The Prevalence and Impact of Chagas Disease Among Latin American Immigrants With Non-Ischemic Cardiomyopathy in Los Angeles, California

Traina et al: Immigrants with Chagas in the US

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Abstract

Background—Chagas disease (CD) is a well-known cause of cardiomyopathy in Latin America, however, 300,000 individuals are estimated to have CD in the United States (US). This study examined the prevalence and impact of Chagas cardiomyopathy (CCM) in a US population. We hypothesized that patients with CCM would have increased morbidity and mortality as compared to patients with non-CCM.

Methods and Results—This is a single-center, prospective cohort study. Enrollment criteria were new diagnosis of non-ischemic CM (left ventricular ejection fraction ≤ 40%) and previous residence in Latin America for at least 12 months. Serologic testing for *Trypanosoma cruzi* was performed at enrollment. The primary end point was all-cause mortality or heart transplantation. The secondary end point was heart failure (HF)-related hospitalization. A total of 135 patients were enrolled, with a median of 43 months of follow-up. CD was diagnosed in 25 (19%) patients. The primary end point occurred in 9 patients (36%) in the CCM group and in 11 patients (10%) in the non-CCM group (hazard ratio [HR]: 4.46, 95% confidence interval [CI]: 1.8 to 10.8, p = 0.001). The secondary end point occurred in 13 patients (52%) in the CCM group and in 35 patients (32%) in the non-CCM group (HR: 2.22, 95% CI: 1.2 to 4.2, p = 0.01).

Conclusions—There is a high prevalence of CD among Latin American immigrants diagnosed with non-ischemic CM in Los Angeles. Advanced CCM portends a poor prognosis and is associated with increased all-cause mortality/heart transplantation and HF-related hospitalization.

Key Words: Chagas heart failure, cardiomyopathy, heart failure, morbidity/mortality

Chagas disease (CD), first described in 1909 by the Brazilian physician Carlos Chagas, is caused by the protozoan *Trypanosoma cruzi* (1). The disease is primarily transmitted to humans via triatomine insects, also known as “kissing bugs”, though other potential routes of transmission include blood transfusion, organ transplantation, contaminated food ingestion, lab accidents, or vertically from mother to fetus. CD is chronic and systemic, with approximately one-third of patients developing cardiac manifestations ranging from conduction abnormalities and dysrhythmias to apical aneurysms and dilated cardiomyopathy (CM) (2).

The World Health Organization estimates that 7-8 million people worldwide are infected with *T. cruzi* (3). Though most infected persons live in Latin America where the disease is endemic, immigration patterns have made CD an important health issue in the US where more than 300,000 individuals are estimated to be infected (4). California has more than 5 million residents who were born in Latin America, and 40% of those live in Los Angeles County alone (5,6). *T. cruzi* has been detected in Los Angeles since 1984 (7). and a small cohort of Chagas heart disease patients from a Los Angeles hospital were reported in 1991 (8). Los Angeles blood banks have estimated seroprevalence rates among all blood donors to be as high as 1 in 3800 (9). and two cases of CD transmitted from heart transplantation in Los Angeles were reported in 2006 (10).

The prevalence of heart failure (HF) in the US continues to rise: there are currently 5.1 million Americans with HF and it is estimated that by 2030 the prevalence of HF will increase 25%. The total costs of HF are significant: the current estimate of $32 billion is expected to increase nearly 120% to $70 billion by 2030 (11). Using available immigration trends and existing prevalence rates, one conservative estimate places the number of Chagas CM (CCM)

cases in the US at 30,000-45,000 (12). These prevalence estimates, combined with available cost information for HF, imply a total cost of at least $200-300 million for CCM in the US.

Despite a growing appreciation for CD in the US, the burden of disease remains poorly defined (13). The purpose of this study is to estimate the prevalence and impact of CD in a population of Latin American immigrants diagnosed with non-ischemic CM in a Los Angeles county hospital. Based on previous studies, we hypothesized that CCM would be associated with increased mortality and hospitalization compared to non-CCM.

