

Original article

# Primary Prevention of Sudden Death in Patients With Valvular Cardiomyopathy



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## ABSTRACT

**Introduction and objectives:** Few data exist on the outcomes of valvular cardiomyopathy patients referred for defibrillator implantation for primary prevention. The aim of the present study was to describe the outcomes of this cardiomyopathy subgroup.

**Methods:** This multicenter retrospective study included consecutive patients referred for defibrillator implantation to 15 Spanish centers in 2010 and 2011, and to 3 centers after 1 January 2008.

**Results:** Of 1174 patients, 73 (6.2%) had valvular cardiomyopathy. These patients had worse functional class, wider QRS, and a history of atrial fibrillation vs patients with ischemic (n = 659; 56.1%) or dilated (n = 442; 37.6%) cardiomyopathy. During a follow-up of  $38.1 \pm 21.3$  months, 197 patients (16.7%) died, without significant differences among the groups (19.2% in the valvular cardiomyopathy group, 15.8% in the ischemic cardiomyopathy group, and 17.9% in the dilated cardiomyopathy group;  $P = .2$ ); 136 died of cardiovascular causes (11.6%), without significant differences among the groups (12.3%, 10.5%, and 13.1%, respectively;  $P = .1$ ). Although there were no differences in the proportion of appropriate defibrillator interventions (13.7%, 17.9%, and 18.8%;  $P = .4$ ), there was a difference in inappropriate interventions (8.2%, 7.1%, and 12.0%, respectively;  $P = .03$ ).

**Conclusions:** All-cause and cardiovascular mortality in patients with valvular cardiomyopathy were similar to those in other patients referred for defibrillator implantation. They also had similar rates of appropriate interventions. These data suggest that defibrillator implantation in this patient group confers a similar benefit to that obtained by patients with ischemic or dilated cardiomyopathy.

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◇ The other participants in this work are listed in the [Appendix](#).

## Prevención primaria de muerte súbita en pacientes con miocardiopatía valvular

### RESUMEN

#### Palabras clave:

Miocardiopatía valvular  
Desfibrilador automático implantable  
Prevención primaria de muerte súbita  
cardiaca  
Intervenciones apropiadas  
Intervenciones inapropiadas

**Introducción y objetivos:** Existe escasa evidencia sobre la evolución de los pacientes con miocardiopatía valvular remitidos para implante de desfibrilador por prevención primaria. Se pretende describir la evolución de este subgrupo particular.

**Métodos:** Estudio multicéntrico retrospectivo en 15 centros españoles que incluyó pacientes consecutivos remitidos para implante de desfibrilador en los años 2010 y 2011, y en tres centros desde el 1 enero de 2008.

**Resultados:** De un total de 1.174 pacientes, 73 (6,2%) presentaron miocardiopatía valvular. Comparados con los pacientes con miocardiopatía isquémica (n = 659; 56,1%) o dilatada (n = 442; 37,6%), presentaron peor clase funcional, mayor anchura del QRS y antecedente de fibrilación auricular. Durante un seguimiento de  $38,1 \pm 21,3$  meses, 197 (16,7%) pacientes fallecieron por cualquier causa, sin diferencias significativas entre grupos (19,2% en miocardiopatía valvular, 15,8% en isquémica y 17,9% en miocardiopatía dilatada; p = 0,2). De estos, 136 murieron por causa cardiovascular (11,6%), sin diferencias significativas (12,3%; 10,5% y 13,1%, respectivamente; p = 0,1). Tampoco hubo diferencias en la proporción de intervenciones apropiadas del desfibrilador (13,7%; 17,9% y 18,8%; p = 0,4), pero sí en el de inapropiadas (8,2%; 7,1% y 12,0%, respectivamente; p = 0,03).

**Conclusiones:** Las tasas de mortalidad por cualquier causa y por causa cardiovascular en pacientes con miocardiopatía valvular fueron similares a las del resto de los pacientes remitidos para implante de desfibrilador. También presentaron similares tasas de intervenciones apropiadas. Estos datos parecen indicar que el implante de un desfibrilador en este grupo confiere un beneficio similar al que obtienen los pacientes con miocardiopatía isquémica y miocardiopatía dilatada.

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### Abbreviations

HR: hazard ratio  
ICD: implantable cardioverter-defibrillator

### Exclusion Criteria

The following patients were excluded: those with channelopathies, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, and congenital heart disease.

