**Risk Stratification in Brugada Syndrome**

**Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry**

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**Objectives**

The PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) prospective registry was designed to assess the predictive accuracy of sustained ventricular tachycardia/ventricular fibrillation (VTs/VF) inducibility and to identify additional predictors of arrhythmic events in Brugada syndrome patients without history of VT/VF.

**Background**

Brugada syndrome is a genetic disease associated with increased risk of sudden cardiac death. Even though its value has been questioned, inducibility of VTs/VF is widely used to select candidates to receive a prophylactic implantable defibrillator, and its accuracy has never been addressed in prospective studies with homogeneous enrolling criteria.

**Methods**

Patients with a spontaneous or drug-induced type I electrocardiogram (ECG) and without history of cardiac arrest were enrolled. The registry included 308 consecutive individuals (247 men, 80%; median age 44 years, range 18 to 72 years). Programmed electrical stimulation was performed at enrollment, and patients were followed-up every 6 months.

**Results**

During a median follow-up of 34 months, 14 arrhythmic events (4.5%) occurred (13 appropriate shocks of the implantable defibrillator, and 1 cardiac arrest). Programmed electrical stimulation performed with a uniform and pre-specified protocol induced ventricular tachyarrhythmias in 40% of patients: arrhythmia inducibility was not a predictor of events at follow-up (9 of 14 events occurred in noninducible patients). History of syncope and spontaneous type I ECG (hazard ratio [HR]: 4.20), ventricular refractory period <200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) were significant predictors of arrhythmias.

**Conclusions**

Our data show that VT/VF inducibility is unable to identify high-risk patients, whereas the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic implantable cardioverter defibrillator. (J Am Coll Cardiol 2012;59:37–45) © 2012 by the American College of Cardiology Foundation

Brugada syndrome (BrS) was described in 1992 as a disease that predisposes apparently healthy individuals to sudden cardiac death (1). Patients present with a typical electrocardiographic pattern characterized by a coved type ST-segment elevation in the right precordial leads (V1 to V3) and complete or incomplete right bundle branch block. Such a diagnostic electrocardiographic profile might be
spontaneously present (Fig. 1A) or it might be concealed and unmasked upon intravenous administration of sodium channel blockers (Fig. 1B) such as flecainide, ajmaline, procainamide, or pilsicainide (2). This diagnostic electrocardiographic pattern has a worldwide prevalence in the general population of 1 of 1,000 individuals (3), representing a relevant health care issue.

Although quinidine was proposed as a possible pharmacologic therapy to abate the risk of life-threatening arrhythmias (4), controlled clinical trials that confirm its effectiveness are lacking. Therefore, clinicians are left with the challenging task to select patients who might benefit from an implantable defibrillator.

Pedro and Josep Brugada were the first to propose in 2002, on the basis of data from their registry, that sustained ventricular tachycardia/ventricular fibrillation (VTs/VF) inducibility at programmed electrical stimulation (PES) is useful to identify patients at high risk of sudden death (5). In the same year we were unable to confirm the predictive value of the test in our BrS cohort, and we suggested that the use of PES might lead to the unnecessary insertion of an implantable cardioverter-defibrillator (ICD) due to the high inducibility rate (6). Our data showed the presence of a spontaneous type I electrocardiogram (ECG) and the history of syncope were the only predictors of adverse outcome; accordingly, we proposed a risk stratification scheme that recommends ICD only in the patients with a spontaneous ST-segment elevation and history of syncope.

To sort out the debate on the value of VTs/VF inducibility, a group of experienced investigators convened to discuss the matter and produced a consensus document to support the use of VTs/VF inducibility to identify high-risk patients who should be treated with a defibrillator (7). As a result, VTs/VF inducibility became largely adopted to guide the management of patients. Over the years, in agreement with our initial report, other studies failed to confirm the capability of VTs/VF inducibility to identify high-risk individuals (8). Subsequent data from Brugada et al. confirmed its value (9–11), whereas in 2005 the second consensus conference (9) issued a Class IIa for use of PES in
patients with a spontaneous type I ECG and a Class IIb for PES in patients without a spontaneous type I pattern. In 2006 the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines for prevention of sudden death (12) reflected the ongoing debate and did not provide stringent indication for PES in BrS (Class IIb).

