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Abstract

Background. Detailed information on the profile of Brugada syndrome (BrS) patients presenting their first arrhythmic event (AE) after prophylactic implantation of a cardioverter defibrillator (ICD) is limited.

Objectives. 1) To compare clinical, electrocardiographic, electrophysiologic and genetic profiles of patients who exhibited their first documented AE as aborted cardiac arrest (CA) (group A) with those in whom the AE was documented after prophylactic ICD implantation (group B); 2) To characterize group B patients' profile using the Class II indications for ICD implantation established by HRS/EHRA/APHRS Expert Consensus Statement in 2013.

Methods. A survey of 23 centers from 10 Western and 4 Asian countries enabled data collection of 678 BrS patients with AE (group A, n=426; group B, n=252).

Results. First AE occurred in group B patients 6.7 years later than in group A (46.1$\pm$ 13.3 vs. 39.4$\pm$15.1, P<0.001). Group B patients had a higher incidence of family history of sudden cardiac death (SCD) and *SCN5A* mutations. Of the 252 group B patients, 189 (75%) complied with the HRS/EHRA/APHRS indications whereas the remaining 63 (25%) did not.

Conclusion. BrS patients with first AE documented after prophylactic ICD implantation exhibited their AE at a later age with a higher incidence of positive family history of SCD and *SCN5A* mutations compared to those presenting with an aborted CA. Only 75% of patients who suffered an AE after receiving a prophylactic ICD complied with the 2013 Class II indications, suggesting efforts are still required for improving risk stratification.

Keywords: ICD, arrhythmic risk stratification, sudden cardiac death, genetics, electrophysiologic study.

INTRODUCTION

Brugada syndrome (BrS) is an inherited arrhythmic disorder that may result in sudden cardiac death (SCD).[1] Despite the considerable amount of publications on the topic since the first description of the syndrome[2], the number of patients with documented ventricular arrhythmic events (AE) reported is relatively limited.

Most prior studies have focused on patients with an aborted cardiac arrest (CA) as the presenting AE. The 2 largest European series gathered 62[3] and 25[4] patients presenting with an aborted CA while the largest Asian series from Japan[5], South Korea[6] and Thailand[7] included 84, 77 and 65 patients respectively. Based on these data a profile of BrS patients presenting with aborted CA has been drawn: male patients (>90%) in their fourth decade of life, most of them with spontaneous type 1-Brugada ECG who exhibited their AE without any warning symptoms.

In contrast, detailed information regarding the profile of patients who exhibited their AE after prophylactic implantation of a cardioverter-defibrillator (ICD) is scarce and confined to 3 small series[8-10] comprising up to 14 patients.[9] Gaining insight into the profile of the patients who received and appropriately utilized a prophylactic ICD is important for determining whether ICD indications for these patients complied with those established by the HRS/EHRA/APHRS 2013 Expert Consensus Statement.[11].

We have recently organized a multicenter international survey on AE in BrS (the Survey on Arrhythmic events in BRUgada Syndrome, SABRUS)[12] which collected data on a large cohort of 678 patients with AE's from multiple Western and Asian countries. The present study has 2 main objectives:

1. Compare the characteristics of patients with BrS who underwent a secondary prevention ICD implant with those who underwent a primary prevention device implant.

2. Analyze the profile of patients who exhibited their first AE after prophylactic ICD implantation based on the previously defined Class II indications for ICD implantation.[11]

METHODS

Data source and center selection.

A systematic Medline search was conducted in order to locate the largest academic EP centers having experience in the diagnosis and management of AE's in the setting of BrS. Meta-analyses and case reports were excluded. The centers were requested to state whether their data originated from a single or from multiple institutions and to provide a list of participating institutions in order to prevent any duplication in data collection.

Center recruitment.

