

# Brugada Syndrome: A Brief Review on Diagnostic Approach, Risk Stratification, and Management

Raymond Pranata

Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village - Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

ORCID:

Raymond Pranata: <https://orcid.org/0000-0003-3998-6551>

## Abstract

Brugada syndrome is a congenital channelopathy in cardiac ion transmembrane causing an alteration in the electrical conduction of the heart. ST-elevation, as well as right bundle-branch block in anterior precordial electrocardiography (ECG), is pathognomonic in this syndrome. The patient might be asymptomatic or with a history of syncope and prone to develop ventricular tachyarrhythmia which may spontaneously recover or degenerates to ventricular fibrillation, cardiac arrest and even sudden death. Nevertheless, this can be prevented by implantable cardioverter defibrillator implantation. Therefore, it is of paramount importance that clinical suspicion and identification, interpretation of its characteristic ECG pattern and risk stratification to be properly done to diagnose and to manage Brugada syndrome. The author has also done a systematic review (included in the article) for several noninvasive ECG parameters for risk stratification with promising results. Epicardial ablation is an emerging therapy that may “cure” Brugada syndrome.

**Keywords:** Arrhythmia, Brugada syndrome, risk stratification, sudden cardiac death, syncope

## INTRODUCTION

Brugada syndrome is a genetically determined channelopathy leading to syncope and ventricular tachyarrhythmia causing sudden death in those without evident structural heart disease. It was first mentioned in 1992.<sup>[1,2]</sup> Brugada syndrome was commonly considered as an abnormality found commonly in young males (male: female ratio was 9:1) and Southeast Asian. It frequently manifests at the age of 40 years, causing sudden death frequently during sleep.<sup>[3-5]</sup> Suspicion should arouse when encountering a patient with a history of idiopathic ventricular fibrillation (VF) or polymorphic ventricular tachycardia (VT) that aborts spontaneously and family history of sudden death in young age with or without typical electrocardiography (ECG) findings. The incidence of Brugada syndrome in adults is approximately 0.05%–0.60% and the average age when the diagnosis is established is 41 years old.<sup>[6]</sup>

## GENETIC BASIS AND PATHOPHYSIOLOGY

There are 18 genes that are associated with Brugada syndrome

from BrS1 to BrS18. Basically, there are abnormalities in sodium, calcium, or potassium ion channels located at heart muscles.<sup>[7,8]</sup>

### Sodium flow

BrS1 gene was the first gene to be discovered which involves SCN5A at chromosome 3p21-23 encodes subunit  $\alpha$  of sodium ion channel protein (NaV1.5) which is responsible for depolarization (Phase 0 of action potential). Mutation results in loss-of-function of the sodium channel resulting in less sodium influx into the interior of the cell during depolarization. This mutation was also linked with other cardiac conduction defects (atrioventricular [AV] block, left bundle branch block, and left anterior fascicular block).<sup>[9,10]</sup> BrS2 is responsible for mutations in glycerol-3-phosphate dehydrogenase 1-like protein reducing both the surface membrane expression and the inward sodium current.<sup>[11]</sup> SCN1B plays a role in forming subunit  $\beta$ 1 of sodium ion

**Address for correspondence:** Dr. Raymond Pranata,  
Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia.  
E-mail: [raymond\\_pranata@hotmail.com](mailto:raymond_pranata@hotmail.com)

Submission: 02-Aug-18 Accepted: 27-Sep-18

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DOI:  
10.4103/IJCA.IJCA\_31\_18

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**How to cite this article:** Pranata R. Brugada syndrome: A brief review on diagnostic approach, risk stratification, and management. *Int J Cardiovasc Acad* 2019;5:1-7.

which modifies Nav1.5, thus increasing  $I_{Na}$  was the cause of BrS5.<sup>[12]</sup> Meanwhile, BrS7 gene (SCN3B gene) forms subunit  $\beta 3$  of sodium ion channels which alters Nav1.5 trafficking, thereby decreasing  $I_{Na}$ .<sup>[13]</sup>

