**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 ~1:2000, 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. ECG findings support variable extent of depolarization and repolarization changes, with coved ST elevation ≥2mm 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.

**Abbreviations**

BrS: Brugada syndrome

ICD: implantable cardioverter defibrillator

PVS: programmed ventricular stimulation

RVOT: right ventricular outflow tract

SAE: serious arrhythmic events

SCB: sodium channel blocker

SCD: sudden cardiac death

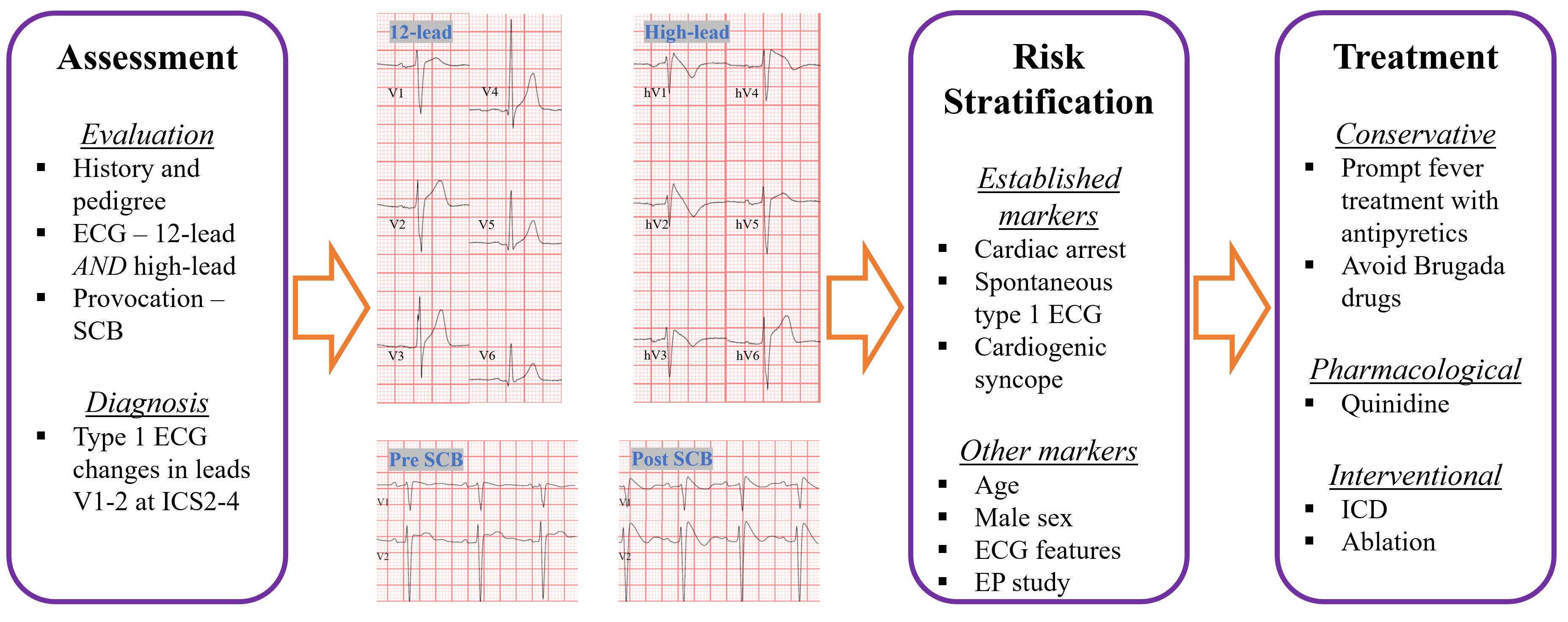
VF: ventricular fibrillation

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**Representative Figure:**

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**Bullet point messages**

* 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

**Introduction**

Brugada syndrome (BrS) is characterized by pathognomonic ECG changes of coved ST-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-elevation and sudden cardiac death (SCD) (1), although documentation of these ECG findings had been described earlier (4). Over 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** and Table 1).

**Pathophysiology**

*Sodium channel structure and function*

Voltage gated sodium channels are transmembrane proteins, composed of an α-subunit and auxiliary β-subunit(s), and are essential for the electrical signaling of neuromuscular cells (5-9). Thus far, nine sodium channels (designated NaV1.1-1.9) have been isolated in humans (8,9). While it is thought that the predominant sodium channel in the human heart is the isoform NaV1.5, studies have indicated that other isoforms (NaV1.4 and NaV1.8) may also be expressed (10,11), albeit at much lower densities.

Cardiac depolarization occurs as a result of sodium channel activation (Figure 1), generally lasting <1ms (12). The activation phase involves conformational changes in the α-subunit, leading to the rapid influx of sodium ions (INa) (5,7). Increasingly, β-subunits are recognized to play an important role in the net INa 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 Brugada syndrome*

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 NaV1.5 sodium channel (16), and can affect the various components including transmembrane proteins, interdomain linkers and the N- or C- terminals (3). These variant NaV1.5 channels show evidence of defective gating properties (activation and/or inactivation) (17), but also reduced trafficking to the cell membrane (18-20). Dysfunctional NaV1.5 channels in patients with BrS results in later activation and earlier inactivation with subsequent shortening of the action potential duration (9). The resultant effect is a reduction of peak INa with a slowing in the upstroke (phase 0) of the action potential (9). Furthermore, experimental models have shown that NaV1.5 function is augmented by changes in ambient temperature (21-23). This becomes especially evident in those with BrS caused by gene variants affecting NaV1.5 (24,25), with additional shortening of action potential duration at higher temperatures (21-23,25).

