



ORIGINAL RESEARCH

Long-Term Outcomes Among a Nationwide Cohort of Patients Using an Implantable Cardioverter-Defibrillator: UMBRELLA Study Final Results

Sem Briongos-Figuero , MD; Arcadio García-Alberola, MD, PhD; Jerónimo Rubio, MD, PhD; José María Segura, MD, PhD; Aníbal Rodríguez, MD, PhD; Rafael Peinado, MD, PhD; Javier Alzueta, MD, PhD; José B. Martínez-Ferrer , MD, PhD; Xavier Viñolas, MD, PhD; Joaquín Fernández de la Concha, MD, PhD; Ignasi Anguera, MD, PhD; María Martín, EngD; Laia Cerdá, Pharm B; Luisa Pérez, MD, PhD; on behalf of the UMBRELLA Investigators*

BACKGROUND: Large-scale studies describing modern populations using an implantable cardioverter-defibrillator (ICD) are lacking. We aimed to analyze the incidence of arrhythmia, device interventions, and mortality in a broad spectrum of real-world ICD patients with different heart disorders.

METHODS AND RESULTS: The UMBRELLA study is a prospective, multicenter, nationwide study of contemporary patients using an ICD followed up by remote monitoring, with a blinded review of arrhythmic episodes. From November 2005 to November 2017, 4296 patients were followed up. After 46.6±27.3 months, 16 067 episodes of sustained ventricular arrhythmia occurred in 1344 patients (31.3%). Appropriate ICD therapy occurred in 27.3% of study population. Patients with ischemic cardiomyopathy (hazard ratio [HR], 1.51; 95% CI, 1.29–1.78), dilated cardiomyopathy (HR, 1.28; 95% CI, 1.07–1.53), and valvular heart disease (HR, 1.94; 95% CI, 1.43–2.62) exhibited a higher risk of appropriate ICD therapies, whereas patients with hypertrophic cardiomyopathy (HR, 0.72; 95% CI, 0.54–0.96) and Brugada syndrome (HR, 0.25; 95% CI, 0.14–0.45) showed a lower risk. All-cause death was 13.4% at follow-up. Ischemic cardiomyopathy (HR, 3.09; 95% CI, 2.58–5.90), dilated cardiomyopathy (HR, 3.33; 95% CI, 2.18–5.10), and valvular heart disease (HR, 3.97; 95% CI, 2.25–6.99) had the worst prognoses. Delayed high-rate detection was enabled in 39.7% of patients, and single-zone programming occurred in 52.6% of primary prevention patients. Both parameters correlated with lower risk of first appropriate ICD therapy, with no excess risk of mortality. The rate of inappropriate shocks at follow-up was low (6%) and did not differ among type of ICD but was lower in SmartShock-capable devices.

CONCLUSIONS: Irrespective of the cause, contemporary ICD patients with heart failure–related disorders had a similar risk of ICD life-saving interventions and death. Current ICD programming recommendations still need to be implemented.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NTC01561144.

Key Words: all-cause death ■ appropriate implantable cardioverter-defibrillator therapy ■ implantable cardioverter-defibrillator ■ inappropriate shock ■ sustained ventricular arrhythmia

Correspondence to: Sem Briongos-Figuero, MD, Servicio de Cardiología. Hospital Universitario Infanta Leonor, Gran Vía del Este, 28030 Madrid, Spain. E-mail: semdoc@hotmail.com

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018108>

*A complete list of the UMBRELLA Investigators can be found in the Appendix at the end of the article.

For Sources of Funding and Disclosures, see page 13.

© 2020 The Authors and Medtronic Iberica S.A. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The present study comprises a large cohort of 4296 implantable cardioverter-defibrillation (ICD) patients with 8 different heart disorders, implanted according to current guidelines and followed up for 46.6±27.3 months.
- A reliable incidence of arrhythmic events and ICD interventions by disease cause was identified by a blinded review of the stored arrhythmic episodes collected through the remote monitoring system.

What Are the Clinical Implications?

- The long-term prognosis of heart failure in patients using an ICD seems to be similar regardless of the disease cause.
- Contemporary primary prevention ICD patients with channelopathies and inherited cardiomyopathies showed a low risk of life-threatening ventricular arrhythmia and death, suggesting that a better risk stratification would be desirable in these subgroups.
- Delayed high-rate detection was enabled in <40% of patients and correlated with a lower risk of appropriate ICD interventions, showing that better implementation of current programming recommendations is required in modern-era patients using an ICD.

Nonstandard Abbreviations and Acronyms

ARVC	arrhythmogenic right ventricular cardiomyopathy
BS	Brugada syndrome
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
ICM	ischemic cardiomyopathy
IS	inappropriate shock
LQTS	long-QT syndrome
PP	primary prevention
RT	randomized trial
SCD	sudden cardiac death
SP	secondary prevention
SVA	sustained ventricular arrhythmia
VA	ventricular arrhythmia
VHD	valvular heart disease

A broad spectrum of cardiovascular disorders have an increased risk of life-threatening ventricular arrhythmia (VA) and sudden cardiac death (SCD), with up to 50% of deaths related to cardiovascular

disease being linked to SCD.¹ Thus, an implantable cardioverter-defibrillator (ICD) is recommended to prevent SCD in patients at high risk of VA. In this setting, the survival benefit is achieved mainly by proper detection and subsequent treatment of life-threatening VA. Current recommendations for ICD therapy in patients with left ventricular systolic dysfunction are robust because they were derived from randomized trials (RTs).² However, many cardiac diseases are not included or are underrepresented in RTs, and the risk of SCD has been inferred from small observational studies by reporting the incidence of VA and ICD interventions.^{3–6} Large observational real-world studies describing ICD populations implanted with modern devices are lacking. Therefore, homogeneous information derived from a wide and diverse population after long-term follow-up is needed to analyze the real incidence of arrhythmia, mortality, and adverse events among patients using an ICD.

The UMBRELLA observational study intended to bridge this gap and to provide further knowledge about real clinical practice and SCD risk stratification. The UMBRELLA study aims to collect a large and contemporary ICD population implanted under current clinical guidelines and followed up by remote device monitoring. The primary objective of the UMBRELLA study was to assess the incidence of arrhythmias in a cohort of patients implanted with Medtronic ICDs in Spain, as well as to analyze the arrhythmic risk and mortality prognosis according to their clinical profiles and ICD indication. The secondary objective was to investigate the existence of additional parameters that could identify ICD patients at higher risk of malignant VA.

The incidence of arrhythmias in the UMBRELLA study population after 2 years of recruitment was published previously.⁷ Herein, we report the results of the entire cohort at the end of follow-up.

METHODS

Study Design

The UMBRELLA study is a multicenter, observational, nationwide study of patients implanted with Medtronic ICDs (Medtronic, Inc) and prospectively followed up through the Medtronic remote device monitoring system (CareLink). The study, which was sponsored by Medtronic Ibérica S.A. and registered at www.clinicaltrials.gov (NTC01561144), was performed in 44 hospitals distributed among 14 of the 17 regions in Spain. Institutional ethics committee approval was acquired according to national requirements, and written informed consent was mandatory for patient enrollment. The enrollment period started in August 2011 and ended in November 2017. For each patient, the

protocol allowed use of the device information from the implant date until study exit or end of follow-up. Thus, remote transmissions stored in the CareLink system before patient enrollment could be included in the study as a contribution to the follow-up of the patient's device.

As an observational study, ICD programming was performed according to regular clinical practice at each site.

The analytic methods and study materials that support the findings of this study will be made available to other researchers from the corresponding author on reasonable request.

Patient Selection

Patients were eligible for inclusion in the UMBRELLA study if they were at least 18 years old and implanted with a Medtronic ICD. In addition, patients were also required to be followed up by the remote monitoring system. Single-, dual-, and triple-chamber ICDs were permitted. The protocol allowed the inclusion of patients at the moment of implantation ("de novo" procedure or device replacement) as well as patients implanted with the device before the moment enrollment.

Data Collection and Follow-Up

The follow-up period ran from the date of the first ICD implant (November 11, 2005) to the end of study follow-up and data collection (November 30, 2017). For each patient, a baseline form was used to collect data on demographics, cardiovascular history, and implant procedure information related to the first device registered in the study database. All device information was automatically stored and collected through the remote monitoring system database. Information on adverse events, including deaths, or study exits was collected when applicable on separate forms. Data on cause-specific mortality were further classified into SCD, non-SCD, heart failure (HF) death, noncardiac death, or death of unknown origin.

A specific quality process was followed regularly throughout the study to ensure consistency in the collected data. Furthermore, twice a year, an analysis was performed of the patients who had not made any CareLink transmission within the previous 7 months.

Electrogram Analysis and Classification of Arrhythmic Events

A committee, composed of 6 expert electrophysiologists, analyzed all electrograms from the arrhythmic events that occurred in study patients. The electrograms were automatically stored in the CareLink

network. Two committee members reviewed each event in a blinded manner, classifying the type of arrhythmia and the effectiveness of the delivered therapy. If the 2 members disagreed on the classification, the event was referred to a third reviewer. If no agreement was reached, the event was reassigned to a new pair of reviewers and, if needed, to a sixth reviewer. If consensus was not reached at this point, the event was finally classified in a joint meeting of all committee members.

