Asymptomatic Brugada Syndrome: Clinical Characterization and Long Term Prognosis

Running title: Sieira et al.; Asymptomatic Brugada Syndrome

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Abstract:

**Background** - Among BS patients, asymptomatic individuals are considered to be at the lowest risk. Nevertheless, arrhythmic events and sudden cardiac death (SCD) are not negligible. Literature focused on this specific group of patients is sparse. The purpose of the present study is to investigate the clinical characteristics, management and long term prognosis of asymptomatic Brugada syndrome (BS) patients.

**Methods and Results** - Patients presenting with spontaneous or drug-induced Brugada type I electrocardiogram (ECG) and no symptoms at our institution were considered eligible. A total of 363 consecutive patients (200 males, 55.1%; mean age: 40.9±17.2 years, 41 (11.3%) with spontaneous type I ECG) were included. Electrophysiological study (EPS) was performed in 321 (88.4%) and ventricular arrhythmias (VA) were induced in 32 (10%). An implantable cardioverter defibrillator (ICD) was implanted in 61 (16.8%). After a mean follow-up time of 73.2±58.9 months, 9 arrhythmic events occurred, accounting for an annual incidence rate of 0.5%. Event free survival was 99.0% at 1 year and 96.2% at 5 years, 95.4% at 10 and 15 years. Univariate analysis identified as risk factors EPS inducibility (HR 11.4, p<0.01), spontaneous type I (HR 4.0, p=0.04) and previous sinus node dysfunction (SND) (HR 8.0, 95% CI 1.0 – 63.9, p=0.05). At the multivariate analysis only inducibility remained significant (HR 9.1, p<0.01)

**Conclusions** - Arrhythmic events in asymptomatic BS patients are not insignificant. VA inducibility, spontaneous type I ECG and presence of SND might be considered as risk factors and used to drive long term management.

**Key words:** Brugada syndrome, risk stratification, asymptomatic, prognosis
Introduction

Brugada syndrome (BS) is an inherited syndrome characterized by coved-type ST-segment elevation in the right precordial leads (V1-V3) and increased risk of sudden cardiac death (SCD) in the absence of structural heart disease\(^1\).

The placement of an implantable cardioverter-defibrillator (ICD) remains the therapy with most proven efficacy to prevent SCD in patients with BS\(^2,3\). Therefore, identifying patients at higher risk for ventricular arrhythmias (VA) is of utmost importance.

Presentation as SCD or syncope has been consistently identified as risk factors for events by different investigators\(^4,5\). Nevertheless arrhythmic events in asymptomatic patients are not insignificant\(^4,6,7\). Risk stratification of asymptomatic BS patients remains challenging and controversial. Literature focused in this group is sparse and usually mixes asymptomatic patients and those with previous syncope\(^8,9\). Furthermore, data on long-term follow-up (longer than 5 years) of BS patients is infrequent; none of the major BS registries have a mean follow-up longer than 40 months\(^10,11\). As the risk of sudden death in BS patients is a lifelong issue, longer follow-up is necessary to help clarify this question.

The purpose of this study was to analyze our single-center 20 years’ experience in asymptomatic BS patients, with focus on arrhythmic events predictors search.

Methods

Study population

Since 1992 all consecutive patients diagnosed with BS have been included in a registry and followed in a prospective fashion. The ethics committee of the Universitair Ziekenhuis Brussel - Vrije Universiteit Brussel approved the study protocol. A total of 549 patients with BS have been included in the registry from 1992 to 2013. Among them, 363 patients (66.1%) had no prior SCD
or syncope. Study inclusion criteria consisted of (1) spontaneous or drug-induced Brugada type I electrocardiogram (ECG) and (2) no previous syncope or SCD. Medical history, physical examination and baseline ECG were obtained and underlying structural cardiac abnormalities were excluded in all patients by means of echocardiography. Other non invasive methods (such as stress test or nuclear magnetic resonance) or invasive methods (coronary angiography, left and right ventriculography, and myocardial biopsies) were used at the discretion of the treating physician. ECGs were classified as Brugada coved-type (type I), saddleback (type II) or normal. An ECG was considered diagnostic of BS if a coved type ST elevation ≥ 2 mm was documented in ≥ 1 lead from V1 to V3 in the presence or absence of a sodium-channel blocker agent. All baseline and drug-induced 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space. Two independent experienced electrophysiologists analyzed all ECGs; in case of disagreement a third physician was consulted.

