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EDITORIAL

Improving the heart team: An interdisciplinary team and integrated practice unit

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Abstract

Heart Team emerged as an important tool in the cardiovascular care, improving the efficiency of decision-making process. In addition to the benefits in patient care, it symbolizes a new culture and mindset. However, beyond the clinical condition, in low/middle-income countries other concerns arise regarding patient's background and these demands are, usually, as challenging as the medical treatment. New models have been proposed face these demands and to assure a holistic care by Integrated Practice Units. Optimization and reorganization of already existing resources and promotion of interdisciplinary and holistic care may be an effective manner to improve outcomes despite socioeconomic barriers.

Key Words: Heart team; Interdisciplinary; Integrated practice units; Cardiovascular; Perioperative; Surgery

Core Tip: Despite emerging technologies and advanced devices, the real-world situation of low- to middle-income countries presents several socioeconomic concerns that jeopardize patients and, consequently, resources and outcomes. Our pioneer project "interdisciplinary heart team and integrated practice unit" emerged as a means by which to address these demands by prioritizing the management of existing resources.

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INTRODUCTION

Heart Team (Table 1) emerged as an important tool in the cardiovascular care, improving the efficiency of decision-making process[1,2]. This multidisciplinary team-based approach has been used for decades in fields as oncology[3] and organ transplantation[4,5] to deliver the best patient care. Although is not a new concept, the term *Heart Team* was incorporated in the cardiovascular care since the publication of SINTAX Trial[6] and, more recently, the PARTNER Trial[7]. Both trials used a collaborative team-based approach to decide the better strategy to the myocardial revascularization (surgical or percutaneous) or valvular replacement (surgical or transcatheter), respectively.

Using the theory of Venn diagrams[8], this expertise's overlap among different specialties may improve the challenging decision-making process. In addition to the benefits in patient care, the *Heart Team* also promotes continue education[1,9] through the share-of-knowledge and the built of respect, trust and lasting professional relationship between its members. Besides, the interdisciplinary rounds[10,11] and the incorporation of new devices[12] has been currently used in intensive care medicine [13], reducing miscommunication and improving the comprehension of goals by all team members and patient/family satisfaction[14].

More than a medical multi-specialty interaction, it symbolizes a new culture and mindset, and it has been adopted in many cardiology fields as cardio-obstetrics[15-17], heart failure[18], valvular disease[19-21] and coronary artery revascularization[3]. Furthermore, recently published professional societies guidelines for valvular[22-24] and coronary diseases[25] includes the *Heart Team* as pivotal to both clinical and interventional therapeutic strategies, especially in complex or high-risk patients.

Beyond the clinical condition, in low/middle-income countries other concerns arise regarding patient's background and these demands are, usually, as challenging as the medical treatment[26]. Notedly on valvular disease, the socioeconomic circumstances are crucial. Low scholarity, malnutrition, limited access to the primary care, a high prevalence of rheumatic fever, management of anticoagulation and delayed time referral to cardiac surgery are some of these concerns[27]. To face these demands, new models have been proposed[28] to assure a holistic care by *Integrated Practice Units*[29].

Our institution is the public biggest cardiovascular center in Latin America, and, beyond the traditional *Heart Team*, a pioneer interdisciplinary perioperative project coordinated and supported by the Management Executive Direction has been implemented in our Valvular Diseases Unit to optimize resources and improve outcomes. Since 2018, are part of this *Interdisciplinary Heart Team* the cardiovascular surgeon, clinical cardiologist, anesthetist, nursing, psychologist, nutritionist, physiotherapist, welfare service and pharmacists. Beyond these professional, we count on a management team responsible for the logistics to optimize further necessary exams, team re-evaluation and surgical scheduling. Before referral to surgery, all-team come together to expose and solve each patients' demands. If no concerns are pending, patient is referred to waiting surgery list.

On the procedure eve the entire preoperative routine is checked by clinician, surgeon and nursing. The intraoperative and intensive care unit, patient is under care according to the clinical, safety and handover protocols. In the ward, besides daily assessment, every patient is reviewed by the entire *Interdisciplinary Heart Team*. Forecast of hospital discharge, referral to backup hospitals and other demands are discussed. At the hospital discharge, nursing and medical team provide guidance to patients and schedule the postoperative return visit consultation.

CONCLUSION

Even with an unfavorable profile (high proportion of rheumatic disease, redo procedures, multivalvular disease and advanced heart failure status) preliminary results demonstrated reduction of waiting for surgery time and lowering mortality rates. As part of an upper-middle income country, optimization and reorganization of already existing resources and promotion of interdisciplinary and holistic care may be an effective manner to improve outcomes despite socioeconomic barriers. There is always a manner to the improvement.

Table 1 Members of the interdisciplinary heart team responsible to solve patient's demands before they are referred to waiting surgery list

Interdisciplinary heart team members	
Clinical cardiologist	Cardiovascular surgeon
Anesthetic	Nursing
Management team	Welfare service
Psychologist	Physioterapist
Nutritionist	Pharmacist

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REVIEW

Chagas heart disease: An overview of diagnosis, manifestations, treatment, and care

Roberto M Saraiva, Mauro Felippe F Mediano, Fernanda SNS Mendes, Gilberto Marcelo Sperandio da Silva, Henrique H Veloso, Luiz Henrique C Sangenis, Paula Simplício da Silva, Flavia Mazzoli-Rocha, Andréa S Sousa, Marcelo T Holanda, Alejandro M Hasslocher-Moreno

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Abstract

Chagas heart disease (CHD) affects approximately 30% of patients chronically infected with the protozoa *Trypanosoma cruzi*. CHD is classified into four stages of increasing severity according to electrocardiographic, echocardiographic, and clinical criteria. CHD presents with a myriad of clinical manifestations, but its main complications are sudden cardiac death, heart failure, and stroke. Importantly, CHD has a higher incidence of sudden cardiac death and stroke than most other cardiopathies, and patients with CHD complicated by heart failure have a higher mortality than patients with heart failure caused by other etiologies. Among patients with CHD, approximately 90% of deaths can be attributed to complications of Chagas disease. Sudden cardiac death is the most common cause of death (55%–60%), followed by heart failure (25%–30%) and stroke (10%–15%). The high morbimortality and the unique characteristics of CHD demand an individualized approach according to the stage of the disease and associated complications the patient presents with. Therefore, the management of CHD is challenging, and in this review, we present the most updated available data to help clinicians and cardiologists in the care of these patients. We describe the clinical manifestations, diagnosis and classification criteria, risk stratification, and approach to the different clinical aspects of CHD using diagnostic tools and pharmacological and non-pharmacological treatments.

Key Words: Chagas disease; Diagnosis; Treatment; Heart failure; Arrhythmia; Stroke

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Core Tip: Chagas heart disease (CHD) is associated with high mortality and a myriad of clinical manifestations, including bradyarrhythmias, tachyarrhythmias, stroke, heart failure, and sudden death. Therefore, adequate care of these patients requires careful follow-up, clinical stratification, and knowledge of possible CHD complications and their treatment. In this review, we present the most up-to-date available data to optimize the care of these patients. We describe the clinical manifestations, diagnosis and classification criteria, risk stratification, and approach to the different clinical aspects of CHD using diagnostic tools and pharmacological and non-pharmacological treatments.

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INTRODUCTION

Chagas disease (CD) is responsible for the highest economic and health burden among parasitic diseases in the Western hemisphere[1]. It is caused by the protozoa *Trypanosoma cruzi* (*T. cruzi*), which infects 6 to 7 million people worldwide[2]. Although it has usually been confined to endemic rural areas in Latin America, migration movements have caused the urbanization of the disease, followed by its spread to other continents. Currently, CD is not only a major cause of death in endemic countries[2], but is also an important cause of morbidity and mortality among immigrant populations in non-endemic countries, such as Spain and the United States [3]. At least 300000 up to 1000000 people living in the United States have chronic CD [4]. Most of them are unaware of their condition but are at risk of developing Chagas heart disease (CHD). For instance, among relatives of patients with CD in California, 7.4% had CD diagnosed after a screening test[5]. The same situation may be reproduced in other countries where significant migration movement from Latin American countries occurred. In Europe, there is an estimated 120000 people living with CD, around 43% of which are in Spain[6], with a prevalence of *T. cruzi* infection among Latin American migrants of 6.08%[7].

The main route of transmission in people born in endemic areas is vector-borne transmission. However, food-borne transmission has recently become a concern in the Amazon region, with an increasing number of acute CD cases[8]. Other routes of transmission may occur in endemic and non-endemic countries, including blood transfusion, congenital, and organ transplantation. Adequate control measures can decrease the risk of transmission by all of these routes; however, patients who are already infected require proper care to prolong their lives, prevent complications, and improve quality of life.

CHD pathophysiology is influenced by parasite persistence, together with an inflammatory response that leads to chronic fibrosing myocarditis, ventricular remodeling, and damage to the electrical conduction system[1,9]. There is evidence that an imbalance favoring an inflammatory response against persistent parasites within the myocardium is one of the main mechanisms for CD progression[10,11]. Other possible mechanisms involved in CD progression include coronary microvascular disease and cardiac autonomic dysfunction[12]. Ultimately, patients will present with a myriad of clinical manifestations, including bradyarrhythmia, tachyarrhythmia, cardioembolic events, heart failure (HF), and sudden death[1,9,12,13]. They present with a high 10-year mortality rate, ranging from 10% in the low-risk group to 84% in the high-risk group[14]. Sudden cardiac death is the main mode of death, followed by HF and stroke[1,9,12]. Importantly, CHD has a higher incidence of sudden cardiac death and stroke than most other cardiopathies, and patients with CHD complicated by HF have a higher mortality than patients with HF caused by other etiologies[15,16].

Specific CD treatment with trypanocidal drugs is indicated during the acute phase of the disease or in cases of reactivation that may occur due to immunosuppression[9]. In patients with chronic indeterminate CD, trypanocide treatment should also be offered because it decreases the rate of CD progression[17,18], the occurrence of a composite outcome of clinical events (HF, stroke, or device implantation with a pacemaker or implantable cardioverter defibrillator)[17], and the risk of congenital transmission. However, in patients with CHD, trypanocide treatment was not associated with improved outcomes[19]. Therefore, the care of patients with CHD relies on measures to prevent or treat CHD complications to improve their survival and quality of life. In this review, we present the most up-to-date available data to help clinicians and cardiologists in the care of these patients. We describe the clinical manifestations, diagnosis and classification criteria, risk stratification, and approach to the different clinical aspects of CHD using diagnostic tools and pharmacological and non-pharmacological treatments.

DEFINITION AND DIAGNOSIS CRITERIA

CD presents with two distinct temporal phases: acute and chronic. The acute phase begins soon after infection, presenting with fever and systemic symptoms, inflammatory physiopathogenesis, and intense parasitemia. Meanwhile, the chronic phase begins after regression of the acute phase and remains throughout life. It is characterized by fibrosis as the main physiopathogenic mechanism and progresses with no or extremely low parasitemia[1,9]. The chronic phase is comprised of three well-defined clinical forms: The first, affecting approximately 60% of patients, is the indeterminate form, which is classically characterized by the absence of symptoms and signs, with no changes identified on electrocardiography (ECG), chest radiography, and gastrointestinal tract examinations; the second is the cardiac form, which presents with rhythm and/or conduction disorders, segmental (most frequent) or global left ventricular (LV) systolic dysfunction with or without HF, and/or thromboembolic events; and the third is the digestive form, which presents with esophageal and intestinal peristaltic dysfunction, with symptoms related to megaesophagus and megacolon[9].

The first study that described CHD was published by Carlos Chagas and Eurico Villela in 1922[20]. This study presented a new cardiopathy observed in 63 patients with CD. It was associated with rhythm and conduction disorders. In the 1940s, Dias *et al*[21] and Laranja *et al*[22] defined the first clinical criteria for CHD and presented it as a well-defined clinical entity that could be distinguished from other chronic heart diseases, in addition to particular ECG changes that were not found in the analysis of similar groups with other heart diseases. In 1956, Dias *et al*[23] presented a pioneering study on an extensive series of patients with CHD from endemic areas, in which they consolidated the histopathological, clinical, and ECG criteria that define this heart disease.

CHD is one of the most frequent and severe clinical presentations of the chronic phase of CD. It is responsible for significant morbidity and mortality[14]. Classically, CHD is diagnosed when the patient presents with a positive serological or parasitological test for *T. cruzi* and ECG shows typical CHD changes in the absence of other heart diseases that may cause these changes[9]. However, patients with the indeterminate form based on ECG criteria may present with wall motion abnormalities in 13% of echocardiograms[24]. Therefore, others use ECG, clinical and echocardiographic criteria to categorize patients into those with definite, probable, and possible CHD diagnoses[25]. The possible presence of wall motion abnormalities in patients with normal or nonspecific changes on ECG indicates that at least one echocardiogram should be obtained for all patients with CD[1]. However, at the primary care level in places with limited access to health resources, the echocardiogram may be postponed until typical CD changes appear on ECG[9].

The ECG changes considered typical (definitive CHD) were systematized by Biolo *et al*[26] and included second- and third-degree right bundle branch blocks, whether or not associated with a left anterior fascicular block; frequent polymorphous or repetitive ventricular premature beats (VPBs) > 1 on ECG; nonsustained ventricular tachycardia (VT); second- and third-degree atrioventricular blocks; sinus bradycardia with a heart rate < 40 beats/min; sinus node dysfunction; second- and third-degree left bundle branch blocks; atrial fibrillation; and electrical inactive segment and primary ST-T wave changes. Nonspecific (non-definitive CHD) changes on ECG include sinus bradycardia with heart rate ≥ 40 beats/min; low voltage QRS; nonspecific ST-T wave

changes; first-degree right bundle branch block; left anterior fascicular block; isolated VPBs; and first-degree atrioventricular block.

CHD CLASSIFICATION

There are several different classification systems for chronic CD that share some similarities, such as the use of ECG and echocardiographic findings as classification criteria, but also disparities that make comparisons between clinical studies and management guidelines complicated. Moreover, current classifications share similar codes for strata classification but with different meanings, which can lead to difficulties when comparing clinical studies and discussing cases. Furthermore, several studies classify patients as symptomatic or asymptomatic. This specific classification is troublesome, as the "asymptomatic patient" class includes patients with both indeterminate and cardiac forms at earlier stages, with isolated changes on ECG or wall motion changes on echocardiography but no HF symptoms.

Here, we will discuss five CD classifications: the Kuschnir classification[27], the Brazilian Consensus on Chagas Disease[9], the modified Los Andes classification[28], the Latin American Guidelines[12] and the American Heart Association (AHA) Statement[1]. They take into account the ECG, chest radiography, echocardiogram, and clinical symptoms of HF, including the New York Heart Association (NYHA) functional class, which have implications on patient prognosis. All of them have some limitations in identifying the risk of events other than HF, such as cardioembolism or sudden cardiac death. In fact, HF is the focus of the question in all these scales. However, sudden cardiac death is a relevant mode of death in CD and manifests frequently without previous symptoms or even without severe LV systolic dysfunction [29].

The Tables 1-5 show the description of these five classifications. Figure 1 presents these different classification systems to facilitate their understanding and shows a comparison of the results from different clinical studies. We assumed that patients with an enlarged heart on radiography would have an abnormal LV ejection fraction to be able to include the Kuschnir classification in Figure 1. However, the Los Andes IB group cannot be compared to other classifications, as it is comprised of patients with normal ECG and abnormal echocardiogram.

It would be interesting to evaluate the discriminatory capacity of each classification system in relation to prognosis. The Kuschnir classification[27] considers only the findings on ECG, radiography, and clinical symptoms, without echocardiogram findings. Therefore, patients with echocardiographic findings, such as mild LV systolic dysfunction, aneurysms, and LV wall motion changes, who have a worse prognosis than patients with isolated ECG changes are not discriminated by this classification. Furthermore, this classification loses the ability to stratify the severity of heart disease.

The Brazilian Consensus Classification[9] was designed to classify patients with CHD into stages with prognostic value. It includes patients with abnormal ECG, since patients with normal ECG findings might have a similar prognosis and risk of death as the population without CD. The classification was derived from a cohort study that observed that global LV systolic dysfunction and HF were the most important markers of prognosis. The mortality rates in 5 years were as follows: stage A, 13%; B (1 and 2), 45%; C, 91%; and D, 98%. Since the difference between stages B and C was significant, stage B was divided into B1 and B2, with a cut-off point at an LV ejection fraction of 45%[9].

The Los Andes classification is divided into four categories. However, two of them include a normal ECG and may have a similar prognostic value. In addition, patients with an abnormal ECG and/or changes in echocardiogram were grouped together in the same stage (stage II), although patients with isolated changes on ECG have a better prognosis[9].

The Latin American Guidelines Classification includes patients with normal ECG (indeterminate chronic form) in stage A. Stage B1 includes those with abnormal ECG and mild echocardiographic alterations in the same group, which decreases the potential for stratification of the classification. The other stages consider the presence of systolic ventricular dysfunction and HF symptoms to discriminate the different prognostic stages (stages B2, C, and D)[12].

The AHA statement classification describes stage A as an indeterminate chronic form without cardiac or digestive abnormalities. Stage B1 includes patients with segmental contractility abnormalities and normal or altered ECG, which mixes different prognoses in the same group. In addition, stage B2 includes patients with

Table 1 Kuschnir classification (1985)[27]

Classification	ECG	X-ray / cardiac symptoms
0	Normal ECG findings	Normal heart size (on chest X-ray)
I	Abnormal ECG findings	Normal heart size (on chest X-ray)
II		Left ventricular enlargement
III		Congestive heart failure

ECG: Electrocardiogram.

Table 2 Brazilian consensus classification[9]

Classification	ECG	Echocardiogram	HF
A	Abnormal	No LV wall motion abnormalities	No
B1	Abnormal	LV wall motion abnormalities with LV ejection fraction (LVEF) ≥ 45%	No
B2	Abnormal	LV wall motion abnormalities with LVEF <45%	No
C	Abnormal	LV wall motion abnormalities	Compensated HF
D	Abnormal	LV wall motion abnormalities	Refractory HF

ECG: Electrocardiogram; HF: Heart failure; LV: Left ventricular.

Table 3 Modified Los Andes classification[28]

Classification	ECG	Echocardiogram	HF
IA	Normal	Normal	No
IB	Normal	Abnormal	No
II	Abnormal	Abnormal	No
III	Abnormal	Abnormal	Yes

ECG: Electrocardiogram; HF: Heart failure.

Table 4 I Latin American guidelines[12]

Classification	ECG /X-ray	Echocardiogram	HF
A	No structural heart disease (normal ECG and chest X-ray)	_	No
B1	ECG changes (arrhythmias or conduction disorders)	Mild contractile abnormalities with normal LVEF	No
B2		Decreased LVEF	No
C		Decreased LVEF	Prior or current symptoms of HF
D			Symptoms of HF at rest, refractory to maximized medical therapy (NYHA functional class IV).

ECG: Electrocardiogram; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association.

mild and severe systolic dysfunction, which also results in a heterogeneous group with different therapeutic approaches and prognoses[1].

We adopted the Brazilian Consensus Classification throughout this review, as we understand that CHD is better stratified into stages of increasing severity and worsening prognosis by this classification system.

Table 5 American Heart Association Statement[1]

Classification	ECG/ Echocardiogram	HF	Digestive changes
A (Indeterminate form - patients at risk for developing HF)	Normal ECG	Neither structural cardiomyopathy or HF symptoms	No
B1	Structural cardiomyopathy evidenced by ECG or echocardiographic changes with normal LVEF	Neither current or previous signs and symptoms of HF	
B2	Structural cardiomyopathy characterized by decreased LVEF	Neither current or previous signs and symptoms of HF	
C	LV systolic dysfunction	Current or previous symptoms of HF (NYHA functional class I, II, III, or IV)	
D		Refractory symptoms of HF at rest despite optimized clinical treatment requiring specialized interventions.	

ECG: Electrocardiogram; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association.

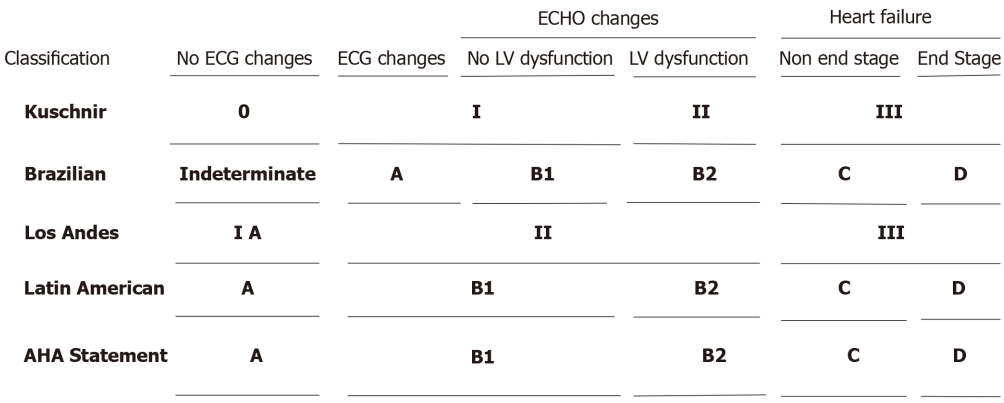

Figure 1 Schematic representation of the different classification systems of Chagas disease. We assumed that patients with an enlarged heart on chest radiography would have left ventricular systolic dysfunction on echocardiography in order to be able to compare all classifications.

ROUTINE ASSESSMENT AND FOLLOW UP

The clinical management of patients with chronic CD should consider the various forms of the disease. Clinical procedures, guidelines, directives, and protocols have been presented in the last decade to improve the comprehensive approach to CD in terms of patient care at the primary, secondary, and tertiary levels[9,12,30,31].

Patients with CD should be clinically evaluated and should undergo an ECG to diagnose CHD. In cases of CHD, it is necessary to identify the degree of myocardial involvement, determine clinical prognosis with emphasis on stratification of the risk of death, and initiate pharmacological management. Patient education should be part of the patients' integrative care.

The initial diagnostic evaluation of patients with CHD includes clinical, epidemiological, and social evaluation[9,32], which is comprised by their medical history, physical examination, and collection of epidemiological and social data. General laboratory evaluations include complete blood count, biochemistry, electrolytes, liver function, and lipid count tests. This initial evaluation is important to identify possible comorbidities, such as essential arterial hypertension, diabetes mellitus, dyslipidemia, obesity, kidney failure, and thyroid disorders. Specifically, B-type natriuretic peptide (BNP and NT-ProBNP) analyses may be useful for diagnosing HF in clinically suspected patients, as well as to define the prognosis[33]. Imaging tests include posteroanterior and lateral chest radiography with the contrasted esophagus, ECG, echocardiography, 24-h Holter monitoring, and cardiac stress test. In the context of primary care and the presence of a normal ECG, echocardiography is not mandatory [9]. In case of ECG changes, an echocardiogram and Holter monitoring are mandatory. If the initial diagnostic evaluation suggests CD with digestive involvement, the patient can be referred for a radiologic contrast study of the esophagus and/or colon, upper

digestive endoscopy, and/or colonoscopy. Patients with a previous history or symptoms suggestive of coronary disease and/or ECG changes compatible with ischemic heart disease should be investigated with diagnostic tests as recommended in specific guidelines. It is important to emphasize that the accuracy of functional tests (cardiac stress test and myocardial scintigraphy) for diagnosing coronary disease is reduced in patients with CHD, and preference is given to invasive (coronary cineangiography) or noninvasive (coronary computed tomography angiography) anatomical tests, which are the best choice according to the estimated pre-test probability of coronary disease.

During routine follow-up, it is essential to characterize and monitor the NYHA functional class. In CHD staging, the algorithm used to evaluate patients with CD is based on ECG and echocardiogram[9]. Asymptomatic patients with ECG changes and normal echocardiograms are included in stage A CHD. Follow-up should be maintained at the primary care level, and patients should undergo ECG annually and echocardiography every 2 years. Asymptomatic patients with ECG changes presenting with LV wall motion changes and LV ejection fraction > 45% are included in stage B1 CHD. Follow-up should be maintained at the primary care level, and patients should undergo ECG annually and echocardiography every 2 years or whenever clinical progression is suspected. Asymptomatic patients with ECG changes and LV ejection fraction < 45% are included in stage B2 CHD. Patients should be referred to the secondary care level, with consults every 3-4 mo, and ECG and echocardiograms performed annually or whenever there are clinical changes. Patients with HF symptoms responsive to treatment are included in stage C CHD and should also be referred to the secondary care level, with consultations every 3 mo, and ECG and echocardiograms performed annually or whenever there are clinical changes. Patients with HF symptoms refractory to conventional treatment are in stage D CHD and should be referred to the tertiary care level. The need for other procedures, such as cardiac resynchronization[34], cardiopulmonary rehabilitation program[35], use of new pharmacological drugs[36], and heart transplantation[37] should be evaluated.

Risk stratification in CHD aims to identify patients with increased mortality risk in order to define therapeutic interventions and closer surveillance. The most powerful predictor of CHD is LV systolic function. The Rassi score is the most commonly used risk score, which includes six independent prognostic factors: NYHA class III or IV (5 points), increased cardiothoracic ratio on chest radiography (5 points), LV systolic dysfunction on echocardiography (3 points), nonsustained VT on 24-h Holter monitoring (3 points), low QRS voltage on ECG (2 points), and male sex (2 points)[14]. Patients were classified into three risk groups: low risk (0–6 points), intermediate risk (7–11 points), and high risk (12–20 points). The 10-year mortality rates for these three groups were 10%, 44%, and 84%, respectively[14]. Other risk score has recently been proposed, including age (10 points per decade), NYHA functional class higher than I (15 points), heart rate ≥ 80 beats/min (20 points), QRS duration ≥ 150 ms (15 points), and abnormal NT-proBNP adjusted by age (55 points). The patients were classified into three risk categories at baseline (low, < 2%; intermediate, ≥ 2% to 10%; high, ≥ 10%). The observed mortality rates in the low-, intermediate-, and high-risk groups were 0%, 3.6%, and 32.7%, respectively[38]. Both scores[14,38] underwent external validation and used all-cause mortality as the endpoint. However, the mechanisms underlying the three main modes of death in CHD may influence the risk scores. Therefore, other scores have been proposed to assess the risk of specific modes of death in CHD. Our group published a score to predict sudden cardiac death based on clinical, echocardiographic, and ECG data, which classifies patients into low, intermediate, and high risk of sudden death[29]. Similarly, our group also proposed a score to identify CHD patients at higher risk of stroke, which includes four variables: LV systolic dysfunction, apical aneurysm, primary ST changes on ECG, and age > 48 years[39].

Many other predictors of poor outcomes in CHD have been published, including right ventricular (RV) systolic dysfunction[40], left atrial (LA) volume and function [41], LV diastolic function[41,42], and biomarkers such as BNP, transforming growth factor β1, and metalloproteinase[33,43-45].

ECHOCARDIOGRAPHY AND NEW IMAGING EXAMS

Echocardiography is a key method for the evaluation and follow-up of patients with CHD due to its wide availability, machine portability, and the information it provides. Echocardiography allows the classification of CHD patients into stages, identification

of complications, and follow-up and risk assessment of patients with CD. Echocardiography can identify chamber size, global and regional LV contractility, LV aneurysms, LV diastolic dysfunction, LA size and function, and RV systolic dysfunction[9,12,41]. Echocardiography is also important to identify the presence of other non-CHD diseases that may be responsible for clinical and/or ECG changes.

In the early stages of chronic CHD, echocardiography may demonstrate segmental LV wall motion abnormalities and diastolic dysfunction[46]. Segmental wall motion disturbances may range from hypokinesis to small or large aneurysms. The LV segments that most commonly present wall motion abnormalities are the inferior and inferolateral walls, and the apex[24] (Figure 2). These wall motion abnormalities can be detected in one or more LV segments in the same patient, and have prognostic implications[47]. LV aneurysm prevalence in patients with CD ranges from only 2% in patients with the indeterminate form to approximately 45% of CD patients with LV systolic dysfunction and HF[48]. Most aneurysms are found in the classic narrow-neck apical location, but they can also be found in other sites, such as the inferolateral and basal inferior walls, the interventricular septum, and even the RV apex[49]. Chagas heart aneurysms have crucial importance because of their relationship with embolic [39,50-52] and arrhythmic[49,53,54] events. Apical aneurysms are more associated with intraventricular thrombi (Figure 3) and stroke risk, while inferolateral aneurysms are more associated with arrhythmia risk. However, apical aneurysms can be missed in conventional 2D apical views due to apical foreshortening, dropout, or near-field artifacts. Therefore, echocardiographic examinations require standard views and modified four- and two-chamber views to detect small apical aneurysms with or without thrombus. Contrast echocardiography, better harmonic imaging, and three-dimensional (3D) applications may allow for more accurate detection of LV aneurysms and thrombi in CD, especially in those with inadequate acoustic windows.

Because of the extensive wall motion abnormalities in CHD, LV volumes and ejection fraction are preferably estimated according to the modified Simpson's rule instead of the Teicholz method.

Even early in the disease, chronic CHD may already affect diastolic function[41]. Usually, the first abnormality is impaired LV relaxation, and as CHD progresses to the late stages, LV pseudo-filling and restrictive patterns increase in prevalence[41]. The prevalence of diastolic function abnormality varies according to study methodologies, but has been described to range from 10% of patients with the indeterminate form to almost 100% of patients with HF[41]. Studies using tissue Doppler imaging have shown that progressive worsening of the e' velocity appears to be a good parameter to identify the progressive nature of LV diastolic dysfunction[41].

As CHD progresses to its late stages, more LV walls are affected and LV dilatation and global LV systolic dysfunction ensue with diffuse hypokinesia. However, even at this stage, LV aneurysms and more pronounced LV wall motion abnormalities in the inferior and inferolateral walls are still present. LV dysfunction has prognostic implications in chronic CHD and is the strongest predictor of death in patients with CD[13].

RV systolic dysfunction has been reported in all CHD stages[40,55]. RV systolic dysfunction can be an isolated finding, but it is most commonly associated with LV dysfunction. Several echocardiographic parameters have been used to assess RV function in CD, including qualitative evaluation, tissue Doppler imaging, myocardial performance index, tricuspid annular plane systolic excursion, speckle tracking strain, and 3D-imaging[13].

Echocardiography of patients with CHD may also reveal mitral and tricuspid regurgitation. Mitral regurgitation is secondary to the distortion of the mitral annulus and the subvalvular apparatus due to LV remodeling and fibrosis of the inferolateral wall. Moderate to severe mitral regurgitation may worsen the symptoms and prognosis of HF[56]. Tricuspid regurgitation is secondary to dilation of the tricuspid annulus, pulmonary hypertension, and/or the presence of a pacemaker lead through the tricuspid valve. Tricuspid regurgitation may worsen right-sided HF symptoms.

