

# Advances in Clinical Practice, Diagnosis and Treatment of Chronic Chagas' Heart Disease

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## Abstract

Chagas disease has become globalized as a result of the migratory process of infected patients to non-endemic areas. With the considerable number of individuals affected by the disease, detection and treatment of its chronic manifestations is a relevant and necessary issue. Growing attention has been paid to chronic Chagas cardiomyopathy (CCC), which includes heart failure, malignant arrhythmias, conduction disturbances and thromboembolic events. Many pharmacological and non-pharmacological treatments for CCC are still extrapolations of existing evidence on the treatment of other clinical conditions, highlighting the need of including this group of patients in future studies. In this review, we will discuss the most recent data from the literature and clinical practice on the diagnosis and treatment of CCC.

## Introduction

Chagas disease (CD) is a neglected tropical disease that affects socially vulnerable individuals that experience stigma, discrimination and high morbidity and mortality, especially those with the cardiac form of the disease.<sup>1,2</sup> Changes in the epidemiological landscape of CD have been described worldwide.

With the migratory phenomenon, CD has become globalized. Especially coming from the Latin America, CD

patients have moved to developed countries for better life conditions. For the time being, it is estimated that 6-7 million people in the world have CD, and approximately 100 million are at risk of contracting the disease (Figure 1).<sup>1,3</sup>

The number of Latin-Americans living in peripheral urban agglomerations has drastically increased.<sup>4</sup> Parallel to the trends of population and urbanization growth, there have been increasing reports of events related to emerging infectious diseases, in which the presence of insect vectors has contributed to dissemination and transmission of zoonoses.<sup>5,6</sup> Estimates have shown that there are 400,000 Latin-Americans with CD living in other continents, especially in the United States, Canada, Europe, Australia and Japan. Although becoming citizens of the world, these individuals still live in poor socioeconomic conditions and limited access to health systems.<sup>7</sup>

In Brazil, it is estimated that at least one million people are infected with *Trypanosoma cruzi* (T. cruzi).<sup>8</sup> In the last 15 years, systematic occurrence of acute cases of CD, outbreaks related either to oral transmission by the ingestion of contaminated foods, mainly in the Amazon region, or to vectorial transmission due to accidental exposure to the wild cycle of the etiologic agent.<sup>7,9</sup> CD has become an urban condition in the 80's, with the rural-urban migration, with a high number of patients currently living in the periphery of large cities.<sup>10,11</sup> Considering the high uncertainty of the Brazilian numbers, a giant step has been taken with the compulsory notification of the cases since 2020 (decree number 1061 of May 18, 2020); however, unfortunately, very little progress has been seen since then, due to the COVID-19 pandemic, and the weakening of programs for the care of CD patients.<sup>12</sup>

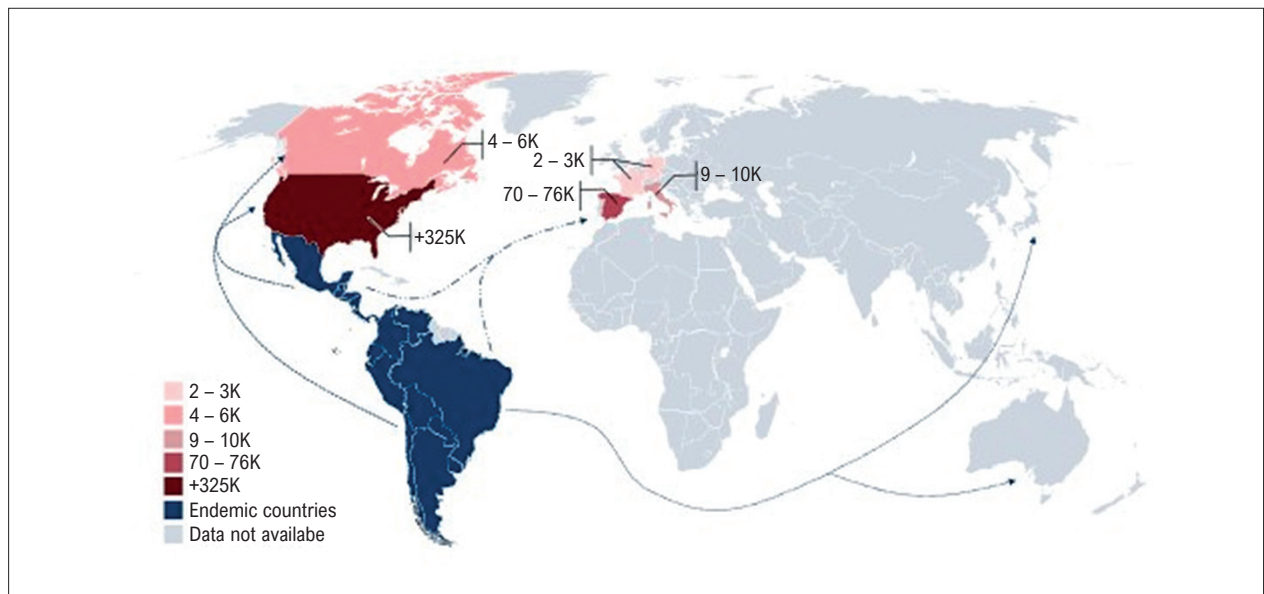
With the increase in life expectancy of the general population, the number of CD patients at older ages and with more comorbidities has dramatically increased.<sup>13</sup> Approximately 25-30% of patients infected with *T. cruzi* develop chronic Chagas cardiomyopathy (CCC),<sup>14</sup> which may lead to arrhythmias, heart failure (HF), thromboembolic phenomena, and changes in the myocardial wall (Figure 2).

