

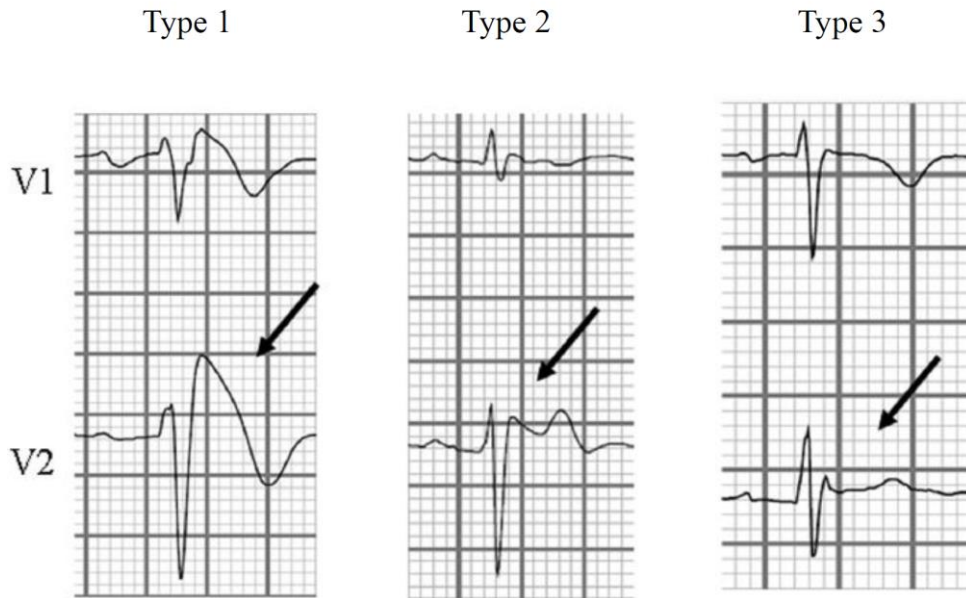


Figure 1. ECG abnormality diagnostic or suspected of Brugada syndrome.

Type 1 ECG (coved-type ST-segment elevation) is the only diagnostic ECG in Brugada syndrome and is defined as a J-wave amplitude or an ST-segment elevation of ≥ 2 mm or 0.2 mV at its peak (followed by a negative T wave with little or no isoelectric separation). Type 2 ECG (saddle-back-type ST-segment elevation), defined as a J-wave amplitude of ≥ 2 mm, gives rise to a gradually descending ST-segment elevation (remaining ≥ 1 mm above the baseline) followed by a positive or biphasic T wave that results in a saddle-back configuration. Type 3 ECG is a right precordial ST-segment elevation (saddle-back type, coved type, or both) without meeting the aforementioned criteria.

Mizusawa Y, Wilde AA. Brugada syndrome. *Circ Arrhythm Electrophysiol.* 2012;5:606-16.

Table 1. Genetic Testing**EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Gene implicated in Brugada Syndrome**

Gene	Locus	Phenotype—syndrome	Protein (functional effect)	Frequency	ClinGen classification
<i>SCN5A</i>	3p22.2	BrS/AD	Loss of $I_{Na1.5}$ channel function	15–30%	Definite

ESC 2022 GL on VA and SCD. Recommendations for genetic testing (Class I)**Proband*****Initial clinical test*****Cornerstone for diagnosis**

ECG and high precordial lead ECG

Sodium channel blockers provocative test^a***Other tests/processes***Exclude phenocopy^b***Follow-up***

1-3 years dependent on level of risk

Relatives***Clinical screening***

ECG and high precordial lead ECG at 10 years

Sodium channel blockers provocative test*: start >16 years unless clinically indicated

Follow-up

Positive phenotype and/or Class IV/V variant: 1-3 years dependent on level of risk

Negative phenotype and no Class IV/V variant: Discharge

a: A phenocopy has characteristics of a genetic disease but is produced environmentally

b: Not in case of a documented type 1 Brugada pattern

Table 2. Diagnosis**ESC 2022 GI on VA and SCD. Recommendations for management of patients with Brugada syndrome*****Diagnosis***

BrS is diagnosed in patients with no other heart disease and a spontaneous type 1 Brugada ECG pattern.	I C
BrS is diagnosed in patients with no other heart disease who have survived a CA due to VF or PVT and exhibit a type 1 Brugada ECG induced by sodium channel blocker challenge or during fever.	I C
Genetic testing for SCN5A gene for probands with BrS.	I C
BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of: • Arrhythmic syncope or nocturnal agonal respiration • A family history of BrS • A family history of SD (>45 years old) with a negative autopsy and circumstance suspicious for BrS.	IIa C
BrS as a diagnosis in patients with no other heart disease who exhibit an induced type 1 Brugada ECG.	IIb C
Sodium channel blocker test is not recommended in patients with a prior type I Brugada pattern.	III C

