

## Are there low risk patients in Brugada syndrome?

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### **Risk stratification in Brugada syndrome**

In the last years risk stratification in Brugada syndrome has become the center of attention for several reasons. First, because the implantable cardioverter defibrillator (ICD) proved to be a very effective treatment for the disease. Second, because the effective ICD treatment is costly, has side effects and is not entirely without risks. Lastly, because accurate identification and treatment of patients at increased future risk of sudden death can save many years of life of young and otherwise healthy individuals.

Active research in the area by several study groups revealed that risk stratification in Brugada syndrome is problematic and led to several controversial issues. The main goal of risk stratification is the prediction of future ventricular fibrillation episodes at any time during life. This is especially difficult in middle age patients who have never had any symptoms and the diagnosis is incidental. Some of these patients will remain lifelong asymptomatic but a minority of these patients will die suddenly without any warning perhaps within 1 week or 20 years after the diagnosis. The identification of the later individuals is very difficult for several reasons. First, the disease is rare and meaningful information can only be derived from large international registries, where the inclusion criteria and the management strategies differ from center to center. Secondly, the event rates in the follow up studies are low, thus it is very difficult to identify statistically meaningful predictors. Lastly, the disease has only been described 14 years ago and up until today, even the longest follow up studies provide information only over a mean of the first 5 years following the diagnosis.

The search for ideal risk predictors continues. The ideal risk factor should be easy to use, cheap, reproducible, little invasive, applicable in all patients and available in all parts of the world. More importantly, it should be sensitive enough to avoid losing healthy young adults due to sudden death and specific enough to avoid unnecessary ICD implantations. However, when judging the usefulness of a risk factor it should be remembered that low sensitivity and positive predictive value (absence of VF in a patient with positive test result) within 5years of follow-up does not mean that the given predictor is not useful, since the disease likely carries a lifelong risk of sudden death. We believe that given the devastating consequences of a false negative test result (sudden death

in a patient with a negative test), the specificity and the negative predictive value of a parameter is even more important.

General agreement exists that survivors of cardiac arrest have a high risk of recurrent life threatening arrhythmic events (17 to 62% in the following 4-7 years) and therefore should receive an ICD (1-5). The current review will focus on the advantages and disadvantages of the currently available risk factors in patients without previous aborted sudden death.

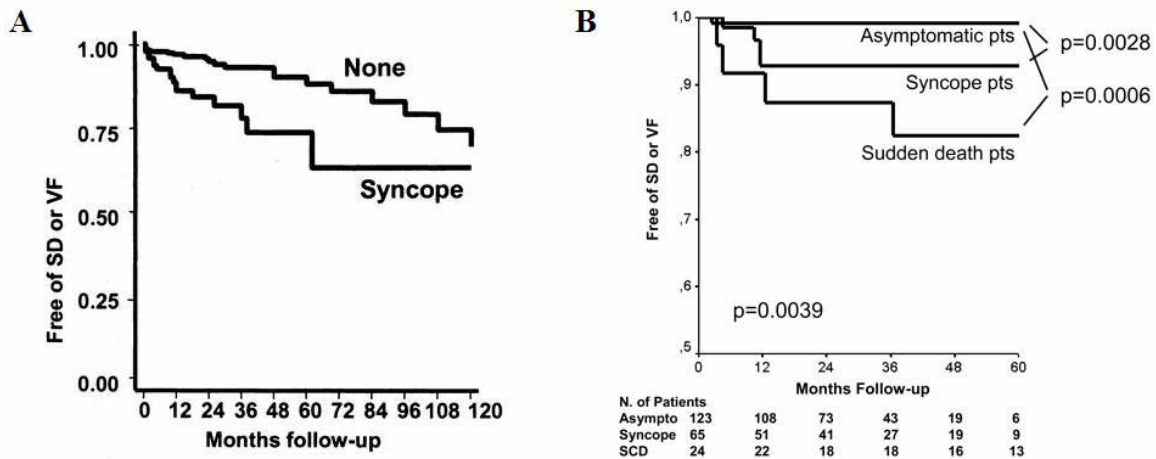
### **Syncope in carriers of Brugada syndrome**

