Risk Stratification of Individuals with the Brugada Electrocardiogram: A Meta-Analysis

ANIL K. GEHI, M.D.,* TRUONG D. DUONG, M.D.,* LOUISE D. METZ, M.D.,† J. ANTHONY GOMES, M.D.,* and DAVENDRA MEHTA, M.D., PH.D.*

From *The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York, USA; and †Department of Medicine, New York University Medical Center, New York, New York, USA

Risk Stratification of Individuals. Objectives: We performed a meta-analysis of prognostic studies of patients with a Brugada ECG to assess predictors of events.

Background: The Brugada syndrome is an increasingly recognized cause of idiopathic ventricular fibrillation; however, there is wide variation in the prognosis of patients with the Brugada ECG.

Methods and Results: We retrieved 30 prospective studies of patients with the Brugada ECG, accumulating data on 1,545 patients. Summary estimates of the relative risk (RR) of events (sudden cardiac death [SCD], syncope, or internal defibrillator shock) for a variety of potential predictors were made using a random-effects model. The overall event rate at an average of 32 months follow-up was 10.0% (95% CI 8.5%, 11.5%). The RR of an event was increased (P < 0.001) among patients with a history of syncope or SCD (RR 3.24 [95% CI 2.13, 4.93]), men compared with women (RR 3.47 [95% CI 1.58, 7.63]), and patients with a spontaneous compared with sodium-channel blocker induced Type I Brugada ECG (RR 4.65 [95% CI 2.25, 9.58]). The RR of events was not significantly increased in patients with a family history of SCD (P = 0.97) or a mutation of the SCN5A gene (P = 0.18). The RR of events was also not significantly increased in patients inducible compared with noninducible by electrophysiologic study (EPS) (RR 1.88 [95% CI 0.62, 5.73], P = 0.27); however, there was significant heterogeneity of the studies included.

Conclusions: Our findings suggest that a history of syncope or SCD, the presence of a spontaneous Type I Brugada ECG, and male gender predict a more malignant natural history. Our findings do not support the use of a family history of SCD, the presence of an SCN5A gene mutation, or EPS to guide the management of patients with a Brugada ECG. (J Cardiovasc Electrophysiol, Vol. 17, pp. 577-583, June 2006)

meta-analysis, Brugada syndrome, sudden cardiac death, risk stratification, prospective studies

Introduction

Since its first description in 1992,1 the Brugada syndrome has been recognized as a major cause of idiopathic ventricular fibrillation.2 3 Overall, the prevalence of a Brugada electrocardiogram has been estimated between 0.5 and 0.7% with an approximately 8:1 male predominance.3-6 However, the incidence of syncope or sudden cardiac death (SCD) varies widely, particularly between patients with and without a history of syncope or cardiac arrest,7-8 and may be especially high in patients of Asian origin.5

The Brugada electrocardiogram (ECG) is characterized by coved (Type I) ST-segment elevation > 1 mm in more than one right precordial lead (V1 to V3) in the presence or absence of a sodium-channel blocker.9 Additionally, there should be no other factor to account for the ECG abnormality. The only genetic abnormality to have been linked to Brugada syndrome is a mutation of the SCN5A gene, though the mutation is present in a minority of cases.9-11

The only effective method of management for Brugada syndrome is an implantable cardioverter defibrillator (ICD).12 However, given the wide variation in the incidence of events,7-11,13 the appropriate indication for ICD implantation remains uncertain. According to the recently published second consensus report,14 patients with a spontaneous or drug-induced Type I Brugada ECG and a history of syncope or SCD should undergo ICD implantation. Asymptomatic patients with a spontaneous Type I Brugada ECG or asymptomatic patients with a drug-induced Type I Brugada ECG and a family history of SCD should undergo electrophysiologic study (EPS) to guide the selection of patients for ICD implantation.

The recommendations for risk stratification from the recently published consensus report, however, are based on a number of studies with disparate findings.14 To better understand the prognosis and predictors of events in patients with a Brugada ECG, we performed this meta-analysis.

