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STATE-OF-THE-ART REVIEW

Brugada Syndrome

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ABSTRACT

Brugada syndrome (BrS) is an "inherited" condition characterized by predisposition to syncope and cardiac arrest, predominantly during sleep. The prevalence is ~1:2,000, and is more commonly diagnosed in young to middle-aged males, although patient sex does not appear to impact prognosis. Despite the perception of BrS being an inherited arrhythmia syndrome, most cases are not associated with a single causative gene variant. Electrocardiogram (ECG) findings support variable extent of depolarization and repolarization changes, with coved ST-segment elevation ≥2 mm and a negative T-wave in the right precordial leads. These ECG changes are often intermittent, and may be provoked by fever or sodium channel blocker challenge. Growing evidence from cardiac imaging, epicardial ablation, and pathology studies suggests the presence of an epicardial arrhythmic substrate within the right ventricular outflow tract. Risk stratification aims to identify those who are at increased risk of sudden cardiac death, with well-established factors being the presence of spontaneous ECG changes and a history of cardiac arrest or cardiogenic syncope. Current management involves conservative measures in asymptomatic patients, including fever management and drug avoidance. Symptomatic patients typically undergo implantable cardioverter defibrillator insertion, with quinidine and epicardial ablation used for patients with recurrent arrhythmia. This review summarizes our current understanding of BrS and provides clinicians with a practical approach to diagnosis and management. (J Am Coll Cardiol EP 2022;8:386–405) © 2022 by the American College of Cardiology Foundation.

Brugada syndrome (BrS) is characterized by pathognomonic electrocardiogram (ECG) changes of coved ST-segment elevation with T-wave inversion in the right precordial leads.[1-3] In 1992, the Brugada brothers initially described a syndrome consisting of right bundle branch block, ST-segment elevation and sudden cardiac death (SCD),[1] although documentation of these ECG findings had been described earlier.[4] During the last 30 years, significant progress has been made in the understanding of this clinical entity. Due to the potential risk for SCD, it is vital for clinicians to be able to accurately identify and manage patients suspected of having BrS. In this review, we summarize the current understanding of BrS and provide a practical framework for its diagnosis, risk stratification, and treatment (Central Illustration, Table 1).

PATHOPHYSIOLOGY

SODIUM CHANNEL STRUCTURE AND FUNCTION. Voltage gated sodium channels are transmembrane

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HIGHLIGHTS

- Recently, there have been significant advances in our understanding of BrS.
- This review provides practical recommendations for the diagnosis and treatment of BrS.
- Further research is required regarding the pathophysiological understanding and risk stratification in BrS.

proteins which are essential for the electrical signaling of neuromuscular cells.[5-9] Thus far, 9 sodium channels (designated $Na_V1.1$-1.9) have been isolated in humans.[8,9] Although it is thought that the predominant sodium channel in the human heart is the isoform $Na_V1.5$, studies have indicated that other isoforms ($Na_V1.4$ and $Na_V1.8$) may also be expressed,[10,11] albeit at much lower densities. $Na_V1.5$ is comprised of an α-subunit whereby 4 homologous domains—each consisting of 6 segments—co-assemble into a pore-forming channel, and auxiliary β-subunits.[5,7-9]

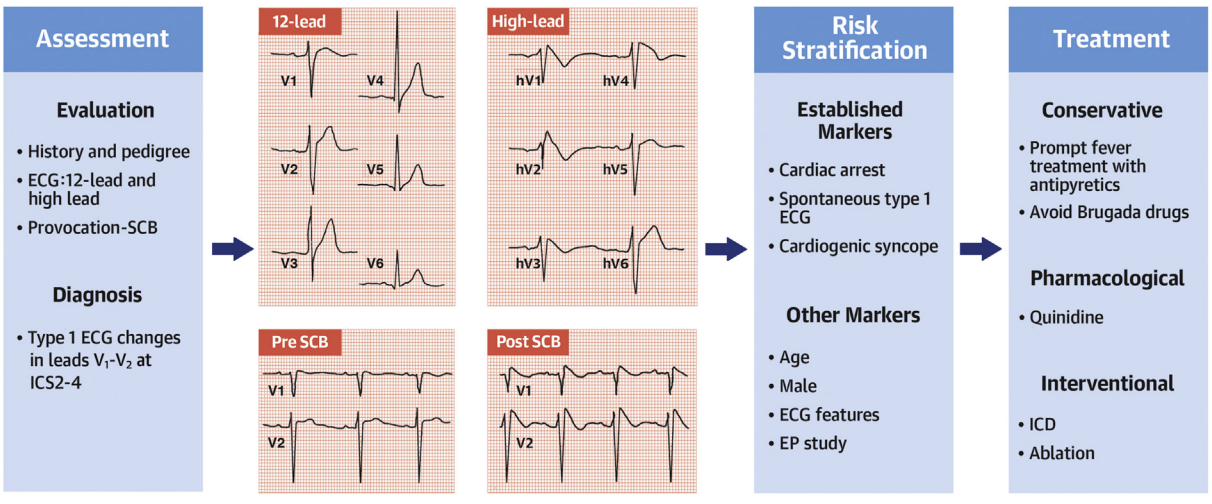
Cardiac depolarization occurs as a result of sodium channel activation (**Figure 1**), generally lasting <1 ms.[12] The activation phase involves conformational changes in the α-subunit, leading to the rapid influx of sodium ions (I_{Na}).[5,7] Increasingly, β-subunits are recognized to play an important role in the net I_{Na} due to their ability to modulate densities of sodium channels at the cell membrane, and in the recruitment of ancillary proteins required for normal sodium channel function.[13-15]

GENETICS OF BrS. Initial genetic studies indicated that familial BrS was primarily due to loss-of-function variants in the *SCN5A* gene, which encodes for the α-subunit of the $Na_V1.5$ sodium channel[16] and can affect the various components including transmembrane proteins, interdomain linkers, and the N- or C-terminals.[3] These variant $Na_V1.5$ channels show evidence of defective gating properties (activation and/or inactivation),[17] but also reduced trafficking to the cell membrane.[18-20] Dysfunctional $Na_V1.5$ channels in patients with BrS result in later activation and earlier inactivation with subsequent shortening of the action potential duration.[9] The resultant effect is a reduction of peak I_{Na} with a slowing in the upstroke (phase 0) of the action potential.[9] Furthermore, experimental models have shown that $Na_V1.5$ function is augmented by changes in ambient temperature.[21-23] This becomes especially evident in those with BrS caused by gene variants affecting $Na_V1.5$,[24,25] with additional shortening of action potential duration at higher temperatures.[21-23,25]

ABBREVIATIONS AND ACRONYMS

BrS = Brugada syndrome
ECG = electrocardiogram
ICD = implantable cardioverter-defibrillator
PVS = programmed ventricular stimulation
RVOT = right ventricular outflow tract
SAE = serious arrhythmic event
SCB = sodium channel blocker
SCD = sudden cardiac death
VF = ventricular fibrillation

CENTRAL ILLUSTRATION Clinical Approach to Brugada Syndrome



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BrS = Brugada syndrome; EP = electrophysiology; ICD = implantable cardioverter defibrillator; ICS = intercostal space; MRI = magnetic resonance imaging; SCB = sodium channel blocker.

