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Implantable Cardioverter-Defibrillators in Children and Adolescents With Brugada Syndrome

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ABSTRACT

BACKGROUND Young patients presenting with symptomatic Brugada syndrome have very high risks for ventricular arrhythmias and should be carefully considered for implantable cardioverter-defibrillator (ICD) placement. However, this therapy is associated with high rates of inappropriate shocks and device-related complications.

OBJECTIVES This study investigated clinical features, management, and long-term follow-up of young patients with Brugada syndrome and ICD.

METHODS Patients diagnosed with Brugada syndrome, who underwent implantation of an ICD at an age of ≤20 years, were studied.

RESULTS The study included 35 consecutive patients. The mean age at ICD placement was 13.9 ± 6.2 years. Ninety-two percent were symptomatic; 29% presented with aborted sudden cardiac death and 63% with syncope. During a mean follow-up period of 88 months, sustained ventricular arrhythmias were treated by the ICD in 9 patients (26%), including shocks in 8 patients (23%) and antitachycardia pacing in 1 patient (3%). Three patients (9%) died in an electrical storm. Seven patients (20%) experienced inappropriate shocks, and 5 patients (14%) had device-related complications. Aborted sudden cardiac death and spontaneous type I electrocardiogram were identified as independent predictors of appropriate shock occurrence.

CONCLUSIONS ICD therapy is an effective strategy in young patients with symptomatic Brugada syndrome, treating potentially lethal arrhythmias in >25% of patients during follow-up. Appropriate shocks were significantly associated with previously aborted sudden cardiac death and spontaneous type I electrocardiograms. However, ICDs are frequently associated with complications and inappropriate shocks, both of which remain high regardless of careful device implantation and programming. (J Am Coll Cardiol 2018;71:148-57) © 2018 by the American College of Cardiology Foundation.

Brugada syndrome is an inherited disease characterized by a coved-type ST-segment elevation in the right precordial leads and increased risk of sudden cardiac death (SCD) (1). The phenotypic expression of the disease extends from the completely asymptomatic subject to the individual who experiences potentially lethal arrhythmias and SCD. The disease typically manifests in the fourth decade of life, but severe cases have clinical expression during childhood and can lead to life-threatening arrhythmias (2,3).

The placement of an implantable cardioverter-defibrillator (ICD) remains the only therapy with proven efficacy for the management of ventricular arrhythmias and prevention of SCD in young patients with Brugada syndrome. Young patients experiencing aborted SCD represent a small group, but they are at a very high risk of recurrence of potentially lethal events during follow-up (4). This population has a clear class I indication for ICD implantation (5).

Data on young patients with Brugada syndrome that underwent an ICD implantation are sparse (6).

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In a previous publication from our center (4), we reported that almost 25% of high-risk patients with an ICD received an appropriate therapy and that the mean time that elapsed from the device implantation to therapy occurrence was 1 year.

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The purpose of this study was to analyze our single-center experience with ICD in a young cohort (≤20 years old) with Brugada syndrome over the past 25 years, since the first description of the syndrome. Particularly, we aimed to assess the clinical features and the long-term follow-up of this group, with a focus on appropriate therapies versus adverse events including inappropriate shocks.

METHODS

STUDY POPULATION. Since 1992, all consecutive patients diagnosed with Brugada syndrome have been included in a family registry and followed in a prospective fashion. The ethics committee of Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel approved the study protocol. A total of 1,638 patients, coming from 428 families with Brugada syndrome were included in the registry from 1992 to 2016. Among them, 210 patients were ≤20 years old. Study inclusion criteria in this subset of the population consisted of the following: 1) spontaneous or drug-induced Brugada type I electrocardiographic pattern; 2) ICD therapy; and 3) continuous follow-up at our institution for ≥6 months post-device implantation. Thirty-five patients (16%) fulfilled inclusion criteria. Two international patients were excluded because follow-up data could not be obtained.

Patients were considered symptomatic if they presented with severe syncope and/or aborted SCD. Arrhythmic syncope was suspected in the absence of prodrome or specific triggering circumstances.

All patients with aborted SCD or severe syncope underwent a careful diagnostic work-up for arrhythmic origins of the events before ICD implantation. The work-up included a careful examination of the patient's history, a 12-lead electrocardiography, a transthoracic echocardiography or cardiac magnetic resonance imaging, and a Holter monitoring or other event recorder means when indicated.

Electrocardiograms were considered diagnostic of Brugada syndrome 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. 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 the electrocardiograms.

Twelve-lead electrocardiograms and Holter monitoring tracings were reviewed to identify sinus node dysfunction and atrial arrhythmias. Sinus node dysfunction was defined as inappropriate sinus bradycardia according to age and activity level (7), sinus pause/arrest >2.5 s, and chronotropic incompetence. Chronotropic incompetence was defined as failure to achieve 85% of the age-predicted maximum heart rate during the exercise test (8). Atrial arrhythmias were defined as sustained atrial tachycardia, atrial fibrillation, and atrial flutter for the purposes of this study.

