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ABOUT COVER

Peer Reviewer of *World Journal of Cardiology*, Tolga Aksu, MD, Associate Professor, Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli 41000, Türkiye. aksutolga@gmail.com

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The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

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EDITORIAL

Congenital heart "Challenges" in Down syndrome

Maria Drakopoulou, Panayotis K Vlachakis, Costas Tsioufis, Dimitris Tousoulis

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Maria Drakopoulou, Panayotis K Vlachakis, Costas Tsioufis, Dimitris Tousoulis, Department of First Cardiology, Hippokration General Hospital, Athens Medical School, National and Kapodistrian University of Athens, Athens 11527, Greece

Corresponding author: Maria Drakopoulou, FESC, MD, MSc, PhD, Lecturer, Department of First Cardiology, Hippokration General Hospital, Athens Medical School, National and Kapodistrian University of Athens, 114 Vasilissis Sophia Avenue, Athens 11527, Greece. mdrakopoulou@hotmail.com

Abstract

In this editorial, we comment on the article by Kong *et al* published in the recent issue of the *World Journal of Cardiology*. In this interesting case, the authors present the challenges faced in managing a 13-year-old patient with Down syndrome (DS) and congenital heart disease (CHD) associated with pulmonary arterial hypertension. In this distinct population, the Authors underscore the need for early diagnosis and management as well as the need of a multidisciplinary approach for decision making. It seems that the occurrence of CHD in patients with DS adds layers of complexity to their clinical management. This editorial aims to provide a comprehensive overview of the intricate interplay between DS and congenital heart disorders, offering insights into the nuanced diagnostic and therapeutic considerations for physicians.

Key Words: Down syndrome; Congenital heart disease; Atrioventricular septal defect; Pulmonary hypertension; Right heart catheterization

Core Tip: Addressing the health challenges of individuals with Down syndrome (DS) poses intricate challenges, with congenital heart disease (CHD) being notably prevalent. The complexity of managing DS and CHD is heightened by diagnostic delays and difficulties in symptom assessment due to intellectual disabilities. Incorporating this unique population into comprehensive studies and randomized trials, with careful consideration of informed consent and a multidisciplinary research framework, is crucial.

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INTRODUCTION

In this editorial we comment on the article by Kong *et al*[1] published in the recent issue of the *World Journal of Cardiology* [1]. In this interesting case, the Authors present the challenges faced in managing a 13-year-old patient with Down syndrome (DS) and congenital heart disease (CHD) associated with pulmonary hypertension (PH). In this article, the Authors underscore the high incidence of CHD in patients with DS and the need for early diagnosis and management. Indeed, about half of infants born with DS are identified with CHD, a stark contrast to the general population's approximate 1% incidence[2]. Moreover, Authors, highlight the need of a multidisciplinary approach for decision making in this distinct population with DS and concomitant CHD associated with PH. Based on recently published European Society of Cardiology (ESC) guidelines, shunt closure (intracardiac and/or extracardiac) in the presence of pulmonary arterial hypertension seem not to be appropriate in patients with increased pulmonary vascular resistance (> 5 WU) and may only be considered after careful evaluation in specialized centers and individualization. Most importantly, in the aforementioned guidelines as well as current ESC guidelines in adult CHD there is no referral to patients with DS and data concerning this population management is limited[3].

It was in 1866 when Down[4] first described the features of DS, and in 1959 when Lejeune *et al*[5] linked the syndrome to the chromosomal abnormality of trisomy 21[1,4]. Since then, DS has constituted one of the most common chromosomal abnormalities, affecting nearly 11.8 *per* 10000 live births[6]. In tandem with the joy of these unique individuals comes the intricate challenge of managing associated health complications, with CHDs standing out prominently.

Recognition of the diverse clinical presentations of CHDs in DS is imperative for timely diagnosis and intervention. So far, atrioventricular septal defect (AVSD) remains the most common CHD in this susceptible population (Figure 1)[7]. In a population-based study from 1985 to 2006 in northeastern England, 42% of infants with DS exhibited cardiovascular abnormalities. Among 821 infants, 23% had multiple anomalies, with atrial septal defect (ASD) or patent ductus arteriosus (PDA) being common secondary lesions. Primary lesions included complete-AVSD (37%), ventricular septal defect (31%), ASD (15%), partial-AVSD (6%), Tetralogy of Fallot (5%), and PDA (4%). Miscellaneous anomalies constituted 2%[8]. Data revealed a shift in the distribution of CHD in DS over time, noting a tendency toward simpler lesions in recent years. One hypothesis is that this trend might be influenced by improved survival rates in simple lesions. Alternatively, it could indicate a higher incidence of prenatal diagnosis and an increased likelihood of terminating pregnancies involving more complex defects[9].

Diagnostic modalities tailored to the distinctive features of DS patients are pivotal. A consensus document recently published by Dimopoulos *et al*[9] on behalf of the DS international network supports systematic screening for the detection of CHDs in newborns diagnosed with or suspected of having DS[10]. This comprehensive screening involves clinical examination, electrocardiogram, and, where available, echocardiography. In health systems equipped with obstetric ultrasound screening, it is advisable to screen fetuses with suspected or confirmed DS during the second trimester[10]. Fetal echocardiography should be considered, particularly for women with conditions linked to high rates of CHD or when fetal ultrasound suggests a potential abnormality[11]. In cases of prenatal diagnosis of both CHD and DS, it is crucial to establish a delivery plan with expert support to effectively manage the complications arising from CHD and associated lesions.

The landscape of CHD treatment underwent a transformative shift in the 1960s and early 1970s with the widespread of open-heart surgery[12]. Initially excluded, DS patients gradually became candidates. Improved outcomes and successful cardiac repairs shifted societal attitudes, making surgery standard for DS patients with CHD. Referral to a specialized center for management is advised for all individuals with DS and CHD, with the timing and nature of repair contingent on CHD type, clinical presentation, and the specific risk of developing PH. For infants amenable to biventricular repair, early CHD repair is recommended, irrespective of DS presence, as DS doesn't pose a higher perioperative risk for most CHD types[9]. Despite increased perioperative risk, individuals with DS and single ventricle physiology should be considered for Fontan palliation when suitable[13].

Regular assessment for PH is essential for all individuals with DS and CHD, both before CHD repair and at intervals thereafter. The management of individuals with DS and PH is often complicated, leading to delays in diagnosis and treatment initiation or escalation. Defining symptomatology can be challenging due to intellectual disabilities, rendering traditional assessments like the 6-minute walk test less reliable[14]. Additionally, the higher prevalence of comorbidities in these individuals, such as obstructive sleep apnea, lung disease, and others, further complicates the clinical presentation and response to therapies. Limited data on the efficacy of PH therapy in DS individuals highlight the importance of their identification and referral to specialist centers for comprehensive care[15,16]. Diagnosing PH, identifying its causes, and determining optimal management require specialized expertise.

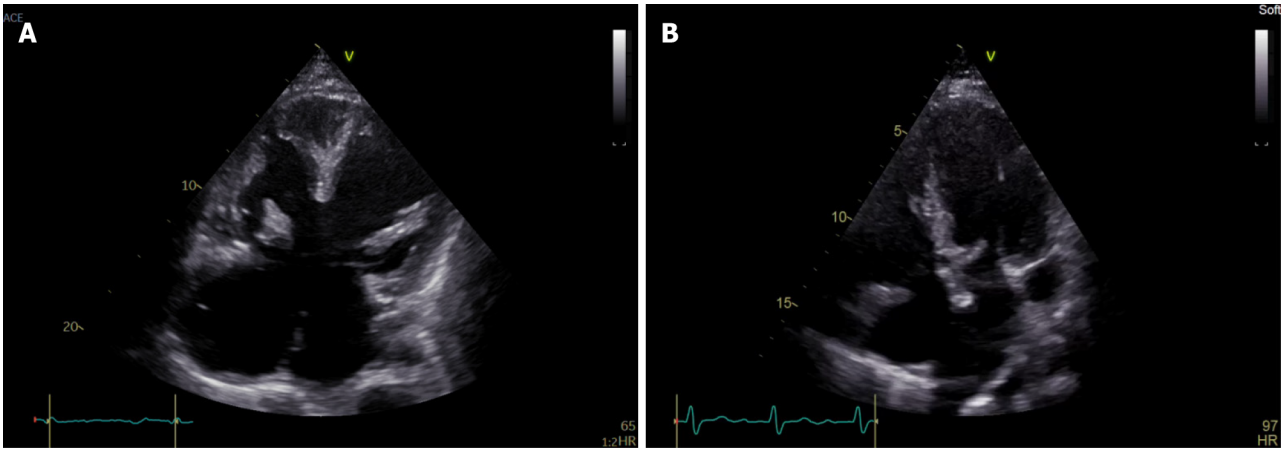

Figure 1 Echocardiographic images of patients with atrioventricular septal defect and Down syndrome. A: 26-year-old patient with Down syndrome unrepaired complete atrioventricular septal defect (AVSD) and Eisenmenger syndrome; B: 53-year-old patient with Down syndrome and repaired partial AVSD.

CONCLUSION

In conclusion, fostering multidisciplinary collaboration and advancing ongoing research initiatives are pivotal for a patient-centric approach to CHDs in individuals with DS. Unraveling the complexities of this intersection provides clinicians with the insights needed for optimal care. The imperative for research persists, focusing on early diagnosis, person-centered follow-up, health-related quality of life assessment, and the timing of interventions. Encouraging the inclusion of individuals with DS in randomized trials and comprehensive studies, supported by informed consent and a multidisciplinary research framework, is pivotal for addressing the unique challenges associated with intellectual disability in this population.

FOOTNOTES

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ORCID number: Maria Drakopoulou 0000-0002-0022-0332; Panayotis K Vlachakis 0000-0003-0736-4942; Costas Tsioufis 0000-0002-7636-6725; Dimitris Tousoulis 0000-0001-7492-4984.

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EDITORIAL

Portal vein pulsatility: An important sonographic tool assessment of systemic congestion for critical ill patients

Stavros Dimopoulos, Michael Antonopoulos

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Stavros Dimopoulos, Michael Antonopoulos, Cardiac Surgery ICU, Onassis Cardiac Surgery Center, Kallithea 17674, Greece

Co-first authors: Michael Antonopoulos and Stavros Dimopoulos.

Corresponding author: Stavros Dimopoulos, PhD, EDIC, Director, Cardiac Surgery ICU, Onassis Cardiac Surgery Center, No. 356 L. Syggrou, Athens, 17674, Greece. stdimop@gmail.com

Abstract

In this editorial we comment on the article by Kuwahara *et al*, published in the recent issue of the *World Journal of Cardiology*. In this interesting paper, the authors showed a correlation between portal vein pulsatility ratio, examined by bedside ultrasonography, and prognosis of hospitalized patients with acute heart failure. Systemic congestion is being notoriously underdetected in the acutely ill population with conventional methods like clinical examination, biomarkers, central venous pressure estimation and X-rays. However, congestion should be a key therapeutic target due to its deleterious effects to end organ function and subsequently patient prognosis. Doppler flow assessment of the abdominal veins is gaining popularity worldwide, as a valuable tool in estimating comprehensively congestion and giving a further insight into hemodynamics and patient management.

Key Words: Systemic congestion; Organ perfusion; Hemodynamics; Central venous pressure; Point of care ultrasound; Venous excess ultrasound

Core Tip: Venous excess ultrasound score incorporates the assessment of the inferior vena cava and the Doppler flow patterns of hepatic, portal and renal veins. It can provide valuable information about volume status, guide fluid management decisions in the acutely ill and obviate the deleterious effects of congestion to the peripheral organs.

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INTRODUCTION

In this observational study[1], the authors included 56 patients who were hospitalized for decompensated acute heart failure (AHF) and 17 controls without AHF. They calculated the portal vein pulsatility ratio (PVPR) by ultrasonography on admission and on discharge. On admission, PVPR was significantly higher in patients with AHF compared with controls and was decreased at discharge after guideline directed medical therapy. The authors suggest this PVPR amelioration might reflect venous congestion and HF condition, as there was noted concomitant improvement in clinical, laboratory (total bilirubin, brain natriuretic peptide) and echocardiographic [inferior vena cava (IVC) diameter, tricuspid regurgitation pressure gradient] indices. They also showed that patients with a higher PVRP at discharge had worse prognosis (cardiac death and HF hospitalization) at 1 year of follow up, implying that PVRP could be a novel prognostic marker for hospitalized patients with AHF.

THE ROLE OF VENOUS CONGESTION

In acutely ill patients, the complex interplay between cardiac dysfunction (especially right heart failure), vascular tone dysregulation, systemic inflammation and neurohormonal activation, often leads to venous congestion. In this setting, the superimposed acute kidney injury with subsequent sodium and fluid retention, aggravates considerably clinical management. Systemic congestion is the hallmark of AHF, leads to peripheral organ dysfunction (liver, kidney, lungs, intestines) and is associated with dismal prognosis of the critically ill patients[2,3]. As in the current paper[1], there is a considerable proportion of HF patients with residual congestion after a recent hospitalization. These patients have a high risk (up to 60%) for death or HF hospitalization at 12 months, especially if they have untreated congestion[4,5]. In the DOSE trial[6] only 15% of patients were free from congestion at 72 h of diuretic therapy, which rose to 42% in the recent ADVOR trial[7]. Congestion is often underdiagnosed and undertreated and should be a key therapeutic target in hospitalized patients with AHF. It seems that reduction in congestion is more important even than improvement in cardiac output, in order to prevent further renal failure or mortality[8-10].

TRADITIONAL BEDSIDE ASSESSMENT OF VENOUS CONGESTION IS PROBLEMATIC

The presence of classic clinical findings (peripheral edema, JVP, third heart sound and rales) is useful but has low sensitivity for the detection of ongoing congestion[11], and its absence does not exclude congestion. The same is true for chest X ray, as 20% of patients with AHF in the emergency department have normal radiological findings[12]. Estimation of IVC size and respiratory variations with ultrasonography, although it may help with fluid tolerance, is a poor marker for intravascular volume and fluid responsiveness[13]. IVC size and collapsibility are influenced by intrathoracic and intraabdominal pressures, by cardiac pathology (tricuspid regurgitation, pulmonary hypertension, severe diastolic dysfunction) and by obstructive pathology (tension pneumothorax, tamponade, pulmonary embolism), where it reflects more pressure than volume burden[14]. Central venous pressure (CVP), measured at the bedside through a central catheter, is a static marker of cardiac preload which does not specify in which part of the Starling curve the patient is functioning. Except from extreme values, CVP has failed to guide fluid management[15] and should be interpreted together with cardiac output, as dictated by the Guytonian physiology, in order to comprise both cardiac and venous return function of the circulatory system[16]. CVP is also influenced by thoracic, abdominal and pericardial pressures, which makes its interpretation difficult in the complex clinical setting[17].

VENOUS EXCESS ULTRASOUND SCORE

Doppler evaluation of the venous system help us estimate the downstream effects of elevated Right atrial pressure (RAP). Venous excess ultrasound (VExUS) protocol was introduced by Beaubien-Souligny *et al*[18] to quantify systemic congestion in a comprehensive manner and was validated in cardiac surgery patients. It comprises ultrasonographic estimation of IVC size and collapsibility, along with the Doppler flow patterns of the hepatic, portal and renal parenchymal veins. Depending on flow alterations, a score is derived (grade 0 = no congestion, grade 3 = severe congestion), which indicates the estimated degree of splanchnic congestion. VExUS score severity is strongly associated with elevated CVP levels[19] and has a good sensitivity and specificity to predict an elevated RAP[20]. It may predict AKI in various settings[21-23] and has been used to guide various interventions (diuretic therapy, ascites drainage, hemodialysis)[24]. A key advantage of these Doppler waveforms is that they are dynamic and allow monitoring the

Table 1 Summary of main limitations of sonographic splanchnic vein flow assessment

Inferior vena cava	Cylinder effect (misaligned diameter measurement in long axis)
	Abdominal aorta misinterpreted as inferior vena cava
	Presence of thrombus or obstruction
	Normally distended in young individuals and athletes due to increased venus reserve
	Distended in mechanically ventilated patients (PEEP, mean airway pressure)
	Diameter influenced by respiratory effort in spontaneous breathing patients
	Collapsed in abdominal hypertension
	Distended in tricuspid regurgitation, pulmonary hypertension, severe diastolic dysfunction, cardiac tamponade, tension pneumothorax, pulmonary embolism
Hepatic vein	Difficult interpretation in presence of arrhythmias and pacing (ECG tracing imperative)
	In case of tricuspid regurgitation, does not alone reflect venous congestion
	Decreased venous phasicity in parenchymal liver disease (cirrhosis, occlusive disease)
Portal vein	Enhanced pulsatility in thin healthy individuals
	Unreliable in parenchymal liver disease (cirrhosis, severe steatosis, occlusive disease, arteriovenous fistulas)
	Unreliable in severe portal hypertension (stagnant/retrograde flow, low velocities)
Renal vein	Technically the most challenging
	Influence of body habitus and mechanical ventilation
	Results differ between cortical versus hilar vessel interrogation
	Unknown reliability in renal parenchymal diseases and kidney transplantation

response to decongestive therapy in real time[25]. In patients with AHF, VExUS was shown to predict AKI and have prognostic implications[23,26], as in the current paper by Kuwahara *et al*[1].

In particular portal vein Doppler, which was used by the authors of this paper, is less technically demanding and is affected only by parenchymal hepatic pathology. In a recent trial, the author's conclusions were similar as Kuwahara *et al* [1], portal vein pulsatility ≥ 50% was highly prevalent in a population of patients hospitalized with AHF and was most closely associated with RV dysfunction. After decongestive therapy, patients with abnormal PVPR at discharge had poorer long-term clinical outcomes when compared with those with normal PVPR pattern[27].

The term extended venous excess ultrasound score (E-VExUS) or extended VExUS has been proposed to include Doppler interrogation of additional veins such as internal jugular, splenic, and femoral veins[28], or even sonographic estimation of the intestinal wall[29].

PITFALLS OF VEXUS

Doppler evaluation of venous congestion comes with various limitations. It is operator dependent and this may affect image acquisition and interpretation. Ultrasound penetration and Doppler sensitivity depends also on the probe and ultrasound machine available. Severe obesity, supine position, drainage tubes, surgical wounds, pain and agitation, may hamper ultrasound examination of visceral venous blood flow in the acute setting.

IVC is influenced by thoracic, abdominal and pericardial pressures and particularly mechanical ventilation positive pressures. Hepatic vein flow may be altered by arrhythmias, pacing, tricuspid regurgitation and pulmonary hypertension, even without fluid overload. Renal vein flow is the most challenging to obtain and is affected in renal parenchymal disease[30]. Portal vein flow is more advantageous, as it remains less affected by arrhythmias, pacing, tricuspid regurgitation and pulmonary hypertension; however, it may be altered in patients with cirrhosis and portal hypertension and should be cautiously considered. In Table 1, we summarize the main limitations regarding ultrasound evaluation of splanchnic venous flow[13,18,31].

VExUS may quantify congestion but may not indicate the reason of congestion, nor differentiate between pressure or volume overload. This is why the physician should interpret Doppler findings in the clinical context and combine clinical assessment with information from laboratory tests, echocardiography or even right heart catheterization[25,28] in more challenging cases.

CONCLUSION

Congestion is often underdiagnosed and undertreated in the acutely ill patients, leading to excessive morbidity and mortality. Although congestion relieve should be a key therapeutic target, traditional bedside assessment is problematic. Ultrasound interrogation of the splanchnic veins emerge as an effective tool to quantify congestion and estimate effects of right atrial pressure to peripheral organs. It should be assessed along with other echocardiographic, hemodynamic and clinical indices to determine how much congestion contributes to organ dysfunction. Additional research is needed for splanchnic vein flow assessment as a valid diagnostic and prognostic tool to guide therapeutic decisions and improve prognosis.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Stavros Dimopoulos 0000-0003-2199-3788; Michael Antonopoulos 0000-0003-2071-9445.

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EDITORIAL

Cardiovascular mechanisms of thyroid hormones and heart failure: Current knowledge and perspectives

Viktor Čulić

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Viktor Čulić, Department of Cardiology and Angiology, University Hospital Centre Split, University of Split School of Medicine, Split 21000, Croatia

Corresponding author: Viktor Čulić, MD, PhD, Full Professor, Senior Scientist, Department of Cardiology and Angiology, University Hospital Centre Split, University of Split School of Medicine, Šoltanska 2, Split 21000, Croatia. viktor.culic@st.t-com.hr

Abstract

A multiple hormonal imbalance that accompanies heart failure (HF) may have a significant impact on the clinical course in such patients. The non-thyroidal illness syndrome (NTIS), also referred to as euthyroid sick syndrome or low triiodothyronine syndrome, can be found in about 30% of patients with HF. NTIS represents a systemic adaptation to chronic illness that is associated with increased cardiac and overall mortality in patients with HF. While conclusions on thyroid-stimulating hormone, free triiodothyronine, total and free thyroxine are currently unresolved, serum total triiodothyronine levels and the ratio of free triiodothyronine to free thyroxine seem to provide the best correlates to the echocardiographic, laboratory and clinical parameters of disease severity. HF patients with either hyper- or hypothyroidism should be treated according to the appropriate guidelines, but the therapeutic approach to NTIS, with or without HF, is still a matter of debate. Possible treatment options include better individual titration of levothyroxine therapy, combined triiodothyronine plus thyroxine therapy and natural measures to increase triiodothyronine. Future research should further examine the cellular and tissue mechanisms of NTIS as well as new therapeutic avenues in patients with HF.

Key Words: Heart failure; Non-thyroidal illness syndrome; Low triiodothyronine syndrome; Therapy; Thyroxine; Triiodothyronine

Core Tip: The non-thyroidal illness syndrome, also referred to as euthyroid sick syndrome or low triiodothyronine syndrome, can be found in about 30% of patients with heart failure (HF). Serum total triiodothyronine levels and the ratio of free triiodothyronine to free thyroxine seem to correlate the best with the echocardiographic, laboratory and clinical parameters of the severity of HF. Future research should further explore cellular and tissue mechanisms of this syndrome as well as possible therapeutic options in patients with HF.

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INTRODUCTION

The cardinal symptoms of heart failure (HF) are fatigue and shortness of breath, which in more severe cases may be accompanied by signs such as peripheral edema, pulmonary crackles and elevated jugular venous pressure[1]. HF is caused by a structural and/or functional abnormality of the heart producing increased ventricular filling pressures and/or impaired cardiac output. According to the left ventricular ejection fraction (LVEF), HF is divided into the 3 subgroups: HF with preserved ejection fraction and LVEF ≥ 50%, HF with mildly reduced ejection fraction in those with LVEF between 41% and 49%, and HF with reduced ejection fraction and LVEF ≤ 40%[1]. In developed countries, primarily due to population ageing and significant advances in the management of cardiovascular diseases, the overall incidence of HF is continuously and substantially increasing[2,3].

HF: MULTIPLE HORMONAL IMBALANCE SYNDROME

A body of evidence suggests that HF is accompanied by a multiple hormonal imbalance which may affect the clinical course of such patients[4]. In older men with HF, a lower endogenous testosterone level contributes to the occurrence of HF[5] due to a lack of testosterone's favorable cardiac and peripheral effects[6], particularly on diastolic function[7]. Since estrogen's cardiovascular effects somewhat protect against HF, estrogen stimulation in postmenopausal women may be useful for improving cardiac functioning in this disease[8,9]. However, in men with HF, circulating levels of estradiol are also inversely associated with diastolic dysfunction independently of circulating testosterone levels and other clinical variables[10], whereas both low and high levels of estradiol are predictors of a poorer prognosis[11]. The multiple hormonal deficiency syndrome associated with HF also encompasses down-regulation of anabolic axes of growth hormone, its tissue effector insulin-like growth factor-1, and insulin signaling[4]. Finally, we now realize that alterations in the serum level, tissue concentration and metabolism of thyroid hormones (TH) are common hormone disturbances which accompany HF.

TH METABOLISM, NON-THYROIDAL ILLNESS SYNDROME AND HF

By stimulating TH receptors present in the heart and vascular endothelial tissue, TH directly regulate the dynamics of the cardiovascular system and may modulate cardiovascular risk factors, primarily arterial hypertension, hyperlipidemia and thrombogenesis. Fluctuation of the TH concentration in both peripheral tissues and circulation substantially affect cardiovascular function, whereas both hyperthyroidism and hypothyroidism may induce HF. Untreated hyperthyroidism may lead to a hyperdynamic state with increased cardiac output caused by increased myocardial contractility and heart rate coupled with increased cardiac preload due to reduced systemic vascular resistance[12]. The long-term consequences of hyperthyroidism include cardiac hypertrophy, chronically increased preload and development of cardiac arrhythmias, all of which may lead to HF[13]. In contrast, hypothyroidism is associated with reduced myocardial contractility, heart rate and cardiac output, and increased peripheral vascular resistance[14]. Both overt[15] and subclinical[16,17] hypothyroidism may be associated with systolic dysfunction of the left ventricle (LV).

Besides hyper- or hypothyroidism, the non-thyroidal illness syndrome (NTIS), also referred to as euthyroid sick syndrome or low triiodothyronine (T_3) syndrome, can be found in about 30% of patients with HF[18,19]. NTIS is not an isolated pathophysiological condition; it is rather a systemic adaptation to chronic illness. NTIS affects the pathophysiology of TH at the level of the hypothalamic-pituitary-thyroid axis, including organ and tissue levels[20]. This syndrome is characterized by a decrease in serum T_3 levels, an increase in reverse T_3 and a reduction in serum thyroxine (T_4). Absent is the expected rise in the serum levels of thyroid-stimulating hormone (TSH)[20]. Changes in serum TH levels have been suggested as an independent predictor of cardiac and overall mortality associated with NTIS[18,21,22]. This is not surprising since TH have important cardioprotective effects against HF at the level of the myocytes, the interstitium and the vasculature, with a strong antiapoptotic effect on myocytes, and reduction of interstitial fibrosis[19]. At the same time, increased reverse T_3, the inactive TH metabolite, is an important predictor of both acute- and long-term

Table 1 The chief areas of future research of non-thyroidal illness syndrome in heart failure

Area of research	Clinical parameters
Best correlations of TH with clinical, echocardiographic and laboratory parameters of HF	Total serum T_3 (LVEF, LVDD, NT-proBNP)
	Free T_3/free T_4 ratio (cardiac chamber diameters, LVEF, NYHA class)
	Reverse T_3 (predictor of mortality)
Possible treatment options	Better individual titration of levothyroxine therapy
	Combined T_3 + T_4 therapy
	Natural measures to increase T_3
Parameters of clinical status/improvement monitoring	LVEF
	LVDD
	NT-proBNP
	HF cardinal symptom attenuation/alleviation
	HF signs attenuation/alleviation

HF: Heart failure; TH: Thyroid hormones; LVEF: Left ventricular ejection fraction; LVDD: Left ventricular diastolic dysfunction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; T_3: Triiodothyronine; T_4: Thyroxine.

mortality[19].

CURRENT KNOWLEDGE AND UNANSWERED QUESTIONS

Given the body of evidence linking NTIS with poor prognosis in HF, three clinically relevant questions remain unanswered: (1) Which TH are most associated with the cardiovascular parameters and should be measured to identify those who should be treated; (2) when and how such patients should be treated; and (3) what parameters should be monitored to assess the efficacy of the therapy (Table 1).

Clinical research has provided some insight into the correlation of particular TH with the clinical parameters of HF. In general, the findings regarding TSH[23-25], free T_3 (fT_3)[25,26], total T_4 and free T_4 (fT_4)[25,27] are, at best, inconclusive. On the other hand, findings on two other TH indicators, although also relatively scarce, seem less contradictory. It has been suggested that total T_3 is closely associated with LVEF[25], LV diastolic dysfunction (LVDD)[25,27] and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels[25,28]. The role of T_3 as the most important TH in HF was strongly supported by a 2008 study by Pingitore *et al*[26]. This study showed that intravenous T_3 administered to patients with chronic HF due to dilated cardiomyopathy produced a significantly improved neuroendocrine profile and ventricular performance expressed through LV end-diastolic volume. Moreover, the stroke volume was increased without change in external and intra-cardiac workload, and was probably mediated through inodilating properties, *i.e.*, positive inotropic effect and a favorable effect of T_3 on diastolic dysfunction and vascular resistance[26]. Additionally, it has been suggested that fT_3/fT_4 ratio is associated with cardiac chamber sizes, LVEF and NYHA class[23,29]. Therefore, it seems that total T_3 and fT_3/fT_4 ratio may serve as the best correlates to cardiac function, clinical status and progression of HF.

TREATMENT POSSIBILITIES

HF patients with either hyper- or hypo-thyroidism should be treated according to the appropriate guidelines. However, the therapeutic approach to NTIS, with or without HF, is still a matter of debate. In the case of persistent symptoms despite previous substitutional levothyroxine therapy and serum TSH values within the reference range, the T_4 plus T_3 combination has been suggested as a treatment option by the European Thyroid Association[30] regardless of reported contradictory findings[31,32]. Perhaps natural measures to raise T_3, such as lowering stress levels, having a healthy diet, along with emphasis on regular exercise[33] and selenium intake[34], may achieve clinically relevant improvement through changes in TH levels in HF patients.

Obviously, it is difficult to distinguish persistent hypothyroid symptoms despite achieved normal TSH from the typical HF symptoms. In this light, the whole concept of NTIS, more commonly called low T_3 syndrome when associated with HF, should be additionally explored in better-designed randomized clinical trials with rigorous selection criteria. The effect of any explored therapeutic option could be assessed by a change in LVEF, LVDD and NT-proBNP levels or through HF symptom alleviation, and correlated with TH improvement. Still, although these suggested therapeutic interventions appear useful and logical, we must be prepared for disappointment, as demonstrated by testosterone supplementation in HF within the physiologic range[35] after several decades of seemingly promising results[36].

CONCLUSION

TH are among the chief regulators of the cardiovascular system. At present, it seems that serum total T_3 levels and a fT_3/fT_4 ratio show the best correlation to echocardiographic, laboratory and clinical parameters of the severity of HF. Future research should further explore the role of hormonal changes in HF, particularly cellular and tissue mechanisms of NTIS as well as possible therapeutic options.

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Country of origin: Croatia

ORCID number: Viktor Čulić 0000-0002-4026-0195.

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OPINION REVIEW

Management of cerebral amyloid angiopathy and atrial fibrillation: We are still far from precision medicine

Liuba Fusco, Zefferino Palamà, Antonio Scarà, Alessio Borrelli, Antonio Gianluca Robles, Gabriele De Masi De Luca, Silvio Romano, Luigi Sciarra

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Liuba Fusco, Department of Cardiology, University Hospital of Northamptonshire, Northampton NN1 5BD, United Kingdom

Zefferino Palamà, Department of Cardiology, Casa di Cura Villa Verde, Taranto 70124, Italy

Zefferino Palamà, Antonio Gianluca Robles, Gabriele De Masi De Luca, Silvio Romano, Luigi Sciarra, Department of Life, Health and Environmental Sciences, University of l'Aquila, L'Aquila 67100, Italy

Antonio Scarà, Alessio Borrelli, Department of Cardiology, GVM Care and Research, San Carlo di Nancy Hospital, Rome 00100, Italy

Corresponding author: Zefferino Palamà, MD, Research Fellow, Department of Cardiology, Casa di Cura Villa Verde, Taranto 70124, Italy. zefferino.palama@icloud.com

Abstract

The use of anticoagulation therapy could prove to be controversial when trying to balance ischemic stroke and intracranial bleeding risks in patients with concurrent cerebral amyloid angiopathy (CAA) and atrial fibrillation (AF). In fact, CAA is an age-related cerebral vasculopathy that predisposes patients to intracerebral hemorrhage. Nevertheless, many AF patients require oral systemic dose-adjusted warfarin, direct oral anticoagulants (such as factor Xa inhibitors) or direct thrombin inhibitors to control often associated with cardioembolic stroke risk. The prevalence of both CAA and AF is expected to rise, due to the aging of the population. This clinical dilemma is becoming increasingly common. In patients with coexisting AF and CAA, the risks/benefits profile of anticoagulant therapy must be assessed for each patient individually due to the lack of a clear-cut consensus with regard to its risks in scientific literature. This review aims to provide an overview of the management of patients with concomitant AF and CAA and proposes the implementation of a risk-based decision-making algorithm.

