Predictors of Mortality and Mode of Death in Patients Treated with an Implantable Cardioverter-Defibrillator: ICD-LABOR: a Latin American Regional Study

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ON BEHALF OF THE ICD-LABOR INVESTIGATORS

Summary

The widespread use of cardioverter-defibrillators (ICDs) for malignant ventricular therapy has rapidly increased over the last decade. Many patients in different regions of the world now have access to this therapy. Nevertheless, the various clinical features and diseases of these populations render the evaluation of clinical results difficult. The Latin American Biotronik Ongoing Registry (ICD-LABOR) summarizes the experience of 665 patients with an antecedent of malignant ventricular arrhythmias or aborted sudden death treated with an implantable ICD. The follow-up period was 25 ± 23 months, and all-cause mortality was 17% ± 9.5% (113 deaths). Ejection fraction (EF), NYHA functional class, and gender were significant predictors of risk of cardiac death. In our study, only males had a higher risk of death with increasing age. The mode of death was related to the abovementioned predictors of risk of death: low EF suggests a higher probability of non-sudden cardiac death, while high EF reflects the opposite. Conversely, in the cardiomyopathy groups (Chagas disease and dilated cardiomyopathy) sudden cardiac death occured significantly more frequently than non-sudden cardiac death, which could explain why the ejection fraction could not identify those patients at high risk of death within the cardiomyopathy groups.

Key Words

Implantable cardioverter-defibrillator (ICD), mode of death

Introduction

Indications for electrical treatment of lethal ventricular arrhythmias have increased over the last 10 years. ICD therapy has been established as an effective method of preventing sudden death compared to drug treatment [1-4]. For a careful evaluation of the benefits of ICD therapy it is necessary perform a reliable analysis as to the exact cause of death. We explored the mode of outcome in 113 deaths reported in our Latin American registry.

Materials and Methods

The ICD-LABOR (Latin American Biotronik Ongoing Registry) is a prospective, non-randomized study. For all patients, the ICD indication was considered a secondary prevention according to the "Consensus Statement on Indications, Guidelines for Use and Recommendations for Follow-up of Implantable Cardioverter Defibrillators" [5]. The database was completely registered through the Internet and a personal password was assigned to each group of investigators, so that they could freely manage their own information center. The patients´ follow-up and new implantations were able to be registered instantaneously via the Internet. For this presentation, data collected from June 1994 to December 2003 was considered. During this period 134 investigators participated in the registry and 665 patients were included from

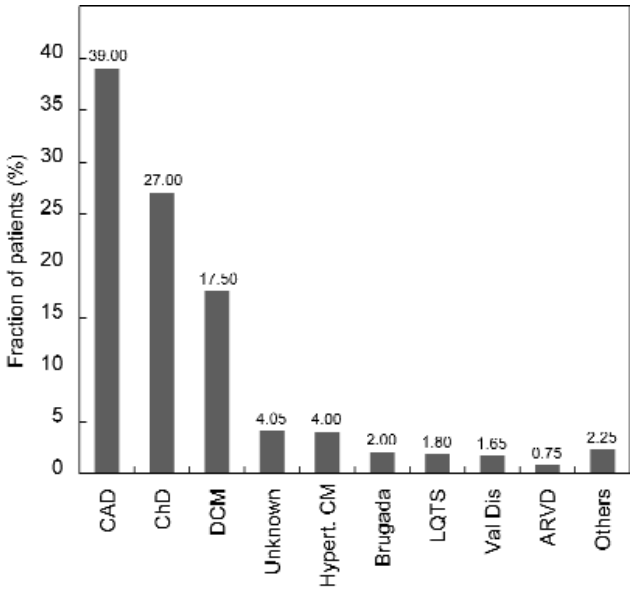

Figure 1. Pathology distribution CAD = coronary artery disease, ChD = Chagas disease, DCM = dilated cardiomyopathy, Hypert. CM= hypertrophic cardiomyopathy, Brugada = Brugada Syndrome, LQTS= long QT syndrome, Val dis = valvular disease, ARVD = arrhythmogenic right ventricular dysplasia.

93 different medical centers within seven different countries (Argentina, Brazil, Uruguay, Chile, Mexico, Cuba, and Venezuela). In total, 113 deaths were reported and classified as follows:

- Cardiac death
- Non-cardiac death
- Unknown

Cardiac deaths were divided as: sudden death (all cardiac deaths 1 hour after onset of acute symptoms) and non-sudden death (all cardiac deaths not classified as sudden death). In addition, sudden cardiac death was sub-classified as: witnessed sudden death or unwitnessed sudden death (if the patient had been free of symptoms 6 hours before being found dead, or if death occurred while the patient was sleeping). Memory Holter devices were useful when the actual time of death and the reporting of fatal ventricular events coincided.