Provocative tests with ajmaline were performed in cases of normal baseline electrocardiogram. Ajmaline (1 mg/kg) was administered intravenously over a 5-min period. The test was considered positive for Brugada syndrome if a coved-type electrocardiogram pattern was documented in ≥1 right precordial lead from V_1 to V_3.

Electrophysiological studies were performed in patients with severe syncope and type I electrocardiographic pattern. Programmed ventricular stimulation consisted of a maximum of 3 ventricular extrastimuli with a minimal coupling interval of 200 ms delivered from ≥1 ventricular site. The study was considered positive in the case of induction of ventricular fibrillation or sustained ventricular tachycardia lasting ≥30 s. Genetic testing with sequence analysis of *SCN5A* was recommended for all patients with diagnoses of Brugada syndrome starting in 2010.

ICD INDICATION AND IMPLANTATION. The indications for ICD therapy were determined using the recommendations of the most recent expert consensus conference, adapted to our pediatric population (5). The decision to perform epicardial versus endocardial lead implantation, and 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. Defibrillation testing was systematically performed in the operating room both for transvenous and epicardial systems. The protocol included induction of ventricular fibrillation and delivery of an initial 10-J shock in patients of <25 kg, and 15-Js shocks in patients ≥25 kg (9). Defibrillation was achieved in all

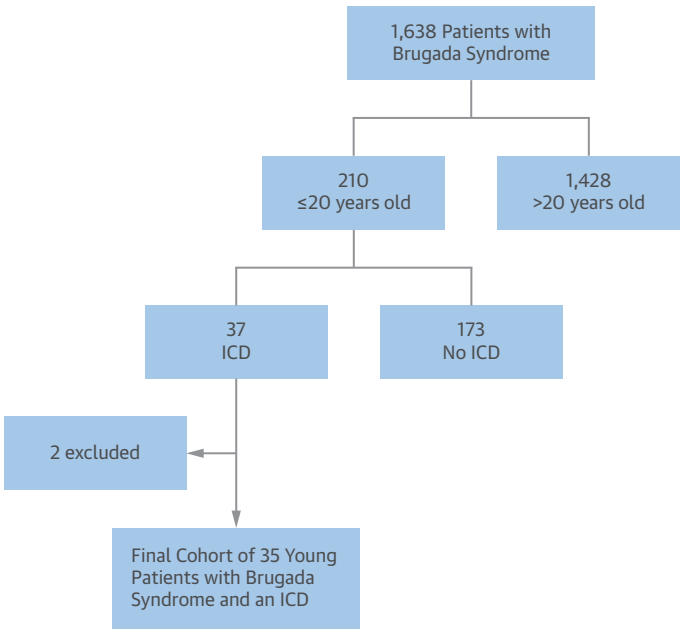
ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

ICD = implantable cardioverter-defibrillator

SCD = sudden cardiac death

FIGURE 1 Study Population



This flowchart shows the study population. Since 1992, a total of 1,638 patients, coming from 428 families with Brugada syndrome were included in a prospective family registry. Among them, 210 patients were ≤20 years of age. From these, 37 patients received an implantable cardioverter-defibrillator (ICD). Two international patients were excluded because follow-up information could not be obtained, resulting in a final cohort of 35 pediatric and adolescent patients with Brugada syndrome and implantable cardioverter-defibrillation therapy.

patients with the initial shock. All patients were programmed with the first shock set at the strength that resulted as successful during the test, with the maximum output for subsequent shocks and reverse polarity for the last 2 shocks. Additional device programming was adapted to patient's age and level of activity, with a single ventricular tachycardia zone at 240 beats/min. Long detection intervals between 30 and 40 s were used to avoid unnecessary therapies. A monitor zone was usually programmed between 200 and 240 beats/min. These settings were adjusted during follow-up on the basis of increasing age, level of individual clinical history, and to avoid recurrences of inappropriate interventions.

FOLLOW-UP. Clinical follow-up of patients consisted of physical examinations and electrocardiography after cardioverter implantation. Follow-up of the device was performed at 1 and 3 months after implantation and thereafter every 6 months. From 2006, home monitoring devices were implanted either de novo or at battery change, in case of prior implantation. Device memory was interrogated in each regular visit and during post-therapy visits. All available electrograms of appropriate and inappropriate shocks were analyzed by ≥2 investigators independently. Electrograms were derived from various bipolar configurations involving the tip and ring electrodes, or shocking coils on the pacing or defibrillating leads, or a wide bipolar recording between 1 of the ventricular electrodes and the device casing. In those patients that presented arrhythmias during follow-up, discrimination between rapid polymorphic ventricular tachycardia and ventricular fibrillation was performed when possible on the basis of the electrocardiographic patterns derived from multiple channels. Monomorphic ventricular tachycardia was defined as an arrhythmia with constant electrographic configuration and a stable rate within a few beats. On the other hand, polymorphic ventricular tachycardia had a changing rate and demonstrated varying configurations. Finally, ventricular fibrillation was defined as rapid and continuously varying electrograms with irregular cycle lengths. Appropriate therapies were defined as shocks or antitachycardia pacing delivered for ventricular arrhythmias. On the contrary, inappropriate therapies were defined as those delivered in the absence of ventricular events. Finally, electrical storms consisted of ≥3 sustained episodes of ventricular arrhythmias with or without appropriate ICD interventions during a period of 24 h.