Newer imaging methods have potential utility in the diagnosis of cardiac complications and prediction models for CD. However, cost-effectiveness studies are necessary before they are implemented in clinical practice. Reviews of new imaging tools for CD can be found elsewhere[13]. Briefly, newer echocardiographic methods such as speckle tracking echocardiography can be used in early CHD stages to identify early changes in myocardial contractility or strain[57-59]. Analysis of the LV strain may also yield a new prognostic index for CHD. In a short-term follow-up of a population comprised of patients with HF due to CD and idiopathic dilated cardiomyopathy, LV longitudinal strain was an independent predictor of cardiovascular events [60]. Another new echocardiographic method is 3D echocardiography (3DE), which can be potentially useful in CHD because of the more accurate evaluation of the LV

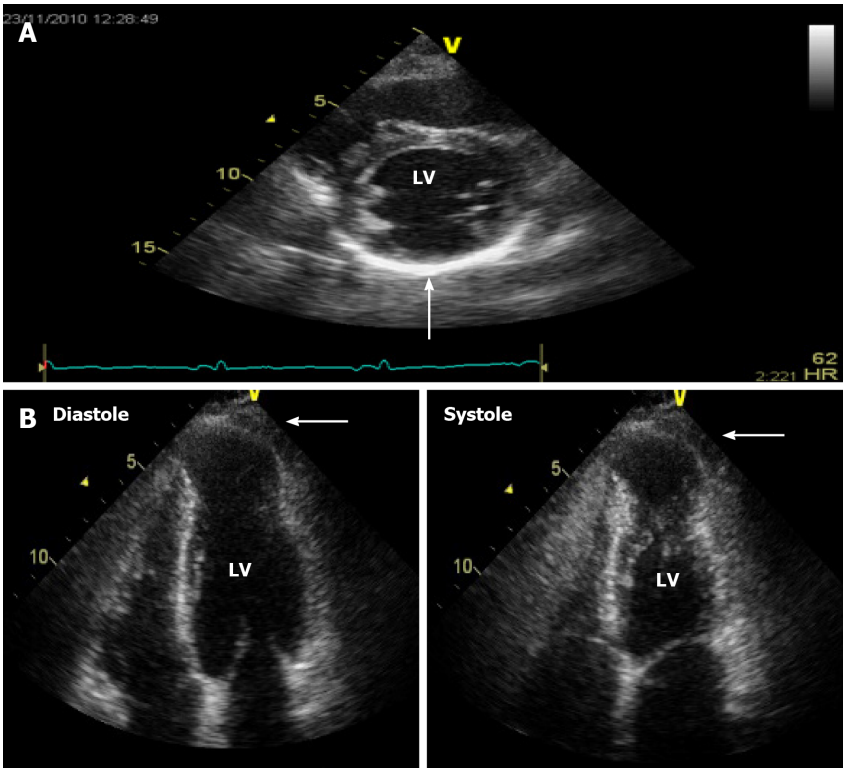

Figure 2 Note the hyperrefringent akinetic area in the basal inferolateral left ventricular wall (A) and the left ventricular apical aneurysm in the diastolic and systolic left ventricular images (B).

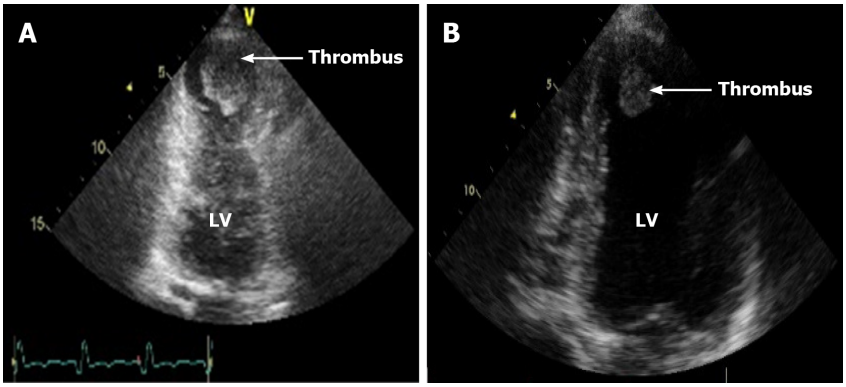

Figure 3 Note the thrombi in the apical location in a patient with a large apical aneurysm (A) and a patient with severe left ventricular dilation and dysfunction (B).

apex, avoiding LV foreshortening. In addition, 3DE is more accurate than 2D Simpson's biplane rule for assessing LV volumes and ejection fraction in patients with significant wall motion abnormalities. LA volume and function assessed by 3DE and strain may be able to predict atrial fibrillation in CD[61].

Cardiac magnetic resonance imaging (MRI) can improve the evaluation of chamber volume and segmental and global function over bidimensional echocardiography, identify aneurysms and intracardiac thrombi[13], and evaluate the extension of myocardial fibrosis (Figure 4), which correlates with increased risk of VT[62] even in the absence of global LV systolic dysfunction[13], and is an independent predictor of the combined endpoint of cardiovascular death and sustained VT[63], and all-cause mortality[64]. Cardiac MRI can identify areas of fibrosis in 20% of patients with the indeterminate form of CD and in 43.7% of patients with CHD stage A. Cardiac fibrosis is detected in 89% to 100% of patients in the late stages of CHD[13].

Another imaging method with potential utility in risk stratification of CD is myocardial scintigraphy using iodine-123 metaiodobenzylguanidine testing. This can identify areas of myocardial sympathetic denervation, which are associated with the

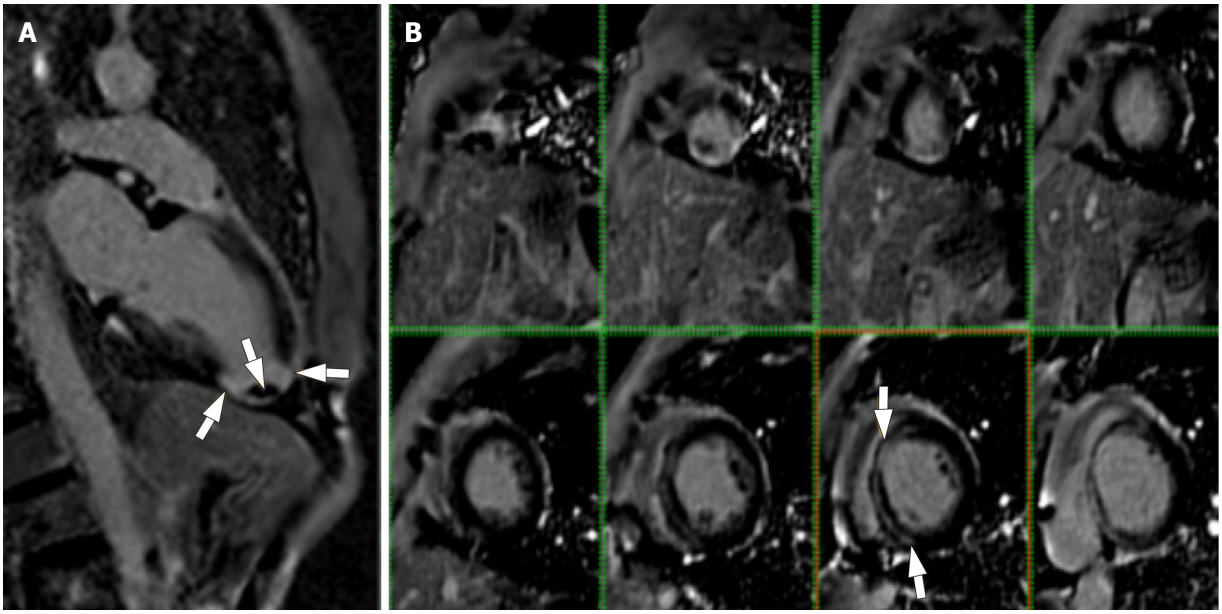

Figure 4 Cardiac magnetic resonance imaging of a patient with stage B1 Chagas heart disease. A: Myocardial delayed enhancement on 2-chamber apical slice depicts areas of cardiac fibrosis in the apical segments and an apical thrombus; B: Myocardial delayed enhancement protocol on left ventricular short-axis slices depicts areas of cardiac fibrosis in the apical and basal left ventricular walls of a patient at stage B1 of Chagas heart disease.

risk of VT in CHD[13]. The detection of areas of cardiac fibrosis by single-photon emission computed tomography and areas of myocardial sympathetic denervation identify patients at risk of developing malignant ventricular arrhythmia[65].

ARRHYTHMIA

Arrhythmias in CHD can either be bradyarrhythmias or tachyarrhythmias.

In the case of bradyarrhythmias, patients may present with presyncope, syncope, fatigue, atypical chest pain, or exertional dyspnea, even with preserved LV systolic function. ECG, 24-h Holter monitoring, and electrophysiological studies are usually enough to clarify the diagnosis. Advanced atrioventricular block and symptomatic sick sinus syndrome are the main reasons for pacemaker implantation. However, all medications capable of worsening heart conduction should be withheld prior to pacemaker implantation. Recommendations for pacemaker implantation in CHD follow the same guidelines for other conditions. However, some aspects need to be highlighted. The RV electrode position should be midseptal due to possible excessive fibrosis at the apex[66] and the LV systolic function may worsen after pacemaker implantation due to LV systolic dyssynchrony related to LV pacing. Another aspect to bear in mind is that whenever it is anticipated that a pacemaker-derived rhythm will predominate or patients already have a left bundle branch block, a resynchronization device should be chosen.

With regard to ventricular arrhythmias, isolated VPBs are the most common, and they do not need treatment unless symptomatic. Asymptomatic nonsustained VT also does not require treatment in patients with preserved LV systolic function, and pharmacological treatment of patients with symptomatic nonsustained VT or asymptomatic nonsustained VT with LV systolic dysfunction is controversial[67]. On the other hand, malignant ventricular tachyarrhythmias are the main cause of sudden death in CHD and require treatment. Amiodarone is the drug of choice in patients with CHD as it improves symptoms and decreases the density of ventricular arrhythmia[68]. However, amiodarone has side effects, and there is no convincing evidence that amiodarone decreases mortality in patients with CHD[68,69]. Nevertheless, amiodarone should be used in high-risk patients with LV systolic dysfunction and nonsustained VT with symptoms. In addition, amiodarone should be considered in patients with a high percentage of ventricular ectopic beats and nonsustained VT on 24-h Holter monitoring because these can result in tachycardiomyopathy.

Another approach to secondary prophylaxis against malignant ventricular arrhythmias in patients with CHD is an implantable cardioverter defibrillator (ICD).

ICDs are indicated in patients with HF and LV ejection fraction < 35% with or without a previous history of VT[70]. However, the studies that supported this recommendation included only a few patients with CHD. Currently, ICDs are recommended in CHD for secondary prevention after documented VT, ventricular fibrillation, or aborted sudden death; in patients with LV ejection fraction < 35% and documented syncope secondary to VT; in patients with LV ejection fraction > 35% who have experienced syncope secondary to VT; and in patients with syncope and inducible sustained VT during electrophysiological study[12]. In a single study, patients with CHD and LV ejection fraction < 40% with documented prior life-threatening arrhythmia had better survival with ICDs than patients given amiodarone[71]. Amiodarone should be considered even after ICD placement to decrease the number of shocks, because CHD patients have intense ventricular arrhythmic activity[72] and a high number of shocks may cause myocardial necrosis and worse LV systolic function [73].

It is important to identify patients with an increased risk of VT, as sudden death can be the first manifestation of a malignant arrhythmia. In the previous sections of this review, we have discussed the prognostic value of cardiac MRI and the detection of areas of myocardial sympathetic denervation by myocardial scintigraphy with iodine-123 metaiodobenzylguanidine to identify patients at increased risk of sustained VT. We also discussed a score based on clinical, echocardiographic, and ECG data (QT dispersion, syncope, premature ventricular contractions, and LV function) to predict sudden cardiac death. This score classifies patients into low (0–2 points), intermediate (3–4 points), and high (> 5 points) risk of sudden death[14]. Nevertheless, ICD implantation for primary VT prophylaxis based on such findings in complementary examinations is still not indicated in clinical practice.

Ablation therapy (catheter-based) is an option to treat recurrent VT in patients with CHD, as VT in CHD is typically reentrant[74]. Most reentrant circuits are located in the same LV walls that are frequently affected in CHD[75]. However, the fibrosis pattern in CHD is not necessarily subendocardial or transmural, as in ischemic cardiomyopathy, but can also be midwall and subepicardial[59]. Therefore, careful electrophysiological mapping is necessary to achieve successful ablation[76]. The recommendation for VT ablation in CHD follows the indication for other clinical conditions[77]: Symptomatic sustained monomorphic VT, including VT terminated by ICD, that recurs despite drug therapy or when antiarrhythmic drugs are not tolerated or not desired, and when there is a suspected trigger that can be targeted for ablation; control of incessant sustained monomorphic VT or VT storm that is not the result of a transient reversible cause; and bundle branch reentrant or interfascicular VT.

STROKE

CD is responsible for up to 20% of stroke cases in endemic areas[78]. The main mechanism of stroke in CD is cardioembolism from thrombi arising mainly in apical ventricular aneurysms. However, as patients with CD have a high prevalence of atrial fibrillation[79,80], thrombi originating from the LA and the LA appendage also contribute to stroke in CHD[81]. The risk factors already identified for stroke in CHD are apical aneurysm, LV thrombus, severe atrial dilation, LV systolic dysfunction, older age, and atrial fibrillation[39,52]. Recently, risk factors for atrial fibrillation were identified, including LA function[61] which could possibly become a new risk factor for stroke in CHD. Importantly, CHD patients are aging, and other possible mechanisms for stroke related to comorbidities (hypertension, dyslipidemia, smoking), such as small vessel disease and large vessel atherosclerosis, may also play an important role in CHD[50]. Moreover, proinflammatory and prothrombotic disease states[50,82,83] and endothelial dysfunction may also contribute to a higher incidence of stroke in CHD.

The most frequent signs and symptoms presented by CHD patients with stroke are related to ischemia in the distribution of the anterior or middle cerebral arteries in the brain, and include unilateral weakness and/or numbness, facial droop, and speech deficits ranging from mild dysarthria and mild aphasia to global aphasia[50]. Stroke may also contribute to cognitive impairment and dementia in endemic areas[84,85]. Stroke can be the first clinical manifestation of a patient with CHD[51,86] and examinations for CD must be part of the diagnostic work-up when investigating stroke in patients with epidemiological history positive for CD.

Transthoracic echocardiography is indicated in all patients with CD and thromboembolic events in order to rule out LV mural thrombi, especially in LV apical

aneurysms. Transesophageal echocardiography must also be performed in cases of documented or suspected atrial fibrillation in order to investigate thrombi within the LA and the LA appendage. Holter monitoring is also indicated to investigate occult paroxysmal atrial fibrillation, whenever the source of cardioembolism is still unclear [79]. Cardiac MRI may detect intracardiac thrombi, but its routine use in patients with CHD and stroke is not warranted[87].

Secondary prophylaxis with anticoagulation is indicated in all patients with a previous history of stroke. The timing of initiating anticoagulation in case of a stroke or transient ischemic attack (TIA) due to atrial fibrillation is within 14 d after the onset of neurological symptoms[88] but can be delayed beyond 14 d in cases that are at high risk for hemorrhagic conversion (*i.e.*, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhagic tendency)[88]. Consultation with a specialist is advisable, as most neurologists recommend starting anticoagulation within 96 h of the event in patients with small strokes without hemorrhagic transformation or TIA, and halting anticoagulation for more than 14 d in case of symptomatic hemorrhagic transformation; however, there is little consensus on the exact timing to initiate anticoagulation in other cases[89]. Given that most stroke cases in CHD patients are related to LV thrombi, most neurologists recommend an earlier start of anticoagulation therapy in such cases. In cases of acute stroke in CHD, the experience with thrombolysis is limited, but short-term treatment with thrombolytics seems to have similar success compared to non-Chagas stroke[90,91].

Antiplatelet agents for secondary prophylaxis in patients with CD and stroke considered to be non-cardioembolic are recommended based on studies with non-CD patients, and must follow the published guidelines[88].

Regarding primary prophylaxis, few studies have addressed stroke prediction models for CHD. Our group identified four variables associated with stroke occurrence in patients with sinus rhythm: LV systolic dysfunction, apical aneurysm, primary ST changes, and age > 48 years[39]. A score was created with two points attributed to LV systolic dysfunction and one point for each of the other variables. The annual risk of stroke was 4.4% among patients with a score of 4 or 5, and anticoagulation is indicated in such patients. For patients with a score of 2 to 3, the risk of stroke is lower and may be similar to the risk of bleeding; hence, either anticoagulation or aspirin can be prescribed. Patients with a score of 1 had a low incidence of ischemic events, and we recommend treatment with aspirin or no treatment at all is recommended[39]. Anticoagulation for primary prophylaxis is also indicated whenever intracardiac thrombi are diagnosed by cardiac imaging. In cases of paroxysmal or permanent atrial fibrillation, primary stroke prophylaxis follows the same recommendations for non-CD patients[9].

The drug of choice for anticoagulation in CHD is warfarin, which is the drug that cardiologists have the largest experience with in clinical practice in CHD. At present, no study has compared warfarin with direct oral anticoagulants in CD. However, patients with contraindications or those who cannot tolerate warfarin may be treated with direct oral anticoagulants, especially patients with atrial fibrillation. Regarding LV thrombi, the experience with direct oral anticoagulants is still limited, but a meta-analysis of five retrospective observational studies suggested that both warfarin and direct oral anticoagulants have a similar rate of thrombus resolution, major bleeding, and stroke or systemic embolization. However, none of these studies included patients with CD[92].

HEART FAILURE

CHD has an important burden on the public health system due to frequent cardiovascular complications[93]. One of the most important CHD complications is HF with reduced ejection fraction (HFrEF).

Patients with CD and HFrEF usually present a dilated cardiomyopathy with a large amount of fibrosis, ventricular remodeling, and damage to the electrical conduction system. These changes ultimately lead to bradyarrhythmias, tachyarrhythmias, and progressive LV global systolic dysfunction[12] with hemodynamic and neurohormonal responses similar to those observed in other cardiomyopathies. This common pathophysiology suggests that the treatment usually recommended for HFrEF could also be prescribed to CHD patients with HF[1]. However, most previous studies that tested such medications in HF included a small proportion of CHD patients.

Right-sided HF are more prominent than left-sided HF symptoms and signs in CHD patients with HF[1]. Typical physical examination reveals deviated and sustained ictus of the LV, usually with prominent RV, third heart sound, and varying degrees of mitral and tricuspid regurgitation. Splitting of the second heart sound may be associated with right bundle branch block. Edema, jugular venous distention, dyspnea, and fatigue are common symptoms, but orthopnea is less common than in other cardiomyopathies[15]. In addition to ECG, echocardiography is essential in patients with HF, as outlined in the "Imaging Exams" section of this review.

In a meta-analysis of 143 studies, CD was responsible for 13% of all HF cases in Latin America[94]. Patients with HF due to CD have a more dismal prognosis than patients with HF due to other etiologies, which includes a higher proportion of hospital admissions due to HF and arrhythmia, pacemaker implantation, and stroke [15]. Moreover, the importance of HF as a mode of death in CHD has increased in recent years[95]. Patients with asymptomatic LV systolic dysfunction should be started on angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers, as recommended by the HF guidelines[36].

Non-pharmacological treatment strategies for HF are described in a specific section of this review.

The pharmacological treatment in patients with HF due to CD follows the recommendations of HF guidelines[36] and CD consensus[1,9,12] and includes a neurohumoral block (beta-blockers, ACEI or angiotensin receptor blockers, and mineralocorticoid receptor antagonists). However, the recommended full doses of these drugs are often not reached, as patients with CHD have a high prevalence of atrioventricular block and autonomic nervous system disorders. Carvedilol is the most frequently used beta-blocker in CHD, although the quality of evidence is low and based on a meta-analysis that included 69 participants and found a lower all-cause mortality in the carvedilol group than in the placebo group[96].

Patients with HF due to CD receive amiodarone more often because of a higher risk of ventricular malignant arrhythmias. The same occurs with anticoagulants due to a higher frequency of cardioembolic events[1].

Diuretics should also be added to the patients' prescription whenever there is clinical evidence of congestion, and the doses should be tapered to the lowest possible dosage in order to avoid electrolyte and metabolic disorders[1].

In case the patient persists with symptoms compatible of NYHA functional class III or above despite neurohumoral block and diuretics, digitalis may be added to the prescription. Another indication for digitalis is the presence of atrial fibrillation with a rapid ventricular response. However, it is necessary to monitor digitalis serum levels and the occurrence of atrioventricular block[1].

The experience with new drugs recently added to the HF treatment portfolio is very limited. Regarding ivabradine, a *post hoc* sub-analysis of the SHIFT trial suggested that ivabradine was associated with improvement in NYHA functional class and a trend toward reduction in mortality[97]. However, the indication for ivabradine in CD patients is limited due to electrical conduction system disturbances characteristic of CHD[12]. Regarding sacubitril/valsartan, only 7.6% of Latin American patients with HFrEF randomized to angiotensin receptor-neprilysin inhibitors in the PARADIGM-HF and ATMOSPHERE trials had CHD. An underpowered analysis suggested that patients with CHD treated with sacubitril/valsartan had a lower risk of cardiovascular death or HF hospitalization[98]. Therefore, a specific multicenter, prospective, randomized, controlled phase 4 study including only patients with HFrEF due to CD, named PARACHUTE-HF study, is currently in progress in order to testing the superiority of sacubitril/valsartan over enalapril in improving the composite endpoint of cardiovascular death or first HF hospitalization (NCT04023227).

When overt and refractory HF occurs, alternative therapies are still possible for CHD. Orthotopic heart transplantation (OHT) and cardiac resynchronization therapy are such therapies. Although there is a risk of CD reactivation after OHT, advances in immunosuppression protocols and careful reactivation monitoring after surgery allowed successful OHT in CHD. In fact, CD is the third most common indication for OHT in South America[12]. The selection criteria are the same as those in the general OHT evaluation, but an active pre-transplantation search for chronic digestive complications (megaesophagus and megacolon) is necessary to avoid postoperative complications. The mortality rate is high for CHD patients on the waiting list, suggesting the need for earlier intervention. On the other hand, post-OHT survival is higher, despite the risk of reactivation, perhaps because the patients included in the previous series were younger, with fewer comorbidities and less risk of pulmonary hypertension. Monitoring of reactivation throughout life is mandatory, especially during increases in immunosuppression therapy for transplant organ rejection.

Universal trypanocidal prophylactic therapy before OHT is not recommended, but benznidazole is the drug of choice in cases of reactivation[1,9].

Different devices for cardiac assistance could be used in patients with end-stage HFrEF due to CD. These could be applied as a bridge to transplantation, a bridge to recovery, or even as a destination therapy. Unfortunately, the limited access to health services in endemic countries makes this option uncommon, but some successful experiences have been described[99].

NON-PHARMACOLOGICAL STRATEGIES

Several non-pharmacological strategies based on lifestyle modifications have demonstrated beneficial effects in the clinical management of patients with CHD, including nutritional counseling, pharmaceutical care, and exercise-based cardiac rehabilitation (CR). The first approach involves dietary guidelines, encouragement to self-care, adherence to treatment, regular physical activities, and prohibition of alcohol and tobacco use. These strategies are usually easy to implement and have a low maintenance cost; therefore, they should be included in clinical practice.

Nutritional counseling

CHD promotes physiological changes that can directly influence nutritional status. In this setting, nutritional counseling aims to provide adequate calories and nutrients to maintain an ideal body composition[9], especially considering patients who progress with cardiac cachexia. Nutritional counseling should consider the eating behaviors and cultural habits of each patient, as well as access to food and the presence of other clinical conditions, such as dysphagia, intestinal constipation, dyslipidemia, diabetes mellitus, and hypertension[9].

For patients with HF, nutritional intervention also includes the control of salt consumption, limiting it to 3 to 4 g/d for those with mild to moderate disease, and less than 2 g/d for more severe cases (decompensated HF)[9]. The restriction of sodium consumption can cause low adherence to dietary recommendations[100,101], due to low food palatability, resulting in insufficient food intake with energy and nutrient supply below the recommendation. Culinary preparations using spices, herbs, condiments, and different techniques have been recommended to improve palatability and encourage healthy food consumption[102]. In severe HF, restriction of fluid intake is necessary, and patients should be encouraged to closely control their body weight [9].

Pharmaceutical care

Considering that as high as 30% to 40% of patients with CD will develop cardiac or digestive symptoms that chronically require medical assistance and pharmacological treatment[9], pharmaceutical care emerges as an important auxiliary strategy to improve medication compliance, minimize adverse drug events, and improve quality of life[103]. Therefore, pharmaceutical care is an important strategy that should be implemented in the follow-up of patients with CHD and HF, as it could help to identify adverse drug events and suggest alternatives to minimize these side effects [104].

Exercise-based cardiac rehabilitation

Exercise-based CR has emerged as an important strategy to improve functional capacity and quality of life in patients with CHD complicated by HF[35]. Before participating in an exercise program, patients must undergo a clinical evaluation including anamnesis, physical examination, and complementary tests to minimize the risk of adverse events during exercise practice. The anamnesis should include information regarding the stage of CHD, history of arrhythmias, organ damage, comorbidities, devices (pacemaker or ICD), previous hospital admissions, allergies, and history of physical activity. On physical examination, cardiac and pulmonary auscultation are important, together with evaluation of musculoskeletal limitations, surgical scars, and any other signs of diseases that may limit exercise practice. A basic laboratory investigation with a complete blood count, lipid profile, and coagulation factors is also important.

A resting ECG should be performed to assess rhythm disturbances, and a maximal exercise test (with or without gas exchange analysis) should be performed to evaluate clinical, hemodynamic, and electrocardiographic responses during exercise. If not available, a submaximal test (*e.g.*, the 6-min walk test) can provide parameters for

monitoring functional capacity. Exercise tests must be performed under the usual medications, especially for patients with chronotropic negative drugs, such as beta-blockers, digitalis, or antiarrhythmics, to mimic the condition that they will be in during physical training sessions. An echocardiographic evaluation is also useful, as it provides additional information for risk stratification[105].

During exercise sessions, electrocardiographic monitoring should be performed to detect malignant exercise-induced arrhythmias. Heart rate monitors can also be used, but the CR team must pay attention to possible errors due to electrical interference and check with manual verification, if necessary. Blood pressure and oxygen saturation should also be assessed before, during, and after exercise. Blood glucose measurements can be performed before and after exercise sessions for diabetic patients.

Ideally, the CR training program should be comprised of 150 to 300 min per week (divided into 3 to 5 wkly sessions) of moderate-intensity activities, including aerobic, strength, stretch, and balance exercises. The intensity of aerobic exercise usually ranges from 70% to 85% of the peak heart rate obtained in the exercise test or 90% to 110% of the ventilatory threshold obtained in the maximal exercise test with gas exchange analysis. The perception of effort scale (*i.e.*, Borg scale) is also a valuable instrument that can be used to control exercise intensity. Resistance exercises should be performed at least twice a week at moderate intensity, with greater emphasis on large muscle groups (upper limbs, lower limbs, and trunk), which can be performed using free weights, elastic bands, and resistance equipment. Stretching and balance exercises improve performance of functional activities, reduce cardiovascular overload in some daily situations, decrease the risk of falls, and improve autonomy[106].

In addition to low aerobic capacity and peripheral muscle weakness, inspiratory muscle weakness is estimated in 30% to 50% of patients with CHD[107]. Inspiratory muscle training (IMT) alone and associated with aerobic training[108,109] may improve exercise capacity in HF patients by reducing diaphragmatic metaboreflex activity and respiratory muscle fatigue[110]. IMT should be considered in CR, in combination with aerobic endurance or peripheral resistance training[111]. IMT should start at 30% of maximal inspiratory pressure (MIP), followed by a gradual increase to 60% MIP, for 20 to 30 min per session, with a frequency of 3 to 5 exercise sessions per week[112]. Despite the growing recommendation of IMT to become a part of CR, little is known about this strategy for CHD. Recently, two IMT protocols (30% and 60% of MIP) have been safely tested in patients with CHD[107].

CONCLUSION

CHD is still a major cause of hospital admissions, cardiac device implantations, stroke, and death in endemic Latin American countries. CHD must also be investigated as a cause of cardiac complications in migrant populations in non-endemic countries. The routine performance of diagnostic examinations and therapies described here can help identify CHD complications and minimize their consequences in order to improve quality of life and, possibly, survival.

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REVIEW

Cardiovascular benefits from SGLT2 inhibition in type 2 diabetes mellitus patients is not impaired with phosphate flux related to pharmacotherapy

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Abstract

The beneficial cardiorenal outcomes of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus (T2DM) have been substantiated by multiple clinical trials, resulting in increased interest in the multifarious pathways by which their mechanisms act. The principal effect of SGLT2i (-flozin drugs) can be appreciated in their ability to block the SGLT2 protein within the kidneys, inhibiting glucose reabsorption, and causing an associated osmotic diuresis. This ameliorates plasma glucose elevations and the negative cardiorenal sequelae associated with the latter. These include aberrant mitochondrial metabolism and oxidative stress burden, endothelial cell dysfunction, pernicious neurohormonal activation, and the development of inimical hemodynamics. Positive outcomes within these domains have been validated with SGLT2i administration. However, by modulating the sodium-glucose cotransporter in the proximal tubule (PT), SGLT2i consequently promotes sodium-phosphate cotransporter activity with phosphate retention. Phosphatemia, even at physiologic levels, poses a risk in cardiovascular disease burden, more so in patients with type 2 diabetes mellitus (T2DM). There also exists an association between phosphatemia and renal impairment, the latter hampering cardiovascular function through an array of physiologic roles, such as fluid regulation, hormonal tone, and neuromodulation. Moreover, increased phosphate flux is associated with an

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associated increase in fibroblast growth factor 23 levels, also detrimental to homeostatic cardiometabolic function. A contemporary commentary concerning this notion unifying cardiovascular outcome trial data with the translational biology of phosphate is scant within the literature. Given the apparent beneficial outcomes associated with SGLT2i administration notwithstanding negative effects of phosphatemia, we discuss in this review the effects of phosphate on the cardiometabolic status in patients with T2DM and cardiorenal disease, as well as the mechanisms by which SGLT2i counteract or overcome them to achieve their net effects. Content drawn to develop this conversation begins with proceedings in the basic sciences and works towards clinical trial data.

Key Words: Sodium-glucose cotransporter 2; Phosphate; Hyperphosphatemia; Cardiovascular; Canagliflozin; Dapagliflozin; Empagliflozin; Endothelial

Core Tip: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have received increased attention regarding their pleiotropic effects given their markedly impressive performance in cardiovascular outcome trials (CVOT). Preliminary evidence shows that their role as antidiabetic agents is not their sole mechanism in achieving these cardiorenal protective properties. Therefore, investigation in the auxiliary properties that they hold concomitant with glucose control, vindicated by not only CVOTs, but meta-analyses, retrospective studies, and case reports has led to increased interest in delineating their global pharmacodynamic effects across the spectrum of gene expression and molecular modulation to end-organ translational biology. Such a full profile of their effects is not yet understood given the refractory period between clinical evidence supporting their utilization and a proclivity for their implementation in practical clinical environments. In this review, we answer inquiries regarding how *via* a multifarious avenues, SGLT2 inhibitors, while carrying a negative effect of induced phosphatemia (which is deleterious to the heart), compensate for this phenomenon, retaining their propensity for net cardiac benefit upon pharmacotherapeutic administration under appropriate clinical circumstances.

