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Predictors of mortality and heart transplantation in patients with Chagas' cardiomyopathy and ventricular tachycardia treated with implantable cardioverter-defibrillators

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Aims Data on long-term follow-up of patients with Chagas' heart disease (ChHD) receiving a secondary prevention implantable cardioverter-defibrillator (ICD) are limited and its benefit is controversial. The aim of this study was to evaluate the long-term outcomes of ChHD patients who received a secondary prevention ICD.

Methods and results We assessed the outcomes of consecutive ChHD patients referred to our Institution from 2006 to 2014 for a secondary prevention ICD [89 patients; 58 men; mean age 56 ± 11 years; left ventricular ejection fraction (LVEF), 42 ± 12%]. The primary outcome included a composite of death from any cause or heart transplantation. After a mean follow-up of 59 ± 27 months, the primary outcome occurred in 23 patients (5.3% per year). Multivariate analysis showed that LVEF < 35% [hazard ratio (HR) 4.64; $P < 0.01$] and age ≥ 65 years (HR 3.19; $P < 0.01$) were independent predictors of the primary outcome. Using these two risk factors, a risk score was developed, and lower- (no risk factors), intermediate- (one risk factor), and higher-risk (two risk factors) groups were recognized with an annual rate of primary outcome of 1.4%, 7.4%, and 20.4%, respectively. A high burden of appropriate ICD therapies (16% per year) and electrical storms were documented, however, ICD interventions did not impact on the primary outcome.

Conclusion Among ChHD patients receiving a secondary prevention ICD, older age (≥65 years) and left ventricular dysfunction (LVEF < 35%) portend a poor outcome and were associated with increased risk of death or heart transplantation. Most patients received appropriate ICD therapies, however, ICD interventions did not impact on the primary outcome.

Keywords Chagas' disease • Ventricular tachycardia • Implantable cardioverter-defibrillator • Heart transplant • Mortality

Introduction

Chagas' disease results from infection with the protozoan parasite Trypanosoma cruzi and poses a substantial social and public health burden in Latin America[1] and has become a worldwide problem due to growing immigration from endemic areas.[2,3] Chronic Chagas' heart disease (ChHD) is its most important clinical presentation and is characterized by conduction system abnormalities, segmental wall

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What's new?

- Our data show that older age (≥65 years) and left ventricular dysfunction (left ventricular ejection fraction <35%) were independent predictors of death or heart transplantation in Chagas' heart disease patients with sustained ventricular arrhythmias treated with implantable cardioverter-defibrillators (ICDs).
- Using these two risk factors, a risk score was developed, and lower- (no risk factors), intermediate- (one risk factor), and higher-risk (two risk factors) groups were recognized. The primary outcome occurred at an annual rate of 1.4%, 7.4%, and 20.4% among patients without any risk factor, one risk factor, and two risk factors, respectively.
- Despite the high burden of appropriate ICD therapies and electrical storms in our cohort, these ICD interventions did not impact on the primary outcome.

motion abnormalities (aneurysms), thrombo-embolic events, ventricular arrhythmias (VAs), and dilated cardiomyopathy that may lead to sudden cardiac death or death due to worsening heart failure.[4,5]

Because ChHD patients with sustained VAs are at increased risk for sudden cardiac death (SCD), secondary prevention implantable cardioverter-defibrillator (ICD) has become an emerging therapy in the contemporary clinical practice,[6,7] however, the long-term benefit of ICDs in these patients is inconclusive and may be attenuated by non-arrhythmic death.

In the present observational study, we aimed to assess (i) the long-term outcomes and predictors of death from any cause or heart transplantation in a cohort of hospital-based ChHD patients who received a secondary prevention ICD and (ii) the impact of ICD-delivered therapies on outcomes.

Methods

Patient population

We included 89 patients with ChHD, consecutively referred to our Institution from January 2006 to December 2014 for a secondary prevention ICD therapy. The exclusion criteria were age <18 years old, previous pacemaker or cardiac resynchronization device at the time of the ICD placement ($n = 24$ patients).

Study protocol

Before ICD implantation, patients underwent a comprehensive evaluation including clinical examination, 12-lead electrocardiography, two-dimensional echocardiography, electrophysiological study (EPS), and general laboratory exams. The absence of clinically significant coronary artery disease as the cause of the cardiomyopathy was confirmed by coronary angiography. The diagnosis of Chagas' disease was based on epidemiological data and at least two positive serological reactions. The study complies with the Declaration of Helsinki, the research protocol was approved by the Human Research Ethical Committee of our Institution, and the informed consent for study participation was obtained from all patients. All patients received commercially available ICDs, which were implanted transvenously without thoracotomy. All devices provided back-up bradycardia pacing and were capable of storing intracardiac electrograms. In general, devices were programmed with three tachycardia detection zones [a monitor zone, an antitachycardia pacing (ATP) shock zone, and an initial shock zone] at discretion of the treating physician. Devices were interrogated every 3–6 months, and each stored arrhythmia episode was reviewed and classified by two experienced electrophysiologists (W.L.G. and A.V.L.S.) according to the following definition criteria: ventricular fibrillation (VF) was defined as VA with rate ≥250 b.p.m, fast ventricular tachycardia (VT) as VA with rate ≥188 b.p.m. and <250 b.p.m., and slow VT as VA with rate <188 b.p.m. Appropriate ICD therapy was defined as shocks and/or ATP delivered in response to VA. Inappropriate ICD therapy was defined when triggered by a rapid ventricular rate due to supraventricular tachyarrhythmias or device malfunction. Electrical storm (ES) was defined as the occurrence of VT or VF, resulting in device intervention (shocks and/or ATP) three or more times within a 24 h period. Recurrent appropriate ICD therapies or ESs were managed mainly by modification of the doses of amiodarone and/or beta-blockers and ICD reprogramming. Percutaneous endocardial and transthoracic epicardial VT ablation using a 3-dimensional (3D) mapping system (CARTO 3, BiosenseWebster, Diamond Bar, CA, USA) and surgical left cardiac sympathetic denervation were used when available. The cumulative right ventricular (RV) pacing was calculated at each ICD interrogation, and its value at the last follow-up was considered for analysis.