Arrhythmic episodes were classified as sustained VA (SVA), non-SVA, and nonventricular episodes. SVA was defined as ventricular episodes lasting ≥ 30 seconds and/or requiring ICD therapy, and was further classified into sustained monomorphic ventricular tachycardia (VT) or sustained polymorphic VT/ventricular fibrillation (VF). Non-SVA was defined as VA lasting < 30 seconds and terminated before the delivery of any ICD therapy. Nonventricular episodes were classified as atrial fibrillation (AF), sinus tachycardia, other regular supraventricular tachycardia, T-wave oversensing, false detection, or noise.

Appropriate ICD therapy was defined as any therapy (antitachycardia pacing or high-energy shocks) delivered to treat SVA episodes. Inappropriate shock (IS) was defined as any shock delivered to nonsustained ventricular episodes or nonventricular episodes.

All of the arrhythmic events described in this article come from the adjudication of the expert committee.

Subgroup Analysis and Outcomes

The entire cohort was clustered into subgroups according to the underlying heart disease and ICD indication. The resulting study subgroups were ischemic cardiomyopathy (ICM), nonischemic dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), valvular heart disease (VHD), long-QT syndrome (LQTS), Brugada syndrome (BS), arrhythmogenic right ventricular cardiomyopathy (ARVC), and adult congenital heart disease.

The study outcomes were SVA, first appropriate ICD therapy, all-cause death, and IS.

Statistical Analysis

Continuous variables are expressed as mean \pm SD, and categorical data are expressed as numbers and percentages. Parametric tests were used for comparisons: Student *t* test and χ^2 test for continuous and categorical variables, respectively. Cumulative incidence was described using the Kaplan-Meier method, and comparisons between the estimated curves were performed using the log-rank test.

Cox proportional hazards regression analysis was used to identify unadjusted risk factors for the study outcomes. After proportional hazard assumptions

were tested, a multivariable Cox regression analysis was performed to assess independent predictors of appropriate ICD therapy, all-cause death, and IS. The multivariate Cox regression model was adjusted for age, sex, hypertension, diabetes mellitus, hypercholesterolemia, smoking, history of AF, previous stroke, chronic kidney disease, family history of SCD, left ventricular ejection fraction (LVEF), QRS width, and heart disease, as well as the following ICD characteristics: type of device, ICD indication, detection zones enabled, and delayed high-rate detection programming. SmartShock technology was also included in the multivariate analysis of IS outcome. Data are expressed as hazard ratios (HRs) and 95% CIs. Analyses were performed using IBM Statistical Package for Social Sciences, version 25.0 (IBM SPSS, Inc, Chicago, IL). A 2-sided $P < 0.05$ was considered significant for all tests.

RESULTS

Population Characteristics

A total of 4618 patients were enrolled in the study, with 74.7% (n=3449) corresponding to first implants. Figure 1 shows the patient distribution according to available follow-up. A total of 322 patients (7%) were implanted and then included in the CareLink system but had no record of a remote transmission being made. As no follow-up information could be obtained, these patients were excluded from the analysis. Thus, the final study sample was composed of 4296 patients (follow-up population) in whom at least one remote transmission was performed. The mean follow-up was 46.6 ± 27.3 months (median, 44 months; maximum, 143 months). The baseline characteristics of the follow-up population and study subgroups are summarized in Table 1 and Tables S1 and S2.

ICD Type and Programming

Device models used in the UMBRELLA study are depicted in Table S3. ICD programming extracted from the first remote transmission is given in Table 2. Briefly, many primary prevention (PP) patients had a VT zone enabled (47.4%), and delayed high-rate detection programming was only enabled in 39.7% (n=1704) of follow-up population. Delayed high-rate programming was defined according to current consensus⁸ and comprised patients with a cutoff rate ≤ 320 ms and number of intervals to detect $\geq 30/40$ within the VF zone. Nevertheless, adherence to programming recommendations increased through the study period (Table S4).

SVA and Appropriate ICD Therapies

At study closure, a total of 27 472 stored arrhythmic episodes had been collected in 2048 patients

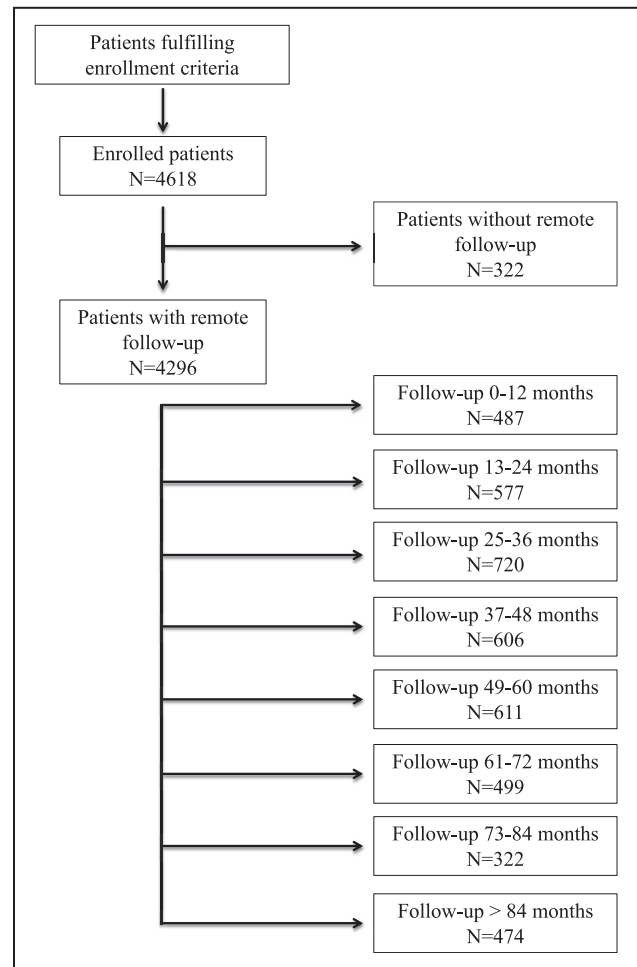


Figure 1. Flow diagram of patient distribution.

(47.7%). After blinded analysis of the electrograms, 11 405 were catalogued as non-SVA or nonventricular episodes. Therefore, 1344 patients (31.3% of follow-up population) experienced 16 067 episodes of SVA; 1054 episodes (6.6%) were catalogued by the committee as VF/sustained polymorphic VT and 15 013 (93.4%) were catalogued as sustained monomorphic VT. The overall cumulative incidence of SVA was 23% (95% CI, 22%–24%) at 1 year, 34% (95% CI, 33%–35%) at 3 years, and 54% (95% CI, 53%–55%) at 6 years. The incidence rates of SVA, appropriate ICD therapy, and all-cause death on the basis of the underlying heart disease and ICD indication are given in Table 3.

An appropriate ICD therapy was delivered to 85.7% (n=13 767) episodes of SVA in 1173 patients (event rate, 27.3%). A total of 1334 episodes of the untreated SVA occurred in a monitor zone (58.4%). The remaining 966 events (41.6%) corresponded to episodes of SVA that terminated before the delivery of the programmed therapy. Among the treated events, 346 episodes (2.7%) of sustained monomorphic VT

Table 1. Baseline Characteristics at Implantation in the Follow-Up Population and Study Subgroups

