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To cite this version:

Vincent Probst, C. Veltmann, L. Eckardt, P. G. Meregalli, F. Gaita, et al.. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry.. Circulation, American Heart Association, 2010, 121 (5), pp.635-43. 10.1161/CIRCULATIONAHA.109.887026 . hal-00910144

HAL Id: hal-00910144
https://hal.archives-ouvertes.fr/hal-00910144
Submitted on 27 May 2014

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Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome

Results From the FINGER Brugada Syndrome Registry

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Background—Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac death (SCD). Fundamental questions remain on the best strategy for assessing the real disease-associated arrhythmic risk, especially in asymptomatic patients. The aim of the present study was to evaluate the prognosis and risk factors of SCD in Brugada syndrome patients in the FINGER (France, Italy, Netherlands, Germany) Brugada syndrome registry.

Methods and Results—Patients were recruited in 11 tertiary centers in 4 European countries. Inclusion criteria consisted of a type 1 ECG present either at baseline or after drug challenge, after exclusion of diseases that mimic Brugada syndrome. The registry included 1029 consecutive individuals (745 men; 72%) with a median age of 45 (35 to 55) years. Diagnosis was based on (1) aborted SCD (6%); (2) syncope, otherwise unexplained (30%); and (3) asymptomatic patients (64%). During a median follow-up of 31.9 (14 to 54.4) months, 51 cardiac events (5%) occurred (44 patients experienced appropriate implantable cardioverter-defibrillator shocks, and 7 died suddenly). The cardiac event rate per year was 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. Symptoms and spontaneous type 1 ECG were predictors of arrhythmic events, whereas gender, familial history of SCD, inducibility of ventricular tachyarrhythmias during electrophysiological study, and the presence of an SCN5A mutation were not predictive of arrhythmic events.

Conclusions—In the largest series of Brugada syndrome patients thus far, event rates in asymptomatic patients were low. Inducibility of ventricular tachyarrhythmia and family history of SCD were not predictors of cardiac events. (Circulation. 2010;121:635-643.)

Key Words: Brugada syndrome ■ death, sudden ■ electrophysiology ■ genetics ■ tachyarrhythmias

Brugada syndrome (BrS) is an arrhythmogenic disease characterized by a typical ECG pattern of ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac death (SCD) due to ventricular fibrillation.1

Clinical Perspective on p 643

Patients displaying the BrS ECG pattern were initially considered at high risk of SCD, but recent studies have demonstrated that at least asymptomatic patients have a low risk of arrhythmic events.2-5 Risk stratification and therapeutic approach in asymptomatic patients are still controversial. The second consensus report on BrS, published in 2005, considered an electrophysiological study (EPS) as the cornerstone of the therapeutic strategy.6,7 EPS was described as a valuable stratification tool in asymptomatic patients, and, if positive, implantation of an implantable cardioverter-defibrillator (ICD) was recommended (class II recommendation).7 Several other studies, however, have failed to identify the inducibility of ventricular tachyarrhythmias as a predictor for SCD.2-5

Received June 15, 2009; accepted October 29, 2009.
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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.109.887026

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The aim of the present study was to evaluate the prognosis and risk factors of SCD in BrS patients in the FINGER (France, Italy, Netherlands, Germany) Brugada registry.

**Methods**

Consecutive patients were included at the following university hospitals: Academic Medical Centre, Amsterdam (n=159) (Netherlands); University of Muenster (n=77) and University Hospital of Mannheim (n=80) (Germany); Cardinal Massaia Hospital of Asti, University of Torino (n=192) (Italy); and the reference center for arrhythmic diseases in Nantes (n=521) (France), which includes patients from the university hospitals of Bordeaux, Brest, Rennes, Tours, Angers, Poitiers, Strasbourg, and Nantes (France). This international registry also contains follow-up data on patients included in a previous study published in 2005 and recently reported Italian patients.2,4,8

From the present study comprising 1029 patients, 212 patients were initially described in *Circulation* in 2005.2 The follow-up of this population was 40±50 months. These patients represent most of the population included in the registry before 2003. In this population of 305 individuals, we obtained a follow-up of 69 months. The Italian group included 192 patients in the registry; of them, 166 have also been described in *Europace*.8

Finally, 378 of the 1029 patients have already been included in a publication, which means that 657 patients are new. We can consider that over a total follow-up of 1029×37=38 073 months, the patients from the Eckardt publication represent 212×40=8480 months of follow-up, and the patients from the *Europace* publication from the Italian group represent 166×30=4980 months, for a total of 13 460 months. Finally, the FINGER registry presents 24 613 new months of follow-up. Only patients displaying a type 1 ECG at baseline or after provocation with a class I antiarrhythmic drug and at least 1 follow-up visit available were included (Figure 1). Children younger than 16 years were excluded.

