Implantable cardioverter-defibrillators for treatment of sustained ventricular arrhythmias in patients with Chagas’ heart disease: comparison with a control group treated with amiodarone alone

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Received 30 September 2013; accepted after revision 10 December 2013; online publish-ahead-of-print 30 January 2014

Aims Evidence is inconclusive concerning the benefit of implantable cardioverter-defibrillators (ICDs) for secondary prevention of mortality in patients with Chagas’ heart disease (ChHD). The aim of this study was to compare the outcomes of ChHD patients with life-threatening ventricular arrhythmias (VAs), who were treated either with ICD implantation plus amiodarone or with amiodarone alone.

Methods and results The ICD group [76 patients; 48 men; age, 57 ± 11 years; left ventricular ejection fraction (LVEF), 39 ± 12%] and the historical control group treated with amiodarone alone (28 patients; 18 men; age, 54 ± 10 years; LVEF, 41 ± 10%) had comparable baseline characteristics, except for a higher use of beta-blockers in the ICD group (P, 0.0001). Amiodarone was also used in 90% of the ICD group. Therapy with ICD plus amiodarone resulted in a 72% reduced risk of all-cause mortality (P = 0.007) and a 95% reduced risk of sudden death (P = 0.006) compared with amiodarone-only therapy. The survival benefit of ICD was greatest in patients with LVEF < 40% (P = 0.01) and was not significant in those with LVEF ≥ 40% (P = 0.15). Appropriate ICD therapies occurred in 72% of patients and the rates of interventions were similar across patients with LVEF < 40% and ≥ 40%.

Conclusion Compared with amiodarone-only therapy, ICD implantation plus amiodarone reduced the risk of all-cause mortality and sudden death in ChHD patients with life-threatening VAs. Patients with LVEF < 40% derived significantly more survival benefit from ICD therapy. The majority of ICD-treated patients received appropriate therapies regardless of the LV systolic function.

Keywords Chagas’ disease • Implantable cardioverter-defibrillator • Amiodarone

Introduction Chagas’ disease is a major cause of morbidity and mortality in Latin America, and has become a worldwide problem due to growing immigration from endemic areas. Chagas’ heart disease (ChHD) manifests as heart failure, segmental wall motion abnormalities (aneurysms), thrombo-embolic events, conduction system disturbances, ventricular arrhythmias (VAs), and sudden death. Because of its frequent association with sudden death, sustained VAs in the setting of ChHD have become an emerging indication for implantable cardioverter-defibrillator (ICD) therapy; however, most of the data on which these recommendations are based were derived

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What’s new?
- Our observational study with the control group provides the most precise estimate available in the literature concerning the survival benefit of the implantable cardioverter-defibrillator (ICD) over amiodarone for secondary prevention of mortality in Chagas’ heart disease (ChHD).
- Our data show that ChHD patients with life-threatening ventricular arrhythmias can expect a 72% relative risk reduction in all-cause mortality and a 95% relative risk reduction in sudden death when treated with ICDs plus amiodarone, as compared with amiodarone therapy alone.
- Patients with left ventricular ejection fraction < 40% derived significantly more survival benefit from ICD therapy.
- The majority of ICD-treated patients received appropriate therapies regardless of the left ventricular systolic function.

from randomized controlled trials conducted in patients with other cardiac diseases, such as ischaemic and non-ischaemic cardiomyopathy (but not including ChHD),9 and whether ICD therapy would also decrease all-cause mortality in the setting of ChHD remains unproven.

All previously published studies reporting on the use of ICD in ChHD consisted of observational studies, which were limited by a lack of control groups, precluding the evaluation of the survival benefit of the ICD.10–13 Furthermore, the results of these studies have been somewhat inconsistent,10–13 and there is controversy over whether ICD therapy may have a deleterious impact on patients’ outcome as a result of repetitive appropriate ICD shocks.5,12,14 Therefore, the aim of this study was to compare the outcomes of ChHD patients with sustained VAs who were treated either with ICD implantation plus amiodarone or with amiodarone alone.

