% sensitivity and 51.2% specificity; $P = 0.001$). Likewise, Ozsin *et al*[49] analyzed the RDW levels in 93 patients who underwent off-pump CABG surgery. 24 patients developed PSAF while 69 did not. RDW was significantly correlated with PSAF and was also found to be predictive for PSAF (79.2% sensitivity and 65.2% specificity; $P = 0.001$).

Pilling *et al*[50] analyzed the RDW levels in 240477 healthy volunteers (40 ± 70 at baseline) during a follow-up period of ≤ 9 years. Higher RDW levels (≥ 15% variation, $n = 6050$) was associated with AF (sHR 1.37: 1.21 to 1.55). RDW was also predictive of new-onset AF.

Han *et al*[51] investigated the effects of low altitude (3.5 m above the sea level) and high altitude (2260 m above the sea level) on RDW levels of 303 patients with nonvalvular AF. RDW levels were higher in AF than control individuals ($P < 0.05$) and higher in persistent AF than paroxysmal AF ($P < 0.05$) in both low and high altitudes. Moreover, RDW, was independently associated with AF in low altitude

(RDW, OR: 1.687, 95%CI: 1.021–2.789; $P < 0.05$), whereas it was an independent predictor for AF (RDW, OR: 1.755, 95%CI: 1.179–2.613; $P < 0.05$) in high altitude.

Jurin *et al*[52] recruited 579 patients with AF, 412 with non-permanent AF and 167 with permanent AF, and followed-up the patients with non-permanent AF during a median time of 21 mo. The main endpoint was progression of non-permanent AF to permanent AF. 109 patients (26.6%) progressed to permanent AF. Moreover, increased RDW levels showed a significant independent association with the progression to permanent AF (HR 1.19, 95%CI: 1.03–1.39, $P = 0.022$).

Finally, Li *et al*[53] recently examined the relationship between RDW and AF in a general Chinese population (106998 subjects). The authors concluded that RDW was significantly related to a higher prevalence of AF; the OR (95%CI) of AF for increasing tertiles of RDW were 1.00 (reference), 1.08 (0.69, 1.67), and 2.65 (1.75, 4.07) (P for trend < 0.0001), respectively.

Taken together, the results of these epidemiological studies, as well as results from two systematic reviews and meta-analysis recently published[54,55], are all virtually concordant to emphasize that an enhanced RDW value not only is a predictive factor and a marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events (including new-onset stroke) and mortality.

ANISOCYTOSIS IN ATRIAL FIBRILLATION: ACTIVE PLAYER OR BYSTANDER?

There are at least two biological explanations which can be brought for justifying the strong epidemiological association observed between anisocytosis and AF, either of which is plausible (Figure 2).

The first and rather predictable scenario is that the same causative factors for AF may also impair erythropoiesis, and thereby the observation of an increased RDW value may only be a coincident epiphenomenon in AF[56]. For example, a high RDW value is commonplace in patients with recent blood transfusions or severe anemia[13], and both RBC transfusion[57] and anemia[58] are associated with an excess incidence of AF, as consequence of onset of heart failure and impairment of renal function. Inflammation is probably the most frequent cause of anisocytosis[59], but its contribution to the pathogenesis of AF is now almost unquestionable, since many inflammatory cytokines are known to impair atrial electrophysiology and structure[60]. Oxidative stress is another important inducer of anisocytosis[61], whilst the oxidation of myofibrillar protein and cardiomyocyte membrane lipids is also a well-recognized mechanism leading to AF[62]. Finally, it is now clearly acknowledged that renal diseases may generate a kaleidoscope of inflammatory, neurohumoral, metabolic and hemodynamic stresses to the heart[63], whilst impaired erythropoiesis and anisocytosis are also commonplace in patients with impaired renal function, mainly due to impaired erythropoietin production[13] (Figure 2).

On the other hand, a support to the thesis that anisocytosis not only may be an innocent bystander in AF, but may also trigger, or contribute to worsening, AF has emerged from a discrete number of studies. Hirayama *et al* showed that the onset of arrhythmias is strongly associated with reduced erythrocyte deformability[64], which is a conventional hallmark of anisocytic erythrocytes[65]. A large variation of erythrocytes volume is also associated with a greater cholesterol content in the RBC membrane, which can then be directly transferred to atherosclerotic plaques enriched in erythrocytes[66,67], thus finally promoting atherogenesis and ultimately predisposing to cardiac arrhythmias, since AF atherosclerosis and AF are now considered two strictly intertwined disorders[68]. Finally, the presence of anisocytic erythrocytes has also been involved in the mechanisms underlying adverse cardiac remodeling[69], thus leading to atrial fibrosis and predisposing the patients to a higher risk of developing AF[70].

CONCLUSION

The value of the RDW can be automatically generated, along with the other parameters of the complete blood cell count, by the majority of modern hematological analyzers. It can therefore be considered an easier, faster and less expensive test compared to other potentially useful biomarkers in AF[1]. Regardless of the fact that anisocytosis may be a simple bystander or an active player in the pathogenesis of AF and of its life-threatening complications, the current epidemiological evidence convincingly suggests that routine measurement of RDW may provide valuable

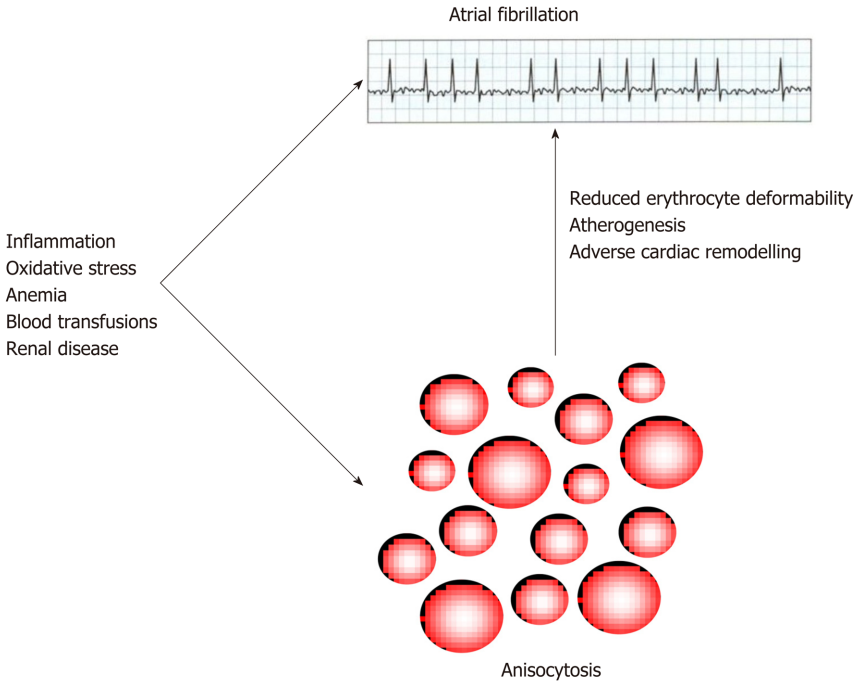


Figure 2 The interplay between atrial fibrillation and anisocytosis.

clinical information for diagnosis and management of AF, alone or combined with traditional risk scores such as CHADS2 and CHA2DS2-VASc[71]. In particular, the strong and often independent association observed between high RDW values and unfavorable outcomes (*e.g.*, recurrence of AF, heart failure, bleeding, thromboembolic events and death) (Table 1), would lead us to conclude that AF patients with RDW values exceeding the local reference range may be more aggressively investigated and managed, in order to identify and reduce the impact of possible underlying disorders causing both anisocytosis and AF (Figure 2), and also for preventing the possible risk of adverse events potentially attributable to anisocytosis. Additional studies are then advised to define whether the inclusion of RDW within conventional risks scores may be effective in providing more accurate risk stratification in AF.

REFERENCES

1 **O'Neal WT**, Venkatesh S, Broughton ST, Griffin WF, Soliman EZ. Biomarkers and the prediction of atrial fibrillation: state of the art. *Vasc Health Risk Manag* 2016; **12**: 297-303 [PMID: 27486329 DOI: 10.2147/VHRM.S75537]

2 **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64**: e1-76 [PMID: 24685669 DOI: 10.1016/j.jacc.2014.03.022]

3 **Melgaard L**, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. *JAMA* 2015; **314**: 1030-1038 [PMID: 26318604 DOI: 10.1001/jama.2015.10725]

4 **Jacobs V**, May HT, Bair TL, Crandall BG, Cutler M, Day JD, Weiss JP, Osborn JS, Muhlestein JB, Anderson JL, Mallender C, Bunch TJ. The impact of risk score (CHADS2 versus CHA2DS2-VASc) on long-term outcomes after atrial fibrillation ablation. *Heart Rhythm* 2015; **12**: 681-686 [PMID: 25546809 DOI: 10.1016/j.hrthm.2014.12.034]

5 **Ruff CT**, Giugliano RP, Braunwald E, Murphy SA, Brown K, Jarolim P, Mercuri M, Antman EM, Morrow DA. Cardiovascular Biomarker Score and Clinical Outcomes in Patients With Atrial Fibrillation: A Subanalysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial. *JAMA Cardiol* 2016; **1**: 999-1006 [PMID: 27706467 DOI: 10.1001/jamacardio.2016.3311]

6 **Fernández-Ruiz I**. Atrial fibrillation: New score for stroke risk. *Nat Rev Cardiol* 2016; **13**: 634-635 [PMID: 27629514 DOI: 10.1038/nrcardio.2016.156]

7 **Hijazi Z**, Oldgren J, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Yusuf S, Granger CB, Siegbahn A, Wallentin L; ARISTOTLE and RE-LY Investigators. A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score. *Eur Heart J* 2018; **39**: 477-485 [PMID: 29069359 DOI: 10.1093/eurheartj/ehx584]

8 **Hijazi Z**, Lindahl B, Oldgren J, Andersson U, Lindbäck J, Granger CB, Alexander JH, Gersh BJ, Hanna

M, Harjola VP, Hylek EM, Lopes RD, Siegbahn A, Wallentin L. Repeated Measurements of Cardiac Biomarkers in Atrial Fibrillation and Validation of the ABC Stroke Score Over Time. *J Am Heart Assoc* 2017; 6 [PMID: 28645934 DOI: 10.1161/JAHA.116.004851]

9 **Imataka K**, Nakaoka H, Kitahara Y, Fujii J, Ishibashi M, Yamaji T. Blood hematocrit changes during paroxysmal atrial fibrillation. *Am J Cardiol* 1987; **59**: 172-173 [PMID: 3812234 DOI: 10.1016/s0002-9149(87)80099-1]

10 **Takahashi N**, Ashida T, Kiraku J, Fujii J. Increase in erythrocyte volume in patients with chronic atrial fibrillation. *Jpn Heart J* 1997; **38**: 387-391 [PMID: 9290573 DOI: 10.1536/ihj.38.387]

11 **Lippi G**, Pavesi F, Bardi M, Pipitone S. Lack of harmonization of red blood cell distribution width (RDW). Evaluation of four hematological analyzers. *Clin Biochem* 2014; **47**: 1100-1103 [PMID: 24925288 DOI: 10.1016/j.clinbiochem.2014.06.003]

12 **Fischbach FT**, Dunning MB. A manual of laboratory and diagnostic tests. 9th ed. Philadelphia: Wolters Kluwer Health; 2015;

13 **Sarma PR**. Red Cell Indices. Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. Boston; 1990; 720-723

14 **Salvagno GL**, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci* 2015; **52**: 86-105 [PMID: 25535770 DOI: 10.3109/10408363.2014.992064]

15 **Lippi G**, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width and cardiovascular disorders. Does it really matter which comes first, the chicken or the egg? *Int J Cardiol* 2016; **206**: 129-130 [PMID: 26788688 DOI: 10.1016/j.ijcard.2016.01.122]

16 **Lippi G**, Cervellin G. Risk assessment of post-infarction heart failure. Systematic review on the role of emerging biomarkers. *Crit Rev Clin Lab Sci* 2014; **51**: 13-29 [PMID: 24410541 DOI: 10.3109/10408363.2013.863267]

