



The Cardiac Society of Australia and New Zealand

Position Statement on the Diagnosis and Management of Brugada Syndrome

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Genetics Council Writing Group

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KEY POINTS

Brugada Syndrome (BrS) is an autosomal dominant channelopathy with variable penetrance affecting the sodium channel. It reduces the transport of sodium ions essential for proper generation of the cardiac action potential. The resulting inhomogeneous repolarization in areas of the RV epicardium causes malignant ventricular arrhythmias.

BrS is diagnosed by typical cove shaped ST elevation of > 2mm in ≥ 1 RV precordial lead V1, V2 occurring spontaneously or after provocative drug test with IV administration of Class 1 antiarrhythmic drug such as flecainide or ajmaline.

The incidence of BrS is variable being higher in South East Asians and is generally quoted as 1;2000. It is responsible for 20% of sudden arrhythmic deaths in those without structural heart disease. Typical presentation is syncope or resuscitated sudden death and symptoms usually occur at night or at rest. Fever is a common trigger, particularly in children.

Genetic testing for BrS is a Class 2A indication and the yield has increased recently to nearly 40%. Genetic testing assists with family screening.

Management of Brugada syndrome

Resuscitated cardiac arrest and cardiac syncope are Class 1 indication for implantation of an ICD. All family members of BrS patients should be screened and those with normal or nondiagnostic ECGs should be offered flecainide test. ICD implantation in BrS has a significant complication rate and should be avoided in asymptomatic patients. Family history of sudden death is not an indication for ICD implantation. Asymptomatic patients should be advised life style measures such as avoidance of 'Brugada drugs', prompt treatment of fever and avoiding excess of alcohol and big carbohydrate meals at night.

Risk assessment of asymptomatic Brugada syndrome patients

Event rate in those with spontaneous type 1 ECG has been reported as 0.24 to 1.7% per year. Drug induced BrS pattern ECG patients are at minimal risk. Several major trials have reported that programmed electrical stimulation is not helpful in risk stratification.

Fragmentation of QRS on the ECG, RV ERP of ≤ 200 msec, history of syncope and spontaneous type 1 Brugada pattern on the ECG, put the patient in higher risk category.

Treatment of arrhythmic storms: Isoprenaline infusion is effective in acute situation and quinidine is the only effective drug in long term treatment.

1 Clinical Characteristics

1.1 Definition and prevalence

Brugada Syndrome (BrS) was described as a clinical entity in 1992. (1) The diagnosis is made by electrocardiogram (ECG) and is defined by the presence of an atypical right bundle branch block (RBBB) pattern with a characteristic cove-shaped ST elevation in leads V₁ to V₃, in the absence of obvious structural heart disease, electrolyte disturbances or ischaemia. Inheritance can be autosomal dominant with incomplete penetrance, or be polygenic.(2, 3) It can also appear as a consequence of structural changes in the right ventricular outflow tract from a variety of causes. BrS is reported to be responsible for 4% of all sudden deaths and 20% of sudden deaths in those without structural heart disease and is a leading cause of death in subjects under the age of 40 years. A family history is present in about 20 to 30% of patients. It is difficult to estimate the exact incidence of BrS in the general population but the prevalence is quoted as 1 in 2000. (4-6) The condition is particularly common in South East Asia and amongst migrants of South Asian origin and in the Japanese population the prevalence is reported to be 0.5-1 per 1000. BrS has also been reported as Sudden Unexplained Death Syndrome (SUDS) or Sudden Unexplained Nocturnal Death Syndrome (SUNDS).(7) The ECG changes of BrS are dynamic and can vary spontaneously.

BrS appears to be a channelopathy, which, besides electrophysiological changes, there have also been reports of subtle structural changes in the atria and the right ventricular outflow tract (RVOT). (4)

1.2 Clinical presentation

The most typical presentation is syncope or resuscitated sudden death in the third or fourth decade of life due to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). Symptoms typically occur at night, or at rest during the day but also uncommonly during exercise.(2) Monomorphic VT is rare and is more prevalent in children and infants, among whom fever is the commonest trigger.(8, 9) The diagnosis of BrS may also be made on family screening of patients with BrS or incidentally following a routine ECG. More than 80% of adult patients are males but in children there is an equal male:female ratio. Many subjects remain asymptomatic throughout life.

