

Brugada syndrome: a review of the literature

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ABSTRACT

Brugada syndrome is an example of a channelopathy caused by an alteration in the transmembrane ion currents that together constitute the cardiac action potential. Approximately 20% of the cases of Brugada syndrome have been shown to be associated with mutations in the gene coding for the sodium ion channel in the cell membranes of the muscle cells of the heart. Patients with Brugada syndrome are prone to develop ventricular tachyarrhythmias that may lead to syncope, cardiac arrest or sudden cardiac death. Many clinical situations have been reported to unmask or exacerbate the electrocardiography (ECG) pattern of Brugada syndrome. Genetic testing for Brugada syndrome is clinically available. Here we report two cases of Brugada syndrome followed by a comprehensive review of the literature.

KEYWORDS: Brugada syndrome, atrial fibrillation, sudden cardiac death, syncope, channelopathy

Introduction

Brugada syndrome (BS), first described in 1992,¹ is a major cause of sudden cardiac death (SCD),² syncope and ventricular tachyarrhythmia in young people with no structural heart disease.¹ About 5% of survivors of cardiac arrest have no clinically identified cardiac abnormality. About half of such cases are thought to be due to BS.³

The syndrome should be suspected in patients with documented idiopathic ventricular fibrillation, self-terminating polymorphic ventricular tachycardia, a family history of sudden cardiac death in a young person and/or syncope with the characteristic electrocardiography (ECG) changes. BS is usually diagnosed in adulthood, with an incidence of 0.05–0.60% in adults, and is very rarely diagnosed in children; the average patient age at diagnosis was 41 years in two large studies.⁵ The Brugada pattern is much more common in men with a ratio of 9:1 in one study;⁶ men had a higher rate of syncope and sudden cardiac death in a large prospective registry study.⁷ The syndrome characterised by right bundle branch block (RBBB) with ST elevation in leads V1 to V3 on electrocardiogram can transiently normalise for a period of time, making it difficult to diagnose.⁸

We report two cases here, one presenting with atrial fibrillation who developed ventricular fibrillation after being treated with flecainide, unmasking the Brugada ECG pattern, and the other admitted with a history of collapse. These cases are followed by a comprehensive review of the published literature.

Case 1

A 25-year-old man was admitted to the accident and emergency (A&E) department with a history of collapse. There was no significant previous history. His blood pressure was 129/65 mmHg and pulse was 160 beats per minute. Otherwise, examination was unremarkable.

An ECG showed atrial fibrillation (Fig 1a). Metoprolol 5 mg intravenous (IV) bolus had no effect. He was then given flecainide 150 mg over 30 minutes, but after 20 minutes of flecainide loading he became very pale and developed ventricular tachycardia leading to ventricular fibrillation (Fig 1b). One shock of 360 J resulted in return of spontaneous circulation (ROSC) and reversion to sinus rhythm. His repeat ECG showed RBBB with ST elevation in V1 to V2, suggesting Brugada syndrome Type 1 (Fig 1c). A repeat ECG after 3 hours proved to be normal without any feature of Brugada-type ECG pattern (Fig 1d).

Case 2

A 57-year-old male collapsed and lost consciousness while sitting at home. His ECG showed RBBB with ST elevation in V1–V3 (Fig 2). His investigations showed a haemoglobin level of 13.7 g/dl, white cell count $12 \times 10^9/l$, C-reactive protein 35 mg/l, sodium 137 mmol/l, potassium 4.3 mmol/l, creatinine 141 µg/l and urea 7.2 mmol/l. His chest X-ray (CXR) revealed consolidation of the right base and he was treated for chest infection with antibiotics. His transthoracic echocardiogram revealed good left ventricular systolic function with no evidence of structural heart disease. He was referred to an electrophysiologist for further management.

Discussion

Background

Brugada syndrome (BS) is an example of a channelopathy: a disease caused by an alteration in the transmembrane ion currents that together constitute the cardiac action potential. BS is consistent with an autosomal dominant inheritance with a variable expression.