Clinical data of interest were (1) age, (2) gender, (3) circumstances at diagnosis, and (4) family history of SCD. All of the ECGs were reviewed and classified by expert cardiologists (A.A.M.W., V.P., L.E., C.W., F.G.). BrS diagnosis was made according to the criteria of the consensus report.7,9 Intravenous ajmaline or flecainide was used for class I drug challenge. Routine examinations, including at least echocardiography, excluded any underlying structural heart disease, and laboratory tests excluded acute ischemia and metabolic or electrolyte abnormalities.

Three groups were classified according to the circumstances under which the ECG abnormalities were documented: subjects after an episode of aborted SCD, subjects during diagnostic evaluation of syncope (considered to be probably of arrhythmic origin), and asymptomatic subjects who had a type 1 or a suspicious ECG (type 2 or 3) during routine examination or who underwent family screening. Typical different types of ECG are presented in Figure 1. The classification as spontaneous type 1 ECG or drug-induced type 1 ECG was made with regard to the ECG pattern at the time of the diagnosis. The patient group was defined at the time of inclusion in the registry.

EPS was performed in 638 patients. A maximum of 3 ventricular extrastimuli was delivered from 2 ventricular sites. In case of ventricular fibrillation induced with a minimum coupling interval of <200 ms for the last extrastimuli, the EPS was considered negative.2 Patients were treated on the basis of the clinical judgment of the participating centers. During follow-up, patients were considered to have an arrhythmic event if SCD occurred, or, if appropriate, ICD shocks or sustained ventricular tachyarrhythmias were documented.

Mutation analysis of the SCN5A gene followed standard accepted protocols for genetic testing and is described elsewhere.2,10

**Statistical Analysis**

Data were analyzed with the SPSS and SAS packages (SPSS Inc, Chicago, Ill; SAS Institute Inc, Cary, NC), We used the χ² or Fisher exact test to compare categorical variables. The Mann-Whitney and Kruskal-Wallis tests were performed to test for statistical differences in continuous parameters. The mean event rate per year was evaluated by the number of events occurring during the follow-up divided by the number of patients multiplied by the average duration of follow-up. Continuous data are presented as median and inter-quartile range. Time from ECG diagnosis to the first event was analyzed with the Cox proportional hazards model. Hazard ratios (HR) and confidence intervals (CI) are presented in univariate analysis and only with significant P values in multivariable analysis. Survival curves were plotted by the Kaplan–Meier method. Multivariable analysis was performed with the following variables: gender, age, type of symptoms, type 1 ECG, inducibility of ventricular tachyarrhythmias during EPS, and ICD implantation (at the baseline time point). A value of P<0.05 was considered statistically significant.

**Results**

**Patient Population**

The registry included 1029 consecutive individuals (745 men; 72%) with a median age of 45 (35 to 55) years at diagnosis (female 49 [36 to 57] versus male 44 [35 to 55] years; P=0.03); 808 individuals (78%) were index patients (Table). The circumstances of diagnosis were as follows: (1) aborted SCD in 62 patients (6%); (2) syncope in 313 (30%); and (3) lack of symptoms in 654 (64%). Of these, 239 (36.5%) were
identified during family screening, 21 during an ECG performed for palpitation (3.2%), 12 during presyncope (1.8%), and 382 (58.4%) after a routine ECG.

Overall, a spontaneous type 1 ECG was recorded in 468 patients (45%): 31 subjects (50%) from the cardiac arrest group, 169 (54%) from the syncope group, and 268 (41%) from the asymptomatic group ($P$=0.001). Median ST-segment elevation in leads $V_1$ through $V_3$, at baseline, was 2 (0.4 to 3) mm in the cardiac arrest group, 2 (1 to 4) mm in the syncope group, and 2 (0.3 to 3) mm in the asymptomatic group ($P$$=$0.002). In the asymptomatic group, a spontaneous type 1 ECG was found in 45 (19%) of the patients diagnosed during a family screening and in 223 other patients (54%) ($P$$=$0.001). We identified a type 1 ECG limited to the third intercostal space in 43 of 1029 patients.