1.3 Clinical diagnosis

Consensus statements regarding making the diagnosis of Brugada Syndrome

The first consensus report of 2002 proposed using ECG criteria alone. These are shown in Figure 1. Three subtypes of ECG features have been recognised. (3)

- i. *Type 1*: Cove-shaped ST elevation in right precordial leads with J wave or ST elevation of $\geq 2\text{mm}$ (mm) at its peak followed by a negative T wave with little or no isoelectric interval in more than one right precordial leads V_1 - V_3 .
- ii. *Type 2*: The ST segments also have a high take-off but the J amplitude of $\geq 2\text{mm}$ gives rise to a gradually descending ST elevation remaining $\geq 1\text{mm}$ above the baseline followed by a positive or biphasic T wave that results in a saddle back configuration.
- iii. *Type 3*: Right precordial ST elevation of $<1\text{mm}$ of saddle-back type or coved type.

In 2005, at least one of six additional clinical feature was required to make a diagnosis, including documented ventricular fibrillation (VF), polymorphic VT, a family history of sudden cardiac death at <45 years, coved-type ECG in family members, inducibility of VT with programmed stimulation, syncope or nocturnal agonal respiration (attributed to self-terminating polymorphic VT or VF). These additional criteria increased specificity but lowered sensitivity. (2)The latest consensus statement of 2013 does not mention these additional clinical features and only mentions the ECG features. (10)

We suggest that the 2013 criteria be used for the diagnosis. However, presence of one of the clinical features adds confirmation to the diagnosis.

Diagnosis of Brugada Syndrome

Expert Consensus statement ‘Diagnosis and management of patients with inherited primary arrhythmic syndromes 2013’ (11)

1. BrS is diagnosed in patients with ST-segment elevation with type I morphology $\geq 2\text{ mm}$ in ≥ 1 lead among the right precordial leads V_1, V_2 positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.
2. BrS is diagnosed in patients with Type 2 or Type 3 ST-segment elevation in ≥ 1 lead among the right precordial leads V_1, V_2 positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a Type 1 ECG morphology.

Notes on obtaining the ECG

Even in genetically-proven cases of BrS, the morphology of ST segment elevation varies considerably day by day. The chances of finding typical Type 1 cove-shaped elevation increase with repeated ECG recordings and also with placement of precordial leads V_1, V_2 and V_3 up the chest into the 2nd and 3rd intercostal space. This should thus be routinely performed when the diagnosis is suspected but is uncertain on a standard ECG, and in screening of family members of BrS patients.

12-lead Holter recordings with placement of precordial leads V_1 , V_2 and V_3 in the 2nd and 3rd intercostal space are also helpful; a typical Brugada pattern may become apparent during nocturnal bradycardia. ECG changes of BrS can also be brought out following a meal and on standing. Rarely ST changes of BrS may be seen in inferior or lateral leads.

Misdiagnosis of Brugada Syndrome

Spurious BrS type ECG changes can be seen in patients following cardioversion and last for a few hours and may lead to an incorrect diagnosis of BrS. Misdiagnosis of BrS can occur with ECG changes of early repolarization, athlete's heart, right bundle branch block, acute pericarditis, myocardial infarction, Prinzmetal angina, arrhythmogenic right ventricular cardiomyopathy (ARVC), myocarditis, Duchenne muscular dystrophy, electrolyte disturbances and hypothermia. (2)

Other ECG findings in Brugada Syndrome

ECG in BrS patients may also show other changes. The PR interval is often increased (≥ 200 ms) and reflects the presence of an increased HV interval. Also described are: P wave abnormalities (prolonged or biphasic P waves), late potentials detected by signal-averaged ECG and QRS widening and fragmented QRS. (12, 13) Augmentation of ST segment elevation by ≥ 0.5 mV in V_1 to V_3 one to four minutes post exercise has been reported by Makimoto et al in 37% of BrS patients and was a significant independent predictor of cardiac events. (14)

Atrial fibrillation occurs in about 10 to 20% of BrS patients and is associated with increased risk of syncope and sudden cardiac death. (15, 16) Sick sinus syndrome and atrial standstill have also been described. Conduction delays in the RVOT have also been reported.