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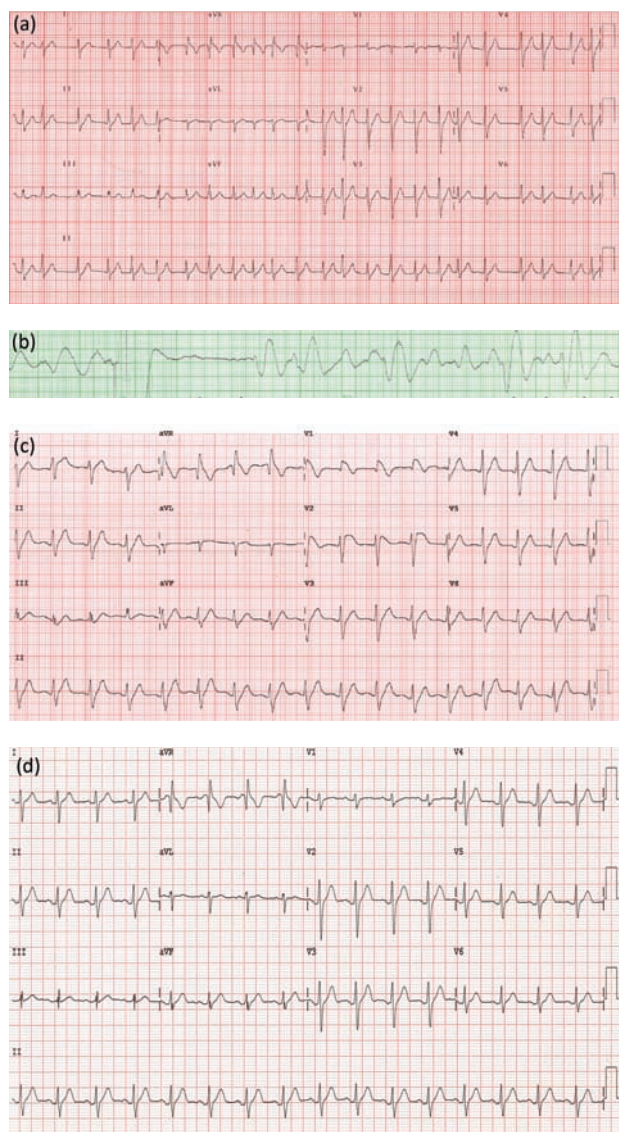


Fig 1. (a) The 12-lead ECG on admission showing atrial fibrillation with fast ventricular rate. (b) The rhythm strip from the monitor showing ventricular fibrillation post flecainide loading. (c) The 12-lead ECG after the shock showing ST right bundle branch block with ST elevation in V1–V2, suggestive of Brugada syndrome type 1. (d) Repeat 12-lead ECG 3 hours later showing no feature suggestive of Brugada syndrome. ECG = electrocardiography.

Several mutations have been identified in genes encoding subunits of cardiac sodium, potassium and calcium channels, as well as in genes involved in the trafficking or regulation of these channels. Accordingly, eight types of BS (from BS1 to BS8) have already been described, involving mutations in the *SCN5A*,⁹ *GPD1-L*,¹⁰ *CACNA1C*,¹¹ *CACNB2*,¹¹ *SCN1B*,¹² *KCNE3*,¹³ *SCN3B*¹⁴ and *HCN4*¹⁵ genes. The prototypical case of BS has been associated with alterations in the sodium channel gene *SCN5A*, of which nearly 300 mutations have been described.¹⁶ Mutations in this gene, located on chromosome 3p21–24, have been found in 18–30% of families.^{2,5,9}

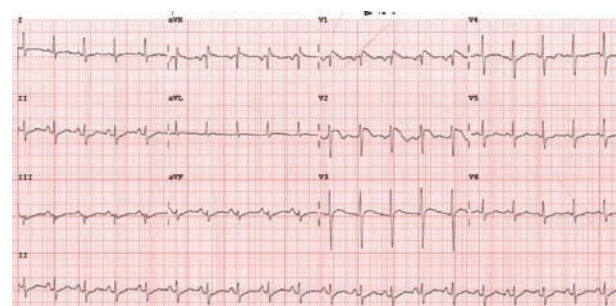


Fig 2. The 12-lead ECG showing Brugada ECG pattern. ECG = electrocardiography.