Key Words: Anticoagulation; Atrial fibrillation; Cerebral amyloid angiopathy; Intracerebral hemorrhage; Stroke; Watchman; Secondary prevention; Left atrial appendage closure

Core Tip: The use of anticoagulation therapy could prove to be controversial when trying to balance ischemic stroke and intracranial bleeding risks in patients with concurrent cerebral amyloid angiopathy (CAA) and atrial fibrillation (AF). This review aims to provide an overview of the management of patients with concomitant AF and CAA and proposes the implementation of a risk-based decision-making algorithm.

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INTRODUCTION

In the last two decades, the management of thromboembolic risk in atrial fibrillation (AF) has dramatically improved, with a continuous reduction of thromboembolic events. Almost all aspects of AF management are based on clear evidence, covering treatment of underlying cardiovascular conditions, rate control or rhythm control, and anticoagulation. However, some clinical settings are yet to be covered by evidence. In particular, the management of patients with both high bleeding and stroke risks could present strong uncertainties in clinical practice. This is the case in patients with concomitant cerebral amyloid angiopathy (CAA) and AF that pose challenges for the risk-benefit balance of anticoagulation therapy. AF, not considered directly life-threatening, is associated with increased cardiovascular diseases (such as heart failure, and pacemaker implantation), ischemic risk (such as stroke) and an overall increased risk of death. Ischemic risk is often reduced by anticoagulants. However, patients with CAA have a high risk of intracerebral hemorrhage (ICH), worsened by anticoagulation therapy[1-3]. This clinical dilemma is increasingly becoming a common scenario, due to the aging of the population. CAA and AF are frequent diseases in older age groups. Both these diseases have seen massive rises in incidence over recent years; with a prevalence of around 5% for moderate to severe CAA in cognitively normal elderly and around 20% for AF in subjects aged > 80 years. In fact, myocardial fibrosis and atrial remodeling play an important role as substrates for AF in the aging heart as well as CAA results from the cerebrovascular deposition of β-amyloid protein in the aging brain. Although CAA could be undetected, based on these epidemiological data, in the elderly population a large cohort has concurrent AF and CAA. In the absence of any specific recommendations regarding anticoagulation management in patients with CAA and AF, all specialists should balance the risk-benefit of each patient's treatment on an individual basis. Many clinical guidelines recommend using validated scores for bleeding and stroke risk. HAS-BLED (hypertension; abnormal renal/liver function; stroke; bleeding history or predisposition; labile international normalized ratio; elderly, age ≥ 65 years; and drugs/alcohol concomitantly) is the common score to predict the risk of major bleeding secondary to anticoagulation, whereas the CHA2DS2-VASc score is used to assess the 1-year risk of stroke in patients with AF and to determine whether anticoagulation therapy is indicated[4,5]. However, these current risk scores might be of limited value for a specific subset of populations, such as patients with concurrent AF and CAA. Better bleeding risk assessment is essential in each older subject. We believe that the increasing impact of CAA in clinical practice and its well-known association with ICH cannot be ignored while establishing whether to start or continue anticoagulant therapies. A search of the literature was carried out to create this review, which aims to provide a clinically oriented update on anticoagulation management for patients with concomitant CAA and AF, focusing on the importance of further factors involved in the risk profile. Specifically, we propose the implementation of a risk-based decision-making algorithm in order to provide a more accurate precision-medicine approach.

CAA and intracranial hemorrhage risk

CAA is a cerebrovascular disorder characterized by the presence of amyloid β-peptide (Aβ) deposits within media and adventitia of small to medium-sized arteries in the cortex and leptomeninges[6,7]. This is a chronic degenerative process that causes changes in blood vessels: loss of smooth muscle cells, fibrinoid necrosis and simultaneous accumulation of Aβ40 species, an eosinophilic hyaline material. That deposition in blood vessel walls can lead to lobar ICH and to smaller areas of bleeding, including cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS). In addition to ICH, CAA can also cause ischemic events such as microinfarcts. Other important clinical manifestations of CAA may include cognitive impairments, transient neurological symptoms, and inflammatory leukoencephalopathy[1,2]. This clinical and pathological heterogeneity could indicate related but distinct phenotypes of CAA, reflected in different clinical syndromes[2-6]. The most common localization is the occipital cortex followed by the frontal, temporal, and parietal cortices[8,9]. Some studies suggest that parieto-occipital regions are related to the most severe CAA[10].

Although the conclusive diagnosis of CAA requires histopathological confirmation, this disease is associated with characteristic magnetic resonance imaging (MRI) biomarkers, including cSS, CMBs, centrum semiovale perivascular spaces, and white matter hyperintensity[2-9]. At present the possible-probable diagnosis is based on a set of pathological parameters, clinical aspects and MRI findings that are termed the Boston criteria 2.0[10,11]. This latest version of diagnostic criteria updates the previous Boston criteria and Modified Boston Criteria (proposed in 1995 and 2010, respectively)[11]. These new criteria take into account hemorrhagic and nonhemorrhagic imaging findings in patients aged ≥ 50 years with spontaneous ICH; transient focal neurological episodes; cognitive impairment or dementia without the presence of deeper hemorrhagic or other causes of hemorrhagic lesions. Probable CAA requires the presence of at

least two strictly lobar hemorrhagic lesions (ICH, cortical CMBs, and cSS or convexity subarachnoid hemorrhage), or at least the presence of a strictly lobar hemorrhagic lesion plus one white matter features[10,11].

Given that the patients with CAA are at notably higher risk of ICH[2], improving accuracy for the diagnosis of CAA is crucial to assess individual bleeding risk and determining the risk-benefit balance for the anticoagulation therapy[12-14]. CAA is one of the most common causes of spontaneous ICH and accounts for 15%-20% of lobar ICHs that are preferentially localized in cortical and subcortical regions[2,15-18]. CAA is also an increasingly recognized cause of recurrent ICH with an annual risk of 9%-10%[18,19]. Within 5 years after the first ICH, 25% of patients with CAA have a new episode.

Some genetic and imaging data have recently shown to be strong predictors of future ICH in patients with CAA and they can help to better stratify the individual bleeding risk such as the presence of cSS, CMBs and apolipoprotein E (ApoE) allele status[12]. cSS represents the hemosiderin deposition in the subarachnoid space that results from extravasation of blood from leptomeningeal vessels. It has been shown to be the strongest predictor of future ICH[12-20] and could represent an independent risk factor for the development of dementia post-ICH[12]. Another important finding for ICH risk stratification is the number and the presence of CMBs. Recent literature has confirmed the association between the presence and number of CMBs and increased incidence of ICH[12-21]. Genetic factors play an important role in the pathophysiology of CAA, such as ApoE genotype; ApoE polymorphisms are associated with an increased risk of lobar ICH[12]. In those carrying ApoE4/E4 and ApoE2/E4, it appears that the E4 allele enhances amyloid deposition in blood vessels in a dose-dependent fashion and the E2 allele is related to the severity of vascular pathology, promoting vessel rupture[12-22].

AF and stroke risk

AF is one of the most common sustained cardiac arrhythmias, and is associated with increased thromboembolic risk[23,24], and, compared to sinus rhythm, it has higher mortality[24]. The rate of stroke (without anticoagulation therapy) can amount to 20% a year, based on the patient's comorbidities[25]. In a large observational cohort, the risk of ischemic stroke in non-anticoagulated subjects with AF ranged from 0.2% to 14.4% yearly. The mortality rates post-stroke ranged from 15% during the first month to 50% during the following 5 years, and the recurrence rate of stroke was high over that period[26]. Antithrombotic prophylaxis with vitamin K antagonists (VKAs) and direct-acting oral anticoagulants (DOACs) is the cornerstone approach to controlling this ischemic risk[5], and it has demonstrated strong protection against first-ever stroke and recurrent events[26-28]. Before the advent of DOACs, warfarin, a VKA, showed effectiveness and safety with a reduction of overall stroke risk by 64%[29,30]. However, there are several practical limitations to using VKAs. These include residual ischemic risk, its narrow therapeutic window, difficulties in achieving it, and monitoring anticoagulation serum levels[26,31,32]. International guidelines have recently prioritized the use of DOACs over VKA for the aforementioned reasons[33].

These new agents do not require frequent therapeutic monitoring due to a predictable pharmacokinetic profile, rapid onset of action, and fewer drug and food interactions[34-35]. These novel drugs have been compared to warfarin in randomized trials and have demonstrated equivalent or improved efficacy in reducing cardioembolic stroke risk in patients with AF, with a lower incidence of ICH[36-39].

At present, several factors can predict stroke in AF: clinical, electrical, genetic and biological markers[4,40]. However, in the current guidelines, the risk stratification model recommended for stroke prediction in patients with AF is the CHA2DS2-VASc score which is based on clinical data[5]. This represents an updated score that has been validated and suggested in the most recent guidelines. Patients with a CHA2DS2-VASc score of ≥ 2 have a stroke risk of around 2.5% annually and should use DOACs or VKAs to reduce this risk. Lower scores are considered to represent a low risk of stroke, with an event rate of around 1% annually. This tool, which helps clinicians to quickly estimate risk relying on only a short set of clinical features (congestive heart failure; hypertension; age ≥ 75 years; diabetes; stroke; vascular disease; age 65-74 years; and sex category), could be insufficient and inaccurate in complex patients that present with other ischemic risk factors[41-43].

Management of ischemic and bleeding risk

The most difficult dilemmas occur when patients with AF and concomitant CAA have an indication for antithrombotic therapy. This is because evaluating the interaction of the many factors involved may prove challenging. Unfortunately, this scenario is becoming progressively common in clinical practice. The prevalence of CAA and AF is strongly age related[1-3,44,45] and increasing rapidly due to improved diagnostic procedures and aging of the global population[2]. The prevalence of moderate-to-severe CAA based on pathology and imaging was around 5% in cognitively normal elderly and up to 50% in patients with lobar ICH[1]. The prevalence of AF is around 1% for individuals younger than 60 years, around 12% for those aged 75-84 years, and up to 20% for people aged > 85 years[2,3,46,47]. The main issue is that in some cases antithrombotic strategies could theoretically do more harm than good.

Even in subjects with low baseline ICH risk, anticoagulation therapy is significantly associated with a higher risk of ICH and ICH-related mortality. Specifically, warfarin increases the risk of ICH by five times compared to placebo, while DOACs showed a 2-3-fold increase in ICH risk[4,47-49]. In a recent systematic review and meta-analysis, all DOACs showed a lower risk of ICH than VKA compared with VKAs, dabigatran reduced the risk of ICH by 60%, apixaban by 57%, edoxaban by 56% and rivaroxaban by 41%[50]. Anticoagulation-associated ICH has a worse outcome than non-OAC ICH, with 50% mortality[47,48]. As discussed above, some providers recommend using CHA2DS2-VASC for ischemic risk score as well as different bleeding scores to determine the risk of major bleeding events secondary to anticoagulation [5,47,51]. The most commonly used is the HAS-BLED score. This bleeding risk score has shown to have moderate predictive abilities and to perform better than other scores[51-53]. However, this approach may be insufficient to estimate the risk of ICH in CAA, as some markers of ICH risk factors such as cSS or lobar CMBs are not systematically included [47-54].

Possible strategies for bleeding risk reduction: management of comorbidities and additional therapies: The correct management of patients with concomitant AF and CAA, besides anticoagulation therapy, includes controlling cardiovascular risk factors (hypertension and statin use) and considering alternatives to anticoagulation [*i.e.*, left atrial appendage closure (LAAC)].

Hypertension is a well-known risk factor for both ischemic and bleeding events and its rigorous control can reduce rates of ICH in primary and secondary prevention[55]. It is plausible that hypertension could play an important role in altering the forces upon the vessel wall, leading to the rupture of the vessel and changing perivascular clearance[48]. A subanalysis of a progress trial showed a risk reduction of 77% in patients with a probable diagnosis of CAA with intensive treatment of hypertension[56], confirming the results from other studies that show a net benefit in patients with CAA to keep blood pressure (BP) < 120/80 mmHg[57]. A single-center observational cohort study also demonstrated an association between BP and the risk of recurrent ICH. The association between elevated BP and ICH recurrence appeared to become stronger with the worsening severity of hypertension[58]. Visit-to-visit BP variable parameters have been shown to be related to the evolution of CMBs and white matter lesions, which could explain the association between high BP and ICH risk[59]. These data strongly suggest the importance of BP control in patients with CAA[58]. Future research could help to individualize the BP-lowering strategy in patients with CAA.

Strong scientific evidence shows the established benefits of statins on cardiac and cerebrovascular diseases, for both primary and secondary prevention[59-63]. However, some studies have suggested a relationship between the use of statins and an increased risk of cerebral hemorrhage. A prospective, randomized, placebo-controlled trial of stroke prevention by aggressive reduction in cholesterol levels demonstrated a beneficial effect of statins on the risk of recurrent stroke, along with an increase in the incidence of ICH in the statin arm compared to the placebo arm[60]. A retrospective review in patients with spontaneous ICH demonstrated an association between statin treatment and an increased number of microbleeds[64]. A recent analysis that used a decision analytic model calculated that statin therapy is predicted to raise the annual probability of lobar ICH recurrence from 14% to 22%[65]. In contrast, many studies have demonstrated a positive effect of statin therapy on ICH risk[66]. A recent nationwide observational study showed that statins were associated with a lower risk of ICH compared with non-statin therapy[67]. Another nationwide follow-up cohort study observed that patients with ICH after therapy with hydrophilic statins had a significantly lower risk of recurrent ICH compared to subjects using lipophilic statins[68]. Currently, in patients with CAA and clear indication for statin therapy according to guidelines, there is no evidence to avoid statin treatment[12].

Most of the thromboembolism in AF that causes ischemic stroke originates from the LAA[69,70]. Closure of the LAA represents a safe and effective strategy for stroke prevention, targeting patients with high bleeding risk[12], and a few clinical data support some devices for percutaneous LAAC. A recent observational cohort study demonstrated that, in subjects with CAA, LAAC was a safe and valid approach to stroke prevention, even without long-term anticoagulant therapy[71]. Nonsurgical LAA closure with a Watchman device has been shown not to be inferior to anticoagulation therapy for ischemic stroke prevention, with an 85% reduction in hemorrhagic stroke[71]. The net benefit of this strategy can be assessed in large prospective studies but at present there is no conclusive evidence.

Discussion and implementation of risk stratification: Aging of the global population and higher survival rates have led to a substantial increase in the prevalence of cerebrovascular diseases associated with chronic cardiac conditions. As a result, clinical practitioners have to deal with increasingly complex decision-making when administering therapy to patients with both high bleeding and ischemic risks. In addition, current guidelines do not set out any clear-cut recommendations as to how to balance the risk-benefit of antithrombotics in a specific subgroup of patients. The suggested risk scores and decisional algorithm do not consider some neurological conditions that can increase hemorrhagic risk. The risk of OAC-ICH in patients with CAA can be calculated based on several clinical and MRI findings. In addition, recent evidence has demonstrated that an integrated care approach in patients with a chronic complex conditions such as AF is associated with an overall benefit in terms of cardiovascular outcomes[72-75]. For those reasons, the international guidelines recommend a holistic approach to managing the AF population. This includes multidisciplinary team care, the use of technology, and comprehensive management of patients' conditions (*e.g.*, comorbidity and cardiovascular risk factors)[76,77]. This approach called the AF better care pathway, has three main components: A covers anticoagulation therapy to avoid stroke; B means better symptom management; and C includes optimization of cardiovascular and other comorbidity risks. The first component encompasses the optimal management of anticoagulation which means maintaining a stable time in the therapeutic range (higher than 65%-70%) for warfarin treatment and appropriate dosage for DOAC treatment. Symptoms management is included in the second component. The last component covers control of cardiometabolic and lifestyle risk factors[78]. Many studies have shown that there is a serious suboptimal prescription of DOACs, especially in elderly patients. The frequent underuse of oral anticoagulants in this high-risk population could be due to many reasons, including worries about cerebral bleeding[79-81]. Older patients, often affected by multiple comorbidities, could complicate the therapeutic decision-making process in optimizing the risks and benefits of OAC[82]. Deeper knowledge about the bleeding risk of each subject can help clinicians better assess the risk/benefit ratio for anticoagulation treatment.

The expansion of an integrated chronic care program could lead to a change in the risk/benefit balance of anticoagulation therapy by encompassing a more accurate evaluation of neurological conditions that can worsen the bleeding risk. We think that CAA may be one of the additional bleeding factors that ought to be suspected in everyday clinical evaluation in elderly people who are candidates for anticoagulation therapy. To go further in this direction, we emphasize the need for an integrated approach with neurological and geriatric assessment, by systematically integrating the probable presence of CAA in elderly candidates for anticoagulation therapy. Randomized trials are urgently needed to evaluate the exact weight of emergent ICH risk factors, implement risk scores, and identify viable ways of decreasing

this risk. For the latter, the following ought to be assessed systematically in patients aged > 75 years (Figure 1): (1) Baseline risk of ICH without anticoagulation; (2) additional ICH risk (by phenotype) in patients with possible/probable CAA; (3) ischemic stroke risk without anticoagulation; (4) management of BP; and (5) evaluation of alternatives to anticoagulation discussion with patients.

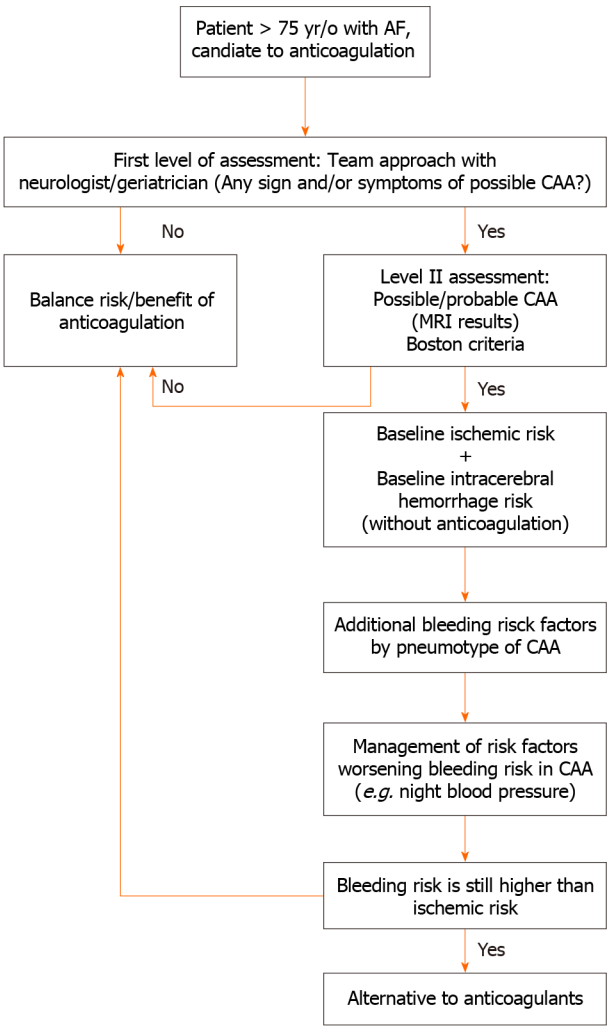

Figure 1 Proposed work flow to evaluate the ischemic stroke and intracranial bleeding risks in patients with concurrent cerebral amyloid angiopathy and atrial fibrillation. CAA: Cerebral amyloid angiopathy; MRI: Magnetic resonance imaging; AF: Atrial fibrillation.

CONCLUSION

Evidence increasingly points to difficulties/limitations in stroke and bleeding risk assessments in AF and CAA. Current guidelines and risk scores do not consider all of the factors involved. Precise identification of these risk factors and their magnitude of risk will promote patient-tailored management for ischemic stroke prevention in the setting of AF. This review aims to reduce the gap between guidelines and precision medicine, helping clinicians in the management of anticoagulation solutions.

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Zefferino Palamà 0000-0002-9262-6654; Antonio Gianluca Robles 0000-0002-2150-3788; Luigi Sciarra 0000-0002-9669-1330.

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REVIEW

Sodium glucose cotransporter-2 inhibitors and heart disease: Current perspectives

Sunetra Mondal, Subhodip Pramanik, Vibhu Ranjan Khare, Cornelius James Fernandez, Joseph M Pappachan

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Sunetra Mondal, Vibhu Ranjan Khare, Department of Endocrinology, NRS Medical College, Kolkata 700020, West Bengal, India

Subhodip Pramanik, Department of Endocrinology, Neotia Getwel Multispecialty Hospitals, Siliguri 734010, West Bengal, India

Cornelius James Fernandez, Department of Endocrinology and Metabolism, Pilgrim Hospital, United Lincolnshire Hospitals NHS Trust, Boston PE21 9QS, United Kingdom

Joseph M Pappachan, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9HT, United Kingdom

Joseph M Pappachan, Faculty of Science, Manchester Metropolitan University, Manchester M15 6BH, United Kingdom

Joseph M Pappachan, Faculty of Biology, Medicine & Health, The University of Manchester, Manchester M13 9PL, United Kingdom

Corresponding author: Joseph M Pappachan, MD, FRCP, Academic Editor, Professor, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Sharoe Green Lane, Preston PR2 9HT, United Kingdom. drpappachan@yahoo.co.in

Abstract

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are antidiabetic medications with remarkable cardiovascular (CV) benefits proven by multiple randomised controlled trials and real-world data. These drugs are also useful in the prevention of CV disease (CVD) in patients with diabetes mellitus (DM). Although DM as such is a huge risk factor for CVD, the CV benefits of SGLT-2i are not just because of antidiabetic effects. These molecules have proven beneficial roles in prevention and management of nondiabetic CVD and renal disease as well. There are various molecular mechanisms for the organ protective effects of SGLT-2i which are still being elucidated. Proper understanding of the role of SGLT-2i in prevention and management of CVD is important not only for the cardiologists but also for other specialists caring for various illnesses which can directly or indirectly impact care of heart diseases. This clinical review compiles the current evidence on the rational use of SGLT-2i in clinical practice.

Key Words: SGLT2 inhibitors; SGLT2i; Cardiovascular disease; Heart failure; Atherosclerotic cardiovascular disease; Diabetic kidney disease

Core Tip: The new antidiabetic medication class sodium glucose cotransporter-2 inhibitors (SGLT-2i) are found to have remarkable cardiovascular (CV) benefits proven by multiple randomised controlled trials and real-world observational studies. They are also useful in prevention of CV disease (CVD) in patients with diabetes mellitus. The CV benefits of SGLT-2i are not just because of antidiabetic effects. The preventive and management effects of SGLT2i molecules in diabetic and nondiabetic renal disease also translate into CV benefits. This clinical update review compiles the up-to-date evidence on the molecular mechanisms of SGLT-2i in prevention and management of CVD for empowering clinicians to rationalise the use of these molecules in day-to-day medical practice.

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INTRODUCTION

Patients with type 2 diabetes mellitus (T2DM) are predisposed to develop atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), increased cardiovascular (CV) mortality, and renal disease. The cardiac manifestations can include coronary artery disease (CAD), HF, atrial fibrillation (AF), as well as ischemic strokes as and peripheral arterial diseases. Also, diabetes increases the risk of developing albuminuria, and chronic kidney disease (CKD), both of which are independent risk factors for CVD. Thus, the combination of diabetes and cardio-renal comorbidities lead to a cumulative increase in the risk for CV events and mortality.

The first Sodium-linked glucose co-transporter-inhibitor (SGLTi) to be isolated was dihydrochalcone phlorizin, a nonselective SGLTi extracted from apple tree roots. Later, the aromatic O-glycoside sergliflozin and the aromatic C-glycoside dapagliflozin became the first selective SGLTi[1]. Currently several SGLT2i molecules like ipragliflozin, dapagliflozin, canagliflozin, empagliflozin, luseogliflozin, and tofogliflozin are available for treating T2DM, while ipragliflozin and dapagliflozin have also been approved for type 1 diabetes mellitus (T1DM) in some countries[1]. Though the cardio-vascular outcome trials (CVOTs) were conducted to demonstrate CV safety of the anti-diabetic agents, the remarkable results with Empagliflozin and Canagliflozin in the Empagliflozin CV Outcome Event Trial in T2DM Patients (EMPA-REG OUTCOME) and Canagliflozin Cardiovascular Assessment Study (CANVAS) trials demonstrating the beneficial effects of SGLT2i on CV events and HF as well as on renal outcomes revolutionised the management of heart disease in diabetes[2,3]. Soon, the CV and renal benefits of SGLT2i became apparent in patients without diabetes[4,5]. Initially marketed as an anti-diabetic agent, SGLT2i soon became a favourite medicine for cardiologists and nephrologists.

SGLT2I IN PATIENTS WITH ASCVD

Cardiovascular outcome trials of SGLT2i in T2DM

Since 2008 the United States Food and Drug Administration (FDA) required CVOTs to demonstrate CV safety for all new antidiabetic medications. These studies were primarily designed to assess whether new medications are non-inferior with respect to placebo for CV events. Generally, these trials do not assess efficacy for glycemic control, but enroll subjects with high CV risk to gather enough CV events in a short time. SGLT2 inhibitors have been evaluated in dedicated CVOTs and real-world studies for their CV safety and benefit. Given the huge benefits observed in different CV risk factors (hypertension, dyslipidemia, body weight, arterial stiffness, endothelial dysfunction), CVOTs of all 4 agents have been completed and the results are summarized in Table 1. A few meta-analyses and real-world data are also published and discussed below.

The EMPA-REG OUTCOME was designed to test the CV safety of Empagliflozin[6]. In this study, 7020 patients with T2DM and established CVD were randomized to receive either 10 or 25 mg of Empagliflozin or placebo over a median observation period of around 3 years. All the participants received the existing standard of care in terms of CV protection and received antiplatelets, lipid-lowering medications, and blockers of the renin-angiotensin-aldosterone system (RAASi). This study showed a significantly lower percentage (10.5%) of the primary outcome, 3 point - major adverse CV event [(3P-MACE), which was a composite of death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke], in the Empagliflozin group compared to the group receiving placebo (12.1%), with a hazard ratio (HR) in the empagliflozin group: 0.86, 95%CI: 0.74-0.99; P = 0.04 for superiority. Regarding the secondary outcomes, empagliflozin treatment resulted in a 32% reduction of mortality from any cause, a 38% reduction in death from CV causes, and 35% lesser rates of hospitalization for HF, although no significant effect was observed in nonfatal MI and stroke rates. Intriguingly, the CV event curves of the empagliflozin and placebo groups started to diverge early after trial initiation.

Table 1 Major cardiovascular outcome trials of sodium glucose cotransporter 2 inhibitors

	EMPA-REG outcome	CANVAS	DECLARE-TIMI 58	VERTIS-CV	SCORED
Intervention	Empagliflozin 10 and 25 mg *vs* placebo	Canagliflozin 100 and 300 mg *vs* placebo	Dapagliflozin 10 mg *vs* placebo	Ertugliflozin 5 and 15 mg *vs* placebo	Sotagliflozin *vs* placebo
Population	*n* = 7020, T2DM with established CV disease	*n* = 10142 patients, T2DM with established CV disease or ≥ 2 CV risk factors	*n* = 17160 patients, T2DM with established CV disease or risk factors for atherosclerotic CV disease	*n* = 8246, T2DM with established CV disease	10584 patients with T2DM and established CV disease or risk factors for athero-sclerotic CV disease
Established CV disease (%)	99	66	41	99	48.6
Follow up period (yr)	3.1	3.6	4.2	3.5	1.3
HbA1c (%) at baseline	7.0% to 10.0% (for those on a stable background therapy); 7.0%-9.0% (for medication-naive patients)	7.0% to 10.5%	6.5% to 12.0%	7.0% to 10.5%	> 7%
Estimated GFR	≥ 30	≥ 30	≥ 60	≥ 30	25-60
Primary outcome, HR (95%CI)	3P-MACE, 0.86 (0.74-0.99)	3P-MACE, 0.86 (0.75-0.97)	3P-MACE, 0.93 (0.84-1.03); CV death or hospitalization for HF, 0.83 (0.73-0.95)	3P-MACE, 0.97 (0.85-1.11)	Total no. of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF 0.74 (0.63-0.88)
Key secondary outcome (s), HR (95%CI)	4P-MACE, 0.89 (0.78-1.01)	All-cause mortality (as below); CV death (as below); progression of albuminuria, 0.73 (0.67-0.79); CV death or hospitalization for HF 0.78 (0.67-0.91)	≥ 40% decline in eGFR to < 60 mL/min/1.73 m^2 or new onset end-stage renal disease or renal/CV mortality, 0.76 (0.67-0.87); all-cause mortality (as below)	CV death or hospitalization for HF, 0.88 (0.75-1.03); CV death (as below); renal death or dialysis/transplant or doubling of serum creatinine from baseline, 0.81 (0.63-1.04)	Total No. or hospitalizations for HF and urgent visits for HF HR: 0.67 (0.55-0.82); deaths from cardiovascular causes (as below)
Other secondary outcomes					
CV death, HR (95%CI)	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.92 (0.77-1.11)	0.90 (0.73-1.12)
All-cause mortality, HR (95%CI)	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.93 (0.80-1.08)	0.99 (0.83-1.18)
Fatal or non-fatal myocardial Infarction, HR (95%CI)	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77 − 1.01)	1.04 (0.86-1.26)	0.68 (0.52-0.89)
Fatal or non-fatal stroke, HR (95%CI)	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	1.06 (0.82-1.37)	0.66 (0.48-0.91)
Hospitalization for HF, HR (95%CI)	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.70 (0.54-0.90)	0.67 (0.55-0.82)

EMPA-REG outcome: Empagliflozin and canagliflozin in the empagliflozin cardiovascular outcome; event trial in type 2 diabetes mellitus patients; CANVAS: Canagliflozin cardiovascular assessment study; DECLARE-TIMI 58: Dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction 58; T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; GFR: Glomerular filtration rate; HR: Hazard ratio; 3P-MACE: 3 point - major adverse CV event; HF: Heart failure; eGFR: Estimated glomerular filtration rate.

The number-needed-to-treat for the empagliflozin group was only 39, indicative of the fact that 39 patients would need treatment with empagliflozin for 3 years to prevent one case of CV mortality.

The CANVAS Program was a composite of two sub-trials: The CANVAS, designed to assess CV safety of Canagliflozin, and the CANVAS-R study (CANVAS-Renal), designed to investigate the effect of canagliflozin on albuminuria[7]. The trial recruited a total of 10142 patients with T2DM, of whom 66% were having established CV disease while 34% had multiple CV risk factors. Patients were randomized to receive Canagliflozin 100 mg, 300 mg, or placebo and the mean follow-up was 3.6 years. Like EMPA-REG OUTCOME, participants were patients treated with routine CV protective regimens using statins, antiplatelets, and RAASi. The primary outcome was significantly lower in the canagliflozin group compared to placebo (26.9 *vs* 31.5 participants per 1000 patient-years; HR: 0.86; 95%CI: 0.75-0.97; P < 0.001 for noninferiority; P = 0.02 for superiority) Additionally, canagliflozin was found to reduce the rate of hospitalization due to HF by 33%. However, there was no significant effect was on all-cause mortality or CV mortality.

The largest CVOT done with dapagliflozin was the 'Dapagliflozin Effect on CV Events-Thrombolysis in MI 58' (DECLARE-TIMI 58) study[8]. A total of 17160 patients with T2DM and established ASCVD (41%) or multiple risk factors for ASCVD (59%) were randomized to receive either dapagliflozin 10 mg or placebo for a median period of 4.2 years. Among two primary outcomes, dapagliflozin was seen to reduce the composite outcome of CV death or hospitalization for HF by 17%, but no beneficial effects were seen in terms of 3P-MACE. Hospitalization due to HF was reduced by 37% and that was the driving factor behind meeting the primary outcome, but no effect was seen in CV death or all-cause mortality. In terms of secondary endpoints, dapagliflozin reduced the composite renal outcome by 24% [≥ 40% decrease in estimated glomerular filtration rate (eGFR) to < 60 mL/min/1.73 m^2, new end-stage renal disease, or death from renal or CV causes], but did not affect the all-cause mortality.