TABLE 1 Diagnosis and Management Summary for BrS

Diagnosis		
At Risk	**Evaluation and Testing**	**Diagnostic Criteria**
Symptomatic • Cardiogenic syncope • Ventricular arrhythmias • Resuscitated cardiac arrest *Asymptomatic* • Type 1 ECG • Type 2/3 ECG • Family screening of first-degree relatives	*Initial* • Clinical: syncope, family history, medical history, medications • ECG with high leads • Echocardiogram: exclude structural abnormalities *Discretionary* • SCB provocation • Holter monitor • Further cardiac imaging as indicated • EP study • Cardiac MRI	*Definite* • Spontaneous type 1 ECG changes in V_1-V_2 at ICS2-4 *Probable* • Type 1 ECG changes in V_1-V_2 at ICS2-4 with fever or SCB provocation
Management		
Conservative	**Pharmacologic**	**Interventional**
Avoid Brugada drugs, triggers and promptly treat fever • For all patients with definite BrS • Recommended for all patients with probable BrS *Re-evaluation* • Yearly follow-up with cardiologist *Other considerations* • Promptly report any episodes of syncope or seizures • Inform and screen family members	*Quinidine* • Recurrent appropriate ICD therapies • Consider for patients who qualify for ICD but decline • Consider for medical management of atrial arrhythmias • Consider low-dose therapy (≤600 mg/d) to prevent side effects • Requires regular blood count monitoring *Isoproterenol* • During acute ventricular arrhythmias	*ICD* • Secondary prevention in resuscitated cardiac arrest • Recommended for primary prevention in patients with spontaneous type 1 ECG and syncope • Consider for primary prevention in patients with provoked type 1 ECG and syncope • Consider for primary prevention in asymptomatic patients with spontaneous type 1 ECG and additional high-risk features *Ablation* • Quinidine intolerance • Arrhythmic events despite quinidine

BrS = Brugada syndrome; ECG = electrocardiogram; EP = electrophysiology; ICD = implantable cardioverter defibrillator; ICS = intercostal space; MRI = magnetic resonance imaging; SCB = sodium channel blocker.

Of note, only *SCN5A* gene variants are considered to be definitely disease causing for BrS.[26] Currently, however, an identifiable *SCN5A* variant is found only in ~20% of patients with BrS.[27,28]

Other genes that have been implicated in BrS include *SCN10A* encoding for the α-subunit of the $Na_V1.8$ sodium channel,[28-30] those encoding for $Na_V1.5$ β-subunits,[31] those involved in $Na_V1.5$ trafficking or expression,[32,33] potassium channel genes (responsible for the transient outward current, I_{to}, during phase 1 of the action potential),[34] and calcium channel genes (responsible for late calcium current, I_{CaL}, during phase 2 of the action potential).[35] The net effect is a relative reduction of inward sodium and calcium current or a relative increase in outward potassium current.[36] However, when applying updated criteria for pathogenicity from ClinGen,[37] the significance of these other gene variants for causing BrS is disputed.[26]

Recently, it has been suggested that common genetic variation modulates the phenotypic expression of BrS within families.[38,39] From genome-wide association studies, it appears that the presence of multiple single nucleotide polymorphisms may account for the majority of BrS cases.[40] Importantly, this mechanism may still explain the familial occurrence of BrS without the identification of a single pathogenic variant.

DEPOLARIZATION VERSUS REPOLARIZATION HYPOTHESES. The underlying mechanism of BrS remains the subject of contention and debate.[36,41]

Advocates for a primary depolarization disorder, due to reduced I_{Na} and conduction discontinuity, note the presence of conduction delay in the right ventricular outflow tract (RVOT) in association with the presence of late potentials in patients with BrS.[41,42] This conduction delay results in heterogeneity of depolarization around the RVOT, which is thought to be arrhythmogenic.[43,44]

In contrast, those advocating for a primary repolarization disorder, due to a relatively increased outward potassium current (I_{to}) during phase 2 of the action potential, note a dispersion of transmural

(epicardial-endocardial gradient) action-potentials in canine models of pharmacologically induced BrS.[41,45] Heterogeneity of repolarization between the epicardium and endocardium is postulated to cause arrhythmias by phase 2 re-entry.[45,46] Interestingly, the prominence of I_{to} within the atria is thought to cause atrial disease and atrial arrhythmias in patients with BrS.[47,48]

Others have found that both depolarization and repolarization abnormalities are present in patients with BrS,[49-52] although it is suggested that repolarization changes may occur secondary to a primary depolarization disorder.[53] Given the spectrum of diagnostic and clinical presentations including phenocopies, there is likely to be a confluence of factors leading to a common ECG that may not be explained by a single mechanism.

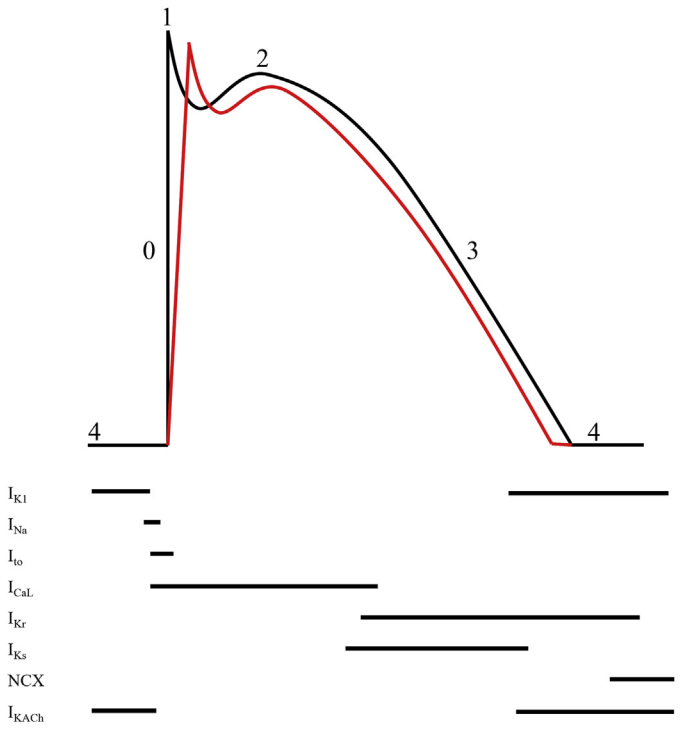
RVOT CHANGES. Cardiac structural changes are also noted in patients with BrS, providing support for a primary depolarization disorder. Initial histopathological studies suggested a potential overlap between those with BrS and arrhythmogenic cardiomyopathy.[54] Subsequent studies indicate that patients with BrS display functional changes in the epicardial aspect of the right ventricle compared with healthy controls,[55,56] but to a lesser extent than when compared with those with arrhythmogenic cardiomyopathy.[55,57]

In this context, an additional pathophysiological hypothesis relates to cardiac neural crest cell migration.[58,59] Cardiac neural crest cells are important in the development of the outflow tracts, the conduction system, the great arteries, and the neighboring structures.[58,60-62] Furthermore, cardiac neural crest cells express connexin-43, which is important in providing electrical coupling between cardiomyocytes.[63] Histopathological studies have shown that patients with BrS have increased collagen and fibrosis within the anterior RVOT,[64,65] along with the presence of inflammatory infiltrates and a reduction in connexin-43.[64,65] In conjunction with electroanatomic mapping, these histopathological changes correlate with areas of low voltage and the presence of abnormal fractionated electrograms.[64,65] Targeted ablation of these areas may correct the phenotypic ECG changes and prevent ventricular arrhythmias.[64,66]

EPIDEMIOLOGY

In a comprehensive review of global studies, Mizusawa and Wilde[2] showed that the overall prevalence of BrS with type 1 ECG is ~1:2,000, whereas the prevalence of type 2/3 ECG pattern is ~1:500; it is most common in Asia followed by Europe and the United States. Males are more commonly affected than females, accounting for ~80%-90% of diagnosed cases,[67] although this is only apparent after adolescence.[68,69] The phenotypic expression appears to be age dependent,[70] and, despite the original Brugada case series including 3 children (38%),[1] the prevalence of BrS in children appears extremely low (~1:20,000).[71] BrS accounts for up to 28% of SCD cases with an apparently normal heart[72] and ~5%-10% of cases of resuscitated cardiac arrest,[73,74] although these estimates vary depending on the age and ethnic background of the cohort.

