

## Approach to the Asymptomatic Patients with Brugada Syndrome

Azza A.Katta MD  
Arrhythmia and Device Therapy  
department  
National Heart Institute

- Brugada Syndrome (BrS) was first described in 1992 in 8 patients with recurrent episodes of aborted sudden death .

**Right Bundle Branch Block, Persistent ST Segment Elevation  
and Sudden Cardiac Death: A Distinct Clinical and  
Electrocardiographic Syndrome**

**A Multicenter Report**

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD\*†

*Aalst, Belgium and Barcelona, Spain*

- When characterising a new disease it is congruent that the most severe phenotype is described first.
- However, it is now clear that there is a marked spectrum in phenotype reflecting a variable degree of penetrance between individuals from those who are symptomatic with spontaneous type I ECG changes to asymptomatic individuals who only manifest characteristic ECG changes in response to a pharmacological challenge.

- Brugada syndrome (BrS) is among the more common familial arrhythmia syndromes, with an estimated prevalence of 1 to 5 per 10 000 persons.

- It is characterized by a right ventricular conduction delay, dynamic or persistent ST-segment elevations in the precordial leads V 1–3, and an elevated risk of syncope and SCD due to VF in young adults without structural heart disease.

- ◉ While high risk subsets of Brugada are easily managed , it is the asymptomatic ones that bother us.

- ◉ Even after great scientific progress, identifying those patients at risk remains challenging and controversial.
- ◉ Few studies have directly addressed this issue and most available registries are limited to a relative short follow-up period, which makes it impossible to evaluate the whole BS spectrum.
- ◉ As patients remain at risk lifelong, studies with a long follow-up are necessary.

- Clinical practice guidelines are focused on those patients at higher risk and do not offer specific recommendations concerning the management of individuals who have never suffered an aborted SCD.

*The following are some of the difficult questions, a cardiologist faces when dealing with patients, who exhibit only Brugada pattern in ECG.*

- **Should He(she)** go for an EP specialist ?
- **Will He** require an ICD implantation ?
- **Does He** carry a significant risk of dying suddenly ?
- **Does He** need a genetic test for sodium channel mutation ?

## Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome

### Results From the FINGER Brugada Syndrome Registry

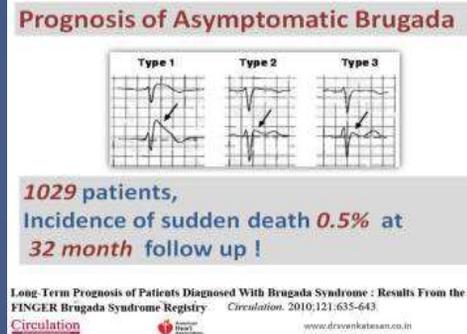
V. Probst, MD, PhD<sup>\*</sup>; C. Veltmann, MD<sup>\*</sup>; L. Eckardt, MD<sup>\*</sup>; P.G. Meregalli, MD<sup>\*</sup>; F. Gaita, MD;  
H.L. Tan, MD, PhD; D. Babuty, MD, PhD; F. Sacher, MD; C. Giustetto, MD;  
E. Schulze-Bahr, MD, PhD; M. Borggrefe, MD, PhD; M. Haissaguerre, MD; P. Mabo, MD, PhD;  
H. Le Marec, MD, PhD; C. Wolpert, MD, PhD; A.A.M. Wilde, MD, PhD

## Brugada syndrome : *FINGER* registry



- The registry included 1029 consecutive individuals
- (1) Aborted SCD (6%);
- (2) Syncope unexplained (30%);
- (3) Asymptomatic patients (64%).

In the follow-up of 31.9 (14 to 54.4) months . A total of 7 death occurred .



