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REVIEW

Brugada Syndrome: Clinical Care Amidst Pathophysiological Uncertainty

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Brugada syndrome (BrS) is a complex clinical entity with ongoing conjecture regarding its genetic basis, underlying pathophysiology, and clinical management. Within this paradigm of uncertainty, clinicians are faced with the challenge of caring for patients with this uncommon but potentially fatal condition. This article reviews the current understanding of BrS and highlights the "known unknowns" to reinforce the need for flexible clinical practice in parallel with ongoing scientific discovery.

Keywords Brugada syndrome • Risk stratification • Sudden death • Arrhythmogenesis • Implantable cardioverter-defibrillator • Non-device management

Introduction

Brugada syndrome (BrS) is an inherited arrhythmogenic heart disease defined by the classic electrocardiographic feature of coved ST-segment elevation in the right precordial leads and an increased risk of sudden death. Although some suspicion of an association of right bundle branch block, early repolarisation and idiopathic VF had been raised by Martini et al. in 1989 [1], the first formal description of the clinical syndrome was reported by Brugada et al. in 1992 [2]. Nademanee et al. [3] reported the same electrocardiographic features in those resuscitated from the Sudden Unexplained Nocturnal Death Syndrome.

The prevalence of type 1 Brugada electrocardiogram (ECG) pattern has been reported to be in the range of 1 in 2,000, but the true incidence of BrS is difficult to define because of variable penetrance, dynamic electrocardiographic features and concealed phenotypes. Moreover, large ethnic differences exist with prevalence reported to be 10-fold higher in South-East Asian populations compared to European and North American cohorts [4]. Males are much more commonly affected than females, and the average age at diagnosis is in the fourth decade [5].

Pathophysiology of BrS

A schema of our current understanding of the pathophysiology of BrS is summarised in Figure 1. Despite the recognition of BrS as a clinical entity for almost three decades [2], the underlying pathophysiological mechanisms remain contentious. Brugada syndrome has historically been considered a channelopathy, requiring a structurally normal heart by definition and there has been vibrant debate between the predominant electrophysiological theories of abnormal repolarisation and depolarisation [6]. Recent advances in non-invasive imaging, improved electrophysiological characterisation and potentially curative ablation, as well as histological observations have prompted a reassessment of the interplay between structural and functional changes and the complex heterogenous drivers of BrS and its phenocopies.

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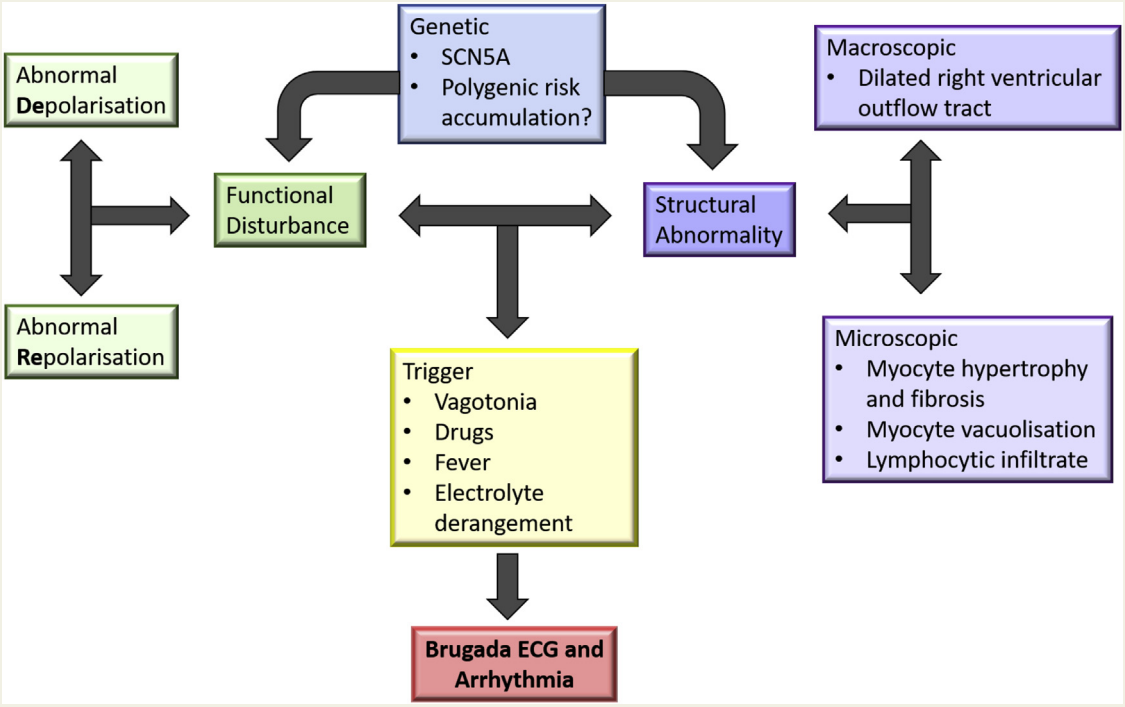