Out of 27 centers contacted, 23 (85%) agreed to participate. Sixteen centers (69.5%) reported their sole experience and 7 (30.5%) collected the experience of multiple institutions. A total of 678 patients were recruited from 10 Western (415 patients; 61%) and 4 Asian (263 patients; 39%) countries (Supplemental Table 1).

The study was approved by the Institutional Committee on Human Research at the Tel Aviv Sourasky Medical Center.

Data acquisition.

Study inclusion criteria consisted of 1) a typical Brugada type 1 ECG either spontaneously or following the intravenous administration of a sodium blocker drug; 2) a first documented AE.

Anonymous patient information was collected using a predefined questionnaire regarding the following: 1) mode of AE documentation (Group A or Group B, see below); 2) age at the time of the first AE; 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 Brugada-ECG type 1; 9) inducibility of ventricular fibrillation (VF) at electrophysiologic study (EPS) and 10) results of genetic testing.

In patients who had an AE documented after receiving a prophylactic ICD but did not comply with the 2013 guidelines indications[11], the presence of QRS fragmentation (QRS-f) in leads V1-V3 (13), which was previously reported as a good predictor for AE[8,13] was also collected.

Definitions.

Patient groups according to mode of AE documentation:

- Group A: Patients with documented aborted CA in whom the diagnosis of BrS was made *a posteriori*.
- Group B: Patients with an *a priori* diagnosis of BrS in whom prophylactic ICD implantation was performed and an AE triggering appropriate ICD shock therapy was documented during follow-up.

Arrhythmic events: AE was defined as any sustained ventricular tachyarrhythmia documented during initial aborted CA (group A) or triggering ICD shock therapy (group B).

HRS/EHRA/APHRS Expert Consensus Statement[11]: Current guidelines recommend prophylactic ICD implantation in patients with either spontaneous type 1 Brugada-ECG presenting with syncope judged likely to be caused by ventricular arrhythmia (Class IIa indication) or spontaneous or drug-induced type 1 ECG with inducible VF by programmed ventricular stimulation (Class IIb indication).

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

Statistical analysis.

Assumptions of normality of the age distributions amongst patient subgroups were assessed by Kolmogorov–Smirnov test and Q-Q plots. Differences between group age means were assessed using a Welch t-test for two groups or a one-way ANOVA test for three groups. Differences in proportions were assessed by a Chi-square test or a Fisher's exact test as appropriate. Significance of linear trends for ordinal variables was calculated using a Mantel-Haenszel test. To assess factors influencing dichotomous variables in a multivariate fashion a binary logistic model method was utilized using influencing variables as independent variables. Statistical significance was defined as $P<0.05$. All calculations were performed using SPSS vs. 24 (IBM, Armonk, NY, USA).

RESULTS

The clinical, ECG, EP and genetic findings of the 678 SABRUS patients in respect to mode of AE presentation (groups A and B) are presented in Table 1.

Comparison between group A and group B.

Demographics. The male/female ratio was similar in group A (10.5) and group B (10.8). Group B patients were 6.7 years older than group A patients at time of first AE (46.1 ± 13.3 vs. 39.4 ± 15.1 years, $P<0.001$). Since the survey recruited more patients from Western than Asian countries, there were more Caucasians in both groups but the proportion of Asians with AE was greater in group A (45% vs. 31% in group B, $P<0.001$).

Proband status. The great majority (80%) of SABRUS patients were probands with a greater proportion in group A (84%) than in group B (74%) ($P<0.001$)

Clinical data. A family history of SCD was more frequently noted in group B (29%) compared with group A (17%) (P<0.001), as was a history of syncope (63% vs. 25%, P<0.001).

ECG data. Spontaneous type 1 Brugada-ECG was observed in similar proportions of groups A and B patients (65% and 69%, respectively) (P=0.214).

EP data. Group B patients underwent more EPS than group A (79% vs. 47%, P<0.001) and had a greater proportion of positive results (72% in group B vs 55% in group A, P<0.001).

