Characterization and Management of Arrhythmic Events in Young Patients With Brugada Syndrome

Profile of Young Patients with Brugada Syndrome and Arrhythmic Events; Characterization, Management and Risk factors for Arrhythmia Recurrence.

Yoav Michowitz, MD et al.

Department of Cardiology, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv, Israel

Word count : 3888.
Funding: None.
Disclosures: None.

Address for correspondence:
Bernard Belhassen, MD
Department of Cardiology
Tel-Aviv Sourasky Medical Center
Weizman St 6, Tel-Aviv, 64239, Israel
E-mail: bblhass@gmail.com
Phone: 972.52.4.266.856
Fax: 972.153.52.4.266.856

Abstract

Background: Information on young patients with Brugada syndrome (BrS) and arrhythmic events (AEs) is limited. We aim to describe their characteristics and management as well as risk factors for AE recurrence.

Methods: SABRUS is a multicenter Survey on 678 BrS patients with first AE. Fifty seven patients (aged ≤20 years) including 47 SABRUS and 10 new recruited patients were divided into pediatric (≤12 years old, n=26) and adolescents (13-20 years old, n=31) . The adult SABRUS group comprised 631 patients aged ≥21 years.

Results: The young cohort median age at time of first AE was 14 years, with the majority constituting by males (73.7%), Caucasians (70.2%), probands (78.9%) and presenting as aborted cardiac arrest (ACA) (84.2%). A significant proportion of patients (28.1%) exhibited fever-related AE. Family history of sudden cardiac death (SCD), prior history of syncope, spontaneous type 1 Brugada-ECG, inducible ventricular fibrillation at electrophysiologic study and *SCN5A* mutations were present in 26.3%, 49.1%, 64.9%, 28.1% and 58.1% of patients, respectively. The young patients differed from the older in a greater proportion of females, Caucasians, fever-related AEs, initial presentation as ACA, *SCN5A* mutation rates and lower arrhythmia inducibility. The pediatric group differed from the adolescents thru a greater proportion of females, Caucasians, fever-related AEs, and spontaneous type 1-ECG. During follow-up, 68% of pediatric and 64% of adolescent patients had recurrent AE with median time to recurrence of 9.9 and 27 months, respectively. About one third of recurrent AE occurred on quinidine therapy. Risk factors for recurrent AE included sinus node dysfunction, atrial arrhythmias, intraventricular conduction delay or large S wave on ECG lead I in the pediatric group and the presence of *SCN5A* mutation among adolescents. Pediatric patients with any of these risks

factors or adolescents who were *SCN5A* mutation carriers had substantially higher AE recurrence within a median time of 2.3 and 4.5 months, respectively.

Conclusions: Young BrS patients with AE represent a small, albeit very arrhythmogenic group. Current management after first arrhythmia episode is associated with high recurrence rate. Knowledge regarding risk factors for repeat events could help in clinical management of these patients.

Key words: Brugada syndrome, pediatric, adolescence, quinidine, ablation, *SCN5A* mutation.

Introduction

Brugada syndrome (BrS) is an inherited arrhythmic disease that may cause potentially fatal ventricular tachyarrhythmias mainly in males aged 38-48 years old.[1] The initial description of the disease in 1992 included 3 (37.5%) children[2], however later reports mainly focused on adults who constitute the immense majority of symptomatic patients.[3, 4]

Currently, the literature on children and adolescents with BrS and arrhythmic event (AE) is limited. The few published large series on young patients with BrS include 30-128 patients, of whom only a minority (1-10 patients) presented with aborted cardiac arrest (ACA) or developed (1-4 patients) an AE during follow up.[5-10] Several risk factors for malignant ventricular tachyarrhythmias in young BrS patients have been suggested: a previous history of ACA or malignant syncope, spontaneous type 1 Brugada-ECG, atrial arrhythmias and conduction abnormalities.[5-10] However, estimation of the utility of all proposed parameters for predicting the occurrence of AE in young BrS patients is hampered by the small patient population size studied. We recently reported the results of a multicenter international survey on AE in BrS (SABRUS) in a large cohort of 678 BrS-patients with their first ever documented AE, including a non-negligible number of young patients.[1, 11-13]

The purpose of the present paper was threefold: 1) to describe the clinical, ECG, electrophysiologic and genetic characteristics of a large cohort of young BrS patients ($\leq$20 years) with documented AE and to compare them with those of their older counterparts ($\geq$21 years); 2) to compare the characteristics of the pediatric ($\leq$12 years) and adolescent groups (13-20 years); 3) to describe the management and follow-up of the young patients ($\leq$20 years) after their first AE and assess possible predictors for AE recurrence.

Methods

Patient selection.

Patients were included if they fulfilled the following two criteria 1) Presence of spontaneous or drug-induced typical type 1 Brugada-ECG; 2) Documented episode of first AE (sustained ventricular tachyarrhythmia).

As detailed elsewhere[1] a total of 678 BrS-patients with first AE were recruited from 23 centers worldwide which agreed to collaborate in the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS). For the current project, all 23 centers were requested to provide additional baseline and follow-up data (see below) on all their patients aged ≤ 20 years who belonged to the original SABRUS cohort. Also, all centers were asked to provide data on any new young BrS patients (≤ age 20 years) with an AE treated in their institution since the initial patient recruitment in April 2016. In addition, a new center was recruited following its published experience in young BrS patients with AE.[8-10] Overall, this enabled the collection of 57 young BrS patients with AE (including 10 new patients) who originated from a total of 24 centers. Of note, the current young cohort included some patients already previously reported.[5-7, 10]

The study was approved by the Institutional Review Board committees of all participating centers.

Data acquisition.

As detailed elsewhere[1] the following data were collected for all study patients: 1) Age at the time of the first AE; 2) mode of AE documentation (group A or group B, see below); 3) gender; 4) proband status; 5) ethnicity (Caucasian, Asian, other or unknown); 6) family history of SCD; 7) prior history of syncope; 8) presence of spontaneous or drug-induced type 1 Brugada-ECG; 9) whether or not the AE

was associated with fever; 10) inducibility of sustained polymorphic ventricular tachycardia or ventricular fibrillation (VF) at electrophysiologic study (EPS) and 11) presence of *SCN5A* mutation. For the young patient cohort the following information was added: The presence or absence of: 1) sinus node dysfunction (SND) as defined elsewhere[9]; 2) atrial arrhythmias; 3) first degree atrio-ventricular (AV) block (i.e. PR interval > 200 ms); 4) intraventricular conduction delay defined as QRS duration ≥ 110 ms; 5) QRS fragmentation, defined as ≥ 4 spikes in a single lead or ≥ 8 spikes in leads V1, V2, and V3[14] and 6) S wave in ECG lead I (amplitude ≥ 0.1 mV or duration ≥ 40 ms).[15] Further collected data included whether sodium channel blocker challenge test with ajmaline was performed and whether this was associated with ventricular arrhythmias[6, 16]. Information on patient management was also requested: 1) mode of management and follow up after the first AE and 2) clinical manifestation of the second AE if it occurred.

Definitions.

Age groups: Young BrS patients were defined as aged ≤ 20 years old. This group of patients was further divided into a pediatric (age ≤ 12 years old) and adolescent groups (age ≥13 and ≤ 20 years old).

Patient presentation: The patients were classified into 2 groups according to their mode of AE documentation. Group A: Patients with documented ACA in whom the BrS-diagnosis was made during work-up performed after CA; Group B: Patients with a BrS-diagnosis in whom prophylactic ICD implantation was performed for any reason and in whom an AE requiring appropriate ICD shock therapy was documented during follow-up by ICD interrogation.