Methods

Ethics statement: This study was approved by the Institutional Review Board of the Olive View-UCLA Education and Research Institute. All participants provided written informed consent prior to study enrollment.

Study location: Olive View-UCLA Medical center is a 377-bed Los Angeles county hospital which serves a population of 1,584,000 adults (18 and over) covering 1,123 square miles. This population is 43% White, 38% Latino, 14% Asian, 3% Black, and 2% other. Thirty-one percent of adults have an income < 200% of the federal poverty level, and 28% of residents (ages 18-64) are uninsured all or part of the year. These statistics were not significantly different when compared to the entire population of Los Angeles County (14).

Study population: All Latin American immigrant patients with newly-diagnosed non-ischemic CM at Olive View-UCLA Medical center were asked to participate in this study. From May 2007 to October 2011, 135 patients were prospectively enrolled into the study and followed until June 2012. Inclusion criteria were: CM with left ventricular ejection fraction (LVEF) ≤ 40% as documented by either echocardiography, gated single-photon emission computed tomography

(SPECT), or left ventriculography during cardiac catheterization, age ≥ 18 years, and prior residence in Latin America (Mexico, Central, and South America) for at least 1 year. Exclusion criteria were: coronary artery disease (evidence of ischemia or infarct on non-invasive stress testing or >70% stenosis on coronary angiography), severe valvular disease, history of any substance abuse, thyroid disease, severe uncontrolled hypertension, or a history of uncontrolled tachyarrhythmias. There was no compensation for participation. No information was collected on individuals who refused to participate, though only one individual refused to participate. Once enrolled, no participant was lost to follow-up or withdrew from the study.

Demographic variables: At the time of study enrollment, participants were interviewed to assess basic demographic information, previous and current living situations, past medical history, and current medication use. Due to low counts, response categories for country of origin were collapsed into 4 categories: Mexico, El Salvador, Guatemala, and other (Honduras, Nicaragua, Argentina, Colombia). Similarly, response categories for type of Latin American house were collapsed into 3 categories: concrete, adobe, and other (brick, thatched, wood).

Objective data: At the time of study enrollment, all patients underwent a standard 12-lead electrocardiogram and transthoracic echocardiogram. Electrocardiographic abnormalities were classified according to the Minnesota Code Manual of Electrocardiographic Findings (15). Echocardiography was used to determine LVEF by visual estimation and left ventricular end-diastolic diameter (LVEDD) from the standard parasternal long axis view (16). Electrocardiograms and echocardiograms were interpreted by two board-certified cardiologists blinded to the study; discrepancies were resolved by a third board-certified cardiologist with consensus opinion.

Diagnosis of CD: Serologic testing was performed upon study enrollment by the Centers for Disease Control and Prevention (CDC) Parasitic Diseases Laboratory using Immunofluorescence Assay (IFA) and Enzyme-Linked Immunosorbent Assay (ELISA, Chagatest ELISA recombinate v. 3.0, Wiener Laboratorios, Argentina) tests. Participants were considered seropositive only if both tests were positive.

End points: The primary end point was all-cause mortality or heart transplantation. Death or heart transplantation was confirmed by reviewing medical records, contacting patients/family members, and accessing social security databases. The secondary end point was HF-related hospitalization. HF-related hospitalizations were confirmed by reviewing medical records and/or contacting patients/family members. For the purposes of this study, the diagnosis of HF was made when the terms "CHF", "CHF exacerbation", and/or "fluid/volume overload" were documented as discharge diagnoses on the discharge summary. One investigator with a medical background ascertained and interpreted the information regarding end points with the assistance of non-medical study personnel. The time from study enrollment until the primary and/or secondary end points occurred was used for survival analysis.

Statistical analysis: Categorical variable frequencies and proportions (%) are reported, while continuous variables are reported with medians and quartiles (25%, 75%). The p value for comparing baseline differences was determined by the Fisher's exact test for categorical data or Wilcoxon rank sum test for continuous data.