EPS was performed in 638 individuals (62%). In 262 patients (41%), sustained ventricular tachyarrhythmias were inducible. The rate of inducible ventricular tachyarrhythmia was higher in previously symptomatic patients (125/269) than in asymptomatic individuals (137/369) (46% versus 37%; $P$$=$0.02).

Among 516 index patients in whom genetic analysis was performed, an SCN5A mutation was found in 115 (22%). In 70 (52%) of the 134 screened family members, an SCN5A mutation was found.

**Treatment**

ICD implantation was performed in 54 of 62 patients from the cardiac arrest group (87%), in 208 of 313 syncope group patients (66%), and in 171 of 654 asymptomatic patients (26%). An ICD was implanted in 118 of 137 (86%) of the asymptomatic patients with a positive EPS.

The ICD implantation rate was higher in symptomatic than in asymptomatic patients (69.9% versus 26.1%; $P$$<$0.001). Eight patients from the cardiac arrest group did not undergo ICD implantation because of severe brain damage.

Eight patients were treated with hydroquinidine; 3 of them were diagnosed after aborted SCD, 2 were diagnosed after syncope, and 3 were asymptomatic.

**Follow-Up Data**

The median follow-up period for the entire study population was 31.9 (14 to 54.4) months. Follow-up was significantly longer in the cardiac arrest group patients (44 [26 to 68] months) than in the syncope group (34 [14 to 58] months) or the asymptomatic group (31 [13 to 53] months; $P$$=$0.003). During follow-up, 51 arrhythmic events occurred: appropriate ICD shocks (44 patients) and SCD (7 patients). The mean event rate per year for the entire population was 1.6%. Seven patients died from noncardiac causes (Figure 2).

During follow-up, 22 of 62 patients (35%) from the cardiac arrest group, 19 of 313 patients (6%) from the syncope group, and 10 of 654 (1.5%) patients from the asymptomatic group had an arrhythmic event. The mean event rates per year were 7.7%, 1.9%, and 0.5%.

**Univariate Analysis**

**Symptoms**

Time to first event was shorter in the cardiac arrest group patients than in the asymptomatic group patients (HR, 12.4; CI, 5.6 to 27.3; $P$$<$0.001). Furthermore, time to first event was shorter in the syncope group patients than in the asymptomatic group patients (HR, 3.4; CI, 1.6 to 7.4; $P$$=$0.002) (Figure 3).

In the asymptomatic group, there was no difference in the time to first event between patients diagnosed during familial screening and patients diagnosed during other circumstances (HR, 0.7; CI, 0.2 to 2.8; $P$$=$0.63).

**ECG Pattern at Time of Diagnosis**

Patients with a spontaneous type 1 ECG had a shorter time to first arrhythmic event than patients in whom the type 1 ECG

<table>
<thead>
<tr>
<th>Table. Patient Characteristics According to Their Clinical Presentation</th>
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<tbody>
<tr>
<td>Cardiac Arrest Group</td>
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<tr>
<td>No. of patients</td>
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<td>Index patients, %</td>
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<tr>
<td>Male, n (%)</td>
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<td>Age at diagnosis, y</td>
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<td>Family history of SCD, n (%)</td>
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<td>PR, ms</td>
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<td>ST elevation, mm</td>
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<tr>
<td>Spontaneous type 1 ECG, n (%)</td>
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<tr>
<td>EPS performed, n (%)</td>
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<tr>
<td>Inducible VT/VF, n (%)</td>
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<tr>
<td>SCN5A mutations, n (%)</td>
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<tr>
<td>Follow-up,* mo</td>
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<tr>
<td>No. of patients with events during follow-up</td>
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<td>Mean event rate per year, %</td>
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VT/VF indicates ventricular tachycardia/ventricular fibrillation.