Standard cardiac testing, including echocardiography, stress testing and cardiac magnetic resonance imaging (MRI), often reveals no structural abnormalities. BS may be categorised as a disorder that occurs in hearts that are apparently normal, as some evidence suggests that there may be subtle structural or microscopic abnormalities, including dilation of the right ventricular outflow tract (RVOT) and localised inflammation and fibrosis.^{17,18}

Clinical presentation

Sudden cardiac arrest (SCA) may be the first and only clinical event in BS, occurring in up to one-third of patients with BS. Arrhythmic events are more common at night and during sleep;¹⁹ SCA in patients with BS is usually not related to exercise.²⁰

The most significant clinical manifestations of BS are ventricular arrhythmias, although these patients may also be at risk of atrial arrhythmias, most notably atrial fibrillation (AF),^{21,22} as seen in Case 1. The incidence of AF is higher in BS patients than in control subjects²² and the presence of AF has been associated with increased disease severity and a higher risk of ventricular fibrillation (VF).²¹

Over a 3-year follow up in 59 patients with BS and 31 matched control subjects, AF occurred in 12 (20%) of the BS patients but none of the control subjects. Patients with AF had a higher incidence of syncope (60% vs 22% of patients without AF), and VF (40% vs 14%).²¹

Characteristic BS patterns on an electrocardiogram may be present at all times or may be elicited by the administration of particular drugs. Many events unmask or exacerbate the ECG pattern of BS. Examples include: febrile state, hyperkalaemia, hypokalaemia, hypercalcaemia, alcohol or cocaine intoxication, and the use of certain medications, including sodium channel blockers, vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, heterocyclic antidepressants and a combination of glucose and insulin.²³

Diagnosis and types

Brugada syndrome is diagnosed in patients with typical ECG findings (coved ST elevation in leads V1–V3) plus at least one additional criterion from: a personal or family history of syncope, ventricular arrhythmias, or similar ECG findings in other family members.²⁴ The

