Long-Term Follow-Up of Patients with Brugada Syndrome: Foremost Risk Factors Associated with Arrhythmic Events

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Abstract

Background: Brugada syndrome (BS) is characterized by ST segment elevation in right precordial leads (V1-3), ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death (SCD) in individuals without structural heart disease. The aim of this study was to assess parameters associated with arrhythmic events in patients with BS.

Methods: A total of 68 patients diagnosed with BS or had Brugada Type ECG Change (BTEC) between January 1997 and July 2012 at the Department of Cardiology of Başkent University Faculty of Medicine, Ankara, Turkey were included. Patients were screened every 6 months for arrhythmia-related syncope, SCD, appropriate and inappropriate defibrillation (shock), AF development and death; collectively defined as “arrhythmic events” and were the primary endpoints. Patients with and without arrhythmic events were compared.

Results: The mean age was 34.9 ± 12.2 years (9-71 years), and 52 (76.5%) patients were male. Mean follow-up was 49.6 ± 37.6 months (4-188 months). Univariate analysis showed that male sex (p = 0.004), Type 1 electrocardiographic pattern (p = 0.008), SCD (p = 0.036), VT/VF history (p = 0.046), requirement for electrophysiological studies (p = 0.034), implantable cardioverter-defibrillator (ICD) placement (p = 0.014) was found to demonstrate significant differences in patients with and without arrhythmic events. In multivariable analyzes, spontaneous Type 1 ECG presence (HR = 8.54, 95% CI: 0.38-26.37; p = 0.003) and VT/VF history (HR = 9.21, 95% CI: 0.004-1.88; p = 0.002) were found to be independently associated with arrhythmic events.

Conclusion: We found the presence of spontaneous type 1 ECG and a history of VT/VF to be associated with increased likelihood of arrhythmic events in BS.

Keywords
Brugada syndrome, Sudden cardiac death, Ventricular tachyarrhythmia, Risk factors, Implantable cardioverter-defibrillator

Introduction

Brugada syndrome (BS) was first described by the Brugada brothers with the presentation of 8 cases in 1992 [1]. BS is characterized by ST segment elevation in right precordial leads (V1-3), ventricular tachycardia (VT), ventricular fibrillation (VF) and sudden cardiac death (SCD) in individuals without structural heart disease [1]. It is estimated that BS is responsible for 20% of SCDs in the population without structural heart disease while it accounts for 4-12% of all SCDs [2]. Its prevalence is thought to be around 5/10,000 worldwide with the majority being males, but this figure may not reflect true prevalence due to varying electrocardiography (ECG) findings and the fact that most patients have the masked BS phenotype. Some patients may be completely asymptomatic throughout their life, while some develop SCD [3,4] which is most frequently encountered in the 5th decade of life [5,6].

The only treatment with proven efficacy in patients with BS is implantable cardioverter-defibrillator (ICD) implantation [7,8]. However, the cost of this treatment...
is high, and complications and/or inappropriate interventions are reported between 20-36% after ICD implantation in patients with BS [9,10]. Currently, it is recommended that patients with BS should be treated with ICD, as the risk of SCD is higher in patients with a history of syncope and ventricular arrhythmia [11-13]. Although there is no consensus, it is recommended that other patients should be followed without treatment according to relevant guidelines [11-14]. There is conflicting information in the literature regarding parameters associated with BS prognosis or risk of sudden death [4,13,15]. Nonetheless, current literature recommends several parameters to be used as indicators of poor prognosis, including syncope, spontaneous Type 1 ECG, induction of arrhythmia after electrophysiological study (EPS), and VT/VF history [13,15]. However, many of the studies on this topic are limited by low patient count, short follow-up period, omission of parameters, or partial or complete combinations of these limitations.

Therefore, our aim was to contribute to the controversial issue of determining variables that were associated with arrhythmic events (poor prognosis) in patients with BS.

Methods

This study was initiated after obtaining approval from Baskent University Clinical Research Ethics Committee, with the project number: KA09/51, dated March 4, 2009.