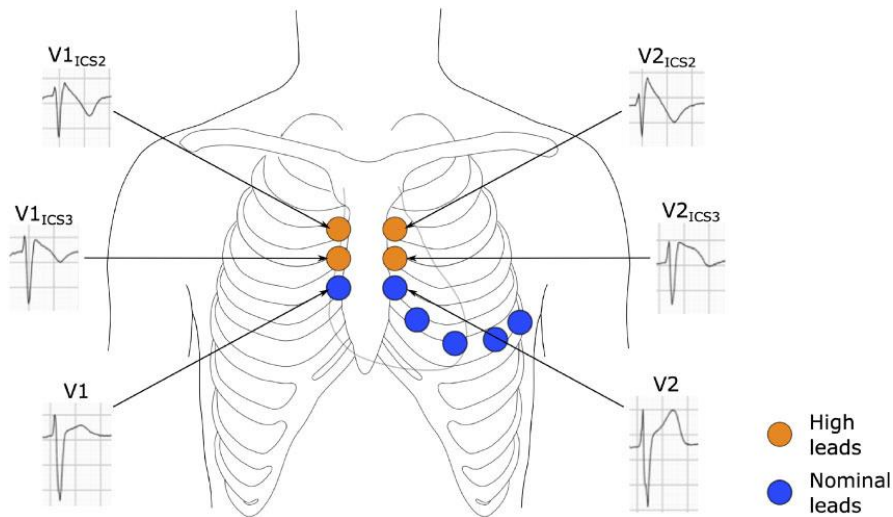


Figure 2. High lead placement and type 1 Brugada ECG pattern.

In the high lead placement, leads V1 and V2 are placed in the 3rd and 2nd ICSs; this correlates with RVOT location and increases ECG sensitivity in BrS. The ECG tracings shown were recorded from high and nominal leads V1 and V2. Type 1 Brugada ECG pattern, characterized by a coved ST-segment elevation ≥ 2 mm followed by a negative T wave, is evident in the high but not the nominal leads. V1_{ICS2}, lead V1 in the 2nd ICS; V2_{ICS2}, lead V2 in the 2nd ICS; V1_{ICS3}, lead V1 in the 3rd ICS; V2_{ICS3}, lead V2 in the 3rd ICS.

Behr ER, et al. Brugada syndrome and reduced right ventricular outflow tract conduction reserve: a final common pathway? *Eur Heart J.* 2021;42:1073-1081.

Table 3. APHRS/EHRA/HRS/SOLAECE 2015 consensus report on J-wave syndromes. Differential diagnosis and modulating factors in Brugada syndrome

A. Differential diagnosis	B. Modulating factors
• Atypical right bundle branch block • Ventricular hypertrophy • Early repolarization (especially in athletes) • Acute pericarditis/myocarditis • Acute myocardial ischemia or infarction (especially of the right ventricle) • Pulmonary thromboembolism • Prinzmetal angina • Dissecting aortic aneurysm • Central and autonomic nervous system abnormalities • Duchenne muscular dystrophy • Friedreich ataxia • Spinobulbar muscular atrophy • Myotonic dystrophy • Arrhythmogenic right ventricular dysplasia • Mechanical compression of the right ventricular outflow tract (e.g., pectus excavatum, mediastinal tumor, hemopericardium, • Hypothermia • Postdefibrillation ECG	• Electrolyte abnormalities: ◦ Hyperkalemia ◦ Hypokalemia ◦ Hypercalcemia ◦ Hyponatremia • Temperature: hyperthermia (fever), hypothermia • Hypertestosteronemia • Treatment with: ◦ Antiarrhythmic drugs: sodium channel blockers (Class IC, Class IA), calcium antagonists, beta-blockers ◦ Antianginal drugs: calcium antagonists, nitrates, potassium channel openers ◦ Psychotropic drugs: tricyclic/tetracyclic antidepressants, phenothiazines, selective serotonin reuptake inhibitor, lithium, benzodiazepines ◦ Anesthetics/analgesics: propofol, bupivacaine, procaine ◦ Others: histamine H₁ antagonist, alcohol intoxication, cocaine, cannabis, ergonovine

Antzelevitch C, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. *Europace.* 2017;19:665-694.

Table 4. Common Drugs Associated With the Brugada Syndrome

Drug Class	Drugs	Incidence of Drug- Induced Brugada Syndrome, %	Incidence of Ventricular Arrhythmias, %	Mechanism of Action
Antiarrhythmic drugs	Ajmaline	39–48.2*	0.15–1.8 (adults)* 10 (children)*	I_{Na} blockade
	Pilsicainide	...	11–18*	
	Flecainide	...	...	
	Procainamide	...	...	
	Propafenone	...	...	
Tricyclic antidepressants	Amitriptyline	2.3–15.3†	0	I_{Na} blockade
	Desipramine			
	Imipramine			
	Nortriptyline			
Anesthetics/analgesics	Bupivacaine	...	...	I_{Na} blockade
	Procaine		...	
	Propofol		...	
Miscellaneous	Alcohol	...	...	I_{CaL} blockade
	Cocaine	...	...	I_{Na} blockade
	Lithium	...	...	I_{Na} blockade
	Loxapine	...	...	I_{Na} blockade
	Oxcarbazepine	...	...	I_{Na} blockade
	Trifluoperazine	...	...	I_{Na} blockade

I_{CaL} indicates L-type calcium channel; I_{Na} , sodium channel; and ..., unknown.