Proband status: Proband was defined as the first patient of a family who has been diagnosed with the type-1 Brugada-ECG (spontaneous or drug-induced). A non-proband was defined as a family member of a known BrS-patient.

Genetic analysis: When a *SCN5A* mutation was identified it was classified by its known pathogenicity.

Statistical analysis.

Differences in nominal variables between groups were assessed using a Pearson's chi-square test or a Fisher's exact test as appropriate. Differences in continuous and ordinal variables between groups were assessed using a Mann-Whitney U test. Continuous and ordinal variables are shown as median [IQR] and nominal variables as n (%). Length of follow-up was evaluated using reverse censoring method. Univariate Cox regression was used to evaluate the association between each variable and AE recurrence. Kaplan-Meier curve was used to describe event recurrence during the follow-up time. The first AE was set as start of follow-up which continued until the recurrent AE or end of follow-up. Log rank test was used to compare event recurrence between the two age groups and the potential risk factors.

Significant p values were considered when $p<0.05$. All calculations were done using R version 3.3.2 from R Foundation for Statistical Computing (Vienna, Austria) or SPSS version 25 (IBM, Armonk, NY, USA).

Results

Main characteristics of the young BrS group (≤ 20 years) with AE.

Table 1 displays the main characteristics of the young patient group. The cohort comprised 57 patients, median age (IQR) of 14 (3-18) at time of first AE, most being males (n=42, 73.7%), Caucasians (n=40, 70.2%), probands (n=45, 78.9%) and initially presenting with ACA (n=48, 84.2%). The AE was fever-related in 28.1% of patients. A positive family history of SCD and a prior history of syncope were present in 26.3% and 49.1% of patients, respectively. A

spontaneous type 1 Brugada-ECG was observed in 64.9% of patients. Most of the patients (56.1%) underwent an EPS during which VF was inducible in only 28.1%. Genetic testing was performed in 75.4% of patients revealing an *SCN5A* mutation in 58.1%.

Comparison of young (age ≤ 20) versus older BrS patients (age ≥ 21) with AE.

As presented in **Table 1** a higher proportion of females and Caucasians were noted among the young BrS patients. Also, young BrS patients presented more with ACA (84.2% vs. 61.3% in the older group, P<0.001) while only 9 (15.8%) of the young group exhibited their AE after prophylactic ICD implantation as compared to 244 (38.7%) of the older patients (p<0.001). There were 9-fold more fever-related AEs among the young patient group. EPS was performed in a similar proportion of patients in the 2 groups and showed a significantly lower inducibility rate of VF in the young group (28.1% vs. 65.2% in the older group, P<0.001). The young group also exhibited higher *SCN5A* mutation rates (58.1% vs. 26.9% in the older group, P<0.001). The other parameters including proband status, presentation with an arrhythmic storm, family history of SCD, prior history of syncope, and presence of spontaneous type 1 ECG, were not significantly different between the 2 groups.

Comparison between the pediatric (age ≤ 12) and adolescent (13 ≤ age ≤ 20) groups.

Main comparative results are shown in **Table 2**. A higher proportion of females and Caucasians were noted in the pediatric group. In both groups (~ 84%) ACA was the initial manifestation of the disease. More AEs were associated with fever in the pediatric group. More patients in the pediatric group had spontaneous type 1 ECG while other basic ECG features or the presence of SND or atrial arrhythmias was equally distributed among the 2 groups. Other variables including proband status, presentation with an arrhythmic storm, family history of SCD, prior history of

syncope, VF inducibility at EPS, occurrence of AE during Ajmaline test and presence of *SCN5A* mutation were not significantly different between the 2 groups.

Management and follow up after the first AE in the young group.

Follow-up and management data were available for 52 patients; 24 from the pediatric and 28 from the adolescent group. **Table 3** summarizes patients' follow-up and management after their first AE. Regarding the pediatric group, 6 patients (25%) died during follow-up including 2 who died shortly after the first AE from neurologic sequelae secondary to prolonged resuscitation. One patient died due to intractable ventricular tachyarrhythmia and 2 patients exhibited post discharge recurrent AE and SCD after 3.5 and 6.1 months, respectively following their initial AE (ICD was not implanted in these patients). One patient who had an AE at the age of 2, had an AE recurrence 9.9 months later; he died 16 years after his initial presentation from VF storm despite having an ICD implanted[17]. None of these 6 patients were treated with quinidine. Another 11 patients had a recurrent second AE, including an arrhythmic storm in one (overall 62.5% had either arrhythmic death or recurrent ventricular tachyarrhythmia during follow-up). These events occurred without anti-arrhythmic therapy (6 patients) or while on quinidine therapy (5 patients, including 1 with VF storm). Of note, quinidine levels after the second AE were measured for 2 of these patients and were found below the therapeutic range in both cases. Concerning the adolescent group, no patient died during follow-up. However, 18 (64%) patients had a recurrent second AE: in 5 patients (including 1 with VF storm) it occurred during quinidine treatment while in the remaining 13 (including 1 with VF storm) with no antiarrhythmic therapy. The recurrent second AE was treated with endocardial right ventricular outflow tract ablation (n=1) and epicardial ablation of the right ventricle (n=3). There were no AEs recurrences following the ablation procedures in these 4 patients. Kaplan-Meier curves describing time to recurrent AE in

the pediatric and adolescent groups are presented in **Figure 1**. Both age groups demonstrated a similar high recurrence AE rate (p=0.27) with median time to recurrence of 9.9 months and 27.2 months, respectively. The 12-month recurrence AE rates were 59.1% and 35.7% for the pediatric and adolescent groups, respectively.

Predictors of AE recurrence in the young BrS group.

Of the 52 patients with available follow-up, 2 patients from the pediatric group were excluded from the current analysis since they died shortly after the first AE from neurological sequelae secondary to prolonged resuscitation; therefore, whether they were at risk for recurrent AE cannot be determined. Thus, the current analysis included 22 patients from the pediatric group and 28 patients from the adolescent group, of whom 15 and 18 patients had a recurrent AE, respectively. **Table 4** summarizes the variables that were significantly associated with AE recurrence. As shown, intraventricular conduction delay, the presence of S wave in ECG lead 1, SND and atrial arrhythmias were associated with recurrent AE in the pediatric group, while *SCN5A* mutation was associated with AE recurrence in the adolescent group [HR of 5.0 (95% CI, 1.03-23.8, P=0.045)]. Pediatric patients with one or more AE recurrence risk factors (intraventricular conduction delay, the presence of S wave in ECG lead 1, SND and atrial arrhythmias) compared to patient without any of these variables had a HR of 6.9 (95% CI, 1.9-25.2, P=0.004) for recurrent AE. **Figure 2** shows Kaplan Meier curve for AE recurrence in pediatric patients with 1 or more risk factors compared to none. The median time for recurrent AE of pediatric patients with risk factors ≥1 was 2.3 months while it was not reached in the subgroup of pediatric patients without any risk factor (P=0.001). **Figure 3** shows Kaplan Meier curve for AE recurrence in adolescent patients with or without *SCN5A* mutation. The median

time for recurrent AE in *SCN5A* mutation carriers was 4.5 months while it was 105.5 months in patients not carrying the *SCN5A* mutation (P=0.03).

All other variables including gender, ethnicity, proband status, mode of AE documentation, fever-related AE, VF storm, family history of SCD, history of syncope, presentation with VF storm, spontaneous type 1 ECG, first degree AV block, QRS fragmentation and EPS results, were not associated with AE recurrence.