### Calcium flow

CACNA1C mutation results in BrS3 and CACNB2 cause BrS4. They are responsible for a defective unit of the L-type calcium channel. These mutation cause dysfunctions in subunit  $\alpha$  and  $\beta$  resulting in loss of function and reduced calcium influx culminating in shortening of the plateau phase of action potential. The *CACNA2D1* gene was reported as responsible for BrS. The  $\alpha 2/\delta$ -subunit of voltage-dependent calcium channels regulates current density and activation/inactivation kinetics of the calcium channel.<sup>[7,8]</sup>

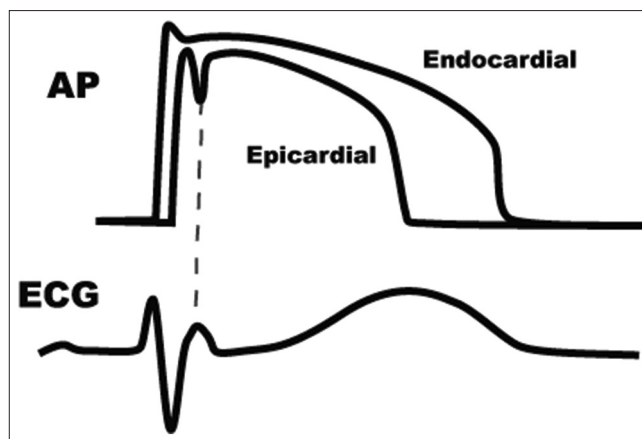
### Potassium flow

KCNE3 gene plays a role in the formation of MiRP2 protein ( $\beta$ -subunit that regulates the potassium channel  $I_{to}$ ) and modulates some potassium currents in the heart. A recent study revealed that enhanced  $I_{to}$  current gradient in the right ventricle was associated with KCND3 gain-of-function mutations (Kir4.3 protein). Another gene associated with BrS is *KCNJ8*, which was previously related to early repolarization syndrome and a marker of gain-of-function in the cardiac K (ATP) Kir6.1 channel. The *KCNE5* gene, which is located in the X chromosome, encodes an auxiliary  $\beta$ -subunit for K channels causing gain-of-function effects on  $I_{to}$ .<sup>[7,14]</sup>

The most prevalent is SCN5A mutation (20% of cases), these dysfunctions resulted in an imbalance between outward and inward positive currents during repolarization causing heterogeneous loss of action potential dome during phase 2. Increased dispersion of repolarization and refractoriness within epicardium and across the wall are associated with phase 2 re-entry mechanism resulting in ventricular arrhythmias.<sup>[15]</sup> Most of the genetic variants found in Brugada syndrome remain of unknown significance because no comprehensive cellular studies have been performed. Genetic variants other than SCN5A may be responsible for only 2%–5% of diagnostic cases. Recently, there is a notion that Brugada syndrome may not be caused by a single mutation but rather by multiple susceptibility variants [Figure 1].

## CLINICAL MANIFESTATION AND DIAGNOSIS

VF or aborted sudden cardiac death (SCD), syncope, nocturnal agonal respiration, palpitations, and chest discomfort are associated with Brugada syndrome. These symptoms frequently occur during rest or sleep, fever, excess eating or binge drinking resulting in excess vagotonic condition nonetheless they rarely manifest during exercise.<sup>[8,16]</sup> Symptoms occurring at young age signals an aggressive form of the disease. Overall 20% experienced at least 1 syncope and only 10%–14% suffered cardiac arrest before 60 years old as was shown by international registries and meta-analysis.<sup>[6,17]</sup> Drugs such as bupivacaine, cocaine, propafenone, methoxamine,  $\beta$ -blocker, potassium channel activator (pinacidil), a tricyclic



**Figure 1:** Difference in action potential in epicardial and endocardial myocyte in Brugada syndrome. Repolarization disorder hypothesis stated that the difference between action potential in the epicardial and endocardial myocyte resulted in the typical ST-elevation in Brugada syndrome