1.4 Mechanism of BrS (4)

During phase 1 of the normal action potential, the inward Na^+ current and transient outward K^+ current, I_{To} , cause a normal spike and dome morphology. In the presence of weak Na^+ current, the unopposed outward K^+ current I_{To} and I_{Ca} , cause accentuation of the action potential notch in the RV epicardium, resulting in accentuated J wave and ST segment elevation associated with the Brugada pattern. As these changes occur in the epicardium but not in the endocardium, they create a transmural voltage gradient. (Figure 2) Arrhythmias develop because of inhomogeneous repolarization in different areas of the RV epicardium leading to the so-called phase 2 re-entry and to the development of closely coupled extrasystoles leading to VT/VF. Triggering extrasystoles have left bundle branch morphology, have a close coupling interval and arise from the RVOT. Successful ablation of initiating ectopics has been performed in BrS patients who have arrhythmic storms. Both androgens and oestrogens modulate inward Na^+ and Ca^+ and outward I_{To} currents. The male preponderance in adult patients with onset after puberty is probably explained by the fact that the transient outward current I_{To} in the RV epicardium is stronger in men than women.

1.5 Drug Challenge

Intravenous administration of Na⁺ channel blocking drugs like ajmaline, flecainide, pilscanide and, to a variable extent, procainamide, are useful in bringing out Type 1 Brugada pattern on the ECG when ECG changes are not diagnostic.(17) Ajmaline is an ideal drug for this purpose because of its short duration of action (1mg/kg over ten minutes, maximum of 80mg) and higher sensitivity than flecainide, but as it is not available in Australia; flecainide (2mg/kg maximum 150mg in 10 minutes) is the drug commonly used. The sensitivity and specificity of flecainide test in *SCN5A* mutation-positive probands and their families has been reported as 77% and 80%, respectively. (18)

Indication

Pharmacological provocation should only be performed when the baseline ECG is not diagnostic of BrS, but BrS needs to be excluded after cardiac arrest or in asymptomatic family members of BrS and where the baseline ECG shows Type 2 or 3 changes.

Contraindications

1. Type 1 BrS pattern in the baseline ECG (there is no advantage and possibly a risk of inducing VT/VF);
2. PR prolongation in the baseline ECG (risk of inducing AV block).

Precautions

Drug challenge should be performed under strict monitoring of blood pressure (BP) and 12-lead ECG and facilities for cardioversion and resuscitation should be available. Diagnostic yield is improved by moving leads V₁ to V₃ up to the 2nd intercostal space. Drug administration should be stopped if a Type 1 pattern becomes apparent on the ECG, if the patient develops ventricular arrhythmias, if the QRS widens to ≥ 130% of the baseline, or if a total of 150mg flecainide or 1mg/kg up to 80mg of ajmaline is administered over ten minutes. The patient needs to be monitored for three hours or until the ECG is normalized as late positive tests have been reported. (19) Plasma half-life of flecainide is 20 hours, and of ajmaline is five minutes. Isoprenaline infusion may be employed to counteract if serious ventricular arrhythmias develop. The incidence of serious arrhythmia is low if the drug is not administered to patients who already have Type 1 ECG at baseline.

2 Molecular Genetics

BrS is a genetically heterogeneous channelopathy as disease-causing variants have been identified in at least 16 genes to date. (20) Most genes have in common a link to the cardiac sodium ion channel Na_v1.5. However, these only account for approximately 35% of all cases.

Hence, at least two-thirds of individuals with a clinical diagnosis of BrS or an isolated Type 1 Brugada ECG pattern do not have a known mutation. (21) The majority of mutations in BrS are novel, found in single individuals or single families. Genotype-phenotype correlations are mostly still unavailable. (22) Mutations often demonstrate incomplete disease penetrance and significantly variable clinical expression.