*The follow-up is the time between the first event or the last new date and the diagnosis ECG date.
was shown only during drug challenge (mean event rate per year, 2.3% versus 1.07%; HR, 2.1; CI, 1.2 to 3.6; \( P < 0.01 \)) (Figure 4).

**Gender**

Male gender tended to be associated with a shorter time to first event, but this difference did not reach statistical significance (mean event rate per year, 3.0% for men versus 0.9% for women; HR, 1.9; CI, 0.9 to 4.2; \( P = 0.08 \)).

**Genetic Data**

There was no difference in time to first event between SCN5A mutation carriers and noncarriers (HR, 1.1; CI, 0.5 to 2.2; \( P = 0.8 \)).

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**Figure 2.** Mean event rate per year during follow-up in the entire population. The results are divided according to the type of ECG and the presence of symptoms. Results of EPS are also given in the different groups. FU indicates mean follow-up in months in the group.

**Figure 3.** Kaplan–Meier curves of arrhythmic events during follow-up in the 3 different groups. Patients from the cardiac arrest group (n=62) had a shorter time to first arrhythmic event than patients from the asymptomatic group (n=654), and patients from the syncope group (n=313) had a shorter time to first arrhythmic event than patients from the asymptomatic group.
**Family History of SCD**
Overall, a family history of SCD at a young age (<45 years) was found in 264 patients (26%). This information was not available for 12 patients (1%). The event rates per year did not differ between patients with a family history of SCD and those without (1.29% versus 1.7%). A family history of SCD was not predictive of arrhythmic events in either the group of symptomatic or the group of asymptomatic patients (symptomatic patients, 3.3% versus 3.0%; asymptomatic patients, 0.5% versus 0.6%).

**Electrophysiological Study**
At univariate analysis, patients with inducible ventricular tachyarrhythmias (n=262; 41%) had a significantly shorter time to first arrhythmic event than patients with a negative EPS (n=376; 59%) (mean event rates per year, 2.3% versus 1.2%; HR, 1.9; CI, 0.9 to 3.9; P=0.05; Figure 5).

**Multivariable Analysis**
In a multivariable analysis, symptoms before inclusion (P<0.001), SCD versus asymptomatic status (HR, 11; CI, 4.8 to 24.3; P<0.001), syncope versus asymptomatic status (HR, 3.4; CI, 1.6 to 7.4; P=0.002), and spontaneous type 1 ECG versus drug-induced type 1 ECG (HR, 1.8; CI, 1.03 to 3.33; P=0.04) were predictors of a shorter time to first arrhythmic event. The results of the EPS (P=0.48), age (P=0.27), and gender (P=0.60) were not predictive of a shorter time to first arrhythmic event, however.

If introduced in the multivariable analysis, ICD implantation (HR, 3.9; CI, 1.4 to 10.6; P=0.007) was found to be a predictor of a shorter time to first arrhythmic event.

**Asymptomatic Patients**
A separate analysis was performed in asymptomatic patients. Neither spontaneous type 1 ECG (event rate per year, 0.8% versus 0.4%; HR, 2.0; CI, 0.5 to 7.4; P=0.26) nor male gender (0.7% versus 0.2%; HR, 3.0; CI, 0.3 to 22; P=0.35) nor age (HR, 0.9; CI, 0.3 to 3.3; P=0.92) was predictive of a shorter time to the first arrhythmic event during follow-up.

Results of EPS were available in 369 asymptomatic individuals. In univariate analysis, patients with positive EPS (n=137; 37%) had a shorter time to first arrhythmic event compared with those with a negative EPS (n=232; 63%; event rate per year, 1.1% versus 0.4%; HR, 5.2; CI, 1 to 25.8; P=0.05). The multivariable analysis, restricted to the asymptomatic patients, showed no independent predictive value: EPS (P=0.09), male gender (P=0.42), spontaneous type 1 ECG (P=0.38), and age (P=0.97).

If introduced in the multivariable analysis, ICD implantation (HR, 10.1; CI, 1.7 to 58.7; P=0.01) was found to be a predictor of a shorter time to first arrhythmic event.

**Analysis of Patients Diagnosed Before 2003**
In 305 patients, the diagnosis was performed before 2003. In this subpopulation, the average follow-up was 66 (56 to 82) months. During follow-up, 34 arrhythmic events occurred (event rate per year, 1.9%): 15 of 31 cardiac arrest group patients (48%), 11 of 101 syncope group patients (11%), and 8 of 173 asymptomatic group patients (4.5%) had an arrhythmic event. Thus, the event rates per year were 7.4%, 1.8%, and 0.8%, respectively (Figure 6).

