Outcome after Implantation of Cardioverter-Defibrillator in Patients with Brugada Syndrome: A Multicenter Study – Part 2

Running title: Sacher et al.; Brugada syndrome and ICD

Frédéric Sacher, MD1; Vincent Probst, MD, PhD2; Philippe Maury, MD3; Dominique Babut, MD, PhD4; Jacques Mansourati, MD5; Yuki Komatsu, MD6; Christelle Marque, MD7; Antonio Rosa, MD8; Abou Diallo, MD, MPH1; Romain Cassagneau, MD9; Claire Loizeau, MD1; Raphael Martins, MD10; Michael E. Field, MD1; Nicolas Derval, MD1; Shinsuke Miyazaki, MD6; Arnaud Denis, MD1; Akihiko Nogami, MD11; Philippe Ritter, MD1; Jean-Baptiste Gourraud, MD2; Sylvain Ploux, MD1; Anne Rollin, MD3; Adlane Zemmoura, MD1; Dominique Lamaison, MD12; Pierre Bordachar, MD1; Bertrand Pierre, MD4; Pierre Jaïs, MD1; Jean-Luc Pasquié, MD, PhD13; Méleze Hocini, MD1; François Legal, MD14; Pascal Defaye, MD9; Serge Boveda, MD8; Yoshito Iesaka, MD6; Philippe Mabo, MD10; Michel Haïssaguerre, MD1

1Hôpital Cardiologique du Haut-Lévêque, CHU de Bordeaux, L’Institut de Rythmologie et de modélisation Cardiaque, INSERM 1045, Bordeaux, France; 2Institut du thorax, CHU de Nantes, Nantes, France; 3CHU de Toulouse, Toulouse, France; 4CHU de Tours, Tours, France; 5CHU de Brest, Brest, France; 6Tsuchiura Kyodo Hospital, Tsuchiura, Japan; 7CHU de Lille, Lille, France; 8Clinique Pasteur, Toulouse, France; 9CHU de Grenoble, Grenoble, France; 10CHU de Rennes, Rennes, France; 11Yokohama Rosai Hospital, Yokohama, Japan; 12CHU de Clermont-Ferrand, Clermont-Ferrand, France; 13CHU de Montpellier, Montpellier, France; 14CHU de Poitiers, Poitiers, France

Address for Correspondence:
Frédéric Sacher, MD
Hôpital Cardiologique du Haut-Lévêque
CHU de Bordeaux
33604 Bordeaux-Pessac, France
Tel: 33-5-57656471
Fax: 33-5-57656509
E-mail: fréderic.sacher@chu-bordeaux.fr

Abstract

**Background**—Implantable Cardioverter-Defibrillator (ICD) indications in Brugada Syndrome (BrS) remain controversial especially in asymptomatic patients. Previous outcome data is limited by relatively small number of patients or short follow-up duration. We report the outcome of BrS patients implanted with an ICD in a large multicenter registry.

**Methods and Results**—378 patients (310 male, 46±13 years) with a type 1 Brugada ECG pattern implanted with an ICD (31 for aborted sudden cardiac arrest (SCA), 181 for syncope and 166 asymptomatic) were included. Fifteen patients (4%) were lost to follow-up. During a mean follow-up of 77±42 months, 7 patients (2%) died (1 due to inappropriate shock (IS)) and 46 patients (12%) had appropriate device therapy (5±5 shocks/patient). Appropriate device therapy rates at 10 years were 48% for patients whose ICD indication was aborted SCA, 19% for those whose indication was syncope and 12% for the patients who were asymptomatic at implantation. At 10 years, rates of IS and lead failure are 37% and 29%, respectively. IS occurred in 91 patients (24%, 4±4 shocks/patient) because of lead failure (n=38), supraventricular tachycardia (n=20), T-wave oversensing (n=14), or sinus tachycardia (n=12). Importantly, introduction of remote monitoring as well as programming a high single VF zone (>210/220 bpm) and a long detection time were associated with a reduced risk of IS.

**Conclusions**—Appropriate therapies are more prevalent in symptomatic BrS patients but are not insignificant in asymptomatic patients (1%/year). Optimal ICD programming and follow-up reduce dramatically IS. However lead failure remains a major problem in this population.

**Key words:** Brugada syndrome, implantable cardioverter-defibrillator, outcome, Lead Failure
Introduction

Brugada syndrome (BrS) is an arrhythmogenic disease characterized by an ECG pattern of right bundle-branch block, ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac arrest (SCA) as a result of polymorphic ventricular tachyarrhythmias or ventricular fibrillation (VF)\(^1\). Whereas ICD is considered as the main therapy in symptomatic patient, we \(^2\) and others \(^3\)-\(^7\) have reported the low prevalence of arrhythmic events as well as a high risk of complications in this young otherwise healthy population. However, these studies were limited by the relatively small number of patients and/or short duration of follow-up. We continued our initial registry in the same 14 centers to obtain a longer-term follow-up and evaluate the evolution of ICD management in BrS patients.