antidepressant, an opioid analgesic, lithium, and propofol exacerbates ECG pattern and potentially precipitating arrhythmia (visit [Brugadadrugs.org](http://Brugadadrugs.org)). Diagnostic criteria of Brugada syndrome according to 2013 HRS/EHRA/APHS expert consensus statement is with ST-segment elevation with type I morphology  $\geq 2$  mm in  $\geq 1$  lead among the right precordial leads V1, V2 positioned in the 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs or in patients with type 2 or type 3 ST-segment elevation in  $\geq 1$  lead among the right precordial leads V1, V2 positioned in the 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.<sup>[16]</sup> According to international consensus conference on BrS ST-segment elevation of  $\geq 2$  mm in at least two of three precordial leads (V1–V3) with coved morphology associated with complete or incomplete right bundle-branch block was the ECG criteria to fulfill. Other ECG abnormalities that might be found are AV block and atrial fibrillation (10%–25% of patients).<sup>[8,18–21]</sup> These atrial arrhythmias in Brugada syndrome were associated with genetic variants impairing the sodium channel function along with structural remodeling that promote AF by prolonging refractoriness and slowing conduction velocity which may be heterogeneous and facilitates the development of unidirectional block and re-entry, giving rise to atrial fibrillation, atrial flutter, and AV-nodal re-entry tachycardia.<sup>[22]</sup>

There are three typical ECG patterns in patients with Brugada syndrome. In type 1 there is a Coved ST-segment elevation  $\geq 2$  mm followed by T inversion in  $>1$  precordial leads (V1–V3). ST-T segment saddleback configuration followed by positive or biphasic T wave is seen in type 2 ECG. Meanwhile, type 3 may show coved or saddleback with ST-segment elevation  $<1$  mm [Figure 2]. Typical ST segment changes might be found in patients with concealed form or type 2 or 3 ECG during provocation or fever. Therefore, in

**Table 1: Proposed Shanghai Score System for diagnosis of Brugada syndrome**

	Points
ECG (12-Lead/Ambulatory)	
Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
Only award points once for highest score within this category. One item from this category must apply.	
Clinical History*	
Unexplained cardiac arrest or documented VF/polymorphic VT	3
Nocturnal agonal respirations	2
Suspected arrhythmic syncope	2
Syncope of unclear mechanism/unclear etiology	1
Atrial flutter/fibrillation in patients <30 years without alternative etiology	0.5
Family History*	
First- or second-degree relative with definite BrS	2
Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
Unexplained SCD <45 years in first- or second-degree relative with negative autopsy	0.5
Genetic test result	
Probable pathogenic mutation in BrS susceptibility gene	0.5
Score (requires at least 1 ECG finding). >3.5 points: Probable/definite BrS. 2-3 points: Possible BrS <2 points: Non-diagnostic	

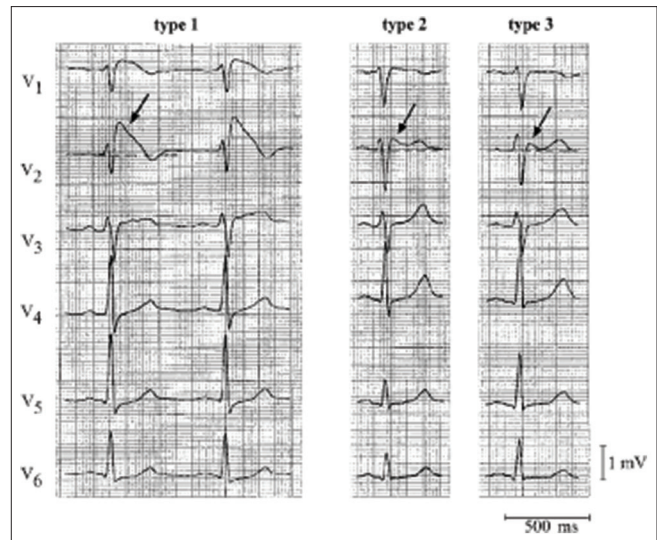
\*Only award points once for highest score within this category.

