Age of First Arrhythmic Event in Brugada Syndrome: Data From the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 Patients.

Age of First Arrhythmic Event in Brugada Syndrome: Data from the Survey on Arrhythmic Events in Brugada Syndrome (SABRUS) in 678 Patients

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Abstract

Background. Data on the age at first arrhythmic event (AE) in Brugada syndrome (BrS) are from limited patient cohorts. The aim of this study is twofold: 1) to define the age of first AE in a large cohort of BrS-patients; 2) assess the influence of the mode of AE documentation, gender and ethnicity on the age of first AE.

Methods and Results. A survey of 23 centers from 10 Western and 4 Asian countries gathered data from 678 BrS-patients (91.3% males) with first AE documented at time of aborted cardiac arrest (Group A, n=426) or after prophylactic ICD-implantation (Group B, n=252). The vast majority (94.2%) of the patients were 16-70 years old at the time of AE while pediatric (<16 years) and elderly patients (>70 years) comprised 4.3% and 1.5%, respectively. Peak AE rate occurred between 38-48 years (mean 41.9$\pm$14.8, range 0.27 to 84 years). Group A patients were younger than in Group B by a mean of 6.7 years (46.1$\pm$13.2 vs. 39.4$\pm$15.0 years, P<0.001). In adult patients ($\geq$16 years), females experienced AE 6.5 years later than males (P=0.003). Caucasians and Asians exhibited their AE at the same median age (43 years).

Conclusions. SABRUS presents the first analysis on the age distribution of AE in BrS, suggesting 2 age cut-offs (16 and 70 years) that might be important for decision-making. It also allows gaining insights on the influence of mode of arrhythmia documentation, patient gender and ethnic origin on the age of AE.

Keywords: Sudden Cardiac Death, ICD, Caucasian, Asian, Screening

Brugada syndrome (BrS) is an inherited arrhythmic disorder that may result in sudden cardiac death (SCD)[1]. BrS is estimated to account for 4% of all SCDs and for 20% of all SCDs in patients with apparently normal hearts[2]. BrS is more prevalent in Asia than in Europe and in the United States[1]. Despite its autosomal-dominant mode of transmission there is a male predominance among patients with aborted cardiac arrest (CA), even more so in those originating from South-East Asia[3,4]. Malignant ventricular arrhythmic events (AE) are documented either at patient presentation due to aborted cardiac arrest (CA) or after prophylactic ICD-implantation. The first AE typically occurs in male patients aged 40-50 years[5-8] and rarely during childhood[9,10] or in the elderly[11,12].

However, these data are from limited patient cohorts, the largest in Europe being the FINGER Brugada syndrome registry[5] that gathered 62 patients with aborted CA from 4 European countries.

In order to clarify the issue of AE in BrS we have recently organized a multicenter international survey (Survey on Arrhythmic events in BRUgada Syndrome, SABRUS) that enabled data collection on a large cohort of 678 BrS-patients with AE from multiple Western and Asian countries.

The present study has 2 objectives: 1) to define the age of first AE in a large cohort of BrS-patients originating from Western and Asian countries; 2) to assess the influence of the mode of AE documentation, gender and ethnic origin on the age of first AE.

METHODS

The data that support the findings of this study are available from the corresponding author or the first author (anatmilman@gmail.com) upon reasonable request.

DATA SOURCE AND CENTER SELECTION. A Medline search was used to locate academic electrophysiology (EP) centers involved in BrS. The search, limited to English language articles published between 1992 - year of the principle publication of the syndrome[13] - and April 2016, included all clinical publications with no limitation to patient age. All major EP-centers with publications reporting AE in BrS were eligible for inclusion.

Meta-analyses and case reports were excluded. When data from multicenter studies were provided, the data-origin of each center was specifically requested and carefully checked in order to prevent any duplication in data collection.