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 which have been implicated in BrS include *SCN10A* encoding for the α-subunit of the NaV1.8 sodium channel (28-30), those encoding for NaV1.5 β-subunits (31), those involved in NaV1.5 trafficking or expression (32,33), potassium channel genes (responsible for the transient outward current, Ito, during phase 1 of the action potential) (34), and calcium channel genes (responsible for late calcium current, ICaL, 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 influences 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 INa 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 (Ito) 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 Ito 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 confluence of factors leading to a common ECG that may not be explained by a single mechanism.

*Right ventricular outflow tract 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 to healthy controls (55,56), but to a lesser extent than when compared to 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, conduction system, along with the great arteries and 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 electro-anatomical 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 showed that the overall prevalence of BrS with type 1 ECG is ~1:2000, while the prevalence of type 2/3 ECG pattern is ~1:500; and is most common in Asia followed by Europe and the United States (2). 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.

**Diagnosis**:

*Guideline recommendations*

Recommendations for the diagnosis of BrS have evolved over 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 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 below).

*Clinical manifestations*

The clinical manifestations of BrS are syncope and cardiac arrest or SCD resulting from ventricular fibrillation 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 30-50 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, ~1/3 of patients will have syncope while ~2/3 are asymptomatic, though 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 decline 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 medications may provoke the diagnosis of BrS in some cases (98).

*Baseline ECG*

Initially, three 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 elevation ≥2mm with a negative T-wave in the right precordial leads, which are felt to be representative of pathophysiological changes in the RVOT (36). Originally described for standard lead positions in V1-3 (75), it is now recognized that leads V1-2 – at either the 2nd, 3rd or 4th intercostal spaces (Figure 3) – increases the sensitivity for diagnosis due to individual variations in the anatomical position of the RVOT (99). The use of high lead positions is thought to increase the diagnostic yield by ~1.5 times compared to 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., who systematically examined the effects of various antiarrhythmic medications in patients with BrS and found that class 1a anti-arrhythmic drugs (procainamide or disopyramide in their study) augmented the classical ST segment changes in BrS patients, but not controls (90).

Due to differences in global availability of these drugs (73,103,104), four 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 four SCB is on NaV1.5, and the inhibition of INa (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 V1 and V2 in both standard and high lead positions (104), as this increases test sensitivity while maintaining specificity (101).

While SCB challenge testing is an important diagnostic test for BrS, not all SCBs are created equal. Differences in the mechanisms of NaV1.5 inhibition – with class 1a agents acting during the activated state, and class 1c agents acting during the inactivated state (106) – leads 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 Ito) 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). While 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. determined that 8% of positive ajmaline challenges were confounders in families with a history of cardiac arrest or SCD (113), while Hasdemir et al. reported that 27% of patients with atrioventricular node reentrant tachycardia and 4.5% of otherwise “healthy” controls may exhibit type 1 ECG changes with ajmaline administration (114). 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), as 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), since the pathogenicity of other reported putative genes is tenuous in all but exceptional circumstances. This may be considered in consultation with a genetic 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. Again, if SCB testing is negative, additional testing can be avoided.

*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 (SAE), 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 SAE. 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 which have the greatest impact on SAE 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 SAE even when adjusting for other factors (125-132). In a pooled analysis of prospective studies involving 1312 patients, Sroubek et al. found that patients with BrS and syncope had a 2.5% annual incidence of SAE compared to 0.7% for those who did not have syncope (67). Similarly, the documentation of a spontaneous type 1 ECG resulted in a 2-6x relative risk for SAE when adjusting for other factors (125,126,128,131,133-135). In a systematic review of studies involving 4099 patients, Rattanawong et al. found that patients with spontaneous type 1 ECG had a 2.4% annual incidence of SAE compared to 0.65% for those with SCB induced BrS (136). 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 SAE (88).

Overall, patient age and sex do not appear to have a significant impact on the risk of SAE in patients with 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 30-50 years (136). While rare, there are reports of SAE occurring in pediatric age groups (138), even as young as <1 year of age (139). SAE in this group of patients are also associated with the presence of syncope and spontaneous ECG changes (86). Interestingly, significantly less SAE 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 to the general population (140). In addition, while 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. and Berthome et al. found that women had a significantly lower SAE rate compared to men, although this did not adjust for other important factors including the presence of spontaneous ECG changes (132,143). 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 SAE or SCD requires clarification. While one study found a positive family history to be predictive for SAE (144), this has not been confirmed in numerous subsequent studies (126,128,133,135). Interestingly, Sieira et al. found that while a family history of SCD was not associated with increased SAE, the presence of early familial (first degree relative age <35 years) SCD was associated with SAE (145), 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 which demonstrated 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 SAE (133), which has recently been corroborated in a large multi-center study (131). Furthermore, a higher proportion of spontaneous type 1 ECGs during clinical follow-up has been found to correlate with more SAEs (147), while the temporal burden of ST-segment changes on 24-hour Holter monitoring is associated with the occurrence of cardiac events (composed of SAE 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 morphological 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 which 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 SAE in BrS (137,154), while 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.