Methods

Study Selection

We performed a literature search using the PubMed database to identify articles published between January 1990 and March 2005 of the prognosis of patients with a Brugada ECG. These date limits were chosen because the Brugada syndrome was first described in 1992.1 The following Medical Subject Heading search terms were used: bundle-branch block, prospective studies, follow-up studies, predictive value of tests, arrhythmia, sudden death, ventricular tachycardia, and ventricular fibrillation. In addition, we used the search
term Brugada. The search was restricted to English language literature. A review of the bibliographies of all articles identified and a search of articles published by authors identified in the initial search were performed to identify additional articles for review.

Studies were included if they met all of the following criteria: (1) prospective cohort studies of the natural history of patients with a Brugada-type ECG, (2) study includes >10 human subjects, (3) provides primary data on cardiac events (syncope, SCD, or ICD shock) in identified patients with at least 6 months and >90% follow-up, (4) states clearly that structural cardiac disease was ruled out.

Two investigators (AG and TD) independently reviewed the titles and abstracts of the articles from the initial search and excluded those that clearly would not meet the inclusion criteria. A consensus was reached on which articles should be completely reviewed for potential inclusion in the study.

Data Abstraction

Two investigators (AG and TD) independently reviewed potential articles for this study blinded to the author, journal, and institutions of the articles. Data for each article were abstracted, including: patient characteristics (number, mean age, percent men, country of recruitment), Brugada ECG type, endpoints of the study, average follow-up, and raw data on outcomes at follow-up. Outcomes were stratified by several prespecified predictors of events when available, including: history of syncope or SCD, sex, family history of SCD, spontaneous versus sodium-channel blocker induced Brugada ECG, inducibility of sustained ventricular arrhythmia at EPS, and presence of an SCN5A mutation.

Statistical Analysis

We calculated a pooled event (SCD, syncope, ICD shock) rate and 95% confidence interval (CI) of all the included studies, weighted by study sample size. When multiple studies from a research group were eligible for inclusion, only the most recent and comprehensive study was used.

Summary estimates (relative risk and risk difference with 95% CI) of predictors of events in patients with a Brugada ECG were made using the DerSimonian and Laird meta-analytic statistical method, which is based on a random effects model. Summary estimates were made for the previously described predictors. Studies were included for calculation of summary estimates if there were at least 10 subjects with and without the specified risk factor. To avoid computational errors, a small sample correction of 0.5 was added to each cell. A test for homogeneity using the Mantel-Haenszel statistic was performed for all summary estimates of predictive events. A P value <0.10 was considered statistically significant for heterogeneity.

Publication bias was assessed for each predictor of events using a funnel plot and the correlation coefficient, Kendall’s Tau, comparing sample size to RR. A sensitivity analysis, including only those studies with patients having a spontaneous or drug-induced Type I Brugada ECG, showed no significant difference in the overall or region specific event rate. Summary estimates using the DerSimonian and Laird random-effects model of the univariate RR of events and absolute risk difference of events for the previously described risk predictors are presented in Table 2. The summary RR for an event was increased in patients with a history of syncope or SCD, in men compared with women, and in patients with a spontaneous compared with drug-induced Brugada ECG. The Mantel-Haenszel test for homogeneity was >0.10 for
TABLE 1
Summary Characteristics of Individual Prospective Studies of Patients with a Brugada ECG

