Preliminary Results from the Implantation and Follow-up of 279 Cardioverter-Defibrillators: The Latin American Biotronik Ongoing Registry

R. PESCE, E. VALERO
Universidad René G. Favaloro, Buenos Aires, Argentina

R. GARILLO
Universidad del Salvador, Buenos Aires, Argentina

M. MARTÌNEZ
Hospital San Roque, San Roque, Argentina

ON BEHALF OF THE ICD-LABOR STUDY INVESTIGATORS GROUP

Summary

From June 1994 to September 2001, a non-randomized, retrospective-prospective Latin American registry study, the ICD Latin America Biotronik Ongoing Registry (ICD-LABOR), was performed. In total, 317 patients with antecedents of malignant ventricular tachyarrhythmia or aborted sudden death who received an implantable cardioverter-defibrillator (ICD) were enrolled. Follow-up was completed in 279 patients, of whom 210 were male (75%). The primary pathology was coronary artery disease in 113 (40.5%), followed by Chagas disease in 77 (27.6%), and idiopathic dilated cardiomyopathy in 52 patients (18.6%). During the follow-up time (average 22.3 ± 18.9 months, range 3 − 83 months), 45 deaths were reported, of which 34 (75.5%) were attributed to cardiac causes. Total mortality due to cardiac cause was 12.2%. The annual adjusted mortality rate was 5.3% ± 1.72% (range 3.5% − 7.0%). The Cox proportional-hazards regression model established two independent risk factors: age and left ventricular ejection fraction. The worst prognosis corresponded to the combination of advanced age and low left ventricular ejection fraction. Despite the differences in terms of gender and pathologies between the ICD-LABOR study and most well-known trials, the parallel evolution observed reaffirms the predictive value of age and left ventricular ejection fraction. The development of modern technology related to devices and shock coils is shortening the ICD implantation procedures and in some respect has eliminated the need to determine certain values, for instance the true defibrillation threshold. The primary life-threatening risk factor for patients receiving an ICD is congestive heart failure. In patients with antecedents of sudden cardiac death with advanced age and low left ventricular ejection fraction, the indication for an ICD with resynchronization capabilities might be considered.

Key Words

Implantable cardioverter-defibrillator (ICD), registry study

Introduction

An assessment for the performance of implantable cardioverter-defibrillators (ICD) was developed in Latin America. The ICD Latin America Biotronik Ongoing Registry (ICD-LABOR) was a non-randomized, retrospective-prospective registry. The end point was the results from the analysis of indications, patient characteristics, pathology, technical aspects of the implantation procedure, and outcome of the population undergoing ICD treatment. The registry began in June 1994, and the preliminary results were concluded in

Pathology	No.	Gender	Mean age (years)
Hypertrophic cardiomyopathy	10	9m, 1f	54.6
No heart disease	7	5m, 2f	54.0
Valvular disease	5	3m, 2f	54.8
Hypertensive cardiomyopathy	5	4m,1f	67.4
LQTS	4	4f	41.0
ARVD	3	2m, 1f	38.3
Brugada syndrome	2	2m	39.5
CTGV	1	1m	55.0
Total	37	26m, 11f	52.7 ± 14.5

Table 1. Age and gender in the patient group without coronary artery disease, Chagas disease, or idiopathic dilated cardiomyopathy, which were included as miscellaneous causes. f = female; m = male; ARVD = arrhythmogenic right ventricular dysplasia; LQTS = long QT syndrome; CTGV = corrected transposition of great vessels.

September 2001. Five countries (Argentina, Uruguay, Brazil, Chile, and Cuba), 39 medical centers, 91 investigators, and 317 patients were included.

Materials and Methods

A specific protocol was designed for the medical centers. Every patient implanted with an ICD (Biotronik all models) signed an informed consent prior to the procedure. In all cases, the indication for ICD implantation was Class I, based on the "Consensus Statement on Indications, Guidelines for Use, and Recommendations for Follow-up of Implantable Cardioverter-Defibrillators" from NASPE [1]. The study population was comprised of 317 patients, of whom only 279 (88%) completed the protocol. The entire group consisted of 210 males, 62.8 ± 11.5 years (range 22 – 90 years) and 69 females, 61.0 ± 12.2 years (range 26 – 85 years). In all cases the myocardial condition at the time of implantation was evaluated by means of two-dimensional echocardiography, scintigraphy, or invasive methods (hemodynamic study).