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

*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 60/217 (28%) patients with PVS induced ventricular arrhythmias had spontaneous VF during follow-up compared to 5/221 (2%) of patients who were non-inducible (160). Additional studies, predominantly from the same cohort of patients, have provided support for these findings (126,145,161,162). In contrast, two large prospective multi-center registries, FINGER with 1029 patients and PRELUDE with 308 patients (124,125), failed to corroborate a utility for PVS. In a systematic review and pooled analysis of prospective observational studies of 1312 patients with BrS (which included patients from FINGER and PRELUDE), Sroubek et al. found that inducibility during PVS was associated with a 2.7 odds ratio of SAE, which was greater if induction occurred with only 1 or 2 extra-stimuli (67). However, while this study adjusted for age, sex and the presence of spontaneous ECG changes, additional non-invasive ECG parameters were not included, and the positive predictive value of the test remained low. Hence, it is possible that non-invasive ECG parameters, some of which are independently associated with high odds ratios for SAE, 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. found that by including other ECG parameters, the presence of f-QRS and early repolarization on ECG were independently associated with SAE while PVS was not (150). In a recent retrospective, multi-center study of 1110 patients, Honarbakhsh et al. found that early repolarization and type 1 ECG changes in peripheral leads (along with spontaneous ECG and syncope) were independently associated with SAE (131). While PVS was not found to be predictive in this cohort, it should be noted that PVS findings were only available for ~1/3 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 extra-stimuli) may be considered as a ‘tie-breaker’ in certain circumstances – for example, a young male 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 indicated 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, as 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. found that the Sieira score did not allow for adequate risk stratification of intermediate risk patients (169). 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.

An up-to-date list of drugs which can precipitate Brugada ECG changes can be found at <https://www.brugadadrugs.org/> (93), including both prescription and non-prescription medications (94). For clinicians, this includes anti-arrhythmic (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, non-prescription 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 SAE in patients with BrS (91). Pediatric patients with BrS appear to be particularly susceptible to SAE in the context of fever (69,171). Thus, it is imperative that patients with BrS are educated regarding the early institution of anti-pyretic 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), while metabolic disturbance such as hypokalemia, hyperkalemia and metabolic acidosis has been reported to uncover Brugada ECG changes (173,174).

*Pharmacological*

Quinidine, and its related compounds quinine and hydroquinidine, is useful in the pharmacological 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 ICaL current during phase 2 of the action potential (178). Mechanistically, it is thought that the inhibition of Ito 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, immunological reactions (thrombocytopenia, anemia, fever, lupus reactions), neurological effects and pro-arrhythmia (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 SAE in patients taking hydroquinidine therapy.

Quinidine has also been shown to reduce VF inducibility at PVS. In a cohort of 60 BrS patients with inducible VF, Belhassen et al. demonstrated that administration of quinidine resulted in non-inducibility in 54 (90%) patients (180). 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 ~1/3 of patients (180,182). The use of low-dose quinidine (200-600mg/day of quinidine sulfate) may improve tolerance while providing reasonable anti-arrhythmic benefit (185,186), while 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 ventricular fibrillation (79,187,188). Its predominant anti-arrhythmic effect in BrS is through increase in ICaL (45,79). Additional pharmacological therapy which may be considered in BrS include phosphodiesterase III inhibitors (cilostazol or milrinone), also acting via potentiation of ICaL (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 SAE in excess of 1.4%, and this represents the highest risk group (67,136). By contrast, a meta-analysis of 1539 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 1613 patients with BrS and a mean follow-up of 6.5 years, Probst et al. presented that the incidence of SCD to be ~0.19% in BrS patients without an ICD compared to ~0.10% in those with an ICD (169), suggesting the possibility of “missed opportunities” for SCD prevention.

Nevertheless, the authors would recommend a primary prevention ICD for patients with BrS syndrome (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 versus 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 BrS patients 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 BrS patients with breakthrough SAE 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 BrS patients undergoing epicardial substrate ablation, Pappone et al. 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 over a median follow-up of 10 months (210). Currently however, ablation is mostly reserved for patients with recurrent ICD shocks which cannot be managed with medical therapy, or those in whom an ICD is indicated but not implanted (e.g., strong patient preference). There are insufficient data to support its use in asymptomatic patients.

**Future directions**

The pathophysiologic understanding of BrS remains incomplete, with a confluence of factors contributing to a heterogenous phenotype of impaired RVOT conduction reserve (36). While disorders of NaV1.5 are the most commonly reported ion channel abnormality, the additional and relative contributions of Ito and ICaL are yet to be determined. Clearly related is the confounding genetic basis for BrS, as 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). While 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 non-invasive markers have been suggested, including cardiac imaging changes (215), although the lack of systematic investigation and reporting limits their current applicability. Thus, a study which can analyze multiple non-invasive 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 end-points should further refine our ability to advise intermediate risk individuals within a shared decision-making framework.

The reported results of ablative treatment for BrS appears 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.

