Contemporary Characteristics and Outcomes in Chagasic Heart Failure Compared With Other Nonischemic and Ischemic Cardiomyopathy

BACKGROUND: Chagas' disease is an important cause of cardiomyopathy in Latin America. We aimed to compare clinical characteristics and outcomes in patients with heart failure (HF) with reduced ejection fraction caused by Chagas' disease, with other etiologies, in the era of modern HF therapies.

METHODS AND RESULTS: This study included 2552 Latin American patients randomized in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure) trials. The investigator-reported etiology was categorized as Chagasic, other nonischemic, or ischemic cardiomyopathy. The outcomes of interest included the composite of cardiovascular death or HF hospitalization and its components and death from any cause. Unadjusted and adjusted Cox proportional hazards models were performed to compare outcomes by pathogenesis. There were 195 patients with Chagasic HF with reduced ejection fraction, 1300 with other nonischemic cardiomyopathy, and 1057 with ischemic cardiomyopathy. Compared with other etiologies, Chagasic patients were more often female, younger, and had lower prevalence of hypertension, diabetes mellitus, and renal impairment (but had higher prevalence of stroke and pacemaker implantation) and had worse health-related quality of life. The rates of the composite outcome were 17.2, 12.5, and 11.4 per 100 person-years for Chagasic, other nonischemic, and ischemic patients, respectively—adjusted hazard ratio for Chagasic versus other nonischemic: 1.49 (95% confidence interval, 1.15–1.94; *P*=0.003) and Chagasic versus ischemic: 1.55 (1.18–2.04; *P*=0.002). The rates of all-cause mortality were also higher.

CONCLUSIONS: Despite younger age, less comorbidity, and comprehensive use of conventional HF therapies, patients with Chagasic HF with reduced ejection fraction continue to have worse quality of life and higher hospitalization and mortality rates compared with other etiologies.

CLINICAL TRIAL REGISTRATION: PARADIGM-HF: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01035255; ATMOSPHERE: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00853658.

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WHAT IS NEW?

- Patients with heart failure with a reduced ejection fraction because of Chagas' disease continue to have worse quality of life and higher hospitalization and mortality rates, compared with other pathogeneses, despite their younger age, less comorbidity, and comprehensive use of conventional heart failure therapies.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Better understanding of the mechanism and natural history of Chagasic heart failure is needed in the future studies to identify strategies for improving its prognosis.

Chagas' disease, caused by the protozoan *Trypanosoma cruzi*, is estimated to affect 6 to 7 million people in Latin America and ≈300 000 people in the Unites States of America.[1–10] Indeed, concern about the growing prevalence of *T. cruzi* infection has led to screening of donations to the blood banks in the United States of America.[11] More recently, cases of Chagas' disease have been reported in Europe.[12] Up to 30% of affected individuals exhibit evidence of a chronic cardiomyopathy 2 to 3 decades after infection, ranging from asymptomatic ECG abnormalities to structural heart disease, with some patients ultimately developing heart failure with a reduced ejection fraction (HFrEF).[1–10] Despite the high prevalence of Chagas' disease, little is known about the morbidity and mortality in patients with HFrEF caused by Chagas' disease, compared with other etiologies, especially in the modern era of heart failure (HF) therapies.[13–21] We pooled the 2 largest and most recent trials in HFrEF, the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and the ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients With Heart failure Trial), to look further into investigator-reported Chagasic HF in Latin America.[22,23]

METHODS

Study Population

This study consisted of 2552 Latin American patients with HFrEF randomized in the PARADIGM-HF and ATMOSPHERE trials. The design and primary results of both studies have been published.[22,23] Briefly, in PARADIGM-HF patients had New York Heart Association class II to IV symptoms, a left ventricular ejection fraction ≤40% (changed to ≤35% by amendment), and an elevated plasma natriuretic peptide level (B-type natriuretic peptide [BNP] ≥150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL). Patients with lower natriuretic peptide levels (BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL) were eligible if they had been hospitalized for HF within 12 months. Patients were required to receive an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (equivalent to enalapril ≥10 mg daily), along with a stable dose of a β-blocker (unless contraindicated) and a mineralocorticoid receptor antagonist (if indicated), for at least 4 weeks before screening. In ATMOSPHERE, patients had New York Heart Association class II to IV symptoms, HF with a reduced left ventricular ejection fraction (≤35%), and an elevated plasma natriuretic peptide level (same criteria as in PARADIGM-HF). Patients were required to be treated with an angiotensin-converting enzyme inhibitor (equivalent to enalapril ≥10 mg daily), a stable dose of a β-blocker (unless contraindicated) for at least 4 weeks before screening, and could be treated with a mineralocorticoid receptor antagonist if felt to be indicated by the investigator. Both trials used a composite of cardiovascular death or HF hospitalization as the primary outcome. Both trials were approved by the ethics committee in each study center. All patients gave written informed consent.