Characteristic	Follow-Up Population	ICM	DCM	VHD	HCM	ARVC	LQTS	BS	ACHD
No. (%)	4296 (100)	2150 (50)	1166 (27.1)	119 (2.8)	294 (6.8)	71 (1.7)	43 (1)	143 (3.3)	60 (1.4)
Age, mean±SD, y	61.9±12.9	65.6±10.1	62.1±12.1	63.5±12.6	52.6±15.1	47.4±11.9	51.1±18.5	50.3±12.6	45.6±14.2
Sex (men)	3527 (82.1)	1938 (90.2)	878 (75.3)	90 (75.6)	216 (73.5%)	51 (71.8)	12 (27.9)	120 (83.9)	34 (56.7)
Hypertension	2275 (54.4)	1358 (65)	598 (52.4)	60 (52.2)	109 (37.7)	14 (20.6)	11 (25.6)	24 (16.8)	11 (18.3)
Diabetes mellitus	1178 (28.3)	758 (36.4)	312 (27.5)	24 (21.1)	30 (10.3)	0 (0)	3 (2.3)	9 (5.6)	4 (6.7)
Hypercholesterolemia	2040 (52.5)	1291 (65.8)	462 (43.8)	40 (39.6)	111 (41.6)	16 (24.6)	6 (12.5)	33 (25.6)	13 (22)
Smoking status	1415 (37.7)	852 (45.2)	345 (33.8)	21 (21.4)	69 (26)	10 (15.9)	3 (7.7)	40 (32.5)	10 (16.9)
History of atrial fibrillation	1235 (29.4)	608 (29)	401 (35.1)	62 (63)	89 (30.5)	3 (4.3)	7 (16.3)	5 (3.5)	13 (21.7)
Previous stroke	252 (6.8)	145 (7.9)	60 (5.9)	9 (9)	17 (6.1)	1 (1.7)	3 (7.9)	2 (1.6)	3 (5.1)
Chronic kidney disease	633 (15.3)	380 (18.4)	183 (16.3)	17 (14.8)	19 (6.6)	3 (4.3)	3 (7)	4 (2.8)	4 (6.7)
Family history of SCD	356 (8.7)	48 (2.4)	93 (8.3)	3 (2.7)	104 (36.4)	15 (22.1)	10 (23.8)	44 (31.9)	14 (23.7)
LV ejection fraction, %									
≤35	2841 (66.4)	1633 (76.3)	996 (85.6)	64 (53.8)	34 (11.6)	11 (15.5)	1 (2.3)	1 (0.7)	25 (41.7)
36–50	631 (14.7)	379 (17.7)	131 (11.3)	27 (22.7)	35 (11.9)	11 (15.5)	5 (11.6)	5 (3.5)	9 (15)
>50	806 (18.9)	128 (5.9)	36 (3.1)	28 (23.5)	224 (76.5)	49 (69)	37 (86)	137 (95.8)	26 (43.3)
QRS width, ms									
<120	2202 (52.4)	1154 (53.7)	389 (34)	42 (35.9)	196 (68.3)	65 (91.5)	35 (81.4)	127 (90.1)	23 (40.4)
120–150	877 (20.9)	479 (22.3)	249 (21.7)	32 (27.4)	48 (16.7)	5 (7)	5 (11.6)	11 (7.8)	9 (15.8)
>150	1119 (26.7)	466 (21.7)	507 (44.3)	43 (36.8)	43 (15)	1 (1.4)	3 (7)	3 (2.1)	25 (43.9)
Previous heart failure	2973 (69.8)	1564 (73.1)	986 (85.4)	89 (75.4)	133 (45.2)	26 (36.6)	11 (25.6)	23 (16.1)	40 (66.7)
Type of device									
VR	2027 (47.2)	1107 (51.5)	356 (30.5)	46 (38.7)	137 (46.6)	48 (67.6)	16 (37.2)	133 (93)	23 (38.3)
DR	972 (22.6)	511 (23.8)	168 (14.4)	20 (16.8)	142 (48.3)	23 (32.4)	26 (60.5)	10 (7)	21 (35)
CRT-D	1297 (30.2)	532 (24.7)	642 (55.1)	53 (44.5)	15 (5.1)	0 (0)	1 (2.3)	0 (0)	16 (26.7)
Primary prevention	2758 (64.2)	1342 (62.4)	899 (77.1)	53 (44.5)	228 (77.6)	22 (31)	4 (9.3)	110 (76.9)	37 (61.7)

Data are given as number (percentage) unless otherwise noted. ACHD indicates adult congenital heart disease; ARVC, arrhythmogenic right ventricular cardiomyopathy; BS, Brugada syndrome; CRT-D, cardiac resynchronization therapy-defibrillator; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; LQTS, long-QT syndrome; LV, left ventricular; SCD, sudden cardiac death; and VHD, valvular heart disease.

Table 2. ICD Programming

Variable	Follow-Up Population (N=4296)	Primary Prevention (N=2758)	Secondary Prevention (N=1538)	P Value
Detection zones enabled				
Single zone*	1853 (43.2)	1451 (52.6)	402 (26.2)	<0.001
Multiple zones	2440 (56.8)	1305 (47.4)	1135 (73.8)	
VF detection interval, ms	302.7±19.4	302.9±18.7	302.4±20.4	0.396
NID				
<30/40	2490 (58)	1508 (54.7)	982 (63.8)	
≥30/40	1805 (42)	1249 (45.3)	555 (36.2)	
Fast VT detection zone enabled†	1557 (36.3)	879 (31.9)	678 (44.1)	<0.001
Fast VT detection interval, ms†	266.5±29.4	263.7±26	270±32.9	<0.001
VT detection interval, ms‡	361.6±25.3	358.7±20.4	366.7±31.5	<0.001
NID‡				
≤16	1395 (57.2)	740 (56.7)	655 (57.7)	
≥20	1045 (42.8)	565 (43.3)	480 (42.3)	
SmartShock technology–capable device	2930 (72.1)	1890 (72.6)	1040 (71.0)	0.267

Data are given as number (percentage) or mean±SD. ICD indicates implantable cardioverter-defibrillator; NID, number of intervals to detect; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Patients with fast VT zone enabled through VF zone, but without any other VT zone activated, were also considered as single-zone detection patients.

†Through VF detection zone.

‡Applies only to multiple-zone detection programming patients.

received high-energy shocks, 11 074 (85.7%) received antitachycardia pacing, and 1508 (11.6%) received both therapies, whereas 615 episodes (73.3%) of sustained polymorphic VT/VF received high-energy shocks, 63 (7.5%) received antitachycardia pacing, and 161 (19.2%) received both therapies. The overall cumulative incidence of appropriate ICD therapy was 14% (95% CI, 13%–15.2%) at 1 year, 26% (95% CI, 24.7%–27.7%) at 3 years, and 36% (95% CI, 34.4%–38.2%) at 6 years. A higher risk of first appropriate ICD therapy was observed in patients with VHD (HR, 1.94; 95% CI, 1.43–2.62; $P<0.001$), ARVC (HR, 1.84; 95% CI, 1.28–2.66; $P=0.001$), ICM (HR, 1.51; 95% CI, 1.29–1.78; $P<0.001$), and DCM (HR, 1.28; 95% CI, 1.07–1.53; $P=0.005$), whereas patients with HCM (HR, 0.72; 95% CI, 0.54–0.96; $P=0.027$) and BS (HR, 0.25; 95% CI, 0.14–0.45; $P<0.001$) were at significantly lower risk (Figure 2A). A trend toward lower risk was seen in LQTS (HR, 0.49; 95% CI, 0.22–1.09; $P=0.082$), whereas no differences in risk were observed in adult congenital heart disease (HR, 1.30; 95% CI, 0.85–1.99; $P=0.218$). Furthermore, the risk of appropriate ICD therapy was higher in secondary prevention (SP) patients than in PP patients (HR, 2.27; 95% CI, 2.02–2.54; $P<0.001$). The event incidence rate was 40.1% versus 20.4%, respectively (Figure 2B).

In the multivariate analysis (Table 4), age, sex, previous AF, SP, LVEF ≤35%, and QRS width (120–150 ms) emerged as clinical predictors of appropriate ICD therapy, whereas the implantation of a cardiac resynchronization therapy-defibrillator correlated

with lower risk. Among causative subgroups, an independently higher risk of appropriate ICD therapy was found in patients with DCM, VHD, and ARVC, whereas patients with BS exhibited a lower risk. Among ICD settings, delayed high-rate detection in PP patients (Figure 3A) and single-zone programming were associated with a lower risk of first appropriate ICD therapy.

All-Cause Death

At the end of follow-up, 590 deaths (event rate, 13.4% of follow-up population) had been reported. The causes of death are given in Table S5. The cumulative incidence of all-cause death was 5% (95% CI, 4%–6%) at 1 year, 13% (95% CI, 12%–14%) at 3 years, and 25% (95% CI, 24%–26%) at 6 years. Patients with ICM (HR, 3.90; 95% CI, 2.58–5.90; $P<0.001$), DCM (HR, 3.33; 95% CI, 2.18–5.10; $P<0.001$), and VHD (HR, 3.97; 95% CI, 2.25–6.99; $P<0.001$) had worse prognoses (Figure 2C), and prognosis was significantly better in patients with BS (HR, 0.11; 95% CI, 0.01–0.67; $P=0.017$). ICD indication lacked a statistical relationship with mortality (HR, 1.19; 95% CI, 0.91–1.41; $P=0.076$). The event rate was 14.7% in PP patients and 13.9% in SP patients (Figure 2D).

In the multivariate analysis, sex, increasing age, previous AF, chronic kidney disease, diabetes mellitus, and impaired LVEF emerged as independent predictors of all-cause death (Table 4). No excess risk of mortality was associated with any ICD setting.