Medical therapy and follow-up

Treatment for heart failure with evidence-based medical therapies such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists were optimized in all patients. Amiodarone was administered at discretion of the treating physician to reduce ICD interventions. After a loading dose of amiodarone of 10 g during 3 weeks, patients received amiodarone at a dose of 200–400 mg daily thereafter.

Outcomes and definitions

The primary outcome of the study was a composite of death from any cause or heart transplantation. The secondary outcome was any ICD-delivered therapy, including appropriate (shocks and/or ATP) and inappropriate therapies. The cause of death was ascertained by reviewing medical records and contacting patients/family members. Causes of death were categorized according to a modified Hinkle–Thaler classification.[8]

Statistical analysis

Continuous data were expressed as mean ± standard deviation and were compared by Student's *t*-test or Mann–Whitney exact tests. Categorical data were presented as the number of patients and percentage of the total sample and were compared by the χ^2 analysis or with the Fisher's exact test. Receiver-operating characteristic (ROC) curves were analysed to assess the best cut-off value of left ventricular ejection fraction (LVEF) to predict the primary outcome. To identify the variables that are independently predictive of the primary outcome, a subsequent stepwise multivariate analysis using Cox's regression model was performed, including all variables that had a predictive value of *P*-value <0.05 in the univariate analysis. Event-free survival rates, defined as free of death from any cause or heart transplantation, were determined by the Kaplan–Meier method and were compared by the log-rank test with adjustment for multiple comparisons. Analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA). For all tests, a *P*-value of <0.05 was considered significant.

Table 1 Baseline characteristics of the study population

	All group ($n = 89$)	Alive ($n = 66$)	Death/heart transplantation ($n = 23$)	*P*-value
Age (years)	56 ± 11	55 ± 10	62 ± 14	0.01
Age ≥65 years	19 (21%)	9 (13%)	10 (43%)	<0.01
Men	58 (65%)	43 (65%)	15 (65%)	0.99
Syncope	44 (49%)	33 (50%)	11 (47%)	0.85
NYHA functional class				
NYHA I/II	88 (98%)	66 (100%)	22 (95%)	0.25
LVEDD (mm)	57 ± 7	56 ± 7	62 ± 6	<0.01
LVEF				
LVEF <35%	27 (30%)	13 (19%)	14 (60%)	<0.01
Mean LV ejection fraction (%)	42 ± 12	45 ± 11	34 ± 11	<0.01
Conduction disorders				
Mean QRS width (ms)	122 ± 26	120 ± 26	127 ± 26	0.32
RBBB	40 (44%)	31 (46%)	9 (39%)	0.51
LBBB	4 (4%)	2 (3%)	2 (8%)	0.27
Mean cumulative RV pacing	27 ± 36	27 ± 36	28 ± 35	0.98
Cumulative RV pacing >40%	25 (28%)	17 (25%)	8 (34%)	0.40
Medications				
ACEI/ARB	75 (84%)	55 (83%)	20 (86%)	1.00
Beta-blocker	80 (89%)	58 (87%)	22 (95%)	0.43
Spironolactone	51 (57%)	33 (50%)	18 (78%)	0.01
Amiodarone	82 (92%)	60 (90%)	22 (95%)	0.67
Mean amiodarone dose (mg)	256 ± 133	227 ± 107	339 ± 164	<0.01
Appropriate ICD therapy	69 (77%)	51 (77%)	18 (78%)	0.92
Electrical storm	39 (43%)	27 (40%)	12 (52%)	0.34

Data are expressed as mean ± standard deviation or *n* (%) of patients. The χ^2 test or Fisher's test for categorical variables; the *t*-test or Mann–Whitney test for continuous variables.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle branch block; RV, right ventricular.

Results

Baseline characteristics

The study population consisted of 89 patients and their baseline characteristics are shown in *Table 1*. Overall, 58 patients (65%) were men, mean age was 56 ± 11 years (range 30–80 years). Most patients were in New York Heart Association functional class (NYHA FC) I or II (88 patients, 98%) and mean LVEF was 42 ± 12% before ICD placement. Of the 89 patients, 82 (92%) were taking amiodarone (mean dose 256 ± 133 mg; range 100–600 mg), 80 (89%) were taking beta-blockers, and 75 (84%) ACEIs or ARBs. The ICD indication was tachycardia arrest in 7 patients (8%), symptomatic sustained VT in 74 (83%), or syncope with inducible VT at EPS in 8 patients (9%). Seventy-five patients underwent an EPS, and sustained monomorphic VTs were induced in 53 (71%). There were no significant differences between patients with inducible sustained VT at the EPS ($n = 53$) and those without VT induction ($n = 22$) with respect to baseline characteristics and to the primary outcome ($P = 0.37$). A single-chamber ICD was implanted in 10 patients (11%), and a dual-chamber ICD in 79 (88%).