Genetic data. A greater proportion of patients in group A underwent genetic testing (74% and 67% for groups A and B, respectively, P=0.03). An *SCN5A* mutation was more frequently observed in group B (36%) than in group A (26%) (P=0.016); however, the difference did not reach statistical significance when comparing only proband patients (32.8% vs. 24.3%, P=0.070).

Among patients with a family history of SCD, the proportion of patients with an *SCN5A* mutation was slightly higher in group B (42.1% vs. 35.8% in group A) but the difference was not statistically significant (P=0.474).

Most of the *SCN5A* mutations were identified as pathogenic (56.34%) and likely pathogenic (23.24%) while 10.9% were classified as a "variant of unknown significance", 0.8% as "benign" and for 9.9% the classification was unknown (Supplemental Figure 1). All *SCN5A* mutations are listed in Supplemental Table 2.

Detailed characteristics of group B patients.

Group B patients were divided into 3 subgroups based on the 2013 consensus statement on class II indications for ICD[11]: a) Group B1 (Class IIa indication): 112 (44%) patients; b) Group B2 (Class IIb indication): 77 (31%) patients; c) Group B3

(neither Class IIa nor Class IIb indications): 63 (25%) patients. The clinical, ECG, EP and genetic findings in these subgroups are presented and compared in Table 2.

Although the proportion of females in group B3 (13%) was greater than in group B1 (9%) and group B2 (6%), this difference was not statistically significant. Group B3 included a smaller proportion of patients aged 16-70 than the other 2 groups. A family history of SCD was more frequently noted in group B2 (39%) and group B3 (30%) as compared to group B1 (22%) (P=0.01). No significant differences were observed between the 3 subgroups with regard to age at first AE, ethnic origin and the presence of *SCN5A* mutation. However, when comparing between B3 patients vs. the remainder of the group B patients (B1+B2), there was a trend for more *SCN5A* mutation carriers in Group B3 (48% vs. 32%, P=0.067) (Supplemental Table 3).

As expected by group definition criteria, prior syncope and spontaneous type 1 Brugada-ECG predominated in group B1. Similarly, VF inducibility predominated in group B2 and was absent in group B3.

Characteristics of group B3.

The clinical, ECG, EP and genetic findings in the 63 group B3 patients are presented in Table 3. In 33 (52%) patients (group B3a) EPS was performed but yielded negative results while in the remaining 30 (48%) patients (group B3b) EPS was not performed. Table 4 provides detailed patient characteristics of these 2 subgroups.

The only striking difference between these 2 subgroups of patients was the higher proportion of females in the non-inducible group (18% vs. 7%) but this difference did not reach statistical significance (P=0.261). QRS-f was found in ~ 30% of patients of either subgroup (30.3% and 30%, respectively) regardless of the presence of spontaneous type 1 Brugada-ECG.

When dividing group B into 3 equal subgroups according to the date of ICD implantation (from 9/1987 to 6/2016) there was a rise over the years of the proportion of patients who received an ICD without complying with conventional guidelines (Figure 1) (P=0.021 for trend). There was no difference in clinical characteristics of B3 patients (age, gender, ethnicity, familial history of SCD, prior syncope, ECG type) between the 3 periods.

Using a logistic regression multivariate model, no single parameter identified group B3 patients (besides the definition of not having a conventional class II indication) (Supplemental Table 4).

DISCUSSION

The strength of SABRUS comes from its large cohort of BrS patients who suffered their first documented AE either at the time of aborted CA or after a prophylactic ICD implantation.

Comparison between group A and group B.

The profile of group A patients from SABRUS was similar to previously reported in largest studies of CA survivors.[3,4,5-7] However, besides the similarity in the male predominance (>90%) and the presence of spontaneous type 1 Brugada-ECG in about two thirds of patients in both groups, there were marked differences between the 2 groups with regards to the other clinical, EP and genetic characteristics.