Table 3. Incidence of Study End Points, According to the Underlying Heart Disease and ICD Indication

Variable	SVA	P Value	Appropriate ICD Therapy	P Value	All-Cause Death	P Value
ICM (n=2150)	730 (34.0)		658 (30.6)		371 (17.3)	
Primary prevention (n=1342)	349 (26.0)	<0.001*	310 (23.1)	<0.001*	235 (17.5)	0.686*
Secondary prevention (n=808)	381 (47.2)		348 (43.1)		136 (16.8)	
DCM (n=1166)	355 (30.4)		306 (26.2)		167 (14.3)	
Primary prevention (n=904)	223 (24.8)	<0.001*	187 (20.8)	<0.001*	131 (14.6)	0.656*
Secondary prevention (n=268)	132 (49.4)		119 (44.6)		36 (13.4)	
HCM (n=294)	65 (22.1)		49 (16.7)		9 (3.1)	
Primary prevention (n=228)	38 (16.7)	<0.001*	25 (10.1)	<0.001*	5 (2.2)	0.108*
Secondary prevention (n=66)	27 (40.9)		26 (39.4)		4 (6.1)	
VHD (n=119)	49 (41.2)		43 (36.1)		19 (16)	
Primary prevention (n=53)	17 (33.1)	0.071	16 (30.2)	0.226*	8 (15.1)	0.816*
Secondary prevention (n=66)	32 (48.5)		27 (40.9)		11 (16.7)	
ARVC (n=71)	31 (43.7)		27 (38)		1 (1.4)	
Primary prevention (n=22)	7 (31.8)	0.178*	6 (27.3)	0.211*	1 (4.5)	0.310*
Secondary prevention (n=49)	24 (49)		21 (42.9)		0 (0)	
LQTS (n=43)	8 (18.6)		5 (11.6)		1 (2.3)	
Primary prevention (n=4)	0 (0)	0.424*	0 (0)	0.598*	0 (0)	0.746*
Secondary prevention (n=39)	8 (20.5)		5 (12.8)		1 (2.6)	
BS (n=143)	13 (9.1)		10 (7)		1 (0.7)	
Primary prevention (n=110)	5 (4.5)	0.002*	3 (2.7)	0.001*	1 (0.9)	0.583*
Secondary prevention (n=33)	8 (24.2)		7 (21.2)		0 (0)	
ACHD (n=60)	23 (38.3)		19 (31.7)		5 (8.3)	
Primary prevention (n=37)	11 (29.7)	0.082*	8 (21.6)	0.034*	3 (8.1)	0.936*
Secondary prevention (n=23)	12 (52.2)		11 (47.8)		2 (8.7)	

Data are given as number (percentage). ACHD indicates adult congenital heart disease; ARVC, arrhythmogenic right ventricular cardiomyopathy; BS, Brugada syndrome; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; LQTS, long-QT syndrome; SVA, sustained ventricular arrhythmia; and VHD, valvular heart disease.

*Comparison of the proportion of primary vs secondary prevention patients within the same cardiomyopathy subgroup.

Inappropriate Shocks

A total of 1375 patients (32% of follow-up population) had 11 405 episodes catalogued as non-SVA or non-VA. Inappropriate ICD therapy was given in 13.2% (n=1503) of these episodes, but only 257 patients (6%) experienced an IS. The most frequent cause of an IS was AF and other supraventricular tachycardia (Table S6). The incidence of IS was higher in patients with HCM (9.4%; $P=0.007$), and a trend toward higher risk was seen in patients with ARVC (10.7%; $P=0.065$), but it was lower in patients with BS (1.3%; $P=0.015$) and ICM (5%; $P=0.008$). No significant differences were found in patients with DCM (6.8%; $P=0.153$), VHD (4.9%; $P=0.477$), adult congenital heart disease (3.1%; $P=0.214$), and LQTS (2%; $P=0.232$). The incidence of IS did not differ according to type of device (6.4% versus 6.2% versus 5.2% for VR, DR, and cardiac resynchronization therapy-defibrillator, respectively; $P=0.321$) or ICD indication (6.8% for PP versus 5.5% for SP; $P=0.081$), but it was lower in patients implanted with SmartShock-capable devices (4% versus 8.7%; $P=0.002$; Figure 3B).

In the multivariate analysis (Table 4), previous AF was the only clinical predictor of IS, whereas increasing age correlated with a lower risk. Among ICD settings, single-zone programming was independently related to a lower risk of IS.

DISCUSSION

Our study comprises the largest contemporary cohort of ICD patients implanted according to current clinical guidelines and followed up over a long period of time. We had several key findings. First, left ventricular systolic dysfunction, and subsequent HF, remains the most frequent indication for ICD implantation, with PP as the leading strategy. Second, ICD patients with HF-related disorders had a similar risk of life-threatening VA, appropriate ICD therapies, and death, regardless of the cause (ischemic, dilated, or valvular heart disease). SP patients were more prone to VA and appropriate ICD therapies, but survival was similar to PP patients. In addition,

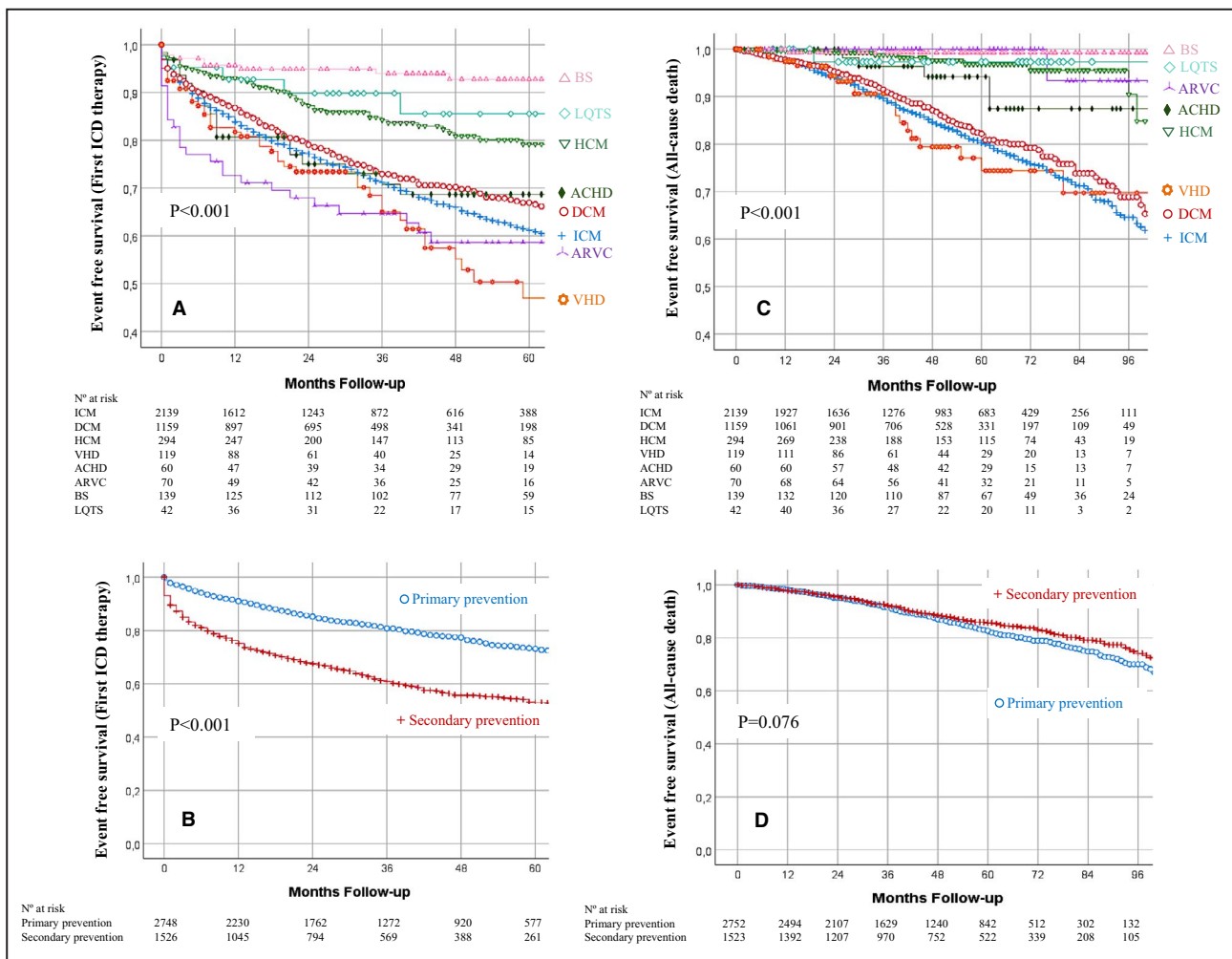


Figure 2. Kaplan-Meier curves for first appropriate implantable cardioverter-defibrillator (ICD) therapy according to underlying heart disease (A) and ICD indication (B); and for all-cause death according to underlying heart disease (C) and ICD indication (D).

ACHD indicates adult congenital heart disease; ARVC, arrhythmogenic right ventricular cardiomyopathy; BS, Brugada syndrome; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; LQTS, long-QT syndrome; and VHD, valvular heart disease.

prophylactic ICD patients with channelopathies and inherited cardiomyopathies presented a low risk of life-threatening VA. Finally, delayed high-rate and single-zone detection programming were poorly implemented in patients with daily clinical ICD, and they were confirmed as essential programming strategies.

To the best of our knowledge, this is the first large-scale study of ICD carriers including patients with no restriction on ICD indication or underlying heart disease. This point allows us to compare the evolution of different populations using an ICD in a real-life scenario. The rigorous follow-up allowed by the remote monitoring guarantees a reliable incidence of arrhythmia and ICD interventions and offers the opportunity to explore the impact that currently recommended programming strategies have on outcomes. A strength of the UMBRELLA study is that it provides a systematic

review of stored arrhythmic events classified by a blinded committee of experts.

