Inappropriate shock in Brugada syndrome: incidence and predictors in patients with a subcutaneous implantable cardiac defibrillator

Short title: S-ICD Inappropriate shocks in Brugada syndrome

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Conflict of interest

G.C. has served as proctor for Boston Scientific. F.B. has served as consultant for St. Jude Medical. The other authors have no conflict of interest to disclosure

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27Abstract

28Background: Subcutaneous implantable cardioverter defibrillators (S-ICDs) avoid complications
29secondary to transvenous leads, but inappropriate shocks (ISs) are frequent. Furthermore, IS data
30from patients with Brugada syndrome (BrS) with an S-ICD are scarce.

31Objective: We aimed to establish the incidence, mechanisms, and predictors of S-ICD in this
32population.

33Methods: We analyzed the clinical and electrocardiographic characteristics, automated screening
34test data, device programming, and IS occurrence in adult patients with BrS with an S-ICD.

35Results: Thirty-nine patients were enrolled (69% male, mean age at diagnosis 46±13 years, mean
36age at implantation 48±13 years). During a mean follow-up of 26±21 months, 18% patients
37experienced IS. Patients with IS were younger at the time of diagnosis (36±8 versus 48±13 years,
38p=0.018) and S-ICD implantation (38±9 versus 50±23 years, p=0.019) and presented with
39spontaneous type 1 Brugada ECG pattern more frequently at diagnosis or during follow-up (71%
40versus 25%, p=0.018). During automated screening tests, patients with IS showed lower QRS
41voltage in the primary vector in the supine position (0.58±0.26 versus 1.10±0.35 mV, p=0.011) and
42lower defibrillator automated screening score (DASS) in the primary vector in the supine (123±165
43versus 554±390 mV, p=0.005) and standing (162±179 versus 486±388 mV, p=0.038) positions.
44Age at diagnosis was the only independent predictor of IS (hazard ratio=0.873, 95% confidence
45interval: 0.767-0.992, p=0.037).

46Conclusion: IS was a frequent complication in patients with BrS with an S-ICD. Younger age was
47independently associated with IS. A more thorough screening process might help prevent IS in this
48population.

49Keywords: Brugada syndrome. Subcutaneous implantable cardioverter-defibrillator. Inappropriate
50shock.

Introduction

An implantable cardioverter-defibrillator (ICD) is recommended in patients with Brugada syndrome (BrS) at a high risk of ventricular fibrillation (VF) to prevent sudden cardiac death (SCD). As these patients are often young, have long life expectancy, and rarely need pacing, a subcutaneous ICD (S-ICD) may be considered to prevent complications associated with transvenous leads. S-ICDs are associated with complications, the most frequent of which is inappropriate shock (IS). In patients with an S-ICD, the main cause of IS has been shown to be related to T-wave oversensing (TWOS) (1;2). Data are lacking on the incidence, mechanisms, and predictors of IS in patients with BrS implanted with an S-ICD. We aimed to determine the incidence and predictors of IS in patients with BrS and an S-ICD.

Methods

Patient population

This was a single-center, ambispective, observational study of a cohort of patients with BrS at a high risk of SCD and implanted with an S-ICD. Patients referred to our center after S-ICD implantation in other institutions were enrolled retrospectively. All patients signed written informed consent before enrollment.

The registry is in accordance with the Declaration of Helsinki, following good-practice guidelines required by the Italian Ministry of Health, and approved by the hospital's ethics committee (approval number: 699).

Inclusion criteria

Inclusion criteria included age >18 years with a diagnosis of BrS at high arrhythmic risk and implanted with an S-ICD. The diagnosis of BrS was made according to the 2015 consensus

(3). Briefly, patients presented with a type 1 BrS electrocardiogram (ECG) pattern in at least one precordial lead (V1 and/or V2) placed in the fourth, third, and/or second intercostal space, either spontaneously or after a provocative test with a sodium channel blocker (ajmaline or flecainide). Patients were considered candidates to ICD implantation if they were survivors of an aborted sudden cardiac arrest, presented arrhythmic syncope, and/or if sustained ventricular arrhythmia was induced during electrophysiological study. At enrollment, the baseline clinical characteristics and electrocardiographic features of all patients were collected.

Screening test

All candidates for S-ICD implantation were screened using the tools provided by the manufacturer (Boston Scientific, Natick, MA), either manual or automated (according to availability), to determine if implantation of an S-ICD was feasible.