STATISTICAL ANALYSIS. Data were reported as mean ± SD, medians (interquartile ranges), or as absolute values and percentages, as appropriate. Comparisons between continuous variables were performed using the unpaired Student's *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. 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 indicated statistical significance. Statistical analyses were conducted using SPSS (version 22, SPSS, IBM, Armonk, New York).

RESULTS

A total of 35 consecutive young patients ≤20 years old (25 male [71%]) received an ICD at our institution from 1992 to 2016 and met the inclusion criteria for this study (Figure 1).

Patients belonged to 27 different families. The mean age at diagnosis was 10.1 ± 6.2 years and the age at ICD implantation was 13.9 ± 6.2 years. Family

histories of SCD were present in 13 patients (37%). Ten patients (29%) presented with aborted SCD before ICD placement. Twenty-two patients (63%) presented with ≥1 episode of syncope, and 3 patients (8%) were asymptomatic before receiving a device.

Five patients (14%) presented with spontaneous (including fever-induced) type I electrocardiographic pattern. The diagnosis was induced by a provocative test in the remaining 30 patients (86%). Among them, 3 patients (9%) experienced drug-induced sustained ventricular arrhythmias.

Eight patients (23%) presented with sinus node dysfunction. Seven patients (20%) had documented episodes of sustained atrial arrhythmias. An electrophysiological study was performed in 26 patients (74%). Sustained ventricular arrhythmias were induced during programmed ventricular stimulation in 4 patients (11%).

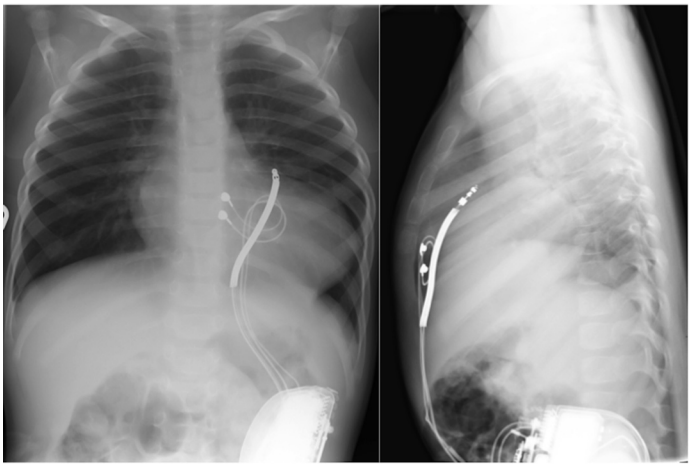
A total of 19 genetic tests (54%) were performed; 7 of them (37%) were positive for mutations in the *SCN5A* gene.

ABORTED SCD. From the group that presented initially with SCD (n = 10), 7 were male (70%), and 3 had a family history of SCD (30%). Three patients (30%) had evidence of spontaneous type I electrocardiogram. The mean age of SCD was 7.0 ± 5.4 years, ranging from 0.1 to 15.0 years. Three infants experienced multiple episodes of aborted SCD before reaching 2 years of age. Aborted SCD was the first clinical manifestation of the syndrome in 7 patients (70%). SCD was preceded by episodes of syncope in 3 patients (30%). Sudden death occurred at rest in 8 patients (80%), of which, 1 was during sleep and 1 during fever.

SYNCOPE. Syncope was the clinical manifestation of the syndrome in 22 patients (63%). Sixteen patients (73%) were male, and 8 (36%) had family histories of SCD. Nine patients (41%) were family members of patients with Brugada syndrome. Spontaneous Brugada type I electrocardiographic pattern was documented in 3 patients (14%). The mean age at the time of the first syncope was 11.7 ± 5.7 years.

ASYMPTOMATIC PATIENTS. Three patients (8%) did not report any symptoms. All of them were family members of a single Brugada syndrome patient that died suddenly in a ventricular fibrillation storm. The indication to place an ICD was based on the presence of multiple electrical abnormalities (including spontaneous type I electrocardiographic pattern, sinus node dysfunction, atrioventricular [AV] block with PR interval >180 ms, severe intraventricular delay with QRS complex >120 ms, and atrial arrhythmias), in the setting of an identified *SNC5A* mutation and first-degree family history of SCD.

FIGURE 2 Epicardial ICD in a 3-Year-Old



This figure shows thoracic and abdominal x-ray front and lateral views of a 3-year-old patient with an epicardial implantable cardioverter-defibrillator (ICD) system. Note the arrangement of an epicardial coil, a bipolar inferior sensing lead, and an abdominal generator.

PROCEDURAL CHARACTERISTICS. Twenty-two patients (63%) received a transvenous ICD, and patients (37%) received single-chamber transvenous devices. No patient received a totally subcutaneous system. Patients that received an epicardial system had a mean age of 7.9 ± 3.8 years.