BrS=Brugada syndrome; SCD=sudden cardiac death; VF=ventricular fibrillation; VT=ventricular tachycardia. Reproduced from Antzelevitch *et al.*<sup>[23]</sup>

patients with type 2 or 3 ECG findings, provocation with sodium channels inhibitor.<sup>[15]</sup> [Figure 2]. There is also new diagnostic criteria of Brugada syndrome (Shanghai score) which was proposed in the consensus statement in 2016 [Table 1].<sup>[23]</sup> It is important to note in this new consensus, that asymptomatic patients with drug-induced type 1 ECG are considered to be at low risk and need some clinical manifestations to be diagnosed with Brugada syndrome.<sup>[23]</sup>

## RISK STRATIFICATION

Almost all studies are in agreement that patient with type 1 baseline ECG and an episode of syncope have a high risk of cardiac arrhythmia in follow-up. The presence of QRS fragmentation and effective refractory period <200 ms were also proposed.<sup>[24-26]</sup> Risk of lethal or near-lethal arrhythmia episode in previously asymptomatic patient is 8%, event rate at 33 ± 39 months follow-up was reported by Brugada *et al.*; 6% event rate in 34 ± 44 months by Priori *et al.*; 1% event rate was found at 40 ± 50 months and 30 ± 21 months follow-up by Eckardt *et al.* and Giustetto *et al.*<sup>[25,27-29]</sup> Even though large registries are in agreement that electrophysiological study (EPS) inducibility was most frequently encountered



**Figure 2:** Electrocardiographic characteristics of Brugada pattern in precordial leads. electrocardiography in Brugada Syndrome. Type 1: Coved ST-elevation  $\geq 2$  mm followed by T wave deflection. Type 2: Gradually decreasing ST-elevation with saddleback pattern with positive or biphasic T wave and Type 3: coved or saddleback with  $\geq 1$  mm ST-elevation.<sup>[32]</sup> From: Wilde AA, Antzelevitch C, Borggrefe M *et al.*; Study Group on the Molecular basis of arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J 2002;23:1648-54

in those who experienced syncope or aborted sudden death, there is no consensus regarding the role of EPS. A study by Siera *et al.* showed 25 ventricular arrhythmia events, which consists of 16 (21.9%) patients in the group that was successfully induced by EPS and 9 (2.7%) patients that are not inducible. The aforementioned arrhythmia resulted in 24 appropriate implantable cardioverter defibrillator (ICD) shocks and 1 resuscitation because of cardiac arrest in those without ICD. The hazard ratio for an arrhythmic event in the future is 8.1 ( $P < 0.01$ ) for those with inducible ventricular arrhythmia during the EPS study.<sup>[30]</sup> EPS is controversial because the protocols are different between studies, for example; only from RV apex by Brugada group, but other groups from both apex and RVOT, up to double or triple extra stimuli, and minimal coupling interval to 200 ms or to 180 ms, etc.). Recently, VF induction up to two extra stimuli is reported to be useful in the risk stratification of patients with Brugada syndrome.<sup>[27,31]</sup>

A study showed a Kaplan–Meier curve of 96.8%–99% event-free survival at 1, 5, 10, and 15 years in noninducible ventricular arrhythmia during EPS. It is concluded that in a patient with asymptomatic clinical presentation alone in those with noninducible groups has 99.2% event-free survival at 1, 5, 10, and 15 years.<sup>[30,32]</sup> Hence, EPS is an excellent predictor in both asymptomatic or those presenting with syncope<sup>[2]</sup> [Figure 3].

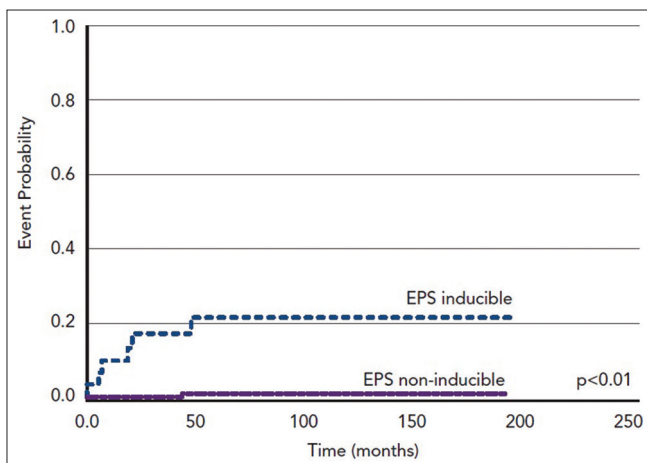
There were also studies that enlist additional tools for the risk stratification mainly Tpeak-end interval (TpTe), Tp-e dispersion, and TpTe/QT ratio [Table 2].<sup>[33-41]</sup> There were five