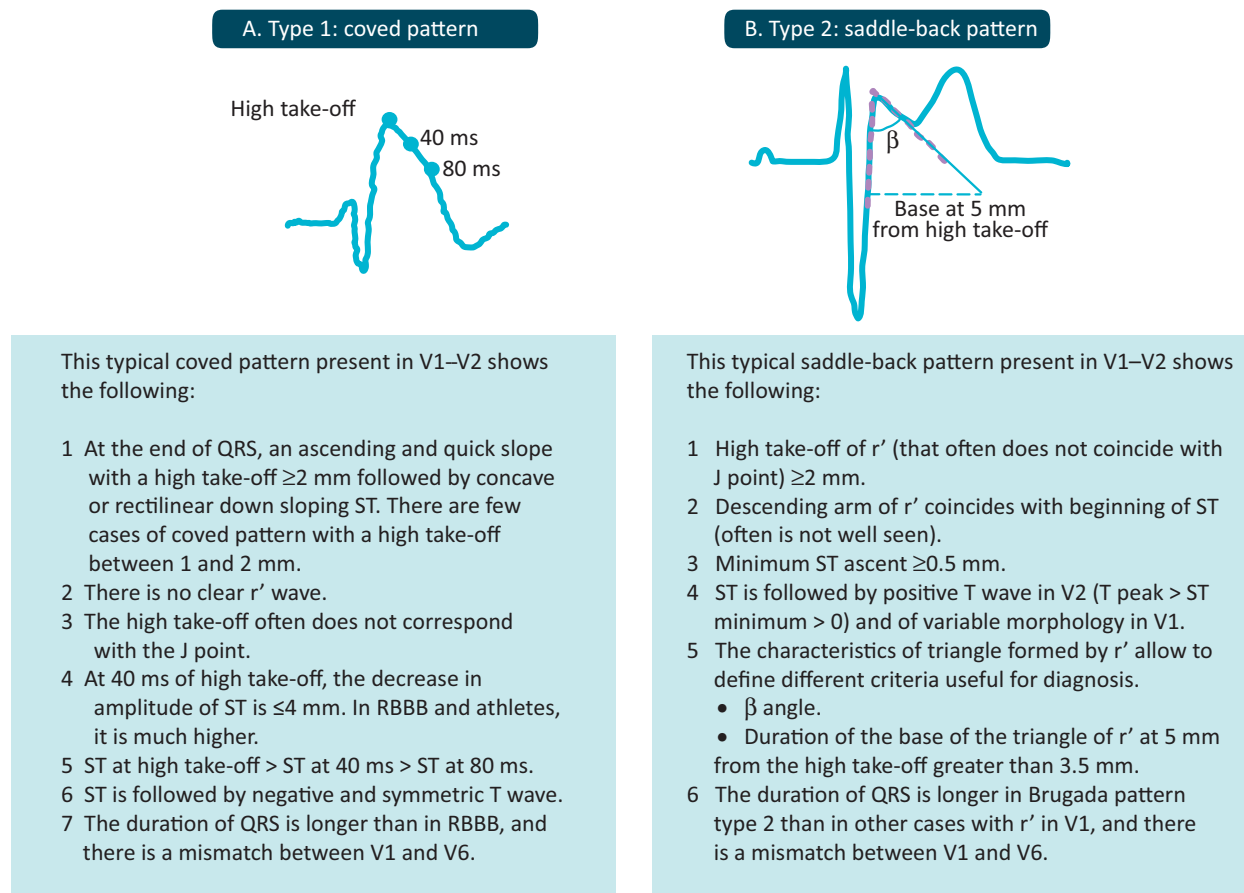


Fig 3. ECG patterns of Brugada syndrome in leads V1–V2. Reproduced with permission from Bayés de Luna et al (2012).²⁵ ECG = electrocardiography.

typical ECG changes alone are considered to represent an idiopathic Brugada ECG – ie the pattern is present, but BS is not.^{2,24} Both ECG and clinical features are important in establishing the diagnosis.^{2,24}

Two different patterns of ST elevation have been described (Fig 3).²⁵

- > In the classic Brugada Type 1 ECG, the elevated ST segment (≥ 2 mm) descends with an upward convexity to an inverted T wave. This is referred to as the ‘coved type’ Brugada pattern.
- > In the Type 2 pattern (combined from the original designation of types 2 and 3 patterns, Table 1),²⁶ the ST segment is ≥ 2 mm elevated and has a ‘saddle back’ ST-T wave configuration, in which the elevated ST segment descends toward the baseline but remains at least 0.5 mm above the isoelectric baseline, and then rises again to an upright or biphasic T wave.

Diagnostic criteria

In view of the clinical variability in presentation and the different ECG manifestations which can be seen in patients with Brugada syndrome, diagnostic criteria have been proposed by professional societies from both Europe and North America.^{2,24}

Type 1

The HRS/EHRA/APHRs expert consensus statement²⁷ recommends that Brugada syndrome is diagnosed when a Type 1 ST-segment elevation (coved type; Fig 3) is observed either spontaneously or after intravenous administration of a sodium channel blocking agent in at least one right precordial lead (V1 and V2),²⁸ which are placed in a standard or a superior position (up to the second intercostal space).^{29,30}

Type 2

The second consensus report² proposed that the diagnosis should be strongly considered in patients with a Type 2 Brugada ECG showing Type 2 ST-segment elevation (saddle-back type; Fig 3) in more than one right precordial lead under baseline conditions, with conversion to Type 1 following challenge with a sodium channel blocker, plus at least one of the following:

- > documented ventricular fibrillation
- > polymorphic ventricular tachycardia (VT)
- > family history of sudden cardiac death at less than 45 years of age
- > family history of Type 1 Brugada pattern ECG changes
- > inducible VT during electrophysiology study
- > unexplained syncope suggestive of a tachyarrhythmia
- > nocturnal agonal respiration.

Key points

- > Brugada syndrome, an autosomal dominant condition, is a disorder characterised by sudden death associated with one of several ECG patterns characterised by incomplete right bundle-branch block and ST-segment elevations in the anterior precordial leads.
- > Patients with Brugada syndrome are prone to develop ventricular tachyarrhythmias that may lead to syncope, cardiac arrest, or sudden cardiac death.
- > Diagnosis is based on clinical findings. Mutations in eight genes (SCN5A, GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3, SCN3B, and HCN4) are known to cause Brugada syndrome.
- > At present, implantation of an automatic implantable cardiac defibrillator (ICD) is the only treatment proven effective in treating ventricular tachycardia and fibrillation and preventing sudden death in patients with Brugada syndrome.
- > No proven pharmacologic treatment for preventing SCD in BS have been found, although Isoproterenol has been proved to be useful for treatment of electrical storm in BS and Quinidine has also shown to be beneficial. Quinidine is currently being used in:
 - patients with ICD and multiple shocks;
 - cases in which ICD implantation is contraindicated; or
 - for the treatment of supraventricular arrhythmias.