Follow-up and primary outcome

After a mean follow-up of 59 ± 27 months (range 1–109 months), the primary outcome occurred in 23 patients (5.3% per year), including death in 21 patients (4.8% per year) and heart transplantation in 2 patients. The causes of death were determined as a cardiac death in 13 patients, resulted from SCD in 1 patient and from progressive heart failure in 12 (63%). Six deaths (31.5%) were attributable to non-cardiac causes: three deaths due to pneumonia, one due to complications from an abdominal sepsis, one due to haemorrhagic stroke, and one due to complications from renal failure. The causes of death were not determined in two patients. The Kaplan–Meier estimates of event-free survival for the entire cohort are displayed in *Figure 2A*. At 1, 3, and 5 years of follow-up, event-free survival rates were 96%, 85%, and 78%, respectively.

The study cohort was subsequently divided into patients who died or underwent heart transplantation during follow-up and those who survived, and the baseline characteristics of the two subgroups were compared by univariate analysis (*Table 1*). All baseline data were comparable between the two groups, except that patients who died or underwent heart transplantation were older (62 ± 14 vs. 55 ± 10 years; $P = 0.01$) and had more advanced left ventricular dysfunction, reflected by lower LVEF (34 ± 11% vs. 45 ± 11%; $P < 0.01$), higher prevalence of patients with LVEF <35% (60% vs. 19%; $P < 0.01$), and had increased left ventricular end-diastolic diameter (LVEDD) (62 ± 6 mm vs. 56 ± 7 mm; $P < 0.01$), and also used a higher daily dose of amiodarone (339 ± 164 mg vs. 227 ± 107 mg; $P < 0.01$).

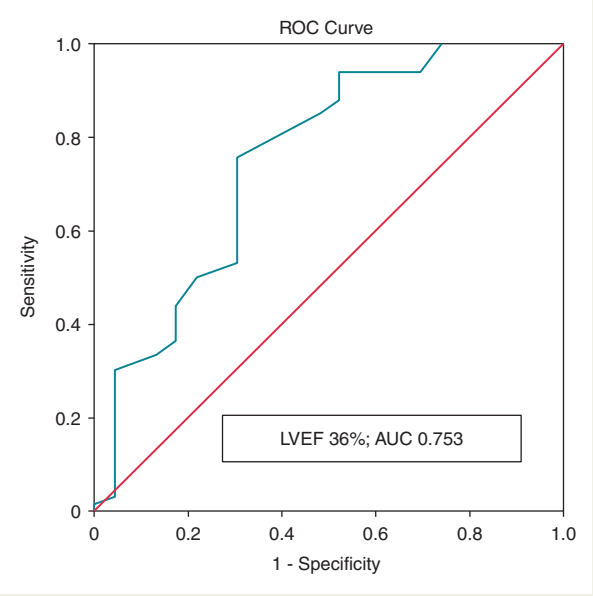


Figure 1 ROC curves of selected risk factors. The ROC curve analysis showed that a LVEF cut-off value of 36% had sensitivity of 75% and specificity of 69% to predict death from any cause or heart transplantation (AUC, 0.753; $P < 0.01$). AUC, area under the curve; LVEF, left ventricular ejection fraction; ROC curve, receiver-operating characteristic curve.

To define the optimal cut-off value for LVEF that predicted the primary outcome of death or heart transplantation, a ROC curve analysis was performed. A cut-off value of 36% (area under the curve 0.753; $P < 0.01$) yielded a sensitivity of 75% and a specificity of 69% in predicting the primary outcome (*Figure 1*).

As shown in *Table 2*, clinical variables associated with increased risk of death or heart transplantation in univariate analysis were age ≥65 years ($P < 0.01$), LVEF <35% ($P < 0.01$), LVEDD ($P < 0.01$), and NYHA FC >2 ($P = 0.02$). However, in multivariate analysis only LVEF <35% [hazard ratio (HR) 4.65, 95% confidence interval (CI) 2.00–10.80; $P < 0.01$] and age ≥65 years (HR 3.19, 95% CI 1.39–7.30; $P < 0.01$) remained significantly associated with the primary outcome. Importantly, ICD-delivered therapies were not associated with the primary outcome.

Based on the results of the multivariate analysis, we performed a subgroup analysis of the study patients according to LVEF dichotomized as ≥35% and <35%, and also according to age dichotomized as ≥65 years and <65 years. The primary outcome occurred in 9 out of 62 patients (3% per year) with LVEF ≥35% and in 14 out of 27 patients (10.6% per year) with LVEF <35%. The Kaplan–Meier estimates of event-free survival according to LVEF classified as ≥35% and <35% are displayed in *Figure 2B*. At 1, 3, and 5 years of follow-up, event-free survival rates were 96%, 93%, and 90%, respectively, for patients with LVEF ≥35% and were 96%, 68%, and 54% for those with LVEF <35% (log-rank $P < 0.01$). The primary outcome occurred in 11 out of 24 patients (9.3% per year) with age ≥65 years and in 12 out of 65 patients (3.7% per year) with age <65 years. The Kaplan–Meier estimates of event-free survival according to age classified as ≥65 years and <65 years are displayed in *Figure 2C*. At 1, 3, and 5 years of follow-up, event-free survival rates were 91%, 77%, and 58%, respectively, for patients with age ≥65 years and were 98%, 88%, and 84% for those with age <65 years (log-rank $P < 0.01$).

