Brugada syndrome or pattern: Management and approach to screening of relatives

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INTRODUCTION

The Brugada syndrome is a genetic disorder that can cause life-threatening ventricular tachyarrhythmias and thereby sudden cardiac arrest (SCA) and sudden cardiac death (SCD); patients have abnormal findings on the surface electrocardiogram (ECG) but do not usually have any apparent cardiac structural abnormalities. The prognosis and management of the Brugada syndrome along with our approach to screening first-degree relatives will be reviewed here.

The following topics discuss other aspects of Brugada syndrome in detail separately:

- (See "Brugada syndrome: Epidemiology and pathogenesis".)
- (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation".)

Other causes of SCA in patients with apparently normal hearts are discussed in detail separately. (See "Approach to sudden cardiac arrest in the absence of apparent structural heart disease".)

DEFINITIONS

The following two terms, distinguished by the presence or absence of symptoms, have been used to describe patients with the typical electrocardiogram (ECG) findings of a pseudo-right bundle branch block and persistent ST-segment elevation in leads V1 to V2 (figure 1):

- **Brugada pattern** – Patients with typical ECG features (figure 1) who are asymptomatic and have no other clinical criteria are said to have the Brugada pattern (sometimes referred to as Brugada phenocopies).

  Distinguishing Brugada syndrome from Brugada pattern is discussed separately. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Brugada pattern versus syndrome'.)

- **Brugada syndrome** – Patients with typical ECG features (figure 1) who have experienced sudden cardiac arrest (SCA) and/or sudden cardiac death (SCD) or a documented sustained ventricular tachyarrhythmia, or who have one or more of the other associated clinical criteria, are said to have the Brugada syndrome. Patients with premature ventricular beats or nonsustained ventricular tachycardia are generally not considered to have Brugada syndrome but only the Brugada pattern.

Persons with either the Brugada pattern or the Brugada syndrome can have identical findings on the surface ECG; the ECG will have one of two distinct patterns of ST elevation described below:

- **Type 1 Brugada ECG pattern** – The elevated ST segment (≥2 mm) descends with an upward convexity to an inverted T wave (figure 1). This is referred to as the "coved type" Brugada pattern.

- **Type 2 Brugada ECG pattern** – The ST segment has a "saddle back" ST-T wave configuration, in which the elevated ST segment descends toward the baseline and then rises again to an upright or biphasic T wave (figure 1).

  The definitions of SCA and SCD are presented and discussed in detail separately. (See "Overview of sudden cardiac arrest and sudden cardiac death", section on 'Definitions'.)

RISK FACTORS FOR ARRHYTHMIA OR SUDDEN CARDIAC ARREST

The management of patients with Brugada syndrome depends on their level of risk for future sustained ventricular arrhythmia, sudden cardiac arrest (SCA), or sudden cardiac death (SCD); therefore, early risk assessment is important to guide treatment strategy.

High-risk symptoms — Among patients with Brugada pattern electrocardiogram (ECG), the following symptoms represent high-risk markers for subsequent arrhythmic events and SCD:

- **SCA** – Compared with asymptomatic patients, those with a previous history of SCA have the highest risk of subsequent arrhythmic events. Two larger studies illustrate these findings [1,2]. In one series of 1029 patients (median age 45 years at diagnosis) with Brugada pattern ECG in the FINGER European Registry, 654 patients were asymptomatic and 62 had prior SCA [2]. Over a median follow-up of 32 months, patients with prior SCA were at higher risk for experiencing a future arrhythmic event compared with asymptomatic patients (7.7 versus 0.5 events per year; hazard ratio [HR] 11; 95% CI 4.8-24.3).

- **Syncope** – Compared with asymptomatic patients, those with a previous history of arrhythmic syncope (unexplained syncope suggestive of a tachyarrhythmia) have the second highest risk of subsequent arrhythmic events after those with SCA [1-4].

  - In the FINGER European Registry of 1029 patients, 313 had prior syncope [2]. Over a median follow-up of 32 months, patients with syncope were at higher risk for experiencing a future arrhythmic event compared with asymptomatic patients (1.9 versus 0.5 events per year; HR 3.4; 95% CI 1.6-7.4).

  - A separate study of 334 patients was similar in that patients with SCA had the highest risk of life-threatening arrhythmic events (SCD or documented ventricular fibrillation), followed by patients with syncope; those who were asymptomatic had the lowest risk of arrhythmic events (figure 2) [1].

- **Sustained ventricular tachycardia** – This includes any such arrythmias that are documented on 12-lead ECG or cardiac monitoring (eg, telemetry or ambulatory ECG monitors) [5]. Sustained ventricular tachycardia is assumed to have a high likelihood of leading to SCD in patients with Brugada syndrome. (See "Sustained monomorphic ventricular tachycardia: Clinical manifestations, diagnosis, and evaluation".)

Nocturnal agonal respiration is a rare finding, but if present it is also considered a high-risk symptom. Nocturnal agonal respiration can be related to sudden unexpected nocturnal death syndrome (SUNDS; also called sudden unexpected death syndrome). These conditions are described in detail separately.

Intermediate-risk factors — The following risk factors place a person at moderate risk of subsequent arrhythmic events and SCD. This is based on our clinical experience and/or supportive studies.

In our experience, **more concerning** intermediate-risk factors are:

- **Syncope that may be nonarrhythmic in origin** – A benign-sounding history of syncope origin (neurocardiogenic features) in the setting of Brugada syndrome; the pretest probability remains high such that there is an intermediate likelihood that the syncope may have been caused by an arrhythmia

The following risk factors still represent intermediate-risk factors for subsequent arrhythmic events and SCD but are less concerning than syncope:

- **Family history of SCA and/or Brugada Syndrome** – Patients with Brugada syndrome who report a familial history of SCA or SCD may be at higher risk for SCA; however, data are mixed [6-8]. In some studies, familial history was not shown to be a strong risk factor for future malignant arrythmia [6,7]. However, in a separate multicenter registry of patients with Brugada syndrome treated with implantable cardiac defibrillator (ICD), familial history of SCD was associated with arrhythmic events [8].