*Patients with suspicion for Brugada syndrome underwent class IC antiarrhythmic challenge, primarily with ajmaline or pilsicainide, and hence represent a population with a high pretest probability. The real-world incidence of drug-induced Brugada syndrome in patients taking class I antiarrhythmic agents is not known.

†Data on the incidence of tricyclic antidepressant-induced Brugada syndrome are available only in patients with overdose. The real-world incidence of drug-induced Brugada syndrome in patients on therapeutic doses of these agents is not known.

Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation*. 2020

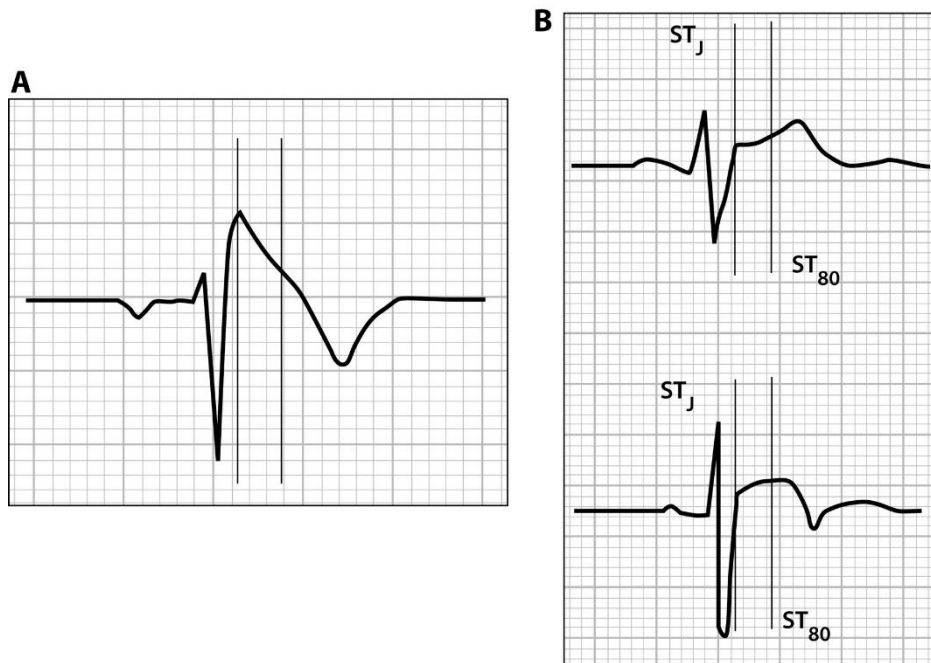


Figure 3. Differential diagnosis between representative right precordial ECG patterns from (A) a Brugada patient and (B) two trained athletes.

Vertical lines mark the J-point (STJ) and the point 80 ms after the J-point (ST80) where the amplitudes of ST-segment elevation are calculated. 'Coved' type ST-segment elevation in the patient with Brugada syndrome is characterized by a 'downsloping' elevated ST-segment with a STJ/ST₈₀ ratio of 1.9. Right precordial early repolarization patterns in both athletes show an 'upsloping' ST-segment elevation with STJ/ST₈₀ ratio <1; 0.7 for the 'concave' toward the top (B, top) and 0.68 for the 'convex' toward the top (B, bottom) ST-segment elevation.

European Association of Cardiovascular Prevention and Rehabilitation. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. Eur Heart J. 2010;31:243-59.