Primary Pathogenesis of HF

The primary HF etiology was collected at the screening visit using a similar, structured, case report form in both trials. We used this information to categorize the patients into 3 mutually exclusive subgroups (ie, investigator-reported Chagas' disease, other nonischemic cardiomyopathy, and ischemic cardiomyopathy).

Study Outcomes

The outcomes of interest in this study included a composite of cardiovascular death or first HF hospitalization and its components, as well as death from any cause. We also examined the 2 major modes of cardiovascular death (ie, sudden death and pump failure death).

Statistical Analyses

Baseline characteristics were summarized as means with SDs for continuous variables and numbers with percentages for categorical variables. Baseline characteristics were compared across HF pathogenesis categories using ANOVA for continuous variables with Bonferroni correction for multiple comparisons and the χ^2 test for categorical variables. The Kansas City Cardiomyopathy Questionnaire clinical summary score[24] and NT-proBNP were not normally distributed and therefore were summarized as medians with the first and third quartile (Q1–Q3) and analyzed using Kruskal–Wallis test with Dunn test and Bonferroni correction for multiple comparisons. Event rates for each outcome according to HF pathogenesis were calculated per 100 patient-years of follow-up. The proportional hazards (Cox) regression analysis was used to calculate the hazard ratio for each outcome with the comparisons of Chagas' disease versus nonischemic cardiomyopathy and Chagas' disease versus ischemic cardiomyopathy. The proportional hazards regression analyses were also performed with adjustment for treatment assignment, age, sex, left ventricular ejection fraction, New York Heart Association class, and NT-proBNP (log transformed) to account for the confounding.

Within-trial clustering was taken into consideration with the use of shared frailty models. A 2-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using Stata version 14 (Stata Corp, College Station, TX).

RESULTS

Overall, 195 patients (7.6% of the total) were reported to have Chagasic cardiomyopathy, 1300 (51%) another type of nonischemic cardiomyopathy, and 1057 (41%) ischemic HFrEF. The largest number of Chagas' patients were enrolled in Brazil (n=112; accounting for 22.7% of all patients randomized in that country), followed by Argentina (n=60; 7.2%) and Colombia (n=16; 5.2%; Table I in the Data Supplement).

Baseline Characteristics

The baseline characteristics of patients with Chagasic HFrEF compared with those with other nonischemic cardiomyopathy and ischemic cardiomyopathy are shown in Table 1.

Notable differences included the younger age of individuals with Chagasic cardiomyopathy, their lower systolic blood pressure, lower body mass index, and lower prevalence of hypertension and diabetes mellitus compared with patients in the other etiology subgroups. Individuals with Chagasic HFrEF were more likely to be female and have a history of stroke and renal impairment than in the other etiology subgroups (especially compared with patients with other nonischemic HFrEF). Right bundle branch block was much more common in patients with Chagasic cardiomyopathy compared with patients with other causes of nonischemic and ischemic HFrEF whereas left bundle branch block was less common in patients with Chagas' disease compared with the other groups.

Patients with Chagasic HFrEF were much more likely than other patients to have a history of pacemaker implantation. β-Blockers were used less often in patients with Chagasic cardiomyopathy compared with other types of HFrEF, but anticoagulant and, especially, amiodarone, treatment was used more frequently.

Patients with Chagasic HFrEF reported significantly worse health-related quality of life as evaluated using the Kansas City Cardiomyopathy Questionnaire with median (Q1–Q3) values of 85 (72–94), 87 (74–96), and 82 (70–92) in patients with ischemic, other nonischemic, and Chagasic cardiomyopathy.

Clinical Outcomes

The rates of the primary composite outcome, its components, and all-cause death are shown in Table 2 and the Figure. Patients with Chagasic HFrEF had a higher unadjusted and adjusted risk of the primary outcome compared with each of the other pathogenic categories, with the adjusted risk ≈50% greater. The adjusted risk of both cardiovascular and all-cause death was ≈40% greater in patients with Chagasic cardiomyopathy than in patients with ischemic HFrEF. The adjusted risk of all-cause death was also higher than in patients with nonischemic HFrEF although the risk of cardiovascular death was not statistically significantly higher.

We also examined the 2 main modes of cardiovascular death (Table 2). The risk of sudden death did not differ significantly by etiology although in Chagasic patients this mode of death was relatively less common than in patients with ischemic cardiomyopathy and relatively more common than in patients with other causes of nonischemic cardiomyopathy (but these trends were not statistically significant). Conversely, pump failure death was more common in Chagasic patients, especially when compared with ischemic cardiomyopathy patients.

Patients with a Chagasic pathogenesis had a substantially elevated risk (60%–80% higher) of HF hospitalization compared with each of the other pathogenic categories. In sensitivity analyses, additional adjustment for right and left bundle branch block did not materially alter the difference in risk between patients with Chagas' disease and those in the other groups (data not shown).