SVA and Appropriate ICD Therapies

The incidence of SVA and appropriate ICD interventions has declined over the past years. In major ICD trials, the incidence of appropriate therapies ranged from 17% to 31% in PP to 54% to 64% in SP studies.⁹ Similar rates were reported in observational registries^{10,11} with short-term follow-up that did not include channelopathies or inherited cardiomyopathies. More modern real-world studies reported a lower rate of life-threatening VA. In the DANISH ICD registry,¹² only 13.5% of the 1609 ischemic patients carrying a prophylactic ICD received an appropriate therapy. Nevertheless, the authors admit some underreporting of therapies, which is rare in the UMBRELLA study

Table 4. Multivariate Cox Regression Analysis of the Study End Points

End Point	Variable	HR (95% CI)	P Value
First appropriate ICD therapy	Clinical parameters		
	Age	1.01 (1.00–1.01)	0.023
	Sex (men)	1.57 (1.26–1.94)	<0.001
	AF	1.29 (1.12–1.49)	<0.001
	Secondary prevention	1.96 (1.67–2.31)	<0.001
	QRS width, ms		
	>150	0.98 (0.81–1.21)	0.896
	120–150	1.32 (1.09–1.61)	0.005
	<120	REF	
	LVEF, %		
	≤35	1.53 (1.18–1.97)	0.001
	36–50	1.21 (0.92–1.58)	0.168
	>50	REF	
	Type of device		
	CRT-D	0.76 (0.61–0.94)	0.011
	Dual-chamber ICD	1.03 (0.88–1.21)	0.711
	Single-chamber ICD	REF	
	ICD settings		
	Single-zone programming	0.69 (0.59–0.81)	<0.001
Delayed high-rate detection*	0.76 (0.61–0.94)	0.012	
Causative subgroups			
DCM	1.30 (1.02–1.66)	0.036	
VHD	1.54 (1.08–2.20)	0.018	
ARVC	1.72 (1.14–2.61)	0.010	
BS	0.32 (0.15–0.67)	0.003	
All-cause death	Clinical parameters		
	Age	1.05 (1.04–1.06)	<0.001
	AF	1.31 (1.09–1.59)	0.004
	Sex (men)	1.43 (1.07–1.93)	0.016
	CKD	1.75 (1.43–2.15)	<0.001
	DM	1.63 (1.35–1.96)	<0.001
	LVEF, %		
	≤35	2.44 (1.65–3.62)	<0.001
	36–50	1.79 (1.14–2.80)	0.011
	>50	REF	
Inappropriate shock	Clinical parameters		
	Age	0.98 (0.97–0.99)	0.001
	AF	2.40 (1.73–3.32)	<0.001
	ICD settings		
	Single-zone programming	0.71 (0.51–0.97)	0.035

AF indicates atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; BS, Brugada syndrome; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy-defibrillator; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HR, Hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; REF, reference group; and VHD, valvular heart disease.

*Among primary prevention patients.

because of the automatic storage of all arrhythmic events. A contemporary but retrospective study from Amara et al¹³ demonstrated 22.3% of appropriate therapies after a 3-year follow-up in a cohort of PP ICD-only patients.

The incidence of appropriate therapies in the UMBRELLA study ranges from 7% in patients with BS to 38% in patients with ARVC. Our cohort is composed of 8 different cardiomyopathies, includes PP and SP, and has long-term follow-up. This kind of

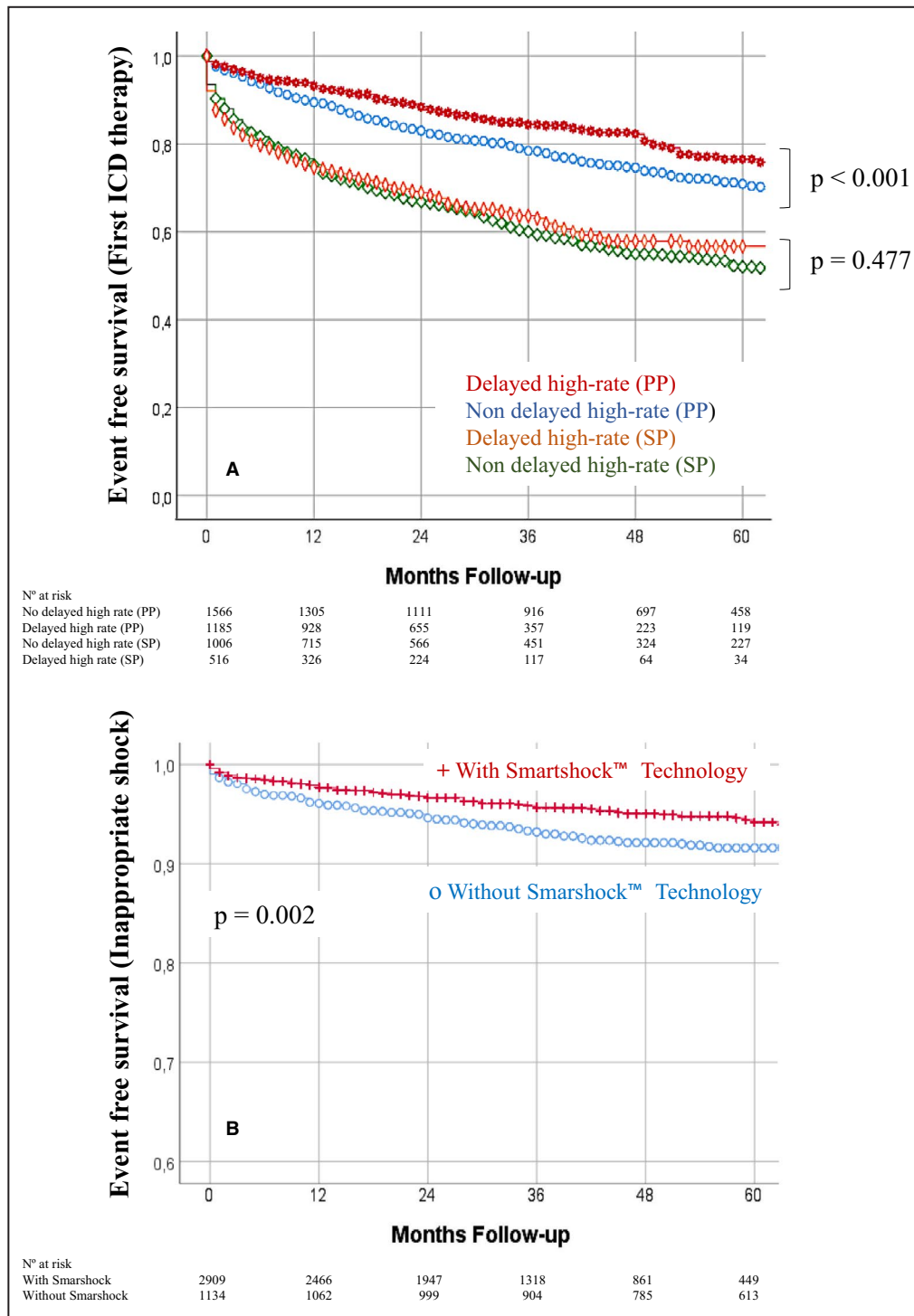


Figure 3. Kaplan-Meier curves for first appropriate implantable cardioverter-defibrillator (ICD) therapy, according to delayed high-rate detection stratified by ICD indication (A), and for inappropriate shock, according to SmartShock technology (B). PP indicates primary prevention; and SP, secondary prevention.

comparison has never been performed. VHD, ARVC, and DCM predicted a higher risk of appropriate ICD therapies, whereas BS correlated with lower risk, which indicates the importance of a pathological myocardial substrate on the risk of SCD. LVEF

≤35% was associated with a 1.5-fold increased risk, whereas cardiac resynchronization therapy-defibrillator patients, who have the chance for improved LVEF, were at significantly lower risk. This is somewhat striking, as concerns about the benefit of ICD

in DCM are still present.¹⁴ Our results suggest that patients with DCM, when carefully selected, are at high risk of life-threatening VA and may obtain a similar benefit as other high-risk populations (ICM/ARVC). In addition, the high arrhythmia risk found in patients with VHD agrees with published data on PP patients.¹⁵ Left ventricle overload and remodeling attributable to valvular dysfunction seem to offer another pathological substrate for the occurrence of life-threatening VA.

ICD shocks are life saving, but they are also associated with an increased risk of complications and death. We found that 14.3% of episodes of SVA did not receive an ICD intervention, which supports the existence of non-life-threatening episodes of SVA. Current consensus recommends shock reduction strategies based on high-rate cutoffs, delayed programming, and single-zone detection.⁸ These recommendations were derived from trials performed mainly in patients with HF. In the UMBRELLA study, high-rate cutoffs were commonly programmed through the VF zone, but number of intervals to detect <30/40 was present in 58% of patients and VT zones were enabled in many PP patients. This may be explained by the 12-year period of patient enrollment in which recommendations were continuously evolving.

Our results endorse the usefulness of single-zone detection and the combination of high-rate intervals with delayed detection. This setting was associated with 24% lower risk of appropriate ICD therapies among PP patients. Thus, despite an increase in the adoption of delayed programming throughout the study period, current programming recommendations still need to be implemented in patients using an ICD.