## Keywords

Chagas disease; Chronic Chagasic Cardiomyopathy; Cardiac insufficiency; Treatment; Diagnosis

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**Figure 1** – Estimated number of immigrants infected with *Trypanosoma cruzi* in non-endemic countries; data-based estimates for the United States (2007), Canada (2006), Europe (2008–2011), Japan (2007), Australia (2011) and New Zealand (2006)+<sup>3</sup>

The mortality rate of patients seen in outpatient care is estimated at 4% a year.<sup>15</sup>

In light of the growing number of patients infected with *T. cruzi* or at risk for CD, and consequently at higher risk of CCC, the understanding of the latest information about the diagnosis and management of these patients is essential for the clinical practice. This will be the focus of our discussion.

## Diagnosis

### Laboratory

The diagnosis of *T. cruzi* infection is established by different laboratory techniques, depending on the stage of disease.<sup>16</sup> In the acute phase, because of parasitemia, it is recommended the direct detection of the parasite in the blood. Although it has a specificity of 100%, sensitivity may vary between the tests. Besides, the continuous training of microscopists should be considered for a positive impact on resource performance.

In the chronic phase, with the reduction of parasites in the blood, a serological diagnosis is required, by applying two tests for the presence of anti-*T. cruzi* IgG antibodies. The most used methods are enzyme-linked immunosorbent assay (ELISA), chemiluminescence microparticle immunoassay, indirect hemagglutination, and indirect immunofluorescence reaction. In case of disagreement, a third test is used for definition of a suspected case.<sup>7,17</sup> Conflicting results may be explained by an insufficient antibody production, and, in these cases, molecular methods for detection of *T. cruzi* DNA have been used as an excellent alternative for these cases.<sup>18-20</sup>

Immunochromatography (rapid test) has been used for point-of-care testing of *T. cruzi* infection among family

members of patients in field works or at outpatient clinics.<sup>21</sup> Serological tests are subsequently performed to confirm.

Recently, one of the largest outbreaks in Brazil has occurred in Pernambuco, and the diagnosis of suspected cases was only possible by real-time polymerase chain reaction (PCR) using the TcSAT-IAM.<sup>18</sup> Besides, this method has been suggested to monitor the etiological treatment in the chronic phase,<sup>22</sup> since today the criteria for cure of CD is antibody decay analyzed by serological techniques, which may take many years.

