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

ORCID number: Roberto M Saraiva 0000-0002-2263-4261; Mauro Felippe F Mediano 0000-0001-6369-3631; Fernanda SNS Mendes 0000-0003-2033-1715; Gilberto Marcelo Sperandio da Silva 0000-0002-0468-4417; Henrique H Veloso 0000-0002-2743-6555; Luiz Henrique C Sangenis 0000-0002-5948-6282; Paula Simplício da Silva 0000-0002-7414-9698; Flavia Mazzoli-Rocha 0000-0003-0972-194X; Andréa S Sousa 0000-0001-8266-4801; Marcelo T Holanda 0000-0002-3125-6610; Alejandro M Hasslocher-Moreno 0000-0002-5430-7222.

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, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro 21040-900, RJ, Brazil

Corresponding author: Roberto M Saraiva, MD, Senior Researcher, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Av. Brasil 4365, Rio de Janeiro 21040-900, RJ, Brazil. roberto.saraiva@ini.fiocruz.br

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

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.

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 micro-vascular disease and cardiac autonomic dysfunction[12]. Ultimately, patients will present with a myriad of clinical manifestations, including bradyarrhythmia, tachyar-rhythmia, 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.

Classification	No ECG changes	ECG changes	ECHO changes		Heart failure	
			No LV dysfunction	LV dysfunction	Non end stage	End Stage
Kuschnir	**0**	**I**		**II**	**III**	
Brazilian	**Indeterminate**	**A**	**B1**	**B2**	**C**	**D**
Los Andes	**I A**	**II**			**III**	
Latin American	**A**		**B1**	**B2**	**C**	**D**
AHA Statement	**A**		**B1**	**B2**	**C**	**D**

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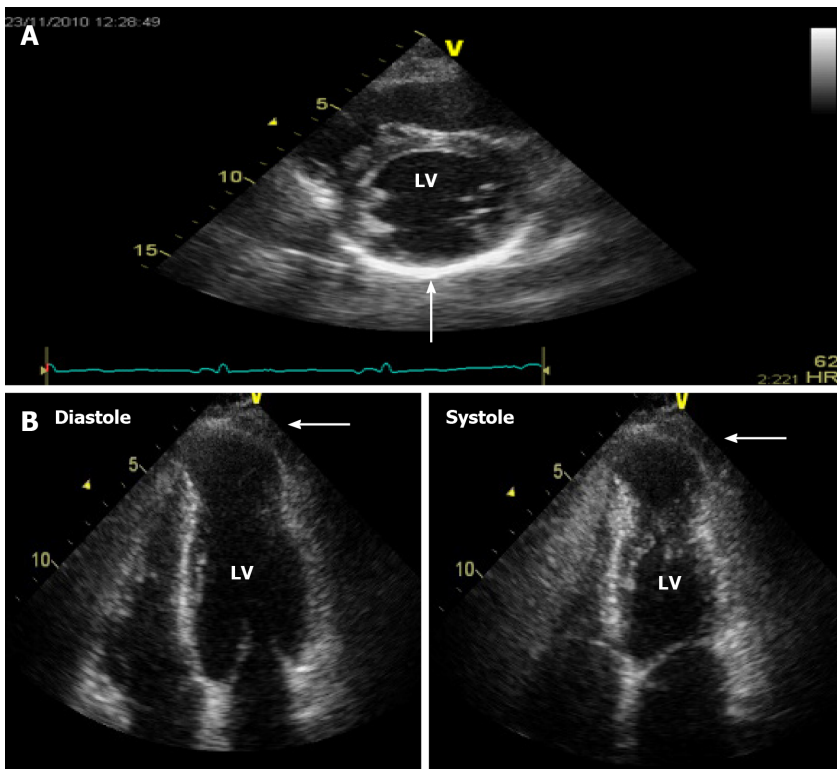
Figure 2 Note the hyperrefringent akinetic area in the basal inferolateral left ventricular wall (A) and the left ventricular apical aneurysm in the diastolic and systolic left ventricular images (B).
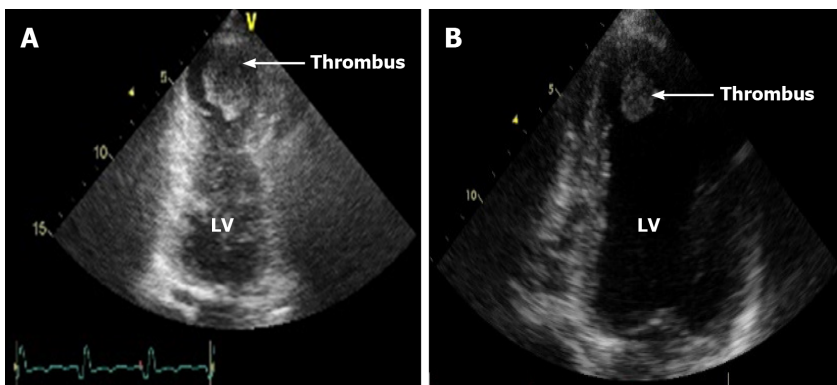

Figure 3 Note the thrombi in the apical location in a patient with a large apical aneurysm (A) and a patient with severe left ventricular dilation and dysfunction (B).