Today, after almost 1 decade, the field is still struggling with the discordant results derived from retrospective analysis of different registries (13–15), and clinicians often still use PES to identify patients in need of an ICD.

To contribute to fill this gap, we organized an Italian multicenter prospective registry called PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) to assess the role of PES and VTs/VF inducibility in patients with BrS in whom there was no history of sustained ventricular tachycardia or ventricular fibrillation. Enrollment of patients was open to all Italian electrophysiology centers willing to participate. The study was endorsed by the Italian Cardiac Arrhythmias Association (Associazione Italiana Aritmologia e Cardiostimolazione).

Objectives of the PRELUDE registry were: 1) to evaluate the impact of different protocols of ventricular inducibility on the predictive value of PES; 2) to evaluate prospectively the predictive value of PES; and 3) to search for novel outcome predictors in BrS.

Methods

Registry design and enrollment criteria. The study was coordinated by the team at the Maugeri Foundation in Pavia; the participating centers are listed in the acknowledgments, and the top 10 enrolling centers coauthored the study.

Patients were considered eligible if they were older than 18 years, presented either a spontaneous or a pharmacologically induced type I ECG pattern with coved ST-segment elevation >2 mm in at least 2 right precordial leads, and had never experienced either cardiac arrest or sustained ventricular tachycardia (7), because this latter group of patients already has a Class I indication for ICD insertion (12). At the time of enrollment an ECG was sent to the coordinating center to validate the presence of a type I ECG and ensure the presence of uniform enrollment criteria in the study population. At enrollment, 2 blinded investigators (C.N., S.G.P.) assessed the following parameters: PR interval, QRS, presence of complete right bundle branch block, QT, corrected QT, and QRS fragmentation (QRS-f) (16) defined as 2 or more spikes within the QRS complex in leads V1 to V3 (Fig. 1C).

The absence of structural cardiac abnormalities or cardiac diseases (such as previous myocardial infarction, cardiomyopathies, angina, or left ventricular hypertrophy) was verified before enrollment by echocardiography and exercise stress test.

All patients underwent PES to assess VTs/VF inducibility. At the present time, there is no agreement on how PES should be performed in BrS, and the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for prevention of sudden cardiac death did not recommend any specific protocol (12). In the absence of guidance, the PRELUDE investigators agreed on a stimulation protocol consisting of 2 drive cycles (600 and 400 ms, S1) and 3 extrastimuli (S2 to S4) according to the protocol reported by Brugada et al. (17,18). Minimum coupling interval of premature beats was set to 200 ms for S2 and S3 and to refactoriness for S4. The inducibility protocol was performed from the apex of the right ventricle and from the right ventricular outflow tract unless the patient had inducible ventricular tachycardia at the first location (9).

“Inducible patients” were defined as those in whom PES induced ventricular fibrillation, sustained polymorphic ventricular tachycardia (>30 s of duration), or polymorphic syncopal ventricular tachycardia requiring direct current shock. This definition closely follows that of Brugada et al. (5). Whenever the physician elected to assess short-term reproducibility of PES, the inducibility protocol was repeated in the inducible patients. The test was considered reproducible (i.e., confirmatory of the result obtained in the first test) when VTs/VF was induced a second time with the same protocol. Measurements of the ventricular refractory period (VRP) (19) (delivery of an S2 at twice the diastolic threshold on a driving cycle of 600 ms with a minimal coupling interval of 200 ms from the apex) were also collected; for the purpose of the analysis, when conduction of the S2 at 200 ms was preserved, it was inferred that VRP was <200 ms.

