Risk Stratification in Patients With Brugada Syndrome Without Previous Cardiac Arrest

– Prognostic Value of Combined Risk Factors –

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Background: Risk stratification in patients with Brugada syndrome for primary prevention of sudden cardiac death is still an unsettled issue. A recent consensus statement suggested the indication of implantable cardioverter defibrillator (ICD) depending on the clinical risk factors present (spontaneous type 1 Brugada electrocardiogram (ECG) [Sp1], history of syncope [syncpe], and ventricular fibrillation during programmed electrical stimulation [PES+]). The indication of ICD for the majority of patients, however, remains unclear.

Methods and Results: A total of 218 consecutive patients (211 male; aged 46±13 years) with a type 1 Brugada ECG without a history of cardiac arrest who underwent evaluation for ICD including electrophysiological testing were examined retrospectively. During a mean follow-up period of 78 months, 26 patients (12%) developed arrhythmic events. On Kaplan-Meier analysis patients with each of Sp1, syncope, or PES+ suffered arrhythmic events more frequently (P=0.018, P<0.001, and P=0.003, respectively). On multivariate analysis Sp1 and syncope were independent predictors of arrhythmic events. When dividing patients according to the number of these 3 risk factors present, patients with 2 or 3 risk factors experienced arrhythmic events more frequently than those with 0 or 1 risk factor (23/93 vs. 3/125; P<0.001).

Conclusions: Syncpe, Sp1, and PES+ are important risk factors and the combination of these risks well stratify the risk of later arrhythmic events. (Circ J 2015; 79: 310–317)

Key Words: Brugada syndrome; Electrophysiological study; Primary prevention; Risk stratification; Syncope

Brugada syndrome (BrS), characterized by ST-segment elevation in the right precordial leads (type 1 Brugada electrocardiogram [ECG]) and a high incidence of ventricular fibrillation (VF) leading to sudden cardiac death (SCD) in young and otherwise healthy adults, has been reported since the initial description of the disease.1 It is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts.2 Clearly, a method for the risk stratification of patients with BrS is required. A number of studies have noted a high recurrence rate of VF in patients with BrS who had previously experienced cardiac arrest.3–7 Further discussion regarding the indications for implantable cardioverter defibrillator (ICD) in these patients (secondary prevention) is unnecessary. The indications for ICD for primary prevention of SCD in patients with BrS without a history of VF or cardiac arrest, however, have not been well evaluated. A recent consensus statement suggested the indication of ICD for these patients based on the following risk factors: spontaneous diagnostic type 1 Brugada ECG (Sp1), history of syncope likely caused by ventricular...
arhythmia (syncope), and development of VF during programmed electrical stimulation (PES+, ie, inducible patients). This statement recommends ICD implantation for primary prevention of SCD as a class IIA indication for patients with Sp1 and syncope and as a class IB indication for patients with PES+. The indication of ICD for the patients who do not meet these conditions, however, remains unclear. Here we hypothesized that these 3 proposed risk factors may be used to stratify the risk of SCD in patients with BrS and without previous cardiac arrest.

Methods

Patients and Baseline Data
Among 612 patients who had been given the diagnosis of BrS at 2 Japanese institutions, Okayama University Hospital or the National Cerebral and Cardiovascular Center between 1996 and 2012, we retrospectively enrolled 218 consecutive patients with type 1 Brugada ECG, without a history of VF or cardiac arrest, who were hospitalized and underwent electrophysiological testing to evaluate the suitability of ICD therapy. All patients were followed for at least 12 months from the start of the investigation. The primary endpoint was the occurrence of VF or SCD. Patients with structural cardiac abnormalities on transthoracic echocardiography were excluded. Written informed consent regarding the data acquisition was obtained from all individuals. The study conforms to the 1975 Declaration of Helsinki as reflected by approval by the Institutional Review Board in both institutions.