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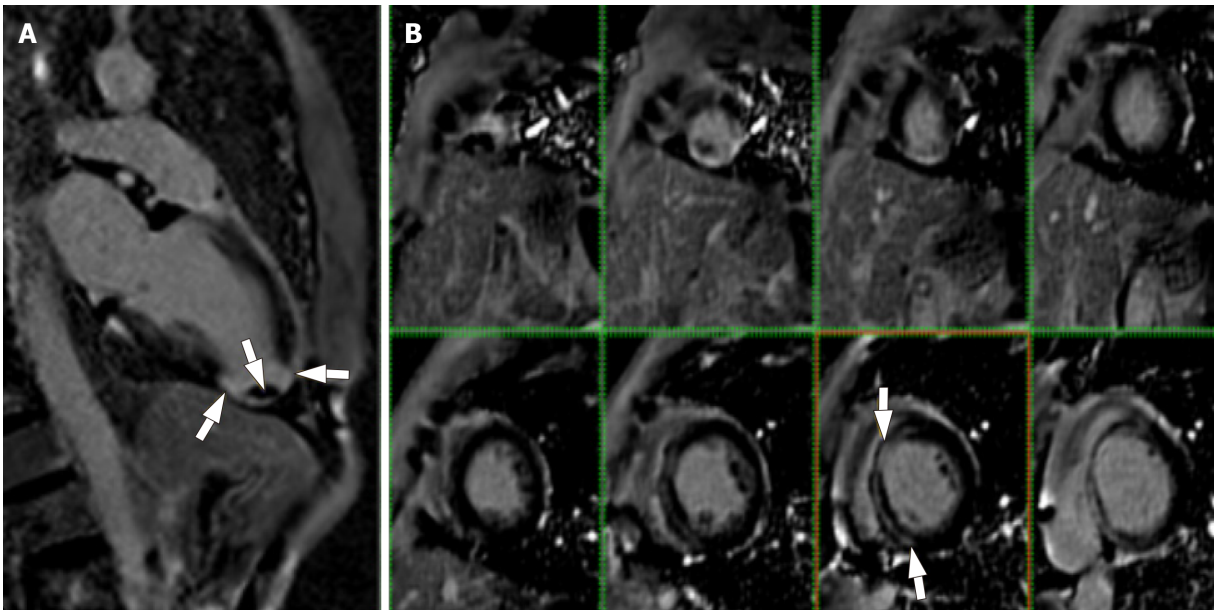
Figure 4 Cardiac magnetic resonance imaging of a patient with stage B1 Chagas heart disease. A: Myocardial delayed enhancement on 2-chamber apical slice depicts areas of cardiac fibrosis in the apical segments and an apical thrombus; B: Myocardial delayed enhancement protocol on left ventricular short-axis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

REFERENCES

1   **Nunes MCP**, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, Dutra WO, Gascon J, Morillo CA, Oliveira-Filho J, Ribeiro ALP, Marin-Neto JA; American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Stroke Council. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. *Circulation* 2018; **138**: e169-e209 [PMID: 30354432 DOI: 10.1161/CIR.0000000000000599]

2   **World Health Organization**. Chagas Disease (American trypanosomiasis). 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis)

3   **Pinto Dias JC**. Human chagas disease and migration in the context of globalization: some particular aspects. *J Trop Med* 2013; **2013**: 789758 [PMID: 23606862 DOI: 10.1155/2013/789758]

4   **Hotez PJ**, Dumonteil E, Betancourt Cravioto M, Bottazzi ME, Tapia-Conyer R, Meymandi S, Karunakara U, Ribeiro I, Cohen RM, Pecoul B. An unfolding tragedy of Chagas disease in North America. *PLoS Negl Trop Dis* 2013; **7**: e2300 [PMID: 24205411 DOI: 10.1371/journal.pntd.0002300]

5   **Hernandez S**, Forsyth CJ, Flores CA, Meymandi SK. Prevalence of Chagas Disease Among Family

Members of Previously Diagnosed Patients in Los Angeles, California. *Clin Infect Dis* 2019; **69**: 1226-1228 [PMID: 31220221 DOI: 10.1093/cid/ciz087]

6   **Basile L**, Jansa JM, Carlier Y, Salamanca DD, Angheben A, Bartoloni A, Seixas J, Van Gool T, Canavate C, Flores-Chavez M, Jackson Y, Chiodini PL, Albajar-Vinas P; Working Group on Chagas Disease. Chagas disease in European countries: the challenge of a surveillance system. *Euro Surveill* 2011; **16** [PMID: 21944556]

7   **Velasco M**, Gimeno-Feliú LA, Molina I, Salas-Coronas J, Solà I, Monge-Maillo B, Torrús-Tendero D, Caylà J, de Guzmán EN, Arellano JP, Pérez-Molina JA. Screening for *Trypanosoma cruzi* infection in immigrants and refugees: Systematic review and recommendations from the Spanish Society of Infectious Diseases and Clinical Microbiology. *Euro Surveill* 2020; **25** [PMID: 32127121 DOI: 10.2807/1560-7917.ES.2020.25.8.1900393]

8   **Santos VRCD**, Meis J, Savino W, Andrade JAA, Vieira JRDS, Coura JR, Junqueira ACV. Acute Chagas disease in the state of Pará, Amazon Region: is it increasing? *Mem Inst Oswaldo Cruz* 2018; **113**: e170298 [PMID: 29742200 DOI: 10.1590/0074-02760170298]

9   **Dias JC**, Ramos AN Jr, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, Torres RM, Melo JR, Almeida EA, Oliveira W Jr, Silveira AC, Rezende JM, Pinto FS, Ferreira AW, Rassi A, Fragata AA Filho, Sousa AS, Correia D, Jansen AM, Andrade GM, Britto CF, Pinto AY, Rassi A Jr, Campos DE, Abad-Franch F, Santos SE, Chiari E, Hasslocher-Moreno AM, Moreira EF, Marques DS, Silva EL, Marin-Neto JA, Galvão LM, Xavier SS, Valente SA, Carvalho NB, Cardoso AV, Silva RA, Costa VM, Vivaldini SM, Oliveira SM, Valente VD, Lima MM, Alves RV. 2 nd Brazilian Consensus on Chagas Disease, 2015. *Rev Soc Bras Med Trop* 2016; **49Suppl** 1: 3-60 [PMID: 27982292 DOI: 10.1590/0037-8682-0505-2016]

10   **Dutra WO**, Menezes CA, Magalhães LM, Gollob KJ. Immunoregulatory networks in human Chagas disease. *Parasite Immunol* 2014; **36**: 377-387 [PMID: 24611805 DOI: 10.1111/pim.12107]

11   **González FB**, Villar SR, Pacini MF, Bottasso OA, Pérez AR. Immune-neuroendocrine and metabolic disorders in human and experimental T. cruzi infection: New clues for understanding Chagas disease pathology. *Biochim Biophys Acta Mol Basis Dis* 2020; **1866**: 165642 [PMID: 31866417 DOI: 10.1016/j.bbadis.2019.165642]