FIGURE 1 Action Potential



Black line indicates normal ventricular action potential; **red line** indicates delayed upstroke of action potential in Brugada syndrome. Action potential phases: 0, rapid depolarization; 1, rapid/early repolarization; 2, plateau; 3, terminal repolarization; 4, resting potential.

DIAGNOSIS

GUIDELINE RECOMMENDATIONS. Recommendations for the diagnosis of BrS have evolved during the past 2 decades.[75-77] Until 2016, the documentation of type 1 ECG changes (spontaneous or induced) was considered diagnostic for BrS. However, the recently

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TABLE 2 Shanghai Score

		Points
ECG findings[a,b]		
A	Spontaneous type 1 ECG	3.5
B	Fever-induced type 1 ECG	3
C	Type 2/3 ECG that converts to type 1 ECG with SCB provocation	2
Clinical history[a]		
A	Unexplained cardiac arrest or documented VF/polymorphic VT	3
B	Nocturnal agonal respirations	2
C	Suspected arrhythmic syncope	2
D	Syncope of unclear etiology	1
E	AF/flutter age <30 y without clear etiology	0.5
Family history[a]		
A	First- or second-degree relative with definite BrS	2
B	Suspicious SCD (fever, nocturnal, Brugada-aggravating drug) in a first- or second-degree relative	1
C	Unexplained SCD age <45 y in first- or second-degree relative with negative autopsy	0.5
Genetic testing		
A	Probable pathogenic mutation in BrS susceptibility gene	0.5

[a]Highest point in category. [b]Testing at both standard and high leads. Proposed diagnostic criteria: probable/definite ≥3.5 points, possible 2-3 points, nondiagnostic <2 points. Modified with permission from Antzelevitch et al.[78]

AF = atrial fibrillation; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

developed Shanghai score (Table 2) recognizes the limitations of induced type 1 ECG changes in isolation, and recommends additional information (clinical history, family history, and/or genetic testing results) to make a definite diagnosis.[78] Pragmatically, a type 1 pattern without an obvious trigger is clearly diagnostic, but there is no current consensus regarding whether a drug- or fever-induced type 1 pattern is diagnostic, with subsequent implications for management recommendations (see the following).

CLINICAL MANIFESTATIONS. The clinical manifestations of BrS are syncope and cardiac arrest or SCD resulting from ventricular fibrillation (VF) most often initiated by short-coupled premature ventricular complexes,[1,79] although initiation by late-coupled premature ventricular complexes has been reported.[80] Presentation with monomorphic ventricular tachycardia is reported but is rare,[81] usually seen in *SCN5A* variant carriers, and should prompt clinicians to exclude other potential pathology such as arrhythmogenic cardiomyopathy.[82] The age at which patients experience their first arrhythmic event is usually between 30 and 50 years, although females have a bimodal distribution of events and commonly experience their first event either in childhood or later life.[83] Although rare, life-threatening events and SCD can occur in pediatric cohorts including infants.[68,69,84-86]

At the time of diagnosis, approximately one third of patients will have syncope whereas approximately two-thirds are asymptomatic, although this is likely influenced by ascertainment and referral bias.[67,87] In patients who present with syncope, a detailed clinical assessment is required to differentiate likely cardiogenic syncope from other potential causes such as vasovagal syncope.[88,89] Based on contemporary data, up to 4% of patients may be diagnosed after an antecedent cardiac arrest event, although this figure is likely to further decrease with increased screening.[87] The clinical manifestations are known to be precipitated by various factors such as fever, certain drugs, large meals, and alcohol.[90-96]

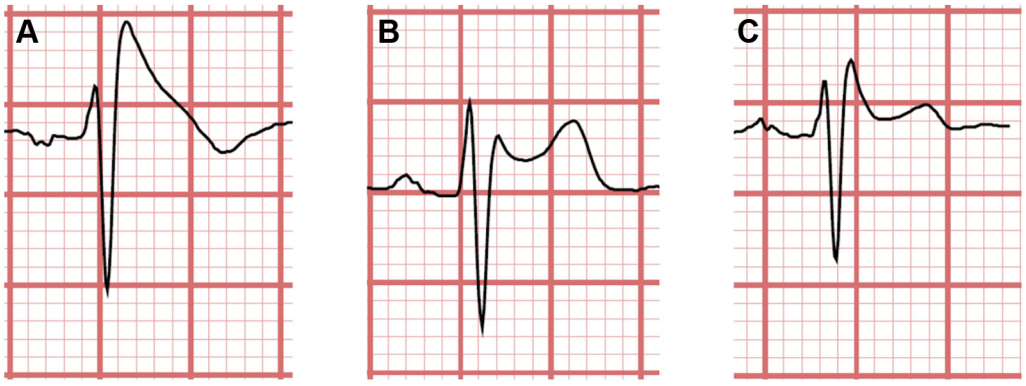
Atrial arrhythmias are common in patients with BrS. Based on 2 large cohort studies, the prevalence of atrial arrhythmias in BrS is ~10%.[97,98] Not surprisingly, the treatment of atrial arrhythmias with a class 1c antiarrhythmic medication may provoke the diagnosis of BrS in some cases.[98]

BASELINE ECG. Initially, 3 ECG pattern types were described in patients with BrS,[75] although only type 1 changes are considered diagnostic (Figure 2).[77] A type 1 Brugada ECG consists of coved ST-segment elevation ≥2 mm with a negative T-wave in the right precordial leads, which are thought to be representative of pathophysiological changes in the RVOT.[36] Originally described for standard lead positions in V_1 to V_3,[75] it is now recognized that leads V_1 to V_2—at either the second, third, or fourth intercostal spaces (Figure 3)—increase the sensitivity for diagnosis due to individual variations in the anatomic position of the RVOT.[99] The use of high-lead positions is thought to increase the diagnostic yield by ~1.5 times compared with standard lead positions.[100,101]

In keeping with the clinical manifestations, these ECG changes may also be sporadic, fluctuating spontaneously, as well as under the influence of fever or medications.[90,91] As a result, provocation testing with sodium channel blockers (SCBs) is considered an important adjunct in the assessment of patients for BrS.[102]

PROVOCATION TESTING. Provocation testing with SCB is indicated in patients with a baseline type 2 or 3 Brugada pattern ECG or those with a suspicion for BrS based on clinical or family history.[78] The basis for SCB challenge for the diagnosis of BrS originates from Miyazaki et al,[90] who systematically examined the effects of various antiarrhythmic medications in patients with BrS and found that class 1a antiarrhythmic drugs (procainamide or disopyramide in their study) augmented the classical ST-segment changes in patients with BrS, but not controls.

FIGURE 2 **Brugada Pattern Electrocardiograms**



Representative type 1 **(A)**, type 2 **(B)**, and type 3 **(C)**. Brugada pattern electrocardiogram traces originally proposed by Wilde et al.[75] All feature J-point elevation ≥2 mm. Type 1 pattern consists of coved ST-segment elevation (J-point elevation with a gradual down-sloping ST-segment) with T-wave inversion. Type 2/3 patterns consist of saddleback ST-segment configuration with variable levels of ST-segment elevation. Pragmatically, only a type 1 pattern is diagnostic for Brugada syndrome, whereas patients with type 2/3 patterns should undergo sodium channel blocker provocation testing.