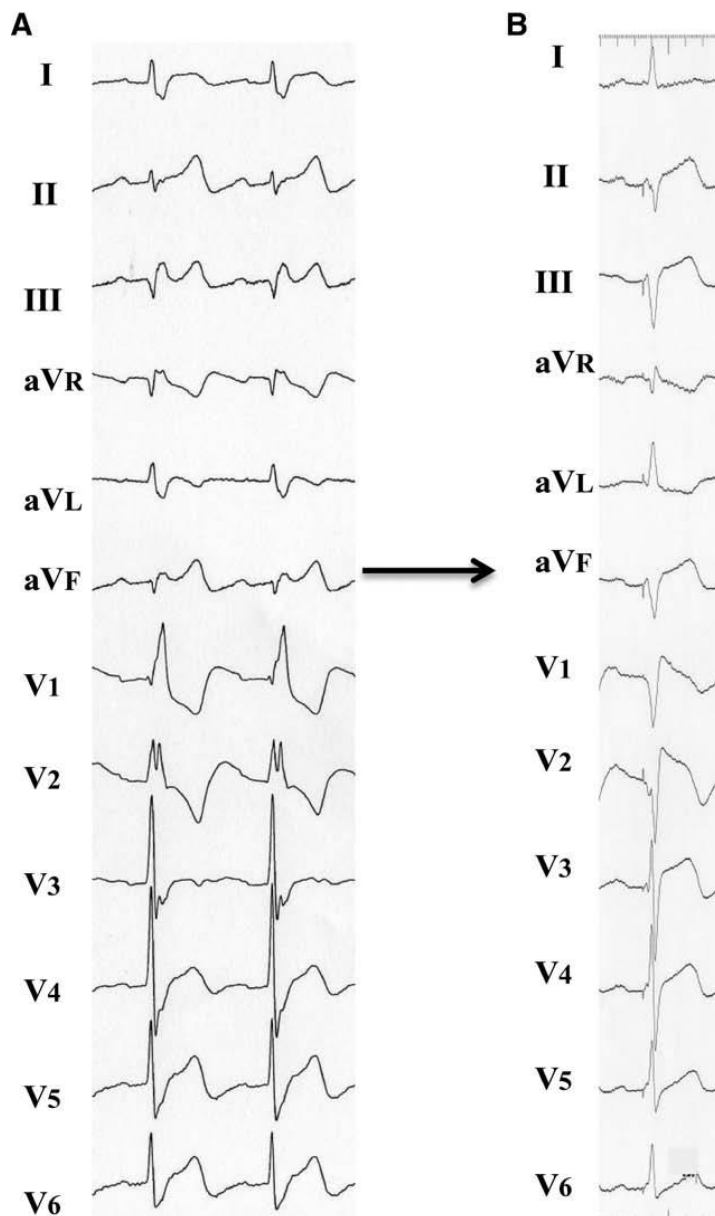


Figure 4. The complete RBBB pattern at baseline (A) was normalized by right ventricular pacing (B). The QRS became narrow with left-axis deviation, and leads V1 and V2 showed coved-type ST-segment elevation (B).

Aizawa Y, et al. Brugada syndrome behind complete right bundle-branch block. *Circulation*. 2013;128:1048-1054.

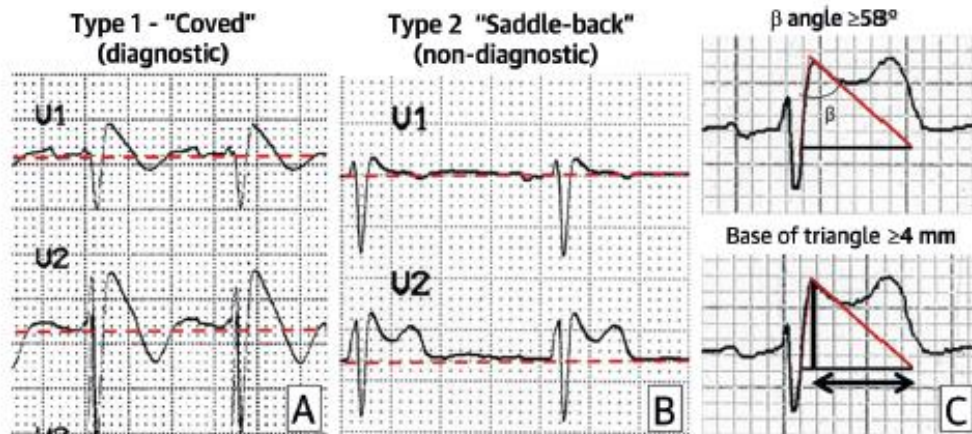


Figure 5. Electrocardiographic Patterns in Brugada Syndrome

(A) Type 1 Brugada electrocardiogram pattern showing a concave ST-segment elevation $\geq 2 \text{ mm}$ in ≥ 1 right precordial lead, followed by a negative T-wave. (B) Type 2 Brugada electrocardiogram pattern showing a convex ST-segment elevation $\geq 0.5 \text{ mm}$ (generally $\geq 2 \text{ mm}$) in ≥ 1 right precordial lead followed by a positive T-wave. (C) Additional criteria for the diagnosis of Brugada electrocardiogram pattern type 2 (top: the b angle; bottom: the length of the base triangle of the r' wave 5 mm below the maximum rise point).

Brugada J, et al. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2018;72:1046-1059.