Survival curves for the primary and secondary end points were estimated by the Kaplan-Meier method, and the p values for differences in survival curves between groups were computed by the log-rank test. The crude mortality rate is the number of deaths for all patients in that group divided by the total number of person-months of follow-up for all patients in that

group. The crude hospitalization rate is similar, with the numerator representing the total number of hospitalizations for that group.

Univariate Cox proportional-hazards models were used to compute the hazard rate ratio for comparing time-dependent primary and secondary end point event rates between groups. The proportional hazard assumption was examined in all Cox models using the Supremum test. There was no evidence that the proportional hazard assumption was violated. There were insufficient events to perform valid multivariate Cox proportional-hazards models. All p values are two-sided, with $p < 0.05$ considered significant for all analyses. Analyses were conducted with SAS software, version 9.4 (SAS Inc, Cary NC).

Results

A total of 135 participants were followed for a median of 43 months (3.6 years), with CD diagnosed in 25 (19%) patients. The baseline characteristics of the study population are shown in Table 1, categorized by the presence or absence of CD. As a group, 57% of participants were male. The median age of the overall group was 57 years old. The prevalence of CCM, in decreasing order, was 38% for El Salvador, 25% for Guatemala, and 8% for Mexico. There were no differences in location (rural vs urban) or type of house (concrete, adobe, or other) among the CCM or non-CCM groups, however those with CCM spent more time in their native country (41 vs. 26 years, $p = 0.002$) and less time in the US (13 vs. 24 years, $p = 0.01$). Clinical variables such as the prevalence of hypertension, hyperlipidemia, tobacco and alcohol use were not clinically or significantly different between CCM and non-CCM groups, but diabetes mellitus was less prevalent in the CCM group (4% vs. 34%, $p = 0.002$). Therapeutic variables including the use of beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II

receptor blockers (ARB), aldosterone-antagonists, or HMG-CoA reductase inhibitors ("statins"), were no different between CCM and non-CCM groups, but amiodarone (40% vs. 6%, $p < 0.001$) and implantable cardioverter-defibrillator (ICD) use (36% vs. 7%, $p = 0.001$) was more common in the CCM group.

Electrocardiographic and echocardiographic characteristics of the study group are shown in Table 2. The presence of right-bundle branch block (RBBB) (20% vs. 1%, $p < 0.001$) was more common in the CCM group, but all other electrocardiographic variables were similar between the two groups. As a study group, the mean LVEDD was mildly dilated at 62 mm while the median LVEF was severely depressed at 25%. There were no differences in LVEDD or LVEF among CCM or non-CCM groups.

Table 3 displays the results of the unadjusted crude outcomes. All-cause mortality or heart transplantation occurred in 9 patients (36%) in the CCM group and in 11 patients (10%) in the non-CCM group (hazard ratio [HR]: 4.46, 95% confidence interval [CI]: 1.8 to 10.8, $p = 0.001$). The primary end point was driven almost entirely by all-cause mortality, since only 1 heart transplantation occurred in a CCM patient. HF-related hospitalization occurred in 13 patients (52%) in the CCM group and in 35 patients (32%) in the non-CCM group (HR: 2.22, 95% CI: 1.2 to 4.2, $p = 0.01$). Kaplan-Meier survival curves for all-cause mortality/heart transplantation and heart-failure related hospitalization are shown in Figure 1.

Discussion

This is the first and largest prospective study of patients with CCM in the US. We followed a group of 135 Latin American immigrants diagnosed with advanced non-ischemic CM (median LVEF 25%) at a Los Angeles county hospital for a median of 43 months. CD was diagnosed by

positive IFA and ELISA tests in 25 patients, yielding a 19% prevalence of advanced CCM (at least intermediate risk by the Rassi criteria (17)). This prevalence estimate is similar to the 13% prevalence found in a smaller study of Latin American immigrants diagnosed with dilated cardiomyopathy in New York City (18). This finding cannot be emphasized enough, as multiple investigators have documented an increased mortality among patients with various stages of CCM as compared to those with non-CCM. Our data corroborate these findings, as CCM was associated with a primary end point of mortality or heart transplantation that was 4.46 times higher than non-CCM (Figure 1A) despite similar LVEDD and LVEF. This HR estimate is in accordance with previous estimates of 3.29-6.09 for CCM-related mortality (19-21).