EPICARDIAL ICD IMPLANTATION TECHNIQUE. In those patients that received an epicardial system (n = 13), a single coil transvenous lead was implanted via a left thoracotomy approach. A bipolar pace-sense lead was placed on the right ventricle for sensing and pacing purposes. To avoid cardiac strangulation, no more than 30% of the heart's circumference was covered, and the coil was sewn to the pericardium. A left lateral, subfascial generator pocket was created beneath the anterior rectus sheath. The pocket was placed below the left costal margin, creating an effective vector for defibrillation. The ventricular lead sensing and pacing thresholds were tested. Impedance measurements were obtained both in the ventricular epicardial pacing lead and in the coil. Finally, defibrillation threshold testing was performed for all the systems as previously described. Figure 2 depicts a thoracic and abdominal x-ray of a 3-year-old patient with an epicardial ICD arrangement.

LONG-TERM FOLLOW-UP. After a mean follow-up period of 88 months (range: 7 to 238 months),

TABLE 1 Characteristics of Patients That Presented With Electrical Storms Resulting in Death During Follow-Up

Patient #	Proband	Sex	Diagnosis Age (yrs)	Symptom	SND	AT	CoAb	aECG	Ind	Gen	ICD	Age at ICD Implantation (yrs)	Age at Event (yrs)	Follow-Up (yrs)
1	Yes	M	3.2	SCD	Yes	Yes	Yes	Yes	No	ND	Yes	17.2	18.2	15
2	Yes	M	13.3	Syncope	Yes	Yes	Yes	Yes	Yes	Pos	Yes	13.5	20.1	6.6
3	Yes	M	15.3	Syncope	No	Yes	Yes	Yes	No	Neg	Yes	15.5	22.6	7.1

aECG = abnormal electrocardiogram; AT = atrial tachycardia; CoAb = conduction abnormality; Gen = genetic test; ICD = implantable cardioverter-defibrillator; Ind = inducibility in electrophysiology study; M = male; ND = not done; Neg = negative; Pos = positive; SCD = sudden cardiac death; SND = sinus node dysfunction.

spontaneous sustained ventricular arrhythmias were documented in 10 patients (29%). Sustained ventricular arrhythmias were treated by ICD shocks in 8 patients (23%) and by antitachycardia pacing in 1 patient (3%). In 1 patient, the ventricular arrhythmias stopped spontaneously at 32 s, and therapy was aborted.

Seven patients (20%) experienced inappropriate shocks. An electrical storm occurred in 3 subjects (9%). A spontaneous Brugada type I electrocardiographic pattern could be documented on ≥1 occasion during the follow-up period in 9 patients (26%). After ICD placement, 1 patient (3.5%) experienced episodes of vasovagal-mediated syncope. In this patient, the rate of ventricular pacing was <1%, and no ventricular arrhythmias were detected in the device memory. Among initially asymptomatic patients, none experienced syncope during follow-up. Six patients (17%) developed paroxysmal atrial fibrillation during follow-up: 5 in the asymptomatic group (83%), and 1 in the symptomatic group (17%). Two patients (6%) with ICDs and drug-resistant atrial fibrillation underwent pulmonary vein isolation by means of cryoballoon ablation. At last follow-up, a total of 4 patients (11%) with documented atrial arrhythmias were under pharmacological treatment with sotalol or beta-blockers. One patient presented atrial flutter and underwent ablation. Two patients underwent ablation of typical AV nodal re-entrant tachycardia.

ELECTRICAL STORMS AND MORTALITY. Three young patients (9%) died during follow-up due to noncontrolled ventricular arrhythmias. All of them were male and presented with atrial arrhythmias and/or sinus node dysfunction, but only 1 had evidence of spontaneous type I electrocardiogram (Table 1).

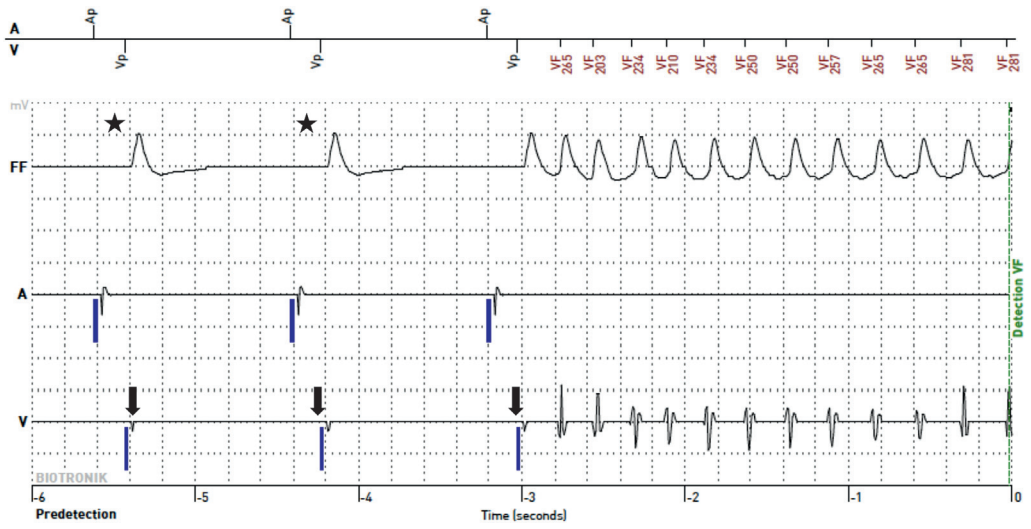
The youngest patient belonged to the first family ever diagnosed with Brugada syndrome. He had presented at 3 years of age with syncope and recurrent aborted SCD, in the setting of spontaneous type I electrocardiogram. He also presented with severe sinus node dysfunction, with clinical evidence of severe bradycardia and long sinus pauses. He had a PR interval of >200 ms and a QRS interval of >150 ms. He presented with early onset of atrial arrhythmias, rapidly evolving to atrial fibrillation and atrial standstill. 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, the antiarrhythmic therapy was discontinued. The patient died suddenly 11 months after the device implantation in 2009, at 18 years of age, due to ventricular fibrillation refractory to both internal and external defibrillations.