### Electrocardiogram

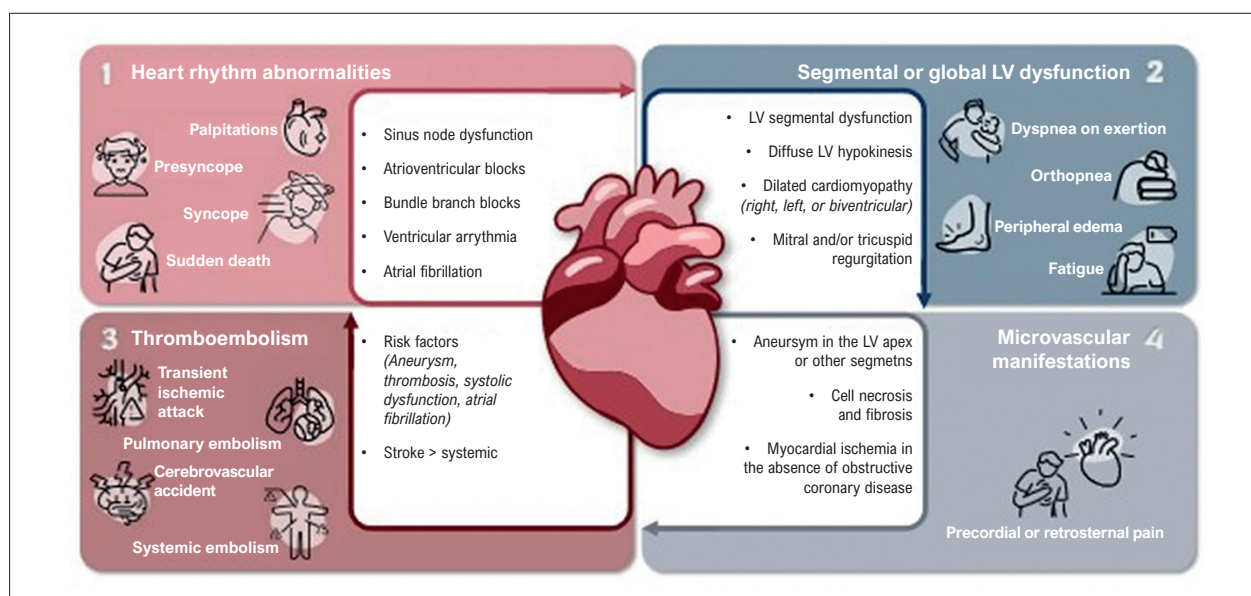
Based on current knowledge of the natural history of CD, electrocardiographic changes precede the occurrence of symptoms, abnormalities on physical examination and chest X-ray.<sup>23</sup> A positive predictive value of 35% and a negative predictive value of 98% were seen in the diagnosis of systolic ventricular dysfunction in patients with abnormal ECG.<sup>24</sup> Therefore, ECG is an important diagnostic and prognostic instrument.

ECG should be performed for suspected or confirmed cases of CD and regularly repeated to assess the emergence or progression of abnormalities. Complete or incomplete right bundle branch block (RBBB) is one of the most common conduction disorders (10-50% of patients) and is frequently associated with anterior-superior fascicular block (the most common combination in chronic heart disease). Left bundle branch block (LBBB) is rare.<sup>25-27</sup>

### Cardiac images

#### Echocardiogram

Transthoracic echocardiogram is the most commonly used imaging method in the assessment, follow-up and staging of



**Figure 2** – Clinical presentations in chronic Chagas cardiomyopathy; LV: left ventricular.

heart diseases. Left ventricular (LV) segmental changes may be present in up to 10% of patients in initial stages and in 50% of patients with ventricular dysfunction and dilation. Abnormal contractility and aneurysms are predictors of LV deterioration and arrhythmias.<sup>28-30</sup> Apical aneurysms are atypical, and more common in patients with systolic dysfunction; they may be associated with intraventricular mural thrombus, and are considered important risk factors for systemic embolism, including cerebrovascular accident.<sup>31,32</sup>

Transthoracic echocardiogram is a crucial test for the initial assessment and follow-up of patients with CCC, especially due to its low cost and easy access. New echocardiographic techniques have added gains. Contrast echocardiography may be useful in the detection of aneurysms and ventricular thrombus, for improving echocardiographic endocardial border delineation, influencing physicians' clinical decision-making about the need of anticoagulation. The use of global longitudinal strain may help in the evaluation of the heterogeneity of systolic contraction, already related to arrhythmic events, regardless of LV the ejection fraction.<sup>33</sup> Three-dimensional echocardiography allows a more accurate evaluation of LV apex and LV ejection fraction using the Simpson method, including the ventricular geometry, which may be distorted in CCC.

### Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) may be useful when other imaging techniques are not enlightening. The major advantage of the method is the possibility of evaluating and characterizing the myocardium, identifying areas of myocardial fibrosis (MF). MF may be present in all stages of the disease, affecting up to 68% of patients.<sup>34</sup> The early detection of edema and/or MF is correlated with the risk of disease progression, severity of LV systolic dysfunction

and risk of arrhythmias.<sup>35</sup> Recently, MF mass and MF area have been correlated with all-cause mortality, cardiac transplantation, shock delivered by implantable cardioverter defibrillator implantable and aborted sudden cardiac death; 76% of CCC patients had MF with a mass equal to or superior to 12.3 grams.<sup>36</sup>

