Profile of Brugada Syndrome Patients Presenting with Their First Documented Arrhythmic Event. Data from the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS)

Profile of Brugada Syndrome Patients Presenting with their First Documented Arrhythmic Event. Data from the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS)

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

Milman. Age of First Arrhythmic Event in Brugada Syndrome

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

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

[3]LIRYC Institute, INSERM 1045, Bordeaux University Hospital, Bordeaux, France

[4]Cardiology and Vascular Disease Division, Rennes University Health Centre, 35033 Rennes Cedex, France

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

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

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

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

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

[10]Arrhythmia Services, Sunnybrook Health Sciences Centre,
Toronto, Ontario, Canada.

[11]Heart Centre AMC, department of clinical and experimental Cardiology, AMC, University of Amsterdam, Amsterdam Netherlands.

[12]Cardiovascular Institute, Hospital Clínic Pediatric Arrhythmia Unit, Hospital Sant Joan de Déu University of Barcelona, Barcelona, Spain

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

[14]Service de Cardiologie et CNMR Maladies Cardiaques Héréditaires Rares, Hôpital Bichat, Paris, France

[15]Université Paris Diderot, Sorbonne, Paris, France

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

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

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

[19]Department of Molecular Medicine, University of Pavia, Pavia, Italy

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

[21]Cardiovascular Genetics Center, Institut d'Investigació Biomèdica Girona-IdIBGi, Spain

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

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

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

[25]The Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, and Department of Medicine and Surgery, University of Copenhagen, Copenhagen, Denmark

[26]Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Japan

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

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

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

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

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

Address for correspondence:

Bernard Belhassen, MD

Department of Cardiology

Tel Aviv Medical Center

6 Weizman Street

Tel Aviv 6423906, Israel

Telephone: +972-3-6974762

Fax: +972-3-6974418

Email: bblhass@tasmc.health.gov.il

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) Compare the clinical, electrocardiographic, electrophysiologic and genetic profile 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) 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 21 centers from 10 Western and 3 Asian countries enabled collecting data from 628 BrS patients (group A, n=383; group B, n=245).

Results. First AE occurred in group B patients 6 years later than in group A (46.2 $\pm$ 13.2 vs. 40.1 $\pm$ 14.2, $p<0.001$). Group B patients had a higher incidence of family history of sudden cardiac death (SCD) and *SCN5A* mutations. Of the 245 group B patients, 183 (74.7%) complied with the HRS/EHRA/APHRS indications whereas the remaining 62 (25.3%) did not.

Conclusion. BrS patients implanted appropriately with a prophylactic ICD 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.

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 by the Brugada brothers in 1992 (2), the number of patients with documented arrhythmic events (AE) reported is relatively limited, in agreement with the low prevalence of the disease among patients with apparently normal hearts who exhibit SCD.

Most prior studies have focused on patients with an aborted cardiac arrest (CA) as the presenting AE. The FINGER registry, published in 2010 (3), is a multicenter study that gathered 62 patients (out of a total of 1029 patients) from 4 European countries (France, Italy, Netherlands, Germany). The Pedro Brugada group (4), during a 20-year period, observed 25 patients who suffered an aborted CA. Similarly, the largest Asian series of aborted CA 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). No previous study compared these patients with those presenting with aborted CA. Gaining insight into the profile of the patients who received a prophylactic ICD is important for determining whether ICD indications in these patients complied with those

established in the HRS/EHRA/APHRS 2013 Expert Consensus Statement (11). This could help in identifying other subgroups of patients who could draw benefit from prophylactic ICD implantation without sharing these consensual indications.

We have recently organized a multicenter international survey on AE in BrS (the Survey on Arrhythmic events in BRUgada Syndrome, SABRUS) which collected data from a large cohort of 628 patients from multiple Western and Asian countries. The present study has 2 main objectives:

1. Compare the clinical, electrocardiographic (ECG), electrophysiologic (EP) and genetic profile of patients who exhibited their first documented AE as aborted CA with those in whom the AE was documented after prophylactic ICD implantation.
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 systemic Medline search was conducted by one investigator (A.M) 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 multiple institutions and to provide a list of participating institutions in order to prevent any duplication in data collection.