Enrollment of patients in the PRELUDE registry did not influence therapeutic strategies: physicians were free to choose with their patients the preferred management option. Similarly, the physicians and patients were free to decide whether genetic testing should be performed.

Personal history of syncopal spell and family history of BrS or unexplained sudden cardiac death were collected. Syncope was defined as an abrupt loss of consciousness occurring at rest or a loss of consciousness during sleep with agonal respiration reported by bystanders. The first follow-up visit for patients who received an ICD was scheduled 3 months after surgery.

“Arrhythmic events” at follow-up were defined as the occurrence of ventricular fibrillation or appropriate ICD interventions on the basis of the clinical judgment of the cardiologist in charge of the patient. Documentation of ICD shocks was collected by the coordinating center at the Maugeri Foundation.

Follow-up visits were scheduled every 6 months. Data entry was performed at each center on a web-based case report form; each patient was attributed an anonymous code, and no personal data/identifiers were part of the case report form. Only physicians in charge of patients were able to retrieve the identity of patients. The ethics committee of each participating center approved the study protocol and the informed consent for patients. Separate institutional review board-approved consent forms were used for genetic testing. Enrollment in the PRELUDE registry started in July 2004 and ended in March
and backward elimination (likelihood ratio method). In all analyses, inducibility proved to be nonsignificant and was removed in backward analysis. All other covariates proved to be significant.

Results

Study population. A total of 308 patients were enrolled, and their demographic profile is reported in Table 1. Patients had a mean age at enrollment of 45 ± 12 years; as expected (3,6,11,13,14), most patients were men (n = 247, 80%).

Diagnosis of BrS was established on the presence of a type I ECG pattern in the absence of structural abnormalities. Type I ECG was spontaneously present in 56% of subjects (n = 171), whereas in the remaining patients it was induced upon intravenous drug challenge with ajmaline (1 mg/kg) or flecainide (2 mg/kg, max 150 mg) (Figs. 1A and 1B). The ECG parameters are presented in Table 1. QRS-f (Fig. 1C) was present in 25 of 308 patients (8.1%). Genetic analysis was performed in 123 patients and, in agreement with previous findings (6,20), an SCN5A mutation was identified in 20% of tested patients (n = 24). Sixty-five patients (21%) reported at least 1 syncopal spell in their clinical history, whereas >1 event occurred in 16 of 65 patients (25%). The first syncopal episode occurred an average of 2.92 years before enrollment (range 0 to 12 years). Mean age at syncpe was 45 ± 13 years; none of the patients experienced syncpe before age 18.

At follow-up, 14 of 308 (4.5%) patients experienced cardiac arrest (Fig. 1D) and/or documented ventricular fibrillation: all patients were resuscitated (13 by the ICD, and 1 by the emergency medical service); therefore, no sudden death or permanent cerebral damage occurred in the study. The clinical profile of the 14 patients with arrhythmic events at follow-up is presented in Table 2.

PES and arrhythmic events at follow-up. Programmed electrical stimulation was performed in all 308 patients; 126 of 308 patients (41%) met the criteria for inducibility

<table>
<thead>
<tr>
<th>Patient ID #</th>
<th>Sex</th>
<th>Age (yrs)*</th>
<th>Family History of SCD</th>
<th>Spontaneous Type 1 ECG</th>
<th>History of Syncope</th>
<th>Inducibility</th>
<th>VRP &lt;200 ms</th>
<th>QRS-f</th>
<th>SCN5A Mutation</th>
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<td>4</td>
<td>M</td>
<td>43</td>
<td>-</td>
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<td>73</td>
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<td>58</td>
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<td>+</td>
<td>-</td>
<td>N.A.</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ICD shock</td>
</tr>
</tbody>
</table>