A total of 68 patients diagnosed with BS or Brugada-type ECG Change (BTEC) between January 1997 and July 2012 at the Department of Cardiology of Başkent University Faculty of Medicine, Ankara, Turkey, were included in the study. Twenty-four of the participants were diagnosed with BS before March 2009, and thus, pre-study data were assessed retrospectively. The remaining 44 were patients diagnosed with BS or BTEC after this date and were assessed prospectively. Retrospective data prior to the study start date were obtained from hospital records. Information after this date was obtained by calling the patients who were identified both retrospectively and prospectively for a control check every 6 months or by phone calls. Patients who could not be followed up, whose information could not be accessed retrospectively or prospectively, who had electrolyte imbalances that may cause arrhythmias before ECG recording, and those who were using drugs that could cause BS-like ECG were excluded from the study.

BS diagnosis

ECGs were obtained by experienced technicians using 12-channel ECG devices (Pagewriter XLI, Hewlett Packard, USA). All records were taken in the supine position at a 25 mm/sec speed and 10 mm/mV calibration. While taking the 1st ECG, the leads were placed as recommended in the standard ECG recording. The second ECG was performed by moving only the V1, V2 and V3 leads to an upper intercostal space, without lifting the patient and without changing the other leads [16,17].

The ECGs obtained were analyzed by two different arrhythmologists who were aware of the demographic and clinical characteristics of the participants. Results were interpreted in accordance with the diagnostic criteria of the Brugada Consensus Conference 2005 (17) for BTEC, and the findings were noted in the relevant patient records. Three types of ECG were recorded. Briefly, ≥ 2 mm (0.2 mV) dome-type ST segment/J point elevation in V1-V3 followed by a negative T wave was defined as “Type 1 ST segment elevation”. A change in saddleback appearance with ≥ 2 mm ST elevation (with ≥ 1 mm ST elevation in the pil) followed by a positive or biphasic T wave was defined as “Type 2 ST segment elevation”. Finally, “Type 3 ST segment elevation” was defined as saddleback or dome-type < 1 mm ST segment elevation [2]. Type 1 ST segment elevation is referred to as “Brugada ECG”, while Types 2 and 3 are not considered to be diagnostic. The diagnosis of BS was definitively established in the presence of Type 1 ST segment elevation (Brugada ECG) in more than one right precordial lead (spontaneously or with the use of a sodium channel blocker) in the presence of at least one of the following: (i) Documented VF; (ii) Polymorphic VT, family history of SCD under 45 years of age, Type 1 ECG in family members; (iii) Induction of VT with Programmed Electrical Stimulation (PES); (iv) Syncope; (v) Nocturnal agonal respiration [11,18]. In the presence of specific changes observed in the ECG without symptoms, the findings can be classified as being BTEC in the current literature [19]. ECGs in which both observers separately agreed to a BTEC definition were classified as such.

Ajmaline test

Ajmaline was given at a dose of 1 mg/kg intravenously (IV) within 5 minutes before ECG. During the test, continuous ECG recording at 10 mm/sec and 12 lead ECG recordings at 25 or 50 mm/sec (in between) were taken. The presence of type 1 ECG findings in at least two of the V1, V2 or V3 leads with Ajmaline was accepted as the positivity criterion of the test [20].

Propafenone test

Propafenone was given IV at a dose of 1 mg/kg within 10 minutes before ECG. During the test, continuous ECG recording at 10 mm/sec and 12 lead ECG recordings at 25 or 50 mm/sec (in between) were taken. The presence of type 1 ECG findings in at least two of the V1, V2 or V3 leads with propafenone was accepted as the positivity criterion of the test [21].

Study protocol

Demographic, clinical, laboratory and ECG features of all patients were recorded. The symptoms or findings
that led to initial diagnosis (manifesting symptom) were also identified and recorded in each patient (syncope, syncpe and palpitation, palpitation, SCD, family screening, incidental). Echocardiography was performed in patients to exclude structural heart disease. Biochemical tests were performed to exclude electrolyte imbalances that may cause arrhythmias. The treatment of the patients or the examinations that needed to be performed were not intervened within the study. The patient’s examination and treatment plans were arranged by the arrhythmologist who followed up the patient, taking into account relevant treatment guidelines [11,12,14] at the time of the patient’s application. Within the scope of the research, ajmaline and/or propafenone tests were performed in patients with suspected BS when sodium channel blocker testing was advised by the following physician. Family members of patients diagnosed with BS were also screened for the disease. While performing family screening, clinical history and ECG recordings of the patients were obtained. ECG recordings were obtained in two ways: Standard and upper-level recordings. Family members who were diagnosed with BS or had Type 2 or 3 ECGs were also scheduled for follow-up.

