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AHA SCIENTIFIC STATEMENT

Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management

A Scientific Statement From the American Heart Association

Endorsed by the Inter-American Society of Cardiology

BACKGROUND: Chagas disease, resulting from the protozoan *Trypanosoma cruzi*, is an important cause of heart failure, stroke, arrhythmia, and sudden death. Traditionally regarded as a tropical disease found only in Central America and South America, Chagas disease now affects at least 300 000 residents of the United States and is growing in prevalence in other traditionally nonendemic areas. Healthcare providers and health systems outside of Latin America need to be equipped to recognize, diagnose, and treat Chagas disease and to prevent further disease transmission.

METHODS AND RESULTS: The American Heart Association and the Inter-American Society of Cardiology commissioned this statement to increase global awareness among providers who may encounter patients with Chagas disease outside of traditionally endemic environments. In this document, we summarize the most updated information on diagnosis, screening, and treatment of *T cruzi* infection, focusing primarily on its cardiovascular aspects. This document also provides quick reference tables, highlighting salient considerations for a patient with suspected or confirmed Chagas disease.

CONCLUSIONS: This statement provides a broad summary of current knowledge and practice in the diagnosis and management of Chagas cardiomyopathy. It is our intent that this document will serve to increase the recognition of Chagas cardiomyopathy in low-prevalence areas and to improve care for patients with Chagas heart disease around the world.

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American trypanosomiasis or Chagas disease, caused by the protozoan *Trypanosoma cruzi*, is responsible for the highest disease burden of any parasitic disease in the Western Hemisphere. In the absence of successful treatment, infection persists for a lifetime, causing serious cardiac disease in one-third of those infected.[1] Early in the disease course, chronic Chagas heart disease can be clinically silent but can progress to dilated cardiomyopathy with heart failure, ventricular arrhythmias and conduction disturbances, stroke, and other systemic or pulmonary embolisms.

Nearly 6 million people are currently estimated to have Chagas disease.[1] Although the majority of these infected individuals reside in Mexico, Central America, and South America, migration patterns have resulted in large numbers of infected individuals in formerly nonaffected areas, including Europe, Japan, Australia, Canada, and the United States,[2,3] with an estimated 300 000 individuals in the United States alone. Chagas disease has been targeted by the Centers for Disease Control and Prevention (CDC) as 1 of 5 neglected parasitic infections in the United States. The CDC provides educational resources for communities and providers and supports physicians by assisting with diagnostic testing and release of antitrypanosomal drugs.

Despite this, Chagas disease outside of Latin America remains poorly recognized.[4,5] Most US immigrants from endemic countries have limited knowledge of Chagas disease or of their risk of being infected, and many have limited access to diagnostic and treatment facilities because of insurance or immigration issues.[6] Infected individuals are widely scattered across >40 states,[7] making comprehensive assessment and screening challenging. Most US healthcare practitioners have limited awareness and knowledge of Chagas disease and thus are unlikely to screen those at risk.[8,9]

Similar difficulties are seen in Europe, where the high diversity of health systems and high mobility of migrants among the states of the European Union create additional challenges in the management of Chagas disease.[10] The control of this disease is also difficult in other areas with smaller high-risk immigrant populations, including Japan and Australia.

As globalization continues, healthcare providers and health systems outside of Latin America need to be equipped to recognize, diagnose, and treat Chagas disease and to prevent further disease transmission. Indeed, transmission of *T cruzi* is not confined to endemic countries only but also occurs in nonendemic countries through various nonvector pathways, including blood transfusion, congenital transmission, and organ transplantation.

Although local vector-borne transmission occurs in the southern half of the United States, the vast majority of infected US residents are immigrants from endemic countries of Latin America. In addition, transmission can occur in nonendemic areas through blood transfusion, organ transplantation, and congenital transmission from an infected mother.

In recognition of this, the American Heart Association and the Inter-American Society of Cardiology commissioned this statement to increase global awareness among providers who may encounter patients with Chagas disease outside of traditionally endemic environments.

In this document, we summarize the most updated information on diagnosis, screening, and treatment of *T cruzi* infection, focusing primarily on its cardiovascular aspects. This document also provides quick reference tables, highlighting salient considerations for a patient with suspected or confirmed Chagas disease. It is our intent that this document will serve to increase the recognition of Chagas cardiomyopathy in low-prevalence areas and to improve care for patients with Chagas heart disease around the world.

DEFINITIONS

The term *Chagas disease* is used for the general disease. Chagas cardiomyopathy encompasses all cases of Chagas disease with cardiac involvement, defined by the presence of at least a typical electrocardiographic abnormality in those patients who have positive serological tests against *T cruzi*. Dilated Chagas cardiomyopathy refers to the hemodynamic pattern of the Chagas cardiomyopathy that is characterized by left ventricular (LV) enlargement with segmental or global systolic function impairment, regardless of electrocardiographic findings.

EPIDEMIOLOGY, TRANSMISSION, AND CONTROL

Epidemiology

In the Americas, Chagas disease is responsible for ≈7.5 times as many disability-adjusted life-years lost as malaria.[11] Strategies targeting vector and transmission control have led to a substantial decline in global prevalence, now estimated at 6 million people compared with 8 million in 2005 and 18 million in 1990.[12,13] Despite these improvements, in the 21 endemic countries, 13% of the population is thought to remain at risk.[1] The estimated national infection is highest in Bolivia (6.1%), followed by Argentina (3.6%) and Paraguay (2.1%), whereas the largest number of individuals living with Chagas disease, 42% of all cases, reside in Brazil (nearly 1.2 million people) and Argentina (1.5 million

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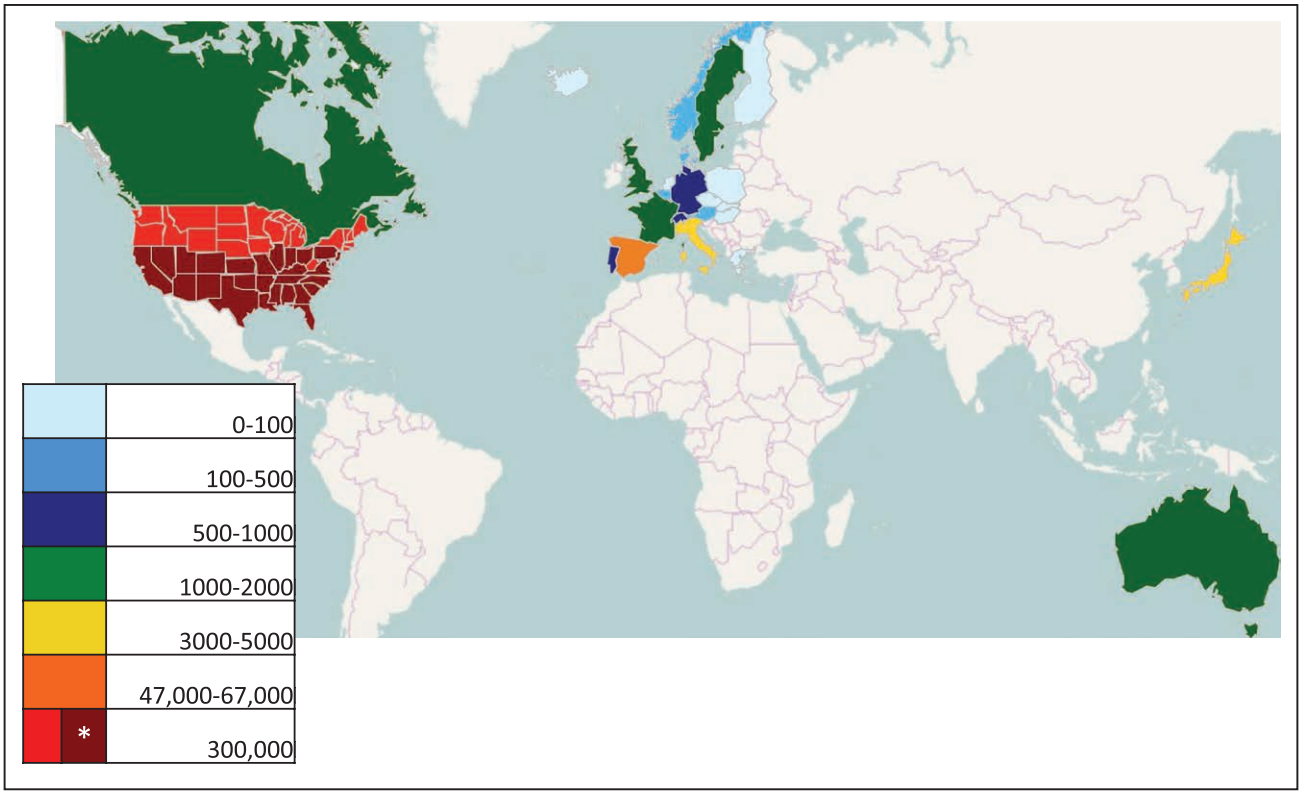

Figure 1. Estimated number of Chagas disease cases outside of Latin America.
*States with documented Triatomine species making vector transmission possible. Data compiled from Bern et al,[18] Bern and Montgomery,[14] Gascon et al,[3] and Navarro et al.[2]

people). Nearly 1.2 million people in these countries are thought to have Chagas cardiomyopathy.[1]

International migration has brought *T cruzi* infection to countries outside of traditionally endemic areas. An estimated 300 000 infected immigrants live in the United States, and at least 42 000 infected people live in Spain.[2,3,14] Infected residents have been reported in Switzerland, France, Italy, Canada, Australia, and Japan.[3] In 2007, control efforts in Latin America were formally joined by an initiative to address the globalization of Chagas disease that was based on the presence of imported cases in Europe, North America, and Japan and the potential for local transmission through nonvectorial routes[15–17] (Figure 1).

In addition to infected immigrants from endemic Latin American countries, an unknown number of people have been infected by local transmission in the United States.[18,19] Recent evidence suggests that locally acquired *T cruzi* infection can result in cardiomyopathy,[20] but existing data are not adequate to assess the magnitude of this problem or to map the areas of highest risk.

Transmission and Control

T cruzi originated as an enzootic disease.[21] The host, the Triatomine insect, is naturally found on the American continents from latitudes 46°N to 46°S. The parasite, *T cruzi*, is thought to have infected animals for >10 million years. Domestic and peridomestic infestation and transmission developed with the arrival of humans to the Americas, deforestation, increasing agriculture, and raising of livestock, which combined to bring the vector closer to human habitation.[22] More than 100 species of these blood-sucking insects have been described, but only about a dozen are implicated as important transmitters of *T cruzi*, having adapted to living in earthen walls and thatch roofs of rural dwellings. Domiciliary Triatomine infestation results in endemic *T cruzi* transmission among impoverished rural populations throughout Latin America.[18]

Vector control programs have been highly effective in reducing domestic and peridomestic *T cruzi* transmission.[23,24] Domestic infestation by *Triatoma infestans* has been eliminated from Chile, Uruguay, Brazil, and some areas of Peru and Paraguay,[25] and *Rhodnius prolixus* has been eliminated from Central America.[25,26] However, success has not been universal. In the Gran Chaco, an ecological zone shared among Bolivia, Argentina, and Paraguay, intense infestation of adobe (mud brick) houses, low effectiveness of residual insecticide application on local housing materials, and emerging insecticide resistance combine to maintain high levels of transmission.[27–29] In villages in the Bolivian Chaco,

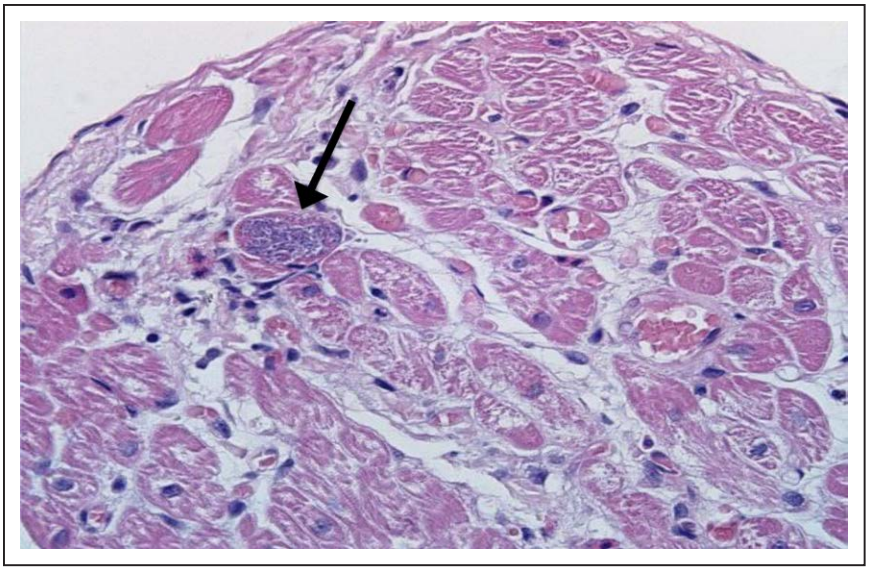

Figure 2. The myocardium in acute Chagas disease.
The myocardium of a patient with acute Chagas reactivation after cardiac transplantation. Parasitism of the muscle fibers is seen with amastigote forms of *Trypanosoma cruzi* leading to the formation of pseudocysts (arrow).

infection prevalence reaches 80% in adults and 20% in children, reflecting ongoing transmission and rapid reinfestation after vector control interventions.[30,31]

Starting in the mid-20th century, rapid urbanization brought Chagas disease into the cities of Latin America. For example, in the city of Santa Cruz, Bolivia, *T cruzi* infection is found in nearly 20% of pregnant women and 60% of patients with heart disease.[32,33] In cities, vector-borne transmission is rare, and alternative routes of transmission predominate. Nonvectorial routes include congenital transmission, blood component transfusion, organ transplantation, and laboratory contamination; oral transmission through contaminated food with vector materials is a peculiar form of transmission.

The United States cannot be classified as non-endemic in the same sense as Europe or Japan. The southern half of the United States has enzootic cycles of *T cruzi*, involving 11 Triatomine vector species and mammalian hosts such as raccoons, opossums, wood rats, and domestic dogs.[18,34] Recent US data estimate that 5.5% to 7.5% of *T cruzi*–infected blood donors may have locally acquired infection.[19] However, most *T cruzi*–infected individuals in the United States, including most of the 30 000 to 40 000 estimated to have Chagas cardiomyopathy, are immigrants from endemic areas of Latin America.[5,14] US blood banks instituted screening of donors for Chagas disease on January 1, 2007. In data collated by the American Association of Blood Banks through October 27, 2017, 3480 confirmed seropositive donations have been detected in 46 states, with the largest numbers found in California, Florida, and Texas.[35]

Although *T cruzi* screening is not mandated by law, an estimated 95% of the US blood supply is currently screened.