- **Drug-induced type 1 ECG pattern** – Some studies have suggested that a type 1 "coved type" Brugada ECG pattern is associated with increased arrhythmic risk (figure 1). (See 'Definitions' above.)

  Patients with a spontaneous type 1 ECG pattern may have a higher arrhythmic risk compared with patients who develop this pattern with a drug challenge; however, evidence is mixed [2,9,10]. A cohort of 421 patients with type 1 Brugada pattern ECG (19 percent spontaneous) were followed over a median of 63 months. Arrhythmic event rates were higher among patients with spontaneous type 1 ECG compared with a drug-induced type 1 Brugada pattern (2.3 versus 1.1 percent per year) [9].

  In the FINGER Brugada registry of 1029 patients with Brugada pattern ECGs, the arrhythmic event rate for asymptomatic patients was low (0.5 percent per year). Patients with spontaneous type 1 ECG had similar rates of arrhythmic events compared with those with drug-induced type 1 ECG pattern (0.8 versus 0.4 percent). [2].

- **Atrial fibrillation (AF)** – AF occurs more frequently in patients with the Brugada ECG pattern compared with the general population. Additionally, patients with the Brugada ECG pattern who experience AF have a higher risk of future ventricular tachyarrhythmias; this was shown in a series of 73 patients with Brugada syndrome in whom 14 percent had AF [11]. Compared with patients free of AF, those with AF had a higher incidence of syncope (60 versus 22 percent) and ventricular fibrillation (40 versus 14 percent).

Possible risk factors — Whereas male sex [3,12] and presence of inferolateral ECG abnormalities [13] may also be markers of increased risk in patients with a Brugada pattern ECG, there is limited evidence that these have clinical utility.

MANAGEMENT

General measures in all patients — All patients with Brugada syndrome or Brugada pattern electrocardiogram (ECG) in the absence of symptoms or other risk factors should undergo routine follow-up and be counseled on the following general measures aimed at preventing potential malignant arrythmia:

- **Antipyretics** – If they develop a fever for any reason, it should be promptly treated with an antipyretic agent. (See "Pathophysiology and treatment of fever in adults", section on 'Selection of antipyretic'.)

- **Avoiding specific medications** – Patients should avoid medications that are known to increase the risk of ventricular arrhythmias in patients with Brugada pattern ECG (a full list is available at www.brugadadrugs.org) [14,15]. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Drug challenge for type 2 or equivocal ECG'.)

  Selected drugs that should be avoided in patients with Brugada syndrome or pattern are summarized below:

  - **Class I antiarrhythmic drugs aside from** quinidine – In particular, sodium channel blockers may be deleterious and should not be used for therapy (eg, flecainide, ajmaline, or procainamide); these can transiently induce the characteristic type 1 ECG changes and are frequently used as part of a drug challenge to diagnose the Brugada ECG pattern (table 1) [16-20]. In addition, sodium channel blockade can induce premature ventricular beats or ventricular tachycardia in patients with Brugada syndrome, particularly in symptomatic patients (6 out of 10 in one report) [21].

  - **Some psychotropic drugs** – Tricyclic antidepressants, lithium, and oxcarbazepine should be avoided. These drugs can also cause sodium channel blockade and potentially precipitate arrhythmias.

  - **Some anesthesia medications** – Procaine, bupivacaine, and prolonged propofol infusion should be avoided.

- **Avoid excessive alcohol intake** – Patients with Brugada pattern ECG should avoid excessive alcohol intake, as this has been shown to trigger arrythmia [22,23].

High-risk patients — The treatment of high-risk patients with Brugada syndrome is primarily focused on the prevention of sudden cardiac arrest (SCA) and sudden cardiac death (SCD) through termination of any ventricular tachyarrhythmias (algorithm 1).

Initial therapy with implantable cardiac defibrillator — For high-risk patients with the Brugada syndrome (ie, those who have survived SCA or those with a history of syncope from ventricular tachyarrhythmias), we recommend an implantable cardiac defibrillator (ICD) rather than antiarrhythmic drug therapy. (See 'High-risk symptoms' above.)

This recommendation is consistent with society guidelines published in 2013 and 2017 (algorithm 2) and is endorsed by numerous professional societies and experts worldwide [5,24-26].

Patients with the Brugada syndrome who experience recurrent ventricular arrhythmias resulting in ICD shocks may require additional therapy with an antiarrhythmic drug or catheter ablation to reduce the frequency of ICD shocks. (See 'Patients with ICD with high arrhythmic burden' below.)

We approach treatment of patients with sudden unexpected nocturnal death syndrome (SUNDS; also called sudden unexpected death syndrome) in an identical fashion as patients with Brugada syndrome with high-risk features. (See 'High-risk symptoms' above.)

In patients with the Brugada syndrome, ICDs are effective for terminating life-threatening arrhythmias [5,8,17,27-29]. While several studies have looked at the effectiveness of ICD therapy in patients with the Brugada syndrome, there are no randomized trials comparing ICDs with antiarrhythmic drug therapy (or no drug therapy) in patients with Brugada syndrome.