### **The cardiac event rates per year was**

- **7.7% in patients with Aborted SCD,**
- **1.9% in patients with syncope**
- **0.5% in Asymptomatic patients.**

### **Predictors of cardiac event**

- Previous syncope
- Spontaneous type 1 ECG

### **Non predictors ( Surprisingly there were more non predictors ! )**

- Gender has no predictive role
- Familial history of SCD,
- Inducibility of ventricular tachy-arrhythmias during EP study,
- Presence of an SCN5A mutation

## Asymptomatic Brugada Syndrome Clinical Characterization and Long-Term Prognosis

Juan Sicra, MD; Giuseppe Ciconte, MD; Giulio Conte, MD; Gian-Battista Chierchia, MD;  
Carlo de Asmundis, MD; Giannis Baltogiannis, MD; Giacomo Di Giovanni, MD;  
Yukio Saitoh, MD; Ghazala Irfan, MD; Rubén Casado-Arroyo, MD; Justo Julià, MD;  
Mark La Meir, MD; Francis Wellens, MD; Kristel Wauters, MD; Gudrun Pappaert, RN;  
Pedro Brugada, MD

**Background**—Among Brugada syndrome patients, asymptomatic individuals are considered to be at the lowest risk. Nevertheless, arrhythmic events and sudden cardiac death are not negligible. Literature focused on this specific group of patients is sparse. The purpose of this study is to investigate the clinical characteristics, management, and long-term prognosis of asymptomatic Brugada syndrome patients.

**Methods and Results**—Patients presenting with spontaneous or drug-induced Brugada type I ECG and no symptoms at our institution were considered eligible. A total of 363 consecutive patients (200 men, 55.1%; mean age, 40.9±17.2 years; 41 [11.3%] with spontaneous type I ECG) were included. Electrophysiological study was performed in 321 (88.4%) patients, and ventricular arrhythmias were induced in 32 (10%) patients. An implantable cardioverter defibrillator was implanted in 61 (16.8%) patients. After a mean follow-up time of 73.2±58.9 months, 9 arrhythmic events occurred, accounting for an annual incidence rate of 0.5%. Event-free survival was 99.0% at 1 year, 96.2% at 5 years, and 95.4% at 10 and 15 years. Univariate analysis identified as risk factors: electrophysiological study inducibility (hazard ratio, 11.4;  $P<0.01$ ), spontaneous type I (hazard ratio, 4.0;  $P=0.04$ ), and previous sinus node dysfunction (hazard ratio, 8.0; 95% confidence interval, 1.0–63.9;  $P=0.05$ ). At the multivariate analysis, only inducibility remained significant (hazard ratio, 9.1;  $P<0.01$ ).

**Conclusions**—Arrhythmic events in asymptomatic Brugada syndrome patients are not insignificant. Ventricular arrhythmia inducibility, spontaneous type I ECG, and presence of sinus node dysfunction might be considered as risk factors and used to drive long-term management. (*Circ Arrhythm Electrophysiol*. 2015;8:1144-1150. DOI: 10.1161/CIRCEP.114.003044.)

## Asymptomatic Brugada Syndrome Clinical Characterization and Long-Term Prognosis

Juan Sicra, MD; Giuseppe Ciconte, MD; Giulio Conte, MD; Gian-Battista Chierchia, MD;  
Carlo de Asmundis, MD; Giannis Baltogiannis, MD; Giacomo Di Giovanni, MD;  
Yukio Saitoh, MD; Ghazala Irfan, MD; Rubén Casado-Arroyo, MD; Justo Julià, MD;  
Mark La Meir, MD; Francis Wellens, MD; Kristel Wauters, MD; Gudrun Pappaert, RN;  
Pedro Brugada, MD

**Background**—Among Brugada syndrome patients, asymptomatic individuals are considered to be at the lowest risk. Nevertheless, arrhythmic events and sudden cardiac death are not negligible. Literature focused on this specific group of patients is sparse. The purpose of this study is to investigate the clinical characteristics, management, and long-term prognosis of asymptomatic Brugada syndrome patients.