### INTRODUCTION

Current evidence indicates that implantable cardioverter-defibrillators (ICDs) reduce mortality in patients with ischemic and nonischemic dilated cardiomyopathy.<sup>1–5</sup> However, individuals with left ventricular dysfunction secondary to valve disease are underrepresented in this subgroup, and the outcome data for these patients are less robust.<sup>6</sup>

The aim of the present study was to describe the outcomes of patients with acute left ventricular dysfunction secondary to valve disease referred for ICD implantation for primary prevention of sudden death compared with those of patients with “ischemic cardiomyopathy” or “dilated cardiomyopathy”.

### METHODS

This multicenter retrospective study was performed in 15 Spanish centers with experience in ICD implantation and follow-up of these patients. Consecutive patients with first implantations for primary prevention from 2010 and 2011 were included, as well as consecutive patients from 3 centers with implantations performed after 1 January 2008.

### Inclusion Criteria

The present study included patients referred for defibrillator implantation for primary prevention with or without resynchronization therapy according to current recommendations.<sup>7</sup>

### Definitions of the Variables

Cardiovascular mortality included sudden death and death attributed to myocardial infarction or heart failure. Sudden death was defined as death in the first hour after symptom onset or unexpected death in a person who lived alone and was feeling well within the previous 24 hours. Death due to refractory heart failure was defined as death in a patient with decompensated heart failure who failed to respond to medical treatment, in the absence of any other cause of death. Death due to myocardial infarction was considered to have occurred when the infarction caused electrical or mechanical complications leading to early death. The remaining deaths were considered noncardiac deaths.

Finally, valvular cardiomyopathy was defined as cardiomyopathy secondary to replacement or repair of the aortic or mitral valve or severe valve disease causing ventricular dysfunction in the absence of other causes explaining the dysfunction before device implantation.<sup>8</sup>

### Baseline Risk Stratification

The MADIT<sup>9</sup> and SHOCKED<sup>10</sup> scales were used to stratify the baseline risk of the population. The variables included in these scales and their scores are summarized in [Table 1](#).

### Statistical Analysis

Gaussian continuous variables in an initial descriptive analysis are expressed as mean and standard deviation and non-Gaussian continuous variables as median (minimum and maximum).

**Table 1**  
Variables Included in the 3 Models Used for Predicting Mortality and the Scoring Systems

Scale	Variables	Categories
MADIT II	Age > 70 years (1 point) QRS width > 120 ms (1 point) AF (1 point) NYHA > II (1 point) BUN > 26 mg/dL (1 point)	Low risk: score of 0 Intermediate risk: score of 1 or 2 High risk: score $\geq$ 3
SHOCKED	Age $\geq$ 75 years (62 points) NYHA III (36 points) AF (27 points) COPD (62 points) Chronic kidney disease (100 points) LVEF $\leq$ 20% (28 points) Diabetes mellitus (41 points)	The abbreviated model equation is represented in the form of nomograms with a maximum of 360 points. The rates of mortality are based on risk quintiles The highest risk quintile is > 202

AF, atrial fibrillation; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

To identify differences among the study groups (valvular, ischemic, and dilated cardiomyopathy), the parametric analysis of variance test was used for Gaussian variables and the Kruskal-Wallis test was used for non-Gaussian variables. Categorical variables were compared with a chi-square test. Kaplan-Meier life table and competitive risk analyses were performed. All-cause mortality and cardiovascular mortality were calculated for each type of cardiomyopathy using Cox regression models. In these models, p-spline smoothing was used for continuous variables to determine the linearity of the variables. Various multivariate Cox models were used to identify the best explanatory model and the model with the highest plausibility or Atkinson  $R^2$  test and best c-statistic was selected. Cox regression models were used to analyze appropriate and inappropriate ICD interventions (presence or absence). The following variables were included: age, sex, MADIT and SHOCKED scales, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, New York Heart Association functional class, chronic obstructive pulmonary disease, dyslipidemia, obstructive sleep apnea syndrome, history of atrial fibrillation, QRS width, creatinine clearance, heart rate at the time of implantation, blood urea nitrogen, bundle branch block at the time of implantation, hypertension, ischemic cardiomyopathy, incomplete revascularization, body mass index, and use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, antialdosterone agents, and digoxin. *P* values were obtained with a 2-tailed test, and  $P < .05$  was considered statistically significant. All statistical analyses were performed using SPSS 19 and Stata 13 (*stcomp*) software and the free software R (*survival* package).

For the univariate analysis, the category "ischemic cardiomyopathy" was considered a reference subcategory for the explanatory variable "type of cardiomyopathy".