Risk score

All risk factors that proved to be significant during multivariate analysis (age ≥65 years, LVEF <35%) were used to develop a risk model. Patients without any risk factors were considered as low-risk and had a primary outcome of death or heart transplantation in 3 out of 43 patients (1.4% per year), patients with one risk factor were considered as an intermediate-risk and had a primary outcome in 15 out of 41 patients (7.4% per year), and patients with two risk factors were considered a high-risk and had a primary outcome in 5 out of 5 patients (20.4% per year) during follow-up. The Kaplan–Meier estimates of event-free survival for the three risk groups are displayed in *Figure 3*. At 3, 5, and 7 years of follow-up, event-free survival rates were 97%, 97%, and 93% for the low-risk group, were 75%, 60%, and 55% for the intermediate-risk group and were 60%, 40%, and 0%, respectively, for the high-risk group (log-rank $P < 0.01$). In patients with two risk factors, the cause of death was progressive heart failure in four patients and resulted from abdominal sepsis in one. Compared with the low-risk group, the intermediate-risk group had a HR for the primary outcome of 7.40 (95% CI 2.13–25.66; $P < 0.01$) and the high-risk group had a HR of 16.87 (95% CI 3.97–71.61; $P < 0.01$).

Implantable cardioverter-defibrillator-delivered therapies

Over a mean follow-up of 59 ± 27 months, of the 86 patients with intracardiac electrograms available for analysis, 69 (80%) patients received appropriate ICD therapies (shocks and/or ATP) (16% per year), with 56 (65%) patients requiring at least one shock for terminating an episode of VA (13% per year). Sustained VT was observed in 64 patients (74%) and VF in 6 patients (7%). The mean cycle length of the VAs was 396 + 70 ms (range 155–580 ms). Of the 2470 episodes of VAs detected by the ICD, slow VT occurred in 2317 episodes (93.8%), fast VT in 140 (5.6%), and 13 episodes (0.6%) were classified as VF. Eighty-four percent of VAs was terminated by ATP, 11.4% by shock after failed ATP, 1% by primary shocks, and 3.6% terminated spontaneously after ICD detection but before therapy. The mean period between ICD implantation and the first appropriate therapy was 424 days (range 1–1686 days). Survival-free of appropriate ICD therapies was 55%, 26%, and 23% after 1, 3, and 5 years of follow-up, respectively (*Figure 4A*). As shown in *Figure 4B*, survival free of appropriate ICD therapy was not different between patients with LVEF ≥35% and LVEF <35% ($P = 0.23$).

Electrical storm episodes were observed in 39 patients (43.8%), and there were no significant differences between patients with and without ES with respect to baseline characteristics such as age (56 ± 11 vs. 56 ± 12 years; $P = 0.97$), gender, LVEF (41 ± 14 vs. 43 ± 11%; $P = 0.19$), and use of medications for heart failure, even though patients with ES were treated with higher daily dose of amiodarone (312 ± 154 vs. 212 ± 93 mg; $P < 0.01$). The primary outcome was similar among patients with and without ES episodes (log-rank $P = 0.71$). The Kaplan–Meier estimates of event-free survival according to occurrence of ES are displayed in *Figure 5A*. At 1, 3, and 5 years of follow-up, event-free survival rates were 97%, 89%, and 75% for