DISCUSSION

Approximately 8% of patients enrolled in ATMOSPHERE and PARADIGM-HF in Latin America had HFrEF attributed to Chagas' disease. Although higher rates have been reported in some registers from more endemic regions, the proportion in our study is consistent with 2 prior studies from the GESICA group (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) where 9.3% and 5.7%, respectively, of patients had HFrEF because of Chagas' disease.[25,26] Our cases also showed a geographic distribution consistent with the known epidemiology of Chagas' cardiomyopathy.[27]

Although several prior studies have compared individuals with Chagasic HFrEF to others with ischemic or nonischemic cardiomyopathy (but not both concomitantly), these have been mainly single-center reports of often highly selected cohorts (eg, transplant referrals) usually markedly undertreated by contemporary standards.[12–20,28] These prior reports included between 25 and 246 patients with Chagas' cardiomyopathy and 50 to 454 patients in the comparator group, usually did not report detailed characterization of participants (eg, in relation to prior history and biomarkers) and often did not adjust for differences in a multivariable analysis when comparing outcomes across etiologic groups.[13–21,28]

Table 1. Baseline Characteristics in Patients With Chagasic Heart Failure Compared With Those With Nonischemic Cardiomyopathy and Those With Ischemic Cardiomyopathy in Latin America in the Combined Data Sets of PARADIGM-HF and ATMOSPHERE

	Chagasic	Other Nonischemic	Ischemic	*P* Value	
	n=195	n=1300	n=1057	Chagasic vs Other Nonischemic	Chagasic vs Ischemic
Age, y	59.6±10.7	61.1±12.5	65.8±10.1	0.291	<0.0001
Male sex, n (%)	129 (66.2)	897 (69.0)	828 (78.3)	0.424	<0.0001
Race, n (%)				<0.0001	<0.0001
White	107 (54.9)	554 (42.6)	449 (42.5)		
Black	34 (17.4)	147 (11.3)	46 (4.4)		
Asian	0 (0.0)	0 (0.0)	2 (0.2)		
Other	54 (27.7)	599 (46.1)	560 (53.0)		
BMI, kg/m^2	26.0±4.6	27.6±5.2	27.4±4.5	<0.0001	0.001
Blood pressure, mm Hg					
Systolic	111.4±12.5	120.3±15.9	120.7±15.0	<0.0001	<0.0001
Diastolic	71.4±8.8	74.3±10.7	72.9±10.1	0.001	0.206
Heart rate, beats/min	65.5±10.3	72.0±12.0	70.2±11.3	<0.0001	<0.0001
LVEF, %	28.5±6.2	27.1±6.3	28.5±6.1	0.015	0.999
NYHA class, n (%)				0.103	0.070
I	11 (5.7)	80 (6.2)	47 (4.5)		
II	170 (87.6)	1054 (81.1)	868 (82.2)		
III	13 (6.7)	165 (12.7)	140 (13.3)		
IV	0 (0.0)	1 (0.1)	1 (0.1)		
Medical history, n (%)					
Current smoker	14 (7.2)	110 (8.5)	74 (7.0)	0.545	0.929
Previous HF hospitalization	100 (51.3)	727 (55.9)	525 (49.7)	0.224	0.679
Myocardial infarction	1 (0.5)	35 (2.7)	748 (70.8)	0.064	<0.0001
Angina	4 (2.1)	35 (2.7)	223 (21.1)	0.600	<0.0001
CABG or PCI	1 (0.5)	28 (2.2)	396 (37.5)	0.121	<0.0001
Hypertension	85 (43.6)	874 (67.2)	739 (69.9)	<0.0001	<0.0001
Diabetes mellitus	15 (7.7)	290 (22.3)	341 (32.3)	<0.0001	<0.0001
Atrial fibrillation	63 (32.3)	380 (29.2)	182 (17.2)	0.380	<0.0001
Stroke	27 (13.8)	56 (4.3)	88 (8.3)	<0.0001	0.014
Medication/devices, n (%)					
Digitalis	75 (38.5)	543 (41.8)	284 (26.9)	0.382	0.001
Diuretics	158 (81.0)	1086 (83.5)	785 (74.3)	0.381	0.044
ACE inhibitor or ARB	113 (100.0)	699 (99.4)	616 (99.8)	0.422	0.668
β-Blocker	166 (85.1)	1187 (91.3)	984 (93.1)	0.006	<0.0001
MRA	133 (68.2)	763 (58.7)	539 (51.0)	0.011	<0.0001
Antiplatelet	61 (31.3)	576 (44.3)	763 (72.2)	0.001	<0.0001
Anticoagulant	54 (27.7)	285 (21.9)	161 (15.2)	0.073	<0.0001
Amiodarone	80 (41.0)	150 (11.5)	100 (9.5)	<0.0001	<0.0001
Pacemaker	59 (30.3)	77 (5.9)	83 (7.9)	<0.0001	<0.0001
CRT	5 (2.6)	23 (1.8)	15 (1.4)	0.445	0.241
ICD	15 (7.7)	40 (3.1)	48 (4.5)	0.001	0.064

(*Continued*)