Statistical analysis of metric data was performed using the two-sided unpaired t-test, and analysis of dichotomous proportions was done using Fisher's test. A p-value < 0.05 was considered statistically significant.

Cardiac death	Sudden cardiac death	Witnessed	21 patients
		Unwitnessed	11 patients
	Non-sudden cardiac death		41 patients
Non-cardiac death			31 patients
Deaths not classifiable			8 patients

Table 1. Classification of mode of death.

Sepsis	10	(32.3%)
Pneumonia	7	(22.7%)
Stroke	4	(12.9%)
Cancer	4	(12.9%)
Systemic disease	2	(6.4%)
Subdural hematoma	1	(3.2%)
Mesenteric infarction	1	(3.2%)
Acute renal insuffuciency	1	(3.2%)
Total	31	(100.0%)

Table 2. Deaths due to non-cardiac causes.

	NYHA I	NYHA II	NYHA III	NYHA IV
Mortality	2.4%	7.2%	16.4%	40.0%

Table 3. Mortality according to NYHA functional class. Fisher's test 2x4 contingency table yields $p < 0.0005$.

Results

Distribution of the underlying cardiac diseases is summarized in Figure 1. The three main underlying cardiac diseases (83.5%) were coronary artery disease (CAD), Chagas disease (ChD), and dilated cardiomyopathy (DCM). The remaining patients were included in a miscellaneous group (MISC). Of the whole population, 499 patients were male (75%). The average age at the time of implantation was 59 ± 13 years (range 6 to 88 years), the follow-up time was 25 ± 23 months, and the global mortality was 17.0% ± 9.5% (113 deaths).

The relationship between mortality and the underlying cardiac disease was as follows: 260 CAD with 50 deaths (19.2%), 179 ChD with 34 deaths (18.9%), and 116 DCM with 18 deaths (15.5%). In the miscellaneous group (110 patients) 11 deaths were reported (10%). As seen in Table 1, there were 74 cardiac