Outside of the Americas, congenital transmission, transmission through blood transfusion, and transmission through organ donation are the main sources of new infection. Transmission through these routes is a global problem and can occur wherever infected individuals reside.[36]

PATHOLOGY AND PATHOGENESIS OF CHAGAS HEART DISEASE

Pathology

In acute Chagas disease, a widespread immunological reaction is characterized by diffuse lymphadenopathy, hepatomegaly, and splenomegaly. High-grade parasitemia and intense direct tissue parasitism may result in inflammation of the heart, gastrointestinal tract (mainly esophagus and colon), meninges, and central and peripheral nervous tissues.[37]

Generalized cardiac enlargement, involving all 4 cardiac chambers, and pericardial effusions may occur. Myocarditis is typically diffuse with myocyte necrosis, interstitial edema, vascular dilation, and mononuclear and polymorphonuclear infiltration. The inflammatory process may extend to the endocardium, resulting in mural thrombosis, and may involve the conduction system as well as the intramural and extracardiac neuronal ganglia.[38] Vasculitis and microangiopathy with microvascular thrombosis have been described in experimental models of the disease.[37,39] Histological specimens during acute cardiac involvement are characterized by a large number of parasite amastigote forms in the myofibers, leading to the pseudocysts that ultimately rupture (Figure 2). Myocyte necrosis occurs both local to and distant from parasite multiplication sites.[40,41]

In vivo studies of patients with the indeterminate form of Chagas disease demonstrate histopathological alterations in >50% of patients.[42,43] These findings have been reproduced in the canine model of *T cruzi* chronic

infection, showing small foci of mild chronic myocarditis, with interstitial edema, early fibrosis, and infiltration by lymphocytes, macrophages, and plasma cells.[44]

Pathological features of chronic Chagas heart disease are distinct.[40,41] On autopsy, there is typically cardiomegaly and increased cardiac mass, thinning of the ventricular walls, and aneurysmal lesions in various regions of the LV and right ventricle (RV).[45] In patients who die after the onset of heart failure, liver enlargement and other signs of systemic and pulmonary congestion are common. Intracardiac mural thrombosis is a frequent finding, and in autopsy studies, up to 50% of patients with cardiomyopathy had evidence of embolic events.[46]

Histological examination demonstrates focal, mild, chronic myocarditis. Scattered mononuclear cell infiltrates surround myocytes undergoing various stages of degeneration and necrosis, and immunohistochemical techniques targeting anti–*T cruzi* antibodies or polymerase chain reaction (PCR) methods to detect genomic fragments typically correlate with inflammatory foci.[47–49] Cardiac fibrosis is a prominent finding, diffusively scattered and involving both the myocardium and the conduction system.[50] Microvascular changes include decapillarization, interstitial edema, intravascular platelet aggregation, thickening of the vascular basement membrane, and striking cardiac neuronal depopulation.[41,44,51]

Pathogenesis

The pathogenesis of chronic Chagas heart disease is complex and incompletely understood. Two primary mechanisms, parasite-driven immune response and autoreactivity triggered by the infection, likely initiate and drive both acute and chronic myocarditis, with 2 secondary mechanisms, neurogenic disturbances and coronary microvascular derangements, being responsible for associated cardiac alterations.[12,52–54] Pathogenic differences in *T cruzi* strains and host susceptibility also likely play a role in the clinical pattern and disease severity.[55]

Tissue Parasitism and the Immune Response

Cardiac inflammation and damage during the acute phase of Chagas disease result from high-grade parasitemia and intense direct tissue parasitism. Although intensely questioned and debated historically,[41,56,57] the development of more sensitive diagnostic techniques has shown that chronic Chagas heart disease is indeed an infectious cardiomyopathy, with incessant, low-grade inflammation resulting from the continued presence of *T cruzi* in cardiac tissues.[47,48,58–62] Autopsy studies and myocardial biopsies from living patients show a close correlation between the *T cruzi* amastigote tissue burden and the site and intensity of the myocardial inflammatory process,[63–65] and human and animal models have shown that the severity and distribution of ongoing myocarditis correlate with the severity and pattern of heart failure.[66,67] Finally, experimental models have demonstrated that treatment to decrease host parasite load attenuates,[68–70] whereas increasing host parasite burden exacerbates cardiac inflammation.[71–73] In addition, apoptosis that occurs in the advanced stages of heart failure supports the possibility that direct myocyte aggression by the parasite also contributes to ongoing inflammation, with gradual clonal exhaustion in the $CD8^+$ T-cell population.[74]

The exact mechanism whereby parasitism causes tissue damage in the chronic phase is not clear. A direct parasite-targeted immune response and infection-triggered autoreactivity likely combine to produce substantial and ongoing inflammation, myocytolysis, and the superimposed reactive and reparative fibrosis characteristic of the chronic phase of Chagas cardiomyopathy.[54,57,75–82]

The response of the host immune system to *T cruzi* invasion may be the most important factor determining the severity of chronic disease. A period of relative symbiosis occurs between most infected individuals and their pathogen, as evidenced by the asymptomatic indeterminate clinical form, which can persist for decades or lifelong.[12] Patients in the indeterminate stage display a balanced production of inflammatory and anti-inflammatory cytokines, whereas patients who develop heart disease appear to lose this coregulation.[12,55,80–82]

Neurogenic Disturbances

Characteristic parasympathetic neuronal depopulation is seen in the heart, esophagus, and colon of *T cruzi*–infected humans and animal models of Chagas disease.[83–87] Although similar neuronal depopulation occurs in other cardiomyopathies, the absolute reduction is more severe and extensive in patients with Chagas disease.[51,88–92]

Most patients with Chagas disease, including those with the indeterminate and digestive forms, show loss of parasympathetic cardiac control before the development of myocardial dysfunction.[83,93–97] The parasympathicopriva Chagas cardiopathy theory proposed that parasympathetic impairment led to catecholamine-induced cardiomyopathy.[41,98] However, the considerable individual variability of vagal denervation is not correlated with the severity of LV dysfunction. Moreover, sympathetic denervation can be detected in many patients.[54,90,99,100]

Despite these drawbacks of the theory, parasympathetic dysautonomia probably leads to impairment of the control of the coronary microcirculation.[44,101] It has also been hypothesized that early parasympathetic impairment could be responsible for triggering malignant arrhythmia and sudden death,[102] a notion

indirectly supported by pathological reports of small, highly denervated hearts among patients with Chagas disease with sudden death.[85,88] However, the genesis of arrhythmia is probably multifactorial, as shown by iodine-123 meta-iodobenzylguanidine scintigraphy studies demonstrating the focus of ventricular tachycardia (VT) in patients with Chagas disease to be associated with the adrenergically denervated myocardium.[103,104] In addition, a cholinesterase inhibitor recently was shown to have a cardioprotective effect in a murine model of chronic *T cruzi* infection, suggesting abnormal neuroimmunomodulatory anti-inflammatory functions of the parasympathetic nervous system.[98]

Microvascular Derangements

It is likely that vascular endothelial cell damage, driven by *T cruzi* presence or immune reaction, secondarily results in microvascular deregulation.[53,57,65,105,106] Microvascular perfusion derangements are known to play a role in the development of Chagas cardiomyopathy,[54,107,108] potentially leading to ischemia-like symptoms (Chagas chest pain syndrome), electrocardiographic ST- and Q-wave changes, and regional wall motion impairment.[100,109–111] Several coronary microvascular abnormalities, including increased platelet activation, microthrombi, focal spasm, and endothelial dysfunction, have been reported in patients and animal models of *T cruzi* infection.[53,112,113]

In humans, cardiac biopsy and necroscopy specimens from *T cruzi*–infected patients show findings similar to transient microvascular ischemia.[114,115] The role of the microvasculature is emphasized by studies showing myocardial perfusion abnormalities in patients with Chagas with angiographically normal coronary arteries and sequential Tc-99m-sestamibi perfusion scans correlating deterioration of LV systolic function with increase in irreversible perfusion defects over time.[99] In addition, it is plausible that microinfarctions may coalesce into the hallmark Chagas ventricular aneurysms that typically occur in watershed coronary areas.[116,117]

Parasitic Strain Variation and Genetic Susceptibility

There is substantial geographic and interpersonal variation in the predominant clinical features of chronic Chagas disease. Parasitic strain variation, genetic susceptibility, and the effects of both on the host immune response likely play a role, but the clinical variation within Chagas disease remains one of the least understood and most intriguing targets for future studies.

Differences in *T cruzi* strains are thought to influence disease development through unique tissue tropism[118,119] and differential effects on the host immune response.[120–122] Marked phenotype and genotype diversity occurs among *T cruzi* strains[123] and may be responsible for the pathological and clinical differences between infected hosts and geographic regions. Other factors, including parasitic load during acute infection, occurrence of reinfection,[33,124–128] and response to therapy,[129,130] may also influence chronic-phase pathology.

Host susceptibility, likely reflected by variations in host immune response, also contributes to the development of chronic Chagas cardiomyopathy (CCC).[82] Functional polymorphisms in IL-1 (interleukin-1), CCR5 (C-C chemokine receptor type 5), MCP-1 (monocyte chemoattractant protein-1), TNF (tumor necrosis factor)-α, and IL-10 (interleukin-10) have been associated with Chagas cardiac disease.[82] Gene polymorphisms outside of the immune response, including galectin-3, COX-2 (cyclooxygenase-2), actin, and vasoactive intestinal peptide, have also shown differential associations with clinical presentation and severity in Chagas disease.[82] However, results of genetic investigations remain inconclusive, and the field is open to further investigation; most studies have been targeted to specific populations and not widely replicated.[131]

NATURAL HISTORY

Chagas disease is a heterogeneous condition with a wide variation in clinical course and prognosis. The majority (60%–70%) of infected individuals remain asymptomatic throughout life. Although some develop only conduction defects and mild segmental wall motion abnormalities, others develop severe symptoms of heart failure, thromboembolic phenomena, and life-threatening ventricular arrhythmias. Of note, sudden cardiac death (SCD) is frequent and manifests often in the absence of previous significant symptoms or signs of advanced CCC.[132]

Chagas disease evolves through acute and chronic phases. Acute Chagas disease occurs with primary infection. Chronic Chagas disease is subdivided into 4 clinical presentations—indeterminate, digestive, cardiac, or mixed (both digestive and cardiac)—and may be staged on the basis of severity of involvement according to the American Heart Association and American College of Cardiology guidelines for the diagnosis and management of heart failure in adults[132a,133,134] (A–D in Table 1).

Contemporary information on the natural history of established CCC was recently provided by the placebo group of the BENEFIT trial (Benznidazole Evaluation for Interrupting Trypanosomiasis).[130] This prospective, multicenter, multinational randomized study compared benznidazole with placebo in 2854 patients with established CCC with follow-up data available up to 7 years (mean, 5.4 years). Most patients (97%) were classified as having New York Heart Association class I to II heart failure, with a mean LV ejection fraction (EF) of 55%. In the placebo group (1423 patients), there were 203 deaths (14.3%) resulting from cardiovascular causes, 41 patients (2.9%) with sustained VT, 122

Table 1. Definitions and Progression of Chagas Disease

Chagas Disease: Infection With the Parasite *Trypanosoma cruzi*					
Acute Phase	**Chronic Phase**				
Patients infected by *T cruzi* with findings compatible with acute Chagas disease	**Indeterminate form**	**Chagas cardiomyopathy**			
	A	**B1**	**Chagas dilated cardiomyopathy/heart failure**		
	Patients at risk for developing HF. They have positive serology, neither structural cardiopathy nor HF symptoms. Normal ECG. No digestive changes.	Patients with structural cardiopathy, evidenced by electrocardiographic or echocardiographic changes, but with normal global ventricular function and neither current nor previous signs and symptoms of HF	**B2**	**C**	**D**
			Patients with structural cardiopathy characterized by global ventricular dysfunction and neither current nor previous signs and symptoms of HF	Patients with ventricular dysfunction and current or previous symptoms of HF (NYHA FC I, II, III, or IV)	Patients with refractory symptoms of HF at rest despite optimized clinical treatment requiring specialized interventions

Note that arrhythmias and conduction system disease can occur from B1 through D presentation forms. HF indicates heart failure; and NYHA FC, New York Heart Association functional class.

patients (8.6%) with new or worsening heart failure, 125 patients (8.8%) requiring pacemaker or implantable cardioverter-defibrillator (ICD) insertion, and 61 patients (4.3%) with stroke. New electrocardiographic abnormalities occurred in 35.6% of patients at 2 years and in 38.2% at 5 years. Despite the apparent slow progression and the relatively well-preserved LV systolic function at study enrollment, a significant proportion of deaths were related to either heart failure or SCD, highlighting the need for optimal heart failure treatment.[130]

Acute Infection

The incubation period for *T cruzi* ranges from 1 to 2 weeks after vector-borne transmission[12] and up to 3 to 4 months after transfusion or transplant transmission.[136] The acute phase of Chagas disease typically lasts 8 to 12 weeks and often remains undiagnosed because the majority of patients are asymptomatic or manifest mild and nonspecific symptoms such as fever, malaise, and splenomegaly. In a small percentage of patients, acute infection is marked by inflammation at the site of inoculation: the pathognomonic chagoma (*T cruzi* skin abscess) or Romaña sign (unilateral conjunctivitis and painless swelling of the upper and lower eyelids).

When the acute phase is detected, mild cardiac anomalies such as tachycardia out of proportion to fever are often noted. The ECG during mild acute disease shows sinus tachycardia and PR/QT prolongation, low-voltage QRS complexes, and repolarization abnormalities. When more advanced electrocardiographic findings are present, including right bundle-branch block (RBBB), atrial fibrillation, or ventricular arrhythmias, they signal a worse prognosis.[137]

A small proportion of patients present with fulminant acute disease, displaying acute myocarditis, pericardial effusion, meningoencephalitis,[138] or death.[139] These more severe manifestations typically affect immunocompromised individuals[140] and those contracting *T cruzi* through oral transmission, thought to be the result of increased parasite load, associated with an intrinsic permeability of the upper mucosae to the parasite and heightened invasiveness of trypomastigotes exposed to gastric acid.[141,142] In the largest oral outbreak, affecting 103 individuals in Caracas, Venezuela, 75% of the infected were symptomatic, 59% had electrocardiographic abnormalities, 20% were hospitalized, and 1 patient died secondary to complications of acute myocarditis.[143] Untreated symptomatic patients face a roughly 1% chance of death in the acute period, usually the result of severe myocarditis or meningoencephalitis.[134]

Regardless of symptoms, microscopically detectable circulating trypomastigotes mark the acute phase. After 8 to 12 weeks, parasitemias typically fall below levels detectable by microscopy. Untreated patients then enter the chronic phase of *T cruzi* infection. Chronically infected patients remain infectious to vectors and can transmit the disease through congenital transmission, blood transfusion, or organ donation.[11]

Indeterminate Form

After the acute phase of infection, most patients pass into a chronic indeterminate form,[137,144,145] defined by positive anti–*T cruzi* serology, the absence of physical signs or symptoms of disease, a normal ECG, and normal radiographs of the chest, esophagus, and colon.[146,147] Characterization of the indeterminate form has been challenging and is imperfect because early manifestations can be subtle. Extensive radiological evaluation is needed to fulfill the strict criteria, and most patients are not subjected to full radiological evaluation of the gastrointestinal tract to exclude digestive disease because this adds individual discomfort and cost at little clinical value.[145,148] The current recommendation for the evalu-

ation of a patient in the United States with suspected or newly diagnosed Chagas disease includes serological confirmation, based on 2 different assays for anti–*T cruzi* immunoglobulin G, a history, a physical examination, an ECG, and a 30-second rhythm strip. Additional cardiac and gastrointestinal workup is recommended only when this first evaluation raises clinical suspicion of more advanced disease forms.[133]

Even when the standard clinical workup does not reveal myocarditis, it is possible for patients who meet the criteria for the indeterminate form to have subclinical myocarditis. *T cruzi* is found in endocardial biopsies from patients without clinical heart disease,[62] and pathological changes, such as myocyte degeneration, inflammatory infiltrates, and ongoing fibrosis, have been documented in animal[149] and human subjects[62,150] with the indeterminate form of disease. In addition, patients with the indeterminate or clinically isolated digestive form may demonstrate impaired segmental systolic wall motion,[151–154] chronotropic incompetence,[155] or ventricular arrhythmias.[152,156]

Indeterminate Chagas disease will progress to clinically manifest disease, most commonly dilated cardiomyopathy,[12] at a rate of 1.85% to 7% annually.[144,157,158] The progression rate can vary, and the prevalence of the indeterminate form depends on the age of the population. In younger cohorts, >50% of patients have the indeterminate form. It is very relevant to emphasize that as long as their ECG remains normal, the prognosis for these patients is good, with most surviving without major complications for >5 to 10 years and carrying the same risk of death as the general population.[137,144,145,159,160] Among more senior asymptomatic Chagas populations, true indeterminate disease is rare because, given time, most infected individuals will develop characteristic electrocardiographic changes.[161,162]

Gastrointestinal Manifestations

Gastrointestinal involvement is less common than Chagas heart disease and is seen mainly in the countries of the Southern Cone (Argentina, Bolivia, Chile, Paraguay, southern Peru, Uruguay, and parts of Brazil). It is hypothesized that geographic specificity results from differences in *T cruzi* genotypes (TcII, V, and VI in the Southern Cone versus TcI north of the equator),[163,164] but where regional overlap exists, phenotypic specificity has not been documented.[163]