17 **Lippi G**, Buonocore R, Cervellin G. Value of Red Blood Cell Distribution Width on Emergency Department Admission in Patients With Venous Thrombosis. *Am J Cardiol* 2016; **117**: 670-675 [PMID: 26718227 DOI: 10.1016/j.amjcard.2015.11.024]

18 **Lippi G**, Favalor EJ, Simundic AM. Biomedical research platforms and their influence on article submissions and journal rankings: an update. *Biochem Med (Zagreb)* 2012; **22**: 7-14 [PMID: 22384515]

19 **Horne BD**, May HT, Kfoury AG, Renlund DG, Muhlestein JB, Lappé DL, Rasmusson KD, Bunch TJ, Carlquist JF, Bair TL, Jensen KR, Ronnow BS, Anderson JL. The Intermountain Risk Score (including the red cell distribution width) predicts heart failure and other morbidity endpoints. *Eur J Heart Fail* 2010; **12**: 1203-1213 [PMID: 20705688 DOI: 10.1093/eurjhf/hfq115]

20 **Providência R**, Ferreira MJ, Gonçalves L, Faustino A, Paiva L, Fernandes A, Barra S, Pimenta J, Leitão-Marques AM. Mean corpuscular volume and red cell distribution width as predictors of left atrial stasis in patients with non-valvular atrial fibrillation. *Am J Cardiovasc Dis* 2013; **3**: 91-102 [PMID: 23785587]

21 **Liu T**, Shao Q, Miao S, Liu E, Xu G, Yuan R, Li G. Red cell distribution width as a novel, inexpensive marker for paroxysmal atrial fibrillation. *Int J Cardiol* 2014; **171**: e52-e53 [PMID: 24360079 DOI: 10.1016/j.ijcard.2013.11.112]

22 **Ertaş G**, Aydin C, Sönmez O, Erdoğan E, Turfan M, Tasal A, Bacaksiz A, Vatankulu MA, Uyarel H, Ergelen M, Zeybek R, Göktekin Ö. Red cell distribution width predicts new-onset atrial fibrillation after coronary artery bypass grafting. *Scand Cardiovasc J* 2013; **47**: 132-135 [PMID: 23035619 DOI: 10.3109/14017431.2012.736636]

23 **Ertaş G**, Sönmez O, Turfan M, Kul S, Erdoğan E, Tasal A, Bacaksiz A, Vatankulu MA, Altıntaş O, Uyarel H, Göktekin O. Neutrophil/lymphocyte ratio is associated with thromboembolic stroke in patients with non-valvular atrial fibrillation. *J Neurol Sci* 2013; **324**: 49-52 [PMID: 23084070 DOI: 10.1016/j.jns.2012.09.032]

24 **Kurt M**, Tanboga IH, Buyukkaya E, Karakas MF, Akçay AB, Sen N. Relation of red cell distribution width with CHA2DS2-VASc score in patients with nonvalvular atrial fibrillation. *Clin Appl Thromb Hemost* 2014; **20**: 687-692 [PMID: 23430929 DOI: 10.1177/1076029613478157]

25 **Güngör B**, Özcan KS, Erdinler İ, Ekmekçi A, Alper AT, Osmonov D, Çalık N, Akyuz S, Toprak E, Yılmaz H, Yıldırım A, Bolca O. Elevated levels of RDW is associated with non-valvular atrial fibrillation. *J Thromb Thrombolysis* 2014; **37**: 404-410 [PMID: 23821044 DOI: 10.1007/s11239-013-0957-1]

26 **Adamsson Eryd S**, Borné Y, Melander O, Persson M, Smith JG, Hedblad B, Engström G. Red blood cell distribution width is associated with incidence of atrial fibrillation. *J Intern Med* 2014; **275**: 84-92 [PMID: 24112470 DOI: 10.1111/joim.12143]

27 **Sarikaya S**, Şahin Ş, Akyol L, Börekçi E, Yilmaz YK, Altunkaş F, Karaman K. Is there any relationship between RDW levels and atrial fibrillation in hypertensive patient? *Afr Health Sci* 2014; **14**: 267-272 [PMID: 26060490 DOI: 10.4314/ahs.v14i1.41]

28 **Gurses KM**, Yalcin MU, Kocyigit D, Evranos B, Ates AH, Yorgun H, Sahiner ML, Kaya EB, Ozer N, Oto MA, Aytemir K. Red blood cell distribution width predicts outcome of cryoballoon-based atrial fibrillation ablation. *J Interv Card Electrophysiol* 2015; **42**: 51-58 [PMID: 25510648 DOI: 10.1007/s10840-014-9959-y]

29 **Korantzopoulos P**, Sontis N, Liu T, Chlapoutakis S, Sismanidis S, Siminelakis S, Apostolakis E. Association between red blood cell distribution width and postoperative atrial fibrillation after cardiac surgery: A pilot observational study. *Int J Cardiol* 2015; **185**: 19-21 [PMID: 25777283 DOI: 10.1016/j.ijcard.2015.03.080]

30 **Wan H**, Yang Y, Zhu J, Huang B, Wang J, Wu S, Shao X, Zhang H. The relationship between elevated red cell distribution width and long-term outcomes among patients with atrial fibrillation. *Clin Biochem* 2015; **48**: 762-767 [PMID: 26054582 DOI: 10.1016/j.clinbiochem.2015.06.001]

31 **Lee KH**, Park HW, Cho JG, Yoon NS, Kim SS, Kim MR, Kim MC, Cho KH, Kim HK, Kim CH, Kim KH, Jun SJ, Kim WJ, Lee KJ, Jeong HC, Cho JY, Park KH, Sim Ds, Yoon HJ, Kim KH, Hong YJ, Kim JH, Ahn Y, Jeong MH, Park JC. Red cell distribution width as a novel predictor for clinical outcomes in patients with paroxysmal atrial fibrillation. *Europace* 2015; **17** Suppl 2: ii83-ii88 [PMID: 26842121 DOI: 10.1093/europace/euv210]

32 **Zhao J**, Liu T, Korantzopoulos P, Fu H, Shao Q, Suo Y, Zheng C, Xu G, Liu E, Xu Y, Zhou C, Li G. Red blood cell distribution width and left atrial thrombus or spontaneous echo contrast in patients with non-valvular atrial fibrillation. *Int J Cardiol* 2015; **180**: 63-65 [PMID: 25438214 DOI: 10.1016/j.ijcard.2014.11.145]

33 **Aksu T**, Baysal E, Guler TE, Golcuk SE, Erden İ, Ozcan KS. Predictors of atrial fibrillation recurrence after cryoballoon ablation. *J Blood Med* 2015; **6**: 211-217 [PMID: 26170730 DOI: 10.2147/JBM.S81551]

34 **Korantzopoulos P**, Kyrlas K, Liu T, Li G, Goudevenos JA. Red blood cell distribution width and atrial fibrillation in patients with sick sinus syndrome. *J Cardiol* 2016; **67**: 551-554 [PMID: 26321105 DOI: 10.1016/j.jjcc.2015.07.013]

35 **Karataş MB**, Çanga Y, İpek G, Özcan KS, Güngör B, Durmuş G, Onuk T, Öz A, Şimşek B, Bolca O. Association of admission serum laboratory parameters with new-onset atrial fibrillation after a primary percutaneous coronary intervention. *Coron Artery Dis* 2016; **27**: 128-134 [PMID: 26693808 DOI: 10.1097/MCA.0000000000000333]

36 **Yanagisawa S**, Inden Y, Kato H, Miyoshi A, Mizutani Y, Ito T, Kamikubo Y, Kanzaki Y, Hirai M, Murohara T. Elevated Red Blood Cell Distribution Width Predicts Recurrence After Catheter Ablation for Atrial Fibrillation in Patients With Heart Failure - Comparison With Non-Heart Failure Patients. *Circ J* 2016; **80**: 627-638 [PMID: 26823143 DOI: 10.1253/circj.CJ-15-1152]

37 **Vizzardi E**, Sciatti E, Bonadei I, Pezzali NL, Lombardi CM, Metra M. Red cell distribution width and chronic heart failure: prognostic role beyond echocardiographic parameters. *Monaldi Arch Chest Dis* 2016; **84**: 59 [PMID: 27374035 DOI: 10.4081/monaldi.2015.59]

38 **Geçmen Ç**, Babür Güler G, Erdoğan E, Hatipoğlu S, Güler E, Yılmaz F, Unkun T, Cap M, Bengi Bakal R, Bayram T, Deniz Acar R, Candan Ö, Özdemir N. SYNTAX score predicts postoperative atrial fibrillation in patients undergoing on-pump isolated coronary artery bypass grafting surgery. *Anatol J Cardiol* 2016; **16**: 655-661 [PMID: 27488747 DOI: 10.5152/AnatolJCardiol.2015.6483]

39 **Zhang Q**, Qin Y, Zhao DS, Zhao HP, Zhou L. Prognostic Value of Red Blood Cell Distribution Width on Bleeding Events in Nonvalvular Atrial Fibrillation Patients Taking Dabigatran (110 mg b.i.d.) after Catheter Ablation. *Cardiology* 2017; **136**: 215-221 [PMID: 27802430 DOI: 10.1159/000449461]

40 **Al-Kindi SG**, Kim CH, Morris SR, Freeman ML, Funderburg NT, Rodriguez B, McComsey GA, Dalton JE, Simon DI, Lederman MM, Longenecker CT, Zidar DA. Brief Report: Elevated Red Cell Distribution Width Identifies Elevated Cardiovascular Disease Risk in Patients With HIV Infection. *J Acquir Immune Defic Syndr* 2017; **74**: 298-302 [PMID: 27828877 DOI: 10.1097/QAI.0000000000001231]

41 **Liu T**, Shao Q, Korantzopoulos P, Miao S, Zhang Z, Xu G, Yuan R, Li G. Relation of red blood cell distribution width with $CHADS_2$ and CHA_2DS_2-VASc score in Chinese patients with non-valvular atrial fibrillation. *Int J Cardiol* 2017; **228**: 861-864 [PMID: 27889552 DOI: 10.1016/j.ijcard.2016.11.255]

42 **Saliba W**, Barnett-Griness O, Rennert G. Red cell distribution width and all-cause mortality in patients with atrial fibrillation: A cohort study. *J Arrhythm* 2017; **33**: 56-62 [PMID: 28217230 DOI: 10.1016/j.joa.2016.06.001]

43 **Kaya A**, Tukkan C, Alper AT, Gungor B, Ozcan KS, Tatlisu MA, Tekkesin AI, Karadeniz FO, Gok G, Kayapinar O. Increased levels of red cell distribution width is correlated with presence of left atrial stasis in patients with non-valvular atrial fibrillation. *North Clin Istanb* 2017; **4**: 66-72 [PMID: 28752145 DOI: 10.14744/nci.2017.72324]

44 **Cha MJ**, Lee HS, Kim HM, Jung JH, Choi EK, Oh S. Association between red cell distribution width and thromboembolic events in patients with atrial fibrillation. *Eur J Intern Med* 2017; **46**: 41-46 [PMID: 28781193 DOI: 10.1016/j.ejim.2017.07.028]

45 **Nam JH**, Park KH, Lee JH, Lee CH, Son JW, Kim U, Park JS, Shin DG. Discordant Relationships between Systemic Inflammatory Markers and Burden of Oxidative Stress in Patients with Atrial Fibrillation. *Korean Circ J* 2017; **47**: 752-761 [PMID: 28955393 DOI: 10.4070/kcj.2017.0024]

46 **Wasilewski J**, Pyka Ł, Hawranek M, Tajstra M, Skrzypek M, Wasiak M, Suliga K, Bujak K, Gąsior M. Prognostic value of red blood cell distribution width in patients with left ventricular systolic dysfunction: Insights from the COMMIT-HF registry. *Cardiol J* 2018; **25**: 377-385 [PMID: 28353308 DOI: 10.5603/CJ.a2017.0037]

47 **Cerşit S**, Kalçik M, Öcal L, Bayam E. Association between atrial fibrillation and red cell distribution width in patients with acute coronary syndrome. *Medeniyet Medical Journal* 2018; **33**: 89-93 [DOI: 10.5222/MMJ.2018.58234]