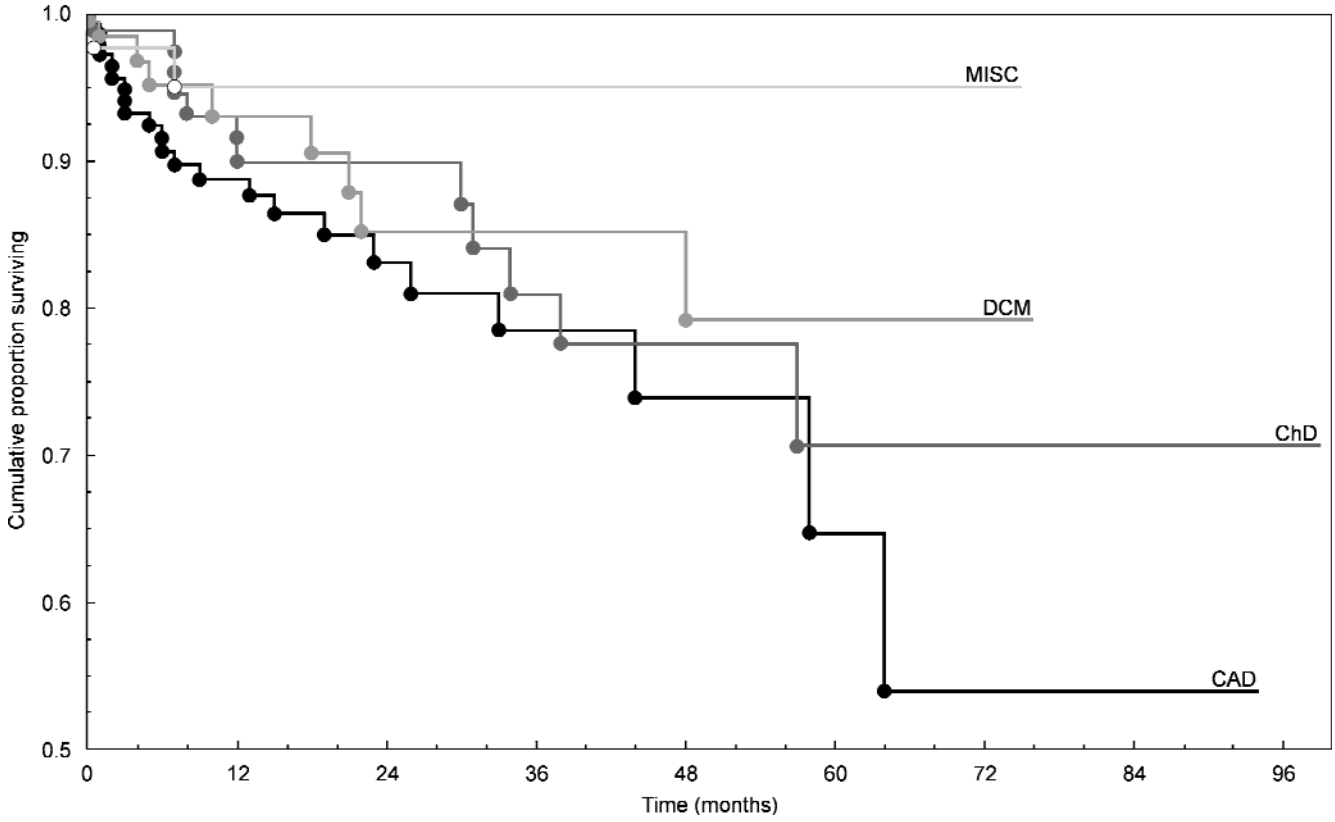

Figure 2. Kaplan-Meier analysis of the probability of survival for cardiac diseases. Dots = deaths, CAD = coronary artery disease, ChD = Chagas disease DCM = dilated cardiomyopathy, MISC = miscellaneous (all others).

deaths; 41 (55.4%) were non-sudden cardiac deaths and 33 (44.6%) were sudden cardiac deaths (witnessed 22, unwitnessed 11). Table 2 shows non-cardiac causes of death. The most common cause of non-cardiac death was infection (sepsis and pneumonia in 17 of 31 cases). In the remaining eight patients the cause of death could not be determined. Post-mortem analysis of the memory Holter program could be retrieved in 40 deaths (35%). In four situations (3.5%) electromechanical dissociation, preceded by episodes of ventricular tachycardia or fibrillation, were documented.

Fatal Ventricular Arrhythmias

Four deaths under special circumstances were reported: one case after an ablation procedure where the lead was damaged, two cases with lead dislodgement, and one case where the antitachycardia pacing and ventricular shock programs were disabled.

Cumulative Proportion Surviving

Over a mean follow-up period of 25 ± 23 months, a similar outcome was observed in the CAD, ChD, and DCM groups (Figure 2). In the CAD group, non-sudden cardiac death was found significantly more frequently than in the ChD or DCM groups ($p < 0.038$). In the miscellaneous group, mortality due to cardiac causes was significantly lower than in the three main underlying cardiac disease groups (Fisher's test, p-value < 0.030).

Ejection Fraction (EF)

Among cardiac deaths, the EF in the sudden death group was 32.9% ± 10.8%, while in the non-sudden death group the EF was 27.4% ± 9.6% ($p < 0.029$). When the follow-up period and left ventricular function were analyzed in the CAD group, the EF was statistically lower in patients who died during the first year after implantation (early deaths) EF: 25.0% ± 8.1%, compared to those who died after the first year (late deaths) EF: 35.5% ± 13.9%, ($p < 0.0079$). In the cardiomyopathy groups (ChD, DCM) the EF could not discriminate between early and late deaths.

Functional Class
During the follow-up period and according to NYHA functional class, patients belonging to classes 1 – 2 had a 5% mortality rate, while in classes 3 – 4 the mortality rate was 18% ($p < 0.0005$). No relationship could be found between the mode of outcome (sudden or non-sudden) and the functional class (Table 3).

Gender
For the entire male group (498), 63 deaths due to cardiac causes were reported, while among the 166 women, only 10 deaths due to cardiac causes were reported (Fisher´s test p-value < 0.015). Sudden deaths occurred exclusively in the cardiomyopathy groups (ChD, DCM), yet due to the small number, they could not be confirmed by statistical tests.

Age
In the female group, the relationship between living and deceased patients was 57.2 ± 14.4 years and 62.3 ± 13 years respectively (not significant). Conversely, for the male group, the relationship was 59.8 ± 13.9 years and 63.0 ± 10.3 years ($p < 0.032$). No correlation could be found between mode of outcome and patient's age.