**Conclusion**

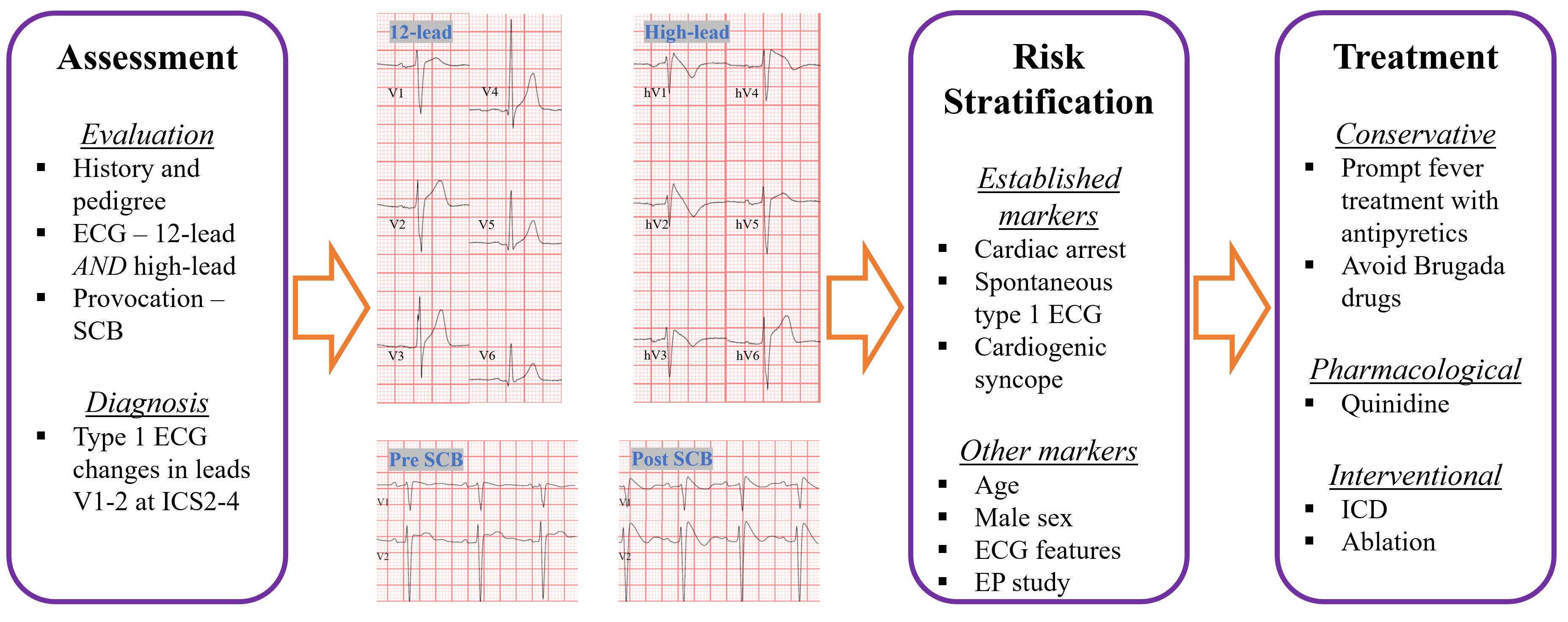
BrS represents a complex clinical problem with a pathognomonic ECG phenotype, although its pathophysiologic basis is incompletely understood, and likely heterogenous in nature. Assessment of clinical and ECG factors are important to both the diagnostic evaluation and risk stratification of patients with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

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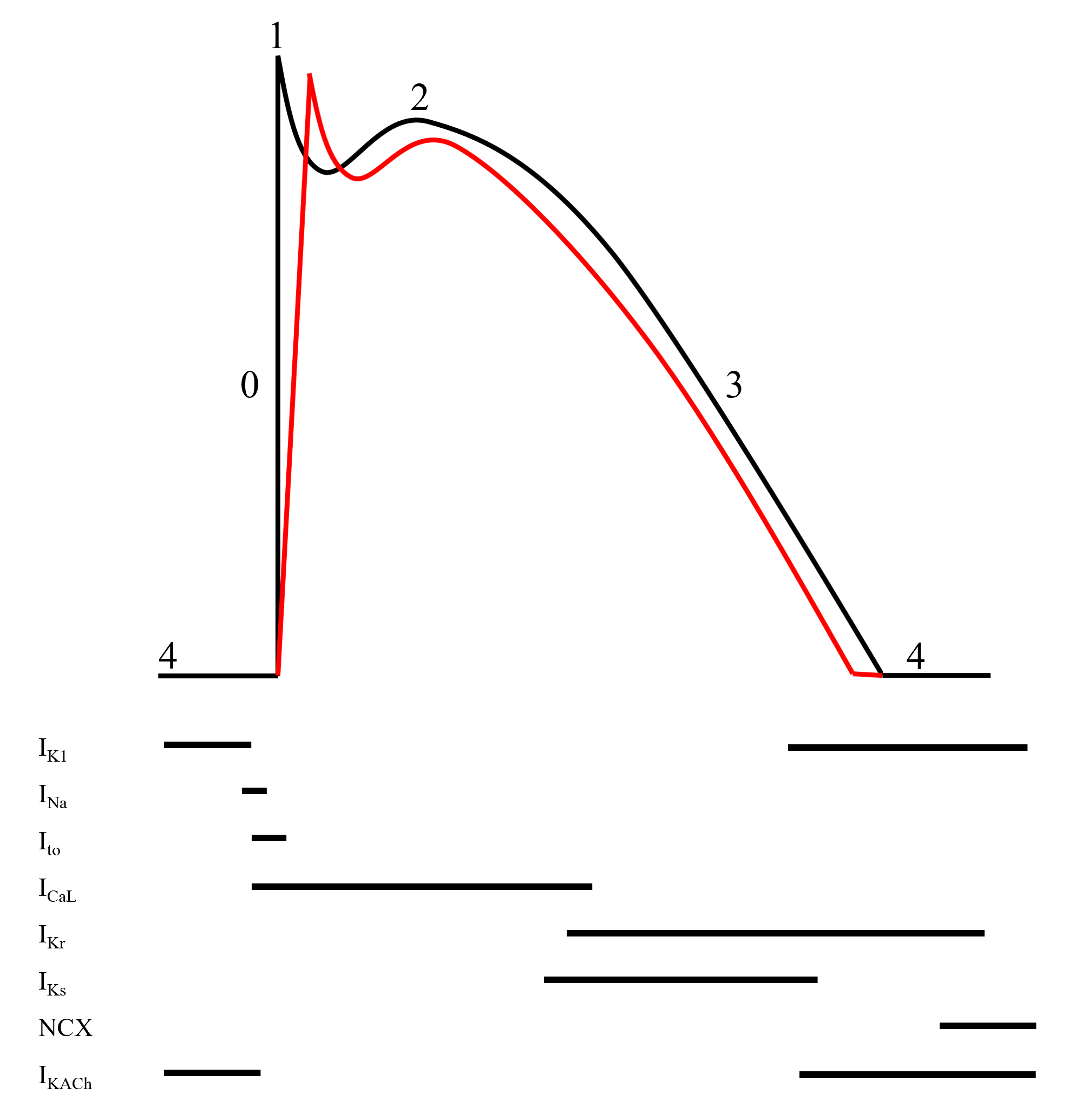
Dr. Krahn receives support from the Sauder Family and Heart and Stroke Foundation Chair in Cardiology (Vancouver, BC), the Paul Brunes Chair in Heart Rhythm Disorders (Vancouver, BC) and the Paul Albrechtson Foundation (Winnipeg, MB). The study was supported by the Heart in Rhythm Organization (Dr. Krahn, Principal Investigator) that receives support from the Canadian Institute of Health Research (RN380020 – 406814). Dr Behr receives funds from the Robert Lancaster Memorial Fund. Dr. Hamilton is funded by a Canadian Institutes of Health Research grant, a Waugh Family Innovation grant from the Labatt Family Heart Centre (2019-2021) to R.M.H., a Freeman Innovation Award from the Heart and Stroke Richard Lewar Centre of Excellence (2019), the Caitlyn Elizabeth Morris Memorial Foundation, the Alex Corrance Memorial Foundation, and Meredith Cartwright L. L.B. Dr. Laksman receives support from The University of British Columbia, Department of Medicine and the School of Biomedical Engineering, The University of British Columbia Cardiology Academic Practice Plan. Dr. Han receives grant support from the RACP Foundation, Australia.

