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A Clinical Score Model to Predict Lethal Events in Young (≤ 19 years) Patients With the Brugada Syndrome

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Abstract

Risk stratification in Brugada syndrome among young patients remains challenging. We investigated the clinical characteristics, prognosis, and risk of young patients with the Brugada syndrome. We studied 95 patients with the Brugada syndrome and aged ≤ 19 years. Median age at diagnosis was 12.9 years. Clinical presentation was sudden cardiac death in 7%, and syncope in 21%. The remaining 72% were asymptomatic at diagnosis. Electrical abnormalities were present in 36%, including spontaneous type-I electrocardiogram (12%), sinus node dysfunction (9%), atrioventricular block (17%), intraventricular conduction delay (16%), and atrial arrhythmias (8%). An electrophysiological study was performed in 75%; ventricular arrhythmias were induced in 3%. An implantable cardioverter-defibrillator was placed in 25%. During a mean follow-up of 59 months, 9 patients presented with arrhythmic events (event rate: 1.9% per year). Variables significantly associated with events were: presentation with sudden cardiac death or syncope, spontaneous type-I electrocardiogram, sinus node dysfunction and/or atrial tachycardia, conduction abnormality, and induction of ventricular arrhythmias during programmed ventricular stimulation. A model including the previous four main clinical variables (1- sudden cardiac death or syncope, 2- spontaneous type-I electrocardiogram, 3- sinus node dysfunction and/or atrial tachycardia, and 4- conduction abnormality) had a high predictive power (C: 0.93) for the risk of lethal events. A score ≥ 4 conferred a 5-year event probability of 30% that increased to 53% if the score was ≥ 6 . In conclusion, our study validated a model to predict risk for young patients with Brugada syndrome, which takes into account 4 clinical measures.

Keywords: Brugada syndrome, risk stratification, sudden cardiac death, syncope, ventricular fibrillation.

Introduction

Brugada syndrome is an inherited disease characterized by coved-type ST-segment elevation in the right precordial leads and increased risk of sudden cardiac death in the absence of structural heart disease¹. The phenotypic expression of the disease extends from the completely asymptomatic subject to the individual who experiences sudden cardiac death. The disease typically manifests in the fourth decade of life, but severe cases have clinical expression during childhood^{2,3}. The purpose of this study was to analyze our experience with young patients with Brugada syndrome, focusing on the search for potentially lethal arrhythmic event predictors. Therefore, we aimed to construct a simple risk score system that could help manage young patients with Brugada syndrome.

Methods

Since 1992, all consecutive patients diagnosed with the Brugada syndrome have been included in a registry and followed-up in a prospective manner. Patients ≤ 19 years of age with spontaneous or drug-induced Brugada type I electrocardiogram and follow-up longer than 1 year were identified in the family registry from 1992 through 2016, and included in the study cohort. An electrocardiogram was considered diagnostic of Brugada syndrome if a coved type ST elevation ≥ 2 mm was documented in ≥ 1 lead from V1–V2, in a standard or a superior position (up to the second intercostal space)⁴, as analyzed by 2 independent electrophysiologists.

A cohort of young patients with Brugada syndrome was created. Each patient was initially evaluated with a physical examination, a personal and family medical history, a baseline electrocardiogram, and a provocative test with ajmaline in cases of normal baseline electrocardiogram; most patients also underwent exercise test, Holter monitoring, and an electrophysiological study. The absence of underlying structural cardiac abnormalities was confirmed in all patients by echocardiography. Most patients were also tested with cardiac magnetic resonance imaging or computed tomography.

Clinical or electrical markers for symptomatic Brugada syndrome were identified, including syncope, sudden cardiac death, ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation), atrial arrhythmias (sustained ectopic atrial tachycardia, atrial flutter, or atrial fibrillation), conduction abnormalities, or sinus node dysfunction. Syncope was defined as a non-traumatic and reversible loss of consciousness, and was considered of arrhythmia origin in the absence of prodrome or triggering circumstances. Sinus node dysfunction was assessed both clinically and invasively during the electrophysiological study. Clinically, sinus node dysfunction was evaluated by 12-lead electrocardiograms, Holter monitoring, and exercise tests, and defined as inappropriate sinus bradycardia according to age and activity level ⁵, 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 ⁶. Conduction abnormalities included PR and QRS prolongation, and were evaluated in 12 lead electrocardiograms. Prolongation of PR, QRS, and QT intervals were defined as those values above the 98 percentile for age ⁵.

