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MINIREVIEWS

Heart disease in Friedreich's ataxia

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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

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.

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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.

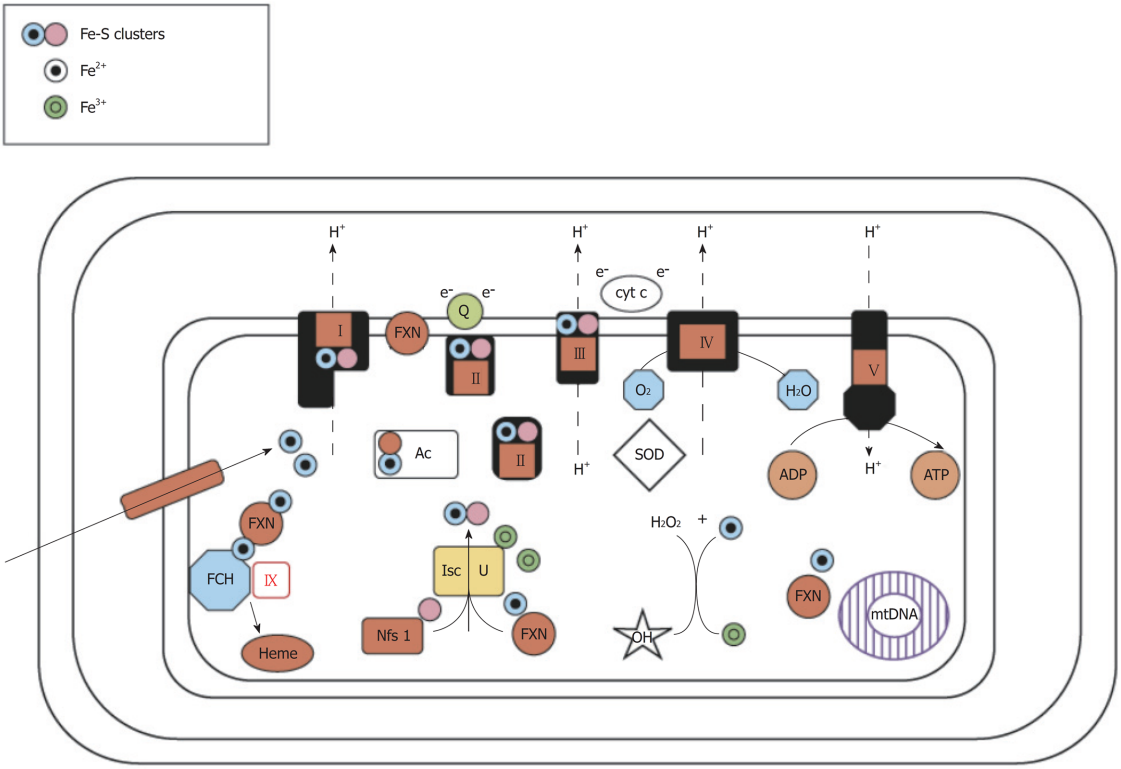

Figure 1 Postulated functions of frataxin. (1) Frataxin is a general iron chaperone that provides Fe^{2+} to ferrochelatase (FCH) for heme biosynthesis, mitochondrial iron-sulfur (Fe-S) cluster biogenesis, and maintenance of the mitochondrial aconitase (Ac) Fe-S cluster; (2) Frataxin may directly interact 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).

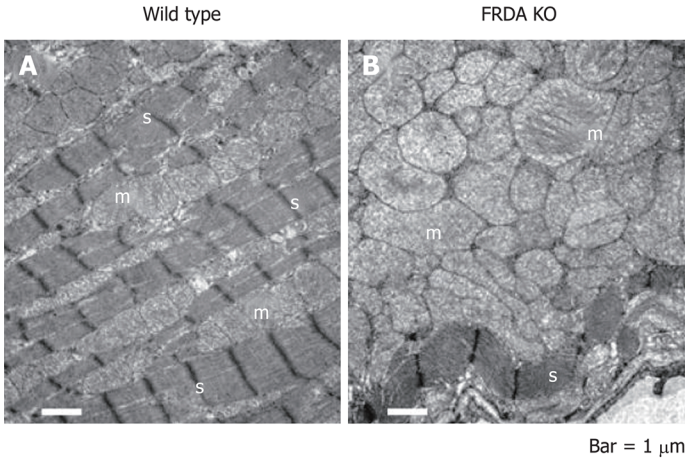

Figure 2 Electron microscopy of Friedreich's ataxia-knockout and wild-type control mouse heart tissues from 28-d-old littermates. A: Wild type mouse showing normal mitochondria ("m") in rows between abundant, well-ordered sarcomeres ("s"); B: Conditional Friedreich's ataxia-knockout (FRDA KO) mouse with 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,