In both screening protocols, ECG electrodes were placed in the same position as the S-ICD sensing electrodes (ECG electrode LL was placed at the fifth intercostal space along the middle axillary line, to represent the intended location of the implanted pulse generator; ECG electrode LA 1 cm left lateral of the xiphoid midline, to represent the intended location of the proximal sensing node of the implanted electrode; and ECG electrode RA 14 cm superior to the ECG electrode LA, to represent the intended position of the distal sensing tip of the implanted electrode). The device has three available sensing vectors: primary (sensing from the proximal electrode ring on the subcutaneous electrode to the active surface of the device), secondary (sensing from the distal sensing electrode ring on the subcutaneous electrode to the active surface of the device), and alternate (sensing from the distal sensing electrode ring to the proximal sensing electrode ring on the subcutaneous electrode).

For manual screening, a standard ECG recorder was used to obtain ECGs from each of the three lead vectors at gains 5, 10, and 20 mV for 10 seconds at a paper speed of 25 mm/s, with patients in the supine and standing positions. The maximal R- or S-waves of all QRS complexes and T-waves must fit within the boundaries of a template provided by the manufacturer to be considered acceptable. The automatic screening was performed using the Model 3120 Programmer (Boston Scientific). After ECG lead connection, the system automatically assesses the acceptability of each of the three sensing vectors in both positions. For patients screened with the automated tool, T-wave and QRS voltages and defibrillator automated screening score (DASS) were analyzed for each vector. The DASS takes into account the T-wave and QRS voltages and is automatically calculated by a built-in software of the manufacturer device programmer. The DASS must be ≥100 to consider the vector acceptable. Patients were considered suitable for implant of the S-ICD if at least one sensing vector was acceptable in the supine and standing positions during screening test.

Device programming

After implantation, the sensing vector was chosen automatically by the programmer according to the best QRS/T-wave ratio, and two therapy zones were programmed: conditional shock cutoff between 200 and 230 beats/minute and shock therapy cutoff between 220 and 250 beats/minute. A high-pass filter (SMART Pass; Boston Scientific) was programmed when available.

Follow-up of patients and data collection

Patients were routinely followed every six months at our outpatient clinic. On each visit, patients were asked whether they experienced any adverse events or shocks, and device interrogations were performed. Additional follow-up visits took place in the event of shock delivery, symptoms, or individual device-related complications.

Shock therapy was considered appropriate when used to treat ventricular tachycardia (VT) or VF at a rate equal or superior to the programmed therapy zones.

An IS was defined as a shock delivered when the patient's heart was in sinus rhythm, when the patient experienced a supraventricular arrhythmia, or when the shock was secondary to causes unrelated to VT/VF (e.g., TWOS, oversensing of myocardial or muscular potentials, or electromagnetic interference).

All events were evaluated by two cardiologists with extensive experience in device follow-up and programming. The programmed sensing vector at the time of the first shock was used for signal analysis.

Statistical analysis

Values are expressed as percentage, mean±SD, or median when appropriate. *T*-test was used to compare continuous data, and Wilcoxon signed rank test and Mann-Whitney U test for non-normally distributed data. Receiver operator characteristic (ROC) curve analysis was performed to obtain the cutoff values to predict inappropriate shocks. The optimal cutoff value was defined as the value for which the sum of sensitivity and specificity was maximized. Kaplan-Meier analysis was used to estimate inappropriate shock-free survival probabilities. Variables selected from the univariate analysis (p value ≤ 0.10) were entered into multivariate Cox proportional hazards regression models to estimate predictors of inappropriate shock. A p value <0.05 was considered significant. Statistical analysis was performed using SPSS Statistics 23 software (SPSS Inc. Chicago, IL).

Results

In total, 39 high-risk patients with BrS implanted with an S-ICD were enrolled in the study from February 2013 to December 2019. Twenty-three patients (59%) were enrolled

prospectively. Twenty-eight patients (72%) were implanted at diagnosis, and 11 patients (28%) were implanted due to newly developed symptoms (arrhythmic syncope) during follow-up.

Baseline characteristics

Baseline characteristics and ECG features of the population are summarized in Table 1.