## RESULTS

Of the 1185 patients included in this study, 11 were excluded due to missing follow-up data (final  $n = 1174$ ). Patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or channelopathies were not included in the database and it is unknown how many were excluded for these reasons. The date of implantation was before 2010 in 281 of the 1174 patients (in 3 specific centers: *Hospital Clínico Universitario de Santiago de Compostela*, *Hospital Universitario Marqués de Valdecilla*, and *Hospital Clínico Universitario de Valencia*); in the other patients, the date of implantation was after 2010 ( $n = 893$ ). There were no relevant differences between the risk profiles of the patients implanted before and after 2010 or among the proportion of

cardiomyopathy type in each category (25% ischemic, 18% valvular, and 21% dilated;  $P = .1$ ).

## Baseline Characteristics

Of the 1174 patients included in the study, 73 had valvular dilated cardiomyopathy (10 patients also had coronary disease with consequent complete revascularization but the dysfunction was attributed to valve disease).

The baseline characteristics of the overall population and cardiomyopathy subtypes are shown in Table 2; notably, patients with valvular cardiomyopathy showed worse functional class, wider QRS, and a history of atrial fibrillation.

Significant drug treatment-related differences were found according to cardiomyopathy type. Overall, 85.9% of the patients received beta-blockers (86.5% of those with ischemic cardiomyopathy, 87.1% with dilated cardiomyopathy, and 75.3% with valvular cardiomyopathy;  $P = .02$ ) and 4.8% were treated with calcium antagonists (6.2% of those with ischemic cardiomyopathy, 3.2% with dilated cardiomyopathy, and 1.4% with valvular cardiomyopathy;  $P = .02$ ). Digoxin was taken by 13.9% (27.4% of those with valvular cardiomyopathy, 19.0% with dilated cardiomyopathy, and 8.9% with ischemic cardiomyopathy;  $P < .01$ ). Significant differences were seen in antialdosterone use among the 3 groups (63.0% of those with valvular cardiomyopathy, 55.0% with dilated cardiomyopathy, and 45.9% with ischemic cardiomyopathy;  $P < .01$ ). Acetylsalicylic acid was taken by 54.0% of patients (80.1% of those with ischemic cardiomyopathy, 16.4% with valvular cardiomyopathy, and 21.5% with dilated cardiomyopathy;  $P < .01$ ). Oral anticoagulants were taken by 34.7% and their use was significantly higher in those with valvular cardiomyopathy (80.1% vs 28.6% with ischemic cardiomyopathy and 36.2% with dilated cardiomyopathy;  $P < .01$  (Table 2).

Patients with valvular cardiomyopathy had a worse risk profile according to the MADIT (mean and standard deviation scores of the valves) and SHOCKED (idem) scales than the ischemic cardiomyopathy or dilated cardiomyopathy groups.

## Overall and Cardiovascular Mortality According to Cardiomyopathy Subgroup

During a mean follow-up of  $38.1 \pm 21.3$  months, 197 patients (16.7%) died: 14 (19.2%) of those with valvular cardiomyopathy, 104 (15.8%) with ischemic cardiomyopathy, and 79 (17.9%) with dilated cardiomyopathy ( $P = .2$ ) (Figure).

**Table 2**

Baseline Characteristics of the Overall Population and by Cardiomyopathy Subgroup. In the Last Column, the Differences Among the 3 Groups Were Calculated Using the Analysis of Variance Test