CENTER RECRUITMENT. Twenty-three (85%) of the 27 contacted centers agreed to participate. Sixteen (69.5%) centers provided data from their institution only, whereas the remaining 7 (31.5%) provided data from multiple institutions from their countries. The French center that coordinated FINGER (France, Italy, Netherlands, Germany BrS-registry)[5] provided data from multiple (n=20) French centers only. The number of patients provided by each of the 23 centers ranged from 7 to 105 patients. All 23 centers but 2 attested that there was no limitation of age in the recruitment of patients.

The survey gathered 678 patients in total: 415 (61.2%) from 10 Western countries and 263 (38.8%) patients from 4 Asian countries. The countries of origin of the patients are listed in Supplemental Table 1.

DATA ACQUISITION. The study was approved by the Tel-Aviv Medical Center Institutional Review Board committee. Study inclusion criteria consisted of 1) a typical Brugada type-1 ECG either spontaneously or following the intravenous administration of a sodium channel blocker; 2) a first documented AE. Participating centers were sent a questionnaire and were asked to provide anonymous information on clinical, ECG, EP and genetic findings for each of their patients, including: 1) mode of AE documentation (group A or group B, see below); 2) patient's age at the time of their first AE; 3) patient's gender; 4) patient's proband status; 5) patient's ethnicity (Caucasian, Asian, other or unknown). Only patients for whom the entire questionnaire was completed were included.

The patients were classified in 2 groups according to the mode of AE documentation: Group A: Patients with documented aborted CA 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 therapy was documented during follow-up by ICD interrogation.

In addition, 22 of the 23 centers were able to provide the age and gender distribution of the entire BrS-population followed at their own center (with or without prior AE). The centers from Western and Asian countries were assumed to include Caucasian and Asian patients, respectively (see Results section below). The number of AE collected in SABRUS by these same centers was also determined. An "estimated AE rate" for each age group by gender, mode of AE documentation and ethnicity was calculated by dividing the number of patients

with AE collected in SABRUS by the number of patients collected in the BrS-registry from the same centers.

DEFINITIONS.

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.

Age cut-offs: We defined an upper age cut-off of 16 years for the pediatric patient group based upon the exclusion of patients aged <16 years in the FINGER Registry[5] and the fact that 70% of AE occurred before age of 15 years in the largest pediatric series[10]. Taking into account the results of 2 studies showing the rarity of AE in BrS-patients >70 years[11,12], we also defined an upper age cut-off of 70 years for the elderly. Patients' age at time of AE was allocated to 5 bins of 11 years between these 2 age cut-offs.

STATISTICAL ANALYSIS. Assumptions of normality of the general age distribution and the age distribution amongst patient subgroups were assessed by Kolmogorov–Smirnov test and Q-Q plots. Differences in means 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. Ratio differences were examined by a Chi-square test or a Fisher's exact test as appropriate. Significance of differences between curves of cumulative event occurrence by age was assessed using a Mantel–Cox test. Statistical significance was defined as $P<0.05$. Numerical data are presented as mean±SD for normally distributed variables or as Median [IQR] for not normally distributed variables. All calculations were performed using SPSS version 24 (IBM, Armonk, NY, USA).

RESULTS

STUDY PATIENT COHORT (Table 1). Complete information was provided for 678 patients, 619 (91.3%) males and 59 (8.7%) females aged 41.9±14.8 years at the time of their first AE. Most patients (n=426, 62.8%) belonged to group A while the remaining 252 (37.2%) belonged to group B. Of the 678 patients, 364 (53.7%) were Caucasians, 270 (39.8%) patients were Asians and 14 (2.1%) were of other ethnic origin. Ethnicity was unavailable for 30 (4.4%) patients. Seven (1.7%) of the 415 patients from Western countries had an Asian origin while no patient from Asian countries was Caucasian.

The great majority (79.9%) of the survey patients were probands, 13% of patients were diagnosed during family member screening while no information on the proband status was available for the remaining 7.1%. Distribution of proband status by age group is shown in Supplemental Fig. 1.