Genetic testing with sequence analysis of SCN5A was recommended for all patients with diagnosis of BS.

**Ajmaline challenge**

Ajmaline (1 mg/kg) was administered intravenously over a 5 minutes period to unmask the diagnostic ECG pattern of BS in case of non-diagnostic baseline ECG. The test was considered positive for BS only if coved type I ECG was documented in ≥1 right precordial leads (V1-V3). Ajmaline infusion was discontinued before reaching the target dose if QRS prolongation exceeded 30% compared to baseline interval, when frequent premature ventricular beats (PVCs) or type I Brugada ECG occurred or in the case of development of high-degree AV-block. Ajmaline-induced sustained VA was defined as the occurrence of VF or sustained VT.
Electrophysiological study

EPS included basal measurements of conduction intervals and programmed ventricular stimulation. As reported elsewhere\textsuperscript{12}, the protocol used a single site of stimulation (right ventricular apex), 3 basic pacing cycles (600, 500, and 430 ms), and introduction of 1, 2, and 3 ventricular premature beats down to a minimum of 200 ms. A patient was considered inducible if a sustained ventricular arrhythmia (ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), or monomorphic VT lasting more than 30 seconds or requiring emergency intervention) was induced.

ICD implantation

Beginning from 2005, the indication to ICD therapy was determined using the recommendations of the second Brugada consensus conference\textsuperscript{5}. Patients with inducible VA during EPS were considered at high risk of future arrhythmic events\textsuperscript{8,12} and the implantation of an ICD was considered. The choice between single- and dual-chamber devices was driven by the presence of previous episodes of supraventricular arrhythmias or the evidence of sinus node dysfunction (SND). The device was usually programmed to treat ventricular rates over 200 beats/min and occasionally a VT monitoring zone was added. However, these settings were adjusted on the basis of the individual clinical history and to avoid recurrences of inappropriate interventions during the follow-up\textsuperscript{13}.

Follow-up

Clinical follow-up of patients consisted of physical examination and ECG performed at least every 6 months in case of device therapy patients and every 2 years elsewise. Clinical data were regularly collected. Follow-up of ICDs was performed at 1 and 3 months after implantation and thereafter every 6 months. All available electrograms of appropriate and inappropriate shocks
were analyzed by at least two investigators independently. Appropriate therapies were defined as shocks or anti-tachycardia pacing (ATP) delivered for VT or VF and inappropriate therapies were defined as those delivered in the absence of VA. Electrical storm was defined by 3 or more sustained episodes of VT, VF, or ICD appropriate shocks within 24 hours.

Statistical analysis
Data are presented as mean ± standard deviation or as absolute values and percentages where appropriate. Comparison between continuous variables were performed using the unpaired Student’s t-test or U Mann-Whitney test as appropriate. The chi-square test or the Fisher’s exact test were used to compare categorical variables. Sensitivity, specificity and area under the curve were created by means of a receiver operating characteristic curve analysis. Event-free survival was estimated by Kaplan-Meier method and compared by log-rank test. Hazard ratios were calculated using Cox proportional hazards regression models. Cox regression analysis was used to create a predictive model. The variables included were those that showed statistical significance at the univariate analysis. A p value less than 0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS software (SPSS v22, Chicago, IL, USA).

Results
Study population
A total of 363 consecutive BS patients (200 males, 55.1%; mean age: 40.9±17.2, ranging from 0.5 to 80.9 years) fulfilled inclusion criteria. Baseline clinical characteristics of study population are shown in Table 1.

At the time of diagnosis, 42 patients (11.6%) were younger than 18 years and 23 (6.3%) older than 65. Eighty seven (23.9%) were probands and the remaining 276 (76.0%) patients were
diagnosed during family member screening. They belonged to 199 different families. One hundred eighty two (50.1%) had familial history of SCD, 33 (37.9%) among 87 probands and 149 (54.0%) out of 276 familial screening patients.