Age at onset of AE. Priori et al. noted that BrS-patients with a first AE documented after prophylactic ICD implantation[8] were 14 years older than those presenting with aborted CA. [14] In SABRUS the initial AE occurred 6.7 years later in group B. There are 2 possible explanations for this late occurrence of AE in group B patients: a) the arrhythmias in group A patients could have a more malignant character striking the patient at a younger age; b)

the lack of effective ECG screening and arrhythmic risk assessment in the younger patient group contrasting with a better stratification in the older group.

Ethnicity. In SABRUS a greater proportion of Asian patients were observed in group A. This difference in the mode of AE presentation between Caucasians and Asians could suggest a more malignant presentation of AE in Asians and/or a less effective screening recognition in Asian countries.

Family history of SCD. A higher incidence of family history of SCD was found in group B (29%) compared with group A patients (17%). It is noteworthy that in 3 large series of BrS patients[3,4,8] and in the prospective study of Sarkozy et al[15], the incidence of family history of SCD was highest in asymptomatic patients (30-58.7%), lowest in CA survivors (10-40%), and intermediate (20-51%) in patients presenting with syncope. The reason for the concordant findings of a higher incidence of a family history of SCD in patients who *did not present with aborted CA* has not been previously addressed. One possible explanation could be that a substantial number of these patients were identified after routine familial screening following the SCD of a family member that notably increased their family history of SCD rate as compared to patients with aborted CA.

Prior history of syncope. Priori and coworkers previously reported that a history of syncope was more frequently noted in patients with AE documented after prophylactic ICD implantation (50%)[3] than in CA survivors (23.5%).[4] Similar results were found in SABRUS with figures of 63% and 25%, respectively. Such difference is likely due to the fact that a previous syncope was one of the inclusion criteria in the B1 subgroup fulfilling Class IIa indication.

*Arrhythmia inducibility***.** The results of SABRUS also showed a higher proportion of patients with inducible VF in group B (72% vs. 55% in group A). Such results are consistent with the fact that arrhythmia inducibility was the inclusion criterion in the

B2 subgroup fulfilling Class IIb indication. In addition, it is possible that the stimulation protocols used in group B patients were more aggressive (in order to minimize false negative results) than in group A (where EPS was mainly performed for academic purpose since the EP results were unlikely to affect patient management with ICD).

Genetic findings. The latest meta-analysis by Wu et al.[16] indicated that an *SCN5A* gene mutation did not increase the risk for future cardiac events. In contrast, a recent Japanese study showed that an *SCN5A* mutation was a significant predictor of cardiac events in BrS probands.[17] In SABRUS, an *SCN5A* mutation was more frequently observed in group B (36%) than in group A (26%) (P=0.007).

The fact that a greater proportion of group B patients had a family history of SCD (29% vs. 17% in group A, P<0.001) and that a greater (albeit non-significant) incidence of *SCN5A* mutation was found among those patients with a family history of SCD in group B could explain our findings.

Profile of group B patients.

In addition to groups B1 and B2 who fulfilled Class II indications, the survey showed for the first time another sizeable group (B3) comprising 25% of group B patients, who did not fulfill these indications. Besides a higher incidence of a family history of SCD in group B2 and group B3 as compared to group B1 as well as intergroup differences due to group criteria definitions, there were no significant differences between these 3 groups in regard to patients' age at time of AE, ethnic origin, and the presence of *SCN5A* mutation.

The fact that group B1 comprised more patients than group B2 is consistent with the results of the Multicenter Japanese study on the long-term prognosis of BrS patients with no previous CA, based on Class II indications for ICD implantation.[18] Such

results validate the classification adopted in the Expert Consensus Statement[11] establishing that patients with Class IIa indication exhibit an increased risk as compared to those with Class IIb indication.

Characteristics of group B3 patients.

This group comprised 2 subgroups of similar size: one in whom EPS did not induce arrhythmias (n=33) and the second in whom EPS was not performed (n=30). Interestingly the proportion of Caucasians and Asians in group B3 among group B patients was similar (25% and 24.3%, respectively).