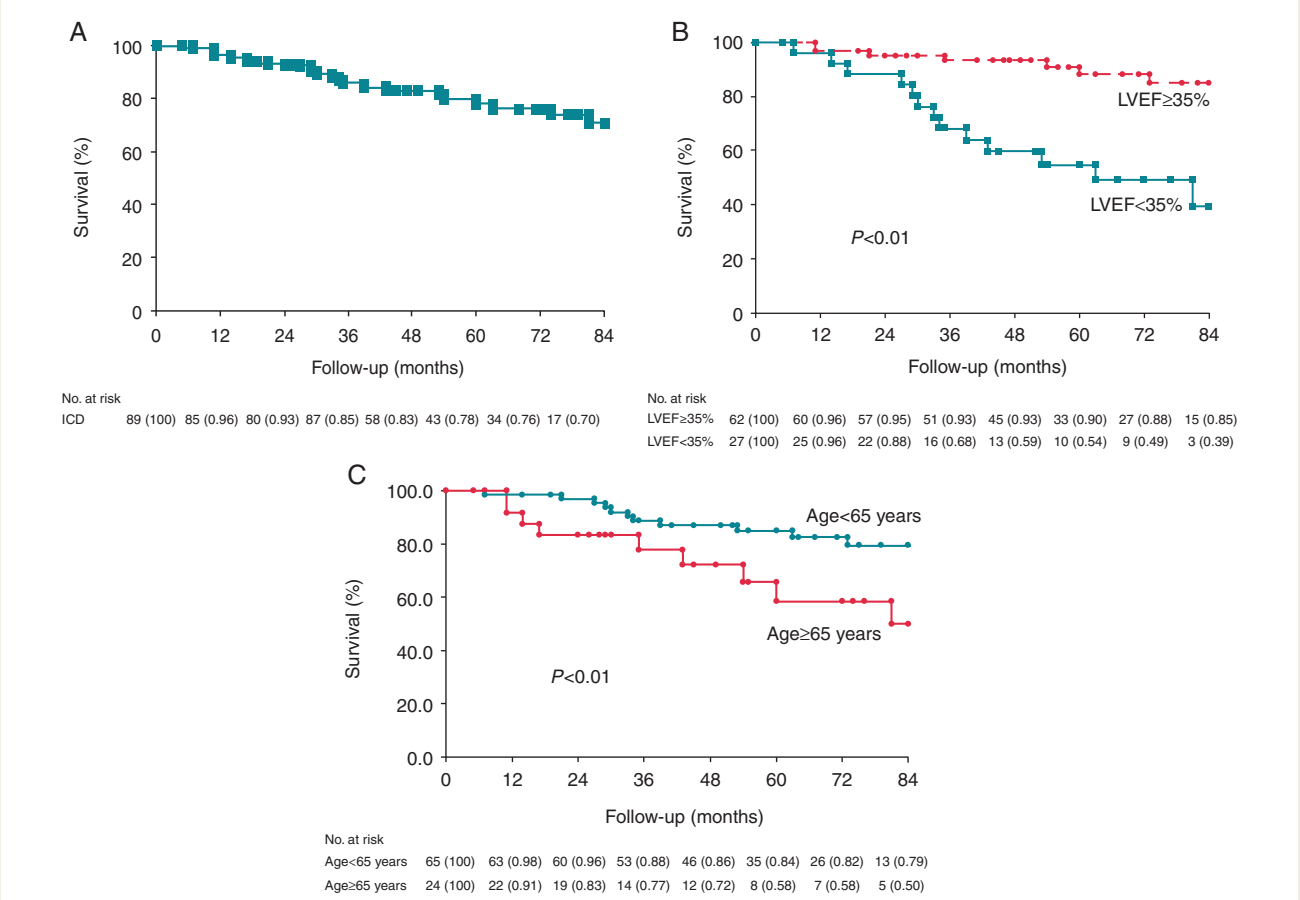


Figure 2 (*A*) The Kaplan–Meier estimates of event-free survival (death or heart transplantation) for all patients who received secondary prevention ICD. (*B*) Event-free survival according to LVEF dichotomized to ≥35% and <35%. (*C*) Event-free survival according to age dichotomized to ≥65 years and <65 years. The numbers below the figures refer to patients at risk. ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.

patients who had ES and were 95%, 82%, and 82%, respectively, for those without ES (log-rank $P = 0.71$). Inappropriate shocks occurred in eight patients (9.3%), in seven related to atrial fibrillation and in one patient due to inappropriate ICD sensing.

Recurrent ICD therapies or ES were managed in 34 patients by modification of the doses of amiodarone and/or beta-blockers and ICD reprogramming, and in two patients this clinical management was associated with surgical left cardiac sympathetic denervation. Six patients underwent endocardial and epicardial VT ablation, which was successful in five patients. In regard to the specific treatment of the ES episodes, there were no significant differences between patients who underwent successful VT ablation and those treated by modification of the doses of amiodarone and/or beta-blockers with respect to baseline characteristics such as age (56 ± 3 vs. 56 ± 11 years; $P = 0.71$), gender, LVEF (44 ± 18 vs. 40 ± 13%; $P = 0.81$), and use of medications for heart failure. Moreover, the primary outcome was not different between patients who underwent successful VT ablation and those treated with increasing doses of amiodarone and/or beta-blockers (log-rank $P = 0.51$). The Kaplan–Meier estimates of event-free survival for the two groups are displayed in *Figure 5B*.

Cumulative RV pacing >40% was observed in 25 patients (28%), and the primary outcome was not different in patients with and without RV pacing >40% (HR 1.15, 95% CI 0.48–2.74; $P = 0.76$).

Discussion

The present observational study extends the existing literature by providing further insights on long-term outcomes of patients with ChHD who received a secondary prevention ICD. The main findings can be summarized as follows: (i) despite the substantial burden of appropriate ICD therapies, we found a very low rate of SCD in our cohort; (ii) the primary outcome of death from any cause or heart transplantation was 5.3% per year, which was significantly lower than those reported in previous secondary prevention ICD studies; (iii) older age (≥65 years) and left ventricular dysfunction (LVEF < 35%) were independent predictors of death or heart transplantation; (iv) these two independent predictors of the primary outcome were used to develop a risk model, and lower- (no risk factors), intermediate- (one risk factor), and higher-risk (two risk factors) groups were recognized; (v) despite the high burden of

appropriate ICD therapies and ESs in our cohort, these ICD interventions did not impact on the primary outcome.

Previous observational studies reported that ICDs can effectively terminate life-threatening VAs and prevent SCD in patients with ChHD. Our results are consistent with these other series, showing that, despite the substantial burden of appropriate ICD interventions, the rate of SCD was very low, and was seen in only one patient in our series. Indeed, our results are in line with Gali *et al.*[7] who compared ChHD patients with sustained VAs treated either with ICD plus amiodarone or with amiodarone alone, and reported a 72% risk reduction in all-cause mortality and a 95% risk reduction in SCD among those treated with ICD plus amiodarone. In contrast, a higher mortality rate (16.5% per year) was described by Cardinalli-Neto *et al.*[9] among 90 ChHD patients who received secondary prevention ICDs. These authors reported that the number of shocks during the first month after ICD implantation was a major predictor of mortality, which may have resulted from the inadequate behaviour of the ICDs in their series.