12   **Andrade JP**, Marin-Neto JA, Paola AA, Vilas-Boas F, Oliveira GM, Bacal F, Bocchi EA, Almeida DR, Fragata Filho AA, Moreira Mda C, Xavier SS, Oliveira Junior WA, Dias JC; Sociedade Brasileira de Cardiologia. I Diretriz Latino Americana para o Diagnóstico e Tratamento da Cardiopatia Chagásica. [I Latin American guidelines for the diagnosis and treatment of Chagas cardiomyopathy]. *Arq Bras Cardiol* 2011; **97**: 1-48 [PMID: 21952638]

13   **Nunes MCP**, Badano LP, Marin-Neto JA, Edvardsen T, Fernández-Golfín C, Bucciarelli-Ducci C, Popescu BA, Underwood R, Habib G, Zamorano JL, Saraiva RM, Sabino EC, Botoni FA, Barbosa MM, Barros MVL, Falqueto E, Simões MV, Schmidt A, Rochitte CE, Rocha MOC, Ribeiro ALP, Lancellotti P. Multimodality imaging evaluation of Chagas disease: an expert consensus of Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI). *Eur Heart J Cardiovasc Imaging* 2018; **19**: 459-460n [PMID: 29029074 DOI: 10.1093/ehjci/jex154]

14   **Rassi A Jr**, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, Rassi GG, Hasslocher-Moreno A, Sousa AS, Scanavacca MI. Development and validation of a risk score for predicting death in Chagas' heart disease. *N Engl J Med* 2006; **355**: 799-808 [PMID: 16928995 DOI: 10.1056/NEJMoa053241]

15   **Shen L**, Ramires F, Martinez F, Bodanese LC, Echeverría LE, Gómez EA, Abraham WT, Dickstein K, Køber L, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Jhund PS, Gimpelewicz CR, McMurray JJV; PARADIGM-HF and ATMOSPHERE Investigators and Committees. Contemporary Characteristics and Outcomes in Chagasic Heart Failure Compared With Other Nonischemic and Ischemic Cardiomyopathy. *Circ Heart Fail* 2017; **10** [PMID: 29141857 DOI: 10.1161/CIRCHEARTFAILURE.117.004361]

16   **Terhoch CB**, Moreira HF, Ayub-Ferreira SM, Conceição-Souza GE, Salemi VMC, Chizzola PR, Oliveira MT Jr, Lage SHG, Bocchi EA, Issa VS. Clinical findings and prognosis of patients hospitalized for acute decompensated heart failure: Analysis of the influence of Chagas etiology and ventricular function. *PLoS Negl Trop Dis* 2018; **12**: e0006207 [PMID: 29432453 DOI: 10.1371/journal.pntd.0006207]

17   **Hasslocher-Moreno AM**, Saraiva RM, Sangenis LHC, Xavier SS, de Sousa AS, Costa AR, de Holanda MT, Veloso HH, Mendes FSNS, Costa FAC, Boia MN, Brasil PEAA, Carneiro FM, da Silva GMS, Mediano MFF. Benznidazole decreases the risk of chronic Chagas disease progression and cardiovascular events: A long-term follow up study. *EClinicalMedicine* 2021; **31**: 100694 [PMID: 33554085 DOI: 10.1016/j.eclinm.2020.100694]

18   **Viotti R**, Vigliano C, Lococo B, Bertocchi G, Petti M, Alvarez MG, Postan M, Armenti A. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole *vs* no treatment: a nonrandomized trial. *Ann Intern Med* 2006; **144**: 724-734 [PMID: 16702588 DOI: 10.7326/0003-4819-144-10-200605160-00006]

19   **Morillo CA**, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A Jr, Rosas F, Villena E, Quiroz R, Bonilla R, Britto C, Guhl F, Velazquez E, Bonilla L, Meeks B, Rao-Melacini P, Pogue J, Mattos A, Lazdins J, Rassi A, Connolly SJ, Yusuf S; BENEFIT Investigators. Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. *N Engl J Med* 2015; **373**: 1295-1306 [PMID: 26323937 DOI: 10.1056/NEJMoa1507574]

20   **Chagas C**, Villela E. Cardiac form of American Trypanosomiasis. *Mem Inst Oswaldo Cruz* 1922; **14**: 3-54

21   **Dias E**, Laranja FS, Nobrega G. Clinical and therapeutic Chagas disease. *Medicina (Mex)* 1948; **28**: 224-236

22   **Laranja FS**, Dias E, Nobrega G. [The electrocardiogram in chronic cardiopathy of Chagas' disease]. *Bras Med* 1948; **62**: 51-53

23   **Dias E**, Laranja FS, Miranda A, Nobrega G. Chagas' disease; a clinical, epidemiologic, and pathologic study. *Circulation* 1956; **14**: 1035-1060 [PMID: 13383798 DOI: 10.1161/01.cir.14.6.1035]

24   **Viotti RJ**, Vigliano C, Laucella S, Lococo B, Petti M, Bertocchi G, Ruiz Vera B, Armenti H. Value of echocardiography for diagnosis and prognosis of chronic Chagas disease cardiomyopathy without heart failure. *Heart* 2004; **90**: 655-660 [PMID: 15145872 DOI: 10.1136/hrt.2003.018960]

25   **Sabino EC**, Ribeiro AL, Salemi VM, Di Lorenzo Oliveira C, Antunes AP, Menezes MM, Ianni BM, Nastari L, Fernandes F, Patavino GM, Sachdev V, Capuani L, de Almeida-Neto C, Carrick DM, Wright D, Kavounis K, Goncalez TT, Carneiro-Proietti AB, Custer B, Busch MP, Murphy EL; National Heart, Lung, and Blood Institute Retrovirus Epidemiology Donor Study-II (REDS-II), International Component. Ten-year incidence of Chagas cardiomyopathy among asymptomatic Trypanosoma cruzi-seropositive former blood donors. *Circulation* 2013; **127**: 1105-1115 [PMID: 23393012 DOI: 10.1161/CIRCULATIONAHA.112.123612]

26   **Biolo A**, Ribeiro AL, Clausell N. Chagas cardiomyopathy--where do we stand after a hundred years? *Prog Cardiovasc Dis* 2010; **52**: 300-316 [PMID: 20109600 DOI: 10.1016/j.pcad.2009.11.008]