AGE AT FIRST ARRHYTHMIC EVENT. The age of first AE was not normally distributed, with a left tail representing a higher occurrence in the pediatric group. Exclusion of pediatric patients resulted in a normally distributed age with a mean age of 43.5±12.9 years. Ages in the entire cohort ranged from 0.27 to 84 years. The vast majority of patients (n=639, 94.2%) were 16 to 70 years old, 29 patients (4.3%) belonged to the pediatric group (age <16 years) and 10 patients (1.5%) to the elderly group (age >70 years) (Fig. 1A). Peak AE rate occurred in the 38-48 years age group (n=204 patients, 30.1% of all study patients). The AE rate more than doubled from 4.3% (n=29, 86.2% from group A) before age 16 to 9.7% between ages 16-26 years (n=66, 78.8% from group A). In the pediatric group,

the median age was 4 [1.6-10.4] years and 17 (58.6%) of the 29 AE occurred in children aged ≤5 years old. In the elderly group the 2 oldest patients were 84 years old.

MODE OF AE DOCUMENTATION. The mean age at first AE was significantly lower in group A than in group B (39.4±15.0 vs. 46.1±13.2 years, P<0.001) (Fig. 2A). The majority of pediatric patients (86.2%) and two thirds of the elderly patients belonged to group A. Overall, group A maintained a significant earlier occurrence of AE (P<0.001) (Fig. 2B).

GENDER DISTRIBUTION. Age was normally distributed in males, while the female distribution was abnormal due to a high prevalence of AE in females in the pediatric group. Females exhibited their AE at a similar median age as males (46 [28-58] vs. 42 [33-52], P=0.255) (Fig. 3A). After filtering out pediatric patients from the entire cohort, both gender groups were normally distributed and age at onset of AE was significantly higher in females (mean 49.5±14.4 vs. 43.0±12.7, P=0.003). In the pediatric group (age<16, n=29), the male predominance was significantly lower than in the rest of the cohort (65.5% vs. 92.4%, P<0.001). Above the age of 49 years, male predominance was also lower (87.7% vs. 92.8%, P=0.029). Fig 3B highlights how the occurrence of AE at an earlier age depends on gender and age group (i.e. AE occurs earlier in females up to 38-48 years, then this trend reverses afterwards).

ETHNIC DISTRIBUTION. Due to the small number of patients of other ethnicity, only comparisons between Caucasians and Asians were performed. Caucasians and Asians exhibited their AE at the same median age (43 [31-53] and 43 [34.8-51.2] years, respectively, P=0.285) (Fig. 4A). Only 1 of 26 patients with known ethnicity in the pediatric group and 2 of 9 patients in the elderly group were

Asian (Fig. 4A), but overall there was no ethnical difference in the age at onset of AE (Fig. 4B).

Patients from Japan (n=119), South Korea (n=79), and Taiwan (n=40) exhibited their AE at similar ages (45.0±12.3 vs. 43.2±12.3 vs. 42.4±14.1 years, respectively, P=0.442). However, patients from China (n=25) exhibited their AE at a younger age than patients from the other Asian countries (37.0±7.0 vs. 43.9±12.6 years, P<0.001)

MULTIFACTORIAL ANALYSIS. The age of onset at AE was similar in males and females from both group A and group B (Supplemental Table 2A). The age of onset at AE in both groups was not affected by patient ethnicity (Supplemental Table 2A).

The age of onset of AE in both females and males was higher in group B patients (P<0.05) and not affected by ethnicity (Supplemental Table 2B). The age of onset at AE in both Caucasian and Asian patients was higher for group B (P<0.001) and not affected by gender (Supplemental Table 2B).

BrS REGISTRY AND ESTIMATED AE RATE.

Data on patient gender and age distribution were provided by 22 SABRUS centers and included as the BrS registry. The registry comprised 6441 patients (73.4% males). The vast majority (92.5%) of patients were 16-70 years old, while pediatric (<16 years) and elderly patients (>70 years) comprised 4.7% and 2.8%, respectively (Fig. 1B). Age distribution of the 6441 registry-patients showed a single peak in the 38-48 years age group in males (28.2% of the male patients) and a single peak in the 49-59 years age group in females (26.8% of the female patients) (Fig. 5A). There were significantly less

patients of Asian ethnicity in the extreme age groups of <16, 16-26 and >70 ($p<0.005$) of the registry (Fig. 5B).