The three largest registries including patients with Brugada syndrome and a history of syncope reported that during a follow up of 24 to 39 months 6 to 19 % of the patients suffered an arrhythmic event (documented ventricular fibrillation or SD) (2-5). In our international registry consisting of the largest number of patients without previous cardiac arrest (547 patients, 124 patients with syncope) the presence of syncope in both univariate and multivariate analysis was a significant predictor of future arrhythmic events; hazard ratio 2.79 (95% CI: 1.5-5.1),  $p=0.002$  and 2.5 (95% CI:1.2-5.3),  $p=0.017$ , respectively (Figure 1/a) (5). In the second largest European registry, involving 212 patients with or without cardiac arrest (including 65 patients with syncope), in the presence of low statistical power due to the low event rates, in univariate analysis the presence of syncope was still a significant predictor of future arrhythmic events ( $p=0.0028$ ) (result of the multivariate analysis was not reported in this study) (Figure 1/b) (3). Finally, the third largest Italian registry involving 200 patients with saddle or coved type ECG, with or without cardiac arrest (including 34 patients with syncope), reported that in multivariate analysis syncope in itself was not a predictor of future arrhythmic events. However, syncope in combination with the presence of spontaneous ST segment elevation was a significant predictor ( $p<0.002$ ) (Figure 3/b) (2). Therefore, general consensus exists that the presence of a history of syncope is a useful predictor of future cardiac events in patients with Brugada syndrome but without previous cardiac arrest. However, based on the first two mentioned registry data, the first two groups recommend ICD implantation in all patients with a history of syncope of unknown origin (3,5), while the Italian study group only if the syncope is coupled with the presence of spontaneous ST elevation (coved or saddle) (2). General agreement exists that the absence of a history of syncope (and aborted sudden death) identifies a patient group with a lower risk of future arrhythmic events.

However, there are several problematic issues with the presence of syncope as a risk factor. First, the diagnosis of the exact etiology of syncope is not always clear. In the young patient population of Brugada syndrome vasovagal syncope is also likely to occur frequently. In some incidentally identified patients, the detailed history frequently reveals an episode of syncope

occurring in unclear circumstances 10-20 years prior to the current presentation. For example, in our primary prophylactic ICD population of 47 patients, 4 patients had recurrent, most likely vasovagal syncope during follow-up, indicating that the syncopal episodes of these patients prior to the ICD implantation were likely also vasovagal in origin. In these patients, the presence of a history of syncope likely falsely suggests an increased risk of sudden death. However, in our opinion, the risk associated to a misdiagnosis and wrong treatment (not implanting an ICD) is much too high, being sudden death at a very young age.

Figure 1.



Kaplan-Meier analysis of arrhythmic events (sudden cardiac death [SD] or documented ventricular fibrillation [VF]) during follow-up depending on presence or absence or a history of syncope (A). From: Brugada et al: *Circulation* 2003;108:3092-3096

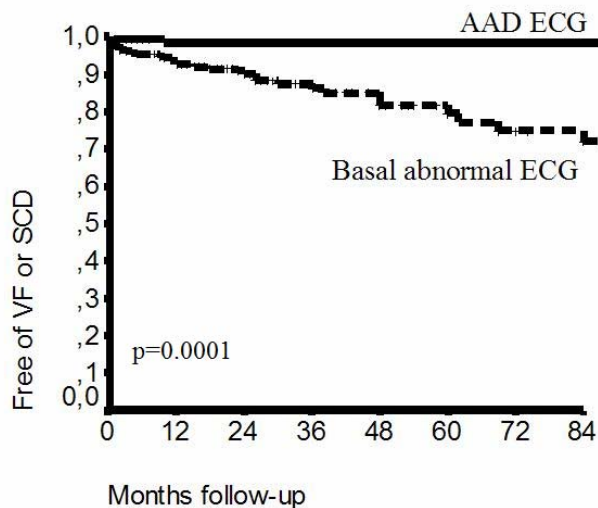
Kaplan-Meier analysis of arrhythmic events (sudden cardiac death or documented ventricular fibrillation) during follow-up depending on clinical presentation when abnormal ECG was identified. P=0.0039 represents overall comparison. From Eckardt et al: *Circulation* 2005;111:257-63