CENTER RECRUITMENT.

Out of 25 centers contacted, 21 (84%) agreed to participate. Fourteen centers (66.6%) reported their sole experience and 7 (33.3%) collected the experience of multiple institutions. The French center that coordinated FINGER (3) provided data from 20 French institutions.

A total of 628 patients were recruited from both Western (10 centers, 405 patients; 64.5%) and Asian countries (3 centers, 223 patients; 35.5%) (Supplemental Table 1). The number of patients provided by each center ranged from 7 to 105 patients.

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

DATA ACQUISITION.

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) ethnicity (Caucasian, Asian, other or unknown); 5) family history of SCD; 6) prior history of syncope ; 6) presence of spontaneous or drug-induced Brugada-ECG type 1; 7) inducibility of ventricular fibrillation (VF) at EP study (EPS); 8) results of genetic testing.

In patients who had AE documented after receiving a prophylactic ICD but did not meet the 2013 guidelines for prophylactic ICD implantation (11), the relevant participating centers were asked to search for QRS fragmentation (QRS-f) in leads V1-V3 (12), which was previously reported as a good predictor for AE (8,12).

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 requiring appropriate ICD therapy was documented during follow-up.

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

HRS/EHRA/APHRS Expert Consensus Statement (11): Current international guidelines recommend prophylactic ICD implantation in 2 groups of patients: a) those with spontaneous type 1 Brugada-ECG presenting with syncope judged likely to be caused by ventricular arrhythmias (Class IIa indication); b) those with a spontaneous or drug-induced type 1 ECG with inducible VF by programmed ventricular stimulation (Class IIb indication).

STATISTICAL ANALYSIS.

Assumptions of normality of the age distributions amongst patient subgroups were assessed by Kolmogorov–Smirnov test and Q-Q plots. Differences between means of two groups of normally distributed ages were assessed using a Welch t-test. Differences between non-normally distributed ages were assessed using a Mann–Whitney U test for two groups, or a Kuraskal-Wallis test for three groups. Differences in proportions were assessed by a Chi-square test or a Fisher's exact test as appropriate. Statistical significance was defined as $p<0.05$. All calculations were performed using SPSS vs. 24 (IBM, Armonk, NY, USA).

RESULTS

THE SURVEY GROUP

Of the 628 patients enrolled in SABRUS, 575 (91.6%) were males and 53 (8.4%) females aged 0.27 to 84 (mean 42.5 ± 14.1) years old at the time of their first AE. The vast majority (96%) of patients were 16 to 70 years old. There were 355 (56.5%) Caucasians, 230 (36.6%) Asians and 43 (6.9%) who had other (2.1%) or unknown (4.8%) ethnic origin. Most patients (n=383, 61%) belonged to group A while the remaining 245 (39%) belonged to group B. A family history of SCD was noted in 138 (22%) patients, a prior history of syncope in 244 (38.9%) and a spontaneous type 1 Brugada-ECG pattern in 412 (65.6%). VF was induced in 242 (64.9%) of the 373 patients in whom EPS was performed. An *SCN5A* mutation was found in 131 (30.1%) of the 435 patients who underwent genetic testing.

COMPARISON BETWEEN GROUP A AND GROUP B

The clinical, ECG, EP and genetic findings of the patients in the 2 groups are presented in Table 1.

Demographics. The male/female ratio was similar in group A (n=11.3) and group B (n=10.1) (p=0.679). Group B patients were ~ 6 years older than group A patients at time of first AE (46.2 $\pm$ 13.2 vs. 40.1 $\pm$ 14.2 years, p<0.001). The incidence of AE was higher before age 37 in group A (43.3%) vs. group B (24.9%). 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 (41.5% vs. 29% in group B, p=0.001).

Clinical data. A family history of SCD was more frequently noted in group B (29%) compared with group A (17.5%) ($p<0.001$), as was a history of syncope (62% vs. 24%, $p<0.001$).

ECG data. Spontaneous type 1 Brugada-ECG was observed in similar proportions of groups A and B patients (63.4% and 69%, respectively) ($p=0.154$).

EP data. Group B patients underwent more EPS than group A ($P<0.001$) and had a greater proportion of positive results (73.2% vs 55.9% in group A, $p<0.001$).