Priori et al.[8] and Sieira et al.[9] previously reported small cohorts of patients without Class IIa or IIb ICD indications who exhibited an AE during follow-up after prophylactic ICD implantation.

Taking into account that arrhythmia inducibility is a critical factor for deciding upon prophylactic ICD implantation in BrS, aggressiveness of the protocol of programmed ventricular stimulation (PVS) used is of paramount importance.[19,20] In addition, in SABRUS the non-inducible subgroup (B3a) included a relative high proportion of females who have been shown to exhibit a lower inducibility rate of VF than males.[21] Although it is tempting to speculate that aggressive PVS protocols[19,20] could have resulted in a higher inducibility rate of arrhythmias and enabled inclusion of the inducible patients in the B2 group, one should recognize that doing so might increase the number of false positive responses and unnecessary ICD implants.

The issue of patients in whom EPS was not performed and who received a prophylactic ICD not based on Class II indications (subgroup B3b), just to exhibit an AE during follow-up has not been previously addressed. Our data showed that the proportion of such patients has been growing over the years, probably due to the increasing doubts of the EP community concerning the role of EPS in predicting

arrhythmic risk in BrS. It is likely that performance of EPS in subgroup B3b would have yielded positive results in some of them, thus enabling their inclusion in group B2.

Careful analysis of the B3 group characteristics failed to identify any obvious clinical or laboratory criteria used as single factor that could raise suspicion of the very high arrhythmic risk of these patients.

It is noteworthy that the total number of patients treated with a prophylactic ICD without appropriate shocks based on non-conventional indications such as in group B3 was unknown from our survey results.

Study limitations.

The survey is not a multicenter prospective study but rather a retrospective cumulative analysis of results from the largest EP centers which have experience with BrS. The definitions of family history of SCD and syncope, as well as the PVS protocol were left at the discretion of the participant centers. There was no information about the patients' or physicians' involvement in the decision to implant a prophylactic ICD in those patients who did not fulfill Class II indications.

Clinical implications.

The results of SABRUS confirm the validity of Class II indications established by the Expert Committee[11] in 75% of the SABRUS patients without previous CA. However, the fact that the remaining 25% of patients exhibited AE despite the fact they did not fulfill the conditions justifying this implantation based on these guidelines, is of a great concern. A strict application of the guidelines recommendations in these patients would have discarded ICD implantation and could have had a fatal outcome. On the other hand widening the indications for prophylactic ICD implantation in BrS based on the data provided by SABRUS in group B3 is likely to result in unnecessary ICD

implantations in a considerable amount of patients. Thus, our data suggest that major efforts should be made to assign these patients to group B1 or B2. However, one should admit that despite these efforts it might be that the patient's clinical and familial history as well as the patient's and the family's wishes will lead to ICD implantation despite the lack of strict adherence to Class II indications. We believe that this possibility should be kept to the minimum. Although there might well be a larger pressure for patients, families and doctors to implant a prophylactic ICD in the case of familial SCD, this is not currently supported by guidelines because of the high chances of unnecessary exposure to invasive ICD therapy and its associated risks. Taking into account the limitations and inconsistencies with taking a family history of SCD in the current retrospective study, there is certainly a need for more robust family history data in BrS patients.

Conclusions.

For the first time SABRUS describes the profile of patients with BrS who developed an AE after prophylactic ICD implantation in a large patient population. The profile of these patients differs from that of CA survivors including a non-negligible proportion of patients who did not comply with the conventional guidelines. Major efforts are still necessary for improving arrhythmic risk stratification in BrS.

REFERENCES

1. Mizusawa Y, Wilde AA. Brugada syndrome. Circ Arrhythm Electrophysiol. 2012;5:606-616.

2. Brugada P, Brugada J. Right bundle branch block, persistent ST-segment elevation and sudden cardiac death. J Am Coll Cardiol. 1992;20:1391–1396.

3. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome results from the FINGER Brugada Syndrome Registry. Circulation 2010;121:635–643.

4. Conte G, Sieira J, Ciconte G, et al. Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience. J Am Coll Cardiol. 2015;65:879-888.

5. Takagi M, Aonuma K, Sekiguchi Y, Yokoyama Y, Aihara N, Hiraoka M; Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. The prognostic value of early repolarization (J wave) and ST-segment morphology after J wave in Brugada syndrome: multicenter study in Japan. Heart Rhythm. 2013;10:533-539.

6. Kim JY, Kim SH, Kim SS, et al. Benefit of implantable cardioverter-defibrillator therapy after generator replacement in patients with Brugada syndrome. Int J Cardiol. 2015;187:340-344.

7. Makarawate P, Chaosuwannakit N, Vannaprasaht S, Tassaneeyakul W, Sawanyawisuth K. Clinical characteristics and treatment outcomes of patients with Brugada syndrome in northeastern Thailand. Singapore Med J. 2014;55:217-220.

8. Priori S, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome. Results of the PRELUDE registry. J Am Coll Cardiol 2012;59:37–45.

9. Sieira J, Conte G, Ciconte G, et al. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20 years experience. Circ Arrhythm Electrophysiol. 2015;8:777-784.

10. Sieira J, Ciconte G, Conte G, et al. Asymptomatic Brugada syndrome: clinical characterization and long term prognosis. Circ Arrhythm Electrophysiol. 2015;8:1144-1150.

11. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. 2013;15:1389-1406.

12. Milman A, Andorin A, Gourraud J-B, et al. Age of first arrhythmic event in Brugada syndrome: Data from the survey on arrhythmic events in Brugada syndrome (SABRUS) in 678 patients. Circ Arrhythm Electrophysiol 2017;10:e005222. DOI: 10.1161/CIRCEP.117.005222 (in press)

13. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation 2008;118:1697–1704.

14. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation. 2002;105:1342-1347.

15. Sarkozy A, Sorgente A, Boussy T, Casado R, Paparella G, Capulzini L, Chierchia GB, Yazaki Y, De Asmundis C, Coomans D, Brugada J, Brugada P. The value of a family history of sudden death in patients with diagnostic type I Brugada ECG pattern. Eur Heart J. 2011;32:2153-2160.

16. Wu W, Tian L, Ke J, Sun Y, Wu R, Zhu J, Ke Q. Risk factors for cardiac events in patients with Brugada syndrome: A PRISMA-compliant meta-analysis and systematic review. Medicine (Baltimore). 2016;95:e4214.

17. Yamagata K, Horie M, Aiba T, et al. 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

18. Takagi M, Sekiguchi Y, Yokoyama Y, Aihara N, Hiraoka M, Aonuma K; Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. Long-term prognosis in patients with Brugada syndrome based on Class II indication for implantable cardioverter-defibrillator in the HRS/EHRA/APHRS Expert Consensus Statement: multicenter study in Japan. Heart Rhythm. 2014;11:1716-1720.

19. Belhassen B, Michowitz Y. Arrhythmic risk stratification by programmed ventricular stimulation in Brugada syndrome: the end of the debate? Circ Arrhythm Electrophysiol. 2015;8:757-759.

20. Belhassen B. Management of Brugada syndrome 2016: Should all high risk patients receive an ICD? Alternatives to implantable cardiac defibrillator therapy for Brugada syndrome. Circ Arrhythm Electrophysiol. 2016;9. pii: e004185.

21. Sacher F, Meregalli P, Veltmann C, et al. Are women with severely symptomatic Brugada syndrome different from men? J Cardiovasc Electrophysiol. 2008;19:1181-1185.

Legends

Figure 1. Evolution over the years of the indication of prophylactic ICD implantation in Group B patients who exhibited arrhythmic events (n=252). Patients who exhibited arrhythmic events after prophylactic ICD implantation were divided into 3 equal subgroups according to the date of ICD implantation. A rise is noted over the years of the proportion of patients who received an ICD without complying with conventional guidelines indication (Group B3).