**Central Illustration**

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Abbreviations as per Table 1.

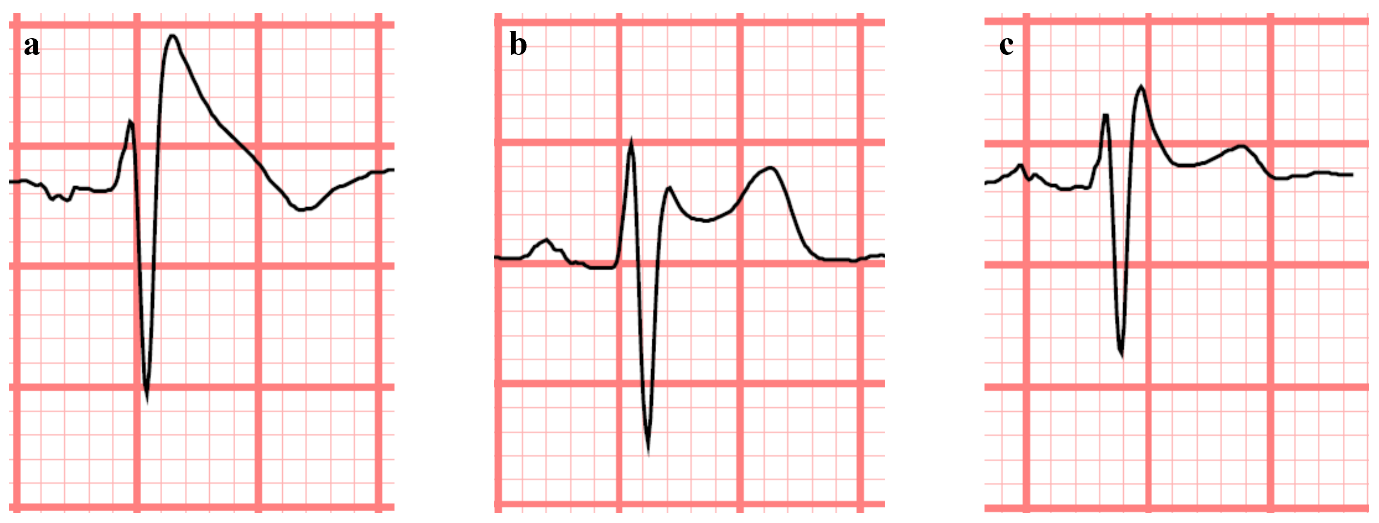
**Figure 1. Action potential**

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Black line indicates normal ventricular action potential; red line indicates delayed upstroke of action potential in Brugada syndrome