Genetic data. A similar proportion of patients in both groups underwent genetic testing (71.5% and 65.7% for groups A and B, respectively). An *SCN5A* mutation was more frequently observed in group B (37.9%) than in group A (25.5%) ($p=0.007$). Among patients with a family history of SCD, the proportion of *SCN5A* mutation was slightly higher for group B patients (42.9% vs. 36.1% in group A), but the difference did not reach statistical significance ($p=0.452$).

DETAILED CHARACTERISTICS OF GROUP B PATIENTS.

Group B patients were divided into 3 subgroups according to their adherence with the Class II indications for ICD (11): a) Group B1 (Class IIa indication): 106 (43.3%) patients; b) Group B2 (Class IIb indication): 77 (31.4%) patients; c) Group B3 (neither Class IIa nor Class IIb indications): 62 (25.3%) patients. The clinical, ECG, EP and genetic findings of group B patients are presented in Table 2.

Although the proportion of females in group B3 was greater than in the other 2 groups, this difference was not statistically significant. However, a family history of SCD was more frequently noted in group B2 (39%) and group B3 (30.6%) as compared to group B1 (20.8%) ($p<0.01$ and $p<0.05$, respectively). No significant

difference was observed between the 3 subgroups in regard to age at first AE, ethnic origin and the presence of *SCN5A* mutation.

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 of the 62 group B3 patients are presented in Table 3. In 32 (51.6%) patients (group B3a) EPS was performed but yielded negative results while in the remaining 30 (48.4%) patients (group B3b) EPS was not performed. Table 4 provides a flowchart of the 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 (18.8% vs. 6.7%) but this difference did not reach statistical significance (p=0.258). QRS-f was found in ~ 30% of patients of either subgroup (31% and 30%, respectively) irrespectively of the presence of spontaneous type 1 Brugada-ECG.

When dividing group B into 3 almost equal subgroups according to the date of ICD implantation, there was a rise over the years of the proportion of patients who received an ICD without complying with conventional guidelines (Supplemental Table 2). 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.

We could not identify a single parameter uniting group B3 patients (besides the definition of not having a conventional class II indication) using a logistic regression multivariate model (Supplemental Table 3).

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.

MAIN SURVEY RESULTS.

The results gathered from these 628 BrS patients demonstrated 2 main findings: 1. Group B patients exhibited a later occurrence of AE and a higher incidence of family history of SCD and *SCN5A* mutations than group A; 2. Although ~ 75% of group B patients complied with the Class IIa and IIb indications for primary ICD implantation established by the Expert Consensus Statement, the remaining 25% patients did not.

COMPARISON BETWEEN GROUP A AND GROUP B.

The profile of group A patients from SABRUS was similar to previously reported 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 from both groups, there were marked differences between the 2 groups in regard to the age at onset of AE, patient ethnicity, family history of SCD, prior history of syncope, arrhythmia inducibility and genetic findings.

Age at onset of AE. Priori et al. noted that patients with first AE documented after prophylactic ICD implantation (8) were 14 years older than those presenting with aborted CA (13) (47 ± 12 vs. 33 ± 13 years, respectively). In SABRUS the initial AE occurred at a

mean age of 40.1 and 46.2 years in groups A and B, respectively, i.e ~ 6 years later in group B. This difference was attested by our data showing a higher incidence of AE in group A patients aged $\leq$ 37 years (43.2%) than in group B (24.9%). There are 2 possible explanations for this marked 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. Interestingly, in FINGER (3) (the largest European BrS series), the CA survivors group included only 62 patients while the syncope group and the asymptomatic group included 313 and 654 patients, respectively. In contrast, in the largest Asian BrS series from Thailand (7) (that were not included in SABRUS), 65 patients presented with aborted CA, 14 with unexplained syncope and 11 were asymptomatic. This difference in the mode of AE presentation between Caucasians and Asians could suggest a more malignant presentation of AE in Asians or a less effective screening program 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 (17.5%). It is noteworthy that in 3 large series of BrS patients (3,4,8) and in the prospective study of Sarkozy et al. (14), 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. These results cannot be directly compared to those of our survey since only a small proportion of the patients in the above mentioned studies exhibited AE during follow-up as compared to our group B patients who all exhibited AE. 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 that was documented after prophylactic ICD implantation (50%) (3) than in CA survivors (23.5%) (13). Similar results were found in SABRUS with figures of 62% and 24%, respectively. Such differences could be due to the fact that a previous syncope was one of the inclusion criteria in the B1 subgroup fulfilling Class IIa indications.