A provocative test was performed in young patients suspected of having Brugada syndrome, in the case of a normal baseline electrocardiogram. The test was performed with an ajmaline intravenous infusion (maximum dose of 1 mg/kg) administered over a 5-min period. Ajmaline infusion was terminated before reaching the target dose in the case of diagnostic type I Brugada electrocardiogram, QRS prolongations >30% above baseline, presence of high-degree atrio-ventricular block, or ventricular arrhythmias.

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 second, third and fourth intercostal space according to the prescribed guidelines ⁴. All electrocardiograms were analyzed before and after ajmaline administration, with measurement of PR intervals, QRS durations, and QTc intervals (determined using Bazett's

formula), by averaging hand-measurements on three consecutive beats⁴. Maximal ST-segment elevations were measured at the J point in the right precordial leads (V₁–V₃), and analyses of ST-segment elevation were performed in leads V₁ and V₂.

Electrophysiologic studies were performed to stratify risk. Measurements included baseline intervals, sinus node recovery time, corrected sinus node recovery time, and sino-atrial conduction time⁷. The atrio-ventricular conduction system was evaluated by measuring the Wenckebach cycle length and the atrio-ventricular nodal effective refractory period in each case. Atrial and ventricular stimulation protocol were performed.

Starting in 2010, genetic testing to specifically analyze the *SCN5A* gene sequence was performed. In mutation-positive index cases, family members were also screened for specific *SCN5A* genetic mutations.

Recommendations made in the Brugada consensus reports⁴ were used to determine candidacy for implantable cardioverter-defibrillator therapy. Decisions to place epicardial versus endocardial leads, and the appropriate location for the generators were made based on an individual patient's body size, age, and activity level.

Clinical follow-up was performed yearly in the case of asymptomatic young patients and every 6 months in case of symptomatic patients or after implantable cardioverter-defibrillator. During the follow-up period, potentially lethal event outcomes occurred when patients experienced the following: (i) sudden cardiac death; (ii) recordings of sustained ventricular tachycardia or ventricular fibrillation during electrocardiograms, Holter monitoring, implantable loop recorder, implantable cardioverter-defibrillator memory, or (iii) appropriate implantable cardioverter-defibrillator shocks with tracings recorded in the device's memory.

Data were analyzed using SPSS version 23 (IBM SPSS Statistics, IBM Corporation,

Armonk, New York). The chi-squared or Fisher's exact tests were used to compare categorical variables. Mean comparisons for continuous measures were performed with Student's *t*-tests, Mann–Whitney, and Kruskal–Wallis tests. Mean data were presented with standard deviation. Event-free survival was estimated by the Kaplan-Meier method and compared by the log-rank test. Hazard ratios were calculated using Cox proportional hazards models. Incidence rates were expressed as the number of events per 100 person-year. A predictive model containing all variables related with events in the univariable analysis was constructed. Predictive power was evaluated by means of C-statistic. Among the reduced models, the simplest one with a predictive power loss of less than 10% was selected as the final model. $P < 0.05$ was considered statistically significant.

Results

Ninety-five young patients with Brugada syndrome fulfilled the inclusion criteria with a median age at diagnosis of 12.9 years [9.0–17.3]. Table 1 shows the baseline characteristics, dividing patients according to age group into children (0–13 years) and adolescents (13–19 years). There were no significant differences between these two age groups.

Patients displaying only fever-induced Brugada type 1 ECG pattern were included in the spontaneous type I group. Among the 11 patients that presented spontaneous type I electrocardiogram, 5 patients displayed the pattern only during fever, 2 patients presented severe syncope during fever, and 1 presented SCD during a viral infection (probably febrile).

Electrophysiological studies were performed in 72 patients (75% of total population, 85% of patients > 13 years old). Patients who did not have a programmed ventricular stimulation were very young asymptomatic patients (< 7 years old) ($n = 10$), had high risk owing to aborted sudden cardiac death ($n = 5$), refused it ($n = 5$), or developed ventricular arrhythmia during the

provocative test ($n = 3$). Sustained ventricular arrhythmias were induced in 3 patients (4%), all of them > 13 years old.