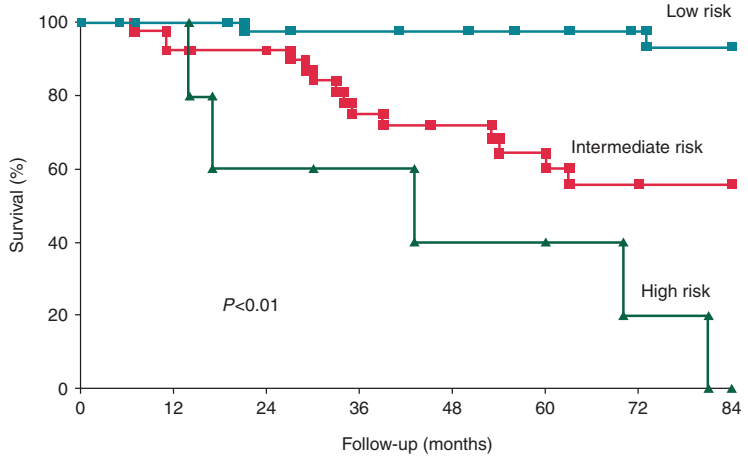
Table 2 Univariate and multivariate predictors of death from any cause or heart transplantation using Cox proportional-hazards analysis

Variables	HR (95% CI)	*P*-value[a]
Univariate analysis		
Age (≥65 vs. <65 years)	2.97 (1.30–6.78)	<0.01
Gender (female vs. male)	1.07 (0.45–2.57)	0.88
NYHA (Class 3 vs. 1, 2)	11.69 (1.44–95.00)	0.02
LVEF (<35% vs. ≥35%)	4.43 (1.91–10.28)	<0.01
LVEDD (mm)	1.10 (1.04–1.17)	<0.01
ACEI or ARB (yes vs. no)	1.38 (0.41–4.66)	0.60
Beta-blocker (yes vs. no)	2.26 (0.30–16.83)	0.42
Spironolactone (yes vs. no)	2.91 (1.08–7.87)	0.03
Amiodarone (yes vs. no)	2.64 (0.34–20.20)	0.35
Cumulative RVP (>40% vs. ≤40%)	1.15 (0.48–2.74)	0.76
Appropriate ICD therapy (yes vs. no)	1.26 (0.46–3.46)	0.65
Electrical storm (yes vs. no)	1.16 (0.51–2.67)	0.72
Multivariate analysis		
Age (≥65 vs. <65 years)	3.19 (1.39–7.30)	<0.01
LVEF (<35% vs. ≥35%)	4.65 (2.00–10.80)	<0.01

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RVP, right ventricular pacing.
[a]P<0.05.

In our study, after a mean follow-up of 59 ± 27 months, the primary outcome occurred in 23 patients (5.3% per year), including death in 21 patients (4.8% per year), mostly due to progressive heart failure or non-cardiac cause, and heart transplantation in 2 patients. These findings were consistent with a previous series from Gali *et al.*,[7] where they reported an annual mortality rate of 4.8% among ChHD patients treated with ICD plus amiodarone. These results stand out because annual mortality rates were significantly lower than those reported in previous ICD-treated ChHD patients, which ranged from 7.1% to 16.5% per year.[9–13] The reasons for these discrepancies in the mortality rates between the present study, Gali's report[7] and the other series remain conjectural, and may be related to the differences in the study populations, duration of follow-up, ICD programming characteristics, or concomitant use of amiodarone and medical therapies for heart failure.

In this respect, it is interesting to note that the survival rates reported in all these series paralleled the concomitant use of medications for heart failure and for suppressing VAs, such as amiodarone and beta-blockers. Thus, in the seven series of ICD-treated ChHD



No. at risk							
Low risk	43 (100)	43 (100)	41 (0.97)	40 (0.97)	35 (0.97)	27 (0.97)	22 (0.97)	11 (0.93)
Intermediate risk	41 (100)	37 (0.92)	35 (0.92)	24 (0.75)	21 (0.71)	14 (0.60)	10 (0.55)	6 (0.55)
High risk	5 (100)	5 (100)	3 (0.60)	3 (0.60)	2 (0.40)	2 (0.40)	2 (0.40)	0 (0.00)

Figure 3 The Kaplan–Meier estimates of event-free survival of three distinct risk groups [lower- (no risk factors), intermediate- (one risk factor), and higher-risk (two risk factors)] according to the risk factors identified during multivariate analysis (age ≥65 years and LVEF <35%). The numbers below the figure refer to patients at risk. LVEF, left ventricular ejection fraction.