All-Cause Death

Mortality was lower in the UMBRELLA study than in other observational reports,^{11–13,16} which may be related to the inclusion of low-risk populations. Our study reinforces the idea that ICM has an unfavorable prognosis. In addition, the prognosis of DCM was similar to ICM; thus, death in patients with left ventricular systolic dysfunction seems to be barely influenced by the cause of HF. Another important finding is that patients with VHD were not only at high risk of life-threatening VA, but also death. Therefore, they probably represent a subgroup of patients with HF who may obtain a similar benefit from ICD as other patients with left ventricular systolic dysfunction.¹⁵ However, the relationship between a high risk of malignant VA and death is not always present, as with ARVC, which is mainly an electrical disease. Taken together, the results indicate that the risk of death in

patients using an ICD is influenced mainly by patient comorbidities and LVEF.

Predictors of death found in the UMBRELLA study are in agreement with the results of developed risk models.^{17–19} Increasing age, AF, chronic kidney disease, diabetes mellitus, and impaired LVEF are well-established predictors of death in patients using an ICD. Nevertheless, most of the models were performed with cohorts of PP and ischemic patients.

Other Subgroups

In the UMBRELLA study, the risk of arrhythmic events and death was low among HCM, LQTS, and BS carriers of a prophylactic ICD. As RTs are lacking, recommendations for ICD implantation have been derived from small observational reports.^{3–6} Several stratification methods have been proposed to determine the minimum risk of SCD that could justify a prophylactic ICD. A 5-year risk of SCD $\geq 6\%$ supposes a class IIa recommendation for an ICD in patients with HCM,³ and BS patients with 2 risk factors had a 5-year risk of arrhythmic events of 10.2% in a recently developed score.⁶ In the UMBRELLA study population of patients with HCM, LQTS, and BS, the risk of appropriate ICD therapy after a mean follow-up of 46 months ranged from 0% to 10.1%, in PP setting. Therefore, in the absence of RTs, better stratification methods are necessary to select PP candidates with enough 5-year risk of SCD to support the implantation of an ICD.

Inappropriate Shocks

Current programming recommendations led to a reduction of IS rates to $<5\%$.⁸ This tendency was confirmed in the UMBRELLA study, with an annual rate of 1.53%. Our results also agree with contemporary recommendations, as single-zone detection correlated with 29% lower risk of IS.

AF was the leading cause of IS and correlated with a 2.4-fold increased risk, but we also found that age was associated with a lower risk of IS. Although elderly patients are more prone to developing AF, the probability of rapid ventricular conduction may be lower. Thus, IS reduction strategies should be enhanced among younger patients using an ICD.

In theory, dual-chamber devices have more power to discriminate between supraventricular tachycardia and VA, but several studies have failed to demonstrate this.⁸ We think that our heterogeneous population supposes a barrier to identifying any potential benefit. We reported an independently lower risk of IS among dual-chamber ICDs in the UMBRELLA study population of PP patients with HF.²⁰ SmartShock technology consists of 6 discrimination algorithms that are nominally activated to distinguish between true VA and other

rhythms. As observed in previous reports,²¹ the use of SmartShock technology in modern-era ICD patients with real-world programming led to a low IS rate in the UMBRELLA study.

Limitations

This study has limitations inherent to the observational design. The UMBRELLA study is a single-brand ICD study and, as such, extrapolation of the conclusions to other brands should be made with caution. Nevertheless, characteristics of the UMBRELLA study population are similar to the characteristics of patients included in the last Spanish ICD Registry²² (Table S7), which enrolled >90% of the devices implanted in our country. Therefore, we believe our sample might represent a real picture of the Spanish population using an ICD. ICD programming evolved throughout the 12-year period of patient inclusion. We did not study temporal trends in programming because this topic is currently being analyzed in another study by our group. Although we included several populations that are underrepresented in RTs, the small size of these subgroups and the lack of specific predictors of death (ie, wall thickness in HCM) limit the power to extract stronger conclusions.

CONCLUSIONS

This contemporary nationwide study involved a broad ICD population with long-term follow-up. We observed a decrease in the incidence of SVA, appropriate ICD therapies, IS, and death compared with previous observational and randomized studies. Patients with myocardial substrate derived from an impaired LVEF (ICM, DCM, and VHD) were at higher risk of appropriate ICD interventions and death than those with channelopathies and HCM.

A better SCD risk stratification is necessary in PP ICD patients with channelopathies and inherited cardiomyopathies. A strategy based on delayed high-rate detection and single-zone programming still needs to be implemented in modern-era patients using an ICD.

APPENDIX

Principal investigators and participating centers of the UMBRELLA study: Ricardo Pavón, Hospital Nuestra Señora De Valme (Sevilla); José María Arizón, Hospital Universitario Reina Sofía (Córdoba); Miguel Álvarez López, Hospital Universitario Virgen De Las Nieves (Granada); Javier Alzueta, Hospital Virgen De La Victoria (Málaga); Ernesto Díaz Infante, Hospital Universitario Virgen Macarena (Sevilla); David Calvo, Hospital Universitario Central De Asturias (Asturias); Juan Carlos Rodríguez, Hospital Insular De Gran Canaria (Gran Canaria); Aníbal

Rodríguez, Hospital Universitario De Canarias (Tenerife); Luis Álvarez, Hospital Universitario Nuestra Señora De La Candelaria (Tenerife); Juanjo Olalla, Hospital Universitario Marqués De Valdecilla (Santander); Javier Jiménez Díaz, Hospital General De Ciudad Real (Ciudad Real); Javier Balaguer, Hospital General Y Universitario De Guadalajara (Guadalajara); Miguel Ángel Arias, Hospital Virgen De La Salud (Toledo); Jerónimo Rubio, Hospital Clínico Universitario De Valladolid (Valladolid); Marisa Fidalgo, Hospital De León (León); Francisco-Javier García, Hospital Universitario De Burgos (Burgos); Xavier Viñolas, Hospital De La Santa Creu I Sant Pau (Barcelona); Josep Brugada, Hospital Clínico De Barcelona (Barcelona); Ignasi Anguera, Hospital De Bellvitge (Barcelona); Roger Villuendas, Hospital Germans Trias I Pujol (Barcelona); Rosa Porro, Hospital San Pedro De Alcántara (Cáceres); Joaquín Fernández de la Concha, Hospital Infanta Cristina (Badajoz); Luisa Pérez, Complejo Hospitalario Universitario A Coruña (A Coruña); Enrique García Campo, Complejo Hospitalario Universitario De Vigo (Pontevedra); Ignacio Fernández Lozano, Hospital Universitario Puerta De Hierro (Majadahonda); Adolfo Fontenla, Hospital 12 De Octubre (Madrid); Julián Villacastín, Hospital Clínico San Carlos (Madrid); Ángel Arenal, Hospital General Universitario Gregorio Marañón (Madrid); Roberto Muñoz Aguilera, Hospital Infanta Leonor (Madrid); Antonio Hernández, Hospital Universitario Ramón Y Cajal (Madrid); Rafael Peinado, Hospital Universitario La Paz (Madrid); Arcadio García Alberola, Hospital Clínico Universitario Virgen De La Arrixaca (Murcia); Fernando Pérez Lorente, Hospital General Universitario Reina Sofía (Murcia); Nuria Basterra, Hospital de Navarra (Navarra); María Fe Arcocha, Hospital de Basurto (Vizcaya); Andrés Bodegas, Hospital de Cruces (Baracaldo); Francisco Zumalde, Hospital de Galdakao-Usansolo (Vizcaya); José B. Martínez Ferrer, Hospital Universitario De Álava (Álava); José María Porres, Hospital Universitario Donostia (Guipúzcoa); José Moreno Arribas, Hospital Clínico San Juan (Alicante); Ricardo Ruiz, Hospital Clínico Universitario De Valencia (Valencia); Aurelio Quesada, Hospital General Universitario De Valencia (Valencia); Juan Gabriel Martínez, Hospital General Universitario De Alicante (Alicante); María José Sancho-Tello, Hospital Universitario Y Politécnico De La Fe (Valencia).

ARTICLE INFORMATION

Received October 6, 2020; accepted October 28, 2020.

Affiliations

From the Hospital Universitario Infanta Leonor, Madrid, Spain (S.B.-F.); Universidad Complutense de Madrid, Madrid, Spain (S.B.-F.); Hospital Virgen de la Arrixaca, Murcia, Spain (A.G.-A.); Hospital Clínico Universitario de Valladolid, Valladolid, Spain (J.R.); Hospital Reina Sofía de Córdoba, Córdoba, Spain (J.M.S.); Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain (A.R.); Hospital Universitario La Paz, Madrid, Spain (R.P.);

Hospital Universitario Virgen de la Victoria, Málaga, Spain (J.A.); Hospital Universitario de Árabá, Álava, Spain (J.B.M.-F.); Hospital Santa Creu i Sant Pau, Barcelona, Spain (X.V.); Hospital Infanta Cristina, Badajoz, Spain (J.F.d.); Hospital Universitario de Bellvitge, Barcelona, Spain (I.A.); Medtronic Ibérica, Madrid, Spain (M.M., L.C.); and Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain (L.P.).

Acknowledgments

The authors appreciate the efforts made by the investigators of the UMBRELLA study and Medtronic personnel who have contributed to the success of this project.