27   **Kuschnir E**, Sgammini H, Castro R, Evequoz C, Ledesma R, Brunetto J. [Evaluation of cardiac function by radioisotopic angiography, in patients with chronic Chagas cardiopathy]. *Arq Bras Cardiol* 1985; **45**: 249-256 [PMID: 3835868]

28   **Carrasco HA**, Barboza JS, Inglessis G, Fuenmayor A, Molina C. Left ventricular cineangiography in Chagas' disease: detection of early myocardial damage. *Am Heart J* 1982; **104**: 595-602 [PMID: 7113900 DOI: 10.1016/0002-8703(82)90232-0]

29   **de Souza AC**, Salles G, Hasslocher-Moreno AM, de Sousa AS, Alvarenga Americano do Brasil PE, Saraiva RM, Xavier SS. Development of a risk score to predict sudden death in patients with Chaga's heart disease. *Int J Cardiol* 2015; **187**: 700-704 [PMID: 25919755 DOI: 10.1016/j.ijcard.2015.03.372]

30   **Ministério da Saúde (BR)**. [Protocolo Clínico e Diretrizes Terapêuticas da doença de Chagas, no âmbito do Sistema Único de Saúde - SUS. 2018]. Available from: http://conitec.gov.br/images/Protocolos/Relatorio_PCDT_Doenca_de_Chagas.pdf

31   **Panamerican Health Organization**. Guidelines for the diagnosis and treatment of Chagas disease. 2018. Available from: https://iris.paho.org/bitstream/handle/10665.2/49653/9789275120439_eng.pdf?sequence=6&isAllowed=y

32   **Ferreira AM**, Sabino ÉC, Oliveira LC, Oliveira CDL, Cardoso CS, Ribeiro ALP, Damasceno RF, Nunes MDCP, Haikal DSA. Impact of the social context on the prognosis of Chagas disease patients: Multilevel analysis of a Brazilian cohort. *PLoS Negl Trop Dis* 2020; **14**: e0008399 [PMID: 32598390 DOI: 10.1371/journal.pntd.0008399]

33   **Sherbuk JE**, Okamoto EE, Marks MA, Fortuny E, Clark EH, Galdos-Cardenas G, Vasquez-Villar A, Fernandez AB, Crawford TC, Do RQ, Flores-Franco JL, Colanzi R, Gilman RH, Bern C. Biomarkers and mortality in severe Chagas cardiomyopathy. *Glob Heart* 2015; **10**: 173-180 [PMID: 26407513 DOI: 10.1016/j.gheart.2015.07.003]

34   **Menezes Junior ADS**, Lopes CC, Cavalcante PF, Martins E. Chronic Chagas Cardiomyopathy Patients and Resynchronization Therapy: a Survival Analysis. *Braz J Cardiovasc Surg* 2018; **33**: 82-88 [PMID: 29617506 DOI: 10.21470/1678-9741-2017-0134]

35   **de Souza Nogueira Sardinha Mendes F**, Mediano MFF, de Castro E Souza FC, da Silva PS, Carneiro FM, de Holanda MT, Saraiva RM, Xavier SS, Americano do Brasil PEA, de Sousa AS. Effect of Physical Exercise Training in Patients With Chagas Heart Disease (from the PEACH STUDY). *Am J Cardiol* 2020; **125**: 1413-1420 [PMID: 32171439 DOI: 10.1016/j.amjcard.2020.01.035]

36   **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2016; **68**: 1476-1488 [PMID: 27216111 DOI: 10.1016/j.jacc.2016.05.011]

37   **Echeverría LE**, Figueredo A, Rodriguez MJ, Salazar L, Pizarro C, Morillo CA, Rojas LZ, Gómez-Ochoa SA, Castillo VR. Survival after heart transplantation for Chagas cardiomyopathy using a conventional protocol: A 10-year experience in a single center. *Transpl Infect Dis* 2021; **23**: e13549 [PMID: 33345420 DOI: 10.1111/tid.13549]

38   **Di Lorenzo Oliveira C**, Nunes MCP, Colosimo EA, de Lima EM, Cardoso CS, Ferreira AM, de Oliveira LC, Moreira CHV, Bierrenbach AL, Haikal DSA, Peixoto SV, Lima-Costa MF, Sabino EC, Ribeiro ALP. Risk Score for Predicting 2-Year Mortality in Patients With Chagas Cardiomyopathy From Endemic Areas: SaMi-Trop Cohort Study. *J Am Heart Assoc* 2020; **9**: e014176 [PMID: 32157953 DOI: 10.1161/JAHA.119.014176]

39   **Sousa AS**, Xavier SS, Freitas GR, Hasslo
cher-Moreno A. Prevention strategies of cardioembolic ischemic stroke in Chagas' disease. *Arq Bras Cardiol* 2008; **91**: 306-310 [PMID: 19142374 DOI: 10.1590/s0066-782x2008001700004]

40   **Nunes Mdo C**, Rocha MO, Ribeiro AL, Colosimo EA, Rezende RA, Carmo GA, Barbosa MM. Right ventricular dysfunction is an independent predictor of survival in patients with dilated chronic Chagas' cardiomyopathy. *Int J Cardiol* 2008; **127**: 372-379 [PMID: 17689706 DOI: 10.1016/j.ijcard.2007.06.012]

41   **Nascimento CA**, Gomes VA, Silva SK, Santos CR, Chambela MC, Madeira FS, Holanda MT, Brasil PE, Sousa AS, Xavier SS, Hassloch
er-Moreno AM, Cunha AB, Saraiva RM. Left atrial and left ventricular diastolic function in chronic Chagas disease. *J Am Soc Echocardiogr* 2013; **26**: 1424-1433 [PMID: 24055123 DOI: 10.1016/j.echo.2013.08.018]

42   **Rocha MO**, Nunes MC, Ribeiro AL. Morbidity and prognostic factors in chronic chagasic cardiopathy. *Mem Inst Oswaldo Cruz* 2009; **104** Suppl 1: 159-166 [PMID: 19753471 DOI: 10.1590/s0074-02762009000900022]