Patients were screened every 6 months (by phone or in-person visit) to check for syncope, other symptoms, cardiac arrest, arrhythmias other than ventricular arrhythmias, and appropriate or inappropriate interventions in patients with ICD. Arrhythmia-related syncope, SCD, appropriate and inappropriate defibrillation (shock), AF development and death are defined as “arrhythmic events” and were determined as the primary endpoints of our study. Appropriate defibrillation, death, or arrhythmia-related syncope in a patient without ICD were also identified as arrhythmic events. Patients with ICD were checked for battery life, lead problems, and defibrillator settings that could be related to arrhythmia, shock, and ICD, and necessary information was recorded.

Statistical analysis

While evaluating the findings of the study, the SPSS 17.0 statistical package program (Statistical Package for the Social Sciences, version 17.0, SPSS, Chicago, IL, USA) was used for statistical analysis. Results were expressed as n (%) values for categorical variables and mean ± standard deviation values for continuous variables. For all statistical investigations, statistical significance was set at a p value of < 0.05. Categorical variables were compared by Chi-square tests and the Fisher’s exact test. Independent samples t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used to compare non-normally distributed continuous variables. Regression analysis was performed to determine multiple variables that were associated with the study endpoints.

Results

The mean age of the patients was 34.9 ± 12.2 years (9-71 years), and the number of male patients was 52 (76.5%). Mean follow-up was 49.6 ± 37.6 months (range: 4-188 months). Considering the initial application ECGs of the patients, 2 (2.9%) had normal ECG, while 13 patients (19.1%) had Type 1, 15 patients (22.1%) had Type 2, 36 (52.9%) patients had Type 3 ECG patterns. Furthermore, 1 patient (1.5%) had LBBB and 1 (1.5%) had RBBB. At the time of application to the cardiology clinic, 52 of the patients (other than patients with definite Type 1 ECG pattern) were further tested with sodium channel blockers using ajmaline and/or propafenone to reveal masked ECG findings. After these tests, Type 1 ECG was identified in 40 patients (58.8%), Type 2 ECG in 4 patients (5.9%), and Type 3 ECG in 24 patients (35.3%).

The distribution of manifesting symptoms according to ECG types is given in Table 1. Of 40 patients with type 1 ECG, 11 were diagnosed with syncope, 9 with syncope and palpitation, 6 with palpitation, 2 with SCD, and 9 with family screening. At the time of application to the cardiology clinic, 52 of the patients (other than patients with definite Type 1 ECG pattern) were further tested with sodium channel blockers using ajmaline and/or propafenone to reveal masked ECG findings. After these tests, Type 1 ECG was identified in 40 patients (58.8%), Type 2 ECG in 4 patients (5.9%), and Type 3 ECG in 24 patients (35.3%).

The distribution of manifesting symptoms according to ECG types is given in Table 1. Of 40 patients with type 1 ECG, 11 were diagnosed with syncope, 9 with syncope and palpitation, 6 with palpitation, 2 with SCD, and 9 with family screening, while 3 cases were incidentally diagnosed. Of 4 patients with type 2 ECG, 1 was diagnosed with syncope and palpitation, 1 with palpitation, 2 with family screening. Of 24 patients with type 3 ECG, 4 were diagnosed with syncope, 6 with syncope and palpitation, 5 with palpitation, 8 with family screening, and 1 incidentally.

Table 1: Manifesting symptoms according to ECG types.