Chagas gastrointestinal disease is the result of enteric nervous system impairment, creating disordered esophageal or colonic motility.[165–167] Esophageal involvement ranges from mild achalasia to severe megaesophagus,[165] characterized by dysphagia, odynophagia, esophageal reflux, weight loss, aspiration, cough, regurgitation, and increased risk of esophageal carcinoma.[168,169] Colonic involvement typically manifests as constipation with megacolon,[137,165,170] which can be complicated by fecaloma, volvulus, and bowel ischemia. The prognosis for patients with digestive forms of the disease is generally good except in those with advanced forms and complications that occasionally cause death.[170]

Typically, gastrointestinal imaging and functional evaluation (eg, manometric studies) are warranted in the presence of symptoms, but subtle abnormalities may be present before symptoms appear. In a recent study in northeastern Brazil of 186 individuals with chronic Chagas disease, contrast radiography of the esophagus and colon demonstrated a 7% prevalence of megaesophagus, 12.9% with megacolon, and 3.8% with combined involvement.[171] Isolated digestive and cardiodigestive forms were detected in both symptomatic and asymptomatic patients, highlighting that functional changes precede clinical manifestations.[171] Similarly, among a Bolivia-originated cohort of patients living in Spain, gastrointestinal tract involvement affected almost one-quarter of patients (21%), with an 11% prevalence of megaesophagus and 14% prevalence of megacolon.[172]

Evolution to Chagas Heart Disease

Although uncommon (<10%), patients can progress directly from acute Chagas disease to the chronic cardiac form.[173] This phenomenon, described in the endemic area of Bambuí, Brazil,[173] is now infrequent because most apparent acute cases are being treated and cured. Even in a hyperendemic region of the Bolivian Chaco, electrocardiographic abnormalities were found in only 1.1% of teenagers (10–19 years of age) infected by *T cruzi*, suggesting that the direct progression to the cardiac form is rare in this population.[174]

More commonly, chronic Chagas heart disease develops after several decades of the indeterminate form of the disease, reflecting the establishment of a new status of imbalance between parasite and host immune response. Drivers of progression are incompletely understood, although longitudinal studies have highlighted male sex, exposure to reinfection, parasite strain, genetic background, African ancestry, age, severity of acute infection, nutritional status, alcoholism, and other concomitant diseases as potential risk factors.[137] More recently, there is evidence that the persistence of high parasitemia and tissue parasitism,[63,128,175] a proinflammatory immunological profile[55,176] with sustained oxidative stress,[81,177] and genes related to natural killer/CD8$^+$ T-cell cytotoxicity[178] may be determinant in the development of Chagas cardiomyopathy, although the exact mechanism remains to be elucidated.

Predicting which patients will progress to Chagas heart disease is an ongoing challenge and a high-priority area of research. The most commonly used and simplest monitoring parameter is the ECG.[179] Electrocardiographic changes, often RBBB with or without left

anterior hemiblock,[180] usually mark the transition from the indeterminate to chronic cardiac form,[179] and the presence of a typical electrocardiographic abnormality is associated with increased risk of progression to more severe cardiomyopathy.[154–156,159–161,181–183]

A sensitive and specific early serum biomarker has been elusive.[184–186] Elevation of BNP (B-type natriuretic peptide) or NT-proBNP (N-terminal pro-BNP) is sometimes seen before advanced heart disease,[185,187] but elevations can be subtle, are inconsistent, and have not been proven clinically valuable. Indeed, BNP increase is a good marker of the presence of LV systolic dysfunction and diastolic dysfunction in Chagas cardiomyopathy.[188,189] Other methods such as echocardiography, stress testing, and Holter monitoring can sometimes elucidate cardiac findings in patients believed otherwise to have the indeterminate form. If seen, ventricular arrhythmias during cardiac stress testing[190,191] or Holter monitoring[192] and regional wall motion abnormalities on echocardiogram[193] denote the development of Chagas heart disease and may carry a higher risk of aggravation of the cardiomyopathy. However, assessment of heart disease with advanced cardiac imaging is not routinely indicated in asymptomatic patients.[179]

Table 2. Cardiac Rhythm Abnormalities More Commonly Detected in Chagas Cardiomyopathy[179,196]

More Typical Findings	Less Commonly Seen
Bradyarrhythmias and conduction system abnormalities	
RBBB±left anterior fascicular block	Incomplete RBBB, left bundle-branch block
First-degree atrioventricular block	Isolated left anterior fascicular block
Second- and third-degree atrioventricular block	Sinus bradycardia with HR ≤40 bpm
Sinus bradycardia with HR >40 bpm	Sinus node dysfunction
Atrial tachyarrhythmias	
Atrial fibrillation	
Ventricular tachyarrhythmias	
Frequent PVCs, often polymorphic	Isolated monomorphic PVCs
Nonsustained VT	
Other	
Primary ST- and T-wave abnormalities	Nonspecific ST- and T-wave abnormalities
Pathological Q waves or electric inactive areas	Low limb lead voltage

HR indicates heart rate; PVC, premature ventricular contraction; RBBB, right bundle-branch block; and VT, ventricular tachycardia.

CHAGAS HEART DISEASE

Chagas cardiomyopathy is the most important clinical manifestation of Chagas disease, resulting in the majority of Chagas morbidity and mortality.[134] Although generally classified as having a hemodynamic pattern of dilated cardiomyopathy, the typical predominant distribution of fibrosis to the posterior and apical regions of the LV and involvement of the sinus node and electric conduction system distinguish Chagas disease from other cardiomyopathies. Clinical manifestations of Chagas heart disease result from electric conduction abnormalities, myocardial contractile dysfunction, arrhythmias, or thromboembolism.[194] In most studies, sudden death is the most common overall cause of death (55%–60%), followed by heart failure (25%–30%) and embolic events (10%–15%), but the proportions vary depending on the population studied.[132,195]

Cardiac Manifestations

Arrhythmias

Chagas heart disease is considered an arrhythmogenic cardiomyopathy characterized by atrial and ventricular arrhythmias and a wide variety of abnormalities of the conduction system. Electrocardiographic rhythm changes are predictors of both disease severity and outcome.[159–161,182]

Cardiac arrhythmias can be the sole manifestation of Chagas heart disease, the so-called arrhythmic syndrome, but usually occur in combination with heart failure or thromboembolic events.[196] The severity of electric abnormalities ranges from the incidental finding of sinus bradycardia to mild conduction abnormalities on the ECG (eg, incomplete RBBB) to advanced atrial or serious ventricular arrhythmia noted on Holter or provoked by cardiac stress testing to syncope and sudden death.[197] No single electrocardiographic finding is pathognomonic for Chagas disease (Table 2); multiple electrocardiographic findings are common; and as the Chagas population ages, ECGs can also reflect other comorbid conditions such as hypertension and ischemic heart disease.[161] Other significant changes found in Chagas disease include pathological Q waves (simulating previous myocardial infarction), low voltage, and primary changes of the T wave, all 3 potentially related to poor prognosis.[161,198,199]

Palpitations are commonly reported by patients with Chagas heart disease and warrant further investigation. Syncope is an ominous sign when resulting from sustained VT or advanced atrioventricular block, less so when resulting from intermittent block at the atrioventricular node.[200,201] Sudden death, most commonly associated with malignant ventricular arrhythmia, can interrupt the course of the disease at any time, even before the development of symptoms or heart failure.[202] In the early reports on the disease, sudden death was soon highlighted. In his early reports, Carlos Chagas stated, "Individuals, not rarely, die in their youth with an apparently healthy condition and no signs of heart disease."[203]

Bradyarrhythmia and Conduction System Abnormalities

Chagas disease is an important cause of bradyarrhythmias and pacemaker implantation in Latin America.[204] Widespread fibrosis shows a predilection for the cardiac conduction system, affecting the sinus node, atrioventricular node, and bundles of His.[205,206] Sick sinus syndrome can manifest as bradycardia, sinus pauses, sinoatrial block, and, in severe cases, bradycardia-tachycardia syndrome.[161,207] On electrophysiological study, patients with Chagas disease can demonstrate abnormal sinus node recovery time and sinoatrial conduction, even when overt sick sinus syndrome is not present.[208] Fibrotic sinus node dysfunction can be further exacerbated by dysautonomia, leading to chronotropic insufficiency despite preserved LV function.[155,209]

Patients can present with first-, second-, or third-degree atrioventricular block.[207,210] In a population-based study in an endemic area, patients self-reporting Chagas disease were 4 times more likely to present with second- or third-degree atrioventricular block and 13 times more likely to have an implanted pacemaker compared with the general population, even after covariable adjustment.[207] RBBB (incomplete and complete) is the most common intraventricular conduction abnormality and often one of the first manifestations of Chagas disease. RBBB is seen in 10% to 50% of patients[159,161,180,207,211–213] with chronic Chagas disease, 7 to 10 times more frequently than in serologically negative individuals.[161,180,207] The combination of RBBB and left anterior fascicular block is strongly suggestive of Chagas disease and should prompt a search for risk factors and serological evaluation of those at risk. Left bundle-branch block is seen much less frequently[161,180,207] but is directly related to LV size and function[214] and indicative of worse prognosis.[211]

Atrial Tachyarrhythmias

Atrial fibrillation is the most common supraventricular arrhythmia, found in up to 5% of electrocardiographic tracings of patients with chronic Chagas disease.[2,3,5,9–12] Most typically, atrial fibrillation is seen in patients with dilated cardiomyopathy, often indicating advanced myocardial damage.[215] Small cohort studies have identified intra-atrial block, frequent supraventricular and ventricular premature contractions, severe left atrial enlargement, and pulmonary artery hypertension as risk factors for the development of atrial fibrillation.[216,217] Commonly in patients with atrial fibrillation, concurrent LV systolic dysfunction and atrioventricular and intraventricular conduction delays result in slow ventricular rate response.[205] Development of atrial fibrillation is a predictor of mortality[161,205,218] and an important risk factor for stroke, independent of LV function.[215,219,220] Isolated premature atrial contractions are rarely associated with chronic Chagas disease in youth but become more common with age and are associated with worse prognosis in the elderly.[161]

Ventricular Tachyarrhythmias

Patients with Chagas disease can develop a wide spectrum of ventricular tachyarrhythmias that are associated with substantial morbidity and mortality and are the leading cause of sudden death in these patients.[195,221,222] Monomorphic or polymorphic premature ventricular complexes (affecting 5%–66% of seropositive individuals), ventricular couplets, and runs of nonsustained VT are common findings on an ECG, Holter monitoring, and exercise stress testing. The presence and complexity of ventricular arrhythmias typically correlate with the severity of cardiac segmental wall motion abnormalities,[152,192] but ventricular arrhythmias also are often seen in patients with normal global ventricular function.[223] Frequent or complex extrasystoles on an ECG[159,161] and nonsustained VT on Holter monitoring or stress testing are independent predictors of mortality.[198,224]

The main ventricular arrhythmogenic substrates in Chagas heart disease are necrotic and fibrotic myocardial lesions.[112] These lesions disrupt the intercellular junctions, change the cardiac electric potential,[225] and form the basis of reentrant circuits for ventricular arrhythmias.[225–227] Although ventricular arrhythmia can arise from various locations, there is good topographic correlation among myocardial perfusion deficits, wall motion abnormalities, and foci of VT.[228] The LV inferolateral region is the most common focus. The extension of myocardial fibrosis as assessed by delayed enhancement on cardiac magnetic resonance (CMR) imaging can identify high-risk patients.[224,229,230] Alternatively, the use of the Selvester QRS scoring system, which estimates scar size by quantifying changes in Q-, R-, and S-wave duration, amplitude, and morphology on the 12-lead ECG,[231] has shown good correlation with magnetic resonance imaging and retrospectively with a history of VT.[230]

Cardiac dysautonomia also likely contributes to the frequency and lethality of ventricular arrhythmias in patients with Chagas disease.[54,232] It is hypothesized that the coexistence of denervated and hypersensitive partly denervated or hyperinnervated ventricular myocardium results in electrophysiological heterogeneity that predisposes to malignant ventricular arrhythmia.[103,233] Further supporting these hypotheses, sympathetic innervation defects (detected by iodine-123 meta-iodobenzylguanidine scintigraphy) have been associated with sustained VT in this population.[103] There has been documentation of autonomic-driven abnormal heart rate dynamics preceding VT in patients with Chagas disease.[234]

Heart Failure

Chagas heart failure is typically caused by a progressive dilated cardiomyopathy. Regional wall motion abnormalities usually precede decreases in global LV function,

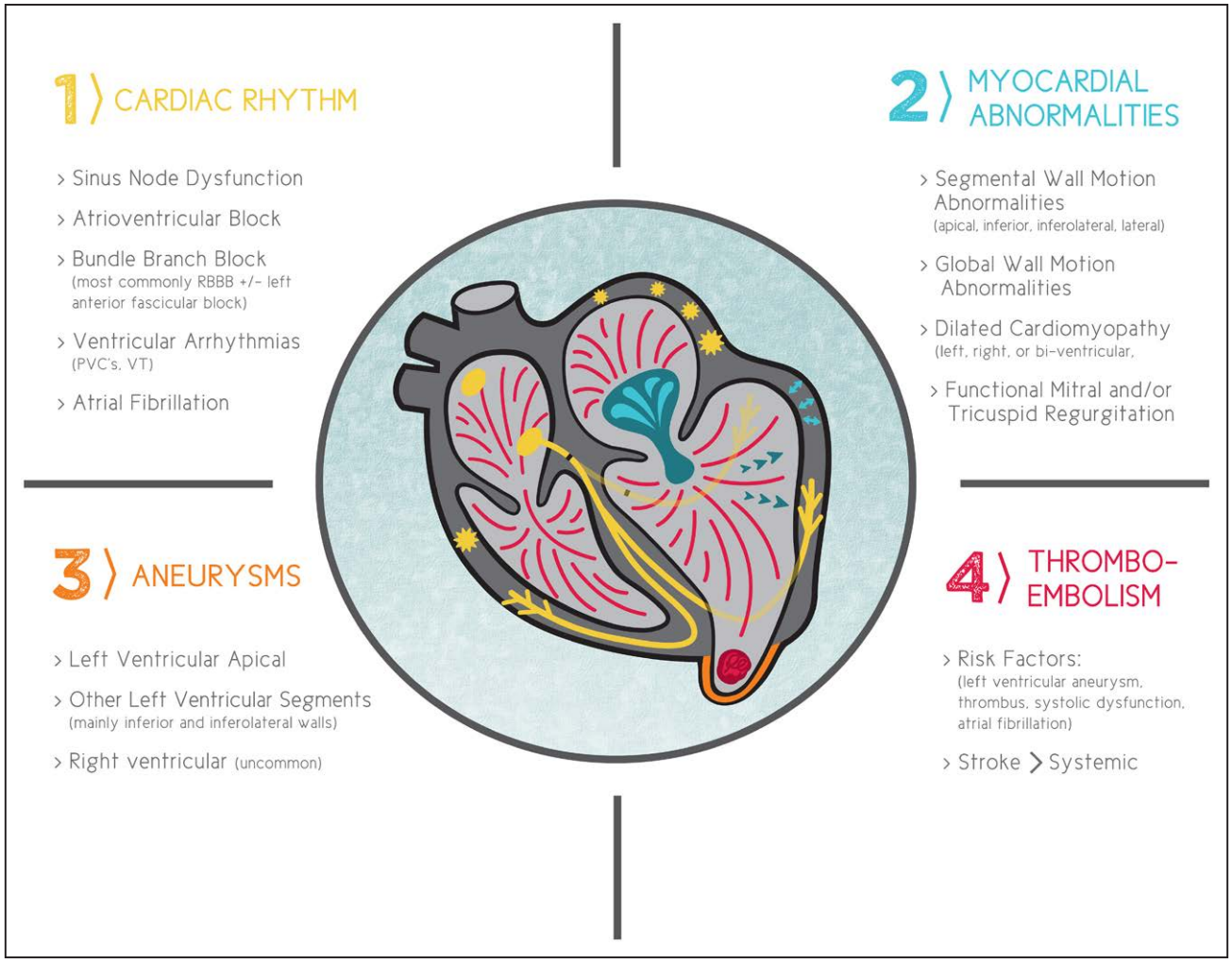

Figure 3. Illustration of the most common findings in patients with Chagas cardiomyopathy.
PVC indicates premature ventricular contraction; RBBB, right bundle-branch block; and VT ventricular tachycardia.

which can become severe.[193] Abnormalities of systolic and diastolic function coexist[235] with cardinal symptoms related to pulmonary congestion. In some patients, right-sided heart failure can be more prominent than left-sided systolic failure and can be a hint for the diagnosis of CCC as the cause of heart failure. Isolated right-sided heart failure is not frequent, and RV dysfunction usually is associated with LV dysfunction in advanced stages of Chagas cardiomyopathy (Figure 3). The reason is that, although RV dysfunction may be present at early stages of Chagas disease, it is only when this chamber faces an increased afterload secondary to LV dysfunction, at later stages, that its functional impairment becomes apparent.[236,237] Functional mitral and tricuspid insufficiencies are often associated with severe biventricular global systolic dysfunction.