Ertugliflozin was studied in the VERTIS CV Trial, where a total of 8246 patients underwent randomization for ertugliflozin 5 mg, 15 mg, and placebo and were followed for a mean of 3.5 years[9]. Patients treated with Ertugliflozin showed noninferiority for 3P-MACE as compared with placebo (HR: 0.97; 95%CI: 0.85-1.11; $P < 0.001$ for noninferiority). Hospitalization due to heat failure was reduced by 12%, but no benefit was observed in the reduction of CV death, all-cause mortality, or renal outcomes. The basic characteristics of CVOTs are depicted in Table 1.

Sotagliflozin CV outcome trial, SCORED[10], was published recently. It included 10584 patients with established CVD (48.6%) and with multiple risk factors (51.4%) and was randomized between sotagliflozin and placebo and followed up for 1.3 years. Patients treated with sotagliflozin demonstrated a 26% reduction in primary outcome (total number of deaths from CV causes, hospitalizations for HF, and urgent visits for HF) HR: 0.74; 95%CI: 0.63-0.88; $P < 0.001$. There was a 33% reduction in HF, but no benefit was observed for the reduction of CV death. Genital mycotic infections, diarrhea, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than with a placebo.

SGLT2I AND HEART FAILURE

The use of SGLT2i in HF has drastically changed the therapeutic outcomes of these patients. Initially introduced as an agent for glycemic control, SGLT2i gained recognition in the management of HF after the EMPA-REG OUTCOME trial showed a significant reduction in hospitalisation due to HF (HHF) in the empagliflozin group compared to the placebo [2]. This trial and those that were performed in the later years suggested that independent of its glucose-lowering effect, SGLT2i must have a direct effect on HF. The current classification of HF is based on the ejection fraction (EF), with HF with reduced EF (HFrEF) defined as EF ≤ 40%, HF with preserved EF (HFpEF) defined as EF > 50%, and HF with mildly reduced EF (HFmrEF) defined as EF between 40% to 50%[11].

SGLT2i in HFrEF

The DAPA-HF trial recruited patients having HF with an EF ≤ 40% and an eGFR ≥ 30 mL/min per 1.73 m^2. Dapagliflozin was found to reduce the primary composite CV outcomes (which included death from CV causes, hospitalization for HF, or an urgent hospital visit resulting in intravenous therapy for HF) by 24%[4]. The EMPEROR-Reduced trial included patients with HF with a mean EF of 27% and an eGFR ≥ 20 mL/min per 1.73 m^2. There was 22% reduction in the primary composite outcome of CV death or hospitalization for HF in the group receiving empagliflozin[12].

SGLT2i in HFpEF or HFmrEF

In the earlier studies, the beneficial effect of the SGLT2i was demonstrated only in patients with HFrEF, but the EMPEROR-Preserved trial in 2022 showed that empagliflozin improved CV outcomes even in patients with HFpEF[13]. The EMPEROR-Preserved trial was the first trial of SGLT2i which included patients with HFmrEF and HFpEF regardless of whether they had diabetes or not. It was found that with the use of empagliflozin, there was a 19% reduction in the primary composite outcome of CV death and HHF[13]. The recently published DELIVER trial also enrolled patients with HFmrEF and HFpEF. There was an 18% reduction in the primary composite endpoint of worsening HF or CV death[14].

Although the newest addition to the HF therapies, SGLT2i helps in a significant reduction of morbidity and mortality in the entire range of EF. Thus, they form an important pillar in the management of HF. The details of the landmark trials of SGLT2i in HFrEF or HFpEF are outlined in Table 2.

SGLT2i in acute heart failure

In a meta-analysis of RCTs involving 1831 patients with acute HF (AHF), SGLT2i improved the Kansas City Cardiomyopathy Questionnaire scores (mean difference: 4.12; 95%CI: 0.1.89-6.53) and reduced the risk of rehospitalization due to HF (OR: 0.52; 95%CI: 0.42-0.65). However, no significant effect on all-cause mortality was observed. Initiating SGLT2i in patients with AHF did not increase the risk of hypotension or acute kidney injury (AKI)[15].

While SGLT2i use reduces levels of plasma NT-proBNP and improves diastolic function of the heart, improvement in left-ventricular EF was observed only in patients having HFrEF who are in stage C HF. The benefits were not very prominent in patients with HFpEF with HF stages A or B.

SGLT2I AND CV EFFECTS IN T2DM - REAL-WORLD DATA

Real-world data, which possibly better represent everyday clinical practice, do exist in favor of SGLT2i for CV outcome. An observational study from Denmark, Norway, and Sweden by Birkeland *et al*[16] included a total of 91320 patients,

Table 2 Major heart failure trials with sodium glucose cotransporter 2 inhibitors

Trial and medication name	Primary endpoint	Median follow-up	Outcomes
HFrEF			
DAPA-HF (dapagliflozin)	Primary composite outcome: Worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for HF) + cardiovascular death	18 months	Reduction in the primary composite outcome by 24%
EMPEROR-reduced (empagliflozin)	Primary composite outcome: Hospitalisation for heart failure + cardiovascular death	16 months	Reduction in the primary composite outcome by 22%
HFpEF			
EMPEROR-preserved (empagliflozin)	Primary composite outcome: Hospitalisation for heart failure + cardiovascular death	26 months	19% reduction in the primary composite outcome
DELIVER (dapagliflozin)	Primary composite outcome: Worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for HF) + cardiovascular death	28 months	18% reduction in the primary composite endpoint

HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HR: Hazard ratio.

among which 22830 patients with T2DM were on SGLT2i (most commonly Dapagliflozin) and a total of 68490 patients were being treated with other anti-diabetic agents[15,16]. They were observed for a follow-up of around 0.9 years. One-fourth of them already had established CV disease. It was seen that SGLT2i use was associated with a significantly reduced risk of major adverse CV events, CV mortality, and HF-related hospitalisation in comparison to other glucose-lowering drugs. However, the difference in nonfatal MI or stroke was not significant.

SGLT2I IN THE PRIMARY PREVENTION OF CV DISEASES

Though the DECLARE-TIMI 58 and other trials suggested that SGLT2i can reduce the CV composite outcome in patients without established ASCVD, a meta-analysis including data from three major CVOTs with 34322 patients, 39.8% of whom did not have established ASCVD, SGLT2i was found to reduce MACE by 11% (HR: 0.89, 95%CI: 0.83-0.96, $P = 0.001$][17]. However, on subgroup analysis, the benefits were only seen in patients who had established ASCVD [0.86 (0.80-0.93)] but not in those without [1.00 (0.87-1.16), P for interaction = 0.05][16]. The reduction in the composite of CV death or HHF by 23% [0.77 (0.71-0.84), $P < 0.0001$] could, however, be in patients with and without ASCVD and with and without a history of HF. The renal benefits were also seen in both the groups with and without ASCVD. The magnitude of the benefit of SGLT2i differed according to the baseline renal function, with a greater decline in hospitalisations for HF ($P = 0.007$) and a lesser reduction in the progression of CKD ($P = 0.03$) seen in patients with more severe kidney disease at baseline.

CARDIOVASCULAR BENEFIT IN NON-DIABETIC INDIVIDUALS

Some of the SGLT2 trials evaluating kidney and HF outcomes have deliberately enrolled patients without T2DM, but none of these studies were powered to study their effects on atherosclerotic outcomes. Specially, MACE was not included as an outcome in the primary hierarchy of analyses in any of the HF trials like Empagliflozin Outcome Trial in Patients with Chronic HFrEF (EMPEROR Reduced)[17], Empagliflozin Outcome Trial in Patients with Chronic HFpEF (EMPEROR-Preserved)[18], and Dapagliflozin and Prevention of Adverse Outcomes in HF (DAPA HF)[19]. Although in the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA CKD). 3P-MACE (CV death, MI, and stroke) was included as a prespecified, exploratory outcome, but the comparative efficacy of dapagliflozin for this outcome were not presented by baseline T2DM status. Additionally, MACE was seen to occur in only 3% of the trial cohort, meaning that the power was likely insufficient for meaningful MACE analyses classified by T2DM status[20]. Further studies evaluating 3P-MACE in individuals without diabetes may answer this question in the future.

EFFECTS OF SGLT2I ON DIFFERENT CV RISK FACTORS

Trials with various SGLT2i have consistently shown marked benefits in various CV outcomes. This indicates that there might be a class effect of SGLT2i on CV parameters. This benefit cannot be solely attributed to their glucose-lowering effect as significant improvements in different CV outcomes have been found even in patients without diabetes. Instead, the CV benefit is because of the effect of SGLT2i on the various risk factors associated with heart disease most importantly blood pressure control, weight loss, and dyslipidemia. We will now briefly discuss the major CV risk factors and how they are ameliorated by SGLT2i.

Effects on glucose levels

The first indication of SGLT2i after they were designed was to control blood glucose. By inhibiting the SGLT2 co-transporters in the proximal convoluted tubules, they lower the blood glucose and have been found to reduce the HbA1c by around 0.5% in various trials[21]. This would reduce the glucotoxicity and oxidative stress on the cardiac tissues. However, the rapid efficacy observed with the SGLT2i on cardiac endpoints, starting days after the initiation of the drug, suggests other mechanisms playing a role in this cardio-protection.

Effects on body weight

With the use of SGLT2i, there is a loss of glucose in the urine leading to the loss of calories which, in turn, results in the mobilisation of the fatty acids from the adipose tissue stores resulting in weight loss. This has been consistently observed in various trials and metanalyses suggest that the weight reduction is around 2-3 kg[22]. In DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved trials, weight reduction of 0.9 kg, 0.8 kg, and 1.3 kg were observed respectively as compared to the placebo[4,12,13]. Again, this modest weight reduction cannot entirely explain the CV benefit provided by the SGLT2i.

Effects on blood pressure

Hypertension is a very strong adverse risk factor for both HFrEF and HFpEF. Because of the osmotic and diuretic effects of the SGLT2i, there is a modest reduction in blood pressure. In the DAPA-HF trial, there was a mean difference of around -1.4 mmHg in the systolic BP after 8 months which was significant when compared to the placebo. In the EMPEROR-Reduced trial, compared to the placebo, empagliflozin showed a greater reduction (-2.4 *vs* -1.7 mmHg) but it was not significant[4,12]. These modest reductions, although not entirely, will affect the cardiac and vascular remodelling and afterload, leading to improvement in hemodynamics.

Effect on lipid parameters

Although there is a debate regarding the effect of SGLT2i on low-density lipoprotein (LDL) cholesterol, most of the studies showed that there is a minor increase in LDL cholesterol with its use. A study published in 2013 showed an increase in LDL cholesterol by 11.7% with the use of canagliflozin for 52 wk in patients with T2DM[23]. Still SGLT2i has a cardioprotective effect and this paradox can be explained by the fact that SGLT2i might decrease the small dense LDL and increase the large buoyant LDL as was seen with the use of dapagliflozin for 12 wk in T2DM[24]. SGLT2i also resulted in an increase of high-density lipoprotein cholesterol by around 10%-11% with the use of canagliflozin in one study[25]. Moreover, SGLT2i also decreases lipid deposition in the visceral fat, decreases lipid oxidation, and affect the transport of lipid into the cells[26]. All these taken together would provide a cardioprotective benefit with the use of SGLT2i.

Effects on albuminuria and progression of CKD

CV events are the chief cause of mortality in patients with CKD and the risk progressively increases with a decline in eGFR or increasing degrees of albuminuria, making the latter an independent predictor of CV risk[27]. In addition to their glycemic lowering properties and effects on body weight and systemic blood pressure, SGLT2i can reduce intraglomerular pressure, and therefore albuminuria and also slow down GFR decline[28]. Recent data also suggest that SGLT2i can directly reduce oxidative stress, and angiotensinogen levels as well as reduce NLRP3 inflammasome activity in the kidney[29]. The promising results of Canagliflozin in the CREDENCE trial led to it being stopped early and showed a significant reduction in the primary composite end point of ESRD, doubling of serum creatinine, or renal or CV death with up to 32% risk reduction for development of ESRD[28]. It also demonstrated clear benefits on CV outcomes in the advanced CKD group[3]. The DAPA-CKD study with Dapagliflozin was similar except that one-third of the population had other one-third had CKD without T2DM and the endpoints were slightly different. The HR for the renal composite outcome of a sustained decline in eGFR of > 50%, ESRD, or death from renal causes was 0.56 (95%CI: 0.45-0.68; $P < 0.001$) [5].

Effects on uric acid levels in serum

Several studies and meta-analyses have verified the effectiveness of SGLT2i in improving hyperuricemia. The uricosuric effects of dapagliflozin, empagliflozin, and canagliflozin have been seen in patients with or without diabetes[30,31]. The likely mechanism involves the GLUT9 isoform 2. By preventing reabsorption, SGLT2i can increase the concentration of glucose reaching the collecting ducts, which in turn compete with urate for reabsorption *via* the GLUT9 isoform 2 leading to the excretion of more uric acid. Other mechanisms involving activation of the xanthine oxidase by sirtuin activation and alteration of URAT1 transporter have been also proposed[32]. In a nationwide study from Taiwan, that investigated the association, the use of SGLT2i was associated with a lower incidence of gout (HR: 0.89; 95%CI: 0.82-0.96) than DPP4 inhibitors, and this was particularly seen in patients receiving dapagliflozin[33]. Up to 15% reduction in the risk of gout was observed with SGLT2i. Another meta-analysis of 62 studies, including 34941 patients, however, reported that although all the SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, tofogliflozin, luseogliflozin, or ipragliflozin) significantly decreased uric acid levels, empagliflozin resulted in the most superior reduction[30]. No consistent dose-related effects were observed.

Effects on haematocrit

All SGLT2i has been associated with a modest increase in haematocrit between 2%-4%. This effect was seen with empagliflozin in patients with T2DM and stage 2 or 3 CKD, but not stage 4 CKD. Though initially thought to be due to its diuretic effects, the urine volume returns to baseline within 1 wk of SGLT2i, whereas the increase in haematocrit

continues beyond 2 months. In patients with diabetes mellitus, increased glucose uptake by SGLT2 in the proximal tubular epithelial cells results in increased ATP consumption by the Na^+/K^+ pump. There is increased oxygen consumption by the proximal tubular mitochondria to meet the high demand for ATP, resulting in a relative hypoxia within the renal cortical cells[34]. Selective damage to the proximal tubular epithelial cells as seen in diabetic kidney disease induces trans-differentiation of the erythropoietin-producing fibroblasts into myofibroblasts[35], which loses the capacity to produce erythropoietin and starts producing fibrogenic molecules. Low erythropoietin levels have been demonstrated even in patients with T2DM with normal kidney function[36]. This might be due to metabolic stress associated with excessive glucose resorption by the tubular epithelial cells causing a hypoxic microenvironment. SGLT2i can reduce this metabolic stress and reduce ATP consumption by the Na^+/K^+ pump, causing a possible reversion of myofibroblasts to erythropoietin-producing fibroblasts and elevation of the haematocrit. Additionally, the nephroprotective effect of SGLT2i which prevents progression of CKD can also improve erythropoietin levels.

Effects on inflammatory markers

Inflammation is a key component in the development of atherosclerosis and plaque destabilisation/rupture. Indeed, SGLT2 inhibitors have all been shown to reduce inflammation in Apo E -/- mice[37]. Reduced IL-1β, IL-6 and IL-10 levels have been seen with empagliflozin, while dapagliflozin has demonstrated reduced NLRP3, IL-1β and IL-18 levels[38]. Canagliflozin has demonstrated significant reduction in the adhesion molecules, VCAM-1 and MCP-1, while increasing the TIMP-1 inhibitor[37,38]. These anti-inflammatory and vaso-protective effects might explain some of the major mechanisms involved in the CV and nephroprotective benefits of sodium glucose cotransporter-2 inhibitors (SGLT-2i) molecules.

Effects on metabolic syndrome-associated fatty liver disease

The effects of SGLT2i on body weight and their antioxidant and anti-inflammatory effects make them promising candidates for the management of MAFLD. In addition to decreases in in insulin and glucose levels in T2DM, SGLT2i can lead to reduction in the de-novo lipid synthesis in the liver[39]. Also, the glucagon-secreting alpha cells express SGLT2, and inhibition of this reduces intracellular glucose concentration in them thus increasing the secretion of glucagon[40]. The high glucagon levels and elevated glucagon/insulin ratio can stimulate β-oxidation leading to a shift from carbohydrate to fatty acid metabolism and reduction in the hepatic triglyceride content[41]. Thus, SGLT2i can play an important role in reducing hepatic lipid content by reduction in de novo lipid synthesis due to reduced blood glucose and insulin levels along with increased beta-oxidation of fatty acids.

A study comparing ipragliflozin to Pioglitazone found that while pioglitazone demonstrated benefit in terms of reduction in serum ALT and HbA1c; reductions in body weight and visceral fat were seen in those with Ipragliflozin[42]. Canagliflozin has been found to significantly reduce FIB-4 index and ferritin levels in T2DM patients with MAFLD, suggesting improvement in hepatic fibrosis[43]. Dapagliflozin has also been shown to reduce Fibroblast Growth Factor 21 levels and indices of hepatocyte injury[44]. A study using serial liver biopsies showed Canagliflozin use for 24 wk showed remarkable histologic improvement of metabolic-associated steatohepatitis (MASH); with even demonstration from MASH to borderline or non-MASH status[45].

Effects on obstructive sleep apnea

Obstructive sleep apnea (OSA) is related to CVD development and has been identified as a modifiable CV risk factor[46]. SGLT2i have been found to reduce apnea-hypopnea index in patients with T2DM with OSAS in small studies, though their beneficial effects on OSA or sleep-disordered breathing have not been substantiated by other studies or meta-analyses[47-49]. Apart from weight reduction, other postulated beneficial mechanisms could include rostral nasal fluid shift due to diuresis and reduction of circadian sympathetic nerve activity, nocturnal hypertension, and oxidative stress by which SGLT2i might reduce the incidence or the CV effects of OSA[50,51]. Further studies are required to elucidate the benefits of SGLT2i in this regard. The CV benefits of SGLT2i are depicted in Figure 1.

CARDIOVASCULAR BENEFITS WITH SGLT2I - POSSIBLE MECHANISMS

The mechanisms that drive the CV benefits of SGLT2i can be grossly categorised into hemodynamic alterations, metabolic changes, and direct effects on the cardiomyocytes. The CV benefits with Empagliflozin were seen as early as 12 wk after randomization, when the patients treated with empagliflozin were found to have lower rates of HHF (0% *vs* 2.9%), of the composite of HHF/CV deaths (0.2% *vs* 4.1%), and of the composite of HHF or all-cause mortality (0.2% *vs* 4.1%)[52]. A posthoc analysis of the EMPAREG-OUTCOME trial showed that the reduction in risk for empagliflozin *vs* placebo reached a significance at day 17 for HHF, day 27 for the composite of CV death/HHF, and day 59 for CV deaths[53]. The direct effects on the cardiomyocytes have been seen in several in-vitro studies and animal models, but the time taken for these effects to manifest as beneficial effects on the functioning of the human heart is not clear.

Given that the cardioprotective effects of glycemic or weight reduction and other metabolic effects would take more time to manifest, the hemodynamic alterations and effects on the cardiomyocyte actions with SGLT2i may have a more important role behind the early benefits. However, in the long run, the metabolic effects become equally important as the benefits are sustained throughout use[53]. The effects of SGLT2i on different hemodynamic and metabolic risk factors that drive ASCVD or HF are discussed in an earlier section. In the ensuing part, we have discussed the direct effects of SGLT2i on the structure and functioning of the myocardium and blood vessels.

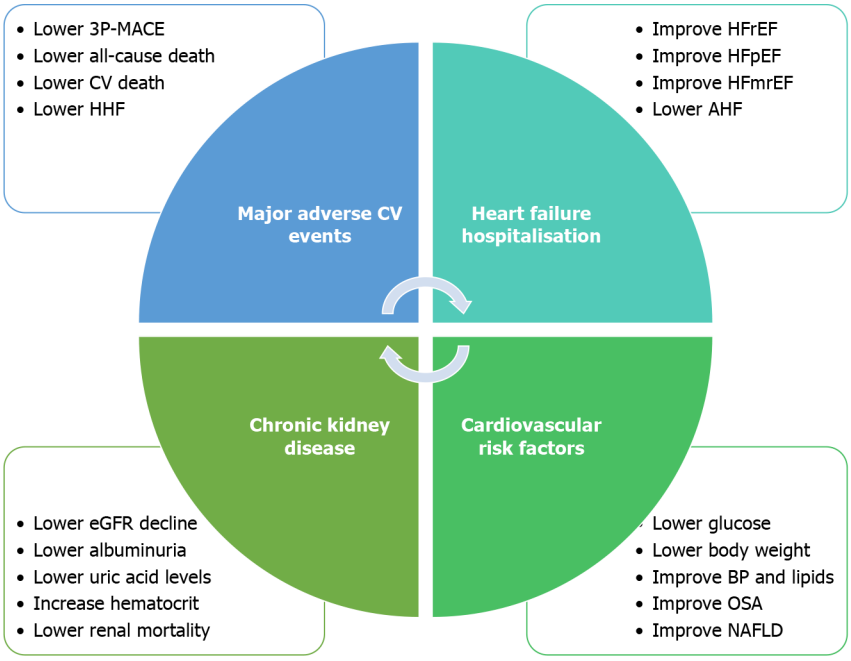

Figure 1 Cardiovascular benefits of sodium glucose cotransporter 2 inhibitors - the evidence from trials. CV: Cardiovascular; HHF: Hospitalisation due to heart failure; 3P-MACE: 3 point - major adverse cardiovascular event; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; AHF: Acute heart failure; OSA: Obstructive sleep apnea; NAFLD: Non-alcoholic fatty liver disease; eGFR: Estimated glomerular filtration rate; BP: Blood pressure.

SGLT2I - DIRECT EFFECTS ON MYOCARDIUM AND BLOOD VESSELS

Studies with SGLT2i suggest that the effects of SGLT-2i may not cause significant changes in cardiac stroke volume or output in patients with or without established CV disease. However, diastolic function appears to be directly influenced by SGLT-2i and significant decreases in left ventricular mass have been documented following treatment with SGLT2i [54]. Both of these are associated with endothelial dysfunction, and it is possible that SGLT-2i, by improving endothelial dysfunction, inhibits negative cardiac remodelling and improves diastolic function. The receptors and mediators through which SGLT2i exert their direct effects on the cardiomyocytes remain to be fully elucidated. Cardiomyocytes have been found to express SGLT1, which may be one of the targets for SGLT2i[54]. However, the effects of SGLT2i on HF may not only be mediated by their target receptors. SGLT2i have been found to directly inhibit Na^+/H^+ exchanger-1 (NHE1) in cardiomyocytes. Also, dapagliflozin has been found to directly activate AMP-activated protein kinase (AMPK) leading to reduced lipopolysaccharide-induced myocardial fibrosis[55]. Other cardiac sodium channels like Nav1.5 have also been found to be the targets for SGLT2i and inhibiting these sodium channels can ameliorate dysfunctional calcium overload [56].

Effects on myocardial fuel energetics

Under physiologic circumstances, cardiomyocytes prefer fatty acids as the predominant metabolic fuel for energy generation which account for 70%-90% of ATP synthesis. Although fatty acid metabolism produces more ATP than glucose, complete oxidation of the former also requires more oxygen. In those with diabetes mellitus, due to lesser glucose uptake in cardiomyocytes, they utilise more fatty acids and less glucose as the preferred substrate for oxidative metabolism, leading to greater oxygen consumption and decreased pumping efficiency of the heart[57,58]. SGLT2i has been found to benefit myocardial energy metabolism by increased GLUT1 expression and therefore increased glucose uptake in the human and murine myocardium. Enhanced rates of glycolysis and glucose oxidation have also been demonstrated in the myocardium of db/db mice[59,60]. In mouse models with diabetes, it has been demonstrated that there is increased expression of the O-palmitoyl transferase (CPT) isoform CPT1b on the outer mitochondrial membrane, which facilitates mitochondrial transport and β-oxidation of fatty acids in cardiomyocytes. Empagliflozin was found to reduce mRNA and protein expression of CPT1b[61]. Additionally, empagliflozin has been found to inhibit the mRNA and protein expression of CD36, which serves a downstream mediator of PPAR-γ in cardiomyocytes[62,63]. Following activation of PPAR-α, fatty acid uptake is enhanced compared to glucose. Thus, this effect of SGLT2i might reduce the uptake and accumulation of fatty acids within the myocardium.

One meta-analysis of RCTs showed that SGLT2i can increase adiponectin levels in T2DM[61]. Adiponectin has a negative correlation with serum triglycerides and higher adiponectin levels lead to enhanced utilization of glucose and fatty acids by muscle tissue. SGLT2i increases myocardial utilization of ketone bodies to increase ATP production. Although empagliflozin has not been seen to directly improve the efficiency of myocardial ketone body utilization, empagliflozin can increase levels of ketone bodies in serum, predominantly by promoting expression of the enzyme HMG CoA Synthase which is necessary for ketone body production[64]. The "thrifty" or frugal fuel hypothesis suggests

that ketonemia and ketone body utilisation by cardiomyocytes can increase the efficiency of cardiac mitochondrial oxidation[65].

Effects on myocardial mitochondria

Cardiac mitochondrial dysfunction is a factor behind diabetic cardiomyopathy. Under hyperglycemic conditions, mitochondria within cardiomyocytes undergo dynamin-related protein 1 (Drp1)-mediated fission, ultimately leading to fragmentation, ROS production, and increased oxidative stress. Dapagliflozin significantly reduced myocardial mitochondrial Drp1 level thereby reversing this impairment[66]. Similarly, SGLT2i have been found to normalise the alteration in proteins like MFN1, MFN2 and OPA1 which are responsible for mitochondrial fusion[66]. Additionally, empagliflozin has been seen to reverse the downregulation of *PGC-1α*, *NRF-1*, and *mtTFA* in rat models of T2DM[67]. These allow increased transcription and replication of mitochondrial DNA and activation of mitochondrial electron transport chain (ETC). Hyperglycemia increases O-GlcNAcylation, which in turn leads to decreased activity of ETC complexes I, III, and IV. Dapagliflozin and other SGLT2i can directly reduce O-GlcNAc transferase activity, leading to improvement in the functioning of the mitochondrial respiratory chain[68].

Effects on endothelial cells

Empagliflozin leads to activation of AMPK and inhibition of Drp1 by serine phosphorylation, leading to anti-inflammatory effects on arterial endothelial cells[69]. Dapagliflozin activates voltage-dependent K^+ channels, also known as the Kv channels, which are responsible for maintaining the membrane resting potential and vascular tone. Opening of these channels will lead to hyperpolarization and endothelial-independent vascular smooth muscle relaxation and vasodilation. SGLT2i have been found to inhibit TNFα-induced ROS generation and therefore reduced NO consumption in coronary arterial endothelial cells. Reduced serum uric acid concentrations with SGLT2i can also lead to increased NO synthase activity and improved NO synthesis[55]. Improved flow-mediated dilation has been seen with dapagliflozin, which might be dependent on COX-2 inhibition and reduction in ROS production[70]. SGLT2i have been found to inhibit COX-2 mRNA expression[71].

Effects on ventricular compliance, myocardial fibrosis, and infarct size

Chronic hyperglycaemia increases formation of AGEs by nonenzymatic glycation of proteins. AGEs activate the receptor for AGE (RAGE) leading to proliferation, function, and migration of cardiac fibroblasts, ultimately ending in myocardial fibrosis and cardiac aging. Empagliflozin has been shown to inhibit the AGE/RAGE axis in the kidney, though this action has still now not been demonstrated in the heart[72]. SGLT2i acts directly on cardiomyocyte NHE1 to reduce cytosolic Na^+ and thereafter Ca^{2+} accumulation within the cardiomyocyte[69].

People living with diabetes have larger size of myocardial infarcts than non-diabetics. SGLT2i can promote angiogenesis by reducing the loss of CD31+ micro-vessels, leading to reduction in the size of perfusion defects in diabetes model mice[73]. SGLT2i improves ventricular remodelling and reduces myocardial fibrosis by modulating macrophage polarization in the cardiomyocytes and reducing myocardial expression of collagen I and collagen III proteins as also pro-fibrotic molecules like TGF-β1, p-Smad2, and p-Smad3[71].

Empagliflozin has been found to improve ventricular remodelling in diabetic patients. Empagliflozin increases NO and cGMP concentrations as well as sGC and PKGIα activity leading to a decrease in cardiomyocyte stiffness[74]. Empagliflozin has been shown to reduce left ventricular mass in patients with T2DM and improve left ventricular hypertrophy[75].

Effects on oxidative stress

Canagliflozin and empagliflozin have been found to activate and restore eNOS activity in the myocardium, while the former also reduced iNOS levels, which in turn decreased superoxide and nitrate[76]. In animal T2DM models, SGLT2i has been shown to increase lipid hydroperoxide and MDA levels significantly compared to the control group, while reducing levels of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD). Empagliflozin has the potential to reverse the imbalance between pro-oxidant molecules like lipid hydroperoxide and MDA levels and anti-oxidant molecules like GSH-Px and SOD in T2DM models, possibly by activation of the Nrf2/HO-1 pathway[77]. SGLT2i also activates Silencing information regulator 2 related enzyme 1 (SIRT1) and corresponding downstream pathways, which might explain how SGLT2i can decrease oxidative stress in diabetic cardiomyopathy *via* the SIRT1/Nrf2 signalling pathway in T1DM or the Sirt1/fork head box[69].

Protective effects against myocardial apoptosis

Diabetes is known to promote programmed cell death of cardiomyocytes. The SGLT2i inhibits caspase-3 activity in the myocardium, as also inhibits the ERK1/2 pathway and promotes the STAT3 pathway, ultimately leading to decreased cardiomyocyte apoptosis[78]. Dapagliflozin has been seen to reverse the increased NLRP3, ASC, IL-1β, or caspase-1 in mice models with T2DM, which reflects increased NLRP3-inflammasome complex formation and risk for pyroptosis (a highly inflammatory type of programmed cell death)[79].

Empagliflozin has been reported to inhibit enhanced crease autophagy of cardiomyocytes by downregulation of *NHE1* and *NHE1*-related genes like *Beclin 1* which induce autophagy[80,81]. ER stress leads to the accumulation of misfolded or unfolded proteins thus initiating an unfolded protein response (UPR) that leads to apoptosis of cells. In ER stress models induced by pressure overload or ischemic injury, SGLT2i, *via* SIRT1 activation and GRP78 reduction can inhibit the increase in p-PERK and its downstream molecules which are associated with ER stress[82,83].

OTHER MECHANISMS OF CARDIOVASCULAR BENEFIT WITH SGLT2I

Effects on the intestinal microbiota

Dapagliflozin has shown favourable alteration in the gut microbiota, including an increased abundance of *Akkermansia muciniphila*[84]. This has been associated with improved glycemic profile and improved generalized vascular functioning in mice with T2DM. Induction of the expression of tight junctions in the gut also reduces endotoxemia-related inflammation and prevents atherosclerosis. Luseogliflozin was found to increase the abundance of other bacteria like *Syntrophothermus lipocalidus*, *Parabacteroidesdistasonis distasonis*, and *Anaerotignum sp*, which produce short-chain fatty acids (SCFAs) which leads to improvement in diabetes and CV function[85]. However, these changes in gut microbiota have not been confirmed in patients with T2DM. The possible mechanisms of CV benefits from SGLT2i are summarised in Figure 2.

Effects on sympathetic nervous system activity

Since sympathetic nervous system hyperactivity is intricately linked with the initiation, progression, and deterioration (poor prognosis) of chronic human HFrEF, in a mechanism akin to β-blockers, SGLT2i, by suppressing sympathetic neural activity can protect the failing myocardium against adrenergic overstimulation. In the EMPA-REG OUTCOME Trial, empagliflozin was found to reduce heart rate somewhat unexpectedly. Consistent with this, Luseogliflozin was also found to cause bradycardia in patients with baseline elevated heart rate. Studies have shown that the FFAR3 (GPR41) receptors are abundant on sympathetic ganglia and nerve endings; and while SCFAs, *via* their stimulation of FFAR3 leads to activation of sympathetic neuronal firing, the ketone body 3-hydroxybutyrate can block it leading to reduced norepinephrine release from sympathetic nerve terminals. The SGLT2i, by their potential to increase production of ketone bodies in humans, could potentially exert sympatholysis by this mechanism[86].