Spontaneous type 1 ECG was present in 41 (11.3%) patients with a mean ST elevation of 2.7±1.2 mm. The remaining 322 (88.7%) were diagnosed after a pharmacological challenge test. It was performed in 301 (93.5%) patients with ajmaline, in 6 (1.9%) with procainamide and in 15 (4.7%) with flecainide.

Three hundred twenty one (88.4%) patients underwent an EPS. Among whom, in 32 (10.0%) a sustained VA was induced. In 27 (84.4%) of these latter, ventricular fibrillation was the induced rhythm and in 5 (15.6%) it was VT. Inducible subjects were more frequently males (84.4% vs 52.6%, p<0.01), presented more spontaneous type I pattern (50.0% vs 8.7%, p<0.01) and had a wider QRS (107.7±14.8 vs 93.8±19.4, p<0.01), as compared to non-inducible subjects with EPS (n=289).

A total of 224 genetic tests (61.7%) were obtained and 49 of them (21.9%) resulted positive for mutation in the SCN5A gene.

**Time evolution**

The clinical profile of the patients evolved over the time (Table 2). Patients before 2005 presented more frequently spontaneous type I pattern (16.4% vs. 7.8% p=0.02) and had a broader QRS (99.9±16.1 ms vs. 82.4±24.1 ms, p<0.01). These BS patients were less frequently probands (14.4% vs. 30.7%, p<0.01) and had more history of AF (13.0% vs. 2.3%, p<0.01) Of note, inducibility rates dropped from 15.9% before 2005 to 5.8% from 2005 and the rate of ICD implantation was also lower after this year, although not statistically significant (23.3% and 12.2%, p=0.16).
Management

An ICD was implanted in 61 (16.8%) patients. Reasons for implantation were: spontaneous Brugada type I ECG and sustained VA induced during EP study in 11 patients (18.0%), spontaneous Brugada type I ECG and family history of SD in 7 patients (11.5%) and sustained VA during ajmaline challenge in 5 patients (8.2%). The remaining patients received an ICD because of ajmaline-induced Brugada type I ECG with sustained VA induced during EP study in 20 (32.8%) patients or family history of SD in 13 (21.3%) patients, 1 (1.6%) had a spontaneous non sustained polymorphic VT registered, 1 (1.6%) had nocturnal palpitations and 2 (3.3%) for personal preference. One patient (1.6%), initially asymptomatic, received an ICD after an aborted SCD.

Follow up

Among the entire population, a follow-up longer than 6 months was available for 303 (83.5%) patients. Among these, during a mean follow up of 73.2±58.9 months 9 patients presented arrhythmic events. These consisted in 6 appropriate shocks delivered by the ICD, 2 SCD and 1 aborted SCD. Table 3 summarizes clinical characteristics of patients with events.

Event rate was 0.5% / year. Kaplan Meier event free survival was 99.0% at 1 year and 96.2% at 5 years, 95.4% at 10 and 15 years. Figure 1 shows cumulative event free survival according to Kaplan Meier method.

Arrhythmic event free survival in patients in whom an ICD was implanted was 94.8% at 1 year and 89.5% at 5 years and 86.7% at 10 and 15 years. Event free survival in patients without an ICD was 100% at 1 year and 97.9% at 5 years and beyond. This difference was statistically significant (p<0.01), figure 2.
ICD patients follow up

Among 61 patients with ICD, after a mean follow up of 96.8±72.3 months (no patient was lost), 6 appropriate therapies were documented. All of them were due to VF, with a cycle length lower than 300 ms. Sixteen (26.2%) were male with mean age at diagnosis of 45.8±15.9, spontaneous type I was present in 21 (34.4%) patients. EPS was performed in 56 (91.8%) individuals and inducible VA during EPS were observed in 31 (50.8% of patients who underwent EPS).

Incidence of events in this group was 1.4% year (SE: 0.6). Significantly higher to non ICD patients, who presented 3 events (among 242 patients with a mean follow up of 67.8 ±54.3 months), which corresponds to 0.22% year (SE: 0.12), (Cox regression HR 7.7, 95% CI 1.9 – 30.6, p<0.01). Five (83.3%) patients with events were males, 4 (66.6%) presented spontaneous type I and 5 (83.3%), presented inducible VA arrhythmias during EPS.