Sources of Funding

The UMBRELLA study was supported by Medtronic Iberica.

Disclosures

Dr Briongos-Figuero reports personal fees and nonfinancial support from Medtronic Iberica and personal fees from Boston Scientific. Dr Garcia-Alberola reports grants from Medtronic. Dr Rubio reports personal fees from Medtronic, St. Jude, and Boston Scientific. Dr Segura reports personal fees from Medtronic and grants from Boston Scientific. Dr Peinado reports personal fees from Medtronic and grants from Medtronic, Boston Scientific, and Abbot. Dr Martínez-Ferrer reports personal fees and non-financial support from Medtronic. Drs Martín and Cerdá are employees of Medtronic.

Supplementary Material

Tables S1–S7

REFERENCES

1. Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. *Nat Rev Cardiol*. 2010;7:216–225.
2. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europe. *Eur Heart J*. 2015;36:2793–2867.
3. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010–2020.
4. Orgeron GM, James CA, Te RA, Tichnell C, Murray B, Bhonsale A, Kamel IR, Zimmerman SL, Judge DP, Crosson J, et al. Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular dysplasia/cardiomyopathy: predictors of appropriate therapy, outcomes, and complications. *J Am Heart Assoc*. 2017;6:e006242. DOI: 10.1161/JAHA.117.006242.
5. Schwartz PJ, Spazzolini C, Priori SG, Crotti L, Vicentini A, Landolina M, Gasparini M, Wilde AAM, Knops RE, Denjoy I, et al. Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them? Data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry. *Circulation*. 2010;122:1272–1282.
6. Sieira J, Conte G, Ciconte G, Chierchia G-B, Casado-Arroyo R, Baltogiannis G, Di GG, Saitoh Y, Julia J, Mugnai G, et al. A score model to predict risk of events in patients with Brugada syndrome. *Eur Heart J*. 2017;38:1756–1763.
7. Fontenla A, Martínez-Ferrer JB, Alzueta J, Vinolas X, Garcia-Alberola A, Brugada J, Peinado R, Sancho-Tello MJ, Cano A, Fernandez-Lozano I. Incidence of arrhythmias in a large cohort of patients with current implantable cardioverter-defibrillators in Spain: results from the UMBRELLA Registry. *Europace*. 2016;18:1726–1734.
8. Wilkoff BL, Fauchier L, Stiles MK, Morillo CA, Al-Khatib SM, Almendral J, Aguinaga L, Berger RD, Cuesta A, Daubert JP, et al. 2015 HRS/EHRA/APHS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Heart Rhythm*. 2016;13:e50–e86.
9. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol*. 2006;97:1255–1261.
10. van Welsenes GH, van Rees JB, Borleffs CJW, Cannegieter SC, Bax JJ, van Erven L, Schalij MJ. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. *Europace*. 2011;13:389–394.
11. MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P, Birnie D, Simpson CS, Khaykin Y, Pinter A, et al. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. *Ann Intern Med*. 2012;156:195–203. DOI: 10.7326/0003-4819-156-3-201202070-00007.
12. Weeke P, Johansen JB, Jorgensen OD, Nielsen JC, Moller M, Videbaek R, Hojgaard MV, Riahi S, Jacobsen PK. Mortality and appropriate and inappropriate therapy in patients with ischaemic heart disease and implanted cardioverter-defibrillators for primary prevention: data from the Danish ICD Register. *Europace*. 2013;15:1150–1157. DOI: 10.1093/europace/eut017.
13. Amara N, Boveda S, Defaye P, Klug D, Treguer F, Amet D, Perier M-C, Gras D, Algarrondo V, Bouzeman A, et al. Implantable cardioverter-defibrillator therapy among patients with non-ischaemic vs. ischaemic cardiomyopathy for primary prevention of sudden cardiac death. *Europace*. 2018;20:65–72.
14. Kober L, Thune JJ, Nielsen JC, Haarlo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375:1221–1230. DOI: 10.1056/NEJMoa1608029.
15. Rodríguez-Mañero M, Barrio-López MT, Assi EA, Expósito-García V, Bertomeu-González V, Sánchez-Gómez JM, González-Torres L, García-Bolao I, Gaztañaga L, Cabanas-Grandío P, et al. Primary prevention of sudden death in patients with valvular cardiomyopathy. *Rev Esp Cardiol (Engl Ed)*. 2016;69:272–278. DOI: 10.1016/j.rec.2015.05.016.
16. Al-Khatib SM, Hellkamp A, Bardy GH, Hammill S, Hall WJ, Mark DB, Anstrom KJ, Curtis J, Al-Khalidi H, Curtis LH, et al. Survival of patients receiving a primary prevention implantable cardioverter-defibrillator in clinical practice vs clinical trials. *JAMA*. 2013;309:55–62. DOI: 10.1001/jama.2012.157182.
17. van Rees JB, Borleffs CJW, van Welsenes GH, van der Velde ET, Bax JJ, van Erven L, Putter H, van der Bom JG, Schalij MJ. Clinical prediction model for death prior to appropriate therapy in primary prevention implantable cardioverter defibrillator patients with ischaemic heart disease: the FADES risk score. *Heart*. 2012;98:872–877. DOI: 10.1136/heartjnl-2011-300632.
18. Levy WC, Lee KL, Hellkamp AS, Poole JE, Mozaffarian D, Linker DT, Maggioni AP, Anand I, Poole-Wilson PA, Fishbein DP, et al. Maximizing survival benefit with primary prevention implantable cardioverter-defibrillator therapy in a heart failure population. *Circulation*. 2009;120:835–842. DOI: 10.1161/CIRCULATIONAHA.108.816884.
19. 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;60:1647–1655. DOI: 10.1016/j.jacc.2012.07.028.
20. Briongos-Figuero S, Sánchez A, Pérez ML, Martínez-Ferrer JB, García E, Viñolas X, Arenal Á, Alzueta J, Basterra N, Rodríguez A, et al. Single-brand dual-chamber discriminators to prevent inappropriate shocks in patients implanted with prophylactic implantable cardioverter defibrillators: a propensity-weighted comparison of single- and dual-chamber devices. *J Interv Card Electrophysiol*. 2019;54:267–275. DOI: 10.1007/s10840-018-0494-0.
21. Auricchio A, Schloss EJ, Kurita T, Meijer A, Gerritse B, Zweibel S, AlSmadi FM, Leng CT, Sterns LD. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results. *Heart Rhythm*. 2015;12:926–936. DOI: 10.1016/j.hrthm.2015.01.017.
22. Fernandez Lozano I, Osca Asensi J, Alzueta RJ. Spanish Implantable Cardioverter-Defibrillator Registry: 15th Official Report of the Spanish Society of Cardiology Electrophysiology and Arrhythmias Section (2018). *Rev Esp Cardiol (Engl Ed)*. 2019;72:1054–1064.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics according to date of ICD implant.

	2005-2009	2010-2014	2015-2017
N (%)	344 (8)	2744 (63.9)	1208 (28.1)
Age (years), mean (\pm SD)	61.5 \pm 13.7	61.9 \pm 13.2	62.3 \pm 12.0
Sex (male)	290 (84.3)	2259 (82.4)	978 (81.0)
Hypertension	158 (47.7)	1449 (54.4)	668 (56.3)
Diabetes	72 (21.9)	742 (28.0)	364 (30.8)
Hypercholesterolaemia	157 (49.5)	1315 (52.0)	568 (54.7)
Smoking status	115 (39.9)	867 (35.4)	433 (42.8)
History of atrial fibrillation	116 (34.8)	745 (27.9)	374 (31.4)
Previous stroke	18 (6.0)	167 (6.8)	67 (7.0)
Chronic kidney disease	42 (12.9)	410 (15.6)	181 (15.4)
Family history of SCD	29 (9.0)	241 (9.3)	86 (7.3)
LV ejection fraction			
\leq 35%	217 (63.5)	1807 (66.1)	817 (68.0)
36-50%	57 (16.7)	399 (14.6)	175 (14.6)
$>$ 50%	68 (19.9)	528 (19.3)	210 (17.5)
QRS width			
$<$ 120 ms	160 (47.6)	1398 (52.0)	644 (54.9)
120-150 ms	72 (21.4)	575 (21.4)	230 (19.6)
$>$ 150 ms	104 (31.0)	717 (26.7)	298 (25.4)
Previous heart failure	152 (76.8)	1088 (82.8)	481 (83.2)
Type of device			
VR	159 (46.2)	1237 (45.1)	631 (52.1)
DR	77 (22.4)	682 (24.9)	213 (17.6)
CRT-D	108 (31.4)	825 (30.1)	364 (30.1)
Primary prevention	210 (61.0)	1735 (63.2)	818 (67.7)

Data are given as n (%) unless otherwise noted. CRT-D: cardiac resynchronization therapy defibrillator; LV: left ventricle; SCD: sudden cardiac death; SD: standard deviation.

Table S2. Number of patients in whom baseline data are available.