Table 1. Continued

	Chagasic	Other Nonischemic	Ischemic	*P* Value	
	n=195	n=1300	n=1057	Chagasic vs Other Nonischemic	Chagasic vs Ischemic
ECG findings, n (%)					
Atrial fibrillation	37 (19.0)	283 (21.8)	114 (10.8)	0.367	0.001
Left bundle branch block	23 (11.8)	402 (31.0)	228 (21.7)	<0.0001	0.002
Right bundle branch block	46 (23.6)	92 (7.1)	96 (9.1)	<0.0001	<0.0001
Q waves	7 (3.6)	70 (5.4)	311 (29.5)	0.288	<0.0001
Left ventricular hypertrophy	7 (3.6)	334 (25.8)	187 (17.8)	<0.0001	<0.0001
Laboratory measures					
eGFR, mL/min per 1.73 m^2	69.2±19.8	75.1±28.0	70.1±21.8	0.006	0.999
eGFR <60 mL/min per 1.73 m^2, n (%)	67 (34.4)	334 (25.7)	345 (32.6)	0.011	0.639
Serum creatinine, mg/dL	1.10±0.28	1.03±0.30	1.08±0.30	0.011	0.999
NT-proBNP, pg/mL	1753 [793–3247]	1539 [840–3367]	1486 [808–2973]	0.999	0.583
Symptoms, signs, and HRQL, n (%)					
Dyspnea on effort	176 (90.7)	1113 (85.6)	921 (87.2)	0.054	0.171
Dyspnea at rest	4 (2.1)	19 (1.5)	22 (2.1)	0.526	0.985
Orthopnea	8 (4.1)	113 (8.7)	98 (9.3)	0.030	0.018
Paroxysmal nocturnal dyspnea	4 (2.1)	40 (3.1)	49 (4.6)	0.435	0.101
Fatigue	71 (36.6)	419 (32.2)	387 (36.6)	0.227	0.989
Edema	23 (11.9)	198 (15.2)	185 (17.5)	0.217	0.052
Jugular venous distention	24 (12.4)	192 (14.8)	168 (15.9)	0.376	0.209
Third heart sound	9 (4.6)	105 (8.1)	61 (5.8)	0.092	0.527
Rales	9 (4.6)	64 (4.9)	86 (8.1)	0.864	0.090
KCCQ clinical summary score*	82 [70–92]	87 [74–96]	85 [72–94]	0.006	0.255

Plus–minus values are mean±SD. NT-proBNP and KCCQ clinical summary score are summarized as median (the first quartile to the third quartile). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ATMOSPHERE, Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure; BMI, body mass index; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HRQL, health-related quality of life; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PARADIGM-HF, Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; and PCI, percutaneous coronary intervention.

*Values of the KCCQ clinical summary score (on a scale from 0 to 100, with higher scores indicating better health-related quality of life) were available for 1101 patients with nonischemic cardiomyopathy, for 848 patients with ischemic cardiomyopathy, and for 189 patients with Chagas disease.

Despite these differences, it is possible to make some comparisons with our findings. In both the prior studies and in ours, Chagasic patients were notable by their younger age and lower preponderance of males (especially when compared with patients with ischemic HFrEF). The high prevalence of right bundle branch block, prior pacemaker implantation, and amiodarone use are also characteristic features of patients with Chagasic cardiomyopathy.[29]

Our cohort, recruited according to standardized trial inclusion and exclusion criteria, does, however, highlight other striking differences. The low prevalence of diabetes mellitus and history of hypertension, compared with patients with other nonischemic and ischemic HFrEF, is striking, and the latter is consistent with the much lower systolic blood pressure in the Chagasic group. Similarly, the markedly higher prevalence of prior stroke (in the absence of a substantially higher prevalence of atrial fibrillation) is consistent with concerns about high risk of thromboembolism in patients with Chagasic cardiomyopathy (and reflected in the higher use of anticoagulant therapy in these individuals).[30]

We noted worse renal function in Chagasic patients, compared with the others, despite younger age and less diabetes mellitus and hypertension. Why this finding has not been previously reported and the reason for it is uncertain, the greater use of mineralocorticoid receptor antagonist in Chagasic patients and lower systolic blood pressure may have played a role.

One finding which, notably, was not significantly different, with respect to etiology, was baseline NT-proBNP level (although this was numerically highest in the Cha-

Table 2. Outcomes According to Pathogenesis in Latin America in the Combined Data Sets of PARADIGM-HF and ATMOSPHERE