Arrhythmia inducibility. The results of SABRUS also showed a higher proportion of patients with inducible VF in group B (73.2% vs. 55.9% in group A). Such results are consistent with the fact that arrhythmia inducibility was the inclusion criterion in the B2 subgroup fulfilling Class IIb indications. 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. (15) indicated that an *SCN5A* gene mutation did not increase the risk of future cardiac events. In contrast a recent Japanese study showed that *SCN5A* mutation was a significant predictor of cardiac events in BrS probands (16). In SABRUS, an *SCN5A* mutation was more frequently observed in group B (37.9%) than in group A (25.5%) (p=0.007). The fact that a greater proportion of group B patients had a family history of SCD (29% vs. 17.5% 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 patients could explain our findings.

PROFILE OF GROUP B PATIENTS.

In addition to group B1 and group B2 who fulfilled Class IIa and IIb indications, respectively, the survey showed another sizeable group (B3, 25.3% of 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 patient 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 (17). In this latter study the incidence of AE during > 5 years follow-up was much higher in patients who fulfilled Class IIa indications (12%) than in those who fulfilled Class IIb indications (3%, p = 0.01). 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.

For the first time SABRUS presented in a large cohort of patients that AE can occur after prophylactic ICD implantation in a significant percentage of patients (25.3%) who do not fulfill Class II indications. This group comprised 2 subgroups of similar size: one in whom EPS did not induce arrhythmias (n=32) 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 (25.3% and 25%, respectively). Analysis of the PRELUDE results (8) showed that out of 14 patients without previous CA who exhibited an AE (after prophylactic ICD implantation in 13 patients) 5 (36%) did not fulfill Class IIa or Class IIb indications. The Pedro Brugada group (9) also reported a group of 6 non-inducible patients (2 asymptomatic and 4 with prior syncope) who did not comply with Class II indications and presented 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. In this regard, it is possible that the non-aggressive PVS protocol in the Pedro Brugada's laboratory (9,18) could have played a role in the non inducibility of the arrhythmias in their patients (9). However, a small annual incidence of AE (0.23 – 0.78) has also been observed in patients who had no arrhythmias induced using "standard" PVS protocols (19). In addition, in SABRUS the non-inducible group (B3a) included a relative high proportion of females who have been shown to exhibit a lower inducibility rate of VF than males (20). Thus it is tempting to speculate that a more aggressive PVS protocol (18,21) could have resulted in a higher inducibility rate of arrhythmias, enabling inclusion of the inducible patients in the B2 group.

The issue of patients in whom EPS was not performed and who received a prophylactic ICD not based on Class II indications, 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. This subgroup of patients represented a non-negligible fraction of group B patients in SABRUS (12.2%). They shared similar clinical and ECG characteristics as the subgroup of patients with negative EPS (B3a). However it is likely that performance of EPS in this subgroup of patients 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 that could raise suspicion of the very high arrhythmic risk of these patients. In this regard it is noteworthy that the total number of patients unnecessarily treated with a prophylactic ICD based on such non-conventional indications was unknown from our survey results.

CLINICAL IMPLICATIONS.

The results of SABRUS emphasize the need for improving diagnosis and screening of young patients with BrS in order to decrease the relatively high AE rate in this patient population. In addition they do 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 in spite 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. Our data suggest that major efforts should be made to assign these

patients to group B1 or B2: a) patients experiencing syncope should be thoroughly evaluated for differentiating neurally-mediated syncope from suspected arrhythmic syncope (22); b) when a spontaneous type 1 Brugada-ECG is not initially documented, close ECG monitoring should be instituted in order to detect its occurrence during follow-up especially in those patients who initially presented with syncope; c) patients who initially refused to undergo EPS for risk stratification should be encouraged to do so; d) repetition of double extrastimulation at the shortest coupling intervals (18) might be considered in order to increase sensitivity of the PVS protocol without affecting its specificity. However, one should recognize 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 that will prove justified despite the lack of strict adherence to Class II indications. We believe that this possibility should be kept to the minimum.