### Treatment

Clinical management of patients with CCC involves monitoring of disease progression, non-pharmacological interventions, antitrypanosomal therapy in specific subgroups and supporting treatment for the main cardiovascular complications, including HF, malignant arrhythmias, electrical conduction disturbances and pulmonary and systemic thromboembolic events.<sup>14</sup>

### Non-pharmacological treatment

The greatest challenge in the treatment of chronic diseases is adherence to treatment, be it pharmacological or not.<sup>37</sup> Several factors are added to the complexity of HF, such as polypharmacy, side effects and systemic repercussions with mobility restrictions. The patient and family members affected by the disease stigma live farther from the big cities, making the access to specialized health care services more difficult. Also, these individuals have limited access to free medications, low purchasing power, low educational attainment; they are hence socially, economically and psychologically vulnerable people that require an integral care, with biopsychosocial approach by a multidisciplinary team.

In the last decades, advances have been made in the management of myocardial pathologies, especially by the change of paradigms towards educational interventions for self-care,

which has become as important as pharmacological therapies and implantable devices. Interdisciplinary interventions in the follow-up of HF patients are recommended in self-care, hospitalization and outpatient scenarios.<sup>37-39</sup>

In this context, the multidisciplinary team plays a key role in the integral care, considering each patient individually, helping in the establishment of the most appropriate therapeutic, with few complications and better quality of life for the patients, and capacitate them self-care (Figura 3).<sup>40,41</sup> According to patient needs, accessible technologies should be prioritized, facilitating the understanding of the interventions proposed. In addition, multifaceted approaches, such as those on warning signs of decompensation and anti-alcohol programs have been evaluated.

Another pillar of CCC treatment is rehabilitation. A randomized, controlled, single blind study with 40 patients demonstrated improvement of functional capacity and quality of life with exercises.<sup>42</sup> Another study correlated physical training with improvement of microvascular function in these patients.<sup>43</sup> Despite their benefits, rehabilitation clinics are not widely available. Remote monitoring (telehealth) has been a support strategy to increase the access to specialized professionals.

National and international experiences have shown that the formation of associations of patients has played a fundamental role in the recognition of similarities, helping in the elucidation of the disease and its development process.

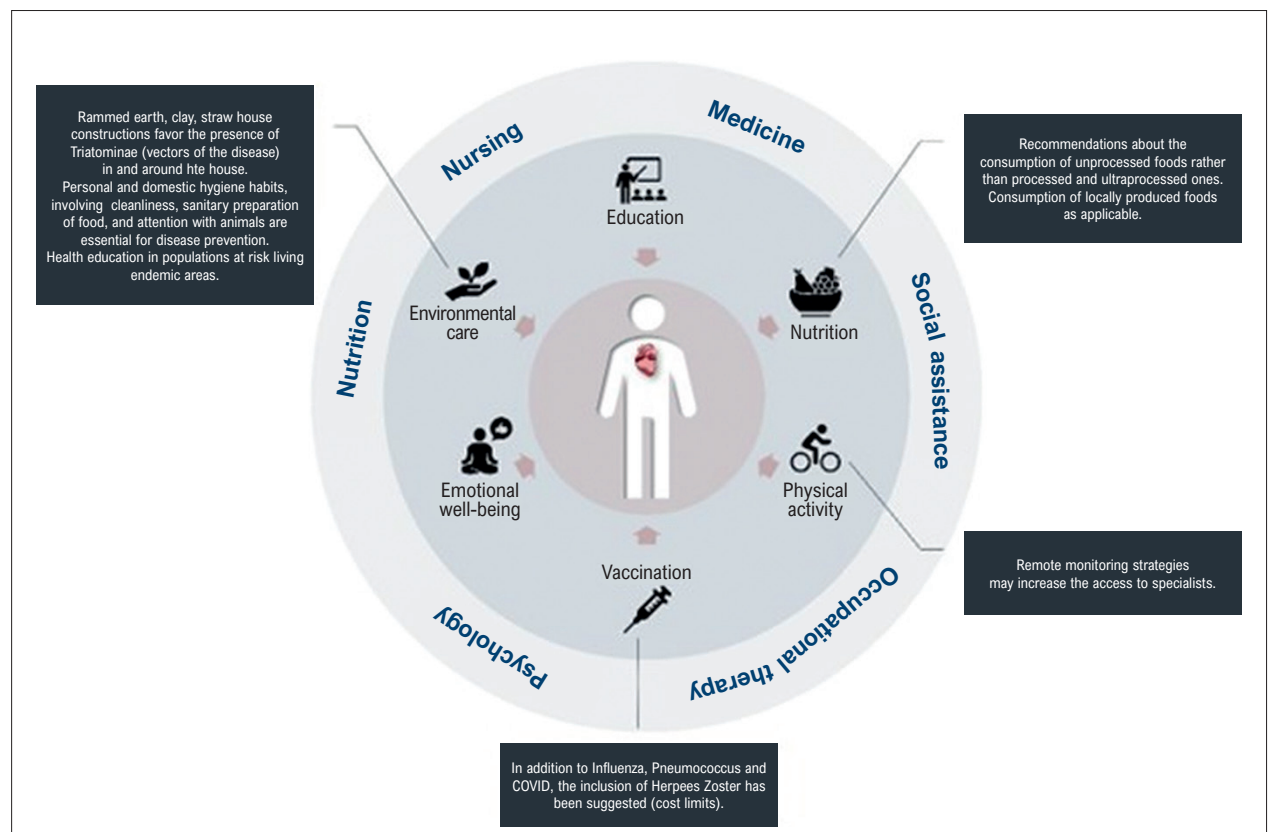
An active role of the patient should be encouraged, to stimulate its critical awareness of their rights and needs, favoring the decision making about health and collectivity. The associations focused on patient well-being try to contribute to a solid identity and citizenship.