The second patient presented with severe syncope at the age of 13 years. He did not present with spontaneous type I electrocardiogram but had early onset of atrial fibrillation that evolved to standstill in <1 year. He had a PR interval of >200 ms and a QRS interval of >160 ms. He received an ICD at age 13.2 years and was asymptomatic for 7 years before presenting the electrical storm that resulted in his death.

The third patient presented with SCD during sleep at 15 years old. He was subsequently implanted of an ICD and remained asymptomatic during 4 years. The ICD memory during the event that resulted in his death during sleep showed initiation with noncaptured ventricular pacing beats followed by ventricular fibrillation refractory to therapy (Figure 3).

APPROPRIATE SHOCKS. Eight patients (23%) experienced ≥1 appropriate shock during the follow-up period. Moreover, 1 patient (3%) received successful antitachycardia pacing for monomorphic ventricular tachycardia. Considering the group of patients that received appropriate shocks, all of them were male and presented with symptoms before the implantation. In 3 patients, the initial symptom was syncope, and in 4 patients, it was SCD. The rate of appropriate shocks was significantly higher in patients presenting with aborted SCD compared with the patients that presented with syncope (40% vs.

FIGURE 3 **ICD Telemetry Transmission Preceding a Ventricular Fibrillation Storm**



Patient #3's implantable cardioverter-defibrillator (ICD) telemetry recording during the event that resulted in his death. Note that the event happened at night during sleep. The sequence starts by sinus bradycardia with atrial and ventricular pacing, but no ventricular capture **(black arrows).** There is a slow escape idioventricular rhythm **(black stars)** that is followed after the third beat by a fast ventricular tachycardia that degenerates later in ventricular fibrillation refractory to cardioversion.

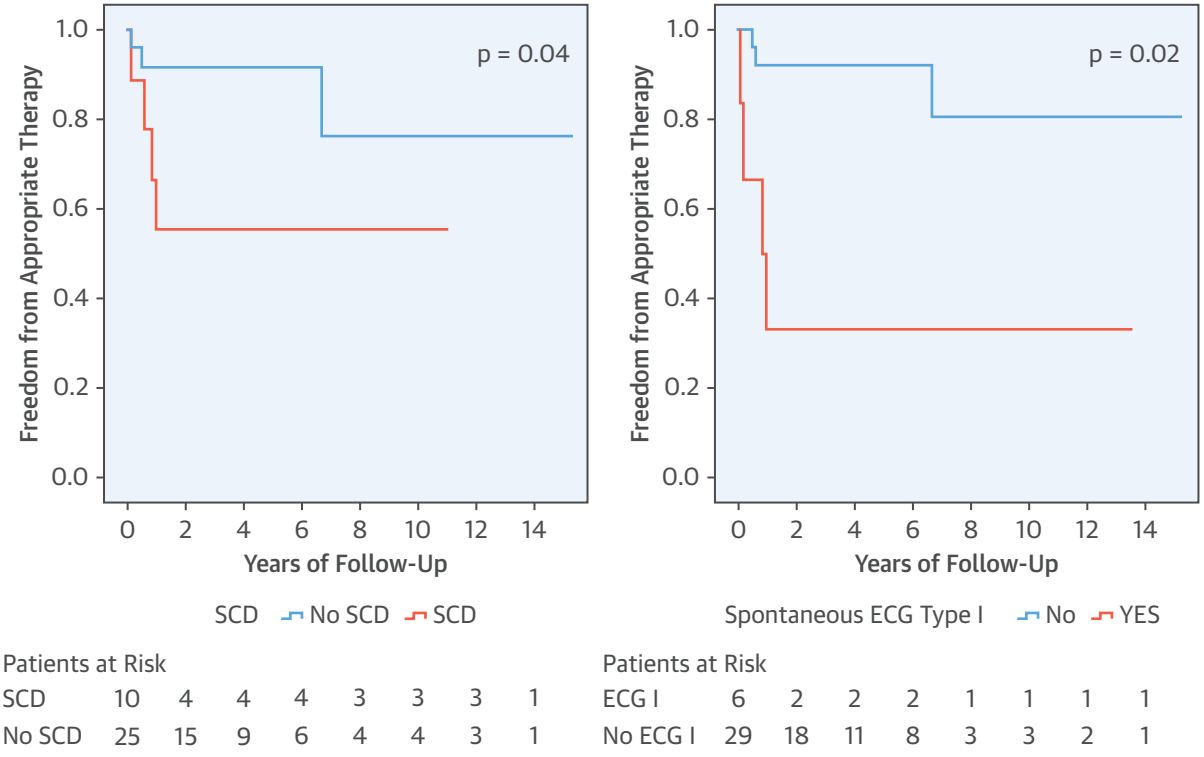
14%; $p < 0.1$). Only 40% of the patients that received an appropriate shock presented with a spontaneous Brugada type I electrocardiographic pattern. The median time from implantation to first therapy was 7.2 months (interquartile range: 1.9 to 11.5 months). Six patients (75%) received the first appropriate shock within 1 year of the implantation. The mean number of shocks delivered per patient was 2.4. Six patients (75%) had 1 shock, 1 (12%) experienced 2 shocks, and 1 (12%) received 10 appropriate shocks due to repetitive ventricular fibrillation episodes initiated by right ventricular outflow extrasystolic activity. This patient underwent subsequently epicardial right ventricular outflow ablation. The therapy-triggering arrhythmia in all the cases was ventricular fibrillation, with ventricular rates >240 beats/min. Of note, none of the asymptomatic patients presented with an appropriate shock.