Mean number of appropriate shocks delivered per patient was 3.8±5.5. Mean time until first shock was 15.7±28.3 months with a range from 0.1 to 48.2 months. A non-sustained VT was documented in 1 patient.

Nine patients (14.8%) had inappropriate shocks after a mean of 34.2±36.8 months Mean number of inappropriate shocks delivered per patient was 2.0±1.4. Inappropriate shocks were due to sinus tachycardia in 1 patient, noise on the ventricular channel after lead fracture 1 patient, T-wave over-sensing in 1 patient and 6 patients due to AF with high ventricular rate.

During follow-up, 6 patients (9.8%) experienced device-related complications. Complications consisted in fracture of ventricular electrode and subsequent extraction and replacement in 5 patients and infection in 1 other.

Mortality

Six patients (1.7%) died during follow up. Causes of death were: SCD in 2 patients, acute
myocardial infarction with myocardial rupture and cardiogenic shock in 1 from non-cardiac causes in the remaining 3.

**Univariate and multivariable analysis**

Univariate Cox regression model showed a statistical significant relation between events and inducible VA during EPS (HR 11.4, 95% CI 2.7 – 41.8, p<0.01). Events in the inducible VA group were 5/31 and 3/240 in the non inducible group. Sensitivity of EPS for predicting arrhythmic events was 75.0% and specificity was 91.3%. Positive predictive value was 18.2% and negative predictive value 98.3%. ROC operative analysis showed an area under the curve of 0.83 (95% CI 0.64 – 1.0, p<0.01).

Spontaneous type I ECG and previous SND showed also a significant relationship (HR 4.0, 95% CI 1.1– 14.9, p=0.04 and HR 8.0, 95% CI 1.0 – 63.9, p=0.049, respectively). Events in the spontaneous type 1 group were 3/42 and 6/261 in the non spontaneous group. Regarding patients with SND, they presented 1/4 events as compared with 8/299 in patients without SND.

Variables that failed to show significant relation with arrhythmic events were: male sex, age at diagnosis, proband status, previous , SCD family history and diagnosis before 2005.

A Cox regression multivariable model including the variables that showed a significant statistical relation with arrhythmic events in the univariate analysis were included. VA inducibility, spontaneous type 1 and previous SND were introduced. Inducible VA remained statistically significant (HR 9.1 95% CI 1.8– 46.8, p<0.01). Spontaneous type 1 ECG and previous SND lost its significance (HR 1.3 95% CI 0.2 – 7.1, p= 0.75 and HR 5.1 95% CI 0.5– 48.6, p=0.16, respectively). Table 4 shows univariate and multivariable analysis.

**Discussion**

More than 20 years after the first description of the BS, management of asymptomatic patients
remains challenging and controversial. When considering the whole spectrum of BS patients, several risk factors, such as spontaneous type I or presence of symptoms, have been consistently identified and therefore are universally accepted\textsuperscript{10,11,14}. As the risk of SCD in BS patients persists lifelong, very long-term follow-up is of utmost importance.

Despite that asymptomatic status represents the biggest subgroup in BS patients\textsuperscript{15}, a lack of robust evidence based recommendations exits. The relatively low event rate in this group and the limited follow-up time of published studies might be responsible of this situation\textsuperscript{11,16}. Furthermore, heretofore no study has focused only in this subgroup of patients to address these questions.

We present the long term follow up of one of the biggest cohorts of asymptomatic patients with BS. To the best of our knowledge, the follow up in our study is the longest reported up to date. Nine arrhythmic events occurred (2 SCD, 1 aborted SCD and 6 ICD appropriate shocks), accounting for an annual incidence of 0.5%.