Atypical chest pain that mimics ischemic disease is often present and is secondary to alterations in the microcirculation.[106,134,238]

The typical physical examination reveals a prominent apical impulse, regurgitation murmurs from mitral and tricuspid valves, and wide splitting of the second heart sound caused by RBBB. An accentuated pulmonic component of the second heart sound caused by pulmonary hypertension can also be detected. Enlargement of the LV and deterioration in overall systolic function are features of the final stages of Chagas disease, a common pathway of all dilated cardiomyopathies.

Chagas cardiomyopathy carries a poor prognosis compared with other forms of cardiomyopathy, including hypertensive heart disease,[239] idiopathic dilated cardiomyopathy,[240] and ischemic cardiomyopathy.[241] When the severity of ventricular dysfunction and other covariates are controlled for, Chagas emerges as an independent predictor of mortality.[239–241] Poor outcomes have been attributed to the aggressive ventricular remodeling observed in patients with Chagas disease, which puts them at higher risk for fatal arrhythmias and other adverse events.[239]

Echocardiographic Findings in Chagas Disease

Increasing availability of echocardiography for assessment of acute Chagas disease is improving our under-

Table 3. Most Common Echocardiographic Findings in Chronic Chagas Disease

Segmental wall motion abnormalities: hypokinesis, akinesis, or dyskinesia
Inferior-inferolateral wall, usually basal segments
LV apex
Preserved septal contraction
LV aneurysm
LV diastolic dysfunction
Dilated cardiomyopathy
RV dysfunction
Mural thrombus, mainly at LV apex
Mitral and tricuspid regurgitation

LV indicates left ventricular; and RV, right ventricular.

standing of early cardiac involvement, which is essentially a myopericarditis. The majority of patients who have had echocardiographic assessment during oral outbreak typically had more severe disease. The most common findings from the 3 largest surveys include pericardial effusion (42%–50%), with almost one-quarter in a single series showing cardiac symptoms, regional wall motion abnormalities (0%–28%), and globally decreased left ventricular ejection fraction (LVEF; 0%–35%).[242–244]

A spectrum of anatomic and functional abnormalities are associated with chronic Chagas disease, the severity of which depends on the stage.[154] Cardiac impairment is generally a progressive process that can be classified into stages (A–D), according to international recommendations adapted to Chagas disease (Table 1).[133,134] The most common echocardiographic findings in chronic Chagas disease are summarized in Table 3.

As previously discussed, asymptomatic patients with a normal ECG, referred to as being in the indeterminate form, make up stage A. Once electrocardiographic changes manifest, which reflects progression to the cardiac form, patients move to stage B. Echocardiography has shown that up to 13% of patients in stage B have segmental wall motion abnormalities[154,245] despite preserved global biventricular systolic function.[254,245–247] In addition, prolonged isovolumic contraction times, indicative of early contractile abnormalities, have been seen during this phase on tissue Doppler evaluation.[153,248] The development of symptoms of heart failure marks the transition to stage C, in which LV systolic dysfunction and electrocardiographic abnormalities become ubiquitous.[140] Stage D marks the decline to New York Heart Association functional class IV with progression to decompensated heart failure. Mortality is high, 50% at 2 years, and complications such as thromboembolism, arrhythmia, and sudden death are common.[182,249]

Ventricular Aneurysms

Ventricular aneurysms, most typically apically located, are seen on echocardiography in 2.0% to 8.6% of asymptomatic patients and in 24% to 64% (mean, 55%) of patients with moderate to severe myocardial involvement.[154,245,250–256] Necroscopy studies show even higher prevalence (30%–92%)[110,140,257,258] and wider distribution (82% in the LV apex, 9% in the RV apex, and 9% in both) in patients dying of Chagas heart disease. Aneurysm size is variable, ranging from small "hollow punch" lesions to large aneurysms hardly distinguishable from those seen with myocardial infarction[140,245] (Figure 4). Use of 3-dimensional echocardiography and contrast injection can help delineate and measure aneurysms that are small, atypically located, and present in patients with poor acoustic windows.[245]

The presence of ventricular aneurysm predicts the development of mural thrombus and stroke[253,256,259–262] and contributes to the substrate for ventricular arrhythmias but has not been shown to be an independent predictor of mortality apart from LV systolic function.[254,263,264]

Systolic Function

Segmental wall motion abnormalities, most commonly in the apical and inferolateral walls, are common in patients with Chagas heart disease and typically precede global changes in systolic function (Figure 5). Although much less available in most clinical settings, 3-dimensional is more accurate than 2-dimensional echocardiography for assessing LVEF in patients with wall motion abnormalities, including aneurysms (Figure 6).

Regional functional deficits are of great importance because they predict the risk of progression to global systolic dysfunction[193] and may sometimes be associated with ventricular arrhythmias even at early stages of the disease.[152] Under pharmacological stress, asymptomatic patients may demonstrate regional or global contractile impairments.[265,266] In advanced Chagas disease, there can be significant LV dilation and depression of global LV systolic function, the severity of which is directly correlated to risk of death.[134,140]

Assessment of myocardial strain through speckle-tracking echocardiography is emerging as an additional modality to detect early myocardial deficits in Chagas disease. Subtle changes in regional and global contractility have been found and offer increased sensitivity for early myocardial involvement compared with conventional echocardiography.[250,267–270] Global radial strain[250,267] may be decreased in some patients in the indeterminate stage, even with a normal ECG and conventional echocardiography, but the real prevalence of such derangement requires further evaluation.[268] However, twist-torsion analysis revealed no differences between normal control subjects and those with indeterminate or early cardiomyopathy.[271] Strain may also offer some utility as a predictor of ventricular arrhythmia because it can map the heterogeneity of myocardial contraction times (mechanical dispersion), shown in 1

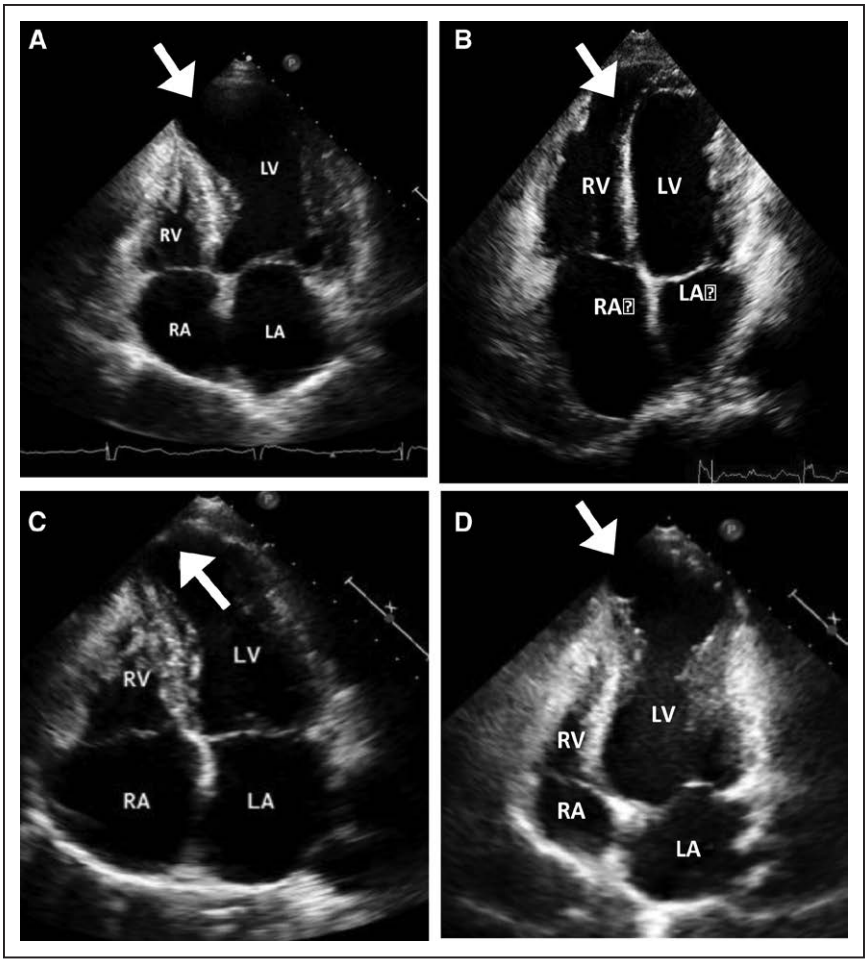

Figure 4. Ventricular aneurysms in several patients with Chagas cardiomyopathy. A range of ventricular aneurysms in patients with Chagas cardiomyopathy. **A**, **C**, and **D**, Left ventricular (LV) apical aneurysm. **B**, Right ventricular (RV) apical aneurysm. LA indicates left atrium; and RA, right atrium.

study to be independently associated with malignant ventricular arrhythmia in Chagas disease.[272]

RV systolic impairment can also occur in Chagas disease. Assessment of RV function by conventional echocardiography remains challenging and largely qualitative, but new modalities, including 3-dimensional echocardiography and cardiac strain, provide some promise for improvements. Subtle changes in RV function have been detected in early-stage disease,[95,248,273] but it is generally accepted that RV dysfunction clinically manifests as concomitant with LV dysfunction and elevated pulmonary artery pressure,[237,268] thus reflecting extensive myocardial involvement impairing overall contractility. RV impairment also serves as a marker of overall severity of cardiac disease and indicates a worse prognosis.[274]

Diastolic Function

The sustained myocardial replacement with scattered fibrosis seen with Chagas disease also impairs ventricular relaxation and diastolic filling.[140,196] A wide range of diastolic dysfunction tracks the severity of overall cardiac involvement and systolic dysfunction,[254,268,275] being found in 92% of patients with systolic heart failure.[268] Subtle early abnormalities have also been reported, with some studies reporting diastolic dysfunction in up to 10% of patients with the indeterminate form of disease,[268] whereas others' findings in this group were normal.[250,276] Most typically, changes in diastolic function progress from prolonged ventricular relaxation times to reduced LV compliance. This leads to increased left atrial pressure and changes in transmitral and pulmonary venous flow velocity pressures.[196,205,268,269] Diastolic dysfunction contributes to left atrial remodeling and dysfunction.[254,268,277,278] Left atrial volumes can be increased at all stages of Chagas disease,[268] and atrial function is more compromised in Chagas disease compared with idiopathic dilated cardiomyopathy,[279] leading some to hypothesize that a component of direct atrial myopathy might also contribute. In contrast, a previous study using strain echocardiography to assess atrial function in Chagas cardiomyopathy showed that it is impaired to a degree similar to that of idiopathic cardiomyopathy.[280]

Echocardiography in Risk Stratification

LV global dysfunction, usually expressed by low LVEF, as classified previously, is the most important predictor of death in Chagas disease.[134,140,198,245,263,281,282] A cohort of 538 patients grouped in 4 stages of disease progression (A–D) showed dramatic 5-year mortality increases

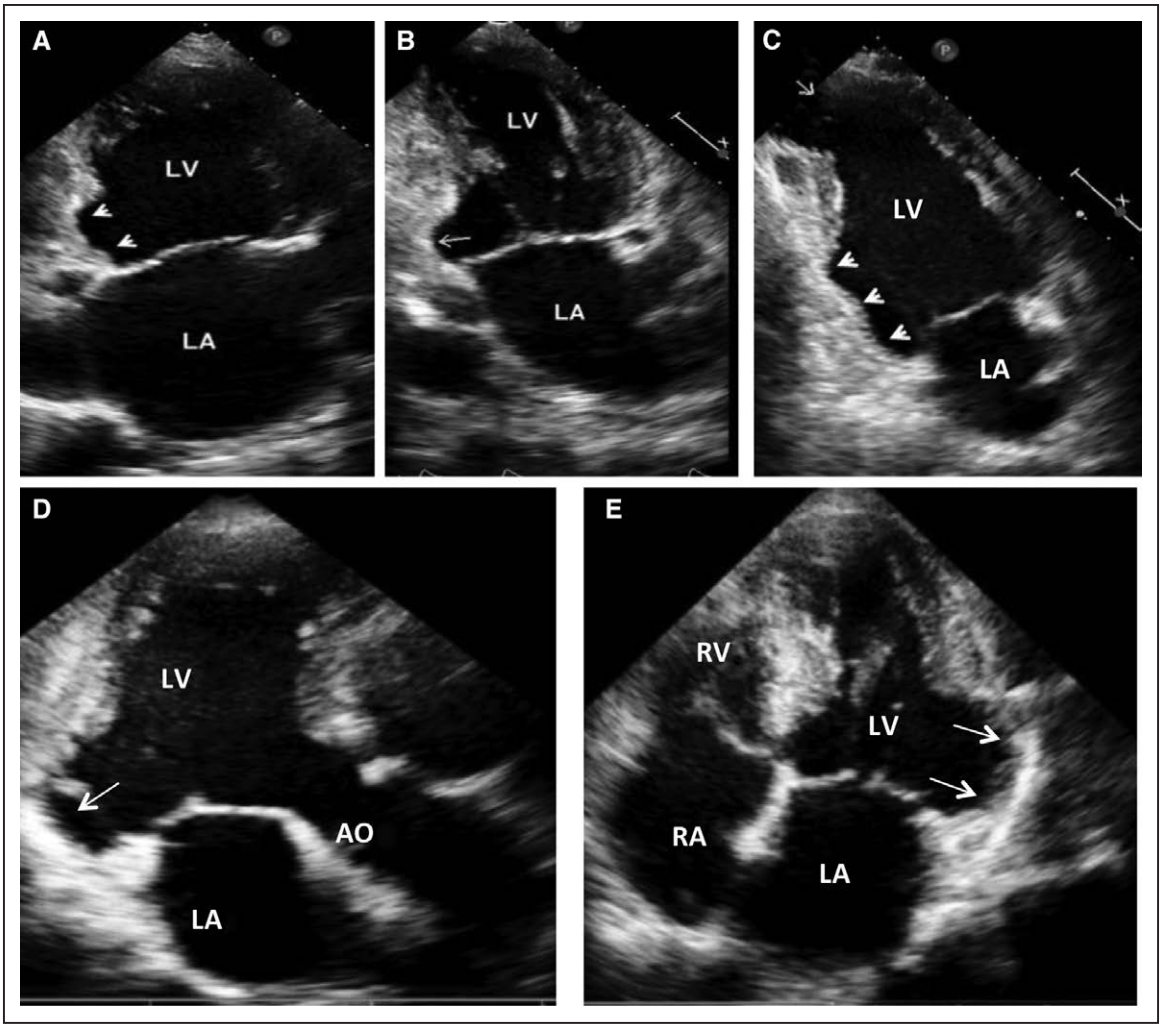

Figure 5. Classic segmental wall motion abnormalities in patients with Chagas cardiomyopathy.
This is most commonly seen in the inferolateral and lateral walls of the left ventricle (LV). AO indicates aorta; LA, left atrium; RA, right atrium; and RV, right ventricle.

with increasing stage: 98%, 91%, 45%, and 13%[283] for stages D, C, B, and A, respectively. Worsening LV diastolic dysfunction,[263,268] left atrial enlargement,[254] decreased left atrial contractility,[268] and RV dysfunction[274] are also independent predictors of mortality and adverse outcomes, and assessment of multiple parameters may increase risk prediction beyond that of only LV systolic function.[198,268,284–293] Studies looking at echocardiographic predictors of adverse outcome are summarized in Table 4.