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INTRODUCTION

In addition to serving a role as antidiabetic agents by mediating glycemic control, the cardiovascular benefits associated with sodium-glucose cotransporter 2 inhibitors (SGLT2i) administration is a boon for patients with type 2 diabetes mellitus (T2DM) given that such patients suffer immensely from increased risk of microvascular and macrovascular complications attributable to T2DM, such as diabetic nephropathy and major adverse cardiovascular events (MACE), respectively[1]. It is noteworthy to state these sequelae are not mutually exclusive when one discusses the cardiovascular health of patients with T2DM and the renal considerations of phosphate dynamics with SGLT2i administration on MACE. An example highlighting these interdigitated cardiorenal pathways can be appreciated when considering that cardiovascular demise in patients with T2DM may predispose to acute kidney injury (AKI) through hypoperfusion and consequently, a diminished capacity to efficiently maintain glomerular filtration rate (GFR). Conversely, pathologic nephropathy from T2DM unveils baneful circumstance within the nephron conducive to MACE *via* mismanagement of fluid and ion flux as well as pathologic neurohormonal activation *via* the renin-angiotensin-aldosterone system (RAAS)[2-4].

Estimates suggest that T2DM is prevalent in roughly 40% of chronic kidney disease (CKD) patients in the United States[5]. Epidemiological studies further contextualize this association, with one United States Renal Data System (USRDS) report implicating diabetes in 44% of end-stage renal disease (ESRD) cases[6]. Moreover, examinations of 10-year cumulative mortality profiles of participants in the Third National Health and Nutrition Examination Survey (NHANES III) linked with the National Death Index has shown that among individuals with diabetes and kidney disease, standardized mortality was 31.1% (95%CI: 24.7%-37.5%) relative to 7.7% within the reference group, a patient populous defined as that without diabetes or kidney disease (95%CI: 7.0%-8.3%)[7]. This represents a statistically significant absolute risk difference of 23.4% (95%CI: 17.0%-29.9%, $P < 0.01$). Such emphasis on the baleful aspects of T2DM is important as cardiovascular disease (CVD) burden and T2DM presents with a similarly grim association, as seen in an incidence-based study by Straka *et al*[8], which followed 29863 patients (5501 with T2DM and 24362 without T2DM). In this study, it was observed that patients with T2DM exhibited a statistically significant relative risk of 1.53 for myocardial infarction (MI), 1.1 for coronary artery disease (CAD), 2.12 for heart failure, and 1.58 for stroke.

With an expanded understanding of the pathophysiologic pathways that stem from T2DM and branch towards its sequelae comes a paradigm shift in which T2DM is no longer focused solely as a disorder of hyperglycemia and aberrant insulin regulation warranting the reduction of hemoglobin A1C (HbA1C) for adequate clinical management[9-12]. Rather, an appraisal of diabetic complications is giving rise to a change in therapeutic approaches that target T2DM sequelae in tandem with glucose and insulin dynamics for expanded, and flexible T2DM treatment strategies. This can be appreciated by the advent of pharmacotherapeutic options with various mechanisms of action and pleiotropic effects, in addition to the Food and Drug Administration's shift towards expectations that antidiabetic agents being considered for approval undergo scrutiny that is validated by trial data that takes into account the systemic effects of T2DM (with an emphasis on microvascular and macrovascular pathophysiology)[13]. Evidence for this change in doctrine can be seen in the elevation of SGLT2i to more preferential recommended therapeutic options for complicated T2DM by authoritative bodies and medical societies such as the American College of Cardiology (ACC), the American Diabetes Association (ADA), and Kidney Disease Improving Global Outcomes (KDIGO)[14-17].

Affirmation for the beneficial clinical outcomes with SGLT2i pharmacotherapy is validated by favorable results in landmark clinical outcome trials. These aforementioned trials scrutinized the effects of multiple SGLT2i agents (namely, empagliflozin, dapagliflozin, and canagliflozin) in their ability to reduce endpoints defined by cardiovascular mortality, hospitalizations for heart failure, and renal considerations of associated cardiovascular demise such as death from renal failure and end-stage renal disease exacerbation, to name a few[18-21]. These drugs work (as illustrated in Figure 1) by blocking the reabsorption of glucose *via* the SGLT2 protein, which is responsible for the reuptake of the vast proportion of glucose in the proximal renal tubule. The latter causes glucosuria and decreased serum glucose levels, which inhibits the salient pathophysiologic pathways in T2DM triggered by hyperglycemia. The degree of glucosuria varies depending on drug metabolism, SGLT2 protein expression as well as distribution, and diabetic status. However, narrative reviews backed by quantitative estimates of the nephron's functional capacity and a general window of SGLT2i efficacy suggest that the glucosuria induced can lead to the excretion of up to 150 g of glucose daily with pharmacotherapy[22].

Associated with such glucosuria is also the liberation of fluid with SGLT2i therapy among patients with T2DM. In normal, healthy adults, the kidneys have the propensity to filter roughly 180 g of glucose per daily, the vast majority of which is usually reabsorbed at the proximal convoluted tubule (PCT) *via* sodium-glucose cotransport[23]. Due to insulin resistance exhibited in patients with T2DM, peripheral GLUT4 expression is decreased in T2DM, leading to increased serum glucose, and increased filtered glucose load through the glomerulus once perfusion reaches the nephron. The low affinity-high capacity properties of the SGLT2 protein within the PCT, allows for substantial glucose reabsorption, with reabsorption dynamics reaching up to 90% in certain physiologic scenarios[24,25]. By inhibiting where the majority of glucose reabsorption at the PCT, there remains feeble opportunities for glucose reabsorption to take place along downstream sites within the nephron, resulting in an increase in osmotic pressure to the flow en route to eventual urinary output[26]. Subsequently, an increased osmotic pressure from a rise in SGLT2i mediated increase in luminal glucose prevents the egress of glucose across tubule cells (and by proxy, the interstitial compartments) resulting in increased urinary volume[27-29] and liberation

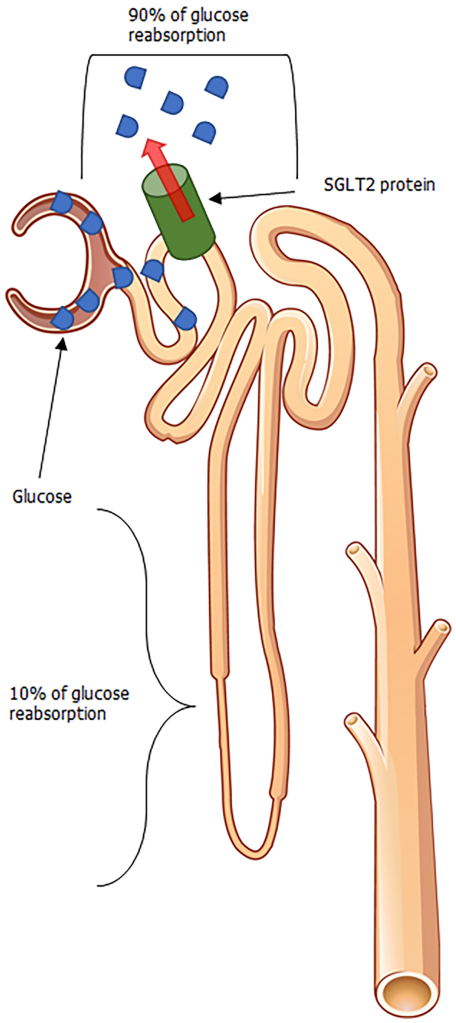

Figure 1 Glycosuria mediated from sodium-glucose cotransporter 2 inhibition. Adapted from OpenStax College, which is licensed under a Creative Commons Attribution 3.0 Unported License. SGLT2: Sodium-glucose cotransporter 2.

of systemic fluid.

The natriuresis involved in SGLT2i pharmacotherapy has recently been scrutinized and there are mixed views as to the degree of natriuresis involved in SGLT2i therapy, as while there is an osmolarity of sodium that would have been tethered for sodium-glucose cotransport, inhibition does not preclude this sodium from undergoing reabsorption at other sites, with some sites even performing compensatory roles in sodium reabsorption after transient natriuresis has been completed[30]. For example, in the thick ascending loop of Henle the Na-K-Cl cotransporter shunts luminal sodium that would have been excreted in urine. Then sodium is discharged into the blood *via* ATP-dependent sodium-potassium pump, resulting in retention of sodium. While playing a minor role, sodium reabsorption also takes place in the distal convoluted tubule through a sodium-chloride symporter that harvests urinary sodium that is also discharged *via* ATP-dependent sodium-potassium pumps. Nevertheless, studies with SGLT2i administration over a 4-week course of empagliflozin resulted in a 30%-60% increase in urinary sodium (which pulls water along for excretion) in patients with T2DM ($P \leq 0.001$), and was positively correlated to the degree of glucosuria ($P \leq 0.001$) [31]. The cumulative effects of this fluid loss can be appreciated from a cardiovascular perspective as a reduction in blood pressure as vindicated by the landmark trials, implying a reduced afterload. Moreover, studies show that the fluid loss in SGLT2i therapy occur *via* losses in intravascular compartments, implying a reduction in preload. This dual reprieve in those with heart disease promotes a physiologic status that leads to improved ventricular loading without maladaptive compensatory changes such as remodeling, and may be partially responsible for positive CVOT results, although it shown be mentioned there are many pleiotropic effects of these drugs under investigation[32-34].

SLGT2i also promote cardiovascular benefits in patients with T2DM through auxiliary avenues deeply rooted in diabetic sequelae such as through the blunting of harmful reactive oxygen species (ROS), modulating detrimental neurohormonal activation, improving oxygen flux, and preserving a positive vascular biology profile [35-38]. However, since the capacity for SGLT2i agents hinder the cotransport and reabsorption of sodium and glucose, the sodium gradient is therefore retained for sodium-dependent phosphate cotransporters (SLC34A1 and SLC34A3) as referenced in Figure 2[39-41]. The consequence of this shift in renal cotransporter dynamics is a resultant increase in phosphate reabsorption at the site of the proximal tubule, resulting in hyperphosphatemia. Albeit a recognized a process, ramifications of phosphate flux with SGLT2i administration within the literature have largely been centered upon a controversial dialogue on whether or not these agents contribute to deficits in bone mineral density of significance to subsequently provoke bone fractures [42-44]. Scant in the literature however, is a commentary highlighting the role of serum phosphate changes mediated by SGLT2i on CVD, considering CVOT have vindicated SGLT2i in mitigating CVD burden. Nevertheless, the pharmacology of SGLT2i theoretically induces increased serum phosphate, which is associated with vascular calcification and stiffness, cardiac remodeling, and other pathologic changes conductive to MACE (observed in settings independent of SGLT2i administration), especially in populations with aberrant metabolic derangements such as T2DM and diabetic CKD[45-49]. A discussion of the relative degrees of phosphate induction with SGLT2i therapy in relation to the attenuation of T2DM and its sequelae conferred with therapy (as is supported by multiple clinical trials) is prudent for giving full context on the pharmacology of SGLT2i while affirming that these drugs are still associated with remarkably beneficial cardiovascular benefit.

The effects of phosphate on cardiovascular function and also renal physiology which thereby impacts cardiovascular function is well documented. While discussed primarily within the scope of the nephron, hyperphosphatemia as a side effect associated with SGLT2i administration has been vindicated in human studies. In one study by Blau *et al*[50], among 25 research participants receiving Canagliflozin 300 mg over placebo, a marked increase in sodium excretion with an increase in associated serum phosphate levels were noted, giving validation for the sodium-phosphate cotransporter mechanism of SGLT2i mediated phosphatemia. Moreover, Canagliflozin administration was associated with a 16% increase in serum phosphate levels over placebo ($P < 0.001$).

In another *post-hoc* analysis of a double-blind, randomized, crossover trial in 31 patients with T2DM and early-stage diabetic kidney disease (defined as an albumin-to-creatinine ratio between 100 and 3500 m/g, eGFR ≥ 45 mL/min per 1.73 m^2, and 11.4% > HbA1c ≥ 7.2%, patients were randomized to dapagliflozin 10 mg daily or placebo. Dapagliflozin administration increased serum phosphate by 9% (95%CI: 4%-15%, $P = 0.002$)[51]. Interestingly, this increase in phosphate was not correlated with changes in eGFR or 24-h albumin excretion, a known marker of renal and by proxy, cardiovascular impairment[52-54]. Such an increase in phosphate with dapagliflozin administration is noteworthy when considering that a 2016 analysis incorporating over an ethnically diverse cohort of 94989 patients stratified for population-based phosphorus quartiles by ethnicity demonstrated that 0.5 mg/dL serum phosphorus increases were associated with adjusted hazard ratios of increased renal mortality[55]. Examinations of NHANES III with incident ESRD and elevated phosphate (> 4 mg/dL) proved elevated ESRD incidence compared to those with lower phosphate levels (RR = 1.90; 95%CI: 1.03–3.53; $P = 0.04$)[56]. The latter two studies show a disparity between the dogma of phosphatemia and empiric findings of studies using dapagliflozin.

Associated with hyperphosphatemia is the elevation of fibroblast growth factor 23 (FGF23)[57,58]. This protein has received interest in its clinical applications due to its potential in mediating aberrant metabolic pathways associated with cardiovascular health, as marked by its associated with MACE providing a link between hyperphosphatemia and the heart[59-61]. There is a growing body of evidence that FGF23 is a key player in signaling pathways related or as a biomarker related to distinct pathologic avenues of diminished cardiovascular function- these include left ventricular hypertrophy (LVH), endothelial cell dysfunction, arterial fitness, and atherosclerosis[60,62]. Nevertheless, we can appreciate that SGLT2i, despite promoting hyperphosphatemia (and subsequently FGF23 as marked by the Canagliflozin and Dapagliflozin phosphate studies) mitigate cardiovascular disease buden[50,51]. We speculate that despite being central to pathways that hamper cardiovascular disease outcome, the mechanisms by which phosphatemia and FGF23 expression induce these impairments are also attenuated by SGLT2i in their pleiotropic effects, with even more

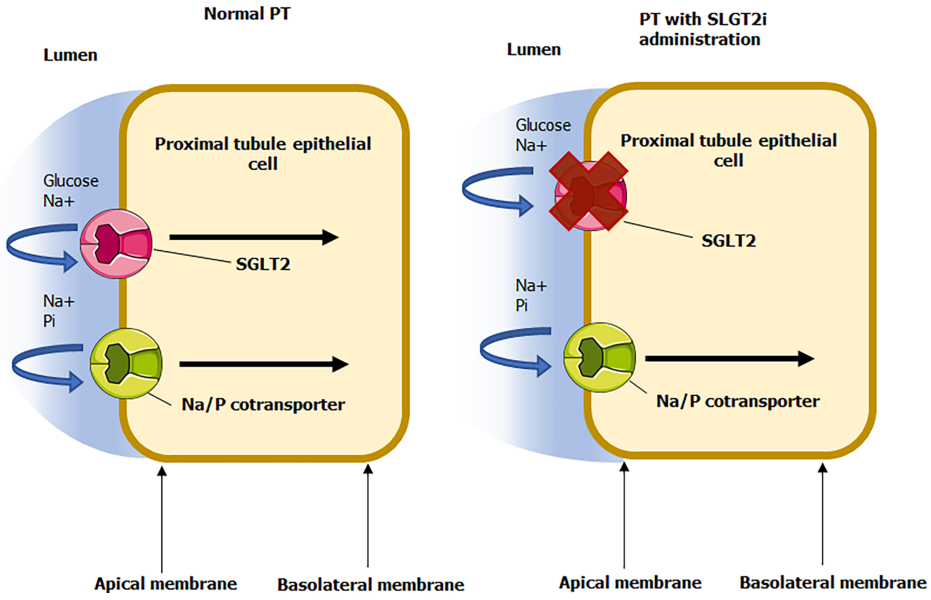

Figure 2 Glycosuria mediated from sodium-glucose cotransporter 2 inhibition. Adapted from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 Unported License. PT: Proximal tubule; SGLT2i: Sodium-glucose cotransporter 2 inhibitors.

mechanisms of cardiovascular benefit and thus, leading to a "net" positive outcome. The course of this review will outline these pathways from a phosphate metabolism perspective, and subsequently *via* commentaries on how SGLT2i overlap with these pathways and go beyond these collective pathways to further support cardiovascular health.

Moreover, the associated osmotic diuresis promotes the loss of sodium and water, which decreases blood pressure and improves oxygen flux and hemodynamic status. For example, in EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes), 7020 patients with established coronary artery disease and T2DM were slated to receive 10 mg empagliflozin (n = 2345), 25 mg empagliflozin (n = 2342) or placebo (n = 2333)[63]. The results were reductions in the risk of cardiovascular (CV) death by 38% relative to placebo (3.7% *vs* 5.9%, HR = 0.62; 95%CI: 0.49-0.77; P < 0.001). An exploratory mediation analysis of EMPA-REG attempted to identify elements influencing CVD death risk reduction with empagliflozin by analyzing *post hoc* mediators through Cox regression[64]. A significant finding of this audit of trial covariates and their influence in survival identified that hematocrit and hemoglobin mediated roughly 50% of the propensity of empagliflozin to improve CV survival relative to placebo. One possible reason for this rise in red blood cell (RBC) magnitude may be due to more efficient erythropoiesis *via* the renoprotective properties of SLGTI2[65,66]. Support for this theory can be found in a small-scale study of 66 patients administered empagliflozin over four weeks, with a 31% increase in erythropoietin (P = 0.0078) seen in 64 patients[31]. Similar improvements in erythropoiesis have been observed in other classes of SGLT2i, dapagliflozin and canagliflozin[67,68]. The role for this phenomenon in CV survival is not well studied however and can be attributed from improvements in oxygen flux and global metabolic resource allocation. Alternatively, parsimony would suggest that osmotic diuresis and improved handling of fluid would result in an increase in RBC constituents *via* dilution-concentration dynamics, and the CV survival observed would be attributable to the mitigation of edema and ventricular stress. Nevertheless, lessons from SGLT2i therapy show us that the improved prospects for patients with T2DM are pleiotropic in nature and extend beyond correction of hyperglycemia. This concept is congruent with the focus in this work that multiple axes promote improved outcomes notwithstanding phosphate metabolism. Such principles will be reinforced throughout this commentary.

PHOSPHATE METABOLISM, DIABETES, HEART DISEASE- LOADING SGLT2 IN THE PICTURE

Within the context of the pleiotropic effects of SLGT2i administration and phosphate metabolism, it is noteworthy to mention that the ramifications of phosphate metabolism occur peripherally and not directly within the heart itself. The SGLT2 protein is not expressed within cardiac tissue, as demonstrated by sequencing studies [69]. Therefore, to make remarks about SGLT2 inhibition within the context of phosphate metabolism, a query of phosphate metabolism beginning within the nephron is warranted.

In normal settings of serum hyperphosphatemia, the parathyroid glands address this homeostatic imbalance through the secretion of parathyroid hormone (PTH). PTH acts on the PT to inhibit sodium/phosphate cotransport, resulting in the excretion of phosphate through urine. There is also a secondary implication of increased sodium flux on the cotransporters hosted on distal portions of the nephron and their relative dynamics Moreover, PTH also has an auxiliary role of promoting phosphate absorption from the small intestine as well as bone, shuttling phosphorus into serum. It also has a role in the activation of vitamin D *via* secondary hydroxylation, which has cardiorenal implications which will later be discussed. For brevity and completeness, this activation of vitamin D is implicated in the absorption of calcium and phosphate within the intestine, with less reliance on phosphate flux on Vitamin D, resulting in a net decrease of phosphate[70].

However, the metabolism of phosphorus and its associated compounds in the context of contemporary lifestyle and diet with an emphasis on heart disease and T2DM has caused a paradigm shift in how this homeostatic mechanism plays out for such patients. Current diets, especially in the western world, are dense in phosphate and have ramifications in a populous that has a significant burden of T2DM and heart disease[71,72]. Animal studies conducted have shown that both genetically impairing sodium-phosphate cotransporter function as well as hyperphosphatemia-induced *via* diet in wild-type mammals results in a phenotype akin to metabolic syndrome, which includes loss of lean skeletal muscle mass, increased reactive oxygen species formation, and renal impairment and cardiopulmonary deficits[73]. This dual-approach of the elicitation of increased serum phosphate with similar end-point results confirmed by histologically analyses was cited as giving credence towards the notion that absolute hyperphosphatemia was the end insult responsible for these findings [73]. These findings mirror the components of derangements seen in patients with T2DM and cardiovascular disease.

For example, earlier animal studies show support for hyperinsulinemia promoting reductions in the fractional excretion of phosphate in dogs, caused mainly by abatement in the ratio of tubular fluid to plasma phosphate domineered primarily by proximal tubular phosphate reabsorption ($P < 0.02$), lending an association between dysfunctional glucose metabolism and phosphate flux with consequences in disease states such as cardiovascular disease[74]. Further evidence for an association between derangements in glucose and phosphate are furthered by one human study, ^{31}P magnetic resonance spectroscopy (MRS) assessing the effects of a hyperglycemic-hyperinsulinemic clamp experiment augmented on study subjects noted an increase in inorganic phosphate and reductions in phosphocreatinine (PCr)[75]. The reductions in PCr have direct implications in heart disease, as one study by Bhella *et al*[76] recruited healthy patients and those with heart failure with preserved ejection fraction (HFpEF) to perform lower limb exercises with MRI scanning evaluation to assess myocyte function. HFpEF patients were noted to have reduced rates of oxidative phosphorylation rates, with an increase in refractory period to normalization of phosphocreatine when compared to healthy sedentary age-matched controls. Blunted PCr replenishment can cause concern as it functions as a phosphate derivative that skeletal muscle may opt to metabolically activate when ATP reserves are not high enough to sustain a respective workload. Reductions in PCr as seen in hyperphosphatemic states show an increased in the proclivity for cardiomyocytes to undergo apoptosis or irregular phenotypes[77].

Irregularities in phosphate in hyperinsulinemic states as mentioned above have also been directly studied in patients with T2DM, setting the foundation for investigation in diabetic heart disease and phosphate metabolism, with SGLT2i. ^{31}P MRS scanning the vastus lateralis of patients with T2DM compared to healthy, aged-controlled matches showed an absolute decrease in PCr, (PCr 28.6 ± 3.2 *vs* 24.6 ± 2.4, $P < 0.002$), which is supported by a negative correlation between PCr and HgbA1C ($r = -0.63$, $P < 0.01$)[78]. These findings support that the diabetic state as well as the cardiovascular

state are impacted by sequelae related to hyperphosphatemia, especially in patients with conditions related to insulin resistance where SGLT2i utilization would be warranted given appropriate consideration considering their increased use in patients with diabetes and cardiovascular disease.

Another derangement observed in the Ohnishi study was renal impairment seen in the form of renal arteriole calcification with apoptotic cells upon histology directly associated with heavy phosphate burden, indicative of maladaptive renal calcification. Such observations have been observed in humans, with ramifications of CKD and ESRD[79]. Prevailing theories include phosphate aggravating vascular smooth cells or the buildup of calcium byproducts in the form of nephrocalcinosis[80]. Similar derangements, albeit by different constituents, occur in T2DM. Such processes both however heavily similarly impact the cardiovascular benefits in patients with T2DM. Patients with T2DM experience insulin resistance and as result experience blunted responses to glucose attenuation, precluding euglycemia. The excess of glucose tends to undergo nonenzymatic glycosylation with amine groups of the glomerular basement membrane of the kidney, causing protein leakage which occludes the arterial lumen. This process propensity to impact the efferent arteriole sooner and with more impact than the afferent arteriole, causing an increase in intraluminal pressure and GFR[81].

One consequence of this relative mismatch in luminal caliber is an initial hyperfiltration cascade that ultimately damages the renal mesangium. Subsequent hyalinization of the afferent arteriole decreases GFR, ultimately manifesting as diabetic kidney disease and subsequently, CKD. The decrease in afferent lumen caliber is noted by afferent baroreceptors and elicits renin secretion by the juxtaglomerular cells. Subsequently this promotes the renin-angiotensin-aldosterone system (RAAS) cascade [82]. Ramifications of the RAAS system include an increase in blood pressure as marked by the activity of angiotensin II on the systemic vasculature, causing an increase in afterload as well as sodium retention. Chronically, this can lead to left ventricular hypertrophy and subsequently MACE. We will see that phosphate ultimately impacts the heart in a critical manner similarly, however, the net benefit of SGLT2i through their pleiotropic effects negate the deleterious effects of increased phosphate levels and lead to beneficial cardiorenal outcomes.

Compromised kidneys, such as in the case of phosphate and T2DM flux promotes a physiologic equilibrium that is acclimated to the retention of metabolic toxins which directly serve as insults to the heart and kidney in cardiorenal syndrome as defined by KDIGO[3]. In normal physiologic circumstances, increased congestion caused by edema results in stretch of native mechanosensory nerve fibers scattered throughout the abdominal and pelvic wall[83]. This leads to a phenomenon known as the renorenal reflex, by which activation of this system attenuates efferent renal sympathetic nervous system activity (ERSNA)[84,85]. Decreased ERSNA is associated with a higher threshold for α1-adrenoceptor activation. These receptors play a vital role in the activation of transporters in the proximal tubule that lead to a state of net sodium reabsorption. By decreasing their function, the renorenal reflex induces natriuresis and relief of central congestion. However, chronic kidney disease and ESRD is associated with dysregulation of the renorenal reflex[86,87]. SGLT2i therapy approaches this consequence of renal impairment and promotes homeostatic renal function by offering liberating sodium. Patients with T2DM experience an increase in filtered glucose, which is reabsorbed along with sodium in the proximal tubule with a higher affinity[88]. SGLT2i, mitigates the reabsorption of glucose of up to 90%, with concomitant sodium loss, disinhibiting the juxtaglomerular apparatus from promoting the hyperfiltration loop. Sodium is subsequently diuresed, sparing the kidney from edema and congestion.

In spite of phosphate mediated renal decline, SGLT2i have been shown to improve cardiovascular as well as renal health in patients with T2DM and CKD. CANVAS-Renal (Canagliflozin and cardiovascular and renal events in type 2 diabetes) was one trial that elucidated the effects of canagliflozin on cardiorenal outcomes[89]. Primary outcomes of interest were drawn from composites of cardiovascular death (CVD), nonfatal myocardial infarction (MI), and nonfatal stroke. Death from any cause, CVD related death, albuminuria exacerbation, and heart failure hospitalization. The primary outcome showed improvements in patients receiving canagliflozin compared to placebo (HR = 0.86; 95%CI: 0.75-0.97, P = 0.02)[20]. Cardiovascular secondary outcomes did not demonstrate superiority, (death from any cause, P = 0.24), and thus hypothesis testing was discontinued[20]. However, we will see that other SGLT2i have differential profiles conducive to cardioprotection in spite of phosphate mediated damage, and this example of CANVAS-Renal was included to illustrate that phosphate mediated nephrotoxicity with SGLT2i is not a significant factor as

demonstrated by clinical trial data as will be discussed. Interestingly, it is noted that magnesium modifies the cardiovascular mortality profile of patients undergoing hemodialysis in a positive respect[90]. In one meta-analysis, it was shown that SGLT2i improved serum magnesium levels with the potential to attenuate PTH, and was implicated as a potential underlying factor in cardiorenal mortality benefits in one SGLT2i trial[91]. This is just one of the multiple pleiotropic effects of SGLT2i.

As we see the continuous deleterious effects of hyperphosphatemia, a query in its mechanisms naturally arises. Investigations into the mitochondrial physiology has shown that oxidative stress, as seen in patients with T2DM, can exacerbate phosphate mediated toxicity and cause insulin and glucose dysregulation[92]. Mitochondrial deficits are the central theme in reactive oxygen species (ROS) formation belief in which by hyperglycemia mediates ROS formation, which impacts nodes of cardiorenal significance[35].

HYPERPHOSPHATEMIA, SGLT2, AND CARDIORENAL IMPLICATIONS

One prevailing study directly linking increased intracellular phosphate with cardiovascular incidents a la ROS is through endothelial dysfunction, which act by various mechanisms such as nitric oxide mitigation leading to decreased vascular compliance, vascular apoptosis, and the promotion of atherosclerotic plaques[91-93]. It has also been shown to promote arterial stiffness in healthy individuals[94]. The aggregate effect of these processes limits vascular compliance and the ability for the heart to adapt to hemodynamic instability. T2DM overlays this effect by inducing the formation of one member of the ROS family, NF-κB, which increases cardiomyocyte tension through activating processes related to pressure-induced remodeling and fibrosis as well as upregulates pro-coagulant factors such as tissue factor VIII and by proxy, downregulates anticoagulant factors such as plasminogen and urokinase[95, 96]. The net effect of both processes would have ramifications in oxygen flux and the propensity for the cardiovascular system to abate vascular injury caused by shear stress, with potential consequences being thrombosis and embolization, and subsequently MACE. An overview of these processes can be seen in Figure 3.

Maladaptive ramifications of MACE are vast, and may include arrhythmia from hypertrophy and disequilibrium of the electromechanical conduction system of the heart in relation to cardiac geometry, to coronary events or heart failure. Both T2DM and aberrant phosphate toxicity have been implicated in modulating the redox state of mitochondria, causing disruptions in important cardiomyocyte channel regulators such as MAPK and calcium flux *via* SERCA with the propensity to cause abnormal heart rhythm[97-99].

Yet, evidence with SGLT2i continue to redeem their propensity to bolster the cardiovascular profile of patients with T2DM. The EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) was one of the initial SLGT2i trials that gave insight into the utilization of SGLT2i for patients with a high cardiovascular risk profile[89]. In the study, three randomized groups were given empagliflozin 10 mg (n = 2345), empagliflozin 25 mg (n = 2342), or placebo (n = 2333). EMPA-REG defined its primary outcomes to note a composite of CVD death, nonfatal MI(s) (not including silent MI), or nonfatality associated with primary endpoint considerations. Unstable angina culminating in hospitalizations were designated as the secondary outcome[90]. Reports from this trial noted relative risk reduction (RRR) of around 13% in the primary outcome group taking both empagliflozin dosages when compared to placebo (HR = 0.86; 95%CI: 0.74-0.99; superiority P = 0.04)[18]. Secondary outcome was not statistically significant (12.8% *vs* 14.3%, HR = 0.89; 95%CI: 0.78-1.01; superiority P = 0.08).

Moreover, Sato *et al*[100] examined 46 patients with T2DM given SGLT2i and observed their QTc_d (the absolute range of QT-intervals in a 12-lead electrocardiogram, and a surrogate for ventricular depolarization. It was shown that SGLTi pharmacotherapy resulted in a reduction of QTc_d by roughly 9%. It is believed that this reduction in QTc_d is not related to glycemic control, but blood pressure reduction. These findings are interesting as the show the propensity to regulate ventricular depolarization, and shedding a potential perspective to one pleiotropic effect of mortality reduction in EMPA-REG as a substantial portion of the cohort in of hypertensive EMPA-REG cohort participants were designated as having left ventricular hypertrophy per ECG findings[101,102]. Cardiovascular benefits that deviate from the antidiabetic effects of SGLT2i such as a decrease in blood pressure show that these agents may hold promise

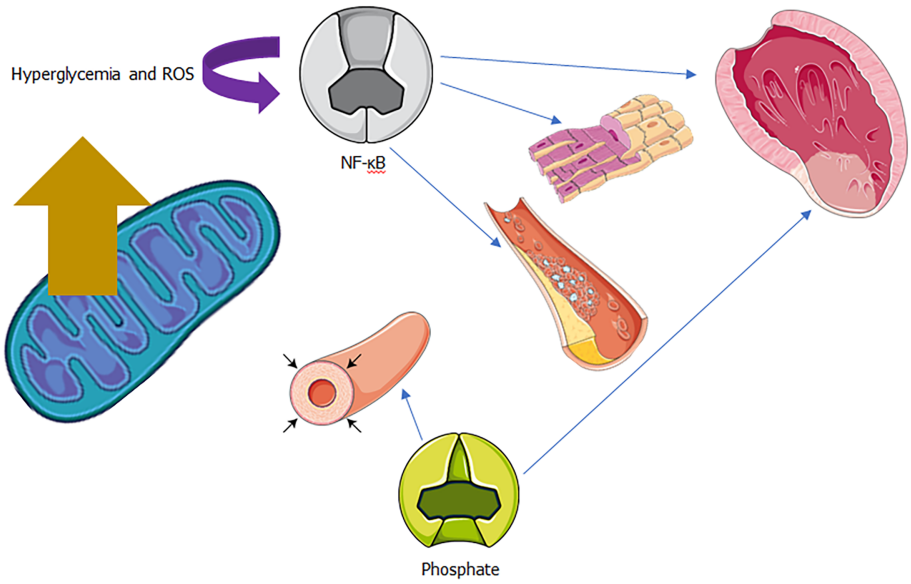

Figure 3 Examples of deleterious cardiovascular pathways associated with hyperphosphatemia and reactive oxygen species. Adapted from Servier Medical Art, which is licensed under a Creative Commons Attribution 3.0 Unported License. ROS: Reactive oxygen species; NF-κB: Nuclear factor kappa-B.

in counterbalancing the deleterious effects of ROS and phosphate on multiple fronts.