**Event rate**

When assessing the risk of SCD in BS patients, special attention should be paid to the annual event rate. In our study the annual incidence of arrhythmic events was 0.5%. This rate is lower than the initially reported by our group\textsuperscript{6} but similar to more recent registries such as the FINGER registry (0.5%)\textsuperscript{11}. This striking difference may be due to a selection bias, as initial reports included patients at higher risk. BS patients characteristics and risk profile have changed over the years. After 2005, fewer patients presented with spontaneous type 1 and inducibility rate has also dropped after 2005. Female sex has been related to better outcome\textsuperscript{4}. One interesting finding of the present study is that women constitute the 45% of the entire population. Male predominance has been universally reported in major BS studies: 80% in the Prelude registry\textsuperscript{10}, 70% in the
Finger registry\textsuperscript{11}. The reason that may explain this finding could be the proactive search of BS and an exhaustive familial screening program established at our institution. The population characteristics of this study might fit better with the actual BS profile and it is similar to recent series.

An annual event rate of 0.5\% in these asymptomatic BS patients might appear low. We must not forget that our population is formed by healthy individuals with a mean age of 40.9 years and therefore a long life expectancy. Though evolution of arrhythmic risk over years is uncertain\textsuperscript{17}, taking into consideration the previous facts, this figure becomes significant.

**Risk factors**

With only 9 events in the entire population, the search of predictors of arrhythmic events is challenging (see limitations section). Nevertheless, we identified inducible VA arrhythmias during EPS strongly associated with events (HR 9.1). Spontaneous type 1 ECG pattern and previous history of SND presented a univariate significant association (HR 4.0 and 8.0, respectively), which was lost in the multivariate model. Male sex presented a borderline association (HR 6.7, p=0.07).

No study, focused only in asymptomatic patients, with enough power is found in the literature. The FINGER registry\textsuperscript{11} performs an analysis in the asymptomatic subgroup. This group consisted in 654 individuals who presented 10 events over a mean follow up of 31.9 months. Our present study doubles this follow up. They report a univariate statistical significant association between inducible VA arrhythmias during EPS and events with a HR of 5.2. No other variables were associated with the outcomes. These investigators constructed a multivariate predictive model introducing age, sex, spontaneous type I and inducibility, where this latter lost the statistical signification. Considering the number of events such analysis might be
underpowered and extracting conclusions of it should be done with caution.

The PRELUDE registry\textsuperscript{10} offers valuable and unique information about the role of EPS in BS patients without prior SCD. Of note, this registry includes patients with prior syncope and no analysis is performed in the asymptomatic subgroup patients. Syncope, spontaneous type I ECG, ventricular refractory period lower than 200 ms and fragmented QRS showed a statistical association with arrhythmic events during follow up. Inducibility was not associated with a higher risk of SCD. A lower event rate and inducibility is found in our study (0.5% and 10% respectively) as compared to the PRELUDE registry (1.5% and 40%). This point might be of importance. Our stimulation protocol involves only one site (right ventricular (RV) apex) whilst the PRELUDE registry uses a two-site protocol (RV apex and RV outflow tract). If the PRELUDE protocol stimulation was only performed at the RV apex, the inducibility rate would be significantly reduced (55% of VA induced were achieved at the RV apex). Summarizing, the population characteristics and protocol of PRELUDE and our study differ significantly and therefore are not completely comparable.

The relation between SND and arrhythmic events is of special interest and has never been described before. Though when introduced in the adjusted model, SND loses its significance, the limited number of patients exhibiting SND might be responsible, making the model underpowered to demonstrate this relation. Conduction disturbances in BS have been associated with a worst outcome\textsuperscript{18} and relation between SND, sodium channelopathies and BS are well known\textsuperscript{19-21}. The mechanism responsible for this is not clear; a more expressive form of the disease might be involved. Specific studies with biggest population and follow-up should be performed to clarify this issue.

It is universally accepted that cardiogenic syncope in BS patients confers a highest risk of
events, as it is attributed to VA. In this scenario, SND may lead to a misdiagnosis of the subjacent mechanism, attributing the event to a VA when bradycardia is the real cause. Interestingly, if SND is related with a worst prognosis, syncope due to this will also confer a higher risk and therefore a more aggressive management should be taken.

We believe that EPS in BS patients has a high performance. It might identify subjects at higher risk, confirm the presence of SND, clarify the cause of syncope or treat supraventricular arrhythmias that eventually might lead to inappropriate ICD therapies.

