JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 9, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.12.031

Implantable Cardioverter-Defibrillator Therapy in Brugada Syndrome

A 20-Year Single-Center Experience

Giulio Conte, MD,* Juan Sieira, MD,* Giuseppe Ciconte, MD,* Carlo de Asmundis, MD,* Gian-Battista Chierchia, MD,* Giannis Baltogiannis, MD,* Giacomo Di Giovanni, MD,* Mark La Meir, MD,† Francis Wellens, MD,† Jens Czapla, MD,† Kristel Wauters, MD,* Moises Levinstein, MD,* Yukio Saitoh, MD,* Ghazala Irfan, MD,* Justo Julià, MD,* Gudrun Pappaert, RN,* Pedro Brugada, MD*

ABSTRACT

BACKGROUND Patients with Brugada syndrome and aborted sudden cardiac death or syncope have higher risks for ventricular arrhythmias (VAs) and should undergo implantable cardioverter-defibrillator (ICD) placement. Device-based management of asymptomatic patients is controversial. ICD therapy is associated with high rates of inappropriate shocks and device-related complications.

OBJECTIVES The objective of this study was to investigate clinical features, management, and long-term follow-up of ICD therapy in patients with Brugada syndrome.

METHODS Patients presenting with spontaneous or drug-induced Brugada type 1 electrocardiographic findings, who underwent ICD implantation and continuous follow-up at a single institution, were eligible for this study.

RESULTS A total of 176 consecutive patients were included. During a mean follow-up period of 83.8 ± 57.3 months, spontaneous sustained VAs occurred in 30 patients (17%). Eight patients (4.5%) died. Appropriate ICD shocks occurred in 28 patients (15.9%), and 33 patients (18.7%) had inappropriate shocks. Electrical storm occurred in 4 subjects (2.3%). Twenty-eight patients (15.9%) experienced device-related complications. In multivariate Cox regression analysis, aborted sudden cardiac death and VA inducibility on electrophysiologic studies were independent predictors of appropriate shock occurrence.

CONCLUSIONS ICD therapy was an effective strategy in Brugada syndrome, treating potentially lethal arrhythmias in 17% of patients during long-term follow-up. Appropriate shocks were significantly associated with the presence of aborted sudden cardiac death but also occurred in 13% of asymptomatic patients. Risk stratification by electrophysiologic study may identify asymptomatic patients at risk for arrhythmic events and could be helpful in investigating syncope not related to VAs. ICD placement is frequently associated with device-related complications, and rates of inappropriate shocks remain high regardless of careful device programming. (J Am Coll Cardiol 2015;65:879–88) © 2015 by the American College of Cardiology Foundation.

Brugada syndrome (BS) is an inheritable syndrome characterized by coved-type ST-segment elevation in the right precordial leads (V_1 to V_3) and increased risk for sudden cardiac death (SCD) in the absence of structural heart disease (1).

Today, the placement of an implantable cardioverter-defibrillator (ICD) remains the only therapy with proven efficacy for the management of ventricular arrhythmias (VAs) in patients with BS (2). Patients experiencing syncope or aborted SCD, who are considered to be the patients with BS at higher

From the *Heart Rhythm Management Centre UZ Brussel-VUB, Brussels, Belgium; and the †Cardiac Surgery Department, UZ Brussel-VUB, Brussels, Belgium. Dr. Brugada has received research grants from Biotronik, Medtronic, St. Jude Medical, and Sorin. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Conte and Sieira contributed equally to this work.

Manuscript received June 3, 2014; revised manuscript received December 7, 2014, accepted December 12, 2014.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BS = Brugada syndrome
CI = confidence interval
ECG = electrocardiographic
EPS = electrophysiologic study
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
SCD = sudden cardiac death
SND = sinus node dysfunction
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia

risk for recurrent arrhythmic events during follow-up, are the best candidates to undergo ICD therapy (3,4). However, although appropriate ICD therapies are more prevalent in symptomatic patients, they are not insignificant in asymptomatic ones (5). To date, risk assessment of patients with asymptomatic BS has not been well established, and device-based management in this setting remains controversial.

Data on long-term follow-up (>6 years) of patients with BS with ICDs are sparse. In our previous study, 15% of 47 patients who underwent primary prophylactic ICD therapy experienced appropriate interventions during a 4-year follow-up period (6). But ICD implantation was not without problems, including high rates of inappropriate shocks and device-related complications.

SEE PAGE 889

The purpose of this study was to analyze our single-center experience with ICD therapy in patients with BS over the past 20 years, since the first description of the syndrome. Particularly, we aimed to assess the clinical features and the long-term follow-up of patients with BS who underwent ICD placement and the evolution of device-based management over the past 2 decades.

METHODS

STUDY POPULATION. Since 1992, all consecutive patients diagnosed with BS have been included in a registry and followed in a prospective fashion. The ethics committee of UZ Brussel-VUB approved the study protocol. A total of 524 patients with BS were included in the registry from 1992 to 2012. Among them, 181 patients (34.5%) received ICD therapy. Study inclusion criteria consisted of 1) spontaneous or drug-induced Brugada type 1 electrocardiographic (ECG) pattern, (2) ICD implantation, and (3) continuous follow-up at our institution. One-hundred seventy-six patients (97.2%) fulfilled the inclusion criteria. Five patients (2.8%) were not included because of a follow-up time of <6 months. Medical history, physical examination, and baseline electrocardiography were performed, and underlying structural cardiac abnormalities were excluded in all patients. All patients with syncope before receiving ICDs underwent careful diagnostic work-up for arrhythmic origins of the events. The work-up included a careful examination of the patient's history, 12-lead electrocardiography, transthoracic echocardiography, and Holter monitoring. Electrophysiologic study (EPS) was performed in patients with syncope potentially related to supraventricular arrhythmias. Arrhythmic syncope was suspected in the absence of prodromes and specific triggering circumstances and in the presence of brief loss of consciousness and rapid return to consciousness or severe trauma. A tilt-table test was performed in patients with suspected vasovagal syncope. ECG patterns were classified as Brugada coved type (type 1) or saddleback (type 2) or normal. An electrocardiogram was considered diagnostic of BS if a coved-type ST-segment elevation of ≥2 mm was documented in ≥1 lead from V_1 to V_3 in the presence or absence of a sodium-channel blocker. Abnormal fragmentation of the QRS complex was defined as the presence of multiple spikes within the QRS complex (≥4 spikes in 1 lead or ≥8 spikes in leads V_1, V_2, and V_3) (7). All baseline and drug-induced 12-lead electrocardiograms were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV, with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space. Two independent experienced electrophysiologists analyzed all electrocardiograms; in cases of disagreement, a third physician was consulted. Patients were considered symptomatic if they presented with syncope and/or aborted SCD. EPS was performed at the investigators' preference to assess risk stratification. Programmed ventricular stimulation consisted of a maximum of 3 ventricular extrastimuli with a minimal coupling interval of 200 ms delivered from 1 ventricular site unless ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) lasting at least 30 s, accompanied with syncope or requiring intervention for termination was induced. Genetic testing with sequence analysis of *SCN5A* was recommended for all patients with diagnoses of BS.