Another class of SGLT2i, Dapagliflozin, has also been vindicated and shows propensity to leverage the negative vasoconstrictive effects of phosphate and hyperglycemia mediated ROS as demonstrated by Li *et al*[103]. The ability for SGLT2i to reduce blood pressure was examined *via* application of dapagliflozin on the aortic rings of male New Zealand white rabbits. Subsequently, vasodilatory events were noted due to the activation of voltage-dependent potassium channels. Moreover, it was shown that SGLT2i had the ability to affect cellular signaling pathways *via* protein kinase G, which has been speculated to play a role in the opening of calcium-activated potassium channels, with a concomitant influx of positive ions into the vasculature, resulting in cellular hyperpolarization, relaxation, and vasodilation. SGLT2i still had the propensity to induce vasodilation after the aortic rings were removed of their endothelium with nifedipine, a calcium channel blocker, or with administration of nitric oxide inhibitors. Voltage-dependent potassium channels and protein kinase G inhibitors however resulted in amelioration of vasodilation, suggesting that SGLT2i may work *via* signaling pathways to attenuate extraneous negative players in cardiovascular health.

DECLARE TIMI-58 (Dapagliflozin Effect on CardiovascuLAR Events) is yet another clinical trial redeeming the cardioprotective profile of SGLT2i in spite of phosphate mediated increases with pharmacotherapy. This trial recruited 17160 patients with T2DM[104]. DECLARE TIMI-58 defined their co-primary endpoints as MACE (defined by CVD, MI, or ischemic stroke), with positive results (HR = 0.93; 95%CI: 0.84-1.03). Second co-primary endpoints included HF hospitalization or CVD death composites with results yielding a 18% relative risk reduction (4.9% *vs* 5.8%; HR = 0.83; 95%CI: 0.73-0.95). Second co-primary endpoints in this study were attributed to a relative risk reduction of 27% regarding heart failure hospitalizations (HR = 0.73; 95%CI: 0.61-0.88).

While the clinical data supports that an increase in phosphate and potential roles it has on vascular calcification, ROS modulation, and exacerbation in the patient with T2DM has no effect and in fact, is shown to improve cardiovascular mortality with SGLT2i, multiple questions arise to how. Glucosuria induced by SGLT2i in patients with T2DM has been shown to reduce the maximal renal glucose transport in addition to the threshold for glucosuria, resulting in a loss of glucose that would otherwise be used to help procure deleterious ROS in the inflamed mitochondria. As demonstrated previously, however, the effects of SGLT2i to taper phosphate effects go beyond antidiabetic properties, and include rhythm control, cellular signaling pathways, hemodynamics, and mineral turnover. More work needs to be done to elucidate the mechanisms of mineral turnover in the nephron given the total variants of SGLT2 proteins in the kidney as well as the pharmacotherapeutic agents, and this work will help understand contextually the full scope of cardiovascular mortality benefits seen with this drug and as validated by clinical trial data.

SGLT2i and other electrolytes: An annotation towards inclusive insight in pharmacodynamics

While this review focused on the effect of phosphate in relation to its changes with SGLT2i therapy correlated with cardiovascular mortality, a brief commentary on the other electrolytes affected by SGLT2i pharmacotherapeutics offers a proclivity to understand the global influence of these drugs. Moreover, these electrolytes have their own cardiorenal effects, and a succinct commentary is warranted given that scope. Therefore, we will include a remark on the current literature using the same standards regarding a focus on evidence-based medicine indexed to translational biology and clinical explanations to share the effects that SGLT2i have on such electrolytes.

A meta-analysis that included a query which successfully harvested random clinical trial (RCT) data of 15309 patients with T2DM taking four SGLTi (canagfliflozin, dapagliflozin, empagliflozin, and iprafliglozin) offers significant insight on the administration of SGLT2i and magnesium levels[89]. Meta-regression analyses for each agent was implemented by the authors of the aforementioned meta-analysis to evaluate the dose-dependent effects for each SGLT2i given the different classes involved. Scrutinization of this study showed that SGLT2i therapy have the propensity to elevate serum magnesium levels 0.08–0.2 mEq/L in T2DM patients compliant with pharmacotherapy. One limitation of this meta-analysis was that patients with CKD are not mentioned in this study. Both magnesium metabolism is impacted in this population group, and there is significant evidence to show a considerable proportion of SGLT2i-eligible patients with CKD are not prescribed in this population despite guideline recommendations for their utilization in this population[19]. Nevertheless, there is some evidence that shows canagliflozin as an agent is beneficial in magnesium retention in patients who have T2DM and CKD (defined as $30 \leq \text{eGFR} \leq 50$ mL/min/1.73 m^2) giving reassurance that these agents may be indicated for the regulation of cardiorenal pertinent electrolytes[104,105].

It should be noted in the scope of cardiovascular disease; magnesium levels hold value as supported by another meta-analysis able to aggregate 313,041 patients. Of these patients, 11995 cardiovascular disease risk stratification[106]. It was determined that each increase in 0.2 mmol/L of serum magnesium conferred a 30% decreased risk of CVD acquisition (RR = 0.70; 95%CI: 0.56-0.88 per 0.2 mmol/L step-size in the physiologic range).

There are many interesting insights to gain from the role of other electrolyte influences in cardiovascular mortality, especially when compared to phosphate metabolism and its seemingly deleterious effects that were offset by SGLT2i. Cohort studies using CKD patients as a model for hyperphosphatemia show those with lower magnesium levels exhibited increased cardiovascular mortality[107]. Cardiovascular mortality risk in the setting of hyperphosphatemia has been shown to be blunted in those who have normal to high serum magnesium levels. These same cohort studies show evidence that that magnesium, in-vitro, offsets hyperphosphatemia mediated sequelae conducive to a MACE phenotype, such as the induction of vascular smooth muscle cell calcification that may affect endothelial cell function. Moreover, higher serum magnesium levels hampered the progression of CKD in patients with hyperphosphatemia, highlighting a shared cardiorenal protective nature with SGLT2i.

There are multiple mechanisms by which magnesium may achieve this affect. With respect to the heart, magnesium has been shown to stimulate ATPase, critical for the maintenance of the sodium-potassium pump within the ventricular myocardium[108]. Further investigations have shown that deficiencies in magnesium lead to aberrant potassium and sodium balances, leading to an increased risk of arrhythmia. Moreover, magnesium serves a role as mitochondrial enzyme cofactors, and its dearth leads to a deficient mitochondrial metabolic status, leading to increased reactive oxygen species, a propensity for thrombus formation, and endothelial dysfunction[109]. These antiarrhythmic affects may explain have played a role in the reduction of arrhythmias as marked by stability of QT_c observed in one study that attempted to elucidate the affects SGLT2i therapy had on the positive clinical end-outcomes in the EMPA-REG outcome trial, showing that Empagliflozin helped mitigate abnormal heart rhythms, and was attributed to be a major cause of mortality and morbidity reduction[110,111]. Magnesium is also noted to be a $Gaba_A$ potentiator in the central nervous system, and its binding has been hypothesized to promote a decrease in blood pressure, decreased sympathetic tone, and the mitigation of tachyarrhythmias *via* parasympathetic and anxiolytic properties[100].

Magnesium wasting is common in patients with T2DM and it is believed that SGLT2i help normalize magnesium levels through an array of mechanisms. For example, T2DM is associated with an increase in transporters that promote

magnesium transport across to the luminal side of the nephron lead in diuresis of magnesium, and reduction of hyperglycemia is believed to give a reprieve from this wasting of magnesium[112]. The proposed mechanism are that in-vivo studies have noted increased magnesium increased magnesium reabsorption at the distal convoluted tubule within the nephron through an insulin dependent mechanism that activates increased expression of TRMP6, an ion channel that allows for entry of luminal magnesium ions into the distal convoluted tubule. Within the tubule, a sodium-magnesium that is believed to be putative in nature, represents the proclivity for basolateral transit of magnesium[113]. This process functionally represents the most terminal opportunity for magnesium reabsorption in the nephron beyond the loop of Henle[114]. It should be noted that this mechanism is partially sodium dependent and may involve increased absorption due to the increased tubular retention of sodium that would have otherwise been excreted in the proximal convoluted tubule by the sodium-glucose cotransporter without SGLT2i therapy[114, 115]. In insulin resistance, there is a decrease in TRMP6 expression, leading to decreased tubular magnesium ion flow, and loss of magnesium in urine. This is consistent with the association of low magnesium levels in patients with T2DM. Moreover, intra-pancreatic magnesium has been shown to improve insulin sensitivity by serving as a potentiator of depolarization of pancreatic β-cells responsible for insulin release[116]. However, deficits in insulin utilization and magnesium availability may lead to a cycle in which the diabetic status is exacerbated. This represents an opportunity for SGLT2i therapeutics to normalize insulin-magnesium dynamics and could be used to explain some components of positive clinical endpoint response. It should be noted that markedly decreased magnesium levels in lieu of activating parathyroid hormone when mildly depressed, prevent parathyroid hormone secretion. The purported mechanism for this phenomenon is that some basal level of magnesium ions is required for the function of the calcium-sensing receptor (CaSR) expressed in the parathyroid gland and renal tubules, and is responsible for regulating calcium by regulating the release of parathyroid hormone (PTH)[117].

This leads to our second ion of consideration in SGLT2i therapy- calcium. Calcium serves multiple roles as a protein activator or inhibitor, can form pathologic deposits, or mediate neurologic signaling- all important in cardiovascular health. Within electrophysiologic considerations, calcium ions are important during the phase 0 upstroke stage in pacemaker action potentials when voltage-gated calcium channels open, and due to their relatively lower negative resting potential, fast-voltage gated sodium channels expressed remain permanently inactivated. This results in a "lag" effect that the AV node utilizes to prolong potential transmission from the atria to the ventricles for a unified beat. In the myocardium, calcium plays an important role in the maintenance of depolarization. As depolarization begins, intracellular potassium channels open and are released to bring the membrane potential to equilibrium, which would terminate the depolarization sequence. However, voltage-gated calcium channels promote the inward flux of calcium ion that activates further calcium release from the sarcoplasmic reticulum, maintaining a plateau that prolongs myocyte contraction and adequate myocardial tension to initiate the stroke volumes needed to maintain perfusion. It is postulated the calcium channel itself in myocardiocytes is dependent upon calcium for its closing[118]. A hypocalcemic state leads to slower calcium leakage within the myocardial membrane, meaning a longer time to reach a concentration to close the L-Type calcium channels, extending the action potential, and by proxy, initiating QT prolongation[119]. In the previously mentioned study by Blau *et al*[50], the 25 research participants who received 300 mg Canagliflozin over placebo for 5 d revealed no change in the serum concentration and ionized-calcium concentration among the participants over this period. However, calcium excretion defined as (mmol/d)/(grams of creatinine) as a function of the day on which urine was collected revealed a statistically significant differential decrease in urinary calcium excretion on day 4 (1.50 *vs* 1.78; $P = 0.04$)[50]. The subsequent day showed a trend, albeit not statistically significant, towards the same trajectory of urine calcium dynamics (day 5, 1.40 *vs* 1.66; $P = 0.09$).

Within the biomarkers assessed in the Canagliflozin study, fibroblast growth factor 23 (FGF23) was tracked. FGF23 is known to be provoked by increased phosphate, and the latter also provokes PTH excretion. Therefore, by proxy, SGLT2i by increasing phosphate, increase both FGF23 and PTH[120,121]. Within this small study, FGF23 levels peaked roughly 12 h after phosphate reached its maximus, consistent with physiologic studies of FGF23 expression[122]. FGF23 acts on the proximal tubule, inhibiting NPT2, a cotransporter of sodium and phosphate (which may further explain why natriuresis is not the predominant mechanism of urinary loss within SGLT2i administration after phosphate levels subsequently reach clinically relevant concen-

trations)[123]. Interestingly, FGF23 suppresses 1-α-hydroxylation of Vitamin D to activate it , while PTH promotes 1-α-hydroxylation resulting in a mismatch of calcium reabsorption[121]. The dynamics of this small-scale Canagliflozin study that measured FGF23, PTH, and 1,25-dihydroxyvitamin D levels on a daily basis implied that early FGF23 expression resulted in a transient hypocalcemia. The decrease in 1,25-dihydroxyvitamin D theoretically decreased the gastrointestinal harvest calcium ion, further stimulating PTH, which has already been induced by SGLT2i mediated phosphatemia. PTH in this cohort may have resulted in net renal tubular reabsorption of calcium ion by the relative influence of SGLT2i. The effect of hypercalciuria may have been a temporary transient effect of osmotic diuresis, as it resolved by day 5. A study involving higher power may be needed to elucidate the effects of SGLT2i on calcium metabolism, as FGF23 expression has been noted to promote paracrine regulation resulting in left ventricular hypertrophy, contraindicative to net positive CVOT outcomes, while also promoting degenerative vascular changes in the kidney [124].

It seems however based on data related electrolyte flux, calcium may not be as significant player in SGLT2i therapy. The only CVOT trial in which bone fractures (a surrogate for phosphate and calcium metabolism) seemed to exhibit a differential risk for bone fractures was CANVAS, a Canagliflozin based trial. Total fracture incidence for bone fracture was more prominent in the canagliflozin group relative to placebo (15.4 *vs* 11.9 fractures among participant per 1000 patient-years; HR = 1.26, 95%CI: 1.04–1.52)[20]. However, this trial when compared to the plethora of dapagliflozin and empagliflozin CVOT trials employed a larger proportion of T2DM diagnosis, female gender, and degree of obesity- all factors associated with bone fractures and by proxy, calcium and phosphate flux relative to other SGLT2i. CREDENCE, another canagliflozin trial, did not report a differential fracture risk among patients. Nevertheless, scrutinizing the role of calcium in SGLT2i therapy has important ramifications when discussing the role they pose in cardiac electrophysiology, wasting in those with CKD, their ability to act as signal transduction messengers, and other downstream factors to explain their role in SGLT2i mediated health benefits.

CONCLUSION

Through the use of translational biology, a known side-effect of SGLT2i, phosphatemia, was able to be shown as diminutive relative to the pleiotropic effects of these new class of antidiabetic agents. Commentaries such as these show that despite theoretical contraindications to pharmacotherapy, the full spectrum of drug effects may outweigh what seems to be harmful, resulting in a net positive clinical profile. Yet, more work needs to be done on elucidating the pathways by which SGLT2i act peripherally beyond the nephron. There is a slew of research implicating cytokine modulation, gene expression, and inflammasome activation in avenues not previously discovered that may give new insight into how these agents have propelled their way to shifting from antidiabetic agents to pharmacotherapeutic options with cardiovascular benefits.

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REVIEW

Current role and future perspectives of cardiac rehabilitation in coronary heart disease

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Abstract

Ischaemic heart disease (IHD) is a major cause of morbidity and mortality worldwide. While there have been major advances in this field, these patients are still a higher risk subgroup. As such, strategies to mitigate risk and tailor secondary prevention measures are of the utmost relevance. Cardiac rehabilitation (CR), encompassing several domains including exercise training, cardiovascular risk factor optimization, nutritional and psychological assessments, as well as other ancillary interventions has shown to be one of the pillars in the contemporary management of patients with IHD. Indeed, CR is associated with several benefits in this population, ranging from functional capacity to improvements in outcomes. Whilst this, there are still several issues concerning the optimal application of CR which are still not fully ascertained, such as lack of referral and completion, as well as questions related to programme design (particularly among patients with multiple comorbidities). In this review, we aim at presenting a pragmatic overview on the current role of CR in the management of individuals with IHD, while also discussing some of the caveats in the current data, as well as future concepts which could help improve the uptake and personalization of this pivotal time-tested intervention.

Key Words: Cardiac rehabilitation; Secondary prevention; Myocardial infarction;

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Core Tip: Ischaemic heart disease (IHD) is a leading cause of morbidity and mortality. Cardiac rehabilitation (CR) programmes have evolved over the years, as to provide comprehensive frameworks encompassing several domains of secondary prevention and forming an integral part of the contemporary management of individuals with IHD. Whilst this, the optimal application of these programmes, in diverse subsets of patients, remains an evolving and challenging field. In this review, we present a pragmatic overview on the current data concerning CR in IHD, while also discussing some of the caveats and future perspectives in this topic.

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INTRODUCTION

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality worldwide[1-3]. Ischaemic heart disease (IHD) is one of its most common presentations, and though significant advances have been made in terms of both its diagnosis and management, patients with IHD still represent a higher risk subgroup[4-6]. Given this background, strategies focused on optimizing overall secondary preventive measures have been the focus of increased interest[4,7,8].

Cardiac rehabilitation (CR) programmes are one of the pillars of the contemporary management of individuals with IHD, being associated with improvements in both morbidity and mortality[6,7,9,10]. Over the years, these programmes have evolved into comprehensive and multidimensional secondary prevention frameworks encompassing several domains ranging from exercise training (ET) to lifestyle counselling, cardiovascular risk factor (CVRF) optimization, psychological interventions, as well as nutritional support and other ancillary interventions[11,12]. While the central role of CR programmes in the management of IHD is currently consensual, there are still several hinderances concerning its optimal application, as manifest by the diversity in programme designs, availability, and patient enrolment [11,13-15]. Moreover, tailoring of these programmes for traditionally less referred subgroups of patients such as women and the elderly, as well as the role of novel strategies to improve referral and completion are also areas of intense interest[8,16-18].

In this review, we aim at presenting a focused and pragmatic overview of the role of CR programmes in the management of individuals with IHD, as well as reviewing some of the challenges and future perspectives concerning this intervention.

CR IN ISCHAEMIC HEART DISEASE

General concepts

Over the last decades, the important role of exercise in the management of individuals with IHD has come under the spotlight[19,20]. Though its potential role in the modulation of anginous symptoms is often ascribed to the classical work of Heberden in the 18th century, the first descriptions of exercise-based rehabilitation in individuals after a myocardial infarction were only reported several years later, well into the 20th century[19,21,22]. Importantly, these early pioneers had a crucial role in changing the then-current *status quo* of prolonged immobilization, by reporting on the benefits of exercise (adapted to the individual patient) in this specific setting[19]. Since these pivotal landmarks, several studies have extensively reported on the myriad benefits of ET in individuals with IHD[8,9,23,24].

Exercise can have a profound impact on the cardiovascular (CV) system, both in the heart as well as in the peripheral vasculature[10,20,25-27]. Interestingly, though its effect on left ventricular systolic function *per se* can vary (depending on factors such as the population under study, timing of introduction and type of protocol), data concurs as to the improvements in functional capacity [as assessed by surrogates such as the peak oxygen consumption (pVO2)][20,28-30]. In addition, its impact on other sites such as the pulmonary and musculoskeletal systems should also be kept in mind, particularly when analysing data related to overall functional capacity as well as its impact in the face of the complex multimorbidity patient[20,31-33]. Moreover, and given recent reports illustrating the putative role of inflammation in IHD, the potential modulation of inflammatory pathways by physical activity has also been postulated as being one of the mechanisms underlying the benefits of exercise-based CR[25,34]. Of note, however, that while some mechanistic as well as clinical data have supported this hypothesis, further research is still needed to fully ascertain the potential relative contribution of inflammatory modulation and metabolic substrate utilization to the overall improvements in individuals undergoing CR[25,34-36].

The role of exercise in preventing CVD has been extensively explored, as depicted by the data showing its relevance in reducing the incidence of several pathologies such as heart failure (HF) and mortality[4,37,38]. Interestingly, though some reports have explored the notion that intense ET could potentially lead to detrimental CV effects, as manifest by phenomena ranging from elevations in cardiac biomarkers (such as cardiac troponin and natriuretic peptides) to coronary artery calcification and myocardial fibrosis, data has consistently shown the beneficial effects of moderate regular exercise[27,38-41]. As such, though these factors should be taken into consideration, particularly in terms of exercise prescription and personalization, the plethora of benefits associated with ET should be further highlighted, namely in the setting of IHD[9,10,42] (Figure 1).

CURRENT EVIDENCE CONCERNING CR

As discussed above, there are several potentially beneficial biological effects of ET[25,38,43] (Figure 1). In accordance with these data, it has become one of the central components in the management of IHD[4,6-8]. While the contribution of ET is undisputable, CR programmes have progressively incorporated increasingly different facets, as to provide a comprehensive approach to the individual patient[8,11,12,44]. This progression mirrors the growing complexity of both patients (including multiple comorbidities, the inclusion of older individuals as well as differences in terms of socio-cultural backgrounds) as well as of therapeutic modalities, and as such the need to provide an ever more patient-centred intervention, as to improve outcomes[11,44-46]. Interestingly, as the concept of global CV risk (comprising different CVRF, as well as modulators which could have varying levels of influence) becomes paramount in the CV assessment, the utility of CR in tackling different components of CVD gains additional relevance[4,8,11]. Indeed, reports have shown the benefits of comprehensive programmes, when compared to isolated interventions[44,47]. These concepts are reflected in the current recommendations by different societies, which reinforce the need for CR programmes to include multiple components, as to provide optimal risk management strategies[11,48-50]. In this regard, the European Association of Preventive Cardiology (EAPC) has recently provided guidance on the core components of CR programmes in individuals with IHD (as well as in other CVD), while also presenting a position statement concerning standardization of this intervention[8,11].

Different studies have assessed the impact of CR programmes in the setting of IHD [9,23,51,52]. A meta-analysis performed by Anderson *et al*[23] reported on significant benefits in terms of CV mortality, hospitalizations, and quality of life. Subsequently, and as to address the relevance of this intervention in a contemporary setting, the CROS-II meta-analysis (including only individuals enrolled by 1995 or later) provided further evidence on CR, as attested by reductions in mortality[9]. The benefits for patients undergoing CR in this setting have also been reported in observational real-word studies[53-55]. Importantly, the CROS-II study also reinforced the need for standardization across different programmes, as to allow further assessments[9,51]. This point should be particularly taken into consideration when analysing data from studies which do not report on benefits in terms of outcomes[51,56-58], as differences in programme design, ET compliance and intensity could (at least partially) explain some of these discrepancies[59-63]. This latter point should be further considered, and

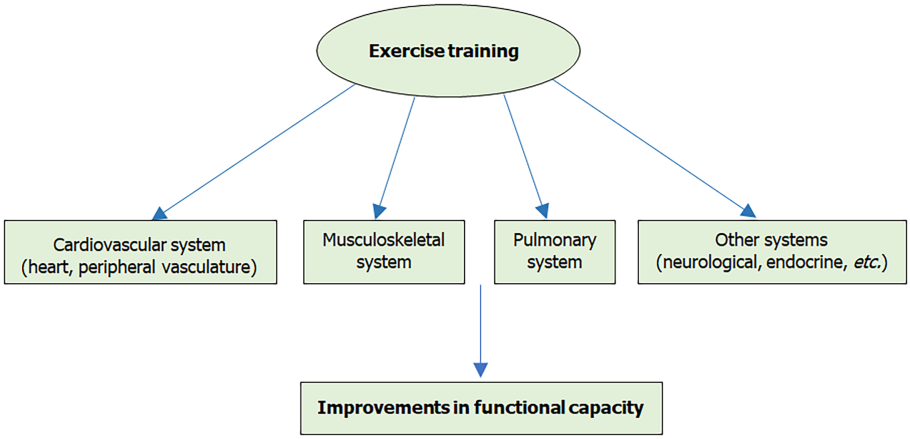

Figure 1 Overview of some of the sites related to the overall effects of exercise training.

it has also been explored when addressing different training methodologies[62,63]. In this regard, albeit high-intensity interval training (HIIT) showed interesting results when compared to moderate continuous training, three large randomized controlled trials in coronary artery disease (CAD), HF with reduced and preserved ejection fractions (respectively) failed to show an advantage of HIIT in terms of the pVO2[62-64]. Importantly, exercise prescription played a pivotal role, as acknowledged by the authors, reinforcing the need for a personalized and highly integrated approach[62,63]. It should also be recalled that the number of CR sessions performed can influence results, as illustrated by data showing that performing a smaller number can lead to worse outcomes[65,66]. These concepts had previously been elegantly raised by Sandercock *et al*[56] by comparing the case of ET to the prescription of pharmacological therapies, where in both cases dosing issues could affect the overall results of the intervention.

Differential responses should also be further explored, as studies have shown that the functional response to CR (namely as expressed by the pVO2) can be associated with outcomes[67,68]. In this regard De Schutter *et al*[67], assessing data from 1171 individuals with coronary heart disease (CHD) who underwent a phase II CR programme, showed significant differences in mortality when comparing those who had improvements in pVO2 to those who did not. When assessing pVO2 as a continuous variable, a 1 mL/kg/min improvement in pVO2 was reported as being associated with a 10% reduction in mortality[67]. Recently, Carbone *et al*[68] also reported that among individuals with CHD undergoing CR, pVO2 at the end of the CR programme was a predictor of mortality. Notably, associations between pVO2 and CV events have also been reported in other settings, further reiterating the need for rigorous programme designs, namely in terms of exercise prescription[8,11,68,69]. Of mention, the timing of CR initiation (after an acute event) should also be taken into consideration as this can be associated not only with reduced uptake and completion but can also influence the response to ET[10,28,29,70].

Another issue which should be discussed pertains to the cost-effectiveness of CR[8,23]. Some studies have suggested the cost-effectiveness of CR among individuals with IHD, while an analysis by Hinde *et al*[70] also supports potential benefits in expanding overall CR coverage[71-73]. Though these data concur as to the relevance of CR, as discussed by Barradas-Pires, differences in terms of programmes and population under study should also be noted, as standardization of CR programmes (as discussed above) would allow further analysis of the best ways to optimize this intervention, while potentially streamlining patient care[71,74]. Beyond this, it should also be referred that differences in terms of overall policies (when comparing world regions) could also influence CR programmes (namely in terms of accessibility and uptake), a factor which should also be acknowledged[13,14].

While the abovementioned caveats should be kept under consideration, the wealth of data supporting the relevance of CR in individuals with IHD in terms of both morbidity and mortality reinforces its role in this group of patients. This is reflected by current guidelines by both the European Society of Cardiology and the American Heart Association/American College of Cardiology, which attribute these programmes high levels of recommendation in this setting, highlighting the paramount role of contemporary CR in the optimal management of IHD[4,6,7,75,76].

CHALLENGES TO CR

As stated above, CR programmes are endorsed as part of the standard management strategy of IHD[4,6,7,75]. Whilst this, data has shown that CR is often underutilized and that even in those who are referred for this intervention, many do not complete the pre-specified programme[8,13,14,77,78]. Notably, while the issue of CR underutilization can affect a substantial number of individuals, as illustrated by data from the ESC-EORP EUROASPIRE V study where less than half of individuals with CAD were referred for CR, this can particularly affect certain subgroups such as women and older patients[77-81].

A seminal work derived from the European Cardiac Rehabilitation Inventory Survey showed that asymmetries could affect different phases of CR, while also noting geographical differences[14]. This latter issue was also reported on a study assessing CR availability worldwide, showing important differences according to location[13]. Though outside the scope of the present report, several factors encompassing patient-related, physician-related, and system-related barriers can affect CR referral as well as completion[5,14,82-84] (Table 1). As such, and as reviewed by Chindhy *et al*[83], strategies directed at each of these components should be the focus of further tailoring, as to allow increased CR uptake. Strategies such as physician and patient education on the benefits of CR, automatic patient referral, flexible hours as well as optimization of expense coverage and early appointments after hospital discharge have been among some of the modalities postulated as to tackle some of these barriers[14,83,85]. Additionally, the potential utilization of alternative modalities should also be reflected upon, to mitigate some of these barriers[82,86-88]. Interestingly, and as discussed below, home-based CR (HBCR) as well as the incorporation of different technologies (such as sensors) could also be of interest, as to address some of these gaps[82,83,89,90]. As detailed in a statement concerning HBCR, this could be an option to overcome several barriers to CR such as scheduling, access, and transportation issues, as well as enrolment delays, though pitfalls such as less intensive training, monitoring and safety concerns related to higher risk patients have also been noted as some of its potential disadvantages[89,91,92]. Importantly, data has shown that this strategy can be performed safely while providing several benefits[89,91,93]. Whilst this, differences in programme designs (including patient characteristics as well as programme duration and frequency) should be considered when analysing comparisons with centre-based CR[89]. Interestingly, although older individuals have traditionally been less represented, a study has shown that a home-based programme was associated with significant functional benefits among the elderly, thus showcasing its possible relevance in this subgroup[92,94]. Notwithstanding the major advances facilitated by the growing digitalization of healthcare, adaptation of facilities as to provide the different facets of contemporary CR (including not only ET but also testing, educational sessions and other interventions) should also be reflected upon, as to maximize resource utilization[11,95].

One important aspect pertains to the presence of multiple comorbidities among individuals with IHD[8,96,97]. Indeed, as patients present with increasingly complex clinical contexts (such as in the elderly, as well as those with HF and polyvascular disease), tailoring of CR programmes can be particularly challenging[8,96-98]. Notably, ET can be associated with functional improvements such as walking distance in patients with peripheral artery disease (PAD), being recommended as an important part of the management of individuals with intermittent claudication[8,99]. Whilst this, studies have shown that functional benefits can differ when comparing patients with CAD with those who present with both CAD and PAD[96,98,100]. Another frontier field which is rapidly expanding relates to cardio-oncology rehabilitation[8,101]. Importantly, attending to the specificities related both to CV pathophysiology as well as to the potential impact of the oncologic disease and its associated treatments, the most adequate programme should be highly individualized and structured on a multidisciplinary setting[101-104]. Given these backgrounds, optimization of CR programmes in these frontier fields should be the focus of further research.

As mentioned above, the response to CR is an important aspect, as this has been shown in some studies to be associated with outcomes[67,68]. While some factors such as age and gender have been associated with modulation of the response to CR, several others have been postulated as having a role in explaining some of the differences in this response[17,25,67,81]. As expertly reviewed by Gevaert *et al*[25], the overall determinants to the complex individual response to CR should be further ascertained, as to allow improvements in its application. In this context, both clinical research as well as translational data, supplemented by the possible inclusion of insights gained from the application of novel instruments such as artificial intelligence

Table 1 Some of the challenges concerning cardiac rehabilitation uptake and completion

Suboptimal referral rates
Limited access (centre availability, geographical issues, transportation, *etc.*)
Challenges concerning programme design (working hours, participant characteristics, *etc.*)
Low participation of different subsets of patients (women, elderly, patients with multiple comorbidities, *etc.*)
Language barriers
Socio-economic issues
Low motivation and/or low self-efficacy
Challenges in the patient/provider relationship
Lack of knowledge concerning cardiac rehabilitation

and multi-omics technologies could improve current knowledge on the pathways involved in the response to CR in different individuals[25,105].