Methods

Patient population

We compared the outcomes of the two groups of ChHD patients with sustained VAs: (i) a contemporary group treated with ICDs in combination with amiodarone and consecutively enrolled at our Institution from March 2006 to December 2011, and (ii) an historical control group treated with amiodarone alone and consecutively enrolled at Medical School of Ribeirão Preto from May 1996 to July 2001, before ICD therapy was available at this tertiary reference centre. The clinical characteristics of the control group have been partially reported in a previous manuscript.15 Indications for ICD implantation followed the Brazilian Guidelines.7,8

Study protocol

In both the groups, before initiation of amiodarone and/or ICD implantation, patients underwent a baseline clinical assessment including medical history, 12-lead electrocardiography, two-dimensional echocardiography, electrophysiological study (EPS), and general laboratory examinations. 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 Ethics Committee of each Institution, and the informed consent for study participation was obtained from all patients.

Implantable cardioverter-defibrillator therapy

All ICD group 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., 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 and < 250 b.p.m., and slow VT as VA with rate < 188 b.p.m. Appropriate ICD therapy was defined as an ICD shock or ATP overdrive pacing 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 was defined as the occurrence of VT or VF, resulting in device intervention (shock and/or ATP) three or more times within a 24 h period. 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 or angiotensin receptor blockers and aldosterone were optimized in all patients. Amiodarone was administered to all control patients, and to ICD-treated patients, at discretion of the treating physician, to reduce the rate of ICD interventions. After a loading dose of amiodarone of 10 g during 3 weeks, patients received amiodarone at a dose of 300–400 mg daily thereafter.

Outcomes and definitions

The primary endpoint of the study was all-cause mortality, and the secondary endpoints were cause-specific mortality and appropriate ICD therapies (shocks and/or ATP). The cause of death was ascertained by reviewing the medical records, or by telephone contact with the patient’s family. Causes of death were categorized according to a modified Hinkle–Thaler classification into four groups: cardiac death, non-cardiac death, sudden death, and heart failure death.17

Statistical analysis

Continuous data are expressed as mean ± standard deviation, and categorical data are presented as absolute values and percentages. The baseline characteristics of the two groups were compared with the use of two-sample t-test or Mann–Whitney exact test for continuous variables, considering the normality of the data distribution, and χ² test or with the Fisher’s exact test for categorical variables, as appropriate. Survival and survival-free-events were estimated by the Kaplan–Meier method and compared by log rank. The Cox proportional hazards model was used to adjust for covariates and to estimate the hazard ratio (HR) for death with the corresponding 95% confidence interval (CI) in the ICD group compared with the control group. Analyses were performed using SAS software, version 9.1.3. For all tests, a P < 0.05 was considered statistically significant.
Results

Baseline characteristics

Table 1 compares the baseline characteristics of the ICD group with the control group. The ICD group (76 patients; 48 men; age, 57 ± 11 years; left ventricular ejection fraction (LVEF) 39 ± 12%) and the control group (28 patients; 18 men; age, 54 ± 10 years; LVEF, 41 ± 10%) had comparable baseline characteristics; however, patients in the ICD group were more frequently treated with beta-blockers (90 vs. 17%; \( P < 0.0001 \)). Also, carvedilol mean doses and metoprolol doses converted to equivalent doses of carvedilol were lower in the control group patients (9.3 vs. 21.2 ± 12.5 mg; \( P = 0.007 \)), as compared with ICD-treated patients. There was a trend towards a higher frequency of moderately or severely reduced LVEF in the ICD group (\( P = 0.08 \)).

All control group patients presented with symptomatic spontaneous sustained VT and none had an aborted cardiac arrest before inclusion in the study. In the ICD group, the indications for ICD implantation were aborted cardiac arrest in 3 patients (4%), symptomatic sustained VT in 56 (74%), and syncope with inducible sustained VT at the EPS in 17 (22%). A single-chamber ICD was implanted in 7 patients (9%), a dual-chamber ICD in 62 (82%), and 7 patients (9%) received ICDs with cardiac resynchronization therapy. Amiodarone was used in 90% of the ICD-treated patients. Two patients from the ICD group and two patients from the control group underwent successfully radiofrequency catheter ablation of VT.