Figure 1 Pathophysiology of Brugada Syndrome.
Abbreviation: ECG, electrocardiograph.

The repolarisation hypothesis is based upon the regional variation in electrophysiological properties of cardiac myocytes. Data from *in vitro* studies using perfused sections of canine myocardium demonstrated differential expression of transient outward potassium current (I_{to}) between endocardial and epicardial myocytes which, when coupled with a reduced phase 0 inward sodium current (I_{Na}) due to sodium channel dysfunction, creates a transmural gradient across the myocardium causing the characteristic ST-segment elevation of BrS [7]. This dispersion of repolarisation between myocardial layers has also been implicated in the development of phase 2 re-entry mediated extrasystolic events; a proposed mechanism for ventricular arrhythmias in BrS [7].

By contrast, the depolarisation hypothesis, based largely on clinical observations, postulates that reduced phase 0 I_{Na} causes conduction delay across the right ventricle, most marked in the right ventricular outflow tract (RVOT) [6]. This leads to the development of a gradient between the right ventricle (RV) and the more delayed RVOT causing initial ST elevation in the high precordial leads which overlie the RVOT. In the later stage of the action potential, the gradient reverses, shifting net membrane potential back from the RVOT to RV accounting for T-wave inversion as current travels away from the high precordial leads [8].

A unifying point between these two apparently divergent hypotheses is that the RVOT is the primary site of arrhythmogenesis. Electrophysiological studies have demonstrated delayed conduction [9,10], electro-anatomical abnormalities characterised by low voltage, fractionated electrograms localised to the RVOT [11] and increased arrhythmic inducibility during stimulation from the RVOT [12]. Cardiac magnetic resonance (CMR) imaging has shown significantly increased RVOT size in BrS patients compared with controls [13] and recent studies have confirmed that these structural changes are isolated to the outflow tract, as opposed to the more generalised right ventricular changes seen in arrhythmogenic right ventricular cardiomyopathy [14].

Histopathological studies have revealed structural changes in BrS patients but no pathognomonic pattern has been identified [1,15]. Resolution of BrS ECG changes and reduction of spontaneous arrhythmic events have been reported following catheter ablation in the RVOT [10,16,17]. This is perhaps the most compelling evidence for the importance of the RVOT in arrhythmogenesis in BrS. Collectively, this has led to the proposal that BrS may be considered an inherited cardiomyopathy rather than a primary arrhythmia syndrome in some cases. The ECG phenotype of BrS may be the final common pathway for expression of a potential gradient of structural and electrical changes affecting both depolarisation and repolarisation, resulting in an arrhythmogenic RVOT [18]. No single hypothesis fits all of the clinical observations.

Genetic Basis of BrS

Brugada syndrome has endured a tortuous journey of genetic discovery since the first report of causative mutations in the sodium channel gene *SCN5A* in 1998 [19]. Even at this early stage, the mechanistic complexity of genotype-