A total of 36 genetic tests (38%) were obtained, and 24 (67%) were positive for the *SCN5A* gene mutation. This high diagnostic yield may be justified by the fact that genetic screening was frequently preceded by the identification of a familial mutation.

A cardioverter-defibrillator was implanted in 24 young patients (25%); the median age at implantation was 13.4 years [8.4–17.2]. The indications for implantable cardioverter-defibrillator included: aborted sudden cardiac death ($n = 7$ [29%]), inducible ventricular arrhythmias observed during either provocative tests or electrophysiology studies ($n = 3$ [13%]), and high risk ($n = 14$ [58%]) due to either multiple occurrences of severe syncope recalling arrhythmic events in the setting of positive genetic tests and/or family history of malignant Brugada syndrome. Eleven implantable cardioverter-defibrillators were transvenous system (46%, median age at implantation: 15.4 years [13.3–18.8]). Thirteen patients received an epicardial lead implantation with an abdominal system (54%, median age at implantation: 9.6 years, [6.4–16.4]). High-risk patients receiving an implantable cardioverter-defibrillator were more frequently male ($n = 16$ [67%]), 8 presented with spontaneous type I electrocardiogram (33%), and 6 (25%) presented with concomitant sinus node dysfunction. Interestingly, this subgroup also presented with more conduction abnormalities (67% vs. 39%, $p = 0.06$), including a longer PR interval (181.6 ± 53.3 ms vs. 161.3 ± 30.5 ms, $p = 0.006$) and broader QRS (117.9 ± 30.7 ms vs. 102.3 ± 21.0 ms, $p < 0.01$).

After implantable cardioverter-defibrillator implantation, 3 patients (12%) experienced a device-related complication requiring re-interventions: a dislocation of the abdominal generator that led to revision of the device 1 week after implantation, and 2 lead-related complications (1 lead fracture and 1 lead dislocation).

After a median follow-up of 33.8 months [9.0–97.7], potentially lethal events occurred in 9 patients (9%). This accounted for an annual event rate of 1.9 for the global young population. The clinical characteristics of the young patients that presented with potentially lethal events during follow-up are presented in Table 2. Figure 1 depicts the individual time line in years for each of these patients; marking the timing of diagnosis, implantable cardioverter-defibrillator implantation, events, and follow-up.

Considering the high-risk population who received an implantable cardioverter-defibrillator implantation, 8 patients (33%) presented with potentially lethal events (2 electrical storms and 6 polymorphic ventricular arrhythmias), corresponding to an annual event rate of 5.3.

Of note, one young patient in our cohort died without an implantable cardioverter-defibrillator; this corresponds to the 2-year-old girl in whom the disease was initially described. Two patients died of an electrical storm despite several implantable cardioverter-defibrillator shocks.

Univariable and multivariate analysis was performed to investigate different clinical variables associated with the occurrence of potentially lethal events during follow-up. Young patients with clinical symptoms had a worse prognosis than asymptomatic individuals. The hazard differed substantially between patients that presented with syncope compared to those that presented with sudden cardiac death. The presence of symptoms conferred a hazard ratio of 25.39 (95% confidence interval, 3.15–204.36; $p < 0.01$). Sudden cardiac death conferred a hazard ratio of 26.77 (95% confidence interval, 6.66–107.60; $p < 0.01$), while syncope presented a hazard ratio of 4.9 (95% confidence interval, 1.3–18.39; $p = 0.01$). The overall incidence rate of events was 6.90% per year for symptomatic patients (16.17% per year for patients presenting with sudden cardiac death and 2.57% per year for syncope), and 0.28% per year for those who were asymptomatic.

Patients with spontaneous type I electrocardiogram were at a high risk (hazard ratio, 8.83; 95% confidence interval 2.35–33.10; $p < 0.01$). The event incidence rate was 5.54% per year for patients with spontaneous type I electrocardiogram and 0.98% per year for those with drug-induced findings.