**The ECG in Brugada syndrome**

The predictive value of the presence of a spontaneous ECG abnormality has also been investigated by the three registry study groups. In our registry of 547 patients with or without syncope but without previous cardiac arrest, univariate analysis showed that a spontaneously abnormal ECG was a significant predictor of arrhythmia occurrence; hazard ratio:7.69 (95% CI:1.9-33.3), p=0.0001 (Figure 2) (5). In multivariate analysis the presence of a spontaneously abnormal ECG was no longer an independent predictor (hazard ratio: 2.86 (95% CI 0.7-12.3), p=0.103. However, in combination with the presence or absence of syncope and inducibility or non-inducibility during electrophysiologic (EP) study it was useful to differentiate between low and high

risk patients. In logistic regression analysis, in the presence of spontaneous ECG abnormality (depending on the presence of syncope and inducibility) the 2 year probability of arrhythmic events varied between 1.8 to 27%, while in the absence of spontaneous abnormality between 0.5 to 9.7% (5). The second largest European registry involving 212 patients with or without cardiac arrest, in the presence of low statistical power due to the low event rates, in univariate analysis the presence of spontaneous type I ECG tended to be a predictor of future arrhythmic events ( $p=0.046$ ) (result of the multivariate analysis was not reported in this study) (Figure 3/a) (3). Finally, in the Italian registry involving 200 patients with saddle or coved type ECG, with or without cardiac arrest, in life-tables method analysis (which considers the age of the patients instead of the length of follow up) baseline spontaneous ST segment elevation (saddle or coved) was a significant predictor of future events ( $p<0.001$ ). In multivariate analysis the spontaneous presence of ST elevation in itself was not a significant predictor of future arrhythmic events (hazard ratio 2.1 (95% CI:0.7-6.9)  $p>0.05$ ). However, as we mentioned previously, the presence of spontaneous ST segment elevation in combination with syncope was a significant predictor ( $p<0.002$ ) (Figure 3/b) (2). Based on these findings, general agreement exists that the presence of spontaneous ECG abnormality likely identifies a group of patients with higher risk of future arrhythmic events.