The estimated total AE-rates, based on the 500 AE documented in these 22 centers, ranged from 6.6% to 7.8% up to age 70 before dropping to 3.9% thereafter (mean 7.1%) (Fig. 6A). The mean estimated rates of AE presenting as aborted CA (group A) or after a prophylactic ICD-implantation (group B) were 4.8% and 2.9%, respectively ($p<0.001$) (Fig. 6B). The mean estimated AE-rates were significantly higher in males (8.6%) as compared to females (2.9%) ($P<0.001$) (Fig. 6C). The estimated AE-rate in Asian patients (25.5%) was significantly greater than that in Caucasians (4.7%) ($P<0.001$) (Fig. 6D).

DISCUSSION

SABRUS includes the largest cohort of BrS-patients with documented AE ever reported. The results gathered from 678 BrS-patients confirm those previously reported regarding the male prevalence (91.3%) and the mean age of AE between the 4th and 5th decade. The survey highlights 5 main findings: 1) the distribution of the age at AE occurrence in BrS-patients and the paucity of AE in the pediatric and elderly population (4.3% and 1.5%, respectively); 2) the absence of male predominance in pediatric and elderly patients; 3) an earlier age at onset of AE (by a mean of 6.7 years) in patients who presented with aborted CA, compared to those who suffered from an AE documented after prophylactic ICD-implantation; 4) a later presentation (by a mean of 6.5 years) of first AE in female adults; 5) no difference between the age at onset of AE in Caucasian and Asian patients.

AGE AT FIRST AE IN BRUGADA SYNDROME. Information on the age of onset of AE in BrS is limited to relatively small series mainly involving CA survivors. FINGER, the

largest European multicenter study included 62 CA survivors[5]. The age of patients at AE ranged from 35 to 54 (mean 43) years; however, this study did not include patients aged <16 years. Makarawate et al. from Thailand[3] reported 65 patients with aborted CA aged 44.2±8.8 years. Kawata et al.[6] reported on 49 BrS-patients with VF from 2 Japanese institutes; the age of patients at AE ranged from 22 to 73 (mean 46±13) years. In a Japanese multicenter study involving 33 patients, VF occurred at a mean age of 49±14 years[7]. The report of the 20-year experience of the Pedro Brugada group by Conte et al.[8] identified 25 CA-survivors with a mean age of 39.5±15.6 years (range 6 days to 61 years) at the time of CA. The results of SABRUS in a large cohort of patients with AE documented during aborted CA or after prophylactic ICD-implantation, that were obtained from 23 centers (21 of them with no age limitation at recruitment) revealed a wide range of ages from 0.27 to 84 years. The vast majority (94.2%) of AE's occurred between 16 and 70 years of age, whereas AE's were rare (4.3%) in patients aged <16 years and even more so (1.5%) in those aged >70 years. The latter 2 findings are consistent with the paucity of publications dealing with these 2 patient populations[9-12].

SABRUS showed that 98.9% of males and 94.9% of females exhibited their AE at age ≤70 years. Sarkozy et al.[14] excluded patients aged >65 years in their assessment of the possible predictive role of familial SCD in future AE. The present study suggests that a positive family history of SCD might still be clinically relevant up to 70 years of age in the affected family member although the risk of AE resulting from coronary heart disease is higher in this patient-population.

AGE OF AE AND THE MODE OF AE DOCUMENTATION. In SABRUS, most (62.8%) patients exhibited their initial AE at the time of their CA without an ICD (group A),

while the remainder (37.2%) experienced their AE after prophylactic ICD-implantation (group B). In group A, the AE occurred 6.5 years earlier. This confirms previous results by Priori et al. who also found a significant age difference (14 years) between patients presenting with aborted CA (33±13 years)[15] compared to those who had AE documented after prophylactic ICD-implantation (47±12 years)[16].