*Age at enrollment.
CA = cardiac arrest; ICD shock = appropriate implantable cardioverter-defibrillator intervention; N.A. = deoxyribonucleic acid not available; SCD = sudden cardiac death; other abbreviations as in Table 1.
We also analyzed the inducibility on the basis of the number of premature stimuli delivered. All 308 patients were tested with a single premature extra-stimulus that induced arrhythmias in 7 of 308 (2.3%) patients; 2 premature stimuli were tested in 301 patients (the 7 patients inducible with 1 premature beat were not further tested). Of 301 patients, 56 (19%) were inducible with 2 premature beats. Finally, the 245 patients who were not inducible with 1 or 2 premature beats completed the protocol up to 3 extrastimuli, and 63 of 245 patients (26%) were inducible. Overall, of the 126 inducible patients, 5.5% were induced with 1 premature beat, 44.5% with 2 premature beats, and 50% with 3 premature beats. As expected, the number of inducible patients is higher when more aggressive protocols are used. No significant difference in the duration of follow-up was present between inducible and noninducible patients (35 ± 16 months vs. 37 ± 16 months, p = 0.4).

The site of inducibility was equally distributed between right ventricular outflow tract (59 of 126; 46.8%) and right ventricular apex (58 of 126; 46.0%): 9 (7.2%) patients were inducible both from the outflow tract and the apex. Of 126 inducible patients, a second inducibility test was performed in 111 (88%) patients as part of the short-term reproducibility of PES study elective protocol (see the Methods section). In analogy with what we reported in 2002 (21), a reproducible outcome of PES was achieved only in the minority of patients (i.e., in 38 of 111 subjects [34%]) (Fig. 2).

An ICD was inserted in 98 of 126 (78%) inducible patients and in 39 of 182 (21%) noninducible patients. It is possible that the medico-legal implications of nonimplanting patients who developed VT/VF during PES influenced the physicians to recommend an ICD for the inducible patients even if the protocol allowed for a decision “not to implant.”

After a mean follow-up of 36 ± 8 months (range 5 to 73 months), 14 events were observed in the 308 patients (4.5%), corresponding to an annual event rate of 1.5%. Kaplan-Meier survivorship analysis showed no statistical difference in the outcome of inducible versus non-inducible patients (5 arrhythmic events in 126 inducible subjects [3.9%] vs. 9 arrhythmic events in 182 non-inducible patients [4.9%; log-rank 0.67]) (Fig. 3A, Table 3). Furthermore, when we restricted Kaplan-Meier survivorship analysis to the patients inducible with 1 and 2 premature stimuli, we were similarly unable to demonstrate the ability of the test to discriminate between patients with and those without arrhythmic events at follow-up (log-rank p = 0.89) (Fig. 3B, Table 3).

The sensitivity and specificity of VTs/VF inducibility with up to 3 premature beats to predict outcome were 35.7% (95% confidence interval [CI]: 16% to 60%) and 58.8% (described in the Methods section). We also analyzed the inducibility on the basis of the number of premature stimuli delivered. All 308 patients were tested with a single premature extra-stimulus that induced arrhythmias in 7 of 308 (2.3%) patients; 2 premature stimuli were tested in 301 patients (the 7 patients inducible with 1 premature beat were not further tested). Of 301 patients, 56 (19%) were inducible with 2 premature beats. Finally, the 245 patients who were not inducible with 1 or 2 premature beats completed the protocol up to 3 extrastimuli, and 63 of 245 patients (26%) were inducible. Overall, of the 126 inducible patients, 5.5% were induced with 1 premature beat, 44.5% with 2 premature beats, and 50% with 3 premature beats. As expected, the number of inducible patients is higher when more aggressive protocols are used. No significant difference in the duration of follow-up was present between inducible and noninducible patients (35 ± 16 months vs. 37 ± 16 months, p = 0.4).

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(95% CI: 57.9% to 60%), respectively (Table 3). When patients inducible with 1 or 2 premature beats were analyzed, sensitivity and specificity of PES were 25% and 74.2%, respectively (Table 3).