Additionally, treatment of HFD-fed mice with dapagliflozin has demonstrated diminished tyrosine hydroxylase activity in the medulla, primarily by inhibition of G-protein coupled receptor kinase 2 (GRK2) leading to reduced noradrenaline levels. GRK2 has inhibitory effects on the α2-adrenergic receptor (α2-AR) which mediates the feedback mediated reduction in catecholamine release from sympathetic nerve terminals. Downregulated GRK2 by Dapagliflozin can thus lead to increased α2-AR mediated feed-back and an overall reduced catecholamine release from the nerve terminals[87].

Notably, while SGLT2 inhibition can affect sympathoinhibition in some critical target organs, such as the heart and the kidneys, dapagliflozin has been shown to promote sympatho-excitation in white adipose tissue. Increased mRNA levels of the brown adipose tissue-selective gene Ucp1 and its upstream mediator, Pgc-1 has been demonstrated suggestive of "beiging" effect of dapagliflozin[87]. Thus, available evidence suggests SGLT2i can potentially reduce secretion of catecholamines and their effects on the myocardium but promotes sympathetic overactivity of white adipose tissue.

ROLE OF SGLT2I IN ATRIAL FLUTTER/FIBRILLATION

The presence of diabetes mellitus independently predicts the risk for AF[2], and diabetes is part of the CHA_2DS_2-VASc score used to predict stroke risk in patients with AF. HF increases the risk of arrhythmias including atrial flutter and/or fibrillation and the presence of AF is associated with adverse outcomes in patients with HFrEF and HFpEF. In the DECLARE-TIMI 58 trial, dapagliflozin was found to reduce the relative risk of AF by 19% (HR: 0.81, 95%CI: 0.68-0.95)[8]. Also, empagliflozin has demonstrated a greater absolute benefit on renal and HF-related events in individuals with a history of AF (HR: 0.58, 95%CI: 0.36-0.92) and without AF (HR: 0.67, 95%CI: 0.55-0.82, $P_{interaction}$ = 0.56)[88]. The reduction in AF events was seen regardless of the presence of HF, and ASCVD. Other CVOTs of patients with diabetes mellitus also reported lower rates of AF with SGLT2i inhibitor, though the absolute reduction was small ranging between 0.1% to 0.2% per year. However, no consistent reduction in stroke was found. Factors that may contribute to a reduction in atrial tachyarrhythmias could be reduced rates of HF and atrial stretch, reduction in blood pressure and improvements in cardiomyocyte energetics, and arterial compliance. There needs to be additional studies to confirm the reliability and clinical importance of this finding.

ROLE OF SGLT2I IN CARDIAC AUTONOMIC NEUROPATHY

Patients with long-standing diabetes can have cardiac autonomic neuropathy (CAN), in which sympathetic tone predominates over parasympathetic activity. This significantly increases CV morbidity and mortality with a high risk for sudden cardiac death. Unfortunately, to date, there is no definitive treatment for CAN. SGLT2i, by its property to reduce sympathetic nervous system activity, offers hope in the management of CAN. Small studies have demonstrated that SGLT2i can reduce the risk of recurrence of vasovagal syncope, which is related to altered autonomic system function, as evaluated by heart rate variability (HRV), and by ^{123}I-metaiodobenzylguanidine myocardial scintigraphy indexes and also improve HRV and heart rate turbulence parameters while decreasing the frequency of ventricular premature beats[89]. However, in a preliminary analysis of data from the EMPA-HEART CardioLink-6 trial, Holter monitoring analyses and automated algorithms to determine HRV domain measures over 6 months found that the observed cardiac benefits of empagliflozin were not likely associated with modulation of autonomic tone in patients with T2DM and stable CAD[90].

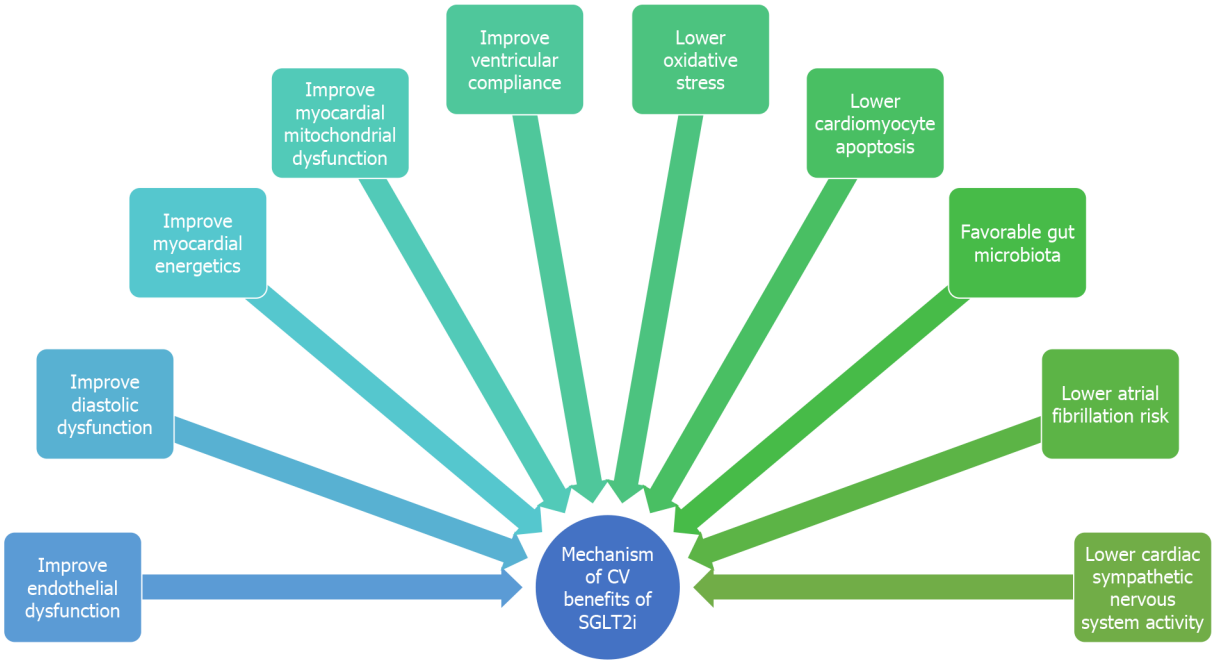

Figure 2 Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 inhibitors. CV: Cardiovascular; SGLT2i: Sodium glucose cotransporter-2 inhibitors.

CAUTION AND CONTRAINDICATIONS TO THE USE OF SGLT2I IN HEART DISEASE

SGLT2i have been associated with different adverse effects. The glucosuric effect of SGLT2i leads to higher urine glucose levels and thus predisposes patients to urinary tract and genital infections. The data regarding urinary tract infection is conflicting among different studies, but most studies report neutral findings. In the large three CVOT outcome trials, the rates of UTI were not significantly increased when compared with placebo[6-8]. In 2013, one meta-analysis reported a higher incidence of UTI between SGLT2i and either placebo or active competitors[91]. But two subsequent metanalysis refuted this finding[92,93]. Available real-world data highlight the fact that SGLT2i do not increase the frequency of UTIs compared to either DPP 4 inhibitors or GLP1 receptor agonists[94,95]. However, genital mycotic infections have been consistently found to be more frequent in patients on SGLT2i in all three major CVOT outcome trials[6-8] as well as in different meta-analyses[92,93]. Risk factors for genital mycotic infection include female gender and previous history of genital infection. However, the genital infection tends to be non-severe and manageable with systemic or topical antifungal agents without the need for treatment discontinuation[96].

SGLT2i have an osmotic diuretic effect, thus a mild volume depletion state can be observed with them. A slight reduction in blood pressure, orthostatic hypotension, and dizziness can occur with these agents especially when combined with diuretics. A meta-analysis did not find a higher volume depletion with SGLT2i compared to placebo[97]. Still, it is recommended to review the dose of diuretics while initiating a patient with SGLT2i to prevent postural hypotension.

The use of SGLT2i is associated with increased circulating ketone bodies. The incidence of euglycemic diabetic ketoacidosis varies from study to study. CANVAS and EMPAREG trials reported a nonsignificant increase of euglycemic DKA, but DECLARE-TIMI 58 reported a small but significant increase of the same[6-8]. Two meta-analyses reported a nonsignificant increase in the rates of DKA among SGLT2i versus placebo or other anti-diabetic agents[98,99]. Real-world data however suggests slightly higher rates of DKA among SGLT2i users[100,101]. This difference of results might be due to the controlled conditions of RCTs and the cautious selection of participants. Risk factors for euglycemic DKA included T1DM, presence of dehydration, excess alcohol intake, critical illness, post-operative period and intake of very low-carbohydrate diet.

The FDA had issued a warning for AKI with dapagliflozin and canagliflozin in 2016 based on few case reports submitted to the FDA adverse events reporting system (FARES). The possible mechanisms that mediate renal damage by SGLT2i could be related to volume depletion by osmotic diuresis, decreased trans glomerular pressure, and hypoxic injury to the renal medulla[102]. However, none of the CVOTs[6-8] reported a higher incidence of AKI with SGLT2i and the dedicated renal outcome trials reported SGLT2i to be beneficial for renal outcome[20,103,104]. The real-world data also suggest the use of SGLT2i is not associated with an increased risk for AKI[105]. However, a careful selection of patients initiated on an SGLT2i and close monitoring of eGFR would be useful to reduce the likelihood of AKI in the real-world clinical practice settings.

There was a postulation that SGLT2i may affect bone mineral density and bone quality, thereby increasing the risk for fragility fractures. Initial studies with canagliflozin reported a mild increase in serum phosphate, parathyroid hormone, bone resorption markers, and bone formation markers and a slight reduction in total hip bone mineral density without affecting the rest of the skeleton[106,107]. In the CANVAS trial, the risk for fracture was significantly higher with

canagliflozin versus placebo but the same finding was not replicated in other two large CV outcome studies with empagliflozin and dapagliflozin[6-8]. The underlying mechanism for increased incidence of fracture with canagliflozin can be a direct effect on bone metabolism, or it can be due to an increased risk for falls due to orthostatic hypertension associated with SGLT2i. Recently three meta-analyses[108-110] did not find any increased incidence of bone fractures with SGLT2i compared to either placebo or active treatment, thus reassuring about the fracture risk of this class of drugs.

An increased incidence of lower limb amputations was seen with canagliflozin compared to placebo (6.3 *vs* 3.4 participants with amputation per 1000 patient-years) in CANVAS trial[7] as well as in a pharmacovigilance analysis of FARES data[111], but not with other SGLT2i. The difference can be partly explained by the differences in study design and data collection regarding lower limb amputation. A recent meta-analysis[112] of 14 RCTs reported no increase in lower limb amputation with SGLT2 inhibitor as a class. However, upon subgroup analysis there was a higher fracture risk with canagliflozin versus placebo or non-SGLT2i antidiabetic drugs. The fact that there is inter-SGLT2i differences in the risk for fractures and for lower limb amputation remains to be confirmed yet.

A concern regarding an increase in bladder malignancies in male patients receiving dapagliflozin was raised in initial studies but was not clear whether it was due to earlier diagnosis of malignancies in the sub-clinical phase or there indeed was a true increase in rates of bladder cancer[95]. Possible mechanisms for tumor genesis with an SGLT2i could be the enhanced tumor growth from bladder epithelium due to persistent glycosuria in as well as the effects of chronic cystitis or recurrent urinary tract infections. However, one metanalysis[113] did not confirm any significant increase in malignancies with the use of SGLT 2 inhibitors, and further research is needed in this field.

SGLT2 IN THE PREVENTION/MANAGEMENT OF HEART DISEASES: RECOMMENDATIONS

Table 3 summarises the current position of different bodies regarding the use of SGLT2i in patients with heart disease with and without diabetes. While they don't specifically prefer one SGLT2i over another, for a particular indication, all the bodies recommend using SGLT2i that have proven benefits in that aspect.

CHOICE OF SGLT2I - ARE THEY ALL THE SAME?

Although an overall beneficial effect is obvious, there is some heterogeneity in the findings from different SGLT2i CVOTs. Also, although no head-to-head comparison data between the SGLT2i are available, there has been some numerical differences in their results. Whether the differences arise from variation in the pharmacologic properties of the various SGLT2 inhibitors or are the result of disparities in trial design and/or baseline characteristics of the study participants remain unclear. However, the latter limits direct comparability of the CVOTs.

One postulated mechanism has been the differences in specificity of the molecules to the SGLT2 receptor over SGLT1, which is greater than 2500-fold for empagliflozin, 2235-fold for ertugliflozin, 1200-fold for dapagliflozin and 200-fold for canagliflozin[114]. In the EMPA-REG trial, empagliflozin users showed a mean improvement in HbA1c by 0.24% over 206 wk, while canagliflozin over 188 wk resulted in improvement by 0.58% in the CANVAS program.

A network meta-analysis of 38 RCTs including canagliflozin, dapagliflozin or empagliflozin that were published up to November 2015 found that canagliflozin 300 mg reduced HbA1c, FPG and systolic blood pressure and increased LDL cholesterol to a greater extent compared to other SGLT2i or to 100 mg Canagliflozin[115].

However, contrary to the biologic plausibility based on SGLT2 selectivity, the CV superiority for 3P-MACE has been seen with empagliflozin in the EMPA-REG and to some extent with canagliflozin use in the CANVAS and CREDENCE studies, but it has not been seen with dapagliflozin in the DECLARE-TIMI, or with ertugliflozin in the VERTIS-CV trials [6-9].

Although the half-lives, metabolism and elimination of these drugs are quite similar, their oral bioavailability is variable, lowest being for canagliflozin (65%) and the highest for ertugliflozin (100%). There is also some variation in the volume of distribution and plasma protein binding. But to what extent these differences translate into clinically important discrepancies is yet unknown[116].

All the SGLT2i so far have demonstrated non-inferiority for 3P-MACE compared to placebo, and superior outcomes with respect to HHF outcomes, except for ertugliflozin which failed to demonstrate superiority in the VERTIS-CV trial. The studies included population with different co-morbidities and risk factors which can significantly reduce the incidence of CV or renal events during the study period. In the EMPA-REG and VERTIS-CV trials, all the participants had established ASCVD whereas in the CANVAS trial, 66% had ASCVD and in the DECLARE-TIMI, 41% had ASCVD whereas the remaining participants had multiple CV risk factors[6-9]. With regards to HF, the initial CVOTs were inconsistent in their reporting of whether the baseline HF status was HFrEF or HFpEF. A higher proportion of participants in the VERTIS-CV trial had HF (24%) at baseline, compared to the other major CVOTs (approximately 10%-15%), of whom 80% had HFpEF, which might have skewed the results of the trial[9].

The beneficial effects seen in the DECLARE-TIMI trial with respect to the combined outcome of CV death or HHF was driven mainly by gross reduction in HHF. The decrease in all-cause mortality seen in the EMPA-REG and DAPA-HF trials was predominantly due to reduction in CV mortality. Regarding 3P-MACE, it is believed that the differences in the number of participants with HF, specifically HFpEF in the VERTIS-CV trial and also low rates of CV events in the DECLARE-TIMI trial might explain why the superiority of SGLT2i for 3-PMACE couldn't be demonstrated in these trials although this was evident in the EMPA-REG and CANVAS trials.

Table 3 Role of sodium glucose cotransporter 2 inhibitors in the management a prevention of diabetes - position of different guidelines

Organize groups	Position of different guidelines
ADA, 2023	Among people with T2DM who have established ASCVD (a SGLT2i with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. (LOE: A)
	In people with T2DM who have established ASCVD, multiple atherosclerotic cardiovascular disease risk factors, or DKD, a SGLT2i with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. (LOE: A)
	In people with T2DM and established ASCVD or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a SGLT2i and a GLP1-RA may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. (LOE: A)
	In people with T2DM and established heart failure with either preserved or reduced ejection fraction, a SGLT2i with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. (LOE: A)
	In people with T2DM and established heart failure with either preserved or reduced ejection fraction, a SGLT2i with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. (LOE: A)
AACE, 2023	SGLT2i should be started irrespective of glycemic target or other T2DM therapies in patients with T2DM and ASCVD or at high risk for ASCVD (albuminuria/proteinuria, hypertension and left ventricular hypertrophy, LV systolic or diastolic dysfunction, ankle-branchial index < 0.9)
ACC/AHA, 2022	In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalisation for heart failure and CV mortality, irrespective of the presence of type 2 diabetes. (COR: 1, LOE: A)
	In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalisation and CV mortality (COR: 1, LOE: A)
	In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalisation and CV mortality (COR: 1, LOE: A)
ESC, 2022	SGLT2i are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death. (COR: 1, LOE: A)
	SGLT2i are recommended in patients with T2DM and LVEF > 40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death. (COR: 1, LOE: A)
	SGLT2i are recommended in patients with T2DM with multiple ASCVD risk factors or established ASCVD to reduce the risk of HF hospitalization. (COR: 1, LOE: A)

ADA: American Diabetes Association; AACE: American College of Clinical Endocrinologists; ACC/AHA: American College of Cardiology/American Heart Association; ESC: European Society pf Cardiology; HFrEF: Heart Failure with reduced ejection fraction; HFmrEF: Heart Failure with mildly reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; COR: Class of recommendation; LOE: Level of evidence; T2DM: Type 2 diabetes mellitus; ASCVD: Atherosclerotic cardiovascular disease; SGLT2i: Sodium glucose cotransporter 2 inhibitors; LV: Left ventricle.

Notably, conflicting results have been seen between different trials with the same drug, for example empagliflozin in the EMPA-REG and EMPEROR-preserved) or dapagliflozin in the DECLARE-TIMI and DAPA-HF trials with respect to CV or all-cause mortality[13,19]. Mortality reduction with empagliflozin was seen in the EMPAREG-OUTCOME trial but not in the EMPEROR-reduced trial. Participants in the HF outcome trials (DAPA-HF and EMPEROR-reduced) were different from participants of older CVOTs like EMPAREG or DECLARE-TIMI, as, in the former group, most of the participants had HFrEF, lower BMI, systolic blood pressure and mean eGFR, and a significant proportion was non-diabetic. However, on comparing the HF trials DAPA-HF (dapagliflozin) and EMPEROR-reduced (empagliflozin), significant reduction in the risk of CV deaths was seen in the DAPA-HF trial, but not with empagliflozin in the EMPEROR-reduced trial[35,45] thus raising a question on whether baseline characteristics alone account for the changes or there is a role of individual pharmacologic property of the SGLT2i. Following the results of the DAPA-HF and EMPEROR-reduced trials, it became clear that the beneficial effects on CV death or HHF was observed in participants irrespective of the presence of diabetes.

A recent real-world study involving 25315 patients (empagliflozin: 5302, dapagliflozin: 4681, canagliflozin: 4411, other SGLT2 inhibitors: 10921), the authors reported no significant differences in the risk of developing HF, MI, AP, stroke, and AF among the individual SGLT2 inhibitors. The robustness of the results was also confirmed through a multitude of sensitivity analyses[117].

Overall, till date, there is insufficient evidence to suggest the superiority of any SGLT2i over the other with regards to different CV outcomes and it appears to be a class-effect. Data from available CVOTs may aid in making a choice of one particular SGLT2i over the other depending on the clinical scenario and the purpose of use. Thus, in patients with established ASCVD, empagliflozin appears to have an upper hand when it comes to mortality reduction and empagliflozin and canagliflozin both seem to score over dapagliflozin in reduction of 3P-MACE or the composite of HHF and CV death. However, in those with HFrEF, dapagliflozin seems to score better than empagliflozin in mortality reduction. Ertugliflozin is not a prudent choice in any scenario, whereas for HFpEF, both dapagliflozin and empagliflozin

are equal and can be used irrespective of the presence of diabetes. Talking of those without established ASCVD, a 300 mg dose of Canagliflozin can be a prudent choice based on its effects on the risk factors like the greater degrees of weight loss, BP and HbA1c% reduction. However, this is more of a personalised opinion rather than an evidence based one and the choice must be balanced against the cost in individual countries, availability, and the risk for adverse effects.

SGLT2I FOR CARDIO-PROTECTION IN TYPE 1 DIABETES? - THE CURRENT STATUS

It is a known fact now that children and adults with type 1 diabetes have insulin resistance and display features of metabolic syndrome like obesity, dyslipidemia, hypertension. A significant proportion of T1DM patients go on to develop ASCVD and HF, thus raising the question of the role of SGLT2i as adjuncts to insulin in these patients[118].

The metabolic benefits of SGLT2 inhibition like weight reduction and better Hba1c reduction have been demonstrated in type 1 diabetes in three phase 3 clinical trials- the EASE (empagliflozin), DEPICT (dapagliflozin), and inTandem (sotagliflozin, a dual SGLT1/2 inhibitor)[119].

In 2019, the European Medicines Agency (EMA) had approved dapagliflozin 5 mg as an adjunct pharmacotherapy for overweight-obese individuals with type 1 diabetes with overweight[120]. However, the FDA declined the applications for dapagliflozin and empagliflozin due to risk concerns for DKA[121]. Indeed, SGLT2i-induced glucosuria can lead to negative caloric balance and promote ketone generation. Ketosis can sometimes occur without hyperglycaemia, known as euglycemic DKA, which makes detection more difficult. In most clinical trials, the risk of DKA was dose-dependent and not seen in participants receiving very low doses of SGLT2 inhibitors like dapagliflozin 5 mg or empagliflozin 2.5 mg [118].

But again, it is unclear whether the cardiorenal protection seen with SGLT2i would manifest at such low doses. Also, the risk of DKA could be higher outside the ideal settings of a clinical trial. The EMA approval of dapagliflozin in T1DM was first made subject to a condition of strict risk mitigation strategy and close supervision by prescribers and consequently, was abruptly reversed in October 2021[122]. It is reassuring to note that most real-world data do not show an alarming increase in DKA risk with SGLT2i in T1DM[123].

CONCLUSION

The discovery of the cardioprotective effects of SGLT2i have brought about a paradigm shift in the management of T2DM with a shift of focus towards a holistic approach to target organ protection in T2DM rather than glycemic control alone. While their roles in HF and cardiac risk factors are well established, they have the potential to be used in other heart diseases like diabetic cardiomyopathy and cardiac autonomic neuropathy as well.

FOOTNOTES

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Country of origin: United Kingdom

ORCID number: Sunetra Mondal 0000-0003-3064-466X; Subhodip Pramanik 0000-0002-3196-1192; Cornelius James Fernandez 0000-0002-1171-5525; Joseph M Pappachan 0000-0003-0886-5255.

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COVID-19 and cardiac complications: Myocarditis and multisystem inflammatory syndrome in children

Muhammed Güneş, Öner Özdemir

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Muhammed Güneş, Department of Pediatric Cardiology, Research and Training Hospital of Sakarya, Adapazarı 54100, Sakarya, Türkiye

Öner Özdemir, Department of Pediatric Allergy and Immunology, Research and Training Hospital of Sakarya, Sakarya University Medical Faculty, Adapazarı 54100, Sakarya, Türkiye

Corresponding author: Öner Özdemir, MD, Professor, Department of Pediatric Allergy and Immunology, Research and Training Hospital of Sakarya, Sakarya University Medical Faculty, Adnan Menderes cad, Adapazarı 54100, Sakarya, Türkiye. ozdemir_oner@hotmail.com

Abstract

Coronavirus is an important pathogen causing disease in humans and animals. At the end of 2019, an investigation into an increase in pneumonia cases in Wuhan, Hubei Province, China, found that the cause was a new coronavirus. This disease, which spread rapidly across China and caused an outbreak worldwide, resulted in a pandemic. Although this virus has previously been referred to as 2019-nCoV, which causes coronavirus disease 2019 (COVID-19), later it was named severe acute respiratory syndrome coronavirus 2. Children were usually asymptomatic and rarely severely affected. In April 2020, reports from the United Kingdom indicated that children may have Kawasaki disease or a clinical condition similar to toxic shock syndrome. This clinical picture was later defined as multisystem inflammatory syndrome in children. Since then, similarly affected children as well as cases with other cardiac complications have been reported in other parts of the world. In this review, we aimed to evaluate COVID-19 in terms of cardiac involvement by reviewing the literature.

Key Words: COVID-19; Cardiac complication; Myocarditis; Multisystem inflammatory syndrome in children; SARS-CoV-2

Core Tip: In April 2020, reports from the United Kingdom indicated that children may have Kawasaki disease or a clinical condition similar to toxic shock syndrome. This clinical picture was later defined as multisystem inflammatory syndrome in children. Since then, similarly affected children as well as cases with other cardiac complications have been reported in other parts of the world. In this review, we aimed to evaluate coronavirus disease 2019 in terms of cardiac involvement by reviewing the literature.

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INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) caused by coronavirus disease 2019 (COVID-19) in children can lead to death, if not diagnosed early. After it was first identified in the United Kingdom in April 2020, similar cases were reported in Europe and America[1-5]. Polymerase chain reaction (PCR) tests or antibodies were found to be positive in most of these children and were associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Various forms of cardiac involvement have been reported in the literature during MIS-C disease. These forms may affect the course of the disease. After the World Health Organization defined the picture as MIS-C in May 2020, guidelines on diagnosis and treatment have been continuously updated[6]. In this review, cardiac involvement that may occur during COVID-19 and MIS-C are discussed in light of the current literature.

PATHOGENESIS OF MYOCARDIAL DAMAGE AND HEART FAILURE IN COVID-19

The mechanisms of myocardial damage in COVID-19 are not clearly defined. Different variants of the virus may cause myocardial damage in children by various mechanisms. One theory suggests that entry of the virus into the host cell is facilitated by the binding of the spike protein to the angiotensin converting enzyme (ACE) 2 receptor. The virus causes a local inflammatory reaction with T-cell infiltration and B lymphocytes[7]. Permanent cell damage may lead to fibrosis formation and finally to the development of dilated cardiomyopathy[7,8]. Postmortem histological examination revealed local inflammation and the presence of a viral genome in the myocardial tissue. Accordingly, the negativity of markers indicating systemic inflammation in blood indicated the presence of direct damage caused by the virus itself[9].

In another study, researchers suggested that the cause of myocardial damage in adults was due to ischemia in the coronaries leading to a weakening of the blood supply to the heart muscle[10]. The main sign of myocardial damage in COVID-19 is thought to be endothelial inflammation leading to bleeding, thrombosis, and necrosis in intramural arteries. There is no correlation between markers of inflammation and myocarditis and no evidence that the virus directly triggers myocarditis. As a result, the theory that immune damage to the endothelium and microthrombosis formation play a role in the pathogenesis of myocarditis has been strengthened[11].

However, the etiology of heart failure due to COVID-19 is multifactorial. (1) Virus-induced infiltration of the myocardium by inflammatory cells that can impair cardiac function; (2) necrosis of the myocardium due to pro-inflammatory cytokines (monocyte chemoattractant protein-1, interleukin-1β; interleukin-6, tumor necrosis factor-α); (3) damage to the endocardium by endothelial damage due to microthrombosis; and (4) heart failure caused by acute respiratory distress syndrome and severe hypoxia due to respiratory failure[7].

ACUTE MYOCARDITIS IN COVID-19 PATIENTS

COVID-19 usually proceeds with mild respiratory symptoms in children[12]. As with other viral agents, COVID-19 has the potential to cause myocarditis. The prevalence of myocarditis due to COVID-19 is not yet known. The approach in COVID-19 patients presenting with acute myocarditis is not different to other classical viral myocarditis. All types of rhythm disturbances can be seen in acute myocarditis cases. In a case presented by Kohli *et al*[9], atrial fibrillation developed, and cardioversion was required[13].

Unlike adults, cases of acute fulminant myocarditis due to SARS-CoV-2 infection with left ventricular dysfunction are rarely seen[14]. Recently, rare cases of acute fulminant myocarditis have been reported and these patients required treatment in intensive care units. In these patients, acute myocarditis develops before respiratory symptoms develop[9, 13]. Extracorporeal membrane oxygenation (ECMO) was applied in an infant with fulminant myocarditis with a fatal course reported by Kesici *et al*[14], but the patient died[9]. In the cases of acute fulminant myocarditis presented in the literature, adolescents presenting with chest pain, fever, palpitations, weakness, and pallor, as well as infants presenting with fever, vomiting, pallor, rapid breathing, and decreased sucking can be seen. ECMO was applied in a patient with sustained ventricular tachycardia presented by Tseng *et al*[15]. The presented cases had a fulminant course and this is not

a condition frequently encountered in other forms of viral myocarditis. The reason for this is still unclear. Histological cardiac evaluations are needed for this. Therefore, acute myocarditis due to COVID-19 should be kept in mind in patients who develop malignant arrhythmia in the absence of fever and respiratory symptoms (Figure 1).

Symptomatic treatment is usually applied according to the severity of myocarditis. In all of these cases, severe left ventricular failure developed and they received various inotropic treatments as well as intravenous immunoglobulin (IVIG) and steroid treatments.

COVID-19 AND MIS-C DEVELOPMENT

In April 2020, reports from the United Kingdom indicated that children may have Kawasaki disease or a clinical condition similar to the described shock syndrome. Since then, similarly affected children have been reported in other parts of the world. This clinical definition is called MIS-C[16]. In both Kawasaki disease (KD) and MIS-C, symptoms and organ dysfunction result from a cytokine storm[17].

It was observed that the inflammatory storm was more prominent in MIS-C[18]. According to Rodriguez-Smith *et al* [19], the measured levels of S-100 and interleukin (IL)-18 are similar in MIS-C and KD. Therefore, interferon-γ-stimulated chemokine ligand 9 is an indicator that may be important in differentiating MIS-C from KD. The main mediator of coronary artery inflammation in KD is IL-1. However, the main mediators of MIS-C are IL-6 and IL-8 and the inflammatory response seems to be triggered by these factors[17].

A mucosal biopsy from a COVID-19 patient with gastrointestinal system involvement and symptoms showed the presence of SARS-CoV-2 in endothelial cells. Recent studies have reported autoantibodies targeting antigens in mucosal and cardiac tissues in MIS-C patients[20]. At the beginning of the pandemic, pediatric patients were not considered to be at high risk for severe COVID-19 symptoms such as severe acute respiratory syndrome due to the lower presence of ACE 2 receptors in epithelial cells[21]. Later in the pandemic, more serious COVID-19-related complications such as thrombotic events, myocardial dysfunction, and coronary artery disease or aneurysms have been observed in pediatric patients with MIS-C[22]. In a study published in the United States, it was shown that the most common finding in children with MIS-C was cardiac dysfunction with a rate of 40.6%[23]. Serological evidence for SARS-CoV-2 or a history of contact with a COVID-19 patient was found in all patients[24,25]. It has been shown that vaccinated children are less frequently diagnosed with MIS-C[26].

PATHOGENESIS OF MIS-C DEVELOPMENT IN COVID-19

Many hypotheses related to the pathogenesis of MIS-C have been presented, but none of them have been fully proven. Some researchers think that there is a delayed immune response that occurs 2 to 6 wk after infection[27,28]. In childhood, the early and pulmonary stages of COVID-19 are mild or asymptomatic. In the early stage, macrophages are activated and T helper cells begin to release cytokines. Subsequently, plasma and B cells produce antibodies and cause the immune response to intensify. This response results in the hyperinflammatory condition called MIS-C[28]. The fact that most children with MIS-C have positive serology and negative PCR tests supports this view. In addition, it has been reported that autoantibody responses against intestinal and endothelial cells are produced in children with MIS-C[29,30]. The fact that MIS-C is more common, especially in Africans shows the importance of genetic factors[31]. Another hypothesis suggests that neutrophil extracellular traps (NETs) play a role in the pathophysiology of MIS-C. The function of NETs is to trap the virus inside the cell. NETs stimulated by viruses cause hyperimmune and hyperinflammatory responses. These are thought to be increased in patients with respiratory failure and severe disease manifestations[32]. More studies are needed to elucidate the exact mechanism of myocardial damage seen in MIS-C.

MIS-C DIAGNOSTIC CRITERIA

According to the American Centers for Disease Control and Prevention, in a person younger than 21 years of age, MIS-C criteria (Figure 2) without an alternative diagnosis are as follows:

Clinical criteria

Minimum 24-h history of subjective or objective fever ≥ 38.0°C; severe illness requiring hospitalization; two or more organ systems affected (*i.e.* cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, neurological).