Methods

Study Population

All patients diagnosed with Brugada syndrome and implanted with an ICD in 14 centers between 1993 and 2005 were included in our initial study \(^2\)(group 1). We continued their follow-up as well as inclusion of all additional BrS patients implanted with an ICD, up to December 2011 in the same 14 centers. Group 2 includes BrS patients implanted between 2006 and 2011. The diagnosis was made after an episode of aborted SCA, during evaluation of syncope, in asymptomatic patients with suggestive ECG pattern recorded during routine examination or as a consequence of familial screening after the diagnosis of BrS in a family member. This registry was approved by the institutional review committee and the subjects gave informed consent.

Diagnosis, Clinical Data and Electrophysiological Testing

Patients were included in this study only if they had a type 1 Brugada pattern on ECG at baseline on at least one occasion or after provocation with a class I antiarrhythmic drug. A type 1 ECG
was defined as a prominent coved ST-segment elevation displaying J-wave amplitude or ST-segment elevation $\geq 0.2$ mV at its peak followed by a negative T wave. The choice of class I drug was determined by its availability in the participating hospitals. Intravenous ajmaline (1mg/kg body weight at a rate of 10 mg/min), flecainide (2mg/kg body weight over 10 minutes with a maximum of 150mg), or pilsicainide (1mg/kg body weight over 10 min) were used. In addition, treadmill exercise testing and biochemical analysis excluded acute ischemia and metabolic or electrolyte disturbances. Echocardiography was performed to rule out underlying structural heart disease.

The following clinical data were collected in all 14 participating centers: circumstances of diagnosis, indication for ICD implantation, age at diagnosis, gender, family history of sudden cardiac death (before the age of 45 years), results of pharmacological testing for unmasking the characteristic coved-type ECG pattern and invasive electrophysiological testing (EPS) when performed. Patients with a previous history of presumed arrhythmic syncope, documented sustained ventricular arrhythmia or aborted SCA were considered symptomatic.

Electrophysiological study (EPS) indication has evolved throughout the study duration and was performed at the discretion of the electrophysiologist. A maximum of 3 ventricular extrastimuli were delivered from 2 ventricular sites unless an inducible ventricular arrhythmia was elicited at a previous step. Premature beats were started in late diastole and coupling intervals were then reduced in 10 ms or 20 ms decrements to 200 ms or until refractoriness was reached. This protocol did not use higher stimulus current nor repetition of double and triple extrastimulation at the shortest coupling intervals. Inducible ventricular arrhythmia was defined as any ventricular arrhythmia lasting $>30$ seconds, or causing syncope / circulatory collapse, or requiring intervention to be terminated. Therefore, patients with inducible asymptomatic
nonsustained ventricular arrhythmia that terminated spontaneously before syncope were classified as non-inducible. The minimum syncope work-up included careful patient history, 12-lead ECG, echocardiography, stress test and Holter monitoring. Syncope classification was mainly based on clinical features in the absence of ECG monitoring during the syncopal event. An arrhythmic origin was suspected in the absence of (or brief) prodrome, the absence of specific triggering circumstance, a brief loss of consciousness, a fast return to consciousness and/or a severe trauma.

**Follow-up**

In the absence of symptoms or device therapy, patients were seen routinely every 3 to 6 months for clinical review and device interrogation, according to local practice and every 6 to 12 months for patients with ICD remote monitoring capabilities. ICD programming was at the discretion of the referring electrophysiologists but after our initial study in 2006, we recommended programming a single VF zone above 210/220 bpm.

In the event of a shock, patients were seen at the ICD clinic within 24 hours and the device interrogated. Appropriate therapies were defined as shocks or anti-tachycardia pacing (ATP) delivered for ventricular tachycardia (VT) or ventricular fibrillation (VF) and inappropriate shocks defined as those delivered in the absence of ventricular arrhythmia. Only the first appropriate therapy, the first inappropriate shock and the first lead failure were considered for analysis. Data were collected until December 2011. Follow-up was extended up to 6 months for patients who had been implanted from July to December 2011 to provide at least 6 months of follow-up for all patients.

**Statistical Analysis**

All quantitative variables were normally distributed according to the Shapiro-Wilk test except
the delay between ICD implantation and lead failure. Data were expressed as mean ± standard
deviation or as median (25th, 75th percentile) for the delay between ICD implantation to lead
failure. One-way ANOVA was performed to compare continuous variables. Two by two
comparisons of quantitative variables were compared with the Student’s t-test. Chi-square test
was used to compare categorical variables. Comparison between Kaplan-Meier survival curves
was made using the log-rank test. A p-value <0.05 was considered statistically significant.