FUTURE PERSPECTIVE

As detailed in the current review, contemporary CR provides an ample secondary prevention framework, able to provide a comprehensive approach to the complex patient with IHD[4,6,8,10]. Nevertheless, questions related to the optimal application of CR among distinct subsets of patients (with a focus on those with different comorbidities) as well as the asymmetries in patient referral and completion still present highly important challenges.

The use of novel technologies has steadily made an impact across different fields of Medicine, including CR[25,90,105-107]. Though the interest in HBCR has been present over the years, with data showing that this could be an interesting option in different subsets of patients, the recent COVID-19 pandemic has markedly expanded the interest in novel models (including hybrid ones) of CR[89,90,108,109]. In this background, models which incorporate concepts of telehealth (namely encompassing different technologies) have been proposed as to allow continuity of care, while minimizing risk[110,111]. Of note, beyond this transitioning phase, these have been postulated as being of potential use to allow for future improvements in overall CR access[90]. Though the use of tele-rehabilitation has made great strides over the last years, as to mitigate some of the barriers associated with CR (particularly in terms of transportation, timing, and potentially cost), questions related to the relative role of hybrid models, as well as of the individuals who could benefit most from these, should be the focus of further study[90,94,109,112]. Moreover, the inclusion of digital tools such as mobile applications as well as sensors (to address not only data related to ET but also to different physiological facets including weight and diet as well as possible CVRF control) should also be a cornerstone of research[90,106,113,114]. Interestingly, some studies highlight the potential in the use of digital applications (often included in the broader concept of mHealth, as the use of wireless technologies with the aim of improving health outcomes) in CR[114]. These could improve access to CR (namely when applied in the framework of HBCR) and allow for more intensive monitoring of different parameters (such as CVRF and physical activity)[90,106,114]. Indeed, some reports have shown that telemonitoring could be of interest in IHD, namely being associated with benefits in functional capacity, whereas the integration of other modalities could allow additional options to address psychological parameters[113,115,116]. In this regard, a randomized study comparing the use of a wrist heart rate monitor with standard training showed that this could be associated with similar increases in pVO2 at twelve weeks, whereas another randomized study (the REMOTE-CR trial, assessing 162 individuals with CHD) showed that cardiac telerehabilitation could lead to comparable results in terms of pVO2[117,118]. While highly promising, questions related to the optimal application of mHealth in CR, particularly in terms of its inclusion across different moments in the CR continuum, should be the focus of additional research[110,114,118,119]. Beyond this, studies aimed at defining the most adequate platforms for a given programme (as well as their comparison to standard methodologies and subsequent validation) and further large, randomized trials would also be of importance, as to allow for an increasingly personalized approach[90,94,120-

122].

Another aspect worthy of mention pertains to the functional assessment methodology. While this point has been comprehensively reviewed in a position statement by the EAPC, novel insights (as discussed above) could also add interesting data[11,42,120,121]. While exercise testing (namely cardiopulmonary exercise stress testing) has a central role, other methods have also been described as of potential interest[11,42,90,123,124]. In this regard, the use of the 6-min walk test in assessing exercise progression has been proposed, whereas another recent study (albeit in a small number of individuals) reported on the use of the 200-m fast walking test in tailoring exercise in low to moderate risk CHD patients undergoing HBCR[123,124]. The relative role of these parameters (namely in the face of data derived from digital platforms) should also be further ascertained[121,125].

Finally, the concept of programme standardization will continue to have a central place when addressing the data for CR[8,11,12]. Data from different CVD shows that there are still variances across CR programmes in ET prescription, a fact which should be considered[126,127]. As mentioned above, standardization (and potential certification) of CR programmes could be of marked importance as to allow benchmarking and process optimization, across varied settings[11,12]. In this regard, also the evolution of preventive cardiology as a highly specialized area of Cardiology, as endorsed by the recently published core curriculum in Preventive Cardiology by the EAPC, could allow for further developments in this specific setting[11,128-130].

CONCLUSION

While substantial advances have been made in the management of IHD, this remains a major cause of morbidity and mortality. Contemporary CR programmes encompass a broad range of interventions, aimed at providing a comprehensive secondary prevention approach to these challenging individuals. Though differences in programme design and application should be considered, data has shown its relevance in improving outcomes, across different contexts. Importantly, the optimal strategy in different groups of patients (such as the elderly and other traditionally less represented individuals) remains an evolving field.

As the complexity of IHD in terms of patient characteristics and different therapeutic strategies (with an increasing focus on mitigating residual risk) grows, the central role of CR as a highly tailored intervention will grow ever more relevant, in the era of precision-based personalized medicine.

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MINIREVIEWS

Dabigatran in cardiovascular disease management: A comprehensive review

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Abstract

Dabigatran, a direct thrombin inhibitor, has robust data for the treatment of deep venous thrombosis and pulmonary embolism, stroke prevention in non-valvular atrial fibrillation, and the prophylaxis of venous thromboembolism (VTE) after knee and hip replacement. Recent studies have evaluated dabigatran to determine its safety and efficacy in such conditions as VTE in malignancy, coronary artery disease, mechanical and bioprosthetic valves, and antiphospholipid syndrome. This article provides a comprehensive review on the role of dabigatran in various cardiovascular diseases.

Key Words: Dabigatran; Anticoagulation; Thrombus; Bleeding; Atrial fibrillation; Deep venous thrombosis; Stroke

Core Tip: Direct oral anticoagulants (DOACs) have plethora of data for the use in medical field and particularly in cardiovascular medicine. This review is focused on the dabigatran which is one of the DOAC and it is prudent for all the physicians to be familiar with this drug.

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INTRODUCTION

Warfarin, a vitamin K antagonist (VKA) and systemic anticoagulant, has been used for decades in clinical practice for a variety of clinical indications including nonvalvular atrial fibrillation, deep venous thrombosis (DVT) and pulmonary embolism (PE). Given warfarin's indirect mechanism of action, maintaining a goal international normalized ratio (INR) is a constant challenge. Patients often experience periods of over- and under-treatment and may therefore be exposed to increased risk for adverse outcomes. The two classes of direct-acting oral anticoagulants (DOACs) include direct thrombin inhibitors (DTI) and factor Xa inhibitors and both have emerged as attractive alternatives to warfarin[1,2]. Dabigitran, a DTI, and three factor Xa inhibitors including apixaban, edoxaban, and rivaroxaban are currently approved by the Food and Drug Administration (FDA) for ischemic stroke prevention in non-valvular atrial fibrillation (AF), treatment of venous thromboembolism (VTE) and the prevention of VTE after hip and knee arthroplasty[3]. Dabigatran etexilate is a small molecule prodrug that is rapidly converted by serum esterase to dabigatran, a competitive and reversible direct inhibitor of thrombin. Dabigatran is predominantly (80%) excreted through the kidneys and does not require INR[4]. The purpose of this review is to provide a comprehensive review of the current and potential indications for dabigatran use.

ANTICOAGULATION IN NONVALVULAR ATRIAL FIBRILLATION

Atrial fibrillation is a prothrombotic condition that may lead to thrombus formation in the left atrial appendage and with subsequent systemic embolization causing a cerebrovascular accident (CVA) or stroke[2,5]. The efficacy of dabigatran in non-valvular atrial fibrillation was studied in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) multicenter randomized controlled trial. In this study, patients were randomized to dabigatran 110 or 150 mg twice daily (BID) *vs* dose-adjusted warfarin. Compared to warfarin, dabigatran dosed at 150 mg twice daily was found to reduce the risk of systemic embolism and similar rates of major hemorrhage. Dabigatran was the first DOAC that received FDA approval in 2010 and by the European Medicines Agency (EMA) in 2011 for treatment of non-valvular atrial fibrillation. The recommended doses are 150 mg BID for patient with eGFR > 30 mL/min and 75 mg BID (not tested in the Re-LY trial) for patients with an eGFR of 15-29 mL/min[6]. In a meta-analysis, dabigatran was found to be associated with a lower risk of ischemic stroke, major bleeding, mortality, a similar risk of myocardial infarction, and a greater risk of gastrointestinal bleeding when compared to warfarin [7].

According to the 2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Focused Update of the 2014 guidelines for the management of atrial fibrillation, dabigatran has a class 1 recommendation (level of evidence A) for the treatment of non-valvular atrial fibrillation and, similar to other DOACs, is recommended over warfarin. Dabigatran is associated with a lower risk of serious bleeding and has been proven to be either non-inferior or superior to warfarin in preventing stroke and systemic embolism[8].

TREATMENT OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Venous thromboembolism (VTE) includes the clinical entities of deep venous thrombosis (DVT) and pulmonary embolism (PE) and is a major cause of morbidity and mortality. The role of dabigatran in the treatment of acute VTE was evaluated in the randomized, double-blind Phase III clinical trials of RE-COVER and RE-COVER II. These trials included patients with DVT and PE who were initially treated with a parenteral anticoagulant therapy for 5-10 d. Dabigatran at a dose of 150 mg twice daily was compared to dose-adjusted warfarin with an INR target of 2-3 for a 6-mo period. In both trials, dabigatran was found to be non-inferior to warfarin in reducing

recurrent VTE. In both trials, dabigatran and warfarin had similar bleeding rates and other adverse effects, while patients on dabigatran were more likely to have dyspepsia as compared to warfarin in the RE-COVER trial, presumably due to the tartaric acid component.

The extended treatment of VTE was studied in the RE-MEDY and RE-SONATE trials. The RE-SONATE trial included patients that had been previously treated for an acute DVT or PE with anticoagulant therapy for 6-18 mo. This trial found that dabigatran use had a significant reduction in symptomatic VTE and related deaths. While the RE-MEDY trial included patients, who had been previously treated for an acute DVT and PE with anticoagulant therapy for 3 to 12-mo, dabigatran 150 mg twice daily demonstrated noninferiority to dose-adjusted warfarin. An increased risk of acute coronary syndrome was observed in the RE-MEDY trial although there was no difference observed in the RE-SONATE trial[9]. In 2014, the FDA approved dabigatran 150 mg twice daily for the treatment of DVT and PE in patients with an eGFR > 30 mL/min while its use is not recommended for patients with a GFR < 30 mL/min.

The American College of Chest Physicians 2016 guidelines recommend dabigatran, along with other DOACs, over warfarin for the treatment of acute VTE in patients without cancer (Grade 2B) and recommend 3 mo of treatment for the management of DVT and PE (Grade 1B)[10]. The American Society of Hematology 2020 guidelines for VTE recommend DOACs over VKAs (conditional recommendation based on a moderate certainty in evidence) and this recommendation does not apply to a patient with low creatinine clearance, moderate to severe liver disease, or antiphospholipid syndrome. This panel does not suggest one DOAC over another (conditional recommendation based on low certainty in evidence)[11].

POSTOPERATIVE VTE PROPHYLAXIS AFTER HIP AND KNEE SURGERY

VTE is the third most common cause of cardiovascular death after myocardial infarction and stroke and has high morbidity and mortality. Major orthopedic surgeries such as total hip and knee arthroplasty are responsible for 50% of thromboembolic events in the absence of VTE prophylaxis[12]. Oral dabigatran (220 mg or 150 mg once daily) was compared to subcutaneous enoxaparin for the primary prevention of VTE in patients undergoing elective total hip or knee arthroplasty in four randomized, double-blind, non-inferiority trials[13].

Prevention of postoperative thromboembolism after knee replacement

RE-MODEL was a randomized, double-blinded trial conducted in Europe and included patients undergoing total knee replacement. In this trial, the patients were assigned to oral dabigatran 150 mg or 220 mg once daily and were compared to enoxaparin 40 mg subcutaneously once daily. Enoxaparin was given the evening before surgery while dabigatran was administered 1–4 h after completion of surgery. Treatment was continued for a total of 6–10 d and patients were assessed for 3 mo after surgery. The primary outcome (total VTE and mortality during treatment) and safety outcome (bleeding events) showed no difference between the two therapies. Dabigatran (150 mg or 220 mg) was as effective as enoxaparin and had a similar safety profile for the prevention of VTE after total knee replacement surgery[14].

RE-MOBLIZE was a double-blind, randomized trial conducted in the United States and Canada and used enoxaparin 30 mg twice daily as compared to the 40 mg daily dose used in the RE-MODEL trial. Patients with unilateral total knee arthroplasty were randomized to receive dabigatran 220 or 150 mg once daily starting 6 to 12 h after the surgery, or enoxaparin 30 mg subcutaneously twice daily starting the morning after surgery. The treatment was continued for 12-15 d. Dabigatran showed inferior efficacy to enoxaparin 30 mg twice daily while major bleeding rates were found to be similar [15].

Prevention of postoperative thromboembolism after hip surgery

The RE-NOVATE randomized phase III, double-blinded trial was conducted in Europe. This trial compared dabigatran 150 mg and 220 mg once daily to enoxaparin 40 mg subcutaneously once daily for the prevention of VTE in patients undergoing total hip replacement. The treatment duration was 28-35 d. Both dabigatran doses were found to be non-inferior to enoxaparin and the incidence of major bleeding was not significantly different[16]. The RE-NOVATE II randomized phase III, double-blinded trial was the follow-up study to further evaluate the efficacy and safety of the dabigatran 220 mg dose in a more diverse population. This trial compared dabigatran

220 mg to enoxaparin 40 mg once daily in patients undergoing total hip arthroplasty. Patients were randomized to 28–35 d of treatment of dabigatran 220 once daily or enoxaparin 40 mg subcutaneously. Subcutaneous enoxaparin was given the evening before surgery while dabigatran 110 mg was given 1–4 h after completion of surgery followed by a full dose of dabigatran 220 mg the morning after surgery. Dabigatran was as effective as enoxaparin for preventing VTE and superior to enoxaparin for reducing the risk of major VTE and major bleeding risk while adverse effects were the same for both groups[17].

In 2015, the FDA approved dabigatran 110 mg on the day of surgery followed by 220 mg the next day for prophylaxis of DVT and PE in patients undergoing hip replacement surgery. The recommended duration of prophylaxis is a minimum of 10-14 d and can be extended up to 35 d. The same dose is being used off-label for the prophylaxis of VTE after knee replacement[18]. The American College of Chest Physicians' guidelines recommend using antithrombotic prophylaxis over no prophylaxis in patients undergoing total hip and knee arthroplasty and suggest extending thromboprophylaxis for up to 35 d (Grade 1B recommendation)[19]. The American Society of Hematology 2019 guidelines also recommends using pharmacological prophylaxis for patients undergoing hip fracture repair (conditional recommendation based on very low certainty in evidence) and recommend using aspirin or a systemic anticoagulant, preferably DOACs, for prophylaxis in patients undergoing total hip or knee arthroplasty (conditional recommendation based on low certainty in evidence)[20].

ROLE IN CORONARY ARTERY DISEASE

The randomized controlled RE-DUAL and RE-DEEM trials assessed the efficacy and safety of DOACs in patients with coronary artery disease (CAD) including acute coronary syndrome (ACS) and stable CAD in patients with atrial fibrillation. RE-DUAL was a noninferiority trial that showed dual-pathway therapy with dabigatran 150 mg or 110 mg twice daily plus clopidogrel or ticagrelor reduced the risk of the primary bleeding outcome compared to triple therapy in patients with atrial fibrillation undergoing PCI. This dual-pathway regimen also demonstrated noninferiority for the secondary efficacy outcome (thromboembolic events, death), although there was an increase in MI and stent thrombosis in dual pathway therapy when compared to triple therapy[21]. The RE-DEEM phase II trial investigated the safety and efficacy of dabigatran in ACS. Patients with STEMI and NSTEMI were randomly assigned to dabigatran 50 mg twice daily, 75 mg twice daily, 110 mg twice daily, 150 mg twice daily or placebo. Patients already on DAPT were continued on this regimen until the end of the study. Dabigatran was found to have no association with ischemic benefit and showed a dose-dependent increase in the rate of the primary safety outcome (bleeding rate) when compared to placebo. A Phase III investigation was not conducted following the RE-DEEM trial[22].

ROLE IN TREATMENT OF VTE WITH CANCER

Patients with cancer are at four-to-seven fold higher risk of developing VTE than those without cancer. Therefore, VTE is an important cause of morbidity and mortality in patients with cancer. The role of dabigatran in the treatment of acute VTE was evaluated in the RE-COVER and RE-COVER II trials as reported above. Data from these two randomized trials were pooled to determine the primary efficacy (recurrent VTE and related death) and safety (major and non-major bleeding) outcomes of dabigatran in active cancer patients who were diagnosed with cancer in the previous 5 years. No significant difference in efficacy between dabigatran and warfarin was found. Although major bleeding and non-major bleeding events were more frequent in patients with cancer than without cancer, there were no differences in the safety outcomes between dabigatran and warfarin[23].

DABIGATRAN USE IN MECHANICAL AND/OR BIOPROSTHETIC VALVE REPLACEMENT

In the Dabigatran phase III clinical trials for atrial fibrillation, patients with mechanical heart valves were excluded. The RE-ALIGN study randomized patients with recent mechanical aortic or mitral valve replacement in a 2:1 ratio to receive dabigatran or warfarin. The patients received dabigatran doses of 150 mg, 220 mg or 300 mg twice daily based on creatinine clearance. The study was discontinued early due to more bleeding and thromboembolic events in the dabigatran-treated group. The DAWA study was initiated to evaluate the efficacy and safety of dabigatran in patients with bioprosthetic mitral and/or aortic valve replacement but the study was terminated early due to limited enrollment[24,25].

ROLE IN TREATMENT OF LEFT VENTRICULAR THROMBUS

Although DOACs have been used off-label for the treatment of left ventricular thrombus, there are currently no randomized controlled trials evaluating the safety and efficacy for this indication. There is conflicting evidence based on various observational studies and a recent systematic review recommended against DOACs for the treatment of left ventricular thrombi[26].On the other hand, a single centered, retrospective, small observational study carried out at tertiary care center found that dabigatran use in patients with left ventricular thrombus is both safe and effective[27]. Additional studies are needed the clarify the role of dabigatran in the treatment of left ventricular thrombus.

USE AFTER LEFT ATRIAL APPENDAGE OCCLUSION

Left Atrial Appendage Occlusion (LAAO) is an established alternative to oral anticoagulation in patients with atrial fibrillation and a contraindication to oral anticoagulation to prevent the risk of stroke. LAAO device placement is associated with increased postoperative stroke risk and requires anticoagulation after device implantation[28]. There is no randomized clinical trial to compare the safety and efficacy of anticoagulants after LAA occlusion. Although warfarin was used after LAAO in landmark trials DOACs have been used in the real-world setting[29].

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia leading to arterial, venous, and microvascular thrombosis. Post hoc analyses compared dabigatran with warfarin in patients with APS for the treatment and prevention of VTE and found no significant difference in symptomatic VTE or VTE-related deaths between groups. The dabigatran group showed fewer bleeding events, but differences did not reach statistical significance. The EMA recommends against the use of DOACs in patients with APS, especially those with triple positive (lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein antibodies) disease[30].

CONSIDERATION IN KIDNEY DISEASE

A meta-analysis published by some researchers evaluated the safety and efficacy of dabigatran, apixaban and rivaroxaban in patients with renal insufficiency. DOAC use was compared to warfarin in patients with mild (defined as eGFR 50–79 mL/min) and moderate (defined as eGFR of 30–49 mL/min) renal impairment and found that DOAC use reduced the risk of stroke, systemic embolism and major and non-major bleeding[31]. Dabigatran 150 mg twice daily was approved by the FDA for atrial fibrillation for patients with eGFR > 30 mL/min and 75 mg twice daily for patients with eGFR 15-29 mL/min[6]. Based on real-world data, the use of DOACs is strongly discouraged in patients with end-stage renal disease (ESRD)[31]. After RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE trials, the FDA approved dabigatran 150 mg BID (after 5-10 d of parenteral anticoagulation) for the treatment of DVT and PE in

patients with eGFR > 30 mL/min and recommends against the use in patients with eGFR < 30 mL/min[9]. In 2015, based on the RE-SONATE and RESONATE II trials, the FDA approved dabigatran 220 mg once daily for VTE prophylaxis in patients undergoing hip arthroplasty. This dose is used off-label in patients with knee arthroplasty; dabigatran is contraindicated for VTE prophylaxis in patients with eGFR < 30 mL/min[32]. The doses of dabigatran for various indications are shown in Table 1.

CONSIDERATION IN LIVER DISEASE

As all approved DOACs undergo some degree of hepatic metabolism, liver dysfunction may increase the risk of bleeding. Patients with liver disease have been excluded from the trials of DOACs, therefore, unlike guidelines for DOAC use in renal disease, no guidelines are available for patients with liver impairment. Dabigatran has 3%-7% bioavailability and a small fraction is metabolized in the liver while 80% is excreted through the kidney. Based on pharmacokinetic and pharmacodynamics studies, the FDA does not recommend dose adjustments for patients with mild or moderate hepatic impairment. The EMA recommends against dabigatran use in patients with elevated liver function tests (twice the upper limit of normal)[33].

CONSIDERATION IN OBESITY

The efficacy and safety of DOACs in the obese population have not been investigated in any large randomized controlled trial. DOACs are as effective as warfarin in phase III randomized trials of atrial fibrillation and VTE, however, patients weighing ≥ 100 kg were underrepresented and accounted for 20% of enrolled patients. The Scientific and Standardization Subcommittee of the International Society on Thrombosis and Hemostasis recommends against the use of DOACs in patients with a BMI > 40 kg/m^2 or a weight >120 kg[3,34].

COST-EFFECTIVENESS ANALYSIS

There is no consensus on the most cost-effective DOAC agent and future head-to-head clinical studies among DOACs are needed. One Canadian study demonstrated dabigatran to be highly cost-effective among patients with atrial fibrillation for the prevention of stroke and systemic embolism as compared to other alternatives[35]. Similarly, in the United Kingdom, Belgium, Denmark, and Taiwan studies have demonstrated dabigatran to be cost-effective in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism[35-39]. Dabigatran was found to be a cost-effective alternative compared to both warfarin and rivaroxaban for the treatment of acute VTE in the United Kingdom[40]. In one study comparing rivaroxaban and dabigatran with enoxaparin, dabigatran was found to be more cost-effective than enoxaparin and less cost-effective than rivaroxaban for thromboprophylaxis in patients undergoing total hip and knee replacements[41].

SAFETY

Dabigatran is associated with a high risk of gastrointestinal bleeding when used at higher doses. Similarly, bleeding risk increases with in treatment with concomitant aspirin use or in those with a history of bleeding[42]. According to the Beers criteria, Dabigatran should be used with caution in patients age 75 and above given an increased risk of gastrointestinal bleeding[43]. Due to the mechanism of absorption, dabigatran use is not recommended in patients with a history of gastrointestinal or bariatric surgery[44,45].

REVERSAL AGENT

Idarucizumab is a humanized monoclonal antibody fragment approved by the FDA and EMA to reverse the anticoagulant effects of dabigatran. The recommended dose of

Table 1 Indications and dosage of dabigatran

Indication	Renal function	Doses
Non-valvular atrial fibrillation	CrCl > 30 mL/min	150 mg BID
	CrCl 15-30 mL/min	75 mg BID
	CrCl < 15 mL/min	Avoid use
Venous thromboembolism treatment	CrCl > 30 mL/min	150 mg BID
	CrCl < 30 mL/min	Avoid use
Venous thromboembolism prophylaxis following hip/knee replacement surgery	CrCl > 30mL/min	110 mg one dose followed by 220 mg daily
	CrCl < 30 mL/min	Avoid use

BID: Twice daily.

idarucizumab is 5 g administered as two separate 2.5 g doses intravenously for rapid reversal of uncontrolled bleeding in dabigatran-treated patients[46]. Glund *et al*[47] conducted a randomized, controlled, phase I study in which patients received idarucizumab 20 mg to 8 g as 1-hour intravenous infusion or 1, 2, or 4 g as 5 min infusion and was found to be safe and well-tolerated in all administrated doses. In the multicenter, prospective cohort study, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial, Idarucizumab was found to reverse the anticoagulant effect of dabigatran in 88% to 98% of the patients[48].

CONCLUSION

Dabigatran has strong data supported by randomized-controlled trials, observational studies, systemic reviews, and meta-analysis for its role in stroke prevention in non-valvular atrial fibrillation, treatment and prophylaxis of VTE, and treatment of VTE in cancer patients. It has also been used off-label for the treatment of left ventricular thrombus and post LAAO, but further randomized trials are needed to determine the safety and efficacy of dabigatran in these indications. Current data do not support the use of dabigatran in patients with mechanical or bioprosthetic valves and acute or chronic CAD.

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MINIREVIEWS

Pulmonary artery catheterization in acute myocardial infarction complicated by cardiogenic shock: A review of contemporary literature

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Abstract

Acute myocardial infarction (AMI) with left ventricular (LV) dysfunction patients, the most common cause of cardiogenic shock (CS), have acutely deteriorating hemodynamic status. The frequent use of vasopressor and inotropic pharmacologic interventions along with mechanical circulatory support (MCS) in these patients necessitates invasive hemodynamic monitoring. After the pivotal Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial failed to show a significant improvement in clinical outcomes in shock patients managed with a pulmonary artery catheter (PAC), the use of PAC has become less popular in clinical practice. In this review, we summarize currently available literature to summarize the indications, clinical relevance, and recommendations for use of PAC in the setting of AMI-CS.

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Core Tip: The unstable hemodynamic status in acute myocardial infarction-cardiogenic shock patients and frequent use of vasopressor and inotropic medications along with mechanical circulatory support devices, may suggest a role for invasive hemodynamic monitoring with a pulmonary artery catheter (PAC) to help improve outcomes. In this review, we summarize the currently available literature to summarize the indications, clinical relevance, and recommendations for use of PAC in the setting of acute myocardial infarction-cardiogenic shock.

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INTRODUCTION

Cardiogenic shock (CS) is a high-acuity hemodynamically diverse state of end-organ hypoperfusion that is frequently associated with multisystem organ failure. Acute myocardial infarction (AMI) with left ventricular (LV) dysfunction remains the most frequent cause of CS[1,2]. AMI related CS (AMI-CS) continues to be associated with high mortality (30%-40%) even in the contemporary era of early reperfusion, increasing use and availability of MCS devices and multidisciplinary shock teams[3-5]. In contrary to conventional teaching, the hemodynamic profile of CS patients is dynamic across a wide clinical spectrum depending on its stage of development[6]. The acutely deteriorating hemodynamic status in AMI-CS patients and nearly ubiquitous use of vasopressor and inotropic medication along with mechanical circulatory support (MCS) devices, underscore the importance of invasive hemodynamic monitoring to help in providing optimal therapies for these patients.

Although earlier randomized clinical trials (RCTs) including the pivotal Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial failed to show a significant improvement in clinical outcomes in shock patients managed with a pulmonary artery catheter (PAC), this data may not be representative of AMI-CS patients as it involved hemodynamically stable patients with heart failure and specifically excluded CS patients[7].

Earlier data from RCTs also failed to show mortality benefit in CS with use of PAC [8-11]. But CS is not a homogeneous disorder and AMI-CS being a distinct entity with markedly different therapeutic/interventional options and management protocols were grossly under-represented (5%-20%) in those studies. Extrapolation of data from these prior studies in the realms of heart failure and critical care and applying it to AMI-CS population may warrant caution and further deliberation[12]. Recent registry-based data allude to improved mortality especially in patients with heart failure and CS with use of PAC[13]. The 2016 European Society of Cardiology guidelines for treatment of heart failure also suggest use of PAC in patients with refractory CS despite pharmacological treatment LOE IIb [C] or being considered for MCS or heart transplantation LOE I [A][14].

Although there are a few earlier reviews on PAC use, they were focused on diagnosis and management of CS patients undergoing MCS[15,16]. However, the use of PAC in AMI-CS subset of patients requires more critical discussion due to multiple recent studies in this arena and addition of intriguing new data regarding its clinical utility. In this review, we intend to explore the indications and recommendations for use of PAC in the setting of AMI-CS and review the recent literature supporting it.

Epidemiological trends of PAC use in AMI-CS

After the data from ESCAPE trial was published, there was a notable decrease in PAC use for hemodynamically unstable patients except for AMI-CS. A recently published studies of a nationally representative population of AMI-CS and HF showed up to 75% decrease in PAC use between 2000 and 2014 despite a concomitant increase in patient acuity[13,17]. Significantly higher PAC use was seen in younger patients, patients of white race and those with higher baseline comorbidity, non-cardiac organ failure, and on MCS[17]. Interestingly, PAC was utilized 10 times more frequently in patients with HF and CS as compared to HF patients without CS between 2004 and 2014[13]. Another study involving medicare beneficiaries looked at 457193 hospitalized patients with PACs and showed that the use of PAC decreased by about 2/3^{rds} from 6.28 per 1000 admissions in 1999 to 2.02 per 1000 admissions in 2013 ($P < 0.001$). The study also noted that the decrease use of PAC was more pronounced in patients with respiratory failure [29.9 PACs placed per 1000 admission in 1999 to 2.3 in 2013 (92.3% reduction), $P < 0.001$ for trend] as compared to PAC use for AMI [20.0 PACs placed per 1000 admissions in 1999 to 5.2 in 2013 (decreased by 74.0%) $P < 0.001$]. Interestingly, the study also noted a nadir in 2009 followed by a subsequent increase in use of PAC for heart failure patients (9.1 PACs placed per 1000 admissions in 1999 to 4.0 in 2009 to 5.8 in 2013) and this was also associated with improved in-hospital mortality, 30-d mortality, and reduced length of stay[18]. A study by Khera *et al*[19] looking at the trends in PAC use among HF patients in the United States from the National Inpatient Sample (NIS) data, 2001 to 2012 showed a decrease in PAC use in CS from 8.2% in 2001 to 6.7% in 2007, but then there was an upward trend up to 14% in 2012 and its use was more common in the larger academic facilities with advanced HF therapies. Similarly, more recent studies using NIS data from 2000-2014, looking at 364001 admissions with AMI-CS showed that PAC was used in 8.1% of patients but there was a 75% decrease during over the study period (13.9% to 5.4%)[17]. While another NIS based study looking at more recent data of 1531878 hospitalized patients with CS (0.3% of total hospital admissions) from January 1, 2004-December 31, 2018, showed a significant increase in the trend for utilization of PAC in CS patients (both AMI-CS and non AMI-CS) reaching up to 17% in 2018 as compared to 10% utilization in the immediate post-ESCAPE trial era (P-trend < 0.001)[20].

In the European literature, a study by Sionis *et al*[6] using an observational, prospective, multicenter, European registry showed that CS patients treated in aca-demic centers noted PAC use 82 (37.4%) of the 219 patients over a course of 2 years. Rossello *et al*[21] noted that a PAC was used in 64% of patients with CS from 2005-2009. In Japan, the use of PAC was seen in 16.8% of patients[22]. Overall, the use of PAC is more common in European countries than in United States and other non-European countries. Earlier studies also noted higher use of PAC in patients with higher socio-economic status and with insurance coverage, large urban hospitals and in patients with MCS which may relate to social disparities in care among this population and paradigm shift in the management of AMI-CS using newer per-cutaneous MCS devices that may require constant hemodynamic data feedback for effective and safe utilization[17].