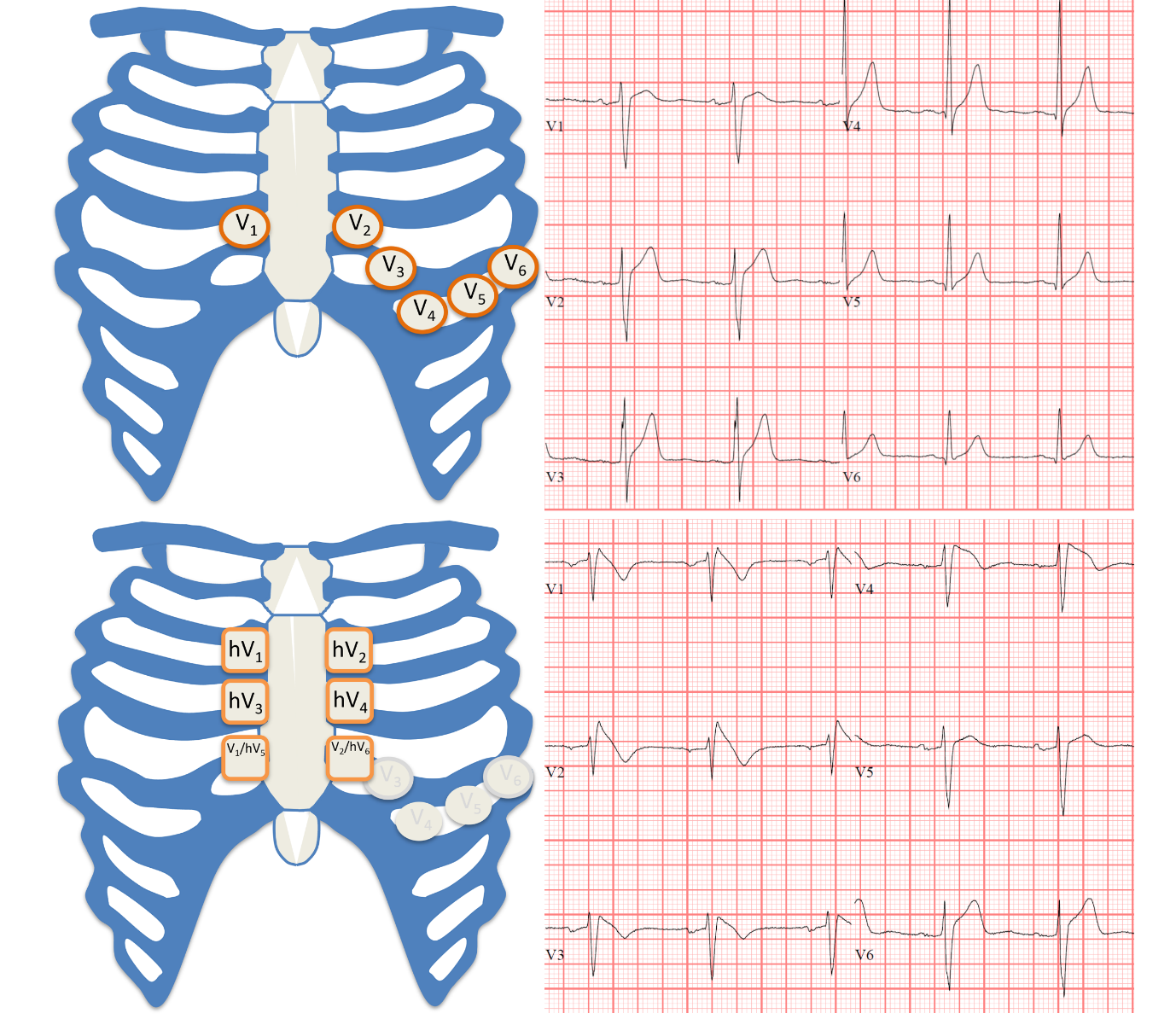
Action potential phases: 0, rapid depolarization; 1, rapid/early repolarization; 2, plateau; 3, terminal repolarization; 4, resting potential

**Figure 2. Brugada pattern ECGs**

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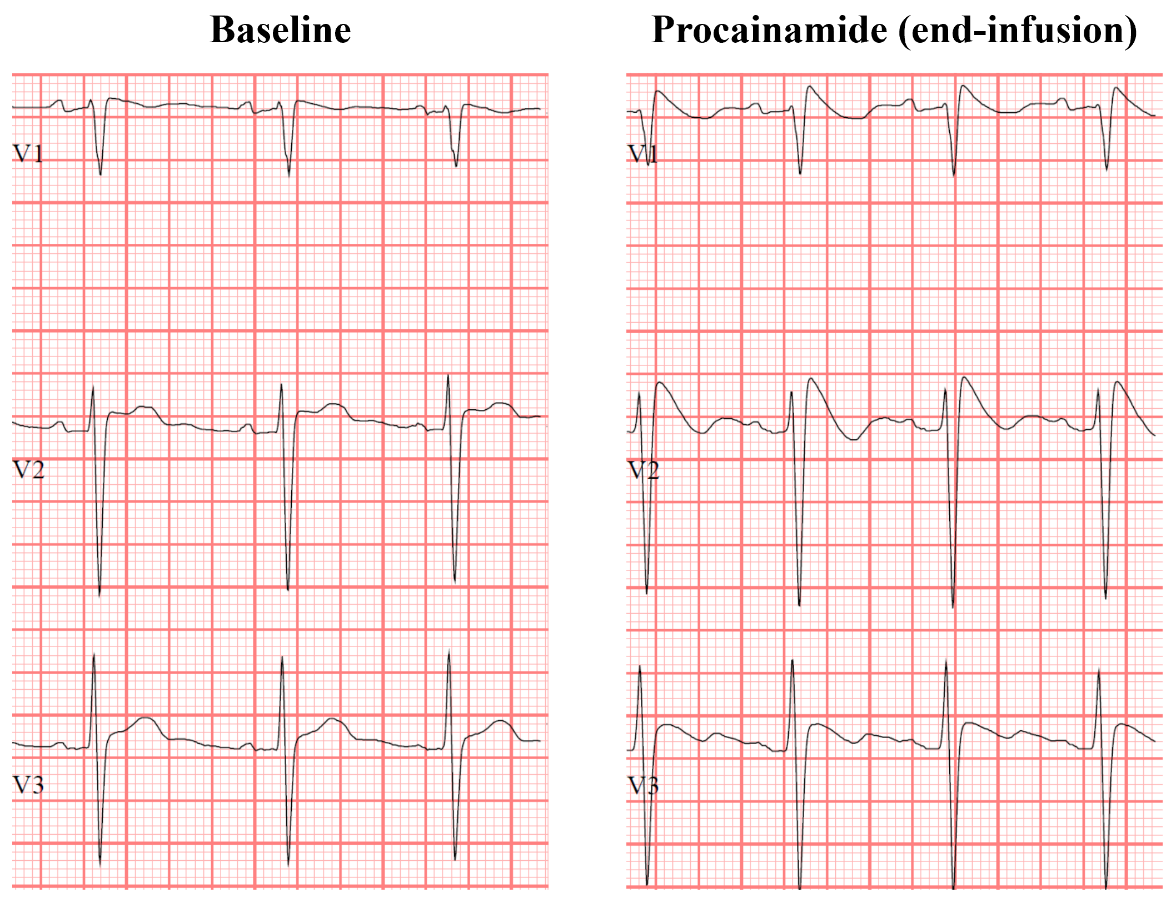
Representative type 1 **(a)**, type 2 **(b)**, and type 3 **(c)**. Brugada pattern ECG traces originally proposed by Wilde et al (75). All feature J-point elevation ≥2mm. Type 1 pattern consists of coved ST elevation (J-point elevation with a gradual down-sloping ST-segment) with T-wave inversion. Type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