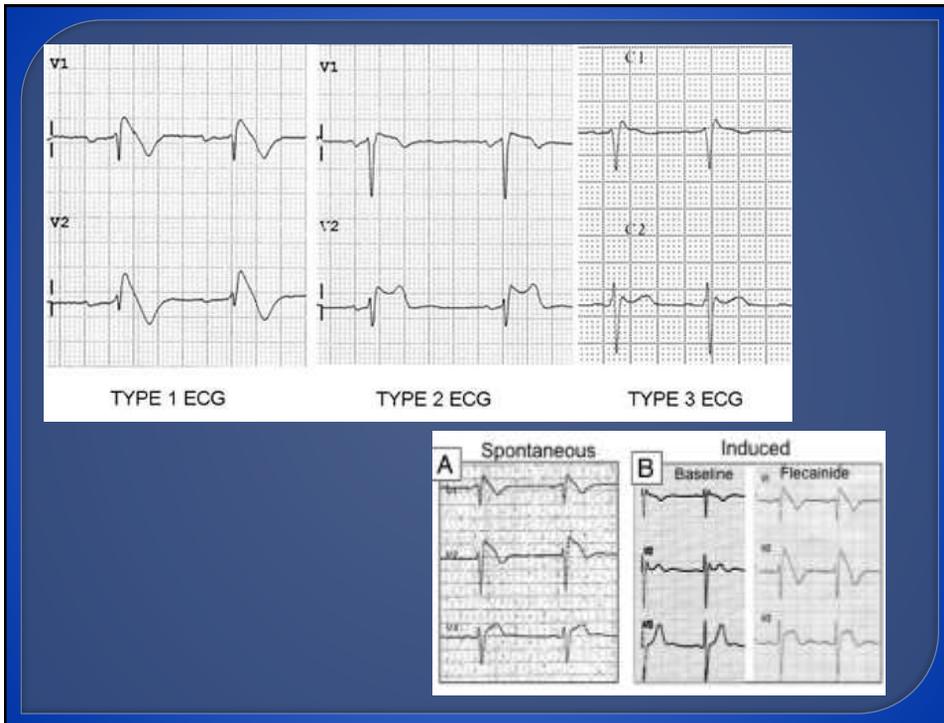
**Methods and Results**—Patients presenting with spontaneous or drug-induced Brugada type I ECG and no symptoms at our institution were considered eligible. A total of 363 consecutive patients (200 men, 55.1%; mean age, 40.9±17.2 years; 41 [11.3%] with spontaneous type I ECG) were included. Electrophysiological study was performed in 321 (88.4%) patients, and ventricular arrhythmias were induced in 32 (10%) patients. An implantable cardioverter defibrillator was implanted in 61 (16.8%) patients. After a mean follow-up time of 73.2±58.9 months, 9 arrhythmic events occurred, accounting for an annual incidence rate of 0.5%. Event-free survival was 99.0% at 1 year, 96.2% at 5 years, and 95.4% at 10 and 15 years. Univariate analysis identified as risk factors: electrophysiological study inducibility (hazard ratio, 11.4;  $P<0.01$ ), spontaneous type I (hazard ratio, 4.0;  $P=0.04$ ), and previous sinus node dysfunction (hazard ratio, 8.0; 95% confidence interval, 1.0–63.9;  $P=0.05$ ). At the multivariate analysis, only inducibility remained significant (hazard ratio, 9.1;  $P<0.01$ ).

**Conclusions**—Arrhythmic events in asymptomatic Brugada syndrome patients are not insignificant. Ventricular arrhythmia inducibility, spontaneous type I ECG, and presence of sinus node dysfunction might be considered as risk factors and used to drive long-term management. (*Circ Arrhythm Electrophysiol*. 2015;8:1144-1150. DOI: 10.1161/CIRCEP.114.003044.)

- Arrhythmic events in asymptomatic BS patients are not negligible, with an annual incidence rate of 0.5%.
- Risk stratification is specially challenging in this specific group.
- VA inducibility at EPS, spontaneous type I ECG, and presence of SND might be considered as risk factors and used to drive long-term management.

### **Correct recognition of the diagnostic BrS ECG pattern**

- 1) One true diagnostic brugada pattern, two others may suggest the disease.
- 2) Drug challenge to help with diagnosis.



Drug	Dosage	Route of administration
Ajmaline	1 mg/kg over 5 minutes	IV
Flecainide	2 mg/kg over 10 minutes	IV
	400 mg	PO
Procainamide	10 mg/kg over 10 minutes	IV
Pilsicainide	1 mg/kg over 10 minutes	IV

- Dynamic character of the Br ECG
- Drug challenge for diagnosis of BS is indicated in cases in which the disease is suspected, but the basal ECG is normal (e.g.: familial screening) or suspicious, but not diagnostic (types 2 or 3).
- It is recommended to place the right precordial leads up to the 2nd intercostals space , because it may increase the sensitivity of the ECG (basal and during drug challenge with class I AAD) for detecting the diagnostic BS pattern

### **Exclude other causes for a Br ECG pattern**

- Many conditions may develop ST-segment elevation, mimicking the BS ECG pattern.
- some drugs may also produce a Brugada-like ST-segment elevation.