### Antitrypanosomal therapy

The main data on antitrypanosomal therapy in patients with CCC derive from the BENEFIT study. This multicenter, randomized, controlled study involving 2854 patients with CCC and mild hemodynamic repercussions, and not including severely ill patients, did not show significant effects of benznidazole in preventing clinical deterioration of patients with established Chagas cardiomyopathy.<sup>44</sup> Based on these data, the antitrypanosomal therapy is not performed routinely in this group of patients.

### Heart failure treatment

The treatment of CCC is mostly based on the evidence from the treatment of other conditions that lead to HF with ventricular dysfunction. However, many of the established clinical trials with medications that reduced mortality did not include patients with Chagas cardiomyopathy. The few studies that have evaluated treatment in this population have methodological limitations regarding randomization, blinding, sample size and study closure.<sup>45,46</sup>



**Figure 3** – Integral care of patients with chronic Chagas cardiomyopathy.



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The routine treatment of CCC includes the combination of beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), digoxin, diuretics, and anticoagulants.<sup>47</sup> New therapies including angiotensin receptor neprilysin inhibitor (ARNI) and sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown important results.<sup>48-50</sup>

### ACEI and ARB

The ACEIs have been the basis of treatment of HF with reduced ejection fraction (HFrEF) for more than two decades, since enalapril demonstrated a reduction in the risk of death in symptomatic patients.<sup>51,52</sup> A double-blind, controlled study with 42 CD patients also showed the benefits of using ACEIs, even before the introduction of BB, showing improvement of the functional class and reduction of brain natriuretic peptide levels.<sup>45</sup> These studies have supported the use of ACEI in CCC, but with an important caveat regarding the fact that these patients have more borderline blood pressure levels and may become symptomatic with the use of these drugs.<sup>53</sup> ACEIs are also recommended for patients with CCC who have segmental involvement of the ventricular wall, even in the absence of LV dysfunction.<sup>47</sup>

The effects of ARB on mortality have been inconsistent.<sup>54,55</sup> This class of drugs is indicated in case of intolerance to ACEIs only.<sup>56</sup>

### Beta-blockers

Patients with CCC frequently have autonomic dysfunction, bradycardia and blocks. Based on this, greater attention has been given to the efficacy and safety of sympathetic blockade by the use of these drugs in this population.<sup>57</sup> With clinical practice, the use and importance of BB in HFrEF has increased over the years, and subanalyses have shown their safety and benefits in the treatment of CCC.

Important studies involving BB have shown a reduction in mortality both in patients with mild to moderate symptoms of HF<sup>58</sup> and in patients with severe symptoms, reducing the combined relative risk of death and hospitalization by 31%.<sup>59</sup>

In a randomized, double-blind, placebo-controlled trial in 42 patients with CCC, the use of carvedilol was well tolerated, and not associated with symptomatic bradycardia.<sup>45</sup> An observational study showed an association between BB and increased survival of CCC patients.<sup>60</sup> This result was also reported in a subanalysis of the REMADHE trial.<sup>57</sup>

Although large studies on BB have not included CD patients in the baseline, there is no biological plausibility to question the benefits of this class of drugs in the treatment of this population.<sup>53</sup>

### Mineralocorticoid receptor antagonists

The Randomized Aldactone Evaluation Study (RALES), published in 1999, evaluated the use of spironolactone (25-50 mg daily) or placebo by patients with HFrEF ( $\leq 35\%$ ) and functional class III-IV. The trial was discontinued early after an analysis determined satisfactory results in mortality,

with a relative risk reduction of 35%.<sup>61</sup> Although patients with CCC have been poorly represented, there has been no evidence against the use of spironolactone in this population.