Pathology	Age (years)			p-value
	Mean ± SD	Median	Range	
CAD	65.8 ± 8.96	66	47 – 90	n.s.
Ch	62.1 ± 11.4	63	38 – 85	n.s.
DCM	61.9 ± 11.5	63	22 – 81	n.s.
Miscellaneous	52.7 ± 14.5	57	25 – 73	0.00005

Table 2. Age of the different patient groups. CAD = coronary artery disease, DCM = idiopathic dilated cardiomyopathy, Ch = Chagas disease. A Kruskal-Wallis test was used for independent group comparison. n.s. = not significant; SD = standard deviation.

Results

Age, Gender, and Pathology

The comparison of ages in both sexes showed no statistical differences ($p = 0.273$, not significant). The etiology of cardiac disease was predominantly ischemic (coronary artery disease, CAD) in 113 patients (40.5%), followed by Chagas disease (Ch) in 77 patients (27.6%), and idiopathic dilated cardiomyopathy (DCM) in 52 patients (18.6%). The remaining pathologies were included as miscellaneous causes in 37 patients (13.3%) (Table 1). Among the principal pathologies (CAD, Ch, DCM), the average ages were similar, but the population of the miscellaneous group was statistically younger than the other groups (Table 2; Kruskal-Wallis $p < 0.00005$). The follow-up timeframe (22.7 months ± 20.2 months) was similar for the four groups.

Ventricular Function

Among CAD, Ch, and DCM, there were no statistical differences concerning the left ventricular ejection fraction (LVEF) average (33.7 % ± 11.3%, 37.9% ± 11.7%, and 32.2% ± 11.4%, respectively). In contrast, the LVEF average in the miscellaneous group was clearly higher (46.7% ± 15.3%; Kruskal-Wallis, $p < 0.00001$).

Defibrillation Threshold

During the implantation procedure in 95 patients (34%), the "true defibrillation threshold" was measured by inducing multiple ventricular fibrillation episodes and testing different energy shock levels (biphasic shock) to rescue the heart rhythm (average 12.9 ± 4.98 J, median 13 J, range 4.5 – 30 J). In the remaining 184 patients (66%), a predefined energy shock was employed. In this group, the average energy shock level was 13.8 ± 3.56 J, median 15 J, range 7 – 30 J. The comparison between both groups was statistically significant (Mann-Whitney, $p < 0.028$).

		Death	Alive	Total
Age	> 66 years	24	94	118
Age	< 66 years	10	151	161
Total		34	245	279

Table 3. A 2x2 contingency table of all cardiac deaths versus age. Threshold age has been determined by a receiver operator characteristic (ROC). χ^2 test, p-value < 0.00073; sensitivity = 70.6, specificity = 61.6; odds-ratio = 3.85, odds-ratio 95% confidence interval = 1.66 – 9.08.

		Death	Alive	Total
LVEF	< 31 (%)	21	89	110
LVEF	≥ 31 (%)	13	156	169
Total		34	245	279

Table 4. A 2x2 contingency table of all cardiac deaths versus left ventricular ejection fraction (LVEF). Threshold LVEF has been determined by a receiver operator characteristic (ROC). χ^2 test, p-value < 0.008; sensitivity = 61.8, specificity = 63.7; odds-ratio = 2.83, odds-ratio 95% confidence interval = 1.27 – 6.32.

Mortality

During the follow-up examinations (average 22.3 ± 18.9 months, range 3 – 83 months), 45 deaths were reported, of which 34 (75.5%) were attributed to cardiac causes. Total mortality due to cardiac cause was 12.2% [2]. The annual adjusted mortality rate was 5.3% ± 1.72% (range 3.5% – 7.0%). The Cox proportional-hazards regression model established two independent risk factors: age (Table 3) and LVEF (Table 4). According to the "death likelihood ratio," the increasing risk was divided into four groups, with the worst prognosis corresponding to the combination of advanced age and low LVEF (Table 5). Gender and pacing thresholds determined during the implantation procedure had no impact on the patient's prognosis.