Discussion

Causes of death have been researched since the very beginning of medical history. Determination of cause of death is extremely useful, particularly in ICD recipients in which the prevention of arrhythmic death is the objective of the device. Different death classifications have been developed and utilized over the last 20 years [6,7]. A NASPE Policy Statement, Standardized Reporting of ICD Patient Outcome, [8] was published in 1993. This paper attempts to apply this classification to our population.

Fatal Events: Reliability of the Classification
Diagnoses of non-cardiac deaths were obtained from many clinics and complementary studies, giving us reliable confirmation of the events leading up to the fatal episode. Most non-sudden cardiac deaths occurred in the hospital and the mode of outcome could be firmly established. The classification of some deaths as "sudden deaths" was the most difficult issue. A witnessed abrupt death, without prior collapse of circulation, was classified as sudden cardiac death without any doubt; unwitnessed deaths were classified as sudden deaths only if the subject was proven to have been free of symptoms 6 hours prior to his/her death or if he/she had died in his/her sleep. At times, the ICD's Holter memory could help determine the cause of death.

Predictors of Mortality
Some trials developed under the concept of "evidence-based" medicine have established indications for ICD implantation [9,10] and note that ejection fraction, functional class, age, and gender are predictors of risk of cardiac death. A registry such as ICD-LABOR applies the guidelines and recommendations that have emerged from these trials. As a point of comparison, our daily clinical practice constitutes "experience-based" medicine, which fortunately includes many parallels to "evidence-based medicine." With regards to EF and mortality, we found similar results with previously published studies. Ejection fraction and global cardiac mortality were as follows:

- EF < 20% mortality = 25.0%
- EF 20 – 29% mortality = 17.5%
- EF 30 – 39% mortality = 14.5%
- EF > 39% mortality = 4.2%

Once again, when we compared cardiac risk of death (an NYHA functional class), the results were similar to previously published ones. Among patients in classes 1 – 2, the crude cardiac mortality was 5.3%, while for patients in classes 3 – 4, it was 22%. With regards to age and mortality, our results deviate slightly from published statistics. We found no statistical difference between living and deceased subjects in the female group, but a significant difference was found between living and deceased subjects in the male group [11].
Finally, the differences in terms of cardiac mortality among the main groups and between both sexes were significant, as some previous publications have noted [12,13]. Men with antecedents of sudden cardiac death or malignant ventricular tachycardia had a worse prognosis than women (adjusted for age and EF).
The miscellaneous group must be considered as a completely different population, because the patients were significantly younger than the CAD, ChD, and DCM patients (46.2 ± 17.5 years vs. 61.9 ± 11.1 years, $p < 0.0001$). The average EF was better as well, documenting a statistical significance (53.1% ± 15.0% vs.

34.2% ± 11.0%, $p < 0.0001$). These differences were also expressed in global mortality (8.5% vs. 18.4%, $p < 0.027$) and global cardiac mortality (4.8% vs. 12.4%, $p < 0.041$).

Possibility of Predicting the Mode of Outcome in Patients Treated with ICDs

Although predictors of risk of death have been studied extensively, the mode of death attributed to those risk factors has received considerably less attention. In this paper, we would like to highlight several of our results [14,15]. Low EF suggests higher probabilities of non-sudden cardiac death, while high EF reflects the opposite. Our findings also show that underlying heart disease plays a role in the mode of death. In CAD, the most common mode was non-sudden cardiac death, and it was related to a low EF. For the cardiomyopathy groups (ChD, DCM) sudden cardiac death was found more frequently than non-sudden cardiac death, which could explain why the EF could not identify those patients at high risk of death within cardiomyopathy groups.

Limitations of the Study

A registry signifies the participation of a large group of patients as well as a large number of medical centers, which often employ different criteria and techniques. Based on these realities, patients might have to wait a long time to receive the device, which would allow their clinical condition to worsen prior to receiving the therapy that they need.

Conclusion

Despite the benefits of ICD therapy in increasing the survival rate among patients rescued from sudden death or malignant ventricular tachycardia episodes, it is still necessary to increase our knowledge in this field. Application of the guidelines that randomized and prospective studies have already established allows us to foresee practical results within the general population. In this paper, we would like to reinforce the value of the EF, the NYHA functional class, and gender as predictors of risk of cardiac mortality within our population. Even though we found some differences in some publications related to age, perhaps this is because a large number of the patients in our registry having endemic local disease (Chagas Disease). And lastly, with regard to outcomes, we feel that we have identified clinical conditions in this paper that allow time for therapy adjustment in order to avoid these potentially fatal future events.

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