AJMALINE CHALLENGE. Ajmaline (1 mg/kg) was administered intravenously over a 5-min period to unmask the diagnostic ECG pattern of BS in case of a nondiagnostic baseline electrocardiogram. The test was considered positive for BS only if coved-type ECG pattern was documented in ≥1 right precordial lead (V_1 to V_3). Ajmaline infusion was discontinued before reaching the target dose if QRS prolongation exceeded 30% compared with the baseline interval, when frequent premature ventricular beats or Brugada type 1 ECG pattern occurred or in case of development of high-degree atrioventricular block. Ajmaline-induced VAs were defined as the occurrence of sustained episodes of VF or VT.

ICD IMPLANTATION. Beginning in 2005, the indications for ICD therapy were determined using the

recommendations of the second Brugada consensus conference (4). The decision to perform epicardial or endocardial lead implantation or to place the device in a thoracic or subcostal pocket was made according to the patient's age, anthropometric characteristics, and level of physical activity. The choice between single- and dual-chamber devices was driven by the presence of previous episodes of supraventricular arrhythmias or evidence of sinus node dysfunction (SND). ICD programming at the time of implantation changed over time. After our initial experience, the VF detection rate was increased from 180 to more than 200 beats/min for primary prevention implantations, and a monitor zone was added (6,8). In accordance with more recently published data, apart from setting a high cutoff rate, long detection intervals (30 of 40 intervals) were adopted to avoid unnecessary therapies (9–11). Conversely, in patients undergoing ICD therapy for secondary prevention, a monitor zone (>150 beats/min) and a fast VT zone (180 to 200 beats/min) with antitachycardia pacing and shocks were programmed in all cases, and supraventricular tachycardia discriminators were activated if available. These settings were adjusted during follow-up on the basis of individual clinical history and to avoid recurrences of inappropriate interventions.

FOLLOW-UP. Clinical follow-up of patients consisted of physical examinations and electrocardiography at least every 6 months. Follow-up of the device was performed at 1 and 3 months after implantation and thereafter every 6 months. Clinical data were regularly collected. From 2006, home monitoring devices were implanted either de novo or at battery change, in case of prior implantation, in all patients younger than 12 years and in 30% of older patients.

Arrhythmic events receiving ICD therapies were pre-defined according to the cycle lengths of the arrhythmias. All available electrograms of appropriate and inappropriate shocks were analyzed by at least 2 investigators independently. Electrograms were derived from various bipolar configurations involving the tip and ring electrodes or shocking coils on the pacing or defibrillating lead or a wide bipolar recording between one of the ventricular electrodes and the ICD casing. For primary prevention implantations, the VF detection rate was usually higher than 180 to 200 beats/min (according to the year of implantation). For these patients, an attempt to discriminate rapid polymorphic VT and VF was made when possible on the basis of the electrographic configuration derived from multiple ICD channels. Monomorphic VTs were defined as arrhythmias with constant electrographic configuration and a stable rate within a few beats. Polymorphic VTs had a changing rate and demonstrated varying configurations and rate between 180 and 200 beats/min. Conversely, an arrhythmia was characterized as VF if the cycle length was irregular and had a rate higher than 200 beats/min and/or occurred in the presence of electrograms of continuously varying configuration.

Appropriate therapies were defined as shocks or antitachycardia pacing delivered for VT or VF, and inappropriate therapies were defined as those delivered in the absence of VAs. Electrical storm was defined by 3 or more sustained episodes of VT, VF, or appropriate ICD shocks within 24 h.

STATISTICAL ANALYSIS. Data are presented as mean ± SD or as absolute values and percents as appropriate. Comparisons between continuous variables were performed using the unpaired Student *t* test or analysis of variance as appropriate. The chi-square test was used to compare categorical variables. Event-free survival was estimated by the Kaplan-Meier method and compared by the log-rank test. Hazard ratios (HRs) were calculated using Cox proportional hazards regression models. Cox regression analysis was used for the predictor model. Variables were selected on the basis of univariate significance and/or if they were known predictors in published research. The final model was selected by stepwise regression on the basis of likelihood ratios. A p value of <0.05 was considered to indicate statistical significance. Statistical analyses were conducted using SPSS version 22 (SPSS, Inc., Chicago, Illinois).

RESULTS

BASELINE CHARACTERISTICS. A total of 176 consecutive patients (118 male [67%]; mean age 43.3 ± 16.8 years; range: 2 to 77 years) received ICDs at our institution from 1992 to 2012 and met the inclusion criteria for this study. Baseline clinical and procedural characteristics of the study population are shown in Table 1. Patients belonged to 92 different families. At the time of implantation, 19 patients (10.8%) were younger than 18 years. Family histories of SCD were present in 90 patients (51%). Twenty-five subjects (14.2%) presented with aborted SCD before ICD placement. One-hundred five patients (59.7%) had at least 1 episode of syncope, and 46 (25.1%) were completely asymptomatic before receiving ICDs. Twenty-four patients (13.6%) had documented episodes of sustained atrial arrhythmias (atrial fibrillation [AF] or atrial flutter). Moreover, 9 patients (5.1%) presented with SND. Spontaneous Brugada type 1 ECG pattern was documented in 37 patients (21%).