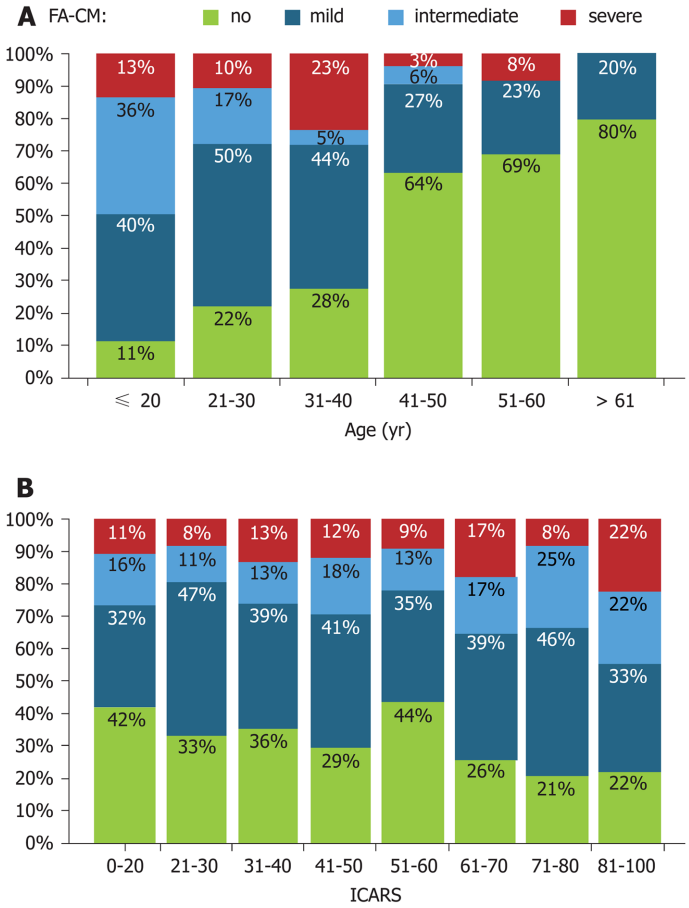

Figure 3 The more severe Friedreich's ataxia cardiomyopathy groups were found at younger ages (A), in contrast, the severity of the Friedreich's ataxia cardiomyopathy was independent of neurological involvement measured by the International Cooperative Ataxia Rating Scale score (B).

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.

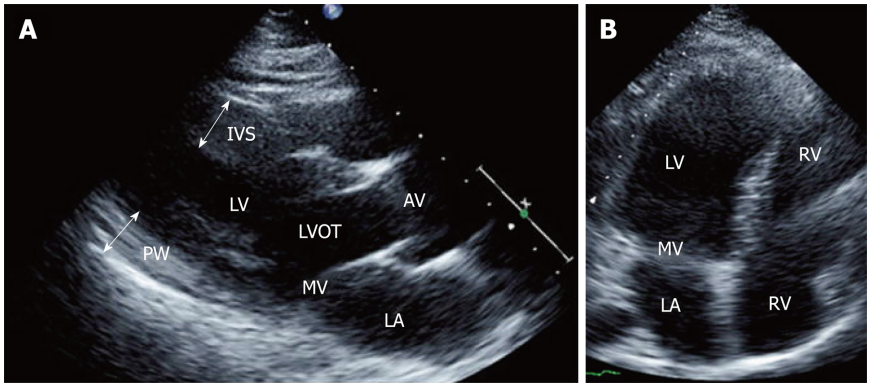

Figure 4 Two-dimensional echocardiographic still frames from a patient with Friedreich's ataxia. A: Parasternal long-axis view showing thickening of the interventricular septum and posterior wall; B: Apical four-chamber view showing dilatation of left ventricular cavity. IVS: Interventricular septum; 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