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Country</th>
<th>Men (%)</th>
<th>Mean Age (Years)</th>
<th>Brugada ECG Type</th>
<th>History of Symptoms</th>
<th>Follow-Up (Months)</th>
<th>Risk Factors Used in Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nademanee et al. (1997)</td>
<td>16</td>
<td>Thailand</td>
<td>100</td>
<td>40</td>
<td>I</td>
<td>Yes</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>Matsuo et al. (1999)</td>
<td>12</td>
<td>Japan</td>
<td>100</td>
<td>46</td>
<td>I or II</td>
<td>Yes</td>
<td>26</td>
<td>None</td>
</tr>
<tr>
<td>Hermida et al. (2000)</td>
<td>60</td>
<td>France</td>
<td>85</td>
<td>36</td>
<td>II</td>
<td>No</td>
<td>49</td>
<td>None</td>
</tr>
<tr>
<td>Kakishita et al. (2000)</td>
<td>19</td>
<td>Japan</td>
<td>100</td>
<td>47</td>
<td>I</td>
<td>Yes</td>
<td>35</td>
<td>None</td>
</tr>
<tr>
<td>Atarashi et al. (2001)</td>
<td>96</td>
<td>Japan</td>
<td>94</td>
<td>45</td>
<td>I or II</td>
<td>Both</td>
<td>36</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Takenaka et al. (2001)</td>
<td>11</td>
<td>Japan</td>
<td>100</td>
<td>41</td>
<td>NA</td>
<td>No</td>
<td>43</td>
<td>None</td>
</tr>
<tr>
<td>Gasparini et al. (2002)</td>
<td>21</td>
<td>Italy</td>
<td>86</td>
<td>34</td>
<td>NA</td>
<td>Both</td>
<td>20</td>
<td>None</td>
</tr>
<tr>
<td>Kanda et al. (2002)</td>
<td>34</td>
<td>Japan</td>
<td>97</td>
<td>44</td>
<td>I or II</td>
<td>Yes</td>
<td>41</td>
<td>EPS</td>
</tr>
<tr>
<td>Masaki et al. (2002)</td>
<td>11</td>
<td>Japan</td>
<td>92</td>
<td>52</td>
<td>I or II</td>
<td>Both</td>
<td>29</td>
<td>None</td>
</tr>
<tr>
<td>Nanke et al. (2002)</td>
<td>20</td>
<td>Japan</td>
<td>90</td>
<td>51</td>
<td>NA</td>
<td>Both</td>
<td>44</td>
<td>None</td>
</tr>
<tr>
<td>Priori et al. (2002)</td>
<td>200</td>
<td>Italy</td>
<td>76</td>
<td>41</td>
<td>I or II</td>
<td>Both</td>
<td>34</td>
<td>Symptoms, sex, EPS, SCN5A, spontaneous vs drug-induced ECG</td>
</tr>
<tr>
<td>Brugada et al. (2003)</td>
<td>547</td>
<td>International</td>
<td>75</td>
<td>41</td>
<td>I</td>
<td>Both</td>
<td>24</td>
<td>Symptoms, sex, EPS, SCN5A, spontaneous vs drug-induced ECG</td>
</tr>
<tr>
<td>Morita et al. (2003)</td>
<td>41</td>
<td>Japan</td>
<td>100</td>
<td>45</td>
<td>NA</td>
<td>No</td>
<td>28</td>
<td>EPS</td>
</tr>
<tr>
<td>Park et al. (2003)</td>
<td>15</td>
<td>Korea</td>
<td>87</td>
<td>44</td>
<td>I</td>
<td>Both</td>
<td>19</td>
<td>None</td>
</tr>
<tr>
<td>Sakabe et al. (2003)</td>
<td>64</td>
<td>Japan</td>
<td>97</td>
<td>48</td>
<td>I or II</td>
<td>No</td>
<td>48</td>
<td>None</td>
</tr>
<tr>
<td>Bordachar et al. (2004)</td>
<td>59</td>
<td>France</td>
<td>74</td>
<td>43</td>
<td>NA</td>
<td>Both</td>
<td>32</td>
<td>None</td>
</tr>
<tr>
<td>Mok et al. (2004)</td>
<td>50</td>
<td>China</td>
<td>94</td>
<td>53</td>
<td>NA</td>
<td>Both</td>
<td>25</td>
<td>Symptoms, EPS</td>
</tr>
<tr>
<td>Eckardt et al. (2005)</td>
<td>212</td>
<td>Germany, France</td>
<td>72</td>
<td>45</td>
<td>I</td>
<td>Both</td>
<td>40</td>
<td>Symptoms, sex, EPS, SCN5A, spontaneous vs drug-induced ECG</td>
</tr>
<tr>
<td>Ajiro et al. (2005)</td>
<td>46</td>
<td>Japan</td>
<td>96</td>
<td>46</td>
<td>I</td>
<td>Both</td>
<td>44</td>
<td>None</td>
</tr>
</tbody>
</table>

N = number of patients; I = coved-pattern; II = saddleback pattern; NA = not available; EPS = electrophysiological study; FH = family history; SCN5A = SCN5A gene mutation.

These three summary estimates, demonstrating that there was no heterogeneity of the combined studies.

Summary estimates demonstrated no significant difference in the risk of events based on whether or not patients had a family history of SCD or a mutation of the SCN5A gene (Table 2). With the studies available, we had 80% power at a two-tailed alpha of 0.05 to detect a RR of 2.24 for a family history of SCD and a RR of 2.89 for the presence of the SCN5A mutation. Again the Mantel-Haenszel test for homogeneity was >0.10 for these two summary estimates demonstrating that there was no heterogeneity of the studies combined.