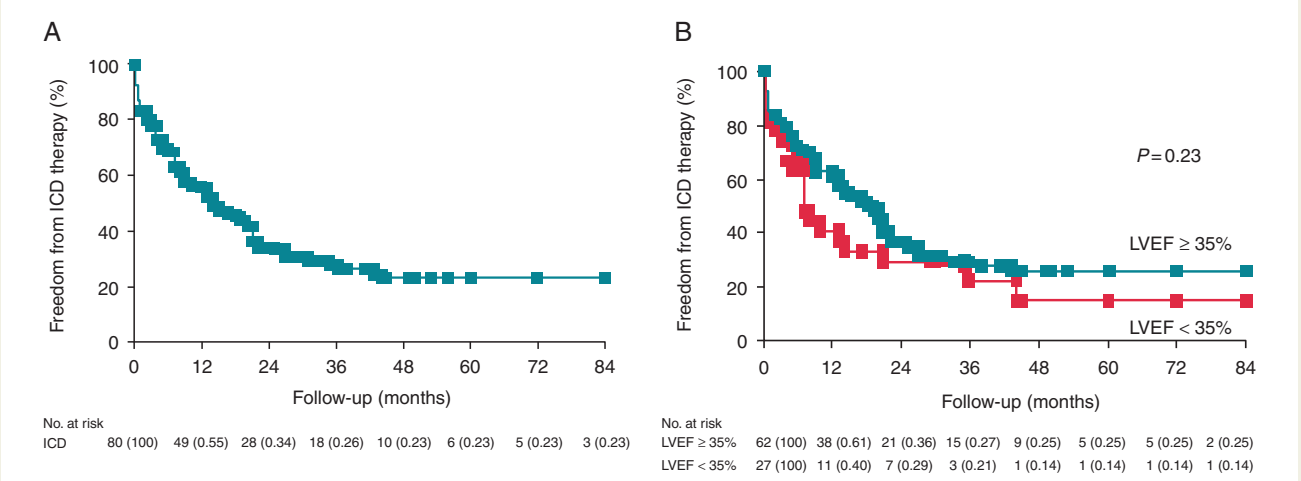


Figure 4 (*A*) The Kaplan–Meier curves depicting time to first appropriate ICD therapy. (*B*) Time to first appropriate ICD therapy according to LVEF dichotomized to ≥35% and <35%. ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.

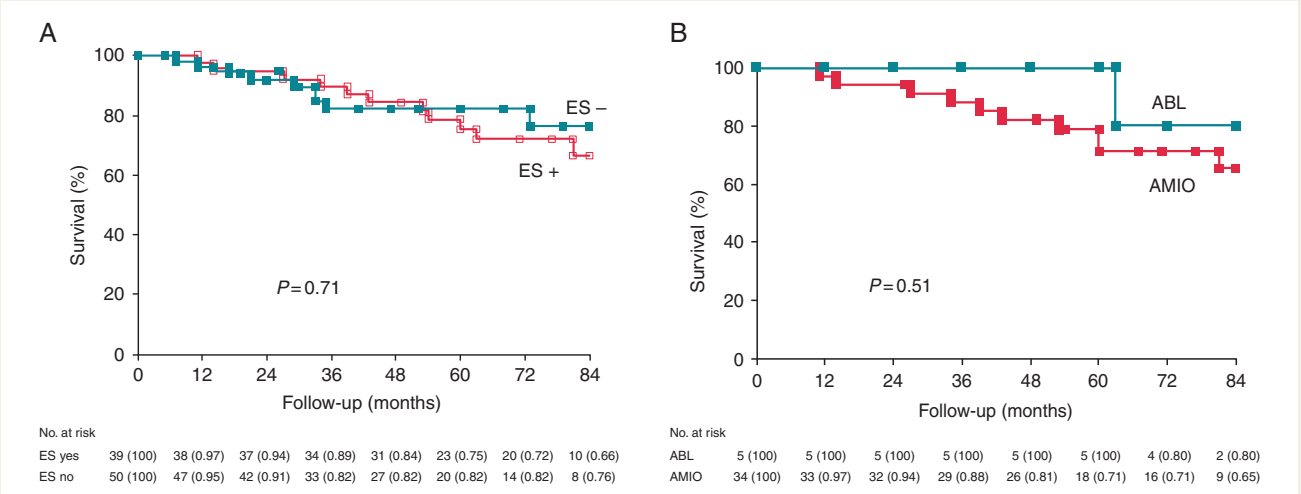


Figure 5 (*A*) The Kaplan–Meier estimates of event-free survival (death or heart transplantation) according to ES, dichotomized to presence (ES+) or absence (ES-) of electrical storms. (*B*) Event-free survival for patients with electrical storms successfully treated with VT ablation (ABL) or amiodarone (AMIO). The numbers below the figures refer to patients at risk. ES, electrical storm; VT, ventricular tachycardia.

patients, including our own here reported, amiodarone was used in 100%, 92%, 63%, 78%, 94%, 90%, and 92% of the patients, beta-blockers were used in 40%, 54%, 49%, 33%, 64%, 90.0%, and 89%, and the annual mortality rate was 16.5%, 12.3%, 10.3%, 7.1%, 8.4%, 4.8%, and 4.8%, respectively, reported by Cardinalli-Neto *et al.*,[9] Barbosa *et al.*,[13] di Toro *et al.*,[10] Martinelli *et al.*,[11] Pavão *et al.*,[12] Gali *et al.*,[7] and our own present series. These observations are clinically important because they may account for some of the discrepancies in the mortality rates across the previous ICD-treated series and our own here reported.

In the present study, we report a LVEF cut-off value of 35% that had the best accuracy for predicting the primary outcome of death or heart transplantation. Multivariate analysis showed that older age (≥65 years) and left ventricular dysfunction (LVEF < 35%) significantly predicted poor prognosis and were associated with increased rates of death or heart transplantation, while ICD-delivered therapies were not associated with the primary outcome. The poor outcomes of ChHD patients with left ventricular dysfunction treated with ICDs have already been reported by Martinelli *et al.*,[11] di Toro *et al.*,[10] Pavão *et al.*,[12] and Gali *et al.*[7] However, these results contrast with the study of Cardinalli-Neto *et al.*,[9] where most patients who died shortly after the ICD implantation had a preserved left ventricular function, even though these findings might be related to inadequate behaviour of the ICDs, with the number of ICD shocks during the

first month of follow-up predicting increased mortality. Traditional predictors of mortality in ChHD are left ventricular dysfunction, severity of HF symptoms, and sustained or non-sustained VAs, which are commonly used for risk stratification. However, in a previous study, di Toro *et al.*[10] reported that advanced age (>65 years), in addition to LVEF <30%, was also associated with increased risk of mortality in patients with ChHD.