Discussion

The current study includes the largest cohort of young BrS patients with an AE ever reported and shows 3 main findings: 1) There were marked differences between the characteristics of the young and older BrS patient populations as well as between the pediatric and adolescent groups; 2) Very high AE recurrence rates were found among the pediatric and adolescent young subgroups with short median time to recurrence; 3) Several predictors for AE recurrence (i.e. more malignant disease) were defined for each of these 2 subgroups.

Previous studies.

Despite the huge number of publications on BrS since its first description by the Brugada brothers in 1992[2], the number of BrS patients with AE reported in the literature is relatively small.[1] Even more so in the young population, as attested in SABRUS, where the pediatric group (<16 years) represented a minority of 4.3%.[1] In 2007 Probst and colleagues[5] published the first largest pediatric series (age <16 years) that included 30 BrS children. Of this cohort, one child presented with ACA and 3 other patients experienced SCD or appropriate ICD therapy during follow up. Conte et al[6] published a series of 40 children ≤12 years of age of whom 2 presented with ACA and 2 had AE during follow up.

Lately, Gonzalez Corcia et al.[8-10] published several papers dealing with BrS in the young, in which high age cutoffs for young age varied between 19 and 25 years old. Of the studied cohorts, up to 10 patients presented with aborted CA and up to 4 others had an AE during follow up after diagnosis of BrS.

The young cohort and its characteristics compared to adult patients.

Several characteristics of the current young cohort as compared to older patients are in agreement with previously published reports. In the young group patient, there were more females and Caucasians[1, 13], more fever- related AEs[12] and lower VF inducibility rates.[6, 8] The higher proportion of young patients presenting with ACA (84.2% vs. 61.3% in the adult population) is an indication of the difficulty to predict and prevent life-threatening arrhythmia in this young population. Finally, the lower inducibility rate of VF at EPS in the young patients compared to adults renders more difficult the use of EP-guided quinidine therapy[18] in this patient group.

Pediatric compared to adolescent BrS patients.

An advantage of the current study is the relatively high number of young patients included which enabled to characterize pediatric compared to adolescent patients separately. Among the main differences found between these 2 groups was the higher proportion of females in the pediatric group as compared to the adolescent group. In addition, this study emphasized our previous observation that an Asian origin was rare amongst young patients[1], especially in the pediatric group. Asians represented a minority of 4.2% (1 out 24) in the pediatric group with known ethnicity vs. 37% (10 out 27) of the adolescent group (P=0.01). The study also confirms our previous report[12] on the predominant occurrence of fever-related AE in the pediatric population.

As in adults, spontaneous type 1 Brugada-ECG is a known risk factor for AE in the young[5, 7-9] and was observed in a substantial proportion (80.8%) of pediatric patients with an AE in our study. Of course, its absence cannot be totally reassuring, as one fifth of patients did not have type 1-ECG. Interestingly type 1-ECG was not found to be a predictive variable for AE recurrence (see below). A possible explanation could relate to the nature of our study which exclusively included patients with an AE, thereby lessening the additional value of spontaneous type 1-ECG as a risk factor. Also, the very high prevalence of 80% found in the pediatric cohort might preclude utilizing this variable for further risk stratification.

***SCN5A* mutation.**

In the general population with BrS, *SCN5A* mutation rates vary between 14-26%.[3, 4, 19, 20] Initial studies, which included mainly adult patients[3, 4] did not support a prognostic significance for the presence of *SCN5A* mutation. However, a selection bias was suspected due to the inclusion of probands as well as family members with the same clinical presentation. Indeed, lately, Yamagata and colleagues[19] demonstrated in a large cohort of Japanese probands (aged 46 $\pm$ 14 years old), that *SCN5A* mutation carriers have higher event rates. In addition, Nishii et al[20] showed in a cohort of adult Asians that *SCN5A* mutation is associated with AE recurrence and a meta-analysis[21] suggested that *SCN5A* mutation is associated with AEs mainly in Asians, symptomatic patients or individuals with type 1 ECG.

The present study found higher mutation rates in the *SCN5A* gene of the young BrS patients compared to adults with AE (58.1% vs 26.9%, $p<0.001$). Conflicting results regarding the clinical significance of *SNC5A* mutations among young BrS patients have been reported. An earlier study by Andorin et al[7] found *SCN5A* mutations in 77% of their 75 BrS patients aged < 19 years, and in all their 9 patients (100%) who had an AE. Our group previously reported a much

lower mutation rate (29.4%) in 201 asymptomatic BrS patients aged < 16 years old.[13] However, Gonzalez Corcia et al.[8] reported mutations rates of 45% (9 out of 20) in symptomatic BrS patients (most with syncope) compared to mutation rates of 73% (24 out of 33) in asymptomatic patients aged ≤ 25 years old. The latter results could be due to a bias related to screening of families with known *SCN5A* mutation causing artificial elevated number of asymptomatic patients with mutation. Overall, it seems that mutation rates among symptomatic young BrS patients are higher than in symptomatic adults, however whether *SCN5A* mutations are associated with higher event rates needs to be studied further. Nevertheless, the only predictor of recurrent AEs in the adolescent population was a positive *SCN5A* mutation.

Patient management.

Several risk factors have been implicated as portending higher risk for AE in BrS. Undoubtedly, the most important risk factor is a previous AE.[3, 22, 23] In various reports the incidence of recurrent AE among ACA BrS survivors ranged from 40-70% at 10 year follow up with a median time for recurrent AE more than 24 months.[10, 22, 23] Gonzalez Corcia and colleagues[10] reported a 40% AE recurrence rate in a smaller cohort of 10 BrS patients aged ≤ 20 years. In our cohort we found similar AE recurrence rates of 68% and 64% in pediatric and adolescent patients, respectively. However, median time for AE recurrence was significantly shorter in patients exhibiting risk factors for recurrent AE, equaling 2.3 and 4.5 months in the pediatric and adolescent patients, respectively. The risk factors that were found predictive of AE recurrence, include SND, intraventricular delay, atrial arrhythmias and S wave in ECG lead I in the pediatric population and *SCN5A* mutation among adolescents. Of note, the presence of S wave in ECG lead I which is a known risk factor for AEs in BrS[15], was not previously examined in the pediatric population. Thus, it seems that besides ICD implantation urgent prudent measures

should be taken to prevent AE recurrence in patients exhibiting any of these risk factors. Gonzales Corcia et al[10] reported 3 (8.5%) deaths due to VF storm in a cohort of young BrS patients wearing an ICD, which further strengthens the notion that ICD implantation without further treatment in high risk patients may not be sufficient.

Measures to prevent AE recurrence.