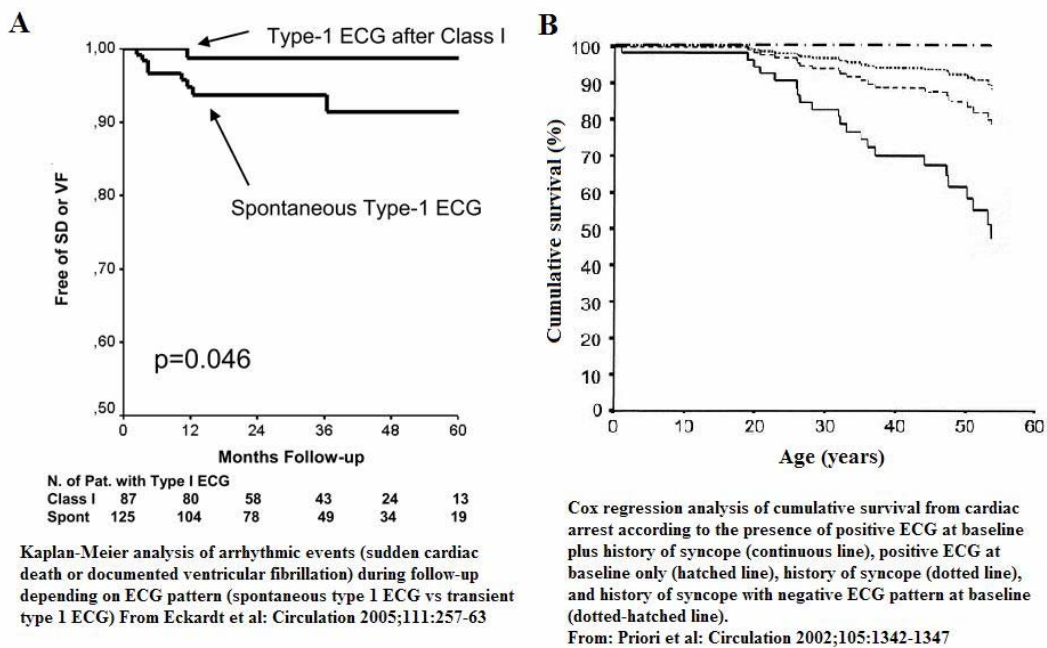
Figure 2.



Kaplan-Meier analysis of arrhythmic events (sudden cardiac death [SD] or documented ventricular fibrillation [VF]) during follow-up depending on the presence of basal spontaneously abnormal abnormal ECG. AAD ECG = abnormal ECG after antiarrhythmic drug challenge  
Data is based on Brugada et al: Circulation 2003;108:3092-3096

However, there remain several unresolved issues about the presence of a spontaneous ECG abnormality as a risk factor. First of all, as mentioned above, some studies considered the spontaneous presence of both saddle and coved type ECG abnormalities, while others only considered the presence of coved type I ECG. Secondly, it is well known that the presence of spontaneous type I ECG is variable. Our recent single center analysis of a primary prophylactic ICD population, where a large number of ECGs are available in each patient, indicates that the type I ECG pattern is intermittent in all patients if a sufficient number of ECGs is recorded. Furthermore, our data suggests that in patients who had at least one documented spontaneous type I ECG, if all the available ECGs of the given patient are analyzed, only about 25% of the ECGs show the diagnostic coved type I pattern (data to be presented on the World Congress of Cardiology, Barcelona, 2006).

Figure 3.



### EP study

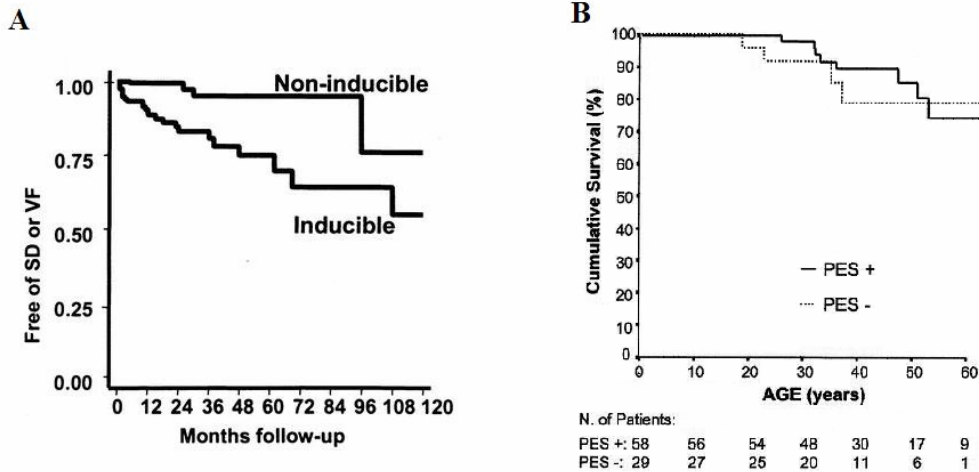
Currently, the most controversial issue in risk stratification of patients with Brugada syndrome is the usefulness of the EP study. Our group has repeatedly analyzed the registry data in general and in different subpopulations (symptomatic, asymptomatic) with consistent results. In