**Table 2: Role of Tpeak-Tend, Tpeak-Tend/QT ratio, and Tpe dispersion as additional noninvasive electrocardiography parameters for predicting ventricular tachycardia/fibrillation in patients with Brugada Syndrome**

Authors	Year	Study design	Samples	Subjects	Outcome of interest	Results
Morita H <i>et al.</i>	2018	Case-control study	62	Brugada-type ECG	Initial VF	OR of difference Tpe interval (V1) $\geq +10$ ms: 11.0, CI: 2.6-46.1, $P=0.001$
Morita H <i>et al.</i>	2018	Retrospective Cohort	471	BrS	VF	TpTe (ms) $V2 \geq 95$ was associated with HR 3.03 1.26-9.01 0.0143
Zumhagen	2016	Case-control study	78	BrS	VT/VF/aborted SCD	TpTe $\geq 77$ ms, 63.6% and 74.1%; AUC 0.675, TpTe/QT ratio $\geq 0.205$ , 72.7% and 68.5%; AUC 0.673
Maury P	2015	Case-control study	325	BrS	Sudden death/ appropriate ICD shocks	Maximum Tpe $> 100$ ms OR of 9.61 (95% CI 3.13-9.41) ( $P < 0.0001$ ). Sensitivity 84% and Specificity 68%, PPV 19%, NPV 98%
Mugnai	2017	Cohort	448	BrS	VT/VF/SCD/ appropriate ICD shocks	No significant difference was observed in TpTe, TpTe/QT, maximum TpTe, and TpTe dispersion
Kawazoe	2016	Case-control study	143	BrS	VF	Tpe dispersion OR 1.069 (1.03-1.10), $P: 0.001$ independent predictor
Letsas	2010	Case-control study	23	BrS	VT/VF inducibility	TpTe V2 (88.82 $\pm$ 15.70 vs. 78.33 $\pm$ 4.08 ms, $P=0.02$ ) and V6 (76.33 $\pm$ 10.08 vs. 66.66 $\pm$ 5.16 ms, $P=0.04$ ) Greater Tpeak-Tend/QT ratio in lead V6 (0.214 $\pm$ 0.028 vs. 0.180 $\pm$ 0.014, $P=0.009$ )
Hevia JC	2006	Cohort	29	BrS	VT/VF	QTc $> 460$ ms in V2 TpTe and Tp-e dispersion were significantly prolonged in patients with recurrences versus patients without events TpTe cut-off point $> 100$ ms; Sensitivity 77.8% and specificity 70%; AUC 0.7861 Tp-e dispersion Cut-off point $> 20$ ms; Sensitivity 66.7% and specificity 90%; AUC 0.7722

TpTe: Tpeak-Tend interval, SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, ECG: Electrocardiography, OR: Odds ratio, CI: Confidence interval, AUC: Area under the curve, PPE: Positive predictive value, NPE: Negative predictive value, BrS: Brugada Syndrome, HR: Hazard ratio



**Figure 3:** Kaplan–Meier curve showing high event-free survival of EPS noninducible patients. Patients had 96.8%–99% event free survival at 1, 5, 10 and 15 years in non-inducible ventricular arrhythmia during electrophysiological study<sup>[32]</sup>

studies that showed TpTe was reliable in predicting VT/VF in patient with Brugada syndrome, the cut-off points varied between precordial leads from  $\geq 80$  ms to  $\geq 100$  ms in which two studies reported a sensitivity 77.8%–84% and specificity 68%–70%; positive predictive value 19%, negative predictive value 98%, odds ratio (OR) 9.61 (95% confidence interval 3.13–9.41) ( $P < 0.0001$ ), area under the curve (AUC) 0.7861 with  $\geq 100$  ms. Morita *et al.* indicated TpTe progression of  $> 10$

ms on repeat ECG was associated with OR 11.6 ( $P = 0.001$ ). Zumhagen *et al.* showed that TpTe/QT ratio is reliable in predicting VT/VF in which a ratio of  $\geq 0.205$  has sensitivity 72.7% and specificity 68.5%; AUC 0.673. Two studies reported that Tp-e dispersion was associated with VT/VF one of which reported Cut-off point  $> 20$  ms; sensitivity 66.7% and Specificity 90%; AUC 0.7722. Only Mugnai *et al.* revealed the nonsignificant relation of the aforementioned parameters and VT/VF. Letsas *et al.* indicated that TpTe and greater TpTe/QT ratio in lead V6 are related to VT/VF inducibility, but the latter was not related to the arrhythmic outcome. Spontaneous type 1 ECG, syncope, early repolarization pattern, age (the elderly is at lower risk), and SCN5A mutation (pore lesion) were also associated with higher risk.<sup>[42-44]</sup>