On univariate analysis, a spontaneous Brugada type I electrocardiographic pattern (hazard ratio: 9.3; 95% confidence interval: 1.2 to 15.5; $p = 0.02$) and aborted SCD (hazard ratio: 3.7; 95% confidence interval: 1.4 to 15.5; $p = 0.04$) were shown to confer a high risk for experiencing an appropriate shock during follow-up. The **Central Illustration** shows the freedom from appropriate therapy survival curves for patients presenting with SCD and spontaneous type I electrocardiogram.

INAPPROPRIATE SHOCKS. Seven patients (20%) had inappropriate shocks after the ICD implantation. The mean number of inappropriate shocks delivered per patient was 1.1, with a minimum of 1 shock in 6 patients (85%) and a maximal of 2 shocks in 1 patient (15%). Inappropriate shocks were caused due to supraventricular tachycardia in 2 patients (29%), lead fracture resulting in noise on the ventricular channel in 3 (42%), and T-wave oversensing in 2 (29%). The supraventricular tachycardias resulting in shock consisted of atrial fibrillation in 1 patient and sinus tachycardia during exercise in the other patient. The patient with atrial fibrillation underwent pulmonary vein isolation due to drug-resistant paroxysmal atrial fibrillation. The patient who experienced an inappropriate shock because of exercise-related sinus tachycardia at rates of 200 beats/min had his ventricular fibrillation window increased to 240 beats/min and did well afterward, with no recurrence of events. Of note, the incidence of inappropriate shocks did not differ depending on patient's age at symptoms or implantation, the presence of atrial fibrillation, sinus node dysfunction or AV block, the localization of the ICD (epicardial vs. transvenous system), or the presence of complications (**Table 2**).

DEVICE-RELATED COMPLICATIONS. Five patients (14%) experienced a device-related complication during follow-up. The complications included a

CENTRAL ILLUSTRATION **ICD in Pediatric Patients With Brugada Syndrome: Event-Free Survival Based on Kaplan-Meier Method**



Gonzalez Corcia, M.C. et al. J Am Coll Cardiol. 2018;71(2):148–57.

The event-free survival was estimated by the Kaplan-Meier method and compared by the log-rank test. This figure shows graphics analyzing freedom from appropriate shocks according to previous sudden cardiac death (SCD) **(left)** and spontaneous type I electrocardiographic (ECG) pattern **(right).** The time is measured in years since device implantation. Note that the incidence of appropriate therapy at 5 years post ICD implantation is 50% in patients that initially presented with SCD, and 70% in those patients that presented with a spontaneous type I ECG pattern.

fracture of the ventricular electrode in 3 patients (60%), a lead dislocation in 1 patient (20%), and a pulse generator migration in 1 patient (20%). All the complications resulted in the immediate revision of the device. Two of the patients that had a lead fracture experienced inappropriate shocks caused by noise in the ventricular channel. Interestingly, we could not identify any clinical or device-related difference between the group of patients that suffered complications and those that did not (Table 3).

The incidence of adverse events related to ICD changed over time. When the evaluation was done between implantation eras, inappropriate shocks occurred less frequently among those patients whose devices were implanted after 2010 (from 33% before or during 2010 to 10% after 2010; p= 0.1). The percentage of patients presenting with an ICD complication decreased by >50% between these 2 eras (26% before or during 2010 and 10% after 2010; p = 0.36).