To assess the contribution of baseline patient characteristics in predicting the likelihood
of first appropriate therapy from the ICD and first lead failure during follow-up, multivariable
Cox proportional-hazard regression analysis was used. Only variables with p-value<0.20 in
univariable analysis were used for the multivariable analysis. For appropriate therapy, sex, age,
symptoms, period of inclusion, family history of sudden cardiac arrest, spontaneous type 1 ECG,
positive EPS and SCN5a mutation were tested in univariable analysis. Only symptoms and
spontaneous type 1 ECG had a p-value <0.20. For lead failure, we tested the following
parameters: age, sex, symptoms, family history of SCA, date of ICD implantation (before or after
2006), type of ICD lead. Only the family history of SCA and the type of ICD leads had p<0.20 in
univariable analysis. All authors had full access to and take full responsibility for the integrity of
the data. All authors have read and agree to the manuscript as written.

Results

Clinical characteristics and indication for ICD implantation.

The percentage of BrS patients implanted with an ICD dropped over the years from 30% until
2005 (group 1) to 22% between 2006 and 2011 (group 2) (p=0.001) (figure 1). Study population
characteristics are summarized in Table 1 (378 patients; 82% male; mean age: 46 ±13 years at
diagnosis). The vast majority of patients were Caucasian (91%) with Asian and African ethnicity
accounting for 8% and 1% of patients respectively. In 226 individuals (60%), a spontaneous type 1 ECG was present at baseline. In the remaining individuals, class I antiarrhythmic drug administration unmasked the diagnostic type 1 ECG. EPS was less likely to be used to risk stratify patients after 2005 (90% in group 1 vs 72% in group 2; p<0.001). A SCN5A mutation was found in 41 (26%) of 160 patients in whom the results of genetic testing were available. A family history of SCA was found in 135 patients (36%).

Before ICD implantation, 166 patients (44%) were asymptomatic, 181 (48%) previously had at least one episode of syncope with no clear extracardiac cause, and 31 patients (8%) had been resuscitated from SCA. Among the 166 asymptomatic patients, indications included: (i) inducible ventricular arrhythmias at EPS (n=139), (ii) no inducible ventricular arrhythmia but a family history of Brugada syndrome and SCA (n=21), (iii) spontaneous non-sustained ventricular arrhythmia (n=3) and (iii) a spontaneous type 1 Brugada pattern along with electrophysiologist and/or patient preference for ICD (n=3) (Figure 2). ICD indication dramatically changed over time (Table 1) with less asymptomatic patients and more patients with syncope implanted. Whereas asymptomatic BrS patients represented 52% of patients with ICD before 2006 (group 1), their proportion dropped to 33% since 2006 (group 2) (p<0.001) mainly due to the decrease in the number of EPS performed (198 in group 1 vs 113 in group 2; p<0.001).

At implantation, R wave amplitude was > 5mV in 330/366 patients (12 missing data) and small diameter recalled ICD leads (Medtronic Sprint Fidelis or St Jude Medical Riata) were used in 82/378 patients (22%).

**Outcome**

During a mean follow-up of 77 ±42 months (median 76 months; range 6 to 220 months)
following ICD implantation, 15 (4%) patients were lost to follow-up and 7 (1.8%) died. Mean age of death was 59 ±12 years with cause of death including malignancy (n=3), suicide (n=2), severe trauma without preceding syncope (n=1) and inappropriate ICD discharge due to lead failure (n=1). During follow-up, a mean of 1.5 ±0.6 [1-4] ICD/patient were implanted. Twelve percent (46 pts) of the patients experienced appropriate therapy. Its rate differed according to ICD indication (aborted SCA: 39% -6.9%/year-, syncope: 12% -2%/year-, asymptomatic 7% -1%/year- ; p<0.001) (Figure 3) and the mean delay to first therapy after ICD implantation was much shorter for patients with previous aborted SCA (18 months) versus patients with previous syncope (4 years) or asymptomatic patients (4 years) (Table 2). The rate of appropriate therapy 10 years after ICD implantation was 48% in patients with aborted SCA, 19% in patients with syncope, 12% in asymptomatic patients (Table 3). First appropriate shock could occur as late as 13 years after initial ICD implantation. Eleven patients had only one shock whereas 24 patients had 2 to 10 shocks. Eleven patients (24% of patients with shocks) presented with an arrhythmic storm (≥3 episodes within 24 hours) and were treated with quinidine (n=6) and/or ablation (5 patients) after acute use of isoproterenol in 4. They had a mean of 13 ±5 shocks versus 3 ±2 for those without arrhythmic storm (p<0.001).