43   **Saraiva RM**, Waghabi MC, Vilela MF, Madeira FS, Sperandio da Silva GM, Xavier SS, Feige JJ, Hassloch
er-Moreno AM, Araujo-Jorge TC. Predictive value of transforming growth factor-β1in Chagas disease: towards a biomarker surrogate of clinical outcome. *Trans R Soc Trop Med Hyg* 2013; **107**: 518-525 [PMID: 23787193 DOI: 10.1093/trstmh/trt050]

44   **Heringer-Walther S**, Moreira MC, Wessel N, Saliba JL, Silvia-Barra J, Pena JL, Becker S, Siems WE, Schultheiss HP, Walther T. Brain natriuretic peptide predicts survival in Chagas' disease more effectively than atrial natriuretic peptide. *Heart* 2005; **91**: 385-387 [PMID: 15710733 DOI: 10.1136/hrt.2003.026856]

45   **Lima-Costa MF**, Cesar CC, Peixoto SV, Ribeiro AL. Plasma B-type natriuretic peptide as a predictor of mortality in community-dwelling older adults with Chagas disease: 10-year follow-up of the Bambui Cohort Study of Aging. *Am J Epidemiol* 2010; **172**: 190-196 [PMID: 20581155 DOI: 10.1093/aje/kwq106]

46   **Barros MV**, Machado FS, Ribeiro AL, Rocha MO. Diastolic function in Chagas' disease: an echo and tissue Doppler imaging study. *Eur J Echocardiogr* 2004; **5**: 182-188 [PMID: 15147660 DOI: 10.1016/S1525-2167(03)00078-7]

47   **Pazin-Filho A**, Romano MM, Almeida-Filho OC, Furuta MS, Viviani LF, Schmidt A, Marin-Neto JA, Maciel BC. Minor segmental wall motion abnormalities detected in patients with Chagas' disease have adverse prognostic implications. *Braz J Med Biol Res* 2006; **39**: 483-487 [PMID: 16612471 DOI: 10.1590/s0100-879x2006000400008]

48   **Rassi A Jr**, Rassi A, Marin-Neto JA. Chagas disease. *Lancet* 2010; **375**: 1388-1402 [PMID: 20399979 DOI: 10.1016/S0140-6736(10)60061-X]

49   **Borges-Pereira J**, Xavier SS, de Sousa AS, de Castro JA, Zauza PL, Coura JR. [Prevalence of left ventricular aneurysms among chronic Chagas disease patients from two areas in the State of Piauí, Brazil]. *Rev Soc Bras Med Trop* 2007; **40**: 521-526 [PMID: 17992406 DOI: 10.1590/s0037-86822007000500006]

50   **Carod-Artal FJ**, Vargas AP, Horan TA, Nunes LG. Chagasic cardiomyopathy is independently associated with ischemic stroke in Chagas disease. *Stroke* 2005; **36**: 965-970 [PMID: 15845889 DOI: 10.1161/01.STR.0000163104.92943.50]

51   **Carod-Artal FJ**, Vargas AP, Falcao T. Stroke in asymptomatic Trypanosoma cruzi-infected patients. *Cerebrovasc Dis* 2011; **31**: 24-28 [PMID: 20980750 DOI: 10.1159/000320248]

52   **Nunes MC**, Kreuser LJ, Ribeiro AL, Sousa GR, Costa HS, Botoni FA, de Souza AC, Gomes Marques VE, Fernandez AB, Teixeira AL, da Costa Rocha MO. Prevalence and risk factors of embolic cerebrovascular events associated with Chagas heart disease. *Glob Heart* 2015; **10**: 151-157 [PMID: 26407510 DOI: 10.1016/j.gheart.2015.07.006]

53   **Rodriguez-Salas LA**, Klein E, Acquatella H, Catalioti F, Davalos V V, Gomez-Mancebo JR, Gonzalez H, Bosch F, Puigbo JJ. Echocardiographic and Clinical Predictors of Mortality in Chronic Chagas' Disease. *Echocardiography* 1998; **15**: 271-278 [PMID: 11175040 DOI: 10.1111/j.1540-8175.1998.tb00607.x]

54   **Benchimol Barbosa PR**. Noninvasive prognostic markers for cardiac death and ventricular arrhythmia in long-term follow-up of subjects with chronic Chagas' disease. *Braz J Med Biol Res* 2007; **40**: 167-178 [PMID: 17273653]

55   **Nunes Mdo C**, Barbosa Mde M, Brum VA, Rocha MO. Morphofunctional characteristics of the right ventricle in Chagas' dilated cardiomyopathy. *Int J Cardiol* 2004; **94**: 79-85 [PMID: 14996479 DOI: 10.1016/j.ijcard.2003.05.003]

56   **Koelling TM**, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 2002; **144**: 524-529 [PMID: 12228791 DOI: 10.1067/mhj.2002.123575]

57   **García-Álvarez A**, Sitges M, Regueiro A, Poyatos S, Jesus Pinazo M, Posada E, Bijnens B, Heras M, Gascon J, Sanz G. Myocardial deformation analysis in Chagas heart disease with the use of speckle tracking echocardiography. *J Card Fail* 2011; **17**: 1028-1034 [PMID: 22123367 DOI: 10.1016/j.cardfail.2011.08.007]

58   **Barbosa MM**, Costa Rocha MO, Vidigal DF, Bicalho Carneiro Rde C, Araújo RD, Palma MC, Lins de Barros MV, Nunes MC. Early detection of left ventricular contractility abnormalities by two-dimensional speckle tracking strain in Chagas' disease. *Echocardiography* 2014; **31**: 623-630 [PMID: 25232573 DOI: 10.1111/echo.12426]

59   **Gomes VA**, Alves GF, Hadlich M, Azevedo CF, Pereira IM, Santos CR, Brasil PE, Sangenis LH, Cunha AB, Xavier SS, Saraiva RM. Analysis of Regional Left Ventricular Strain in Patients with Chagas Disease and Normal Left Ventricular Systolic Function. *J Am Soc Echocardiogr* 2016; **29**: 679-688 [PMID: 27086044 DOI: 10.1016/j.echo.2016.03.007]

60   **Santos Junior OR**, da Costa Rocha MO, Rodrigues de Almeida F, Sales da Cunha PF, Souza SCS, Saad GP, Santos TADQ, Ferreira AM, Tan TC, Nunes MCP. Speckle tracking echocardiographic deformation indices in Chagas and idiopathic dilated cardiomyopathy: Incremental prognostic value of longitudinal strain. *PLoS One* 2019; **14**: e0221028 [PMID: 31437176 DOI: 10.1371/journal.pone.0221028]