In addition to increased mortality/heart transplantation, our study demonstrated an increased burden of HF-related hospitalization in patients with CCM. HF-related hospitalization was 2.22 times higher in CCM compared to non-CCM (Figure 1B) despite similar LVEDD and LVEF. These findings are of paramount importance in the era of Medicare's Hospital Readmission Reduction Program, in which hospital admissions and readmissions for HF are increasingly scrutinized and tied to reimbursement (22). Our study provides the first insight into HF-related hospitalization for CCM in a US population.

Identifying CD in a patient with CM not only helps with prognostication, but also aids in clinical treatment decisions. For instance, the antiarrhythmic amiodarone has been shown to have direct anti-*T. cruzi* effects by disrupting calcium homeostasis *in vitro* (23), with a case report of decreased parasitemia and improved LVEF (24,25). Our center uses amiodarone liberally in patients with CCM, thus explaining the significant difference in amiodarone use observed in our study between the CCM and non-CCM groups (40% vs. 6%, $p < 0.001$). The high burden of malignant ventricular arrhythmias which can involve the epicardium, right ventricle, or apical

aneurysm, are important considerations when contemplating ICD therapy or radiofrequency ablation in patients with CD (26-29). Lastly, it is now recognized that survival in patients with CCM after heart transplant may be better than those patients with other forms of non-ischemic CM, however reactivation rates as high as 26.5% to 42.9% have been reported and require a unique post-transplant surveillance process to monitor for reactivation and provide prompt antiparasitic treatment (30,31).

Many baseline characteristics were found to be associated with CD in this study. Although the majority of participants originated from Mexico (53%), those diagnosed with CCM were predominantly from El Salvador (54%). These findings may be due to sampling error, since the heterogeneous geographical distribution of CD in Mexico makes it possible that the Mexican immigrants included in our study were not from highly endemic areas within Mexico (32,33). However, one small study of Chagas heart disease patients in Los Angeles also reported the highest prevalence among those from El Salvador (8). The fact that El Salvador has the highest prevalence of CD in Central America likely also plays a role in these findings (2). We also found that participants who lived in their native country longer were more likely to have acquired CD, presumably due to increased exposure to the causative agent. Finally, the finding of RBBB on EKG was associated with CCM as has been previously reported (2).

Despite our prospective cohort of CCM patients representing the largest in the US, one of the major limitations of our study was the small sample size. Since CD is not endemic to the US, our sample of CCM was relatively small compared to similar studies conducted in Brazil which have study populations of CCM exceeding 200 patients (19-21). However, since our entire CCM cohort originated from Mexico, El Salvador, or Guatemala, this cohort represents an area of Latin America not previously studied with respect to risk factors and outcomes. Furthermore,

Central America and Brazil are populated with different strains of *T. cruzi*, which may affect the virulence and clinical course of CD (2,34,35). Another limitation of the study is the assumption that seropositivity for CD meant that the parasitic infection had caused CM. To address this issue, we excluded patients with other known etiologies of non-ischemic CM. Since it is entirely possible that CD and another etiology of non-ischemic CM may coexist in the same person, the prevalence of CD in our study group may not accurately reflect the true prevalence of CCM among Latin American CM patients in Los Angeles. Moreover, because only advanced cases of CCM were enrolled in this study our results should not be misconstrued to represent outcomes of all patients with CD. Previous research has shown that seropositivity for CD with little or no cardiac involvement is associated with a more indolent disease course (2,17).