Using the six studies, which stratified outcomes of patients by whether or not they were inducible at EPS, the summary RR demonstrated that there was a nonsignificant (P = 0.27) increased risk of events in patients who were inducible (Table 2, Fig. 2). The Mantel-Haenszel test for homogeneity of these six studies was <0.001 demonstrating that there was significant heterogeneity of the combined studies. A sensitivity analysis of the involved studies showed that the heterogeneity was sensitive only to the study of Brugada et al. Excluding this study, the RR for events in patients inducible compared with noninducible at EPS remained nonsignificant (P = 0.64) at 0.89 (95% CI 0.53, 1.48).

Because there was variability in the ECG criteria for inclusion into the studies included in the above analyses, a sensitivity analysis including only those studies with patients having a spontaneous or drug-induced Type I Brugada ECG was performed. The sensitivity analysis showed no significant difference in the RR of any of the risk factors outlined in Table 2.

Using funnel plots and the correlation coefficient Kendall’s Tau, we found no evidence of publication bias for any of the risk factor analyses performed in this meta-analysis.

Discussion

To our knowledge, we have conducted the first meta-analysis of the overall risk of events and predictors of events in a wide variety of patient populations with the Brugada ECG, accumulating prospective data on over 1,500 patients. Overall, we have found that patients with a Brugada ECG have an approximately 10% risk of SCD, syncope, or ICD shock at an average 2.5 years follow-up. The event rate was...
significantly confidence in Asian compared with European patients. We found that patients with a history of syncope or SCD, men, and patients with a spontaneous compared with a drug-induced Type I Brugada ECG all had a 3- to 4-fold increased risk of events. The risk of events was not significantly increased in patients inducible at EPS although there was significant heterogeneity of the combined studies. Finally, we found that neither a family history of SCD nor the presence of a mutation in the SCN5A gene increased the risk of events. 

These findings have several clinical implications for management. The high risk associated with a history of syncope or SCD would support the implantation of an ICD in any symptomatic patient with a Type I Brugada ECG. Although we did not have sufficient data to accurately measure the overall risk of events in asymptomatic women with a Type I Brugada ECG or asymptomatic patients with only a drug-induced Type I Brugada ECG, our data suggest that these patient groups likely have a low risk for future events and could potentially be followed closely with no further interventions. Our findings do not firmly support the use of EPS for risk stratification of patients with an intermediate risk of events. Our findings also do not support assessing the presence of the SCN5A mutation in an intermediate risk group. Our data suggest that patients of Asian compared to European background may have a higher risk of events though no individual study compared the risks directly. This last finding should only be taken as hypothesis generating for future study.

Overall, 141 (37%) of 383 patients tested in our study had a mutation of the SCN5A gene. We did not find the presence of an SCN5A gene mutation to be predictive of future events, although we had limited power to identify a minor increase in risk. The SCN5A gene which encodes for the alpha subunit of cardiac sodium channel gene is thus far the only gene discovered to be linked to the Brugada syndrome. However, as demonstrated in our study, a minority of individuals with the Brugada syndrome will have a mutation of the SCN5A gene. It is likely that other genes responsible for the Brugada syndrome have not yet been identified, possibly accounting for the heterogeneity of presentation of individuals with a Brugada ECG. As suggested by the current consensus statement, knowledge of a specific genetic mutation is unlikely to provide specific prognostic information at this time.

The use of EPS to further risk stratify intermediate risk patients with a Brugada ECG remains controversial.65,66 Although Brugada et al. support the use of EPS based on the results from the largest series of patients studied with Brugada syndrome,13 two other large series have not confirmed these findings.7,11 This heterogeneity was found in our meta-analyses of six studies such that the summary RR demonstrated no overall prognostic value to EPS. The heterogeneity found in the use of EPS for risk stratification may be due to methodological differences in the stimulation protocols used for EPS or in the criteria used for a positive or negative EPS.7,11,14 The use of EPS for risk stratification was also not further stratified based on whether or not patients had a history of symptoms. It is also possible that patients in the Brugada series, who are primarily recruited as referrals from other institutions, are a more highly selected patient population resulting in significant referral bias.14 According to Priori and Napolitano, a remarkably high rate of SCD among the individuals enrolled in the study of Brugada et al. due to referral bias accounts for the difference in the use of EPS for risk stratification.66 According to Brugada et al., the inclusion of individuals other than those with a Type 1 ECG primarily accounts for the difference in the use of EPS.65 Fundamentally, the short follow-up of current Brugada registries may limit any definitive conclusions.66 The role of EPS for risk stratification in patients with a Brugada ECG may not be resolved until the Programmed Electrical stimulation predictive value in Brugada syndrome (PRELUDE) study is completed.66