**ICD population**

ICD asymptomatic BS patients constitute a subgroup of special interest as they are considered at special high risk of SCD. Among 61 patients with ICD, 6 appropriate therapies were documented. Annual events rate in this subgroup is 1.4%. This incidence is significantly higher than the non ICD patients and slightly higher to that reported by other groups (12% at 10 years reported by Sacher\(^1\)). All of them but one were males, 66.6% had spontaneous type I and 66.6% presented inducible VA during EPS. Very few information has been published about this specific subgroup. Sacher\(^1\) reports that among the 12 asymptomatic patients that received a shock all had spontaneous type I ECG and all but one were inducible. Similar findings were reported by our group\(^8\).

The balance between benefits and complications after ICD implantation is particularly important when dealing with asymptomatic patients. Nine (14.8%) patients experienced inappropriate shocks and 6 (9.8%) had device related complications. These figures might seem high but we have to consider that 3 of the arrhythmic events were sudden cardiac death and two of these patients actually died. Taking into account these considerations, the benefit outweighs the risks.
Limitations

The fact of being a single center experience spanning for a 20-year period, makes the population to present heterogeneous clinical characteristics. However, period of diagnosis did not behave as a confounding factor. Despite it is one of the studies in asymptomatic BS with a longer follow-up, patients with BS present a lifelong risk of arrhythmias, therefore, a mean follow up of 6 years might be considered short. Screening of structural heart disease is in line with other major BS registries\textsuperscript{10,11}, involving echocardiography in all patients and other advanced imaging techniques in selected patients at the discretion of the responsible clinician. The main limitation is clearly the low event rate which limits the power for searching variables associated with the outcomes.

Furthermore, the lack of association of some characteristics might be due to this fact. It is important to consider that, secondary to this, all tests are done at a nominal level of 0.05, without consideration for type I error inflation and consequently false relationships could have been included. The multivariate analysis should be taken with precaution as its power is limited.

Conclusions

Arrhythmic events in asymptomatic BS patients are not negligible, with an annual incidence rate of 0.5%. Risk stratification is specially challenging in this specific group. VA inducibility at EPS, spontaneous type I ECG and presence of SND might be considered as risk factors and used to drive long-term management.

Conflict of Interest Disclosures: None.

References


Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation. 2010;121:635-643.


Table 1: Baseline clinical characteristics of study population

<table>
<thead>
<tr>
<th>Study population (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (±sd), range</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
</tr>
<tr>
<td>Spontaneous type I ECG, n (%)</td>
</tr>
<tr>
<td>Proband, n (%)</td>
</tr>
<tr>
<td>Family history of SCD, n (%)</td>
</tr>
<tr>
<td>Previous atrial fibrillation, n (%)</td>
</tr>
<tr>
<td>Previous SND, n (%)</td>
</tr>
<tr>
<td>PR, ms (±sd)</td>
</tr>
<tr>
<td>QRS, ms (±sd)</td>
</tr>
<tr>
<td>HV, ms (±sd)</td>
</tr>
<tr>
<td>PES inducible, n (%)*</td>
</tr>
<tr>
<td>SCN5A mutation, n (%)*</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
</tr>
</tbody>
</table>

PES: programmed electrical stimulation, SCD: sudden death, SND: sinus node dysfunction. *Percentages are calculated only among patients who underwent the test (321 patients underwent PES and 224 genetic test).
Table 2: Baseline clinical characteristics of study population according to diagnosis year