SCN5A

BrS occurs due to loss-of-function mutations in one copy of the *SCN5A* gene in 20-25% of all cases. (23) Higher diagnostic yield is reported in children and in individuals with spontaneous Type 1 ECG or associated conduction delay. (24) The *SCN5A* gene encodes the pore-forming α -subunit of the cardiac Na^+ channel, $\text{Na}_v1.5$, which is the principal sodium channel protein in the heart and is concentrated at the intercalated discs. (23) $\text{Na}_v1.5$ channels play a key role in generation of the cardiac action potential and propagation of the electrical impulse in the heart. Mutated sodium channels may lead to loss of function through a number of mechanisms such as reduced rate of recovery from inactivation, faster inactivation and protein trafficking defects. Loss of function causes a decrease in Na current (I_{Na}), which in turn impairs the fast upstroke of phase 0 of the action potential, causing slowing of cardiac conduction. (25)

Over 300 different *SCN5A* mutations have now been identified, although the causal role of these mutations in BrS is not always clear. (17, 26) ECG findings predictive of *SCN5A* mutations include the presence of longer and progressive conduction delays (PQ, QRS and HV intervals). (27) The degree of ST elevation and the occurrence of arrhythmias appear to be similar between individuals with and without an *SCN5A* mutation. (20) Accordingly, the presence or absence of an *SCN5A* mutation does not have any effect on the incidence of sudden cardiac death in BrS.

BrS is not the only condition attributed to *SCN5A* mutations; Long QT 3 (gain-of-function mutations), progressive cardiac conduction disease (Lenegre's disease), idiopathic VF, sick sinus syndrome, dilated cardiomyopathy and familial atrial fibrillation are other disorders linked to *SCN5A* mutations and overlapping syndromes have been described. (28)

Other genes

In 2007, Anzelevitch et al identified loss of function mutations involving the L-type calcium channel subunits, encoded by the *CACNA1C*, *CACNB2B* and *CACNA2D1* genes respectively, in probands with BrS. These genes only account for a small percentage of BrS. (29) The mutations reduce basal L-type calcium current and carriers tend to present with short QT intervals. Mutation yield in these three genes may be as high as 50% in patients with Type 1 Brugada ECG pattern and concomitant short QT intervals. (24)

Since 2007, many more BrS susceptibility genes have been identified. These mutations result in either 1) reduction of cardiac Na channel – *GPD1L*, *SCN1B*, *SCN3B* and *MOG1* genes; 2) increase in the transient outward K (I_{to}) current – *KCNE3*, *KCNE5* and *KCND3*; 3) increase in I_{KATP} current – *KCNJ8*; or 4) reduction in pacemaker current – *HCN4*. (24) The causal role for these genes in BrS remain unclear, and each accounts for <1-2% of cases. (23) In 2013, Liu *et al* identified mutations/rare variants in the *TRPM4* gene in 20/331 (6%) unrelated probands with BrS. (30) Most probands (18/20) had cardiac conduction block (incomplete or complete RBBB, bifascicular block). The pathophysiology of *TRPM4* variants is unclear, but it may reduce the availability of $Na_v1.5$ channels. (30)

SCN10A

In 2014, Hu *et al* significantly advanced the genetic landscape of BrS by identifying mutations in the *SCN10A* gene in 25/150 (16.7%) adult probands with BrS. (21) Functional expression studies of two of the identified *SCN10A* missense variants showed a significant reduction in sodium channel current, likely due to a reduced expression of *SCN5A* in the heart. The diagnostic yield of *SCN10A* testing therefore approaches the historical diagnostic yield of *SCN5A* testing in BrS. Further cohorts should be tested to assess the true genetic contribution of *SCN10A* coding variants to BrS.

Polygenic inheritance

BrS is commonly accepted as an autosomal dominant channelopathy, however recent observations suggest that it follows a more complex polygenic inheritance model. BrS can result from the presence of several rare and common variants which confer susceptibility to the phenotype in a given individual. A single presumed pathogenic mutation may be insufficient to cause BrS on its own. Bezzina *et al* conducted genome-wide association studies (GWAS) in 312 patients with BrS to explore the role of common variants in disease susceptibility. (22, 31) They found that a small but significant percentage of the variance in disease susceptibility could be explained by the cumulative effect of common polymorphisms acting as independent “risk alleles”. Three SNPs (single nucleotide polymorphisms) showed association signals which reached genome wide-significance on GWAS. One SNP was located in intron 14 of *SCN10A*, the second SNP was located within *SCN5A*, and the third SNP was located downstream of the *HEY2* gene. These findings were replicated in two further case-control GWAS studies. The risk of manifesting the phenotype increased consistently with increasing numbers of carried “risk alleles” in the one individual, consistent with a multifactorial disease model. (31)

In some *SCN5A* families with BrS, the presence of the presumed pathogenic mutation is not even mandatory. Probst *et al* studied 115 *SCN5A* mutation carriers from 13 large families, all with a different mutation. (32) Eight individuals from 5 families were found to be

mutation-negative but phenotype-positive, with 3 individuals having AICD implantation due to inducible VF/VT on EPS.