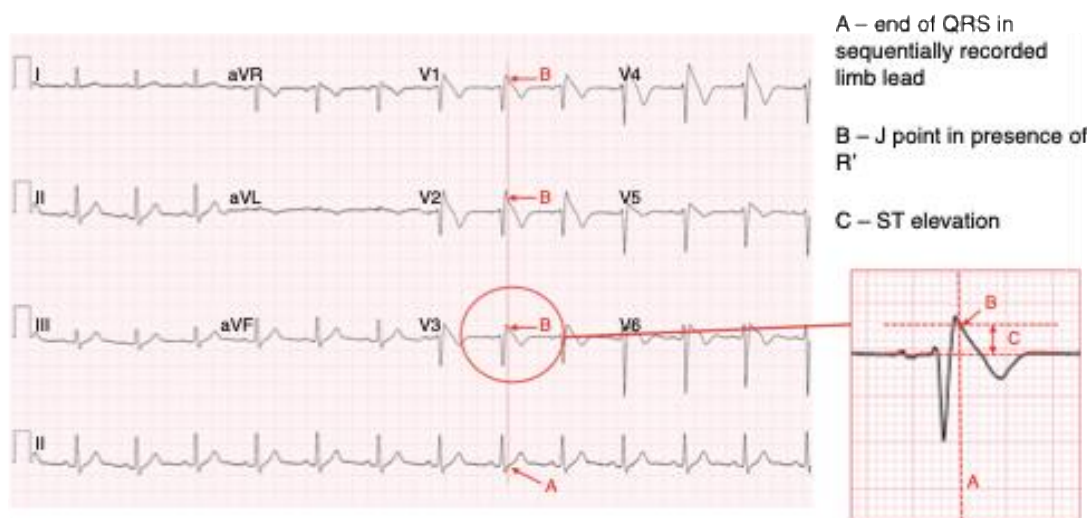


Figure 6. Identifying the J point (defined as the end of the QRS) can be challenging in the presence of R'. The end of the QRS can be identified in a sequentially recorded limb lead. The intersect (B) identifies the J point and C is the degree of ST elevation, from the isoelectric line (PQ and TP segments excluding any U wave) and J point. V1 and V2—fourth intercostal space, V3 and V4—third intercostal space, and V5 and V6—second intercostal space.

Behr ER, et al. The diagnostic role of pharmacological provocation testing in cardiac electrophysiology: a clinical consensus statement of the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC, the ESC Working Group on Cardiovascular Pharmacotherapy, the Association of European Paediatric and Congenital Cardiology (AEPC), the Paediatric & Congenital Electrophysiology Society (PACES), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). *Europace*. 2025;27.

Table 5. Genetic testing

AHA/ACC/HRS 2017 GL on VA/SCD. Brugada Syndrome

Genetic counseling and mutation-specific genetic testing in first-degree relatives of patients who have a causative mutation for Brugada syndrome. I-B-NR

Genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives of patients with suspected or established Brugada syndrome. IIb-C-EO

EHRA/HRS/APHRS/LAQRS 2022 Consensus Statement on genetic testing.

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
Brugada syndrome	+	+	+

Recommendations

Should do

Genetic testing with sequencing of SCN5A for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history.

Variant-specific genetic testing for family members and appropriate relatives following the identification of the disease-causative variant.

May do

Targeted sequencing of variant(s) of unknown significance in SCN5A with a population allele frequency $<1 \times 10^{-5}$ identified in an index case concurrently with phenotyping for family members, following genetic counselling, to assess variant pathogenicity through co-segregation analysis.

Predictive genetic testing (of pathogenic SCN5A variants) in related children from birth onward (any age).

Do not do

Rare variants in genes with a disputed or refuted gene disease clinical validity should not be reported routinely* for BrS genetic testing in a diagnostic setting.

*: Unless in a research setting.