<table>
<thead>
<tr>
<th>Diagnosis type</th>
<th>Type 1 (n = 40)</th>
<th>Type 2 (n = 4)</th>
<th>Type 3 (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>11 (27.5)</td>
<td>0</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Syncope and palpitation</td>
<td>9 (22.5)</td>
<td>1 (25.0)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>6 (15.0)</td>
<td>1 (25.0)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>SCD</td>
<td>2 (5.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family screening</td>
<td>9 (22.5)</td>
<td>2 (50.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Incidental</td>
<td>3 (7.5)</td>
<td>0</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

Data are given as frequency (percentage); SCD: Sudden Cardiac Death
of arrhythmic events showed that male sex (p = 0.004), Type 1 ECG pattern (p = 0.008), SCD (p = 0.036), VT/VF history (p = 0.046), requirement of EPS (p = 0.034), and ICD placement (p = 0.014) were associated with arrhythmic event development. Vasovagal syncope (p = 0.037) was significantly associated with the absence of arrhythmic events (Table 3).

Multiple variable analyses were performed to determine factors independently associated with arrhythmic event development at follow-up. Spontaneous Type 1 ECG presence (HR = 8.54, 95% CI: 0.38-26.37; p = 0.003) and VT/VF history (HR = 9.21, 95% CI: 0.004-1.88; p = 0.002) were found to be associated with arrhythmic event development (Table 4).

Discussion

It is well accepted that the etiology of BS is multifactorial, including genetic, environmental, and hormonal components. In addition, some clinical features have been identified as high-risk markers for poor prognosis in BS [22]. However, risk stratification in BS remains a difficult issue. Some clinical, electrocardiographic, and genetic risk factors appear to be important predictors of future major arrhythmic events [23]. Symptomatic patients with recurrent syncpe, sleep apnoea breathing, or unknown seizures have been shown to be at risk of SCD and need an ICD. However, the value of risk stratification parameters such as electrophysiological inducibility in asymptomatic patients is still a subject of debate [24]. Our aim in this study was to determine factors that could potentially be used to determine poor prognosis in BS. Our results show that having a spontaneous type 1 ECG and developing VT/VF during follow-up are associated with arrhythmic events, and therefore, could be used to stratify risk.

Patients with BS are usually asymptomatic. Nevertheless, lifetime presentation with syncpe or SCD as a result of ventricular arrhythmia have been reported to be between 10-15% [3,4]. However, these values do not include undiagnosed asymptomatic patients. Approximately 38% of patients presenting with SCD have a previous history of syncpe [25]. In addition,

### Treatments administered

Of the 40 type 1 patients, 25 of the symptomatic patients were recommended an ICD implantation. 18 of these patients received ICD, whereas 7 declined ICD implantation. Type 1 patients without ICD were followed up with medical treatment. All the type 2 patients were followed up medically. ICD was implanted in 2 of the 24 patients with type 3 ECG pattern. The patients with type 3 ECG without ICD were also followed up with medical treatment.

### Follow-up findings

Two of 40 patients died in the follow-up. One of the patients died due to SCD, the other patient also had muscular dystrophy and died of pneumonia. During follow-up, an appropriate shock was found to have been delivered in 7 of the patients. All of these patients had VF and one developed AF and VF simultaneously. Inappropriate shock was observed in 3 patients. In 2 of the patients, inappropriate shock was observed due to sinus tachycardia, and the VT/VF rate recognition zone of the ICD was corrected. In 1 patient, inappropriate shock was observed due to AF. The diagnosis of 2 patients with type 3 ECG pattern changed at follow-up period. One of the 2 patients with ICD was diagnosed with dilated cardiomyopathy (DCM) and the other was diagnosed with arrhythmogenic right ventricular dysplasia (ARVD), and both patients had received shocks. The patient who was diagnosed with ARVD experienced inappropriate shocks due to AF and sinus tachycardia and AV node ablation was performed on this patient. The events seen during follow-up according to definitive diagnosis are summarized in Table 2.