Evidence for efficacy of ICDs for specific patient subgroups includes the following:

- **Efficacy**

  - **Adult patients** – In a 2019 meta-analysis of 1539 patients from 28 nonrandomized studies, 79 percent had an ICD for primary prevention after a mean follow-up of nearly five years; 18 percent of patients received an appropriate shock [29]. There was a very low cardiac mortality rate of 0.03 per 100 patient-years. A caveat is that present programming methods that have reduced inappropriate shocks in several other conditions were not routinely applied in most of the studies included in the 2019 meta-analysis. Another study with a longer follow up of 10 years described higher rates of

appropriate shocks, ranging from 19 percent for patients with an ICD placed for syncope to 48 percent for patients with an ICD placed for SCA [30].

- **Pediatric patients** – In one series of 35 patients ≤20 years of age (mean age 14 years, 92 percent symptomatic) who underwent ICD implantation and were followed for an average of 7.3 years, 26 percent received appropriate ICD therapy [31]. Nine percent of patients died in an electrical storm, 20 percent experienced inappropriate shocks, and 14 percent had device-related complications.

- **Patients with SUNDS** – ICD therapy is also beneficial for patients with SUNDS. In the DEBUT trial, which randomized 66 patients who were considered definite or probable SUNDS survivors to treatment with an ICD or beta blockers, the trial was prematurely terminated after a mean follow-up of 24 months because of four deaths in the beta blocker arm, compared with none in the ICD arm [32]. Seven patients in the latter group had recurrent ventricular fibrillation that was appropriately terminated by the ICD.

- **Complications** – Although ICD therapy is generally safe in patients with Brugada syndrome, the following complications have been described in this patient population:

  - **Inappropriate ICD shocks** – In patients with Brugada syndrome who have an ICD, the rate of inappropriate shocks is relatively high. In a metanalysis of 1539 nonrandomized studies, 18 percent received inappropriate shocks after an average of 2.5 years [29]. Another cohort study of 378 patients with Brugada syndrome who had an ICD showed that 37 percent received an inappropriate shock after an average of 13 years [30].

  - **Lead complications** – In a series of 41 adult patients with Brugada syndrome, 20 percent had a lead-related complication (eg, lead fracture, subclavian stenosis, lead dislodgement, lead/ device infection) [33]. In a separate series of 35 pediatric patients with Brugada syndrome who underwent ICD implantation (mean age 14 years), 29 percent had a lead complication (including three with lead fractures and one patient with lead dislodgement) [31].

  It is uncertain whether a subcutaneous ICD system reduces the risk of some lead complications in patients with Brugada syndrome. (See "Subcutaneous implantable cardioverter defibrillators".)

  The periprocedural and long-term complications of ICDs are described in detail separately. (See "Implantable cardioverter-defibrillators: Overview of indications, components, and

functions", section on 'Complications' and "Cardiac implantable electronic devices: Long-term complications".)

Alternative initial therapy with antiarrythmics — Pharmacologic therapy for ventricular tachyarrhythmia prevention is not usually first-line therapy for patients at high risk of SCA; this approach has been tried in the Brugada syndrome with relatively little success. The exception is if the patient is not a suitable candidate for an ICD or does not want to have one placed after a detailed shared decision-making discussion. (See "Implantable cardioverter-defibrillators: Overview of indications, components, and functions", section on 'ICD not recommended'.)

In both circumstances, we suggest initial therapy with either quinidine or amiodarone, although catheter ablation is also an option. (See 'Catheter ablation' below.)

For patients with Brugada syndrome, there have not been any clinical trials comparing initial antiarrhythmic therapy with initial ICD placement.

The evidence for efficacy of quinidine and amiodarone in patients with Brugada syndrome is largely extrapolated from studies of these medications in other ventricular tachyarrhythmia syndromes. The doses and rationale for the use of these medications in patients with Brugada syndrome are described as follows:

- Quinidine – The dose is 1 to 1.5 g/day of quinidine sulfate or 600 to 900 mg/day of hydroquinidine (not available in the United States), typically divided into two or three equal daily doses. Small studies have suggested that lower doses of quinidine (300 to 600 mg/day) may be effective in some patients [34].

  The beneficial effect of quinidine may be mediated by its blockade of I_{to}, which is a transient outward electrical current in myocardial cells. This current may promote premature ventricular beats that act as the trigger for ventricular tachycardia or fibrillation [35].The potential efficacy of quinidine in patients with Brugada syndrome has been shown only in small series of patients. In one study, invasive electrophysiologic testing was performed on 25 patients with Brugada pattern ECGs (15 symptomatic and 10 asymptomatic) before and after treatment with quinidine bisulfate (mean dose 1.4 g/per day) [36]. Ventricular fibrillation was inducible in all patients at baseline compared with only three patients after quinidine loading. In the 19 patients who continued treatment with quinidine for an average of 56 months, none had a ventricular arrhythmia or arrhythmic syncope. In another small study of 50 patients who completed a 36-month, double-blind, placebo-controlled study of hydroquinidine (with crossover to the other group for all patients at 18 months), there were no arrhythmic events in the

hydroquinidine group while on treatment [37]. However, 26 percent of patients stopped the medication due to side effects.

Adverse effects of quinidine are discussed in detail separately. (See "Major side effects of class I antiarrhythmic drugs", section on 'Quinidine'.)

- Amiodarone – The dose is 200 mg daily after an appropriate initial loading dose (typically 400 mg twice daily or 200 mg three times daily for one to two weeks).

  Amiodarone is the most effective agent for the prevention of ventricular tachyarrhythmias, although there are more potential side effects with its use than with most other antiarrhythmic agents, particularly in younger patients in whom therapy might be expected to last for decades. The efficacy of amiodarone for treatment of ventricular arrythmias is discussed in greater detail elsewhere. (See "Amiodarone: Clinical uses", section on 'Amiodarone for ventricular arrhythmias' and "Amiodarone: Adverse effects, potential toxicities, and approach to monitoring".)

