Long-Term Follow-up of Patients with Indication for a Implantable Defibrillator for Primary Prevention of Death

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Summary

Background: Recent MADIT II and SCD-HeFT trials have led to an expansion of indications for use of prophylactic Implantable Cardioverter Defibrillator (ICD) in patients with severe left-ventricular impairment. This therapy has not been fully adopted in our health care system, mainly due to its high cost.

Objective: To assess total mortality of SCD-HeFT-like patients from our daily practice who are under stable, optimal medical treatment and who have not received an ICD; and to compare it to that of the placebo arm of the SCD-HeFT Trial.

Methods: SCD-HeFT-like patients identified from office medical records were included in our study. Total mortality was assessed by telephone contact. Statistical analysis was performed by Student's t-Test, Mann-Whitney Test or χ^2 test, depending on the type of variable. Cumulative mortality rates were calculated according to the Kaplan-Meier method.

Results: Our study comprised 102 patients (seventy-four of which were men) with a median age of 64 years, and an overall median ejection fraction of 25%. We found no differences between our patients and SCD-HeFT patients across these 3 variables. Over a 19.6-month follow-up period, 21 patients died (20.6%) *vs* 28.8% of the SCD-HeFT patients. This difference was not statistically significant (p = 0.08).

Conclusion: SCD-HeFT-like patients from our practice had no difference in mortality rate than patients enrolled in the placebo arm of the SCD-HeFT trial. These results suggest that the SCD-HeFT population is representative of our patients. (Arq Bras Cardiol 2008; 90(5): 311-315)

Key words: Heart failure, congestive/mortality; defibrillators, implantable; death, sudden.

Introduction

Patients with congestive heart failure (CHF) have an increased risk of all-cause mortality and can die suddenly from arrhythmia despite the use of proven useful medical therapies, such as beta-blockers, angiotensin converting enzyme inhibitors (ACEI) and spironolactone[1-11]. Use of amiodarone has also been evaluated in these patients with inconclusive findings[12,13]. Although this drug reduced incidence of all-cause mortality and sudden cardiac death in the GESICA trial, beta-blockers were not used as widely as they are nowadays in this kind of patient[14]. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) tested the additional effect of amiodarone and an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden death among patients with New York Heart Association (NYHA) class II-III CHF and left ventricular ejection fraction (LVEF) of 35% or less[15]. Outcome in the amiodarone group was similar to that of the placebo group, while ICD implantation was associated with a significant (23%) reduction in all-cause mortality after a 5-year follow-up period. In agreement with these findings, MADIT-II Trial showed reduced mortality following ICD implantation in patients with previous myocardial infarction and reduced LVEF[16]. These concordant results have led to an expansion of indications for prophylactic ICD in patients with severe LVEF impairment[17].

However, implementation of this therapy would represent a significant economic impact. This is possibly the main reason hindering broader adoption of ICD therapy for primary prevention of sudden death in CHF patients in our health care system.

In order to test whether SCD-HeFT results can be extrapolated to our population, we set out to assess the outcomes of SCD-HeFT-like patients from our daily practice, and to compare them to those of the placebo arm of the SCD-HeFT Trial.

Methods

Patients from the CHF section of the Cardiovascular Service of our hospital, who fulfilled SCD-HeFT inclusion criteria, were included in the present study. Patients were at least 18 years old and had NYHA class II-III chronic, stable CHF due to ischemic or nonischemic causes and a LVEF of no more than 35 percent. Patients who had already received an ICD or had valvular heart disease were excluded.

Baseline characteristics and clinical data from our patients

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were obtained from office medical records. Total mortality was assessed by telephone contact.

This study was approved by the Research Ethics Committee of our institution, according to the Declaration of Helsinki.

Statistical analysis

Continuous variables with parametric distribution were expressed as mean ± standard deviation, while nonparametric variables were expressed as median and interquartile range (IR). For statistical analysis we used the Student's *t*-test for continuous variables with parametric distribution, Mann-Whitney test for those with nonparametric distribution and chi-square test for categorical data. Cumulative mortality rates were calculated according to the Kaplan-Meier method and Cox-Mantel test.

Results

Of 116 patients who fulfilled inclusion criteria, 102 (87.9%) were successfully contacted by telephone and comprised our study group. Mean age was 63.5 ± 10.9 years and 72.5% were male. Etiology of dilated cardiomyopathy was ischemic in 65 patients (63.7%) and nonischemic in the remaining 37 (36.3%). Sixty-nine patients (67%) were in NYHA class II and median LVEF was 25% (IR 21 to 30). With regard to standard treatment for CHF, 89.7% of patients were receiving ACEI, 69.2% beta-blockers, 43.2% spironolactone, 35.3% digoxin and 45.9% amiodarone.