TABLE 1 Baseline Clinical and Procedural Characteristics of the Study Population According to Year of Implantation

	Overall (n = 176)	Group I (n = 82)	Group II (n = 94)	p Value
Age, yrs	43.3 ± 16.8	42.5 ± 15.3	44.0 ± 18.2	0.46
Male	118 (67.0)	62 (75.6)	56 (59.6)	0.02
Spontaneous type 1 ECG pattern	37 (21.0)	28 (34.1)	9 (9.6)	<0.01
Aborted SCD	25 (14.2)	15 (18.3)	10 (10.6)	0.15
Syncope	105 (59.7)	39 (47.6)	66 (70.2)	<0.01
Asymptomatic	46 (26.1)	28 (34.1)	18 (19.1)	0.01
Family history of SCD	90 (51.1)	47 (57.3)	43 (45.7)	0.13
Previous atrial arrhythmias	24 (13.6)	14 (17.1)	10 (10.6)	0.22
Previous SND	9 (5.1)	6 (7.3)	3 (3.2)	0.31
Inducible on EPS*	72 (43.6)	58 (75.3)	14 (15.9)	<0.01
SCN5A mutation*	23 (21.9)	13 (21.7)	10 (22.2)	0.95
Abdominal implantation	19 (10.8)	6 (7.3)	13 (13.8)	0.19
Epicardial lead placement	8 (4.5)	3 (3.7)	5 (5.3)	0.73

Values are mean ± SD or n (%). Group I included patients who underwent ICD placement before 2005, and group II included patients who underwent ICD placement during or after 2005. *Percents refer to patients who underwent EPS and genetic testing.

ECG = electrocardiographic; EPS = electrophysiologic study; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; SND = sinus node dysfunction.

The diagnosis was induced by ajmaline challenge in the remaining 139 patients (79%). Among them, 9 patients (6.5%) experienced drug-induced sustained VAs. EPS was performed in 165 patients (93.7%). Sustained VAs were induced during programmed ventricular stimulation in 72 patients (43.6%). A total of 105 genetic tests (59.7%) were performed; 23 of them (21.9%) were positive for mutations in the *SCN5A* gene.

The clinical profile of the patients who received ICDs during the 20-year study period changed over time (Table 1). In particular, the rate of asymptomatic patients significantly decreased after 2005 (from 34.1% before 2005 to 19.1% during or after 2005; $p = 0.01$). Similarly, there was a significant reduction in the number of patients with inducible arrhythmias during EPS (from 75.3% before 2005 to 15.9% during or after 2005; $p < 0.01$). Conversely, the rate of patients with syncope increased (from 47.6% before 2005 to 70.2% during or after 2005; $p < 0.01$). No significant temporal difference was found in the number of patients presenting with aborted SCD or in those with family histories of SCD in whom ICDs were placed before or after 2005. Moreover, the number of patients with spontaneous Brugada type 1 ECG pattern undergoing ICD placement decreased over time (from 34.1% before 2005 vs. 9.6% during or after 2005; $p < 0.01$).

SYMPTOM STATUS. A total of 130 patients (73.8%) presented with syncope and/or aborted SCD before ICD implantation. The remaining 46 patients were asymptomatic. Clinical characteristics of patients according to their symptom status are shown in Table 2. No significant difference was found in the clinical features among patients presenting with syncope and aborted SCD and asymptomatic patients.

Aborted SCD. Twenty-five patients (14.2%) presented with previous episodes of aborted SCD due to spontaneous sustained VAs. Sixteen (64%) were male, and 10 (40%) had family histories of SCD. Spontaneous Brugada type 1 ECG pattern was documented in 7 patients (28%). The mean age at the time of SCD was 39.5 ± 15.6 years, ranging from 6 days to 61 years. One infant and 1 child experienced multiple episodes of aborted SCD before reaching 2 years of age. Aborted SCD was the first clinical manifestation of the syndrome in 20 patients (11.3%). SCD was preceded by episodes of syncope and by palpitations in 4 patients and 1 patient, respectively. Sudden death occurred at rest in 16 patients, during exercise in 5, during sleep in 3, and during a febrile episode in 1.

Syncope. Syncope was the clinical manifestation of the syndrome in 105 patients (59.7%). Sixty-six (62.8%) were male, and 53 (50.4%) had family histories of SCD. Forty-eight patients (45.7%) were family members of patients with BS. Spontaneous Brugada type 1 ECG pattern was documented in 19 patients (18.1%). The mean age at the time of first syncope was 43.2 ± 17.2 years. The mean number of episodes of syncope per patient was 1.2 ± 0.8. Syncope occurred at rest in 72 patients (68.6%) and during exercise in 27 subjects (25.7%). Syncope was associated exclusively with fever in 6 patients (5.7%).

Asymptomatic patients. Forty-six patients (26.1%) did not report any symptoms before receiving ICDs. Twenty-seven (58.7%) were family members of BS patients. Indications for ICD therapy in these patients were: 1) the presence of spontaneous Brugada type 1 ECG pattern and family history of SCD in 2 patients (4.3%); 2) spontaneous Brugada type 1 ECG pattern and sustained VA induced during EPS in 9 patients (19.6%); and 3) sustained VA during ajmaline challenge in 5 patients (10.9%). The remaining 30 patients (65.2%) received ICDs because of ajmaline-induced Brugada type 1 ECG pattern with sustained VA induced during EPS (n = 17) or family histories of SCD (n = 13).

PROCEDURAL CHARACTERISTICS. One-hundred nine patients (62%) received single-chamber transvenous devices, and 59 (33.5%) underwent dual-chamber transvenous ICD implantation. Single and dual epicardial leads were implanted in 6 and 2 patients (4.5%), respectively. No patient received a totally subcutaneous system. Nineteen subjects (10.8%)

underwent abdominal pulse generator placement. Mean R-wave amplitude at implantation was 11.3 ± 4.7 mV. After ICD implantation, 4 patients (2.3%) experienced device-related early complications: 2 pneumothoraxes, 1 episode of pericarditis that occurred 1 month after epicardial lead placement, and a dislocation of the abdominal generator that led to the revision of the device 1 week after implantation.