During follow-up, 8 patients experienced an arrhythmic event. The annual arrhythmic event rate was found to be 4.8% patient/year. An arrhythmic event was observed in 24% of symptomatic Type 1 patients, and the annual event development rate was found to be 5.8% patient/year. Arrhythmic events were observed in 13.3% of asymptomatic patients, resulting in an arrhythmic event rate of 3.2% patient/year. Univariate comparisons based on the presence/absence of arrhythmic events showed that male sex (p = 0.004), Type 1 ECG pattern (p = 0.008), SCD (p = 0.036), VT/VF history (p = 0.046), requirement of EPS (p = 0.034), and ICD placement (p = 0.014) were associated with arrhythmic event development. Vasovagal syncope (p = 0.037) was significantly associated with the absence of arrhythmic events (Table 3).

### Table 2: Follow-up findings according to ECG type.

<table>
<thead>
<tr>
<th>Definitive diagnosis</th>
<th>Type 1 (n = 40)</th>
<th>Type 2 (n = 4)</th>
<th>Type 3 (n = 24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (5.0)</td>
<td>0</td>
<td>0</td>
<td>0.486</td>
</tr>
<tr>
<td>Syncope</td>
<td>4 (10.0)</td>
<td>0</td>
<td>1 (4.2)</td>
<td>0.581</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>4 (10.0)</td>
<td>0</td>
<td>1 (4.2)</td>
<td>0.581</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>7 (17.5)</td>
<td>0</td>
<td>2 (8.3)</td>
<td>0.418</td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>3 (7.5)</td>
<td>0</td>
<td>1 (4.2)</td>
<td>0.753</td>
</tr>
<tr>
<td>Revision due to infection</td>
<td>1 (2.5)</td>
<td>0</td>
<td>0</td>
<td>0.701</td>
</tr>
<tr>
<td>Atrioventricular node ablation</td>
<td>0</td>
<td>0</td>
<td>1 (4.2)</td>
<td>0.394</td>
</tr>
</tbody>
</table>

Data are given as frequency (percentage).
Table 3: Comparison of groups with and without arrhythmic events.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with an event (n = 8)</th>
<th>Patients with no event (n = 32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>34 ± 11</td>
<td>35 ± 13</td>
<td>0.832</td>
</tr>
<tr>
<td>Male sex</td>
<td>3 (37.5)</td>
<td>29 (90.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Manifest Type1 ECG</td>
<td>6 (75.0)</td>
<td>7 (21.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Symptom (at admission)</td>
<td>6 (75.0)</td>
<td>25 (78.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Palpitation</td>
<td>4 (50.0)</td>
<td>14 (43.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Syncope</td>
<td>4 (50.0)</td>
<td>21 (65.6)</td>
<td>0.444</td>
</tr>
<tr>
<td>Vasovagal syncope</td>
<td>0</td>
<td>13 (40.6)</td>
<td>0.037</td>
</tr>
<tr>
<td>SCD</td>
<td>2 (25.0)</td>
<td>0</td>
<td>0.036</td>
</tr>
<tr>
<td>VT/VF history</td>
<td>3 (37.5)</td>
<td>2 (6.3)</td>
<td>0.046</td>
</tr>
<tr>
<td>Agonal respiration</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0.200</td>
</tr>
<tr>
<td>Family history of BS</td>
<td>4 (50.0)</td>
<td>14 (43.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Family history of syncope</td>
<td>3 (37.5)</td>
<td>12 (37.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>3 (37.5)</td>
<td>13 (40.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Positive ajmaline test</td>
<td>3 (37.5)</td>
<td>28 (87.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Positive propafenone test</td>
<td>2 (25.0)</td>
<td>4 (12.5)</td>
<td>0.580</td>
</tr>
<tr>
<td>AF in the basal ECG</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0.200</td>
</tr>
<tr>
<td>EPS</td>
<td>8 (100.0)</td>
<td>18 (56.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>EPS, arrhythmia</td>
<td>5 (62.5)</td>
<td>11 (34.4)</td>
<td>0.229</td>
</tr>
<tr>
<td>ICD</td>
<td>7 (87.5)</td>
<td>11 (34.4)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Data are given as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables.