Cumulative Probability of Survival and Death

The Kaplan-Meier analysis of cumulative probability of survival was similar among the three main groups (CAD, Ch, DCM). Conversely, the miscellaneous group's cumulative probability of survival, based on a lower average age and higher LVEF average, was statistically much better (log rank test, $p < 0.00006$). The main cause of all cardiac deaths was congestive heart failure (CHF) in 18 patients (53%), followed by sudden cardiac death (SCD) in 13 patients (38%) [3]. The remaining cardiac deaths only represented 9% of the total cardiac mortality.

Discussion

Evidence-based medicine has increased in importance during the last decade. Numerous randomized trials [4-6] have been employed in establishing new guidelines in the therapy of multiple pathologies. Despite its utility, some have criticized the selection of patients and the reliability of the procedures [7,8]. This has prompted the medical community to develop a renewed interest in registries in recent years. To that end, the development of a registry for patients treated with ICDs was undertaken in Latin America to offer a snapshot representing the diversity of this region. Latin America is a large community with similar cultural habits, economic problems, scarce resources, and particular endemic pathologies, such as Chagas disease. Within this region, an increasing number of new patients are receiving ICD therapy every year, which is creating new challenges related to indications, implantation procedures, and clinical follow-up.

What has the ICD-LABOR study taught us and how can we apply these data toward the improvement of our daily medical activities? The primary point to emphasize is the close correlation, in terms of average age and cumulative probability of survival, between the ICD-LABOR study and most well-known randomized trials. This agreement has occurred despite the higher percentage of females in the ICD-LABOR study and the presence of a large number of patients with Chagas disease (27.6%). Due to these factors, the rate of CAD was markedly lower than in the classic randomized trials.

Age (years)	LVEF (%)	Annual mortality (%)
< 65	> 31%	3.7
≤ 65	≤ 30%	10.0
> 66	> 31%	13.3
≥ 66	≤ 30%	30.3

Table 5. Annual mortality death likelihood ratio from the Cox regression model. LVEF = left ventricular ejection fraction.

Related to the small difference found between the true defibrillation threshold and an empiric value, we concluded that in our experience it is not necessary to induce multiple ventricular fibrillation episodes. Moreover, with modern devices and biphasic shocks, a successful test employing 50% of the maximal energy should be considered safe enough for patients [9]. Nevertheless, the concept of "upper limit of vulnerability" [10-12], that is a shock strength above which ventricular fibrillation cannot be induced, was employed during some occasions to obtain a "true defibrillation threshold" without subjecting the patients to repeated episodes of circulatory arrest.

When causes of mortality were investigated, CHF, as other authors have previously reported, appeared as the most common cause of death [13,14]. In elderly patients with low LVEF, 50% of the deaths due to CHF were observed in the first year post implantation [15]. As a result, these high-risk patients must be under close clinical surveillance and the indication for ICD plus resynchronization therapy should be considered.

Study Limitation

There are several limitations to our study. It was observational, non-randomized, and some parts of the registry were retrospective. Different types of implantable cardioverter-defibrillators were used, and there was no standard programming of devices for arrhythmia treatment.

Conclusion

- Despite the differences in terms of gender and pathologies among the ICD-LABOR study and most well-known trials, the parallel evolution that was observed reaffirms the predictive value of age and LVEF; this was similar in all cases and was independent of all other factors.
- The development of modern technology related to devices and shock coils might shorten the ICD implantation procedures and in some respect could eliminate the need to determine certain values, for instance the true defibrillation threshold.
- The primary life-threatening risk factor for patients receiving an ICD is CHF.
- In patients with antecedents of SCD with advanced age and low LVEF, the indication for an ICD with resynchronization capabilities might be considered.