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. Despite our repeated efforts, we could not recruit more centers from other Asian countries (especially Thailand). The definitions of family history of SCD and syncope were left to the discretion of the participating centers. The information requested from the participant centers about the Brugada-ECG type only dealt with the patient's ECG pattern at ICD implantation; we cannot exclude that some of the patients with initial drug-induced type 1 Brugada ECG developed it later spontaneously. The protocol of PVS most probably varied among the survey centers, however the immense majority of centers used up to 3 extrastimuli from 1-2 right

ventricular sites. 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.

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 those of CA survivors. Although comprising mainly patients who complied with Class II indications for ICD established by the HRS/EHRA/APHRS Expert Committee, this group of patients also included a non-negligible proportion of patients who did not comply with these indications. 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, 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, Wilde AA 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, 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, Julià J, Pappaert G, Brugada P. 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;10:533-9.

6. Kim JY, Kim SH, Kim SS, Lee KH, Park HW, Cho JG, Uhm JS, Joung B, Pak HN, Lee MH, Park SJ, On YK, Kim JS, Lim HE, Shim J, Choi JI, Park SW, Kim YH, Lee WS, Kim J, Nam GB, Choi KJ, Kim YH, Oh YS, Lee MY, Rho TH. 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, Della Bella P, Ghidini Ottonelli A, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. 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, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, Saitoh Y, Irfan G, Casado-Arroyo R, Juliá J, La Meir M, Wellens F, Wauters K, Van Malderen S, Pappaert G, Brugada P. 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, Chierchia GB, de Asmundis C, Baltogiannis G, Di Giovanni G, Saitoh Y, Irfan G, Casado Arroyo R, Julià J, La Meir M, Wellens F, Wauters K, Pappaert G, Brugada P. Asymptomatic Brugada syndrome: clinical characterization and long term prognosis. *Circ Arrhythm Electrophysiol.* 2015;8:1144-1150.

11. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C; Document Reviewers, Ackerman M, Belhassen B, Estes NA 3rd, Fatkin D, Kalman J, Kaufman E, Kirchhof P, Schulze-Bahr E, Wolpert C, Vohra J, Refaat M, Etheridge SP,

Campbell RM, Martin ET, Quek SC. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace.* 2013;15:1389-1406.

12. 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.

13. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation*. 2002;105:1342-1347.

14. 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.

15. 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.

16. 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* (in press)

17. 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.

18. 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.

19. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K, Zorzi A, Champagne J, Kostopoulou A, Yin X, Napolitano C,Milan DJ, Wilde A, Sacher F, Borggrefe M, Ellinor PT, Theodorakis G, Nault I, Corrado D, Watanabe I, Antzelevitch C, Allocca G, Priori SG, Lubitz SA. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: A pooled analysis. *Circulation.* 2016;133:622-630.

20. Sacher F, Meregalli P, Veltmann C, Field ME, Solnon A, Bru P, Abbey S, Jaïs P, Tan HL, Wolpert C, Lande G, Bertault V, Derval N, Babuty D, Lacroix D, Boveda S, Maury P, Hocini M, Clémenty J, Mabo P, Lemarec H, Mansourati J, Borggrefe M, Wilde A, Haïssaguerre M, Probst V. Are women with severely symptomatic Brugada syndrome different from men? *J Cardiovasc Electrophysiol.* 2008;19:1181-1185.

21. 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 Nov;9(11). pii: e004185.

22. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N, Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. *Heart Rhythm.* 2015;12:367-375.