BS: Brugada Syndrome; ICD: Implantable Cardioverter Defibrillator; EPS: Electrophysiological Study; VT: Ventricular Tachycardia; VF: Ventricular Fibrillation; AF: Atrial Fibrillation; SCD: Sudden Cardiac Death

Table 4: Factors independently associated with arrhythmic events (appropriate shock, inappropriate shock, death, syncope, atrial fibrillation).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of spontaneous Type 1 ECG</td>
<td>8.54</td>
<td>0.385-26.37</td>
<td>0.003</td>
</tr>
<tr>
<td>VT/VF history</td>
<td>9.21</td>
<td>0.004-1.88</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CI: Confidence Interval; OR: Odds Ratio; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia

Although univariate analyses demonstrated a number of differences between groups, only the presence of spontaneous type 1 ECG and history of VT/VF were confirmed to be associated with arrhythmic events by multivariate analysis. In the univariate analyses of the study conducted by Brugada, et al. the development of arrhythmic events during follow-up were found to be associated with previous syncope history, spontaneous type 1 BTEC, male sex and ventricular arrhythmia induction in EPS [4]. In the FINGER study, univariate analyses assessing arrhythmic events showed that SCD history, syncope history, presence of spontaneous Type 1 ECG and induction of ventricular tachyarrhythmia in EPS were associated with arrhythmic events in patients with BS [13]. In the PRELUDE study, it was found that history of syncope, spontaneous type 1 ECG, and QRS fragmentation were significant predictors of arrhythmias and were shown to be useful to identify candidates for prophylactic ICD implantation [15]. A recent review supported these possible relationships by reporting that there existed a positive correlation between the number of risk factors and arrhythmic events in patients with BS [23].

Although EPS is utilized commonly, some argue that EPS yields no value, despite the fact that electrophysiological studies have been suggested to enable the identification of asymptomatic patients at higher risk who may benefit from ICD implantation [22]. Brugada and colleagues put forth the suggestion that induction of ventricular arrhythmia was a prognostic factor in EPS. In their initial studies, they found a significant relationship between induction of ventricular arrhythmia in EPS and the development of arrhythmic symptoms such as palpitation, dizziness and neurogenic shock are also observed in patients [26]. In the results of previous studies, the predictors of arrhythmic events in long-term follow-up show considerable diversity. In our study, EPS was performed in 65% of all patients with Type 1 ECG. Of note, EPS had been performed in all (100%) of patients with arrhythmic events, while this value was 56% in patients without arrhythmic events. However, in multivariable analyses, the need for EPS was not found to be a risk factor for arrhythmic events.
events during follow-up and reported that induction of ventricular arrhythmia was an independent predictor of prognosis [4]. However, in their following studies, although they published data indicating that arrhythmia inducibility was detected at a greater frequency in subjects with syncope or fatal arrhythmia, they concluded that EPS was indeed an inadequate variable to assess the risk for fatal arrhythmic events [4,6,25]. The results of our study are in large supportive of prior literature in this context. Considering the well-established diversity in symptoms and clinical course, and the serious risks of arrhythmic events reported in the literature and our study, the importance of predicting the prognosis of BS remains a matter of considerable interest.