48 **Kılıcgedik A**, Naser A, Gurbuz AS, Kulahcioglu S, Bakal RB, Unkun T, Yilmaz F, Kahveci G, Kirma C. Red Cell Distribution Width with CHADS2 and CHA2DS2-VASc score is associated with Post-operative Atrial Fibrillation after Coronary Artery Bypass Grafting. *Heart Surg Forum* 2018; **21**: E170-E174 [PMID: 29893674 DOI: 10.1532/hsf.1886]

49 **Ozsin KK**, Sanri US, Toktas F, Yavuz S. Relationship between red cell distribution width and mean platelet volume with new onset atrial fibrillation afteroff-pump coronary artery bypass grafting. *Bratisl Lek Listy* 2018; **119**: 335-340 [PMID: 29947232 DOI: 10.4149/BLL_2018_063]

50 **Pilling LC**, Atkins JL, Kuchel GA, Ferrucci L, Melzer D. Red cell distribution width and common disease onsets in 240,477 healthy volunteers followed for up to 9 years. *PLoS One* 2018; **13**: e0203504 [PMID: 30212481 DOI: 10.1371/journal.pone.0203504]

51 **Han K**, Su X, Liu J, Yao F, Lu F. Red Cell Distribution Width as a Novel Marker for Different Types of Atrial Fibrillation in Low and High Altitude. *Cardiol Res Pract* 2019; **2019**: 6291964 [PMID: 30984423 DOI: 10.1155/2019/6291964]

52 **Jurin I**, Hadžibegović I, Durlen I, Jakšić Jurinjak S, Mišković D, Ajduk M, Jerkić H, Letilović T. Left atrium size and red cell distribution width predict atrial fibrillation progression from paroxysmal or persistent to permanent. *Acta Clin Belg* 2019; 1-7 [PMID: 30950766 DOI: 10.1080/17843286.2019.1599173]

53 **Li H**, Gu Y, Liu M, Wang X, Chi VTQ, Zhang Q, Liu L, Meng G, Yao Z, Wu H, Bao X, Zhang S, Kumari S, Sun S, Zhou M, Jia Q, Song K, Wu Y, Liu T, Niu K. The relationship between red blood cell distribution width and atrial fibrillation in Asian population: A cross-sectional study. *Pacing Clin Electrophysiol* 2019; **42**: 1197-1203 [PMID: 31397913 DOI: 10.1111/pace.13776]

54 **Shao Q**, Korantzopoulos P, Letsas KP, Tse G, Hong J, Li G, Liu T. Red blood cell distribution width as a predictor of atrial fibrillation. *J Clin Lab Anal* 2018; **32**: e22378 [PMID: 29315856 DOI: 10.1002/jcla.22378]

55 **Weymann A**, Ali-Hasan-Al-Saegh S, Popov AF, Sabashnikov A, Mirhosseini SJ, Liu T, Tse G, Lotfaliani M, Ghanei A, Testa L, D'Ascenzo F, Benedetto U, Dehghan H, Roever L, Sá MPBO, Baker WL, Yavuz S, Zeriouh M, Mashhour A, Nombela-Franco L, Jang JS, Meng L, Gong M, Deshmukh AJ, Palmerini T, Linde C, Filipiak KJ, Biondi-Zoccai G, Calkins H, Stone GW. Haematological indices as predictors of atrial fibrillation following isolated coronary artery bypass grafting, valvular surgery, or combined procedures: a systematic review with meta-analysis. *Kardiol Pol* 2018; **76**: 107-118 [PMID: 28980298 DOI: 10.5603/KP.a2017.0179]

56 **Jagannathan-Bogdan M**, Zon LI. Hematopoiesis. *Development* 2013; **140**: 2463-2467 [PMID: 23715539 DOI: 10.1242/dev.083147]

57 **Alameddine AK**, Visintainer P, Alimov VK, Rousou JA. Blood transfusion and the risk of atrial fibrillation after cardiac surgery. *J Card Surg* 2014; **29**: 593-599 [PMID: 24965706 DOI: 10.1111/jocs.12383]

58 **Ali AN**, Athavale NV, Abdelhafiz AH. Anemia: An Independent Predictor Of Adverse Outcomes In Older Patients With Atrial Fibrillation. *J Atr Fibrillation* 2016; **8**: 1366 [PMID: 27909494 DOI: 10.4022/jafib.1366]

59 **Lippi G**, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009; **133**: 628-632 [PMID: 19391664 DOI: 10.1043/1543-2165-133.4.628]

60 **Hu YF**, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol* 2015; **12**: 230-243 [PMID: 25622848 DOI: 10.1038/nrcardio.2015.2]

61 **Ghaffari S**. Oxidative stress in the regulation of normal and neoplastic hematopoiesis. *Antioxid Redox Signal* 2008; **10**: 1923-1940 [PMID: 18707226 DOI: 10.1089/ars.2008.2142]

62 **Yang KC**, Dudley SC. Oxidative stress and atrial fibrillation: finding a missing piece to the puzzle. *Circulation* 2013; **128**: 1724-1726 [PMID: 24030497 DOI: 10.1161/CIRCULATIONAHA.113.005837]

63 **McManus DD**, Saczynski JS, Ward JA, Jaggi K, Bourrell P, Darling C, Goldberg RJ. The Relationship Between Atrial Fibrillation and Chronic Kidney Disease : Epidemiologic and Pathophysiologic Considerations for a Dual Epidemic. *J Atr Fibrillation* 2012; **5**: 442 [PMID: 28496745 DOI: 10.4022/jafib.442]

64 **Hirayama T**, Roberts D, Allers M, Belboul A, al-Khaja N, William-Olsson G. Association between arrhythmias and reduced red cell deformability following cardiopulmonary bypass. *Scand J Thorac Cardiovasc Surg* 1988; **22**: 179-180 [PMID: 3406694 DOI: 10.3109/14017438809105954]

65 **Patel KV**, Mohanty JG, Kanapuru B, Hesdorffer C, Ershler WB, Rifkind JM. Association of the red cell distribution width with red blood cell deformability. *Adv Exp Med Biol* 2013; **765**: 211-216 [PMID: 22879035 DOI: 10.1007/978-1-4614-4989-8_29]

66 **Tziakas D**, Chalikias G, Grapsa A, Gioka T, Tentes I, Konstantinides S. Red blood cell distribution width: a strong prognostic marker in cardiovascular disease: is associated with cholesterol content of erythrocyte membrane. *Clin Hemorheol Microcirc* 2012; **51**: 243-254 [PMID: 22277951 DOI: 10.3233/CH-2012-1530]

67 **Tziakas DN**, Chalikias GK, Stakos D, Tentes IK, Papazoglou D, Thomaidi A, Grapsa A, Gioka G, Kaski JC, Boudoulas H. Independent and additive predictive value of total cholesterol content of erythrocyte membranes with regard to coronary artery disease clinical presentation. *Int J Cardiol* 2011; **150**: 22-27 [PMID: 20223535 DOI: 10.1016/j.ijcard.2010.02.022]

68 **Willeit K**, Kiechl S. Atherosclerosis and atrial fibrillation--two closely intertwined diseases. *Atherosclerosis* 2014; **233**: 679-681 [PMID: 24569021 DOI: 10.1016/j.atherosclerosis.2013.11.082]

69 **Fujii T**, Nishigaki R, Kawahara K, Yamada N, Onda M, Yokoyama M, Naito Z, Asano G, Shimizu-Suganuma M, Shichinohe K. Ultrastructural changes and immunohistochemical localization of advanced glycation end products in the heart of streptozotocin-treated Mongolian gerbils. *Med Electron Microsc* 1999; **32**: 43-49 [PMID: 11810424 DOI: 10.1007/s007959900021]

70 **Shimano M**, Tsuji Y, Inden Y, Kitamura K, Uchikawa T, Harata S, Nattel S, Murohara T. Pioglitazone, a peroxisome proliferator-activated receptor-gamma activator, attenuates atrial fibrosis and atrial fibrillation promotion in rabbits with congestive heart failure. *Heart Rhythm* 2008; **5**: 451-459 [PMID: 18313605 DOI: 10.1016/j.hrthm.2007.12.010]

71 **Chen JY**, Zhang AD, Lu HY, Guo J, Wang FF, Li ZC. CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. *J Geriatr Cardiol* 2013; **10**: 258-266 [PMID: 24133514 DOI: 10.3969/j.issn.1671-5411.2013.03.004]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 December 26; 11(12): 305-315

DOI: 10.4330/wjc.v11.i12.305

ISSN 1949-8462 (online)

MINIREVIEWS

Myocardial infarction with non-obstructive coronary arteries: A comprehensive review and future research directions

Rafael Vidal-Perez, Charigan Abou Jokh Casas, Rosa Maria Agra-Bermejo, Belén Alvarez-Alvarez, Julia Grapsa, Ricardo Fontes-Carvalho, Pedro Rigueiro Veloso, Jose Maria Garcia Acuña, Jose Ramon Gonzalez-Juanatey

ORCID number: Rafael Vidal-Perez (0000-0001-9944-8363); Charigan Abou Jokh Casas (0000-0002-2005-6322); Rosa Maria Agra-Bermejo (0000-0002-7244-9099); Belén Alvarez-Alvarez (0000-0003-0851-7728); Julia Grapsa (0000-0003-4620-6234); Ricardo Fontes-Carvalho (0000-0003-2306-8393); Pedro Rigueiro Veloso (0000-0003-1879-6601); Jose Maria Garcia Acuña (0000-0003-0119-1710); Jose Ramon Gonzalez-Juanatey (0000-0001-9681-3388).

Author contributions: Vidal-Perez R and Abou Jokh Casas C contributed equally to this work; Vidal-Perez R and Abou Jokh Casas C designed, edited and wrote the paper; Agra-Bermejo RM, Alvarez -Alvarez B, Grapsa J, Fontes-Carvalho R, Rigueiro Veloso P, Garcia Acuña JM and Gonzalez-Juanatey JR contributed to the critical revision and editing of the paper.

Conflict-of-interest statement: No potential conflicts of interest.

Open-Access: This is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

Rafael Vidal-Perez, Charigan Abou Jokh Casas, Rosa Maria Agra-Bermejo, Belén Alvarez-Alvarez, Pedro Rigueiro Veloso, Jose Maria Garcia Acuña, Jose Ramon Gonzalez-Juanatey, Cardiology Department, Hospital Clinico Universitario de Santiago, Santiago de Compostela 15706, Spain

Rosa Maria Agra-Bermejo, Belén Alvarez-Alvarez, Pedro Rigueiro Veloso, Jose Maria Garcia Acuña, Jose Ramon Gonzalez-Juanatey, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Santiago de Compostela 15706, Spain

Julia Grapsa, Cardiology Department, St Bartholomew Hospital, Barts Health Trust, London EC1A 7BE, United Kingdom

Ricardo Fontes-Carvalho, Cardiology Department, Centro Hospitalar Gaia, Vila Nova Gaia 4434-502, Portugal

Ricardo Fontes-Carvalho, Faculty of Medicine University of Porto, Porto 4200-319, Portugal

Corresponding author: Rafael Vidal-Perez, MD, PhD, Doctor, Reader (Associate Professor), Staff Physician, Heart failure unit, Cardiology department, USC University Hospital Complex, Travesía da Choupana s/n, Santiago de Compostela, A Coruña 15706, Spain. rafavidal@hotmail.com

Telephone: +34-981950757

Abstract

Acute coronary syndromes constitute a variety of myocardial injury presentations that include a subset of patients presenting with myocardial infarction with non-obstructive coronary arteries (MINOCA). This acute coronary syndrome differs from type 1 myocardial infarction (MI) regarding patient characteristics, presentation, physiopathology, management, treatment, and prognosis. Two-thirds of MINOCA subjects present ST-segment elevation; MINOCA patients are younger, are more often female and tend to have fewer cardiovascular risk factors. Moreover, MINOCA is a working diagnosis, and defining the aetiologic mechanism is relevant because it affects patient care and prognosis. In the absence of relevant coronary artery disease, myocardial ischaemia might be triggered by an acute event in epicardial coronary arteries, coronary microcirculation, or both. Epicardial causes of MINOCA include coronary plaque disruption, coronary dissection, and coronary spasm. Microvascular MINOCA mechanisms involve microvascular coronary spasm, takotsubo syndrome (TTS), myocarditis, and coronary thromboembolism. Coronary angiography with non-significant coronary stenosis and left ventriculography are first-line tests in the differential study of MINOCA patients.

the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited Manuscript

Received: March 12, 2019
Peer-review started: March 15, 2019
First decision: June 6, 2019
Revised: September 17, 2019
Accepted: October 27, 2019
Article in press: October 27, 2019
Published online: December 26, 2019

P-Reviewer: Li JJ, Lin GM, Petix NR
S-Editor: Tang JZ
L-Editor: A
E-Editor: Zhang YL

The diagnostic arsenal includes invasive and non-invasive techniques. Medical history and echocardiography can help indicate vasospasm or thrombosis, if one finite coronary territory is affected, or specify TTS if apical ballooning is present. Intravascular ultrasound, optical coherence tomography, and provocative testing are encouraged. Cardiac magnetic resonance is a cornerstone in myocarditis diagnosis. MINOCA is not a benign diagnosis, and its polymorphic forms differ in prognosis. MINOCA care varies across centres, and future multi-centre clinical trials with standardized criteria may have a positive impact on defining optimal cardiovascular care for MINOCA patients.