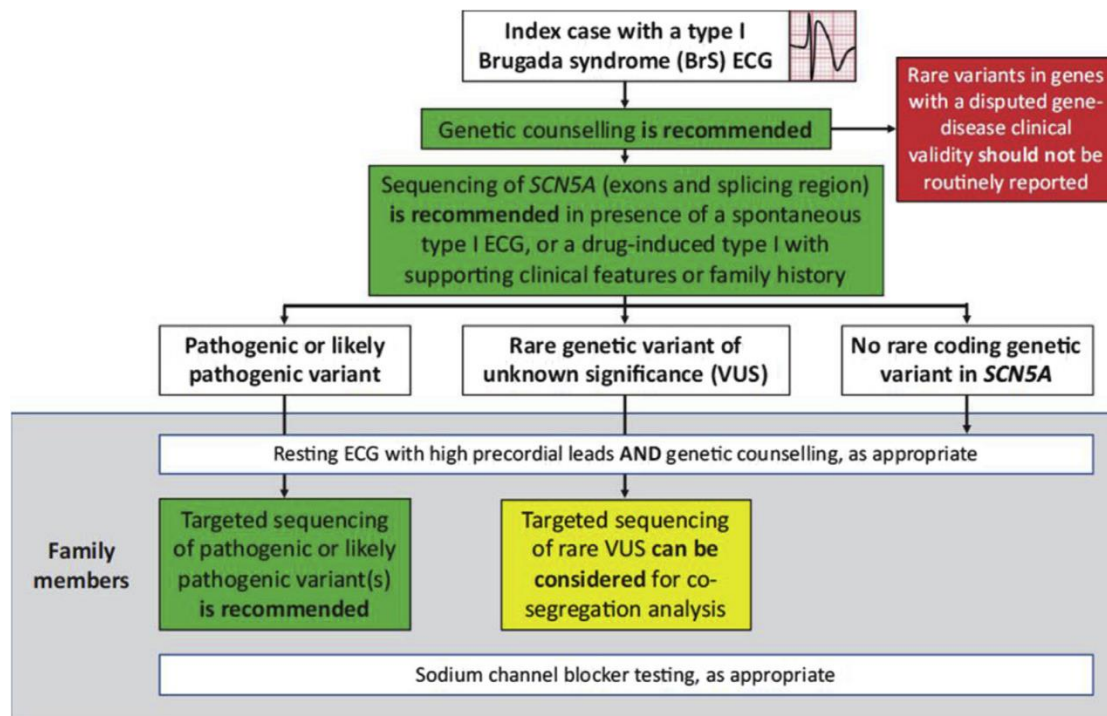


Figure 7. EHRA/HRS/APHRS/LAHRs 2022 Consensus Statement on genetic testing. Clinical algorithm for genetic testing and family screening in Brugada syndrome.

EHRA/HRS/APHRS/LAHRs. Expert Consensus Statement on the state of genetic testing for cardiac diseases. *Europace*. 2022.

Table 6. Risk factors associated with Shanghai score and Sieira scores

Shanghai Score		Sieira Score	
Risk factor	Relative value	Risk factor	Relative value
spontaneous type 1 ECG	3,5	spontaneous type 1 ECG	1
fever induced type 1 ECG	3	-	
drug induced type 1 ECG	2	-	
unexplained SCA or VF	3	SCA	4
nocturnal agonal respiration	2	-	
suspected arrhythmic syncope	2	syncope	2
unclear syncope	1	-	
atrial fibrillation or flutter < 30yo	0,5	-	
familial history of Brs *	2	-	
suspicious familial SCA *	1	-	
unexplained SCA < 45yo *	0,5	early familial SCA < 35yo	1
probable pathogenic mutation	0,5	-	
-		inducible EPS	2
-		SND	3

* in first or second degree relatives ; ECG: electrocardiogram ; SCA: sudden cardiac arrest; VF: ventricular fibrillation ; Brs: Brugada syndrome ; EPS: electrophysiological study ; SND: sinus node dysfunction

Probst V, et al. Robustness and relevance of predictive score in sudden cardiac death for patients with Brugada syndrome. *Eur Heart J*. 2020.

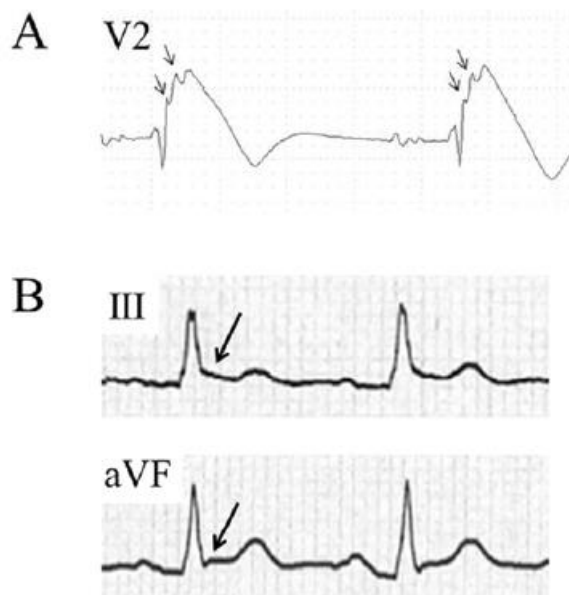


Figure 8. Representative ECGs of fragmented QRS (f-QRS) and early repolarization (ER). (A) Fragmented QRS (f-QRS) was observed in lead V2. Note that there are four spikes (arrows) in this lead. (B) Early repolarization (ER) pattern in the inferior leads.

Note that J-point elevation above the baseline (>1 mm) can be seen in leads III and aVF.

Tokioka K, et al. Electrocardiographic parameters and fatal arrhythmic events in patients with brugada syndrome: Combination of depolarization and repolarization abnormalities. *J Am Coll Cardiol*. 2014 ;63:2131-8.

Table 7. Therapy of Brugada syndrome**AHA/ACC/HRS 2017 GL on VA/SCD. Brugada Syndrome**

Observation without therapy of asymptomatic patients with only inducible type 1 Brugada pattern.	I-B-NR
ICD* in patients with spontaneous type 1 Brugada pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA.	I-B-NR
Quinidine or catheter ablation in patients experiencing recurrent ICD shocks for polymorphic VT.	I-B-NR
Quinidine or catheter ablation in patients with spontaneous type 1 Brugada pattern and symptomatic VA who either are not candidates for or decline an ICD.	I-B-NR
Pharmacological challenge using a sodium channel blocker for diagnosis in patients with suspected Brugada syndrome in the absence of a spontaneous type 1 Brugada pattern.	IIa-B-NR
Programmed ventricular stimulation using single and double extrastimuli in asymptomatic patients and a spontaneous type 1 Brugada pattern.	IIb-B-NR ^{SR}