Those patients presenting with sinus node dysfunction, atrial tachycardia, or a combination of both had a significantly worse prognosis than those without these findings (hazard ratio, 6.79; 95% confidence interval, 1.80–25.58; $p = 0.01$). The incidence rate was 4.53% per year in patients with sinus node dysfunction and/or atrial tachycardia (7.22% per year for atrial tachycardia and 2.98% for sinus node dysfunction), and 1.32% per year in those without either.

A conduction abnormality was diagnosed in the case of atrio-ventricular block or intra-ventricular conduction delay. These two abnormalities conferred a significantly higher risk for events when considered together (hazard ratio, 4.86; 95% confidence interval, 1.01–23.45; $p < 0.05$). The incidence rate was 4.96% per year in patients with conduction abnormalities (3.44% for atrio-ventricular block and 4.46 for intra-ventricular conduction delay), and 1.22 % per year in those without either.

Patients that presented with ventricular arrhythmias induced during programmed ventricular stimulation were at a higher risk (hazard ratio 5.47; 95% confidence interval 1.30–18.39.10; $p = 0.03$). The event incidence rate was 13.33% per year for patients with positive programmed ventricular stimulation and 1.52% per year for those with negative programmed ventricular stimulation.

Additional statistical analysis was performed to evaluate the association of life threatening events with positive *SCN5A* genotype, but was not significant ($p = 0.25$). However, it is important to note that 67% of the patients that presented with events did not undergo genetic testing (6 out of 9 patients), which may interfere with the accuracy of this result.

Risk stratification in young patients with Brugada syndrome is complex, but necessary to guide the indication of an implantable cardioverter-defibrillator. We constructed a clinical risk model with 4 variables that showed a statistical relationship with occurrence of potentially lethal events. All the items included have been validated in our young Brugada syndrome population, resulting in a model with high predictive performance with a C-statistic of 0.93 (95% confidence interval, 0.87–0.99: $p = 0.03$). Four points were attributed to the presence of symptoms, 3 points to spontaneous type I electrocardiogram, 2 points to sinus node dysfunction and/or atrial tachycardia, and 1 point to conduction abnormalities.

Young individuals with a punctuation of 0-3 are in the lowest risk spectrum. They represent mainly asymptomatic patients evaluated in the setting of a familiar screening with an isolated positive ajmaline test. Patients with a score of 1–3 are asymptomatic, but present with isolated conduction abnormalities. Symptomatic patients in the high-risk category with a score of 4–5 could present with syncope with or without any electrical abnormalities. A punctuation of ≥ 6 corresponds to a very high risk. The clinical presentation can be aborted sudden cardiac death or syncope with multiple electrical abnormalities. Patients in this group have indication of an implantable cardioverter-defibrillator. Life-threatening events were present in almost half of the patients in this group during follow-up. Table 3 shows the 4 categories in the proposed risk model, the scores and number of patients from our database belonging to each category, clinical presentation, percentage of implantable cardioverter-defibrillators, and percentage of events per category. Figure 2 shows the Kaplan–Meier event probability according to the score per age, in years.

Discussion

The Brugada syndrome can be a very aggressive disease in the young, resulting in sudden cardiac death. Management of these patients remains challenging and controversial.

Even if the disease was initially described in a couple of siblings¹, data on risk in young patients remains scarce. Priori et al. reported a group of 5 children from a single family that presented with sudden cardiac death and a cardiac sodium-channel mutation⁸. Subsequently, Probst et al. published data on the risk related to presence of a spontaneous type I electrocardiogram and fever in children⁹. More recently, the multi-institutional research study by Andorin et al. reported on the risk related to two clinical parameters: syncope and spontaneous type I electrocardiogram¹⁰. This group proposed a management algorithm for patients with spontaneous type I electrocardiogram. However, their model does not envision those patients without a baseline type I electrocardiogram, but with other electrical abnormalities that place them at a high risk. Our findings show that only around 10% of pediatric patients with Brugada syndrome present with a spontaneous type I electrocardiogram. In our population, from the 9 patients that presented with lethal events during follow-up (Table 2), 75% had abnormal baseline electrocardiogram, but only half of them had a spontaneous type I electrocardiogram. A previous publication from our group³ reported on risk related to electrical markers in a group of young patients (0–25 years old), but did not attempt a scoring system for clinical management.