61   **Saraiva RM**, Pacheco NP, Pereira TOJS, Costa AR, Holanda MT, Sangenis LHC, Mendes FSNS, Sousa AS, Hasslocher-Moreno AM, Xavier SS, Mediano MFF, Veloso HH. Left Atrial Structure and Function Predictors of New-Onset Atrial Fibrillation in Patients with Chagas Disease. *J Am Soc Echocardiogr* 2020; **33**: 1363-1374.e1 [PMID: 32747223 DOI: 10.1016/j.echo.2020.06.003]

62   **Strauss DG**, Cardoso S, Lima JA, Rochitte CE, Wu KC. ECG scar quantification correlates with cardiac magnetic resonance scar size and prognostic factors in Chagas' disease. *Heart* 2011; **97**: 357-361 [PMID: 21245474 DOI: 10.1136/hrt.2010.210047]

63   **Volpe GJ**, Moreira HT, Trad HS, Wu KC, Braggion-Santos MF, Santos MK, Maciel BC, Pazin-Filho A, Marin-Neto JA, Lima JAC, Schmidt A. Left Ventricular Scar and Prognosis in Chronic Chagas Cardiomyopathy. *J Am Coll Cardiol* 2018; **72**: 2567-2576 [PMID: 30466514 DOI: 10.1016/j.jacc.2018.09.035]

64   **Senra T**, Ianni BM, Costa ACP, Mady C, Martinelli-Filho M, Kalil-Filho R, Rochitte CE. Long-Term Prognostic Value of Myocardial Fibrosis in Patients With Chagas Cardiomyopathy. *J Am Coll Cardiol* 2018; **72**: 2577-2587 [PMID: 30466515 DOI: 10.1016/j.jacc.2018.08.2195]

65   **Ribeiro AL**, Moraes RS, Ribeiro JP, Ferlin EL, Torres RM, Oliveira E, Rocha MO. Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas disease. *Am Heart J* 2001; **141**: 260-265 [PMID: 11174350 DOI: 10.1067/mhj.2001.111406]

66   **da Silva Júnior O**, Borges MC, de Melo CS, Nascente GA, Correia D. Alternative sites for right ventricular pacing in Chagas disease: a comparative study of the mid-septum and inflow tract. *Pacing Clin Electrophysiol* 2014; **37**: 1166-1173 [PMID: 24588623 DOI: 10.1111/pace.12368]

67   **Ribeiro AL**, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. *Nat Rev Cardiol* 2012; **9**: 576-589 [PMID: 22847166 DOI: 10.1038/nrcardio.2012.109]

68   **Stein C**, Migliavaca CB, Colpani V, da Rosa PR, Sganzerla D, Giordani NE, Miguel SRPS, Cruz LN, Polanczyk CA, Ribeiro ALP, Falavigna M. Amiodarone for arrhythmia in patients with Chagas disease: A systematic review and individual patient data meta-analysis. *PLoS Negl Trop Dis* 2018; **12**: e0006742 [PMID: 30125291 DOI: 10.1371/journal.pntd.0006742]

69   **Piccini JP**, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2009; **30**: 1245-1253 [PMID: 19336434 DOI: 10.1093/eurheartj/ehp100]

70   **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.592]

71   **Gali WL**, Sarabanda AV, Baggio JM, Ferreira LG, Gomes GG, Marin-Neto JA, Junqueira LF. Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas' heart disease: comparison with a control group treated with amiodarone alone. *Europace* 2014; **16**: 674-680 [PMID: 24481778 DOI: 10.1093/europace/eut422]

72   **Barbosa MP**, da Costa Rocha MO, de Oliveira AB, Lombardi F, Ribeiro AL. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. *Europace* 2013; **15**: 957-962 [PMID: 23376978 DOI: 10.1093/europace/eut011]

73   **Poole JE**, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008; **359**: 1009-1017 [PMID: 18768944 DOI: 10.1056/NEJMoa071098]

74   **de Paola AA**, Horowitz LN, Miyamoto MH, Pinheiro R, Ferreira DF, Terzian AB, Cirenza C, Guiguer N Jr, Portugal OP. Angiographic and electrophysiologic substrates of ventricular tachycardia in chronic Chagasic myocarditis. *Am J Cardiol* 1990; **65**: 360-363 [PMID: 2301265 DOI: 10.1016/0002-9149(90)90302-h]

75   **Sosa E**, Scanavacca M, D'Avila A, Bellotti G, Pilleggi F. Radiofrequency catheter ablation of ventricular tachycardia guided by nonsurgical epicardial mapping in chronic Chagasic heart disease. *Pacing Clin Electrophysiol* 1999; **22**: 128-130 [PMID: 9990612 DOI: 10.1111/j.1540-8159.1999.tb00311.x]

76   **Sosa E**, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. *J Cardiovasc Electrophysiol* 1996; **7**: 531-536 [PMID: 8743758 DOI: 10.1111/j.1540-8167.1996.tb00559.x]

77   **Aliot EM**, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, Della Bella P, Hindricks G, Jaïs P, Josephson ME, Kautzner J, Kay GN, Kuck KH, Lerman BB, Marchlinski F, Reddy V, Schalij MJ, Schilling R, Soejima K, Wilber D; European Heart Rhythm Association (EHRA); Registered Branch of the European Society of Cardiology (ESC); Heart Rhythm Society (HRS); American College of Cardiology (ACC); American Heart Association (AHA). EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). *Heart Rhythm* 2009; **6**: 886-933 [PMID: 19467519 DOI: 10.1016/j.hrthm.2009.04.030]

78   **Cardoso RN**, Macedo FY, Garcia MN, Garcia DC, Benjo AM, Aguilar D, Jneid H, Bozkurt B. Chagas cardiomyopathy is associated with higher incidence of stroke: a meta-analysis of observational studies. *J Card Fail* 2014; **20**: 931-938 [PMID: 25230241 DOI: 10.1016/j.cardfail.2014.09.003]