The mean age was 46±13 years at diagnosis and 48±13 years at S-ICD implantation. The majority of patients were male (n=27, 69%) and underwent implantation for primary prevention of SCD (n=37, 95%). Half of the patients had a family history of SCD (51%), 12 patients presented with spontaneous type 1 BrS ECG pattern at diagnosis (31%) and 13 (33%) presented with a spontaneous type 1 BrS ECG pattern at least once, either at diagnosis or during follow-up. No patients in the study had a history of supraventricular arrhythmias or atrial fibrillation.

Inappropriate shocks

During a mean follow-up of 26±21 months, none of the patients experienced appropriate shock (AS), and seven patients (18%) experienced IS. The mean time from implantation to the first IS was 9±8 months.

Most ISs were due to oversensing (n=4, 57%); other causes included electric noise caused by trapped air escaping from the device header (n=2, 29%) and paroxysmal supraventricular tachycardia (n=1, 14%).

The four patients who experienced IS secondary to oversensing had more shocks per patient (32, 4, 2, and 1, respectively), whereas patients with IS secondary to other mechanisms experienced one IS each (p=0.047).

A detailed description of the number, causes, and programming of IS is listed in Table 2.

Patients with IS were significantly younger at diagnosis (36±8 versus 48±13 years, p=0.018) and at the time of S-ICD implantation (38±9 versus 50±23 years, p=0.019), had a family history of SCD less frequently (14% versus 59%, p=0.04), and presented a spontaneous type 1 BrS ECG pattern at diagnosis or during follow-up more frequently (71% vs 25%, p=0.018). A detailed description of baseline characteristics and ECG features of patients with and without IS is shown in Table 3.

Automated screening data and device programming

Twenty-four patients (62%) underwent automated screening. During the test, the QRS voltage in patients with IS was significantly lower in the primary vector in the supine position (0.58±0.26 versus 1.10±0.35 mV, p=0.011), whereas it tended to be lower in patients with IS in the same vector in the standing position (0.65±0.23 versus 1.02±0.35 mV, p=0.065). The DASS was significantly lower in patients with IS in the primary vector in the supine (123±165 versus 554±390 mV, p=0.005) and standing (162±179 versus 486±388 mV, p=0.038) positions.

After implantation, a high-pass filter (SMART Pass) was available in 30 devices (74%). The SMART Pass filter tended to be less frequently activated in patients with IS (57% versus 86%, p=0.073).

There was no difference between the two groups in terms of sex, device (first-generation versus newer device), indication for implantation (primary or secondary prevention of SCD), type of screening (manual or automated), height, weight, or body mass index (BMI).

Patients did not present other device-related complications during the follow-up.

Predictors of IS

Univariate Cox regression analysis identified significant associations between IS and age at diagnosis and at S-ICD implantation. Spontaneous type 1 BrS ECG pattern and QRS voltage during screening in the primary vector in the supine position showed a trend toward an increased risk of IS.

A multivariate Cox regression model revealed age at diagnosis as the only independent predictor of IS (hazard ratio=0.873, 95% confidence interval: 0.767 to 0.992, p=0.037). A detailed description of the Cox regression analysis is provided in Table 4.

Figure 1 shows the cumulative IS risk based on by age at diagnosis. A cutoff value of 42 years predicted a higher likelihood for IS in our population, with a sensitivity and specificity of 87% and 68% respectively (area under the curve =0.81). IS rate was significantly different between the two groups of population divided by age at diagnosis (log rank p= 0.001). Cumulative IS-free survival curves for IS depending on age at diagnosis are shown in Figure 2.

Discussion

The main findings of the study are as follows: 1) IS is a frequent complication in patients with BrS and S-ICD, mainly due to oversensing; 2) patients experiencing IS were younger at diagnosis and at S-ICD implantation, had a spontaneous type 1 BrS ECG pattern more frequently, had a family history of SCD less frequently, and had a lower QRS voltage and DASS during automated screening in the primary vector; and 3) age at diagnosis independently predicted the occurrence of IS during follow-up.

Incidence of IS

To the best of our knowledge, the present study is the first to describe the incidence of IS in patients with BrS and S-ICD. During a mean 2.5 years of follow-up, no patients had AS and up to 18% had IS, with a mean of 9 months from implantation to the first IS. Our data are consistent with those of previous reports that showed a high incidence of IS in patients with BrS (4;5); however, this is the first report to focus on patients with an S-ICD.