	Total (n = 1174)	Valvular cardiomyopathy (n = 73)	Ischemic cardiomyopathy (n = 659)	Dilated cardiomyopathy (n = 442)	P (global)
Age, y	62.72 (11.1)	64.42 (8.8)	63.66 (10.5)	61.05 (12.3)	< .01
Women, % <sup>a</sup>	218 (18.6)	20 (27.4)	67 (10.2)	131 (29.6)	< .01
Hemoglobin, g/dL <sup>b</sup>	13.5 (8.4-17.9)	12.8 (9.3-17.0)	13.5 (9.0-17.8)	13.5 (8.4-17.9)	< .01
Sodium, mEq/L <sup>b</sup>	139.0 (125-154)	138.3 (125-154)	139.2 (125-154)	138.8 (128-150)	.3
BUN, mg/dL	25.3 (13.7)	25.6 (11.7)	25.0 (12.7)	25.6 (15.4)	.6
Creatinine, mg/dL	1.18 (0.6)	1.19 (0.7)	1.17 (0.4)	1.19 (0.7)	.2
BMI	28.7 (4.7)	28.5 (4.1)	28.4 (4.4)	29.2 (5.2)	.4
Heart rate, bpm <sup>b</sup>	70.7 (30-139)	70.7 (35-104)	69.0 (30-132)	73.0 (30-139)	< .01
QRS duration > 120, ms	127.7 (32.2)	147.9 (32.4)	120.0 (29.8)	135.0 (32.3)	< .01
NYHA III-IV, % <sup>a</sup>	456 (35.3)	47 (64.4)	184 (27.9)	225 (50.9)	< .01
LVEF, % <sup>b</sup>	26.2 (7.6)	25.1 (5.1)	26.8 (6.3)	25.5 (9.8)	.01
History of AF, % <sup>a</sup>	412 (38.8)	52 (71.2)	187 (28.5)	173 (39.1)	< .01
Sinus rhythm at implantation, % <sup>a</sup>	902 (76.8)	31 (42.5)	542 (82.2)	329 (74.4)	< .01
Previous pacemaker, % <sup>a</sup>	71 (6.0)	9 (12.3)	35 (5.3)	27 (6.1)	.06
Hypertension, % <sup>a</sup>	707 (60.2)	40 (54.8)	425 (64.5)	242 (54.8)	.003
Diabetes mellitus, % <sup>a</sup>	387 (33.0)	20 (27.4)	244 (37.0)	123 (27.8)	.004
Active smoking, % <sup>a</sup>	264 (22.5)	8 (11.0)	184 (27.9)	72 (16.3)	< .01
COPD, % <sup>a</sup>	167 (14.2)	11 (15.1)	94 (14.3)	62 (14.0)	.9
OSAS, % <sup>a</sup>	75 (6.4)	7 (9.6)	38 (5.8)	30 (6.8)	.4
CPAP, % <sup>a</sup>	46 (3.9)	5 (6.8)	24 (3.6)	17 (3.8)	.4
Previous admission for HF, %	320 (27.3)	25 (34.2)	152 (23.1)	143 (32.4)	< .01
Dyslipidemia, %	576 (49.1)	24 (32.9)	377 (57.2)	175 (39.6)	< .01
Peripheral arterial disease, %	101 (8.6)	2 (2.7)	81 (12.3)	18 (4.1)	< .01
Previous stroke, %	93 (7.9)	7 (9.6)	61 (9.3)	25 (5.7)	.08
Beta-blockers, %	1009 (85.9)	55 (75.3)	569 (86.5)	385 (87.1)	.02
ACE inhibitors/ARB, %	1026 (87.4)	59 (80.8)	573 (87.1)	394 (89.1)	.12
Calcium antagonists, %	56 (4.8)	1 (1.4)	41 (6.2)	14 (3.2)	.02
Sotalol, %	7 (0.6)	1 (1.4)	3 (0.5)	3 (0.7)	.6
Digoxin, %	163 (13.9)	20 (27.4)	59 (8.9)	84 (19.0)	< .01
Dronedaron, %	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	.4
Amiodarone, %	114 (9.7)	8 (11.0)	61 (9.3)	45 (10.2)	.8
Antialdosterone agents, %	591 (50.3)	46 (63.0)	302 (45.9)	243 (55.0)	< .01
Aspirin, %	634 (54.0)	12 (16.4)	527 (80.1)	95 (21.5)	< .01
Oral anticoagulants, %	407 (34.7)	59 (80.1)	188 (28.6)	160 (36.2)	< .01
Statins, n, %	749 (63.8)	25 (34.2)	528 (80.2)	196 (44.3)	< .01
<b>Device type</b>					
DDD-ICD	222 (18.9)	3 (4.1)	148 (22.5)	71 (16.1)	< .01
VVI-ICD	457 (38.9)	21 (28.8)	326 (49.5)	110 (24.9)	< .01
DDD-CRT-D	385 (32.8)	26 (35.6)	151 (22.9)	208 (47.0)	< .01
VVI-CRT-D	110 (9.4)	23 (31.5)	34 (5.2)	53 (12.0)	< .01
MADIT scale	1.9 (1.4)	3.0 (1.2)	1.6 (1.3)	2.2 (1.3)	< .01
SHOCKED scale	53.0 (40.9)	68.0 (40.2)	47.4 (39.6)	58.64 (41.7)	< .01

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRT-D, cardiac resynchronization therapy-defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSAS, obstructive sleep apnea syndrome.