Definitions of groups B1, B2 and B3 are given in the text.

Table 1: Comparison between group A and group B

		Group A (n=426)	Group B (n=252)	P value
Gender				
	Male	390 (92)	229 (91)	0.763
	Female	36 (8)	23 (9)	
Age at AE				
	All patients (years)	39.4±15.1	46.1±13.3	<0.001
Age distribution	**< 16**	25 (6)	4 (2)	
	16-70	395 (93)	245 (97)	<0.05
	>70	6 (1)	3 (1)	
Ethnicity				
	Caucasian	204 (48)	160 (63)	
	Asian	192 (45)	78 (31)	<0.001
	Other	30 (7)	14 (6)	
Proband status				
	Positive	356 (84)	186 (74)	<0.001
	Negative	40 (9)	48 (19)	
	Unknown	30 (7)	18 (7)	0.961
Family history of SCD				
	Yes	73 (17)	72 (29)	<0.001
	No	315 (74)	153 (61)	
	Unknown	38 (9)	27 (11)	0.443
Prior history of syncope				
	Yes	106 (25)	159 (63)	<0.001
	No	320 (75)	93 (37)	
Spontaneous type 1 ECG				
	Yes	276 (65)	175 (69)	0.214
	No	150 (35)	77 (31)	
VF inducibility during EPS				
	EPS performed	200 (47)	200 (79)	<0.001
	Positive EPS	109 (55)	144 (72)	<0.001
	Negative EPS	91 (46)	56 (28)	
Presence of *SCN5A* mutation				
	Genetics performed	317 (74)	168 (67)	<0.05
	***SCN5A* positive**	82 (26)	61 (36)	<0.05
	***SCN5A* negative**	235 (74)	107 (64)	

All numbers are presented as number of patients (percent of patients in specific group).

AE: arrhythmic event; EPS: electrophysiological study; SCD: sudden cardiac death;

Table 2. Detailed characteristics of group B

		B1 Class II a Syncope + Type 1 ECG	B2 Class II b Inducible VF	B3 No Class IIa or IIb	P-value
No of patients		112 (44.4)	77 (30.6)	63 (25)	
Gender					
	Male	102 (91)	72 (94)	55 (87)	0.445
	Female	10 (9)	5 (6)	8 (13)	
	M/F ratio	10.2	14.4	6.8	
Age at AE					
	All patients (years)	44.7±12.7	48.0±12.5	46.5±15	0.237
Age distribution	**< 16**	1 (1)	0 (0)	3 (5)	0.042#
	16-70	111 (99)	75 (97)	59 (94)	
	>70	0 (0)	2 (3)	1 (2)	
Ethnicity					
	Caucasian	66 (59)	54 (70)	40 (63)	0.113
	Asian	42 (38)	17 (22)	19 (30)	
	Others	4 (4)	6 (8)	4 (6)	
Proband status					
	Positive	91 (81)	56 (73)	39 (62)	0.184
	Negative	17 (15)	16 (21)	15 (24)	
	Unknown	4 (4)	5 (6)	9 (14)	<0.05*#
Family history of SCD					
	Yes	23 (22)	30 (39)	19 (30)	0.010*&
	No	81 (78)	40 (52)	32 (51)	
	Unknown	8 (7)	7 (9)	12 (19)	0.043#
Prior history of syncope					
	Yes	112 (100)	20 (26)	27 (43)	<0.001*&#
	No	0 (0)	57 (74)	36 (57)	
Spontaneous type 1 ECG					
	Yes	112 (100)	37 (48.1)	26 (41)	<0.001*&#
	No	0 (0)	40 (51.9)	37 (59)	
VF inducibility during EPS					
	EPS performed	90 (80)	77 (100)	33 (52)	<0.001&#
	Positive EPS	67 (74)	77 (100)	0 (0)	<0.001&#
	Negative EPS	23 (26)	0 (0)	33 (100)	
Presence of *SCN5A* mutation					
	Genetics performed	71 (63)	53 (69)	44 (70)	0.61
	***SCN5A* positive**	25 (35)	15 (28)	21 (48)	0.136
	***SCN5A* negative**	46 (65)	38 (72)	23 (52)	

All numbers are presented as number of patients (percent of patients in specific group). Abbreviations as in Table 1.