Laboratory confirmation of inflammation

One or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase or interleukin 6; elevated neutrophil or decreased lymphocyte counts; low albumin level.

Laboratory or epidemiological evidence of SARS-CoV-2 infection

PCR, positive SARS-CoV-2 test by serology, or symptoms development after a history of COVID-19 contact 4 wk before the onset of COVID-19[15,23,33].

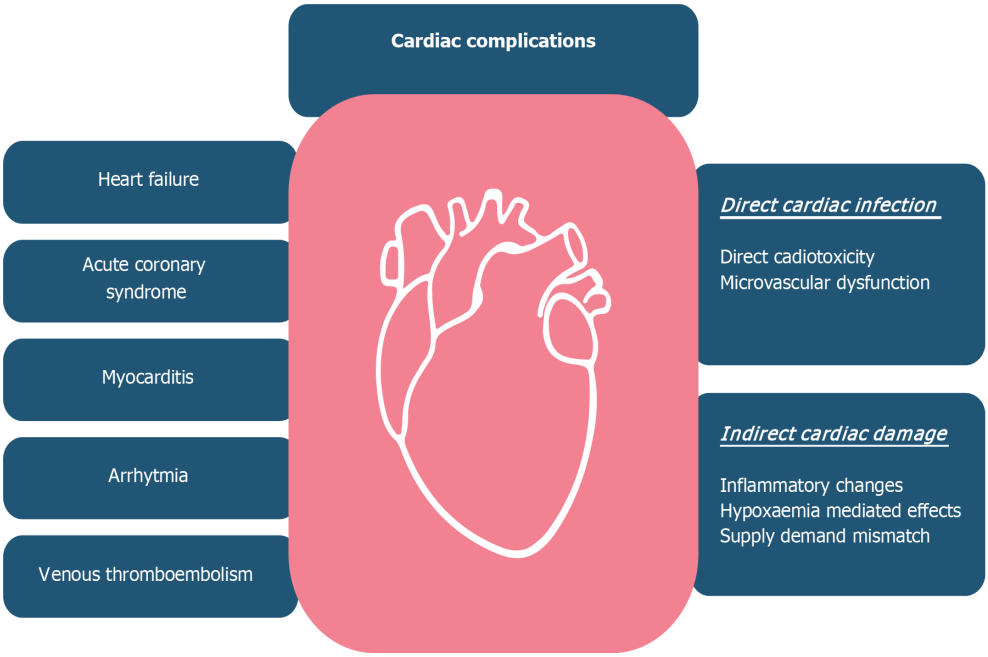

Figure 1 Cardiac complications of coronavirus disease 2019.

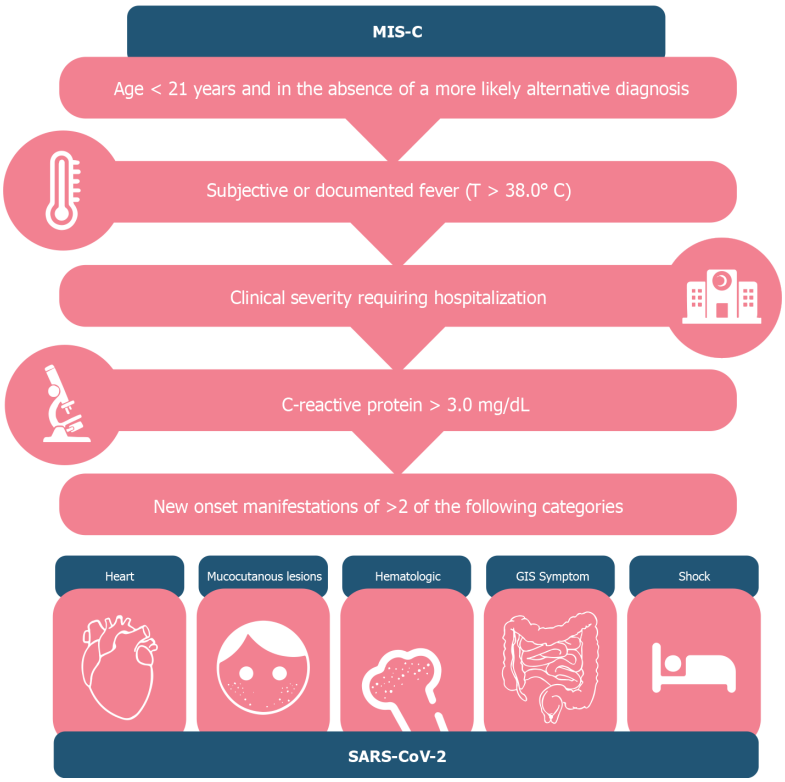

Figure 2 The relation between severe acute respiratory syndrome coronavirus 2 infection and multisystem inflammatory syndrome in children. MIS-C: Multisystem inflammatory syndrome in children; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

MANAGEMENT OF MIS-C

Children with a diagnosis of MIS-C should be hospitalized and followed up by an experienced team. Children who are clinically well enough not to require hospitalization should not be considered to have MIS-C. In these children, close follow-up should be continued as infection markers may increase later. Supportive care is determined according to the severity of the symptoms. Patients presenting with a shock condition should be hospitalized in the intensive care unit as they may need inotropic support and mechanical ventilation[33]. Vasodilatory shock may be seen in some children, and vasopressor drugs should be used in this situation. However, milrinone could be used with caution due to its va-

sodilatory effect[34]. A broad-spectrum antibiotic should be administered until blood culture results are available.

Immunomodulator therapy

Although the exact pathogenesis of MIS-C is not understood, immune dysregulation is suggested to play an important role[35]. Autoantibody production resulting in activation of Fc-y receptors on neutrophils and macrophages and causing secretion of pro-inflammatory cytokines is one of these mechanisms[20,36-38]. Accordingly, immunomodulation is an important step in treatment. IVIG, glucocorticoids, and biological agents constitute the main treatment approaches (Figure 3)[39,40]. Treatment aims to correct cardiac dysfunction and damage in other organs by suppressing inflammation[27,41].

Steroids are used at low doses in patients with moderate to severe disease or at high doses in patients with refractory disease. Biological agents such as anakinra, tocilizumab, or infliximab are preferred in cases resistant to first-line therapies according to new guidelines[42]. In a series of 52 cases (30 MIS-C and 22 severe diseases) reported from Türkiye, it was emphasized that patients presented with different clinical pictures especially conjunctival hyperemia, high CRP values, and a low leukocyte count could be independent parameters used in diagnosis of the disease[43]. IVIG was administered to 30, a steroid to 27 (high dose steroid in 1 patient), anakinra to 26, plasmapheresis to 14, and various vasoactive agents to 13 patients with severe myocardial involvement. No deaths due to MIS-C were reported in this series. The common opinion of authors in the literature related to MIS-C is that mortality in children is very low with correct treatment in those diagnosed early. In the case of cardiac involvement, the importance of treatment under intensive care conditions has been emphasized.

Anti-platelet therapy

Patients with MIS-C are at high risk of thrombotic complications for many reasons including hypercoagulopathy, possible endothelial damage, stasis due to immobilization, ventricular dysfunction, and coronary artery aneurysm. Low-dose aspirin (3-5 mg/kg/d, max. 81 mg) should be started and can be discontinued at 4 wk if there is no coronary artery aneurysm. Treatment with aspirin should be avoided in patients with active bleeding, significant bleeding risk, and/or a platelet count of 80000/μL. Therapeutic anticoagulation with enoxaparin or warfarin is recommended in patients with a coronary artery diameter Z-score > 10[44,45].

FOLLOW-UP OF MIS-C PATIENTS

Echocardiography

For hospitalized MIS-C patients with ventricular dysfunction or coronary artery dilatation, echocardiography (ECHO) should be repeated before discharge or on days 5-7. If the first echocardiogram is normal, it should be repeated on days 7-10. Repeat ECHO is recommended on days 7-10, 4-6 wk, 4-6 mo, and 9-12 mo after discharge[46,47].

Electrocardiography

In MIS-C patients, electrocardiography (ECG) should be performed at 48-h intervals. If grade 1 atrioventricular (AV) block is present, continuous telemetry monitoring is recommended. Holter ECG is recommended on the 7th-10th day after discharge if there is a grade 1 AV block or arrhythmia. Repeat ECG after 4-6 wk and 4-6 months, if there is arrhythmia or 1st-degree AV block, Holter ECG is recommended. After 4-6 months, if arrhythmia persists or ventricular dysfunction and increased troponin, brain-type natriuretic peptide values are present in the initial diagnosis, an exercise stress test is recommended[46,47].

Exercise restriction

Exercise restriction is recommended for 2 wk in the absence of cardiac involvement and 3-6 mo in the presence of cardiac involvement[47,48].

CONCLUSION

Unlike adult patients, COVID-19 has a milder course in children. However, although MIS-C cases due to COVID-19 are rare, they cause deaths in children when not recognized early. Optimal results are obtained with intensive care unit treatments in cases diagnosed early. Early recognition of the disease and consideration of the latest guidelines are very important for the diagnosis and treatment of MIS-C. To clarify the pathogenesis of MIS-C, rational management strategies, and possible preventive measures are important for planning. MIS-C patients need to be registered to keep track of risk factors, and prognosis, and this is possibly the most appropriate way to identify sequelae. Genetic research will be vital to understanding why some children develop MIS-C after SARS-CoV-2 infection.

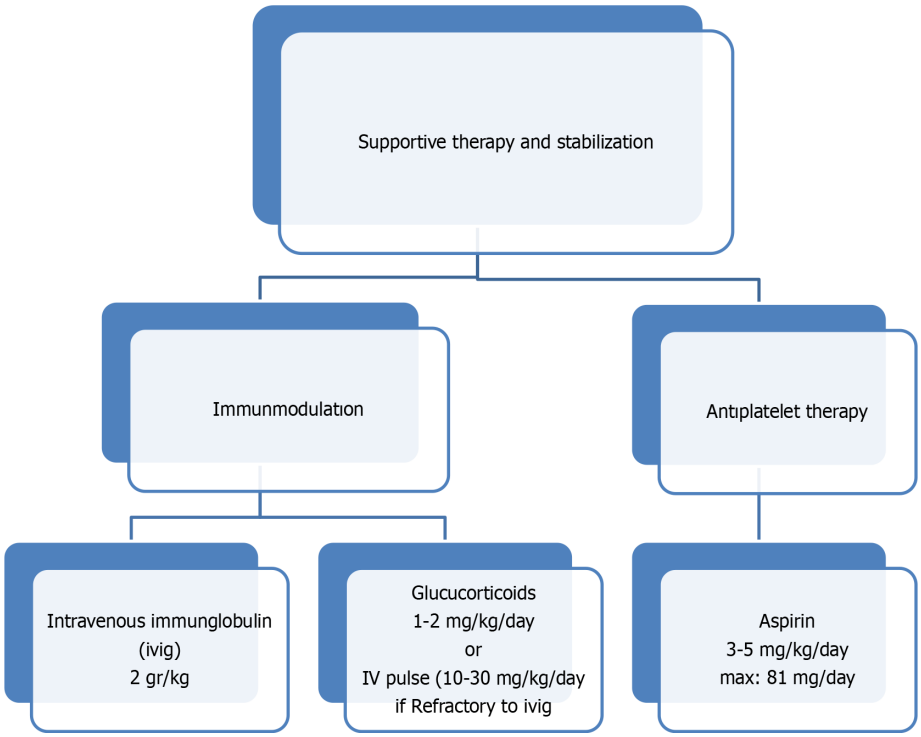

Figure 3 The management algorithm of multisystem inflammatory syndrome in children.

FOOTNOTES

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Country/Territory of origin: Türkiye

ORCID number: Öner Özdemir 0000-0002-5338-9561.

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MINIREVIEWS

Ibrutinib and atrial fibrillation: An in-depth review of clinical implications and management strategies

Moiud Mohyeldin, Shitij Shrivastava, Sai Vishnu Vardhan Allu

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Moiud Mohyeldin, Internal Medicine, University of Medical Sciences and Technology, Khartoum 11111, Sudan

Shitij Shrivastava, Sai Vishnu Vardhan Allu, Internal Medicine, Bronxcare Health System, Bronx, NY 10457, United States

Corresponding author: Moiud Mohyeldin, MD, Doctor, Staff Physician, Internal Medicine, University of Medical Sciences and Technology, Khartoum, Khartoum 11111, Sudan. moiudahmed@gmail.com

Abstract

Ibrutinib, a targeted therapy for B-cell malignancies, has shown remarkable efficacy in treating various hematologic cancers. However, its clinical use has raised concerns regarding cardiovascular complications, notably atrial fibrillation (AF). This comprehensive review critically evaluates the association between ibrutinib and AF by examining incidence, risk factors, mechanistic links, and management strategies. Through an extensive analysis of original research articles, this review elucidates the complex interplay between ibrutinib's therapeutic benefits and cardiovascular risks. Moreover, it highlights the need for personalized treatment approaches, vigilant monitoring, and interdisciplinary collaboration to optimize patient outcomes and safety in the context of ibrutinib therapy. The review provides a valuable resource for healthcare professionals aiming to navigate the intricacies of ibrutinib's therapeutic landscape while prioritizing patient well-being.

Key Words: Ibrutinib; Bruton's tyrosine kinase inhibitor; Atrial fibrillation; Cardiovascular risk; Management strategies

Core Tip: This review examines the association between ibrutinib, a Bruton's tyrosine kinase inhibitor, and atrial fibrillation (AF). It explores the underlying mechanisms, clinical implications, and management strategies for AF in patients treated with ibrutinib. The article emphasizes the need for cardiovascular monitoring and alternative treatments to balance therapeutic efficacy and safety.

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INTRODUCTION

Ibrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, has emerged as a pivotal therapeutic agent for B-cell malignancies, particularly chronic lymphocytic leukemia and mantle cell lymphoma[1,2]. While ibrutinib has demonstrated remarkable efficacy in improving progression-free survival and quality of life, concerns have arisen regarding its association with atrial fibrillation (AF)[3-6]. This comprehensive review aims to dissect the intricate relationship between ibrutinib and AF, encompassing incidence, risk factors, mechanistic underpinnings, clinical implications, and evolving management strategies. By providing valuable insights for informed decision-making, this review seeks to guide healthcare professionals in optimizing therapeutic outcomes while ensuring the cardiovascular well-being of patients receiving ibrutinib.

INCIDENCE AND RISK FACTORS OF ATRIAL FIBRILLATION WITH IBRUTINIB

Several studies have reported an increased incidence of AF in patients treated with ibrutinib[3-5,7,8]. In a pooled analysis of four randomized controlled trials, the incidence of AF was 6.5% in the ibrutinib group, whereas it was 1.6% in the comparator group (relative risk: 4.1; 95%CI: 2.2-7.5)[3]. The median time to AF onset was 2.8 months (range: 0.3-26.6 months)[3]. Risk factors associated with ibrutinib-related AF include older age, hypertension, prior history of AF, and the concomitant use of anticoagulants or antiplatelet agents[3,7]. Recent findings by Tang *et al*[9] further support the association between ibrutinib and cardiac side effects, including AF.

MECHANISTIC LINKS BETWEEN IBRUTINIB AND ATRIAL FIBRILLATION

The mechanisms linking ibrutinib to AF are multifaceted and involve various pathways[5,10-12] (Figure 1). Ibrutinib has been shown to inhibit PI3K-Akt signaling, leading to reduced phosphorylation of the protein kinase Ca^{2+}/calmodulin-dependent protein kinase II, which plays a crucial role in calcium handling and atrial electrophysiology[10-13]. The dysregulation of calcium homeostasis can trigger AF by promoting delayed afterdepolarizations and increasing atrial ectopy[11,12]. Additionally, ibrutinib inhibits the tyrosine kinase CSK, resulting in enhanced activity of Src kinases, which can modulate ion channel function and contribute to atrial remodeling[11,12,14]. Furthermore, ibrutinib has been associated with the inhibition of AMP-activated protein kinase, a key regulator of cellular energy homeostasis, potentially exacerbating oxidative stress and inflammation in the atrial myocardium[11,12]. McMullen *et al*[15] and Xiao *et al*[16] have provided evidence supporting the role of ibrutinib in increasing the risk of AF through inhibition of cardiac PI3K-Akt signaling and C-terminal Src kinase, respectively. Jiang *et al*[17] also highlighted ibrutinib's promotion of AF *via* structural remodeling and calcium dysregulation in the atrium.

CLINICAL IMPLICATIONS AND MANAGEMENT STRATEGIES

The association between ibrutinib and AF necessitates a multidisciplinary approach to patient care involving close collaboration among oncologists, cardiologists, and hematologists[10]. Baseline cardiovascular risk assessment, including electrocardiogram (ECG) and echocardiography, should be performed before initiating ibrutinib therapy[7]. Regular monitoring for signs and symptoms of AF, along with periodic ECG evaluations, is crucial for early detection and intervention[7].

Strategies for managing ibrutinib-associated AF involve a personalized approach tailored to individual patient characteristics and risk profiles[11,18]. In patients with a high risk of thromboembolism (CHA2DS2-VASc score ≥ 2), anticoagulation should be considered while weighing the benefits against the bleeding risk[12]. Novel oral anticoagulants have emerged as a promising option since their safety profile is more favorable than that of warfarin[12,19]. Rhythm control strategies, including pharmacological cardioversion and catheter ablation, may be considered in symptomatic patients or those with persistent AF[5].

Dose reduction or temporary interruption of ibrutinib may be necessary in cases of recurrent or symptomatic AF[7]. Alternative BTK inhibitors with potentially lower AF risk, such as acalabrutinib or zanubrutinib, can be considered in select patients[20,21]. Ongoing research aims to develop risk stratification tools and predictive models to identify patients with a higher risk of developing ibrutinib-related AF, enabling proactive management and personalized treatment decisions[7].

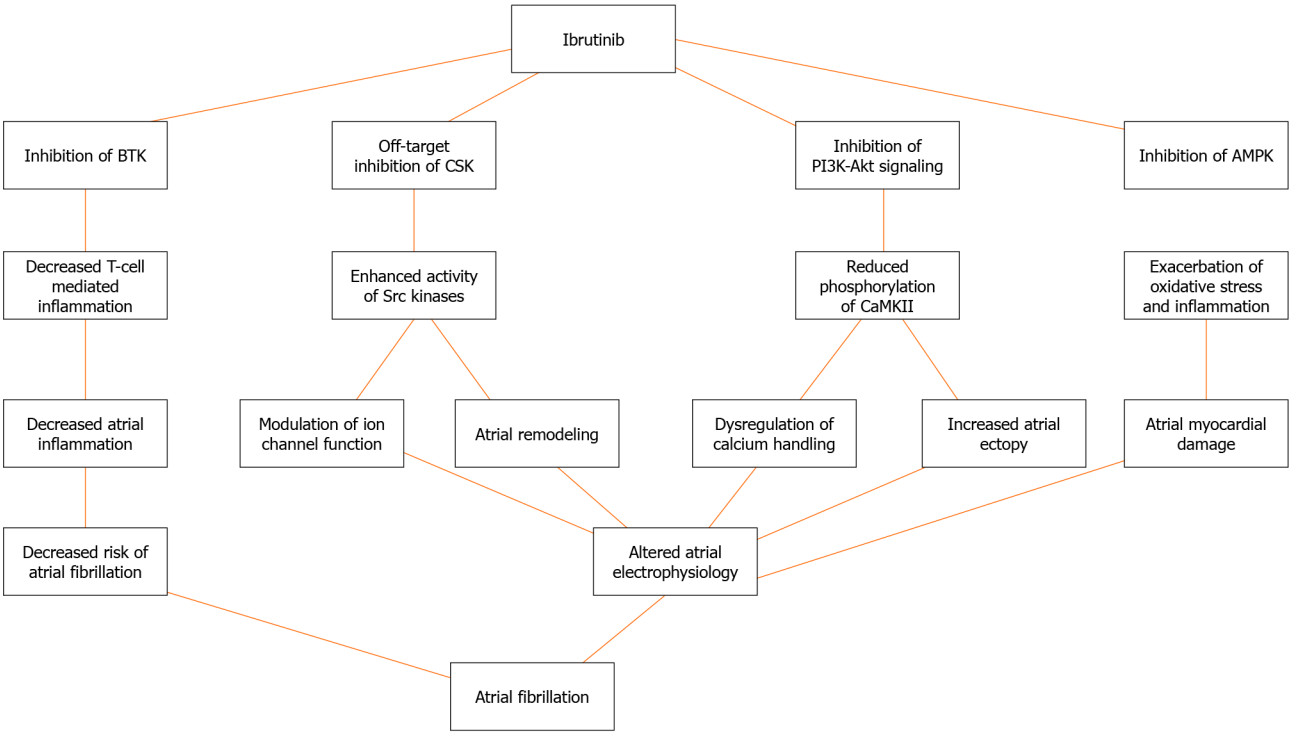

Figure 1 Mechanistic links between ibrutinib and atrial fibrillation. Ibrutinib inhibits various signaling pathways, including PI3K-Akt, CSK, and AMP-activated protein kinase, leading to the dysregulation of calcium handling, atrial remodeling, oxidative stress, and inflammation, ultimately contributing to the development of atrial fibrillation. BTK: Bruton's tyrosine kinase; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; CSK: C-terminal src kinase; AMPK: AMP-activated protein kinase.

CONCLUSION

The association between ibrutinib and AF represents a significant challenge in the management of patients with B-cell malignancies. This comprehensive review highlights the incidence, risk factors, mechanistic links, clinical implications, and evolving management strategies related to this complex relationship. By integrating insights from original research articles, this review provides a robust evidence base to guide healthcare professionals in navigating the intricacies of ibrutinib therapy while prioritizing patient safety and cardiovascular well-being. Multidisciplinary collaboration, personalized risk assessment, and tailored management approaches are paramount in optimizing outcomes for patients receiving ibrutinib. Ongoing research efforts aimed at unraveling the underlying mechanisms, developing risk stratification tools, and exploring alternative therapeutic options could refine the approach to managing ibrutinib-associated AF. As the therapeutic landscape continues to evolve, this review serves as a valuable resource for healthcare professionals seeking to balance the remarkable efficacy of ibrutinib with the need for vigilant cardiovascular monitoring and proactive management strategies. By staying abreast of the latest evidence and adopting a patient-centric approach, clinicians can harness the transformative potential of ibrutinib while minimizing cardiovascular risks and ensuring the best possible outcomes for patients with B-cell malignancies.

FOOTNOTES

Author contributions: Mohyeldin M contributed to conceptualization, methodology, visualization, supervision, and project administration; Mohyeldin M takes responsibility for the integrity of the work as a whole, from inception to published article; Mohyeldin M, Shrivastava S and Allu SVV contributed to investigation, writing - original draft, and writing - review & editing; Shrivastava S and Allu SVV contributed to resources; All authors have read and approved the final version of the manuscript.

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Country of origin: Sudan

ORCID number: Moiud Mohyeldin 0000-0002-5373-2163.

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ORIGINAL ARTICLE

Observational Study

Evaluation of mitral chordae tendineae length using four-dimensional computed tomography

Takuya Mori, Satoshi Matsushita, Terumasa Morita, Abulaiti Abudurezake, Junji Mochizuki, Atsushi Amano

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Takuya Mori, Satoshi Matsushita, Terumasa Morita, Abulaiti Abudurezake, Atsushi Amano, Department of Cardiovascular Surgery, Juntendo University Faculty of Medicine, Tokyo 113-8421, Japan

Takuya Mori, Department of Cardiovascular Surgery, JACCT Japan Animal Cardiovascular Care Team, Osaka 533-0033, Japan

Junji Mochizuki, Department of Radiology, Minamino Cardiovascular Hospital, Tokyo 192-0918, Japan

Corresponding author: Satoshi Matsushita, MD, PhD, Associate Professor, Department of Cardiovascular Surgery, Juntendo University Faculty of Medicine, 2-1-1 Hongo Bunkyo-ku, Tokyo 113-8421, Japan. saty-m@juntendo.ac.jp

Abstract

BACKGROUND

Mitral valvuloplasty using artificial chordae tendineae represents an effective surgical approach for treating mitral regurgitation. Achieving precise measurements of artificial chordae tendineae length (CL) is an important factor in the procedure; however, no objective index currently exists to facilitate this measurement. Therefore, preoperative assessment of CL is critical for surgical planning and support. Four-dimensional x-ray micro-computed tomography (4D-CT) may be useful for accurate CL measurement considering that it allows for dynamic three-dimensional (3D) evaluation compared to that with transthoracic echocardiography, a conventional inspection method.

AIM

To investigate the behavior and length of mitral chordae tendineae during systole using 4D-CT.

METHODS

Eleven adults aged > 70 years without mitral valve disease were evaluated. A 64-slice CT scanner was used to capture 20 phases in the cardiac cycle in electrocardiographic synchronization. The length of the primary chordae tendineae was measured from early systole to early diastole using the 3D image. The primary chordae tendineae originating from the anterior papillary muscle and attached to the A1-2 region and those from the posterior papillary muscle and attached to the A2-3 region were designated as cA and cP, respectively. The behavior and

maximum lengths [cA (ma), cP (max)] were compared, and the correlation with body surface area (BSA) was evaluated.

RESULTS

In all cases, the mitral anterior leaflet chordae tendineae could be measured. In most cases, the cA and cP chordae tendineae could be measured visually. The mean cA (max) and cP (max) were 20.2 mm ± 1.95 mm and 23.5 mm ± 4.06 mm, respectively. cP (max) was significantly longer. The correlation coefficients (r) with BSA were 0.60 and 0.78 for cA (max) and cP (max), respectively. Both cA and cP exhibited constant variation in CL during systole, with a maximum 1.16-fold increase in cA and a 1.23-fold increase in cP from early to mid-systole. For cP, CL reached a plateau at 15% and remained elongated until end-systole, whereas for cA, after peaking at 15%, CL shortened slightly and then moved toward its peak again as end-systole approached.

CONCLUSION

The study suggests that 4D-CT is a valuable tool for accurate measurement of both the length and behavior of chordae tendineae within the anterior leaflet of the mitral valve.

Key Words: Mitral valve; Chordae tendineae; Computed tomography; Four-dimensional; Cardiac cycle

Core Tip: Mitral regurgitation is one of the most common cardiac diseases. Although mitral valvuloplasty with artificial chordae tendineae is a standard procedure for surgical treatment, it has been difficult to evaluate the length and their motion preoperatively. In this study, we used four-dimensional computed tomography to establish accurate measurement of the length of chordae tendineae in the anterior leaflet of the mitral valve.

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INTRODUCTION

Remarkable advancements have occurred in medical x-ray micro-computed tomography (CT), and its applications have expanded with the improvement in multi-slice CT scanning. In cardiovascular medicine, CT is particularly useful in diagnosing coronary artery disease[1]. In recent years, its application has expanded through various guidelines and cases in which images of sufficient quality cannot be obtained with other noninvasive diagnostic equipment[2]. The structure of the mitral valve, which comprises the valve leaflet, annulus, chordae tendineae, papillary muscle, and left ventricular wall, can be comprehensively and three-dimensionally evaluated. The introduction of 320-slice CT has improved temporal resolution to levels approaching those of echocardiography. Conversely, degenerative mitral insufficiency, a prevalent condition, involves myxomatous degeneration of the valve leaflet and chordae tendineae, causing the chordae tendineae to elongate or tear. This results in leaflet deviation of the leaflet and mitral regurgitation (MR)[3,4]. Mitral valvuloplasty, a preferred surgical intervention for MR, offers advantages such as avoiding lifelong anticoagulation therapy and maintaining cardiac function. Numerous techniques for this procedure have been reported[5]. For a long time, resection of the deviated leaflet was the primary method; however, this has limited application for the anterior leaflet. Therefore, chordae tendineae reconstruction (CR) using artificial chordae tendineae is a widely used significantly effective treatment modality for MR caused by anterior leaflet deviation[6]. However, whether CR can be successfully achieved depends largely on the surgeon's experience and skill; hence, it lacks reproducibility and objectivity. Although it would be ideal to form the chordae tendineae by taking differences in their location, characteristics, and length into account, determining their length preoperatively is difficult; furthermore, much remains unknown about their behavior inside the body. When conventional echocardiography is used for preoperative evaluation in mitral valvuloplasty, it is difficult to observe the length and behavior of the chordae tendineae owing to the nature of the technique. In contrast with cardiac CT, it is possible to construct a three-dimensional (3D) image of the beating heart under electrocardiographic synchronization to obtain images, as needed, that are independent of cross-section and angle, which could allow for the dynamic evaluation of mitral chordae tendineae. Furthermore, dual-energy CT, which has received attention recently, combines images from both low-energy and high-energy imaging. This could allow for a more detailed evaluation than that with conventional CT[7]. A better understanding of the *in vivo* behavior and geometry of the chordae tendineae is expected to greatly improve the objectivity and reproducibility of surgeries, and could provide very useful preoperative information, especially in surgeries with restricted surgical field, such as minimally invasive cardiac surgery, which is widely being used.

Therefore, our study aims to assess the detectability of mitral chordae tendineae using four-dimensional CT (4D-CT) and examine variations in their length and behavior throughout the cardiac cycle *in vivo*.

MATERIALS AND METHODS

The participants in this study provided consent for their participation after they receiving detailed information on how their data would be handled. The study protocol was reviewed and approved by the Ethics Committee of Juntendo University School of Medicine (approval #2021080 Juntendo University Medical Ethics).

Eleven adults aged > 70 years without mitral valve disease were included in the study. Data from coronary CT scans performed as part of health checks were analyzed. The Table 1 presents basic data for all participants. None of the participants had any cardiac disease that required medication.

A 64-slice CT scanner (iQon Spectral CT, Philips Healthcare, Amsterdam, Netherlands) was used to obtain CT images. The contrast agent was iopamidol (370 mg/mL, Bayer Pharmaceuticals, Leverkusen, Germany) administered at 3.5 mL/s for at least 10 s. CT imaging was performed with 600 mA tube current, 120 kV tube voltage, and 0.16 pitch factor. The data were reconstructed with an R-R interval of 0%-95% in 5% increments with a thickness of 0.67 mm (Figure 1). Data from 20 phases of the cardiac cycle were sent to a workstation (Aze Virtual Place, Canon Medical Systems, Tochigi, Japan) to create 3D image.

The primary chordae tendineae originating from the anterior papillary muscle (APM) and attached to the A1-2 region were designated as cA, and those originating from the posterior papillary muscle (PPM) and attached to the A2-3 region as cP. The chordae tendineae were measured using the following procedure.

cA or cP was confirmed on the 3D image

The attachment sites of the valve leaflets and corresponding papillary muscle attachments were identified and marked on the image.

Those marks were confirmed on two-dimensional (2D)-multi-planar reformatting (MPR) image of the long axis of the heart corresponding to the 3D image. The angle of the cross-section was fine-tuned so that the two marks appear simultaneously in the 2D-MPR image.

The distance between two points in the 2D-MPR image was measured

Measurements were taken for 11 phases (0%-50%) for cA and cP, respectively. Three measurements were taken per phase in all cases, and the mean value was used as the chordae tendineae length (CL). The maximum CL in the 11 phases for each case was defined as cA (max) and cP (max), and comparisons were made to evaluate the correlation with the body surface area (BSA). The rate of change of CL at each time phase concerning early systole (phase 0%) was graphed to compare the behavior of cA and cP during systole.

Statistical analysis

All data were analyzed with IBM SPSS Statistics version 29 (IBM, Armonk, NY, United States) and presented as mean ± SD. The homoscedasticity of the mean values of each group was confirmed, and an unpaired *t*-test was used to compare them. Pearson's product-moment correlation coefficient was used to analyze the correlation between CL and BSA. Intra-rater reliability was determined by calculating intraclass correlation coefficients (ICC) [ICC (1, 1) and ICC (1, 3)]. The significance level for all statistical tests was < 5%.