More importantly, our results showed an inverse relationship over time between the number of AE presenting as aborted CA and the number documented by appropriate ICD-therapy, with a 1:1 ratio achieved in the 38-48 year age group. These findings may suggest a more malignant character of AEs that strikes patients at a younger age in group A.

AGE OF AE AND GENDER DISTRIBUTION. Previous studies have shown a male predominance of patients experiencing AEs in Western countries (64%-94%)[5,8,17] which is further exaggerated in South Eastern Asian countries (94%-100%)[3,4,6,7]. The electrophysiological mechanism underlying this male predominance and the role of testosterone in the development of Brugada-ECG pattern and VF have been studied previously[18-20]. Also, steroid hormone-responsive elements, particularly sensitive to testosterone in genes involved in BrS such as SCN5A (which encodes the cardiac sodium channel) and CACNA1C (which encodes the L-type calcium channel) have been identified[21]. The SABRUS cohort also showed a strong male predominance (91.3%). However, this predominance disappeared in 2 age groups: a) the pediatric group (<16 years) and b) the group aged >49 years (Fig. 3A). These data raise the possible involvement of female hormones such as estrogens. Estradiol is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity. In contrast, its level is lowest in the pediatric population

and after menopause. Song et al.[22] showed that estrogen may regulate the expression of I_{to}-channels by diminishing the transcription of Kv4.3. This protective nature of a smaller I_{to} density in the right ventricular epicardium of females may decrease the propensity for arrhythmias although this is still debated. One may speculate, however, that in the setting of low estrogenic activity in the pediatric population and after menopause, the propensity for arrhythmias increases. In addition, adult females exhibited their AE much later than males, which might also be explained in part by the relative protective effect of estradiol.

AGE OF AE AND ETHNICITY. A similar age at first AE was observed in Caucasian and Asian patients in our survey. In South-East Asia there is an endemic syndrome of sudden unexpected nocturnal death (SUNDS) occurring in young and middle-aged male patients that has been assumed to be mainly caused by BrS[23-28]. However, the vast majority of decedents in Asians with SUNDS are aged 20 to 40 years[29], i.e. much younger than the Asian patients' age at onset of AE in SABRUS (42.3±14.9 years). Furthermore, a series of 50 British autopsy negative sudden deaths [in the setting of sudden arrhythmic death syndrome (SADS)] of mainly Caucasian origin (Elijah Behr MD, personal communication, 2016) and with a familial diagnosis of BrS, demonstrated a mean age at death of 29.1±10.6 years[30]. A possible explanation for the difference in age at AE between SUNDS and SADS patients and those of our survey could be that these 2 patient populations are a different part of the disease spectrum, failing to survive cardiac arrest and/or being less likely to present with prior warning symptoms than SABRUS cases.

Interestingly, we found a significant difference of age at onset of AE between Japan, Taiwan and South Korea vs. China. Since the Chinese cohort was small, this point

should be interpreted with caution. However, it is possible that this difference could be related to genetic variation between these countries[28] and represent the spectrum of the disease in Asian countries. Another important aspect of ethnicity is found in the extreme age groups of SABRUS, which comprised little if any Asian patients (Fig. 4A). The reason for this finding is unclear.

BrS REGISTRY AND ESTIMATED AE RATE.

Data provided from 22 main SABRUS centers allowed to establish a registry of 6441 patients that comprises ~6-fold and 12-fold more patients than the FINGER[5] and the Pedro Brugada[31] registries, respectively, which are the largest available BrS-registries to date. A male predominance (73.3%) was found that was similar to that observed in FINGER (72%)[5] but higher to that of the Pedro Brugada group (58%)[31]. In addition, males had a peak age at diagnosis in the 38-48 years age group while females were diagnosed later in the 49-59 years age group, in agreement with the FINGER results[5], showing median ages of 45 and 49 years for males and females, respectively (P=0.03). Of note, our registry included 4.6% of pediatric patients as opposed to FINGER that did not include any patients aged <16 years. In addition, the proportion of probands in our survey (79.9%) was similar to that found in FINGER (78%)[5], while non-probands predominated in the Pedro Brugada series (67%) assumedly due to an exhaustive familial screening program established at their institution[31].