During a median follow-up of 19.6 months (range 3.3 to 74.3) 21 patients died (20.6%). Mortality rate was 23.1% among ischemic patients (15 p) and 16.2% in the nonischemic group (6 p); Cox-Mantel test p = 0.52. (Figure 1).

Comparison with SCD-HeFT patients

Baseline characteristics of both groups are summarized in Table 1. Of patients enrolled in the placebo arm of SCD-HeFT trial (n = 847), 655 (77.3%) were male *vs* 72.5% of patients included in this study; p = 0.27. Median age (60, IR 51 to 68) and LVEF (25%, IR 20 to 30) were similar to that of our patients. Seventy percent of SCD-HeFT patients were in NYHA class II *vs* 67% in our study. In both groups ischemic heart disease was the most frequent origin of dilated cardiomyopathy (53.5% in SCD-HeFT *vs* 63.7% in our population; OR 1.52; p = 0.05). Use of ACEI and beta-blockers was similar in both, whereas digoxin was more commonly used in SCD-HeFT patients.

Mortality rate of patients enrolled in the placebo arm of SCD-HeFT trial was 28.8% after follow-up period (median 45.5 months) *vs* 20.6% of patients included in the present study. This difference was not statistically significant: OR 0.64 (CI 95% 0.38-1.05); p = 0.08. Kaplan-Meier estimates of actuarial death from any cause showed similar mortality curves for both populations and an annual mortality rate of 8.25% for our patients *vs* 7.25% for SCD-HeFT patients (p = NS). (Figure 2)

Discussion

Benefit from ICD therapy for secondary prevention of sudden death in patients with severe LVEF impairment has been shown in several trials[18-20]. Early studies showing that ICD improves outcome for primary prevention of sudden death, enrolled patients with coronary artery disease and left ventricular dysfunction who had spontaneous unsustained ventricular tachycardia (VT) and inducible sustained VT at electrophysiological study (EPS)[21,22].

However, ventricular arrhythmia non-inducibility does not necessarily identify a subgroup of patients at lower risk of sudden cardiac death. This fact has been reported both in survivors of cardiac arrest[23-25] and in a recent MADIT-II substudy[26]. Moreover, MUSTT investigators have shown that EP study is of limited value when LVEF is less than 30%[27]. These

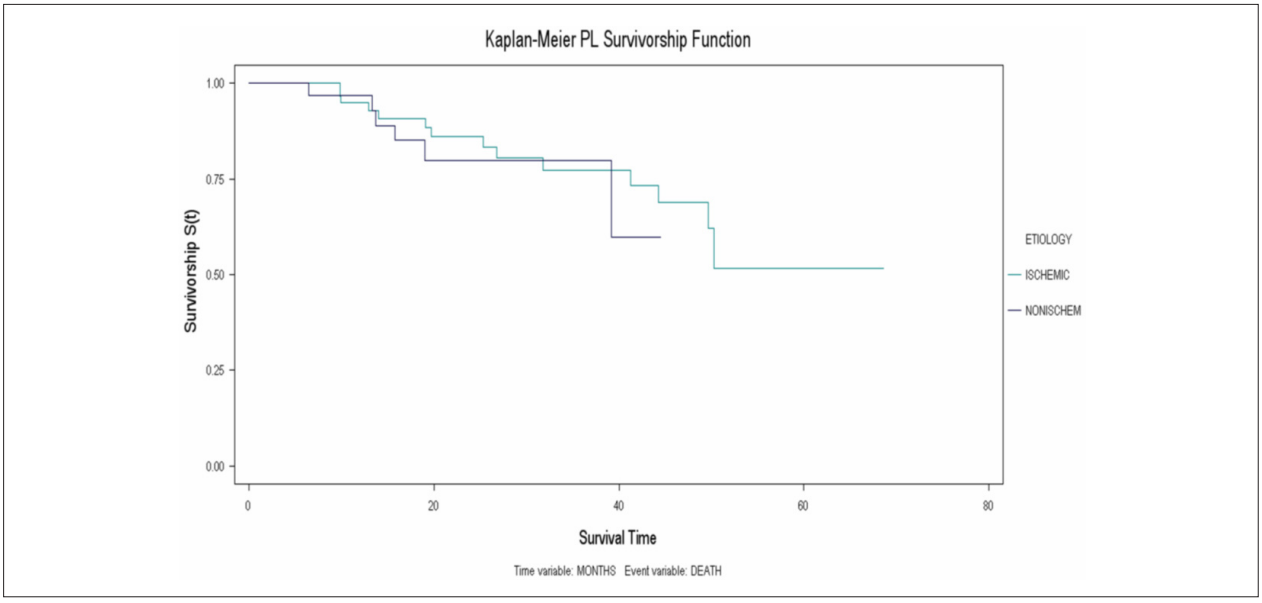

Figure 1 - Kaplan-Meier estimates of the Probability of Survival in our population according to the etiology of CHF.

findings confirm that negative predictive value of programmed ventricular stimulation is low in these patients.