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Group I (n =146)</th>
<th>Group II (n =217)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>41.3±16.8</td>
<td>40.6±17.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>81 (55.5)</td>
<td>119 (54.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Spontaneous type I ECG, n (%)</td>
<td>24 (16.4)</td>
<td>17 (7.8)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Proband, n (%)</td>
<td>21 (14.4)</td>
<td>66 (30.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of SCD, n (%)</td>
<td>75 (51.4)</td>
<td>107 (49.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Previous atrial fibrillation, n (%)</td>
<td>19 (13.0)</td>
<td>5 (2.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous SND, n (%)</td>
<td>3 (2.1)</td>
<td>1 (0.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>PR, ms</td>
<td>169.6±32.0</td>
<td>161.7±32.8</td>
<td>0.13</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>99.9±16.1</td>
<td>82.4±24.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HV, ms</td>
<td>45.9±9.2</td>
<td>44.5±9.7</td>
<td>0.46</td>
</tr>
<tr>
<td>Inducibility, n (%)*</td>
<td>21 (15.9)</td>
<td>11 (5.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCN5A mutation, n (%)*</td>
<td>13 (21.6)</td>
<td>36(22.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>ICD implantation, n (%)</td>
<td>34 (23.3)</td>
<td>26 (12.0)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Group I refers to patients with diagnosis made before 2005 and Group II refers to patients with a diagnosis during or after 2005. Abbreviations: SCD: sudden cardiac death, SND: sinus node dysfunction, ICD: implantable cardioverter defibrillator. *Percentages are calculated only among patients with genetic test.
Table 3: Clinical characteristics patients presenting arrhythmic events during follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Gender</th>
<th>Age</th>
<th>Proband</th>
<th>Family History of SCD</th>
<th>Spontaneous type I</th>
<th>Inducible VA</th>
<th>f-QRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SCD</td>
<td>Male</td>
<td>39.2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2 SCD</td>
<td>Female</td>
<td>47.0</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Patient refused EPS</td>
<td>No</td>
</tr>
<tr>
<td>3 Aborted SCD</td>
<td>Male</td>
<td>53.8</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4 ICD shock</td>
<td>Male</td>
<td>10.7</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5 ICD shock</td>
<td>Male</td>
<td>57.5</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6 ICD shock</td>
<td>Male</td>
<td>47.8</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7 ICD shock</td>
<td>Male</td>
<td>62.6</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8 ICD shock</td>
<td>Female</td>
<td>43.2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9 ICD shock</td>
<td>Male</td>
<td>69.8</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

SCD: sudden cardiac death, Inducible VA: indicates if a ventricular arrhythmia was induced during electrophysiological study, EPS: electrophysiological study, f-QRS: fragmentation of QRS complex, ICD: implantable cardioverter defibrillator.
Table 4: Univariable analysis and multivariable model

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPS inducibility</td>
<td>11.4</td>
<td>2.7 – 41.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Spontaneous type I</td>
<td>4.0</td>
<td>1.1 – 14.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous SND</td>
<td>8.0</td>
<td>1.0 – 63.9</td>
<td>0.049</td>
</tr>
<tr>
<td>Male sex</td>
<td>6.7</td>
<td>0.8 – 53.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.0</td>
<td>0.9 – 1.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Previous AF</td>
<td>1.1</td>
<td>0.1 – 9.0</td>
<td>0.91</td>
</tr>
<tr>
<td>Proband status</td>
<td>2.5</td>
<td>0.6 – 10.1</td>
<td>0.20</td>
</tr>
<tr>
<td>SCD family history</td>
<td>1.1</td>
<td>0.3 – 4.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Diagnosis before 2005</td>
<td>0.9</td>
<td>0.2 – 4.0</td>
<td>0.93</td>
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<tr>
<td><strong>Multivariable model</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>EPS inducibility</td>
<td>9.1</td>
<td>1.8 – 46.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Spontaneous type I</td>
<td>1.3</td>
<td>0.2 – 7.1</td>
<td>0.75</td>
</tr>
<tr>
<td>Previous SND</td>
<td>5.1</td>
<td>0.5 – 48.6</td>
<td>0.16</td>
</tr>
</tbody>
</table>

ICD: implantable cardioverter defibrillator, EPS: Electrophysiological study, SND: Sinus node dysfunction, AF: Atrial fibrillation, SCD: Sudden cardiac death, HR: Hazard ratio, CI: Confidence interval.
Figure Legends:

Figure 1: Kaplan Meier method event rate probability.

Figure 2: Kaplan Meier method event rate probability according to ICD implantation status.
Asymptomatic Brugada Syndrome: Clinical Characterization and Long Term Prognosis
Juan Sieira, Giuseppe Ciconte, Giulio Conte, Gian-Battista Chierchia, Carlo de Asmundis, Giannis Baltogiannis, Giacomo Di Giovanni, Yukio Saitoh, Ghazala Irfan, Ruben Casado Arroyo, Justo Julià, Mark La Meir, Francis Wellens, Kristel Wauters, Gudrun Pappaert and Pedro Brugada

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