Despite apparently promising early results observed with quinidine in the treatment of arrhythmic storms and the prevention of recurrent AEs in adults[18, 24, 25] the current study showed that approximately one third of the recurrent arrhythmias in the young patient occurred during quinidine treatment without major difference between the pediatric and adolescent groups **(Table 3).** Nevertheless, any conclusion regarding the efficacy of quinidine in the young would be premature, for the following reasons: (1) our study is observational and does not compare the prognosis of patients with or without quinidine; (2) doses of quinidine used could have been suboptimal ; (3) problems related to patient compliance may be exacerbated in the pediatric age[26]; accordingly, quinidine levels were measured in only 2 young patients with an AE and were found below the therapeutic range in both; (4) the efficacy of quinidine using EP guided administration[18] previously found to show a high efficacy rate in adults had not been routinely practiced in any of the SABRUS centers in the young. Thus, it seems that until confirmatory studies regarding quinidine efficacy and dosage in various age groups will be available, young patients on quinidine should be followed closely with repeat measurements of serum quinidine level. Also, the practice of EPS to test quinidine efficacy should be considered in case of inducible VF at baseline EPS. Finally, it should be mentioned that all 4 patients in the current cohort who underwent ablation of their arrhythmias remained arrhythmia free during follow up. Although the numbers are too small to draw any significant conclusion, this option should be

considered especially for young patients with recurrent AEs on quinidine or those who exhibit drug intolerance. de Asmundis and colleagues[27] recently reported the feasibility and efficacy of epicardial ablation at the time of abdominal ICD implantation in a 3-year-old child with BrS and recurrent quinidine refractory AEs. Such a case may inaugurate a novel therapeutic approach for children with severe ventricular arrhythmias.

Limitations

The current study is retrospective and observational and therefore any conclusion regarding treatment efficacy or inefficacy should be taken with caution and further validated. Also, the number of Asian young BrS patients is limited especially in the pediatric group; thus, whether young Asians with BrS have a different risk profile than Caucasians should be further studied. Also, despite the study being the largest cohort of young BrS patients with an AE, the total number of patients is not high enough to enable us to perform multivariate analysis to assess which variable is more significant than others in predicting AE recurrence. Yet, it should be emphasized that AE in young BrS patients is very rare. Finally, the current study which is an extension of the SABRUS project focused on young BrS patients presenting with an AE and there is no control group of patients without an AE.

Conclusions

Young patients ($\leq$ 20 years) with BrS and AE are uncommon. These patients display a baseline characteristic profile that is different from older BrS patients. Importantly, a sizeable number of these patients have a very active and malignant disease and measures other than ICD implantation seem mandatory to prevent AE recurrence.

Acknowledgements: We thank Dr. Tomer Ziv-Baran for statistical analysis support.

References

1. Milman A, Andorin A, Gourraud JB, Sacher F, Mabo P, Kim SH, Maeda S, Takahashi Y, Kamakura T, Aiba T, Conte G, Juang JJM, Leshem E, Rahkovich M, Hochstadt A, Mizusawa Y, Postema PG, Arbelo E, Huang Z, Denjoy I, Giustetto C, Wijeyeratne YD, Napolitano C, Michowitz Y, Brugada R, Casado-Arroyo R, Champagne J, Calo L, Sarquella-Brugada G, Tfelt-Hansen J, Priori SG, Takagi M, Veltmann C, Delise P, Corrado D, Behr ER, Gaita F, Yan GX, Brugada J, Leenhardt A, Wilde AAM, Brugada P, Kusano KF, Hirao K, Nam GB, Probst V and Belhassen B. Age of first arrhythmic event in Brugada syndrome: Data from the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 patients. *Circ Arrhythm Electrophysiol*. 2017;10. pii: e005222. doi: 10.1161/CIRCEP.117.005222. Epub 2017 Dec 18.
2. Brugada P and 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.
3. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C and Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635-43.
4. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R and Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59:37-45.
5. Probst V, Denjoy I, Meregalli PG, Amirault JC, Sacher F, Mansourati J, Babuty D, Villain E, Victor J, Schott JJ, Lupoglazoff JM, Mabo P, Veltmann C, Jesel L, Chevalier P, Clur SA, Haissaguerre M, Wolpert C, Le Marec H and Wilde AA. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation*. 2007;115:2042-8.
6. Conte G, Dewals W, Sieira J, de Asmundis C, Ciconte G, Chierchia GB, Di Giovanni G, Baltogiannis G, Saitoh Y, Levinstein M, La Meir M, Wellens F, Pappaert G and Brugada P. Drug-induced brugada syndrome in children: clinical features, device-based management, and long-term follow-up. *J Am Coll Cardiol*. 2014;63:2272-9.
7. Andorin A, Behr ER, Denjoy I, Crotti L, Dagradi F, Jesel L, Sacher F, Petit B, Mabo P, Maltret A, Wong LC, Degand B, Bertaux G, Maury P, Dulac Y, Delasalle B, Gourraud JB, Babuty D, Blom NA, Schwartz PJ, Wilde AA and Probst V. Impact of clinical and genetic findings on the management of young patients with Brugada syndrome. *Heart Rhythm*. 2016;13:1274-82.
8. Gonzalez Corcia MC, Sieira J, Sarkozy A, de Asmundis C, Chierchia GB, Hernandez Ojeda J, Pappaert G and Brugada P. Brugada syndrome in the young: an assessment of risk factors predicting future events. *Europace*. 2017;19:1864-1873.
9. Gonzalez Corcia MC, Sieira J, Pappaert G, de Asmundis C, Chierchia GB, Sarkozy A and Brugada P. A clinical score model to predict lethal events in young patients (</=19 years) with the Brugada syndrome. *Am J Cardiol*. 2017;120:797-802.
10. Gonzalez Corcia MC, Sieira J, Pappaert G, de Asmundis C, Chierchia GB, La Meir M, Sarkozy A and Brugada P. Implantable cardioverter-defibrillators in children and adolescents with Brugada syndrome. *J Am Coll Cardiol*. 2018;71:148-157.
11. Milman A, Andorin A, Gourraud JB, Postema PG, Sacher F, Mabo P, Kim SH, Juang JJM, Maeda S, Takahashi Y, Kamakura T, Aiba T, Conte G, Sarquella-Brugada G, Leshem E, Rahkovich M, Hochstadt A, Mizusawa Y, Arbelo E, Huang Z, Denjoy I, Giustetto C, Wijeyeratne YD, Napolitano C, Michowitz Y, Brugada R, Casado-Arroyo R, Champagne J, Calo L, Tfelt-Hansen J, Priori SG, Takagi M, Veltmann C,

Delise P, Corrado D, Behr ER, Gaita F, Yan GX, Brugada J, Leenhardt A, Wilde AAM, Brugada P, Kusano KF, Hirao K, Nam GB, Probst V and Belhassen B. Profile of patients with Brugada syndrome presenting with their first documented arrhythmic event: Data from the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS). *Heart Rhythm*. 2018;15:716-724.

12. Michowitz Y, Milman A, Sarquella-Brugada G, Andorin A, Champagne J, Postema PG, Casado-Arroyo R, Leshem E, Juang JJM, Giustetto C, Tfelt-Hansen J, Wijeyeratne YD, Veltmann C, Corrado D, Kim SH, Delise P, Maeda S, Gourraud JB, Sacher F, Mabo P, Takahashi Y, Kamakura T, Aiba T, Conte G, Hochstadt A, Mizusawa Y, Rahkovich M, Arbelo E, Huang Z, Denjoy I, Napolitano C, Brugada R, Calo L, Priori SG, Takagi M, Behr ER, Gaita F, Yan GX, Brugada J, Leenhardt A, Wilde AAM, Brugada P, Kusano KF, Hirao K, Nam GB, Probst V and Belhassen B. Fever-related arrhythmic events in the multicenter Survey on Arrhythmic Events in Brugada Syndrome. *Heart Rhythm*. 2018;15:1394-1401.

13. Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, Conte G, Giustetto C, Sarquella-Brugada G, Hochstadt A, Kim SH, Juang JJM, Maeda S, Takahashi Y, Kamakura T, Aiba T, Leshem E, Michowitz Y, Rahkovich M, Mizusawa Y, Arbelo E, Huang Z, Denjoy I, Wijeyeratne YD, Napolitano C, Brugada R, Casado-Arroyo R, Champagne J, Calo L, Tfelt-Hansen J, Priori SG, Takagi M, Veltmann C, Delise P, Corrado D, Behr ER, Gaita F, Yan GX, Brugada J, Leenhardt A, Wilde AAM, Brugada P, Kusano KF, Hirao K, Nam GB, Probst V and Belhassen B. Gender differences in patients with Brugada syndrome and arrhythmic events: Data from a survey on arrhythmic events in 678 patients. *Heart Rhythm*. 2018; 15:1457-1465.

14. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP and Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation*. 2008;118:1697-704.

15. Calo L, Giustetto C, Martino A, Sciarra L, Cerrato N, Marziali M, Rauzino J, Carlino G, de Ruvo E, Guerra F, Rebecchi M, Lanzillo C, Anselmino M, Castro A, Turreni F, Penco M, Volpe M, Capucci A and Gaita F. A new electrocardiographic marker of sudden death in Brugada syndrome: The S-wave in lead I. *J Am Coll Cardiol*. 2016;67:1427-40.

16. Conte G, Sieira J, Sarkozy A, de Asmundis C, Di Giovanni G, Chierchia GB, Ciconte G, Levinstein M, Casado-Arroyo R, Baltogiannis G, Saenen J, Saitoh Y, Pappaert G and Brugada P. Life-threatening ventricular arrhythmias during ajmaline challenge in patients with Brugada syndrome: incidence, clinical features, and prognosis. *Heart Rhythm*. 2013;10:1869-74.

17. Brugada P, Brugada J and Brugada R. When our best is not enough: the death of a teenager with Brugada syndrome. *J Cardiovasc Electrophysiol*. 2009;20:108-9.

18. Belhassen B, Rahkovich M, Michowitz Y, Glick A and Viskin S. Management of Brugada syndrome: Thirty-three-year experience using electrophysiologically guided therapy with class 1A antiarrhythmic drugs. *Circ Arrhythm Electrophysiol*. 2015;8:1393-402.

19. Yamagata K, Horie M, Aiba T, Ogawa S, Aizawa Y, Ohe T, Yamagishi M, Makita N, Sakurada H, Tanaka T, Shimizu A, Hagiwara N, Kishi R, Nakano Y, Takagi M, Makiyama T, Ohno S, Fukuda K, Watanabe H, Morita H, Hayashi K, Kusano K, Kamakura S, Yasuda S, Ogawa H, Miyamoto Y, Kapplinger JD, Ackerman MJ and Shimizu W. Genotype-phenotype correlation of SCN5A mutation for the clinical and electrocardiographic characteristics of probands with Brugada syndrome: A Japanese Multicenter Registry. *Circulation*. 2017;135:2255-2270.

20. Nishii N, Ogawa M, Morita H, Nakamura K, Banba K, Miura D, Kumagai N, Matsunaga A, Kawamura H, Urakawa S, Miyaji K, Nagai M, Satoh K, Nakagawa K, Tanaka M, Hiramatsu S, Tada T, Murakami M, Nagase S, Kohno K, Kusano KF, Saku K, Ohe T and Ito H. SCN5A mutation is associated with early and frequent recurrence of ventricular fibrillation in patients with Brugada syndrome. *Circ J*. 2010;74:2572-8.

21. Rattanawong P, Chenbhanich J, Mekraksakit P, Vutthikraivit W, Chongsathidkiet P, Limpruttidham N, Prasitlumkum N and Chung EH. SCN5A mutation status increases the risk of major arrhythmic events in Asian populations with Brugada syndrome: systematic review and meta-analysis. *Ann Noninvasive Electrocardiol*. 2018:e12589.
22. Conte G, Sieira J, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, La Meir M, Wellens F, Czapla J, Wauters K, Levinstein M, Saitoh Y, Irfan G, Julia J, Pappaert G and Brugada P. Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience. *J Am Coll Cardiol*. 2015;65:879-88.
23. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A, Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A, Nogami A, Ritter P, Gourraud JB, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar P, Pierre B, Jais P, Pasquie JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P and Haissaguerre M. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. *Circulation*. 2013;128:1739-47.
24. Marquez MF, Bonny A, Hernandez-Castillo E, De Sisti A, Gomez-Flores J, Nava S, Hidden-Lucet F, Iturralde P, Cardenas M and Tonet J. Long-term efficacy of low doses of quinidine on malignant arrhythmias in Brugada syndrome with an implantable cardioverter-defibrillator: a case series and literature review. *Heart Rhythm*. 2012;9:1995-2000.
25. Anguera I, Garcia-Alberola A, Dallaglio P, Toquero J, Perez L, Martinez JG, Peinado R, Rubin JM, Brugada J and Cequier A. Shock reduction with long-term quinidine in patients with Brugada syndrome and malignant ventricular arrhythmia episodes. *J Am Coll Cardiol*. 2016;67:1653-1654.
26. Venditti EM, Tan K, Chang N, Laffel L, McGinley G, Miranda N, Tryggestad JB, Walders-Abramson N, Yasuda P, Delahanty L and Group TS. Barriers and strategies for oral medication adherence among children and adolescents with Type 2 diabetes. *Diabetes Res Clin Pract*. 2018;139:24-31.
27. de Asmundis C, Chierchia GB, Baltogiannis GG, Salghetti F, Sieira J, Kolettis TM, Tasi K, Vlahos A, Czapla J, Brugada P and La Meir M. Concomitant Brugada syndrome substrate ablation and epicardial abdominal cardioverter-defibrillator implantation in a child. *HeartRhythm Case Rep*. 2018;4:214-218.

Authors

Yoav Michowitz MD[1,2], Anat Milman MD PhD[2,3], Antoine Andorin MD[4,5], Georgia Sarquella-Brugada MD PhD[6], Maria C. Gonzalez MD[7], Jean-Baptiste Gourraud MD PhD[4,5], Giulio Conte MD PhD[8], Frederic Sacher MD[9], Jimmy JM Juang MD PhD[10], Sung-Hwan Kim MD[11], Eran Leshem MD[1,12], Philippe Mabo MD[13], Pieter G. Postema MD PhD[5,14], Aviram Hochstadt MD[15], Yanushi D. Wijeyeratne MD[5,16], Isabelle Denjoy MD[5,17], Carla Giustetto MD[18], Yuka Mizusawa MD[5,14], Zhengrong Huang MD PhD[19], Camilla H. Jespersen MD[5,20,21], Shingo Maeda MD PhD[22], Yoshihide Takahashi MD PhD[22], Tsukasa Kamakura MD PhD[23], Takeshi Aiba MD PhD[23], Elena Arbelo MD PhD[24], Andrea Mazzanti MD[5,25], Giuseppe Allocca MD[26], Ramon Brugada MD PhD[27,28,29], Ruben Casado-Arroyo MD PhD[30], Jean Champagne MD[31], Silvia G. Priori MD PhD[5,25], Christian Veltmann MD[32], Pietro Delise MD[26], Domenico Corrado MD PhD[5,33], Josep Brugada MD PhD[24], Kengo F. Kusano MD PhD[23], Kenzo Hirao MD PhD[22], Leonardo Calo MD[34], Masahiko Takagi MD PhD[35], Jacob Tfelt-Hansen MD DMSc[5,20,21], Gan-Xin Yan MD PhD[36], Fiorenzo Gaita MD[18], Antoine Leenhardt MD[5,17], Elijah R. Behr MD[5,16], Arthur A.M. Wilde MD PhD[5,14], Gi-Byoung Nam MD PhD[37], Pedro Brugada MD PhD[5,8], Vincent Probst MD PhD[4,5], Bernard Belhassen MD[1,2]