In accordance with the consensus report in 2005, type 1 Brugada ECG was defined as coved-type ST-segment elevation ≥0.2 mV followed by a negative T wave in more than 1 right precordial lead (V1–V3) in the presence or absence of a sodium channel-blocking agent. Although ECG could change during follow-up, Sp1 was defined as spontaneous type 1 Brugada ECG in the absence of a sodium channel-blocking agent at the beginning of the study. ECG was recorded at least 4 different times in each patient. Placement of the right precordial leads in a superior position up to the second intercostal space was performed to increase sensitivity. A sodium channel-blocking agent (i.e., pilsicainide up to 1 mg/kg body weight) was used under careful monitoring to unmask ECG abnormalities when Sp1 was not observed. All patients underwent electrophysiological evaluation to assess the inducibility of VF by PES. The protocol involved up to 3 extrastimuli applied to the right ventricular apex and right ventricular outflow tract at a minimum coupling interval of 180 ms. PES+, however, was defined as VF or polymorphic ventricular tachycardia lasting >30 s or requiring direct current shock induced at a coupling interval ≥200 ms according to the consensus document. Syncope was considered present when a patient had an episode of syncope judged as likely caused by ventricular arrhythmia. Syncope likely due to vasovagal events such as those occurring during abrupt postural changes, exposure to heat and dehydration, or emotional reactions were excluded. Data on family history of SCD prior to age 45 (FH) were also collected. Combinations of the 3 risk factors proposed in the consensus statement, that is, Sp1, syncope, and PES+, were examined for further risk stratification of arrhythmic events.

Follow-up and Arrhythmic Events
Patient treatment, including ICD implantation, was based on physician clinical judgment. All patients were followed up for at least 12 months after the start of the investigation. Patients with ICD were followed every 3 months while those without ICD were followed at least once a year. Arrhythmic events were defined as SCD or appropriate shock delivery by ICD against ventricular tachyarrhythmia.

Statistical Analysis
Data were analyzed using JMP (version 11.0.0, SAS, Cary, NC, USA). For continuous variables, comparisons among groups were made using Student’s t-test. Pearson’s chi-squared test was used for categorical variables. Event analysis over time was performed using the Cox proportional hazard regression model. Risk was quantified as a hazard ratio (HR) with 95% confidence interval. Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test. P<0.05 was considered statistically significant.

Results
Patient Characteristics and Overall Event Rate
A total of 218 consecutive patients were examined. As shown in Table 1, the mean patient age at diagnosis was 46±13 years and most patients were men (n=211, 96%). ICD were implanted in more than half of the patients (n=122, 56%). Sp1 was observed in 159 patients (73%), and 87 patients (40%) had experienced syncope. PES+ was observed in 61 patients (28%), and 64 patients (29%) had FH. During the mean follow-up period of 78±49 months (median, 76 months), 26 patients (12%) experienced at least 1 arrhythmic event. The pe-

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics vs. Presence of SCD or VF</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
</tr>
<tr>
<td>ICD implantation</td>
</tr>
<tr>
<td>ICD period of implantation (months)</td>
</tr>
<tr>
<td>Sp1</td>
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<tr>
<td>Syncope likely caused by arrhythmia</td>
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<tr>
<td>Inducibility of VF (PES+)</td>
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<td>Family history of SCD</td>
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</table>

Data given as n (%) or mean±Standard Deviation. ICD, implantable cardioverter defibrillator; PES, programmed electrical stimulation; SCD, sudden cardiac death; Sp1, spontaneous type 1 Brugada electrocardiogram; VF, ventricular fibrillation.
**Figure 1.** Kaplan-Meier analysis of lethal arrhythmic events during follow-up in 218 patients with Brugada type 1 electrocardiogram but without a history of cardiac arrest, both overall (red line) as well as separately at Okayama University (gray) and the National Cerebral and Cardiovascular Center (NCVC; black). SCD, sudden cardiac death; VF, ventricular fibrillation.

**Figure 2.** Kaplan-Meier analysis of lethal arrhythmic events during follow-up, categorized by risk factors present: (A) spontaneous type 1 Brugada ECG (Sp1− vs. Sp1+); (B) history of syncope judged to be likely caused by ventricular arrhythmias (syncope− vs. syncope+); (C) inducibility of ventricular fibrillation by programmed electrical stimulation (PES− vs. PES+); and (D) family history of SCD (FH− vs. FH+). ECG, electrocardiogram; SCD, sudden cardiac death; VF, ventricular fibrillation.
Risk Assessment in BrS

The proposed risk factors compared to those without it (Sp1, P=0.018, Figure 2A; syncope, P<0.001, Figure 2B; PES+, P=0.003, Figure 2C). FH, however, had no association with event rate (P=0.998, Figure 2D).

Next, univariate and multivariate analysis were used to investigate the possible clinical variables associated with SCD and VF. On multivariate analysis syncope and Sp1 were independent predictors of arrhythmic events during follow-up (HR, 6.81 and 4.51, respectively) as shown in Table 2. PES+, however, was not an independent predictor (HR, 2.03, P=0.078).