DISCUSSION

Clinical Brugada syndrome in young individuals is rare. However, the early manifestation of the disease has very high risk and potentially lethal consequences. When the disease manifests clinically in the early life with syncope or SCD, the physician is faced with many challenges including the choice of a diagnostic strategy, the indication of a therapy, and the possibility of undesirable events during the follow-up period. In children, evaluation of the origin and type of syncope is particularly difficult, even after performing a proper diagnostic work-up. In addition,

TABLE 2 Comparison of Characteristics Between Patients That Received Inappropriate Shock and Those Who Did Not

Shocks	Inappropriate Shocks	No Inappropriate Shock	p Value
Male	4 (60)	21 (75)	0.38
SCD	2 (28)	8 (28)	>0.99
Age at symptoms, yrs	10.2 ± 4.3	9.9 ± 6.5	0.92
Age at ICD implantation, yrs	12.5 ± 4.7	14.2 ± 6.5	0.51
AF	1 (14)	5 (18)	>0.99
SSS	2 (28)	7 (25)	>0.99
AVB	1 (14)	4 (14)	>0.99
Epicardial ICD	4 (60)	9 (32)	0.38
ICD complications	2 (28)	3 (11)	0.25
Total	7	28	

Values are n (%), mean ± SD, or n. Comparison of the characteristics of those patients that received an inappropriate shock and those who did not. Note that the incidence of inappropriate shocks did not differ depending on patient's age at symptoms or implantation; the presence of atrial fibrillation, sinus node dysfunction, or atrioventricular block; the localization of the ICD (epicardial vs. transvenous system); or the presence of complications.

AF = atrial fibrillation; AVB = atrioventricular block; SSS = sick sinus syndrome.

sinus node dysfunction and atrial arrhythmias, 2 frequent markers of severe Brugada syndrome in young patients, can also be responsible for syncope.

On the one hand, the event of a SCD in a youth has a devastating psychological impact in a family and in a society. On the other hand, there are at present no specific guidelines addressing indications for device therapy in children with Brugada syndrome. Currently, ICD therapy is considered in adult patients with the Brugada presenting with episodes of syncope, if no other cause of syncope is found (5). The indication of an ICD is a difficult decision in young patients, but to date, it remains the only strategy that has proven to be effective to protect these patients' lives. In this setting, the decision to recommend an ICD must be taken after a careful evaluation of the episodes and taking into account as many clinical and electrical variables as possible.

We present the results of the largest single-center cohort study of young patients implanted with an ICD for Brugada syndrome. From these 35 patients, 9 patients (26%) received appropriate device therapy during a mean follow-up of 7.3 years. The rate of appropriate device therapy by means of shocks is also very high (23%). This increases to 40% when considering those patients in whom the ICD indication was aborted SCD. Previously, our group, as well as Sacher et al. (10) and Conte et al. (11), reported a similar rate of appropriate shocks after ICD therapy for secondary prevention in an adult population.

When evaluating predictors of a future therapy, SCD has been shown to have a strong predictive power for future arrhythmic events and appropriate shocks in young patients with Brugada syndrome and ICD. The presence of a spontaneous type I electrocardiogram is the other clinical parameter that has predictive value for future arrhythmic events and appropriate shocks. Thus, we consider that symptomatic patients with spontaneous type I electrocardiograms should be considered carefully for ICD therapy.

A previous study from our center reporting on risk factors for lethal events in young patients with Brugada syndrome was able to identify these 2 factors, as well as other independent predictors of future arrhythmic events (4). The other predictors included syncope, sinus node dysfunction, atrial tachycardias and other conduction abnormalities such as AV block, or intraventricular conduction delay. In the present study, including a smaller number of patients, these last variables were not found to be predictors of appropriate shocks.

In this cohort, the inducibility of ventricular arrhythmias during an electrophysiological study failed to identify patients at risk for developing arrhythmic events during follow-up. This mimics our previous reports in young Brugada syndrome patients (4) and contradicts the center experience with adult patients (11). Our group advocates on the importance of performing a complete electrophysiological evaluation in young patients with Brugada syndrome. This study allows collecting valuable information on the sinus node function, the presence of concomitant supraventricular tachycardias, the status of the AV conduction and infra-Hisian conduction, as well as ventricular inducibility.

TABLE 3 Comparison of Characteristics Between Patients That Experienced Device-Related Complications and Those Who Did Not

	Complications	No Complications	p Value
Male	2 (40)	23 (77)	0.12
SCD	1 (20)	9 (30)	>0.99
Age at symptoms, yrs	10.2 ± 8.1	9.9 ± 6.0	0.77
Age at ICD, yrs	13.0 ± 7.1	14.0 ± 6.3	0.75
AF	1 (20)	5 (17)	>0.99
SSS	2 (40)	7 (23)	0.58
AVB	1 (20)	4 (13)	0.56
Epicardial ICD	2 (40)	11 (37)	0.25
Inappropriate shocks	2 (40)	5 (17)	0.25
Total	5	30	

Values are n (%), mean ± SD, or n. The comparison between those patients that experienced device-related complications and those who did not showed no substantial difference in terms of sex, age, electrical characteristics, or type of device.