Baseline characteristics	Valid data, n (%)
Age	4296 (100)
Sex	4296 (100)
Hypertension	4184 (97.4)
Diabetes	4166 (97)
Hypercholesterolaemia	3884 (90.4)
Smoking status	3752 (87.3)
History of atrial fibrillation	4198 (97.7)
Previous stroke	3702 (86.2)
Chronic kidney disease	4132 (96.2)
Family history of SCD	4090 (95.2)
LV ejection fraction	4278 (99.6)
QRS width	4198 (97.7)
Previous heart failure	4259 (99.1)
Type of device	4296 (100)
ICD indication (primary vs. secondary prevention)	4296 (100)
ICD programming	
Detection zones enabled	4293 (99.9)
VF detection interval	4295 (99.9)
NID within VF detection zone	4295 (99.9)
Fast VT detection zone enabled	4293 (99.9)
Fast VT detection interval*	1557 (100)
VT detection interval	4295 (99.9)
NID within VT detection zone**	2440 (100)
SmartShock™ Technology capable device	4065 (94.6%)

ICD: Implantable cardioverter-defibrillator; LV: left ventricle; NID: number of intervals to detect; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

*Data correspond to total of patients with a fast VT zone enabled.

**Data correspond to total of multizone patients.

Table S3. Devices included in UMBRELLA study.

Single-chamber	
Models without SmartShock® Technology	n
EnTrust D154VRC	47
Maximo II VR D264VRM	55
Maximo II VR D284VRC	141
Secura VR D214VRM	35
Secura VR D234VRC	179
Virtuoso II VR D294VRC	58
Virtuoso VR D164VWC	130
Subtotal	645 (29%)
Models with SmartShock® Technology	
Evera MRI S VR DVMC3D4	234
Evera MRI XT VR DVMB2D4	140
Evera S VR DVBC3D1	67
Evera S VR DVBC3D4	171
Evera XT VR DVBB2D1	42
Evera XT VR DVBB2D4	24
Protecta VR D364VRG	135
Protecta VR D364VRM	293
Protecta XT VR D354VRG	115
Protecta XT VR D354VRM	121
Visia AF MRI S VR DVFC3D4	70
Visia AF MRI XT VR DVFB2D4	102
Visia AF MRI™ S VR	5
Visia AF MRI™ XT VR	4
Visia AF S VR DVAC3D1	7
Visia AF XT VR DVAB2D1	12
Subtotal	1542 (71%)
TOTAL	2187

Dual-chamber	
Models without SmartShock® Technology	n
EnTrust D154ATG	20
Maximo II DR D264DRM	17
Maximo II DR D284DRG	44
Secura DR D214DRM	12
Secura DR D234DRG	103
Virtuoso DR D164AWG	57
Virtuoso II DR D294DRG	55
Intrinsic ICD 7288	1
Subtotal	309 (30%)
Models with SmartShock® Technology	n
Evera MRI S DR DDMC3D1	1
Evera MRI S DR DDMC3D4	54
Evera MRI XT DR	7
Evera MRI XT DR DDMB2D4	140
Evera S DR DDBC3D1	39
Evera S DR DDBC3D4	68
Evera XT DR DDBB2D1	38
Evera XT DR DDBB2D4	23
Protecta DR D364DRG	61
Protecta DR D364DRM	105
Protecta XT DR D354DRG	93
Protecta XT DR D354DRM	89
Subtotal	718 (70%)
TOTAL	1027

Cardiac Resynchronization Therapy-Defibrillators	
Models without SmartShock® Technology	n
Concerto C174AWK	63
Concerto II CRT-D D294TRK	28
Consulta CRT-D D214TRM	60
Consulta CRT-D D234TRK	194
Maximo II CRT-D D264TRM	12
Maximo II CRT-D D284TRK	52
Subtotal	409 (29%)
Models with SmartShock® Technology	n
Amplia MRI™ CRTD	8
Amplia MRI™ Quad CRTD	20
Brava CRT-D DTBC2D1	60
Brava CRT-D DTBC2D4	39
Brava Quad CRT-D DTBC2Q1	5
Brava Quad CRT-D DTBC2QQ	134
Claria MRI™ CRTD	17
Claria MRI™ Quad CRTD	45
Compia MRI™ CRTD	7
Compia MRI™ Quad CRTD	13
Protecta CRT-D D364TRG	46
Protecta CRT-D D364TRM	72
Protecta XT CRT-D D354TRG	109
Protecta XT CRT-D D354TRM	87
Viva Quad S CRT-D DTBB2Q1	1
Viva Quad S CRT-D DTBB2QQ	27
Viva Quad XT CRT-D DTBA2Q1	7
Viva Quad XT CRT-D DTBA2QQ	171
Viva S CRT-D DTBB2D1	10
Viva S CRT-D DTBB2D4	10
Viva XT CRT-D DTBA2D1	51
Viva XT CRT-D DTBA2D4	56
Subtotal	995 (71%)
TOTAL	1404

Table S4. Device programming according to date of ICD implant.

	2005-2009 (N=344)	2010-2014 (N=2744)	2015-2017 (N=1208)	p value
Detection zones enabled				< 0.001
• Single-zone *	119 (34.6)	1116 (40.7)	618 (51.2)	
• Multi-zone	225 (65.5)	1627 (59.3)	588 (48.8)	
VF detection interval, ms	302.7 ± 21.4	303.5 ± 19.2	301.0 ± 18.9	0.001
NID				< 0.001
• < 30/40	314 (91.3)	1998 (72.8)	178 (14.6)	
• ≥ 30/40	30 (8.7)	746 (27.2)	1023 (85.3)	
Fast VT detection zone enabled**	119 (34.6)	951 (34.7)	487 (40.4)	0.002
Fast VT detection interval**, ms	270.59 ± 31.7	267.3 ± 31	263.6 ± 24.8	0.014
VT detection interval†, ms	368.4 ± 31.1	362.4 ± 25.4	357.9 ± 22.4	< 0.001
NID †				< 0.001
• ≤16	181 (80.4)	1014 (62.3)	200 (34.0)	
• ≥20	44 (19.6)	613 (37.7)	388 (66.0)	
SmartShock™ Technology-capable device	40 (16.6)	1740 (66.4)	1150 (95.5)	< 0.001

Data are given as n (%) or mean±standard deviation. ICD: Implantable cardioverter-defibrillator; NID: number of intervals to detect; VF: ventricular fibrillation; VT: ventricular tachycardia.

* Patients with fast VT zone enabled through VF zone, but without any other VT zone activated were also considered as single-zone detection patients.

** Through VF detection zone.

† Applies only to multi-zone detection programming patients.

Table S5. Causes of death.

Cause of death	N (%)
Heart failure	214 (36.3%)
Sudden cardiac death	26 (4.4%)
Non-cardiovascular	190 (32.2%)
Unknown	160 (27.1%)
Total deaths	590 (100%)

Table S6. Causes of inappropriate shock.

Cause of inappropriate shock	Episodes, n (%)
Atrial fibrillation	254 (42.3%)
Other SVT*	95 (15.9%)
Non-sustained MVT	52 (8.6%)
T-wave oversensing	95 (15.9%)
Noise	60 (10%)
Sinus tachycardia	24 (4%)
False detection	7 (1.2%)
Possible SVT	13 (2.1%)
Total episodes	600 (100%)

MVT: monomorphic ventricular tachycardia; SVT: supraventricular tachycardia.

*i.e., atrial flutter, atrial tachycardia, atrioventricular node re-entry tachycardia.

Table S7. Comparison between the UMBRELLA population and the patients enrolled in the last Spanish ICD registry.

	UMBRELLA population	Spanish ICD registry ²²
Age (years), mean(\pm SD)	61.9 \pm 12.9	62.4 \pm 13.5
Sex (male)	82.1	82
Hypertension	54.4	57
Diabetes	28.3	30
Hypercholesterolaemia	52.5	48
Smoking status	37.7	35
History of atrial fibrillation	29.4	27
Previous stroke	6.8	6
Chronic kidney disease	15.3	15
Family history of SCD	8.7	9
LV ejection fraction		
\leq 35%	66.4	54
36-50%	14.7	27.4
$>$ 50%	18.9	18.5
QRS width		
$<$ 120 ms	52.4	N/R
120-150 ms	20.9	N/R
$>$ 150 ms	26.7	N/R*
Previous heart failure	69.8	N/R
Type of device		
VR	47.2	50.1
DR	22.6	13.4
CRT-D	30.2	30.6
Primary prevention	64.2	65.7
Underlying heart disease		
ICM	50	52.9
DCM	27.3	26.1
HCM	7.4	7.1
ARVC	1.9	1.1
VHD	2.8	1.6
BS	3.5	2.3
LQTS	1.1	0.6
ACHD	1.4	N/R

Data are given as % unless otherwise noted. ACHD: adult congenital heart disease; ARVC: arrhythmogenic right ventricular cardiomyopathy; BS: Brugada syndrome; CRT-D: cardiac resynchronization therapy defibrillator; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter-defibrillator; ICM: ischaemic cardiomyopathy; LQTS: long QT syndrome; LV: left ventricle; N/R: not reported; SCD: sudden cardiac death; SD: standard deviation; VHD: valvular heart disease.

*39% of patients had QRS $>$ 140 ms.