Identification of other clinical predictors of arrhythmic events. We performed univariate and multivariate analysis to investigate whether other clinical variables are associated with the occurrence of events at follow-up. We first addressed, on the basis of previous studies (6,8,14–17), the univariate association with outcome of the following predictors: spontaneous type I ECG, history of syncope, spontaneous type I ECG and syncope (combined endpoint previously shown as the strongest predictor of arrhythmic events at follow-up), PR duration, and QRS-f. We tested the hypothesis—on the basis of the observations that arrhythmic episodes in BrS are often initiated by a short-coupled beat and that patients present with an abbreviated action potential (22–24)—that the VRP might predict arrhythmic risk (21). Sensitivity and specificity of clinical variables to differentiate between patients with and without events are presented in Table 3.

Kaplan-Meier analysis showed that history of syncope (log rank p = 0.011) and spontaneous type I ECG (log-rank p = 0.004) (Figs. 4A and 4B), VRP (log-rank p = 0.002), and QRS-f (log-rank p = 0.000001) (Fig. 5) were significantly associated with outcome. Interestingly, as previously shown (6), the most powerful predictor of events was the presence of syncope and of a spontaneous ECG pattern (log-rank p = 0.000105) (Fig. 6, Table 3).

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We investigated the effect of each covariate (spontaneous type I ECG, history of syncope, QRS-f, and VRP <200 ms) on VTs/VF inducibility. All covariates retained an independent predictive value, whereas VT/VF inducibility remained unable to predict events (Table 4). Hazard ratios obtained with Cox multivariate analysis (stepwise analysis with backward elimination, likelihood ratio method) when all covariates were tested at the same time were as follows: inducibility with up to 3 premature extrastimuli HR: 1.03 (95% CI: 0.34 to 3.16, p = 0.96); spontaneous type I ECG and history of syncope HR: 4.20 (95% CI: 1.38 to 12.79, p = 0.012); VRP <200 ms HR: 3.91 (95% CI: 1.03 to 12.79, p = 0.045); QRS-f HR: 4.94 (95% CI: 1.54 to 15.8, p = 0.007). After inducibility was removed, significance of other covariates remained the same, thus confirming redundancy of induction.

We calculated the performance of each clinical indicator of arrhythmic risk if used to guide the insertion of an ICD and calculated the expected number of patients receiving insertion to save 1 life (number needed to treat). The number needed to treat values for each clinical variable were as follows: 102.3 for inducibility, 12.4 for history of syncope, 14.5 for spontaneous ECG type I, 6.8 for the combined

### Table 3 Prognostic Accuracy of Predictors of Outcome

<table>
<thead>
<tr>
<th></th>
<th>Inducibility*</th>
<th>Inducibility (With 1 or 2 Extra Stimuli)</th>
<th>Spontaneous Type 1 ECG Pattern</th>
<th>History of Syncope</th>
<th>Spontaneous Type 1 ECG and Syncope</th>
<th>QRS-f</th>
<th>VRP &lt;200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>35.7 (14–64)</td>
<td>25.0 (5.8–50)</td>
<td>92.9 (65–99)</td>
<td>50.0 (25–76)</td>
<td>42.9 (29–69)</td>
<td>42.9 (20–69)</td>
<td>78.6 (49–94)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>58.8 (58–60)</td>
<td>74.2 (78–81)</td>
<td>45.7 (45–47)</td>
<td>80.6 (79–82)</td>
<td>90.5 (89–92)</td>
<td>93.5 (92–95)</td>
<td>62.9 (62–64)</td>
</tr>
<tr>
<td><strong>NNT</strong></td>
<td>102.3 (20–200)</td>
<td>—</td>
<td>14.5 (12–58)</td>
<td>12.4 (6.7–108)</td>
<td>6.8 (3.7–26)</td>
<td>4.7 (2.7–14)</td>
<td>13.2 (9.4–50)</td>
</tr>
<tr>
<td><strong>Univariate log-rank</strong></td>
<td>0.67</td>
<td>0.89</td>
<td>0.004</td>
<td>0.011</td>
<td>0.000105</td>
<td>0.000001</td>
<td>0.002</td>
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</table>

Values are % (95% confidence intervals). *Inducibility = inducibility of VTs/VF during programmed electrical stimulation. NNT = number needed to treat; other abbreviations as in Table 1.
endpoint of spontaneous type 1 and syncope, 4.7 for QRS-f, and 13.2 for VRP <200 ms (Table 3).