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**Figure 4.** Kaplan–Meier curves of arrhythmic events during follow-up depending on the ECG pattern. Patients displaying a spontaneous type 1 ECG (n=468) had a shorter time to first arrhythmic event than patients in whom the type 1 ECG was induced after challenge with sodium channel blockers (n=561); P=0.01.
The aim of this study was to evaluate the prognosis and assess the value of clinical and electrophysiological parameters for risk stratification in a large series of individuals with either a spontaneous or drug-induced type 1 Brugada ECG. The study population consisted of 1029 individuals from 4 different European countries, who were included in the FINGER Brugada syndrome registry. A large group of these patients underwent ICD implantation because of primary or secondary prevention. One of the major characteristics of this population is that patients have been consecutively enrolled in defined geographic regions within the 4 European countries. This registry was built as a result of an exhaustive recruitment of the available clinical data of all of the BrS patients of these areas and, as such, is representative of daily practice in clinical cardiology. Therefore, in contrast to previous studies.

**Figure 5.** Kaplan–Meier curves of arrhythmic events during follow-up depending on the results of the EPS. Patients in whom EPS induced ventricular fibrillation (n=262) had a shorter time to the first arrhythmic event than those with a negative EPS (n=376); P=0.05.

**Figure 6.** Mean event rate per year during follow-up, restricted to the group of patients recruited in the database before 2003. Results are divided according to the type of ECG and the presence of symptoms. FU indicates mean follow-up in months in the group.
based on worldwide registries, which were potentially subject to a referral bias with inclusion of more severely affected subjects, the present findings may more accurately reflect disease severity.

Since the BrS was identified in 1992, major progress has been made in understanding the pathophysiology of the disease and in identifying its genetic basis. The diagnostic workup and the therapeutic approach to BrS have been described extensively in 2 comprehensive consensus reports. Nevertheless, controversy still exists regarding the role of EPS for risk stratification and the manner in which to proceed with asymptomatic patients. In the last consensus report, EPS was offered to patients exhibiting a spontaneous type 1 ECG or patients with a type 1 ECG revealed by drug challenge but with a positive family history of SCD (class II-b). This approach involves performing a large number of EPS, which in turn leads to a high number of ICD implantations. This not only may result in a considerable increase in healthcare costs but also may expose asymptomatic individuals to ICD-related complications.

Overall, the incidence of arrhythmic events in asymptomatic patients in the FINGER registry is low: SCD occurred in 2 (0.4%) of 478 asymptomatic patients in whom an ICD was not implanted. The event rate in asymptomatic patients was 0.5% per year.

Given the low event rate overall, it remains difficult to recommend a suitable therapeutic approach for asymptomatic patients. In multivariable analysis, no predictor for cardiac events could be identified. A risk of 0.5% per year for a period of 40 years (mean life expectancy of a patient diagnosed with BrS) leads to a potential cumulative risk of up to 20%. If this calculation were true, then ICD implantation should be recommended; however, it is currently impossible to estimate the evolution of arrhythmic risk over time in patients with BrS.

To answer this question, we performed a subanalysis of the subjects who were registered before 2003. The event rate per year in this subpopulation was 0.8% in asymptomatic patients, which is similar to the rate of 0.5% found in the entire asymptomatic patient population. Does this mean that the risk of arrhythmic events occurring in this population remains stable over time? Probably not, because it must be noted that in our registry the median age at the time of an arrhythmic event (45 [38 to 57] years) was close to the age of diagnosis (45±14 [35 to 55] years). Thus, even if one extends follow-up from 3 to 6 years, the follow-up period remains close to the peak of event period of time, which may lead to an overestimation of event risk.