Thromboembolism

Stroke and Systemic Embolism

Chagas disease is a major cause of stroke in Latin America, with up to 20% of stroke patients in Chagas-endemic areas serologically positive for *T cruzi*.[296] Despite the growing burden of Chagas in the United States and other traditionally nonendemic areas, *T cruzi* serology is not included in routine stroke investigation, and no data on burden in these high-income nations exist.[297] The incidence of Chagas-associated stroke (CAS) in patients with known Chagas disease ranges from 0.56 to 2.67 per 100 person-years.[260,298–300]

Classically, the cause of CAS was thought be cardioembolic, with intracardiac thrombi resulting from poor ventricular function and atrial arrhythmias.[46,301] Identified risk factors for CAS include apical aneurysm, LV thrombus (Figure 7), severe atrial dilation, LV systolic dysfunction, older age, and atrial fibrillation.[254,261,277,298,302] Although it remains true that the majority of CAS is thromboembolic,[220,260–262,303–306] other types, including small vessel disease (9.5%), large vessel atherosclerosis (8.5%), and cryptogenic (25.5%), have been observed.[219] Hypotheses on the mechanisms of these nonembolic strokes include the presence of concomitant risk factors (hypertension, hyperlipidemia, smoking),[219,307] a proinflammatory and prothrombotic disease state,[219,308–310] and endothelial dysfunction.[311,312] However, these represent preliminary hypotheses, and their contribution to CAS development and specificity to Chagas disease remain to be determined.

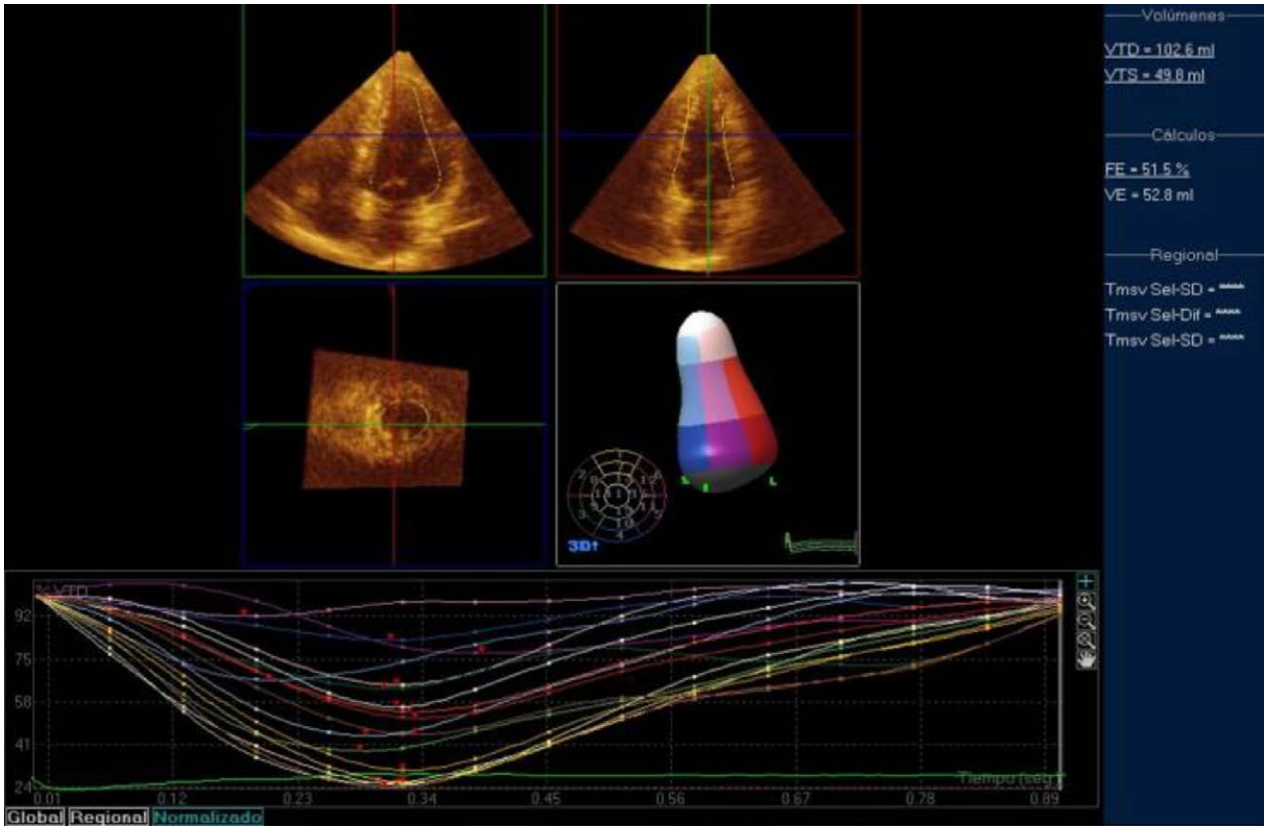

Figure 6. Three-dimensional echocardiography assessment of a patient with Chagas cardiomyopathy.
Normalized segmental contractile analysis from a 3-dimensional apical view of a patient with chronic Chagas disease having mainly electrocardiographic abnormalities and ventricular arrhythmias but without heart failure.

The clinical presentation of CAS reflects the predominantly embolic profile. Between 50% and 70% of patients manifest with immediate onset of partial anterior circulation syndrome, which includes 2 of the following 3 signs: motor or sensory deficit involving the face, arm, and leg; homonymous hemianopia; and higher cerebral dysfunction such as aphasia or visuospatial deficit.[219,262] Less frequently, patients will present with a lacunar or posterior circulation syndrome.[219,262,313]

Several clues point to the diagnosis of Chagas disease as a potential cause of stroke.[259] Patients with CAS may present a history of immigration from an endemic area,[314] may have seen or know about the insect vector (*Triatoma sp*., the "kissing bug"), may reveal a family history of Chagas disease, or may demonstrate additional clinical findings (evidence of cardiac or gastrointestinal involvement). Even with no history, a high index of suspicion is warranted for patients coming from or living in endemic regions because stroke can present as the first and only clinical manifestation of Chagas disease.[220,253,303,304]

CAS may also contribute to cognitive impairment and dementia in endemic regions and appears to be independent of cardiac disease.[315–317] The typical pattern is that of vascular cognitive impairment, with deficits in executive function, processing speed, and visuospatial function, although memory is relatively well preserved.[316-318] Both pathological and clinical studies have documented brain atrophy in CCC independently of brain infarcts.[319–322] White matter disease has also been reported and is associated with impaired autonomic function.[323] In chronic stages of the disease, pathological studies have found no parasites in the brain, and focal vasculitis is rare.[319] Cognitive impairment is probably a combined effect of multiple microinfarcts, low-flow state caused by heart failure, dysautonomia, and the effects of chronic inflammation on the brain.[320,322,324] However, the exact contribution of each of these mechanisms is not well studied, and there are no intervention studies to guide treatment.

Diagnosis and Monitoring

Chagas Disease in the Nonendemic Environment

Detection and diagnosis of chronic Chagas heart disease in traditionally nonendemic environments require a high index of suspicion. A 12-lead ECG may reveal signs of occult chronic Chagas disease in asymptomatic individuals. The most common presenting features in symptomatic patients include those related to heart

Table 4. Echocardiographic Variables as Predictors of Prognosis in Chagas Disease

Reference	Sample Size, n	Chagas Disease Population	Follow-Up Duration	End Points	Echocardiography Prognostic Variables*	Main Results
Rodriguez et al[294] (1998)	283	Indeterminate form and heart disease	48±36 mo	All-cause mortality	M-mode E-point separation ≥22 mm	Age ≥56 y, RBBB, first- and second-degree atrioventricular block; ST-segment elevation on precordial leads, and cardiothoracic ratio ≥0.55 were predictors of mortality.
Viotti et al[284] (2005)	856	Indeterminate form and heart disease without HF	8 y	Progression of the disease or cardiovascular death	LV end-systolic diameter	Age, LV systolic diameter, intraventricular conduction abnormalities, sustained VT, and pathogenetic treatment were associated with disease progression.
Rassi et al[198] (2006)	424	Heart disease	7.9±3.2 y	All-cause mortality	LV systolic dysfunction subjectively estimated	Predictors of mortality were NYHA class III or IV, cardiomegaly, wall motion abnormalities, nonsustained VT, low QRS voltage, and male sex.
Benchimol Barbosa[285] (2007)	50	Indeterminate form and heart disease	84.2±39 mo	Cardiac death or documented VT	Apical aneurysm and LVEF <62%	Ventricular ectopic beats >614/24 h were independent predictors of the composite end point.
Theodoropoulos et al[286] (2008)	127	Dilated cardiomyopathy	25±19 mo	All-cause mortality	LVEF	Lack of β-blockade, digoxin treatment, and low serum sodium levels were predictors of mortality.
Issa et al[287] (2010)†	68	Irreversible chronic HF	1326±39 d	All-cause mortality or heart transplantation	LV end-diastolic diameter	β-Blockers were associated with better survival.
Sarabanda et al[288] (2011)	56	Cardiomyopathy with either sustained VT or nonsustained VT	38±16 mo	All-cause mortality and sudden death	LVEF <40%	VT (either sustained or nonsustained) is a major risk for cardiac mortality in the presence of moderate or severe LV systolic dysfunction.
Ribeiro et al[289] (2011)	113	Indeterminate form and heart disease	106±28 mo	Cardiovascular death	LVEF	Increased T-wave amplitude variability was a predictor of death independent of LVEF, nonsustained VT, and QRS duration.
Bestetti et al[290] (2011)	231	Chronic HF	19 mo	All-cause mortality or heart transplantation	LV end-systolic diameter	Mortality was significantly lower in patients taking β-blockers.
Duarte et al[291] (2011)	56	Dilated cardiomyopathy	21±14 mo	Death or hospitalization	Rassi score	Ventricular dyssynchrony does not have any prognostic value.
Nunes et al[292] (2012)	232	Dilated cardiomyopathy	3.4 y	Death or heart transplantation	LVEF, RVMPI, LA volume, and E/e' ratio	There is an interaction between LVEF and E/e' ratio in predicting prognosis.
Nascimento et al[268] (2013)	251	Indeterminate form and heart disease	842±245 d	All-cause mortality, stroke, heart transplantation, worsening HF, or arrhythmias	E' velocity and peak negative global LA strain	LV diastolic function and LA contractile function were independent predictors of clinical events.
Costa et al[295] (2017)	60	HF with severe LV systolic dysfunction	24.5 mo	Cardiovascular death	Indexed LA volume	Increased indexed LV volume ≥72 mL/m^2 and nonsustained VT were predictors of mortality.

Six patients with HF were enrolled, and Chagas cardiomyopathy was present in 68 patients. HF indicates heart failure; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle-branch block; RVMPI, right ventricular myocardial performance index; and VT, ventricular tachycardia.

*Multivariate analysis

†Clinical trial; n=45.

‡E/e' is the ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity obtained by tissue Doppler imaging.

failure, bradyarrhythmias or tachyarrhythmias, thromboembolic events, and microvascular abnormalities (Table 5). When these signs and symptoms are present without a clear diagnostic confirmation, history of risk factors for *T cruzi* infection should be sought (Table 6), and specific serological tests must be used to confirm or rule out the diagnosis of Chagas disease.

Testing of selected high-risk populations demonstrates clearly that Chagas cardiomyopathy exists in the United States and Europe, but the magnitude of the disease burden remains only roughly estimated.[325–327] Among Latin America–born patients with newly diagnosed nonischemic cardiomyopathy (LVEF ≤40%) in Los Angeles, 19% (25 of 135) had Chagas disease.[326] Similarly, in a sample of New York City immigrants with dilated cardiomyopathy, 13% (5 of 39) had Chagas disease.[325]

The prognosis of infected patients (defined as transplantation-free survival) was poorer than for those with-

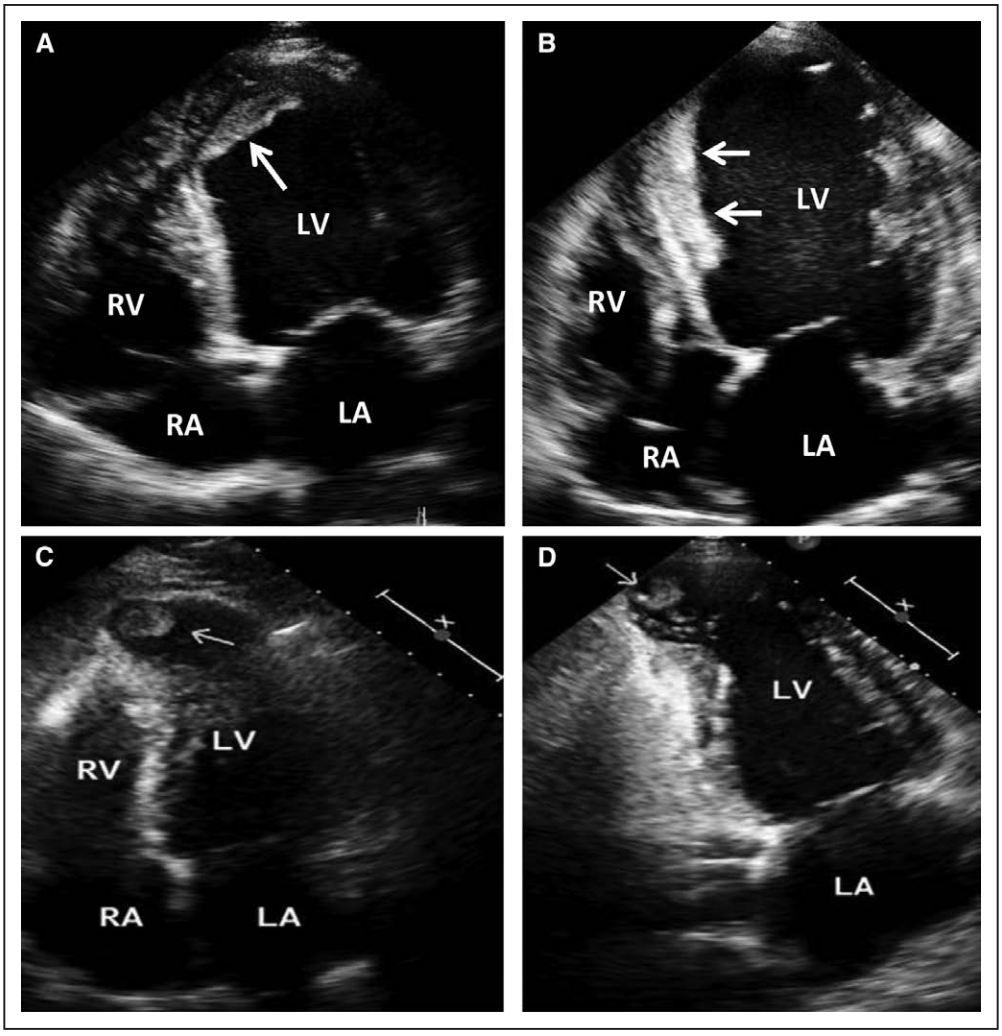

Figure 7. Left ventricular (LV) thrombus in patients with Chagas cardiomyopathy.
Several examples of LV thrombus in patients with Chagas cardiomyopathy. **A** and **B**, Mural thrombi. **C** and **D**, Apical thrombi within an LV aneurysm. Arrows indicate thrombi in different locations within the LV. LA indicates left atrium; RA, right atrium; and RV, right ventricle.

out *T cruzi* infection, a finding consistent with Latin American studies indicating that Chagas cardiomyopathy is associated with poorer survival than cardiomyopathy of similar severity with other causes.[326,328] In the Los Angeles study, a higher percentage of Central American than Mexican patients had *T cruzi* as the cause of their cardiomyopathy.[326] Cardiologists who care for Latin America–born patients should conduct *T cruzi* diagnostic testing for those with consistent clinical and epidemiological characteristics because management decisions may be affected by knowledge of the diagnosis.