Risk Factor Combinations

Figure 3 shows the number of risk factors of Sp1, syncope, and PES+ in each patient, from 0 to 3. The majority of patients had 1 (44%) or 2 (31%) risk factors. Using event-free survival curve according to the number of risk factors, the event-free rate decreased as the number of risk factors increased (Figure 4). The prevalence of arrhythmic events was higher in patients with 2 risk factors compared to patients with 1 risk factor (P<0.001). There was no statistically significant difference in the number of arrhythmic events between patients with 2 and 3 risk factors (P=0.089), and patients without any risk factors had no SCD or VF.

Among patients with either 1 or 2 risk factors, there were no statistical differences in event-free survival rates between

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**Table 2. Predictive Factors of SCD or VF**

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<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
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<th>Multivariate analysis</th>
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<td></td>
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<td>95% CI</td>
<td>P-value</td>
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<td>Male</td>
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<tr>
<td>Sp1</td>
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<td>Syncope</td>
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<td>6.81</td>
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<tr>
<td>Inducibility of VF (PES+)</td>
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<td>0.94</td>
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</table>

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

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Arrhythmic Events

Figure 2 shows the influence of each of the proposed risk factors (Sp1, syncope, and PES+) and FH on the incidence of arrhythmic events during the follow-up period. The prevalence of arrhythmic events was higher in patients with any of the proposed risk factors compared to those without it (Sp1, P=0.018, Figure 2A; syncope, P<0.001, Figure 2B; PES+, P=0.003, Figure 2C). FH, however, had no association with event rate (P=0.998, Figure 2D).

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The period from the start of the investigation to the first arrhythmic event was 51±37 months (median, 54 months). Twenty-four patients received appropriate ICD shock delivery against VF with successful termination, while 2 patients who had refused ICD therapy died suddenly. Figure 1 shows the Kaplan-Meier event-free survival curve for the overall group as well as for each institution. Table 1 also compares the patient characteristics between 2 groups defined according to the presence (n=26) or absence (n=192) of an arrhythmic event during follow-up. The prevalence of ICD was higher and the follow-up period was shorter in patients with an arrhythmic event (92% vs. 51%, P<0.001; 51 months vs. 81 months, P=0.0023, respectively). The period of ICD implantation was also longer in patients without an arrhythmic event (44 months vs. 87 months, P<0.001). The prevalence of SP1, syncope, and PES+ were higher in patients with an arrhythmic event compared to those without (92% vs. 70%, P=0.018; 81% vs. 34%, P<0.001; and 50% vs. 25%, P<0.00077, respectively). There was no difference in FH between the 2 groups (27% vs. 30%, P=0.77).

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Figure 3. Distribution of risk factors. PES+, inducibility of ventricular fibrillation by programmed electrical stimulation; Sp1, spontaneous type 1 Brugada electrocardiogram; syncope, history of syncope judged to be likely caused by ventricular arrhythmia.
Major Finding
This is one of the largest studies on this topic to date, with a subject group of 218 patients with BrS without cardiac arrest who were considered for ICD therapy for primary prevention of SCD. The major finding was that the proposed 3 risk factors, Sp1, syncope, and PES+, successfully stratified the risk of later arrhythmic events in Japanese patients with BrS with-

Discussion

Figure 4. Kaplan-Meier analysis of lethal arrhythmic events during follow-up depending of the number of risks factors present, including syncope, inducibility of ventricular fibrillation, and spontaneous type 1 Brugada electrocardiogram. SCD, sudden cardiac death; VF, ventricular fibrillation.

Figure 5. Kaplan-Meier analysis of arrhythmic events during follow-up depending on the presence of (A) 2 risks (syncope+Sp1 vs. Sp1+PES+ vs. syncope+PES+) or (B) 1 risk (Sp1 vs. syncope vs. PES+). PES+, inducibility of ventricular fibrillation by programmed electrical stimulation; Sp1, spontaneous type 1 Brugada electrocardiogram; syncope, history of syncope judged to be likely caused by ventricular arrhythmia.

subgroups (P=0.33 for 2 risk factors, syncope+Sp1/Sp1+PES+/syncope+PES+; and P=0.79 for 1 risk factor, Sp1/syncope/PES+: Figure 5).