our registry data of 547 patients with or without syncope but without previous cardiac arrest, in univariate analysis inducibility of a sustained ventricular arrhythmia was a strong predictor of arrhythmia free survival with a hazard ratio of 8.33 (95% CI:2.8-25),  $p=0.0001$  (5) (Figure 4/a). In multivariate analysis the presence inducibility during EP study remained an independent predictor with a hazard ratio of 5.88 (95% CI:2-16.7),  $p=0.0001$  (5). The second largest registry involving 212 patients with or without cardiac arrest, in the presence of low statistical power due to the low event rates, reported that inducibility during EP study was not a predictor of future arrhythmic events. In this analysis, in the presence of low event rates, the specificity and the sensitivity were low (50% and 56% respectively) with a very low positive predictive value (5.4%) and a high negative predictive value (95.7%) were noted; all asymptomatic non-inducible patients remained asymptomatic (3). Similarly, in the Italian registry involving 200 patients with saddle or coved type ECG, with or without cardiac arrest, inducibility at the EP study analyzed by the above mentioned life-table method was reported not to be a predictor of future events (Figure 4/b). In this study low specificity and sensitivity (36% and 66%, respectively) with a very low positive (14%) but a high negative (86%) predictive value were reported for programmed electrical stimulation (2).

It is difficult to explain the major differences between the three registries in the predictive value of the EP study. A possible explanation is the higher event rates in our registry as compared to the other 2 registries, as proposed by Eckardt et al, due to a selection bias due to the inclusion of more severe patients and families from the 1990's when the syndrome has been first described (3). At this time only patients and families with the most severe presentations of the disease were diagnosed. To evaluate this explanation, recently we conducted an analysis from our registry data of patients who were entirely asymptomatic and who has had no family history of sudden death or Brugada syndrome (fortuitous individuals). Of the 168 individuals identified the ECG was spontaneously abnormal in 92%. During a mean follow up of 28 months 5 sudden deaths and 7 VF events (6%) occurred. All 5 SD occurred in individuals who did not undergo an EP study and had no ICD (6), emphasizing once more the predictive role of the EP study in the asymptomatic patient population. The different stimulation protocols might also play a role in explaining the discrepancies. Although our registry is also a multicenter study with protocols differing from centre to centre, in our study population the large majority of patients were stimulated only from one site (RV apex) with a maximum of three basic cycle lengths and a maximum of 3 extrasystoles with the minimum coupling interval not shorter than 200 ms. Additionally, the different inclusion criteria, especially the inclusion of patients with the non-diagnostic saddle back type ECG pattern in the Italian registry might also play a role. Additionally, in the other 2 studies the predictive value of the EP study was calculated together for the symptomatic and asymptomatic patients. The different statistical methods, especially the life-time table analysis, when instead of follow up, the age of the

patients is used for analysis (in a study population with a mean age of 41±18 years) might also play a role. Finally, it should be noted that in the presence of very low event rates and relatively short follow up in a disease with lifelong risk of arrhythmias, it is not possible to draw any definitive conclusions over the predictive value of any examination.

Figure 4.



Kaplan-Meier analysis of arrhythmic events (sudden cardiac death [SD] or documented ventricular fibrillation [VF]) during follow-up depending on inducibility of sustained ventricular arrhythmias during electrophysiological study (B).  
From: Brugada et al: Circulation 2003;108:3092-3096

Kaplan-Meier analysis of cumulative survival from cardiac arrest, based on the outcome of PES. PES+ indicates patients with inducible VF (continuous line); PES-, patients without inducible VF (dotted line). Log-rank test, P >0.05, NS.  
From: Priori et al: Circulation 2002;105:1342-1347