In conclusion, this is the first and largest prospective study following a group of Latin American immigrants with CCM in the US. Although somewhat limited by sample size, the data suggest that approximately 1 in 5 Latin American immigrants in Los Angeles with non-ischemic CM may have CD. Immigrants from El Salvador and those who have lived in their native country longer than 40 years were more likely to have CCM. Survival analysis showed that advanced CCM is clearly associated with increased mortality/heart transplantation and hospitalization compared to non-CCM despite similar LVEDD and LVEF. Based on the results of this and other studies, healthcare facilities providing care for Latin American immigrants diagnosed with non-ischemic cardiomyopathy in the United States should consider evaluating for CD as a possible cause of CM (18).

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Disclosures

None.

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Table 1. Baseline characteristics*

Characteristic	CCM (N = 25)	Non-CCM (N = 110)	All (N = 135)†	P Value‡
Demographic				
Male sex - no. (%)	12 (48)	65 (59)	77 (57)	0.37
Median age - yrs (25%, 75%)	58 (50, 66)	56 (46, 66)	57 (47, 66)	0.04
Country of origin				
Mexico - no. (%)	6 (25)	65 (59)	71 (53)	0.005
El Salvador - no. (%)	13 (54)	21 (19)	34 (25)	0.001
Guatemala - no. (%)	5 (21)	15 (14)	20 (15)	0.36
Other - no. (%)	0 (0)	9 (8)	9 (7)	0.36
Location				
Rural - no. (%)	10 (40)	56 (52)	66 (50)	0.38
Urban - no. (%)	15 (60)	52 (48)	67 (50)	0.38
Type of house				
Concrete - no. (%)	11 (46)	48 (44)	59 (45)	1.00
Adobe - no. (%)	9 (38)	44 (41)	53 (40)	0.95
Other - no. (%)	4 (17)	16 (15)	20 (15)	0.76
Median time in native country - yrs (25%, 75%)	41 (26, 56)	26 (16, 35)	29 (16, 42)	0.002
Median time in United States - yrs (25%, 75%)	13 (11, 34)	24 (16, 31)	22 (13, 31)	0.01
Clinical				
Hypertension - no. (%)	10 (40)	47 (43)	57 (42)	0.83
Hyperlipidemia - no. (%)	4 (16)	16 (15)	20 (15)	0.77
Diabetes mellitus - no. (%)	1 (4)	37 (34)	38 (28)	0.002
Tobacco use - no. (%)	8 (32)	21 (19)	29 (22)	0.18

Alcohol use - no. (%)	6 (24)	26 (24)	32 (24)	1.00
Therapeutic				
Beta-blocker - no. (%)	22 (88)	103 (94)	125 (93)	0.39
ACEI/ARB - no. (%)	23 (92)	98 (89)	121 (90)	1.00
Aldosterone-antagonist - no. (%)	7 (28)	32 (29)	39 (29)	1.00
Statin - no. (%)	9 (36)	56 (51)	65 (48)	0.19
Amiodarone - no. (%)	10 (40)	6 (6)	16 (12)	< 0.001
ICD device- no. (%)	9 (36)	8 (7)	17 (13)	0.001

*CCM denotes Chagas cardiomyopathy, Yr year, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, LVEDD left ventricular end-diastolic diameter, ICD implantable cardioverter-defibrillator.

†The following variables had a different number of total patients: country of origin (CCM [N = 24], Non-CCM [N = 110]), location (CCM [N = 25], Non-CCM [N = 108]), type of house (CCM [N = 24], Non-CCM [N = 108]), tobacco use (CCM [N = 25], Non-CCM [N = 109]), alcohol use (CCM [N = 25], Non-CCM [N = 109]).

‡Fisher's exact test (categorical variables) or t-test (continuous variables).