Five patients (11% of patients with appropriate ICD therapies) had therapies for monomorphic VT (4 shocks and 1 ATP, mean VT cycle length: 280 ±47 ms). The patient with VT terminated by ATP suffered myocardial infarction between BrS diagnosis and VT. Forty-one patients had appropriate shocks for polymorphic VT or VF. Of note, 11 patients experienced non-sustained polymorphic VT / VF that did not result in ICD therapy. Three patients with self-terminating polymorphic VT / VF episodes never had any ICD therapy (Figure 4). In 6 patients, non sustained polymorphic VT/VF occurred during sleep and no symptom was noted. The 5
remaining patients experienced lightheadness/near syncope (n=3) or syncope (n=2). Regarding antiarrhythmic drug therapy, 13 patients were on quinidine (6 after arrhythmic storm, 2 for atrial fibrillation). Once quinidine blood level was within therapeutic range (up to 600mg of hydroxyquinidine bid), no patient had ventricular arrhythmia recurrence during follow-up. Concerning ablation, one patient had incomplete ablation due to the absence of PVCs and bleeding during pericardial access that limited the epicardial part of the ablation but he was subsequently well controlled on quinidine therapy. The other 7 patients (5 with arrhythmic storm) with ablation did not have recurrence in the absence of any treatment.

Regarding the 12 asymptomatic patients who received an ICD and subsequently experienced appropriate therapies, 8 had a spontaneous type 1 Brugada ECG pattern at baseline and all but one had inducible ventricular arrhythmia at EPS. Six had a family history of sudden cardiac arrest before the age of 45. All these patients were included before 2006 (initial study).

Of note, 10 other patients (2.6%) with lead failure and subsequent extraction/device deactivation were not reimplanted because of physician or patient decision. Seven were asymptomatic at the time of initial ICD implantation and had received an ICD for positive EPS (n=5) or family history of SCA (n=2) and the remaining 3 had been implanted for syncope. All 10 patients were still alive 44 ±33 months later. The 3 patients with previous syncope have not been reimplanted because of patient preference in a 50 years old male, older age in a 77 years old male and endocarditis in a setting of chemotherapy for cancer in a 66 years old male.

In multivariable analysis, the only factor predictive of appropriate device discharge was the presence of symptoms prior to implantation (HR 2.460 [1.169-5.174] for syncope and 10.149 [4.364-23.607] for resuscitated SCA). Spontaneous type 1 ECG, age, sex and family history of SCA were not predictive in this selected population.
Complications of ICD

Complications after hospital discharge for ICD implantation occurred in 135 patients (36%). The most common complication was inappropriate shock (n=91) followed by lead failure (n=60). Nine patients had infection in relation to the ICD: endocarditis (n=3) or ICD pocket infection (n=6) that required lead extraction in all (surgical approach in one) in addition to intravenous antibiotic therapy. Nine patients suffered from lead dislodgement or pocket hematoma requiring specific re-intervention in 3. Five patients had pericardial effusion treated by pericardiocentesis. Severe depression was diagnosed in 5 patients leading to suicide in 2. Five patients had other types of complications: premature ICD failure due to electric arc n=1, upper limb phlebitis n=1, pulmonary embolism 2 weeks after ICD implantation n=1, transient stroke in patients with patent foramen ovale (PFO) n=2 (few days after lead extraction in one and several months after implantation in one patient whose ICD lead was placed inadvertently in the left ventricle through the PFO). Fifty-one patients had their ICD changed prematurely: 50 because of lead failure and 1 because of an electric arc that shorted out the ICD.

Inappropriate ICD therapy

Inappropriate shocks occurred in 91 (24%) patients (mean 3.8 ±4.2 shocks/pt) 35 ±31 months after ICD implantation with a risk at 10 years of 37% (Table 3). However the rate of inappropriate shocks decreased significantly after 2005 (Figure 5). Remote monitoring was used in 147 patients (39%) with an increasing use since 2006 (31% in group 1 vs 49% in group 2; p<0.001). In the subgroup of patients with lead failure, remote monitoring decreased significantly the occurrence of inappropriate shock from 91% to 44% (p<0.001). Reasons for inappropriate shocks were: lead dysfunction (n=38), supra-ventricular arrhythmias (n=20), T wave oversensing (n=14), sinus tachycardia (n=12), and other reasons (n=7). Two patients
developed VF as a result of an inappropriate shock that could not be terminated by the device because of lead failure. One patient survived owing to prompt resuscitation maneuvers but the second patient died.

Inappropriate shocks occurred only in 2/69 patients (2.3%; 0.7%/year) who had a combination of R wave amplitude >5mV at implantation, long number of interval to detect (NID) duration, high VF rate>210-220 bpm and remote monitoring capabilities vs 3.7%/year in the general study population.