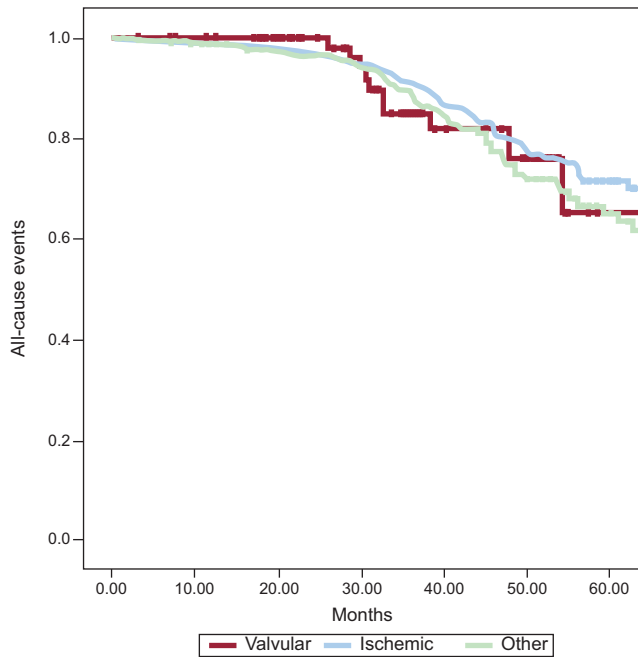
<sup>a</sup> Nonparametric test, with the Kruskal-Wallis used for non-Gaussian variables.

<sup>b</sup> Nonparametric test, with the chi-square test used for non-Gaussian variables.

The cause of death was cardiovascular in 136 of the 197 deaths (11.6%): 9 patients (12.3%) with valvular cardiomyopathy, 69 (10.5%) with ischemic cardiomyopathy, and 58 (13.1%) with dilated cardiomyopathy ( $P = .1$ ).

The crude effect of the analyzed variables on the event “all-cause mortality” is shown in [Table 3](#).

In the adjusted analysis, the independent predictors of all-cause mortality were left ventricular ejection fraction on admission (hazard ratio [HR] = 0.96; 95% confidence interval [95%CI], 0.93-0.97), age (HR = 1.03; 95%CI, 1.01-1.06), serum creatinine (HR = 1.66; 95%CI, 1.36-2.02), male sex (HR = 2.5; 95%CI, 1.27-4.95), chronic obstructive pulmonary disease (HR = 1.73; 95%CI, 1.09-2.75), digoxin therapy



**Figure.** Kaplan-Meier survival curves for all-cause events according to subgroup.

(HR = 1.61; 95%CI, 1.02-2.53), with a c-statistic for this model of 0.71. No relevant changes were seen with a specific analysis of cardiovascular mortality, considering the left ventricular ejection fraction on admission (HR = 0.96; 95%CI, 0.94-0.98), age (HR = 1.02; 95%CI, 1.01-1.04), serum creatinine (HR = 1.58; 95%CI, 1.30-1.91), male sex (HR = 2.35; 95%CI, 1.26-4.38), obstructive pulmonary disease (HR = 1.64; 95%CI, 1.08-2.48), and digoxin therapy (HR = 1.84; 95%CI, 1.23-2.76). The type of cardiomyopathy was not significant in the univariate analysis or in any of the multivariate analyses performed, whether for all-cause mortality or cardiovascular mortality. Regression analysis ruled out the presence of competitive risks.

**Table 3**

Crude and Adjusted Effect of the Type of Idiopathic Valvular and Ischemic Cardiomyopathy on Overall Mortality in Patients Receiving an Implantable Cardioverter-Defibrillator for Primary Prevention. The Overall Mortality of Each Cardiomyopathy Was Compared with the Overall Mortality in Patients with Ischemic Cardiomyopathy (Reference)