Table 2. Electrocardiogrpahic and echocardiographic characteristics*

Characteristic	CCM (N = 25)	Non-CCM (N = 103)†	All (N = 128)	P Value‡
Electrocardiographic				
Rhythm				
NSR - no. (%)	21 (84)	79 (77)	100 (78)	0.60
Atrial fibrillation/flutter - no. (%)	1 (4)	16 (16)	17 (13)	0.19
Paced - no. (%)	3 (12)	6 (6)	9 (7)	0.38
Conduction disease				
LBBB - no. (%)	2 (8)	26 (25)	28 (22)	0.11
RBBB - no. (%)	5 (20)	1 (1)	6 (5)	< 0.001
LAFB - no. (%)	1 (4)	11 (11)	12 (9)	0.46
IVCD - no. (%)	6 (24)	9 (9)	15 (11)	0.08
Other				
Q waves - no. (%)	4 (16)	8 (8)	12 (9)	0.25
LVH - no. (%)	6 (24)	27 (26)	33 (26)	1.00
Echocardiographic				
Median LVEDD - mm (25%, 75%)	66 (59, 73)	62 (56, 69)	62 (55, 69)	0.15
Median LVEF - % (25%, 75%)	20 (8, 33)	25 (18, 33)	25 (18, 32)	0.24

*CCM denotes Chagas cardiomyopathy, NSR normal sinus rhythm, LBBB left bundle-branch block, RBBB right bundle-branch block, LAFB left anterior fascicular block, IVCD intraventricular conduction delay, LVH left ventricular hypertrophy, LVEDD left ventricular end-diastolic diameter, LVEF left ventricular ejection fraction.

†7 EKGs were missing from the non-CCM group.

‡Fisher's exact test (categorical variables) or t-test (continuous variables).

Table 3. Unadjusted outcomes*

Outcome	CCM (N = 25)	Non-CCM (N = 110)	P Value†	Hazard ratio (95% CI)‡
Mortality or heart transplant - no. (%)	9 (36)	11 (10)	0.001	4.46 (1.8, 10.8)
Hazard rates per 1000 person-months - % (95% CI)	11.2 (3.9, 18.5)	2.4 (1.0, 3.8)		
Heart failure-related hospitalization - no. (%)	13 (52)	35 (32)	0.01	2.22 (1.2, 4.2)
Hazard rates per 1000 person-months - % (95% CI)	21.1 (9.6, 32.5)	9.0 (6.0, 12.0)		

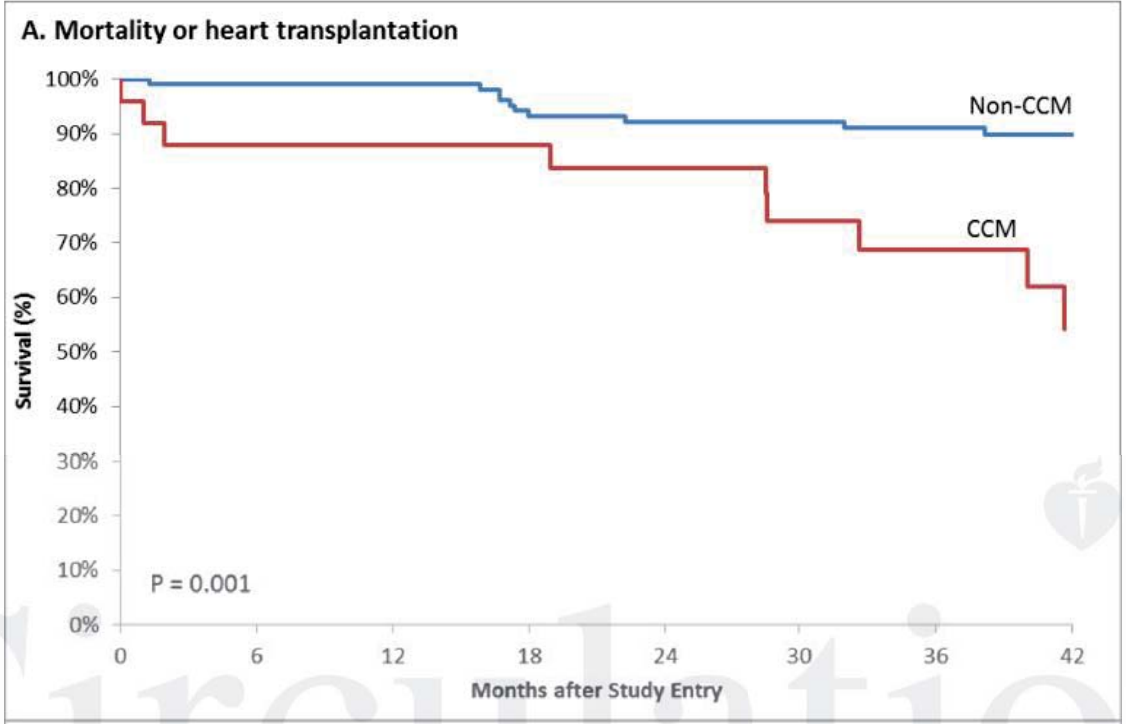
*CCM denotes Chagas cardiomyopathy, CI confidence interval, mos months.