LONG-TERM FOLLOW-UP. After a mean follow-up period of 83.8 ± 57.3 months, spontaneous sustained VAs were documented in 30 patients (17%). Sustained VA was terminated by ICD shocks in 28 patients (15.9%) and by antitachycardia pacing in 2 patients (1.1%). Thirty-three patients (18.7%) experienced inappropriate shocks. Electrical storm occurred in 4 subjects (2.3%). Nonsustained VAs were documented in 10 patients (5.7%). Of note, 30 patients (21.6%) with drug-induced BS presented with spontaneous Brugada type 1 ECG pattern during follow-up. Spontaneous Brugada type 1 ECG pattern could be documented on at least 1 occasion during the follow-up period in 67 patients (38.1%). After ICD placement, 21 patients (11.9%) experienced episodes of syncope. Of them, 5 patients had neurally mediated syncope. In 8 patients with recurrent syncope after ICD implantation, the rate of ventricular pacing was <1%, and no VAs were detected. Among initially asymptomatic patients, 3 (6.5%) experienced syncope during follow-up. Thirty-two patients (18.2%) developed paroxysmal AF: 6 in the asymptomatic group, 21 (20%) in the syncope group, and 5 (20%) in the aborted SCD group (p = 0.58). Six patients (3.4%) with ICDs and drug-resistant AF underwent pulmonary vein isolation by means of radiofrequency energy source (n = 5) or cryoballoon ablation (1 patient). At last follow-up, a total of 19 patients (10.8%) with documented atrial arrhythmias were under pharmacological treatment with sotalol or beta-blockers. Fifty-two patients (29.5%) underwent generator replacement. The mean number of battery changes during the follow-up was 1.27 ± 0.5 per patient.

MORTALITY. Eight patients (4.5%) died during follow-up. The mean age at death was 55.7 ± 20.7 years. The mean time from BS diagnosis to death was 8.1 ± 4.9 years. Cardiac death occurred in 3 patients. One subject died in the hospital because of cardiogenic shock complicating an acute anterolateral wall myocardial infarction that presented with persistent ST-segment elevation. Another patient experienced septic shock with fatal consequences shortly after device revision. A third patient died as consequence of an arrhythmic event (**Central Illustration**). He was the first patient ever diagnosed with BS. He had presented at 3 years of age with syncope and recurrent aborted SCDs and had concomitant SND and AF and atrial flutter. He first received a pacemaker and pharmacologic therapy with amiodarone, beta-blockers, digoxin, and diphenylhydantoin but had 2 further episodes of syncope. Subsequently, he was asymptomatic for 13 years, at which point the family agreed to undergo ICD implantation. After the implantation, antiarrhythmic therapy was discontinued. The patient died suddenly 11 months after ICD implantation, at 18 years of age, because of VF refractory to both internal and external defibrillations. In the remaining 5 cases, death was due to noncardiac causes. None of the asymptomatic patients died.

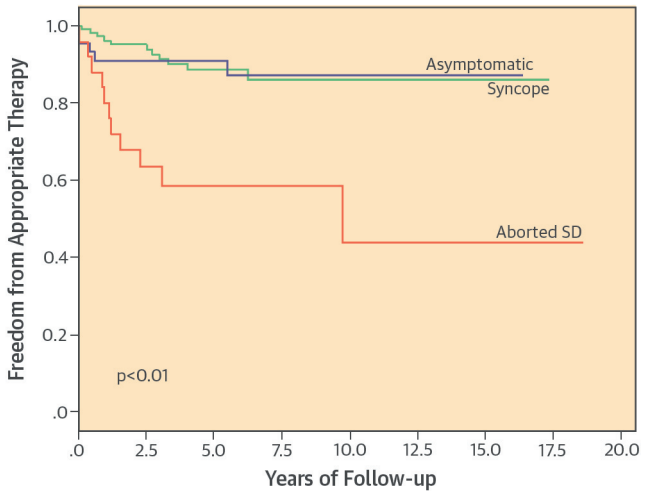
TABLE 2 Clinical Characteristics and Outcomes of Patients According to ICD Indication

	Overall (n = 176)	Aborted SCD (n = 25)	Syncope (n = 105)	Asymptomatic (n = 46)	p Value
Clinical features					
Age, yrs	43.3 ± 16.8	39.5 ± 15.6	43.2 ± 17.2	45.3 ± 16.6	0.41
Male	118 (67.0)	16 (64.0)	66 (62.9)	36 (78.3)	0.17
Proband	92 (52.3)	16 (64.0)	57 (54.3)	19 (41.3)	0.15
Spontaneous type 1 ECG pattern	37 (21.0)	7 (28.0)	19 (18.1)	11 (23.9)	0.47
Family history of SCD	90 (51.1)	10 (40.0)	53 (50.5)	27 (58.7)	0.32
Previous atrial arrhythmias	24 (13.6)	3 (12.0)	14 (13.3)	7 (15.2)	0.92
Previous SND	9 (5.1)	1 (4.0)	5 (4.8)	3 (6.5)	0.87
Inducible on EPS*	72 (43.6)	5 (26.3)	39 (37.9)	28 (65.1)	<0.01
SCN5A mutations*	23 (21.9)	6 (26.1)	9 (15.8)	8 (32)	0.23
Outcomes					
Appropriate shocks	28 (15.9)	11 (44.0)	11 (10.5)	6 (13.0)	<0.01
Time to first therapy, months	20.7 ± 25.9	23.6 ± 32.5	19.9 ± 18.5	15.7 ± 28.3	0.85
Shock rate per year	0.46 ± 1.05	0.23 ± 0.28	0.8 ± 1.56	0.16 ± 0.11	0.38
Inappropriate shocks	33 (18.8)	8 (32.0)	18 (17.1)	7 (15.2)	0.54
Time to first therapy (months)	49.9 ± 46.2	53.9 ± 47.6	54.8 ± 50.4	34.2 ± 36.8	0.66
Shock rate per year	0.47 ± 1.26	0.19 ± 0.19	0.64 ± 1.59	0.17 ± 0.05	0.71
Deaths	8 (4.5)	3 (12.0)	5 (4.8)	0 (0)	0.10

Values are mean ± SD or n (%). *Percents refer to patients who underwent EPS and genetic testing.
Abbreviations as in Table 1.