## Causes of right precordial ST segment Elevation

- Acute myocarditis
- Acute pericarditis
- Hemopericardium
- Right ventricular ischemia/infarction
- Dissecting aortic aneurysm
- Acute pulmonary thromboemboli
- Central and autonomic nervous system abnormalities
- Duchenne muscular dystrophy
- Friedreich's ataxia
- Thiamine deficiency
- Hypercalcemia
- Hyperkalemia
- Mediastinal tumor compressing right ventricular outflow tract
- Arrhythmogenic right ventricular cardiomyopathy
- Long QT syndrome type 3
- Right bundle branch block
- Left bundle branch block
- Left ventricular hypertrophy
- Early repolarization syndrome
- Hypothermia

## Drug-induced Brugada-Like ECG patterns

- I Antiarrhythmic drugs:
  1. Sodium channel blockers:  
Class IC drugs (Flecainide, propafenone, pilsicainide).
  - Class IA drugs (Ajmaline, procainamide, dysopyramide, cibenzoline)
  2. Calcium channel blockers:  
Verapamil
- II Beta-blockers:  
Propranolol, etc.
- III-Antianginal drugs:
  1. Calcium channel blockers:  
Nifedipine, diltiazem
  2. Nitrate:  
Isosorbide dinitrate, nitroglycerine
  3. Potassium channel openers:  
Nicorandil
- III-Psychotropic drugs:
  1. Tricyclic antidepressants:  
Amitriptyline  
Nortriptyline  
Desipramine  
Clomipramine
  - 2- Tetracyclic antidepressants:  
Maprotiline
  - 3-Phenothiazine:  
Perphenazine  
Cyamemazine
  - 4- Selective serotonin reuptake inhibitors:  
Fluoxetine
- IV- Other drugs:  
Dimenhydrinate  
Cocaine intoxication  
Alcohol intoxication

## Risk Stratification

- More than 20 years after the first description of BS, risk stratification remains challenging and controversial.
- Current practical guidelines and consensus address symptomatic BrS patients.
- No specific statement is made for asymptomatic patients. These guidelines do not refer to newly described risk factors and lack recommendations for the low risk, but otherwise frequent, groups.

- Age
- Sex
- Family History
- Genetics
- ECG pattern
- Atrial fibrillation
- Sinus node dysfunction
- Programmed electrical stimulation

## Age

---

- Patients with BS are typically diagnosed during their fourth decade.
- Paediatric and elderly patients

- Asymptomatic children appear to have good outcomes, especially if they do not show the type 1 pattern spontaneously; however, they are not risk free
- Importantly, it is recommended to repeat the test after puberty because up to 25 % of patients with an initially negative drug test become positive.

- BS diagnosed in elderly patients appears to have a benign prognosis.
- Decision for implanting or replacing an ICD in elderly patients must be done individually.
- Establishing the diagnosis is important, as it has family implications.