Pathophysiology of CS and the role of PAC

Regardless of the etiology, CS is a primary pump failure (increased residual volume and intracardiac pressures in one or both ventricles), which could be from right ventricular, LV or biventricular dysfunction, resulting in hemodynamic compromise and multi-organ failure[23-25]. PAC measures direct and indirect parameters which can be used to differentiate right-sided, left-sided, or biventricular dysfunction. For instance, a high central venous pressure (CVP) to pulmonary capillary wedge pressure (PCWP) ratio indicates right-ventricular (RV) failure[26]. Similarly, low pulmonary artery pulsatility index (PAPi), a more accurate measure of RV function, is associated with high CVP, PCWP, mean PA pressure and low cardiac index (CI). In contrast, these parameters measured with other non-invasive parameters such as echocardiography are not as accurate as with PAC[27]. The Society for Cardiovascular Angiography and Interventions (SCAI) recently proposed a five-stage classification system for CS: A – at risk – at risk of developing symptoms of CS but currently asymptomatic; B – beginning – patient who has relative hypotension but no signs of hypoperfusion; C – classic – patients require inotropic or MCS; D – deteriorating – C getting worse with failure to respond to aforementioned therapies; and E – extremis – circulatory collapse and refractory cardiac arrest (Figure 1)[28]. SCAI classification is used for prognostication purposes as the in-hospital mortality has been shown to rise progressively with each advancing SCAI stage[29,30]. Use of PAC measured para-

Figure 1 Stages of cardiogenic shock classified by the Society of Cardiovascular Angiography and Intervention. CPR: Cardiopulmonary resuscitation; ECMO: Extracorporeal membrane oxygenation. Citation: Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, Hollenberg SM, Kapur NK, O'Neill W, Ornato JP, Stelling K, Thiele H, van Diepen S, Naidu SS. SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94(1): 29-37. Copyright© The Authors 2021. Published by John Wiley and Sons. The authors have obtained the permission for figure using from the Wiley Periodicals Inc.

meters and prognostication through SCAI classification can facilitate clinical decision making in deciding the therapy and its clinical utility[31].

Untreated or sub-optimally treated CS results in a state of persistent tissue hypoperfusion with accumulation of lactic acid metabolites which transitions the early potentially reversible hemodynamic insult of CS to a more complex 'hemo-metabolic' cascade with refractory CS (Figure 2)[32]. All aspects of hemodynamic support including adequate circulatory support, optimal LV unloading, restoring myocardial perfusion and achieving significant decongestion must be fulfilled in a timely manner to effectively treat and reverse the hemodynamic compromise of CS[32,33].

Adequate circulatory support is defined by an increase in mean arterial pressure (MAP) and enhanced microvascular blood flow resulting in adequate organ perfusion. Ventricular unloading, which is defined as a reduction in myocardial work and wall stress, is best achieved by reducing native ventricular pressure and volume[32,33]. Myocardial perfusion, increased epicardial and microvascular coronary blood flow, often improves with adequate circulatory and ventricular support. Decongestion refers to a reduction in total body volume resulting in decreased venous filling pressures [32]. The importance of aforementioned aspects of CS is crucial to highlight, since selective therapies such as inotropes and vasopressors although may increase MAP, but they do not improve microvascular organ perfusion[32]. In addition, inotropes and vasopressors disproportionately increase LV afterload, myocardial work/wall stress, and myocardial ischemia eventually culminating refractory CS and increased in-hospital mortality[32].

Clinical utility of hemodynamic parameters from the PAC

The use of hemodynamic parameters obtained through the PAC are essential indicators for decision-making during the selection, initiation, titration and weaning of pharmacological as well as MCS support in AMI-CS patients. Emerging new evidence suggests that the use of PAC among patients with CS is associated with lower mortality and lower in-hospital cardiac arrest possibly by improved patient selection and better utilization of hemodynamic data to guide management[13]. Early acquisition of hemodynamic data like cardiac output (CO), cardiac filling pressures and systemic vascular resistances (SVR) and pulmonary vascular resistances (PVR) would

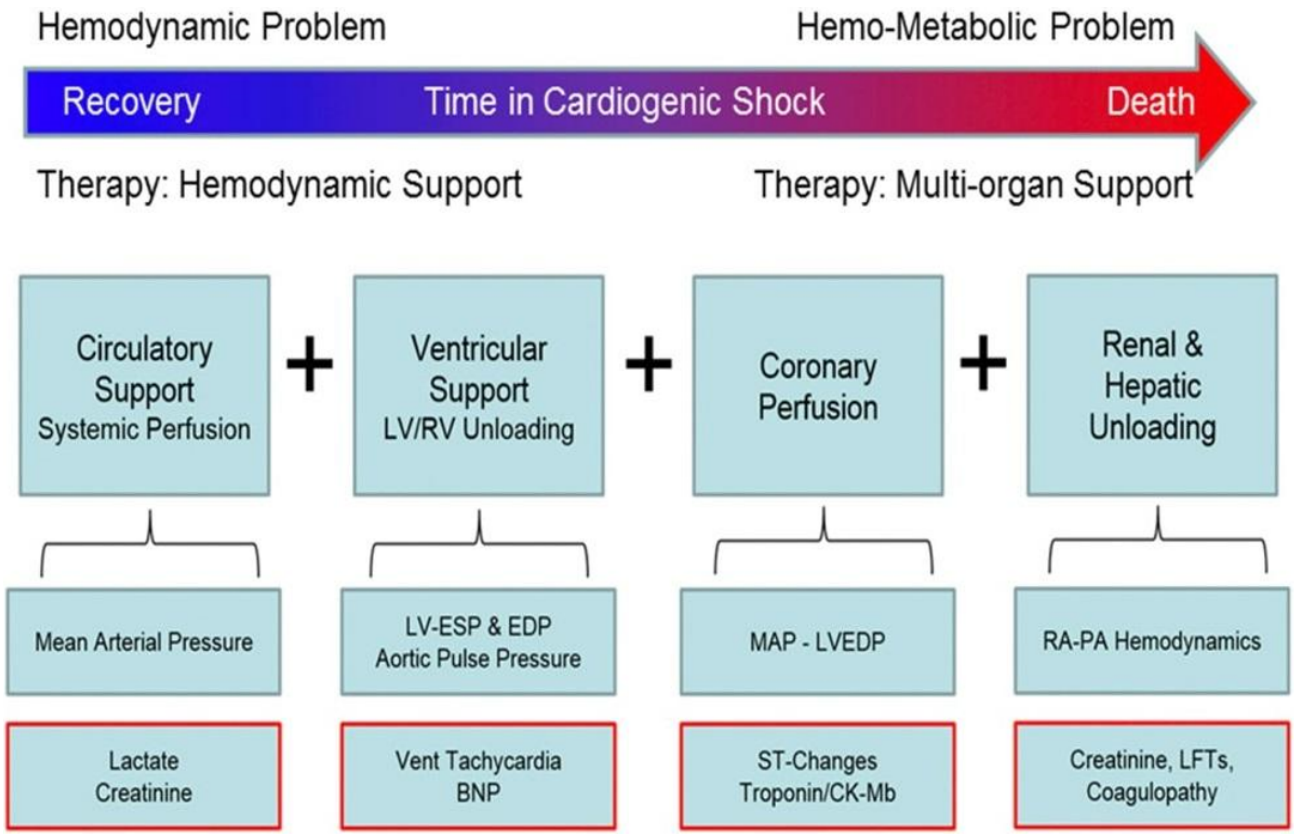

Figure 2 Hemo-metabolic cascade of acute myocardial infarction with cardiogenic shock. BNP: B-type natriuretic peptide; CK: Creatinine kinase; ESP: End-systolic pressure; LFT: Liver function tests; LV: Left ventricular; LVEDP: Left ventricular end-diastolic pressure; MAP: Mean arterial pressure; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricular. Citation: Esposito ML, Kapur NK. Acute mechanical circulatory support for cardiogenic shock: the "door to support" time. F1000Res. 2017 May 22; 6: 737. Copyright© The Authors 2021. Published by Taylor and Francis Group. The authors have obtained the permission for figure using from the Taylor and Francis Group.

help not only to define the nature of CS (univentricular or biventricular) but also to evaluate the patient's response to various advanced therapies[32]. For instance, the use of PAC in such patients would be indispensable in assessing response to therapies, guiding management and optimize device settings especially when escalating or de-escalating MCS and is supported by the current heart failure guidelines (Table 1)[14, 16]. In patients with CS, continuous hemodynamic feedback from a PAC can guide management by helping to optimize volume status, titrate vasoactive medications in a more targeted fashion as well as detect any complications such as pump thrombosis which usually manifests as recurrence of CS with sudden elevation of PA and PCWPs [33,34]. A more recent reanalysis of the ESCAPE trial data published in 2016 showed that advanced heart failure patients with a PAC who achieved a post-treatment goal of PCWP + right atrial pressure (RAP) < 30 mmHg was associated with a 6-mo mortality rate of 8.7%, as compared to 45.3% (P-value < 0.0001) in patients who have failed to achieve that target[35]. A recently released scientific statement from the American Heart Association does endorse use of PAC in difficult clinical scenarios such as when treating patients with cardiorenal syndrome as the real-time hemodynamic data obtained through PAC will help to identify and treat subclinical congestion and avoid over diuresis and intravascular underfilling and thereby improving the hemodynamics and subsequent end organ perfusion to the heart and kidneys[36] (Table 2).

Several algorithms have been proposed to help manage and potentially improve outcomes in patients with AMI-CS and early acquisition of hemodynamic data using a PAC and prompt action remain a central theme across all the various protocols. According to the National Cardiogenic Shock Initiative, in order to achieve four aspects of hemodynamic support equation, it is important to maintain thrombolysis in myocardial infarction - 3 flow, CPO > 0.6 (CPO = MAP × CO/451) and PAPi > 0.90 [PAPi = (systolic pulmonary artery pressure – diastolic pulmonary artery pressure/CVP][37-39]. Four different management pathways could be evaluated from CPO and PAPi. Therefore, the hemodynamics obtained from the use of a PAC are crucial in determining further management.

Table 1 Studies evaluating outcomes with use of pulmonary artery catheter in patients with cardiogenic shock

Author (year)	Study type	Region/sites	Time period	*n*	Study population	Outcomes	Conclusion
Sotomi *et al*[22] (2014)	Prospective observational	Japan-multicenter	2007-2011	1004	ADHF	All-cause mortality	Decreased all-cause mortality in PAC cohort on ionotropic support or lower SBP
Sionis *et al*[6] (2020)	Prospective observational	Europe-multicenter	2010-2012	219	CS, hypotension or severe LCOS	30-d mortality	No mortality difference. CI, CPI, and SVI-predictors of 30-d mortality
Rossello *et al*[21] (2017)	Prospective observational	Spain-single center	2005-2009	179	CS	Short- and long-term mortality	Lower long-term and short-term mortality
Hernandez *et al*[13] (2019)	Retrospective observational	United States-multicenter	2004-2014	9431944	ADHF and CS	Mortality	Lower mortality
Doshi *et al*[54] (2018)	Retrospective observational	United States-multicenter	2005-2014	842369	CS	In-hospital mortality	Lower mortality
Cohen *et al*[55] (1)(2005)	Retrospective observational	International-multicenter	–	26437	ACS	30-d mortality	Higher mortality
Gore *et al*[56](1987)	Retrospective observational	United States-multicenter	1975, 1978, 1981, 1984	3263	AMI	In-hospital and long-term mortality	No mortality difference
Vallabhajosyula *et al*[17](2020)	Retrospective observational	United States-multicenter	2000-2014	364001	AMI-CS	In-hospital mortality	No mortality difference
Zorzi *et al*[52] (2019)	Retrospective observational	Switzerland-single center	2008-2011	91	CS	Mortality	Increase in PAC in first 24 h
Garan *et al*[34] (2020)	Retrospective observational	United States-multicenter	2016-2019	1414	CS	In-hospital mortality	Lower mortality
Cooper *et al*[57] (2015)(3)	Retrospective observational	United States-single center	2002-2008	217	AMI	CS diagnosis	Echocardiography-based criteria can be used to accurately diagnose CS

ACS: Acute coronary syndrome; ADHF: Acute decompensated heart failure; AMI: Acute myocardial infarction; CI: Cardiac index; CS: Cardiogenic shock; CPI: Cardiac power index; HF: Heart failure; LCOS: Low cardiac output syndrome; PAC: Pulmonary artery catheterization; SBP: Systolic blood pressure; SVI: Stroke volume index.

The INOVA Heart and Vascular Institute algorithm adopts a similar 'combat' approach to managing CS and primarily relies on 5 key areas of focus which include rapid identification of shock, early right heart catheterization, expedited initiation and early escalation of percutaneous MCS as appropriate, minimization of vasopressor and inotrope use, and, meaningful patient recovery and survival[40,41]. In addition to the routinely measured hemodynamic parameters using a PAC, the INOVA pathway emphasizes on measurement of CPO (< 0.6), right atrial (RA): PCWP (> 0.63) and PAPi (< 1.5) as well as other metrics such as serum lactate (> 2 mmol/L) and tricuspid annular plane systolic excursion (< 14 mm) to help diagnose the presence of RV failure and need for RV mechanical support in CS as well as guide management including initiating or escalating/de-escalating percutaneous MCS[40].

In another prospective study by Garan *et al*[42] comparing outcomes of veno-arterial extracorporeal membrane oxygenation and a percutaneous ventricular assist device an institutional CS algorithm was used to guide selection of MCS. Of the 51 patients, 31 (76.4%) underwent invasive hemodynamic assessment with a PAC before the first device initiation and both groups had very similar hemodynamic parameters as measured by the PAC including, RA pressure, PCWP, CPO and CI[42]. The Utah Cardiac Recovery Shock Team also emphasizes the importance of multidisciplinary shock team approach and early use of PAC to guide MCS selection and improve in-hospital mortality (61.0% for shock team *vs* 47.9% for control; $P = 0.041$) and 30-d all-cause mortality [hazard ratio (HR): 0.61, 95% cumulative incidence (CI): 0.41-0.93] in refractory AMI-CS[41]. The University of Ottawa Heart Institute adopted a multidisciplinary code shock team approach to CS and demonstrated improved long-term survival[43]. In their study as well, hemodynamic monitoring with a PAC was done in 62% of patients (66% for treatment *vs* 50% for control, $P = 0.13$) for a median duration of 4 d (IQR, 2-6)[43].

Table 2 Current guidelines on pulmonary artery catheterization in cardiogenic shock

Guideline	Recommendation
2011 ACCF/AHA CABG[51]	Invasive hemodynamic monitoring with PAC is required before induction of anesthesia in patients with CS undergoing CABG (Class 1; level of evidence C)
2013 ACCF/AHA HF [52]	Invasive hemodynamic monitoring should be performed in patients with respiratory distress or impaired perfusion – when intracardiac filling pressures could not be determined from clinical assessment (Class 1; level of evidence C)
	Invasive hemodynamic monitoring is also recommended for patients with persistent acute HF symptoms despite empiric HF therapy adjusts and with one of following: (1) Systemic or pulmonary vascular resistance; or fluid status or perfusion is uncertain; (2) Low systolic blood pressure despite initial therapy; (3) Worsening renal function; (4) Candidate for pressor support; and (5) Candidate for MCS or heart transplant (Class IIa; level of evidence C)
The 2013 ISHLT MCS [53]	Patients undergoing procedure MCS device placement should have insertion of large-bore intra-venous line, arterial line, and pulmonary catheter for monitoring and intra-venous access (Class I; level of evidence B)
2016 ESC HF[11]	Routine invasive hemodynamic evaluation is not indicated for diagnosis of HF – PAC could be used in hemodynamically unstable patients with unknown mechanism of deterioration
	PAC could be used for acute HF who have refractory symptoms despite pharmacological treatment (Class IIb; level of evidence C)
	PAC along with right heart catheterization is recommended for evaluation of patients for MCS or heart transplantation (Class I; level of evidence C)
2017 SCAI/HFSA Invasive Hemodynamics[54]	Continuous hemodynamic monitoring is required for patients receiving MCS
	Continuous hemodynamic monitoring is used for withdrawal of MCS and pharmacologic support

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; CABG: Coronary artery bypass grafting; CS: Cardiogenic shock; ESC: European Society of Cardiology; HF: Heart failure; HFSA: Heart Failure Society of America; ISHLT: International Society of Heart and Lung Transplantation; MCS: Mechanical circulatory support; PAC: Pulmonary artery catheter; SCAI: Society of Cardiovascular Angiography and Intervention.

The ratio between the RA pressure and PCWP (RA:PCWP ratio) could help us gain insight into the possibility of RV failure in AMI and prognosis in patients with CS[32]. The RA:PCWP ratio can be used analogous to the classic 2 × 2 table in HF patients to classify patients as hypovolemic, LV-, RV-, or BiV dominant congestion (Figure 3)[44, 45]. Prior studies have successfully demonstrated PAPi as a simple and reliable hemodynamic measure to predict in-hospital mortality after acute inferior wall MI with high sensitivity and specificity as well as predict RV failure after left ventricular assist devices implantation[46,47].

A recent review on AMI-CS emphasizes the need for systems of care with early recognition and transportation of AMI-CS patients to level I dedicated cardiac shock care centers along with use of pre-PCI implantation of MCS devices with "door-to-support" time ≤ 90 min and consistent use of PAC for accurate hemodynamic monitoring to help improve survival and outcomes in these patients[48]. It is important to recognize that PAC does not have any intrinsic therapeutic effect and by itself would not improve outcomes but rather facilitates decisions that could translate to favorable outcomes by prompt and appropriate action guided by the real-time monitoring of hemodynamic data. For instance, escalation of device therapy from a primarily LV support to biventricular device support with Bipella (right and left sided Impella) may be warranted if hemodynamic monitoring with PAC suggests biventricular failure with CPO < 0.6 and PAPI < 0.9 to help reverse the progression of AMI-CS[25].

Differentiating AMI-CS from CS in chronic congestive heart failure

Although CS is often referred to as one homogenous entity the CS phenotype in AMI patients may be very distinct from that in end stage heart failure patients and such early distinction could have significant prognostic and therapeutic implications. There are also considerable differences between CS from AMI *vs* heart failure – chronicity in heart failure along with neurohumoral dysregulation (especially shock) and changes stemming from heart failure therapy[49]. CS from AMI has low filling, lower pulmonary artery pressures, higher oxygen delivery (DO_2), lower oxygen-hemoglobin affinity (P50), and more severe metabolic acidosis in comparison with CS from end-stage heart failure (ESHF)[49]. Further, there is higher inpatient mortality in patients with acute HF related *vs* acute on chronic HF related CS even with similar hemodynamic characteristics such as MAP, CO, cardiac power index (CPI)[50].

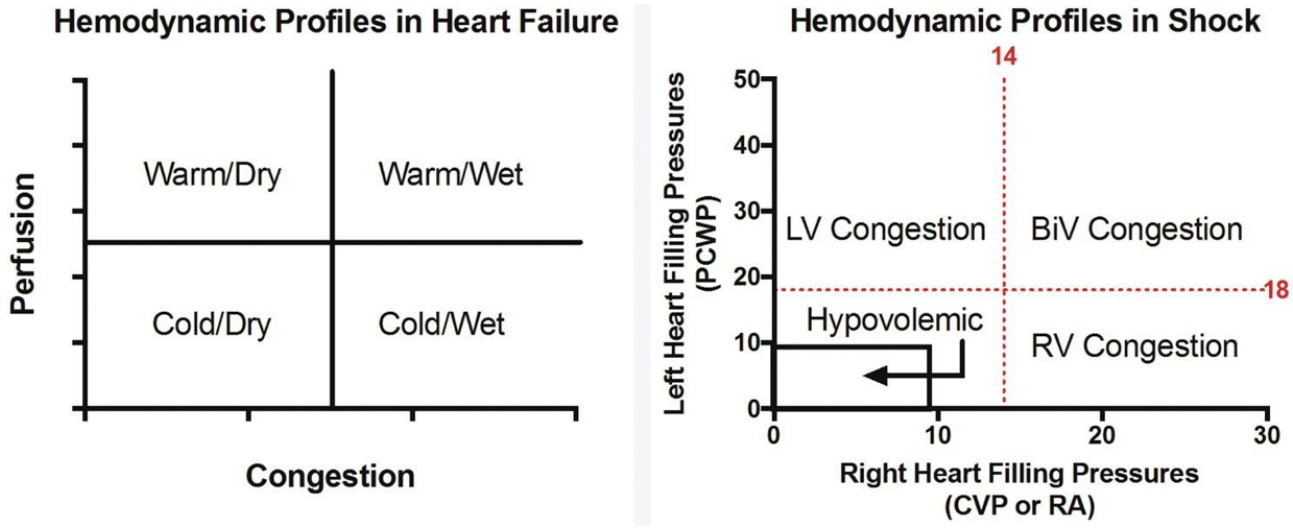

Figure 3 Congestive profiles in cardiogenic shock. Clinical assessment of hemodynamic conditions in decompensated heart failure is traditionally categorized into four groups based on systemic perfusion and congestive status using a two-by-two table. Cardiogenic shock is categorized as having LV-, RV-, or BiV-dominant congestion or hypovolemia. Treatment approaches may be tailored to each of these four categories. BiV: Biventricular; CVP: Central venous pressure; LV: Left ventricular; PCWP: Pulmonary capillary wedge pressure; RA: Right atrial; RV: Right ventricular. Citation: Esposito ML, Kapur NK. Acute mechanical circulatory support for cardiogenic shock: the "door to support" time. F1000Res. 2017 May 22; 6: 737. Copyright© The Authors 2021. Published by Taylor and Francis Group. The authors have obtained the permission for figure using from the Taylor and Francis Group.

A recent single-center study by Lim *et al*[49] looking at patients with CS due to AMI (n = 26) and ESHF (n = 42) who underwent MCS (extracorporeal life support, Impella or temporary ventricular assist devices) suggested that the ESHF-CS patients had higher filling and pulmonary artery pressures but lower oxygen delivery, greater anaerobic metabolism with less severe metabolic acidosis as compared to the AMI-CS patients.

Clinical outcomes in CS patients with PAC and hemodynamic monitoring

More recent data from the CS literature have shown potential short- and long-term mortality implications of invasive hemodynamic data. In the CardShock study, which used an observational, prospective, multicenter, European registry, the CI, CPI and stroke volume index were the strongest 30-d mortality predictors in addition to the previously validated CardShock risk score (Table 1)[6]. Similarly, an earlier study looking at 541 patients with CS who were enrolled in the Should we emergently revascularize Occluded Coronaries for CS (SHOCK) trial registry suggested that CP [odd ratio (OR): 0.60, 95%CI: 0.44-0.83, P < 0.002; n = 181] and CPI (OR: 0.65, 95%CI: 0.48-0.87], P < 0.004; n = 178) are the strongest independent hemodynamic correlate of in-hospital mortality in patients with CS[37], but this was not shown to be predictive in a more recent study involving a large multi-center registry[34]. Data from this large multicenter registry study representing real-world patients with CS in the contemporary acute MCS era suggested that decreased MAP along with an increased RAP significantly associated with higher mortality but PCWP, CPO and CI did not appear to impact mortality consistently[34].

The Nursing Students Competence Instrument shock team protocols used cardiac power output[37], and PAPi[39,51] as hemodynamic criteria for MCS patient selection, assessing response to therapy and for escalation/de-escalation of MCS. In this study, CPO (> 0.6 or < 0.6 W) and lactate (> 4 or < 4 mg/dL) at 12-24 h was shown to have the best prognostic value in predicting survival as patients with persistently higher lactate levels (> 4 mmol/L) and low CPO (< 0.6 W) at 12-24 h while on Impella support will have a higher mortality (50%) and such patients should be evaluated for escalation of MCS[38].

Another retrospective single center study looking at 91 consecutive patients with CS due to primary LV failure, who had PAC within the first 24 h showed that a reduced compliance of the pulmonary artery (CPA), worsened right ventricular dysfunction and was independently associated with increased mortality in patients with CS and increased from 4.5% in the quartile of patients with highest CPA to 43.5% in the lowest CPA quartile[52].

Literature has shown beneficial, non-significant, and deleterious effects of PAC in CS patients (Table 1). In a study by Hernandez *et al*[13] utilizing the NIS database, patients with CS and PAC use had lower mortality (35.1% *vs* 39.2%, OR: 0.91; $P < 0.001$) and lower in-hospital cardiac arrest (14.9% *vs* 18.3%, OR: 0.77; $P < 0.001$) which persisted even after propensity score matching. The Acute Decompensated Heart Failure Syndromes registry which was an prospective, multicenter observational study in which 813 patients (16.8%) were managed with PACs, of which 502 patients (PAC group) were propensity core-matched with 502 controls (control group) showed that PAC guided management in advanced HF patients with CS requiring inotropes (HR: 0.22; 95%CI: 0.08-0.57; $P = 0.002$) and are hypotensive (systolic blood pressure ≤ 100 mmHg; HR: 0.09; 95%CI: 0.01-0.70; $P = 0.021$) had an in-hospital mortality benefit compared to those managed without PAC derived hemodynamic data[22]. Another recent study from the Cardiogenic Shock Working Group looking at 1414 patients with CS showed that use of complete PAC-derived hemodynamic data prior to MCS initiation in 1190 (84%) patients with advanced CS stages was associated with improved survival from CS ($P < 0.001$). Patients with no PAC assessment had worse in-hospital mortality as compared to patients who were assessed with PAC (OR: 1.57; 95%CI: 1.06-2.33)[34]. Another recent study involving 15259 AMI-CS patients treated rapidly with an Impella for MCS along with use of invasive hemodynamic monitoring with a PAC as the first strategy had significantly better survival rates (63%) as compared to the controls (49%) ($P < 0.001$)[53].

Interestingly, a single center study with 129 patients admitted with CS and followed for 5 years showed that the use of PAC in patients with CS was associated with lower short-term (HR: 0.55, 95%CI: 0.35-0.86, $P = 0.008$) and long-term mortality rates (HR: 0.63, 95%CI: 0.41-0.97, $P = 0.035$) even after adjustment for age, gender and the presence of shock upon admission but this benefit was only significant in those patients without acute coronary syndrome (ACS)[21]. This merits future studies on outcomes of PAC in ACS *vs* non-ACS patients.

In contrast, CardShock study was an observational, prospective, multicenter, European registry study in which more than one-third of patients were managed with a PAC. The findings from this study suggest that use of PAC was associated with a more aggressive treatment strategy but did not increase the 30-d mortality[6]. Similarly, a retrospective single center study looking at 91 consecutive patients with CS due to primary LV failure, who had PAC within the first 24 h showed with increased mortality in patients with CS[52]. The discrepancy in the outcomes of mortality with PAC invites future multi-center and international trials as deciding factors to assess the efficacy of PAC in comparison with PAC in AMI-CS sub-set of population.

Limitations

This review is based on the results of currently available observational, single/multicenter, and national cohorts. However, the contribution of confounding factors in these studies in unknown. For instance, use of PAC could be significantly higher in critically ill patients thus confounding the results of in-hospital, 30-d mortality and other relevant clinical outcomes. Therefore, the role of PAC in AMI-CS patients may need to be further explored through well-designed future RCTs.

Future directions

As PAC by itself has no intrinsic therapeutic benefit, future studies focused on testing the workflows and appropriate interventions that would allow prompt acquisition and action on hemodynamic information from the PAC including the timing, selection, management, and weaning of temporary MCS. There is also an ongoing clinical trial looking at whether PAC guided LV mechanical unloading after PCI for acute anterior wall MI will attenuate post-infarct scar and cardiac remodeling. The data from this study may further define the clinical utility of PAC in guiding the need for mechanical LV unloading to help improve clinical outcomes in the setting of AMI-CS.

CONCLUSION

In conclusion, PAC has shown to be useful in monitoring treatment parameters, tailoring treatments, and predict prognosis in AMI-CS patients. Several hemodynamic parameters acquired using PAC are critical to not only defining the etiology of AMI-CS (univentricular or Bi-ventricular) but also vital to the selection, initiation, titration of both pharmacological and MCS devices in these patients that may help better

outcomes. Early identification of CS with a targeted shock to device time of < 90 min along with dedicated multidisciplinary shock teams and designated shock centers will be critical to favorably affecting mortality outcomes in this extremely sick patient population. However, the contradicting benefits of in-hospital and 30-d mortality in AMI-CS requires further understanding of the processes and treatment strategies using larger RCTs.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic value of left atrial size in hypertensive African Americans undergoing stress echocardiography

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Abstract

BACKGROUND

Left atrial (LA) enlargement is a marker of increased risk in the general population undergoing stress echocardiography. African American (AA) patients with hypertension are known to have less atrial remodeling than whites with hypertension. The prognostic impact of LA enlargement in AA with hypertension undergoing stress echocardiography is uncertain.

AIM

To investigate the prognostic value of LA size in hypertensive AA patients undergoing stress echocardiography.

METHODS

This retrospective outcomes study enrolled 583 consecutive hypertensive AA patients who underwent stress echocardiography over a 2.5-year period. Clinical characteristics including cardiovascular risk factors, stress and echocardiographic

(HRPP) and does not replace any other approvals that may be required.

Informed consent statement: This was a retrospective study that the IRB deemed as exempt and so we did not need informed consent forms signed by patients.

Conflict-of-interest statement: The authors have nothing to disclose.

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data were collected from the electronic health record of a large community hospital. Treadmill exercise and Dobutamine protocols were conducted based on standard practices. Patients were followed for all-cause mortality. The optimal cutoff value of antero-posterior LA diameter for mortality was assessed by receiver operating characteristic analysis. Cox regression was used to determine variables associated with outcome.

RESULTS
The mean age was 57 ± 12 years. LA dilatation was present in 9% (54) of patients (LA anteroposterior ≥ 2.4 cm/m^2). There were 85 deaths (15%) during 4.5 ± 1.7 years of follow-up. LA diameter indexed for body surface area had an area under the curve of 0.72 ± 0.03 (optimal cut-point of 2.05 cm/m^2). Variables independently associated with mortality included age [P = 0.004, hazard ratio (HR) 1.34 (1.10-1.64)], tobacco use [P = 0.001, HR 2.59 (1.51-4.44)], left ventricular hypertrophy [P = 0.001 , HR 2.14 (1.35-3.39)], Dobutamine stress [P = 0.003, HR 2.12 (1.29-3.47)], heart failure history [P = 0.031, HR 1.76 (1.05-2.94)], LA diameter ≥ 2.05 cm/m^2 [P = 0.027, HR 1.73 (1.06-2.82)], and an abnormal stress echocardiogram [P = 0.033, HR 1.67 (1.04-2.68)]. LA diameter as a continuous variable was also independently associated with mortality but LA size ≥ 2.40 cm/m^2 was not.

CONCLUSION
LA enlargement is infrequent in hypertensive AA patients when traditional reference values are used. LA enlargement is independently associated with mortality when a lower than "normal" threshold (≥ 2.05 cm/m^2) is used.

Key Words: Mortality; Hypertension; African American; Left atrial enlargement; Stress echocardiography

Core Tip: In hypertensive African American patients referred for stress testing, left atrial (LA) enlargement was infrequent when using the established references values for the general population. Indexed LA Antero-posterior diameter has a superior area under the curve compared to LA diameter alone for discrimination of survivors and non-survivors. LA enlargement is an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or when using a lower reference value derived from our population.