Furthermore, there were significant differences in event-free survival rates between all subgroups with 2 risk factors and 1 risk factor (P<0.001 for syncope+Sp1 vs. 1 risk, P=0.03 for Sp1+PES+ vs. 1 risk and P=0.0036 for syncope+PES+ vs. 1 risk; Figure S1).
Risk Assessment in BrS

Figure 6. Electrocardiogram (V1 and V2) of a patient with a history of syncope who developed ventricular fibrillation during the follow-up. Spontaneous coved-type ST elevation was seen in the superior position (Middle: 3rd intercostal space; Right: 2nd intercostal space) not in the (Left) standard position.

out prior cardiac arrest. In particular, syncope and Sp1 were both independent risk factors. To our knowledge, this is the first study to show that the magnitude of the risk of SCD or VF was stratified by combining these 3 risk factors. When a patient had ≥2 risk factors, the risk of fatal arrhythmic events dramatically increased.

Combining Risk Factors for VF
The idea of combining risk factors arose from the guidelines for non-pharmacotherapy of cardiac arrhythmias published by the Japanese Circulation Society in 2011.9 These guidelines recommended ICD for primary prevention of SCD in patients with BrS according to the number of the following 3 risks factors present: syncope, PES+, and FH. ICD was categorized as a class IIA therapy for patients with ≥2 risk factors and ICD was categorized as class IIb for patients with a single risk factor. Sp1 was not included as a risk factor in these guidelines. Delise et al reported the risk stratification in a similar patient type as in the present study, with a focus on risk combinations.10 Although FH itself failed to predict arrhythmic events, the authors concluded that a multi-parametric approach that included syncope, FH, and PES+ helped to identify patients at high risk. They also reported that the patients at highest risk were those with at least 2 risk factors in addition to Sp1. In this study, we could stratify the risk of arrhythmic events clearly by combining 3 proposed risk factors according to the 2013 consensus report: Sp1, syncope, and PES+.

Japanese Guideline 2011
As noted, the 2011 Japanese guidelines recommended ICD for primary prevention of SCD in patients with BrS according to 3 risk factors: syncope, PES+, and FH. ICD was categorized as a class IIA treatment for patients with ≥2 risk factors and ICD was categorized as class IIb for patients with a single risk factor. Event-free survival curve according to this ICD indication class seemed to well stratify the risk of SCD, although there was a modest but not significant difference between class IIA and class IIb indication (P=0.07; Figure S2A). Among patients with class IIA or class IIb indications, however, there were statistically significant differences in event-free survival rate between subgroups (P=0.049 for class IIA indications, syncope+FH/PES+/syncope+FH/FH/PES+/syncope+PES+; and P=0.035 for class IIb indications, FH/syncope/PES+; Figure S2B,C). These differences seemed to arise from the lack of predictive value of FH and further discussion on this guideline is required.

Spontaneous Coved-Type ECG
The present results demonstrated the importance of Sp1 as a predictor of arrhythmic events, confirming similar findings in other studies.3,10-14 To increase the sensitivity for detecting Sp1, ECG were recorded in the superior position up to the second intercostal space as well as in the normal position in all patients, which may have resulted in the higher incidence of Sp1 (73%) in this study than in other studies (around 55%).6,10,12,15

Figure 6 presents a typical ECG of a patient with a history of syncope who developed VF during the follow-up, and in whom ICD was implanted because Sp1 was recorded in the superior position, not in the normal position. It has been reported that Sp1 can evolve spontaneously within minutes or can be unmasked by fever, although fever-induced Brugada ECG was not observed in this study.16-18 Also, seasonal and circadian distributions of arrhythmic events in patients with BrS have been reported.19 In the present study, ECG were recorded during the day, and circadian variation of ECG pattern was not evaluated. ECG recording immediately after the meal or at various times may further increase the sensitivity for detecting Sp1. Interestingly, ECG recording on deep inspiration has been reported to be useful to identify Brugada ECG.20 Accordingly, repeated recordings of 12-lead ECG should be performed to increase the detection of Sp1.