*: if a meaningful survival of greater than 1 year is expected

ACC/AHA/HRS 2017 GL on syncope. Brugada ECG pattern and syncope

ICD in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology	IIa-B-NR
EPS in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology	IIb-B-NR
ICD is not recommended in patients with Brugada ECG pattern and reflex-mediated syncope in the absence of other risk factors	III-B-NR (no benefit)

ESC 2022 GI on VA and SCD. Recommendations for management of patients with Brugada syndrome**General recommendations**

The following is recommended in all patients with BrS:	I C
(a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org).	
(b) Avoidance of cocaine, cannabis, and excessive alcohol intake.	
(c) Treatment of fever with antipyretic drugs.	

Risk stratification, prevention of SCD and treatment of VA

ICD in patients with BrS who:	
(a) Are survivors of an aborted CA and/or	
(b) Have documented spontaneous sustained VT.	

ICD in patients with type 1 Brugada pattern and an arrhythmic syncope.	IIa C
Implantation of a loop recorder in BrS patients with an unexplained syncope.	IIa C
Quinidine in patients with BrS who qualify for an ICD but have a contraindication, decline, or have recurrent ICD shocks.	IIa C
Isoproterenol in BrS patients suffering electrical storm.	IIa C
Catheter ablation of triggering PVCs and/or RVOT epicardial substrate in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy.	IIa C
PES in asymptomatic patients with a spontaneous type I BrS ECG.	IIb B
ICD implantation in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extra stimuli.	IIb C
Catheter ablation in asymptomatic BrS patients is not recommended.	III C

BrS, Brugada syndrome; CA, cardiac arrest; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; PES, programmed electrical stimulation; PVCs, premature ventricular complexes; PVT, polymorphic ventricular tachycardia; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; SD, sudden death; VA, ventricular arrhythmia; VF, ventricular fibrillation.

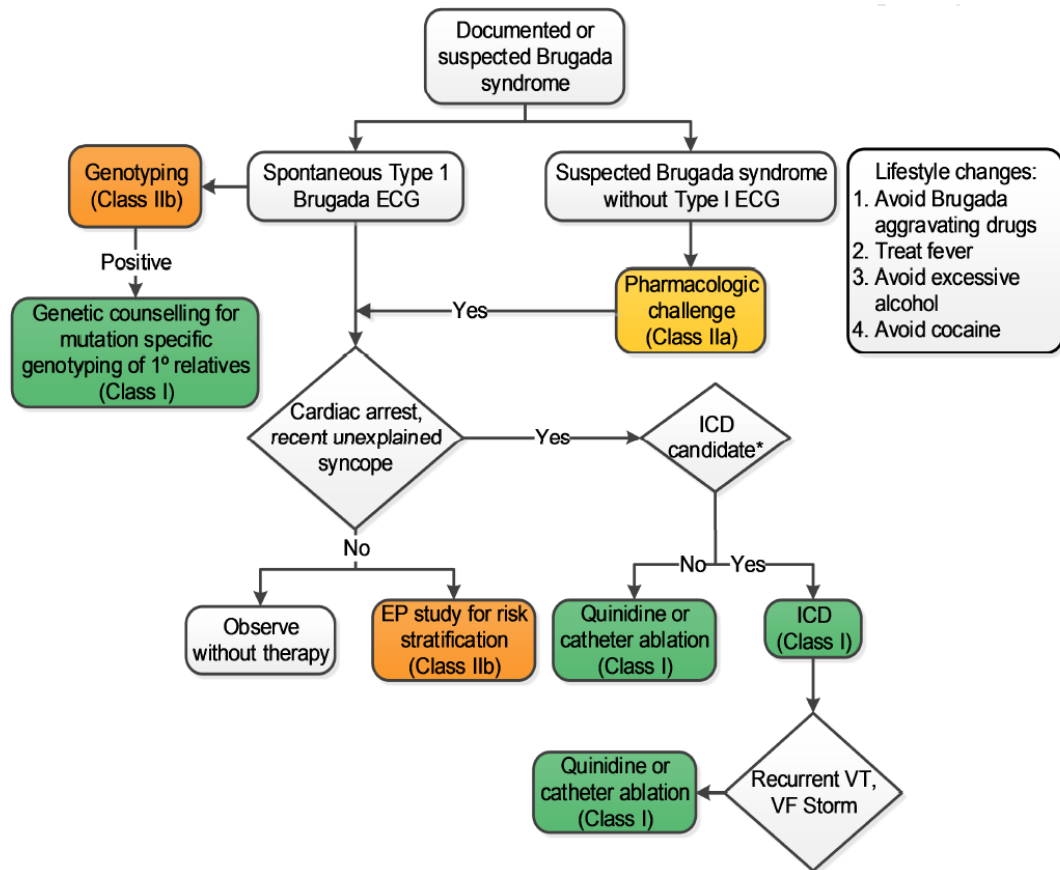


Figure 9. AHA/ACC/HRS 2017 GL on VA/SCD. Prevention of SCD in Patients With Brugada Syndrome

*ICD candidacy as determined by functional status, life expectancy or patient preference.