Laboratory Testing

Early detection of Chagas disease is critical, allowing prompt introduction of therapy.[329] Moreover, identification of infection in blood and organs is crucial to evaluate suitability of a presumed donor for transfusion or transplantation.[330–332]

PCR testing is the most sensitive test in acute infection and for the monitoring of recipients of an organ from a *T cruzi*–infected donor.[333] In the acute phase, PCR may show rising parasite loads before parasites are visible by microscopy.[334] Once parasite levels increase, motile trypomastigotes can be detected through direct microscopic examination of fresh anticoagulated blood or buffy coat.[11] Microhematocrit is a widely used method to identify congenital infection.[335,336]

There is no single gold-standard laboratory test for diagnosing chronic Chagas disease.[334,337] Instead, at least 2 serological tests with different methods for detecting antibodies to *T cruzi* and complementary sensitivity and specificity are needed to confirm infection.[133,336] Conventional approaches include indirect immunofluorescence, hemaglutination, and ELISAs. High sensitivity and specificity with a single test, detection of trypomastigote-excreted and -secreted antigens in an ELISA format, have been achieved.[338] As the ELISA tests were used more broadly in the blood bank setting, the sensitivity of the assays improved, and the current consensus is that a single highly sensitive assay can

Table 5. Most Common Presenting Signs in Patients With CCC

HF: exertional dyspnea, orthopnea, peripheral edema, and fatigue
Bradyarrhythmia/tachyarrhythmia: palpitations, presyncope, syncope, aborted sudden death
Thromboembolic events: symptoms suggesting transient ischemic attack or stroke, pulmonary or systemic emboli
Microvascular abnormalities: precordial or retrosternal chest pain that is atypical for angina without evidence of epicardial coronary artery disease

CCM indicates chronic Chagas cardiomyopathy; and HF, heart failure.

Table 6. Risk Factors for Occult Chronic Chagas Disease in People Living in Nonendemic Environments

Patients who were born in or have lived for an extended period in *Trypanosoma cruzi*–endemic zones
A child of a mother from a *T cruzi*–endemic zone
Travelers with stays in *T cruzi*–endemic zone
Resident or former resident of the southern United States, especially in rural areas of states known to have the vector
Occupation brings patient in contact with *T cruzi* (laboratory transmission)

be used for routine *T cruzi* screening (ie, for ruling out infection when the test is negative)[339] but not for diagnosis, when 2 serological tests using different antigens are needed. In general, *T cruzi* PCR is not used to diagnose chronic infection but is used for early detection of reactivation in immunocompromised patients[340] (eg, recipients of transplants) and in research studies as surrogate criteria of therapeutic failure.[341]

Diagnostic testing for Chagas disease is not widely available in the United States. The CDC Division of Parasitic Diseases and Malaria houses the only laboratory performing *T cruzi* serological and molecular tests under Clinical Laboratory Improvement Amendments standards.[342]

Cardiovascular Assessment and Monitoring

Assessment of cardiac disease in patients with confirmed *T cruzi* infection is essential to detect early cardiac impairment and risk stratification before symptoms develop. Routine and ongoing assessments of electrocardiographic changes, especially of cardiac rhythm, are imperative because conduction abnormalities are typically the first indication of disease progression and can be clinically silent. Improved access to echocardiography has led to incorporation of noninvasive imaging as a more routine part of ongoing evaluation, and at least 1 echocardiogram is now indicated at each stage of disease. Advanced imaging offers complementary testing for patients with more advanced cardiac disease and can be used to help predict those at risk of adverse events and early mortality. Table 7 contains a summary of recommendations for cardiac diagnostic testing in patients with Chagas disease.

Electrocardiogram

The ECG is the single most important test in the initial evaluation of patients with definite or suspected Chagas disease. In those who come from endemic regions but without known infection, the existence of typical electrocardiographic abnormalities on the ECG may raise the clinical suspicion, and it is an additional reason to order a serological test. In patients with a confirmed serological diagnosis of chronic Chagas disease, the ECG can recognize those with established cardiomyopathy, in whom typical electrocardiographic findings will occur or, if normal, can point to the presence of the indeterminate chronic form, which should be confirmed by the absence of clinical manifestations and normal radiological tests (at least a chest x-ray). The presence of some electrocardiographic abnormalities, such as atrioventricular blocks and atrial fibrillation, demands immediate treatment, and a higher number of major electrocardiographic abnormalities is related to a higher risk of death.[141] The ECG should be repeated on a regular basis because the appearance of an electrocardiographic abnormality even in those with a previous abnormal ECG is frequently recognized as a marker of the progression to cardiomyopathy,[159,181] which results in the need for further testing and evaluation. For those with symptoms of cardiac arrhythmias, such as palpitations, syncope, and aborted sudden death, a resting ECG is obligatory before further testing with Holter monitoring, stress testing, or electrophysiologic study.

Unlike individuals with premature ventricular contractions detected on the 12-lead ECG who have no structural cardiac disease and have an entirely benign prognosis, patients with Chagas disease in whom premature ventricular contractions are found on the ECG carry a very high risk of having complex ventricular arrhythmia, and Holter monitoring is mandatory in this clinical setting.

Holter Monitoring

All patients with CCC, regardless of severity, require 24-hour Holter monitoring to assess the presence and density of complex ventricular arrhythmia, sinus node disease, and atrioventricular conduction.[132] Occult nonsustained ventricular arrhythmia is more common than in other cardiomyopathies and increases in frequency as cardiac function declines: 40% of patients with mild wall motion abnormalities and 90% of those with clinical heart failure.[343] Nonsustained VT on Holter monitoring is an independent marker of higher risk of death.[198] Holter monitoring is especially useful in patients with presyncope or syncope because these symptoms may be caused by bradyarrhythmia or tachyarrhythmia and both frequently coexist in patients with Chagas disease.[12] When seen, ST changes and abnormal Q waves must be interpreted cautiously because these changes frequently occur in patients with Chagas disease with no epicardial coronary artery disease.

Table 7. Timing of Cardiovascular Testing in Confirmed Chagas Disease

Test Modality	Indications at Diagnosis	Serial Evaluation*
ECG (12-lead plus minimum 30-s rhythm strip)	Acute Chagas disease Baseline evaluation at diagnosis in chronic phase	Normal ECG: yearly Abnormal: Minor changes: yearly Major changes: biannual ↓LVEF (B2 and C): biannual Clinical status change Arrhythmic episode, including palpitations, syncope, and aborted sudden death Evaluation for device therapy
Chest radiography	Baseline to assess heart size and pulmonary congestion and to detect alternative diseases that may contribute to the patient's symptoms	Decompensated HF
Echocardiography	Acute Chagas disease Baseline evaluation in those who have an abnormal ECG Thromboembolic event Transesophageal echocardiography is reasonable in patients with AF suspected of having cardioembolic stroke if initial transthoracic echocardiography is negative	Preserved LVEF (B1): every 3–5 y LVEF (B2 or greater): 1–2 y Clinical status change (worsening HF, embolic events, developing new electrocardiographic changes) Assessment for pacemaker or ICD device therapy
24-h Holter monitoring	Normal ECG (indeterminate form): only with specific concern Baseline evaluation in those who have an abnormal ECG (B1–D) Presence of symptoms (syncope) or arrhythmias on physical examination (frequent PVCs)	Major electrocardiographic changes: sinus node dysfunction, atrioventricular block, or frequent PVCs Clinical status change (presyncope or syncope) Treatment intervention
Exercise stress testing	Assessment of functional capacity and chronotropic response Presence of symptoms, especially chest pain to rule out myocardial ischemia	Pre-employment assessment to guide activity restrictions Development of symptoms Advanced HF, candidate for cardiac transplantation
Electrophysiology study	Symptoms of arrhythmia with negative Holter Sustained VT Aborted sudden death	Clinical status change with specific concern Recurrent VT for ablation therapy
Nuclear medicine testing	Baseline in Chagas cardiomyopathy for assessment of biventricular function when echocardiography is inadequate	Presence of chest pain for the detection of reversible (ischemic) and fixed (fibrosis) perfusion defects Assessment of the presence and extent of sympathetic denervation (for research purposes)
Cardiac MRI	Selected patients with Chagas cardiomyopathy to evaluate the extension of fibrosis	Presence of complex ventricular arrhythmias, especially VT
Cardiac catheterization and coronary angiography	Disabling atypical chest pain to rule out the concomitance of CAD, especially in patients with multiple risk factors Advanced HF to assess the feasibility of cardiac transplantation Endomyocardial biopsy for the assessment of inflammatory processes after cardiac transplantation, helping to distinguish between organ rejection and reactivation of *Trypanosoma cruzi* infection	

AF indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PVC, premature ventricular contraction; and VT, ventricular tachycardia.

*In addition to routine tests, additional follow-up tests should be requested in the following situations: clinical status change defined as a worsening functional class, development of systemic congestion indicating right-sided HF, or occurrence of a thromboembolic event. Arrhythmic episode defined as new-onset AF, bradyarrhythmias or tachyarrhythmias that cause palpitations, syncope, and aborted sudden death. Evaluation for pacemaker or ICD device therapy defined as the need for device implantation.

Chest X-Ray

In patients with Chagas disease, chest radiography is best performed in the posterior-anterior and lateral projections, facilitating assessment of atrial and ventricular size. Enlargement of all 4 cardiac chambers without pulmonary congestion suggests Chagas cardiomyopathy[236] and should prompt additional cardiac imaging and serological assessment in patients without a confirmed diagnosis of Chagas disease. In the acute presentation of *T cruzi* infection, a chest x-ray can provide helpful information on the presence and extent of pericardial effusion. Asymptomatic patients with a normal ECG should have a chest x-ray to confirm indeterminate Chagas disease.[105,344] In chronic Chagas heart disease, a chest x-ray is important for the evaluation of patients presenting with signs and symptoms of heart failure to assess pulmonary congestion. Cardiomegaly (a cardiac-to-thoracic ratio >50%) is an important predictor of mortality, which is also a component of the Rassi score used to assess mortality risk (adding 5 of a maximum of 20 points).[198]

Echocardiogram

Given the high rates of pericardial effusion and functional deficits and the lack of cross-sectional echocardiography data in this population, echocardiography should be part of the routine assessment of all patients with acute *T cruzi* infection, regardless of symptoms. It is also reasonable to obtain at least 1 echocardiogram for patients diagnosed during the indeterminate stage of Chagas disease. This study establishes a baseline for later comparison and can detect the small percentage of patients with subclinical regional wall motion abnormalities or ventricular aneurysm despite a normal 12-lead ECG. Serologically positive patients with an abnormal ECG should also have an echocardiographic assessment focusing specifically on LV systolic and diastolic function, presence of aneurysm, left atrial size, and RV function. Routine echocardiography is not indicated after this for asymptomatic patients with chronic Chagas heart disease. However, repeat echocardiography is indicated for patients with worsening functional class, developing new electrocardiographic changes, having aborted SCD, and undergoing assessment for pacemaker or ICD devices.

Stress Test With Electrocardiographic Monitoring

Patients with chronic Chagas heart disease typically have relatively preserved exercise capacity,[345] even in the face of marked electrocardiographic changes and depressed ventricular function.[346–349] Therefore, cardiac stress is not aimed primarily at assessing the ability to exercise but to assess chronotropic responses to exercise, which can be diminished as a result of previously described autonomic impairment.[83,346,350,351] Cardiac stress is also useful in uncovering complex ventricular arrhythmias, in particular when Holter monitoring is unavailable.[191,352,353] ST changes, of particular interest in patients with the classic chest pain syndrome of Chagas disease or unclear comorbidities, require cautious interpretations secondary to the background of chronic Chagas ST- and T-wave abnormalities.[354] Results of cardiac stress testing have been shown to be predictive of the risk of continued cardiovascular decline,[190] in particular in the earlier stages of disease.[355,356] Cardiac stress testing should be considered to guide activity restrictions in patients with Chagas disease, especially as a tool to assess occupational safety for participation in manual labor. Finally, cardiac stress testing is recommended in patients with Chagas disease with advanced heart failure for whom cardiac transplantation is under consideration, with a peak oxygen uptake ≤10 $mL \cdot kg^{-1} \cdot min^{-1}$ being a recommended criterion for heart transplantation.[134]

Nuclear Medicine Tests

Nuclear medicine testing can provide helpful complementary information in patients with Chagas disease, in particular in patients with poor acoustic windows or when additional information about RV function, myocardial perfusion, or myocardial sympathetic innervation is required.[357] These methods have been quite useful to elucidate some relevant aspects of the pathogenesis and pathophysiology of CCC. However, because nuclear medicine testing is relatively expensive and not universally available, these tests have typically been used for research with no standardized clinical use recommendations.

Radionuclide Ventriculography (Multigated Acquisition)

Radionuclide ventriculography (multigated acquisition [MUGA]) scans provide the most precise ventricular function information in patients with Chagas disease.[358–362] Unlike M-mode and 2-dimensional echocardiography, in which EF is reliant on a formula that assumes normal ventricular geometry, MUGA averages hundreds of cardiac cycles, can delineate and account for aneurysm, does not depend on geometric assumptions for LVEF calculation, and is not affected by the more spherical shape typically seen in dilated cardiomyopathy. MUGA is also effective for quantification of RV function[95,273] (qualitative by echocardiography) and can be used to assess ventricular dyssynchrony.[363] Tomographic MUGA adds data to myocardial perfusion assessment, allowing correlation between perfusion defects and regional wall motion abnormalities.[364] MUGA can be particularly helpful for the assessment of biventricular systolic function in patients with poor acoustic windows and a contraindication to CMR imaging.

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography has shown that patients with Chagas cardiomyopathy have both fixed perfusion defects, typically associated with areas of fibrosis and wall motion abnormality,[365,366] and reversible perfusion defects, despite normal epicardial coronary on angiography.[110,111] These perfusion defects worsen over time, as fibrosis increases, with fewer reversible and more fixed areas of poor perfusion.[99] In addition, follow-up single-photon emission computed tomography studies have correlated Chagas chest pain syndrome with microvascular perfusion defects, confirming this mechanism as potentially causative of myocardial damage.[110,111,228] Single-photon emission computed tomography imaging has, to date, been used mostly for research purposes, with no routine clinical indications. However, results of this test in selected patients with atypical chest pain, showing the absence or presence of mild, multiple perfusion defects not related to coronary anatomy, are useful to preclude the performance of unnecessary cardiac catheterization.

Myocardial Sympathetic Innervation Imaging

Myocardial scintigraphy can assess the integrity of cardiac sympathetic innervation in patients with Chagas cardiomyopathy, although to date, this has been done

mainly for research. Abnormalities in sympathetic innervation have been shown to be an early finding in Chagas heart disease, preceding other cardiac changes in 33% of patients,[100] and tend to correlate with areas that will later develop regional wall motion and perfusion defects.[367,368] It is plausible to speculate that combining single-photon emission computed tomography assessment of myocardial fibrosis (by detecting fixed perfusion defects) and metaiodobenzylguanidine testing for myocardial sympathetic denervation may be a potential tool for stratifying patients for the risk of developing malignant ventricular arrhythmia.[95,96]

Positron Emission Tomography With Fludeoxyglucose

In a recent case report, a female patient appearing to have takotsubo syndrome but whose CMR imaging findings suggested the presence of an inflammatory condition was studied with fludeoxyglucose positron emission tomography imaging. Enhanced uptake of the positron emission tomography tracer in the peri-aneurysm area was interpreted as meaning active inflammation in the viable myocardium adjacent to the typical apical lesion.[369] This notion is corroborated by studies in animal models of *T cruzi* infection showing that positron emission tomography may be used to detect enhanced myocardial metabolism possibly elicited by inflammatory changes caused by the infection.[370] It is plausible that this method can be used in the future to assess noninvasively the presence of active inflammation in some clinical settings (eg, after cardiac transplantation).

Cardiac Magnetic Resonance

CMR has a superior capability for anatomic and functional evaluation of all cardiac chambers, provides direct measurement of both RVEF and LVEF, detects mural thrombosis, and allows valuable tissue characterization. In particular, late enhancement imaging of gadolinium injected intravenously is useful for the qualitative and quantitative assessment of myocardial fibrosis.[367,371] These studies further highlighted the striking feature Chagas cardiomyopathy, describing patients who develop malignant arrhythmia in the absence of global ventricular systolic dysfunction but showing focal areas of myocardial fibrosis.[229,357,372] Thus, CMR has strong potential for improving the prognostic evaluation of patients with CCC beyond the Rassi score, perhaps allowing restratification of those with intermediate risk of death. Despite some limitations for the widespread use of CMR in low-income countries, the use of this method can be strongly encouraged on the basis of its diagnostic and prognostic capabilities.