## MANAGEMENT

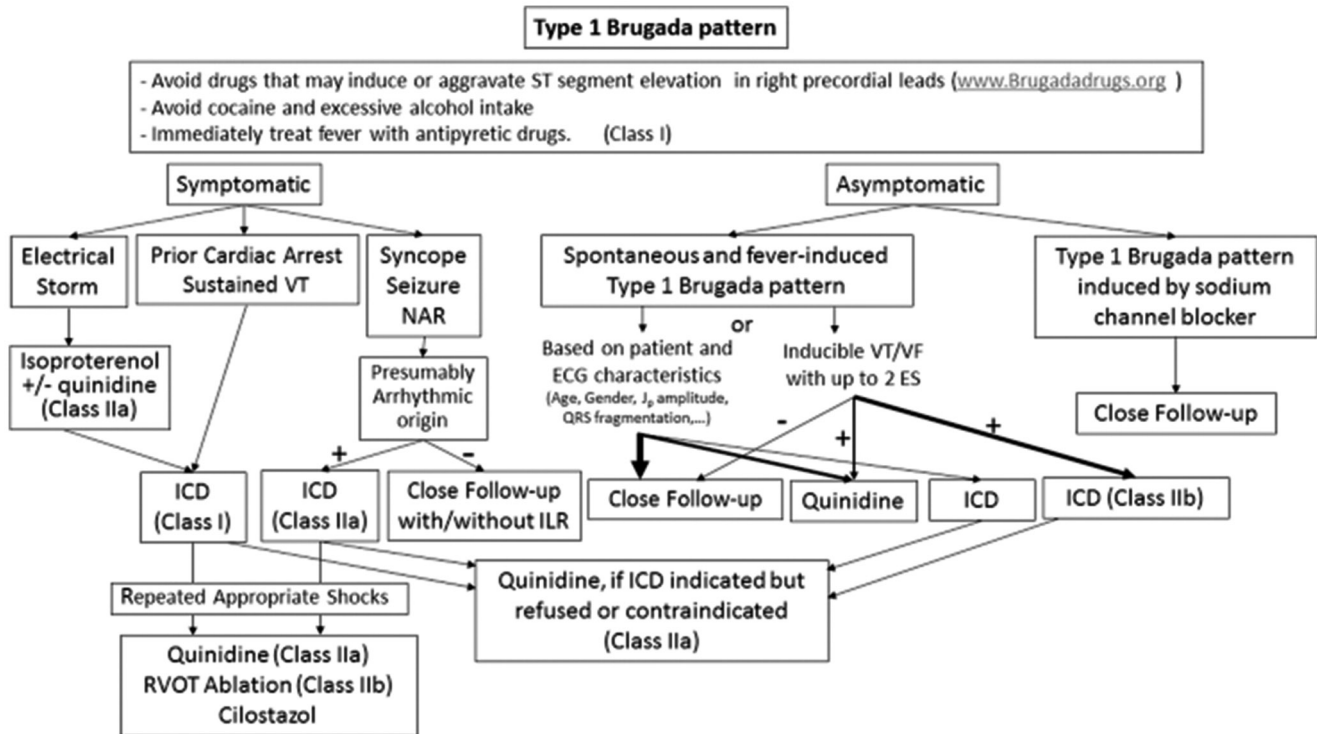
Drugs that may induce or aggravate ST-segment elevation in the right precordial leads should be avoided (visit [Brugadadrugs.org](http://Brugadadrugs.org)). Excessive alcohol intake should be avoided, and immediate treatment of fever with antipyretic drugs are Class I recommendation [Table 3]. ICD implantation is the only effective modality in Brugada syndrome. Brugada syndrome patients who are survivors of a cardiac arrest and/or have documented spontaneous sustained VT with or without syncope had a Class I recommendation for ICD implantation. Implantation of ICD is recommended (Class IIa) in a patient with syncope (if syncope is suspected as arrhythmic origin)

and spontaneously abnormal ECG (without provocation) because those patients have six times increased risk of cardiac arrest compared to those showing type I ECG after provocation.<sup>[2,6]</sup> The risk is very low when the diagnosis was