Abbreviations as in Tables 1 and 2.

The occurrence of a ventricular storm is always a tragic event, even more so when the patient is young. In this series, 3 patients died because of uncontrolled ventricular arrhythmic events despite the presence of well-functioning ICD. All 3 patients presented with early severe electrical conduction abnormalities in their baseline electrocardiograms and Holter monitorings. These included sinus node dysfunction with severe sinus bradycardia and pauses, first-degree AV block with a PR interval of >200 ms, and severe intraventricular conduction delay with a QRS interval of >150 ms. Furthermore, there was an early diagnosis of atrial arrhythmias in all, which progressed rapidly to atrial fibrillation and atrial standstill in 2 of them. None of them presented with an appropriate shock before the occurrence of the electrical storm, and they were on no concomitant medical treatment. Interestingly, the last 2 patients had also evidence of sporadic noncaptured beats in the memory of their pacemakers during follow-up even if the device showed excellent thresholds at each interrogation.

In patients presenting with electrical storms or recurrent appropriate shocks, pharmacologic therapy aimed at rebalancing the currents active during the early phases of the epicardial right ventricular action potentials can be useful to abort and control the arrhythmias. In particular, drugs such as quinidine inhibit the transient outward current, acting to diminish the action potential notch and thus suppressing the substrate and trigger for ventricular arrhythmias (12). Our group has previously warned against the use of quinidine as a strategy to avoid ICD implantation in the pediatric age (2). The QUIDAM (Hydroquinidine therapy for the management of Brugada syndrome patients at high arrhythmic risk) study has recently concluded that even if quinidine seems to be effective in preventing life-threatening ventricular arrhythmias, it could not be an alternative for an ICD implantation (13).

When considering the adverse effects of ICD, inappropriate shocks are among the most important. In this series, 20% of the patients experienced inappropriate shocks due to supraventricular arrhythmias, lead fracture, and T-wave oversensing. No significant difference was found in terms of the rate of inappropriate shocks between patients implanted with epicardial versus transvenous ICD. Younger age, an active profile, and the presence of atrial arrhythmias likely increase the risk for inappropriate shocks, but none of these had statistical significance for this cohort. However, we did find an era effect, with a tendency toward reduction of inappropriate shocks and complications from 2010 onward. Improvements in device technology and programming algorithms have certainly played an important role in improving outcomes and reducing inappropriate therapies. To minimize inappropriate shocks, it is our practice to program a single ventricular fibrillation zone with a high detection rate set at >240 beats/min in young patients, and to adjust these settings on the basis of the individual's clinical history, age, and level of activity. Supraventricular tachycardia discriminators and a prolonged delay in therapy delivery are also used.

The rate of device-related complications of this study is 14% at 7-year follow-up. Even though this rate is high, it is not when compared with other reports in the pediatric literature. A multicenter study on ICD in pediatric and congenital heart disease patients by Berul et al. (14) in 2008 showed that 36% of patients presented with acute or chronic complications. This same study reported 24% of inappropriate shocks in a subcohort <18 years of age. Similar rates had been previously reported by Alexandre et al. (15) on a single-center study from 2004. Most of the adverse events in young patients have their origin in lead abnormalities. In this particularly active category of patients, a lead fracture can occur more frequently and give rise to inappropriate therapies with a significant impact on the quality of life of patients and relatives. Most probably secondary to the small number of patients, no variable with statistical significance could be identified as a risk for complications.

STUDY LIMITATIONS. This study was a single-center retrospective analysis. We report the experience of the largest homogeneous cohort of young patients with Brugada syndrome and an ICD. However, the main limitation remains the small number of the cohort, which could interfere with the statistical results.

CONCLUSIONS

The medical decision to indicate an ICD in young patients with Brugada syndrome remains a challenge. Our study summarizes a single-center experience with 35 patients with Brugada syndrome that received an ICD at an age of ≤20 years. During a mean follow-up of 7.3 years, this therapy was effective to treat potentially lethal arrhythmias in more than 25% of these patients. Appropriate shocks were significantly associated with the presence of previous aborted SCD and spontaneous type I electrocardiogram at diagnosis or follow-up. However, ICD placement is frequently associated with device

complications (14%) and inappropriate shocks (20%). These 2 undesirable events occur despite very careful device implantation and programming in experienced hands. It is thus extremely important to evaluate every patient on an individual basis and discuss with the patient and the family the benefits and potential risks associated with this therapy. Long-term follow-up studies are needed to assess the value of diagnostic electrophysiological testing and of specific genetic mutations in this population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Approximately 1 in 4 patients ≤20 years of age with symptomatic Brugada syndrome and an ICD receive appropriate life-saving interventions over a period of 7 years, although inappropriate shocks and other adverse events occur relatively frequently in this patient population.

TRANSLATIONAL OUTLOOK: Additional studies are needed to assess the value of diagnostic electrophysiological testing and identification of specific genetic mutations in guiding device-based therapy for pediatric patients with Brugada syndrome.

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