**Lead failure**

Sixty patients (16%) experienced lead failure 56 (36-72) months after ICD implantation (Figure 6). Eighty-two patients (22%) had leads involved in a device recall/advisory (St. Jude Medical Riata or Medtronic Sprint Fidelis). They accounted for 27% (16/60) of lead failure. In this particular population (young and active), ICD leads not involved in a recall process also had a high risk of failure (Figure 6). Risk of lead failure increased dramatically 2 years after implantation up to a risk of 29% at 10 years (Table 3). No parameters (age, sex, symptoms, date of implantation, or presence of Sprint Fidelis/Riata leads) were found predictive of lead failure in univariable analysis.

**Discussion**

Six years after ICD implantation, BrS patients implanted with an ICD have twice the rate of inappropriate shock (24%) versus appropriate shock (12%) with an overall complication rate of 36%. A major reason is a 29% risk of lead failure 10 years post implantation in this young otherwise healthy population (Figure 6). These results as well as FINGER⁹ ones provide important data to assist in patient counseling prior to ICD implantation in the setting of BrS.
Another finding is the evolution in the management of these patients since our initial work\textsuperscript{2}. The overall ICD implantation rate decreased in BrS patients from 30\% during our initial study (group 1) to 22\% since then (group 2) (p=0.001). This was particularly true in asymptomatic patients (Table 1). However we are still lacking tools to better risk stratify asymptomatic patients in whom the utility of EP study is questionable\textsuperscript{10}. Of note, none of our asymptomatic patients implanted since 2006 had appropriate shock. Currently, ICD implantation in asymptomatic patients is a case by case decision\textsuperscript{11} with multifactorial approach involving an informed consent discussion with the patient. Although the risk for asymptomatic BrS patients is low, it is not insignificant (0.81%/year in patients with spontaneous type 1 ECG and 0.35%/year in patients with only induced type 1 pattern)\textsuperscript{9} and the consequence of not implanting an ICD in an asymptomatic patient who subsequently goes on to develop VF is extreme. Looking at the subgroup of patients from Bordeaux (n=329; 91 with an ICD, 238 without), 2 asymptomatic subjects with Brugada pattern diagnosed during the period of the study but not implanted with an ICD died suddenly. The first one was a 21 year old male diagnosed after ajmaline test because of familial BrS screening. He had a negative EPS (2 sites, 2 cycles, 3 extrastimuli down to 200ms) but died suddenly during his sleep 8 months later. The second patient, a 56-year-old asymptomatic male, underwent ajmaline test after a routine pre-operative ECG performed before surgery showed a type 2 ECG pattern. He had no family history of SCA and did not undergo EPS. He died suddenly during sleep 16 months later. No autopsy was performed on either patient.

Even in patients with syncope, the decision to implant an ICD can be difficult because non-arrhythmic syncope is present in this young population. In a recent study\textsuperscript{12}, 4/23 BrS patients with ICD implantation for suspected arrhythmic syncope subsequently developed
recurrent syncope without arrhythmia on ICD log. In a BrS patient with syncope for whom the clinical history is not typical of an arrhythmic etiology, an implantable loop recorder may be helpful. This would allow for continued surveillance for ventricular arrhythmia but avoid committing the patient to the potential complications of long-term ICD therapy with the understanding however that the patient would remain unprotected during this monitoring period. To make this decision even more challenging, non-sustained polymorphic VT/VF was recorded on the ICD log in 11 patients from our study population who were either asymptomatic or simply complained of lightheadedness (Figure 4). Because of the complexity of the risk / benefit analysis, we strongly feel that decisions regarding ICD implantation in BrS patients should be performed at experienced centers and after a thorough discussion with the patient and family.

Owing to the results of our initial study, we also modified ICD programming with a single VF zone above 210-220 bpm that helped reducing the inappropriate shock rate (Figure 5). As recently demonstrated in MADIT-RIT, such programming was associated not only with reduction in inappropriate therapy but also with reduction in all-cause mortality in patients with structural heart disease. Veltmann et al. for BrS patients also showed that programming a single high rate VF zone was safe and could prevent inappropriate therapy. Because monomorphic VT was recorded in 5 patients, a monitor zone from 180 to VF zone may be helpful. Importantly, looking at patients with good implantation parameters (R wave amplitude >5mV at implantation), optimal programming (long NID, single high VF zone >210-220bpm) and close follow-up with remote monitoring had a low rate of inappropriate shock (0.7%/year compared to 3.7%/year in the general BrS population).

The other evolution that likely explains the decrease in inappropriate shock rate since 2006 is the incorporation of remote monitoring (Table 1) for the early detection of ICD lead
failure or malfunction\textsuperscript{15}. It has the potential to reduce the morbidity associated with inappropriate shocks and may be even prevent ICD related death (as it occurred in one of our patient and as described in the literature\textsuperscript{16-18}).