In a study evaluating a series of BrS patients with transvenous ICDs, Sarkozy et al. (6) reported that 36% of patients experienced IS, whereas only 15% had AS during a median follow-up of 47.5 months. IS is one of the main causes of morbidity and worsening of the quality of life in these patients (4;5).

Patients' and S-ICD screening characteristics

Patients with BrS are usually young at diagnosis. Remarkably, our study showed that patients with IS were significantly younger both at diagnosis and at S-ICD implantation. Younger individuals are more prone to engage in intense physical activities; hence, they develop exercise-related IS due to electric noise (myopotentials) or TWOS (7-10), owing to the dynamic behavior of R- and T-waves during exercise. In a study by Kooiman et al., 16% patients implanted with an S-ICD experienced IS, with 72% of them secondary to TWOS at exercise during a median follow-up of 21 months. Modification of the sensing vector and ECG template during a maximum exercise test resulted in elimination of IS in 88% of these patients (10).

Patients with IS had a spontaneous type 1 BrS ECG pattern more frequently at diagnosis and/ or during follow-up. The ECG pattern in BrS is often dynamic, either spontaneously or secondary to drugs, fever, and increased vagal tone (11-16), and it is characterized by marked repolarization abnormalities, often leading not only to temporary S-ICD screening unsuitability but also to inadequate sensing and IS.

Interestingly, patients with IS also had a lower QRS voltage amplitude (supine position) and DASS (supine and standing positions) during automated screening in the primary vector.

Our findings suggest the potential benefit of an adequate screening process to select suitable candidates for S-ICD among BrS patients, especially in those diagnosed at a younger age. Besides the classical requirements, the new proposed criteria may include screening patients during an exercise test (7;17) and drug challenge (19), as well as using higher QRS voltage and DASS values and requiring more than one vector passed. The application of these new, stricter criteria plus other strategies, such us pharmacological treatment to reduce heart rate during exercise or advising the patient to avoid certain activities may result in a reduction of this frequent complication, minimizing the need for more aggressive solutions (e.g., repositioning of the electrode and/or the device, replacing the device with a transvenous ICD), or choosing a transvenous device in the first place. Nevertheless, there is no consensus among experts regarding the usefulness of an exercise test(18). Further studies are needed to confirm this hypothesis.

Air entrapment

Two patients presented IS secondary to air escaping from the device header. Residual air around the device and/or the electrode may alter sensing and therapy deliver by the S-ICD, and cause IS. An appropriate surgical technique, including flushing the xiphoid and superior incisions, and the device pocket with sterile saline solution, and massaging the skin along the tract and over the device to expel any residual subcutaneous air may reduce the occurrence of IS by this mechanism (20).

Device programming

The high-pass filter (SMART Pass) was activated in 30 devices (74%) and tended to be more frequently disabled or not available in patients with IS (57% versus 86%, p=0.073). This filter reduces the magnitude of low-frequency waves (T-waves), leaving high-frequency waves (QRS) unaffected and preventing IS due to TWOS. In our series, in accordance with previous studies, TWOS was the main cause of IS. Interestingly, the high-pass filter was active only in 25% of patients experiencing IS secondary to TWOS, whereas it was active in all patients with IS secondary to other mechanisms, supporting the usefulness of this tool for preventing this complication in patients with BrS.

Limitations

The number of patients enrolled was relatively small, and the follow-up was short (26±21 months). Importantly, screening data of patients implanted in other centers were not available. The lack of a significant difference in our results may be owing to the small sample of patients with SMART Pass off and IS due to oversensing.

There was no difference in the number of ISs between patients implanted for primary or secondary prevention of SCD, which may be due to the few patients implanted for secondary prevention of SCD.

Conclusions

IS is a frequent complication in patients with BrS implanted with an S-ICD. Younger age at diagnosis was independently associated with IS. A more thorough screening process including ECG features and device settings may help prevent IS in this patient population.