Patients with ICD with high arrhythmic burden — In patients with an ICD for Brugada syndrome who have recurrent arrhythmias resulting in repeated or concerning ICD shocks, we suggest catheter ablation of arrhythmogenic substrate in the right ventricular outflow tract and right ventricular free wall. Therapy with quinidine or amiodarone is also an option. (See 'Catheter ablation' below.)

In some patients, both catheter ablation and antiarrhythmic therapy may be required to terminate arrhythmia.

Catheter ablation — Radiofrequency catheter ablation for ventricular arrhythmias in patients with the Brugada syndrome can effectively reduce the burden of ventricular arrhythmias and is endorsed as a treatment option (along with quinidine) for patients with or without an ICD who experience recurrent ventricular tachyarrhythmias [26]. We also consider radiofrequency catheter ablation for patients with a Brugada syndrome and significant arrhythmic burden in whom antiarrhythmic drugs have failed. Catheter ablation may also be considered as first-line therapy in patients with a large arrhythmia burden. (See "Overview of catheter ablation of cardiac arrhythmias".)

Radiofrequency ablation of the right ventricular substrate in these patients should be performed at centers experienced in epicardial mapping and ablation.

In patients with Brugada syndrome, observational and nonrandomized trials have shown that catheter ablation is effective at treating ventricular arrhythmia and normalizing ECG [38,39].

Evidence suggests that therapy needs to be individualized and that shared decision-making is important in guiding treatment.

In a large single-cohort procedural study of 135 symptomatic patients with Brugada syndrome, after catheter ablation, patients no longer demonstrated Brugada pattern on ECG and did not have inducible ventricular tachycardia or ventricular fibrillation [39]. Similarly, in the more recent BRAVO trial, 159 patients with Brugada syndrome and spontaneous ventricular fibrillation who underwent percutaneous epicardial substrate ablation had a decrease in ventricular fibrillation burden and frequency of ICD shocks (1.1±2.1 per month before to 0.003±0.14 per month after the last ablation) [40]. Normalization of type 1 Brugada ECG after ablation was seen in 83 percent after one procedure and 94 percent after all procedures and was associated with freedom from ventricular fibrillation (hazard ratio 0.078; 95% CI 0.008-0.753). There were no arrhythmic or cardiac deaths. Complications included hemopericardium in 2.5 percent of patients.

A previous systematic review of 22 nonrandomized studies included 233 patients who underwent catheter ablation for symptomatic Brugada syndrome. The efficacy of ablation differed according to mapping and ablation approach [38]. Epicardial mapping with substrate ablation was shown to be highly effective at eliminating ventricular arrhythmia in 97 percent of patients, ventricular fibrillation triggering-premature ventricular contraction ablation was effective in 80 percent, and endocardial mapping with substrate ablation in only 71 percent of patients.

Drug therapy — Quinidine and amiodarone are two antiarrhythmic options for the treatment of ventricular tachyarrhythmias in patients with the Brugada syndrome who have recurrent arrhythmias resulting in ICD shocks [5,34,36]. While either drug may be effective, we suggest initial adjunctive therapy with quinidine for most patients with ICDs, particularly younger patients in whom there is a desire to avoid the potential toxicities associated with long-term amiodarone. The doses of and rationale for the use of quinidine and amiodarone are discussed above. (See 'Alternative initial therapy with antiarrythmics' above.)

Adverse effect of quinidine and amiodarone are presented separately. (See "Major side effects of class I antiarrhythmic drugs", section on 'Quinidine' and "Amiodarone: Adverse effects, potential toxicities, and approach to monitoring".)

Intermediate-risk patients — For patients Brugada pattern ECG and intermediate-risk factors for future arrythmia and SCA, we perform shared decision-making and consider further risk stratification with a signal averaged ECG, possible electrophysiologic study, and other tests (ie, cardiac monitoring) to further guide diagnosis and therapy. (See "Brugada syndrome: Clinical

presentation, diagnosis, and evaluation", section on 'Risk stratification for those with uncertain diagnosis' and 'Risk factors for arrhythmia or sudden cardiac arrest' above.)

The reason that shared decision-making is important is because tests such as signal-averaged ECG and electrophysiologic studies do not always lead to a definitive diagnosis; they may also have spurious results that could lead to treatments with potential complications and/or adverse effects (eg, ICD or antiarrhythmic medications). For example, although ICDs can prevent SCA/SCD in patients with Brugada syndrome, the rate of inappropriate shocks is relatively high, and therefore when the diagnosis of Brugada syndrome is uncertain, placement of an ICD could have a low ratio of potential benefit relative to harm.

If a patient with suspected Brugada syndrome has intermediate-risk factors for subsequent arrhythmic events, we may perform further risk stratification prior to making therapeutic decisions. This is consistent with 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) expert consensus statement [5]. (See 'Intermediate-risk factors' above.)

If after electrophysiologic study a patient has confirmed Brugada syndrome, we place an ICD and treat the patient as having Brugada syndrome with high-risk features. If a patient has a negative electrophysiologic study, we perform routine follow-up. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Electrophysiology testing'.)

Management of patients with Brugada pattern — In contrast to patients with the Brugada syndrome or SUNDS, asymptomatic patients with only the Brugada ECG pattern and no high- or intermediate-risk factors do **not** require any specific therapy other than the general measures described in detail separately. (See 'General measures in all patients' above.)

ALTERNATIVE APPROACHES: OTHER GUIDELINE GROUPS

Several professional societies have discussed their approach to the treatment of patients with the Brugada syndrome [5,17,26,41]. These approaches are largely consistent with our approach, but there are also some key differences.