The estimated AE rates obtained from 22 centers which provided registry data deserve further discussion. The estimated mean AE-rate for the entire cohort was 7.1%. However, a lower rate (3.9%) was found in the elderly population (P=0.088), a finding that is consistent with the paucity of AE's found in the SABRUS population as well (Fig.

1A). Interestingly the pediatric group had an estimated AE-rate (8%) similar to adult patients suggesting that although BrS is rarely diagnosed in the pediatric population, the arrhythmic risk is not negligible once the diagnosis of BrS is made. However, we cannot exclude that this result could merely be due to detection bias. In addition, our analysis of the estimated total AE-rate after excluding pediatric patients showed a figure (7.75%) similar to that of the FINGER-registry (6%) which did not include pediatric patients. Finally, it confirmed the considerable higher arrhythmic risk in males as compared to females, and in Asians as compared to Caucasians.

CLINICAL RELEVANCE. The results of SABRUS highlight 2 special populations:

1. ***Pediatric population:*** Since the vast majority of our pediatric population presented with aborted CA (86%) and were probands (74% of patients with known proband status), prevention of SCD seems to be a difficult task in children, especially in Caucasians who constituted the vast majority of this age group. In addition, the ideal timing of screening asymptomatic first-degree relatives of BrS-patients is unknown. Taking into account the marked increase of AE rate in patients aged 16-26 years (9.7%) compared to that in patients <16 years (4.3%) observed in our survey, it would seem advisable to recommend screening before age 16. However, performing ECG screening and provocative drug testing during childhood has been shown to carry a low yield for predicting future AE[9,10] and has been associated with serious complications in some patients[9]. In addition, Conte et al.[32] found that in 23% of children (aged 11.4+2.5 years) with a negative Ajmaline challenge test, BrS will be unmasked when the test is repeated several years later (age 20.9+4.2 years). Therefore, in asymptomatic patients with periodical normal ECG adopting a cut-off of 16 years for sodium channel blocker challenge would seem reasonable and in agreement with the cut-off of 15 years

previously suggested by Andorin et al.[10]. This does not preclude periodical ECG and clinical assessment in the under-16 group and careful genetic counseling of the parents if a clear pathogenic variant is present in a family member[9,10].

2. Elderly population: At present, there are no guidelines for an age-limit at which ICD should not be replaced upon battery depletion except for patients with terminal illnesses and projected life expectancy ≤6 months. Thus, ICD should be theoretically replaced until patient's natural death. The results of SABRUS showing the extreme rarity of AE in BrS-patients after age 70 (especially those of Asian ethnicity), along with the relatively low estimated AE rate in the elderly population would support careful consideration and discussion of withholding ICD replacement for those patients who have received a prophylactic ICD and reached the age of 70 years without having AE.

STUDY LIMITATIONS. This is not a multicenter prospective study but rather a retrospective cumulative analysis of results from the largest EP-centers that have experience with BrS. Despite our repeated efforts, we could not recruit more centers from other Asian countries (such as from Thailand). Nevertheless, it is noteworthy that the number of patients provided per Asian center was much higher than that provided per center from Western countries. We cannot exclude that the low reported AE rate in the pediatric and the elderly population may be related in part to misdiagnosis of the etiology of the AE at these ages.

CONCLUSION

SABRUS is a retrospective analysis of multicenter data from 23 well-recognized centers in the management of BrS worldwide. This survey confirms the male predominance and the peak age of AE at the early 4th decade of life. It also presents for the first time the age distribution of AE in BrS, suggesting 2 age cut-offs (16 and 70 years) that may

be important for decision-making. Finally, it allows an analysis of the influence of mode of arrhythmia documentation, patient gender and ethnic origin on the age of onset of AE in a large BrS-population. Hopefully this will ultimately result in both a significant decrease in SCD-rate of BrS-patients and in a decrease of the number of unnecessarily treated patients.