An increasing challenge is the strategy to manage patients after lead failure and extraction. Extrapolation of the lead failure rates seen in \textbf{figure 6} indicates that patients implanted with an ICD in their forties will have an important risk of lead failure during their life (life expectancy $>30-40$ years at implantation). The rate of standard ICD lead failure remains high not just in the small diameter recalled leads (\textbf{Figure 6}). In case of lead failure, should we just reimplant a new ICD system as we often do simply based on the initial decision to implant? One alternative for reimplantation could be the use of recently developed subcutaneous ICD\textsuperscript{19} but this too, is not without risk of complications\textsuperscript{20} and we have currently only short follow-up data on the safety and efficacy of this device. Another alternative is not to reimplant certain patients (especially asymptomatic patients without ventricular arrhythmia recorded by the ICD log during an extended follow-up period) as was the case for 10 patients (2.6\%) in our series. All 10 patients are still alive without symptom after a mean of 44 $\pm$33 months after ICD system extraction or deactivation. However the long term safety of this strategy is unknown. In our series, the first appropriate ICD therapy could occur as late as 13 years after ICD implantation.

We now consider not reimplanting an ICD in asymptomatic Brugada patients without ventricular arrhythmia during follow-up who do not have persistent spontaneous type 1 Brugada pattern ECG. This strategy requires a case-by-case analysis after reviewing of the risks and benefits of reimplantation or not with the patient and his family.

In patients with arrhythmic risk who refuse ICD/lead implantation, quinidine therapy may be an option as it is extremely effective in preventing VF recurrence\textsuperscript{21} when blood concentration
is within therapeutic range.

Finally, psychological and social impact of ICD is often underestimated. In this registry, 2 patients committed suicide and 3 other suffered from severe depression. The social impact of ICD implantation is particularly important in young patients with implications for employment. Psychological evaluation before ICD implant may be valuable identifying more fragile patient requiring closer follow-up.

Study Limitations

This is a retrospective study and the population included was identified from 14 different centers. Although every effort was made to collect the data in a uniform and thorough manner, some measurement bias may be present.

Conclusions

In this large Brugada syndrome population (only 4% of patients lost to follow-up), rates of appropriate shock at 5 and 10 years are 48%/48% for patients implanted because of aborted SCA, 11%/19% for those with syncope and 6%/12% for asymptomatic patients. Optimal ICD programming and follow-up reduce dramatically the inappropriate shock rate. However lead failure remains a major problem in this population (29% at 10 years).

Conflict of Interest Disclosures: None.

References:


**Table 1.** Characteristics of the Brugada syndrome population according to the period of ICD implantation. Group 1: BrS patients from our initial study implanted until 2005; Group 2: Patients with Brugada syndrome implanted with an ICD since 2006 in the same 14 centers.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=220)</th>
<th>Group 2 (n=158)</th>
<th>p-value</th>
<th>Total (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (Male)</strong></td>
<td>183 (83%)</td>
<td>127 (80%)</td>
<td>p=0.48</td>
<td>310 (82%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>46 ±12</td>
<td>47 ±14</td>
<td>p=0.40</td>
<td>46 ±13</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>205 (93%)</td>
<td>138 (87%)</td>
<td></td>
<td>343 (91%)</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (5%)</td>
<td>18 (11%)</td>
<td>p=0.11</td>
<td>30 (8%)</td>
</tr>
<tr>
<td>African</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
<td></td>
<td>5 (1%)</td>
</tr>
<tr>
<td><strong>ICD indication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aborted SCA</td>
<td>18 (8%)</td>
<td>13 (8%)</td>
<td></td>
<td>31 (8%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>88 (40%)</td>
<td>93 (59%)</td>
<td>p=0.001</td>
<td>181 (48%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>114 (52%)</td>
<td>52 (33%)</td>
<td>p=0.001</td>
<td>166 (44%)</td>
</tr>
<tr>
<td>Family history of SCA</td>
<td>91 (41%)</td>
<td>45 (25%)</td>
<td></td>
<td>135 (36%)</td>
</tr>
<tr>
<td>Spontaneous type I ECG</td>
<td>137 (62%)</td>
<td>89 (56%)</td>
<td>p=0.25</td>
<td>226 (60%)</td>
</tr>
<tr>
<td>Number of patients with EPS</td>
<td>198 (90%)</td>
<td>113 (72%)</td>
<td>p&lt;0.001</td>
<td>311 (82%)</td>
</tr>
<tr>
<td>ICD with remote monitoring</td>
<td>69 (31%)</td>
<td>78 (49%)</td>
<td>p&lt;0.001</td>
<td>147 (39%)</td>
</tr>
<tr>
<td>Patients with genetic test</td>
<td>102 (46%)</td>
<td>58 (37%)</td>
<td>p=0.17</td>
<td>160 (42%)</td>
</tr>
<tr>
<td><strong>SCN5a mutation</strong></td>
<td>31 (30%)</td>
<td>10 (17%)</td>
<td></td>
<td>41 (26%)</td>
</tr>
</tbody>
</table>

ICD: Implantable Cardioverter Defibrillator; SCA: Sudden Cardiac Arrest; ECG: Electrocardiogram; EPS: Electrophysiological Study
Table 2. Characteristics and Outcome of the Brugada syndrome population according to ICD indication.