Similar to our approach, the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRA) most strongly recommend implantable cardioverter-defibrillator (ICD) for patients with Brugada syndrome who have survived sudden cardiac arrest (SCA) or who have documented spontaneous sustained ventricular tachycardia [5]. (See 'High-risk symptoms' above and 'Initial therapy with implantable cardiac defibrillator' above.)

The HRS/EHRA/APRA recommendation for ICD implantation for patients with Brugada pattern electrocardiogram (ECG) and a history of syncope is less strong compared with ours. Also, this guideline does not advocate for a role of considering family history of SCA/sudden cardiac death (SCD) or Brugada syndrome in risk stratification, whereas we consider family history an intermediate-risk factor, and we may use this as a reason to perform further risk stratification (in the context of shared decision-making). (See 'Intermediate-risk patients' above.)

Also different from our approach, the second consensus conference on Brugada syndrome, endorsed in 2005 by the HRS and the EHRA, recommended ICD implantation for nearly all patients with the Brugada syndrome, including many with asymptomatic patients [17].

SCREENING RELATIVES

Because of relatively limited data regarding the best approach to screening of first-degree relatives, guidance is primarily based on expert opinion [26].

Clinical and ECG screening — Since Brugada syndrome follows an autosomal dominant genetic pattern with variable penetrance, all first-degree relatives of patients with confirmed Brugada syndrome should undergo screening with a clinical history and 12-lead electrocardiogram (ECG). The clinical history should carefully screen for any prior episodes of syncope, and the 12-lead ECG should be carefully scrutinized for findings characteristic of the Brugada ECG pattern (figure 1).

Genetic testing — We suggest genetic testing for all patients with Brugada syndrome, and if a pathogenic variant is identified, we test all first-degree relatives. We advocate a strategy of testing the proband, then performing targeted genetic testing of family members only if testing of the proband is positive for a known associated mutation. Pathogenic variants in potassium channels are less commonly seen in patients with Brugada syndrome [42]. Pathogenic variants in sodium channel genes can lead to some of the ECG and clinical manifestations of Brugada syndrome; this is discussed in detail separately. (See "Brugada syndrome: Epidemiology and pathogenesis", section on 'Genetics'.)

Still, we do not advocate universal genetic testing of asymptomatic first-degree relatives of patients with confirmed Brugada syndrome, as evidence does not support this approach [43]. In a study of 2022 patients who underwent DNA sequencing for an inherited arrythmia syndrome, 63 persons had a potentially pathogenic variant in *SCN5A* and/or *KCNH2* genes. Patients with potentially pathogenic variants had a similar rate of arrhythmia diagnosis (17 versus 13 percent) compared with patients without these variants [43].

Repeat screening — For first-degree relatives of a patient with Brugada syndrome who initially screen negative, we repeat screening with a clinical history and ECG every one to two years. This is because a Brugada ECG may not develop until later in life. We decrease the frequency of screening after the fifth decade of life, when the incidence of new-onset Brugada syndrome is lower. However, lifelong vigilance for syncope is required in patients with a family history of Brugada.

While provocative pharmacologic testing is also available, we do not perform this part of the screening process for the majority of the first-degree relatives that we screen. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Drug challenge for type 2 or equivocal ECG'.)

Management based on screening result — The management of first-degree relatives of patients with Brugada syndrome depends on the results of screening.

- **Positive results** – Screening may identify patients with both symptomatic Brugada syndrome and asymptomatic Brugada pattern ECGs. The management of relatives at this point is similar to other patients determined to have suspected or confirmed Brugada syndrome. (See 'Risk factors for arrhythmia or sudden cardiac arrest' above and 'Management' above.)

- **Negative results** – Screening may identify patients in whom Brugada syndrome (and Brugada pattern ECG) can be confidently excluded:

  First-degree relatives with no history of syncope and a normal ECG are considered to have a negative screening result. These patients should undergo repeat screening with a clinical history and ECG every one to two years until at least the fifth decade of life, since a Brugada ECG may not develop until later in life. (See 'Screening relatives' above.)

- **Indeterminate results** – Screening may identify patients in whom Brugada syndrome (and Brugada pattern ECG) can neither be diagnosed nor confidently excluded. In such patients, additional testing or ongoing surveillance is needed.

  - First-degree relatives with a history of syncope of suspected arrhythmic origin and a type 2 Brugada ECG pattern or a normal ECG should undergo drug-challenge testing. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Drug challenge for type 2 or equivocal ECG'.)

- First-degree relatives with a concerning history of syncope but a normal-appearing ECG have an indeterminate screening result but may continue to have a high suspicion for the Brugada syndrome. Such patients should have ongoing screening with serial ECGs performed over three to four visits over the course of one to two years.

  First-degree relatives with indeterminate screening should also be considered for provocative testing with a pharmacologic challenge. A negative drug challenge has a specificity of 94 percent and negative predictive value of 83 percent in a similar population, and therefore a negative test makes Brugada syndrome unlikely, and ongoing screening is not mandatory in such patients [20]. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Drug challenge for type 2 or equivocal ECG'.)

  Since the diagnostic ECG changes of Brugada syndrome can appear later in life (in the fourth and fifth decade), symptomatic younger patients (ie, in their teens or 20s) with a first-degree relative with Brugada syndrome should continue to receive annual screening ECGs.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Inherited arrhythmia syndromes" and "Society guideline links: Cardiac implantable electronic devices".)

SUMMARY AND RECOMMENDATIONS

- **Risk factors for arrythmia of sudden cardiac arrest (SCA)** – The most important prognostic risk factors for patients with the Brugada electrocardiogram (ECG) pattern or Brugada syndrome are history of prior SCA, syncope from ventricular tachyarrhythmia, and/or documented sustained ventricular tachycardia. The risk of having a later ventricular arrhythmia is much lower in asymptomatic patients with Brugada pattern ECGs, although subgroups of asymptomatic patients with increased risk can be identified. (See 'Risk factors for arrhythmia or sudden cardiac arrest' above.)