Differential diagnosis

The differential diagnosis for Brugada pattern ECG changes includes other conditions that result in apparent conduction and ST segment abnormalities in leads V1 to V3 on the ECG. A list of such conditions are shown in Box 1.

Box 1. Differential diagnosis of Brugada pattern ECG.

- > Atypical right bundle branch block
- > Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- > Early repolarisation
- > Acute pericarditis
- > Acute myocardial ischaemia or infarction
- > Pulmonary embolism
- > Dissecting aortic aneurysm
- > Hyperkalaemia
- > Hypercalcaemia
- > Hypothermia
- > Pectus excavatum

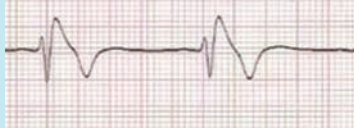
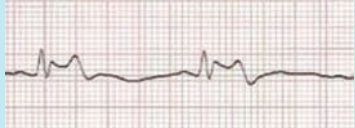

ECG = electrocardiography.

The Brugada pattern on ECG can be seen as an early subclinical manifestation of arrhythmogenic right ventricular cardiomyopathy (ARVC).⁸ An association between ARVC and the Brugada pattern on ECG is suggested by a report of 96 victims of sudden cardiac death (SCD) who were aged ≤ 35 years and had a baseline ECG available.²⁰ Right precordial ST segment elevation with or without RBBB was present in 13 (14%) of these; at autopsy, all but one had ARVC.

In patients with clinical manifestations of ventricular tachyarrhythmias and no apparent cardiac structural abnormalities, a number of other conditions should be considered along with:

- > congenital long QT syndrome (LQTS)
- > acquired LQTS with polymorphic ventricular tachycardia (VT)

Table 1. Diagnostic criteria for Brugada syndrome. ST segment abnormalities in leads V1–V3. 1 mm=0.1 mV; the terminal portion of the ST segment refers to the latter half of the ST segment.

	Type 1	Type 2	Type 3
			
J wave amplitude	≥ 2 mm	≥ 2 mm	≥ 2 mm
T wave	Negative	Positive or biphasic	Positive
ST-T configuration	Coved type	Saddle-back type	Saddle-back type
Terminal part of ST segment	Gradually descending	Elevated ≥ 1 mm	Elevated < 1 mm

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Table 2. Sodium channel blocking agents used to unmask Brugada syndrome.

Drug	Anti-arrhythmic class	Dosage	Route of administration	Duration of administration
Ajmaline ²⁸	1A	1 mg/kg	IV	10 min
Flecainide ²⁸	1C	2 mg/kg	IV	10 min
Flecainide ²⁸	1C	400 mg	Oral	Stat dose
Procainamide ^{29,30}	1A	10 mg/kg	IV	10 min
Pilsicainide ³¹	1C	1 mg/kg	IV	10 min

IV = intravenous.

- > catecholaminergic polymorphic VT
- > idiopathic VT
- > idiopathic ventricular fibrillation
- > short QT syndrome
- > commotio cordis.

Analysis of the ST-T waveform usually permits differential diagnosis between a Brugada ECG and right precordial early repolarisation seen in athlete's heart. Athletes exhibit an upsloping ST-segment with a mean ST_j:ST₈₀ ratio of ≤1, whereas Brugada patients show a downsloping ST-segment with a ST_j:ST₈₀ ratio of >1.³¹ The athlete with a suspected Brugada ECG should be referred to a cardiologist/electrophysiologist for further clinical work up, including a pharmacological test with sodium channel blocking, risk stratification and familial evaluation.