Due to differences in global availability of these drugs,[73,103,104] 4 SCBs are routinely used for provocation testing—Class 1a agents ajmaline (mainly in Europe) and procainamide (mainly in North America), or class 1c agents flecainide (mainly in Europe) and pilsicainide (mainly in Japan). The predominant action of all 4 SCBs is on $Na_V1.5$, and the inhibition of I_{Na}.[12,105]

The SCB challenge testing procedure with recommendations for its practical implementation is shown in Supplemental Table 1, and representative ECG changes for a positive test are shown in **Figure 4**. ECG tracings should be obtained for V_1 and V_2 in both standard- and high-lead positions[104] because this increases test sensitivity while maintaining specificity.[101]

Although SCB challenge testing is an important diagnostic test for BrS, not all SCBs are created equal. Differences in the mechanisms of $Na_V1.5$ inhibition—with class 1a agents acting during the activated state, and class 1c agents acting during the inactivated state[106]—lead to resultant differences in electrophysiological effects including degree of QRS widening, prolongation of effective refractory period, and lengthening of action potential duration.[106,107] Furthermore, these agents exhibit supplemental effects of varying degrees on potassium current (particularly I_{to}) as well as the intracellular release of calcium.[106,108-111] Unsurprisingly, clinical studies have found differences in the diagnostic yield of various SCBs, whereby ajmaline is considered the most potent and procainamide is considered the least potent.[104] Although ajmaline is associated with a high sensitivity for diagnosis,[112] there are concerns regarding its accuracy, particularly at high doses.[113] For example, Tadros et al[113] determined that 8% of positive ajmaline challenges were confounders in families with a history of cardiac arrest or SCD, whereas Hasdemir et al[114] reported that 27% of patients with atrioventricular node re-entrant tachycardia and 4.5% of otherwise "healthy" controls may exhibit type 1 ECG changes with ajmaline administration. Whether these represent actual false-positives or cases of otherwise undiagnosed BrS is yet to be established. Thus, improved standardization for the use of SCB is required in the diagnostic evaluation of BrS.

GENETIC TESTING. Genetic testing is recommended in those exhibiting a type 1 Brugada ECG pattern (either spontaneous or provoked), because this may allow for familial screening.[115] Currently, however, the presence of a likely or definite pathogenic variant in a BrS susceptibility gene in isolation is not considered diagnostic for BrS.[77,78] Furthermore, it has been shown that in families in whom a genetic variant is identified, the penetrance is ~50%, while family members who do not carry the variant may still have clinical BrS.[116] Therefore, familial screening for BrS cannot rely solely on genetic testing and should be based primarily on clinical screening. At present, the authors only perform testing for variants in the *SCN5A* gene[26,117] because the pathogenicity of other

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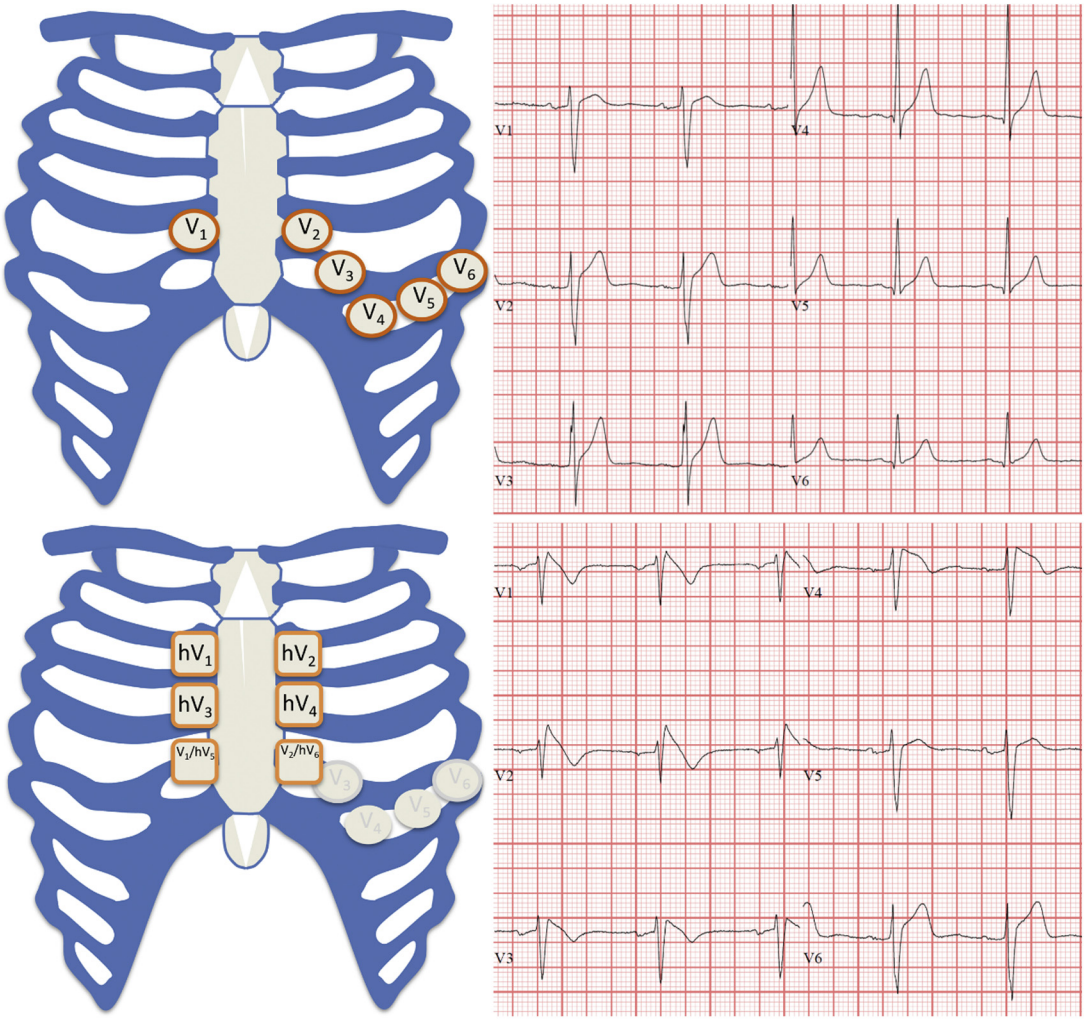
FIGURE 3 Standard- and High-Lead Electrocardiogram Positions

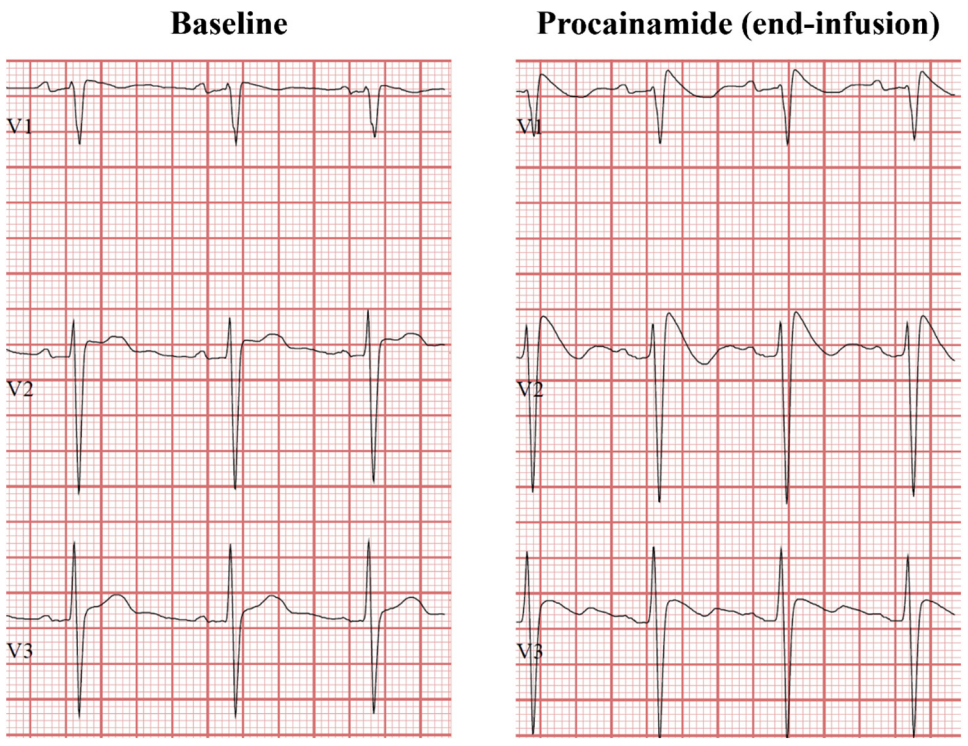


(Top) Standard-lead electrocardiogram positions and corresponding precordial electrocardiogram in a patient with Brugada syndrome. **(Bottom)** High-lead electrocardiogram positions and corresponding electrocardiogram in the same patient. Note that hV_5 and hV_6 on the high-lead electrocardiogram corresponds with V_1 and V_2 on the standard-lead electrocardiogram.

reported putative genes is tenuous in all but exceptional circumstances. This may be considered in consultation with a genetics expert when 2 or more family members are phenotypically affected and *SCN5A* sequencing is negative.