1° indicates primary; ECG, electrocardiogram; EP, electrophysiological; ICD implantable cardioverter-defibrillator; SCD, sudden cardiac death; VT, ventricular tachycardia; and VF, ventricular fibrillation.

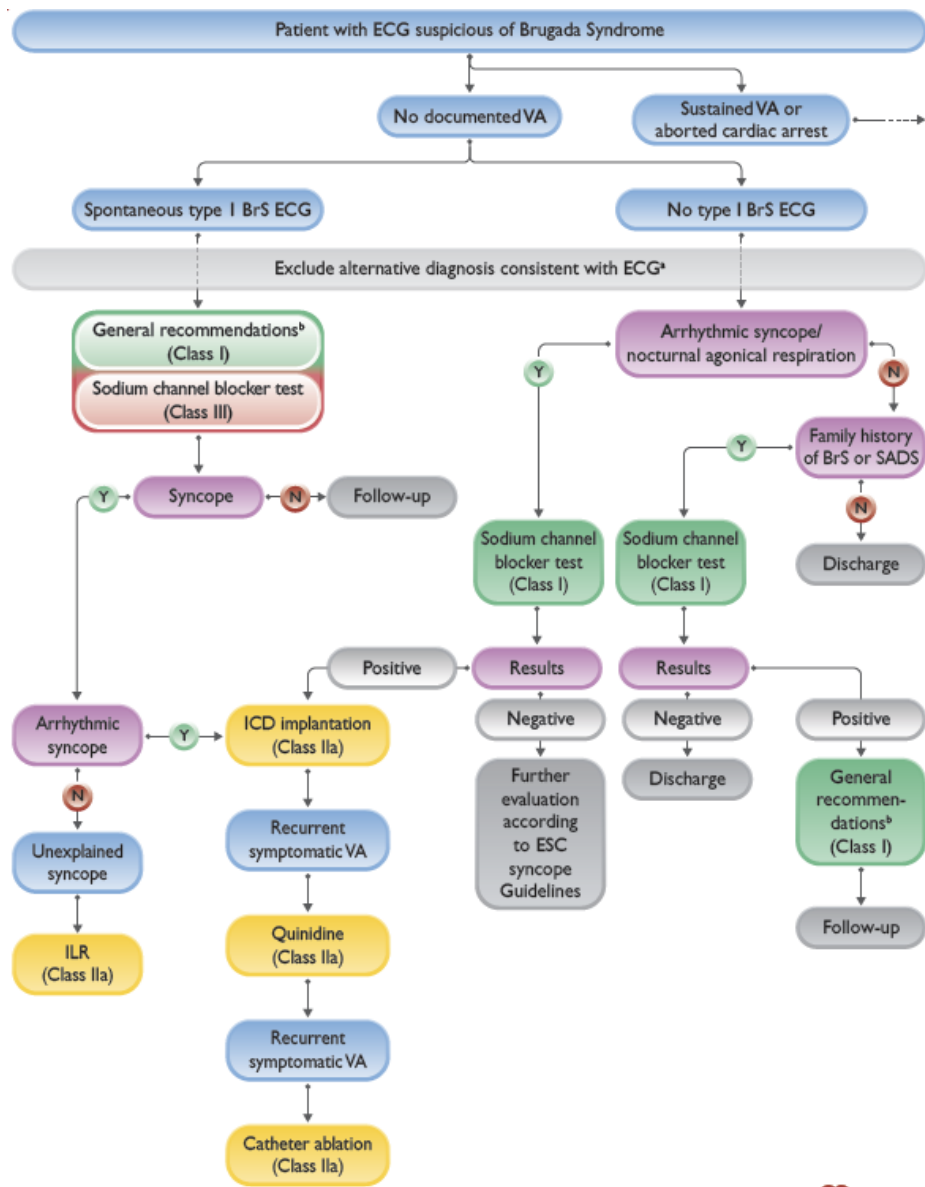


Figure 10. ESC 2022 GL on VA and SCD. Algorithm for the management of patients with Brugada pattern electrocardiogram (Parts 1 and 2).

BrS, Brugada syndrome; CA, cardiac arrest; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; N, No; SADS, sudden arrhythmic death syndrome; VA, ventricular arrhythmia; Y, Yes.

^a Echo, CMR, cardiac CT, CAG indicated according to patient clinical presentation and risk factors.

^b General recommendations: avoidance of drugs that may induce ST-segmentation elevation in right precordial leads (<http://www.brugadadrugs.org>), avoidance of cocaine and excessive alcohol intake, treatment of fever with antipyretic drugs.