## Sex

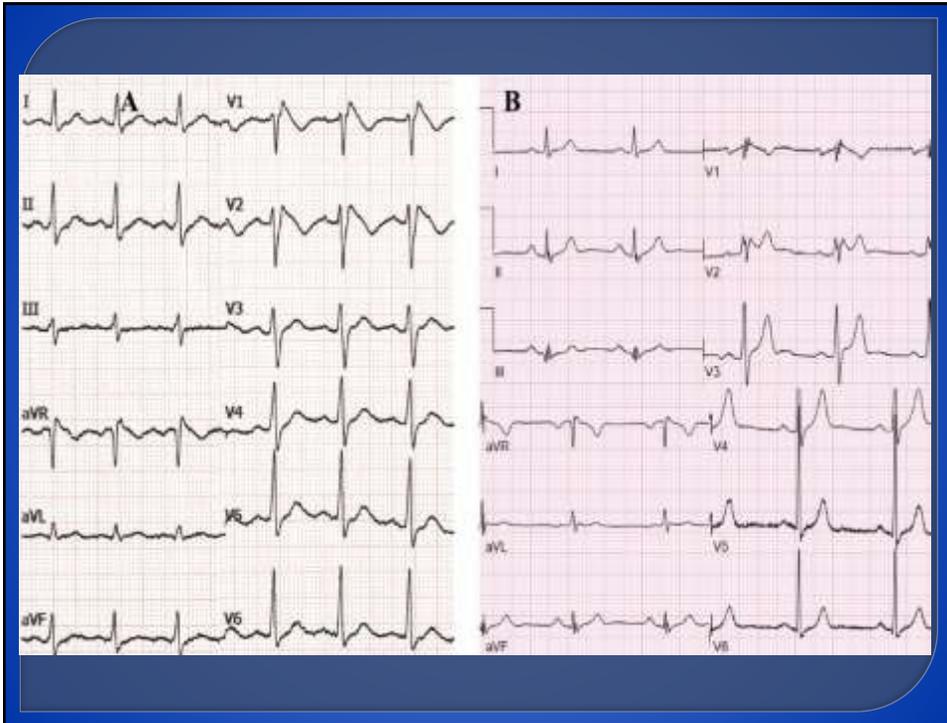
- Males show a tendency to develop more arrhythmic events than women and have a worse prognosis during follow-up

## Genetics

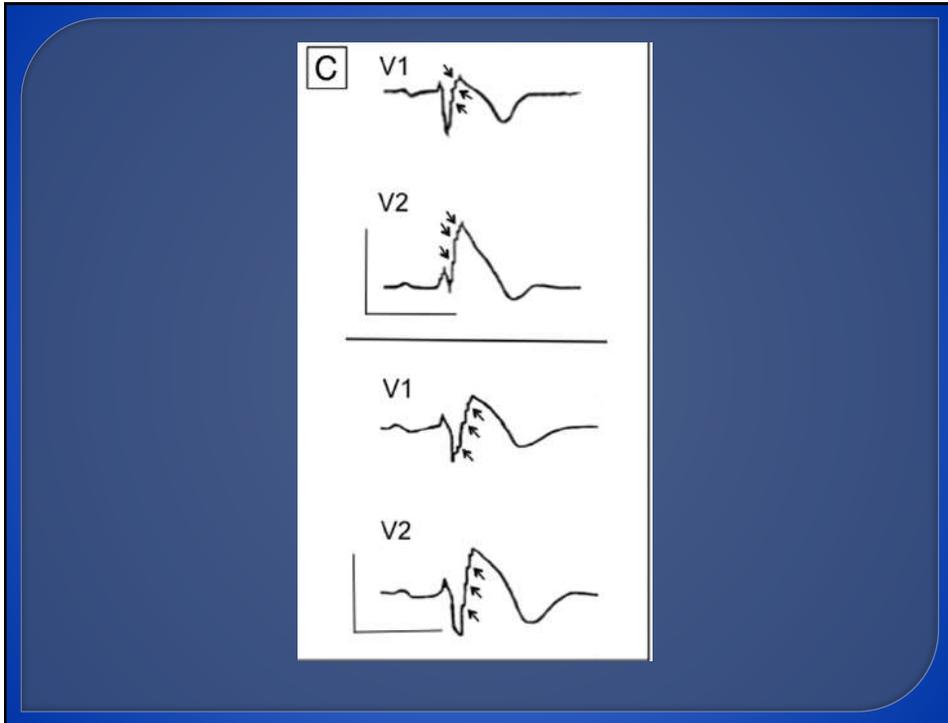
- Mutations can be identified in approximately 20–30 % of patients with BrS.
- The presence of an identifiable mutation has not been clearly linked to a worse prognosis; particularly amongst asymptomatic patients.
- Interestingly, none of the negative genotype patients suffered an event.

## ECG pattern

- The hallmark of the BS diagnosis is the characteristic ST-segment elevation
- Patients displaying the spontaneous pattern have a worse prognosis, with a hazard ratio (HR) of 4.0 for events.
- Although patients diagnosed after a drug challenge have a better outcome, they are still at risk.



- QRS fragmentation has been associated with a worse prognosis and a more expressive clinical presentation of the BS .
- Repolarisation anomalies may have value to stratify patients; present in around 10 % of BS patients and might co-exist with fragmented QRS. They are associated with a more severe clinical presentation and also have an independent prognosis value.