FAMILY SCREENING. Screening of family members for BrS should include all first-degree relatives of patients diagnosed with BrS, or those with otherwise unexplained SCD.[72,118] This should include standard- and high-lead ECG, and consideration of SCB provocation.[119] The routine use of SCB challenge is advocated by some groups. In adult patients, one-time screening is probably adequate if SCB provocation testing is negative. In pediatric family members, the authors would recommend initial standard- and high-lead ECG screening at age 3, and, if negative, additional screening every 3 years until age 15, because of possible age-related phenotypic expression.[71,120] Due to a possible higher risk of adverse events with SCB provocation in children,[121] we would not recommend the routine use of SCB for screening purposes until after age 15 years. Again, if SCB testing is negative, additional testing can be avoided.

FIGURE 4 Provocation Testing



OTHER TESTS. Although not necessary for the diagnosis, a baseline echocardiogram should be performed in all patients being assessed for BrS for the exclusion of structural heart disease. Additional cardiac imaging, including magnetic resonance imaging may be considered in complex cases to delineate RVOT structure and function.[56,122]

RISK STRATIFICATION

Serious arrhythmic events (SAEs), encompassing resuscitated cardiac arrest and SCD, are seldom the first manifestation of symptoms in BrS. Thus, risk stratification in patients with BrS aims to identify those with a greater likelihood of SAEs. These are influenced by various clinical, ECG, and electrophysiological factors, and an understanding of these factors can allow for shared decision-making regarding surveillance and treatment strategies.

CLINICAL. Aside from resuscitated cardiac arrest, the clinical factors that have the greatest impact on SAEs in patients with BrS are a history of cardiogenic syncope and the presence of a spontaneous type 1 ECG, which is validated in both pediatric and adult cohorts (**Table 3**).[85,86,123,124] Consistent evidence from multiple studies have found that a history of cardiogenic syncope results in a 2.5-5x relative risk for SAEs even when adjusting for other factors.[125-132] In a pooled analysis of prospective studies involving 1,312 patients, Sroubek et al[67] found that patients with BrS and syncope had a 2.5% annual incidence of SAEs compared with 0.7% for those who did not have syncope. Similarly, the documentation of a spontaneous type 1 ECG resulted in a 2-6× relative risk for SAEs when adjusting for other factors.[125,126,128,131,133-135] In a systematic review of studies involving 4,099 patients, Rattanawong et al.[136] found that patients with spontaneous type 1 ECG had a 2.4% annual incidence of SAEs compared with 0.65% for those with SCB-induced BrS. The application of both syncope and spontaneous ECG changes allows for additional risk stratification. The annual SAE risk is 2.3%-3.7% for those with cardiogenic syncope and spontaneous ECG, up to 2.0% for those with syncope and SCB-induced BrS, 0.8%-1.2% for those with asymptomatic spontaneous ECG, and ~0.3% for those with asymptomatic SCB-induced BrS (**Figure 5**).[67,131,136] Importantly, patients with syncope that is not cardiogenic in nature are not at increased risk of SAEs.[88]

Overall, patient age and sex do not appear to have a significant impact on the risk of SAEs in patients with

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TABLE 3 Established Risk Stratification Markers

Category First Author/Ref. #	Population	N	Outcome	Risk Marker	Odds Ratio
Clinical					
Kamakura et al[144]	Type 1/2/3	330	SAE	Syncope	NS
Probst et al[125]	Type 1	1,029	SAE	Syncope	3.4
Delise et al[126]	Type 1	320	SAE	Syncope	2.8
Rollin et al[133]	Type 1	323	SAE	Syncope	NS[a]
Takagi et al[127]	Type 1 without CA	376	SAE	Syncope	2.53
Tokioka et al[52]	Type 1	246	SAE	VF Syncope	19.6 28.6
Conte et al[161]	Type 1 with ICD	176	ICD therapies	CA	5.13
Okamura et al[128]	Type 1 without CA	218	SAE	Syncope	6.81
Kawazoe et al[129]	Not specified	143	SAE	Syncope	4.91
Calo et al[137]	Spontaneous type 1 without CA	346	SAE	Syncope	NS
Andorin et al[85]	Type 1 age <19 y	106	SAE	Symptoms	4.7
de Asmundis et al[150]	Type 1	289	SAE	VF Syncope	8.97 9.86
Ueoka et al[130]	Type 1	245	SAE	Syncope	3.28
Yuan et al[142]	Not specified	4,140 (SR)	SAE	Symptoms	4.54
Berthome et al[132]	Type 1 females	494	SAE	CA (or VF) Syncope	69.4 6.8
Subramanian et al[135]	Type 1 without CA	103	SAE	Syncope	NS
Honarbakhsh et al[131]	Type 1	1,110	SAE	Syncope	3.71
ECG					
Kamakura et al[144]	Type 1/2/3	330	SAE	Spontaneous	NS
Probst et al[125]	Type 1	1,029	SAE	Spontaneous	1.8
Delise et al[126]	Type 1	320	SAE	Spontaneous	6.2
Rollin et al[133]	Type 1	323	SAE	Spontaneous	2.43
Takagi et al[127]	Type 1 without CA	376	SAE	Spontaneous	NS
Letsas et al[134]	Type 1 asymptomatic	1,398 (SR)	SAE	Spontaneous	3.56
Okamura et al[128]	Type 1 without CA	218	SAE	Spontaneous	4.51
Kawazoe et al[129]	Not specified	143	SAE	Spontaneous	NS
Rivard et al[152]	Type 1	105	SAE	Spontaneous	10.80
Andorin et al[85]	Type 1 age <19 y	106	SAE	Spontaneous	5.9
Gonzalez Corcia et al[86]	Type 1 age ≤25 y	128	SAE	Spontaneous	8.07
de Asmundis et al[150]	Type 1	289	SAE	Spontaneous	3.88
Berthome et al[132]	Type 1 females	494	SAE	Spontaneous	NS
Subramanian et al[135]	Type 1 without CA	103	SAE	Spontaneous	4.10
Honarbakhsh et al[131]	Type 1	1110	SAE	Spontaneous	3.80

[a]$P = 0.051$.

CA = cardiac arrest; NS = nonsignificant; SAE = serious arrhythmic event; SR = systematic review; other abbreviations as in Tables 1 and 2.