[1] Department of Cardiology, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv, Israel

[2] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Department of Cardiology, Leviev Heart Institute, The Chaim Sheba Medical Center, Tel Hashomer, Israel

[4] L'institut du Thorax, Service de Cardiologie, CHU de Nantes, Nantes, France

[5] European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARDHEART;http://guardheart.ern-net.eu)

[6] Pediatric Arrhythmias, Electrophysiology and Sudden Death Unit Cardiology, Department Hospital Sant Joan de Déu, Barcelona - Universitat de Barcelona, Spain

[7] Pediatric Electrophysiology, Cliniques Universitaires St Luc, Brussels, Belgium

[8] Heart Rhythm Management Centre, UZ-VUB, Brussels, Belgium

[9] Hôpital Cardiologique du Haut-Lévêque & Université Bordeaux, LIRYC Institute, Bordeaux, France

[10] Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

[11] Division of Cardiology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

[12] Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[13] Cardiology and Vascular Disease Division, Rennes University Health Centre, Rennes, France

[14] Heart Centre AMC, Department of Clinical and Experimental Cardiology, AMC, University of Amsterdam, Amsterdam Netherlands

[15] Department of Internal Medicine J, Tel-Aviv Medical Center, Tel Aviv, Israel

[16] Cardiovascular Sciences, St. George's University of London and Cardiology Clinical Academic Group St. George's University Hospitals NHS Foundation Trust, London, UK

[17] Service de Cardiologie et CNMR Maladies Cardiaques Héréditaires Rares, Hôpital Bichat, Paris, and Université Paris Diderot, Sorbonne, Paris, France

[18] Division of Cardiology, University of Torino, Department of Medical Sciences, Città della Salute e della Scienza Hospital, Torino, Italy

[19] Department of Cardiology, the First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

[20] The Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

[21] Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Denmark

[22] Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan

[23] Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan

[24]Cardiology Department, Cardiovascular Institute, Hospital Clinic and IDIBAPS, Barcelona, Catalonia, Spain

[25] Molecular Cardiology, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy.

[26] Division of Cardiology, Hospital of Peschiera del Garda, Veneto, Italy

[27] Cardiovascular Genetics Center, University of Girona-IDIBGI, Girona, Spain

[28] Medical Science Department, School of Medicine, University of Girona, Girona, Spain

[29] Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

[30] Department of Cardiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

[31] Quebec Heart and Lung Institute, Quebec City, Canada

[32] Rhythmology and Electrophysiology, Department of Cardiology, Hannover Medical School, Hannover, Germany

[33] Department of Cardiac, Thoracic and Vascular Sciences University of Padova, Padova, Italy

[34] Division of Cardiology, Policlinico Casilino, Roma, Italy

[35] Division of Cardiac Arrhythmia, Kansai Medical University Medical Center, Moriguchi, Japan

[36] Lankenau Medical Center, Wynnewood, Pennsylvania, USA

[37] Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Table 1: Comparison between young (age ≤ 20 years) and adult (age ≥ 21 years) Brugada syndrome patients with an arrhythmic event.

		Young ≤ 20	Old ≥ 21	P value
		n=57	n=631	
Age at AE in years	median (IQR)	14 (3, 18)	44 (35, 53)	**<0.001**
Gender				
	Male	42 (73.7)	583 (92.4)	**<0.001**
	Female	15 (26.3)	48 (7.6)	
Ethnicity				
	Caucasian	40 (70.2)	332 (52.6)	**0.002**
	Asian	11 (19.3)	262 (41.5)	
	Other/Unknown	6 (10.5)	37 (5.9)	
Proband status				
	Proband	45 (78.9)	505 (80.0)	0.84
	Not Proband	8 (14.0)	81 (12.8)	
	Unknown	4 (7.0)	45 (7.1)	
Mode of AE documentation				
	Group A	48 (84.2)	387 (61.3)	**<0.001**
	Group B	9 (15.8)	244 (38.7)	
Presence of fever during AE				
	Yes	16 (28.1)	21 (3.3)	**<0.001**
	No	37 (64.9)	524 (83.0)	
	Unknown	4 (7.0)	86 (13.6)	
VF storm				
	Yes	7 (12.3)	53 (8.4)	0.33
	No	50 (87.7)	578 (91.6)	
Family history of SCD				
	Yes	15 (26.3)	131 (20.8)	0.41
	No	39 (68.4)	438 (69.4)	
	Unknown	3 (5.3)	62 (9.8)	
History of syncope				
	Yes	28 (49.1)	240 (38.0)	0.12
	No	29 (50.9)	391 (62.0)	
Spontaneous type 1 BrS-ECG				
	Yes	37 (64.9)	421 (66.7)	0.77
	No	20 (35.1)	210 (33.3)	
VF inducibility				
	EPS performed	32 (56.1)	376 (59.6)	0.67
	Inducible	9 (28.1)	245 (65.2)	**<0.001**
	Not inducible	23 (71.9)	131 (34.8)	
Presence of *SCN5A* mutation				
	Testing done	43 (75.4)	446 (70.7)	0.54
	SCN5A mutation	25 (58.1)	120 (26.9)	**<0.001**
	No *SCN5A* mutation	18 (41.9)	326 (73.1)	

AE = arrhythmic event; BrS = Brugada syndrome; EPS = electrophysiological study; SCD = sudden cardiac death; VF = ventricular fibrillation.

Table 2: Comparison between children (age ≤ 12 years) and adolescents (13 ≤ age ≤ 20 years) Brugada syndrome patients with an arrhythmic event.

		age ≤ 12 n= 26	13≤age≤20 n= 31	P value
Age at AE in years	median (IQR)	3 (1.4, 7.1)	18 (16, 19)	**<0.001**
Gender				
	Male	15 (57.7)	27 (87.1)	**0.02**
	Female	11 (42.3)	4 (12.9)	
Ethnicity				
	Caucasian	23 (88.5)	17 (54.8)	**0.01**
	Asian	1 (3.8)	10 (32.3)	
	Other/Unknown	2 (7.7)	4 (12.9)	
Proband status				
	Proband	19 (73.1)	26 (83.9)	0.44
	Not Proband	5 (19.2)	3 (9.7)	
	Unknown	2 (7.7)	2 (6.5)	
Mode of AE documentation				
	Group A	22 (84.6)	26 (83.9)	1
	Group B	4 (15.4)	5 (16.1)	
Presence of fever during AE				
	Yes	14 (53.8)	2 (6.5)	**<0.001**
	No	12 (46.2)	25 (80.6)	
	Unknown	0 (0.0)	4 (12.9)	
VF storm				
	Yes	4 (15.4)	3 (9.7)	0.87
	No	22 (84.6)	28 (90.3)	
Family history of SCD				
	Yes	5 (19.2)	10 (32.3)	0.36
	No	20 (76.9)	19 (61.3)	
	Unknown	1 (3.8)	2 (6.5)	
History of syncope				
	Yes	13 (50.0)	15 (48.4)	1
	No	13 (50.0)	16 (51.6)	
Spontaneous type 1 BrS-ECG				
	Yes	21 (80.8)	16 (51.6)	**0.03**
	No	5 (19.2)	15 (48.4)	
VF inducibility				
	EPS performed	14 (53.8)	18 (58.1)	0.79
	Inducible	3 (21.4)	6 (33.3)	0.69
	Not inducible	11 (78.6)	12 (66.7)	
Presence of *SCN5A* mutation				
	Testing done	24 (92.3)	19 (61.3)	**0.02**
	SCN5A mutation	16 (66.7)	9 (47.4)	0.23
	No *SCN5A* mutation	8 (33.3)	10 (52.6)	
Basic ECG*				
	First degree AV block	9 (40.9)	10 (35.7)	0.77
	IVCD (QRS>110)	11 (45.8)	14 (50)	0.79
	QRS fragmentation	6 (28.6)	11 (40.7)	0.54
	S in lead I	6 (30)	10 (35.7)	0.76
Other arrhythmias*				
	Sinus node dysfunction	7 (30.4)	3 (10.7)	0.15
	Atrial arrhythmias	9 (39.1)	8 (28.6)	0.55
Sodium channel blocker test*				
	performed	13 (54.2)	18 (66.7)	0.4
	AE during test	2 (15.4)	3 (16.7)	1

IVCD= intraventricular conduction delay; other abbreviations are similar to previous Table.