Cardiomyopathy	Ischemic	Valvular	P	Idiopathic	P
No.	659	73		442	
Overall mortality, %	104 (15.8)	14 (19.2)		79 (17.9)	
Crude HR	1 (ref)	1.28 (0.70-2.34)	.55	1.20 (0.88-1.63)	.29
Age-adjusted HR	1 (ref)	1.26 (0.69-2.29)	.45	1.28 (0.95-1.73)	.11
Sex-adjusted HR	1 (ref)	1.45 (0.79-2.64)	.22	1.40 (1.03-1.91)	.02
EF-adjusted HR	1 (ref)	1.21 (0.66-2.20)	.53	1.11 (0.82-1.51)	.48
NYHA functional class-adjusted HR	1 (ref)	1.24 (0.68-2.25)	.48	1.17 (0.87-1.59)	.29
AF presence-adjusted HR	1 (ref)	1.08 (0.58-1.99)	.80	1.15 (0.85-1.56)	.35
COPD presence-adjusted HR	1 (ref)	1.29 (0.71-2.35)	.40	1.24 (0.91-1.68)	.16
Peripheral arterial disease-adjusted HR	1 (ref)	1.40 (0.76-2.56)	.27	1.29 (0.95-1.76)	.09
Serum Cr-adjusted HR	1 (ref)	0.98 (0.49-1.95)	.96	1.13 (0.83-1.55)	.42
Serum Na-adjusted HR	1 (ref)	1.13 (0.55-2.46)	.67	1.14 (0.77-1.69)	.50
Heart rate-adjusted HR	1 (ref)	1.28 (0.68-2.41)	.42	1.06 (0.76-1.47)	.71
Digoxin treatment-adjusted HR	1 (ref)	1.10 (0.60-2.03)	.74	1.12 (0.82-1.53)	.44
Multivariate-adjusted HR*	1 (ref)	1.18 (0.50-2.77)	.96	1.04 (0.65-1.67)	.21

95%CI, 95% confidence interval; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; Cr, creatinine; EF, ejection fraction; HR, hazard ratio; Na, sodium; NYHA, New York Heart Association functional class; ref, reference.

\* Cox regression analysis adjusted by age, sex, ejection fraction, chronic obstructive pulmonary disease creatinine, and digoxin treatment, all at the time of implant.

**Appropriate and Inappropriate Therapies According to Subgroup**

During the study period, 211 patients (18%) received an appropriate device intervention (antitachycardia pacing, shock, or both): 10 patients (13.7%) with valvular cardiomyopathy, 118 (17.9%) with ischemic cardiomyopathy, and 83 (18.7%) with dilated cardiomyopathy (P = .4). In the crude analysis, the only variable associated with a lower risk of appropriate therapy was beta-blockers (HR = 0.63; 95%CI, 0.42-0.93; P = .02). However, for the type of cardiomyopathy variable, after adjustment for age, sex, and beta-blocker therapy, there was no significantly increased risk of appropriate therapy in patients with valvular or nonischemic cardiomyopathy (HR = 0.76; 95%CI, 0.37-1.54; P = .4) vs those with ischemic cardiomyopathy (HR = 1.17; 95%CI, 0.85-1.62; P = .3) (Table 4).

Inappropriate ICD interventions were seen in 106 patients (9%): 6 (8.2%) with valvular cardiomyopathy, 47 (7.1%) with ischemic cardiomyopathy, and 53 (12.0%) with dilated cardiomyopathy (P = .4). In the multivariate Cox analysis, the variables associated with inappropriate therapies were age < 65 years (HR = 2.58; 95%CI, 1.28-5.22; P < .01), history of atrial fibrillation (HR = 2.25; 95%CI, 1.23-4.11; P < .01), and cardiac resynchronization therapy (HR = 0.38; 95%CI, 0.20-0.74; P < .01). No significantly higher risk of inappropriate therapy was found in patients with valvular cardiomyopathy (HR = 2.36; 95%CI, 0.81-6.90; P = .12), but a significantly higher risk was seen in those with nonischemic cardiomyopathy (HR = 1.99; 95%CI, 1.02-3.88; P = .01) vs the reference group of patients with ischemic cardiomyopathy after adjustment for age, sex, left ventricular ejection fraction, heart rate, hypertension, chronic obstructive pulmonary disease, and peripheral arterial disease (Table 4).

**DISCUSSION**

In the present cohort, no notable differences were seen in the rates of all-cause and cardiovascular mortality in patients with left ventricular dysfunction of different causes who received an ICD implantation for primary prevention. There were also no significant differences in the rate of appropriate device interventions,

**Table 4**

Association Between Cardiomyopathy Type and the Incidence of Appropriate and Inappropriate Therapies of Implantable Cardioverter-defibrillators

	Ischemic	Valvular	<i>P</i>	Idiopathic	<i>P</i>
No.	659	73		442	
<i>Appropriate therapies</i>	118 (17.9)	10 (13.9%)		83 (18.8)	
Crude HR	1 (ref)	0.74 (0.37-1.48)	.40	1.06 (0.78-1.45)	.71
Adjusted HR <sup>a</sup>	1 (ref)	0.76 (0.37-1.54)	.45	1.17 (0.85-1.62)	.33
<i>Inappropriate therapies</i>	47 (7.1)	6 (8.3%)		53 (12.0)	
Crude HR	1 (ref)	1.17 (0.48-2.83)	.73	1.77 (1.17-2.68)	< .01
Adjusted HR <sup>b</sup>	1 (ref)	2.36 (0.81-6.90)	.12	1.99 (1.02-3.88)	.04

HR, hazard ratio.