Key words: Myocardial infarction; Non-obstructive coronary; Myocardial infarction with non-obstructive coronary arteries; Management; Prognosis

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Myocardial infarction with non-obstructive coronary arteries (MINOCA) differs from type 1 myocardial infarction regarding patient characteristics, presentation, physiopathology, management, treatment, and prognosis. In the absence of relevant coronary artery disease, myocardial ischaemia might be triggered by an acute event in epicardial coronary arteries, coronary microcirculation, or both. Epicardial causes of MINOCA include coronary plaque disruption, coronary dissection, and coronary spasm. Diagnostic strategies include invasive and non-invasive techniques recently embracing intravascular ultrasound and cardiac magnetic resonance. MINOCA is not a benign diagnosis, and its polymorphic forms differ in prognosis.

Citation: Vidal-Perez R, Abou Jokh Casas C, Agra-Bermejo RM, Alvarez-Alvarez B, Grapsa J, Fontes-Carvalho R, Rigueiro Veloso P, Garcia Acuña JM, Gonzalez-Juanatey JR. Myocardial infarction with non-obstructive coronary arteries: A comprehensive review and future research directions. *World J Cardiol* 2019; 11(12): 305-315
URL: https://www.wjgnet.com/1949-8462/full/v11/i12/305.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i12.305

INTRODUCTION

Remarkable progress in medicine regarding the pathogenesis of heart disease has produced lifesaving and life-extending therapies impacting ischaemic patients worldwide. The definition of angina pectoris is over two hundred years old, but the controversy about the aetiologic role of coronary arteries has never ceased to hold interest. Acute myocardial infarction (MI) without significant coronary artery disease (CAD) was initially described almost 80 years ago by Gross and Sternberg, whereas the term myocardial infarction with non-obstructive coronary arteries (MINOCA) is recent[1,2].

The diagnosis of an acute coronary syndrome should be established according to the fourth universal definition of MI, which is when there is evidence of acute myocardial injury accompanied by clinical data suggesting acute myocardial ischaemia such as relevant symptoms, new ischaemic electrocardiogram (ECG) changes, loss of viable myocardium present in imaging, or identification of coronary thrombus. Several diverse definitions of MI have been used, leading to unbalanced criteria and confusion. Thus, a general universal definition of MI was agreed upon for the first time over 50 years ago with the collaboration of multiple groups that were initially created for epidemiological reasons. With the discovery of cardiac biomarkers, the diagnosis of MI has been simplified, but because an increase in cardiac biomarkers is an entity by itself, it is not pathognomonic of an acute coronary syndrome in isolation. Elevation of cardiac biomarkers, such as cardiac troponin I and T, represents injury to myocardial cells, but such increases do not reflect the underlying pathophysiology because they can arise in a variety of situations, including normal hearts. This variability highlights the need for a global uniform definition of MI and myocardial injury[3-5].

There are multiple classifications of MI. Classically, for discrimination of immediate or delayed treatment strategies, patients who develop new ST-segment elevation in two contiguous leads or new bundle branch block with ischaemic alterations are

designated ST-elevation myocardial infarction (STEMI) patients, whereas the subgroup without ST-segment elevation is diagnosed as non-ST elevation MI (NSTEMI). In addition to those two categories, MI can be classified pathophysiologically[4,5]. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis corresponds to type 2 MI; by definition, acute atherothrombotic plaque rupture excludes type 2 MI. Type 1 MI and MINOCA are two separate entities with different underlying mechanisms, management, and prognosis[5,6].

MINOCA is diagnosed in a patient with features of MI with non-obstructive coronary arteries on angiography, is defined as no coronary artery stenosis ≥ 50% in any potential infarct-related artery and is characterized by the absence of a clinically specific cause of the acute presentation. Clinical criteria and biomarker behaviour of MINOCA remain similar to other acute coronary events[3,6].

PREVALENCE AND CLINICAL FEATURES

MINOCA is not an uncommon presentation of acute coronary syndromes. Large MI registries reflect the universal nature of MINOCA with the prevalence ranging between 5% and 25% in different series, with 11% in a recent prospective observational study[7-9]. Throughout the years, MINOCA has remained prevalent with an increasing incidence, as was observed in a Spanish registry[10]. MINOCA patient characteristics differ from those of other Myocardial Infarction and Coronary Artery Disease (MI-CAD) patients because MINOCA subjects are younger, are more often female, and tend to have fewer traditional cardiovascular risk factors. In the VIRGO study, women had 5-fold higher odds of presenting with MINOCA than men; non-white patients also had increased rates of MINOCA than white patients. Pasupathy *et al*[11] reported that MINOCA patients were less likely to have hyperlipidaemia, whereas a similar distribution was observed regarding hypertension, diabetes mellitus, smoking, and family history of premature coronary disease. Electrocardiographic patterns also differ, generally presenting as STEMI or NSTEMI, with two-thirds of patients having the latter. It has also been suggested that hormonal changes, such as the time of menarche and menopause, may also play a role in MINOCA.

CLASSIFICATION ACCORDING TO PATHOPHYSIOLOGY

In the absence of relevant CAD, myocardial ischaemia may be triggered by a disorder of epicardial coronary arteries and/or malfunction in the coronary microcirculation (Table 1). Both have multiple presentations[7,8].

Epicardial causes of MINOCA

Coronary plaque disruption: Many atherosclerotic plaques are positively remodelled, expand outward, and have a lipid-rich body and thin fibrous cap, making them vulnerable to rupture. The transient and partial thrombosis in this type of plaque causes distal thrombus embolization, with possible superimposed vasospasm, and might be responsible for MINOCA; this mechanism resembles type 1 MI. MINOCA represents 5%-20% of all type 1 MI. Since coronary angiography cannot evaluate the vascular lumen, intracoronary imaging modalities such as intravascular ultrasound (IVUS) might play a determinant role in evaluating the lesion. Ouldzein *et al*[12] performed IVUS in MINOCA patients to evaluate the morphological and quantitative characteristics of the culprit lesion and subsequently classified subjects according to the presence or absence of plaque rupture; the frequency of ruptured plaques in MI patients was estimated to be between 20% and 40%, and patients with plaque rupture had increased plaque burden, plaque volume and positive arterial remodelling.

Coronary dissection: Coronary dissection without visible luminal obstruction and coronary artery intramural haematomas constitute 25% of MI in women younger than 50 years of age. IVUS is a cornerstone in the assessment of coronary dissection. The physiology of this entity is unclear; however, fibromuscular dysplasia is thought to be related. This presentation has a high rate of recurrence[8,13].

Coronary artery spasm: Coronary artery spasm (CAS) represents between 3% and 95% of MINOCA cases depending on the registry. Positive provocative tests with intracoronary, adenosine or ergonovine portend a worse prognosis. The diagnosis does not require confirmation of epicardial coronary spasm, and these tests should only be performed by experienced teams because they have a potential risk of

Table 1 Myocardial infarction with non-obstructive coronary arteries classification, management overview, prevalence and suggested therapy

Mechanism	Diagnosis	Prevalence in coronary syndromes	Therapy
Epicardial causes			
Coronary artery disease	IVUS/OCT, FFR/iFR	5%-20% of MI	Antiplatelet therapy, statins, ACEi/ARB, beta-blockers
Coronary dissection	IVUS/OCT	25% of MI in women under 50 yr of age	Beta-blocker and simple antiplatelet therapy
Coronary artery spasm	Intracoronary nitrates, intracoronary Ach or ergonovine test by experienced teams	3%–95% of MI depending on the registry	Calcium antagonists, nitrates
Microvascular causes			
Microvascular coronary spasm	Objective evidence of ischaemia (ECG, LV wall motion abnormalities, PET). Impaired microvascular function (CFR, intracoronary Ach test, abnormal CMR, slow coronary flow)	As high as 25% depending on the registry	Beta-blockers and nitrates, calcium antagonist, possibly ranolazine
Takotsubo syndrome	Ventriculography, echocardiography, troponin, B-natriuretic peptide, CMR	1%-3% of general STEMI, 5%-6% women with STEMI, concomitant CAD 10%-29%	Heart failure treatment, mechanical support in cardiogenic shock
Myocarditis	CMR, EMB, viral serologies, high c-reactive protein	33% of MINOCA when determined by CMR	Heart failure treatment if complication, autoimmune therapy in autoimmune forms
Coronary embolism	History of potential thromboembolic sources, thrombophilia screen, TTE, TOE, bubble contrast echography	2.9% MI	Antiplatelet therapy, anticoagulation, transcatheter closure or surgical repair

MINOCA: Myocardial infarction with non-obstructive coronary arteries; MI: Myocardial infarction; CAD: Coronary artery disease; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; CMR: Cardiac magnetic resonance; STEMI: ST segment elevation myocardial infarction; PET: Positron emission tomography; FFR: Fractional flow reserve; ECG: Electrocardiogram; iFR: Instantaneous wave-free ratio; EMB: Endomyocardial biopsies; ACEi: Angiotensin-converting-enzyme inhibitors.

arrhythmic complications. Positive testing has been associated with a higher occurrence of death from any cause and cardiac death during follow up, a higher rate of MI readmission and inferior control of angina symptoms; epicardial spasm also showed worse clinical outcomes than microvascular spasm[14].

Microvascular causes of MINOCA

Microvascular coronary spasm: Microcoronary microvascular spasm, also referred to as Syndrome X, can occur in up to 25% of MINOCA patients in some registries and is the cause of persistent angina in up to 36% MINOCA subjects. Catecholamines and endothelin exert transient vasoconstrictive effects primarily in the coronary microvasculature, reducing microvascular blood flow in a transient manner. Objective documentation of myocardial ischaemia should be sought. The presence of four clinical criteria for microvascular angina accomplished a definitive diagnosis: Symptoms of myocardial ischaemia, the absence of obstructive CAD [< 50% diameter reduction in fractional flow reserve (FFR) > 0.80], objective evidence of ischaemia (ECG ischaemic changes, wall motion or perfusion abnormalities), and evidence of impaired coronary microvascular function. This last parameter includes having a coronary flow reserve ≤ 2-2.5, coronary microvascular spasm (reproduction of symptoms, ischaemic ECG shifts) without epicardial spasm in acetylcholine testing, abnormal coronary microvascular resistance indices, or coronary slow flow phenomenon. Diagnostic techniques for the evaluation of microvascular disease include invasive and non-invasive measures. Positron emission tomography (PET) is the most accurate non-invasive outlook of coronary vasomotor function; cardiac magnetic resonance (CMR) can also be applied, although post-processing is technically challenging. Invasive techniques include invasive coronary flow reserve, more recent FFR, and instantaneous wave-free ratio with certain limitations[15]. Plaque burden can be present or absent in MINOCA patients, and a broad spectrum of subtypes have been described, but these usually overlap. The guarded prognosis of these patients justifies an invasive approach[16].