* data available for 24 children and 28 adolescents.

Table 3: Patients management and follow-up after the first AE.

		age ≤ 12	**13 ≤ age ≤20**	**P value**
		n=24	n=28	
Follow up	Duration [median (IQR)]	10.3 [1.3, 27]	14 [4.5, 58.7]	0.15
	Number of patients with 2nd AE*	15 (68.1)	18 (64.3)	1
Treatment	Quinidine during part or all FU*	8 (38.1)	10 (35.7)	1
Clinical Manifestation of 2nd AE	AE on quinidine	4 (26.7)	4 (22.2)	1~
	VF storm on quinidine	1 (6.6)	1 (5.6)	
	Death on quinidine	0 (0.0)	0 (0.0)	
	AE without quinidine	6 (40.0)	12 (66.7)	
	VF storm without quinidine	0 (0)	1 (5.6)	
	Death without quinidine*	4 (26.7)	0 (0.0)	
Death during follow up^		6 (25)	0 (0.0)	**0.007**

AE = arrhythmic event; FU = follow-up; VF = ventricular fibrillation.

*Excluding the 2 patients form the pediatric group who died from neurological complications after the first AE

^Including the 2 patients who died from neurological complications after the first AE.

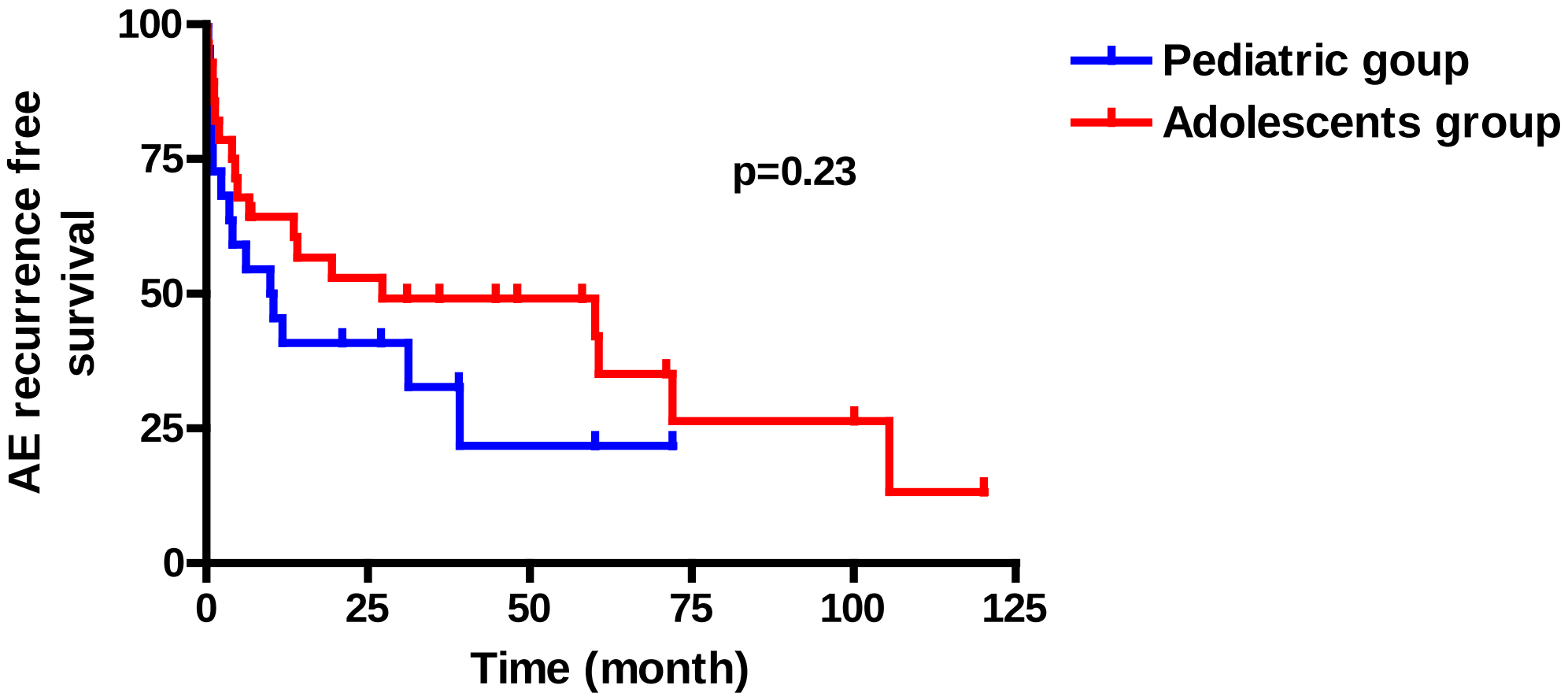
~ comparing the number of AE with or without quinidine in each group

Table 4: Risk factors for recurrent AE

Variable	HR	95% CI	P value
Age ≤ 12			
SND	3.3	1.1-9.7	0.03
Atrial Arhythmias	3	1.07-8.7	0.04
IVCD	3.4	1.2-9.8	0.02
Large S in ECG lead I	3.1	1.04-9.3	0.04
Either vs. none of the above	6.9	1.9-25.2	0.004
Age 13-20			
SCN5A mutation	5	1.03-23.8	0.045