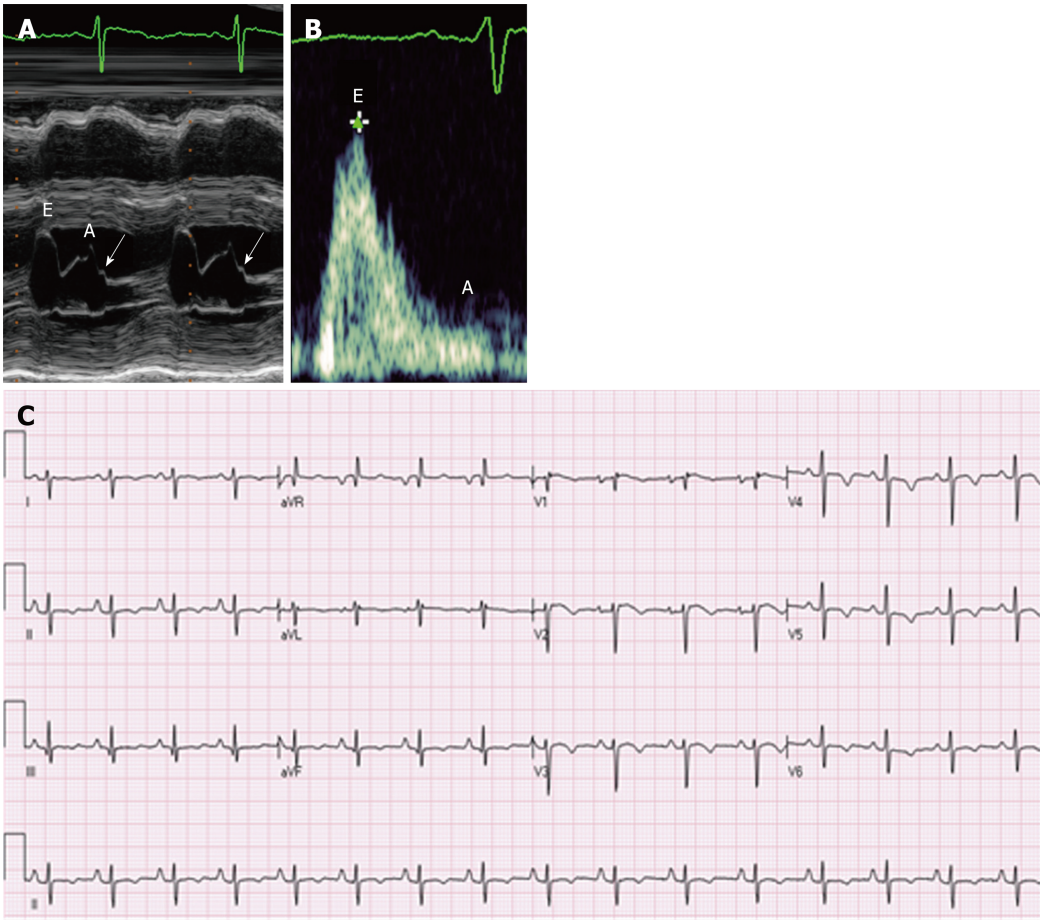

Figure 5 M-Mode image of the mitral valve, Transmitral Doppler flow showing diastolic flow and Twelve-lead electrocardiogram. A: M-Mode image of the mitral valve in the parasternal long-axis view. Mitral valve excursion in early diastole can be seen, as can excursion due to atrial contraction in late 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.

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MINIREVIEWS

Current evidence of drug-elution therapy for infrapopliteal arterial disease

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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

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.

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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.

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ORIGINAL ARTICLE

Retrospective Cohort Study

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

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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

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.

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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