Discussion

Background. The most challenging aspect of BrS is represented by the lack of robust recommendations for the management of individuals presenting with the electrocardiographic diagnosis of the disease without a previous documentation of arrhythmias. The missing elements to formulate recommendations for managing these patients are the lack of agreement on the annual incidence of life-threatening arrhythmias at follow-up (severity of the disease) and the discordant opinions on the value of VTs/VF inducibility to identify patients at higher risk of cardiac arrest.

Incidence of sudden death and role of VTs/VF inducibility for risk stratification. The correct quantification of the annual incidence of arrhythmic events in BrS patients is critical to set indications for the prophylactic implant of a defibrillator. In 1998 Brugada et al. (25) reported no difference in the occurrence of cardiac arrest at follow-up between symptomatic and asymptomatic patients. In this first study they showed an incidence of ventricular fibrillation and sudden death at follow-up of 4.5%/year among previously symptomatic patients (80% had survived cardiac arrest) and of 2.7%/year among asymptomatic patients (25). In the same study the authors also reported inducibility at PES of 80% of patients (78% in symptomatic and 85% in asymptomatic subjects).

In 2003, Brugada et al. (17) reported data in a cohort of 547 patients who had not experienced cardiac arrest (i.e., similar to the patients prospectively followed in the PRELUDE registry) over a mean follow-up of 24 months (range 1 to 160 months). Patients were studied with VTs/VF inducibility protocol up to 3 premature extrastimuli (i.e., the same protocol used in the PRELUDE registry). The inducibility rate was 40%, and the annual incidence of cardiac arrest/death was 4.1%. Interestingly, even though VTs/VF inducibility rate is identical in the PRELUDE registry and in the 2003 study of Brugada et al., the rate of events during follow-up is much lower in the PRELUDE registry (1.5%/year in the PRELUDE registry vs. 4.1%/year in Brugada et al. [17]). Even more important, however, is the evidence that, despite the similar rate of inducibility with the “3 premature beats” protocol, the predictive value of the test was completely different. Interestingly, both studies identified the presence of a spontaneous pattern and the history of syncope as robust prognostic indicators of events at follow-up; however, only the study by Brugada et al. (17) suggested that inducibility at PES is a most informative risk indicator, whereas it has no predictive value in the PRELUDE registry. Remarkably when VTs/VF inducibility was repeated, only 34% of inducible patients were re-induced at the second trial (Fig. 2).
Data from the FINGER (France, Italy, the Netherlands, Germany) study originated from pooling data from 11 European centers also provided information on rate of events and inducibility in BrS (14). The study also included patients with a history of cardiac arrest, but on the basis of reported data, we were able to calculate the inducibility rate in the 967 enrolled patients after the exclusion of individuals resuscitated from ventricular fibrillation (i.e., the subgroup comparable to the population of the PRELUDE registry). In the “no ventricular fibrillation” subgroup of the FINGER study, the inducibility rate with 3 premature stimuli was once more 40% and showed no ability to predict life-threatening events at follow-up. In this group of patients, the annual incidence of events was 1.1% (i.e., similar to that reported in the PRELUDE registry).

The PRELUDE data provide a prospective evaluation of the risk of cardiac arrest in BrS as well as an assessment of the value of VT/VF inducibility to identify affected individuals at high risk of sudden death. The annual rate of cardiac arrest is 1.5% (i.e., much lower than what is consistently reported by the registry of Brugada et al. [2,17]). Furthermore, it is also evident by the results of the PRELUDE registry that, irrespective of the protocol used, the VTs/VF inducibility during PES is not useful to identify high-risk patients in BrS (Table 3). Interestingly, using VTs/VF inducibility to select patients for the implant, we would have performed implantation in 126 individuals and observed an arrhythmic event at 3 years of follow-up in 5 of them.