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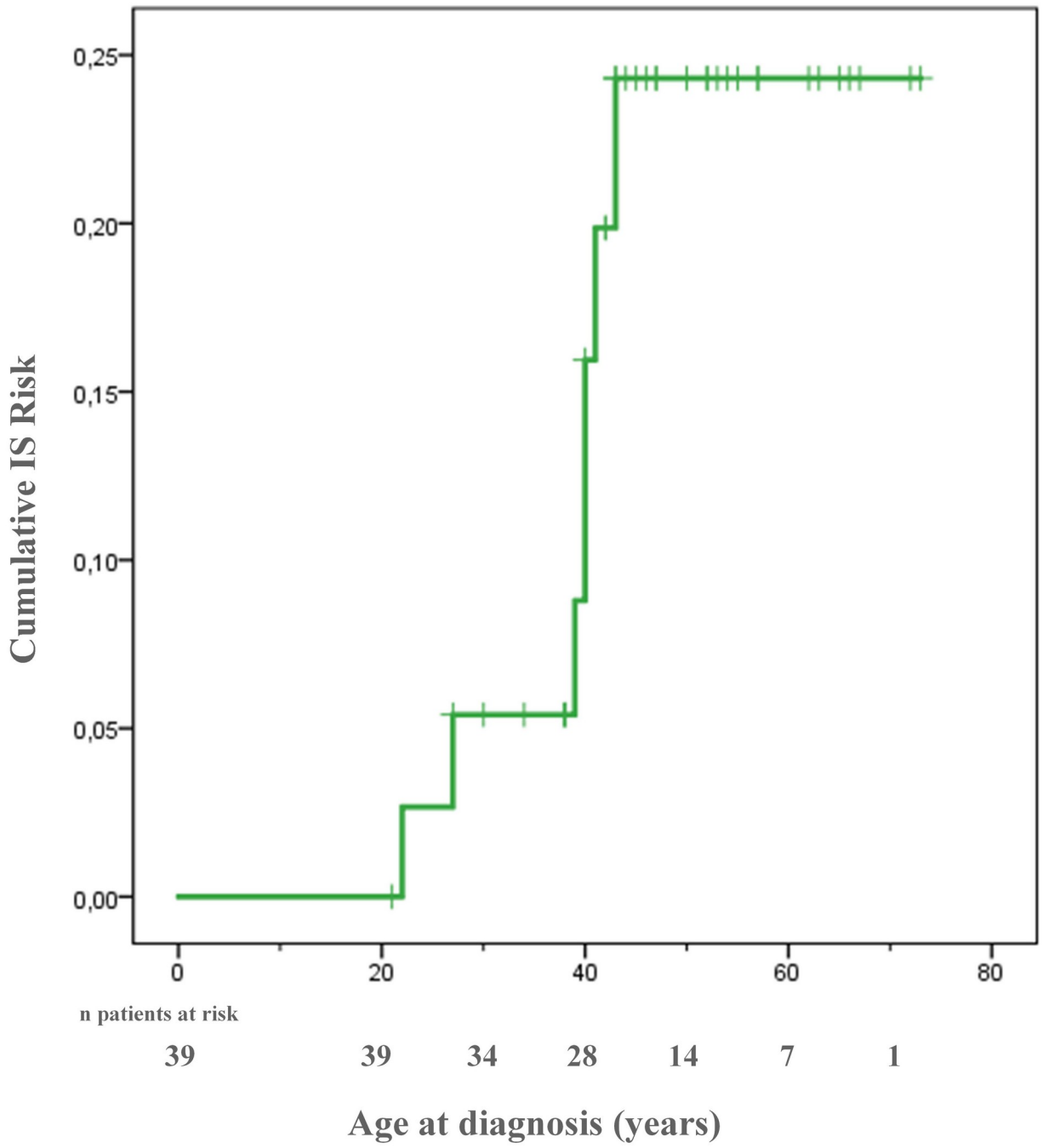
279 Figures