	Event, n (%)			Annual Rate, per 100 Person-Years (95% CI)			Unadjusted HR (95% CI)*		Adjusted HR (95% CI)*†	
	Chagasic (n=195)	Other Nonischemic (n=1300)	Ischemic (n=1057)	Chagas	Other Nonischemic	Ischemic	Chagasic vs Other Nonischemic	Chagasic vs Ischemic	Chagasic vs Other Nonischemic	Chagasic vs Ischemic
CV death or HFH	67 (34.4)	364 (28.0)	264 (25.0)	17.2 (13.6–21.9)	12.5 (11.3–13.8)	11.4 (10.1–12.9)	1.37 (1.06–1.78), *P*=0.017	1.48 (1.13–1.94), *P*=0.004	1.49 (1.15–1.94), *P*=0.003	1.55 (1.18–2.04), *P*=0.002
CV death	46 (23.6)	287 (22.1)	199 (18.8)	10.7 (8.0–14.3)	9.2 (8.2–10.4)	8.1 (7.1–9.4)	1.17 (0.86–1.60), *P*=0.314	1.32 (0.96–1.82), *P*=0.092	1.30 (0.95–1.78), *P*=0.097	1.44 (1.04–2.00), *P*=0.027
HFH	37 (19.0)	175 (13.5)	115 (10.9)	9.5 (6.9–13.1)	6.0 (5.2–7.0)	5.0 (4.1–6.0)	1.56 (1.10–2.23), *P*=0.014	1.86 (1.28–2.69), *P*=0.001	1.64 (1.15–2.35), *P*=0.006	1.83 (1.25–2.67), *P*=0.002
All-cause death	57 (29.2)	336 (25.9)	251 (23.7)	13.3 (10.2–17.2)	10.8 (9.7–12.0)	10.3 (9.1–11.6)	1.24 (0.94–1.64), *P*=0.131	1.30 (0.97–1.73), *P*=0.077	1.36 (1.02–1.80), *P*=0.035	1.43 (1.06–1.91), *P*=0.017
Sudden death	14 (7.2)	101 (7.8)	96 (9.1)	3.3 (1.9–5.5)	3.2 (2.7–3.9)	3.9 (3.2–4.8)	1.00 (0.57–1.75), *P*=0.99	0.81 (0.46–1.43), *P*=0.47	1.11 (0.63–1.94), *P*=0.73	0.89 (0.51–1.58), *P*=0.70
Pump failure death	16 (8.2)	83 (6.4)	41 (3.9)	3.7 (2.3–6.1)	2.7 (2.2–3.3)	1.7 (1.2–2.3)	1.40 (0.82–2.40), *P*=0.22	2.25 (1.26–4.02), *P*=0.01	1.69 (0.98–2.91), *P*=0.06	2.52 (1.40–4.56), *P*=0.002

ATMOSPHERE indicates Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure Trial; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and PARADIGM-HF, Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

*Hazard ratios for combined data were adjusted for within-trial clustering.

†Adjusted covariates: treatment group, age, sex, LVEF, NYHA class, and log 2 base NT-proBNP.

gasic patients). As NT-proBNP is the single most powerful prognostic variable in HF, it is interesting that outcomes were so much worse for patients with Chagas' disease. Why prognosis is worse is, therefore, not clear. Immune or inflammatory mechanisms might be relevant or other biological or nonbiological issues might be important. For example, Chagas' disease is more prevalent in more socioeconomically deprived populations and this may influence health and outcomes in a variety of ways.

Although the protocol for both PARADIGM-HF and ATMOSPHERE required β-blockers to be used in all patients unless not tolerated or contraindicated, fewer patients with Chagasic HFrEF (85%) were treated with an agent from this class than in the other nonischemic patients (91%) or in the ischemic group (93%). Nevertheless, this is a much higher use than reported in most prior studies in Chagasic patients where the rate has been typically ≈40%, usually because of concerns about sinoatrial and conducting system disease.[12–20] Resting heart rate was notably lower (65 beats per minute) in our Chagasic patients, compared with the other nonischemic group (72 beats per minute) and ischemic group (70 beats per minute), despite the different rate of β-blocker use. However, amiodarone use (43%) was common in Chagasic patients (compared with 11% of patients in the other nonischemic group and 9% of those in the ischemic group). In addition, 39% of Chagasic patients were also receiving a digitalis glycoside (compared with 42% of patients in the other nonischemic group and 27% of patients in the ischemic group). While the use of all 3 of these drugs might be concerning, especially in a condition associated with sinoatrial and conduction system disease, 30% of Chagasic patients had a pacemaker and a few more had cardiac resynchronization therapy or an implantable cardioverter defibrillator.

Patients with HFrEF because of Chagas' disease also differed from the others in terms of clinical outcomes. Specifically, their adjusted risk of death (cardiovascular or all-cause) was ≈40% higher than in the other etiology groups and risk of HF hospitalization 60% to 80% greater (despite the higher risk of death). These findings are notable in 2 ways. First, they demonstrate the markedly higher risk in patients with Chagasic cardiomyopathy once HFrEF develops. In the recent BENEFIT (Evaluation of the Use of Antiparasital Drug [Benznidazole] in the Treatment of Chronic Chagas' Disease) trial, where among patients of a similar average age, only about a quarter of patients were in New York Heart Association functional class II or greater and only 17% of patients had a left ventricular ejection fraction <40%, the annual mortality rate was ≈3%.[31] In our patients, it was 13%. However, the excess risk related to Chagas' disease in our cohort was much less than suggested in prior studies.[13–21] Whether this is because of the historical nature