Cardiac Catheterization

Patients with CCC, especially when harboring classic risk factors, are frequently referred to cardiac catheterization because of disabling angina-like symptoms and because the disease mimics coronary artery disease in various ways. In addition to atypical angina, the ECG often shows ST-T changes and pathological Q waves; segmental LV wall motion abnormalities are seen with echocardiography, and ischemic or fixed myocardial perfusion defects are detected in most cases. Despite these similarities, angiography almost always reveals essentially normal epicardial coronary arteries. During the examination, the high spatial resolution of contrast ventriculography allows detection of even very small apical aneurysms and other LV wall motion abnormalities in many patients.[357] Cardiac catheterization is also indicated in patients with advanced heart failure to assess the feasibility of cardiac transplantation, providing the direct measurement of pulmonary vascular resistances.

Cardiac catheterization with endomyocardial biopsy is indicated for the assessment of inflammatory processes after cardiac transplantation to distinguish between organ rejection and reactivation of *T cruzi* infection.

Pathogenic Diagnosis of Stroke

There is no empirical evidence that patients with CAS should undergo a different diagnostic workup than other stroke patients, and the guidelines of the presenting country or institution should be followed. Transthoracic echocardiography is indicated in all patients serologically positive for *T cruzi* who present with thromboembolic events, regardless of electrocardiographic findings. Of consideration, both transthoracic and transesophageal echocardiograms are frequently required to rule out intracardiac thrombi, particularly in the setting of atrial fibrillation, because transthoracic echocardiography is more sensitive for LV aneurysm and thrombus and transesophageal echocardiography is superior for left atrial thrombi.[253] In 1 study, findings on transthoracic echocardiography were more frequent than on transesophageal echocardiography because 23% of patients with Chagas disease had LV thrombus, 47% had LV aneurysm, and only 5% had thrombi in the left atrial appendage.[277] Holter monitoring may unveil occult paroxistic atrial fibrillation as a contributor to the current stroke and a source of future stroke.[373,374] CMR imaging may prove to be a useful technique to detect intracardiac thrombi, mural fibrosis, and inflammation in selected patients.[368]

Risk Stratification in Chagas Heart Disease

Chronic Chagas Cardiomyopathy

When possible, risk stratification scores should be performed in all patients with chronic Chagas disease, with initial use early in the cardiac course. Some risk scores have been developed to predict adverse outcomes in this population. The Rassi score, for patients with established cardiomyopathy, uses 6 factors (a combination

Table 8. Summary of Risk Prediction Score for CCC (Mortality Rassi Score)

Variables assigned points	Number of points
NYHA class III or IV	5
Cardiomegaly	5
Segmental or global wall motion abnormality	3
Nonsustained ventricular tachycardia	3
Low QRS voltage	2
Male sex	2
Summation score assigned risk category	
Low	0–6
Intermediate	7–11
High	12–20
5-year mortality rates (%)	
Low	2
Intermediate	18
High	63
10-year mortality rates (%)	
Low	10
Intermediate	44
High	84

CCC indicates chronic Chagas cardiomyopathy; NYHA, New York Heart Association; and VT, ventricular tachycardia.

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of clinical symptoms, test results, and demographics) with weighted values to classify patients by risk of 10-year mortality: low (10%), medium (44%), and high (84%)[198] (Table 8). The Sousa score, published more recently, uses 4 factors (QT dispersion, syncope, premature ventricular contractions, and LV function) to predict risk of SCD as low (0–2 points), intermediate (3–4 points), and high (>5 points).[375]

Other known predictors of poor outcome in CCC include RV dysfunction, segmental wall motion abnormalities, left atrial volume, E/e' (ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity obtained by tissue Doppler imaging), strain rate, abnormal electrocardiographic ventricular repolarization, and elevated BNP.[193,254,274,376] In addition, newly available data from the BENEFIT trial are the first multinational risk data on patients with mild to moderate CCC at the time of inclusion.[130] The Rassi score, which includes New York Heart Association class III, cardiomegaly, regional wall motion abnormalities, complex ventricular arrhythmias, low-voltage QRS complex, and male sex, applied to this cohort predicted risk of composite cardiac events (death, resuscitated cardiac arrest, sustained VT, insertion of a pacemaker or ICD, cardiac transplantation, new heart failure, stroke or systemic embolism): low-risk patients (score, 0–2), 3%/y; intermediate-risk patients (score, 3–5), 6%/y; and high-risk patients (score >5), 9%/y. The majority of events within the composite outcome were SCD and heart failure. The presence of at least moderate LV dysfunction (EF <40%) at randomization was associated with a 63% (12%/y) event rate compared with 24% (5%/y) when the LVEF was ≥40%. Event rates varied by region, likely with variation of *T cruzi* strains. For example, Colombia and El Salvador (primarily *T cruzi* I) had a primary outcome event rate of 26% (5%/y); Brazil (primarily *T cruzi* II), 38% (7%/y); and Argentina and Bolivia (*T cruzi* V and VI), 19% (4%/y).[130]

Stroke

A prediction model for stroke has been proposed that is based on a 12-year cohort of >1000 patients,[298] but confounders limit the general applicability of this scale, and external validation is needed. Four variables are included: systolic dysfunction (2 points), apical aneurysm (1 point), abnormal ventricular repolarization (1 point), and age >48 years (1 point). According to the risk-benefit analysis, anticoagulation should be indicated in patients with a score of 4 to 5 (annual risk of stroke of 4.4% versus 2% incidence of bleeding). For patients with a score of 2 to 3, the risk of stroke is balanced with the risk of bleeding, and either anticoagulation or aspirin should be considered. In this situation, aspirin should be recommended for patients with higher risk of bleeding. Patients with a score of <1 have a low incidence of ischemic events, and aspirin or no treatment is suggested.[298] However, because the risk-benefit ratio of anticoagulation has not been studied in these high-risk patients, anticoagulation is recommended for those patients in whom a cardioembolic mechanism is most likely, for example, those with a diagnosis of a nonlacunar infarct (computed tomography or magnetic resonance imaging) in the presence of atrial fibrillation, intracardiac thrombus, apical aneurysm, or systolic dysfunction.

Treatment and Management of Chagas Heart Disease

Antitrypanosomal Therapy

Benznidazole and nifurtimox are the only drugs with proven efficacy against Chagas disease.[377,378] Benznidazole is the first-line treatment because it has better tolerance and is more widely available and because more data have been published on its efficacy. Important side effects of benznidazole include dermatitis (which can be severe), leukopenia, peripheral neuropathy, anorexia and weight loss, nausea or vomiting, and insomnia. The drugs are not currently approved by the US Food and Drug Administration, and use in the United States entails consultation with the CDC (contact the Parasitic Diseases Public Inquiries line [404-718-4745 or parasites@cdc.gov], CDC Drug Service [404-639-3670], or CDC Emergency Operations Center [770-488-7100]) and compliance with the requirements of investigative protocols.

Treatment is indicated in all patients with acute Chagas disease regardless of the infection mechanism as soon as parasitological or serological confirmation is obtained, with parasite elimination and cure achieved in 60% to 90%. Success is high in congenital transmission, with >90% of infants treated during the first year of life achieving cure.[379–382] The role and efficacy of antitrypanosomal medications in chronic Chagas disease are less certain. Treatment of children up to 18 years of age with chronic *T cruzi* infection is the standard of care throughout Latin America on the basis of 2 randomized, placebo-controlled double-blind trials of benznidazole that demonstrated 60% cure rates by lytic antibody ELISAs and a 90% decrease in the prevalence of positive xenodiagnosis (the premolecular era test of circulating parasite load).[383,384] However, extension analyses of these 2 studies did not show a benefit of benznidazole on reducing electrocardiographic changes compared with placebo. In long-standing chronic infection (ie, adults), parasite burden is reduced, but it is unclear how often cure can be achieved.[385] Conventional serology takes decades to become negative, and there is no practical test of cure. Quantitative PCR has been shown to be a sensitive, timely indicator of treatment failure.[385] Expert opinions are divided on the role of antitrypanosomal therapy for adults with the indeterminate form of Chagas disease, but the majority of experts believe that there is potential benefit, in particular in younger adults (<40 years of age).[54,133,183,383–386] Challenges with assessing the efficacy of treatment include the fact that many infected individuals will never develop cardiomyopathy and there is no current biomarker to identify those who might benefit from treatment.

Current data indicate that treatment with antitrypanosomal therapy in established cardiac disease is unlikely to change clinical outcomes. The recent BENEFIT trial, a large, multinational, multicenter, randomized controlled trial, demonstrated no significant effect of benznidazole on preventing the progression of established Chagas cardiomyopathy.[130] Further analysis is underway to identify specific subgroups who may derive a benefit from treatment. On the basis of this trial, routine antitrypanosomal treatment of patients with established Chagas cardiomyopathy is not recommended. Expert consensus recommends treatment of women of childbearing age to prevent congenital transmission and of immunocompromised patients with reactivation of the disease[196,340,381] (Table 9).

Benznidazole therapy should be managed by the doctors directly in charge of their patients because they are acquainted with side effects and the pertinent measures to control them. There is no need to refer patients to specialists just to implement the trypanocidal treatment. The following additional guidance is suggested: First, blood count at ≈21 days after the initiation of treatment with benznidazole is mandatory to detect leukopenia (roughly 1/1000 but requires interruption).

Table 9. Recommendations for Antitrypanosomal Treatment in Chagas Disease

Treatment should be given (expert consensus)
Acute infections, regardless of the mechanism of transmission
Congenital infection
Women of childbearing age*
Accidental high-risk contaminations†
All cases of reactivation of *Trypanosoma cruzi* infection
Pediatric patients in chronic phase (children <18 y of age)
Treatment could be offered
Indeterminate form in patients >18 y of age
Chronic cardiomyopathy form; patients not in advanced stages may be offered treatment on the basis of a shared decision with the attending physician.
Treatment should not be given
Patients with established dilated cardiomyopathy

*After a negative pregnancy test because both drugs are contraindicated in pregnancy, and contraceptive methods should be used for women of childbearing age who will receive treatment.

†Contact with living parasites or cultures through skin breakage or mucosal contact, typically in a laboratory, clinical, or necroscopy setting.

Second, mild and moderate dermatitis is readily controlled with prednisone 10 mg once daily for 10 days. Severe exanthema warrants treatment interruption. Third, if peripheral neuropathy supervenes, it occurs by the end of treatment, so drug administration is not interrupted. On the other hand, no empirical treatment has been shown to lead to its remission, and only time will take care of the problem (usually several months).

The recommended dose of benznidazole is 10 $mg \cdot kg^{-1} \cdot d^{-1}$ in children and 5 $mg \cdot kg^{-1} \cdot d^{-1}$ in those with chronic disease for 60 days, divided into 2 doses. The maximum recommended daily dose is 300 mg. For adults weighing >60 kg, the total dose expected should be calculated, extending the treatment time beyond 60 days. Thus, patients weighing 65 kg receive 300 mg daily for 65 days, and patients weighing 70 kg receive this daily dose for 70 days to a maximum of 300 mg. This is a posology regimen that has been empirically implemented to reduce side effects and was used in the second half of the BENEFIT population.[134]

The persistence of a positive serological test is the rule, not the exception, for many years in virtually every patient treated in the chronic phase of Chagas disease. This essentially means that the current protocol treatment may only reduce the whole body parasite load, but it rarely leads to *T cruzi* eradication. Even if this goal is eventually achieved, it will occur at a slow pace, as indicated by the gradual, slow decrease in antibody titers detected with the serology test.

Heart Failure

Treatment of Acute-Phase Cardiac Disease

Treatment of patients presenting with severe acute Chagas disease (5%–10% of those infected) aims to

eliminate *T cruzi (*nifurtimox or benznidazole) and to stabilize the jeopardized hemodynamics. Pericardial effusion and the resulting cardiac tamponade, arrhythmia, and heart failure secondary to Chagas myocarditis need to be recognized and promptly managed.

Medical Therapy for Chronic LV Dysfunction and Heart Failure

Most of the medical treatment for patients with CCC has been extrapolated from data on other forms of heart failure. The vast majority of clinical trials confirming a survival advantage of pharmacological agents did not include patients with Chagas disease, so their efficacy and safety in patients with CCC have not been definitively established. Routine clinical practice includes a combination of β-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, digoxin, diuretics, and anticoagulation. ACE inhibitors are recommended for all patients with CCC and reduced LVEF or with segmental wall motion impairment despite preserved global LV function. The addition of an aldosterone receptor antagonist is recommended for patients who have New York Heart Association class II to IV heart failure and who have LVEF ≤35%. Among the general population with dilated cardiomyopathy, these medications are known to reduce mortality and to improve quality of life in patients with LV dysfunction independent of the functional class.[10–12] A small, single-blind clinical trial of patients with CCC demonstrated that 6 weeks of captopril had a beneficial effect on neurohormones with a reduction in heart rate and decreased incidence of ventricular arrhythmias.[13] In addition, ACE inhibitors and mineralocorticoid receptor antagonists have been shown, in limited study, to improve functional class and to lower BNP, even before the introduction of β-blockade.[387] Aldosterone receptor antagonists seem to be safe in Chagas cardiomyopathy and should be added in patients who are already on ACE inhibitors (or angiotensin receptor blockers) and β-blockers.[196,387]

Unless specifically contraindicated, β-blocker therapy is recommended for all symptomatic or previously symptomatic patients with CCC and reduced EF. Blocking adrenergic response could have specific pathophysiologic relevance in CCC because patients may have autonomic imbalance (resulting from predominant parasympathetic dysautonomia and incompletely denervated myocardium), which has potential for the development of ventricular arrhythmia. In addition, these medications provide general protection against the development of ventricular arrhythmia, and consequently sudden death, further suggesting their usefulness in this scenario.[9] β-Blockers may improve the patient's clinical status,[387] but their effect on survival remains to be demonstrated.[287,388] Although causality is not certain, improved quality of life, a lower BNP, and a significantly increased EF after the addition of carvedilol among patients with CCC already receiving an ACE inhibitor and a mineralocorticoid receptor antagonist have been suggested.[387] Unfortunately, many patients with Chagas cardiomyopathy are intrinsically bradycardic or use amiodarone because of ventricular arrhythmia and may not tolerate the higher doses of β-blockers and ACE inhibitors typically used in clinical trials.[388] In other patients who do not meet these restrictions, the addition of low-dose β-blockade to low-dose ACE inhibitor may still have a protective effect.[286]

As with most medications, there is no direct evidence that digoxin benefits patients with CCC. Data from the generalized heart failure literature support the role of digoxin in improving functional class, reducing cardiac symptoms, and reducing hospitalizations.[15] In CCC, digoxin should be avoided in patients showing conduction abnormalities at or below the atrioventricular node because it prolongs the effective refractory period of atrioventricular nodal tissue and can worsen heart block. This drug may be added to the initial regimen in patients with functional class III to IV symptoms who have not yet responded symptomatically to standard therapy, especially those with atrial fibrillation with fast ventricular response, but close monitoring for the development of atrioventricular nodal dysfunction is recommended.

Diuretics improve the quality of life and relieve congestive symptoms in patients with heart failure, but again, there is no demonstration of an impact on mortality.[134] Their benefits can be sought in patients with symptomatic CCC; thus, diuretics are recommended in patients with Chagas cardiomyopathy and reduced EF who have evidence of fluid retention to improve symptoms. Anticoagulation has increased in importance in CCC compared with other types of dilated cardiomyopathy. Because of a lack of evidence, most practitioners follow recommendations outlined in the only available trial for use of anticoagulation.[298] In general, anticoagulation is recommended for patients with Chagas disease who have permanent/paroxysmal atrial fibrillation, a previous thromboembolic events, or the presence of a cardiac thrombus detected by echocardiography.[134] Anticoagulation may be indicated in patients with apical aneurysms,[319] especially small aneurysms with a narrow neck that are at high risk for thrombus formation. The role of antiplatelet drugs in the prevention of thromboembolic events has yet to be determined in the setting of Chagas disease, but aspirin is empirically used by many practitioners when the bleeding risk is felt to be too high for anticoagulation aiming at the prevention of stroke, as stated previously. Recommendations for the pharmacological treatment of Chagas-related heart failure are summarized in Table 10.