All-cause mortality and sudden death

In the ICD group, six patients were lost to follow-up and two patients underwent heart transplantation and their data were censored at the time of last follow-up. During a mean follow-up of 33 ± 16 months for the ICD group and 35 ± 17 months for the control group (\( P = 0.22 \)), there were 10 deaths (4.7% per year) in the ICD group and 9 deaths (11% per year) in the control group, resulting in a decreased risk of all-cause mortality of 72% (HR, 0.28; 95% CI, 0.11–0.72; \( P = 0.007 \)) among the ICD-treated patients (Table 2). The cumulative rate of all-cause mortality at 1 and 3 years of follow-up were, respectively, 2 and 15% for the ICD group, and 15 and 33% for the control group (Figure 1A).

There was one sudden death in the ICD group, as compared with seven sudden deaths in the control group, resulting in a decreased risk of sudden death of 95% (HR, 0.05; 95% CI, 0.01–0.045; \( P = 0.006 \)) among the ICD-treated patients (Figure 1B). There were five deaths due to heart failure in the ICD group and two in the control group. Three deaths in the ICD group were attributable to non-cardiac causes: two due to pneumonia and one due to complications from an abdominal sepsis.

Predictors of all-cause mortality

As shown in Table 2, clinical characteristics associated with increased risk of all-cause mortality in univariate analysis was female gender (\( P = 0.04 \)) and LVEF < 40% (\( P = 0.006 \)). However, in multivariate
Variable LVEF dichotomized as group analysis using the Cox proportional hazards model with the Based on the results of the multivariate analysis, we performed a subgroup analysis, only LVEF < 40% remained statistically significant and was associated with more than six-fold increased risk of mortality (HR, 6.63; 95% CI, 2.12–20.71; *P = 0.001*). In contrast, ICD therapy was associated with a reduced risk of all-cause mortality of 72% (HR, 0.28; 95% CI, 0.11–0.72; *P = 0.007*).

**Subgroup analysis**

Based on the results of the multivariate analysis, we performed a subgroup analysis using the Cox proportional hazards model with the variable LVEF dichotomized as ≥40 or <40%.

In the subgroup of patients with LVEF ≥ 40%, all deaths were sudden. During follow-up, there was only one death among the 34 patients who received an ICD (1% per year) and three deaths among the 19 patients treated with amiodarone alone (5.7% per year), but there was no significant difference in mortality between the two groups (HR, 0.19; 95% CI, 0.02–1.88; *P = 0.15*) (Figure 2A). In contrast, in patients with LVEF < 40%, there were nine deaths among the 42 patients who received an ICD (7.7% per year) and six deaths among the 9 patients who were treated with amiodarone alone (24% per year), resulting in a decreased risk of all-cause mortality of 77% (HR, 0.23; 95% CI, 0.07–0.72; *P = 0.01*) in ICD-treated patients (Figure 2B).

**Implantable cardioverter-defibrillator therapy**

During follow-up, of the 72 patients with intracardiac electrograms available for analysis, 72% received appropriate ICD therapies (26% per year), with 58% of patients requiring at least one shock for terminating an episode of VA (21% per year). Sustained VT was observed in 49 patients (68%) and VF in 3 patients (4%). The mean cycle length of the VAs was 370 ± 54 ms (range 230–530 ms). Of the 1670 episodes of VAs detected by the ICD, slow VT accounted for 1545 episodes (92.5%), fast VT for 118 (7.1%), and 7 episodes (0.4%) were classified as VF. Eighty-five per cent of VAs were terminated by ATP, 8% by shock after failed ATP, 2.5% by primary shocks, and 4.5% terminated spontaneously after ICD detection but before therapy.

The mean period between ICD implantation and the first appropriate therapy was 282 days (range 1–1322 days). Survival-free of appropriate ICD therapy was 44, 20, and 10% after 1, 3, and 5 years of follow-up, respectively (Figure 3A). As shown in Figure 3B, survival-free of appropriate ICD therapy was not different between patients with LVEF ≥ 40% and LVEF < 40% (*P = 0.07*). Electrical storms
were observed in 25 patients (35%), and mortality rates were not different between patients with and without electrical storms (12 vs. 15%; \( P = 0.7 \)). Inappropriate shocks occurred in eight patients (11%), in seven due to atrial fibrillation and in one due to inappropriate ICD sensing.

There was a trend towards a higher mortality rate in patients with single- or dual-chamber ICDs who had cumulative RV pacing \( \geq 50\% \).

At the 4-year time point, the mortality rate was 43% in patients with cumulative RV pacing \( > 50\% \), as compared with 13% in those with cumulative RV pacing \( \leq 50\% \) (\( P = 0.06 \)).