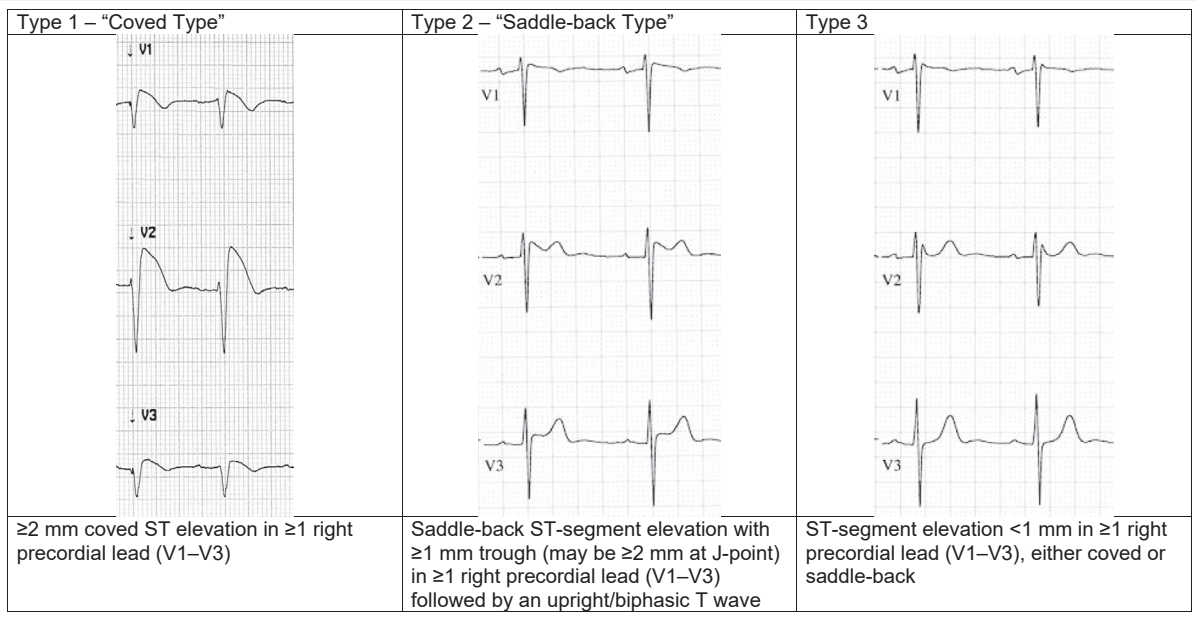

Figure 2 Electrocardiographic Features of Brugada Syndrome.

phenotype interaction in BrS was apparent, with functionally different variants producing electrocardiographic heterogeneity, hinting at the likely role for modifying factors.

Technological advances in genetic testing and the advent of high throughput, next generation sequencing led to an explosion of genetic data and a new set of challenges surrounding variant interpretation. Determining the pathogenicity of a variant is a complex and dynamic process that takes into account evolving evidence such as population data, functional assessment and family studies. At present, the role of diagnostic genetic testing in BrS is limited, with a reported yield of ~20% typically contingent upon the finding of a recognised pathogenic variant in *SCN5A* [20]. It is noteworthy that missense variants in *SCN5A* occur frequently, and may be present in 2–5% of healthy individuals [20]. The pathogenicity of a variant is generally supported when it segregates within a family, but genotype-phenotype mismatch has been reported in families with BrS [21]. Beyond *SCN5A*, hundreds of variants in over 20 genes have been proposed to cause BrS genetic subtypes [22]. The majority of these variants affect sodium channel related genes. However, recent case-control studies and expert gene curation have relegated all non-*SCN5A* genes to "genetic purgatory" such that many clinics currently restrict diagnostic genetic testing in BrS to the *SCN5A* gene only [22]. Moreover, the genetic landscape of BrS is moving from a single gene mechanism to "polygenic risk accumulation" contributing to clinical phenotype, supported by genome wide association studies showing potential "risk alleles" in various sodium channel related genes and genes encoding transcription regulator function [23].

Diagnosis and Risk Stratification

Features of BrS

The ECG is the cornerstone of diagnosis in BrS and three ECG patterns are described (Figure 2). The type 1 pattern is characterised by ≥2 mm ST-segment elevation in at least one of V1 or V2. Type 2 and 3 morphologies are suspicious for BrS but non-diagnostic. The ECG pattern can be mimicked by various pathologies (Table 1) and these should be excluded prior to conferring a diagnosis of BrS [4]. Electrocardiographic changes of BrS fluctuate and are not present in affected patients at all times. Modifiers of the BrS ECG morphology are also listed in Table 1 [4].

Prolonged ECG monitoring is useful given the dynamic nature of the BrS ECG and high precordial lead placement (V1 and V2 in the second and third intercostal spaces) has been shown to increase diagnostic sensitivity [24]. Sodium channel blockers can be used to "provoke" a Type 1 ECG pattern to aid in diagnosis where BrS is suspected but the resting ECG is non-diagnostic. There are currently no imaging criteria for the diagnosis of BrS but CMR imaging may be useful in excluding alternate pathologies, especially arrhythmogenic right ventricular cardiomyopathy [14]. However, it is important to remember that subtle abnormalities in RVOT morphology and function may be observed in patients with BrS.