**Table 3: Recommendation on therapy and intervention in patient with Brugada Syndrome**

Class of Recommendation	Intervention
Class I	The following lifestyle changes are recommended in all patients with diagnosis of BrS Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads Avoidance of excessive alcohol intake Immediate treatment of fever with antipyretic drugs ICD implantation is recommended in patients with a diagnosis of BrS who Are survivors of a cardiac arrest and/or Have documented spontaneous sustained VT with or without syncope
Class IIa	ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmia Quinidine can be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 h Quinidine can be useful in patients with a diagnosis of BrS Who qualify for an ICD but present a contraindication to the ICD or refuse it and/or Have a history of documented supraventricular arrhythmias that require treatment Isoproterenol infusion can be useful in suppressing arrhythmic storms in BrS patients
Class IIb	ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients) Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type 1 ECG Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks
Class III	ICD implantation is not indicated in asymptomatic BrS patients with a drug-induced type 1 ECG and on the basis of a family history of SCD alone

Expert Consensus Recommendations on BrS Therapeutic Interventions. Priori *et al.* SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, ECG: Electrocardiography, BrS: Brugada Syndrome



**Figure 4:** Indications for therapy of patients with Brugada syndrome. The figure above provide flowchart regarding the indications for therapy of patients with Brugada syndrome<sup>[23]</sup>

made after provocation test with sodium ion channel blockers or by identification of pathogenic mutation only. Follow-up may be needed to observe changes in ECG morphology, from previously requiring provocation to display typical ECG into spontaneously abnormal ECG.<sup>[8]</sup> Management in a patient with spontaneously abnormal type I ECG without a history of syncope is controversial, the risk of life-threatening events in this group is two-fold higher in those without spontaneously ST-segment elevation.<sup>[6,17]</sup> EPS may be beneficial in this group. However, its role is still controversial, and ICD implantation (Class IIb) may be considered those who develop VF during programmed electrical stimulation (inducible patients) [Figure 4]. QRS fragmentation in these patients was also associated with a worse prognosis.<sup>[24]</sup> Quinidine, which is the best antiarrhythmic medication available for Brugada syndrome is only used as an adjunct therapy for high-risk patients and to reduce the number of ICD shocks in those with recurrent events.<sup>[8]</sup> Quinidine may be considered in asymptomatic patients with a diagnosis of Brugada syndrome with a spontaneous type I ECG (Class IIb). Catheter ablation can be considered Brugada syndrome patients with a history of arrhythmic storms or repeated appropriate ICD shocks (Class IIb). Finally, ICD implantation is not indicated in asymptomatic Brugada syndrome patients with a drug-induced type I ECG and on the basis of a family history of SCD alone (Class III).

Epicardial ablation is an emerging treatment in the field of Brugada syndrome. Nademanee *et al.* showed that 9 patients with Brugada syndrome experiencing 2–6 incidence of ventricular arrhythmia per month was arrhythmia free in a follow-up of 2 years after ablation.<sup>[41]</sup> Brugada *et al.* reported that ablation of the substrate identified in the presence of flecainide could eliminate the Brugada syndrome phenotype.<sup>[45]</sup> Pappone *et al.* in a study of 50 consecutive patients that underwent ablation showed that ECG pattern normalized in all symptomatic and asymptomatic patients.<sup>[46]</sup> Follow-up of 3 to 20 months showed that the patients showed no Brugada syndrome phenotype and was not VT/VF inducible seemingly “cured” the Brugada syndrome. Pappone stated that ablation could be useful in those that do not meet the recommendation or refuse ICD implantation. A multicenter randomized trial, ablation in Brugada syndrome for the prevention of VF episodes Study was underway. These findings may usher a new era in treating Brugada syndrome, and the possibility of epicardial ablation being a first-line treatment in the future cannot be overruled.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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