- It has recently been reported that in around 16 % of patients with idiopathic VF displaying early repolarisation in the inferior leads, a type 1 Brugada pattern could be recorded in high intercostal leads.

## Sinus Node Dysfunction

- SND can be associated with mutations in the sodium channels.
- So, it can be present in BS patients.
- The underlying mechanism is not clear.
- SND is usually related to a more severe and early disease, and patients are frequently symptomatic.
- It had been recently described that in asymptomatic BS patients, concomitant SND has a worse prognosis that might justify a more aggressive therapeutic attitude.

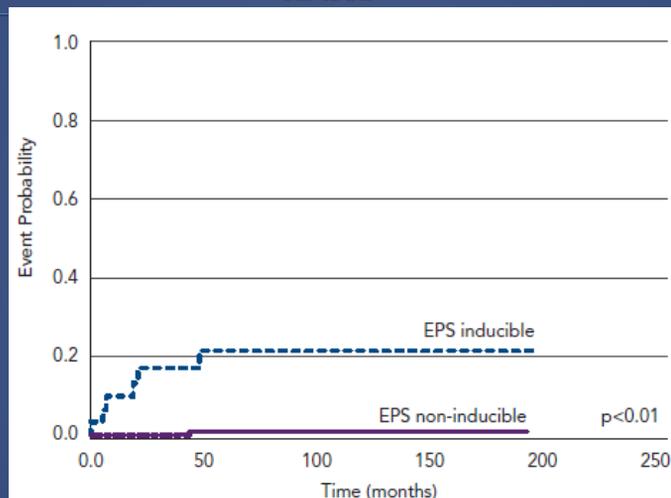
## Atrial Fibrillation

- AF is more common in patients with BS than in the general population.
- Its presence is related to a higher risk patient, with a more expressive clinical presentation and worse long-term outcome.
- Value in asymptomatic patients is not clear. It can just be a marker of a more severe disease and not independently associated with prognosis.

## Electrophysiological testing

- The value of inducibility of sustained ventricular arrhythmias during EP study as a risk predictor tool in BS is still the most controversial .
- The results of the largest BS registry indicates that inducibility during EP study is an independent predictor for cardiac events,
- while the second and third largest registries did not find similar results.

### Risk Factors Associated with Arrhythmic Events in BrS



Sieira J, Conte G, Ciconte G, et al. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20years experience. *Circ Arrhythm Electrophysiol* 2015;8(4):777-84.

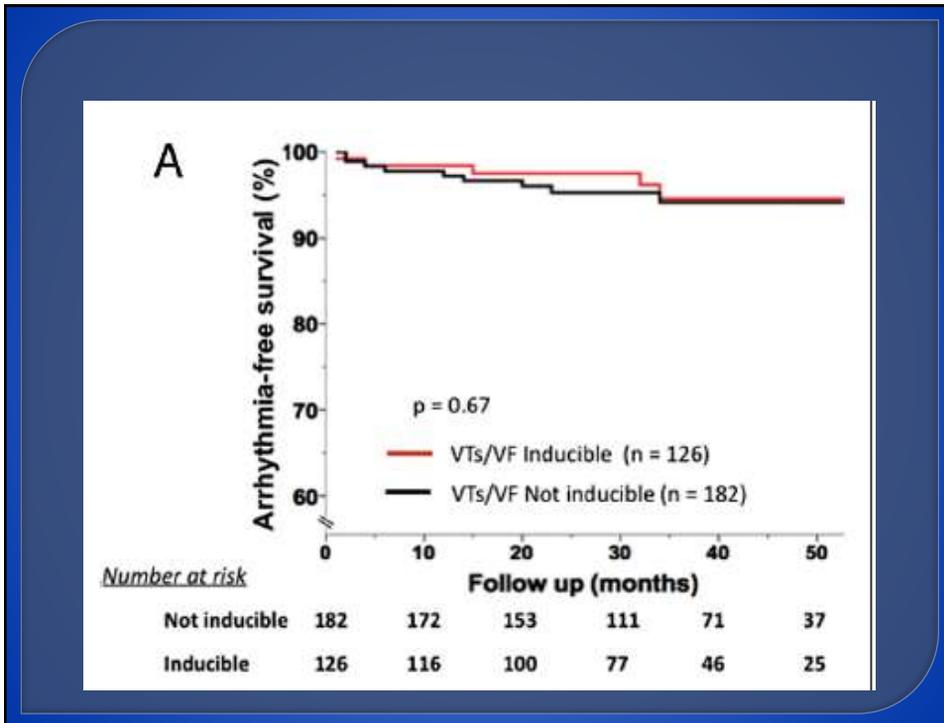
## Risk Stratification in Brugada Syndrome