Takotsubo syndrome: This stress cardiomyopathy represents 1%-3% of all STEMI, with 5%-6% prevalence in female subgroups, and is characterized by apical

ballooning of the left ventricle in the absence of occlusive CAD; although concomitant CAD is described in 10%-29% of Takotsubo syndrome (TTS) cases. The proposed Mayo clinical criteria include transient left ventricle mid-segment wall hypokinesis, akinesis or dyskinesis that extends beyond one vascular territory, absence of significant CAD, new electrocardiographic changes or modest elevation in cardiac biomarkers, and exclusion of pheochromocytoma or myocarditis[17,18]. The more recent international TTS diagnostic criteria (interTAK Diagnostic Criteria) vary from the Mayo criteria by recognizing pheochromocytoma as a secondary cause of TTS by stating that the presence of CAD should not be an exclusion and that cases with wall motion abnormalities restricted to one vascular territory should not be excluded (Table 2 and 3)[19]. The causes and aetiologic mechanisms of TTS are complex and still in debate, but reversible coronary microvascular vasoconstriction is a common mechanism in apical ballooning[20]. Diagnostic tools in TTS diagnosis include ventriculography, transthoracic echocardiogram with adenosine and CMR. In the absence of significant CAD, ballooning ventriculography allows a diagnosis. Contrast echocardiography with adenosine may prove microvascular constriction. CMR provides additional findings suggesting takotsubo; the hyperintense signal on T2 sequences, diffuse or transmural oedema, dysfunctional ventricular contraction matching the TTS typical ballooning, and alterations not restricted to a particular vascular territory in the absence of myocardial necrosis[8,21]. Strain echocardiography and F-18 fluorodeoxyglucose positron emission have shown promising results in the diagnosis of TTS and may play a role in the future[22].

Myocarditis: This polymorphic inflammatory disease can mimic many conditions and can have a prevalence of approximately 33% among MINOCA patients when determined by CMR imaging[24]. Young patients and high C-reactive protein findings were associated with myocarditis, while male sex, previously treated hyperlipidaemia and high troponin ratio were correlated with type 1 MI. Myocarditis also accounts for 5%-12% of young athlete sudden cardiovascular death[25]. The most common pathogens identified in patients are human herpesvirus 6 and parvovirus B19. Diagnosis of myocarditis is challenging; thus, given the poor yield of endomyocardial biopsies (EMB) and viral serologies, standard criteria such as the European Society of Cardiology 2013 Myocarditis Task Force criteria were established (Table 4)[7]. Certain diagnoses and aetiologies of myocarditis require EMB (histology, immunohistology, infectious agents by polymerase chain reaction). CMR imaging should be included in the workup of myocarditis; it provides tissue characterization but does not identify the underlying cause. Late gadolinium enhancement is observed in the majority of patients and can have several phenotypes with different prognostic implications[26].

Coronary embolism: Coronary embolism (CE) can affect coronary microcirculation and/or angiographically visible epicardial vessels. Coronary emboli can arise from coronary or systemic arterial thrombi, and coronary thrombosis may be related to thrombotic disorders. The prevalence of de novo CE MINOCA can be 2.9%. Atrial fibrillation is the most common cause of CE. Case definition can be held according to the National Cerebral and Cardiovascular Center criteria for the diagnosis of CE; the 3 major criteria include angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components, concomitant multivessel CE and concomitant systemic embolization. Minor criteria include CAD with stenosis < 25%, evidence of embolic source detected by imaging, and coexistence of potential thromboembolic disease. Paradoxical embolism due to right-left shunts is a rare cause of MINOCA, and treatment includes trans-catheter device closure or surgical repair. Transthoracic, transoesophageal, and contrast-enhanced echocardiography are the cornerstone methods for uncovering cardiac sources of embolism[8,27].

MINOCA with uncertain etiology

CMR imaging is a cornerstone in determining underlying myocardial tissue pathology. However, 8%-67% of MINOCA patients have no late gadolinium enhancement, myocardial oedema, or wall motion alterations. Vasospastic angina, coronary plaque disease or CE can have normal CMR findings; in these cases, intracoronary imaging may help shed light on the underlying ischaemic trigger. IVUS and CMR provide complementary mechanistic insights into MINOCA patients and may be useful in identifying potential causes and therapies[28].

MINOCA THERAPY ACCORDING TO PATHOPHYSIOLOGY

Epicardial causes of MINOCA

Coronary plaque disruption: Dual antiplatelet treatment for 12 mo is recommended if

Table 2 International takotsubo syndrome diagnostic criteria

Diagnostic criteria
Left ventricular dysfunction usually extending beyond a single coronary territory.
Sometimes triggered by emotional, physical or combined stress.
Acute neurologic disorders, including pheochromocytoma, may become triggers.
New ECG abnormalities. Rare cases can present with without ECG shifts.
Moderate troponin elevation. Usually, significantly high brain natriuretic peptide.
Can have concomitant CAD.
No evidence of infectious myocarditis usually excluded by CMR.
Mostly present in postmenopausal women.

CAD: Coronary artery disease; CMR: Cardiac magnetic resonance; ECG: Electrocardiogram.

allowed by haemorrhage risk, followed by chronic single antiplatelet therapy and statins[8]. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blocker treatment have the same indication as STEMI and NSTEMI guidelines[4,5].

Coronary dissection: There is no effective treatment to reduce long-term risk. A medical strategy is recommended for coronary interventions, and stenting may cause propagation of the dissection. A conservative strategy along with beta-blockers and single antiplatelet treatment is recommended[8,13].

CAS: Chronic medical treatment includes calcium channel blockers and nitrates. Calcium antagonist dose reduction or discontinuation was associated with worse prognosis regarding mortality, supporting the role of epicardial spasm in the occurrence of adverse events[8].

Microvascular causes of MINOCA

Microvascular coronary spasm: There are no specific therapies for microvascular dysfunction, and management of underlying cardiovascular risk factors is recommended. Traditional anti-ischaemic drugs, such as beta-blockers and nitrates, should be first-line therapy; calcium antagonists can be added to treat refractory angina and are recommended when vasomotor tone is increased. The data on ranolazine for angina relief are controversial in this subset[9,15].

TTS: There are no randomized trials to guide evidence-based treatment. Empiric strategies include cardio-selective beta-blockers, avoidance of inotropes, angiotensin-converting enzyme inhibitors for persistent myocardial dysfunction, mechanical support devices in cardiogenic shock, and antiplatelet treatment with statins if associated with CAD[21].

Myocarditis: Myocarditis treatment differs from that of coronary disease because it does not require anti-ischaemic therapies. Myocarditis generally has a favourable prognosis resolving in 2 to 4 wk, while a minor subgroup develops cardiovascular complications such as heart failure and should be treated correspondingly. Autoimmune forms have negative infection findings on biopsy, and specific autoimmune therapy is required in these cases[7].

CE: Standard treatment of thromboembolic events remains individualized. Multiple factors play a role in this entity, such as the time of presentation and the presence or absence of multiple embolic sites. Patients with paroxysmal embolism in the presence of atrial septal defects require percutaneous or surgical closure. These patients have a high rate of recurrence and major adverse cardiovascular events (MACEs) in the follow-up[8,27].

DETERMINING THE CAUSE

MINOCA patients are a conundrum for clinicians; therefore, a systematic global approach should be pursued, and an attempt must be made to determine the specific aetiologic mechanism as prognosis and management vary. The diagnostic arsenal includes invasive and non-invasive techniques. Medical history can suggest a diagnosis of vasospasm angina if the patient has a chronic pattern of recurrent

Table 3 International takotsubo syndrome diagnostic score

Criteria	Points	Diagnosis probability
Female sex	25 points	≤ 70 points
Emotional stress	24 points	Low/intermediate
Physical stress	13 points	TTS probability
No ST-segment depression	12 points	
Psychiatric disorders	11 points	> 70 points
Neurologic disorders	9 points	High TTS probability
QTc prolongation	6 points	

TTS: Takotsubo syndrome.

episodic angina. Regional LV motion alterations corresponding to a finite vascular territory suggest vasospasm or thrombosis. Apical ballooning suggests TTS. A history of atrial fibrillation, dilated cardiomyopathy, prosthetic heart valves, infective endocarditis, atrial myxoma, and patent foramen oval suggest CE. IVUS or optical coherence tomography are encouraged in non-severe coronary angiography findings with less than 50% luminal reduction; if intracoronary imaging reveals normal findings, provocative functional testing is recommended. Transthoracic or transoesophageal echocardiography, LV ventriculography, and CMR are other well-documented techniques. The test flow-chart does not have a specific order and should be performed according to clinical suspicion[4,7,8]. In Figure 1, we summarize our diagnostic and therapeutic workup for MINOCA management.

MINOCA PROGNOSIS

The prognosis of MINOCA patients is heterogeneous and not benign. Patients should be carefully informed about their condition and must not be inaccurately reassured about a favourable course. Because of the aetiological heterogeneity, the extent of MI damage and different inclusion criteria, registries reporting MINOCA prognosis show diverse data regarding major cardiac adverse events during hospitalization and follow-up[10]. In the VIRGO study, similar proportions of cardiac arrest, reduced ejection fraction, and heart failure were observed in patients with MINOCA and MI-CAD, whereas the mortality rates during follow-up were not significantly different. According to a meta-analysis of eight studies that reported all-cause mortality in patients with MINOCA, both in-hospital and 12-month mortality were comparable to MI-CAD[9].

Moreover, different secondary prevention strategies at discharge have been published with discrepancies regarding medical treatment with proven prognostic value, thus possibly interfering with prognosis. In addition, it may be speculated that within the vast spectrum of MINOCA patients, the multiple categories can have dissimilar prognoses and may be under- or overestimated by grouping them together.

Nordenskjöld *et al*[29] conducted an observational study with 9092 MINOCA subjects and found that 24% of the patients presented a new MACE and 14% died during follow-up. Multiple predictors for MACEs and death among MINOCA patients are similar to those previously shown to predict new events in MI-CAD patients, some of which are older age, diabetes, hypertension, current smoking, previous MI, previous stroke, and reduced LVEF. In this study, a cholesterol paradox was observed, where low levels of total cholesterol were significantly associated with the composite endpoint of MACEs and long-term mortality; this phenomenon was primarily observed in the statin-naive group who received statin treatment after MINOCA.

Nordenskjöld *et al*[30] also studied the possible mechanisms and prognosis for reinfarction in MINOCA patients, describing an average time to readmission of 17 mo. With a median follow-up of 38 mo, mortality was similar whether the reinfarction event was MINOCA or MI-CAD. A progression of coronary stenosis is described in approximately half of the patients, and thus, the performance of another angiography in the MI event following MINOCA was relevant; all-cause mortality and cardiovascular mortality were higher among patients who did not undergo a new coronary angiography than among those who did. Repeated episodes of MINOCA are not harmless.

In a recent study of the Chinese population, MACEs in MINOCA patients at the 1-

Table 4 European Society of Cardiology 2013 Myocarditis Task Force definition of clinically suspected myocarditis

Presence of ≥ 1 clinical presentation and ≥ 1 diagnostic criteria:
Clinical presentation:
Acute coronary-like syndrome
New onset or worsening unexplained heart failure
Chronic unexpected heart failure over 3 mo duration
Life-threatening unexplained conditions (including arrhythmias, aborted sudden death, cardiogenic shock)
Diagnostic criteria:
ECG/Holter/stress test shifts: Any degree atrioventricular block or bundle branch block, ST/T or Q wave changes, sinus arrest, cardiac arrest rhythms, low voltage, frequent premature beat or supraventricular tachycardia
Elevated cardiac troponins
Functional and structural abnormalities on cardiac imaging
Oedema and/or late gadolinium enhancement of myocarditis pattern in CMR

CMR: Cardiac magnetic resonance; ECG: Electrocardiogram.

year follow-up were lower than those in MI-CAD patients. Multi-factorial survival analysis showed that older age (≥ 60 years old), female sex, atrial fibrillation, and reduced LVEF are independent risk factors for MACEs in MINOCA patients within one year[31]. The atherosclerotic burden in MINOCA patients may also have an additional role in their prognosis and represents a promising research target in the following years[23].