Aldosterone receptor antagonists appear to be safe in Chagas cardiomyopathy and should be added to patients already taking ACEI and BB.<sup>47</sup>

### Sacubitril / Valsartana

In 2014, the PARADIGM-HF was published. The study validated the use of ARNI and compared it with ACEI (enalapril) in the treatment of HFrEF, showing a reduction in the relative risk of the combined outcome of hospitalizations for HF and cardiovascular mortality by 20%.<sup>50</sup> A post-hoc analysis of a subgroup of 113 CCC patients taking angiotensin-receptor antagonists ( $n=58$ ) showed a lower risk of cardiovascular death and hospitalizations for HF, in either analysis of the composite outcome or by the analysis of the outcomes alone.<sup>62</sup> Despite the low representativeness of patients with Chagas' heart disease in these studies, this class of medications is a valid alternative, already incorporated in the clinical treatment of CCC patients.<sup>53</sup>

Sacubitril/valsartan is currently being investigated in the PARACHUTE study, an ongoing study designed to compare the effectiveness and safety of these drugs with enalapril, by analysis of morbidity, mortality, and variation of NT-proBNP levels in patients with CCC. We believe that these data focusing on CCC patients may help in establishing more fundamental practices in the clinical management of these patients.

### SGLT2 inhibitors

The DAPA-HF<sup>48</sup> and the EMPEROR-Reduced<sup>49</sup> are the main studies so far published on SGLT2 inhibitors in patients with HFrEF. The studies evaluated the use of dapagliflozin and empagliflozin, respectively, against placebo, in patients with ventricular dysfunction. The primary outcome was a composite of cardiovascular death and hospitalization for HF. The results showed a reduction in the risk of the composite outcome and in all-cause mortality as compared with placebo.<sup>48,49</sup> A sub-study<sup>63</sup> of the DAPA-HF evaluated the efficacy and safety of dapagliflozin according to etiology of HF (ischemic or non-ischemic) and found similar results regardless of the etiology.<sup>48,63</sup>

CCC patients have not been represented in these large clinical trials on SGLT-2 inhibitors. However, there are no known interaction mechanisms that may affect the efficacy of this therapy in this group. SGLT2 inhibitors have been part of the therapeutic armamentarium in CCC, with good results, and already incorporated in current guidelines.<sup>53</sup>

### Other drugs used in CCC

#### Digoxin

There are few studies on the safety and efficacy of digoxin in patients with CCC. There are, however, indirect

clinical evidence of symptom improvement and reduction of hospitalizations in patients with HFrEF.<sup>64</sup> In clinical practice, digoxin has been used selectively in patients with persistent functional class III or IV despite optimized clinical treatment, as well as in patients with atrial fibrillation and increased ventricular response.<sup>53</sup>

### Ivabradine

In 2020, the SHIFT<sup>65</sup> study showed the effects of ivabradine on outcomes in patients with HFrEF, heart rate 70 beats per min or higher and in sinus rhythm. The study showed a relative reduction in hospitalizations for heart failure.<sup>65</sup> Years later, a post-hoc analysis<sup>38</sup> of this study was conducted aiming to evaluate the effects of ivabradine in patients with CCC, and showed that the drug was also effective in reducing heart rate and improving functional class of this group of patients.<sup>38</sup> These results should be interpreted with caution due to the limited sample size of patients with this nosologic entity.<sup>38</sup>

### Nitrate and Hydralazine

Evidence of the clinical benefits of the combined therapy of nitrate and hydralazine comes from studies conducted before the eighties, when drug treatment for HF was focused on symptom control, with no effect on mortality. Two main studies have grounded this combined therapy – in 1986, a beneficial, but not significant effect was shown on mortality,<sup>66</sup> and in 1991 additional survival was seen in patients receiving enalapril (18%) versus hydralazine and nitrate.<sup>67</sup>

However, physiological outcomes have suggested that the vasodilator effects of enalapril and the combination of hydralazine and nitrate may be complementary,<sup>67</sup> benefiting patients with congestion, renal dysfunction, or hyperkalemia, which limits the use of ACEI. Nevertheless, there are challenges regarding posology, since the fixed-dose combination medication is not available in Brazil.