**Other risk factors**

**Gender**

It is well documented that among patients with Brugada syndrome the male:female ratio is 3:1 (1-5), with the exception of the south-east asian variant of the disease where the male:female ratio is 8:1 (7). In our registry data in univariate analysis male gender was a predictor of event free survival with hazard ratio of 5.26 (95%:1.6-16.6), p=0.001. However, in multivariate analysis male gender was no longer an independent predictor (5). Similarly, in the other 2 registries male gender was not reported to be a predictor (2,3). However, it should be kept in mind, that the majority of the registry patients are male. Thus, due to the small patient numbers, only little data is available about the characteristics of the disease in female patients. At this point in time, it is not clear whether female patients have a lower risk of arrhythmic events or not.

**Family history of sudden death**

Although in everyday clinical practice, family history of sudden death is frequently considered as an additional risk factor, none of the three registries showed any predictive role for this factor (2-5). However, it should be noted, that in the registries no upper age cut-off was used to avoid the confounding effect of sudden death due to coronary artery disease. Additionally, the possible role of multiple sudden deaths or sudden death of first degree versus second degree relatives has also not been investigated. In spite of the currently available evidence, it is sometimes difficult to neglect the sudden death of a close relative at a young age, especially in the presence of strong psychological factors in the remaining family members. Until further data is available, frequently decisions are made on an individual basis instead of based on strong scientific evidence.

**Age**

Although in the first description of Brugada syndrome in eight patients three patients were children (8), subsequently the registries revealed that Brugada syndrome is extremely rare in the pediatric population. Additionally, population studies revealed that the prevalence of the asymptomatic Brugada ECG pattern is very low (0.005%) even in the Asian pediatric population, as compared to the adults (0.14-0.7%) (9,10). Furthermore, a small study of the family members of 16 SCN5A mutation carrier probands revealed that the penetrance in children was only 17% as opposed to 100% in adults (11). In another single family study of an SCN5A mutation causing both Brugada and long QT-3 syndrome, the ST elevation on the ECG only began to manifest after 5 years of age (12). All this data indicates that for an unknown reason both the ECG phenotype and the symptoms in the large majority of patients manifest in adulthood. Recently, we investigated the follow up data of our asymptomatic pediatric family members who had a positive class I antiarrhythmic drug challenge. During a medium term follow up of this small patient population, none of the patients had any events (data to be presented on the World Congress of Cardiology 2006, Barcelona). This preliminary data needs to be confirmed on a larger patient population, but likely suggests that the asymptomatic pediatric family members have a very low medium term risk for arrhythmic events.

**Other ECG parameters**

In small studies of symptomatic and asymptomatic patients with Brugada syndrome promising results were reported with the use of the signal average ECG (SAECG) as a risk factor



for predicting future arrhythmic events (13,14). However, further data in a larger patient population with prospective follow up is necessary to confirm these observations.

### **Conclusion**

In summary, recent data indicates that patients with Brugada syndrome but without a history of previous cardiac arrest or syncope of unknown origin have a much lower risk of arrhythmic events. In this asymptomatic patient population, the patients with a baseline normal ECG have a future risk of arrhythmic events similar to the general population and thus can be reassured. Based on the currently available data, asymptomatic patients who have a baseline abnormal ECG have a risk of arrhythmic events that is low, but sufficiently high to warrant further risk stratification with the currently available best method; an electrophysiological study. If during the electrophysiological study the patient is not inducible, the patient is considered to be at low risk of future arrhythmic events. Finally, our recent data indicates that the children identified at family screening of a proband, with a baseline normal ECG have also a short term good prognosis. However, in even this low risk population, we consider important to follow recommendations. Most importantly, we ask the patients to contact us immediately in case of syncope. All patients should avoid class I drugs that can worsen Brugada syndrome and if they have fever it should be aggressively treated. Additionally, we recommend in all families the screening of the first degree relatives.

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