APPROPRIATE SHOCKS. Twenty-eight patients (15.9%) experienced at least 1 appropriate shock during the follow-up period (**Central Illustration**). Twenty-four (85.7%) were male, and 22 (78.6%) were symptomatic. Six patients (21.4%) had neither aborted SCD nor previous syncope. Of note, appropriate shocks occurred in 13% of asymptomatic patients. However, the rate of appropriate shocks was significantly higher in patients presenting with aborted SCD compared with the other patients (p < 0.01) (**Table 2**). Sixteen of these patients (53.6%) presented with spontaneous

CENTRAL ILLUSTRATION ICD Therapy in Brugada Syndrome



Number at Risk

Asymptomatic	46	32	26	17	10	3	1	
Syncope	105	77	46	27	16	6	3	
Aborted SD	25	13	8	5	3	2	2	1

Conte, G. et al. J Am Coll Cardiol. 2015; 65(9):879–88.

Kaplan-Meier curve analyzing freedom from appropriate shocks according to implantable cardioverter-defibrillator (ICD) indication. SD = sudden cardiac death.

Brugada type 1 ECG pattern. The median time to first therapy was 11.6 months (interquartile range: 5.3 to 33.0 months). The mean number of shocks delivered per patient was 2.1 ± 2.8. Seventeen patients (60.7%) had 1 shock, 6 (21.4%) experienced 2 shocks, and 5 (17.9%) received 3 or more shocks. Twenty-two patients received ICD shocks for VF and 3 for polymorphic VT. ICD therapy was delivered for monomorphic VT in the remaining 3 patients. All VF and VT episodes had ventricular rates higher than 200 and 180 beats/min, respectively.

On univariate analysis, male sex (HR: 2.95; 95% confidence interval [CI]: 1.02 to 8.53; p = 0.04), spontaneous Brugada type 1 ECG pattern (HR: 2.50; 95% CI: 1.16 to 5.39; p = 0.02), aborted SCD (HR: 4.53; 95% CI: 1.57 to 13.0; p < 0.01), and VA inducibility on EPS (HR: 2.44; 95% CI: 1.18 to 6.02; p = 0.04) were shown to confer a higher risk for experiencing an appropriate shock during follow-up. Implantation after 2005 was shown to be a protective factor (HR: 0.31; 95% CI: 0.12 to 0.77; p = 0.01) (Table 3). Aborted SCD (HR: 5.13; 95% CI: 2.03 to 12.96; p < 0.01) and VA inducibility on EPS (HR: 3.38; 95% CI: 1.33 to 8.59; p = 0.01) remained the only significant predictors of appropriate shocks on multivariate analysis.

TABLE 3 Univariate Cox Regression Analysis Among Patients Experiencing Appropriate Shocks

	β Coefficient	HR (95% CI)	p Value
Age	−0.02	0.98 (0.96-1.0)	0.12
Male	1.08	2.95 (1.02-8.53)	0.04
Proband	−0.35	0.71 (0.33-1.53)	0.38
Spontaneous type 1 ECG pattern	0.91	2.50 (1.16-5.39)	0.02
Symptoms	0.97	2.63 (1.40-4.92)	<0.01
Syncope	−0.08	0.93 (0.32-2.67)	0.89
Aborted SCD	1.51	4.53 (1.57-13.0)	<0.01
Family history of SCD	−0.42	0.66 (0.31-1.42)	0.29
Previous AF	−0.31	0.73 (0.22-2.44)	0.61
Previous SND	0.57	1.77 (0.42-7.50)	0.44
EPS inducibility	0.90	2.44 (1.18-6.02)	0.04
SCN5A mutation	0.29	1.33 (0.24-7.45)	0.74
Implantation during or after 2005	−1.18	0.31 (0.12-0.77)	0.01

The HR for age considers every year increase.
AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

ELECTRICAL STORM. Four patients (2.3%) presented with electrical storm during the follow-up period (Table 4, Figure 1). Three were male (75%). The mean age at the time of electrical storm was 41 ± 10 years. Electrical storm occurred 2.9 ± 2.6 years after ICD implantation. Aborted SCD was the indication for ICD therapy in all patients. Two patients had experienced episodes of appropriate shocks 3 and 5 years before the occurrence of electrical storm. After the electrical storm, 2 patients were treated with quinidine with no further arrhythmic recurrences, and 1 patient underwent VF ablation with no subsequent episodes of electrical storm. The remaining patient who experienced another episode of electrical storm underwent heart transplantation.

INAPPROPRIATE SHOCKS. Thirty-three patients (18.7%) had inappropriate shocks a median of 36.9 months (interquartile range: 9.4 to 75.4 months) after ICD implantation. The mean number of inappropriate shocks delivered per patient was 3.0 ± 5.7. Eighteen patients (54%) experienced 1 shock, and 15 had 2 or more episodes of inappropriate shocks (46%). Inappropriate shocks were due to sinus tachycardia in 5 patients, noise on the ventricular channel after lead fracture in 7 patients, and T-wave oversensing in 6 patients. The remaining 15 subjects experienced inappropriate shocks because of episodes of AF with fast ventricular rate. Among these patients, 3 underwent pulmonary vein isolation because of drug-resistant paroxysmal AF. At follow-up, the remaining 12 patients were under pharmacological treatment with sotalol (n = 10) or beta-blockers and sotalol (n = 2). Conversely, none of the patients who

experienced inappropriate shocks because of sinus tachycardia were treated pharmacologically. Of note, the incidence of inappropriate shocks did not differ depending on patients' previous symptom status (Table 2).