Members of the ICD-LABOR Study Investigators Group

M. Abud, R. Albornoz, L. Aguinaga, V. Arregui, R. Asenjo, D. Azara, A. Baranchuck, D. Boccardo, A. Bolaños, A. Càccavo, C. Cáceres Monie, F. Calleriza, M. Cardona, R. Castellanos, F. Castoldi, N. Citta, L. Cipolleti, J. Cohn, M. Coll, S. Constantini, M. Chambò, C. Chaves, J. Danoviz, D. Dasso, G. de Elizalde, R. De la Fuente, C. de Zuloaga, A. Del Rìo, A. Demozzi, F. Di Tomaso, F. Dorticòs, S. Dubner, E. Dussaut, B. Elencwajg, A. Esteban, M.J. Estebanez, J. Estepo, G. Fernàndez, E. Fernàndez, N. Galizio, R. Garillo, J.L. Gonzàlez, S. Gonzàlez, H. Guillèn, M. Helguera, C. Labadet, S. Lamarca, N. Lanzotti, R. Ledesma, R. Martellotto, M. Martìnez, H. Mazzetti, C. Muratore, O. Oseroff, J.C. Pachòn Mateos, E. Pachòn Mateos, M.A. Parra Pavich, A. Peralta, O. Perez Mayo, R. Pesce, D.L. Pozzer, R. Rabinovich, J.L. Ramos, H. Repetto, E. Retyk, I. Reyes, W. Reyes, R. Rivero Paz, M. Roquinotti, H. Ruffa, J. Sànchez, O. Sànchez, L. Sanziani, D. Schrader, V. Sendra, J.L. Serra, H. Sgarlatta, J. Sirena, M. Solà, J. Suàrez, M.C. Tentori, M.A. Tibaldi, A. Treggia, M. Valentino, E. Valero, J.L. Velarde, A. Ventura, G. Vieyra, A. Villamil, M. Yanguas, E. Ylarri.

References

[1] Winters SL, Packer DL, Marchlinski F, et al. Consensus statement on indications, guidelines for use, and recommendations for follow-up of implantable cardioverter defibrillators. PACE. 2001; 24: 262-266.

[2] Hinkle LE, Thaler HT. Clinical classification of cardiac deaths. Circulation. 1982; 3: 457-463.

[3] Schirdewahn P, Hindricks G, Kottkamp H, et al. Risk stratification and benefit of ICD-therapy in congestive heart failure patients. Prog Biomed Res. 2001; 6: 120-125.

[4] Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest. The Cardiac Arrest Study Hamburg (CASH). Circulation. 2000; 102: 748-754.

[5] Connolly S, Gent M, Roberts R, et al. Canadian implantable defibrillator study (CIDS). A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000; 101: 1297-1302.

[6] The antiarrhythmic versus implantable defibrillators (AVID) investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997; 337: 1576-1583.

[7] Myerburg J, Castellanos A. Clinical trials of implantable defibrillators. N Engl J Med. 1997; 337: 1621-1623.

[8] Hallstrom AP, Anderson JL, Cobb LA, et al. Advantages and disadvantages of trial designs: a review of analysis methods for ICD studies. PACE. 2000; 23: 1029-1038.

[9] Glickson M, Friedman P. Routine arrhythmia inductions for ICD: are they obsolete? PACE. 2001; 24: 915-919.

[10] Dillon SM, Kwaku KF. Progressive depolarization: A unified hypothesis for defibrillation and fibrillation induction by shocks. J Cardiovasc Electrophysiol. 1998; 9: 529-552.

[11] Hwang C, Swerdlow ChD, Kass RM, et al. Upper limit of vulnerability reliably predicts the defibrillation threshold in humans. Circulation. 1994; 90: 2308-2314.

[12] Peng-Shen C, Swerdlow ChD, Hwang Ch. Current concepts of ventricular defibrillation. J Cardiovasc Electrophysiol. 1998; 9: 553-562.

[13] Moss AJ. Implantable cardioverter defibrillator therapy. The sickest patients benefit the most. Circulation. 2000; 101:1638-1640.

[14] Stevenson WG, Stevenson LW, Middlekauff HR, et al. Sudden death prevention in patients with advanced ventricular dysfunction. Circulation. 1993; 88: 2953-2961.

[15] Oseroff O, Rabinovich R, Garillo R, et al. Congestive heart failure as the early death cause in elderly patients with implantable cardioverter defibrillator (abstract). Europace 2002; 3 (Suppl A): A24.

Contact
Ricardo Pesce, MD, Professor of Cardiology
René G. Favaloro University
1093 Buenos Aires
Argentina
Phone: +54 11 43781300
Fax: +54 11 43781300
E-mail: rpesce@ffavloro.org