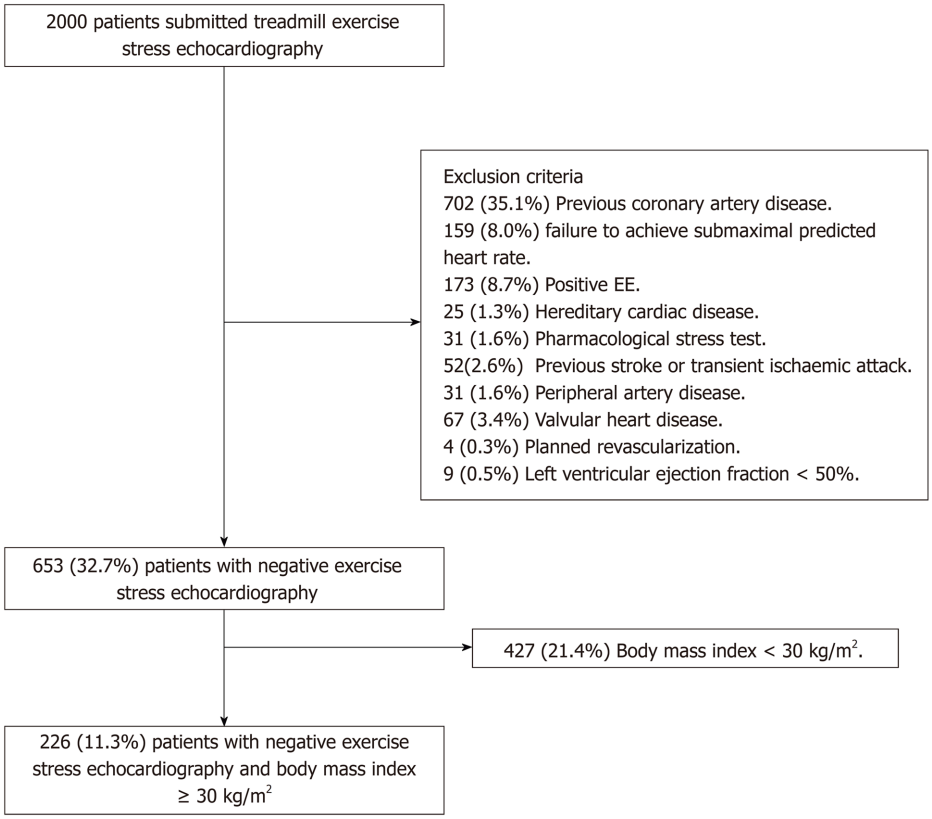


Figure 1 Flowchart of the 2000 patients submitted for exercise echocardiography. EE: Exercise echocardiography.

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.

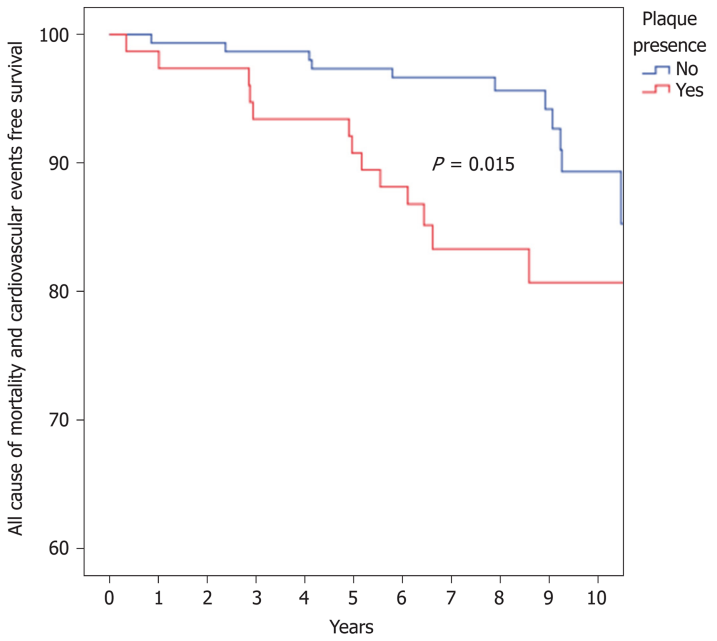
Stockholm[28], CIMT could not predict AE defined as cardiovascular death or cardiovascular events, while CP had a tendency (P = 0.056) to predict them in 809 patients younger than 70 years with clinical suspicion of CAD. Compared to our study, their patients were younger, more frequently male, with a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

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ORIGINAL ARTICLE

Retrospective Study

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

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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%, $P =$

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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

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.

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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.

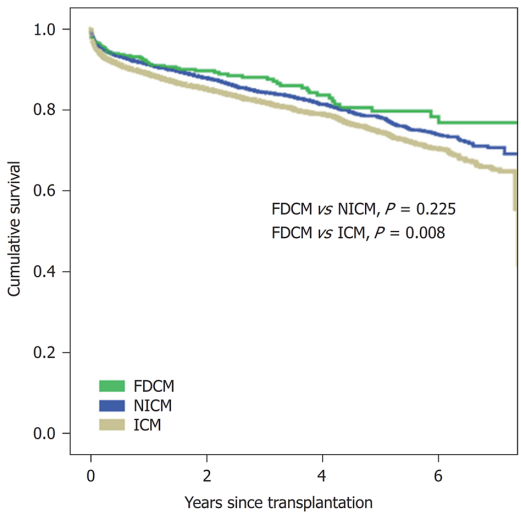

Figure 1 Kaplan-Meir graph showing post-transplant survival in familial dilated cardiomyopathy, non-ischemic cardiomyopathy, and ischemic cardiomyopathy patients. One, three, and five years post-transplant survival of patients with FDCM (91%, 88%, and 80%) was similar to those with NICM (91%, 84%, 79%, *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.

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