DEVICE-RELATED COMPLICATIONS. During follow-up, 28 patients (15.9%) experienced device-related complications. Twenty-one (75%) were younger than 40 years at the time of implantation. Complications consisted of fracture of the ventricular electrode and subsequent extraction and replacement in 14 patients, lead dislocation in 7 patients, and pulse generator migration in 2 patients, leading to revision of the device in all patients. The other 5 patients had device infections, which led to replacement of the devices.

TABLE 4 Clinical Characteristics of Patients Experiencing Electrical Storm

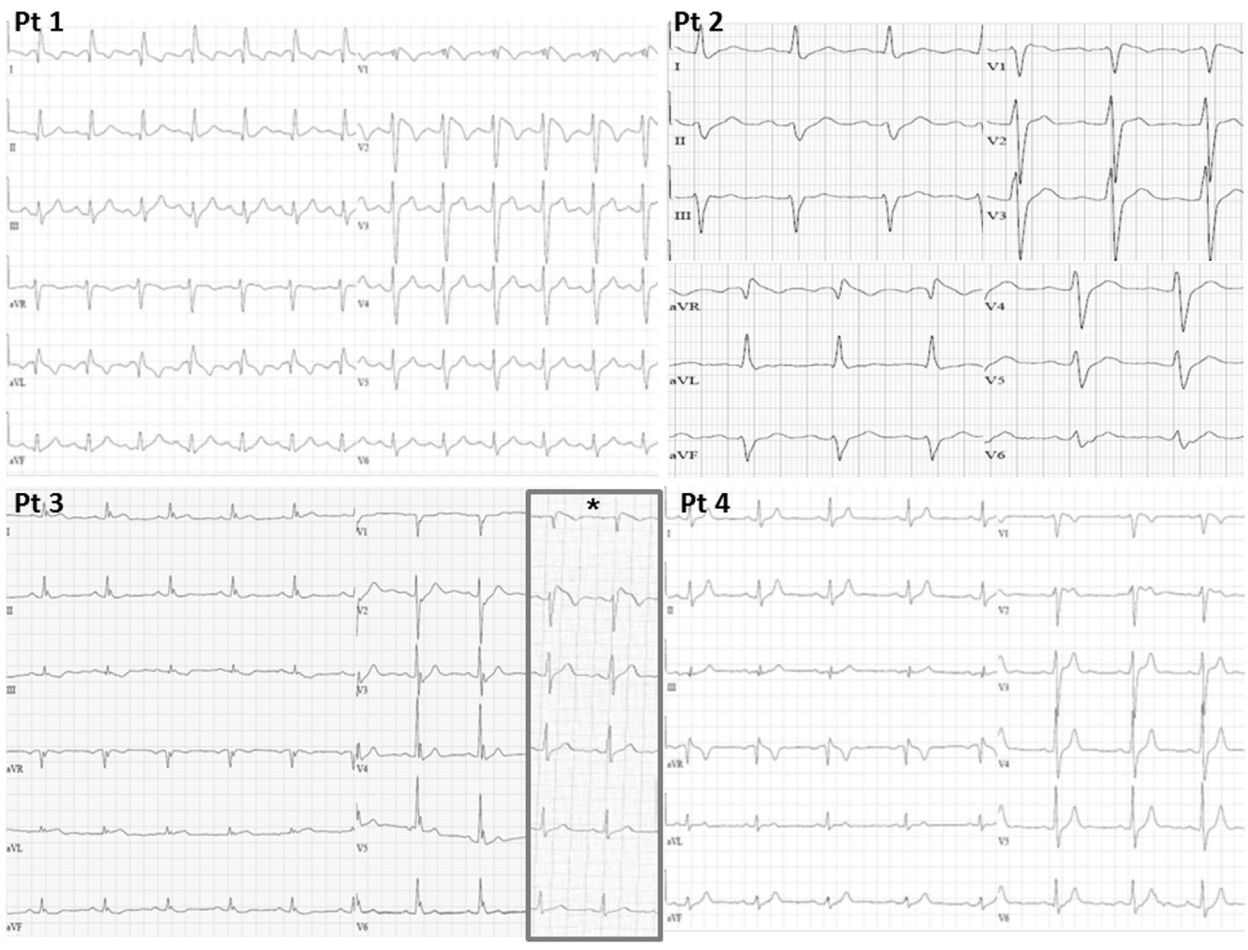
Patient #	Sex	Age (yrs)	Proband	Family History of SCD	Spontaneous Type 1 ECG Pattern	ICD Indication	f-QRS
1	Male	34	No	Yes	Yes	Aborted SCD	No
2	Male	24	No	Yes	Yes	Aborted SCD	No
3	Male	53	Yes	No	No	Aborted SCD	Yes
4	Female	41	No	No	No	Aborted SCD	No

f-QRS = fragmentation of QRS complex; other abbreviations as in Table 1.

DISCUSSION

CLINICAL PROFILE OF PATIENTS WITH BS WHO RECEIVE ICDs. Patients presenting with either symptomatic or asymptomatic BS are usually in their

FIGURE 1 Baseline Electrocardiograms of Patients With Electrical Storm



Fragmentation of the terminal portion of the QRS complex can be appreciated in all leads of the baseline electrocardiogram of Patient #3. *Electrocardiogram after ajmaline challenge. Pt = patient.

fourth or fifth decade of life (3), and in our study, patients with BS receiving ICDs presented with a mean age of 40 years. Most were male, and 74% were symptomatic, presenting with aborted SCD or syncope before ICD placement. Interestingly, the clinical profile of patients undergoing ICD therapy changed during the 20-year study period, particularly after the second Brugada consensus conference recommendations (4). The rate of asymptomatic patients significantly decreased after 2005 (from 34.1% to 19.1%), and there was a significant reduction in the number of patients with inducible arrhythmias during EPS (from 75.3% to 15.9%). Conversely, the rate of patients with syncope increased (from 47.6% to 70.2%). No significant temporal difference was found in the number of patients presenting with aborted SCD or in those with family histories of SCD. Although it has a psychological impact for patients and their families, family history of SCD has not been shown to be predictive of future arrhythmic events in patients with BS, and it does not appear to be of prognostic value in patients with ICDs (12). Thus, asymptomatic patients with family histories of SCD do not have an indication for ICD placement on that basis alone. Clinical follow-up with electrocardiography should be performed every 6 months in these patients, and EPS should be considered for risk stratification purposes. Of note, the rate of patients with spontaneous Brugada type 1 ECG pattern undergoing ICD placement decreased over time (from 34.1% to 9.6%). This could be explained by a more proactive attitude developed after 2005 in the diagnosis of the syndrome in patients with syncope and in asymptomatic family members.