TABLE 1: Comparison between group A and group B

		Group A (n=383)	Group B (n=245)	P value
Gender				
	Male	352 (91.9)	223 (91)	0.679
	Female	31 (8.1)	22 (9.0)	
Patient age at AE				
	All patients (years)	40.1 ± 14.2	46.2 ± 13.2	<0.001
	< 16	15 (3.9)	4 (1.6)	
	16-70	365 (95.3)	238 (97.1)	0.276
	>70	3 (0.8)	3 (1.2)	
Ethnicity				
	Caucasian	195 (50.9)	160 (65.3)	
	Asian	159 (41.5)	71 (29)	<0.01
	Other	29 (7.5)	14 (5.7)	
Family history of SCD				
	Yes	67 (17.5)	71 (29)	<0.001
	No	278 (72.6)	147 (60)	
	Unknown	38 (9.9)	27 (11)	
Prior history of syncope				
	Yes	92(24)	152 (62)	<0.001
	No	291(76)	93 (38)	
Spontaneous type 1 ECG				
	Yes	243 (63.4)	169 (69)	0.154
	No	140 (36.6)	76 (31)	
VF inducibility				
	EPS performed	179 (46.7)	194 (79)	<0.001
	Yes	100 (55.9)	142 (73.2)	<0.001
	No	79 (44.1)	52 (26.8)	
Presence of *SCN5A* mutation				
	Testing done	274 (71.5)	161 (65.7)	0.123
	Yes	70 (25.5)	61 (37.9)	<0.01
	No	204 (74.5)	100 (62.1)	

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		106 (43.3)	77 (31.4)	62 (25.3)	
Gender					
	Male	97 (91.5)	72 (93.5)	54 (87.1)	0.410
	Female	9 (8.5)	5 (6.5)	8 (12.9)	
	M/F ratio	10.8	14.4	6.7	
Age					
	All patients	45 ± 12.6	48 ± 12.5	46.1 ± 14.8	0.294
	< 16	1 (0.9)	0 (0)	3 (4.8)	
	16-70	105 (99)	75 (97.4)	58 (93.5)	$<0.05^{\S,\alpha}$ □
	>70	0 (0)	2 (2.6)	1 (1.6)	
Ethnicity					
	Caucasian	66 (62.3)	54 (70.1)	40 (64.5)	
	Asian	36 (34)	17 (22.1)	18 (29)	0.409
	Others	4 (3.8)	6 (7.8)	4 (6.5)	
Family history of SCD					
	Yes	22 (20.8)	30 (39)	19 (30.6)	$<0.05^{*,\beta}$
	No	76 (71.7)	40 (51.9)	31 (50)	
	Unknown	8 (7.5)	7 (9.1)	12 (19.4)	
Prior syncope					$<0.001^{\ddagger,\beta}$
	Yes	106 (100)	20 (26)	26 (41.9)	
	No	0 (0)	57 (74)	36 (58.1)	
Type 1 ECG					$<0.001^{\ddagger,\Sigma}$
	Yes	106 (100)	37 (48.1)	26 (41.9)	
	No	0 (0)	40 (51.9)	36 (58.1)	
VF inducibility					
	EPS performed	85 (80.2)	77 (100)	32 (51.6)	<0.001
	Yes	65 (76.5)	77 (100)	0 (0)	
	No	20 (23.5)	0 (0)	32 (100)	$<0.001^{\ddagger,\Sigma,\mu}$
***SCN5A* mutation**					
	Testing done	65 (61.3)	53 (68.8)	43 (69.4)	0.448
	Yes	25 (38.5)	15 (28.3)	21 (48.8)	0.118
	No	40 (61.5)	38 (71.7)	22 (51.2)	

§ $p<0.05$ B3 vs B1, α $p<0.05$ B3 vs B2, * $p<0.01$ B1 vs B2, β $p<0.05$ B1 vs B3, ‡ $p<0.001$ B1 vs B2, ∑ $p<0.001$ B1 vs B3, μ $p<0.001$ B2 vs B3.