* Group B1 significantly different from the others, & Group B2 significantly different from the others, # Group B3 significantly different from the others.

Table 3. Comparison between B3 subgroups

		B3a	B3b	P value
		No Class IIa or IIb Non inducible VF	No Class IIa or IIb EPS not performed	
No of patients		33 (52.4)	30 (47.6)	
Gender				
	Male	27 (82)	28 (93)	0.261
	Female	6 (18)	2 (7)	
Age at AE				
	All patients (years)	47.6±16.2	45.2±13.7	0.529
Age distribution	**< 16**	2 (6)	1 (3)	1.00
	16-70	30 (91)	29 (97)	
	>70	1 (3)	0 (0)	
Ethnicity				
	Caucasian	24 (73)	16 (53)	0.197
	Asian	8 (24)	11 (37)	
	Others	1 (3)	3 (10)	
Proband status				
	Positive	22 (67)	17 (57)	0.839
	Negative	8 (24)	7 (23)	
	Unknown	3 (9)	6 (20)	0.289
Family history of SCD				
	Yes	11 (33)	8 (27)	0.909
	No	18 (55)	14 (47)	
	Unknown	4 (12)	8 (27)	0.142
Prior history of syncope				
	Yes	15 (45)	12 (40)	0.662
	No	18 (55)	18 (60)	
Spontaneous type 1 ECG				
	Yes	14 (42)	12 (40)	0.845
	No	19 (58)	18 (60)	
VF inducibility during EPS				
	EPS performed	33 (100)	0 (0)	<0.001
	Positive EPS	0 (0)	0 (0)	N/A
	Negative EPS	33 (100)	0 (0)	
Presence of *SCN5A* mutation				
	Genetics performed	24 (73)	20 (67)	0.601
	***SCN5A* positive**	11 (46)	10 (50)	0.783
	***SCN5A* negative**	13 (54)	10 (50)	

All numbers are presented as number of patients (percent of patients in specific group). Abbreviations as in Table 1.

Table 4. ICD indications in subgroup B3 (group B patients without a class IIa or IIb indication)

		Group B3a (n=33)				Group B3b (n=30)			
EPS		Non-inducible				Not performed			
Symptoms		Asymptomatic 18 (54.5)		Syncope 15 (45.5)		Asymptomatic 18 (60)		Syncope 12 (40)	
ECG		ST1 + 14 (77.8)	ST1 - 4 (22.2)	ST1 + 0 (0)	ST1 - 15 (100)	ST1 + 12 (66.7)	ST1 - 6 (33.3)	ST1 + 0 (0)	ST1 - 12 (100)
M/F		13/1	4/0	-	10/2	12/0	4/2	-	12/0
Fragmented QRS	Yes	5	1	-	4	5	1	-	3
	No	7	1	-	10	3	3	-	7
	N.A	2	2	-	1	4	2	-	2
Proband Positive		10	1	-	11	6	1	-	10
Family history SCD	Yes	4	1	-	6	5	3	-	0
	No	9	1	-	8	3	0	-	9
	N.A	1	2	-	1	4	3	-	3
SCN5A positive		5	2	-	5	5	3	-	2

All numbers are presented as number of patients (percent of patients in specific group).
EPS: electrophysiological study; M: male; F: female; SCD: sudden cardiac death;
ST1 +: spontaneous type 1 Brugada ECG; ST1 - : no spontaneous type 1 Brugada ECG.