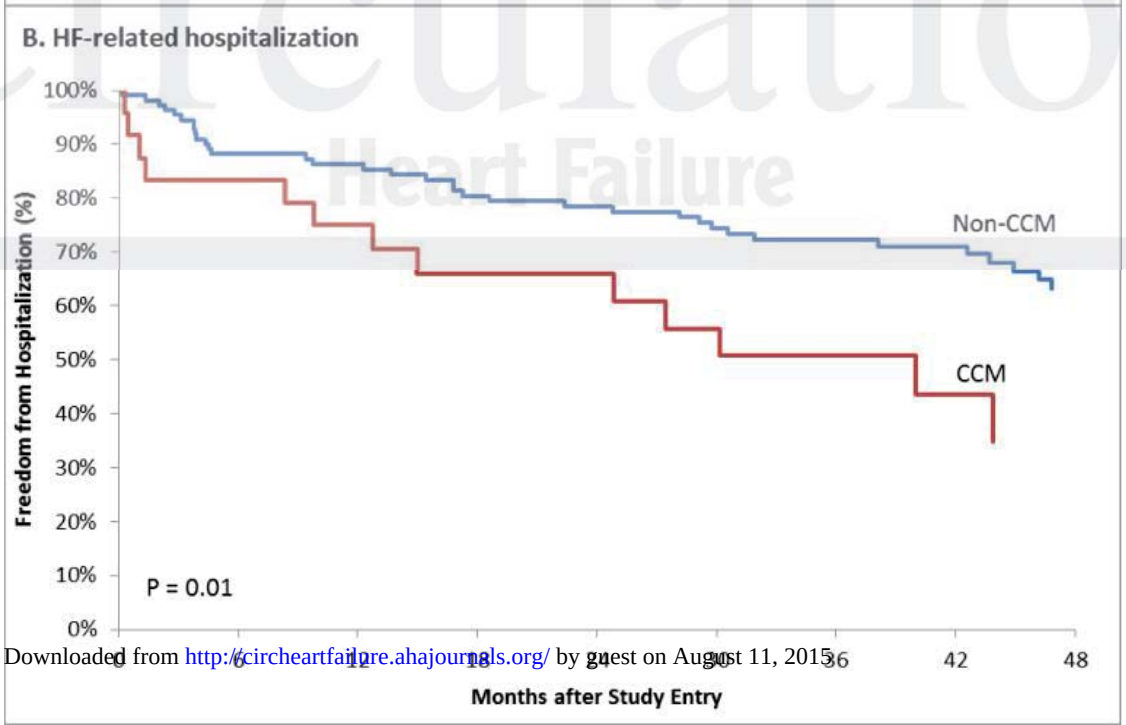
†Log-rank test (Mantel-Cox).

‡Univariate Cox proportional-hazards models.

Figure Legend

Figure 1. Kaplan-Meier Survival Curves for the Primary and Secondary Endpoints. Kaplan-Meier estimates are shown for all-cause mortality/heart transplantation (A) and HF-related hospitalization (B). Differences in the CCM and non-CCM groups were assessed using the log-rank test. CCM = Chagas cardiomyopathy; HF = heart failure.





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