Who should be offered genetic testing?

Cases where there is diagnostic certainty can be offered genetic testing primarily to assist with family cascade screening. However, genetic testing is not recommended for those with an isolated Type 2 or Type 3 Brugada ECG pattern. (27)

Crotti *et al* found that patients with an isolated Type 1 ECG the diagnostic yield of mutation analysis in 12 BrS genes was equivalent to those who fulfilled 2006 task force criteria for a clinical diagnosis of BrS.(26)

Genetic analysis in BrS makes little contribution to diagnosis, prognosis and therapeutic management, in sharp contrast to Long QT syndrome. It does not yet appear to have a useful role in risk stratification. (26, 27) Based on the HRS/EHRA expert consensus statement on genetic testing for channelopathies and cardiomyopathies, mutation analysis for a proband with BrS is given a Class IIa recommendation (“**can be useful**”). In comparison, mutation analysis for index cases with LQTS or HCM is given a Class I recommendation (“**is recommended**”). (27) Mutation-specific genetic testing is recommended for family members following identification of the pathogenic mutation in the proband with BrS, as it is useful for targeting surveillance.

Pre genetic testing counselling

With the advent of next-generation sequencing, patients have access to BrS gene testing in the form of cost-effective multi-gene panels. The benefits and limitations of testing should be discussed in the context of genetic counselling in a clinical genetics clinic, ideally as a combined cardiac genetic clinic. Interpretation of the pathogenicity of novel variants, particularly in *SCN5A*, remains a significant problem and counselling of this to patients in advance of testing is essential.

3 Management

3.1 Affected individuals

While the diagnosis of BrS is essentially made on the ECG and the heart is said to be grossly structurally normal, Recent studies involving cardiac MRI and endomyocardial biopsy have shown discrete morphological abnormalities. However, a recent MRI study reported similar prevalence of right ventricular motion abnormalities in 29 patients with type 1 Brugada pattern and 29 healthy controls. (33) In addition to echocardiography, patients with a presumed diagnosis of Brugada syndrome (particular those being considered for an ICD with

no clear family history of Brugada syndrome), should have an MRI to exclude arrhythmogenic right ventricular cardiomyopathy or myocarditis.

ICD

The second consensus report of 2005(2) recommends ICD implantation in BrS patients who have survived cardiac arrest (Class I) or have a history of syncope and documented ventricular arrhythmia (Class IIA). Electrophysiology Study is only recommended for investigations if there are associated supraventricular arrhythmias.

Drugs

Quinidine, an I_{to} inhibitor, is a drug with some efficacy in BrS; it can normalise the ECG pattern, decrease VF induction, and has been used effectively in VT storm. (34) However it has not yet been demonstrated to improve clinical outcomes in BrS, and is a drug with considerable pro-arrhythmic potential. Unfortunately, this old drug is now difficult to get and is only available under special access scheme in Australia and New Zealand. It is used in patients who have repeated ICD shocks or have an arrhythmic storm. Isoprenaline infusion increases Ca^{+} current and is helpful in emergency treatment of arrhythmic storms in BrS.

Management of repeated ICD shocks and arrhythmic storms

In the acute phase, isoprenaline infusion is effective in suppressing VF and long term treatment with quinidine is effective. (35) Quinidine is available in Australia under special access scheme. Ablation of fractionated electrograms in the epicardial RVOT has been shown to be effective in VF suppression. Disappearance of Type 1 Brugada pattern has recently been reported and appears promising in specialised centres.(36)

Risk stratification

Patients presenting with aborted sudden death are at the highest risk.