79   **Cardoso R**, Garcia D, Fernandes G, He LI, Lichtenberger P, Viles-Gonzalez J, Coffey JO, Mitrani RD. The Prevalence of Atrial Fibrillation and Conduction Abnormalities in Chagas' Disease: A Meta-Analysis. *J Cardiovasc Electrophysiol* 2016; **27**: 161-169 [PMID: 26412204 DOI: 10.1111/jce.12845]

80   **Marcolino MS**, Palhares DM, Benjamin EJ, Ribeiro AL. Atrial fibrillation: prevalence in a large database of primary care patients in Brazil. *Europace* 2015; **17**: 1787-1790 [PMID: 26056188 DOI: 10.1093/europace/euv185]

81   **Samuel J**, Oliveira M, Correa De Araujo RR, Navarro MA, Muccillo G. Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. *Am J Cardiol* 1983; **52**: 147-151 [PMID: 6858902 DOI: 10.1016/0002-9149(83)90085-1]

82   **Echeverría LE**, Rojas LZ, Gómez-Ochoa SA. Coagulation disorders in Chagas disease: A pathophysiological systematic review and meta-analysis. *Thromb Res* 2021; **201**: 73-83 [PMID: 33652329 DOI: 10.1016/j.thromres.2021.02.025]

83   **Herrera RN**, Díaz de Amaya EI, Pérez Aguilar RC, Joo Turoni C, Marañón R, Berman SG, Luciardi HL, Coviello A, Peral de Bruno M. Inflammatory and prothrombotic activation with conserved endothelial function in patients with chronic, asymptomatic Chagas disease. *Clin Appl Thromb Hemost* 2011; **17**: 502-507 [PMID: 20699256 DOI: 10.1177/1076029610375814]

84   **Mangone CA**, Sica RE, Pereyra S, Genovese O, Segura E, Riarte A, Sanz OP, Segura M. Cognitive impairment in human chronic Chagas' disease. *Arq Neuropsiquiatr* 1994; **52**: 200-203 [PMID: 7826247 DOI: 10.1590/s0004-282x1994000200008]

85   **Lima-Costa MF**, Castro-Costa E, Uchôa E, Firmo J, Ribeiro AL, Ferri CP, Prince M. A population-based study of the association between Trypanosoma cruzi infection and cognitive impairment in old age (the Bambuí Study). *Neuroepidemiology* 2009; **32**: 122-128 [PMID: 19088484 DOI: 10.1159/000182819]

86   **Oliveira-Filho J**, Viana LC, Vieira-de-Melo RM, Faiçal F, Torreão JA, Villar FA, Reis FJ. Chagas disease is an independent risk factor for stroke: baseline characteristics of a Chagas Disease cohort. *Stroke* 2005; **36**: 2015-2017 [PMID: 16081855 DOI: 10.1161/01.STR.0000177866.13451.e4]

87   **Lee-Felker SA**, Thomas M, Felker ER, Traina M, Salih M, Hernandez S, Bradfield J, Lee M, Meymandi S. Value of cardiac MRI for evaluation of chronic Chagas disease cardiomyopathy. *Clin Radiol* 2016; **71**: 618.e1-618.e7 [PMID: 27017480 DOI: 10.1016/j.crad.2016.02.015]

88   **Kernan WN**, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**: 2160-2236 [PMID: 24788967 DOI: 10.1161/STR.0000000000000024]

89   **Rybinnik I**, Wong S, Mehta D, Leker RR, Mullen MT, Messé SR, Kasner SE, Cucchiara B. Anticoagulation Choice and Timing in Stroke Due to Atrial Fibrillation: A Survey of US Stroke Specialists (ACT-SAFe). *J Stroke Cerebrovasc Dis* 2020; **29**: 105169 [PMID: 32912570 DOI: 10.1016/j.jstrokecerebrovasdis.2020.105169]

90   **Cougo-Pinto PT**, Dos Santos BL, Dias FA, Camilo MR, Alessio-Alves FF, Barreira CM, Santos-Pontelli TE, Abud DG, Leite JP, Pontes-Neto OM. Safety of IV thrombolysis in acute ischemic stroke related to Chagas disease. *Neurology* 2013; **81**: 1773-1775 [PMID: 24097814 DOI: 10.1212/01.wnl.0000435566.30728.be]

91   **Trabuco CC**, Pereira de Jesus PA, Bacellar AS, Oliveira-Filho J. Successful thrombolysis in cardioembolic stroke from Chagas disease. *Neurology* 2005; **64**: 170-171 [PMID: 15642935 DOI: 10.1212/01.WNL.0000148720.81701.B6]

92   **Al-Abcha A**, Herzallah K, Saleh Y, Mujer M, Abdelkarim O, Abdelnabi M, Almaghraby A, Abela GS. The Role of Direct Oral Anticoagulants Versus Vitamin K Antagonists in the Treatment of Left Ventricular Thrombi: A Meta-Analysis and Systematic Review. *Am J Cardiovasc Drugs* 2021; **21**: 435-441 [PMID: 33354748 DOI: 10.1007/s40256-020-00458-2]

93   **Echeverría LE**, Marcus R, Novick G, Sosa-Estani S, Ralston K, Zaidel EJ, Forsyth C, RIbeiro ALP, Mendoza I, Falconi ML, Mitelman J, Morillo CA, Pereiro AC, Pinazo MJ, Salvatella R, Martinez F,

Perel P, Liprandi ÁS, Piñeiro DJ, Molina GR. WHF IASC Roadmap on Chagas Disease. *Glob Heart* 2020; **15**: 26 [PMID: 32489799 DOI: 10.5334/gh.484]

94   **Ciapponi A**, Alcaraz A, Calderón M, Matta MG, Chaparro M, Soto N, Bardach A. Burden of Heart Failure in Latin America: A Systematic Review and Meta-analysis. *Rev Esp Cardiol (Engl Ed)* 2016; **69**: 1051-1060 [PMID: 27553287 DOI: 10.1016/j.rec.2016.04.054]

95   **Ayub-Ferreira SM**, Mangini S, Issa VS, Cruz FD, Bacal F, Guimarães GV, Chizzola PR, Conceição-Souza GE, Marcondes-Braga FG, Bocchi EA. Mode of death on Chagas heart disease: comparison with other etiologies. a subanalysis of the REMADHE prospective trial. *PLoS Negl Trop Dis* 2013; **7**: e2176 [PMID: 23638197 DOI: 10.1371/journal.pntd.0002176]