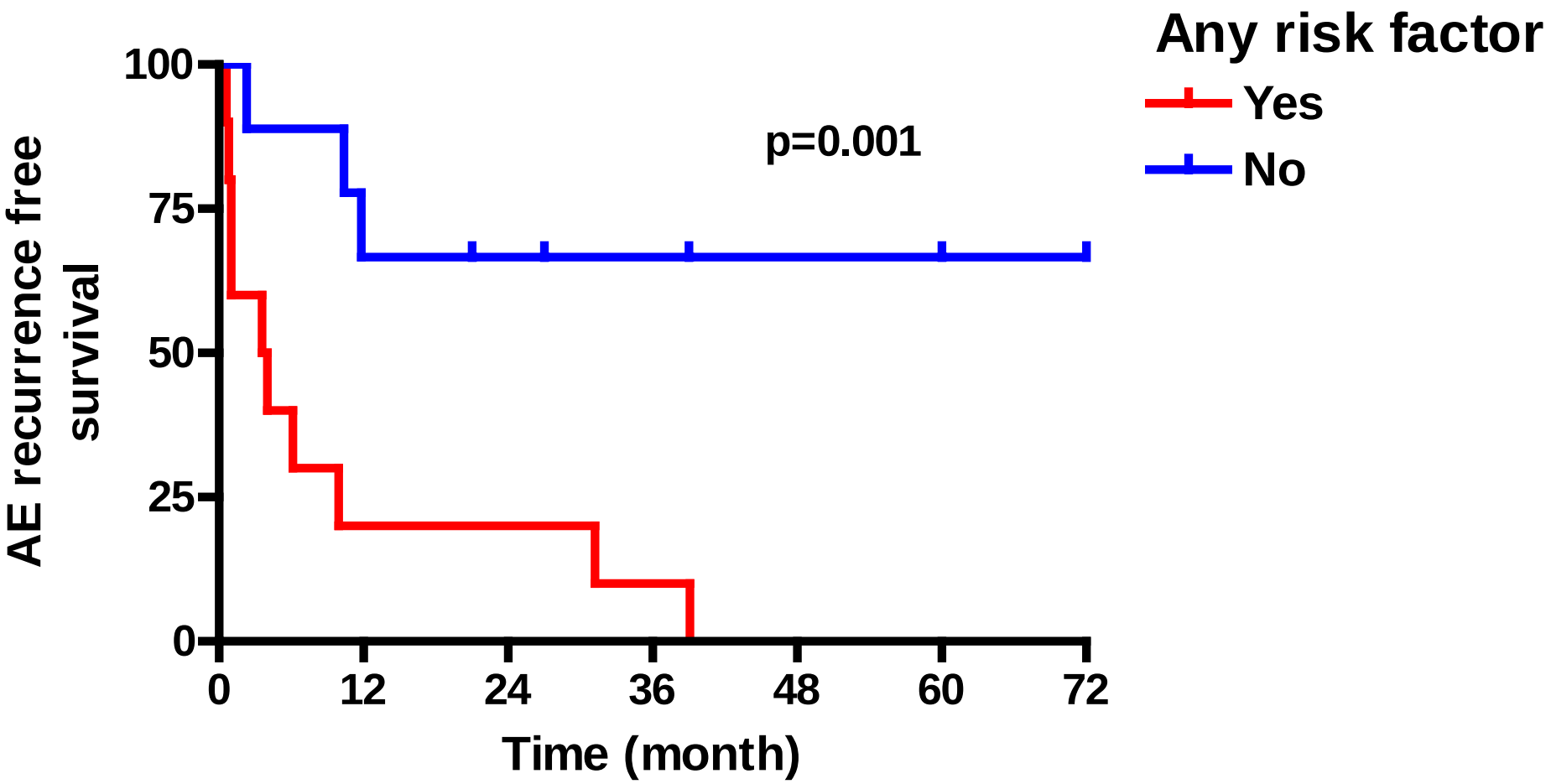
CI = confidence interval; HR = hazard ratio; IVCD = Intraventricular conduction delay (QRS≥110 ms); SND = sinus node dysfunction.

Figure 1



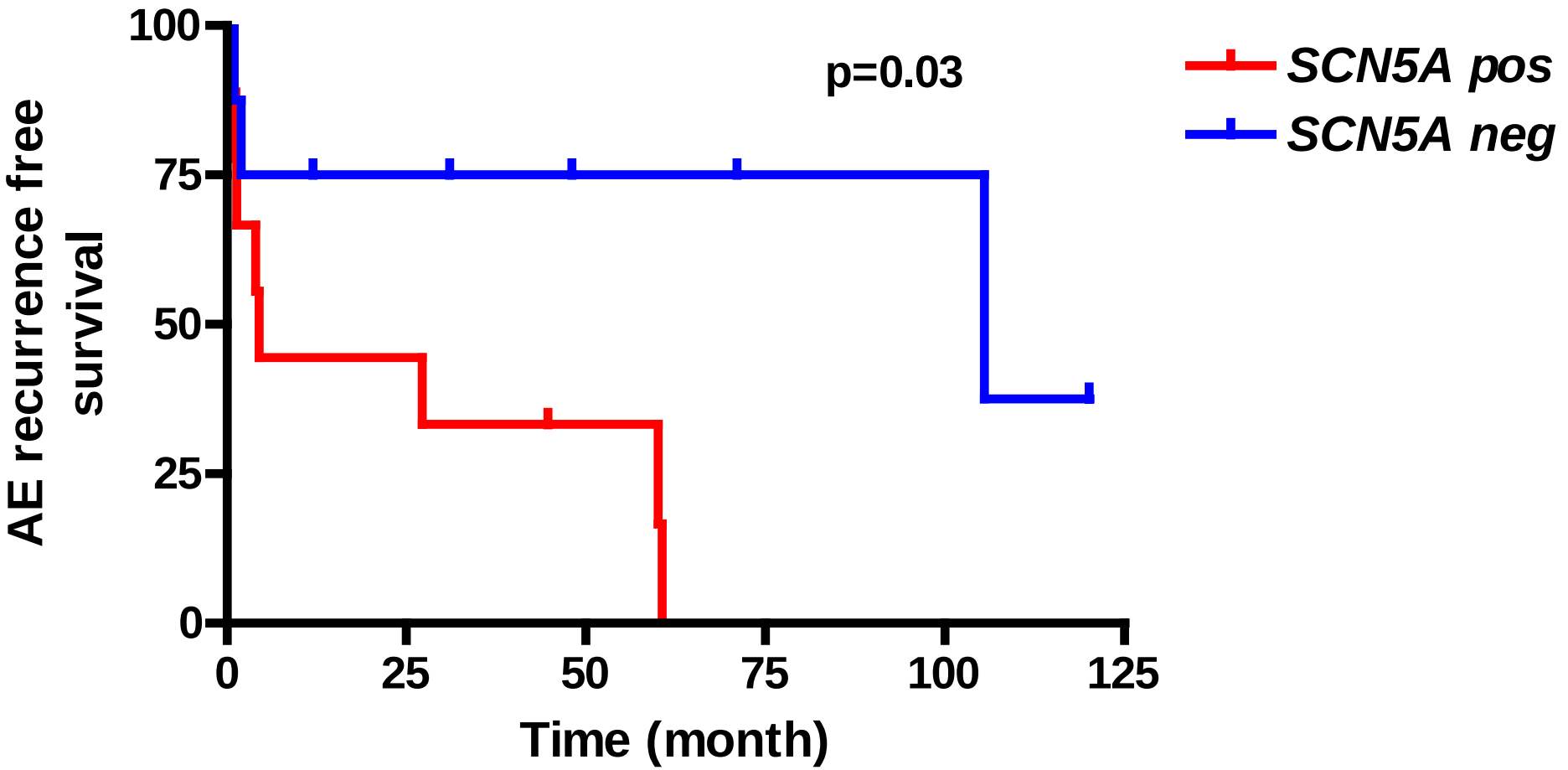
Kaplan-Meier curve for recurrent arrhythmic event among the pediatric and adolescent patients. In both age groups a high recurrence AE rate (59.1% and 35.7% at 12-month, respectively, P=0.27) was observed with median time to recurrence of 9.9 months and 27.2 months, respectively.

Figure 2



Kaplan-Meier curve for recurrent arrhythmic event among the pediatric patients with either none or 1 or more risk factor (risk factors include: atrial arrhythmias, sinus node dysfunction, intra ventricular conduction delay or large S wave in ECG lead I). Patients with risk factors had significantly higher arrhythmic event rate that occurred earlier.

Figure 3



Kaplan-Meier curve for recurrent arrhythmic event among the adolescents with or without *SCN5A* mutation. Patients with positive mutation had significantly higher event rates that occurred earlier.