APPROPRIATE SHOCKS. An important finding of the present study concerns the considerable risk for SCD during long-term follow-up, affecting patients with BS with ICDs for primary or secondary prevention. In our study, 17% of patients experienced documented life-threatening arrhythmias during a mean follow-up period of 7 years. Moreover, 1 patient died because of an arrhythmic event. The rate of appropriate shocks was 16%. The discharge rate was comparable to the rate reported in our previous follow-up study (14.9%) conducted in patients undergoing ICD implantation for prophylactic purposes only (6). This previous study was not able to identify any independent predictors of future arrhythmic events, possibly because of the relatively low event rate in a small patient population. In the present study, including a larger number of patients, aborted SCD (HR: 5.13) and VA inducibility on EPS (HR: 3.38) were found to be the only independent predictors of appropriate shocks in multivariate analysis. Moreover, in univariate analysis, apart from aborted SCD and VA inducibility on EPS, male sex and spontaneous Brugada type 1 ECG pattern were shown to confer a higher risk for experiencing an appropriate shock during follow-up. Although the device-based therapeutic management of BS in asymptomatic patients is challenging, the decision to implant an ICD after an episode of aborted SCD is straightforward. In our study, the appropriate device therapy rate at 7 years was 44% in patients in whom the ICD therapy indication was aborted SCD. Previously, Sacher et al. (5) reported a similar rate of appropriate shocks after ICD therapy for secondary prevention. Although low, the rate of sustained VA in asymptomatic patients with ICD has been reported as 0.81% per year (5). Of note, in our study, it was not as low as previously thought, affecting 13% of previously asymptomatic patients. In patients without histories of VT or VF, the identification of potential predictors of arrhythmic events during follow-up has been assessed in different studies, with controversial results, and the role of EPS has been considered questionable. Data from the PRELUDE (Programmed Electrical Stimulation Predictive Value) study identified the presence of spontaneous Brugada type 1 ECG pattern and history of syncope as the only significant predictors of arrhythmias (13). Conversely, the presence of VT or VF inducibility on EPS failed to identify patients at risk for developing arrhythmic events during follow-up (13). In our study, VA inducibility during EPS appeared to confer a significantly higher risk for experiencing appropriate shocks during follow-up. Therefore, risk assessment on the basis of clinical features, such as male sex, baseline electrocardiography, or the results of EPS, should be always taken into account when considering ICD therapy. Moreover, EPS might be valuable in the clinical evaluation of patients with syncope to rule out the presence of SND or supraventricular arrhythmias as potential causes of the event. Interestingly, in the present study, syncope was not found to be an independent predictor of future VAs, and freedom over time from appropriate shocks did not differ between asymptomatic patients and those with syncope (**Figure 1**). Despite performing a proper diagnostic work-up, in some cases, it remains difficult to determine whether syncope is truly due to VA. All large registries of patients with BS and syncope report that 6% to 19% of patients experience arrhythmic events during follow-up of 24 to 39 months (5,6,8). In our study, 11% of patients with syncope received appropriate shocks. Currently, ICD therapy is considered in order to prevent SCD in patients presenting with episodes of syncope if no

other cause of syncope is found (4). The decision to perform ICD implantation in this setting must be taken after a careful evaluation of the episode, as in this category of patients, it is not always easy to differentiate its origin. In our study, 8% of patients with syncope experienced further episodes of syncope during follow-up, but no VA was detected by the device. Moreover, 18% of patients developed paroxysmal AF. It has been shown that approximately 20% of patients with BS can develop supraventricular arrhythmias that can be a potential cause of syncope (14). Similarly, a prolonged sinus node recovery time and sinoatrial conduction time as well as slowed atrial conduction and atrial standstill have been reported in association with the syndrome and can lead to syncope (15). Thus, in any case of syncope suspected to be attributable to arrhythmic causes other than VAs, an EPS should be always performed to clarify the diagnosis before ICD implantation.

Interestingly, 2% of our study population presented with electrical storm during follow-up, requiring drug therapy initiation, ablation, or cardiac transplantation. Electrical storm occurrence is always a tragic event, even more so when the patient is young. Pharmacologic therapy aimed at rebalancing the currents active during the early phases of the epicardial right ventricular action potentials can be useful to abort electrical storms. In particular, drugs such as quinidine inhibit the transient outward current, acting to diminish the action potential notch and thus suppress the substrate and trigger for VAs (16).

ADVERSE EFFECTS OF ICD THERAPY. Inappropriate shocks are among the most important adverse effects of ICD therapy. In our study, 18.7% of patients experienced inappropriate shocks due to supraventricular arrhythmias, lead fracture, and T-wave oversensing. The frequency of inappropriate shocks in our study is consistent with the data previously reported by other groups. Steven et al. (17) reported a 15% rate of inappropriate shocks in series of 33 patients at 8-year follow-up. Similarly, Sacher et al. (5) reported inappropriate shocks in 24% of patients during 6-year follow-up. On the basis of the results of our previous study (6), in 2006 we started to program a single VF zone with a lower detection rate (>200 beats/min) in patients younger than 50 years and to adjust these settings on the basis of the individual clinical history. However, in this study, no significant temporal difference was found in terms of the rate of inappropriate shocks between patients implanted before or after 2005 (implantation after 2005: HR: 1.1; 95% CI: 0.43 to 2.78; $p = 0.83$). Young age, an active profile, and the predisposition of these patients to atrial arrhythmias likely increase the risk for inappropriate shocks. Moreover, the incidence of atrial arrhythmias has been reported to be higher in patients with ICDs (27%) compared with those without indications for ICD (13%), suggesting a more advanced disease process in patients with spontaneous atrial arrhythmias (18). Apart from setting high rate cutoffs, a strategy to reduce unnecessary therapies might be the insertion of a high VT zone with supraventricular tachycardia discriminators and a prolonged delay in therapy delivery by increasing the number of intervals to detect (11,19,20).