MADIT-II trial enrolled patients with previous myocardial infarction and LVEF < 30%[16]. Despite ventricular arrhythmias or CHF symptoms not being inclusion criteria, 60% of patients were in NYHA class II-III. In this study, ICD therapy significantly reduced mortality by 31% (p = 0.016). MADIT-II was the first trial to demonstrate benefit from ICD therapy for primary prevention of sudden death in non-selected patients with ischemic dilated cardiomyopathy.

The AMIOVIRT trial examined the role of ICD for primary prevention in patients with non-ischemic severe left ventricular dysfunction and nonsustained VT[28]. Compared to amiodarone, there was no difference in mortality, probably due to the small size of the patient sample.

The DEFINITE study enrolled patients with similar characteristics and showed a 35% reduction in mortality with ICD therapy, but this difference did not reach statistical significance (p = 0.08)[29]. Upon more detailed analysis, however, a large reduction in arrhythmic death (RRR 80%; p = 0.006) was observed, whereas there were no differences in death from other causes.

The SCD-HeFT trial included patients with class II-III CHF and LVEF < 35% due to ischemic or non-ischemic causes[15]. Patients were randomized to ICD therapy, amiodarone or placebo in 1:1:1 fashion. The ICD arm was conservatively designed, implanting shock-only, single-lead devices. Because of the potential for antibradychardia pacing to worsen CHF, it was initiated only if the intrinsic rate decreased to less than 34 beats per minute. ICD therapy significantly reduced mortality by 23% compared to placebo, with 14 devices needed to implant to save one life. Although the benefit was observed both in ischemic and non-ischemic CHF, it was restricted to class II CHF patients. Amiodarone had no effect on survival.

In the present study we compared the outcomes of CHF patients from our practice to those of the placebo arm of the SCD-HeFT trial who did not receive amiodarone. Although 45% of our patients received this antiarrhythmic drug, mortality rate was similar in the amiodarone and placebo groups of the SCD-HeFT trial. Therefore, it appears safe to assume that this difference in treatment does not invalidate the comparison at the center of our study. Even though the median follow-up period was different (45.5 months in SCD-HeFT *vs* 19.6 months in our patients), the maximum follow-up was similar in both groups (72.6 *vs* 74.3).

In regard to the remaining medical therapy, there was a larger use of digoxin in SCD-HeFT patients (probably due to a greater proportion of nonischemic CHF), with no different use of other medications in both groups. Although prescription of ACEI and beta-blockers was very similar to that of SCD-HeFT patients, it was clearly greater than that derived from epidemiological data. Indeed, the EuroHeart Failure Survey showed an underuse of recommended medications both in terms of proportion of patients receiving them and the doses employed. This applies particularly to beta-blockers, which were prescribed in only 37% of patients included in that

Table 1 - Baseline characteristics of our patients and of patients enrolled in the placebo group of the SCD-HeFT trial

Variable	Our patients	SCD-HeFT patients
n	102	847
Age (years) *	64 (57 to 71)	60 (51 to 68)
Male sex	72.5%	77%
Ischemic etiology	63.7%	53.5% †
Non-ischemic etiology	36.3%	46.5% †
LVEF *	25 (21 to 30)	25 (20 to 30)
NYHA class II / III	67 / 33 %	70 / 30 %
Rx with ACEI	89.7%	84.8%
Rx with Beta-blockers	69.2%	68.6%
Rx with Digoxin	35.3%	69.5% ‡

*LVEF - Left Ventricular Ejection Fraction; NYHA - New York Heart Association; Rx - Treatment; ACEI: Angiotensin Converting Enzyme Inhibitors. * Variables expressed as median and interquartile range. † p = 0.05. ‡ p < 0.001.*