TTS is a special subset of MINOCA patients with regard to triggers that can be identified in two-thirds of cases and should be exposed because they can influence prognosis. Generally, long-term outcomes of TTS are comparable to those of age- and sex-matched MI patients. TTS related to emotional stress have a favourable short- and long-term prognosis, whereas those secondary to physical stress or medical conditions such as neurological events are associated with higher mortality in follow up; patients with neurological triggers tend to have higher mortality[23].

KNOWLEDGE GAPS AND FUTURE PERSPECTIVE

The present study shows a knowledge gap and heterogeneous management of MINOCA patients that need attention. MINOCA is a polymorphic aggregate with much more to be uncovered, with special emphasis on the pathophysiology. Standard MI protocols do not apply systematically to all MINOCA patients. Variations in revascularization strategies and the use of proven medical therapies exist[9]. The era of eyeball angiographic quantification is evolving, and measuring only the degree of stenosis is insufficient. The plaque burden is multi-faceted, and different plaque content, volume, and distribution along with luminal stenosis can have a divergent clinical impact and prognosis[29]. There is a demand for the use of standard criteria in MINOCA research for effective worldwide communication, as such criteria may help understand and compare international registries. Standardized criteria may provide an investigative structure for mechanistic, diagnostic, prognostic and clinical trial studies aimed at developing MINOCA evidence-based guidelines.

CONCLUSION

MINOCA should be considered a working diagnosis, and challenges must be overcome to identify its underlying cause because its polymorphic nature has various implications. MINOCA is a prevalent, not benign pathology, and misconceptions regarding this condition must be reviewed. Variable practice patterns and disparities in MINOCA care exist. Future multicentric clinical trials will have a strong impact and refine the optimal cardiovascular care of MINOCA patients.

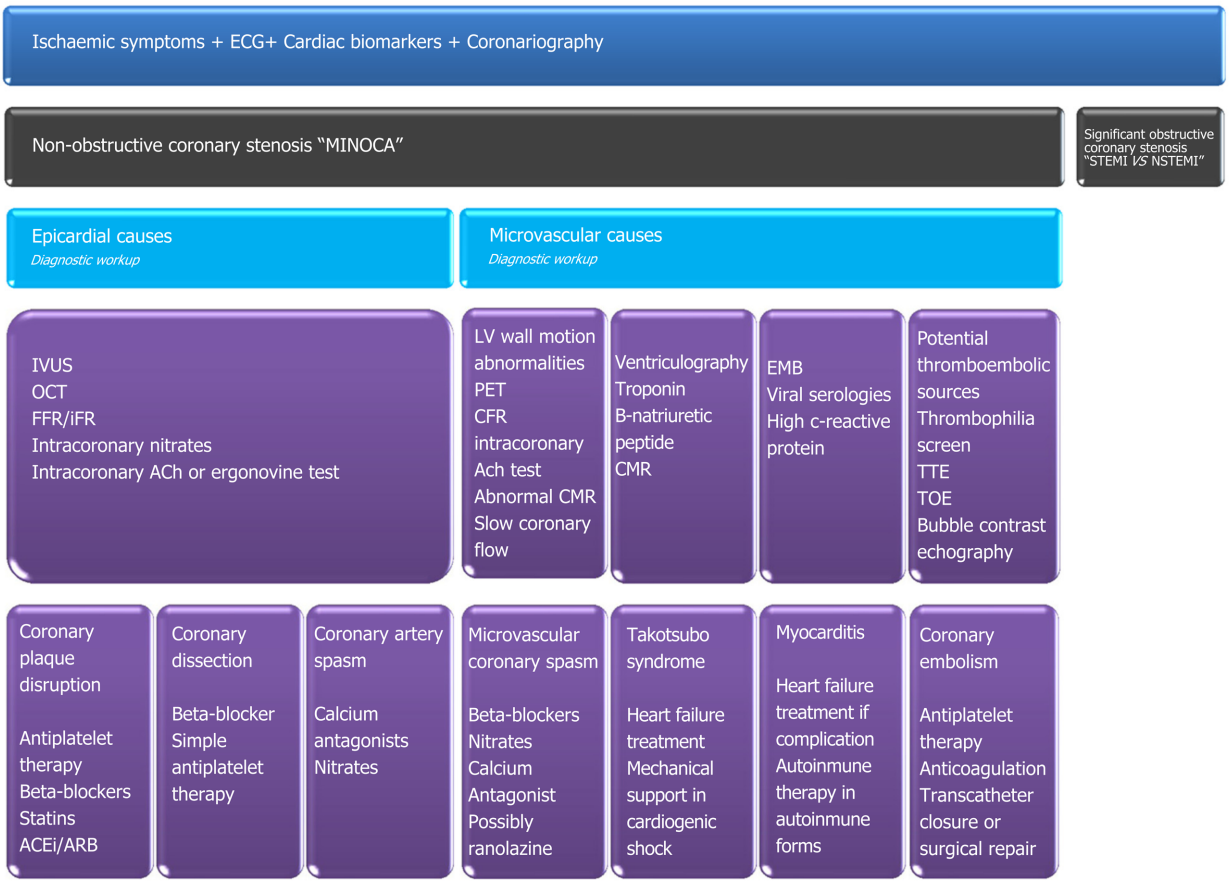


Figure 1 Diagnostic and therapeutic workup for myocardial infarction with non-obstructive coronary arteries. STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; Ach: Acetylcholine; CMR: Cardiac magnetic resonance; EMB: Endomyocardial biopsy; TTE: Transthoracic echocardiography; TOE: Transoesophageal echocardiography; ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin II receptor blockers; MINOCA: Myocardial infarction with non-obstructive coronary arteries; ECG: Electrocardiogram; iFR: Instantaneous wave-free ratio; OCT: Optical coherence tomography; FFR: Fractional flow reserve; IVUS: Intravascular ultrasound; PET: Positron emission tomography.

REFERENCES

1 **Gross H**, Sternberg WH. Myocardial infarction without significant lesions of coronary arteries. *Arch Intern Med (Chic)* 1939; **64**: 249–267 [DOI: 10.1001/archinte.1939.00190020035003]

2 **Alpert JS**, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; **36**: 959-969 [PMID: 10987628 DOI: 10.1016/s0735-1097(00)00804-4]

3 **Thygesen K**, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018; **72**: 2231-2264 [PMID: 30153967 DOI: 10.1016/j.jacc.2018.08.1038]

4 **Ibanez B**, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39**: 119-177 [PMID: 28886621 DOI: 10.1093/eurheartj/ehx393]

5 **Roffi M**, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 267-315 [PMID: 26320110 DOI: 10.1093/eurheartj/ehv320]

6 **Thygesen K**, Mair J, Katus H, Plebani M, Venge P, Collinson P, Lindahl B, Giannitsis E, Hasin Y, Galvani M, Tubaro M, Alpert JS, Biasucci LM, Koenig W, Mueller C, Huber K, Hamm C, Jaffe AS; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010; **31**: 2197-2204 [PMID: 20685679 DOI: 10.1093/eurheartj/ehq251]

7 **Agewall S**, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P; WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2017; **38**: 143-153 [PMID: 28158518 DOI: 10.1093/eurheartj/ehw149]

8 **Scalone G**, Niccoli G, Crea F. Editor's Choice- Pathophysiology, diagnosis and management of MINOCA: an update. *Eur Heart J Acute Cardiovasc Care* 2019; **8**: 54-62 [PMID: 29952633 DOI: 10.1177/2048872618782414]

9 **Safdar B**, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, Reynolds HR, Geda M, Bueno H, Dziura JD, Krumholz HM, D'Onofrio G. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. *J Am Heart Assoc* 2018; **7** [PMID: 29954744 DOI: 10.1161/JAHA.118.009174]

10 **Redondo-Diéguez A**, Gonzalez-Ferreiro R, Abu-Assi E, Raposeiras-Roubin S, Aidhodjayeva O, López-López A, Castiñeira-Busto M, Peña-Gil C, García-Acuña JM, González-Juanatey JR. Long-term Prognosis of Patients With Non-ST-segment Elevation Acute Myocardial Infarction and Coronary Arteries Without Significant Stenosis. *Rev Esp Cardiol (Engl Ed)* 2015; **68**: 777-784 [PMID: 25682572 DOI: 10.1016/j.rec.2014.09.022]

11 **Pasupathy S**, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation* 2015; **131**: 861-870 [PMID: 25587100 DOI: 10.1161/CIRCULATIONAHA.114.011201]

12 **Ouldzein H**, Elbaz M, Roncalli J, Cagnac R, Carrié D, Puel J, Alibelli-Chemarin MJ. Plaque rupture and morphological characteristics of the culprit lesion in acute coronary syndromes without significant angiographic lesion: analysis by intravascular ultrasound. *Ann Cardiol Angeiol (Paris)* 2012; **61**: 20-26 [PMID: 21903196 DOI: 10.1016/j.ancard.2011.07.011]

13 **Hayes SN**, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. *Circulation* 2018; **137**: e523-e557 [PMID: 29472380 DOI: 10.1161/CIR.0000000000000564]

14 **Montone RA**, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Cammà G, Lanza GA, Crea F. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018; **39**: 91-98 [PMID: 29228159 DOI: 10.1093/eurheartj/ehx667]

15 **Taqueti VR**, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018; **72**: 2625-2641 [PMID: 30466521 DOI: 10.1016/j.jacc.2018.09.042]

16 **Ong P**, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN; Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018; **250**: 16-20 [PMID: 29031990 DOI: 10.1016/j.ijcard.2017.08.068]

17 **Prasad A**, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008; **155**: 408-417 [PMID: 18294473 DOI: 10.1016/j.ahj.2007.11.008]

18 **Sachdev E**, Bairey Merz CN, Mehta PK. Takotsubo Cardiomyopathy. *Eur Cardiol* 2015; **10**: 25-30 [PMID: 30310419 DOI: 10.15420/ecr.2015.10.01.25]

19 **Ghadri JR**, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J* 2018; **39**: 2032-2046 [PMID: 29850871 DOI: 10.1093/eurheartj/ehy076]

20 **Galiuto L**, De Caterina AR, Porfidia A, Paraggio L, Barchetta S, Locorotondo G, Rebuzzi AG, Crea F. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome. *Eur Heart J* 2010; **31**: 1319-1327 [PMID: 20215125 DOI: 10.1093/eurheartj/ehq039]

21 **Plácido R**, Cunha Lopes B, Almeida AG, Rochitte CE. The role of cardiovascular magnetic resonance in takotsubo syndrome. *J Cardiovasc Magn Reson* 2016; **18**: 68 [PMID: 27729054 DOI: 10.1186/s12968-016-0279-5]

22 **Ghadri JR**, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur Heart J* 2018; **39**: 2047-2062 [PMID: 29850820 DOI: 10.1093/eurheartj/ehy077]

23 **Ghadri JR**, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, Candreva A, Ding KJ, Micek J, Szawan KA, Bacchi B, Bianchi R, Levinson RA, Wischnewsky M, Seifert B, Schlossbauer SA, Citro R, Bossone E, Münzel T, Knorr M, Heiner S, D'Ascenzo F, Franke J, Sarcon A, Napp LC, Jaguszewski M, Noutsias M, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschöpe C, Pieske BM, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfuß G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Battrawy I, Akin I, Borggrefe M, Horowitz J, Kozel M, Tousek P, Widimský P, Gilyarova E, Shilova A, Gilyarov M, Winchester DE, Ukena C, Bax JJ, Prasad A, Böhm M, Lüscher TF, Ruschitzka F, Templin C. Long-Term Prognosis of Patients With Takotsubo Syndrome. *J Am Coll Cardiol* 2018; **72**: 874-882 [PMID: 30115226 DOI: 10.1016/j.jacc.2018.06.016]

24 **Tornvall P**, Gerbaud E, Behaghel A, Chopard R, Collste O, Laraudogoitia E, Leurent G, Meneveau N, Montaudon M, Perez-David E, Sörensson P, Agewall S. Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: A meta-analysis of individual patient data. *Atherosclerosis* 2015; **241**: 87-91 [PMID:

25967935 DOI: 10.1016/j.atherosclerosis.2015.04.816]
25 **Maron BJ**, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA, Cooper LT, Link MS, Maron MS; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. *Circulation* 2015; **132**: e273-e280 [PMID: 26621644 DOI: 10.1161/CIR.0000000000000239]
26 **Aquaro GD**, Perfetti M, Camastra G, Monti L, Dellegrottaglie S, Moro C, Pepe A, Todiere G, Lanzillo C, Scatteia A, Di Roma M, Pontone G, Perazzolo Marra M, Barison A, Di Bella G; Cardiac Magnetic Resonance Working Group of the Italian Society of Cardiology. Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function: ITAMY Study. *J Am Coll Cardiol* 2017; **70**: 1977-1987 [PMID: 29025554 DOI: 10.1016/j.jacc.2017.08.044]
27 **Shibata T**, Kawakami S, Noguchi T, Tanaka T, Asaumi Y, Kanaya T, Nagai T, Nakao K, Fujino M, Nagatsuka K, Ishibashi-Ueda H, Nishimura K, Miyamoto Y, Kusano K, Anzai T, Goto Y, Ogawa H, Yasuda S. Prevalence, Clinical Features, and Prognosis of Acute Myocardial Infarction Attributable to Coronary Artery Embolism. *Circulation* 2015; **132**: 241-250 [PMID: 26216084 DOI: 10.1161/CIRCULATIONAHA.114.015134]
28 **Reynolds HR**, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, Kalhorn RT, Wood DA, Lobach IV, Hochman JS. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation* 2011; **124**: 1414-1425 [PMID: 21900087 DOI: 10.1161/CIRCULATIONAHA.111.026542]
29 **Nordenskjöld AM**, Baron T, Eggers KM, Jernberg T, Lindahl B. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. *Int J Cardiol* 2018; **261**: 18-23 [PMID: 29563017 DOI: 10.1016/j.ijcard.2018.03.056]
30 **Nordenskjöld AM**, Lagerqvist B, Baron T, Jernberg T, Hadziosmanovic N, Reynolds HR, Tornvall P, Lindahl B. Reinfarction in Patients with Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA): Coronary Findings and Prognosis. *Am J Med* 2019; **132**: 335-346 [PMID: 30367850 DOI: 10.1016/j.amjmed.2018.10.007]
31 **Abdu FA**, Liu L, Mohammed AQ, Luo Y, Xu S, Auckle R, Xu Y, Che W. Myocardial infarction with non-obstructive coronary arteries (MINOCA) in Chinese patients: Clinical features, treatment and 1 year follow-up. *Int J Cardiol* 2019; **287**: 27-31 [PMID: 30826195 DOI: 10.1016/j.ijcard.2019.02.036]
32 **Ghanem AM**, Hamimi AH, Matta JR, Carass A, Elgarf RM, Gharib AM, Abd-Elmoniem KZ. Automatic Coronary Wall and Atherosclerotic Plaque Segmentation from 3D Coronary CT Angiography. *Sci Rep* 2019; **9**: 47 [PMID: 30631101 DOI: 10.1038/s41598-018-37168-4]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2019 December 26; 11(12): 316-321

DOI: 10.4330/wjc.v11.i12.316

ISSN 1949-8462 (online)

CASE REPORT

Left recurrent laryngeal nerve palsy following aortic arch stenting: A case report

Hannah Elisabeth Fürniss, Johanna Hummel, Brigitte Stiller, Jochen Grohmann

ORCID number: Hannah Elisabeth Fürniss (0000-0002-8615-6561); Johanna Hummel (0000-0001-6995-0344); Brigitte Stiller (0000-0002-7657-4647); Jochen Grohmann (0000-0002-8583-6135).

Author contributions: Fürniss HE and Hummel J wrote the paper, Stiller B and Grohmann J performed the interventions and critically revised the manuscript.

Informed consent statement: Informed consent was obtained from the patient's legal guardians for publication of this case report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Hannah Elisabeth Fürniss, Johanna Hummel, Brigitte Stiller, Jochen Grohmann, Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Centre Freiburg - Bad Krozingen, Medical Centre - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg 79106, Germany

Corresponding author: Hannah Elisabeth Fürniss, MD, Resident, Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Centre Freiburg - Bad Krozingen, Medical Centre - University of Freiburg, Faculty of Medicine, University of Freiburg, Mathildenstrasse 1, Freiburg 79106, Germany. hannah.fuerniss@universitaets-herzzentrum.de
Telephone: +49-761-27043230
Fax: +49-761-27044680

Abstract

BACKGROUND

Aortic arch stenting is continuously emerging as a safe and effective option to alleviate aortic arch stenosis and arterial hypertension.

CASE SUMMARY

We present a 15-year-old girl with aortic arch hypoplasia who had undergone implantation of an uncovered 22 mm Cheatham-Platinum stent due to severe (native) aortic arch stenosis. On follow-up seven months later, she presented a significant re-stenosis of the aortic arch. A second stent (LD Max 26 mm) was implanted and both stents were dilated up to 16 mm. After an initially unremarkable post-interventional course, the patient presented with hoarseness five days after the intervention. MRI and CT scans ruled out an intracranial pathology, as well as thoracic hematoma, arterial dissection, and aneurysm around the intervention site. Laryngoscopy confirmed left vocal fold paresis attributable to an injury to the left recurrent laryngeal nerve (LRLN) during aortic arch stenting, as the nerve loops around the aortic arch in close proximity to the area of the implanted stents. Following a non-invasive therapeutic approach entailing regular speech therapy, the patient recovered and demonstrated no residual clinical symptoms of LRLN palsy after six months.

CONCLUSION

Left recurrent laryngeal nerve palsy is a rare complication of aortic arch stenting not previously reported.

Key words: Cardiac catheterization; Congenital heart defects; Hypoplastic aortic arch; Endovascular procedure; Vocal cord paralysis; Case report

Manuscript source: Unsolicited manuscript

Received: July 21, 2019
Peer-review started: July 23, 2019
First decision: August 2, 2019
Revised: August 13, 2019
Accepted: October 18, 2019
Article in press: October 18, 2019
Published online: December 26, 2019

P-Reviewer: Barik R, Nurzynska D, Ueda H
S-Editor: Dou Y
L-Editor: A
E-Editor: Zhang YL

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This case report demonstrates that endovascular therapy of aortic arch hypoplasia with stent implantation in the stenosed segment may, as a rare complication of the procedure, lead to left recurrent laryngeal nerve palsy with subsequent vocal cord paresis.

Citation: Fürniss HE, Hummel J, Stiller B, Grohmann J. Left recurrent laryngeal nerve palsy following aortic arch stenting: A case report. *World J Cardiol* 2019; 11(12): 316-321
URL: https://www.wjgnet.com/1949-8462/full/v11/i12/316.htm
DOI: https://dx.doi.org/10.4330/wjc.v11.i12.316

INTRODUCTION

Hypoplasia of the aortic arch may induce arterial hypertension of the right upper body. Alleviation of aortic arch stenosis is indicated to prevent hypertension-related cardiovascular complications. Endovascular therapy including ballooning and stenting has emerged over the last decade as a safe and effective alternative to surgical reconstruction[1-4]. Acute complications of aortic arch stenting almost exclusively involve aortic wall injury, while stent compression of adjacent structures is uncommon[5,6].

CASE PRESENTATION

Chief complaints

We report a 15-year-old girl who presented with recurrent headaches, arterial hypertension, and a systolic murmur.

History of present illness

Echocardiographic examination in a medical practice had revealed a potential coarctation of the aorta.

History of past illness

The patient had no history of serious illness.

Personal and family history

There were no medically relevant aspects from the patient's personal history. Other than arterial hypertension and coronary artery disease in the patient's grandfather, there was no known cardiac disease within the family.

Physical examination upon admission

The patient presented in good general condition. Body weight was 61 kg and height were 172 cm. Her blood pressure in the right arm with 144/86 [MAP (mean arterial pressure) 110 mmHg] was significantly higher than that in the left arm [118/82 (MAP 96) mmHg] and of the right leg [118/72 (MAP 91) mmHg]. We consistently felt an unequal pulse between the right and left radial arteries (right stronger than left). A 2/6 systolic murmur was identified ventrally in the second and third left intercostal space, and, less prominently, dorsally between the shoulder blades. All other aspects of the physical examination were normal.

Laboratory examinations

No laboratory examinations were done in the diagnostic work-up.

Imaging examinations

Echocardiography and cardiac MRI revealed a hypoplastic native aortic arch with a bi-carotid trunk and a segment just proximal of the left subclavian artery which was stenosed by 75% (Supplemental Figure 1A).

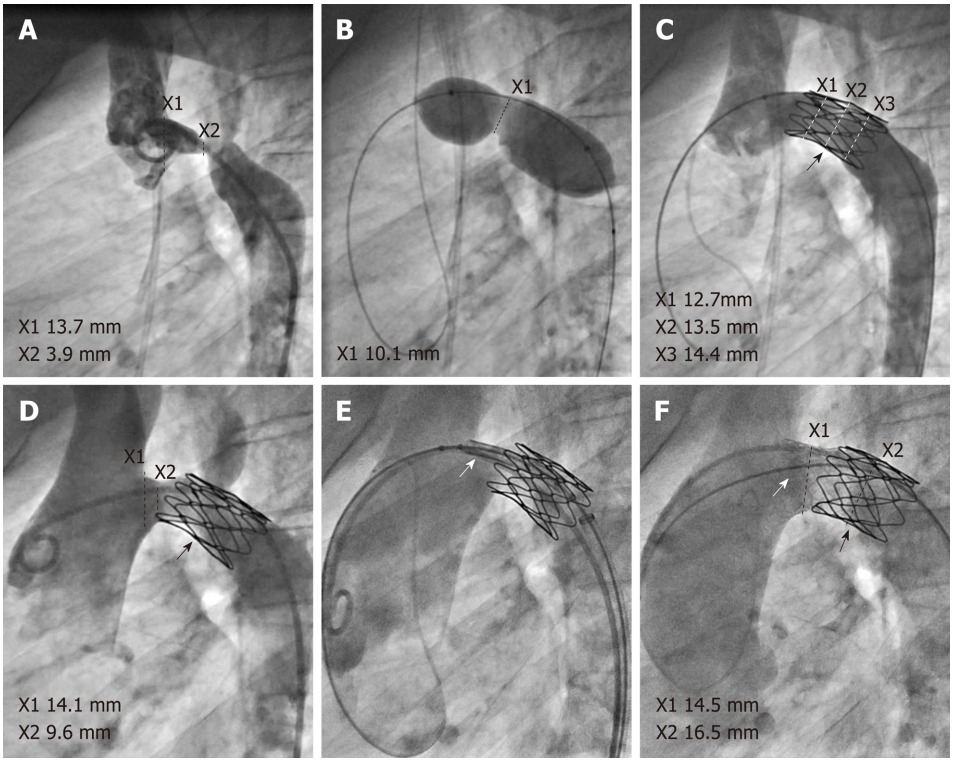


Figure 1 Angiograms in lateral projection (all images, LAO 90°) demonstrating pre-, intra- and post-interventional findings. A: Left aortic arch with bi-carotid trunc and transverse arch hypoplasia with severe native stenosis just proximal to origin of the left subclavian artery; B: Balloon interrogation using an 18 mm Tyshak II that unmasks a relatively high compliance of the stenosis; C: After implantation of a 22 mm Cheatham-Platinum (CP) stent (indicated by black arrow) on 14 mm BiB; D: Re-stenosis proximal of the previously implanted CP stent on follow-up; E: Positioning and implantation of a LD Max 26 mm stent (indicated by white arrow) over the re-stenosis; F: Final result following redilation of both stents with 16 mm Atlas balloon, and proximal stent flaring with 20 mm Cristal balloon.

FINAL DIAGNOSIS

Our final diagnosis was a hypoplastic aortic arch with a bi-carotid trunc and severe coarctation.