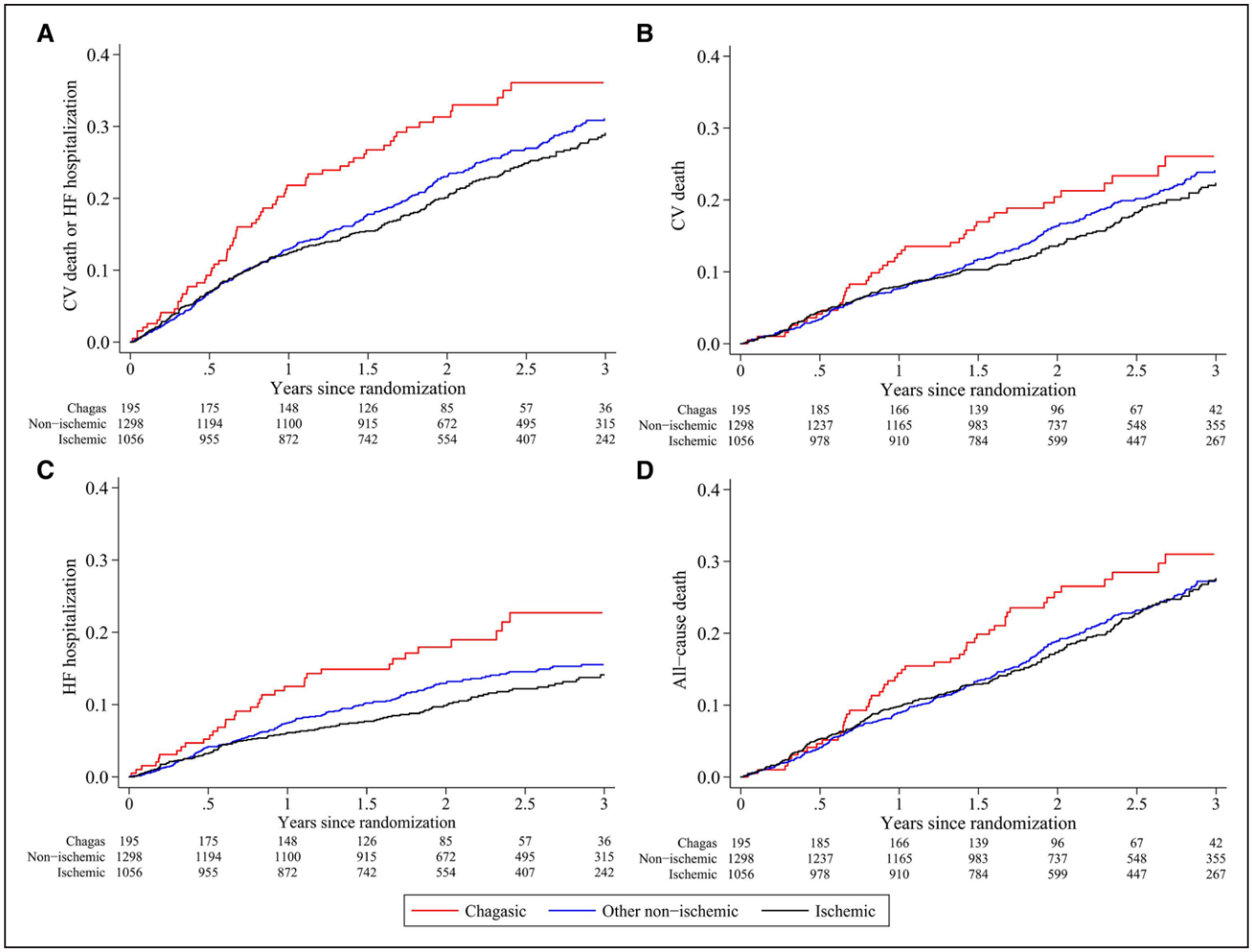

Figure. Kaplan–Meier curves for clinical outcomes according to heart failure etiology (Latin American patients in combined PARADIGM-HF [Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure] and ATMOSPHERE [Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure Trial] data sets).

Kaplan–Meier estimates of the probability of the death from cardiovascular causes or first hospitalization for heart failure (**A**), death from cardiovascular causes (**B**), first hospitalization for heart failure (**C**), and death from any cause (**D**). CV indicates cardiovascular; and HF, heart failure.

of prior studies (with less comprehensive therapy), less complete adjustment for other prognostic variables, smaller and less comprehensive comparator groups, or some other factor or factors is unknown. The most recent study to compare outcomes between patients with Chagasic cardiomyopathy and other patients was undertaken among Latin American Immigrants in the Los Angeles area.[32] Although that study reported a >4-fold higher risk of death or transplantation among Chagasic patients compared with patients with other types of nonischemic cardiomyopathy, it included a total of 135 patients, of which only 25 had Chagasic cardiomyopathy (and there were only a total of 20 events).