- **General measures** – If a patient has Brugada pattern ECG or Brugada syndrome, we counsel them to treat fevers with antipyretics, to avoid medications that provoke Brugada ECG changes, and to avoid excessive alcohol consumption. (See 'General measures in all patients' above.)

- **Management of high-risk patients** – Treatment for patients diagnosed with the Brugada syndrome is primarily focused on prevention of SCA (algorithm 2 and algorithm 1). (See 'Initial therapy with implantable cardiac defibrillator' above.)

  - **Initial therapy** – For patients with the Brugada syndrome who have survived SCA or those with a history of syncope from ventricular tachyarrhythmias, we recommend implantation of an implantable cardioverter-defibrillator (ICD) rather than antiarrhythmic drug therapy (**Grade 1A**). (See 'Initial therapy with implantable cardiac defibrillator' above.)

  - **Alternative initial therapy with antiarrhythmics** – In patients who refuse ICD implantation or are not considered a candidate for ICD implantation due to reduced life expectancy or significant comorbidities, we suggest initial therapy with either quinidine or amiodarone (**Grade 2C**). (See 'Alternative initial therapy with antiarrythmics' above.)

  - **High arrhythmic burden** – In patients with an ICD who have recurrent arrhythmias resulting in ICD shocks, we suggest catheter ablation of arrhythmogenic substrate in the right ventricular outflow tract and right ventricular free wall. (**Grade 2C**). Therapy with quinidine or amiodarone is also an option. (See 'Catheter ablation' above.)

- **Intermediate-risk patients** – For these patients, we perform shared decision-making and consider further risk stratification with signal-averaged ECG, electrophysiologic study, and possibly other tests in order to further guide therapy. (See 'Intermediate-risk patients' above and "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Risk stratification for those with uncertain diagnosis'.)

- **Patients with Brugada pattern ECG who are asymptomatic** – For patients with the Brugada ECG pattern who are otherwise asymptomatic and have none of the criteria that would suggest Brugada syndrome (ie, family history of sudden cardiac death [SCD] or type 1 Brugada ECG pattern), we recommend no treatment (algorithm 1) (**Grade 1B**). (See 'Intermediate-risk patients' above.)

  In these patients, we perform general measures. (See 'General measures in all patients' above.)

- **First-degree relatives** – Since Brugada syndrome follows an autosomal dominant genetic pattern with variable penetrance, all first-degree relatives of patients with confirmed Brugada syndrome should undergo screening with a clinical history and 12-lead ECG. While provocative pharmacologic testing and genetic testing are available, we do not

proceed with these tests as part of the screening process for the majority of patients. (See 'Screening relatives' above.)

For first-degree relatives of a patient with Brugada syndrome who initially screen negative, we repeat screening with a clinical history and ECG every year, since a Brugada ECG may not develop until later in life.

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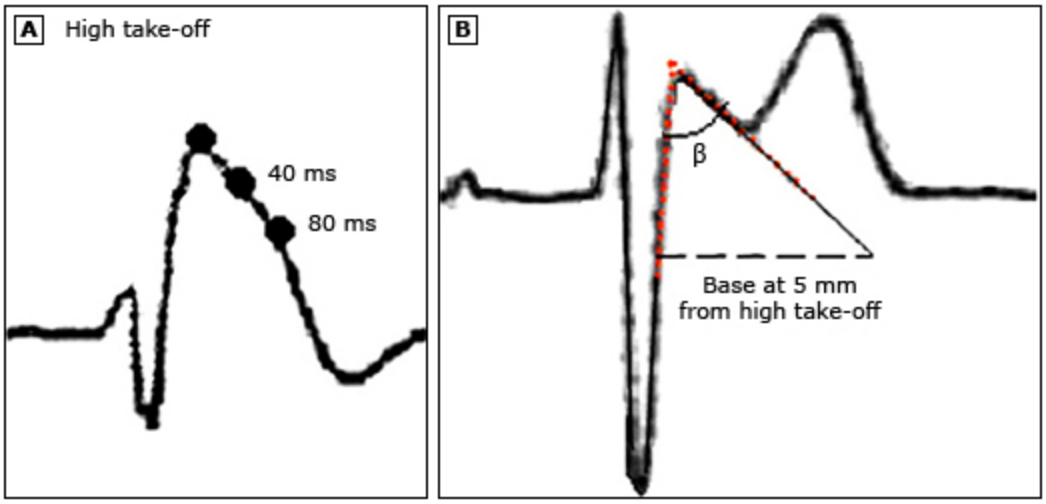
Topic 106760 Version 30.0

GRAPHICS

ECG patterns of Brugada syndrome in leads V1-V2



(A) This typical **coved pattern** present in V1-V2 shows the following:

1. At the end of QRS, an ascending and quick slope with a high take-off ≥2 mm followed by concave or rectilinear downsloping ST. There are few cases of coved pattern with a high take-off between 1 and 2 mm.
2. There is no clear r' wave.
3. The high take-off often does not correspond with the J point.
4. At 40 milliseconds of high take-off, the decrease in amplitude of ST is ≤4 mm. In RBBB and athletes, it is much higher.
5. ST at high take-off N ST at 40 milliseconds N ST at 80 milliseconds.
6. ST is followed by negative and symmetric T wave.
7. The duration of QRS is longer than in RBBB, and there is a mismatch between V1 and V6.