For most conditions in which VT or SCD occurs with no apparent cardiac structural abnormalities, the clinical scenario and the ECG findings can be used to exclude other conditions. For example:

- > Patients with VT or SCD associated with prolongation of the QT interval are more likely to have LQTS than Brugada syndrome, particularly if the patient has been exposed to medications which may prolong the QT interval. Similarly, patients with VT or SCD whose QT interval is markedly shortened are more likely to have short QT syndrome.
- > Patients who experience VT or SCD in the setting of exertion are more likely to have catecholaminergic polymorphic VT than Brugada syndrome, in which symptomatic tachyarrhythmias are more likely to occur at rest.
- > Patients with VT or SCD following blunt chest trauma are more likely to have experienced commotio cord.

Among patients with the Brugada Type 2 ECG pattern, the Brugada Type 1 ECG pattern can occasionally be unmasked by sodium channel blockers (eg flecainide, procainamide, ajmaline and pilsicainide) (Table 2).^{2,32} The reported sensitivity of pharmacologic challenge with these drugs range between 100%³² to as low as 15%.³³

Electrophysiology studies

The role of electrophysiology (EP) testing in patients with known or suspected BS depends largely upon the presence or absence of associated symptoms. Patients with a Brugada ECG pattern and certain high-risk clinical features (ie history of SCA and/or sustained ventricular arrhythmias) are known to

have an increased risk of SCD.^{3,8,19} In asymptomatic patients, EP testing remains debatable.³⁴

In the PRogrammed ELectrical stimulation preDICTive value (PRELUDE) trial, Priori and colleagues enrolled 308 patients with no history of cardiac arrest but with a spontaneous or drug-induced Type I Brugada ECG pattern.³⁵ Seventy-eight of these patients had an implantable cardiac defibrillator (ICD) implanted prophylactically. An EP study with a consistent stimulation protocol was performed. Over a mean follow up of 34 months no differences were found in the incidence of appropriate ICD shocks or cardiac arrest between patients who had or did not have inducible arrhythmias during the EP study.

Management

No proven pharmacologic treatment for preventing SCD in BS have been found, although isoproterenol has been proved to be useful for treatment of electrical storm in BS³⁶ and quinidine has also shown to be beneficial.³⁷

Among 25 patients (15 symptomatic and 10 asymptomatic) before and after treatment with quinidine bisulfate (mean dose 1483±240 mg/day),³⁷ ventricular fibrillation was inducible in all patients at baseline electrophysiology testing, but in only three after a few days of quinidine therapy. Quinidine treatment was continued in 19 patients for a mean of 56 months and none had arrhythmic events. Quinidine is currently being used in patients with ICD and multiple shocks, cases in which ICD implantation is contraindicated or for the treatment of supraventricular arrhythmias.³⁸ A list of potential antiarrhythmic drugs for the treatment of patients with BS are given in Table 3.

Table 3. Potential antiarrhythmic drugs in patients with Brugada syndrome.

Drug category	Drug (generic)	Recommendation*
Anti-arrhythmic drugs	Isoproterenol/ isoprenaline	Class I
	Orciprenaline	Class IIa
	Quinidine	Class I
Other substances	Cilostazol	Class IIb

Reproduced with permission from Postema *et al* (2009).³⁹ *Class I: convincing evidence/opinion; class IIa: evidence/opinion less clear; class IIb: conflicting evidence/opinion.

Table 4. Drugs to be avoided in patients with Brugada syndrome.

Drug category	Drug (generic)	Recommendation*
Anti-arrhythmic drugs	Ajmaline	Class I
	Flecainide	Class I
	Pilsicainide	Class I
	Procainamide	Class I
	Propafenone	Class IIa
Psychotropic drugs	Amytriptyline	Class IIa
	Clomipramine	Class IIa
	Desipramine	Class IIa
	Lithium	Class IIb
	Loxapine	Class IIa
	Nortriptyline	Class IIa
Anaesthetic drugs	Bupivacaine	Class IIa
	Procaine	Class IIa
	Propofol	Class IIa
Other substances	Acetylcholine	Class IIa
	Alcohol (toxicity)	Class IIb
	Cocaine	Class IIa
	Ergonovine	Class IIb

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Some drugs have been reported to induce the Type 1 BS ECG pattern and/or (fatal) arrhythmias in BS patients. Patients with BS can prevent arrhythmias by avoiding these drugs (Table 4 and Table 5)³⁹ or by using them only in controlled conditions.¹⁰

The only treatment with proven efficacy in preventing SCD is an ICD. In a cohort of 63 patients, both amiodarone and β -blockers were found to be inferior to ICD.⁴⁰ Selecting patients for an ICD is challenging. The proposed recommendations of ICD in patients with BS are shown in Fig 4.²⁷

Asymptomatic BS patients do not qualify for an ICD as their risk for life-threatening events is very low.⁴¹ Patients in this group need to be assessed individually based on their gender, age, baseline ECG and inducibility. ■

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Table 5. Drugs preferably avoided in patients with Brugada syndrome.