RESULTS

Evaluation of mitral anterior leaflet chordae tendineae using 4D-CT

The mitral anterior leaflet chordae tendineae could be measured in all cases. In most cases, the cA and cP chordae tendineae could be measured visually, and the leaflets and papillary muscle attachments could be easily identified, even for smaller chordae tendineae that could not be visualized on CT. Individual differences occurred in the number of chordae tendineae originating from the papillary muscles. The number originating from the anterior leaflet of the APM was 3.18 ± 0.60, and that from the anterior leaflet of the PPM was 2.45 ± 0.52, with a significantly higher number originating from the APM. The PPM of Case 10 was smaller than those of the other cases, being displaced toward the apex.

cA and cP measurements and differences

CL exhibited large variations between individuals, with mean cA (max) and cP (max) being 20.2 mm ± 1.95 mm and 23.5 mm ± 4.06 mm, respectively. cP was significantly longer than cA (max). The correlation coefficients (r) with BSA were 0.60 and 0.78 for cA (max) and cP (max), respectively, showing significant correlations (Table 2).

Variation in cA and cP during systole

CL revealed constant variation during systole for both cA and cP, with a maximum 1.16-fold elongation in cA and 1.23-fold elongation in cP from early to mid-systole. For cP, CL reached a plateau at 15% and remained elongated until end-

Table 1 Basic data and underlying diseases of the participants

Case	Age (yr)	Sex	Heigh (cm)	BW (kg)	BSA (m²)	BMI	Underlying disease
1	76	F	149.0	53.4	1.47	24.0	DLp, HT
2	75	M	164.0	61.9	1.67	23.0	None
3	76	F	149.0	50.0	1.43	22.5	Multiple CI
4	80	F	146.0	50.5	1.41	23.6	HT
5	75	M	159.0	65.5	1.68	25.9	CI
6	79	F	148.7	45.0	1.36	20.3	HT
7	85	M	164.2	52.4	1.56	19.4	IP
8	72	F	156.0	53.0	1.51	21.7	CI
9	70	M	170.0	63.4	1.74	21.9	None
10	72	M	162.0	58.5	1.62	22.2	GC, CRC
11	67	F	146.0	51.8	1.43	24.3	DM
Average	75	M: 5, F: 6	155.8	55.0	1.53	22.6	

M: Male; F: Female; BW: Body weight; BSA: Body surface area; BMI: Body mass index; DLp: Dyslipidemia; HT: Hypertension; CI: Cerebral infarction; IP: Interstitial pneumonia; GC: Gastric cancer; CRC: Colorectal cancer; DM: Diabetes mellitus.

Table 2 Maximum chordae tendineae length

Case	cA (mm)	cP (mm)
1	17.6	20.5
2	20.1	23.7
3	18.1	19.6
4	19.5	23.4
5	21.6	25.0
6	18.9	18.8
7	18.2	21.4
8	19.8	23.2
9	22.9	26.0
10	23.2	33.7
11	21.7	22.8
Average	20.2 ± 1.9	23.5 ± 4.1

cA: The primary chordae tendineae from the anterior papillary muscle to the A1-2 region; cP: The primary chordae tendineae from the posterior papillary muscle to the A2-3 region.

systole. Conversely, for cA, after peaking at 15%, CL shortened slightly and then peaked again as end-systole approached (Figure 2).

DISCUSSION

Evaluation of mitral anterior leaflet chordae tendineae using 4D-CT

We were able to measure the length of the mitral anterior leaflet primary chordae tendineae using 4D-CT. The chordae tendineae are small tissues that move at high speeds, making accurate evaluation challenging. Recently, however, several studies have attempted to measure the length of mitral chordae tendineae with transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and cardiac CT. TTE measurements have been used for a relatively overtime owing to their simplicity. However, considering that it is challenging to obtain a cross-section that adequately evaluates

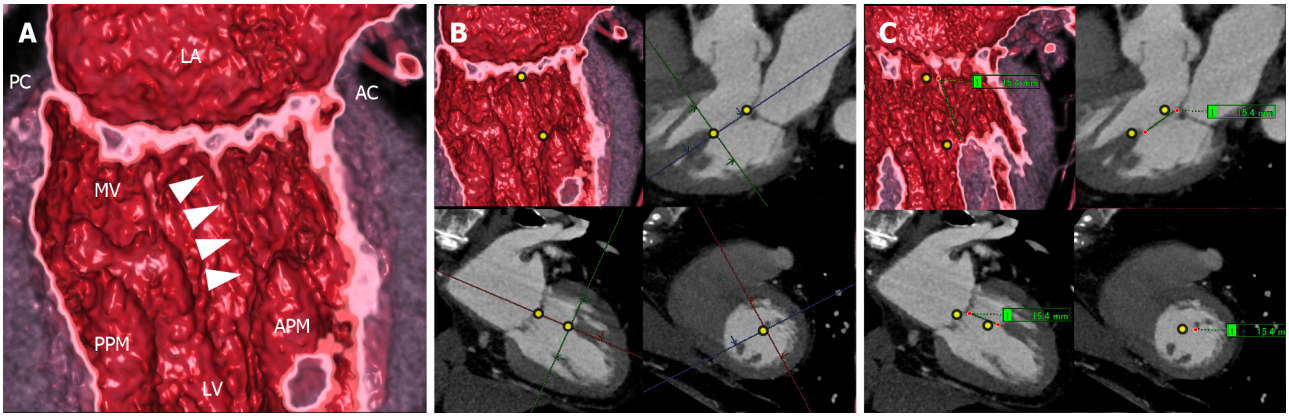

Figure 1 Method of measuring mitral chordae tendineae length. A: The cA was identified after obtaining an overall view of the mitral valve structure on a three-dimensional (3D) image created on the workstation; B: The attachment sites of the cA valve leaflet and papillary muscle were marked on the 3D image, and the marks in the corresponding positions were shown on the two-dimensional (2D)-multi-planar reformatting (MPR) image. The angle of the cross-section was adjusted so that the two marks appear simultaneously in the 2D-MPR image in three directions; C: The distance between the marks in the 2D-MPR image was measured using the measurement tool. The above procedure was also performed for the primary chordae tendineae from the posterior papillary muscle to the A2-3 region, and measurements were made over 11 time phases from 0% to 50%. White arrow: The primary chordae tendineae from the anterior papillary muscle to the A1-2 region (cA). LA: Left atrium; LV: Left ventricle; APM: Anterior papillary muscle; PPM: Posterior papillary muscle; MV: Mitral valve; AC: Anterior commissure; PC: Posterior commissure.

the 3-dimensional length of the mitral chordae tendineae, this method is somewhat lacking in accuracy[8]. Recently, evaluation by TEE has become widely used, while improvements in techniques such as transgastric echocardiography that produce fewer artifacts have been reported[9]. Although TEE is at present considered the standard method for evaluating CL, this method has some drawbacks, such as the mental and physical stress associated with the examination and the skill needed to perform the technique[10,11]. Despite these challenges, with the advent of multi-slice CT, evaluation using cardiac CT has garnered attention. With helical CT, the mitral valve structure can be obtained as volume data; following this, MPR and 3D image can be created to reconstruct optimal cross-sections for chordae tendineae assessment. This allows for direct and accurate measurement of CL, and for all chordae tendineae to be assessed in a single imaging session[12]. However, the characteristics of 3D measurements make them prone to error, while creating suitable cross-sections for 2D-MPR image measurements is time-consuming. Therefore, in the present study, we combined both methods to obtain simple, reproducible, and accurate results. We identified the points to be measured in 3D image, and then accurately measured them in 2D-MPR image. In most instances, we could evaluate the anterior leaflet primary chordae tendineae directly, although in some cases they were blurred from timing artifacts.

cA and cP measurements and differences

In previous reports on autopsies, mitral anterior leaflet CL was 15 mm-20 mm[13] and 17.5 mm ± 0.25 mm[14]. While this study had similar findings, the CLs measured in our study were slightly longer than those measured in previous autopsies. Moreover, CLs measured by the previous studies using TEE tended to be longer than those obtained through autopsies, *i.e.*, 21.3 mm ± 2.8 mm[9] and 19.3 mm ± 0.50 mm[11]. The lengths obtained by autopsies were shorter than those obtained by live measurements because the chordae tendineae in the dead bodies lacked proper tension. In the present study, cP (max) was longer than cA (max) and APM had more chordae tendineae origins than PPM. A similar tendency was observed in a study of pig hearts, with cA 16.04 mm ± 2.16 mm and cP 20.56 mm ± 3.35 mm (Sengda), suggesting that it is possible to accurately measure cA and cP with 4D-CT[14]. The ICC (1, 1) and ICC (1, 3) in our study were 0.963 and 0.987 for cA and 0.970 and 0.990 for cP, respectively, suggesting very high reproducibility of this method.

cA (max) and cP (max) exhibited large individual differences in the present study, and a significant correlation was found between BSA and CL. It is known that left ventricular end-diastolic diameter correlates with BSA in normal hearts; however, larger bodies and hearts may have longer CL[15,16]. Although there have been no reports on differences in CL based on body size, it may be necessary to take body size into account, especially when making preoperative predictions. It could be beneficial to investigate the relationship between heart size and CL by comparing various echocardiographic parameters to CL.

Variation in cA and cP during systole

Variation in CL was observed during systole in the present study. Conventionally, the chordae tendineae were thought to be rigid, non-elastic tissues composed mainly of elastin and collagen; however, recent studies have indicated that they have some degree of elasticity[17-19]. In the present study, a maximum 1.16-fold elongation was observed in cA from early to mid-systole and 1.23-fold elongation in cP. This indicates the importance of timing (15%-40%) in CL measurement, because measuring CL without specifying the timing on cardiac CT may underestimate it. In the present study, cP exhibited a PV loop-like variation with increasing intracardiac pressure, whereas cA exhibited a slight shortening of CL once it peaked, and then another peak toward end-systole. This may distort the pressure applied to the mitral anterior leaflet during systole. *In vitro* studies have suggested that in normal hearts, pressure on the mitral valve is

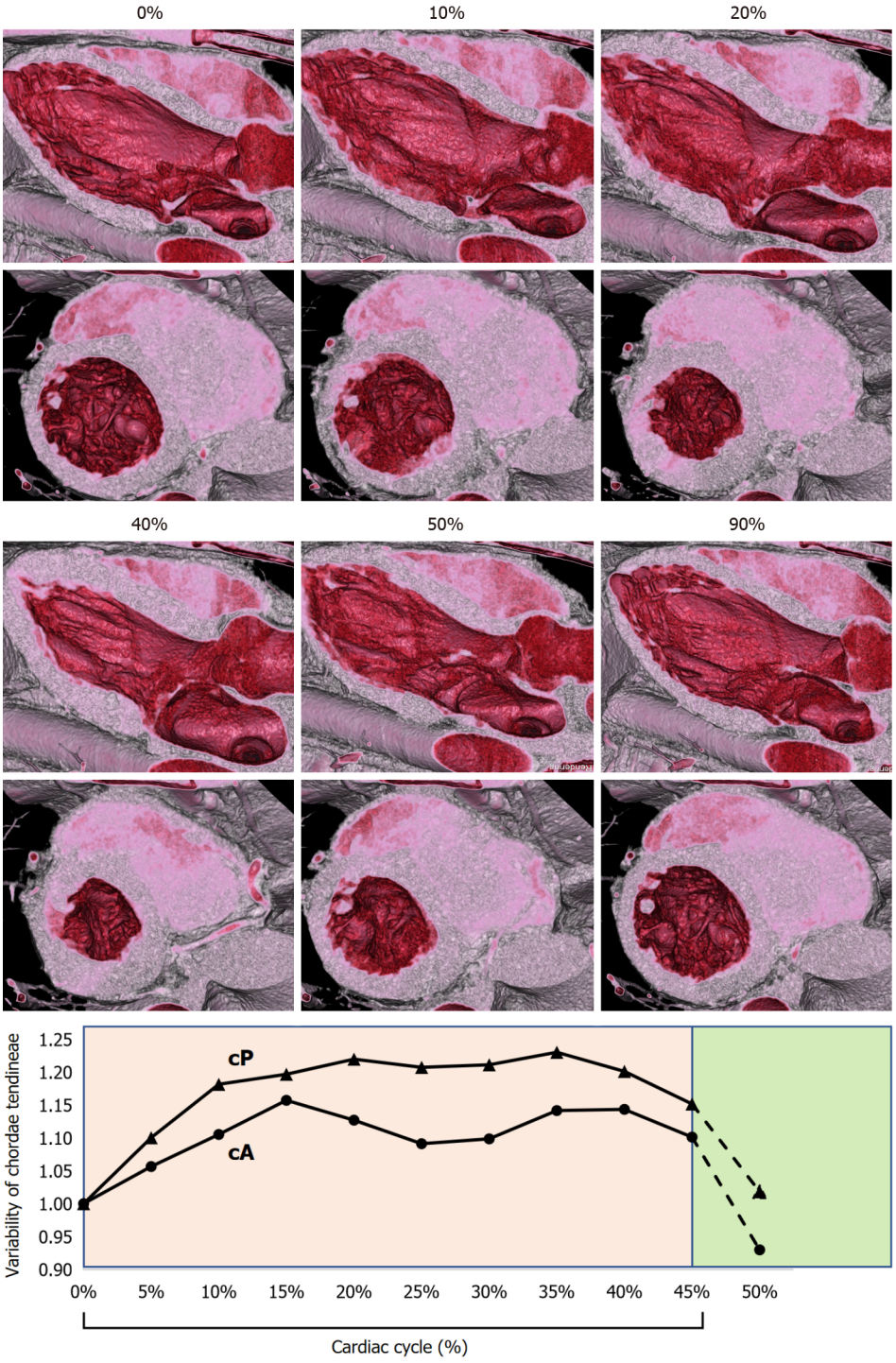

Figure 2 Variability of the mitral valve primary chordae tendineae during systole. The primary chordae tendineae from the posterior papillary muscle to the A2-3 region (cP) plateaued at 15%. The primary chordae tendineae from the anterior papillary muscle to the A1-2 region (cA) peaked at 15%, then shortened slightly and again peaked toward end-systole. 0-40%: Systole, 45-100%: Diastole.

uniform, but the displacement of the papillary muscle may result in non-uniform pressure[20]. The left ventricle is also known to undergo torsional movement during systole, which may have some effect on the displacement of the papillary muscle or the length of chordae tendineae[21]. Moreover, a recent analysis found that intracardiac blood flow is not linear but spiral, suggesting the pressure applied to the mitral valve in the body is not uniform[22]. While we were unable to determine the cause of this, dynamic assessments and blood flow analyses of the papillary muscles and left ventricular wall should be performed going forward.

As described above, while 4D-CT was seen as useful for CT measurements, the risks associated with radiation exposure and the use of contrast media in CT imaging should be taken into consideration when using this technique. That said, this imaging method does not require any special treatment or technique and can be performed simultaneously with coronary artery CT. If an institution routinely performs coronary artery CT as a preoperative examination, this method can be simultaneously implemented with no increase in radiation exposure or other burdens on patients. In the present

study, we focused on two of the more important and thicker chordae tendineae; however, we believe that relatively thin chordae tendineae close to the commissure could also be evaluated if suitable cross-sections were prepared. Variations in the shape of the papillary muscles were also seen in the cases in this study. In case 10, a smaller PPM than that in the other cases was noticed and resulted in a very long cP. It is very important to take these individual differences into account when performing mitral valvuloplasty, and CT is an excellent tool for evaluating the entire mitral valve apparatus, including the papillary muscles. Using this study as a stepping stone, we would like to pursue further research by evaluating patients with pathological conditions to help make 4D-CT a useful preoperative examination for mitral valvuloplasty.

Limitations

The limitations of this study include a small sample size, a narrow range of participants restricted to older individuals, and the absence of direct measurement of chordae tendineae. The chordae tendineae behavior in older individuals may differ from that in younger patients.

CONCLUSION

This study revealed that the primary chordae tendineae of the mitral valve anterior leaflet can be measured using 4D-CT. The lengths of cA and cP differed among individuals and varied during systole. As 4D-CT can measure the mitral complex in three dimensions and at specific timings, it may provide a more accurate evaluation of mitral CL than other modalities. Further research is warranted to explore the applicability of 4D-CT in various clinical scenarios and pathological conditions, enhancing its role as a valuable preoperative examination tool for mitral valvuloplasty.

FOOTNOTES

Author contributions: Mori T, Matsushita S, Morita T, and Amano A designed and conceived the study; Mori T collected and analyzed the data; Abudurezake A and Mochizuki J provided important data analysis support; Mori T wrote the paper; Matsushita S made critical revisions to the paper; all authors gave final approval of the version of the article to be published.

Institutional review board statement: The study was reviewed and approved by the Juntendo University School of Medicine Ethics Committee (approval #2021080 Juntendo University Medical Ethics).

Informed consent statement: All study participants, or their legal guardians, provided informed written consent prior to study enrollment.

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Data sharing statement: No additional data are available.

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Country/Territory of origin: Japan

ORCID number: Takuya Mori 0009-0008-6624-619X; Satoshi Matsushita 0000-0002-1686-6314; Terumasa Morita 0009-0008-1396-2520; Abulaiti Abudurezake 0000-0003-0829-3680; Junji Mochizuki 0000-0001-9548-1430; Atsushi Amano 0000-0003-3698-6871.

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ORIGINAL ARTICLE

Observational Study

Assessment of post-myocardial infarction lipid levels and management: Results from a tertiary care hospital of Pakistan

Rubina Rauf, Muhammad Ismail Soomro, Muhamman Nauman Khan, Mukesh Kumar, Najia Aslam Soomro, Khawar Abbas Kazmi

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Rubina Rauf, Muhammad Ismail Soomro, Khawar Abbas Kazmi, Department of Preventive Cardiology, National Institute of Cardiovascular Diseases, Karachi 75510, Pakistan

Muhamman Nauman Khan, Mukesh Kumar, Department of Adult Cardiology, National Institute of Cardiovascular Diseases, Karachi 75510, Pakistan

Najia Aslam Soomro, Department of Cardiology, Liaquat National Hospital, Karachi 74800, Pakistan

Corresponding author: Rubina Rauf, FCPS, Assistant Professor, Department of Preventive Cardiology, National Institute of Cardiovascular Diseases, Rafiqui (H.J.) Shaheed Road, Karachi 75510, Pakistan. drrubinarauf@gmail.com

Abstract

BACKGROUND

Lipid treatment practices and levels in post-acute myocardial infarction (AMI) patients, which are crucial for secondary prevention.

AIM

To evaluate the lipid treatment practices and lipid levels in post-myocardial infarction (MI) patients at a tertiary care hospital in Pakistan.

METHODS

In this cross-sectional study, we analyzed patients who had experienced their first AMI event in the past 3 years. We assessed fasting and non-fasting lipid profiles, reviewed statin therapy prescriptions, and examined patient compliance. The recommended dose was defined as rosuvastatin ≥ 20 mg or atorvastatin ≥ 40 mg, with target total cholesterol levels set at < 160 mg/dL and target low-density lipoprotein cholesterol (LDL-C) at < 55 mg/dL.

RESULTS

Among 195 patients, 71.3% were male, and the mean age was 57.1 ± 10.2 years. The median duration since AMI was 36 (interquartile range: 10-48) months and 60% were diagnosed with ST-segment elevation MI. Only 13.8% of patients were advised to undergo lipid profile testing after AMI, 88.7% of patients were on the recommended statin therapy, and 91.8% of patients were compliant with statin therapy. Only 11.5% had LDL-C within the target range and 71.7% had total

cholesterol within the target range. Hospital admission in the past 12 months was reported by 14.4%, and the re-admission rate was significantly higher among non-compliant patients (37.5% *vs* 5.6%). Subsequent AMI event rate was also significantly higher among non-compliant patients (43.8% *vs* 11.7%).

CONCLUSION

Our study highlights that while most post-AMI patients received the recommended minimum statin therapy dose, the inadequate practice of lipid assessment may compromise therapy optimization and raise the risk of subsequent events.

Key Words: Lipid profile; Dyslipidemia; Acute myocardial infarction; Secondary prevention; Lipid lowering therapy

Core Tip: Lipid treatment practices and levels in post-acute myocardial infarction (AMI) patients, which are crucial for secondary prevention. This study examined lipid treatment practices and levels in post-AMI patients at a Pakistani tertiary care hospital. Among 195 patients, only 13.8% underwent lipid profile testing post-AMI. While 88.7% received recommended statin therapy, only 11.5% achieved target low-density lipoprotein cholesterol levels. Non-compliance with statin therapy correlated with higher re-admission and subsequent AMI rates. The findings underscore the importance of optimizing lipid assessment practices to reduce the risk of recurrent events in post-AMI patients.

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INTRODUCTION

Acute myocardial infarction (AMI) stands as a global leading cause of mortality. Following AMI, meticulous management of patient's lipid levels for secondary prevention becomes paramount. This specific patient group is at high risk, with a particular focus on reducing low-density lipoprotein cholesterol (LDL-C) levels to recommended ranges, as elevated LDL-C levels significantly contribute to acute coronary events[1]. Despite aggressive cholesterol control with statins in post-MI patients, a lingering risk for further cardiovascular events persists. Shockingly, within the 2 years following an acute coronary event, approximately 20% of survivors experience another coronary event, and their 5-year mortality rate escalates, ranging from 19% to 22%[2].

Assessing and managing the lipid profile serve as the cornerstone of secondary prevention, yet patients typically receive inadequate treatment following an acute coronary event[3,4]. Various studies have illuminated the fact that most patients experience suboptimal dyslipidemia treatment, leading to a heightened future risk of cardiovascular events. Although many patients with acute coronary syndrome (ACS) are prescribed high-intensity statins for secondary prevention, a significant number remains undertreated, failing to achieve therapeutic goals[5,6]. Therefore, the management of hypercholesterolemia in these patients is of paramount importance to mitigate future cardiovascular risks.

International guidelines on lipid management for secondary prevention in post-MI patients exhibit slight variations, emphasizing the significance of assessing individual patient risk in making informed decisions. The 2021 guidelines from the European Society of Cardiology (ESC) advocate for a 50% reduction in LDL-C levels to achieve a value of < 1.4 mmol/L (55 mg/dL) in individuals following an acute coronary event[7]. The ESC guidelines also suggest repeating lipid profiles in patients after an acute coronary event within four to six weeks to optimize lipid-lowering therapy. Conversely, the National Institute for Health and Care Excellence guidelines recommend a 40% reduction in non-high-density lipoprotein cholesterol (non-HDL-C) in patients with ACS, along with a lipid profile reassessment 3 months after initiating lipid-lowering therapy. Furthermore, the third report from the National Cholesterol Education Program Adult Treatment Panel (ATP III) underscores cardiovascular risk reduction through treatment to LDL-C targets[8]. The ATP III guidelines set an LDL-C target of < 100 mg/dL for patients with established coronary artery disease (CAD) and < 70 mg/dL for patients with ACS. Despite these recommendations, achieving guideline-recommended LDL-C goals remains suboptimal in real-world settings[9-11].

Recognizing the pivotal role of statins in minimizing the risk of subsequent cardiovascular events is crucial. However, statin monotherapy may fall short in achieving target goals in many high-risk patients, necessitating the use of statin combination therapy with other non-statin lipid-lowering agents as the optimal therapeutic approach. This underscores the importance of evaluating and ensuring adequate lipid management in patients following an acute cardiovascular event, particularly in those admitted to tertiary care centers, to minimize the future risk of cardiovascular morbidity and mortality. Hence, in this study, we aimed to evaluate the lipid profile treatment practices and lipid levels in post-MI patients at a tertiary care hospital in Pakistan.

MATERIALS AND METHODS

Between August 2022 and February 2023, a single-center cross-sectional study was conducted at the National Institute of Cardiovascular Disease (NICVD) in Karachi, Pakistan. The study aimed to assess post-myocardial infarction (MI) patients visiting the cardiology outpatient clinic for secondary prevention and further management. Eligible participants included individuals aged 18 and above who had experienced their first acute coronary event within the past 3 years. Ethical clearance was obtained from the hospital's ethics committee, and verbal informed consent was acquired from patients, providing a detailed explanation of the study's purpose and benefits.

Our study standards were aligned with the 2021 ESC guidelines on cardiovascular disease (CVD) prevention in clinical practice. These standards included achieving LDL-C levels below 55 mg/dL, which necessitated a 50% reduction from baseline. Additionally, we stipulated that a repeat lipid profile should be obtained six weeks after the initial clinic presentation. For patients who did not reach the lipid reduction target (> 50% LDL-C reduction from baseline or LDL-C < 55 mg/dL), or those who could not tolerate statin therapy, the guidelines recommended the addition of other lipid-lowering agents, in a preferred order, to high-intensity statins. We also documented pre-MI statin use, post-discharge statin type and dose.

High-intensity statin therapy was defined as daily rosuvastatin ≥ 20 mg or atorvastatin ≥ 40 mg, while moderate-intensity statin therapy encompassed daily rosuvastatin between 5 and 19 mg, or atorvastatin between 10 and 39 mg, pravastatin ≥ 40 mg, simvastatin ≥ 20 mg, fluvastatin ≥ 80 mg, lovastatin ≥ 40 mg, and pitavastatin ≥ 2 mg. All other combinations of statin type and dose were considered low intensity.

Data collected for the study encompassed demographics, medical history regarding co-morbid conditions, presentation ["ST-segment elevation MI (STEMI)" or non-STEMI], family history of CAD, diabetes, hypertension, waist circumference (cm), body mass index (kg/m^2), heart rate, systolic blood pressure, lipid profile before the cardiovascular event, and pre-MI statin use. Additionally, last available lipid profiles were assessed for all the patients.

To estimate the proportion of patients meeting guideline-recommended cholesterol targets based on their LDL-C levels and prescribed statin intensity at discharge, we conducted statistical analysis using IBM Statistical Package for Social Sciences 21. Patients were categorized into sub-groups based on their adherence to recommended statin dosages, total cholesterol levels (target < 160 mg/dL), and LDL cholesterol levels (target < 55 mg/dL). Data comparisons between these groups were performed using independent sample *t*-tests or χ^2 tests as appropriate. Univariate and multivariable binary logistic regression analyses were employed to identify clinical and demographic factors associated with achieving target total cholesterol levels, LDL levels, and recommended statin dosages. All analyses were conducted at a significance level of 5%.

RESULTS

Among the 195 post-AMI patients in our study, 71.3% were male, with a mean age of 57.1 ± 10.2 years. The primary diagnosis was STEMI for 60% of patients. The median time since the first acute MI event was 36 (interquartile range: 10-48) months. Most patients (88.7%) were on the recommended statin therapy, predominantly Rosuvastatin (91.8%), with only 2.6% were prescribed Atorvastatin. Lipid profile assessment was advised for only 13.8% of patients after AMI. Compliance with prescribed statin therapy was high at 91.8%. Total cholesterol was within the target range (< 160 mg/dL) in 71.7% of patients, while LDL-cholesterol met the target (< 55 mg/dL) in only 11.5%. Over the past 12 months, 14.4% of patients had at least one hospital admission (Table 1).

The majority of patients (91.8%) demonstrated compliance with their statin therapy, while 8.2% (16) of patients were non-compliant, primarily due to affordability concerns (reported by 15 patients) or dizziness (reported by 1 patient).

Notably, non-compliant patients had a significantly higher hospital admission rate in the past 12 months, with an event rate of 37.5% (6/16), compared to 5.6% (10/179) among compliant patients (P < 0.001). Similarly, the subsequent ACS event rate was significantly higher among non-compliant patients, with an event rate of 43.8% (7/16), compared to 11.7% (21/179) among compliant patients (P < 0.001).

It is worth noting that both univariate and multivariable regression analyses did not reveal any statistically significant clinical factors associated with the target total cholesterol (Table 2).

The univariate and multivariable regression analysis revealed significantly lower prevalence of the target LDL cholesterol levels for the middle aged (41-65 years) patients as compared to younger patients (up to 40 years) with an adjusted odds ratio of 0.17 (95%CI: 0.03-0.85; P = 0.031) (Table 3).

Similarly, the univariate and multivariable regression analysis revealed no statistically significant clinical associates of the recommended dose of statin (Table 4).

DISCUSSION

Recent evidence has solidified the understanding that the primary trigger for atherosclerosis is the retention of cholesterol, primarily LDL, within the arterial walls. The pivotal role of LDL and other apo-B containing lipoproteins in the progression of atherosclerotic CVD (ASCVD) has been substantiated through various genetic, observational, and interventional studies[12]. The results of our study shed light on the crucial aspects of lipid profile management in post-AMI patients, which play a pivotal role in secondary prevention. Our primary aim was to evaluate the practices and lipid levels in this specific patient population to better understand the state of secondary prevention in clinical practice. In our

Table 1 Distribution of demographic and clinical characteristics of post-acute myocardial infarction patients, *n* (%)

	Total	Statin therapy		*P* value
		Not on recommended dose	On recommended dose	
Total	195	22 (11.3)	173 (88.7)	-
Gender				
Male	139 (71.3)	15 (68.2)	124 (71.7)	0.733
Female	56 (28.7)	7 (31.8)	49 (28.3)	
Age (mean ± SD, yr)	57.1 ± 10.2	57.8 ± 11.6	57 ± 10	0.728
≤ 40	11 (5.6)	2 (9.1)	9 (5.2)	0.558
41-65	150 (76.9)	15 (68.2)	135 (78)	
> 65	34 (17.4)	5 (22.7)	29 (16.8)	
Weight (mean ± SD, kg)	73.4 ± 14.7	76.6 ± 15.2	72.9 ± 14.6	0.268
Height (mean ± SD, cm)	155.5 ± 7.7	159.9 ± 7.5	154.9 ± 7.5	0.004
Body mass index (mean ± SD, kg/m^2)	30.4 ± 5.8	30.2 ± 6.6	30.4 ± 5.8	0.857
Underweight (< 18.5)	1 (0.5)	0 (0)	1 (0.6)	0.185
Healthy weight (18.5-22.9)	16 (8.2)	4 (18.2)	12 (6.9)	
Above ideal range (≥ 23)	178 (91.3)	18 (81.8)	160 (92.5)	
Waist circumference (mean ± SD, cm)	97.2 ± 8.8	101.5 ± 11.7	96.7 ± 8.2	0.016
DM	82 (42.1)	11 (50)	71 (41)	0.423
Duration of DM (mean ± SD)	9.1 ± 5.3	9.5 ± 6.2	9.1 ± 5.2	0.832
Well controlled	13 (15.9)	3 (27.3)	10 (14.1)	0.265
HTN	100 (51.3)	12 (54.5)	88 (50.9)	0.745
Duration of HTN (mean ± SD)	8.1 ± 4.4	6.9 ± 3.4	8.2 ± 4.5	0.342
Well controlled	54 (54)	11 (91.7)	43 (48.9)	0.005
Tobacco	83 (42.6)	6 (27.3)	77 (44.5)	0.124
Duration of tobacco use (mean ± SD)	19.1 ± 9.1	15.4 ± 8.2	19.4 ± 9.2	0.296
Chewing	6 (7.2)	2 (33.3)	4 (5.2)	0.073
Chewing, smoking	6 (7.2)	0 (0)	6 (7.8)	
Smoking	71 (85.5)	4 (66.7)	67 (87)	
Family history of coronary artery diseases	101 (51.8)	17 (77.3)	84 (48.6)	0.011
AMI				
STEMI	117 (60)	15 (68.2)	102 (59)	0.406
NSTEMI	78 (40)	7 (31.8)	71 (41)	
Duration science first event of AMI (month)	36 (10-48)	36 (10-72)	30 (10-48)	0.299
Number of hospital admissions (in last 12 months)				
0	167 (85.6)	15 (68.2)	152 (87.9)	0.001
1	23 (11.8)	4 (18.2)	19 (11)	
2	5 (2.6)	3 (13.6)	2 (1.2)	
Lipid profile advised after AMI	27 (13.8)	6 (27.3)	21 (12.1)	0.053
Are you taken statins after 1st event of AMI?	185 (94.9)	12 (54.5)	173 (100)	< 0.001
Duration [median (IQR), month]	24 (9-48)	26 (6.5-66)	24 (10-48)	0.818

What is the dose of statin you are taking?				
Rosuvastatin	179 (91.8)	7 (31.8)	172 (99.4)	-
Not taking	16 (8.2)	15 (68.2)	1 (0.6)	< 0.001
10 mg	7 (3.6)	7 (31.8)	0 (0)	
20 mg	172 (88.2)	0 (0)	172 (99.4)	
Atervastatin	5 (2.6)	4 (18.2)	1 (0.6)	-
Not taking	190 (97.4)	18 (81.8)	172 (99.4)	< 0.001
20 mg	4 (2.1)	4 (18.2)	0 (0)	
40 mg	1 (0.5)	0 (0)	1 (0.6)	
Simvastatin	1 (0.5)	1 (4.5)	0 (0)	-
Not taking	194 (99.5)	21 (95.5)	173 (100)	0.005
10 mg	1 (0.5)	1 (4.5)	0 (0)	
Did you ever lipid profile get done before AMI event?	4 (2.1)	1 (4.5)	3 (1.7)	0.381
Total cholesterol (last lipid profile)				
Available	191 (97.9)	22 (100)	169 (97.7)	-
Level (mean ± SD)	143.1 ± 38.7	143 ± 35.6	143.1 ± 39.2	0.986
Level [median (IQR)]	140 (115-165)	136 (115-165)	144 (115-163)	0.818
Target total cholesterol (< 160)	137 (71.7)	16 (72.7)	121 (71.6)	0.912
LDL-cholesterol (last lipid profile)				
Available	191 (97.9)	21 (95.5)	170 (98.3)	-
Level (mean ± SD)	91.7 ± 34.8	94.7 ± 42.5	91.3 ± 33.8	0.676
Level [median (IQR)]	88 (66-110)	83 (65-94)	88.5 (67-110)	0.989
Target LDL cholesterol (< 55)	22 (11.5)	2 (9.5)	20 (11.8)	0.762
HDL-cholesterol (last lipid profile)				
Available	192 (98.5)	22 (100)	170 (98.3)	-
Level (mean ± SD)	40.9 ± 8.7	41.2 ± 10	40.8 ± 8.6	0.846
Level [median (IQR)]	42 (36-45)	42.5 (37-49)	41.5 (36-45)	0.466
Triglycerides (last lipid profile)				
Available	165 (84.6)	17 (77.3)	148 (85.5)	-
Level (mean ± SD)	167.6 ± 76.4	185.4 ± 125	165.5 ± 69.1	0.311
Level [median (IQR)]	150 (123-190)	152 (125-167)]	150 (123-190)	0.782
Were you taken statins before 1st event of AMI?	3 (1.5)	0 (0)	3 (1.7)	0.534
Duration [median (IQR), month]	36 (12-48)	-	36 (12-48)	-
History of subsequent ACS event	16 (8.2)	3 (13.6)	13 (7.5)	0.324
Compliant to the statin therapy	179 (91.8)	12 (54.5)	167 (96.5)	< 0.001
If no what are the reasons?				
Affordability	15 (7.7)	9 (40.9)	6 (3.5)	< 0.001
Dizziness	1 (0.5)	1 (4.5)	0 (0)	

AMI: Acute myocardial infarction; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; ACS: Acute coronary syndrome; IQR: Interquartile range; DM: Diabetes mellitus; HTN: Hypertension.