We were also able to examine the 2 principal modes of cardiovascular death in the 3 etiology groups studied. This analysis showed that the excess mortality risk in Chagasic patients was because of pump failure rather than sudden death (especially compared with patients with an ischemic etiology). Although this finding might seem surprising in a condition widely considered to be highly arrhythmogenic, it is consistent with the view that modern pharmacological therapy, by reducing the risk of sudden death, may have resulted in pump failure death becoming the major mode of death in Chagas' disease.[33] We have already highlighted the much greater use of β-blockers in the current compared with prior reports. The potential role of amiodarone in preventing sudden death in Chagas's cardiomyopathy is more controversial.

As with any study of this type there are limitations. This was a post hoc analysis. HFrEF etiology was reported by investigators and not verified in any way; however, the characteristics of the patients in the different etiologic subgroups were consistent with what would

be expected, suggesting valid categorization by investigators. The total number of patients with Chagasic HFrEF was relatively small but similar or larger than in other studies comparing etiologies. The protocol required patients to be treated with a β-blocker unless contraindicated or not tolerated and patients had to tolerate enalapril 10 mg twice daily and sacubitril/valsartan 97/103 mg twice daily before randomization, resulting in selection of patients who could tolerate these different treatments. We did not have data on socioeconomic status.

CONCLUSIONS

Despite their younger age, less comorbidity, and comprehensive use of conventional pharmacological therapies for HFrEF, patients with Chagasic HFrEF continue to have worse quality of life and higher hospitalization and mortality rates compared with those with HFrEF because of other nonischemic and ischemic causes.

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FOOTNOTES

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REFERENCES

1. Mendez GF, Cowie MR. The epidemiological features of heart failure in developing countries: a review of the literature. *Int J Cardiol*. 2001;80:213–219.
2. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. *Nat Rev Cardiol*. 2012;9:576–589. doi: 10.1038/nrcardio.2012.109.
3. Bocchi EA, Arias A, Verdejo H, Diez M, Gómez E, Castro P; Interamerican Society of Cardiology. The reality of heart failure in Latin America. *J Am Coll Cardiol*. 2013;62:949–958. doi: 10.1016/j.jacc.2013.06.013.
4. Bocchi EA. Heart failure in South America. *Curr Cardiol Rev*. 2013;9:147–156.
5. Tanowitz HB, Machado FS, Spray DC, Friedman JM, Weiss OS, Lora JN, Nagajyothi J, Moraes DN, Garg NJ, Nunes MC, Ribeiro AL. Developments in the management of Chagas cardiomyopathy. *Expert Rev Cardiovasc Ther*. 2015;13:1393–1409. doi: 10.1586/14779072.2015.1103648.
6. Stanaway JD, Roth G. The burden of Chagas disease: estimates and challenges. *Glob Heart*. 2015;10:139–144. doi: 10.1016/j.gheart.2015.06.001.
7. Bern C. Chagas' disease. *N Engl J Med*. 2015;373:456–466. doi: 10.1056/NEJMra1410150.
8. Ciapponi A, Alcaraz A, Calderon M, Matta MG, Chaparro M, Soto N, Bardach A. Burden of heart failure in Latin America: a systematic review and meta-analysis. *Rev Esp Cardiol (Engl Ed)*. 2016;69:1051–1060.
9. Benziger CP, do Carmo GA, Ribeiro AL. Chagas cardiomyopathy: clinical presentation and management in the Americas. *Cardiol Clin*. 2017;35:31–47. doi: 10.1016/j.ccl.2016.08.013.
10. Kuehn BM. Chagas heart disease an emerging concern in the United States. *Circulation*. 2016;134:895–896. doi: 10.1161/CIRCULATIONAHA.116.024839.
11. Manne-Goehler J, Umeh CA, Montgomery SP, Wirtz VJ. Estimating the burden of Chagas disease in the United States. *PLoS Negl Trop Dis*. 2016;10:e0005033. doi: 10.1371/journal.pntd.0005033.
12. Guerri-Guttenberg RA, Grana DR, Ambrosio G, Milei J. Chagas cardiomyopathy: Europe is not spared! *Eur Heart J*. 2008;29:2587–2591. doi: 10.1093/eurheartj/ehn424.
13. Bestetti RB, Muccillo G. Clinical course of Chagas' heart disease: a comparison with dilated cardiomyopathy. *Int J Cardiol*. 1997;60:187–193.
14. Freitas HF, Chizzola PR, Paes AT, Lima AC, Mansur AJ. Risk stratification in a Brazilian hospital-based cohort of 1220 outpatients with heart failure: role of Chagas' heart disease. *Int J Cardiol*. 2005;102:239–247. doi: 10.1016/j.ijcard.2004.05.025.
15. Oliveira MT Jr, Canesin MF, Munhoz RT, del Carlo CH, Scipioni A, Ramires JA, Barretto AC. Major clinical characteristics of patients surviving 24 months or more after hospitalization due to decompensated heart failure. *Arq Bras Cardiol*. 2005;84:161–166. doi: /S0066-782X2005000200013.
16. Sierra-Johnson J, Olivera-Mar A, Monteón-Padilla VM, Reyes PA, Vallejo M. Epidemiological and clinical outlook of chronic Chagas' heart disease in Mexico. *Rev Saude Publica*. 2005;39:754–760. doi: /S0034-89102005000500009.
17. Pereira Nunes Mdo C, Barbosa MM, Ribeiro AL, Amorim Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: relevance of Chagas disease as an etiological factor. *Rev Esp Cardiol*. 2010;63:788–797.
18. Cardoso J, Novaes M, Ochiai M, Regina K, Morgado P, Munhoz R, Brancalhão E, Lima M, Barretto AC. Chagas cardiomyopathy: prognosis in clinical and hemodynamic profile C. *Arq Bras Cardiol*. 2010;95:518–523.
19. Barbosa AP, Cardinalli Neto A, Otaviano AP, Rocha BF, Bestetti RB. Comparison of outcome between Chagas cardiomyopathy and idiopathic dilated cardiomyopathy. *Arq Bras Cardiol*. 2011;97:517–525.
20. Vilas Boas LG, Bestetti RB, Otaviano AP, Cardinalli-Neto A, Nogueira PR. Outcome of Chagas cardiomyopathy in comparison to ischemic