Drug category	Drug (generic)	Recommendation*	
Anti-arrhythmic drugs	Amiodarone	Class IIb	
	Cibenzoline	Class IIb	
	Disopyramide	Class IIb	
	Lidocaine (lignocaine)	Class IIb	
	Propranolol	Class IIb	
	Verapamil	Class IIb	
	Psychotropic drugs	Carbamazepine	Class IIb
		Cyamemazine	Class IIb
		Doxepin	Class IIb
		Fluoxetine	Class IIb
Imipramine		Class IIb	
Maprotiline		Class IIb	
Perphenazine		Class IIb	
Phenytoin		Class IIb	
Thioridazine		Class IIb	
Anti-anginal drugs		Diltiazem	Class III
	Nicorandil	Class III	
	Nifedipine	Class III	
	Nitroglycerine	Class III	
	Sorbidnitrate	Class III	
	Other substances	Dimenhydrinate	Class IIb
Edrophonium	Class IIb		
Indapamide	Class IIb		

Reproduced with permission from Postema *et al* (2009).³⁹ *Class I: convincing evidence/opinion; class IIa: evidence/opinion less clear; class IIb: conflicting evidence/opinion; class III: very little evidence.

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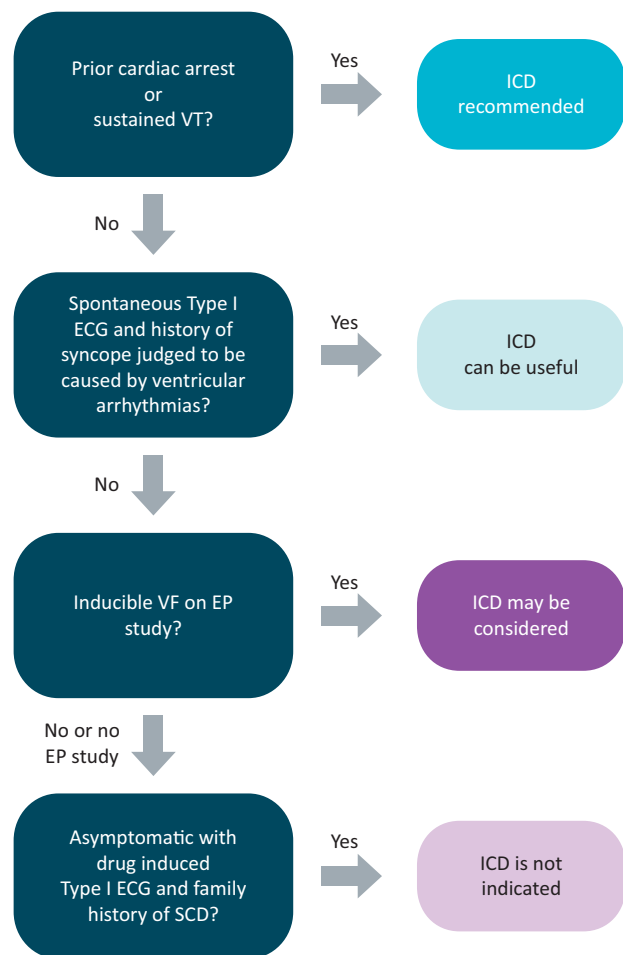


Fig 4. Consensus recommendations for implantable cardiac defibrillators (ICDs) in patients diagnosed with Brugada syndrome. Reproduced with permission from Priori *et al* (2013).²⁷ ECG = electrocardiography; EP = electrophysiology; ICD = implantable cardiac defibrillator; SCD = sudden cardiac death; VT = ventricular tachycardia.

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