Table 2 Univariate and multivariable binary logistic regression analysis for the clinical associates of the target total cholesterol

Target total cholesterol (< 160)	Univariate		Multivariable	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Gender				
Male	1	-	1	-
Female	1.07 (0.53-2.16)	0.845	1.43 (0.61-3.38)	0.411
Age (yr)				
≤ 40	1	-	1	-
41-65	0.23 (0.03-1.88)	0.172	0.18 (0.02-1.53)	0.116
> 65	0.27 (0.03-2.39)	0.238	0.18 (0.02-1.74)	0.137
Body mass index (kg/m^2)				
< 23	1	-	1	-
≥ 23	0.76 (0.24-2.45)	0.650	0.75 (0.2-2.73)	0.657
Waist circumference (cm)	0.99 (0.96-1.03)	0.743	1 (0.95-1.04)	0.859
DM				
Non-DM	1	-	1	-
DM	0.96 (0.51-1.82)	0.901	0.94 (0.47-1.87)	0.864
HTN				
Non-HTN	1	-	1	-
HTN	0.97 (0.52-1.82)	0.925	1.06 (0.55-2.06)	0.854
Tobacco user				
No	1	-	1	-
Yes	1.22 (0.64-2.33)	0.537	1.43 (0.66-3.14)	0.366
Family history of coronary artery diseases				
No	1	-	1	-
Yes	1.03 (0.55-1.93)	0.930	0.94 (0.48-1.81)	0.843
Acute myocardial infarction				
STEMI	1	-	1	-
NSTEMI	0.98 (0.51-1.85)	0.940	1.05 (0.54-2.04)	0.893
Lipid profile advised after acute myocardial infarction				
No	1	-	1	-
Yes	0.71 (0.29-1.7)	0.441	0.58 (0.23-1.47)	0.247
Statin therapy after acute myocardial infarction				
No	1	-	1	-
Yes	0.62 (0.13-3.02)	0.554	0.52 (0.1-2.78)	0.446

OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus; HTN: Hypertension; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction.

cohort of 195 post-AMI patients, we observed some noteworthy trends. Firstly, it is concerning that only 13.8% of the patients were advised to undergo lipid profile testing after their AMI event. This low rate of lipid assessment raises concerns about the adequacy of secondary prevention strategies. Monitoring lipid profiles is a fundamental step in managing cardiovascular risk and tailoring therapeutic interventions. The suboptimal rate of lipid assessment suggests a potential gap in post-AMI care.

Many clinical trials have demonstrated that the CVD risk reduction is proportional to the reduction in LDL-C levels, it is not important which statin is used to achieve the goal, and lower limit of LDL-C levels is not defined[5]. Greater absolute risk reduction in patients with a high or very high risk of future cardiovascular event can be achieved even with

Table 3 Univariate and multivariable binary logistic regression analysis for the clinical associates of the target low-density lipoprotein cholesterol

Target LDL cholesterol (< 55)	Univariate		Multivariable	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Gender				
Male	1	-	1	-
Female	1.18 (0.45-3.06)	0.739	1.09 (0.32-3.72)	0.884
Age (yr)				
≤ 40	1	-	1	-
41-65	0.2 (0.05-0.76)	0.018	0.17 (0.03-0.85)	0.031
> 65	0.18 (0.03-0.97)	0.046	0.14 (0.02-1.07)	0.058
Body mass index (kg/m^2)				
< 23	1	-	1	-
≥ 23	0.57 (0.15-2.17)	0.412	0.34 (0.06-1.84)	0.211
Waist circumference (cm)	1.02 (0.97-1.08)	0.354	1.04 (0.98-1.11)	0.210
DM				
Non-DM	1	-	1	-
DM	0.61 (0.24-1.58)	0.312	0.4 (0.14-1.17)	0.094
HTN				
Non-HTN	1	-	1	-
HTN	0.92 (0.38-2.24)	0.855	0.96 (0.35-2.68)	0.942
Tobacco user				
No	1	-	1	-
Yes	0.6 (0.23-1.54)	0.289	0.59 (0.18-1.93)	0.386
Family history of coronary artery diseases				
No	1	-	1	-
Yes	1.39 (0.57-3.44)	0.470	1.42 (0.53-3.84)	0.485
Acute myocardial infarction				
STEMI	1	-	1	-
NSTEMI	0.4 (0.14-1.12)	0.082	0.41 (0.13-1.31)	0.133
Lipid profile advised after acute myocardial infarction				
No	1	-	1	-
Yes	0.27 (0.04-2.13)	0.216	0.15 (0.02-1.39)	0.095
Statin therapy after acute myocardial infarction				
No	1	-	1	-
Yes	1.04 (0.12-8.76)	0.969	1.45 (0.11-18.39)	0.775

LDL: Low-density lipoprotein; OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus; HTN: Hypertension; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction.

small reduction in LDL-C levels[13]. Treatment goal should be focused on maintaining LDL-C levels to the recommended target, keeping an eye on drug tolerance and affordability. The recommended levels of LDL-C is < 1.4 mmol/L (55 mg/dL) and a > 50% reduction in LDL-C from the baseline is the treatment goal in patients with established CVD.

On a more positive note, a substantial proportion (88.7%) of the patients were on the recommended statin therapy, which includes Rosuvastatin and Atorvastatin at specific doses. Furthermore, our study found that the majority of patients (91.8%) were compliant with their prescribed statin therapy. However, the most concerning aspect of our findings is that only 11.5% of the patients had LDL-cholesterol levels within the target range, and 71.7% had total

Table 4 Univariate and multivariable binary logistic regression analysis for the clinical associates of the recommended dose of statin

Recommended dose of statin	Univariate		Multivariable	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Gender				
Male	1	-	1	-
Female	0.85 (0.33-2.2)	0.733	1.91 (0.55-6.67)	0.325
Age (yr)				
≤ 40	1	-	1	-
41-65	2 (0.39-10.13)	0.402	1.58 (0.25-9.99)	0.395
> 65	1.29 (0.21-7.82)	0.783	0.48 (0.06-4.09)	0.213
Body mass index (kg/m^2)				
< 23	1	-	1	-
≥ 23	2.74 (0.81-9.28)	0.107	14 (2.42-80.95)	0.806
Waist circumference (cm)	0.94 (0.89-0.99)	0.018	0.89 (0.83-0.95)	0.890
DM				
Non-DM	1	-	1	-
DM	0.7 (0.29-1.69)	0.424	0.64 (0.23-1.79)	0.286
HTN				
Non-HTN	1	-	1	-
HTN	0.86 (0.35-2.1)	0.745	1.38 (0.47-4.03)	0.354
Tobacco user				
No	1	-	1	-
Yes	2.14 (0.8-5.73)	0.130	2.08 (0.58-7.51)	0.799
Family history of coronary artery diseases				
No	1	-	1	-
Yes	0.28 (0.1-0.79)	0.016	0.2 (0.06-0.64)	0.098
Acute myocardial infarction				
STEMI	1	-	1	-
NSTEMI	1.49 (0.58-3.84)	0.408	1.6 (0.51-5.06)	0.579
Lipid profile advised after acute myocardial infarction				
No	1	-	1	-
Yes	0.37 (0.13-1.05)	0.061	0.21 (0.06-0.74)	0.130

OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus; HTN: Hypertension; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction.

cholesterol within the target range. These results indicate that, despite a substantial proportion of patients receiving and adhering to statin therapy, many are not achieving the desired lipid profile targets. This could be attributed to various factors, such as inadequate dosage, inadequate medication adjustment over time, or even genetic predisposition. The suboptimal achievement of target lipid levels underscores the importance of ongoing monitoring and personalized adjustments in lipid-lowering therapy.

If the treatment targets are not achieved with the maximum recommended dose of statin, combination with other lipid lowering agent like ezetimabe is recommended. Combination therapy with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibiter is recommended if combination of statin with ezetimabe is not helpful for achieving the target goals [14]. Those patients who are already taking maximum tolerated statin but experience a second cardiovascular event within 2 years of the first CVD event (type may be different), LDL-C levels of 40 mg/dL (1.0 mmol/L) may be the treatment target[14]. Till now none of the clinical trials have demonstrated target goals for HDL-C levels, although high HDL-C is associated with future risk reduction in patients with established ASCVD[14].

A goal-oriented approach to lipid-lowering therapy necessitates regular and timely lipid testing. Our study revealed consistently low lipid testing rates (13.8%) among post-MI patients, and there was no discernible preference for testing in those individuals who required statin dose adjustments. Similarly, the rates of lipid testing remained low for patients who had recently been prescribed statin therapy. Interestingly, a significant majority (88.2%) of patients discharged on a high-intensity statin were more likely to undergo lipid testing. This underscores the importance of targeted lipid management as an integral, multi-step process for secondary prevention. Specifically, post-MI patients who are discharged with a statin prescription must have their lipid levels monitored within 1 to 2 months of initiating treatment.

Patients who have been discharged while on a high-intensity statin regimen may not necessarily require long-term continuation of such an intensive statin therapy. Nevertheless, research findings indicate that patients tend to exhibit higher levels of treatment adherence when they follow the medication regimen prescribed at the time of their discharge [15]. Good adherence to recommended lipid-lowering therapy can be achieved with early and timely follow-up outpatient visits with proper and timely lipid testing[16,17]. Results of a study by Cannon *et al*[18] have shown significant reductions in CVD when statin is combined to ezetimibe to reduce LDL-C levels. Similarly combination of PCSK9 inhibitors to statin in order to reduce the LDL-C levels leads to significant reduction in LDL-C levels[19-21].

Another concerning finding is the history of hospital admissions in the past 12 months, reported by 14.4% of the patients. Even more alarming is that the readmission rate was significantly higher among non-compliant patients (37.5% *vs* 5.6%). This observation highlights the potential consequences of non-compliance with statin therapy. Patients who do not adhere to their prescribed medications may be at higher risk of recurrent cardiovascular events, necessitating hospitalization. In line with this, our study also revealed a significantly higher subsequent AMI event rate among non-compliant patients (43.8% *vs* 11.7%).

It is important to practice lipid testing with early sensitization, and follow guideline-recommended LDL-C targets, lipid lowering therapy optimization, proper lipid monitoring, and after a cardiovascular event with regular follow-up. In our study, we have not observed a single patients on combination therapy, this high-CV risk population that would benefit from a reduction in their high future cardiovascular risk as a result of the LDL-C reduction can be achieved with combination therapy. Shortly, we recommend combination of tolerable highest statin dose with other non-statin lipid-lowering drug for those patients who could not achieve target goal.

The small sample size in our study introduced limitations, as we only included patients who visited the cardiac risk assessment clinic for secondary prevention, potentially introducing selection bias. Larger studies, involving patients recruited from ACS settings, are needed to comprehensively assess lipid management in MI patients.

CONCLUSION

Our study is among the first to conduct a study on dyslipidemia management in post-MI patients in Pakistan. This study underscores the importance of comprehensive lipid profile management in post-AMI patients. While many patients are prescribed and are compliant with statin therapy, achieving target lipid levels remains a challenge. The association between non-compliance and higher hospitalization and subsequent AMI rates underscores the need for interventions to improve medication adherence in this vulnerable population.

However, there were gaps in post MI lipid profile in hospitalized patients, awareness of getting lipid profile before and after cardiovascular event, delays in post-discharge lipid testing and suboptimal achievement of the LDL-C goals. Underutilization of non-statin lipid-lowering therapy amongst those who needed optimization, highlighting some gaps in the secondary prevention of patients with previous MI as recommended by the 2021 ESC guidelines for CVD prevention. Further research and interventions in this area are warranted to reduce the burden of recurrent cardiovascular events in this population.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Long-term outcomes of titanium-nitride-oxide coated stents and drug-eluting stents in acute coronary syndrome: A systematic review and meta-analysis

Muhammad Ahmed Ali Fahim, Afia Salman, Hira Anas Khan, Syed Muhammad Hasan, Muskan Fatima Bhojani, Sarah Aslam, Amna Zia Ul Haq, Vishal Reddy Bejugam, Beena Muntaha Nasir, Wajiha Gul, Abdul Moeed, Abdelrahman S Abdalla, Muhammad Majid, Muhammad Sohaib Asghar, Md Al Hasibuzzaman

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Muhammad Ahmed Ali Fahim, Afia Salman, Hira Anas Khan, Syed Muhammad Hasan, Muskan Fatima Bhojani, Sarah Aslam, Amna Zia Ul Haq, Beena Muntaha Nasir, Wajiha Gul, Abdul Moeed, Department of Internal Medicine, Dow University of Health Sciences, Karachi 74200, Pakistan

Vishal Reddy Bejugam, Department of Internal Medicine, North Central Bronx Hospital, Bronx, NY 10467, United States

Abdelrahman S Abdalla, Department of Urology, Center for Academic Medicine, Stanford University School of Medicine, Palo Alto, CA 33872, United States

Muhammad Majid, Department of Cardiovascular Imaging, Cleveland Clinic, Cleveland, OH 44195, United States

Muhammad Sohaib Asghar, Division of Nephrology and Hypertension, Mayo Clinic Rochester, Rochester, MN 55905, United States

Md Al Hasibuzzaman, Institute of Nutrition and Food Science, University of Dhaka, Dhaka 1000, Bangladesh

Corresponding author: Md Al Hasibuzzaman, MBBS, Doctor, Institute of Nutrition and Food Science, University of Dhaka, Suhrawardi Udyan Road, Dhaka 1000, Bangladesh. al.hasibuzzaman.hasib@gmail.com

Abstract

BACKGROUND

In severe cases of coronary artery disease, percutaneous coronary intervention provide promising results. The stent used could be a drug-eluting stent (DES) or a titanium-nitride-oxide coated stent (TiNOS).

AIM

To compare the 5-year effectiveness and safety of the two stent types.

METHODS

The following systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis

guidelines, and PubMed/MEDLINE, Scopus, and Cochrane Central were searched from inception till August 2023. Primary outcomes were major adverse cardiac events (MACE), cardiac death, myocardial infarction (MI), cardiac death or MI, and ischemia-driven total lesion revascularization (ID-TLR).

RESULTS

Four randomized controlled trials (RCT), which analyzed a sum total of 3045 patients with acute coronary syndrome (ACS) after a median follow-up time of 5 years were included. Though statistically insignificant, an increase in the ID-TLR was observed in patients receiving TiNOSs *vs* DESs. In addition, MI, cardiac death and MI, and definite stent thrombosis (DST) were significantly decreased in the TiNOS arm. Baseline analysis revealed no significant results with meta-regression presenting non-ST elevated MI (NSTEMI) as a statistically significant covariate in the outcome of MACE.

CONCLUSION

TiNOS was found to be superior to DES in terms of MI, cardiac death or MI, and DST outcomes, however, the effect of the two stent types on ID-TLR and MACE was not significant. A greater number of studies are required to establish an accurate comparison of patient outcomes in TiNOS and DES.

Key Words: Stents; Drug-eluting; Major adverse cardiac events; All-cause death; Meta-analysis

Core Tip: Acute coronary syndrome (ACS) is characterized by reduced blood flow to the myocardium. While percutaneous coronary intervention with drug-eluting stents (DES) remains the standard management of ACS patients, titanium-nitride-oxide-coated stents (TiNOS) are a relatively newer intervention with relatively lower host immune reactions. In order to facilitate clinical practice guidelines in ACS patients requiring stent placement, it is imperative to compare and assess the safety and efficacy of DES and TiNOS. Therefore, this meta-analysis compared the two interventions in terms of major adverse cardiac events, cardiac death, myocardial infarction, and ischemia-driven total lesion revascularization outcomes.

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INTRODUCTION

Coronary artery disease (CAD) can be defined as a medical condition where the heart's blood vessels become obstructed, resulting in ischemia and subsequent hypoxia to the cardiac tissue[1]. It is categorized into two groups: acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) with the former differing from the latter mainly in the onset of symptoms[2].

ACS can manifest in a number of ways, namely ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina with subsequent arrhythmias. Clinically, a presentation with chest pain localized to the sternum, often described as a sensation of crushing or pressure can be seen. This discomfort may also radiate to the jaw and/or left arm[3].

Percutaneous coronary interventions (PCI) with drug-eluting stents (DES) have been established as the recommended treatment for ACS owing to their superior efficacy compared to bare metal stents (BMS). The introduction of immunosuppressant and anti-proliferative drugs such as sirolimus, everolimus, paclitaxel, and zotarolimus confers the benefit of lower rates of early cellular proliferation, inflammation, and therefore restenosis[4,5]. However, the comparatively newer titanium-nitride-oxide coated stents (TiNOS) have proven to be at par. The titanium-nitride coating affords the benefit of inducing lower levels of host immune reactions compared to other BMS such as non-coated stainless steel, better early vascular healing, lower rates of malapposition, and better stent coverage[6,7]. Additionally, TiNOS have been reported to require a lower duration of post-procedure anticoagulant therapy, owing to their anti-thrombotic nature[8].

In recent years, there have been several randomized controlled trials (RCT) comparing the clinical outcomes of TiNOSs and DESs in patients with ACS with the latest report being on the 5-year follow-up of patients in the TIDE-ACS trial a study that bears a considerable sample size. This study, and the most recent meta-analysis by Daoud *et al*[9] concluded that TiNOSs are a non-inferior and safe alternative to DES in ACS patients[9,10]. However, there is no meta-analysis to date, which has assessed the long-term efficacy and safety of TiNOSs and DESs with a sufficient sample size. Therefore, we aimed to compare the 5-year effectiveness and safety of the two stent types, using the latest data from the RCTs evaluating outcomes 5 years post-procedure.

MATERIALS AND METHODS

Data sources and search strategy

The following systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines with a PRISMA checklist[11]. The research questionnaire was formulated utilizing the patient, intervention, control, and outcome (PICO) framework[12] and a search strategy based on the aforementioned questionnaire comprising of the Boolean operators "AND" and "OR" along with various MeSH terms was run on three separate databases: PubMed/MEDLINE, Scopus, and Cochrane Central. These databases were then systematically searched from inception till August 2023, without any restrictions or filters on the basis of language, year of publication, author names, country, institution of publication, or any other aspect applied, and all relevant RCTs and observational studies were selected. The terms utilized in the search strategy included 'bioactive', 'Titanium', 'nitride', 'oxide', 'TiNO', 'TNO', 'BAS', 'stent', 'DES', 'drug' and 'eluting stent'. As this study sees publicly available data, study registry and institutional review board approval were not required. A more detailed overview of the search strategy used is given in Supplementary Table 1. Additionally, to identify grey literature ClinicalTrials.gov, Medrxiv.org, and Google Scholar were searched. This systematic review and meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42024534358).

Study selection

Following the comprehensive literature search, all articles retrieved were exported to the EndNote Reference library (Version X7.5; Clarivate Analytics, Philadelphia, PA, United Sates), where duplicates were identified and removed accordingly. Two independent authors (Muhammad Ahmed Ali Fahim and Afia Salman) initially screened the remaining articles on the basis of Title and Abstract, after which full texts were evaluated to confirm relevance. Any disagreements between the two authors were resolved after discussion with a third author (Hira Anas Khan).

Studies complying with the following inclusion criteria were included in our analysis: Presented their findings in english literature; patients above 18 years of age; patients with CAD who received coronary PCI; comparative studies involving implantation of either a TiNOS or DES; outcomes reported at a 5-year follow-up; provided the outcomes as risk ratios (RR), odd ratios or raw data that could be utilized to calculate them; studies reporting one or more of our primary and or secondary outcomes. Our exclusion criteria included conference abstracts, letters, case reports, and studies containing inadequate original data for further analysis.

Study outcomes

We defined our primary outcomes of interest as major adverse cardiac event [MACE, which we defined as a composite of cardiac death, myocardial infarction (MI) or ischemia-driven total lesion revascularization (ID-TLR)], cardiac death, MI, cardiac death or MI and ID-TLR. Our secondary outcomes of interest were defined as all-cause death and definite stent thrombosis (DST).

Statistical analysis

For this study, the program RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used for all meta-analyses and subgroup analysis with the study population being divided into ACS or ACS and CCS subgroups. While Comprehensive Meta Analyst (version 3.7) was used for all meta-regression analyses. A random-effects model was used, for both, and RR along with their 95% Confidence Intervals (CI) were pooled. A P value of > 0.05 was considered statistically significant for all outcomes. Furthermore, heterogeneity was assessed with the Higgins I^2 test. A value of I^2 = 25%-50% was considered mild, 50%-75% moderate, and > 75% significant heterogeneity. Meta-regression results were reported as coefficients (Coeff) and P values.

Data extraction

The study, baseline patient, procedural, and angiographic characteristics were extracted onto an Excel Sheet and verified by two independent authors (Muhammad Ahmed Ali Fahim and Afia Salman). Any disagreements were resolved after consultation with a third author (Hira Anas Khan). Extracted data included, study name, year of publication, study design, study location, sample size, type of DES, study outcomes number of patients in each group, follow-up period, general patient characteristics (age and sex), comorbidities (diabetes mellitus, hypertension), risk factors (smoking, family history) prior cardiac events/procedures [MI, PCI, coronary artery bypass graft (CABG)], cause of PCI (NSTEMI, STEMI, unstable angina), reference vessel diameter, lesion length, total stents per lesion, direct stenting, stents per (culprit) Lesion, stent diameter, primary and secondary endpoints. For certain studies particular baseline and study characteristics were not accessible in the documents pertaining to the 5-year outcomes. As a result, the publication of the same trial for 1-year outcomes was utilized to comprehensively extract these characteristics for further analysis and regression[13-15].

Quality assessment

The Revised Cochrane risk-of-bias tool for randomized trials (ROB 2)[16] tool was used by two independent authors (Muhammad Ahmed Ali Fahim and Afia Salman) to assess the quality of each RCT reported in this meta-analysis. The studies were analyzed according to their randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. All inconsistencies were resolved with discussion and agreement. Additionally, the quality of evidence of each outcome was assessed utilizing GRADEpro[17].

RESULTS

After retrieval of a total of 320 studies from the aforementioned resources, 4 studies[10,18-20], all being RCTs, were narrowed down and included in the meta-analysis. A more detailed explanation of the process is represented in the PRISMA flow chart as shown in Figure 1. The following outcomes of MACE, ID-TLR, cardiac death, MI, cardiac death or MI, DST, and all-cause death were extracted, pooled and analyzed for a sum total of 3045 patients with ACS after a median follow-up time of 5 years. The studies that presented patient data as pooled ACS and CCS were sub-grouped accordingly. Tables 1 and 2 identify the study characteristics and baseline patient, procedural, and angiographic characteristics of the included studies respectively.

Risk of bias assessment

The risks of bias of the included RCTs are demonstrated in Supplementary Figure 1. The overall risk of bias across the RCTs is 75%. Two studies had a high risk of bias for deviation from the intended interventions (TIDE, TITAX-AMI). Additionally, one study represented a high risk of bias for the measurement of the outcomes (BASE-ACS). Furthermore, potential bias existed in one study for the measurement of outcomes (TIDES-ACS). The individual risk of bias summary for each RCT is given in Supplementary Figure 2.

Baseline analysis

An analysis was performed on the following compiled categorical and continuous baseline patient, procedural and angiographic characteristics of age, gender, diabetes mellitus, hypertension, smoking, family history for ischemic heart disease (IHD) or CAD, prior MI, prior PCI, prior CABG, reference vessel diameter, lesion length, stent per (culprit) lesion, stent diameter, total stent length per lesion, direct stenting, and NSTEMI the results of which are given in Supplementary Tables 2 and 3. Analysis results for all revealed a P value of greater than 0.05 indicating no significant differences in characteristics between the 2 arms patients were randomized in.

Primary outcomes

ID-TLR was an outcome of interest across all 4 studies. Upon pooling the results, a slightly increased occurrence of ID-TLR was observed in patients receiving TiNOSs as compared to those receiving DES. However, this disparity did not achieve statistical significance. (RR = 1.06, 95%CI = 0.84-1.35; P = 0.62; I^2 = 0%). Pooling data from three studies that evaluated the incidence of MI underscored a significant risk reduction associated with TiNOSs between the 2 groups (RR = 0.59, 95%CI = 0.43-0.80; P = 0.0008; I^2 = 0%). Additionally, all four studies assessed cardiac death and analysis demonstrated a lower incidence of the outcome in the TiNOS group when compared to the DES group; however, this divergence did not attain statistical significance (RR = 0.54, 95%CI = 0.28-1.03; P = 0.06; I^2 = 44%). The composite endpoint of cardiac death or MI was reported by all 4 studies and a statistically significant reduction in risk was apparent in patients treated with TiNOSs as opposed to those with DESs (RR = 0.59, 95%CI = 0.47-0.75; P < 0.0001; I^2 = 0%). In terms of MACE, a collective analysis of all studies exhibited a decrease in TiNOS in patients randomized between the two groups but no statistically significant divergence (RR = 0.86, 95%CI = 0.70-1.06; P = 0.17; I^2 = 29%). Forest plots for primary outcomes are represented in Figure 2.

Secondary outcomes

DST was evaluated across three out of four studies, revealing a statistically significant decrease in TiNOSs over DESs (RR = 0.31, 95%CI = 0.17-0.58; P = 0.0002; I^2 = 8%). Lastly, the analysis of all-cause death, inclusive of all studies, demonstrated a statistically non-significant decrease in TiNOS patients as compared to DES patients (RR = 0.90, 95%CI = 0.68-1.19; P = 0.45; I^2 = 4%). Forest plots for secondary outcomes are represented in Figure 3.

Subgroup analysis

Studies were sub-grouped according to the representation of patients as ACS or ACS and CCS wherever possible. The outcome of ID-TLR had no heterogeneity overall and this trend continued when studies were sub-grouped. Similar to the overall effect both subgroups presented with the result of a non-significant increase in ID-TLR in TiNOS patients when compared with DES patients. [RR = 1.02, 95%CI = 0.79-1.33, I^2 = 0% P = 0.85; RR = 1.25, 95%CI = 0.71-2.18, I^2 = not available (NA), P = 0.44]. Furthermore, no subgroup differences were found (I^2 = 0%). Similarly, for MI no heterogeneity was present overall or when studies sub-grouped, with both subgroups showing a decrease in MI in the TiNOS patients arm. However, this decrease was significant in the ACS subgroup while insignificant in the ACS and CCS one. (RR = 0.57, 95%CI = 0.41-0.80, I^2 = 0%, P = 0.0010; RR = 0.72, 95%CI = 0.30-1.73, I^2 = NA, P = 0.46). Additionally, no differences between both were shown (I^2 = 0%). When assessing cardiac death mild heterogeneity was shown overall and when studies sub-grouped with the ACS subgroup it showed a slight decrease. The results of both subgroups differed greatly with the ACS subgroup showing a significant decrease in cardiac death while the ACS and CCS subgroup showed a non-significant increase in the aforementioned outcome when TiNOSs were compared with DESs. (RR = 0.46, 95%CI = 0.23-0.90, I^2 = 42%, P = 0.02; RR = 1.23, 95%CI = 0.34-4.50, I^2 = NA, P = 0.75). Subgroup differences having mild heterogeneity were seen (I^2 = 43.9%). No heterogeneity was seen overall or in subgroups for the composite outcome of cardiac death or MI. Both subgroups showed a decrease in the outcome for the TiNOS arm however this decrease was significant in the ACS subgroup and insignificant in the ACS and CCS one. (RR = 0.57, 95%CI = 0.44-0.73, I^2 = 0%, P < 0.0001; RR = 0.85, 95%CI = 0.40-1.77, I^2 = NA, P = 0.66). Slight subgroup differences were shown (I^2 = 1.1%). MACE showed moderate heterogeneity overall but when subgroup analysis was performed and the TIDE study was isolated from the ACS studies the heterogeneity of the ACS subgroup decreased greatly. The results of both subgroups differed with the ACS subgroup

Table 1 Study characteristics

Study name	Year of publication	Study design	Study location	Sample size	Intervention	Control	Study outcomes	Follow-up duration
TIDE	2011	RCT	Switzerland	302	TiNO-coated stent	Zotarolimus-eluting stent	In-stent late lumen loss; MACE; death; cardiac death; MI; clinically-indicated TLR; clinically-indicated TVR; repeat vascular-ization; cardiac death or MI; stroke; cardiac death, MI, or clinically indicated TLR	5 years
BASE ACS	2016	RCT	Finland	827	TiNO-coated stent	Everolimus-eluting stent	MACE; cardiac death; non-cardiac death; total death; non-fatal MI; cardiac death or MI; ischemia-driven TLR; DST	5 years (median)
TITAX AMI	2013	RCT	Finland	425	TiNO-coated stent	Paclitaxel-eluting stent	MACE; cardiac death; recurrent MI; cardiac death or recurrent MI; ischemia-driven TLR; DST; all-cause death	5 years
TIDES ACS	2023	RCT	Five European countries	1491	TiNO-coated stent	Everolimus-eluting stent	Cardiac death; MI; ischemia-driven TLR; major bleeding; cardiac death or MI; stent thrombosis; non-cardiac death; all-cause death	5 years

RCT: Randomized controlled trial; TiNO: Titanium-nitride-oxide; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization; DST: Definite stent thrombosis.