### Diuretics

Diuretics act primarily by relieving of congestive symptoms in HF patients. There is no evidence of their association with mortality reduction. Diuretics are recommended to improve the quality of life of patients with CCC, reduced ejection fraction and congestion.<sup>47</sup>

### Treatment of arrhythmias and conduction disturbances

Chagas cardiomyopathy is characterized by a significant involvement of the myocardium and the conduction system and is an important cause of morbidity and mortality of individuals during their working lifetime. RBBB is frequently associated with anterior-superior fascicular block, and LBBB has a worse prognosis.<sup>25-27</sup> Atrioventricular block (AVB) is common; it may be present in different degrees and be the first manifestation of the disease. Advanced complete AVB and AVB may occur, requiring a permanent pacemaker implantation due to increased risk of sudden death for asystole. Sinus node dysfunction may be manifested with

sinus bradycardia and pauses secondary to sinoatrial block. Atrial fibrillation (5% of ECGs) is usually associated with more pronounced and extensive myocardial damage and is a predictor of worse prognosis.<sup>25,26,68</sup>

Cardiac sudden death is the main cause of death (55-65% of patients) and is often associated with manifestations of HF. The main mechanisms are complex arrhythmias such as ventricular tachycardia and ventricular fibrillation.<sup>69-71</sup>

Table 1 describes CD-related arrhythmias that are predictors of sudden death and their respective treatments.

### Antithrombotic therapy

The incidence of thromboembolic phenomena in patients with Chagas' heart disease is higher in those with ventricular dysfunction, apical aneurysm, left ventricular mural thrombosis and arrhythmias.<sup>47,73</sup>

Anticoagulation is recommended for CCC patients with permanent or paroxysmal atrial fibrillation, previous thromboembolic events or cardiac thrombus detected by imaging tests. It may also be indicated in cases of apical aneurysm.<sup>47</sup> So far, there is no scientific evidence for the use of antiplatelet agents to prevent thromboembolic events in CD, although aspirin can be used for stroke prevention in patients at high risk of bleeding.

### Cardiac transplantation

Cardiac transplantation has become an option for patients with advanced CCC, who are refractory to optimized drug treatment. The selection criteria are no different from those of patients with other etiologies, except for the presence of gastrointestinal disturbances (megaesophagus and/or megacolon) which are relative contraindications to the procedure. Short-term and long-term outcomes of cardiac transplantation in this population have been described as better survival outcomes when compared with other groups of patients undergoing cardiac transplantation.<sup>74</sup>

Immunosuppressive therapy may increase the likelihood of CD reactivation. The immunosuppressive regimen with lower doses has been associated with lower reactivation rates and better outcomes, without increasing the risk of graft rejection.<sup>74,75</sup> Despite the risk of CD reactivation, prophylaxis with antitrypanosomal therapy before the transplantation is not recommended, although the therapeutic response to benznidazole has been satisfactory.<sup>76</sup>

### Conclusion

CD persists as a neglected disease, with an unfavorable course in patients with CCC, considering the high mortality rate and significant impairment of the quality of life. Over the last years, due to emigration of individuals from endemic to non-endemic countries, the disease has taken on global proportions, and become a problem not exclusive to Latin America.

A multidisciplinary support is essential to deliver holistic care to patients. Non-pharmacological measures should be

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**Table 1 – Chagas disease-related arrhythmias, predictors of sudden death, and their respective treatments**