(B) This typical **saddle-back pattern** present in V1-V2 shows the following:

1. High take-off of r' (that often does not coincide with J point) ≥2 mm.
2. Descending arm of r' coincides with beginning of ST (often is not well seen).
3. Minimum ST ascent ≥0.5 mm.
4. ST is followed by positive T wave in V2 (T peak N ST minimum N 0) and of variable morphology in V1.
5. The characteristics of triangle formed by r' allow to define different criteria useful for diagnosis.
   - β angle.
   - Duration of the base of the triangle of r' at 5 mm from the high take-off greater than 3.5 mm.
6. The duration of QRS is longer in BrP type 2 than in other cases with r' in V1, and there is a mismatch between V1 and V6.

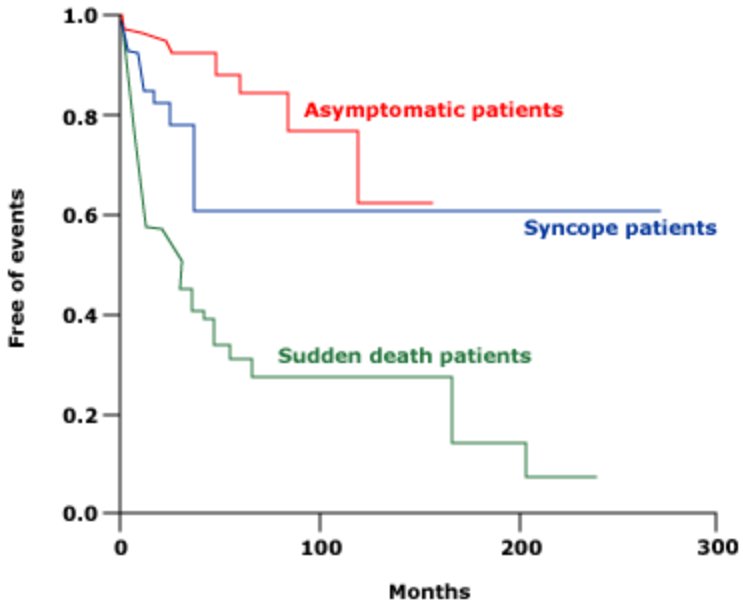
RBBB: right bundle branch block.

Reproduced from: Bayés de Luna A, Brugada J, Baranchuk A, et al. Current electrocardiographic criteria for diagnosis of Brugada

pattern: a consensus report. J Electrocardiol 2012; 45:433. Illustration used with the permission of Elsevier Inc. All rights reserved.

Graphic 91152 Version 2.0

Outcome of patients with Brugada syndrome depends upon the clinical presentation



In a study of 334 patients with the Brugada syndrome, the incidence of arrhythmic events (sudden cardiac death or documented ventricular fibrillation) during follow-up depended upon the clinical presentation. The outcome was best for those who were asymptomatic and presented with an abnormal ECG, intermediate for those presenting with syncope, and worst in patients with aborted sudden cardiac death.

ECG: electrocardiogram.

Data from: Brugada J, Brugada R, Antzelevitch C, et al. Circulation 2002; 105:73.

Graphic 80714 Version 4.0

Revised (2018) Vaughan Williams classification of antiarrhythmic drugs abridged table

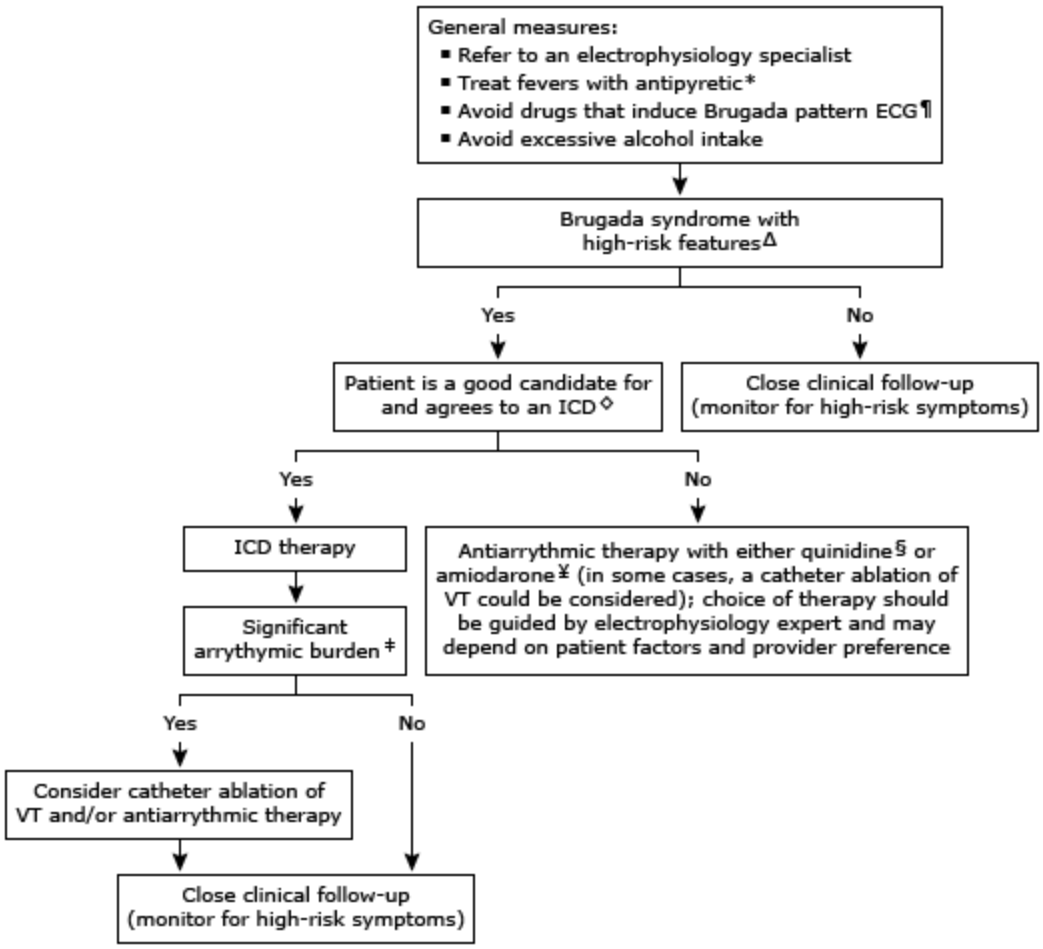
Class 0 (HCN channel blockers)
Ivabradine
Class I (voltage-gated Na+ channel blockers)
Class Ia (intermediate dissociation):
▪ Quinidine, ajmaline, disopyramide, procainamide
Class Ib (rapid dissociation):
▪ Lidocaine, mexilitine
Class Ic (slow dissociation):
▪ Propafenone, flecainide
Class Id (late current):
▪ Ranolazine
Class II (autonomic inhibitors and activators)
Class IIa (beta blockers):
▪ Nonselective: carvedilol, propranolol, nadolol
▪ Selective: atenolol, bisoprolol, betaxolol, celiprolol, esmolol, metoprolol
Class IIb (nonselective beta agonists):
▪ Isoproterenol
Class IIc (muscarinic M2 receptor inhibitors):
▪ Atropine, anisodamine, hyoscine, scopolamine
Class IId (muscarinic M2 receptor activators):
▪ Carbachol, pilocarpine, methacholine, digoxin
Class IIe (adenosine A1 receptor activators):
▪ Adenosine
Class III (K+ channel blockers and openers)
Class IIIa (voltage dependent K+ channel blockers):
▪ Ambasilide, amiodarone, dronedarone, dofetilide, ibutilide, sotalol, vernakalant