In this study, we constructed a non-invasive logistic model combining history of syncope or aborted sudden cardiac death with several baseline spontaneous conduction abnormalities. The major contribution of this algorithm is that it uses simple, universal, and non-invasive parameters to discriminate high-risk for lethal events in young patients with Brugada syndrome. For this reason, our analysis did not include many electrical markers that could be rare, controversial, or more difficult to identify, such as late potentials Tpeak-Tend dispersion, r-J interval, QRS fragmentation, or QT dispersion.

When considering invasive risk stratification, the most recent multicenter data confirms that induction of ventricular arrhythmias during programmed ventricular stimulation is

associated with future ventricular arrhythmia risk in adult patients with Brugada syndrome¹¹. Even if there has been substantial controversy surrounding the utility of programmed stimulation during the last years, our group has supported its use for risk stratification since the original description of the disease. Our results in this study also confirm that programmed ventricular stimulation has a predictive value for future lethal events in the early years of life. Despite these facts, we decided not to include programmed ventricular stimulation in our model, as this practice is not standard of care in most of the pediatric electrophysiology groups at present. We chose a simple score that includes a subset of non-invasive markers, usually available with a 12-lead electrocardiogram and Holter monitoring.

Finally, we acknowledge the importance of positive genetic tests in risk stratification, but we consider that data on specific-mutation risk is still scarce and does not allow us to reach reliable results. We believe that future studies should include results of both programmed ventricular stimulation and genetic tests to address risk stratification of young patients with Brugada syndrome.

A limitation of this study is the small sample size, relatively small for the predictive model. Thus, the adequacy of this scoring method must be validated in a larger prospective study.

In conclusion, this novel logistic model uses 4 simple, non-invasive, clinical parameters to evaluate young patients with Brugada syndrome, validating a high predictive score for lethal events useful for risk stratification in routine clinical practice.

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Figures titles and legends

Figure 1. Individual time line in age in years for patients that presented events during follow-up; marking the timing of diagnosis, implantable cardioverter-defibrillator, events, and age at last follow-up.

Figure 2. Freedom from events according age (in years) in each score category as per Kaplan Meier method.

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Table 1.

Table 1. Demographic data of the young population cohort (n=95) . Patients divided into pediatric and adolescent age groups

Group	Ages < 13 years	13–19 years	Entire Cohort	p-value
Patients	n = 48	n = 47	n = 95	
Male	27 (56%)	26 (55%)	53 (55%)	>0.99
Age at diagnosis (years)	9.0 ± 4.7	17.3 ± 3.1	12.9 ± 8.3	
Family history SCD	24 (50%)	19 (40%)	43 (45%)	0.41
Age familiar SCD (years)	34.0 ± 26.7	22.5 ± 20.7	30.0 ± 21.0	0.47
SCD < 20 years old	6 (12%)	5 (11%)	11 (11%)	>0.99
SCD < 12 years old	2 (4%)	1 (2%)	3 (3%)	>0.99
Clinical presentation				
Asymptomatic	33 (69%)	35 (75%)	68 (72%)	0.65
Symptomatic	15 (31%)	12 (25%)	27 (28%)	0.65
SCD	4 (8%)	3 (6%)	7 (7%)	>0.99
Syncope	11 (23%)	9 (19%)	20 (21%)	0.80
Electrical Characteristics				
Spontaneous ECG type I	6 (12%)	5 (10%)	11 (12%)	>0.99
Sinus Node dysfunction	6 (12%)	3 (6%)	9 (9%)	0.48
Maximal PR (ms)	156.7 ± 38.5	169.2 ± 38.2	162.9 ± 38.6	0.13
First degree AV block	7 (15%)	9 (19%)	16 (17%)	0.59
Maximal QRS (ms)	104.6 ± 24.9	107.9 ± 24.2	106.2 ± 24.6	0.53
QRS fragmentation	5 (10%)	2 (4%)	7 (7%)	0.43
R ≥ 3 mV aVR	10 (21%)	6 (5%)	16 (17%)	0.41
QTc DII (ms)	410.1 ± 34.4	398.8 ± 33.5	402.8 ± 30.0	0.12
Atrial arrhythmias	4 (8%)	4 (8%)	8 (8%)	>0.99
Conduction abnormalities	18 (37%)	17 (36%)	35 (36%)	>0.99
EPS n	32 (67%)	40 (85%)	72 (75%)	0.05
EPS_HV	41.3 ± 9.1	44.7 ± 10.4	43.1 ± 9.8	0.20
Induction V arrhythmias	0 (0%)	3 (6%)	3 (3%)	0.11
Genetic test				
Performed	20 (42%)	16 (34%)	36 (38%)	0.52
SCN5A mutation	13 (27%)	11 (23%)	24 (25%)	0.81
ICD implantation	13 (27%)	11 (23%)	24 (25%)	0.81
Events at follow-up	4 (8%)	5 (10%)	9 (9%)	0.74

Values expressed as mean ± SD or n (%).