Results of the PRELUDE (PRogrammed  
ELectrical stimUlation preDictive valuE) Registry

Silvia G. Priori, MD, PhD,\*†‡ Maurizio Gasparini, MD,§ Carlo Napolitano, MD, PhD,\*‡  
Paolo Della Bella, MD,|| Andrea Ghidini Ottonelli, MD,¶ Biagio Sassone, MD,‡  
Umberto Giordano, MD,\*\* Carlo Pappone, MD,†† Giosuè Mascioli, MD,‡‡ Guido Rossetti, MD,§§  
Roberto De Nardis MD,||| Mario Colombo, MS¶¶

*Parvia, Rozzano, Milano, Lido di Camaiore, Bentivoglio, Palermo, Ravenna, Bergamo, Cuneo,  
and Vicenza, Italy; and New York, New York*

<b>Objectives</b>	The PRELUDE (PRogrammed ELectrical stimulation preDictive valuE) prospective registry was designed to assess the predictive accuracy of sustained ventricular tachycardia/ventricular fibrillation (VTs/VF) inducibility and to identify additional predictors of arrhythmic events in Brugada syndrome patients without history of VT/VF.
<b>Background</b>	Brugada syndrome is a genetic disease associated with increased risk of sudden cardiac death. Even though its value has been questioned, inducibility of VTs/VF is widely used to select candidates to receive a prophylactic implantable defibrillator, and its accuracy has never been addressed in prospective studies with homogeneous enrolling criteria.
<b>Methods</b>	Patients with a spontaneous or drug-induced type I electrocardiogram (ECG) and without history of cardiac arrest were enrolled. The registry included 308 consecutive individuals (247 men, 80%; median age 44 years, range 18 to 72 years). Programmed electrical stimulation was performed at enrollment, and patients were followed up every 6 months.
<b>Results</b>	During a median follow-up of 34 months, 14 arrhythmic events (4.5%) occurred (13 appropriate shocks of the implantable defibrillator, and 1 cardiac arrest). Programmed electrical stimulation performed with a uniform and pre-specified protocol induced ventricular tachyarrhythmias in 40% of patients; arrhythmia inducibility was not a predictor of events at follow-up (9 of 14 events occurred in noninducible patients). History of syncope and spontaneous type I ECG (hazard ratio [HR]: 4.20), ventricular refractory period <200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) were significant predictors of arrhythmias.
<b>Conclusions</b>	Our data show that VT/VF inducibility is unable to identify high-risk patients, whereas the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic implantable cardioverter defibrillator. (J Am Coll Cardiol 2012;59:37-45) © 2012 by the American College of Cardiology Foundation

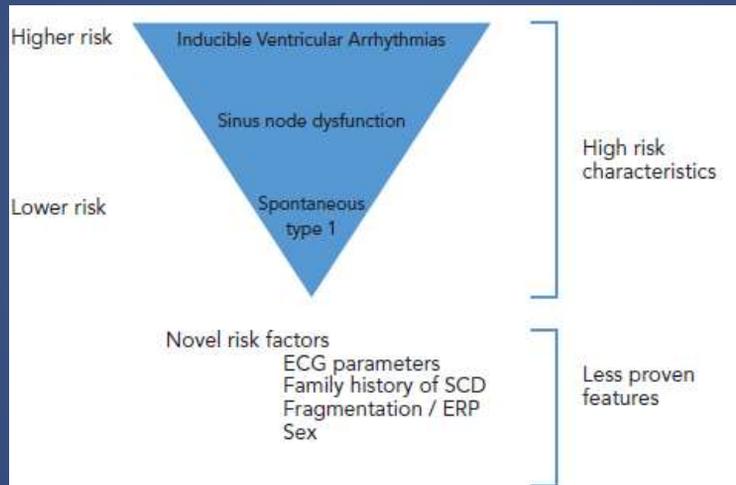


There are several proposed reasons that may account for this differences among the registries:

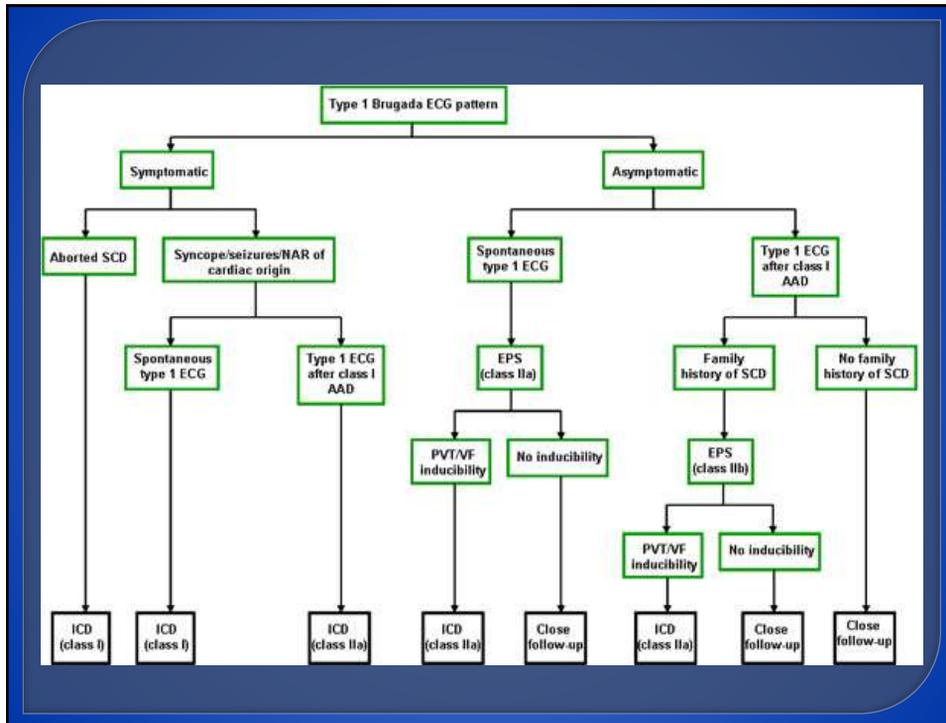
- different inclusion criteria,
- different stimulation protocols,
- different statistical analysis methods, etc.

Prospective studies to elucidate the role of EP study in the risk stratification of these patients are currently being performed.

## Risk of Arrhythmic Events



## Management



- Subcutaneous ICDs (S-ICDs) are a promising option in the BS population.
- Limitations
  - the dynamic ECG pattern in BS patients might lead to inappropriate shocks.
  - BrS patients might need atrial or ventricular pacing (those having concomitant SND,).
  - Monomorphic VT might happen in BrS and effectively respond to ATP.

Consequently, S-ICD implantation in BrS should be considered after taking into account these facts

## Pharmacological therapy

- Quinidine is widely accepted as a treatment for electrical storm or frequent ICD shocks in patients with BS, or as an alternative for patients contraindicated for ICD implantation.
- An EP-based drug therapy involves an aggressive electrophysiological stimulation protocol, with repetition of the test under the drug and regularly follow-up.

## Ablation

- Epicardial RF substrate ablation has emerged as a promising tool for the management of BS.
- First described by Nademanee in 2011, RF of the anterior aspect of the RVOT rendered arrhythmias during electrophysiological testing noninducible, normalised ECG patterns, and had an excellent prognosis at 20 months.
- Further experience and evidence is needed as a prophylactic measure in high-risk asymptomatic patients.

## Recommendations

- Avoid all drugs that may induce a type 1 class ECG
- Avoid fever.
- Patients must contact their cardiologist immediately in case of presenting syncope, seizures or nocturnal agonal respiration.
- Family screening of BS is in first-degree relatives.
- All patients must have regular follow-up, in order to identify the development of symptoms.
- Genetic testing, when available, is recommended