**Figure 3. Standard and high lead ECG positions**



Top panel shows standard lead ECG positions and corresponding precordial ECG in a patient with BrS. Bottom panel shows high lead ECG positions and corresponding ECG in the same patient. Note that hV5 and hV6 on the high lead ECG corresponds with V1 and V2 on the standard lead ECG.

**Figure 4. Provocation testing**

****

**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 (1.04-1.18%), syncope + drug-induced (0.98-1.96%), syncope + spontaneous (3.22-3.66%). Developed using data reported by Probst et al. () (125), Sroubek et al. () (67), Rattanawong et al. () (136), and Honarbakhsh et al. () (131).

**Table 1. Diagnosis and management summary for Brugada syndrome**

|  |  |  |
| --- | --- | --- |
| **Diagnosis and Management of Brugada Syndrome** | | |
|  | | |
| **DIAGNOSIS** | | |
| **At Risk** | **Evaluation & 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 V1-2 at ICS2-4   ***Probable***   * Type 1 ECG changes in V1-2 at ICS2-4 with fever or SCB provocation |
|  | | |
| **MANAGEMENT** | | |
| **Conservative** | **Pharmacological** | **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 (≤600mg/day) 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; EP, electrophysiology; ICD, implantable cardioverter defibrillator; ICS, intercostal space; MRI, magnetic resonance imaging; SCB, sodium channel blocker.

**Table 2. Shanghai score**

|  |  |  |
| --- | --- | --- |
|  |  | Points |
| ECG findings\*# |  |  |
| A | Spontaneous type 1 ECG | 3.5 |
| B | Fever induced type 1 ECG | 3 |
| C | Type 2/3 ECG which converts to type 1 ECG with SCB provocation | 2 |
|  |  |  |
| Clinical history\* |  |  |
| 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 years without clear etiology | 0.5 |
|  |  |  |
| Family history\* |  |  |
| 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 in first or second degree relative with negative autopsy | 0.5 |
|  |  |  |
| Genetic testing |  |  |
| A | Probable pathogenic mutation in BrS susceptibility gene | 0.5 |
|  |  |  |

AF, atrial fibrillation; BrS, Brugada syndrome; SCB, sodium channel blocker; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

\*highest point in category

#testing at both standard and high leads

Proposed diagnostic criteria: probable/definite ≥3.5 points, possible 2-3 points, non-diagnostic <2 points

Reproduced with permission from Antzelevitch et al. (78)

**Table 3. Established risk stratification markers**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Study** | **Population** | **N** | **Outcome** | **Risk marker** | **Odds ratio** |
| **Clinical** | Kamakura (144) | Type 1/2/3 | 330 | SAE | Syncope | NS |
| Probst (125) | Type 1 | 1029 | SAE | Syncope | 3.4 |
| Delise (126) | Type 1 | 320 | SAE | Syncope | 2.8 |
| Rollin (133) | Type 1 | 323 | SAE | Syncope | NS\* |
| Takagi (127) | Type 1 without CA | 376 | SAE | Syncope | 2.53 |
| Tokioka (52) | Type 1 | 246 | SAE | VF  Syncope | 19.6  28.6 |
| Conte (161) | Type 1 with ICD | 176 | ICD therapies | CA | 5.13 |
| Okamura (128) | Type 1 without CA | 218 | SAE | Syncope | 6.81 |
| Kawazoe (129) | Not specified | 143 | SAE | Syncope | 4.91 |
| Calo (137) | Spontaneous type 1 without CA | 346 | SAE | Syncope | NS |
| Andorin (85) | Type 1 age <19y | 106 | SAE | Symptoms | 4.7 |
| de Asmundis (150) | Type 1 | 289 | SAE | VF  Syncope | 8.97  9.86 |
| Ueoka (130) | Type 1 | 245 | SAE | Syncope | 3.28 |
| Yuan (142) | Not specified | 4140 (SR) | SAE | Symptoms | 4.54 |
| Berthome (132) | Type 1 females | 494 | SAE | CA (or VF)  Syncope | 69.4  6.8 |
| Subramanian (135) | Type 1 without CA | 103 | SAE | Syncope | NS |
| Honarbakhsh (131) | Type 1 | 1110 | SAE | Syncope | 3.71 |
| **ECG** | Kamakura (144) | Type 1/2/3 | 330 | SAE | Spontaneous | NS |
| Probst (125) | Type 1 | 1029 | SAE | Spontaneous | 1.8 |
| Delise (126) | Type 1 | 320 | SAE | Spontaneous | 6.2 |
| Rollin (133) | Type 1 | 323 | SAE | Spontaneous | 2.43 |
| Takagi (127) | Type 1 without CA | 376 | SAE | Spontaneous | NS |
| Letsas (134) | Type 1 asymptomatic | 1398 (SR) | SAE | Spontaneous | 3.56 |
| Okamura (128) | Type 1 without CA | 218 | SAE | Spontaneous | 4.51 |
| Kawazoe (129) | Not specified | 143 | SAE | Spontaneous | NS |
| Rivard (152) | Type 1 | 105 | SAE | Spontaneous | 10.80 |
| Andorin (85) | Type 1 age <19y | 106 | SAE | Spontaneous | 5.9 |
| Gonzalez Corcia (86) | Type 1 age ≤25y | 128 | SAE | Spontaneous | 8.07 |
| de Asmundis (150) | Type 1 | 289 | SAE | Spontaneous | 3.88 |
| Berthome (132) | Type 1 females | 494 | SAE | Spontaneous | NS |
| Subramanian (135) | Type 1 without CA | 103 | SAE | Spontaneous | 4.10 |
| Honarbakhsh (131) | Type 1 | 1110 | SAE | Spontaneous | 3.80 |