Class IIIb (metabolically dependent K+ channel openers):
▪ Nicorandil, pinacidil
Class IV (Ca++ handling modulators)
Class IVa (surface membrane Ca++ channel blockers):
▪ Bepridil, diltiazem, verapamil
Class IVb (intracellular Ca++ channel blockers):
▪ Flecainide, propafenone
Class V (mechanosensitive channel blockers):
No approved medications
Class VI (gap junction channel blockers)
No approved medications
Class VII (upstream target modulators)
Angiotensin converting enzyme inhibitors
Angiotensin receptor blockers
Omega-3 fatty acids
Statins

HCN: hyperpolarization-activated cyclic nucleotide-gated; Na: sodium; K: potassium; Ca: calcium.

Graphic 120433 Version 3.0

Treatment of adult patients with Brugada syndrome



ECG: electrocardiogram; ICD: implantable cardioverter-defibrillator; VT: ventricular tachycardia; NSAID: nonsteroidal anti-inflammatory drug.

* Acetaminophen preferred; NSAID may be added if needed in absence of risk factors for NSAID toxicity.

¶ Refer to UpToDate content for further information. Full list of drugs to be avoided is available at https://www.brugadadrugs.org/.

Δ High-risk features include sudden cardiac arrest, arrhythmogenic syncope, documented sustained VT, and family history of Brugada syndrome.

◇ Refer to UpToDate content for further information regarding patients who are good candidates for ICDs.

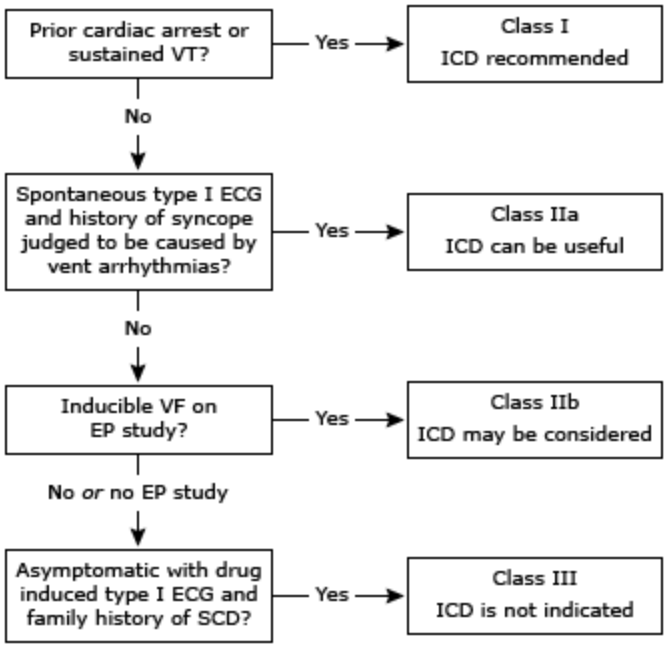
§ Quinidine oral dose is 1 to 1.5 g/day of quinidine sulfate or 600 to 900 mg/day of hydroquinidine (not available in the United States), typically divided into three to four equal daily doses. Small studies have suggested that lower doses of quinidine sulfate (300 to 600 mg/day) may be effective in some patients. Strength of quinidine products available outside the United States may be expressed as salt or quinidine base; refer to local labeling for equivalence before use.

¥ Amiodarone oral dose is 200 mg daily after an initial oral loading dose (typically 400 mg twice daily or 200 mg three times daily for one to two weeks).

‡ Significant burden of sustained ventricular tachycardia.

Graphic 141883 Version 2.0

Consensus recommendations for implantable cardioverter-defibrillators (ICDs) in patients diagnosed with Brugada syndrome



ECG: electrocardiogram; EP: electrophysiology; ICD: implantable cardioverter-defibrillator; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

Graphic 99533 Version 2.0