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Table 1. Main patients characteristics in SABRUS.

		SABRUS
Number of patients		678
Age at AE	Range (years)	0.27-84
	(Mean ± SD)	41.9±14.8
Age distribution	<16 years	29 (4.3)
	16≥ years ≤70	639 (94.2)
	>70 years	10 (1.5)
Group	A	426 (62.8)
	B	252 (37.2)
Gender	Male	619 (91.3)
	Female	59 (8.7)
Country of origin	Western	415 (61.2)
	Eastern	263 (38.8)
Ethnicity	Caucasian	364 (53.7)
	Asian	270 (39.8)
	Unknown	30 (4.4)
	Other	14 (2.1)
Proband	Yes	542 (79.9)
	No	88 (13)
	Unknown	48 (7.1)
Family history of SCD	Yes	145 (21.4)
	No	468 (69)
	Unknown	65 (9.6)
Prior syncope	Yes	265 (39.1)
	No	413 (60.9)
Spontaneous type 1-ECG	Yes	451 (66.5)
	No	227 (33.5)
EPS	Performed	400 (58.9)
Inducible arrhythmia	Yes	253 (63.2)
	No	147 (36.8)
Genetic testing	Performed	485 (71.5)
SCN5A mutation	Yes	143 (29.5)
	No	342 (70.5)

Abbreviations: n (%) unless otherwise indicated.

AE = arrhythmic event; ECG = electrocardiogram; EPS = electrophysiologic study; Group A = cardiac arrest survivors; Group B = patients who received an appropriate discharge from their ICD after prophylactic implantation; SCD = sudden cardiac death.

Figures legends

Figure 1. Age distribution of AE in the 678 SABRUS patients (A) and in the 6441 patients of the Registry (B). In both instances, the age of first AE is normally distributed with a single peak in the 38-48 years age group. Note that the age distribution is similar in both patient groups.

Figure 2. Age distribution by mode of AE documentation in SABRUS.

A. The mean age at first AE is significantly lower in group A than in group B.

B. The occurrence of AE is significantly earlier in group A which is maintained in older age groups.

Figure 3. Age distribution by gender in SABRUS.

A. Age is normally distributed in males, while the female distribution is abnormal due to a high prevalence of AE in females of prepubescent age. Females exhibit their AE at a significantly older age than males.

B. AE occurs earlier in females up to ages 38-48 years then this trend reverses and males suffer more from AE .

Figure 4. AE distribution by ethnicity in SABRUS.

A. Caucasians and Asians exhibit their AE at similar mean ages. Note that only 1 of the 26 patients with known ethnicity in the pediatric group and 2 of the 9 patients of the elderly group are Asians,

B. Cumulative incidence of AE by age in Caucasian and Asian patients. Overall there is no difference in the age of AE.

Figure 5. Data from the 6441 patients of the Registry according to gender (A) and ethnicity (B). Peak incidence for BrS diagnosis for males is observed in the 38-48 years age group in males and in the 49-59 years age group in females (A). Ethnicity distribution does not

differ between Caucasians and Asians, with a similar peak incidence in the 38-48 years age group (B).

Figure 6. Estimated AE rates.

A. In all age groups. The AE rate is similar throughout all age groups with the exception of the elderly group (P=0.088 vs. the non-elderly group).

B. According to mode of AE documentation. The AE rate is higher in group A than group B up to the age of 49, there after there is no difference. *P<0.01, †P<0.001.

C. According to gender. The AE rate is higher in males than females except for the pediatric and elderly patients. *P<0.01, †P<0.001.

D. According to ethnicity. The estimated AE rate is significantly higher in Asians than Caucasians in all age groups except for the pediatric and elderly group (P<0.001). Note that there are no Asians who suffered an AE in the pediatric population. †P<0.001.