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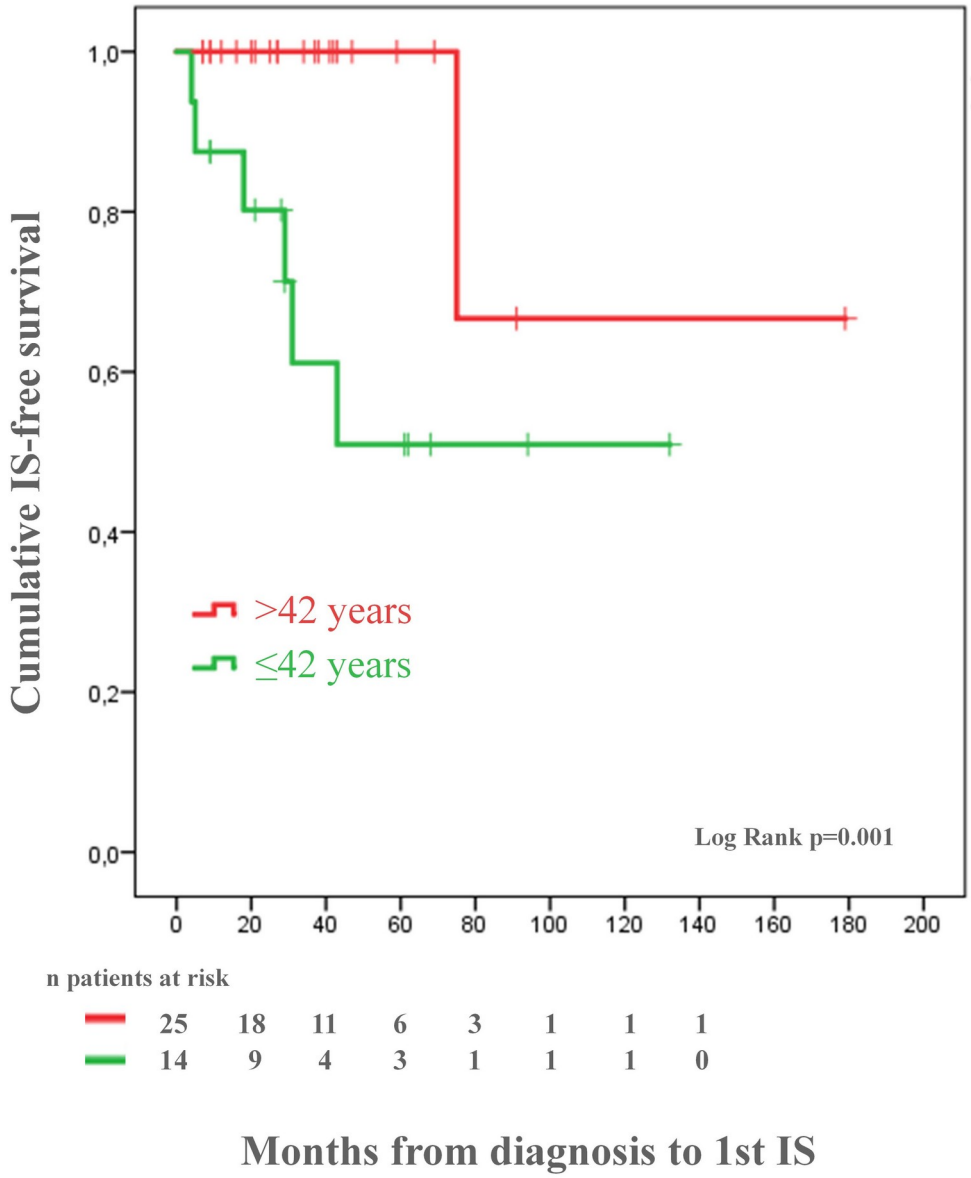
281 Figure 1: Cumulative IS risk showing the incidence of IS based on age at diagnosis. Most of
282 the events occur in patients younger than 40 years at diagnosis. Abbreviations: IS =
283 inappropriate shock.



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285 Figure 2: Kaplan-Meier curves illustrating age at diagnosis significantly correlated with IS.

286 Patients younger than 42 years at diagnosis showed more likelihood of IS. Abbreviations: IS

287 = inappropriate shock.

288 Tables

	n=39
Male, n (%)	27 (69%)
Age at diagnosis (years)	46±13
Age at S-ICD implant (years)	48±13
LVEF (%)	64±5
Weight (Kg)	73±12
Height (m)	1.7±0.07
BMI	25.7±3.5
Proband, n (%)	31 (79%)
Family history of SCD, n (%)	20 (51%)
Supraventricular tachycardia and/or atrial fibrillation before diagnosis	0
Primary prevention of SCD (indication of implant), n (%)	37 (95%)
Indication of implant, n (%) -Aborted SCD -Arrhythmic syncope -Positive EPS	 2 (5%) 29 (74%) 8 (21%)
ECG at diagnosis	
Rhythm	SR
Heart rate (b.p.m.)	71±11
PR interval (ms)	160±24
QRS (ms)	97.6±17
QTc interval (ms)	397±24.8
Mean J point elevation (V2) at diagnosis (mm)	3±1
Spontaneous type 1 pattern at diagnosis, n (%)	12 (31%)
Spontaneous type 1 pattern anytime (at diagnosis or during follow-up), n (%)	13 (33%)
Automated screening test, n (%)	24 (62%)

289Table 1. Baseline characteristics of the study population.