<table>
<thead>
<tr>
<th></th>
<th>Aborted SCA (n=31)</th>
<th>Syncope (n=181)</th>
<th>Asymptomatic (n=166)</th>
<th>p-value between the 3 groups</th>
<th>Total (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 ±13</td>
<td>47 ±13</td>
<td>47 ±12</td>
<td>p=0.30</td>
<td>46 ±13</td>
</tr>
<tr>
<td>Sex (Male, %)</td>
<td>29 (94%)</td>
<td>141 (78%)</td>
<td>140 (84%)</td>
<td>p=0.07</td>
<td>310 (82%)</td>
</tr>
<tr>
<td>Familial History of SCA</td>
<td>6 (19%)</td>
<td>43 (24%)</td>
<td>86 (52%)</td>
<td>p&lt;0.001</td>
<td>135 (36%)</td>
</tr>
<tr>
<td>Spontaneous Type 1 ECG</td>
<td>23 (74%)</td>
<td>111 (61%)</td>
<td>92 (55%)</td>
<td>p=0.12</td>
<td>226 (60%)</td>
</tr>
<tr>
<td>No. of patients with EPS</td>
<td>15</td>
<td>145</td>
<td>150</td>
<td></td>
<td>310</td>
</tr>
<tr>
<td>Inducible at EPS</td>
<td>8 (53%)</td>
<td>90 (62%)</td>
<td>130 (87%)</td>
<td>p&lt;0.001</td>
<td>228 (76%)</td>
</tr>
<tr>
<td>Remote monitoring</td>
<td>8 (26%)</td>
<td>74 (41%)</td>
<td>65 (39%)</td>
<td>p=0.28</td>
<td>147 (39%)</td>
</tr>
<tr>
<td>Mean Follow-up (months)</td>
<td>67 ±49</td>
<td>71 ±44</td>
<td>85 ±36</td>
<td>p=0.004</td>
<td>77 ±42</td>
</tr>
<tr>
<td>Patients with Appropriate shocks n, (%)</td>
<td>12 (39%)</td>
<td>22 (12%)</td>
<td>12 (7%)</td>
<td>p&lt;0.001</td>
<td>46 (12%)</td>
</tr>
<tr>
<td>Mean delay to first shock (months) (min – max)</td>
<td>18 ±20 (2 – 54 months)</td>
<td>47 ±46 (8 days – 156 months)</td>
<td>45 ±36 (27 days – 125 months)</td>
<td>p&lt;0.001</td>
<td>39 ±39 (8 days – 156 months)</td>
</tr>
<tr>
<td>Mean number of shock</td>
<td>5.4 ±5.5</td>
<td>5.4 ±5.8</td>
<td>4.5 ±4.7</td>
<td>p=0.91</td>
<td>5.2 ±5.3</td>
</tr>
<tr>
<td>Patients with Inappropriate shocks n, (%)</td>
<td>6 (19%)</td>
<td>38 (21%)</td>
<td>47 (28%)</td>
<td>p=0.23</td>
<td>91 (24%)</td>
</tr>
<tr>
<td>Mean delay to first shock (months)(min - max)</td>
<td>33 ±36</td>
<td>40 ±32</td>
<td>32 ±30</td>
<td>p=0.04</td>
<td>35 ±31</td>
</tr>
<tr>
<td>Mean number of shock</td>
<td>3.7 ±3.8</td>
<td>4.8 ±5.3</td>
<td>3 ±3</td>
<td>p=0.18</td>
<td>3.8 ±4.2</td>
</tr>
<tr>
<td>R wave amplitude at implantation &lt;5mV</td>
<td>3/30 (10%)</td>
<td>15/178 (8%)</td>
<td>18/158 (11%)</td>
<td>p=0.66</td>
<td>36/366 (10%)</td>
</tr>
<tr>
<td>Lead Failure n, (%)</td>
<td>3 (10%)</td>
<td>29 (16%)</td>
<td>28 (17%)</td>
<td>p=0.60</td>
<td>60 (16%)</td>
</tr>
<tr>
<td>ICD Explantation without reimplantation during follow-up n, (%)</td>
<td>0 (0%)</td>
<td>3 (1.6%)</td>
<td>7 (4%)</td>
<td>p=0.21</td>
<td>10 (2.6%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>p=0.76</td>
<td>15</td>
</tr>
<tr>
<td>Death n, (%)</td>
<td>0 (0%)</td>
<td>3 (1.6%)</td>
<td>4 (2.4%)</td>
<td>p=0.64</td>
<td>7 (1.8%)</td>
</tr>
</tbody>
</table>