Table 1 Mimickers and Modulators of Brugada Syndrome Electrocardiogram Modified From Antzelevitch et al. [4]

Mimickers of the Electrocardiographic Features of Brugada Syndrome	Modulators of the Electrocardiogram in Brugada Syndrome
• Atypical right bundle branch block • Ventricular hypertrophy • Early repolarisation (especially in athletes) • Acute pericarditis/myocarditis • Acute myocardial ischaemia or infarction (especially of the right ventricle) • Pulmonary thromboembolism • Prinzmetal angina • Dissecting aortic aneurysm • Central and autonomic nervous system abnormalities • Duchenne muscular dystrophy • Friedreich ataxia • Spinobulbar muscular atrophy • Myotonic dystrophy • Arrhythmogenic right ventricular dysplasia • Mechanical compression of the right ventricular outflow tract (e.g., pectus excavatum, mediastinal tumour, haemopericardium) • Hypothermia • Post-defibrillation electrocardiogram	• Electrolyte abnormalities: ◦ Hyperkalaemia ◦ Hypokalaemia ◦ Hypercalcaemia ◦ Hyponatraemia • Temperature: hyperthermia (fever), hypothermia • Vagotonia • Hypertestosteronaemia • Treatment with: ◦ Antiarrhythmic drugs: sodium channel blockers (Class IC, Class IA), calcium antagonists, beta blockers ◦ Antianginal drugs: calcium antagonists, nitrates, potassium channel openers ◦ Psychotropic drugs: tricyclic/tetracyclic antidepressants, phenothiazines, selective serotonin reuptake inhibitor, lithium, benzodiazepines ◦ Anaesthetics/analgesics: propofol, bupivacaine, procaine ◦ Others: histamine H_1 antagonist, alcohol intoxication, cocaine, cannabis, ergonovine

Diagnostic Criteria

A key challenge in BrS is the risk of over-diagnosis in healthy individuals. This is particularly relevant for those without a spontaneous Type 1 ECG morphology. The false positive rate of the sodium blocker challenge is unknown because there is no gold standard for the diagnosis of BrS. The prevalence of drug-induced Type 1 ECG pattern has been shown to be five times higher than spontaneous Type 1 pattern and moreover, the outcome of provocation testing varies with sodium channel blocker used. [4,25,26].

In consensus statements published in 2002 and 2005, criteria for diagnosis of BrS required patients to be symptomatic or have additional clinical features (such as family history of sudden cardiac death at age <45 years, ventricular tachycardia [VT] inducibility during programmed electrical stimulation) to satisfy the diagnosis of Brugada syndrome [27,28]. The ECG in isolation was initially referred to as Brugada pattern. Guidelines published in 2013 removed the requirement for symptoms or additional features, such that a type 1 ECG pattern alone (spontaneous or induced) was sufficient for the diagnosis of BrS [29]. Due to concerns about overdiagnosis in cases of drug-induced BrS, Antzelevitch et al. have proposed an empirical scoring system for the diagnosis of BrS, divergent from the most recent consensus statement (Table 2) [4]. It is noteworthy that these so-called Shanghai criteria require validation.

Risk Stratification

Identifying those at risk of ventricular arrhythmias from BrS is a vital step to ensuring personalised therapy in this syndrome with highly variable outcomes. Clinical events are the greatest predictor of future events with nearly half of those who present with cardiac arrest having a ventricular fibrillation (VF) recurrence within 10 years [30]. Brugada syndrome patients with a syncopal event have a four-fold increased risk of VF compared to their asymptomatic counterparts [5]. A detailed history is vital in differentiating arrhythmic syncope and lower-risk vagal syncope [31,32].

Although the risk of events in asymptomatic patients is significantly lower (~0.5–1% per year [5,30]), these patients account for two-thirds of BrS cases and their risk of sudden cardiac arrest is over 100 times that of the general population [5,31]. Risk stratification in the asymptomatic cohort is a far more challenging prospect than for those with symptoms and surrogate markers of risk are under evaluation [31]. Spontaneous type 1 BrS ECG is associated with higher event rates than drug-induced BrS [5,33]. The use of programmed ventricular stimulation (PVS) to identify BrS patients at risk of VF remains controversial. Early studies including a large single centre prospective cohort study and a pooled analysis [34,35] suggested VF inducibility is associated with future arrhythmic risk but several large scale