<sup>a</sup> Adjusted by age, sex, and beta-blocker therapy.<sup>b</sup> Adjusted by age, sex, baseline heart rate, baseline ejection fraction, chronic obstructive pulmonary disease, peripheral arterial disease, and hypertension.

even though these patients showed a more adverse clinical risk profile according to the event prediction scores (MADIT and SHOCKED scales). Thus, patients with valvular cardiomyopathy appear to obtain the same benefit as the rest of the population referred for ICD implantation for primary prevention.

The main objective of this study was to describe the outcomes of this particular population, given that current evidence supporting the use of an ICD for preventing arrhythmic death in patients with left ventricular dysfunction secondary to valve disease is insufficiently robust.<sup>1–5</sup> In fact, this patient type is generally underrepresented in the large randomized studies,<sup>6</sup> and the present work represents one of the largest series available to date. However, evidence indicates that these patients show a substantial rate of arrhythmic events, particularly after valve replacement,<sup>11–14</sup> reaching 25% in some series,<sup>12–14</sup> which can be explained by various mechanisms. It is first important to note the presence of left ventricular hypertrophy, dilatation, and left ventricular dysfunction in this type of pathology.<sup>14–16</sup> Moreover, fibrosis after surgery has been suggested to provide a favorable substrate for the creation of reentry phenomena and consequent ventricular arrhythmias.<sup>13</sup> In fact, in the series reported by Rosenheck et al,<sup>17</sup> antitachycardia pacing was effective in 99% of the ventricular tachycardia episodes, suggesting that reentry would be the main mechanism of ventricular arrhythmia in this population. These characteristics might explain the significant rate of cardiovascular events, which was similar to that of patients with ischemic cardiomyopathy, for example, independently of the correction of the underlying valve disease.

Valles et al<sup>15</sup> published a series of 31 patients with valvular cardiomyopathy and ICD implantation for primary and secondary prevention. In this series, there were no differences (in survival and appropriate discharges) compared with patients with ischemic cardiomyopathy and a control group, although there was a tendency for worse outcomes in patients with ischemic cardiomyopathy. Rosenheck et al<sup>17</sup> described 31 patients with valvular cardiomyopathy and primary and secondary prevention (of a total of 438 individuals). As is inherent to this group, and as in our population, the baseline profile of the patients was different from those with ischemic cardiomyopathy. Although there was a slight tendency for an overall higher cumulative survival than in those patients with ischemic cardiomyopathy and dilated cardiomyopathy, there were no significant differences.

These data, together with the results of our series, seem to indicate that this subgroup of patients can benefit from primary prevention with an ICD, similar to those with cardiomyopathy of other causes. Such conclusions must be analyzed from the perspective that the patients have different clinical characteristics than those with ischemic cardiomyopathy or dilated cardiomyopathy, as reflected in the higher score in the clinical scales for predicting mortality events (MADIT and SHOCKED). In contrast,

these patients show less diabetes, smoking, peripheral arterial disease, and dyslipidemia and, as expected, particularities specific to this group regarding medical treatment (greater use of digoxin and oral anticoagulants), as well significantly wider QRS, which would at least partly explain the significantly larger percentage of implantations of cardiac resynchronization systems.

Finally, another important conclusion from this cohort is that the group of patients with valve diseases did not show a higher rate of inappropriate therapies than patients with ischemic cardiomyopathy (and even showed a lower rate than those with dilated cardiomyopathy). Although the high incidence of atrial fibrillation in patients with valve diseases is presumed to be a risk factor, the current evidence (from our cohort and that of Valles et al<sup>15</sup>) fails to support this claim.

This fact, together with the previously mentioned results, supports the risk/benefit relationship of ICD implantation for primary prevention in patients with valvular cardiomyopathy, as in patients with ischemic cardiomyopathy or dilated cardiomyopathy. Nonetheless, these findings should be confirmed in a series with a larger number of patients and a more homogenous baseline profile.