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INTRODUCTION

Left atrial (LA) enlargement is a known predictor of adverse cardiovascular events including atrial fibrillation, stroke and heart failure[1-3]. Hypertension can induce left ventricular (LV) remodeling resulting in increased LV mass and concentric hypertrophy, both of which are associated with LA enlargement[4,5]. In the general population of patients undergoing stress echocardiography, LA enlargement [defined by an anteroposterior (AP) dimension ≥ 2.4 cm/m^2] has been shown to be predictive of myocardial infarction and death[6,7]. LA enlargement has also been shown to be predictive of an abnormal stress echocardiogram[8]. African Americans (AA) have a high burden of cardiovascular disease as well as risk factors including hypertension and diabetes mellitus. Although morbidity and mortality risk in this population is well established, pharmacotherapy is less commonly utilized and AA have higher mortality relative to other ethnicities[9]. The prognostic value of LA enlargement in AA patients

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undergoing stress echocardiography is less clear. Additionally, it is unclear if reference values for LA enlargement established in white populations should be applied in AA. In African American patients, LA remodeling appears reduced relative to whites even when controlling for risk factors such as obesity, age, increased LV mass, and hypertension[10-12]. The lower incidence of atrial fibrillation in AA may be attributed to their smaller LA size and may be related more to inter-racial differences in antero-posterior diameter rather than volume[10,13,14]. Despite less LA remodeling, AA are at increased for cardiovascular events and mortality compared to white patients[15]. However, LA size may also have prognostic value in this racial group[7,16]. The purpose of this study was to assess the prognostic value of LA size in hypertensive AA patients undergoing stress echocardiography and to determine a threshold value of LA enlargement associated with mortality.

MATERIALS AND METHODS

The Indiana University Institutional Review Board approved this study. The study population comprised of 583 consecutive AA patients with a history of hypertension referred for stress echocardiography at an urban community hospital in Indianapolis over a 2.5-year period.

Clinical characteristics

Clinical characteristics were extracted from the electronic health record. Patients were considered to have a smoking history if they were currently using tobacco or were a former smoker. Hypercholesterolemia was defined as total cholesterol greater than 200 mg/dL or if the patient was receiving lipid-lowering therapy. Obesity was defined as a body mass index ≥ 30 kg/m^2. Patients were considered to have a history of coronary artery disease if they previously suffered a myocardial infarction, underwent a revascularization procedure, or had at least 50% diameter stenosis in one or more major epicardial coronary arteries by angiography. A history of heart failure was noted if there was a previous hospitalization for heart failure or a clinical diagnosis made in an outpatient setting with ongoing medical treatment for heart failure.

Two-dimensional echocardiographic measurements and stress echocardiography

LA diameter was measured as the maximum end-systolic anterior-posterior diameter in the parasternal long- or short-axis views. LA enlargement was defined as a dimension ≥ 2.4 cm/m^2 when indexed to body surface area (BSA) based on studies in the general population[7,17]. LA volume index was not routinely assessed because only a minority of subjects had apical views visualizing the entire LA. In a small subset of patients with apical views that included the entire left atrium, LA volume index was also measured using the biplane Simpson's method. LV diameters and wall thickness were obtained in the parasternal long- or short-axis views at the level of the mitral leaflet tips. LV mass was calculated using linear measurements with the following formula:

LV mass = 0.8 × {1.04 [(LVIDd + PWTd + SWTd)^3 – (LVIDd)^3]} + 0.6 g where:
LVIDd = maximum internal diameter at end-diastole.
PWTd = end-diastole posterior wall thickness.
SWTd = end-diastole septal wall thickness.

Left ventricular hypertrophy (LVH) was defined as an LV mass indexed to BSA greater than or equal to 96 g/m^2 for women and 116 g/m^2 for men[18,19]. Relative wall thickness (RWT) was calculated by the formula (2 × PWTd/LVIDd). LVH was further differentiated into concentric and eccentric hypertrophy if RWT was > 0.42 or ≤ 0.42, respectively. Concentric remodeling was defined as a normal LV mass with RWT > 0.42. Ejection fraction was calculated with either the area length method or with the modified Simpson's method for patients with regional wall motion abnormalities.

Treadmill exercise was performed with protocols chosen based on the patient's age and expected exercise ability. Standard end-points were used[20]. The Dobutamine protocol was conducted with a step-wise infusion using previously described methods and endpoints[21]. Images were obtained in the apical four- and two-chamber views and parasternal long- and short-axis views at rest, low-dose (5-10 μg/kg/min), peak dose and recovery in patients undergoing Dobutamine stress. Baseline and immediate post-stress images were obtained in patients undergoing exercise. Experienced echocardiographers blinded to the clinical data and follow-up interpreted the stress echocardiograms. An abnormal stress echocardiogram was defined by the presence of resting or stress-induced wall motion abnormalities in one or more of 16 myocardial

segments[22].

Follow-up

Follow-up data was obtained retrospectively by review of the electronic health records and the Social Security Death Index database[23]. The end-point for the study was all-cause mortality.

Statistical analysis

Continuous variables were reported as mean ± SD. Patient groups were compared using the Student *t*-test for continuous variables and Chi-square test for categorical variables. A two sided *P*-value < 0.05 was considered significant. Receiver-operating characteristic (ROC) curve analysis was used to determine the best cut-point of LA diameter for predicting mortality. The area under the curve (AUC) was calculated for both LA diameter and LA diameter indexed to BSA. The difference between the two AUC values was compared using the correlated area test statistic. Kaplan-Meier analysis of survival was performed using the best cut-point from ROC analysis. Cox proportional hazards model was used to assess predictors of mortality. Variables with *P* value < 0.05 were included in a multivariate analysis employing a forward conditional method. LA diameter was tested on multivariate analysis both as a continuous variable and as a categorical variable using the cut-point of 2.4 cm/m^2 previously established in the general population and the best cut-point determined from ROC analysis in our study population. The relationship between LA diameter index and LA volume index was assessed by linear regression.

Statistical analysis was performed using SPSS version 18 (SPS, Chicago, IL, United States) and the software package ROCKIT[24].

RESULTS

Patient characteristics

Table 1 shows the clinical and stress echocardiographic characteristics of the patient population. Of the 583 patients, 32% were male and the mean age was 57 ± 12 years. A history of heart failure or coronary atherosclerosis was present in 11% and 19%, respectively. Ninety percent of the patients were on anti-hypertensive therapy and the mean resting systolic blood pressure was 140 ± 17 mmHg. An abnormal stress echocardiogram was noted in 17% of patients. Eleven percent had an ejection fraction less than 50%. LVH was present in 25% and concentric remodeling was present in 52%. Only 9% of the study population had an elevated LA diameter index, using the cut-point of 2.4 cm/m^2 as defined in the general population.

LA size and mortality

During follow-up of 4.5 ± 1.7 years (max 6.9 years), 85 patients (15%) died. ROC analysis showed that LA diameter referenced to body surface area had a larger AUC compared to LA diameter alone (AUC of 0.72 ± 0.03 *vs* 0.66 ± 0.03, *P* = 0.002) for distinguishing survivors and those who died. Figure 1 demonstrates a plot of sensitivity and specificity of LA diameter for death during follow-up at 0.05 cm/m^2 intervals. LA size above the reference value (2.4 cm/m^2) had sensitivity and specificity for mortality during follow-up of 24% and 93%, respectively. The best cut-point for predicting death during follow-up (maximum of sensitivity and specificity) was 2.05 cm/m^2, which produced a sensitivity and specificity of 61% and 72%, respectively.

LA size and survival

Figure 2 shows a Kaplan-Meier analysis of cumulative survival using the best cut-point of 2.05 cm/m^2. Overall, survival was 92% if LA diameter index was ≤ 2.05 cm/m^2 and 72% if LA diameter index was > 2.05 cm/m^2 (*P*-value < 0.001).

Predictors of mortality

Table 2 shows univariate predictors for all-cause mortality. There were six independent predictors of mortality by multivariate analysis using the reference cut-point for LA enlargement (2.4 cm/m^2, see Table 3). These included age, smoking history, heart failure, the need for Dobutamine stress, an abnormal stress echocardiogram, and LVH (Chi-square 102). LA enlargement was not a predictor. In a second multivariate analysis using the ROC defined cut-point of 2.05 cm/m^2 for LA size, LA enlargement was found to be an additional independent predictor (Chi-square 107). A

Table 1 Baseline clinical and echocardiographic characteristics

Clinical		Echocardiographic	
Age (yr)	57 ± 12	Ejection fraction (%)	59 ± 10
Male	32%	Reduced EF	11%
Tobacco	60%	LA Diam (cm)	3.7 ± 0.6
Family history of CAD	34%	LA Diam index (cm/m^2)	1.9 ± 0.4
Hyperlipidemia	50%	Abn LA Diam index	9%
Diabetes mellitus	38%	LV mass (g)	172 ± 59
Obesity	45%	LV mass index (g/m^2)	89 ± 29
CAD	19%	LV hypertrophy	25%
Heart failure	11%	Relative wall thickness	0.51
Atrial fibrillation	3%	LV remodeling pattern	
CKD (GFR < 60)	17%	Normal geometry	22%
Systolic BP (mmHg)	140 ± 17	Concentric remodeling	52%
Hypertensive therapy	90%	Concentric hypertrophy	21%
Diuretic	56%	Eccentric hypertrophy	4%
Calcium channel blocker	33%	Dobutamine study	40%
ACE-I/ARB	55%	Abnormal stress echo	17%
Beta-blocker	46%		

Data are presented as the mean value + standard deviation or percent baseline prevalence. CAD: Coronary artery disease; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; BP: Blood pressure; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; EF: Ejection fraction; LA: Left atrial; LV: Left ventricular.

third multivariate analysis considering LA diameter index as a continuous variable rather than a categorical variable also found LA diameter index to be independently predictive in addition to the other six predictors (Chi-square 109).

Comparison of LA anteroposterior diameter and la volume index

In the 57 patients (10%) in whom LA volume index could be assessed, the *R*-value for the correlation of LA diameter index and LA volume index was 0.76. Fourteen subjects (25%) were identified as having LA enlargement by volume index based on a cut-point of 34 mL/m^2 established in the general population[6].

DISCUSSION

Our study had three main findings. LA enlargement in the AP dimension was infrequent in AA with hypertension using reference values established in the general population. LA diameter indexed for BSA had a superior AUC to LA diameter alone. LA size was an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or using the cut-point of 2.05 cm/m^2 for enlargement derived from our population but not when using the cut-point of 2.4 cm/m^2 derived from the general population.

LA remodeling in AA

In this study, only 9% of hypertensive AA were found to have LA enlargement. This is a lower than expected frequency of LA enlargement when compared to the general population. Among a broad sample of the Framingham study used to validate reference values of LA diameter, 22% of men and 29% of women had LA diameters that exceeded reference limits[2]. Compared to the Framingham study cohort, our population had a higher prevalence of hypertension (100% *vs* 33%), heart failure (11% *vs* 1%), and older age (mean age 57.4 years *vs* 50.8 years), which are all variables associated with LA enlargement[3,25,26]. Multiple studies have shown a higher

Table 2 Univariate predictors of all-cause mortality

Characteristic	Event	No event	Hazard ratio (95%CI)	*P* value
Clinical				
Age	62.9	56.5	1.04 (1.02-1.06)	< 0.001
Male sex	40%	32%	1.43 (0.92-2.20]	0.109
Tobacco	79%	57%	2.55 (1.51-4.29)	< 0.001
Fam. History of CAD	28%	35%	0.73 (0.45-1.28)	0.194
Hyperlipidemia	48%	51%	0.91 (0.59-1.40)	0.662
Diabetes mellitus	52%	36%	1.77 (1.16-2.71)	0.008
Obesity	32%	47%	0.56 (0.35-0.88)	0.010
CAD	33%	17%	2.15 (1.37-3.38)	0.001
Heart failure	27%	9%	3.44 (2.13-5.56)	< 0.001
Atrial fibrillation	7%	2%	2.70 (1.18-6.19)	0.019
CKD (GFR < 60)	29%	15%	2.37 (1.48-3.78)	< 0.001
Systolic BP (mmHg)	141.5	140.0	1.01 (0.999-1.02)	0.438
Echocardiographic				
Reduced EF	25%	9%	2.89 (1.76-4.72)	< 0.001
Abn. LA index (2.40 cut-point)	24%	7%	3.16 (1.91-5.22)	< 0.001
Abn. LA index (2.05 cut-point)	61%	28%	3.35 (2.17-5.18)	< 0.001
LV hypertrophy	52%	21%	3.62 (2.36-5.54)	< 0.001
Relative wall thickness	0.51	0.51	0.94 (0.19-4.57)	0.941
LV diastolic diameter	4.54	4.34	1.57 (1.15-2.13)	0.005
LV systolic diameter	3.24	2.98	1.54 (1.20-1.99)	0.001
Fractional shortening	0.30	0.32	0.05 (0.00-0.57)	0.017
IV septum thickness	1.20	1.11	2.51 (1.19-5.33)	0.016
LV post. wall thickness	1.13	1.07	2.48 (1.04-5.92)	0.040
Dobutamine study	68%	35%	3.55 (2.25-5.60)	< 0.001
Abnormal stress	35%	14%	2.76 (1.77-4.31)	< 0.001

CAD: Coronary artery disease; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; BP: Blood pressure; EF: Ejection fraction; Abn. LA index: Abnormal left atrial diameter indexed to body surface area (cm/m^2); LV: Left ventricular; IV: Intraventricular; Post.: Posterior; See text for further explanation of variables.

prevalence of LA enlargement in white patients with hypertension (weighted average 37.3%)[27-30].

AA have a higher burden of hypertension and cardiovascular mortality with lower rates of pharmacologic interventions[9]. However, when traditional reference values for LA size are used, AA patient mortality risk may be underappreciated. Several studies have shown reduced LA remodeling in AA patients. In a cohort of men with hypertension (58% AA), investigators found that as age increased white patients had a greater mean LA diameter than AA patients[12]. Similarly, in a cohort of 3882 elderly subjects, AA men had significantly smaller mean LA diameter (1.9 mm LA dimension)[11]. Additionally, in a study evaluating the effect of race on the prevalence of atrial fibrillation, AA subjects were demonstrated to have significantly smaller LA diameters (2 mm smaller AP LA dimension)[10].

A more recent evaluation of 129 AA compared with 326 whites showed that in the presence of hypertension, the former had significantly smaller LA size despite similar ventricular relative wall-thickness, diastolic function, and 6-min walk test[31]. Why LA remodeling might be reduced in AA remains unclear although there is speculation that genetic and environmental factors influence the structure of the hearts of AA patients

Table 3 Multivariate predictors of all-cause mortality

	Reference cut-point for Abn. LA Diam			Best cut-point for Abn. LA Diam		
	Chi-square 102			Chi-square 107		
Predictor	Wald	HR (95%CI)	*P* value	Wald	HR (95%CI)	*P* value
Age (per 10 yr)	11.4	1.40 (1.15-1.71)	0.001	8.2	1.34 (1.10-1.64)	0.004
Tobacco	11.9	2.61 (1.51-4.49)	0.001	11.9	2.59 (1.51-4.44)	0.001
Heart failure	6.4	1.92 (1.16-3.20)	0.012	4.7	1.76 (1.05-2.94)	0.031
LVH	17.6	2.54 (1.64-3.93)	<0.001	10.5	2.14 (1.35-3.39)	0.001
Abnormal stress	5.9	1.79 (1.12-2.86)	0.015	4.6	1.67 (1.04-2.68)	0.033
Dobutamine study	8.5	2.09 (1.27-3.43)	0.004	8.9	2.12 (1.29-3.47)	0.003
LA index ≥ 2.40	–	–	NS	[1]	[1]	[1]
LA index ≥ 2.05	[1]	[1]	[1]	4.9	1.73 (1.06-2.82)	0.027

[1]Variable not included in calculation.

Column (Reference cut-point for Abn. LA Diam) demonstrated a multivariate analysis using the reference cut-point of 2.40 cm/m^2 for defining an abnormal left atrium and column (Best cut-point for Abn. LA Diam) demonstrates a multivariate analysis using the best cut-point of 2.05 cm/m^2. ABN: Abnormal; DIAM: Diameter, LVH: Left ventricular hypertrophy; LA index: Left atrium diameter index (cm/m^2).

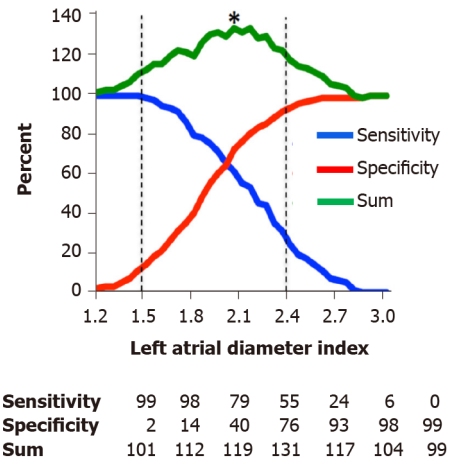

Figure 1 Comparison of sensitivity and specificity of left atrial diameter index cut-points. Sensitivity, specificity, and the summation of sensitivity and specificity are plotted for left atrial diameter index at 0.05 cm/m^2 intervals. Sensitivity is shown in blue, specificity is shown in red, and the summation of the two is shown in green. The reference upper and lower limits of normal (2.4 cm/m^2 and 1.5 cm/m^2, respectively) are indicated with dashed lines. The optimal cut-point that maximizes sensitivity and specificity was 2.05 cm/m^2 and is indicated with an asterisk (*) on the graph.

compared to hearts of white patients. Badertscher *et al*[31] found that AA have lower levels of collagen 1 telopeptide and higher levels of collagen 1 propeptide suggesting that different collagen homeostasis may contribute to atrial remodeling. While AA have a similar average LV mass index as whites, they have significantly smaller LV cavities and thicker LV walls, with a high percentage demonstrating the "concentric remodeling" pattern of cardiac structure[33-35]. This pattern was seen in a majority of our population with 52% displaying concentric remodeling. Similar genetic and environmental factors that produce differences in LV remodeling may also contribute to race related differences in LA remodeling. Gottdiener *et al*[12] proposed the possibility that in parallel with an increased LV wall thickness, there might also be a similar increase in LA wall thickness, which might reduce wall compliance and the resultant cavity size of the LA.

An additional possibility is that reduction of anterior-posterior LA dimension in AA is due to differences in chest and mediastinal structures rather than a consequence of true differences in LA remodeling. The LA is a relatively low-pressure chamber and its size and configuration is influenced by its surrounding structures. Manolio *et al*[11] reported that racial differences in LA dimensions were partially mitigated when

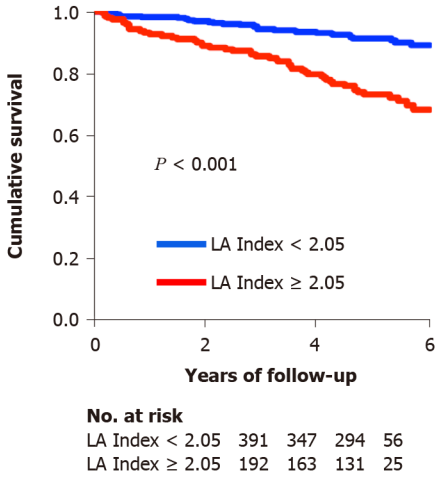

Figure 2 Kaplan Meier curve. Cumulative survival estimates are compared between patients with left atrial (LA) diameter index values above (blue line, LA index < 2.05) and below (red line, LA index ≥ 2.05) the optimal cut-point that maximizes sensitivity and specificity for death. LA: Left atrial.

accounting for chest dimensions and spirometric lung volumes. Given the close proximity of the ascending aorta to the LA, enlargement of the aortic root might limit the ability of the LA to expand in the antero-posterior direction. AA patients are known to have a higher than expected prevalence of aortic regurgitation, which was independently predicted by aortic root size[35]. In the small cohort of patients in our study who had LA volume measurements, the proportion (25%) that had enlargement remained lower than expected.

Prediction of mortality by LA dimension

From ROC analysis, the optimal cut-point for an abnormal LA diameter that predicts mortality in AA was well within the normal reference range. In contrast, the guidelines-defined cut-point had very low sensitivity for predicting mortality in our study population. While LA dilation is infrequent in AA, LA diameter does hold prognostic significance in this population when a lower threshold for abnormal is used.

LA diameter indexed to BSA improved prediction of mortality over LA diameter alone. Indexing of echocardiographic measurements to BSA is currently recommended by the American Society of Echocardiography but it has been argued that correcting for body size inappropriately "forgives" for obesity[36]. Our population included a large proportion of AA females, a population known to have a high prevalence of obesity[37]. Forty-five percent of our population was obese. Therefore, use of indexed LA diameters raises the potential of overcorrection for obesity in our study. However, we found that indexed LA diameter had superior prognostic value over LA diameter alone suggesting that the correction is appropriate in our population. To our knowledge, this is the first study to demonstrate superiority of indexed LA diameter over LA diameter alone.

Comparative long term prognostic value of la dimension

Our data found LA diameter index to be an independent predictor of all-cause mortality in addition to heart failure, age, smoking history, LVH, an abnormal stress echocardiogram, and the requirement for Dobutamine stress. Our study demonstrated that LA diameter predicted long-term outcome as survival curves continued to separate at 6 years of follow-up. Similar to our finding, data from the Framingham study found LA diameter to be predictive of death during 8 years of follow-up[2]. Within an AA cohort of the Atherosclerosis Risk in Communities study, those with the highest quintile of LA diameter had a higher risk of mortality during a median follow-up of 9.8 years[38]. Several investigations have suggested that LA enlargement serves as a marker of chronic diastolic dysfunction over time and thus accounts for the accumulated risk of elevated cardiac filling pressures for cardiovascular events[39]. Our results suggest different reference values are needed for AA patients to accurately evaluate their cardiovascular risk. This may also improve treatment in hypertensive AA patients which may translate to decreased mortality.

Limitations of this study

The primary limitation of this study is our use of LA diameter as opposed to LA volume index. LA volume is currently recommended by the American Society of Echocardiography as the most accurate measure of true LA size[6]. Unfortunately, majority of the patients in our study had truncated apical images utilized for stress echocardiography so we were unable to derive information on LA volume except in a minority of patients. In the small subset of patients there was a reasonable correlation between LA diameter and volume index. While LA volume is clearly a more accurate measure of true LA size, LA volume may be only marginally superior at identifying cardiovascular disease[26,40]. For patients undergoing stress echocardiography, LA diameter index has shown to offer adequate prognostic value and is probably acceptable for those with difficult visualization of the complete LA[7].

An additional limitation of our study was the large percentage of female subjects. Sixty-eight percent of our population was female. How this might affect the applicability of our data for predicting mortality in AA men is unknown, but previous data have suggested that indexing for body size nearly completely accounts for gender differences in LA dimensions[41].

CONCLUSION

LA enlargement is infrequent in AA with hypertension referred for stress testing when using the established references values for the general population. Indexed LA AP diameter has a superior AUC to LA diameter alone for discrimination of survivors and non-survivors. LA enlargement is an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or when using a cut-point derived from our population.

ARTICLE HIGHLIGHTS

Research background

African Americans (AA) have higher cardiovascular (CV) risk factors including hypertension and mortality compared to other races. Left atrial (LA) size has shown prognostic value in white patients.

Research motivation

Prior research has suggested AA have smaller LA volumes and standard references values may not apply.

Research objectives

We investigated the prognostic value of LA size in hypertensive AA patients undergoing stress echocardiography.

Research methods

In this retrospective cohort study, we evaluated 583 consecutive AA patients with a history of hypertension referred for stress testing and evaluated LA diameter in the Antero-posterior window.

Research results

LA dilatation was present in 9% (54) of patients [LA anteroposterior (AP) ≥ 2.4 cm/m^2]. There were 85 deaths (15%) during 4.5 ± 1.7 years of follow-up. LA diameter indexed for body surface area had an AUC of 0.72 ± 0.03 (optimal cut-point of 2.05 cm/m^2). Variables independently associated with mortality included age (P = 0.004), tobacco use (P = 0.001), left ventricular hypertrophy (P = 0.001), need for pharmacologic dobutamine stress (P = 0.003), heart failure history (P = 0.031), LA diameter ≥ 2.05 cm/m^2 (P = 0.027), and an abnormal stress echocardiogram (P = 0.033). LA diameter as a continuous variable was also independently associated with mortality but LA size ≥ 2.40 cm/m^2 was not.

Research conclusions

LA enlargement is infrequent in AA with hypertension referred for stress testing when using the established references values for the general population. Indexed LA AP

diameter has a superior prognostic value to LA diameter alone for discrimination of survivors and non-survivors. LA enlargement is an independent predictor of mortality on long-term follow-up when assessed as a continuous variable or when using a cut-point derived from our population.

Research perspectives

References values for LA size in AA patients may need to be adjusted to more accurately reflect CV risk and which may translate to more aggressive pharmacologic management.

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ORIGINAL ARTICLE

Observational Study

Highly sensitive troponin I assay in the diagnosis of coronary artery disease in patients with suspected stable angina

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ORCID number: Indra Ramasamy 0000-0003-4079-5429.

Author contributions: Ramasamy I was responsible for the conception, design and analysis and presentation of the data and writing the manuscript.

Institutional review board statement: The study was carried out according to the Declaration of Helsinki and the NHS Data Protection Act. The study was approved by the Research and Ethics Committee of the Worcester Acute Hospitals NHS Trust.

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Data sharing statement: The raw data is stored in the Laboratory Quality Management System of The Worcester Royal Hospital, and is available following anonymization of patient identifiable information. The full data set can be requested from the corresponding author upon approval of the paper proposal using the data.

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Abstract

BACKGROUND

Evaluation of suspected stable angina patients with probable coronary artery disease (CAD) in the community is challenging. In the United Kingdom, patients with suspected stable angina are referred by community physicians to be assessed by specialists within the hospital system in rapid access chest pain clinics (RACPC). The role of a highly sensitive troponin I (uscTnI) assay in the diagnosis of suspected CAD in a RACPC in a "real-life" setting in a non-academic hospital has not been explored.

AIM

To examine the diagnostic value of uscTnI (detection limit 0.12 ng/L, upper reference range 8.15 ng/L, and detected uscTnI in 96.8% of the reference population), in the evaluation of stable CAD in a non-selected patient group, with several co-morbidities, who presented to the RACPC.

METHODS

One hundred and seventy two RACPC patients were assigned to either functional or anatomical testing according to the hospital protocol.

RESULTS

The investigations offered to patients were exercise tolerance test 7.6%, 24 h ECG 1.2%, Echocardiogram 14.5%, stress echocardiogram 8.1%, coronary computed tomography angiography (CCTA) 12.8%, coronary angiogram 13.4%, 17.4% were diagnosed with non-cardiac chest pain, 3.5% treated as stable angina, 8.2% reviewed by cardiologists, electronic medical records were not available in 10.4%. Receiver operating characteristic curves for CAD used uscTnI values measured in patients who underwent functional testing, angiogram or CCTA. Values > 0.52 ng/L showed 100% sensitivity and at > 11.6 ng/L showed 100% specificity. In the range > 0.52-11.6 ng/L, uscTnI may not have the same diagnostic potential. In patients assigned to coronary angiogram higher concentrations of uscTnI was

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associated with severe CAD. Low levels of uscTnI and low pre-test probability of CAD (QRISK3) may decrease patient numbers assigned to CCTA.

CONCLUSION
The uscTnI diagnostic cut-off values in a RACPC will depend on patient population and their presenting co-morbidity. In the presence of clinical comorbidities and previous CAD the uscTnI needs to be used in conjunction with clinical assessment.

Key Words: Rapid access chest pain clinic; Suspected stable angina; Troponin I; Coronary artery disease; Coronary angiogram; Coronary computed tomography angiography

Core Tip: In the United Kingdom, patients with suspected stable angina are referred to rapid access chest pain clinic (RACPC) by community physicians for assessment by hospital specialist medical practitioners. We evaluated the value of a new highly sensitive cardiac troponin I assay in the management of patients with suspected coronary artery disease (CAD) in a RACPC. Patients admitted for further assessment and preselected for either coronary computed tomography angiography or coronary angiogram the assay may indicate the severity of CAD. The diagnostic cut-off values of the assay is determined by the patient population and existing co-morbidities.

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INTRODUCTION

Chest pain is a common presenting symptom in primary care, of which there are many possible causes. The most important of these in terms of subsequent morbidity and mortality are the acute chest pain coronary syndromes (acute coronary syndrome, ACS) comprising unstable angina and acute myocardial infarction (AMI). Current medical practice in the United Kingdom is to transfer patients with ACS urgently to hospital emergency care. In contrast, the differential diagnosis of chronic chest pain is wide and includes cardiac pain as exertional chest pain or stable angina. The diagnosis of coronary heart disease (CHD) may be missed in these patients[1].

New models of assessment have been introduced. In the United States, chest pain observation units provide short stay inpatient care where chest pain is monitored and investigated prior to either formal admission or discharge[1]. In England, the government's National Service Framework guideline recommended outpatient rapid access chest pain clinic (RACPC) in which people who develop new symptoms that their community physician thinks might be due to stable angina can be assessed by a specialist within 2 weeks of referral[2]. Unlike patients with ACS, who are investigated in emergency care units, evaluation of patients with stable symptoms and suspected CHD (stable angina) in a RACPC may be a challenge. The ability to recognise the high-risk patient with stable angina and an increased risk of progression to AMI may be difficult on clinical grounds alone and may require further functional testing.

There can be considerable variation in which possible stable angina is assessed in RACPC. The American College of Cardiology (ACC)/American Heart Association (AHA)[3,4] and European Society of Cardiology (ESC) recommend clinical risk scores [5] which incorporate age, sex and chest pain presentation to calculate pre-test probability. Pre-test probability is determined by the Diamond-Forrester Coronary Artery Surgery Study[3,4] and the updated version the Coronary Artery Disease consortium (CADC) clinical risk scores. NICE guidelines, United Kingdom[6] suggest a symptom based clinical assessment followed by coronary computed tomography angiography (CCTA) for those in the possible angina group. CCTA identifies obstructive and nonobstructive coronary artery disease (CAD) and allows the quanti-

fication of coronary artery calcium[7]. Guidelines recommend a stepwise approach for decision making in suspected stable CAD. A clinical assessment of the probability of stable CAD is followed by non-invasive testing, based usually on the availability of non-invasive tests. Characteristics of tests, sensitivity and specificity, used to diagnose CAD are given in the ESC guidelines[5]. Some of the functional tests available are: Exercise electrocardiogram (ECG), exercise stress echocardiography, dobutamine stress echocardiography and coronary CCTA. A variety of factors affect test choice which include local availability of specific tests, local expertise in test performance and interpretation, or the presence of diagnostic or prognostic questions addressed better by one form of test. Local availability and tariff may make clinicians choose one particular test. Current literature either suggest that CCTA and functional tests can serve equally well as first-line tests for patients with suspected CAD[8,9] or that CCTA may have a benefit over more standard testing[10].