TABLE 3. Comparison between B3 subgroups

		B3a No Class IIa or IIb Non inducible VF	B3b No Class IIa or IIb EPS not performed	P value
No of patients		32 (51.6)	30 (48.4)	
Gender				
	Male	26 (81.3)	28 (93.9)	0.258
	Female	6 (18.8)	2 (6.7)	
Age				
	All patients	46.9 ± 16	45.2 ± 13.7	0.651
	< 16 years	2 (6.3)	1 (3.3)	
	16-70	29 (90.6)	29 (96.7)	1.00
	>70 years	1 (3.1)	0 (0)	
Ethnicity				
	Caucasian	24 (77.4)	16 (59.3)	
	Asian	7 (22.6)	11 (40.7)	0.136
	Others	0 (0)	0 (0)	
Family history of SCD				
	Yes	11 (34.4)	8 (26.7)	0.833
	No	17 (53.1)	14 (46.7)	
	Unknown	4 (12.5)	8 (26.7)	
Prior syncope				
	Yes	14 (43.8)	12 (40)	0.765
	No	18 (56.3)	18 (60)	
Type 1 ECG				
	Yes	14 (43.8)	12 (40)	0.765
	No	18 (56.3)	18 (60)	
VF inducibility				
	EPS performed	32 (51.6)	0 (0)	<0.001
	Yes	0 (0)	0 (0)	N/A
	No	32 (100)	0 (0)	
***SCN5A* mutation**				
	Testing done	23 (71.9)	20 (66.7)	0.657
	Yes	11 (47.8)	10 (50)	0.887
	No	12 (52.2)	10 (50)	

TABLE 4. Flow chart of ICD indications in subgroup B3

EPS		EPS: No Inducible Arrhythmias n=32 No Syncope + Spontaneous Type 1 ECG			
Symptoms		Asymptomatic 18 (56.3%)		Syncope 14 (43.8%)	
ECG		ST1 + 14 (77.8%)	ST1 - 4 (22.2%)	ST1 + 0 (0%)	ST1 - 14 (100%)
M/F		13/1	4/0	0/0	9/5
Fragmented QRS	Yes	5	1	0	4
	No	7	1	0	9
	N.A	2	2	0	1
Family history SCD	Yes	4	1	0	6
	No	9	1	0	7
	N.A	1	2	0	1
SCN5A		5	2	0	4

EPS		EPS: Not Performed n=30 No Syncope + Spontaneous Type 1 ECG			
Symptoms		Asymptomatic 18 (60.0%)		Syncope 12 (40.0%)	
ECG		ST1 + 12 (66.7%)	ST1 - 6 (33.3%)	ST1 + 0 (0%)	ST1 - 12 (100.0%)
M/F		12/0	4/2	0/0	12/0
Fragmented QRS	Yes	5	1	0	3
	No	3	3	0	7
	N.A	4	2	0	2
Family history SCD	Yes	5	3	0	0
	No	3	0	0	9
	N.A	4	3	0	3
SCN5A		5	3	0	2

SUPPLEMENTAL TABLE 1: List of participating centers

Country	Center	No Patients (%)
France	Multiple	130 (20.5)
Japan	Multiple	119 (18.9)
Italy	Multiple	84(13.5)
South Korea	Multiple	79(12.6)
Belgium	Multiple	48(7.6)
Netherlands	Single	33(5.3)
Israel	Multiple	31(5.1)
Spain	Multiple	25(4)
China	Multiple	25(4)
UK	Single	20(3.2)
Germany	Single	17(2.7)
Denmark	Single	10(1.6)
Canada	Single	7(1.1)

SUPPLEMENTAL TABLE 2: Proportion of B1, B2 and B3 patients over time.

	1st third (n=81)	2nd third (n=82)	3rd third (n=82)	All group B (n=245)
Periods	01/09/1987- 19/06/2003	25/06/2003 - 04/05/2007	16/05/2007- 04/12/2015	
Group B1	36 (44.4)	36 (43.9)	34 (41.5)	106 (43.3)
Group B2	31 (38.3)	26 (31.7)	20 (24.4)	77 (31.4)
Group B3	14 (17.3)	20 (24.4)	28 (34.1)	62 (25.3)
B3a	10 (12.3)	9 (11)	13 (15.8)	32 (13.1)
B3b	4 (4.9)	11 (13.4)	15 (18.3)	30 (12.2)

SUPPLEMENTAL TABLE 3: Logistic regression analysis

Parameter	OR [95% CI]	p-value
Gender	0.72 [6.29-0.173]	0.173
Ethnicity	0.33 [2.3-0.774]	0.774
Family history of SCD	0.38 [1.91-0.706]	0.706
SCN5A mutation	0.72 [3.4-0.256]	0.256