Heart Transplantation in Chagas Disease

Chagas disease has not been considered a contraindication for heart transplantation since the 1990s. Selection criteria do not differ from the general transplantation evaluation except that the presence of megaesophagus

Table 10. Recommendations for Pharmacological Treatment of Heart Failure in Chagas Disease

Medications that should be recommended
ACE inhibitors or ARBs: Are recommended for all patients with regional wall motion impairment or reduced LVEF
β-Blockers: Are beneficial for all patients with HR >55 bpm and reduced LVEF
Mineralocorticoid/aldosterone receptor antagonists: Can be beneficial for patients classified as having NYHA class II–IV HF and who have LVEF ≤35%
Loop diuretics: Are beneficial for all patients with reduced LVEF who have current or prior evidence of fluid retention
Thiazide diuretics: Are beneficial for patients who are unresponsive to high doses of loop diuretic
Digoxin and other digitalis glycosides: Can be useful for patients with persistent symptoms (NYHA class III–IV and right-sided HF), regardless of the underlying rhythm
Oral anticoagulants: Can be beneficial in patients with paroxysmal or persistent/permanent AF, previous thromboembolic events, and thrombus
Antiplatelet therapy (aspirin): Is reasonable for patients who have indications for anticoagulation but with high risk of serious bleeding
Newer oral anticoagulants: May be considered as an alternative to warfarin
Amiodarone: Can be beneficial used alone or in combination with a β-blocker to suppress symptomatic ventricular arrhythmias in patients with reduced LVEF and in those with a high percentage of ventricular ectopic beats and nonsustained VT by 24-h Holter monitoring; amiodarone is also recommended to decrease the frequency of appropriate ICD shocks

Most drugs have not been tested in randomized controlled trials because there are few randomized trials in patients with Chagas with HF. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and VT, ventricular tachycardia.

or megacolon is a relative contraindication.[390,391] Survival after transplantation at 1 month (83%), 1 year (71%), and 10 years (46%) is better than in the general heart transplantation population.[392]

Despite the risk of *T cruzi* reactivation after transplantation and immunosuppression, universal "prophylactic" antitrypanosomal therapy is not recommended.[393,394] Quantitative *T cruzi* PCR provides sufficient sensitivity to detect a reactivation before complications such as allograft dysfunction develop.[393,395] Benznidazole has been the drug of choice for the treatment of *T cruzi* reactivations. Nifurtimox has not proved to be adequately effective.[394,396] Because treatment does not result in a cure of chronic *T cruzi* infection, patients remain vulnerable to new episodes of reactivation, and lifelong *T cruzi* monitoring is required.

Immunosuppression after heart transplantation for CCC also warrants some particular consideration. Use of lower immunosuppressive regimens has demonstrated fewer reactivations and improved outcomes, with no increase in allograph rejection in patients with CCC.[397,398] Lower immunosuppression may also offer an advantage against the hypothesized development of malignancies, although a high suspicion must be maintained in all immunosuppressed individuals.

Treatment of Arrhythmia and Prevention of SCD

Antiarrhythmic Drugs

Isolated premature ventricular complexes are the most common arrhythmia in CCC and require no treatment in patients with preserved ventricular function. Treatment is similarly not routinely recommended for patients with complex ventricular extrasystoles and asymptomatic nonsustained VT when ventricular function is preserved. Treatment recommendations for patients with nonsustained VT and decreased LV function are not as clear.[195,196,399,400] Amiodarone, the drug of choice in patients with CCC, has high toxicity (eg, dermatitis, the most frequent; pulmonary fibrosis, which is very rare; and thyroid dysfunction, which is common, both hyperthyroidism and hypothyroidism, among others), and there is a lack of evidence that its use alters mortality among all-comers with dilated cardiomyopathy.[401] Although not proven to decrease the risk of SCD in CCC, amiodarone is empirically prescribed to many patients, and it improves symptoms and reduces the density of ventricular arrhythmia.[54,103,193,199,233,234] Amiodarone should be considered in high-risk patients with LV dysfunction and nonsustained VT associated with symptoms, especially dizziness and palpitations, and in patients with delayed enhancement by CMR,[229] late potentials in the signal-averaged ECG,[224] T-wave variability,[289] and T-wave microalternans.[402] In addition, amiodarone should be considered in patients with a high percentage of ventricular ectopic beats and nonsustained VT by 24-hour Holter monitoring because, even without sustained VT, these can result in decreased ventricular function, or tachycardiomyopathy, which may be partly reversible with antiarrhythmic treatment.[403]

Implantable Cardiac Defibrillator

Patients with Chagas heart disease experience a higher rate of malignant ventricular arrhythmia and resultant SCD[195,221] than other populations with dilated cardiomyopathy matched by ventricular dysfunction.[404,405] The CHAGASICS trial (Amiodarone Against ICD Therapy in Chagas Cardiomyopathy for Primary Prevention of Death) is underway to establish the benefit of ICD therapy for the primary prevention of death in patients with Chagas cardiomyopathy.[406] However, until the results of this trial are available, there are no data to support recommendations for the primary prevention of death in patients with Chagas disease.

ICDs are empirically and commonly used for secondary prevention after documented VT, ventricular fibrillation, or aborted sudden death. A few observational in-

vestigations provided mixed results and raised concern compared with historical series of CCC patients treated only with amiodarone.[407] In a single study, ICDs in patients with CCC with documented prior life-threatening arrhythmia were shown to have a survival advantage over amiodarone alone, with a 72% reduced risk of all-cause mortality ($P<0.01$). The greatest survival benefit was seen in patients with LVEF <40%, with no advantage detected for those with LVEF ≥40%.[408] Comparative data between ICDs in CCC and other cohorts show that patients with CCC have more frequent ventricular arrhythmias, a higher percentage of appropriate shocks, and no increase in inappropriate shocks, although no differences in mortality have been seen.[405,409–412]

There is general consensus that patients with CCC who have been resuscitated from SCD and patients with LVEF <35% and documented syncope secondary to VT should be high priority for ICD placement. In addition, ICDs should be considered in patients with LVEF >35% who have experienced syncope secondary to VT and in patients with CCC with syncope and inducible sustained VT during electrophysiological study.[134]

Amiodarone is also an important adjunct therapy after ICD placement. Patients with Chagas heart disease can have frequent shocks as a result of intense ventricular arrhythmic activity,[405] and the number of shocks received may be deleterious,[411] contributing to mortality by causing myocardial necrosis and promoting or exacerbating ventricular dysfunction.[413,414] The combined use of amiodarone and β-blockers was effective in reducing the number of therapies in other cardiomyopathies[413,415] and should be considered in patients with CCC who receive frequent shocks.

Ablation Therapy

Ablation of VT (surgical or catheter based), in particular after medication failure or intolerable side effects, is an option to treat recurrent VT in patients with CCC.[416,417] The VT in Chagas heart disease is typically a reentrant tachycardia,[227] and the goal of ablation is to identify and disrupt the circuit through ablation of critical isthmuses. Careful and extensive mapping is needed because multiple discrete circuits are typically present. The most common site of origin in Chagas cardiomyopathy is the LV basal inferolateral wall.[228,418] However, about one-third of reentrant circuits are located on the epicardial surface, requiring additional epicardial mapping to achieve successful ablation.[419,420]

As stated for other clinical conditions, VT ablation is recommended by expert consensus (Level of Evidence C) for 4 indications in CCC patients[421]: (1) symptomatic sustained monomorphic VT, including VT terminated by ICD, that recurs despite antiarrhythmic drug therapy or when antiarrhythmic drugs are not tolerated or are not desired; (2) control of incessant sustained monomorphic VT or VT storm that is not the result of a transient reversible cause; (3) bundle-branch reentrant or interfascicular VT; and (4) recurrent sustained polymorphic VT or ventricular fibrillation that is refractory to antiarrhythmic therapy and when there is a suspected trigger that can be targeted for ablation.

Pacemaker Implantation

Advanced atrioventricular block and symptomatic sinus sick syndrome are the main indications for pacemaker implantation in Chagas disease. In general, recommendations for pacemaker implantation in Chagas disease are the same as the international guidelines for other conditions. Some recent studies emphasize the detrimental effects of apical implantation of the RV electrode, and midseptal implantation seems to be warranted.[422,423] When patients present with left bundle-branch block (far less common than RBBB) and heart failure, resynchronization therapy can be attempted according to more general heart failure guidelines, but there is scarce evidence to support resynchronization therapy for patients with Chagas cardiomyopathy and RBBB.

Stroke

In Chagas cardiomyopathy, primary stroke prophylaxis with warfarin is indicated in patients with paroxysmal or permanent atrial fibrillation with CHA_2DS_2-VASc score ≥2 or with LV systolic dysfunction.[389]

As previously stated, additional recommendations for anticoagulation include intracardiac thrombi, previous stroke, or transient ischemic attack, especially in the presence of apical aneurysm. Although apical aneurysm is an independent risk factor for stroke in Chagas cardiomyopathy,[261] the indication of anticoagulation in the presence of an apical aneurysm without thrombi is still controversial, and its use should be individualized considering the size of the aneurysm and the patient's risk of hemorrhage.

In patients with CAS, short-term treatment with thrombolysis has been performed with similar rates of success compared with non-Chagas stroke, despite the theoretical concern that intracardiac thrombi may dislodge after systemic thrombolysis.[424,425] There have been no reports of mechanical thrombectomy in CAS. Secondary prophylaxis for stroke in Chagas disease that frequently is cardioembolic will require long-term anticoagulation with warfarin.[426] Although most physicians will prescribe antiplatelet agents for noncardioembolic CAS, actual data on effective treatments are lacking in this rather large subgroup of patients.

SPECIAL CONSIDERATIONS: THE NEED FOR EARLY BIOMARKERS OF THERAPEUTIC RESPONSE

Several key characteristics of Chagas disease make the development of early biomarkers critical. First, the

majority of patients with Chagas disease are asymptomatic until presenting with severe, typically irreversible cardiac or gastrointestinal symptoms and complications.[130] Second, parasites in the chronic form are typically rooted in deep tissues, with only transient low levels of circulating parasites, undetectable by classic parasitological methods. Finally, the gold-standard tool of certificate cure is conventional serology, but negative seroconversion can lag years behind cure.[183,386] Progress has been shown in this area of research, and there has been an attempt to define the ideal characteristics of a biomarker of early treatment response.[427] However, most studies have been conducted in single, homogeneous populations, making comparison and generalization challenging.

PCR has emerged as a sensitive test to detect treatment failure,[385] to monitor for reactivation,[428,429] and to detect congenital transmission, but it has limitations. A negative PCR is not conclusive for cure because of the limitations of the technique itself (ie, limitations in the capacity to detect the number of parasite equivalent per 1 mL)[430] and disease characteristic (amastigotes in deep tissues, intermittence of the peripheral parasitemia).

Biomarkers to assess therapeutic accuracy are also being developed. Those dependent on the detection of parasite antigens with recombinant proteins[431–437] and lytic antibodies[383,438,439] are showing promise in human trials. ELISA for the recombinant *T cruzi* flagellar calcium-binding protein (F29) showed promise during a randomized double-blind controlled study in children,[384] but results were not as encouraging in adult replication studies.[440]

Detection of antibodies specific to the 3 evolutive forms of *T cruzi* using flow cytometry has also recently been described as a valid strategy to monitor therapy efficacy. Reactivity to the amastigote form emerged as an excellent measure of effectiveness; results showed that 100% of patients with therapeutic failure displayed positive antibody reactivity to the amastigote form, whereas all patients who were treated and cured consistently displayed negative results in a 10-year follow-up.[441]

Biomarkers based on host response have also been proposed. The long persistence of the *T cruzi* parasite causes metabolic changes in the host. Hypercoagulability biomarkers[308,310,340] and lipid metabolism[442–447] have been studied as potential biomarkers of therapeutic response. In addition, they may be tools to lead to a better understanding of some of the issues related to the pathogenesis and pathophysiology of the disease.

Because of the complexity of the disease, it is likely that future success will come through a panel of several biomarkers organized through an algorithm, not by a single gold-standard marker of cure. In addition to direct patient benefit, a reliable biomarker would strengthen and shorten clinical trials, facilitating the discovery of new therapeutics for Chagas disease.

FUTURE PRIORITIES TO IMPROVE DISEASE RECOGNITION AND CARE FOR CHAGAS PATIENTS LIVING OUTSIDE OF LATIN AMERICA

Although the pathogenesis of Chagas disease was first described >100 years ago, it remains a largely neglected disease with insufficient diagnostic, therapeutic, and prognostic advances. Whereas patients living in Latin America are by far the largest population affected, those living outside of Latin America are part of a highly vulnerable immigrant population, often without access to consistent-quality medical care. Compounding the healthcare inequality, these patients are often cared for by providers with little knowledge of Chagas disease. High-quality epidemiological research and investment in provider education are urgently needed to improve the recognition of and care for Chagas disease outside of Latin America.

Cost-effective interventions cannot be designed until accurate disease estimates are known. Improved systematic surveillance among immigrant populations around the globe must be a high priority. In the United States, studies to better evaluate the overall burden resulting from locally acquired *T cruzi* are also needed, but they will require large (and therefore expensive) surveys or innovative methods such as vector and animal reservoir infection prevalence surveys followed by adaptive sampling in human populations.[448–450]

Diagnostics must also be improved. A point-of-care diagnostic test could dramatically improve case detection and notification in transient populations. Of particular importance, a rapid test would need to demonstrate good performance characteristics across *T cruzi* genotypes and strains because data from South American populations may not be sufficient to predict test sensitivity in infections acquired in Central America and Mexico.[451,452]

Improved antimicrobial options must be explored. Drugs currently available to treat Chagas disease are of suboptimal efficacy, have substantial toxicity, and are contraindicated in pregnancy. Benznidazole was approved by the US Food and Drug Administration on August 29, 2017, for use in children 2 to 12 years of age.[453] Until it becomes available, the CDC will continue to provide the drug under its existing investigational protocol.[454] Treatment of adults under the current approval will be off-label. A working group has been created to develop guidance for US clinicians because treatment is expected to become more widely available. Because of the high frequency of adverse effects, guidance from Chagas disease experts (at the CDC or elsewhere) is recommended. Nifurtimox is not approved by US Food and Drug Administration but is available under Investigational New Drug from the CDC. Consultations and drug requests should be addressed to the Division of Parasitic Diseases Public Inquiries line (404-718-4745;

email parasites@cdc.gov), the CDC Drug Service (404-639-3670), and, for emergencies after business hours and on weekends and federal holidays, the CDC Emergency Operations Center (770-488-7100). Because of the long persistence of antibodies detected by conventional serology, their presence after treatment is not an indication for retreatment.

Finally, antitrypanosomal treatments are complex, and important uncertainties remain. New biomarkers for early detection of therapeutic efficacy are needed to better evaluate and address antiparasitic treatment[77,133,427,455,456] to develop more accurate treatment recommendations for patients around the globe. In addition, more data are needed on the best practices for the treatment of Chagas cardiomyopathy. Because no specific clinical trials have been conducted, care for patients with Chagas-induced ventricular dysfunction is extrapolated from general heart failure recommendations with unclear efficacy (and potential harm).

ADDENDUM

As of May 14, 2018, benznidazole (manufactured by Exeltis and distributed by Foundation Care) is commercially available in the United States. Prescriptions require submission of a completed Fast Access order form, available at http://www.benznidazoletablets.com/en/ or by contacting Foundation Care at 877-303-7181; 877-620-2849 (fax); or FastAccess@Exeltis.com. The Exeltis Patient Assistance Program ensures that the cost to the patient for the medication will not exceed $60. Depending on resources and insurance, some patients will be eligible to receive the medication at no cost.

ARTICLE INFORMATION

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*Modest.

†Significant.

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