Table 1 lists cardiac event rate per year reported in three large series in patients presenting with cardiac arrest, syncope and asymptomatic spontaneous Type 1 BrS ECG. (8, 37, 38) Brugada et al used programmed electrical stimulation to further risk stratify asymptomatic BrS patients. (38) In a recently published follow up of 1029 BrS patients from four European centres, France, Italy, Netherlands and Germany (FINGER study), Probst et al (39) reported an event rate 7.7, 1.9 and 0.5% per year respectively in these three groups. Risk of life threatening arrhythmias in asymptomatic patients who only have spontaneous Type 1 ECG changes is moderate, between 0.24 and 1.7 % per year. Where Type 1 ST changes appear only after pharmacological provocation, the patients are at minimal risk for arrhythmic events. BrS patients who have atrial fibrillation and fragmentation of QRS complexes in their ECG are reported to be at a higher risk of spontaneous VF. (13)

There is ongoing controversy regarding the role of programmed electrical stimulation (PES) for risk stratification in BrS.(37, 40) Experts agree that PES study have a negative predictive value of 98 to 99% in an asymptomatic individual, but its positive predictive value is controversial. While Brugada et al have found induction of sustained ventricular arrhythmia a strong marker of risk (8 fold risk), other workers, including a large prospective European study in 1,029 BrS patients have found it to be of poor predictive value. The protocol for electrophysiological study used by Brugada et al included measurement of conduction intervals and programmed electrical stimulation from the RV apex with a minimum of 3 ventricular extrastimuli at 3 different pacing rates. The shortest coupling interval was limited to 200ms, and the test was considered positive if sustained arrhythmia lasting >30 s or requiring intervention was induced.

Gehi et al (41) performed a meta-analysis of 30 prospective studies on 1,545 patients and concluded that a history of syncope or sudden death (SCD), the presence of spontaneous Type 1 Brugada ECG and male gender predict a more malignant natural history. Family history of SCD, the presence of *SCN5A* mutation and EPS were not predictive. Priori et al (PRELUDE trial 2012) performed PES in 308 patients (80% males). During a follow up of 34 months 14 arrhythmic events occurred and 9/14 events occurred in non-inducible patients. History of syncope, spontaneous Type 1 Brugada pattern, ERP $\leq$ 200msec and QRS fragmentation were predictive of increased risk. (42)

3.2 Asymptomatic individuals

ICD implantation in BrS has a high complication rate and most authorities do not recommend it for asymptomatic patients.(43) A family history of sudden death does not translate into increased risk in relatives.

As the changes of BrS on ECG are unmasked by a febrile state caused by loss of function of I_{Na} channel, aggressive treatment of all febrile episodes is recommended with antipyretics like aspirin and paracetamol and cold sponges. Hypokalemia, large carbohydrate meals and excessive alcohol and very hot baths have also been incriminated and should be avoided.

Drugs that can cause Brugada-like changes on the ECG are best avoided and include: Class I antiarrhythmic drugs like flecainide, beta blockers, tricyclic and tetracyclic antidepressants, phenothiazines and SSRI like fluoxetine, anaesthetic agents such as bupivacaine, procaine and propofol, alcohol and cocaine intoxication. A website 'www.brugadadrugs.org' gives a list of drugs to be avoided, preferably avoided and potential proarrhythmic drugs in BrS and a letter that can be downloaded and be given to BrS patients to carry.(44) At this stage, apart from quinidine, no other oral drug therapy is available for treatment of BrS. This situation may alter in future; phosphodiesterase inhibitors and tedesamil and dimethyl lithospermate B (dmLSB) a chinese herbal medicine are drugs that are being investigated.

4 Further Information

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Figure Legends

Figure 1

Precordial leads of a resuscitated patient with BrS showing all 3 ECG patterns and dynamic changes over a 8-day period. Arrows indicate J waves.(3) *(Reproduced with permission from: Wilde AA et al. Proposed diagnostic criteria for the Brugada syndrome. Circulation 2002; 106:2514-19)*

Figure 2

Mechanisms of BrS.(4) *(Reproduced with permission from: Antzelevitch C. Brugada Syndrome. PACE 2006;29:1130-59)*

Table 1: Cardiac event rate per year in BrS

Authors (Reference in brackets)	Number of patients	Follow up (months)	Cardiac arrest survivors	Syncope	Asymptomatic Type I ECG
Brugada et al (2005) (37)	724	54 ± 54	18%	8.8%	0.5 (non-inducible) 4.5 (inducible)
Eckardt et al (2005) (38)	212	40 ± 50	5%	1.8%	0.81%
Probst et al (2010) (39)	1,029	14 to 54.4, mean 31.9	7.7%	1.9%	0.5%



Figure 1

Figure 2