An elevated cardiac troponin (cTn) has long been a pre-requisite for the diagnosis of AMI and has become a diagnostic gold standard for AMI[11]. The value of cTnI in stable angina patients, in contrast to those with ACS and myocardial infarction, is not well understood. The high sensitive troponin assays were able to measure troponin in approximately 50% of normal, healthy individuals. In the most very highly sensitive troponin assays (uscTnI) the cTnI is measurable in almost all healthy individuals[12]. Studies have investigated the use of uscTnI in the early diagnosis of CAD in selected groups of patients without known clinically relevant heart disease. In stable symptomatic patients undergoing coronary computed tomography angiography (CCTA) elevated concentrations of uscTnI was associated with CAD[7,13]. The studies suggest that though uscTnI was not sufficient to use the test as a single standalone test, the test may improve the selection of patients for further investigation and treatment [14,15]. The clinical utility of uscTnI is not fully defined in a RACPC either in (1) differentiating non acute chest pain of uncertain origin; or (2) detecting patients with functionally relevant CAD at risk of progression to AMI. Further, the role of uscTnI in the management of patient with established CHD presenting to a RACPC is yet to be evaluated.

In the United Kingdom, QRISK3 calculations are used in the assessment of 10 year risk of cardiac events. In Worcester, RACPC are staffed by specialist cardiac nurses, in a service led by a specialist cardiologist. Currently they use QRISK3 as part of their initial clinical evaluation of patients, prior to stratifying patients into non-invasive techniques or to identify patients requiring further invasive testing or immediate angiography. In this report we describe the use of uscTnI in the investigation of patients, presenting to the RACPC with probable stable angina. Cardiac troponin assays are not currently used in the investigation of patients with suspected stable CAD in the RACPC. The current study, to our knowledge for the first time, describes the use of uscTnI in the investigation of stable CAD in a RACPC in a non-teaching "district general" hospital in the United Kingdom. Unlike previous studies, this study has been carried out in a non-selected group of patients, and included those with previously known cardiac disease, who presented with suspected stable angina to the RACPC.

MATERIALS AND METHODS

Study population

We investigated 172 patients referred to the RACPC at the Worcester Royal Hospital between the period September 2018 and March 2019. Blood samples were taken at the community physician surgery prior to review by RACPC, which was within 2 wk of referral by the community physician. The patients were outpatients whose physicians believed that non urgent cardiovascular testing was necessary for suspected CAD. Patients with stable chest pain or chest pain equivalent and those with previous history of CAD who presented with chest pain were included in the study. Seven patients with previous cardiac pathology were referred to RACPC by their physicians. A sixty two year old male with a prior history of CAD and cardiac stent placement who presented with increasing chest pain was assigned to coronary angiography. Three patients with previous coronary artery bypass graft or stent insertion were classified as non-cardiac chest pain or were already under the care of cardiologists. The mean age of all patients was 62.1 years (range 23-88 years) of which 51.1% were women. The proportion of patients (given as percentage of the study patients) with cardiovascular risk factors were, with hypertension (51%), current or ex-tobacco users (44%), dyslipidemia (48%), diabetes (27%), family history of CAD (68%); increased

BMI was recorded in 29% of the patients. Calculated QRISK3 ranged from 1-88%, mean 16%. Patient electronic medical notes both inpatient and outpatient notes were reviewed and followed for major adverse cardiac events for a period of six months following the end of the study. Receiver operating characteristic curves (ROC), statistical analysis were performed using GraphPad Prism (United Kingdom) and graphs were constructed using the same software.

In addition, the patients had routine tests (renal function, liver enzymes, serum calcium, HbA1c) to which uscTnI was added as part of the performance assessment of pathway that included uscTnI in the clinical evaluation of the patient. The study was carried out according to the Declaration of Helsinki and the NHS data protection policy. Patients were excluded if they required urgent evaluation for suspected ACS.

Patient follow up care

Following clinical assessment the patients with suspected stable CAD were assigned to 24 h monitoring ECG, exercise tolerance test (ETT), echocardiogram (echo), exercise or pharmacological stress echo, CCTA, coronary angiogram and percutaneous coronary intervention (PCI), medical treatment for angina, or were discharged as clinical assessment suggested non-cardiac chest pain. More complex patients were designated for review by specialist cardiologists.

The results of the uscTnI test were not provided to the RACPC staff and subsequent care of the patient was dependent on his or her clinical assessment of the subject, which was independent of uscTnI value.

Diagnostic testing

The patient sera were collected within 24 h of phlebotomy, stored and transported frozen in dry ice (quality controlled by the courier) to Barcelona prior to measurement of uscTnI. uscTnI was measured by the Singulex Clarity (United States) assay. The detection limit of the assay was 0.12 ng/L. The assay CV was 10% at 0.53 ng/L. Imprecision was 3.16% to 12% for the assay. uscTnI was detectable in 96.8% of healthy individuals. The 99th percentile for healthy individuals was 8.15 ng/L. The assay was stated as outperforming other high sensitivity cTnI assays in terms of analytical sensitivity[12,16].

For the exercise tolerance test the Bruce protocol was followed with ECG recording. A semi-supine bike was used for exercise stress echocardiogram (increasing the workload by 25 Watts every 2 min until the 85% or more of target (heart rate) HR is achieved. Target heart rate was calculated by 220 - age). For dobutamine stress echocardiogram with ischaemia the protocol used was: 10 μg/kg/min and infused up to a maximum 40 μg/kg/min in 10/μg/kg/min increments at every 3-5 min according to HR response (to achieve a minimum. of 85% of the target HR for the test to be diagnostic). If target HR was not achieved at 40 μg/kg/min, iv atropine was given. CCTA was done on a 64-slice CT scanner (Toshiba Acquilion Cx or Acquilion Prime, Toshiba). All scans are reported by specialist cardiologists or radiologists. The stenosis was graded as mild (< 50%), moderate (50%-70%) or severe (> 70%).

Following coronary angiogram degree of stenoses was graded as normal, mild (< 50% stenosis), moderate (50%–74% stenosis), severe (> 75%-99% stenosis), and critical (> 99% stenosis). The angiogram was reported by specialist cardiologists.

RESULTS

Patient demographics following clinical assessment by RACPC is shown in Table 1. The flow chart of patients according clinical assessment is given in Figure 1 and the uscTnI values according to further testing carried out for functional CAD is summarised in Table 2. The investigations offered to patients were ETT 7.6%, 24 h ECG 1.2%, Echo 14.5%, stress echo 8.1%, CCTA 12.8%, coronary angiogram 13.4%, 17.4% were discharged with the diagnosis of non-cardiac chest pain, 3.5% were diagnosed and treated as stable angina, 4.1% were further referred to specialist cardiologists, 4.1% were known cardiology patients, electronic medical records were not available in 10.4%, 2.9% were admitted with ACS during the study. The diagnostic conundrum presented by individual patients is summarised according to outcome measures, prior to analysis of the data by ROC curves.

Outcome measures

The patients are divided into follow-up testing subgroups. Clinical details of patients presenting with uscTnI > upper quartile of the reference range (6 ng/L) are described

Table 1 Patient characteristics

	Non-cardiac chest pain	ETT	ECG	Angina	Review	Lost to follow-up	Previous cardiac problems	Stress Echo (negative)	Stress Echo (positive)	Echo (negative)	Echo (pos)	CCTA (negative)	CCTA (positive)	Angiogram (negative)	Angiogram (positive)	ACS
Age (yr)	57 (23-88)	54 (36-66)	66 (62-69)	73 (66-79)	66 (43-84)	64 (41-84)	71 (67-87)	63 (49-82)	68	67 (43-84)	72 (55-83)	53 (34-63)	62 (51-77)	59 (50-65)	58 (46-81)	69 (62-86)
Sex (M/F)	15/15	11/2	0/2	1/5	5/2	4/14	3/4	4/9	1/0	10/9	5/1	4/8	5/5	3/3	12/5	2/3
BMI (> 25 kg/m$^{2)}$ (*n*)	9	4	1	2	4	8	0	2	1	4	0	4	5	1	6	2
Diabetes (*n*)	2	4	0	1	2	1	0	2	0	2	2	2	1	0	4	3
Hyperlipidmia (*n*)	11	8	1	2	4	6	4	6	1	11	5	5	7	2	11	3
Hypertension (*n*)	10	7	2	4	4	7	3	7	1	13	5	4	8	3	11	2
Family History of CAD (*n*)	6	5	1	0	3	7	0	3	0	5	2	8	6	3	10	0
Smoker (*n*)	11	5	0	4	5	9	1	6	0	10	4	3	9	1	8	0
Past History MI/stent/CABG (*n*)	2	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
Aspirin (*n*)	7	2	0	2	1	6	3	4	0	4	2	4	5	2	6	2
Statin (*n*)	5	3	0	2	1	3	5	3	1	7	4	1	2	0	10	1
ISMN/Nitroglycerin (*n*)	9	1	1	5	3	6	4	7	1	7	3	4	5	3	8	2
Anti-hypertensive (*n*)	7	7	1	2	3	2	5	4	1	8	4	2	1	1	14	2
Creatinine (μmol/L) (*n*)	83 (52-122)	79 (54-100)	77 (71-82)	83 (70-103)	82 (51-98)	75 (47-109)	71 (36-95)	72 (56-88)	84	78 (52-102)	83 (63-103)	71 (52-88)	72 (52-99)	78 (56-98)	81 (46-134)	76 (65-86)
QRISK3%	2-> 88	12 (7-40)	9 (5-13)	22 (6-34)	22-41	19 (2-58)	NA	13 (3-36)	32	1 to > 40	12 to 45	9.4 (1-35)	22 (6-37)	8 (2-16)	8 to > 40	
n	30	13	2	6	7	18	7	13	1	19	6	12	10	6	17	5

ETT: Exercise tolerance test; CCTA: Coronary computed tomography angiography; ISMN: Isosorbide mononitrate; ACS: Acute coronary syndrome; CABG: Coronary artery bypass graft; MI: Myocardial infarction; ECG: Electrocardiogram.

in each group.

Patients classified as non-cardiac chest pain: Thirty patients were classified as non-cardiac chest pain and not investigated further by the RACPC. Seventy one year old

Table 2 uscTnI values by patient subgroup according further testing following clinical review

Subgroup	uscTnI ng/L (minimum value)	uscTnI ng/L (average value)	uscTnI ng/L (maximum value)	*n*	*P* value
Referred back to the community practitioner (non-cardiac chest pain)	0.71	2.9	17	30	
Exercise test	0.97	2.6	9.7	13	
24 h ECG	1.9	2.3	2.6	2	
Diagnosed angina, treated with medication	1.8	5.0	9.2	6	
Advised further review by specialist cardiologist	1.0	12	70	7	
Lost to follow up	0.8	2.6	7.5	18	
Previously diagnosed with cardiac problems and under the care of a cardiologist	1.5	7.2	33.2	7	
Echo (normal)	0.46	3.0	8.6	19	
Echo (mild abnormalities)	2.47	6.44	17.0	6	
Stress echo (negative)	0.98	2.1	3.9	13	
Stress echo(positive)	3.1	3.1	3.1	1	
CCTA (negative)	0.58	2.8	9.3	12	NS
CCTA (positive)	1.1	2.7	8.7	10	
Angiogram(negative)	1.1	1.8	2.2	6	< 0.05
Angiogram(positive)	0.94	7.3	49	17	

ECG: Electrocardiogram; CCTA: Coronary computed tomography angiography; NS: Not significant.

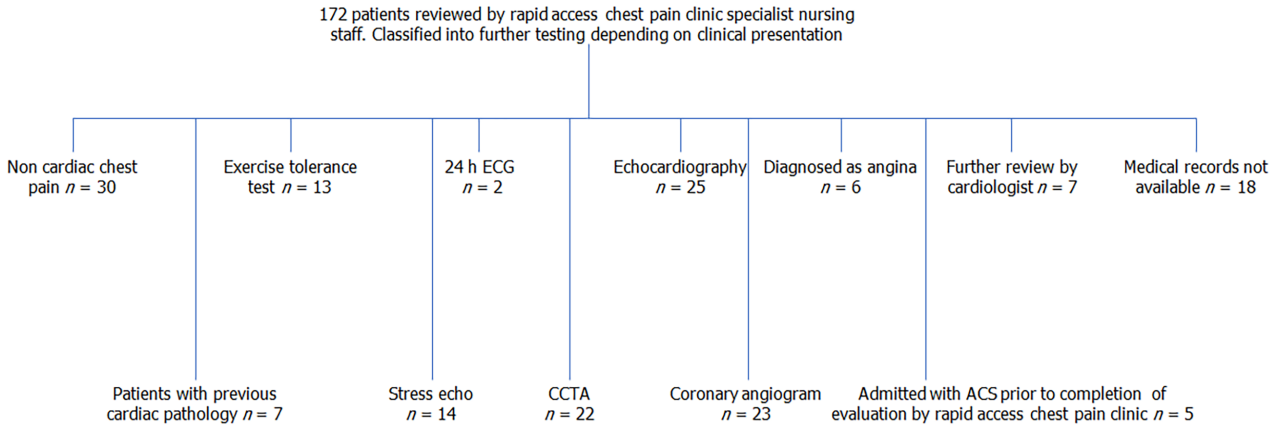

Figure 1 Patient flow chart according to further investigation.

female patient with a past history of AMI, coronary artery bypass surgery and uscTnI = 16.6 ng/L, was referred to the heart failure clinic with severe left ventricular systolic dysfunction. Two patients with uscTnI at the upper quartile of the reference range: 71year old female with persistent gastric reflux and uscTnI = 8.2 ng/L, QRISK3 score = 12%, and 89 year man with a history of pulmonary embolism, idiopathic pulmonary fibrosis and osteoarthritis with a uscTnI=7.7 ng/L, QRISK3 score rated as high, were categorised as non-cardiac chest pain.

Exercise tolerance test: Thirteen patients had a negative exercise tolerance test. A 55 year old male with constant chest pain and an uscTnI value of 9.7 ng/L and QRISK3 score of 9% assigned to ETT developed a non-limiting chest pain during exercise and was described as low risk.

Three patients with ECG changes suggestive of ischemia and a further patient with a normal exercise tolerance test and typical angina pain underwent cardiac catheterisation and coronary angiogram. These patients are included in the section with the group assigned to coronary angiography.

24 h ECG monitoring: Twenty four hour ECG monitoring detected ectopic activity with ventricular and supraventricular ectopics in two patients.

Echocardiography: Twenty five patients were designated for investigation with echocardiography. One 78 year old female with an uscTnI = 8.6 and QRISK3 = 20% was diagnosed with atrial fibrillation. A further 78 year old male with uscTnI at the upper quartile of the reference range, 6.2 ng/L, QRISK3 = 54% and normal systolic and ventricular function was diagnosed with angina and his medication was changed to a beta-blocker. He was diagnosed with adenocarcinoma of the prostate 12 years previously and treated with androgen blockade and radiotherapy. He was referred for further review by cardiology specialists.

Echocardiography diagnosed mild abnormalities in six patients. Two patients were diagnosed with recent onset atrial fibrillation (71 year old male with uscTnI = 9.3 ng/L) and pre-existing left bundle branch block (79 year old male with uscTnI = 17.0 ng/L).

Angina: Six patients were diagnosed with and treated as stable angina. Two patients had measured uscTnI values of 7.9 and 9.2 ng/L.

Review by a specialist in cardiology: Seven patients were further reviewed by a medical specialist in cardiology. A 63 y old male patient with a prior history of cardiovascular accident, subarachnoid haemorrhage and alcohol dependence and uscTnI value of 70 ng/L was treated with beta-blockers and placed under surveillance.

Lost to follow up: Medical notes following RACPC evaluation were not available for eighteen patients. A 74 year old female with an uscTnI = 7.5 ng/L and QRISK3 of 46% was diagnosed with stable angina and referred by RACPC staff for review by specialist cardiologists. Further follow-up of this patient was not recorded in the medical electronic notes.

Patients with previous cardiac pathology: Seven patients with previous cardiology pathology were reviewed by cardiologist. A 72 year old male with prior history of coronary artery bypass graft 9 years previously presented with a uscTnI of 32.2 ng/L. His medication was changed to include statins and ISMN (Isosorbide mononitrate). A further 76 year old female with known AF presented with an uscTnI=6.1 ng/L.

Stress echocardiography: Thirteen patients categorised to stress echocardiography, were classified as normal. A single patient showed mild inducible ischemia.

CCTA: Of the twenty two patients allocated to CCTA 12 were classified as normal, and 6 with mild CAD and 4 with severe disease. The mean uscTnI concentration in patients with obstructive CAD was 2.7 (range 1.1-8.7) ng/L and without CAD was 2.8 (range 0.6-9.3) ng/L. There was considerable overlap between the values. Fifty nine year old female with no relevant previous history and uscTnI = 9.3 ng/L and QRISK3 score 5%, and a 42 year old female with a history of gastroesophageal reflux and uscTnI = 7.1 ng/L and QRISK3 < 2% had normal CCTA. Sixty one year old male with uscTnI = 8.7 ng/L and QRISK3 score of 25% demonstrated severe obstructive disease. A further 62 year old female with a QRISK3 of 17% and uscTnI = 1.2 ng/L demonstrated severe CAD following CCTA and presented with ACS and Non-ST segment elevation myocardial infarction (NSTEMI) prior to completion of investigation. A plot of QRISK3 scores and uscTnI (Figure 2) suggested that 3/22 patients with an uscTnI < 1 ng/L and QRISK3 score < 10% showed a normal CCTA.

Coronary angiography: Twenty three patients underwent coronary angiography. Six patients showed normal coronary arteries. Fifty nine year old male, with definite angina pain, uscTnI = 2.23 ng/L and QRISK3 = 8%, underwent ETT which showed ventricular bigeminy. Investigative echo and coronary angiogram were classified as normal.

Coronary angiography detected severe disease in two patients: 58 year old male with uscTnI = 3.2 ng/L, QRISK3 13%, 53 year old male with uscTnI = 48.5 ng/L and QRISK3 10%. ETT detected ischemic changes in both patients. A further patient, 49 year old male with uscTnI = 1.4 ng/L and QRISK 23%, and normal ETT, and referred for further investigation for 'typical' angina pain, developed NSTEMI prior to

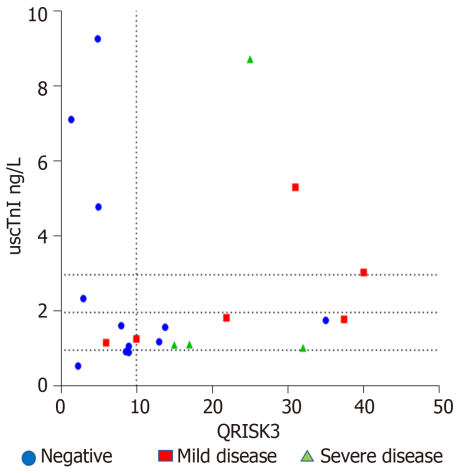

Figure 2 QRISK3 and uscTnI profile in patients assigned to coronary computed tomography angiography. Vertical dotted line represent QRISK3 values of 10%, and the horizontal dotted lines represent uscTnI values of 1, 2 and 3 ng/L. The lower left hand quadrant represents a QRISK value of < 10% and uscTnI values < 1 ng/L. Three patients classified as negative by computerized tomography coronary angiogram fall within the quadrant.

completion of investigation. A 60 year old female uscTnI = 2.9 ng/L and QRISK3 score 8% presented with crescendo angina and a troponin change of 26 ng/L, Coronary angiogram showed severe CAD in both patients. uscTnI increased in patients with the increasing severity of coronary artery occlusion (Table 3). Higher uscTnI was more likely to be associated with severe occlusion of CAD. A plot of QRISK3 and uscTnI in this group showed that patients were not classified within lower quartile (< 1 ng/L uscTnI and QRISK3 score < 10%).

ACS: Two patients presented with ACS and troponin changes prior to assessment by RACPC. A fifty eight year old male with a baseline uscTnI = 1.9 ng/L presented to the emergency department with a cardiac troponin change of 42 ng/L. Coronary angiogram showed mild occlusion. A 63 year old female who was admitted, prior to RACPC assessment, to the hospital with pyelonephritis showed a cardiac troponin change of 23.6 ng/L; coronary angiogram showed severe disease. Baseline uscTnI taken prior to hospital admission was not available in this patient. One 73 year old male and 86 year old female were classified as recent acute cardiac events, a review suggested uscTnI levels of 2290 and 221 ng/L, respectively, prior to review by RACPC. A further 62 year old female with a past history of breast cancer and uscTnI = 3.6 ng/L died of cardiac arrest prior to review by RACPC staff. Patient follow-up over a period of 6 mo after RACPC review did not result in further admissions with ACS.

uscTnI and receiver operating characteristic curves

We examined whether uscTnI can predict the presence or exclude the presence of coronary artery stenosis in patients assigned to ETT, Echo, Stress Echo, CCTA and coronary angiogram using ROC, Figure 3. The analysis included 63 patients who tested negative and 34 patients who tested positive. ROC analysis showed an AUC of 0.63 (95%CI: 0.51-0.73). At a value of uscTnI value > 0.52 ng/L, sensitivity was 100% and specificity 1.6%. At a value of uscTnI > 11.6 ng/L, sensitivity was 10.7% and specificity 100%. We found a single patient (84 year old male) with an uscTnI = 0.46 ng/L with a normal echo. Ten patients with uscTnI > 11.6 ng/L were detected within the study. Three with severe CAD disease following coronary angiogram (uscTnI = 13.4 ng/L, 18.3 ng/L, 48.5 ng/L), one with moderate disease (uscTnI = 22.3 ng/L), left bundle branch block (uscTnI = 17.0 ng/L), known ischemic heart disease (uscTnI = 33.2 ng/L), chronic morbidity for monitoring by cardiologist (70.4 ng/L), a further patient diagnosed with non-cardiac chest pain (uscTnI = 16.6 ng/L), and two with recent previous ACS events (uscTnI = 221 and 2290 ng/L).

DISCUSSION

Early detection of CAD remains an important task as effective treatments are available to relieve symptoms and reduce mortality[5]. Suspected stable angina remains a common presenting complaint. The challenge remains to identify those with CAD and

Table 3 Patients assigned to coronary angiogram

Group	Normal	Mild disease	Moderate disease	Severe disease
Mean uscTnI ng/L	1.8	3.3	7.3	10
Min uscTnI ng/L	1.1	2.0	1.0	0.94
Max uscTnI ng/L	2.2	3.9	22	49
n	6	5	5	7

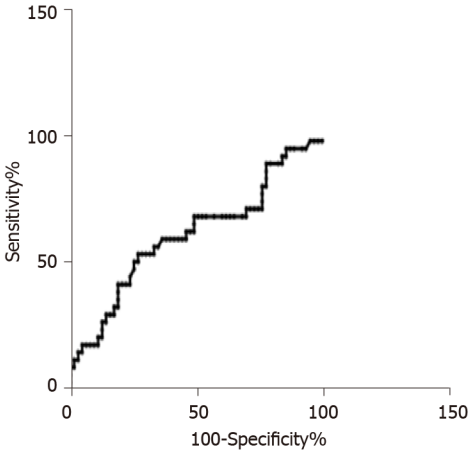

Figure 3 Receiver operating characteristic curves for uscTnI in patients allocated to functional testing (Exercise tolerance test, Echocardiogram, Stress echocardiogram), coronary computed tomography angiography and coronary angiogram. Patients were diagnosed with coronary artery disease based on patient follow-up tests.

those with intermediate pre-test probability who need further functional testing. The pre-test probability of stable CHD is determined by the presence of cardiovascular risk factors, age, sex and the nature of the presenting chest pain[5]. NICE guidelines, United Kingdom suggest that the diagnosis of stable angina is based on clinical assessment alone or clinical assessment and diagnostic testing[6]. In the United Kingdom, RACPC is the first place of referral in the investigation of suspected stable angina. In Worcester specialist nursing staff triage patients using clinical assessment which include among others, detailed clinical history, physical examination, QRISK3 as well as typicality of chest pain. In this study we investigated the use of a very highly sensitive troponin assay, an assay that can detect cTnI in 98% of healthy individuals, in the diagnosis and management of stable angina in the RACPC. In previous studies, uscTnI to rule out functionally relevant CAD was investigated in patients without known previous CAD; in this study we aimed to investigate the application of the assay in an unselected group of patients who presented to the RACPC.

Previous reports have stated that levels of uscTnI were significantly higher in patient with exercise induced ischemia, Using a combination of pre-ETT clinical assessment and uscTnI, the authors suggest a cut-off value of 1.54 ng/L to rule out 15% of patients from further testing, but acknowledge that further refinement is required because even when used with clinical judgement uscTnI provided only moderate diagnostic accuracy[17,18]. This value may be influenced by other structural cardiac abnormalities. In our patient series, the patient co-morbidity included congestive cardiac failure, history of breast cancer and sarcoidosis. In this study, investigation on two patients with uscTnI 3.2, and 48.5 ng/, and abnormal ETT which showed ischemic changes, showed severe CAD. A further patient with a normal ETT, uscTnI = 1.4 ng/L and classified for a coronary angiogram because of "typical angina pain" developed NSTEMI prior to further investigation. Coronary angiogram showed severe CAD. This study suggests overlap in uscTnI values in patients assigned to ETT and classified as with and without CAD. Strategies used to stratify patients into different investigation methods, as well as patient selection for RACPC assessment may influence cut-off levels used for uscTnI.

An additional study, included patients referred for investigation of functionally relevant CAD by rest/stress myocardial perfusion single-photon emission tomography/computer tomography. The patients with clinically relevant cardiac

disease were excluded. An uscTnI value of < 0.5 ng/L ruled out functionally relevant CAD in 10% of patients[15]. The SCOT-HEART trial investigated patients with suspected stable angina assigned to CCTA for obstructive CAD. The median concentration of uscTnI assay in patients without CAD was 1.2 ng/L and with CAD was 1.9 ng/L. Addition of uscTnI to the CADC risk model reduced the number of patients determined to be at intermediate or high risk by the CADC model by 10%[14]. The authors suggest that the study demonstrates that the use of uscTnI as a biomarker can improve the diagnosis of stable obstructive CAD. In the current study there was considerable overlap in uscTnI values between patients with and without obstructive CAD. However a plot of QRISK3, a risk evaluation of cardiac events at 10 years and uscTnI showed that at QRISK3 < 10% and uscTnI < 1 ng/L, 14% of patients with normal CCTA scan were within this quartile. This study confirms previous studies that the assessment of stable angina in patients referred for CCTA may be improved by the addition of uscTnI. Cardiac imaging remains a valuable tool for the assessment of CAD and the early detection of CAD remains an important task, CCTA has recently come under scrutiny due to increased cost, limitations such as increased radiation or user dependent interpretation or used inappropriately in patients with very low pre-test probability of CAD[4,5]. Additional studies are mandatory to elucidate if the rule out of 14% of patients is applicable to a larger cohort of patients pre-selected for CCTA.

Increase in uscTnI occurred in patients referred for coronary angiogram and increased with degree of severity of CAD. Given that previous studies suggest an association between high sensitive cTnI and the presence of CAD without ACS[19], this study confirmed an association between uscTnI and severity of CAD in the patient group referred for coronary angiogram. Further, the use of troponin assays in an RACPC setting may identify patients with recent ACS events and result in earlier assessment and treatment of these patients.

The question remains how these findings and uscTnI can be applied in clinical practice in the RACPC in the United Kingdom. A comparison of ROC curves for patients who underwent both functional testing, CCTA and coronary angiogram did not identify a single uscTnI value with a high enough sensitivity and specificity (and negative and positive predictive value) for stable CAD. In the population referred to the RACPC for further evaluations a low level of uscTnI ≤ 0.52 ng/L may decrease the number of patients required for further investigation and high levels > 11.6 ng/L may identify those who require further evaluation. It is unlikely that uscTnI within the range > 0.52-11.6 ng/L will be a standalone test for suspected stable angina. The cohort we studied included patients with several comorbidities and previous history of CHD that often pose a diagnostic and prognostic challenge as to the cause and significance of the presenting chest pain. This study suggests uscTnI as a sensitive marker of cardiac damage would perform best when combined with clinical assessment of the patient. It must be emphasized that the findings of this study would not mean that in the RACPC clinical judgment can be substituted with uscTnI. Should a single uscTnI be performed in either primary care or at presentation to RACPC, it needs to be interpreted with clinical evaluation.

These findings complement previous data on the use of uscTnI in the diagnosis of CAD in suspected stable angina. To our knowledge this is the first study to investigate the use of a "highly" sensitive cardiac troponin assay in a RACPC. The limitations of this study are that this is a single-centre study and bias may have been introduced due to referral characteristics. We do not believe that lack of access to patient medical records, which was not based on patient demographics led to sample bias. We also need to emphasise that in this institution myocardial ischemia was investigated by several methods in patients with a wide range of clinical probability of CAD based on clinical evaluation.

The study suggests that in the presence of clinical comorbidities and previous CHD the uscTnI needs to be used in conjunction with clinical assessment. Diagnostic cut off values of uscTnI in an RACPC setting depend on patient population and comorbidities. Further work is required to investigate the use of "highly sensitive" cardiac troponin values in the selection of patients suspected with CAD for further investigation and treatment.

CONCLUSION

The study suggests that in the presence of clinical comorbidities and previous CHD the uscTnI needs to be used in conjunction with clinical assessment. Diagnostic cut off

values of uscTnI in an RACPC setting depend on patient population and comorbidities. Further work is required to investigate the use of "highly sensitive" cardiac troponin values in the selection of patients suspected with CAD for further investigation and treatment.

ARTICLE HIGHLIGHTS

Research background

In the United Kingdom rapid access chest pain clinics (RACPC) have been set up in hospital centers to address the problem of non-acute chest pain of uncertain origin. The early detection of coronary artery disease (CAD) in these patients can lead to effective treatment. In this study we looked at the value of a highly sensitive troponin I assay in the rule out of functionally relevant CAD in patients referred for further assessment and investigation in a RACPC. To our knowledge this is the first study to be carried out in a non-teaching hospital in patients who presented with several clinical co-morbidities.

Research motivation

While functional studies and imaging techniques are valuable in the evaluation of patients with suspected CAD, highly sensitive troponin I which detects even minute concentrations of troponin I in the serum may provide further information on cardiac injury that may be associated with CAD.

Research objectives

The aim was to assess the role of troponin in assisting clinical decision making in the setting of a RACPC in a non-teaching hospital. This has not been explored previously.

Research methods

One hundred and seventy two patients admitted to the rapid access clinic were studied. Unlike previous studies, patients with a previous history of CAD were included in the study. Following clinical assessment the patients with suspected stable CAD were assigned to 24 h monitoring electrocardiogram, exercise tolerance test, echocardiogram, exercise or pharmacological stress echo, coronary computed tomography angiography, coronary angiogram and percutaneous coronary intervention, medical treatment for angina, or were discharged as clinical assessment suggested non-cardiac chest pain. More complex patients were designated for review by specialist cardiologists.

Research results

Receiver operating characteristic curves suggest that patients with troponin I ≤ 0.52 ng/L were less likely to present with CAD and values > 11.6 ng/L required further evaluation. In the range > 0.52-11.6 ng/L troponin I was not a standalone test. In all cases troponin was best used in conjunction with clinical assessment. In patients assigned and preselected for coronary computed tomography angiography and coronary angiogram troponin I was an indicator of the severity of CAD. Cut-off levels of troponin I were determined by the patient population cohort.

Research conclusions

The study suggests that in unselected patients presenting with suspected stable angina to a rapid access clinic troponin I is best used in conjunction with clinical evaluation of the patient. Diagnostic cut-off levels are dependent on patient population.

Research perspectives

What is now required is further work with different population groups.

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