CA, cardiac arrest; ICD, implantable cardioverter defibrillator; NS, non-significant; SAE, serious arrhythmic events; SR, systematic review; VF, ventricular fibrillation

\*p=0.051

**Table 4. Other potential risk stratification markers**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Study** | **Population** | **N** | **Outcome** | **Risk marker** | **Odds ratio** |
| **Clinical** | Kamakura (144) | Type 1/2/3 | 330 | SAE | FHx | 3.28 |
| Probst (125) | Type 1 | 1029 | SAE | Age, male | NS |
| Delise (126) | Type 1 | 320 | SAE | Age, male, FHx | NS |
| Rollin (133) | Type 1 | 323 | SAE | FHx | NS |
| Okamura (128) | Type 1 without CA | 218 | SAE | Age, male, FHx | NS |
| Kawazoe (129) | Not specified | 143 | SAE | Age, male | NS |
| Calo (137) | Spontaneous type 1 without CA | 346 | SAE | Age, male, FHx | NS |
| Yuan (142) | Not specified | 4140 (SR) | SAE | Male | 2.06 |
| Berthome (132) | Type 1 females | 494 | SAE | Age, FHx | NS |
| Subramanian (135) | Type 1 without CA | 103 | SAE | Age, male, FHx | NS |
| **ECG** | Takagi (151) | Type 1 | 188 | SAE | R-J interval (V2) ≥90ms  QRSd (V6) ≥90ms | 4.61  4.42 |
| Kamakura (144) | Type 1/2/3 | 330 | SAE | ERP | 2.66 |
| Priori (124) | Type 1 | 308 | SAE | f-QRS | 4.94 |
| Rollin (133) | Type 1 | 323 | SAE | Type 1 (peripheral leads) | 4.58 |
| Takagi (127) | Type 1 without CA | 376 | SAE | QRSd (V2) >90ms  ERP + horizontal ST | >10  2.96 |
| Tokioka (52) | Type 1 | 246 | SAE | f-QRS  ERP | 5.2  2.87 |
| Kawazoe (129) | Not specified | 143 | SAE | R-J interval (V1)  Tp-e dispersion  QRSd (V6) | 1.04  1.07  1.04 |
| Rivard (152) | Type 1 | 105 | SAE | Tp-e ≥100ms  QRSd ≥110ms | 29.73  15.27 |
| Calo (137) | Spontaneous type 1 without CA | 346 | SAE | AF  S-wave (I) ≥40ms | 3.70  39.10 |
| de Asmundis (150) | Type 1 | 289 | SAE | f-QRS  ERP | 6.33  3.77 |
| Ueoka (130) | Type 1 | 245 | SAE | ST elevation ≥0.3mV  SCB induced VAs | 2.80  3.62 |
| Berthome (132) | Type 1 females | 494 | SAE | QRSd (II) >120ms  f-QRS | 4.7  20.2 |
| Subramanian (135) | Type 1 without CA | 103 | SAE | S-wave upslope  f-QRS  Tp-e ≥100ms | 3.84  2.99  3.65 |
| Giustetto (155) | Type 1 | 614 | SAE | QRSd V6 | 1.1 |
| Honarbakhsh (131) | Type 1 | 1110 | SAE | ERP (peripheral leads)  Type 1 (peripheral leads) | 3.42  2.33 |
| **Electrophysiological** | Kamakura (144) | Type 1/2/3 | 330 | SAE | Inducible VAs | NS |
| Probst (125) | Type 1 | 1029 | SAE | Inducible VAs | NS |
| Priori (124) | Type 1 | 308 | SAE | VERP<200ms  Inducible VAs | 3.91  NS |
| Takagi (127) | Type 1 without CA | 376 | SAE | Inducible VAs | NS |
| Letsas (134) | Type 1 asymptomatic | 1104 (SR) | SAE | Inducible VAs | 3.51 |
| Conte (161) | Type 1 with ICD | 176 | ICD therapies | Inducible VAs | 3.38 |
| Okamura (128) | Type 1 without CA | 218 | SAE | Inducible VAs | NS |
| Sroubek (67) | Type 1 | 1312 (SR) | SAE | Inducible VAs | 3.34-3.45 |
| Casado-Arroyo (87) | Type 1 probands | 447 | SAE | Inducible VAs | 3.46 |
| Calo (137) | Spontaneous type 1 without CA | 346 | SAE | Inducible VAs | NS |
| de Asmundis (150) | Type 1 | 289 | SAE | Inducible VAs | NS |
| Berthome (132) | Type 1 females | 494 | SAE | Inducible VAs | NS |
| Subramanian (135) | Type 1 without CA | 103 | SAE | Inducible VAs | NS |

AF, atrial fibrillation; CA, cardiac arrest; ERP, early repolarization pattern; FHx, family history of sudden death; fQRS, fractionated QRS; HR, heart rate; ICD, implantable cardioverter defibrillator; NS, non-significant; QRSd, QRS duration; SAE, serious arrhythmic events; SCB, sodium channel blocker; Tp-e, T-wave peak to end; VAs, ventricular arrhythmias

\*During exercise ECG

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