In the FINGER Brugada registry, the arrhythmic end point was defined as appropriate ICD shock or SCD. Most of the events were appropriate ICD shocks (86%), and only 7 SCDs occurred. This high incidence of appropriate shocks must be taken into account when the results are interpreted. Because ventricular tachyarrhythmias may terminate spontaneously, appropriate ICD shock is not synonymous with SCD. The storage of all ventricular tachycardias (exceeding the monitor zone of the device but still possibly asymptomatic) in patients with an ICD leads to an overestimation of the number of events compared with patients without an ICD. The predictive value of the EPS is difficult to assess because its positive result will most frequently lead to ICD implantation (236/262 patients in the FINGER registry; 90%), whereas a significantly smaller proportion of asymptomatic patients with a negative EPS underwent ICD implantation (102/376 patients; 27%; P<0.0001). Accordingly, the positive predictive value of EPS was found only at univariate analysis and was not confirmed by multivariable analysis, whereas the presence of an ICD was found to be predictive of the occurrence of arrhythmic events. This could certainly explain in part the discrepancy between the different registries.

Until now, the only available treatment that has proven to prevent SCD in BrS patients is ICD implantation. This intervention represents an attractive option to protect patients against SCD. It has been shown recently, however, that the incidence of ICD-related complications is high in this population (up to 28%), and death related to ICD malfunction has also been reported.

Clearly, the risk/benefit ratio of ICD implantation in this population is not easy to assess. Therefore, an open discussion with the patient explaining the potential risks of the disease but also the possible complications of the ICD is a crucial point. Quinidine therapy may be an alternative in patients refusing the ICD or ineligible for ICD implantation, although available data are limited and future prospectively designed studies are needed.

Limitations
Even if the follow-up of this study is the longest published thus far, because patients are usually diagnosed in the fifth decade of life, this follow-up is still too short to draw final conclusions. Risk stratification in the present study is based on 1 basal ECG, whereas fluctuation of the ST-segment elevation over time is a well-demonstrated feature of the syndrome. In all of the published multicenter studies, 1 ECG is used for risk assessment. Not all of the asymptomatic patients underwent an EPS, and therefore a selection bias cannot be completely excluded. Although the number of patients included here is large, the number of asymptomatic patients who underwent EPS is actually relatively small. All of the patients younger than 16 years were excluded from the registry, and therefore no comment can be made on BrS in children in this registry.

Conclusions
The present study demonstrates that, in the largest cohort of patients with BrS thus far, the risk of arrhythmic events is low in asymptomatic patients (event rate per year, 0.5%). The presence of symptoms and a spontaneous type 1 ECG are the only independent predictors of arrhythmic events. Conversely, gender, family history of SCD, inducibility of ventricular tachyarrhythmias during EPS, and presence of a mutation in the SCN5A gene have no predictive value. In view of these results, a revision of the therapeutic strategy proposed in the second consensus report is warranted.

Acknowledgments
We thank Christine Fruchet and Béatrice Guyomarç’h for their assistance, and we also thank the patients for their participation in the study.
Sources of Funding
This study was supported in part by grants from P.H.R.C. 2001 R20/03 and 2004 R20/07 from CHU de Nantes, France; Société française de cardiologie; a Foundation Leducq Trans-Atlantic Network of Excellence grant (05 CVD 01, Preventing Sudden Death); ANR grant 05-MRAR-028; Peter Ospyka Foundation for Clinical and Experimental Electrophysiology; and Netherslands Organization for Scientific Research (NWO, ZonMW VICI 918.86.616).

Disclosures
None.

References
CLINICAL PERSPECTIVE

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac death. Fundamental questions remain on the best strategy for assessing the real disease-associated arrhythmic risk, especially in asymptomatic patients. The aim of the present study was to evaluate the prognosis and risk factors of sudden cardiac death in Brugada syndrome patients in the FINGER (France, Italy, Netherlands, Germany) Brugada syndrome registry. The registry included 1029 consecutive individuals (72% men). In the registry, 36% of the patients were symptomatic, and 64% were asymptomatic. The cardiac event rate per year was 7.7% in patients with aborted sudden cardiac death, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. Symptoms and spontaneous type 1 ECG were predictors of arrhythmic events, whereas gender, familial history of sudden cardiac death, inducibility of ventricular tachyarrhythmias during electrophysiological study, and the presence of an SCN5A mutation were not predictive of arrhythmic events. In the FINGER registry, the rate of cardiac events in the asymptomatic Brugada syndrome patients was low, and the inducibility of ventricular tachyarrhythmias during electrophysiological study did not properly stratify the arrhythmic risk.