TREATMENT

Following discussion with the family and the cardiac surgeons, we opted against surgical treatment in favor of an interventional approach to alleviate the aortic arch stenosis. Cardiac catheterization showed a minimal diameter of 3.8 mm of the stenotic segment (Figure 1A), with a relatively compliant stenosis up to 14 mm on sizing balloon interrogation with a Tyshak II balloon (NuMed, Hopkinton, NY, United States) (Figure 1B). We implanted a short 22-mm uncovered Cheatham-Platinum (CP) stent (NuMed, Hopkinton, NY, United States), which effectively resolved the pressure gradient while preserving good perfusion of the overstented left subclavian artery (Figure 1C). On follow-up seven months later, the patient demonstrated renewed blood-pressure difference between the arms. Re-catheterization revealed re-stenosis with a diameter of 9.5 mm between the brachiocephalic artery's origin and the proximal end of the previously implanted CP stent and a systolic pressure gradient of 18 mmHg under conscious sedation, probably due to slight stent migration towards distal (Figure 1D). The re-stenosis was relieved by implantation of a 26-mm IntraStent LD Max (ev3 - Medtronic, Minneapolis, MN, United States) in telescope technique, proximal flaring of the LD Max stent with a 20-mm Cristal balloon (Balt, Montmorency, France), and (re-)dilation of both stents using a non-compliant 16-mm Atlas balloon (Bard, Tempe, AZ, United States) (Figure 1E and F).

OUTCOME AND FOLLOW-UP

Our interventional result was satisfactory, with a minimum aortic arch diameter of 14.5 mm (Figure 1F) and no relevant residual gradient detectable. Her immediate post-interventional course was unremarkable. However, five days after the

intervention the patient presented with sudden hoarseness and a weakened voice. MRI and CT scans ruled out an aortic aneurysm or dissection, haematoma, thoracic tumour formation, and intracranial pathology such as stroke (Supplemental Figure 1B and C). Otorhinolaryngological examination including laryngoscopy confirmed paresis of the left vocal fold. Due to the anatomically proximity of the left recurrent laryngeal nerve (LRLN) to the implanted stents' region, we attributed the vocal fold palsy to an injury to the LRLN during aortic arch stenting. After careful evaluation, we decided against medical or surgical therapy of the LRLN palsy and took a conservative approach involving regular speech therapy and close otorhinolaryngological monitoring. Fortunately, at follow-up six months later, our patient demonstrated no residual clinical symptoms of LRLN palsy with normal voice sound and speaking volume. For an overview of the time course of this case, see Figure 2.

DISCUSSION

We present a case of LRLN palsy following stent implantation in the transverse aortic arch. Vocal cord paresis is a well-known complication of surgical ligation of patent ductus arteriosus[7], and has also been described secondary to transcatheter closure of patent ductus arteriosus and left pulmonary artery stenting[8-12]. Moreover, LRLN palsy has also occurred after surgical aortic arch reconstruction during the Norwood procedure[13]. However, to our knowledge, LRLN paralysis resulting from transverse arch stenting has not been reported in the MEDLINE database so far. We suggest that, due to the course of the LRLN as is passes underneath the aortic arch in close proximity to the pulmonary artery and the ligamentum arteriosum, stent implantation in a severely hypoplastic aortic arch may either stretch the LRLN as the transverse aortic diameter increases, or compress it between the aortic arch and the pulmonary artery, thereby leading to LRLN damage and left vocal cord paresis. Moreover, after surgical aortic stent-graft placement, additional dilation of the graft is a known independent predictor of LRLN palsy[14]. Therefore, (re-)dilation of the stents in our patient may also have played a significant role in her having developed post-intervention LRLN palsy.

Our patient recovered relatively quickly, most likely due to either nerve growth to accommodate the larger aortic diameter, or due to cessation of an inflammatory reaction or edema following either stretch or compression of the nerve. Contrary to this positive clinical course in our patient, previous reports of LRLN after endovascular therapy of patent ductus arteriosus or left pulmonary artery stenosis have documented persistent vocal cord paralysis after six months in over 50% of patients[8-12]. However, other than the case by Javois and colleagues, who described coughing after their patient drank water[12], there were no previously reported symptoms of LRLN palsy other than hoarseness after transcatheter interventions[8-11]. Presumably due to these relatively mild clinical presentations neither medical therapy nor surgical device removal was performed in any of the cases. Therefore, it remains unclear whether in the case of acute LRLN palsy after aortic arch stent implantation, the administration of medication or decompression of the nerve by surgical stent removal would lead to LRLN recovery. Indeed, further (surgical) manipulation may even aggravate symptoms. Finally, clinicians must carefully assess whether the patient's clinical symptoms justify invasive surgical therapy.

CONCLUSION

LRLN palsy is an extremely rare complication of transverse aortic arch stenting. Interventionalists should be aware of this potential complication and inform their patients accordingly.

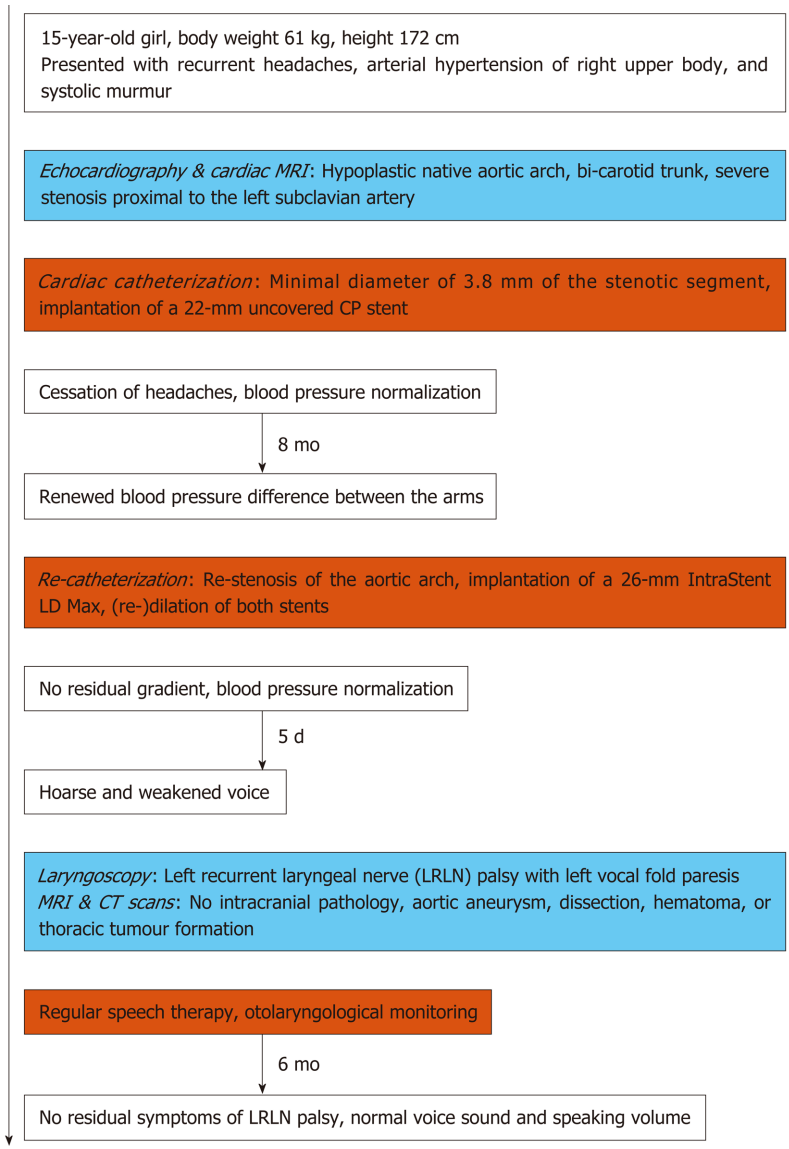


Figure 2 Time line of the case, with clinical findings highlighted in white, diagnostic work-up in blue, and therapeutic procedures in red.

ACKNOWLEDGEMENTS

We thank Carole Cürten for language editing and Stefan Heinz for graphic design.

REFERENCES

1 **Zartner PA**, Neudorf U, Bierbach B, Hart C, Schneider MB. First follow-up of a breakable stent for implantation in infants dedicated for a life-long stay. *Catheter Cardiovasc Interv* 2018; **91**: 1119-1124 [PMID: 29469968 DOI: 10.1002/ccd.27543]
2 **Bentham J**, Shettihalli N, Orchard E, Westaby S, Wilson N. Endovascular stent placement is an acceptable alternative to reoperation in selected infants with residual or recurrent aortic arch obstruction. *Catheter Cardiovasc Interv* 2010; **76**: 852-859 [PMID: 20506213 DOI: 10.1002/ccd.22586]
3 **Holzer RJ**, Chisolm JL, Hill SL, Cheatham JP. Stenting complex aortic arch obstructions. *Catheter Cardiovasc Interv* 2008; **71**: 375-382 [PMID: 18288730 DOI: 10.1002/ccd.21357]
4 **Pushparajah K**, Sadiq M, Brzezińska-Rajszys G, Thomson J, Rosenthal E, Qureshi SA. Endovascular stenting in transverse aortic arch hypoplasia. *Catheter Cardiovasc Interv* 2013; **82**: E491-E499 [PMID: 23494884 DOI: 10.1002/ccd.24735]
5 **Forbes TJ**, Kim DW, Du W, Turner DR, Holzer R, Amin Z, Hijazi Z, Ghasemi A, Rome JJ, Nykanen D, Zahn E, Cowley C, Hoyer M, Waight D, Gruenstein D, Javois A, Foerster S, Kreutzer J, Sullivan N, Khan A, Owada C, Hagler D, Lim S, Canter J, Zellers T; CCISC Investigators. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). *J Am Coll Cardiol* 2011; **58**: 2664-2674 [PMID: 22152954 DOI: 10.1016/j.jacc.2011.08.053]
6 **Gewillig M**, Budts W, Boshoff D, Maleux G. Percutaneous interventions of the aorta. *Future Cardiol*

2012; **8**: 251-269 [PMID: 22413984 DOI: 10.2217/fca.12.10]
7 **Henry BM**, Hsieh WC, Sanna B, Vikse J, Taterra D, Tomaszewski KA. Incidence, Risk Factors, and Comorbidities of Vocal Cord Paralysis After Surgical Closure of a Patent Ductus Arteriosus: A Meta-analysis. *Pediatr Cardiol* 2019; **40**: 116-125 [PMID: 30167748 DOI: 10.1007/s00246-018-1967-8]
8 **Assaqqat M**, Siblini G, Fadley FA. Hoarseness after pulmonary arterial stenting and occlusion of the arterial duct. *Cardiol Young* 2003; **13**: 302-304 [PMID: 12903881]
9 **Baek SM**, Chung H, Kim GB, Song MK, Bae EJ, Noh CI. Vocal Cord Palsy after Left Pulmonary Artery Stent Insertion. *Chonnam Med J* 2018; **54**: 72-73 [PMID: 29399569 DOI: 10.4068/cmj.2018.54.1.72]
10 **Kobayashi D**, Turner DR, Humes RA. Left recurrent laryngeal nerve palsy secondary to left pulmonary artery stent in a child. *Catheter Cardiovasc Interv* 2012; **80**: 482-484 [PMID: 22422720 DOI: 10.1002/ccd.23472]
11 **Liang CD**, Ko SF, Huang SC, Huang CF, Niu CK. Vocal cord paralysis after transcatheter coil embolization of patent ductus arteriosus. *Am Heart J* 2003; **146**: 367-371 [PMID: 12891209 DOI: 10.1016/S0002-8703(03)00125-X]
12 **Javois AJ**, Patel D, Roberson D, Husayni T. Pre-existing left pulmonary artery stenosis and other anomalies associated with device occlusion of patent ductus arteriosus. *Catheter Cardiovasc Interv* 2007; **70**: 83-89 [PMID: 17420999 DOI: 10.1002/ccd.21120]
13 **Pham V**, Connelly D, Wei JL, Sykes KJ, O'Brien J. Vocal cord paralysis and Dysphagia after aortic arch reconstruction and Norwood procedure. *Otolaryngol Head Neck Surg* 2014; **150**: 827-833 [PMID: 24515967 DOI: 10.1177/0194599814522413]
14 **Ohta N**, Kuratani T, Mori T. Vocal cord paralysis after aortic arch surgery with stent-graft placement, a contemporary method of arch surgery. *J Vasc Surg* 2007; **45**: 866 [PMID: 17398405 DOI: 10.1016/j.jvs.2006.12.073]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.