290Abbreviations: b.p.m. = beats per minute; BMI = body mass index; ECG = electrocardiogram; EPS

291= electrophysiological study; LVEF = left ventricular ejection fraction; SR = sinus rhythm; S-ICD =

292subcutaneous implantable cardioverter-defibrillator; SCD = sudden cardiac death.

293

Patient ID #	Cause of IS	n of IS	Management	SMART PASS programming	Vector programming at implant and IS
#1	TWOS	32	TV-ICD recommended, patients refused	Not available	Primary
#2	TWOS	4	Reprograming vector and gain (during exercise test) + bisoprolol	On	Primary
#3	TWOS (exercise)	2	Reprograming vector and gain	Changes to off	Primary
#4	TWOS (exercise)	1	Reprograming vector and gain	Not available	Primary
#5	Noise secondary to air escape from the device header	1	No program modifications	On	Secondary
#6	Noise secondary to air escape from the device header	1	No program modifications	On	Secondary
#7	Paroxysmal supraventricular tachycardia	1	RFA suggested, patient refused	Changes to off	Secondary

Table 2. Number and causes of IS, SMART Pass filter and sensing vector programming in patients with IS.

Abbreviations: IS = inappropriate shock; RFA = radiofrequency ablation; TV-ICD = transvenous implantable cardioverter-defibrillator; TWOS = T-wave oversensing.

	No IS (n, %)	IS (n, %)	p
n, %	32 (82)	7 (18)	
Male, n (%)	21 (66)	6 (86)	NS
Age at diagnosis (years)	48±13	36±8	0.018
Age at S-ICD implant (years)	50±23	38±9	0.019
LVEF (%)	64±5	64±6	NS
Weight (Kg)	73±13	73±9	NS
Height (m)	1.7±0.07	1.66±0.1	NS
BMI	25.6±3.7	26.6±2.5	NS
Proband, n (%)	27 (84)	4 (57)	NS
Family history of SCD, n (%)	19 (59)	1 (14)	0.04
Supraventricular tachycardia and/or atrial fibrillation before diagnosis	0	0	NS
Primary prevention of SCD (Indication of implant), n (%)	30 (94%)	7 (100)	NS
ECG at diagnosis			
Rhythm	SR	SR	
Heart rate (b.p.m.)	70±12	75±9	NS
PR interval (ms)	157±21	168±34	NS
QRS (ms)	93.8±12	109±24	NS
QTc interval (ms)	395±24	401±27	NS
Mean J point elevation (V2) at diagnosis (mm)	2.8±0.9	3.1±1.2	NS
Spontaneous type 1 pattern at diagnosis, n (%)	8 (25)	4 (57)	NS
Spontaneous type 1 pattern anytime (at diagnosis or during follow-up) n (%)	8 (25)	5 (71)	0.018
Automated screening test	20 (63)	4 (57)	NS

297Table 3. Comparison of baseline characteristics and ECG features of patients with and

298without IS. Abbreviations: b.p.m. = beats per minute; ECG = electrocardiogram;

299IS = inappropriate shock; BMI = body mass index; LVEF = left ventricular ejection

300fraction; SR = sinus rhythm; S-ICD = subcutaneous implantable cardioverter-

301defibrillator; SCD = sudden cardiac death.

	Univariate HR (95% CI)	p	Multivariate HR I (95% CI)	p	Multivariate HR II (95% CI)	p
Age at diagnosis	0.93 (0.87-0.99)	0.024	0.87 (0.76-0.99)	0.037		
Age at S-ICD implant	0.93 (0.88-0.99)	0.028			0.89 (0.79-1.00)	0.053
Spontaneous type 1 Brugada ECG pattern at diagnosis and/or during follow-up	0.20 (0.03-1.03)	0.056	0.39 (0.01-14.42)	0.611	0.40 (0.005-31.86)	0.683
QRS voltage, primary vector supine position	0.03 (0.00-1.34)	0.072	0.39 (0-158)	0.763	0.27 (0-171)	0.693

Table 4. Uni- and multivariate Cox regression models for prediction of IS by S-ICD

Abbreviation: BrS = Brugada syndrome; CI = confidence interval; ECG = electrocardiogram; HR = hazard ratio; IS = inappropriate shock; S-ICD = subcutaneous implantable cardioverter-defibrillator.

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