PES
The role of electrophysiological evaluation remains controversial.5 In this study, PES+ did not serve as an independent predictor of SCD or VF, but patients with PES+ had a higher incidence of arrhythmic events than those without it. Although there are several reports on the predictive value of PES+ that suggest that PES+ plays an important role in risk stratification, several studies including the PRELUDE registry reported by Priori et al argued against its usefulness.3,11,12,21 The PRELUDE registry was a prospective study in which patients were followed for an average of 34 months, a much shorter duration...
than that used in the present study. Furthermore, the median period from the start of the study to the arrhythmic event was 54 months in the present study. Short study duration might be one of the reasons for the discrepancy in PES+ importance between the PRELUDE registry and the present findings. The role of PES was also reported in the meta-analysis by Fauchier et al, which suggested the usefulness of PES in asymptomatic patients and in patients with syncope of unknown origin, not in patients with a history of cardiac arrest.21 The present result supports the finding of that meta-analysis. Also, the importance of the negative inducibility of VF by PES should be discussed. In the present study, some patients with negative inducibility of VF developed arrhythmic events as well. The previously mentioned meta-analysis by Fauchier et al also concluded that negative inducibility does not portend a good prognosis. Delise et al, however, reported that no arrhythmic events occurred in patients with negative inducibility of VF.10 Makimoto et al reported that the number of extrastimuli in PES using the minimum coupling interval of 180 ms and the inducibility of VF by up to 2 extrastimuli had significant predictive value for future cardiac events.22 Further discussion of these unresolved issues should be continued.

Family History of SCD
Although we focused on Sp1, syncope and PES in the present study according to the current consensus report published in 2013, we also analyzed the impact of FH on future arrhythmic events, because Kamakura et al reported that FH was one of the predictors of SCD in patients with Sp1.7 Although 45 patients in the Kamakura et al report were included in the present study, the Kamakura et al study included 274 patients without previous cardiac arrest (primary prevention) from 26 institutions across Japan. Also, the Kamakura et al study included patients with aborted SCD (secondary prevention), a patient type that differed from the present study. The FINGER registry, the largest cohort of patients with BrS, also concluded that FH was not a predictor of cardiac events.8 Although there are limited data on FH as a risk factor for lethal arrhythmia, it should not be disregarded. BrS is considered to be an inherited disease to a certain degree and the importance of FH should be discussed on an individual basis. Also, genetic information may provide important information on the relationship between FH and the risk of SCD. Further study is required on this unresolved issue.

Clinical Implications
The HRS/EHRA/APHRS consensus document 2013 provided partial recommendations for ICD therapy for primary prevention of SCD in patients with BrS.8 Recently, Takagi et al reported that class IIa indication in this statement could identify a group of patients with increased risk compared to class IIb indication.23 The indication for ICD for the patients who do not meet the conditions stated in the consensus document, however, remains unclear. In contrast, the combination of the 3 risk factors as proposed in the present study, which was based on the consensus document, covers all patients who are examined for ICD treatment. Patients with ≥2 risk factors are at high risk of SCD, which emphasizes the importance of measuring these 3 risk factors cautiously and exactly. First, repeated 12-lead ECG in the superior position in addition to the normal position should be performed to increase the detection of Sp1. Second, to increase the accuracy of risk estimation, syncope judged as likely caused by vasovagal reflex should be excluded. Third, the PES result is important especially when a patient has either Sp1 or syncope. In this situation, electrophysiological evaluation should be recommended to estimate the risk of VF accurately.

Study Limitations
The retrospective nature of this study is an important limitation. Patients were enrolled from only 2 Japanese institutions and the number of patients in this study was still small. Furthermore, all patients in this study underwent electrophysiological testing to assess suitability for ICD therapy, which was designed to evaluate the 3 proposed risk factors, syncope, Sp1, and PES+. Undoubtedly a certain bias existed in physician decision regarding whether or not to perform PES in each patient. Further prospective studies are needed to reach definitive conclusions.

Conclusions
Syncope, Sp1, and PES+ were important risk factors for SCD and VF in patients with BrS without previous cardiac arrest. The combination of these proposed risk factors according to the consensus report 2013 accurately stratified the risk of arrhythmic events, which could be of assistance when considering ICD therapy in these patients.

Acknowledgments
This work was supported by a research grant for the cardiovascular diseases (grant number H24-033) from the Ministry of Health, Labor, and Welfare.

Disclosures
None.

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Appendix
Number of patients included at each center: Okayama University Hospital, 112; National Cerebral and Cardiovascular Center, 106.

Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier analysis of arrhythmic events during follow-up according to the presence of 2 risks (syncope+Sp1 vs. Sp1+PES+ vs. syncope+PES+) and 1 risk.

Figure S2. (A) Kaplan-Meier analysis of lethal arrhythmic events during follow-up depending on implantable cardioverter defibrillator (ICD) indication class defined in the Japanese guideline 2011.

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-14-1059