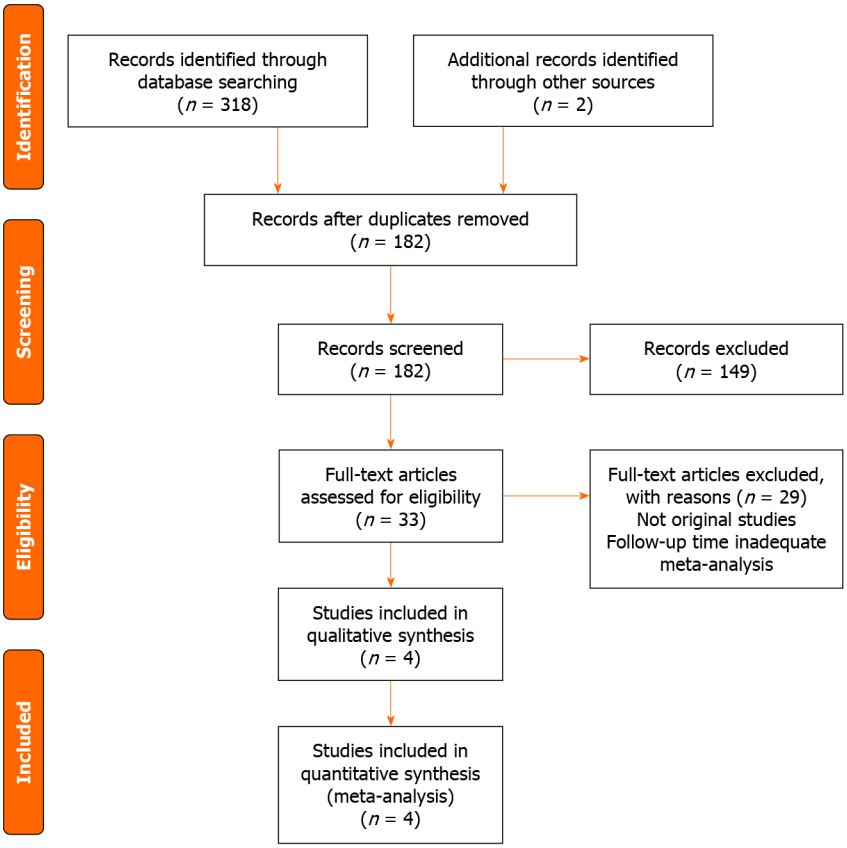


Figure 1 Preferred reporting items for systematic review and meta-analyses flowchart.

showing a significant decrease in MACE while the ACS and CCS subgroup showed a nonsignificant increase in the outcome in patients treated with TiNOSs as compared to DESs. (RR = 0.81, 95%CI = 0.67-0.99, I^2 = 10%, P = 0.04; RR = 1.16, 95%CI = 0.74-1.82, I^2 = NA, P = 0.51). Subgroup differences having moderate heterogeneity were seen (I^2 = 50.3%). The outcome of All-Cause Death revealed slight heterogeneity overall and none in the ACS subgroup. The results of both subgroups were insignificant but differed in the sense that the ACS subgroup showed a decrease in all-cause death while the ACS and CCS subgroups showed an increase in the outcome for the TiNOS arm. (RR = 0.84, 95%CI = 0.63-1.12, I^2 = 0%, P = 0.23; RR = 1.60, 95%CI = 0.68-3.76, I^2 = NA, P = 0.28). Subgroup differences having mild heterogeneity were seen (I^2 = 49.7%).

Table 2 Baseline patient, procedural, and angiographic characteristics, *n* (%)

		TIDE (2011)	BASE ACS (2016)	TITAX AMI (2013)	TIDES ACS (2023)
Sample size *n* (TiNOS/DES)		302 (152/150)	827 (417/410)	425 (214/211)	1491 (989/502)
Age (yr), mean ± SD	TiNOS	65.9 ± 9.0	62.9 ± 12.0	64 ± 11	62.7 ± 10.9
	DES	63.4 ± 10.5	63.0 ± 11.8	64 ± 11	62.6 ± 10.5
Male sex, *n*	TiNOS	124	317	162	745
	DES	118	312	157	383
Female sex, *n*	TiNOS	28	100	52	244
	DES	32	98	54	119
Diabetes mellitus	TiNOS	30 (19.7)	65 (15.6)	48 (22)	140 (14.2)
	DES	28 (18.7)	75 (18.3)	33 (16)	63 (12.5)
Hypertension	TiNOS	105 (69.1)	201 (48.2)	122 (57)	463 (46.8)
	DES	113 (75.3)	212 (51.7)	106 (50)	219 (43.6)
Current smoking/smoking	TiNOS	53 (34.9)	144 (34.5)	113 (53)	309 (31.2)
	DES	43 (28.7)	134 (32.7)	97 (46)	180 (35.9)
Family history of IHD/CAD	TiNOS	45 (29.6)	192 (46.0)	103 (48)	503 (50.9)
	DES	47 (31.3)	185 (45.1)	95 (45)	247 (49.2)
Prior MI	TiNOS	42 (27.6)	56 (13.4)	33 (15)	75 (7.6)
	DES	32 (21.3)	40 (9.8)	20 (9)	45 (9.0)
Prior PCI	TiNOS	39 (25.7)	40 (9.6)	22 (10)	69 (7.0)
	DES	38 (25.3)	43 (10.5)	10 (5)	33 (6.6)
Prior CABG	TiNOS	12 (7.9)	20 (4.8)	16 (7)	6 (6.0)
	DES	4 (2.7)	17 (4.1)	13 (6)	6 (1.2)
STEMI	TiNOS	0 (0)	162 (38.8)	83 (39)	444 (44.9)
	DES	0 (0)	159 (38.8)	97 (46)	239 (47.6)
Unstable angina	TiNOS	14 (9.2)	49 (11.8)	0 (0)	126 (12.7)
	DES	16 (10.7)	64 (15.6)	0 (0)	61 (12.2)
NSTEMI	TiNOS	50 (32.9)	206 (49.4)	131 (61)	458 (46.3)
	DES	63 (42.0)	187 (45.6)	114 (54)	226 (45.0)
Reference vessel diameter (mm), mean ± SD	TiNOS	2.88 ± 0.47	3.13 ± 0.43	3.16 ± 0.45	3.20 ± 0.45
	DES	2.90 ± 0.53	3.14 ± 0.43	3.11 ± 0.50	3.21 ± 0.45
Lesion length (mm), mean ± SD	TiNOS	13.1 ± 8.1	14.4 ± 5.4	13.6 ± 5.6	14.9 ± 6.5
	DES	14.2 ± 8.9	14.3 ± 6.5	13.2 ± 6.4	14.8 ± 5.9
Direct stenting	TiNOS	76 (33.2)	134 (32.1)	26 (12)	225 (22.8)
	DES	66 (29.7)	126 (30.7)	32 (15)	145 (28.9)
Total stent length per lesion (mm), mean ± SD	TiNOS	19.3 ± 11.1	20.8 ± 9.4	18.5 ± 6.4	20.5 ± 7.8
	DES	19.6 ± 10.0	20.6 ± 8.2	19.2 ± 7.2	20.6 ± 7.2
Stents per (culprit) lesion, mean ± SD	TiNOS	1.28 ± 0.55	1.15 ± 0.38	1.1 ± 0.3	1.13 ± 0.38
	DES	1.17 ± 0.45	1.14 ± 0.36	1.1 ± 0.4	1.14 ± 0.37
Stent diameter (mm), mean ± SD	TiNOS	3.02 ± 0.46	3.15 ± 0.44	3.16 ± 0.42	3.22 ± 1.14
	DES	3.01 ± 0.50	3.15 ± 0.45	3.11 ± 0.45	3.19 ± 0.43

n: Number of participants; TiNOS: Titanium-nitride-oxide-coated stent; DES: Drug-eluting stent; IHD: Ischemic heart disease; CAD: Coronary artery

disease; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction.

Meta-regression

We assessed age, male gender, female gender, diabetes mellitus, hypertension, smoking, family history for IHD or CAD, prior MI, prior PCI, prior CABG, NSTEMI, reference vessel diameter, lesion length, direct stenting, total stent length per lesion, stent per (culprit) lesion, and stent diameter as covariates having an impact on specific outcomes. The outcomes assessed in the meta-regression included MACE, ID-TLR, cardiac death, cardiac death or MI, and all-cause death the results for which are represented in Supplementary Tables 4-8. All covariates for all outcomes revealed an insignificant 2-sided *P* value except for the covariate of NSTEMI% which had a significant result when assessed for the outcome of MACE (Coeff: -0.0369, $P = 0.0416$). Scatter plots are presented in the Supplementary Figures 3-87.

Quality assessment of evidence

The quality of evidence was graded 'High' or 'Moderate' after assessment using GRADEpro with the results of ID TLR, Cardiac Death, All Cause Death and MACEs being rated as 'Moderate' quality after downgrading evidence in the field of 'Imprecision' due to individual studies having wide CIs and results being opposite. The remaining outcomes of MI, cardiac death or MI and DST being graded as 'High'. A detailed explanation of each outcome is offered in Supplementary Table 9.

DISCUSSION

The findings of our meta-analysis and systematic review grossly favor TiNOSs over DESs. ID-TLR, the primary outcome being assessed, was found to be numerically higher with TiNOSs, whereas all other outcomes, namely cardiac death, MI, DST, MACE, and all-cause death were significantly lower in PCI with TiNOSs when compared to the occurrence of the same outcomes with DES. Meta-regression was performed for multiple variables such as age (years), male gender, female gender, diabetes mellitus, hypertension, smoking, family history for IHD or CAD, prior MI, prior PCI, prior CABG, reference vessel diameter (mm), lesion length (mm), NSTEMI, stent diameter (mm), total stent per lesion (mm) and stent per (culprit) lesion. However, none were found to be significant contributors to any outcomes being measured in our analysis except for NSTEMI for the outcome of MACE. Furthermore, a baseline analysis found no significant difference between the characteristics of the 2 arms proving that all statistically significant outcomes in our study were not due to any baseline angiographic or procedural discrepancies between the TiNOS or DES groups.

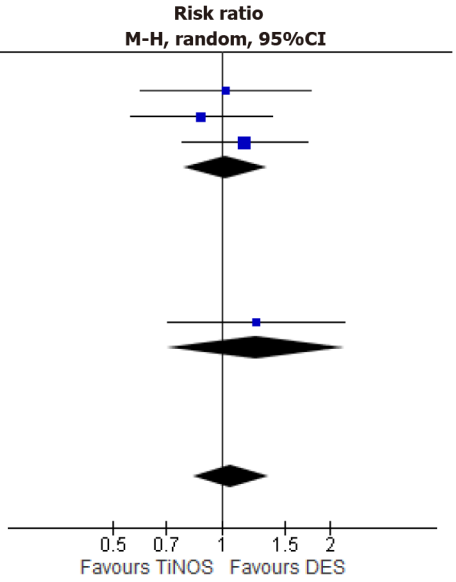
ID-TLR was found to be higher with TiNOSs (RR = 1.06, 95%CI = 0.84-1.35; $P = 0.62$; $I^2 = 0\%$), although statistically insignificant, as compared to DESs which is in coherence with the findings of a previous meta-analysis by Daoud *et al*[9], as well as a comparative study by Limacher *et al*[21]. Although there is insufficient literature highlighting the exact cause of this occurrence, possible reasons for this could be the increased incidence of diabetes mellitus and peripheral arterial disease in patients undergoing PCI with TiNOSs in the TIDE ACS trial, a major contributor to our pooled data. Both factors have been identified as independent predictors of ID-TLR for between 2 and 4 years after PCI by a study conducted by Kurihara *et al*[22]. However, the validity of this hypothesis may be challenged as the mentioned study shows outcomes after treatment with DESs rather than TiNOSs. When assessed through meta-regression diabetes mellitus showed no significant association with this outcome. Early studies, such as one conducted by Varho *et al*[23] suggest that TiNOSs may cause greater early neointimal hyperplasia [Median (interquartile range) neointimal hyperplasia of 203 (106) μm *vs* 42.2 (41) μm] but similar coronary flow reserve, and fractional flow rate (FFR) compared to DES. As FFR has emerged as a valuable predictor of ID-TLR[24], this accentuates the statistical insignificance of increased ID-TLR with the TiNOS arm of this study.

TiNOSs showed statistically significant lower rates of DST *vs* DESs (RR = 0.31, 95%CI = 0.17-0.58; $P = 0.0002$; $I^2 = 8\%$). These findings are consistent with those of Daoud *et al*[9]. According to a study, TiNOSs afford better endothelization than other BMS due to their biocompatibility which results in a less aggressive host response against the inserted stent, lower resultant inflammation, and hence, less likely thrombosis. Additionally, they have exhibited lower fibrinogen and platelet deposition, key modulators in the process[5,6]. Other important contributors to stent thrombosis are stent malapposition and insufficient stent coverage as they create a prothrombotic state due to low endothelial shear stress which causes the production of various chemical factors and according to a cohort study by Sia *et al*[7], Varho *et al*[23] and an RCT by Karjalainen *et al*[25], the incidence of malapposed and uncovered stents is lower with TiNOSs. The clinicians may reconsider their choice of stent types based on the different stent thrombosis outcomes. This also calls for further studies that investigate the optimal patient selection criteria based on the coagulation profile and the medical comorbidities.

These arguments can also be extended to explain the lower rates of MACE (RR = 0.86, 95%CI = 0.70-1.06; $P = 0.17$; $I^2 = 29\%$), cardiac death (RR = 0.54, 95%CI = 0.28-1.03; $P = 0.06$; $I^2 = 44\%$), MI (RR = 0.59, 95%CI = 0.43-0.80; $P = 0.0008$; $I^2 = 0\%$), the composite endpoint of cardiac death or MI (RR = 0.59, 95%CI = 0.47-0.75; $P < 0.0001$; $I^2 = 0\%$), along with the fact that while Varho *et al*[23] reports the opposite, as mentioned earlier, TiNOSs have the advantage of lower neointimal hyperplasia and resultant restenosis as reported by a more recent study conducted on rabbit iliac artery specimens[26]. The overall impact is satisfactory perfusion and therefore, lower probability of cardiac death. However, this is contradicted by Pilgrim *et al*[15] who showed an increased incidence of in-stent late loss, defined as loss in diameter in the

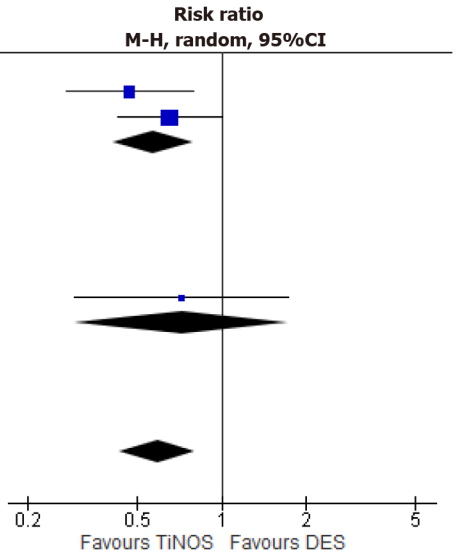
A

Study or subgroup	TiNOS Events	TiNOS Total	DES Events	DES Total	Weight	Risk ratio M-H, random, 95%CI	Year
1.1.1 ACS							
TITAX AMI	24	214	23	211	19.3%	1.03 [0.60, 1.76]	2013
BASE ACS	33	417	37	410	27.8%	0.88 [0.56, 1.37]	2016
TIDES ACS	73	989	32	502	34.8%	1.16 [0.78, 1.73]	2023
Subtotal (95% CI)		**1620**		**1123**	**82.0%**	**1.02 [0.79, 1.33]**	
Total events	130		92				
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%							
Test for overall effect: Z = 0.18 (P = 0.85)							
1.1.2 ACS & CCS							
TIDE	24	152	19	150	18.0%	1.25 [0.71, 2.18]	2011
Subtotal (95% CI)		**152**		**150**	**18.0%**	**1.25 [0.71, 2.18]**	
Total events	24		19				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)		**1772**		**1273**	**100.0%**	**1.06 [0.84, 1.35]**	
Total events	154		111				
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 3 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%							



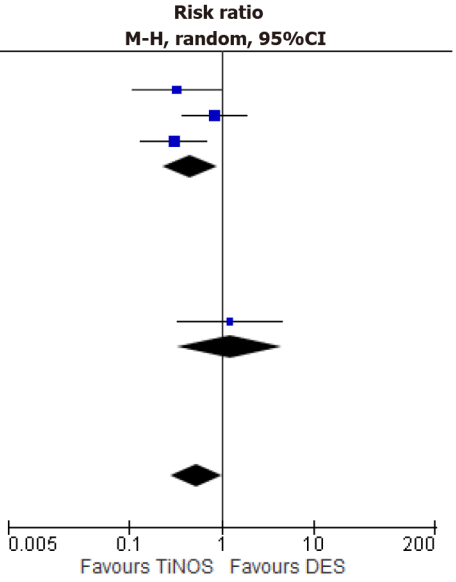
B

Study or subgroup	TiNOS Events	TiNOS Total	DES Events	DES Total	Weight	Risk ratio M-H, random, 95%CI	Year
6.1.1 ACS							
TITAX AMI	18	214	38	211	34.8%	0.47 [0.28, 0.79]	2013
TIDES ACS	45	989	35	502	52.8%	0.65 [0.43, 1.00]	2023
Subtotal (95% CI)		**1203**		**713**	**87.6%**	**0.57 [0.41, 0.80]**	
Total events	63		73				
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%							
Test for overall effect: Z = 3.30 (P = 0.0010)							
6.1.2 ACS & CCS							
TIDE	8	152	11	150	12.4%	0.72 [0.30, 1.73]	2011
Subtotal (95% CI)		**152**		**150**	**12.4%**	**0.72 [0.30, 1.73]**	
Total events	8		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.74 (P = 0.46)							
Total (95% CI)		**1355**		**863**	**100.0%**	**0.59 [0.43, 0.80]**	
Total events	71		84				
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%							
Test for overall effect: Z = 3.35 (P = 0.0008)							
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%							



C

Study or subgroup	TiNOS Events	TiNOS Total	DES Events	DES Total	Weight	Risk ratio M-H, random, 95%CI	Year
3.1.1 ACS							
TITAX AMI	4	214	12	211	21.4%	0.33 [0.11, 1.00]	2013
BASE ACS	11	417	13	410	31.1%	0.83 [0.38, 1.84]	2016
TIDES ACS	9	989	15	502	30.1%	0.30 [0.13, 0.69]	2023
Subtotal (95% CI)		**1620**		**1123**	**82.5%**	**0.46 [0.23, 0.90]**	
Total events	24		40				
Heterogeneity: Tau² = 0.15; Chi² = 3.47, df = 2 (P = 0.18); I² = 42%							
Test for overall effect: Z = 2.27 (P = 0.02)							
3.1.2 ACS & CCS							
TIDE	5	152	4	150	17.5%	1.23 [0.34, 4.50]	2011
Subtotal (95% CI)		**152**		**150**	**17.5%**	**1.23 [0.34, 4.50]**	
Total events	5		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.32 (P = 0.75)							
Total (95% CI)		**1772**		**1273**	**100.0%**	**0.54 [0.28, 1.03]**	
Total events	29		44				
Heterogeneity: Tau² = 0.19; Chi² = 5.34, df = 3 (P = 0.15); I² = 44%							
Test for overall effect: Z = 1.86 (P = 0.06)							
Test for subgroup differences: Chi² = 1.78, df = 1 (P = 0.18), I² = 43.9%							



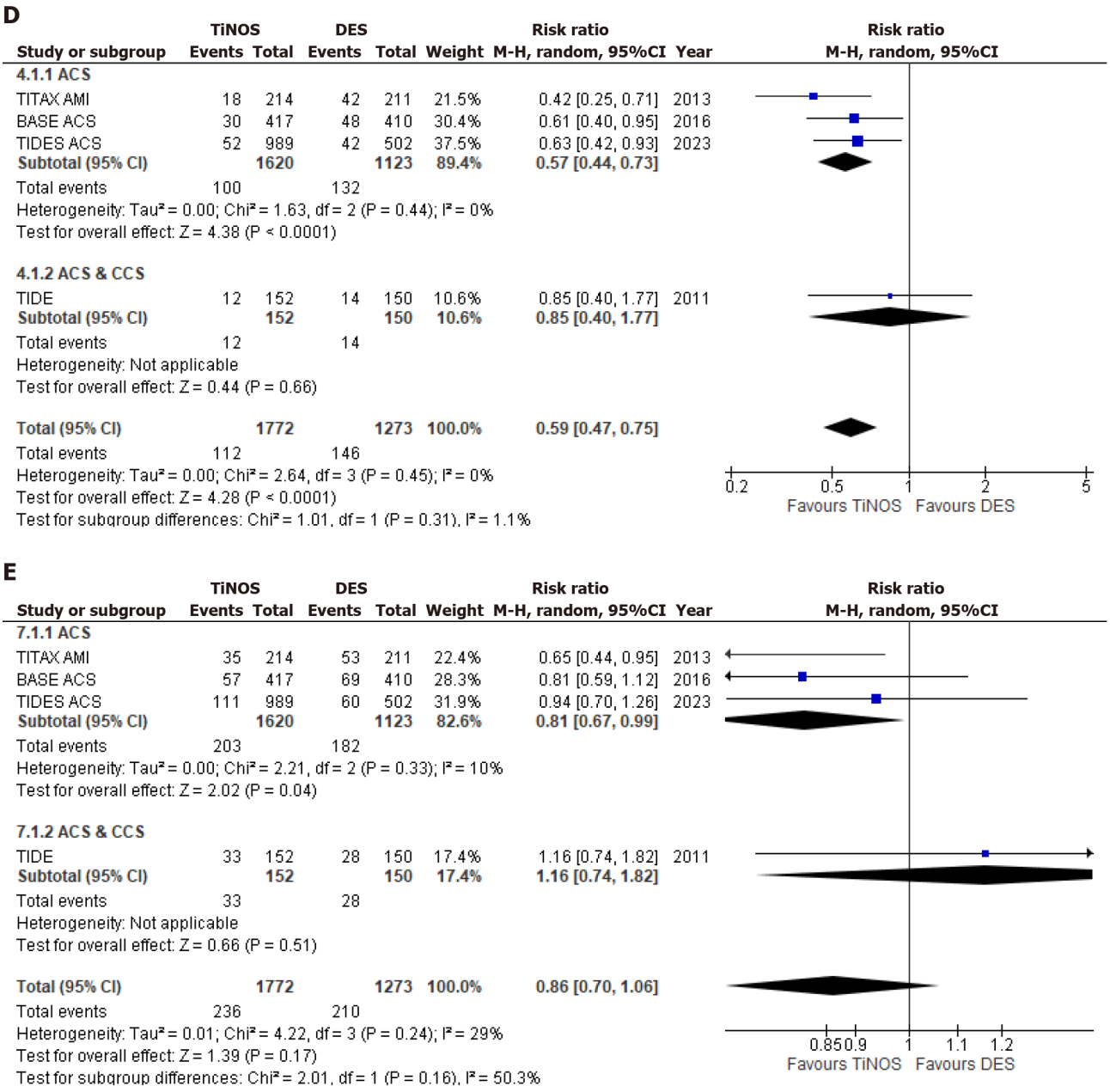


Figure 2 Forest plots for primary outcomes. A: Ischemia-driven target lesion revascularization forest plot; B: Myocardial infarction forest plot; C: Cardiac death forest plot; D: Cardiac death or myocardial infarction forest plot; E: Major adverse cardiovascular event forest plot. TiNOS: Titanium-nitride-oxide-coated stent; DES: Drug-eluting stent; M-H: Mantel-Haenszel; ACS: Acute coronary syndrome; CCS: Chronic coronary syndrome.

lumen following PCI and in segment binary restenosis with TiNOSs compared to DES. However, it is important to note that this study reports outcomes 1-year post-procedure without any further follow-up reports, which were not assessed in our study.

Upon subgroup analysis, the ACS subgroup displayed a statistically significant difference in favor of TiNOSs for MACE (RR = 0.81, 95%CI = 0.67-0.99; P = 0.04) and cardiac death (RR = 0.46, 95%CI = 0.23-0.90; P = 0.02). The significance in ACS-only studies with regard to this result can be explained by the greater likelihood of early stent thrombosis in ACS compared to CCS, as concluded by Yamamoto *et al*[27] which can eventually result in cardiac death as already discussed. In this setting, TiNOSs anticoagulant properties in a thrombotic environment which is found in ACS aid the prognosis in patients. However, our meta-regression reported no significant association of Cardiac death or MI with any of our analyzed covariates. The argument is supported further by Karjalainen *et al*[28], who report a significantly lower incidence of MI and MACE after the use of BMS.

As stated previously, pooling data from three studies underscored a significant risk reduction associated with TiNOSs in MI (RR = 0.59, 95%CI = 0.43-0.80; P = 0.0008; I^2 = 0%). The I^2 = 0% suggests that there was no significant variability among the pool of subjects of all three studies, hence, strengthening the reliability of the pool data analysis. Previous studies such as the one conducted by Bouisset *et al*[10] also display that there is a significant decrease in the risk of MI occurring after using TiNOSs as compared to DESs. Daoud *et al*[9], further support this by highlighting that there is a lower risk of recurrent non-fatal MI occurring when TiNOSs are used.

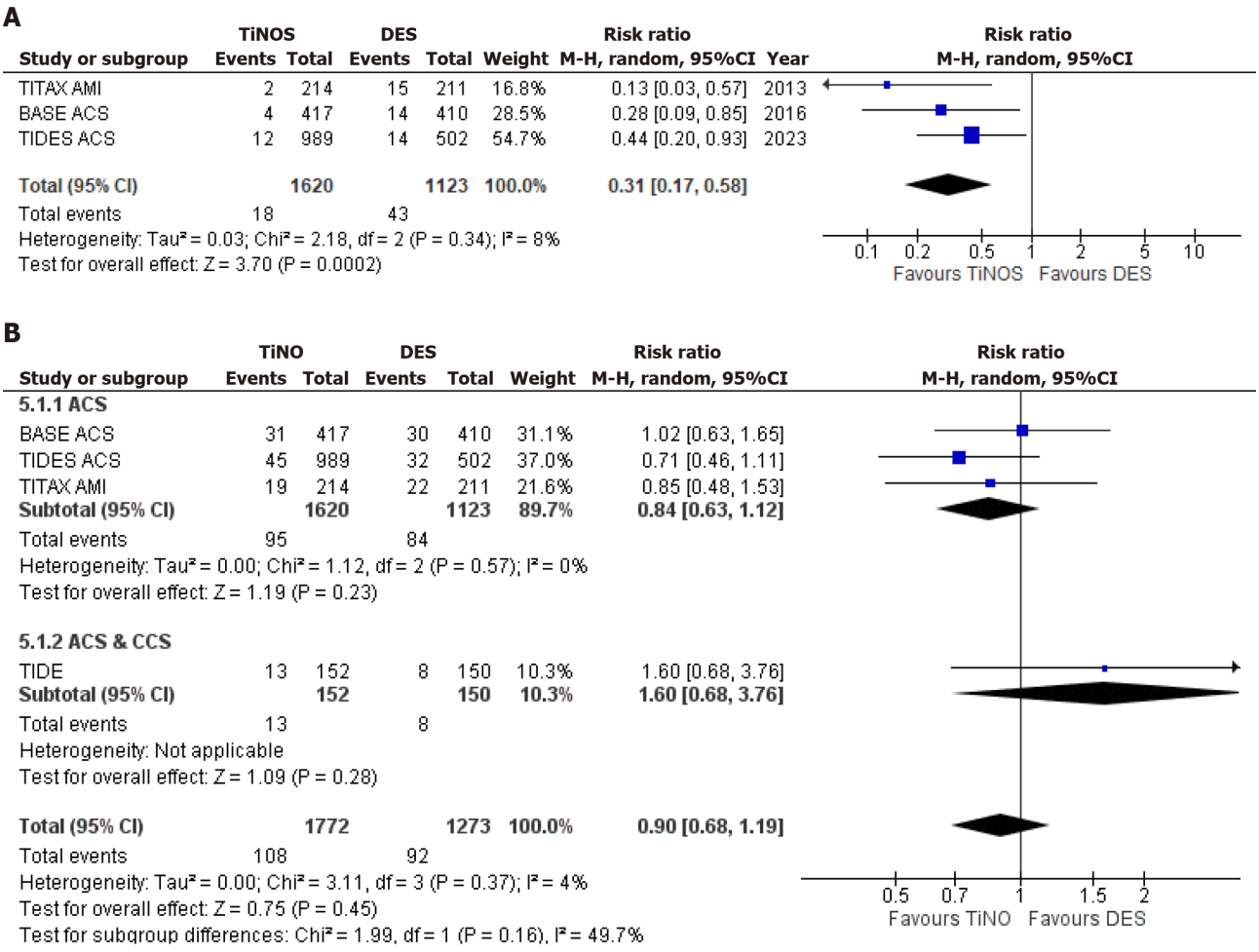


Figure 3 Forest plots for secondary outcomes. A: Definite stent thrombosis forest plot; B: All-cause death forest plot. TiNOS: Titanium-nitride-oxide-coated stent; DES: Drug-eluting stent; M-H: Mantel-Haenszel; ACS: Acute coronary syndrome; CCS: Chronic coronary syndrome.

The analysis of all-cause death suggests a broad measure of mortality. Our analysis of all-cause death, inclusive of all studies, demonstrated no statistically significant distinction between TiNOSs and DESs (RR = 0.90, 95%CI = 0.68-1.19; P = 0.45; I^2 = 4%). This infers that there is a possibility that the observed difference in mortality of the two stents could have occurred due to chance which leads it to being not significant with little variability among the studies. Upon subgroup analysis, as well as regression for the mentioned covariates, the non-significant trend persisted suggesting that the lack of statistical significance is not influenced by subgroup factors without any association between all-cause death and other factors. Similarly, as per the study conducted by Brener *et al*[29], there is no significant difference in cardiovascular *vs* non-cardiovascular mortality post-PCI regardless of the stent used.

While assessing NSTEMI as a covariate to possibly have an effect on the outcomes, we observed a statistically significant association with MACE. A multitude of previous research has presented an association of STEMI with MACE [30-33]. Ours as well as Fath-Ordoubadi *et al*[34] are among the few that have presented the contrary. This may possibly be due to the fact that long-term follow-up studies have smaller sample sizes and incomplete reporting of outcomes of interest[35].

It is important to note that this study may be limited in its extent to elucidate the comparison between TiNOSs and DESs accurately. Due to the limited number of studies, the data may not be representative. Furthermore, all pooled data has been derived from European countries without subgroup studies on participant ethnicities which limits its generalizability. Since the prognosis for ACS and subsequent PCI as a whole is multifactorial including race as a potential risk factor[36], this warrants a detailed study that focuses on the differences in outcomes in people of different races and ethnicities. The data used included patients with both ACS and CCS. However, subgroup studies were conducted to tackle this discrepancy. The trials included also displayed a difference in the type of DES used which could have impacted the results of each and hence, our analysis, even if only to a very limited extent. Another factor that limits the accuracy of our results is the bias due to the deviation from intended intervention specifically in the TIDE and TITAX-AMI studies. For example, in the TITAX-AMI trial, a greater percentage of patients were administered glycoprotein IIa/IIIb inhibitors in patients being treated with TiNOSs than DESs. Additionally, most trials are limited due to the lack of angiographic follow up which may have a possible contribution to the results favoring DESs with regard to ID-TLR or other outcomes favoring TiNOSs over DESs.

The findings of this systematic review and meta-analysis spark international collaborations and consensus efforts among researchers to share larger data sizes in order to optimal stent selection strategies in the management of ACS. Future studies could delve deeper into patient-reported outcomes and quality-of-life measures associated with different stent types. Moreover, the available evidence can be utilized to reinforce the refinement of TiNOSs and further development of novel stent strategies. Further studies can conduct a comparative analysis of healthcare costs associated with different ACS treatment approaches, which can lead to a lesser financial burden on the healthcare systems. Lastly, with the advent of newer technologies, the development of clinical practice guidelines is crucial to the management of ACS patients requiring stent placement.

CONCLUSION

Although DES was deemed to be an evolutionary move from BMS, resulting in their frequent use in PCI, TiNOSs have proved to be comparable if not superior to DESs with regard to efficacy and safety in the management of ACS. It has proven to elicit rapid healing and lower rates of long-term complications such as MI and ST even in patients with comorbidities such as diabetes. Nonetheless, it is important to conduct more studies to further evaluate these findings and fill in gaps in the literature to get better insight into the true potential of these stents.

FOOTNOTES

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Country of origin: Bangladesh

ORCID number: Abdul Moeed 0000-0003-4429-1391; Md Al Hasibuzzaman 0000-0003-0548-4836.

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