SCA: Sudden Cardiac Arrest, ICD: Implantable Defibrillator Cardioverter,
Total on R wave amplitude is 366 instead of 378 because the data is missing for 12 patients.
Table 3. Rate of event post ICD implantation

<table>
<thead>
<tr>
<th></th>
<th>Aborted SCA</th>
<th>Syncope</th>
<th>Asymptomatic</th>
<th>Inappropriate shock rate</th>
<th>Lead failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>25%</td>
<td>3%</td>
<td>1%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Year 2</td>
<td>30%</td>
<td>6%</td>
<td>2%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>Year 3</td>
<td>36%</td>
<td>7%</td>
<td>4%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Year 4</td>
<td>41%</td>
<td>10%</td>
<td>6%</td>
<td>18%</td>
<td>7%</td>
</tr>
<tr>
<td>Year 5</td>
<td>48%</td>
<td>11%</td>
<td>6%</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>Year 10</td>
<td>48%</td>
<td>19%</td>
<td>12%</td>
<td>37%</td>
<td>29%</td>
</tr>
</tbody>
</table>

SCA: Sudden Cardiac Arrest

Figure Legends:

Figure 1. Percentage of ICD implantation in Brugada syndrome patients over the years. The number of patients implanted with an ICD per year is in dark and the number of patients diagnosed with BrS but not implanted with an ICD is in grey. Rate of ICD implantation is displayed on the top of the column. The graph starts in 1998 because before this date very few ICD were implanted for BrS (n=5).

Figure 2. Baseline ECG of the 3 asymptomatic patients (A, B and C) implanted because of 12 leads Brugada pattern and patients/physicians preference.

Figure 3. Kaplan-Meier curve of appropriate shock depending on ICD indication.

Figure 4. Self-terminated ventricular fibrillation recorded by an implantable cardioverter-defibrillator (ICD; Lumax VR-T, Biotronik) in a Brugada syndrome patient leading to lightheadness. The ICD log is composed of 3 channels. On the top line, the V channel represents
the interpretation of the patient’s rhythm by the device (sensed marker). On the middle line, the far-field (FF) channel displays the tracings recorded between the device can and the distal coil. On the bottom line, the V channel represents the electrogram recorded by the distal bipole of the ICD lead. Note that an isolated PVC is present (*) and a second one with a similar morphology on recordings induced a non sustained Ventricular Fibrillation (FV). The ICD detect the episode (Det) but during the capacitor charge the arrhythmia stop and after 3 normal QRS (Vs) the charge end and therefore no therapy is delivered.

**Figure 5.** Kaplan-Meier curve of inappropriate shock depending on the period of implantation.

Note the decreased incidence of shocks in patients from group 2.

**Figure 6.** Kaplan-Meier curve of lead failure depending on the type of ICD lead (Medtronic Sprint Fidelis or St Jude Medical Riata vs other leads).
Goup 2: ICD implanted between 2006-2011

Goup 1: ICD implanted between 1993-2005

Log rank p=0.007

<table>
<thead>
<tr>
<th>Year</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goup 2</td>
<td>158</td>
<td>131</td>
<td>103</td>
<td>82</td>
<td>62</td>
<td>19</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Group 1</td>
<td>220</td>
<td>198</td>
<td>183</td>
<td>175</td>
<td>169</td>
<td>156</td>
<td>140</td>
<td>112</td>
<td>86</td>
<td>52</td>
<td>37</td>
<td>20</td>
<td>11</td>
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</table>

Figure 2
Figure 4

<table>
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<th>5</th>
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<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>166</td>
<td>158</td>
<td>152</td>
<td>144</td>
<td>137</td>
<td>113</td>
<td>97</td>
<td>78</td>
<td>59</td>
<td>36</td>
<td>24</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Syncope</td>
<td>181</td>
<td>166</td>
<td>145</td>
<td>130</td>
<td>113</td>
<td>85</td>
<td>68</td>
<td>54</td>
<td>42</td>
<td>32</td>
<td>24</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Aborted SCA</td>
<td>31</td>
<td>21</td>
<td>16</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 6

Patients with non-advisory ICD leads

Patients with Sprint Fidelis or Riata ICD leads

Log rank

p=0.15

<table>
<thead>
<tr>
<th>Year</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-advisory ICD leads</td>
<td>296</td>
<td>273</td>
<td>245</td>
<td>221</td>
<td>203</td>
<td>165</td>
<td>140</td>
<td>113</td>
<td>87</td>
<td>62</td>
<td>46</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Sprint fidelis or Riata leads</td>
<td>82</td>
<td>79</td>
<td>76</td>
<td>72</td>
<td>66</td>
<td>45</td>
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<td>17</td>
<td>12</td>
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</tbody>
</table>
Outcome after Implantation of Cardioverter-Defibrillator in Patients with Brugada Syndrome: A Multicenter Study - Part 2

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