There are several limitations to our study. Because of the male to female predominance of the Brugada ECG, there

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### Table 2

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Summary Relative Risk (95% CI)</th>
<th>Summary Risk Difference (%) (95% CI)</th>
<th>Average Follow-Up (Months)</th>
<th>N (Patients)</th>
<th>N (Studies)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of syncope or SCD</td>
<td>3.51 (2.14, 5.75)</td>
<td>13.4 (7.2, 19.5)</td>
<td>25</td>
<td>1,105</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men (vs women)</td>
<td>3.47 (1.58, 7.63)</td>
<td>8.7 (5.4, 12.0)</td>
<td>29</td>
<td>788</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>1.04 (0.43, 2.52)</td>
<td>0.5 (−5.2, 6.4)</td>
<td>32</td>
<td>759</td>
<td>2</td>
<td>0.93</td>
</tr>
<tr>
<td>Inducible at EPS</td>
<td>1.88 (0.62, 5.73)</td>
<td>8.8 (−4.4, 22.1)</td>
<td>32</td>
<td>785</td>
<td>6</td>
<td>0.27</td>
</tr>
<tr>
<td>Spontaneous (vs drug-induced) Brugada ECG</td>
<td>4.65 (2.25, 9.58)</td>
<td>8.5 (4.8, 12.3)</td>
<td>30</td>
<td>935</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCN5A mutation</td>
<td>0.60 (0.29, 1.26)</td>
<td>−4.6 (−9.2, 0.1)</td>
<td>37</td>
<td>383</td>
<td>2</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*P < 0.10 for heterogeneity of studies combined.

CI = confidence interval; N = number; SCD = sudden cardiac death; EPS = electrophysiological study; NA = not applicable.

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**Figure 2.** Summary estimate of the relative risk of events (SCD, syncope, or ICD shock) in patients with a Brugada ECG inducible at EPS.
were much fewer women than men included in our study. However, we have accumulated prospective clinical evidence on more women with a Brugada ECG than any other prior study. There was not sufficient data to assess the risk factors for future events further stratified by whether or not patients had a history of symptoms. Although this may have provided the most clinical guidance for patient management, as the management of symptomatic patients is more straightforward, our findings of risk factors associated with future events would likely be independent of a history of symptoms. We were unable to assess the RR of future events comparing patients of European and Asian background, because no studies which included patients recruited from both continents provided this data. However, our pooled event rates suggest an increased risk of events in patients of Asian compared with European background and warrants further evaluation. We used a combined endpoint of SCD, syncope, or ICD shock as the endpoint in our meta-analysis. As discussed above, there may have been inconsistencies among the included studies in the definition of syncope or in the adjudication of an appropriate ICD shock. Our meta-analyses were dominated by large series of patients,7,11,13 however, except for the previously discussed studies of the use of EPS, there was no significant heterogeneity in the findings of these large series and the many smaller series. There was inconsistency among the studies as to whether patients with a Type II Brugada ECG were included. However, a sensitivity analysis, including only those studies which specified that patients had either a spontaneous or drug-induced Type I Brugada ECG, demonstrated no significant difference in the results. Although we found that a family history of SCD was not predictive of future events, there may be differences between studies in what is considered a positive family history of SCD. Finally, as with any meta-analysis, its quality is limited by the quality of the included studies. However, we had stringent criteria for the inclusion of studies and found no evidence of publication bias.

In conclusion, we have conducted the first meta-analysis of predictors of events in patients with a Brugada ECG, accumulating prospective data on over 1,500 patients. Our findings should help understand the natural history of the disease among a variety of patient populations. Furthermore, given the increasing recognized prevalence of this disease and the high cost of management, our findings of predictors of risk in patients with a Brugada ECG should help guide further study and enhance management decisions for patients with this condition.

References