cardiomyopathy. *Int J Cardiol*. 2013;167:486–490. doi: 10.1016/j.ijcard.2012.01.033.
21. Bestetti RB, Otaviano AP, Fantini JP, Cardinalli-Neto A, Nakazone MA, Nogueira PR. Prognosis of patients with chronic systolic heart failure: Chagas disease versus systemic arterial hypertension. *Int J Cardiol*. 2013;168:2990–2991. doi: 10.1016/j.ijcard.2013.04.015.
22. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077.
23. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM; ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med*. 2016;374:1521–1532. doi: 10.1056/NEJMoa1514859.
24. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35:1245–1255.
25. Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, Dubner S, Scapin O, Perrone SV. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators. *Circulation*. 1996;94:3198–3203. doi: https://doi.org/10.1161/01.CIR.94.12.3198.
26. Nul D, Zambrano C, Diaz A, Ferrante D, Varini S, Soifer S, Grancelli H, Doval H; Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina. Impact of a standardized titration protocol with carvedilol in heart failure: safety, tolerability, and efficacy-a report from the GESICA registry. *Cardiovasc Drugs Ther*. 2005;19:125–134. doi: 10.1007/s10557-005-1497-5.
27. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. *Wkly Epidemiol Rec*. 2015;90:33–43.
28. Santos LN, Rocha MS, Oliveira EN, Moura CA, Araujo AJ, Gusmão ÍM, Feitosa-Filho GS, Cruz CM. Decompensated chagasic heart failure versus non-chagasic heart failure at a tertiary care hospital: clinical characteristics and outcomes. *Rev Assoc Med Bras (1992)*. 2017;63:57–63. doi: 10.1590/1806-9282.63.01.57.
29. Marcolino MS, Palhares DM, Ferreira LR, Ribeiro AL. Electrocardiogram and Chagas disease: a large population database of primary care patients. *Glob Heart*. 2015;10:167–172. doi: 10.1016/j.gheart.2015.07.001.
30. Cardoso RN, Macedo FY, Garcia MN, Garcia DC, Benjo AM, Aguilar D, Jneid H, Bozkurt B. Chagas cardiomyopathy is associated with higher incidence of stroke: a meta-analysis of observational studies. *J Card Fail*. 2014;20:931–938. doi: 10.1016/j.cardfail.2014.09.003.
31. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A Jr, Rosas F, Villena E, Quiroz R, Bonilla R, Britto C, Guhl F, Velazquez E, Bonilla L, Meeks B, Rao-Melacini P, Pogue J, Mattos A, Lazdins J, Rassi A, Connolly SJ, Yusuf S; BENEFIT Investigators. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. *N Engl J Med*. 2015;373:1295–1306. doi: 10.1056/NEJMoa1507574.
32. Traina MI, Sanchez DR, Hernandez S, Bradfield JS, Labedi MR, Ngab TA, Steurer F, Montgomery SP, Meymandi SK. Prevalence and impact of Chagas disease among Latin American immigrants with nonischemic cardiomyopathy in Los Angeles, California. *Circ Heart Fail*. 2015;8:938–943. doi: 10.1161/CIRCHEARTFAILURE.115.002229.
33. Ayub-Ferreira SM, Mangini S, Issa VS, Cruz FD, Bacal F, Guimarães GV, Chizzola PR, Conceição-Souza GE, Marcondes-Braga FG, Bocchi EA. Mode of death on Chagas heart disease: comparison with other etiologies. A subanalysis of the REMADHE prospective trial. *PLoS Negl Trop Dis*. 2013;7:e2176. doi: 10.1371/journal.pntd.0002176.