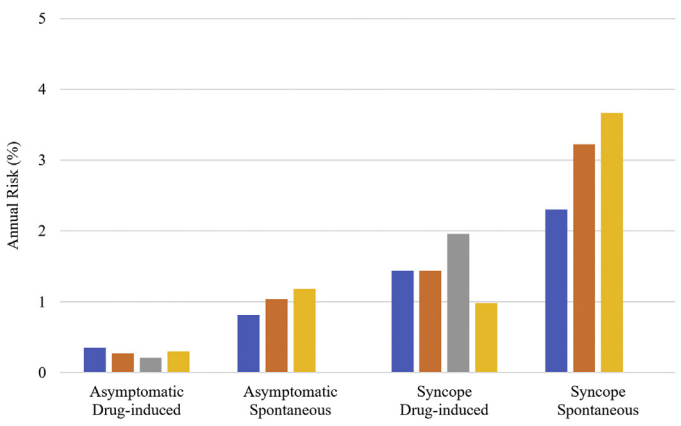
BrS when considering other factors using multivariate analysis (Table 4).[125,126,131,137] Of note, most studies have involved patients with a mean age between 30 and 50 years.[136] Although rare, there are reports of SAEs occurring in pediatric age groups,[138] even as young as <1 year of age.[139] SAEs in this group of patients are also associated with the presence of syncope and spontaneous ECG changes.[86] Interestingly, significantly less SAEs are reported in older patients with BrS,[138,140,141] although it is currently unclear whether this is due to an attenuation of risk with ageing or selection bias of less penetrant cases. Nevertheless, evidence suggests that those who are ≥55 years of age at the time of diagnosis have an annual mortality rate comparable with the general population.[140] In addition, although a systematic review has indicated an increased risk in males with BrS,[142] this has not been confirmed as an independent risk marker in large cohort studies when adjusting for other risk factors.[125,126,137] Similarly, cohort studies by Sieira et al[143] and Berthome et al[132] found that women had a significantly lower SAE rate compared with men, although this did not adjust for other important factors including the presence of spontaneous ECG changes. Thus, age and sex currently have a limited role in the risk stratification in BrS when considering other factors, although older age at initial diagnosis likely reflects a more benign prognosis.

Finally, the potential influence of family history of SAEs or SCD requires clarification. Although one study found a positive family history to be predictive for SAEs,[144] this has not been confirmed in numerous subsequent studies.[126,128,133,135] Interestingly, Sieira et al[145] found that although a family history of SCD was not associated with increased SAEs, the presence of early familial (first-degree relative age <35 years) SCD was associated with SAEs, although other risk factors may not necessarily have been adjusted for.

ECG. In addition to the presence of a spontaneous type 1 ECG pattern, various other ECG parameters may support risk stratification in BrS. Foremost is the concept of "Brugada burden" as proposed by Viskin et al.[146] This term was coined in reference to a study demonstrating that the presence of type 1 ECG changes in peripheral ECG leads (in addition to the right precordial leads) was independently associated with the occurrence of SAEs,[133] which has recently been corroborated in a large multicenter study.[131] Furthermore, a higher proportion of spontaneous type 1 ECGs during clinical follow-up has been found to correlate with more SAEs,[147] whereas the temporal burden of ST-segment changes on 24-hour Holter monitoring is associated with the occurrence of cardiac events (composed of SAEs and syncope).[148] Thus, it appears that both spatial and temporal "Brugada burden" contribute to the severity of the phenotype and influence clinical outcomes.

Numerous morphologic ECG abnormalities have been suggested to provide additional risk stratification (**Table 4**). Changes such as fragmentation of the QRS (f-QRS),[52,124,132,149,150] QRS duration,[129,132,151-155] S-wave duration,[137,155] rJ interval,[129,151] early repolarization pattern,[52,127,131,144,156] Tpeak-end duration,[129,152,157] and QTc[154] have all been suggested to carry prognostic information in BrS, and reflect the underlying perturbations in the continuum between depolarization and repolarization. Evaluation with signal-average ECG, representing depolarization disturbance, may be an additional risk marker.[158,159] However, this has only been shown in small cohort studies that included syncope as an outcome measure,[158,159] with larger studies not necessarily supporting its utility.[52,129] Interestingly, the presence of atrial fibrillation has been found as an independent predictor of SAEs in BrS,[137,154] whereas the presence of sinus node dysfunction may also confer risk.[139,143,145] Many of these parameters likely reflect Brugada burden as well, and large-scale evaluation is warranted to assess the prevalence and potency of these markers after adjusting for recognized risk factors.

FIGURE 5 Risk of Serious Arrhythmic Events Stratified by Clinical Factors



Annual risk of serious arrhythmic events in patients with Brugada syndrome: asymptomatic + drug-induced (0.21%-0.3%), asymptomatic + spontaneous (0.81%-1.18%), syncope + drug-induced (0.98%-1.96%), and syncope + spontaneous (2.3%-3.66%). Developed using data reported by Probst et al[125] **(blue bars)**, Sroubek et al[67] **(orange bars)**, Rattanawong et al[136] **(gray bars)**, and Honarbakhsh et al[131] **(yellow bars)**.

Conceptually, these findings indicate that patients with BrS who have greater quantifiable electrical substrate abnormalities - either spatially or temporally, during depolarization and/or repolarization, affecting both atria and ventricles - are at greater risk for SAEs.

PROGRAMMED VENTRICULAR STIMULATION. The role of programmed ventricular stimulation (PVS) in the risk stratification of patients with BrS remains controversial (**Table 4**). The Brugada brothers were early proponents for the use of PVS in the risk stratification of patients, reporting that 60 of 217 (28%) patients with PVS-induced ventricular arrhythmias had spontaneous VF during follow-up compared with 5 of 221 (2%) patients who were noninducible.[160] Additional studies, predominantly from the same cohort of patients, have provided support for these findings.[126,145,161,162] In contrast, 2 large prospective multicenter registries, FINGER (France, Italy, Netherlands, Germany) with 1,029 patients and PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) with 308 patients,[124,125] failed to corroborate a utility for PVS. In a systematic review and pooled analysis of prospective observational studies of 1,312 patients with BrS (which included patients from FINGER and PRELUDE), Sroubek et al[67] found that inducibility during PVS was associated with a 2.7 odds ratio of SAEs, which was greater if induction occurred with only 1 or 2 extrastimuli. However, although this study adjusted for age, sex, and presence of spontaneous ECG changes, additional noninvasive ECG