| Arrhythmia                                   | General characteristics   | Drug treatment  | Intensive therapy ICD and/or RF ablation  |
|--|---|---|---|
| Ventricular extrasystole (VE)                | <ul style="list-style-type: none"> <li>– 86-88% of patients without HF and in almost all patients with HF</li> <li>– High density: &gt;1000VEs/hour in 45-89% of patients (according to the EF)</li> </ul>                                      | <ul style="list-style-type: none"> <li>– Symptomatic in the absence of ventricular dysfunction<br/>Beta-blockers (nadolol, sotalol or propafenone) may be used</li> <li>– If HFrEF<br/>Amiodarone (200-600mg/day) due to its higher efficacy in reducing VE density</li> </ul>  | <ul style="list-style-type: none"> <li>– Not indicated</li> </ul>   |
| Non-sustained ventricular tachycardia (NSVT) | <ul style="list-style-type: none"> <li>– 40% dos patients</li> <li>– Independent predictor of arrhythmic and global and editor, mainly in patients with a high Rassi score</li> <li>– It increases mortality by up to 15 times in HF</li> </ul> | <ul style="list-style-type: none"> <li>– Without ventricular dysfunction<br/>Similar approach to that of patients with VE</li> <li>– If HFrEF<br/>Beta-blocker<br/>Amiodarone (RCT using amiodarone: GESICA and EPAMSA)</li> <li>–If symptoms<br/>Antiarrhythmics: beta-blockers, sotalol, amiodarone (LV dysfunction and/or fibrosis)</li> </ul>   | <ul style="list-style-type: none"> <li>– Primary prevention in chronic Chagas disease in case of NSVT, LVEF &lt; 35% and optimized treatment (CR II b LE C)**</li> <li>– Awaiting for conclusions of the Brazilian multicentric RCT CHAGASICS, comparing amiodarone vs. ICD in reducing global mortality (primary prevention)</li> </ul>  |
| Sustained ventricular tachycardia (SVT)      | <ul style="list-style-type: none"> <li>– Worse prognosis</li> <li>– Found in 80 - 85% of electrophysiologic studies (EPSS)</li> </ul>   | <ul style="list-style-type: none"> <li>– Based on observational studies comparing amiodarone vs. ICD in Chagas heart disease and on extrapolation of data from RCTs on other heart diseases</li> <li>– Indication for the use of amiodarone according to current guidelines (weighted RL)*:<br/>Stable SVT with EF &gt;40% (LE B)<br/>SVT with syncope and EF&gt;40% (LE B)<br/>Syncope associated with monomorphic ventricular tachycardia induced in an EPS and EF&gt;40% (LE B)<br/>Treatment of spontaneous SVT or symptomatic NSVT with induction of SVT during EPS (LE B)<br/>Patients with strong recommendation of ICD and limited life expectancy or without access to ICD (LE C)</li> </ul> | <ul style="list-style-type: none"> <li>– No evidence of indication of ICD for primary prevention of sudden death</li> <li>– Stable SVT with LVEF &lt;35% and optimized treatment (RL I; LE C)**</li> <li>– Stable SVT with LVEF &gt;35% and optimized treatment (RL IIa; LE C)**</li> <li>– Radiofrequency ablation for recurrent SVT irrespective of optimized treatment, to reduce shocks or arrhythmia storms</li> <li>– Autonomous modulation may be used when ablation is contraindicated (bilateral cervicothoracic sympathectomy)</li> </ul> |

(\*) Brazilian Society of Cardiology guidelines on diagnosis and treatment of patients with Chagas disease cardiomyopathy. (\*\*) 2023 Brazilian guidelines on cardiac implantable electronic devices. ICD: implantable cardioverter defibrillator; RF: radiofrequency; CR: class of recommendation; RCT: randomized clinical trial; EF: ejection fraction; LVEF: left ventricular ejection fraction; RL: recommendation level; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LE: level of evidence; LV: left ventricular.

reinforced at every visit, highlighting the active role and involvement of the patient in the therapies proposed. An appropriate pharmacological management is still hampered by the interests of big pharmaceutical companies. For this reason, much of what we have performed in clinical practice derive from large clinical trials on other conditions that also lead to HF.

The timely detection, integral care, notification, and epidemiological surveillance of individuals with CD should be reinforced not only by the increase of resources but also by capacitation of professionals at all levels of care. Therefore, primary attention seems to play the main role in the progress and control of notification of CD cases, which would contribute to better results in the care of these patients.

## Author Contributions

Conception and design of the research: Alves SMM, Silva BMS, Barbosa ED; Acquisition of data: Alves SMM, Silva BMS, Barbosa ED; Analysis and interpretation of the data: Alves SMM, Silva BMS, Barbosa ED, Medeiros CA, Barros MNDS, Cavalcanti MGAM, Assunção MELSM, Lorena VMB, Albuquerque ALT, Lucena RA, Pereira Júnior CB, Costa LR, Carrazzone CFV; Writing of the manuscript: Alves SMM, Silva BMS, Barbosa ED, Medeiros CA, Barros MNDS, Cavalcanti MGAM, Assunção MELSM, Lorena VMB, Lucena RA, Albuquerque ALT, Montenegro CEL, Pereira Júnior CB, Costa LR, Carrazzone CFV, Oliveira Júnior W; Critical revision of the manuscript for important intellectual content: Alves SMM, Silva BMS, Barbosa ED, Medeiros CA, Barros MNDS, Montenegro CEL, Oliveira Júnior W.

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This article does not contain any studies with human participants or animals performed by any of the authors.



## Review Article

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