### A new risk stratification scheme for BrS?

The evidence that VTs/VF inducibility is not a useful risk indicator opens the need to establish alternative risk stratification metrics. The robust predictive value of a spontaneous type I ECG and history of syncope that we proposed in 2002 (6) and was confirmed by other groups (14,17) is once more supported in the prospective evaluation of the PRELUDE registry, where it is presented in Table 5.

#### Table 5 Comparison of Brugada Syndrome Registries

<table>
<thead>
<tr>
<th></th>
<th>Brugada et al. (11), 2003</th>
<th>FINGER (14) *</th>
<th>PRELUDE</th>
<th>Delise et al. (15), 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>547</td>
<td>967</td>
<td>308</td>
<td>320</td>
</tr>
<tr>
<td>Average follow-up (months)</td>
<td>24</td>
<td>32.5</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Number of patients with syncope before enrollment (%)</td>
<td>124 (23%)</td>
<td>313 (32%)</td>
<td>64 (21%)</td>
<td>105 (34%)</td>
</tr>
<tr>
<td>Spontaneous type 1 ECG (%)</td>
<td>391 (71%)</td>
<td>437 (45%)</td>
<td>171 (56%)</td>
<td>174 (54%)</td>
</tr>
<tr>
<td>Arrhythmic events at follow-up (%)</td>
<td>45 (8.2%)</td>
<td>29 (2.9%)</td>
<td>14 (4.5%)</td>
<td>17 (5.3%)</td>
</tr>
<tr>
<td>Annual arrhythmic event rate (%)</td>
<td>4.1%</td>
<td>1.1%</td>
<td>1.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>VTs/VF inducibility performed (%)</td>
<td>408 (75%)</td>
<td>602 (62%)</td>
<td>308 (100%)</td>
<td>245 (77%)</td>
</tr>
<tr>
<td>Number of patients with inducible VTs/VF (%)</td>
<td>163 (40%)</td>
<td>246 (41%)</td>
<td>126 (41%)</td>
<td>96 (39%)</td>
</tr>
</tbody>
</table>

Values are n, n (%), or %. *Patients with sudden cardiac death have been excluded to allow comparison with the other studies.

FINGER = France, Italy, Netherlands, Germany study; PRELUDE = PRogrammed ELectrical stimUlation preDictive valuE registry; other abbreviations as in Table 1.
associated with a >4-fold increase (HR: 4.2) in the risk of having an arrhythmic event as compared with patients without a spontaneous type I ECG. Furthermore, having the ECG pattern unmasked by a provocative drug test has a very high negative predictive value that reflects the fact that only 1 patient without spontaneous pattern had a cardiac arrest at follow-up (Table 2).

Interestingly, data from the PRELUDE registry identify 2 novel clinical indicators of increased risk of life-threatening events: 1) the presence of QRS-f (16); and 2) the presence of a short VRP.

The idea of using QRS-f was based on the data by Morita et al. (26), who suggested that—in an experimental model of BrS—fragmentation of QRS was a reliable indicator of susceptibility to arrhythmias. The authors also tested in a pilot clinical study the value of this parameter in predicting arrhythmic events and demonstrated that QRS-f but not VTs/VF inducibility might be a good predictor of risk of events (16).

The results of the PRELUDE registry show that PES, irrespective of the number of premature beats used, is not predictive of arrhythmic events. The study confirms the prognostic value of the presence of a spontaneous type I ECG and history of syncope and shows for the first time that QRS-f and a ventricular effective refractory period <200 ms are independent risk indicators in a large cohort of patients prospectively investigated.

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REFERENCES


Key Words: Brugada syndrome • cardiac arrest • electrophysiology • risk factors • ventricular arrhythmias.

APPENDIX

For supplementary materials, please see the online version of this article.