AV indicates atrio-ventricular; ECG, electrocardiogram; EPS, electrophysiology study; ICD,

implantable cardioverter-defibrillator; ms, milliseconds; n, number; SCD, sudden cardiac death; V,

ventricular.

Table 2.

Table 2. Characteristics of patients that presented with events during follow-up

Pt	Pro	Sex	Age	Symp	SND	AT	Co Ab	aECG	Ind	Gen	ICD	Age ICD	Event FU	Ev age	FU	Age FU
1	yes	F	2.3	SCD	yes	yes	yes	yes	nd	nd	no	no ICD	SCD	2.6	0.3	2.6
2	yes	M	3.2	SCD	no	yes	yes	yes	nd	nd	yes	17.6	VF storm/ ICD shock	18.2	15	18.2
3	yes	M	15.3	SCD	no	no	no	no	yes	nd	yes	15.3	VF/ICD shock	15.9	8.1	23.4
4	yes	F	16.5	SCD	no	yes	no	no	no	neg	yes	16.5	MVT/ICD pace	22.1	5.6	22.1
5	yes	M	8.2	syncope	no	no	yes	yes	no	nd	yes	8.2	VT/ICD shock	8.7	4.4	12.6
6	yes	M	15.3	syncope	no	no	yes	yes	no	neg	yes	15.4	VF/ ICD shock	15.5	2.1	17.4
7	yes	M	13	SCD	no	no	yes	yes	nd	nd	yes	13.3	VT/ICD shock	14.1	1.5	14.5
8	no	M	13.5	brady	yes	yes	yes	yes	yes	pos	yes	13.5	VF storm/ ICD shock	20.1	6.7	20.1
9	yes	M	0.9	SCD	no	no	no	yes	nd	nd	yes	0.9	VF/ICD shock	1	2.5	3.4

aECG indicates abnormal electrocardiogram; age, age at diagnosis (years); age ICD, age at implantable cardioverter-defibrillator implantation; age FU, age at last follow-up (years); AT, atrial tachycardia; brady, bradycardia; CoAb, conduction abnormality; ev age, age at event (years); event FU, event at follow-up; F, female; FU, length of follow-up (years); gen, genetic test; ICD, implantable cardioverter-defibrillator; ind, inducibility in electrophysiology study; M, male; MVT, monomorphic ventricular tachycardia; nd, not done; neg, negative; pro, proband; pos, positive; pt, patient; symp, symptom; SCD, sudden cardiac death; SND, sinus node dysfunction; VF, ventricular fibrillation; VT, ventricular tachycardia.

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Table 3.

Table 3. Patient characteristics according to risk score

Risk Category	Score	N	Clinical presentation	ICD (%)	Events (%)
Low Risk	0	53	Asymptomatic with no electrical abnormality	0	0
Intermediate Risk	1 - 3	12	Asymptomatic with electrical abnormality	0	0
High Risk	4 - 5	15	Syncope with or without single electrical abnormality	11 (73%)	2 (13%)
Very High Risk	≥ 6	15	aSCD or syncope with multiple electrical abnormalities	14 (93%)	7 (47%)

aSCD indicates aborted sudden cardiac death; ICD, implantable cardioverter defibrillator; N, number.

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Table 4.

Table 4. Freedom from events according to risk score based on age (years)

Score	Years 5	15	30	p value
0 - 3	100%	100%	100%	<0.01
4 - 5	100%	93%	86%	<0.01
≥ 6	87%	80%	53%	<0.01

Selected risk model to predict events. Event free survival at 5, 15, and 30 years of age, in each category.

p-value refers to the log-rank comparison with the reference category.

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