Patients with BS with ICDs have already been demonstrated to be more difficult to manage, not only because of the high incidence of inappropriate therapies but also because of their long life expectancy compared with the conventional ICD patient population, in which lead failure rates have been reported to range from 15% to 40% after 5 and 8 years, respectively (21). In this study, the rate of device-related complications was 16% at 7-year follow-up, and 75% of patients were younger than 40 years. It is well established that ICD placement in patients with BS is not without potential problems (5,6). Of note, in a previous study from our group, complications affected up to 33% of children with ICDs (22). In this particularly active category of patients, lead fracture can more frequently occur. Moreover, their long life expectancy leads to multiple generator change procedures, with a potential increased rate of device-related complications. Finally, lead-related problems can give rise to inappropriate therapies, with a significant impact on the quality of life of patients and relatives.

STUDY LIMITATIONS. Our study was a single-center experience conducted in a population of patients with heterogeneous clinical characteristics. The nature of this analysis, conducted on ICD implantations performed over 20 years, was retrospective. Thus, the ICD programming evolution over this period of time and the lack of consistent or pre-specified settings might be limitations of the study. EPS with programmed ventricular stimulation and genetic testing were not performed in all patients. Furthermore, in patients with lifelong risk for arrhythmias, a mean follow-up period of 7 years might be too short.

CONCLUSIONS

ICD therapy was an effective strategy in patients with BS, treating potentially lethal arrhythmias in 17% of patients during long-term follow-up. Appropriate shocks were significantly associated with the

presence of aborted SCD, but they also occurred in 13% of asymptomatic patients. On the basis of our findings, risk stratification by means of EPS might identify asymptomatic patients at risk for arrhythmic events and could be helpful in investigating syncope potentially not related to VA. ICD placement is frequently associated with device-related complications, affecting 16% of patients. Moreover, inappropriate shock rates remain high regardless of careful device programming.

REPRINT REQUSTS AND CORRESPONDENCE: Dr. Giulio Conte, Heart Rhythm Management Centre, UZ Brussel-VUB, Laarbeeklaan 101, 1090 Brussels, Belgium. E-mail: giulioconte.cardio@gmail.com.

PERSPECTIVES

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: Before the implantation of ICDs, physicians should explain to patients with BS the potential benefits and risks of device-related complications.

TRANSLATIONAL OUTLOOK: Longer term follow-up studies are needed to better identify patients with BS prone to developing life-threatening arrhythmias and to clarify the value of diagnostic electrophysiologic testing.

REFERENCES

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–6.

2. Brugada J, Brugada R, Brugada P. Pharmacological and device approach to therapy of inherited cardiac diseases associated with cardiac arrhythmias and sudden death. J Electrocardiol 2000;33 Suppl:41–7.

3. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342–7.

4. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659–70.

5. Sacher F, Probst V, Maury P, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. Circulation 2013;128:1739–47.

6. Sarkozy A, Boussy T, Kourgiannides G, et al. Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. Eur Heart J 2007;28:334–44.

7. Morita H, Kusano KF, Miura D, et al. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation 2008;118:1697–704.

8. Sarkozy A, Brugada P, Mont L, Brugada J. Optimizing the clinical use of implantable defibrillators in patients with Brugada syndrome. Eur Heart J 2007;9 Suppl I:I74–80.

9. Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. J Am Coll Cardiol 2008;52:541–50.

10. Gasparini M, Menozzi C, Proclemer A, et al. A simplified biventricular defibrillator with fixed long detection intervals reduces implantable cardioverter defibrillator (ICD) interventions and heart failure hospitalizations in patients with non-ischaemic cardiomyopathy implanted for primary prevention: the RELEVANT [Role of Long Detection Window Programming in Patients With Left Ventricular Dysfunction, Non-Ischemic Etiology in Primary Prevention Treated With a Biventricular ICD] study. Eur Heart J 2009;30:2758–67.

11. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275–83.

12. Sarkozy A, Sorgente A, Boussy T, et al. The value of a family history of sudden death in patients with diagnostic type I Brugada ECG pattern. Eur Heart J 2011;32:2153–60.

13. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (Programmed Electrical Stimulation Predictive Value) registry. J Am Coll Cardiol 2012;59:37–45.

14. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol 2002;40:1437–44.

15. Morita H, Fukushima-Kusano K, Nagase S, et al. Sinus node function in patients with Brugada-type ECG. Circ J 2004;68:473–6.

16. Hermida JS, Denjoy I, Clerc J, et al. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol 2004;43:1853–60.

17. Steven D, Roberts-Thomson KC, Inada K, et al. Long-term follow-up in patients with presumptive Brugada syndrome treated with implanted defibrillators. J Cardiovasc Electrophysiol 2011;22:1115–9.

18. Bordachar P, Reuter S, Garrigue S, Caï X, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. Eur Heart J 2004;25:879–84.

19. Gasparini M, Proclemer A, Klersy C. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. JAMA 2013;309:1903–11.

20. Saeed M, Hanna I, Robotis D, et al. Programming implantable cardioverter-defibrillators in patients with primary prevention indication to prolong time to first shock: results from the PROVIDE study. J Cardiovasc Electrophysiol 2014;25:52–9.

21. Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation 2007;115:2474–80.

22. Conte G, Dewals W, Sieira J, et al. Drug-induced Brugada syndrome in children: clinical features, device-based management and long-term follow-up. J Am Coll Cardiol 2014;63:2272–9.

KEY WORDS Brugada syndrome, implantable cardioverter-defibrillator, sudden cardiac death, ventricular arrhythmias