96   **Martí-Carvajal AJ**, Kwong JS. Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy. *Cochrane Database Syst Rev* 2016; **7**: CD009077 [PMID: 27388039 DOI: 10.1002/14651858.CD009077.pub3]

97   **Bocchi EA**, Rassi S, Guimarães GV; Argentina, Chile, and Brazil SHIFT Investigators. Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial. *ESC Heart Fail* 2018; **5**: 249-256 [PMID: 29266804 DOI: 10.1002/ehf2.12240]

98   **Ramires FJA**, Martinez F, Gómez EA, Demacq C, Gimpelewicz CR, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJV. Post hoc analyses of SHIFT and PARADIGM-HF highlight the importance of chronic Chagas' cardiomyopathy Comment on: "Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial" by Bocchi *et al*. *ESC Heart Fail* 2018; **5**: 1069-1071 [PMID: 30298996 DOI: 10.1002/ehf2.12355]

99   **Benatti RD**, Al-Kindi SG, Bacal F, Oliveira GH. Heart transplant outcomes in patients with Chagas cardiomyopathy in the United States. *Clin Transplant* 2018; **32**: e13279 [PMID: 29744939 DOI: 10.1111/ctr.13279]

100   **Heo S**, Lennie TA, Moser DK, Okoli C. Heart failure patients' perceptions on nutrition and dietary adherence. *Eur J Cardiovasc Nurs* 2009; **8**: 323-328 [PMID: 19589729 DOI: 10.1016/j.ejcnurse.2009.05.005]

101   **Riegel B**, Lee S, Hill J, Daus M, Baah FO, Wald JW, Knafl GJ. Patterns of adherence to diuretics, dietary sodium and fluid intake recommendations in adults with heart failure. *Heart Lung* 2019; **48**: 179-185 [PMID: 30638609 DOI: 10.1016/j.hrtlng.2018.12.008]

102   **Anderson CA**, Cobb LK, Miller ER 3rd, Woodward M, Hottenstein A, Chang AR, Mongraw-Chaffin M, White K, Charleston J, Tanaka T, Thomas L, Appel LJ. Effects of a behavioral intervention that emphasizes spices and herbs on adherence to recommended sodium intake: results of the SPICE randomized clinical trial. *Am J Clin Nutr* 2015; **102**: 671-679 [PMID: 26269371 DOI: 10.3945/ajcn.114.100750]

103   **Chambela MDC**, Mediano MFF, Carneiro FM, Ferreira RR, Waghabi MC, Mendes VG, Oliveira LS, de Holanda MT, de Sousa AS, da Costa AR, Xavier SS, da Silva GMS, Saraiva RM. Impact of pharmaceutical care on the quality of life of patients with heart failure due to chronic Chagas disease: Randomized clinical trial. *Br J Clin Pharmacol* 2020; **86**: 143-154 [PMID: 31659776 DOI: 10.1111/bcp.14152]

104   **Lopes LBDC**, Pereira RR, Andrade PM, Carneiro FM, Mediano MFF, Kilgore SIL, Hasslocher-Moreno AM, Sousa AS, Oliveira MME, Saraiva RM, Holanda MT, Silva GMSD. Adverse drug events and the associated factors in patients with chronic Chagas disease. *Rev Soc Bras Med Trop* 2020; **53**: e20190443 [PMID: 32321092 DOI: 10.1590/0037-8682-0443-2019]

105   **Lacombe SP**, LaHaye SA, Hopkins-Rosseel D, Ball D, Lau W. Identifying patients at low risk for activity-related events: the RARE Score. *J Cardiopulm Rehabil Prev* 2014; **34**: 180-187 [PMID: 24603142 DOI: 10.1097/HCR.0000000000000045]

106   **Ambrosetti M**, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M, Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020 [PMID: 33611446 DOI: 10.1177/2047487320913379]

107   **Frota AX**, Mendes FSNS, Vieira MC, Saraiva RM, Veloso HH, da Silva PS, Sperandio da Silva GM, de Sousa AS, Mazzoli-Rocha F, Costa HS, Rodrigues Junior LF, Mediano MFF. Acute and subacute hemodynamic responses and perception of effort in subjects with chronic Chagas cardiomyopathy submitted to different protocols of inspiratory muscle training: a cross-over trial. *Disabil Rehabil* 2020; 1-8 [PMID: 32779544 DOI: 10.1080/09638288.2020.1800837]

108   **Palau P**, Domínguez E, Núñez E, Schmid JP, Vergara P, Ramón JM, Mascarell B, Sanchis J, Chorro FJ, Núñez J. Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. *Eur J Prev Cardiol* 2014; **21**: 1465-1473 [PMID: 23864363 DOI: 10.1177/2047487313498832]

109   **Adamopoulos S**, Schmid JP, Dendale P, Poerschke D, Hansen D, Dritsas A, Kouloubinis A, Alders T, Gkouziouta A, Reyckers I, Vartela V, Plessas N, Doulaptsis C, Saner H, Laoutaris ID. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: The Vent-HeFT trial: a European prospective multicentre randomized trial. *Eur J Heart Fail* 2014; **16**: 574-582 [PMID: 24634346 DOI: 10.1002/ejhf.70]

110   **Poole DC**, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. *Am J Physiol Heart Circ Physiol* 2012; **302**: H1050-H1063 [PMID: 22101528 DOI: 10.1152/ajpheart.00943.2011]

111   **Bjarnason-Wehrens B**, Predel HG. Inspiratory muscle training - an inspiration for more effective cardiac rehabilitation in heart failure patients? *Eur J Prev Cardiol* 2018; **25**: 1687-1690 [PMID: 30198748 DOI: 10.1177/2047487318798917]

112   **Piepoli MF**, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, McMurray J, Pieske B, Piotrowicz E, Schmid JP, Anker SD, Solal AC, Filippatos GS, Hoes AW, Gielen S, Giannuzzi P, Ponikowski PP. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011; **13**: 347-357 [PMID: 21436360 DOI: 10.1093/eurjhf/hfr017]