### Limitations

This study should be interpreted with the limitations inherent to its retrospective and nonrandomized design. The conclusions should take into account the particularly high percentage of patients in the valvular cardiomyopathy group who were also implanted with a left ventricular electrode for ventricular resynchronization. Therefore, the survival and device discharge rates were probably strongly influenced by resynchronization therapy. However, the proportion of patients with added resynchronization therapy is similar to that in the studies that helped to inform the current guidelines.

Finally, one important limitation is the lack of information on the type of valve disease (aortic, mitral), surgical intervention (valve replacement vs repair), and associated disease (eg, pulmonary hypertension, right ventricular dysfunction), which would surely affect survival and device interventions. Thus, the present work is an initial approach to the study of these patients. These limitations should be taken into account when interpreting its conclusions and by future studies aimed at optimizing the selection criteria of patients with valve diseases referred for an ICD implant.

### CONCLUSIONS

In patients with valve-related left ventricular dysfunction, implantation of an ICD seems to confer a benefit similar to that

obtained by patients with ischemic cardiomyopathy or dilated cardiomyopathy. The rates of all-cause and cardiovascular mortality were similar to those of the other patients referred for an ICD, without significant differences. The patients also showed similar rates of appropriate device interventions (antitachycardia pacing, shock, or both). However, there were baseline differences in the risk profiles and medical treatment of this population vs patients with ischemic cardiomyopathy or dilated cardiomyopathy. Thus, these conclusions should be carefully interpreted and confirmed in future studies focusing specifically on this heretofore underrepresented population.

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#### CONFLICTS OF INTEREST

None declared.

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#### REFERENCES

- Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877-83.
- Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G; Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med.* 1999;341:1882-90.
- Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350:2140-50.
- Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA.* 2004;292:2874-9.
- Stevenson LW, Desai AS. Selecting patients for discussion of the ICD as primary prevention for sudden death in heart failure. *J Card Fail.* 2006;12:407-12.
- Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005;352:225-37.
- Díaz-Infante E, Macías Gallego A, Ferrero de Loma-Osorio A. Registro Español de Ablación con Catéter. XI Informe Oficial de la Sección de Electrofisiología y Arritmias de la Sociedad Española de Cardiología (2011). *Rev Esp Cardiol.* 2012;65:928-36.
- Yang F, Shah B, Iwai S, Markowitz SM, Lerman BB, Stein KM. ICD implantation and arrhythmia-free survival in patients with depressed LV function following surgery for valvular heart disease. *Pacing Clin Electrophysiol.* 2008;31:1419-24.
- Barsheshet A, Moss AJ, Huang DT, McNitt S, Zareba W, Goldenberg I. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. *J Am Coll Cardiol.* 2012;5:2075-9.
- Bilchick KC, Stukenborg GJ, Kamath S, Cheng A. Prediction of mortality in clinical practice for Medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. *J Am Coll Cardiol.* 2012;23:1647-55.
- Konishi Y, Matsuda K, Nishiwaki N, Shimada I, Kitao Y, Ban T, et al. Ventricular arrhythmias late after aortic and/or mitral valve replacement. *Jpn Circ J.* 1985;49:576-83.
- Burke AP, Farb A, Sessums L, Virmani R. Causes of sudden cardiac death in patients with replacement valves: an autopsy study. *J Heart Valve Dis.* 1994;3:10-6.
- Michel PL, Mandagout O, Vahanian A, Cormier B, Iung B, Luxereau P, et al. Ventricular arrhythmias in aortic valve disease before and after surgery. *J Heart Valve Dis.* 1992;1:72-9.
- Biyik I, Ergene O, Oto O. Late ventricular arrhythmias in patients with mechanical heart valves and their relation to associated factors. *J Cardiovasc Surg (Torino).* 2007;48:79-83.
- Valles AG, Khawaja FJ, Gersh BJ, Enriquez-Sarano M, Friedman PA, Park SJ, et al. Implantable cardioverter defibrillators in patients with valvular cardiomyopathy. *J Cardiovasc Electrophysiol.* 2012;23:1326-32.
- Bastante Valiente T, Cano MJ, Delgado JF, Gil ML, Arribas F, Sánchez MA, et al. Implante de desfibrilador como prevención primaria de muerte súbita en pacientes en lista de espera de trasplante cardiaco: experiencia de un centro. *Rev Esp Cardiol.* 2011;64:240-2.
- Rosenheck S, Weiss A, Sharon Z. Therapy success and survival in patients with valvular heart disease and implantable cardioverter defibrillator. *Int J Cardiol.* 2010;144:103-4.