Three types of ECG repolarization changes have been described in the right chest leads (V1-V3) in BS. As mentioned previously, Types 2 and 3 ST segment elevation are not considered definitively diagnostic for BS; whereas Type 1 ST segment elevation is diagnostic in the presence of several other parameters, and therefore, is referred to as Brugada ECG [11,27,28]. Longitudinal analyses have revealed that there is a risk of SCD even in individuals with only type 1 ECG pattern without other criteria [29]. A study comparing patients with type 1 ECG recording in one or more leads found that major cardiac arrhythmia rates were similar after 5 years of follow-up among patients with type 1 ECG recordings in one or more leads. According to the diagnostic criteria taken in the most recent consensus, type 1 ECG change in a single lead is not sufficient for diagnosis, but in this study, it was shown that this group has a similar risk [30]. Furthermore, it is well known that detection of a spontaneous ECG with signs of BS is significantly associated with an increased risk of SCD, ranging from 0.81% per year in asymptomatic patients to 2.3% per year in symptomatic patients [15,31,32]. The spontaneous type 1 ECG pattern may change over time with alterations in J wave elevation over time. Therefore, long-term assessment of type 1 ECG load using Holter recording may be a useful marker for stratifying arrhythmia risk [31]. The presence of SCD or syncope and spontaneous Type 1 ECG were shown as poor prognostic factors in a couple of studies [6,25]. In the FINGER study, the presence of symptoms and spontaneous type 1 ECG were presented as the only independent predictors of arrhythmic events. Conversely, sex, family history of SCD, inducibility of ventricular tachyarrhythmias and genetic factors were not found to be predictors [13]. In a multivariate analysis of another study, type 1 ECG in the peripheral leads was found to be independently associated with malignant arrhythmic events [33]. A comprehensive review noted that annual arrhythmic event rates vary significantly according to history of syncope, presence of a spontaneous type 1 ECG pattern, and arrhythmia induction. The authors showed that the lowest risk was seen in people without syncope and with a drug-induced type 1 pattern, while the highest risk was seen in those with syncope and a spontaneous type 1 pattern [34]. The ECGs of the patients in our study showed that Type 1 ECG represented the majority with 40 patients (58.8%), Type 2 ECG was the rarest (4 patients, 5.9%), and Type 3 ECG was identified in 24 patients (35.3%). Among those with type 1 ECG pattern, 13 (32.5%) patients had been diagnosed spontaneously, whereas the pattern was triggered via medication in 27 (67.5%) subjects. In previous studies, the frequency of spontaneous Type 1 ECG varies between 45-71% [6], indicating a relatively lower frequency in our study. Nonetheless, our multivariable analysis demonstrated that spontaneous Type 1 ECG remained as one of independent factors associated with arrhythmic events, consistent with prior literature.

The annual recurrence risk of a major cardiac event is reported to be 10% within the first 4 years after an initial event. This incidence decreases later, but still maintains its importance and late recurrence can be seen. Therefore, ICD implantation is indicated for all patients with a history of major arrhythmia [31]. Although, the risk of arrhythmia was elevated among patients who received BS diagnosis after syncope, only discontinuous VF-induced syncope has been consistently associated with increased SCD likelihood. Therefore, there is no doubt that an ICD is needed when presented with a case of arrhythmia-induced syncope [9,35,36]. These relationships are supported by various studies. For instance, a study from Japan showed that BS patients with documented VF had worse prognosis for cardiac events than those with syncope without VF and asymptomatic patients [37]. In another comprehensive study, annual arrhythmic event rates per capita were found to be 1.70% for the subgroup with a history of VT/VF, and Cox regression analysis revealed that initial presentation with VT/VF and duration of the P wave were the most important predictors of SCD [13]. In the multivariable analysis of our study, VT/VF history was also found as an independent factor associated with increased arrhythmic event likelihood, like prior studies.

There are some limitations of our study. First, the small number of cases may make it difficult to generalize the results to the population; however, although BS is not an extremely rare disease, identification of patients - especially asymptomatic individuals- is difficult; thus, leading to small study sizes in most of the literature. Second, the effects of other possible risk factors may have been overlooked since our study did not utilize genetic analyses. Third, the difference in group sizes, particularly in relevance to the type 2 ECG group, may have negatively affected the statistical analyses of between-group comparisons.

**Conclusion**

We found the presence of spontaneous type 1 ECG and a history of VT/VF to be poor prognostic factors for BS, as demonstrated by multivariable analyses. A
comprehensive risk assessment approach and a more accurate risk stratification method could assist in making therapeutic decisions in patients with BS, particularly with regard to the need for ICD implantation. For this purpose, more comprehensive studies with a larger number of patients and longer follow-up periods are required.

Conflict of Interest

The author declares that there is no conflict of interest.

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Ethics Committee Approval

This study was initiated after obtaining approval from Baskent University Clinical Research Ethics Committee (Decision number: KA09/51, decision date: 04.03.2009). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration and its later amendments.

Authorship Contributions

Concept: V.C., O.O., I.A.; Design: V.C., O.O.; Data Collection or Processing: V.C., O.O.; Analysis or Interpretation: V.C., O.O.; Literature Search: V.C., O.O.; Writing: V.C., O.O., I.A.

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