**Discussion**

The present observational study provides novel insights for the secondary prevention of mortality in the setting of ChHD. Four findings of the present study are of particular importance. First, we report the
superiority of ICD therapy plus amiodarone in reducing all-cause mortality in ChHD patients with sustained VAs, as compared with amiodarone therapy alone. Secondly, the benefit from ICD therapy resulted from the significant decrease in the risk of sudden death. Thirdly, patients with LVEF < 40% derived the most survival benefit from ICD. Finally, ChHD patients presenting with sustained VAs are at high risk for recurrence of arrhythmias, irrespective of the LV systolic function.

Previous observational studies reporting on the use of ICD in ChHD patients were limited by a lack of control groups and have described divergent results on the survival benefit of ICD.

Muratore et al.,

Martelli et al.,

reported an annual mortality of 6.7% among the 89 ChHD patients who received an ICD mostly for secondary prevention. Martelli et al.,

observed an annual mortality of 7.1% in a case series of 116 ChHD patients who received ICDs for secondary prevention. These results are in agreement with our present data, in which an annual mortality rate of 4.7% was observed in ICD-treated patients. In contrast, Cardinalli-Neto et al.,

reported an unprecedented high mortality rate (16.4% per year) among 90 ChHD patients who received ICDs for secondary prevention. Also, in a more recent recent study, Barbosa et al.,

presented data from 135 patients who received an ICD for secondary prevention, including 65 patients with ChHD. In the latter group, eight patients died (12.3%) during a median follow-up of 9 months.

The reasons for the discrepancies in the mortality rates of ICD-treated patients across these different studies remain conjectural. One possible explanation may be related to the differences in the characteristics of the study populations. Accordingly, Cardinalli-Neto et al.,

and Barbosa et al.,

reported VF episodes during follow-up in 21 and 13% of their study populations, respectively, as opposed to only 4% in our investigation. These differences may be explained by the observation that in both series 91% of the patients has presented an aborted cardiac arrest before enrolment in the study, as opposed to only 4% in our investigation. More importantly, the observation from Cardinalli-Neto’s series that the number of ICD shocks during the first month was a major predictor of mortality raises the question whether ICD therapies, and shocks in particular, led directly to death or were merely a marker for worse outcomes in their study population. In this respect, it should be pointed out that outcomes after ICD implantation may be influenced by occurrence of shocks and also by the arrhythmia subtype treated by ICD shocks. Moreover, it has been reported that VAs terminated by ICD shocks had a higher mortality risk, whereas ATP-terminated VAs were associated with a lower risk. Of note, in our study, the number of ICD therapies and the occurrence of electrical storms were not associated with increased mortality risk, as has been reported in a previous observational study of ICD therapy in ChHD. These findings may be explained by the observation that in our series 85% of the VAs was terminated by ATP and only 10.5% by ICD shocks, as opposed to Cardinalli-Neto’s series, in which 30% of the VAs was terminated by ICD shocks.

Our data show that among control patients treated with amiodarone alone, the rate of fatal events, mainly due to VAs, was highest in the early follow-up period and gradually decreased thereafter. In contrast, in ICD-treated patients, despite a substantial burden of VAs, the rate of fatal events was lower in the early follow-up period, indicating that the arrhythmic deaths averted by the ICD were not offset by a premature increase in the rate of death from non-arrhythmic causes. However, in ICD-treated patients, mortality due to heart failure increased in the late follow-up period, as graphically demonstrated in Figure 1A. This observation, which deserves further study, may be explained in part by the predominance of moderate or severe LV dysfunction among the ICD patients, as compared with the control patients, in which there were more patients with less severe LV dysfunction, but may also be explained by the detrimental effects of RV pacing, as seen in our ICD population and already reported in the other series.