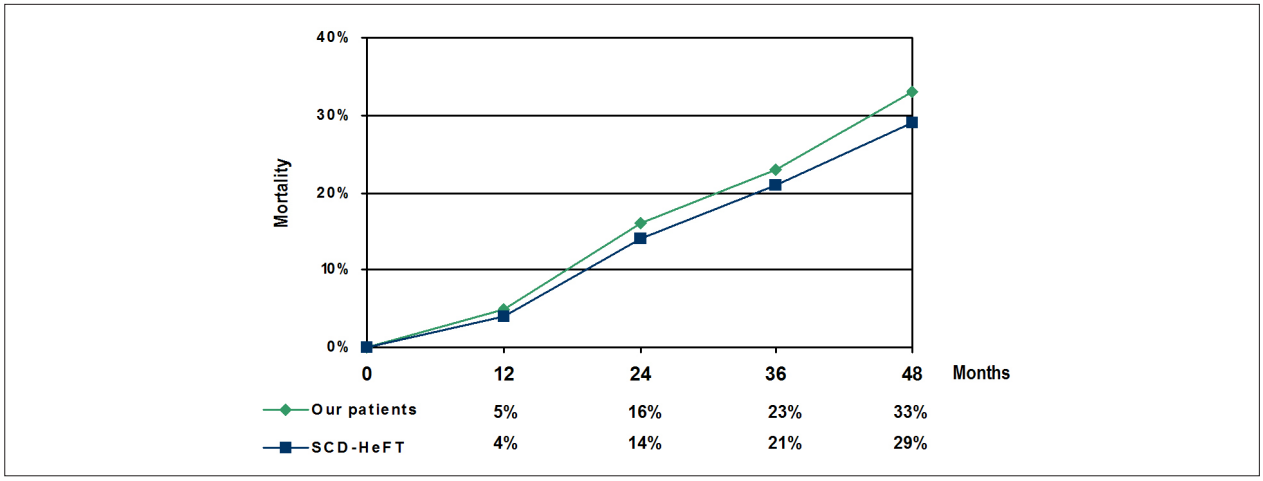

***Figure 2 -** Kaplan-Meier estimates of death from any cause for our patients and for patients enrolled in the placebo arm of the SCD-HeFT trial.*

survey[30]. This difference in treatment reinforces the need for development of specialized areas of health care, such as a Heart Failure Program.

Chagas disease was found to be the etiology of cardiomyopathy in 8/37 patients (21%) of the nonischemic group and it would have been interesting to analyze this population. Owing to the small size of this sample (8% of the whole study group) we considered that those results may not be reliable.

These results show that CHF patients we usually treat have similar characteristics to those in the SCD-HeFT trial. They further argue against the notion that patients included in large clinical trials are not representative of our domestic population, and suggest that our patients might also benefit from ICD therapy. However, it may not be appropriate to extend these results to the general population with CHF, considering that ACEI and beta-blockers remain under-prescribed, as mentioned above. Moreover, MADIT-II authors have suggested that benefits from ICD therapy may be lower in patients who do not receive beta-blockers or who receive suboptimal doses of these drugs[31]. Likewise, it would be interesting to know the outcomes of MADIT-II-like patients who had not been selected according to the presence of CHF or ventricular arrhythmias.

According to study design, clinical characteristics of our patients were collected retrospectively, and the end point (death from any cause) was assessed by telephone contact. Although 14 patients lacking a telephone line could not be followed, their clinical variables did not differ from those of the 102 patients analyzed. Follow-up was completed in 88% of patients, allowing an appropriate data analysis.

Economic impact is probably the main reason precluding full adoption of ICD therapy in class II-III CHF patients in our health care system. Because these patients do not display ventricular arrhythmias and do not require antibradychardia pacing, SCD-HeFT authors proposed to conduct ICD implantation on an outpatient basis, without defibrillation testing. Other authors have identified more than 5% of patients undergoing ICD implant for primary prevention with an inadequate safety margin, indicating that defibrillation threshold testing remains an important part of ICD implantation and should not be omitted[32]. Additionally, under our current health care system the device represents the single highest cost component of the procedure. Hence, outpatient insertion can be potentially risky with negligible benefits in terms of costs. In a cost-effectiveness substudy, SCD-HeFT authors reported that ICD therapy is economically acceptable for the North American Health Care System and suggested that implantation of ICD in class III CHF patients would not be cost-effective[33]. Unfortunately there are no published data concerning cost-effectiveness analysis in our health care system. Perhaps in the future, as the ICD becomes more affordable, indication of this device for primary prevention of sudden death will not elicit the same level of debate that it currently generates in regard to treatment of NYHA class II-III CHF patients.

Conclusion

SCD-HeFT-like patients from our daily practice had no different mortality rate than that of patients enrolled in the placebo arm of the SCD-HeFT trial. These results may indicate that SCD-HeFT population is representative of our patients.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

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