In the present analysis, the two risk factors which proved to be significant during multivariate analysis (age ≥65 years, LVEF <35%) were used to develop a risk model, and lower- (no risk factors), intermediate- (one risk factor), and higher-risk (two risk factors) groups were recognized. Notably, the primary outcome occurred at an annual rate of 1.4%, 7.4% and 20.4% among patients without any risk factors, patients with one risk factor and two risk factors, respectively. Of note, in our series, all five patients with two risk factors (age ≥65 years and LVEF <35%) died during follow-up, four from progressive heart failure and one from abdominal sepsis. Whether the presence of these two risk factors would prevent the benefit of ICD deserves to be investigated. Our study does not allow to speculate on the evolution of ChHD patients older than 65 years and with LVEF <35% but without ICDs. The ICD is expected to exert its benefit on reducing mortality specifically by preventing SCD, and it should not be surprising that during follow-up many ICD-treated patients, mainly those with left ventricular dysfunction or associated comorbidities, ultimately die from heart failure or non-cardiac causes.

The incidence of appropriate ICD therapies was high in our series, despite concomitant therapy with amiodarone. Our data show that 80% of ICD-treated patients received appropriate therapies (16% per year), with 65% requiring at least one ICD shock for terminating an episode of sustained VA (13% per year). This rate is comparable to the rate of appropriate therapies reported in previous secondary prevention ICD studies in ChHD,[9–13] and reflects one of the main features of the ChHD, that is, its striking arrhythmogenic nature,[4,5,14,15] resulting from the ubiquitous presence of ventricular scars leading to re-entrant tachyarrhythmias[14,15] and also possibly related to abnormalities of the cardiac autonomic control.[4,5,16] Importantly, despite the substantial burden of appropriate ICD therapies and episodes of ESs in our cohort, these interventions did not impact on the primary outcome, in contrast with Cardinalli-Neto's series,[9] in which the number of ICD shocks during the first month was a major predictor of mortality. In agreement with our results, ICD interventions in ChHD patients were not associated with increased mortality in several other series.[10–13]

It should be pointed out that ICD therapy cannot be considered a uniform treatment, and outcomes after ICD implantation may be influenced by occurrence of ICD shocks.[17] In addition, the association between ICD interventions and mortality may be further influenced by more aggressive use of ATP-terminated VAs and thoughtful programming of therapy zones.[18]

In the present study, recurrent appropriate ICD therapies or ESs were managed mainly by modification of the doses of amiodarone and/or beta-blockers and ICD reprogramming. Importantly, catheter endocardial and epicardial VT ablation was successfully used in only five patients, and two patients underwent surgical left cardiac sympathetic denervation. We recognize that catheter ablation of VAs was underutilized in our study and a more widespread use of this adjunctive therapy should be attempted in these patients for reducing the substantial burden of VAs, even though there are no data directly comparing catheter ablation with amiodarone and/or beta-blockers for the management of sustained VAs in patients with ChHD. The main limitation to a more widespread use of catheter ablation using a 3D mapping system in this clinical setting is related to financial constraints of the public health system in Brazil, which does not cover this type of ablation procedure.

The 2015 Guidelines from European Society of Cardiology[19] recommend that ICD should be considered in patients with ChHD and LVEF <40% (level of evidence C), primarily based on data from Gali *et al.*[7] Although ChHD patients with left ventricular dysfunction run a major overall risk of cardiac death and SCD, some of them, even with preserved global left ventricular function are also at risk of life-threatening VAs, as shown in a recently reported series of five consecutive patients with preserved left ventricular function who developed fast VT or VF.[20] However, there is no hard evidence that ICD implantation will translate into a better long-term prognosis in these patients. Our study shows that patients with better left ventricular function (LVEF ≥35%) experienced rates of ICD interventions similar to those with worse left ventricular function (LVEF <35%), which supports the concept that patients with LVEF ≥35% are also at increased risk for SCD and may benefit from ICD implantation. Notably, in our series, only 3 out of 43 patients considered as low-risk (age<65 years and LVEF ≥35%) died during follow-up (1.4% per year), even though 29 (67%) received appropriate ICD interventions.

Limitations

Our study has several limitations. First, this is an observational and single centre study and it is subject to all the inherent limitations of such type of analysis. Second, in an attempt to evaluate the impact of RV pacing by ICD on long-term outcomes, we excluded from the analysis nine patients who received ICDs with cardiac resynchronization therapy. Third, despite the high burden of appropriate ICD therapies, only five patients were successfully treated with VT ablation after ES episodes. Then, treatment with ablation may influence recurrence of shocks and mortality rates. Fourth, although we failed to detect differences in primary outcome among patients with and without ESs, our study may have lacked adequate power to detect differences that might exist. Our study design does not allow us to draw definitive conclusions regarding other predictors of death and heart transplantation in ChHD patients who received a secondary prevention ICD.

Conclusions

The present observational analysis shows that in ChHD patients receiving a secondary prevention ICD, older age (≥65 years) and left ventricular dysfunction (LVEF < 35%) portend a poor outcome and were associated with increased risk of death or heart transplantation. Despite concomitant amiodarone therapy, most patients received appropriate ICD therapies, however, these ICD interventions did not impact on the primary outcome. These observations may have important implications for risk stratification and future treatment decisions in the setting of ChHD.

Conflict of interest: none declared.

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