TABLE 4 Other Potential Risk Stratification Markers

Category First Author/Ref. #	Population	N	Outcome	Risk Marker	Odds Ratio
Clinical					
Kamakura et al[144]	Type 1/2/3	330	SAE	FHx	3.28
Probst et al[125]	Type 1	1,029	SAE	Age, male	NS
Delise et al[126]	Type 1	320	SAE	Age, male, FHx	NS
Rollin et al[133]	Type 1	323	SAE	FHx	NS
Okamura et al[128]	Type 1 without CA	218	SAE	Age, male, FHx	NS
Kawazoe et al[129]	Not specified	143	SAE	Age, male	NS
Calo et al[137]	Spontaneous type 1 without CA	346	SAE	Age, male, FHx	NS
Yuan et al[142]	Not specified	4,140 (SR)	SAE	Male	2.06
Berthome et al[132]	Type 1 females	494	SAE	Age, FHx	NS
Subramanian et al[135]	Type 1 without CA	103	SAE	Age, male, FHx	NS
ECG					
Takagi et al[151]	Type 1	188	SAE	R-J interval (V_2) ≥90 ms QRSd (V_6) ≥90 ms	4.61 4.42
Kamakura et al[144]	Type 1/2/3	330	SAE	ERP	2.66
Priori et al[124]	Type 1	308	SAE	f-QRS	4.94
Rollin et al[133]	Type 1	323	SAE	Type 1 (peripheral leads)	4.58
Takagi et al[127]	Type 1 without CA	376	SAE	QRSd (V_2) >90 ms ERP + horizontal ST segment	>10 2.96
Tokioka et al[52]	Type 1	246	SAE	f-QRS ERP	5.2 2.87
Kawazoe et al[129]	Not specified	143	SAE	R-J interval (V_1) Tp-e dispersion QRSd (V_6)	1.04 1.07 1.04
Rivard et al[152]	Type 1	105	SAE	Tp-e ≥100 ms QRSd ≥110 ms	29.73 15.27
Calo et al[137]	Spontaneous type 1 without CA	346	SAE	AF S-wave (I) ≥40 ms	3.70 39.10
de Asmundis et al[150]	Type 1	289	SAE	f-QRS ERP	6.33 3.77
Ueoka et al[130]	Type 1	245	SAE	ST-segment elevation ≥0.3 mV SCB induced VAs	2.80 3.62
Berthome et al[132]	Type 1 females	494	SAE	QRSd (II) >120 ms f-QRS	4.7 20.2
Subramanian et al[135]	Type 1 without CA	103	SAE	S-wave upslope f-QRS Tp-e ≥100 ms	3.84 2.99 3.65
Giustetto et al[155]	Type 1	614	SAE	QRSd V_6	1.1
Honarbakhsh et al[131]	Type 1	1,110	SAE	ERP (peripheral leads) Type 1 (peripheral leads)	3.42 2.33
Electrophysiological					
Kamakura et al[144]	Type 1/2/3	330	SAE	Inducible VAs	NS
Probst et al[125]	Type 1	1,029	SAE	Inducible VAs	NS
Priori et al[124]	Type 1	308	SAE	VERP<200 ms Inducible VAs	3.91 NS
Takagi et al[127]	Type 1 without CA	376	SAE	Inducible VAs	NS
Letsas et al[134]	Type 1 asymptomatic	1,104 (SR)	SAE	Inducible VAs	3.51
Conte et al[161]	Type 1 with ICD	176	ICD therapies	Inducible VAs	3.38
Okamura et al[128]	Type 1 without CA	218	SAE	Inducible VAs	NS
Sroubek et al[67]	Type 1	1,312 (SR)	SAE	Inducible VAs	3.34-3.45
Casado-Arroyo et al[87]	Type 1 probands	447	SAE	Inducible VAs	3.46
Calo et al[137]	Spontaneous type 1 without CA	346	SAE	Inducible VAs	NS
de Asmundis et al[150]	Type 1	289	SAE	Inducible VAs	NS
Berthome et al[132]	Type 1 females	494	SAE	Inducible VAs	NS
Subramanian et al[135]	Type 1 without CA	103	SAE	Inducible VAs	NS

AF = atrial fibrillation; ERP = early repolarization pattern; FHx = family history of sudden death; fQRS = fractionated QRS; HR = heart rate; QRSd = QRS duration; Tp-e = T-wave peak to end; other abbreviations as in Tables 1 to 3.

parameters were not included, and the positive predictive value of the test remained low. Hence, it is possible that noninvasive ECG parameters, some of which are independently associated with high odds ratios for SAEs, may allow for superior risk stratification in patients with BrS. Interestingly, in a subset of patients from the original Brugada cohort, de Asumundis et al[150] found that by including other ECG parameters, the presence of f-QRS and early repolarization on ECG were independently associated with SAEs whereas PVS was not. In a recent retrospective, multicenter study of 1,110 patients, Honarbakhsh et al[131] found that early repolarization and type 1 ECG changes in peripheral leads (along with spontaneous ECG and syncope) were independently associated with SAEs. Although PVS was not found to be predictive in this cohort, it should be noted that PVS findings were only available for approximately one third of patients. This reinforces the need to evaluate the utility of PVS in the setting of all putative risk predictors, including ECG parameters.

Currently PVS (with up to 2 extrastimuli) may be considered as a "tie-breaker" in certain circumstances - for example, a young patient with spontaneous BrS ECG and syncope of uncertain origin whereby easily induced ventricular fibrillation would lead to a recommendation for implantable cardioverter defibrillator (ICD). However, given that PVS is invasive, carrying a potential risk for complications,[163] coupled with potential issues regarding reproducibility,[164] the authors would not recommend routine use of PVS in the risk stratification of patients with BrS.

OTHER CONSIDERATIONS. The genetic risk stratification of BrS is evolving, and recent reports have suggested a utility for *SCN5A* variants in predicting SAE outcomes.[165-168] This includes 2 studies from Japan and Thailand (both cohorts with >97% males) which found that *SCN5A* variants were independent predictors for SAE,[165,166] although this was not seen in the European FINGER registry cohort.[125] In conjunction with the low yield of genetic findings in BrS, the role for genetic risk stratification requires further evaluation.

RISK STRATIFICATION. Various risk stratification scores have been proposed for BrS. These have invariably included the presence of spontaneous ECG changes and cardiogenic syncope as risk markers, along with consideration for undertaking PVS.[126,128,145] Risk stratification is most important in intermediate-risk patients because this has the greatest impact on therapeutic decision making about the potential role of a primary prevention ICD. However, in a study evaluating the performance of the Sieira score, Probst et al[169] found that the Sieira score did not allow for adequate risk stratification of intermediate-risk patients. A recently proposed risk prediction model by Honarbakhsh et al[131] requires external validation, especially in an intermediate-risk cohort. Thus, further work is required to develop a method for the accurate stratification of risk in patients with BrS beyond the presence of spontaneous ECG changes or syncope.

MANAGEMENT

CONSERVATIVE. In all patients who are diagnosed with BrS, conservative measures are advised including the avoidance of drugs that can provoke Brugada ECG changes and rapid antipyretic treatment for fever. In those with asymptomatic drug-induced BrS, conservative measures are typically all that is required.

Postema et al[93] have provided an up-to-date list of drugs that can precipitate Brugada ECG changes, including both prescription and nonprescription medications.[94] For clinicians, this includes antiarrhythmic (predominantly SCB), psychotropic, and anesthetic/analgesic agents. It is crucial for patients to be aware of the medications that are contraindicated in BrS. Patients should also be educated that this also includes alcohol intoxication, nonprescription drugs such as antihistamines, and certain drugs commonly obtained as illicit substances such as cannabis and cocaine, although the published evidence is limited.

Febrile illness has been shown to both unmask the phenotypic manifestation of BrS[95,170] and precipitate SAEs in patients with BrS.[91] Pediatric patients with BrS appear to be particularly susceptible to SAEs in the context of fever.[69,171] Thus, it is imperative that patients with BrS are educated regarding the early institution of antipyretic treatment during febrile illness.

Additional considerations include avoidance of excessive alcohol intake and rapid intervention for acute metabolic disturbance. Alcohol is reported to precipitate syncopal events in patients with BrS,[172] whereas metabolic disturbance such as hypokalemia, hyperkalemia and metabolic acidosis has been reported to uncover Brugada ECG changes.[173,174]

PHARMACOLOGIC. Quinidine, and its related compounds quinine and hydroquinidine, is useful in the pharmacologic management of BrS.[175-177] Quinidine has complex antiarrhythmic properties. Although categorized as a Class Ia agent,[106] thereby

prolonging phase 0 of the action potential, quinidine is also shown to inhibit potassium currents throughout the duration of the action potential and I_{CaL} current during phase 2 of the action potential.[178] Mechanistically, it is thought that the inhibition of I_{to} is most important in the antiarrhythmic effect of quinidine in BrS,[102,175,176] prolonging the effective refractory period.[179] The side effect profile of quinidine is dose related and significant, including diarrhea, immunologic reactions (thrombocytopenia, anemia, fever, lupus reactions), neurologic effects, and proarrhythmia.[178,180] Furthermore, the use of quinidine is limited due to a lack of drug availability.[181]

In the only randomized control trial evaluating the efficacy of hydroquinidine in BrS, the "QUIDAM" study did not demonstrate benefit over placebo, although the study was underpowered.[182] Importantly, however, there were no SAEs in patients taking hydroquinidine therapy.