There are no randomized trials comparing amiodarone and ICD for secondary prevention of mortality in patients with ChHD, and the likelihood of such a trial is currently very low, because most people may consider unethical to compare the outcomes of ICD therapy vs. amiodarone in ChHD patients with life-threatening VAs. In this respect, our observational study with the control group provides the most precise estimate available in the literature concerning the survival benefit of the ICD over amiodarone for treatment of ChHD patients with sustained VAs. Our data show that these patients can expect a 72% relative risk reduction in all-cause mortality and a 95% relative risk reduction in sudden death when treated with ICDs in combination with amiodarone. The 3-year mortality rate in our control group (33%) is comparable with those from secondary prevention trials including patients with ischaemic and non-ischaemic cardiomyopathy. More importantly, in our study, the mortality rate at 3 years was reduced to 15% after ICD implantation, resulting in an absolute risk reduction of 18%. Thus, an ICD would have to be implanted in 5.5 patients to save one life at 3 years. These results are superior to those reported by the secondary prevention trials, in which an 11.3% absolute risk reduction was afforded by AVID [number needed to treat (NNT = 9)], a 7.7% by CASH (NNT = 13), and a 3.7% by CIDS (NNT = 27) at the 3-year time period, and highlights the potential benefit of ICD therapy over amiodarone for secondary prevention of mortality in ChHD patients.

The incidence of appropriate ICD therapies was high in our study, despite concomitant therapy with amiodarone. Our data show that 72% of patients treated with an ICD received appropriate therapies (26% per year), with 58% of patients requiring a shock (21% per year) for terminating VAs. This rate is comparable with the rate of appropriate therapies reported in previous studies of ICD therapy in ChHD, and reflects one of the main features of this cardiomyopathy, that is, its striking arrhythmogenic nature, resulting from the ubiquitous presence of ventricular scars leading to entrant tachyarrhythmias and also possibly related to abnormalities of the cardiac autonomic control. In addition, our data show that patients with relatively preserved LVEF (≥40%) experienced rates of appropriate ICD interventions similar to those seen in patients with moderate-to-severe LVEF (<40%), which suggests that patients with LVEF ≥40% are also at risk for sudden death and potentially may also benefit from ICD implantation. Importantly, despite the high occurrence of appropriate ICD therapies in our study population, our data did not confirm the concern that recurrent ICD therapies would increase the risk of mortality in ChHD patients.

In this respect, appropriate ICD therapies were managed by modification of the doses of amiodarone and/or beta-blockers. ICDs for treatment of sustained VAs in patients with ChHD
reprogramming, or catheter ablation of sustained VAs. In the present study, substrate catheter ablation of sustained VT was used in only two ICD-treated patients; however, we recognize that a more widespread use of this adjunctive therapy should be attempted in these patients for reducing the substantial burden of VAs, even though Chagas’ disease substrates often involve complex VT circuits that are partly or predominantly epicardial, thereby necessitating both endocardial and pericardial mapping and ablation with a three-dimensional mapping system.

Although our study was not powered to evaluate differences within subgroups, we found important interactions between LVEF and ICD benefit. Patients with relatively preserved LVEF (≥40%) obtained a survival benefit from ICD, whereas those with moderate-to-severe LVEF (<40%) obtained a significant benefit from the ICD. These findings are consistent with the results of a meta-analysis from secondary prevention trials, in which there was a survival benefit from ICD only in patients with LVEF < 35%.

Study limitations
Some limitations of the present study must be acknowledged. First, this is an observational, non-randomized study, and is subject to all the inherent limitations of such type of analysis. Our study design does not allow us to draw definitive conclusions regarding the impact of ICD therapy on secondary prevention of mortality in ChHD. Secondly, there was a lower use of beta-blockers in the control group, which can be explained by the risk of exacerbation of bradyarrhythmias with the concomitant use of amiodarone and beta-blockers in CHD patients without an implanted cardiac pacemaker. Thirdly, the use of amiodarone in almost all ICD-treated patients may have changed their natural history, precluding the quantification of the survival benefit of the ICD implantation itself. Finally, the small sample size and event rates limit our ability to perform subgroup analysis pertaining to specific LVEF values.

Conclusions
Our results show that ICD therapy plus amiodarone significantly reduced the risk of all-cause mortality and sudden death in ChHD patients with life-threatening VAs, as compared with amiodarone-only therapy. Patients with LVEF < 40% derived significantly more survival benefit from ICD therapy than patients with LVEF ≥ 40%. Despite concomitant amiodarone therapy, most ICD-treated patients received appropriate ICD therapies regardless of the LV systolic function. The findings of the present analysis may be considered hypothesis generating and further studies are warranted to assess the impact of ICD therapy in this understudied patient population.

Conflict of interest: none declared.

References