Quinidine has also been shown to reduce VF inducibility at PVS. In a cohort of 60 patients with BrS with inducible VF, Belhassen et al[180] demonstrated that administration of quinidine resulted in noninducibility in 54 (90%) patients. Moreover, quinidine is an important adjunct in patients with recurrent ICD shocks or electrical storm.[183] Quinidine is also an important therapeutic consideration for rhythm control in patients with concomitant atrial fibrillation.[98,184]

Despite the observed efficacy of quinidine in patients with BrS, its use is limited by difficulties with access and its side effect profile, which leads to therapy cessation in approximately one third of patients.[180,182] The use of low-dose quinidine (200-600 mg/d of quinidine sulfate) may improve tolerance while providing reasonable antiarrhythmic benefit,[185,186] and evening administration allows theoretical protection against overnight events.[186] Pragmatically, monitoring of serum levels may provide some guidance when lower doses or other preparations (such as quinidine gluconate) are used,[180] and concomitant administration of cholestyramine may alleviate associated diarrhea without impacting efficacy.[175]

In patients with BrS who experience electrical storm, intravenous isoproterenol is recommended where the mechanism is due to short-coupled premature ventricular complex-induced VF.[79,187,188] Its predominant antiarrhythmic effect in BrS is through an increase in I_{CaL}.[45,79] Additional pharmacologic therapy that may be considered in BrS includes phosphodiesterase III inhibitors (cilostazol or milrinone), also acting via potentiation of I_{CaL}.[189]

DEVICE. In patients with BrS and a history of resuscitated cardiac arrest, a secondary prevention ICD is indicated.[190] The decision regarding implantation of a primary prevention ICD is more challenging, requiring consideration about the absolute risk of SCD balanced against the absolute risk of device-related complications.[191] As noted, those with BrS and cardiogenic syncope have an annual incidence of SAEs in excess of 1.4%, and this represents the highest risk group.[67,136] By contrast, a meta-analysis of 1,539 patients with BrS and an ICD found a 3.3% annual rate of inappropriate shocks, and a 4.5% annual rate of other complications such as lead malfunction, device infection, and psychological consequences.[192] Finally, in a study including 1,613 patients with BrS and a mean follow-up of 6.5 years, Probst et al[169] presented that the incidence of SCD was ~0.19% in patients with BrS without an ICD compared with ~0.10% in those with an ICD, suggesting the possibility of "missed opportunities" for SCD prevention.

Nevertheless, the authors would recommend a primary prevention ICD for patients with BrS (either spontaneous or provoked) and a history of cardiogenic syncope. In patients with a spontaneous type 1 ECG and vasovagal syncope or syncope of uncertain origin, an implanted loop recorder may be considered, recognizing that the evidence to support this recommendation is modest.[193-195] In patients with a spontaneous type 1 ECG who are asymptomatic, we would advocate for close follow-up due to the current limitations of other risk stratification methods, generally avoiding a primary prevention ICD unless other markers of risk are considered relevant in consultation with an expert.

For patients undergoing ICD implantation, certain considerations are relevant in the decision regarding a transvenous vs a subcutaneous device. Because patients with BrS—especially those carrying an *SCN5A* variant—are prone to atrial arrhythmias,[98,196] a dual-chamber transvenous system offers the capability of atrial pacing in those with sinus node dysfunction or provision of discrimination in patients with atrial tachyarrhythmias. Conversely, a subcutaneous device, mitigating intravascular infection risk, may be preferred in young patients who do not require pacing. Of note, however, ~15% of patients with BrS will fail initial sensing screening,[197-199] and SCB provocation or exercise testing may identify additional patients with inappropriate morphology analysis.[200,201] Reassuringly though, preliminary reports of patients with BrS with subcutaneous ICD indicate that they are not necessarily at greater risk of inappropriate shocks.[202,203] In younger and smaller children, an

epicardial approach with a subcostal device may be considered.[204]

RADIOFREQUENCY ABLATION. Radiofrequency ablation is an important adjunctive treatment in patients with BrS with breakthrough SAEs despite optimized medical therapy, or in those who are intolerant of medications.[205] A combined epicardial and endocardial approach allows for epicardial substrate modification[66,206,207] and endocardial elimination of triggers.[208,209] Pharmacologic provocation with SCB during the procedure may be useful for identifying additional arrhythmogenic substrate areas.[66,206,207] A proposed end-point for ablation is the resolution of J-point elevation despite pharmacologic provocation.[207] In a large series of 135 patients with BrS undergoing epicardial substrate ablation, Pappone et al[210] showed that amelioration of ajmaline-provoked ECG changes was achieved acutely in all patients with persistence of ECG normalization (despite ajmaline provocation) in 133 (98.5%) patients during a median follow-up of 10 months.[210] Currently, however, ablation is mostly reserved for patients with recurrent ICD shocks that cannot be managed with medical therapy or for those in whom an ICD is indicated but not implanted (eg, strong patient preference). There are insufficient data to support its use in asymptomatic patients.

FUTURE DIRECTIONS

The pathophysiological understanding of BrS remains incomplete, with a confluence of factors contributing to a heterogenous phenotype of impaired RVOT conduction reserve.[36] Although disorders of $Na_V1.5$ are the most commonly reported ion channel abnormality, the additional and relative contributions of I_{to} and I_{CaL} are yet to be determined. Clearly related is the confounding genetic basis for BrS because contemporary changes to the interpretation of genetic testing have resulted in a diminution of the number of cases attributable to a genetic variant.[26,37,211,212] In addition, there appears to be a weak relationship between *SCN5A* variants, sodium channel function, and clinical phenotype.[213] Perhaps then, polygenic factors are important for both the phenotypic expression of BrS and clinical outcomes.[38,39]

Based on findings of myocardial inflammation,[65] additional diagnostic tests are in development and show promise. If validated, autoantibodies to certain cardiac-specific proteins such as α-cardiac actin, α-skeletal actin, keratin, and connexin-43 may accurately differentiate patients with BrS.[214] The implications of this for screening, prognostication, and therapeutic considerations are exciting, analogous to the use of HbA1C in patients with diabetes.

The current risk stratification for BrS is suboptimal, with uncertainty for those at intermediate risk.[77,190] Although the utility of PVS has been extensively investigated,[67] its widespread implementation is lacking due to its invasive nature and concerns regarding reproducibility.[124] Furthermore, multiple potential noninvasive markers have been suggested, including cardiac imaging changes,[215] although the lack of systematic investigation and reporting limits their current applicability. Thus, a study that can analyze multiple noninvasive markers in conjunction with PVS may significantly advance our ability to provide risk stratification in patients with BrS. Escalation of international collaborations with accurate phenotyping and sufficient endpoints should further refine our ability to advise intermediate-risk individuals within a shared decision-making framework.

The reported results of ablative treatment for BrS appear promising,[66,206,207] although larger prospective studies are required.[216] Currently indicated for those who experience recurrent ICD shocks despite medical therapy or for those who are intolerant to medical therapy, refinement of techniques for RVOT substrate modification along with additional outcomes data may eventuate in ablation strategies being recommended earlier in the course of clinical management for BrS.

CONCLUSIONS

BrS represents a complex clinical problem with a pathognomonic ECG phenotype, although its pathophysiological basis is incompletely understood and likely heterogenous in nature. Assessment of clinical and ECG factors are important to both the diagnostic evaluation and risk stratification of patients with BrS. Management in BrS requires an understanding of the various conservative, pharmacologic, and interventional treatment modalities.

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KEY WORDS **Brugada syndrome, serious arrhythmic events, sudden cardiac death, ventricular fibrillation**

APPENDIX **For a supplemental table, please see the online version of this paper.**