Table 2 Shanghai Score – a proposed system for diagnosis of Brugada Syndrome reprinted from Antzelevitch et al. [4]

Criteria	Points
ECG (12-Lead/Ambulatory)	
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	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 mechanism/ unclear aetiology	1
E. Atrial flutter/fibrillation in patients <30 years without alternative aetiology	0.5
Family History	
A. First- or second-degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
C. Unexplained SCD ≤45 years in first- or second-degree relative with negative autopsy	0.5
Genetic Test Result	
A. Probable pathogenic mutation in BrS susceptibility gene	0.5
Score *(only include the highest appropriate point value from each of the 4 categories)* ≥3.5 points: Probable/definite BrS 2–3 points: Possible BrS 0-2 points: Non-diagnostic	

Abbreviations: BrS, Brugada syndrome; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia; ECG, electrocardiogram.

registries have failed to show a consistent association between VF inducibility and clinical events, especially when other clinical factors have been included on multivariate analysis [5,33]. Some of this variation can be accounted for by the use of different induction protocols [36]. No definitive correlation has been shown between family history of sudden cardiac death (SCD) or *SCN5A* mutation and an individual's risk of suffering an arrhythmic event in the future [5,31,33]. Emerging electrocardiographic markers of risk are under ongoing investigation and outlined in Table 3.

Current Approach to Management of BrS

Family screening is paramount. First degree relatives should undergo resting ECG with normal and high precordial lead placement. The merits of sodium channel blocker challenge should be discussed if a spontaneous type 1 ECG is not observed on resting ECG or Holter monitoring.

All patients should be educated about lifestyle modifications including aggressive fever management with antipyretics, avoidance of excessive alcohol, and any new medication checked for safety at brugadadrugs.org [4,29,37]. Exercise restriction is not currently recommended for patients with BrS [37].

More invasive interventions are guided by risk stratification (Figure 3). Implantable cardioverter-defibrillators (ICD) remain the mainstay for prevention of sudden death. Medical therapy with quinidine and more recently, catheter ablation may have emerging roles in reducing arrhythmic events.

ICDs in BrS: The Goldilocks dilemma

Guidelines [29,37,38] recommend ICDs for BrS patients at high risk of ventricular arrhythmia to reduce the risk of sudden cardiac death, but the BrS population has higher rates of transvenous ICD-related complications compared to other cohorts [39]. ICD therapy has a class Ia indication for those with previous cardiac arrest or spontaneous VT and IIa recommendation for those with a spontaneous type 1 BrS ECG and syncope. The unclear utility of PVS is reflected in the IIb recommendation for ICD in BrS patients with inducible arrhythmia. Device complications including inappropriate shocks, lead malfunction and infections have been reported to occur at up to twice the rate of appropriate shocks in asymptomatic BrS patients [30]. Even in the setting of more stringent patient selection in the contemporary era, a metanalysis in 2016 reported that 20% of patients experienced an inappropriate shock and 20% had a device-related complication (including lead malfunction and infection) during follow-up with an annual event rate of 3.9% and 3.4% respectively [39]. Subcutaneous ICDs may overcome some of the potential complications of device therapy but surface ECG morphology screening is vital to avoid inappropriate shocks due to T-wave oversensing. A recent study including 61 BrS patients showed that nearly 20% were ineligible for subcutaneous devices on standard screening and that a further 15% of those previously considered appropriate, failed screening following drug challenge [40].

Discussions surrounding ICD implantation are particularly challenging in lower risk patients. For asymptomatic patients, clinicians must suppress the "oculo-defibrillator"

Table 3 Emerging Electrocardiographic Risk Markers in Brugada Syndrome

Support	Potential Risk Marker	Refute
Ajiro et al. 2005 [48] Ikeda et al. 2005 [49] Huang et al. 2009 [50]	**Late potentials on SAECG**	Leong et al. 2019 [51]
Morita et al. 2008 [52] Priori et al. 2012 [33] Take et al. 2012 [53] Tokioka et al. 2014 [54]	**Fractionated QRS**	Sakamoto et al. 2016 [55]
Junttila et al. 2008 [56] Ohkubo et al. 2011 [57]	**QRS width**	Probst et al. 2010 [5] Priori et al. 2012 [33] Maury et al. 2013 [58] Tokioka et al. 2014 [54]
Kamakura et al. 2009 [59] Sarkozy et al. 2009 [60] Tokioka et al. 2014 [54]	**Early repolarisation in inferior leads**	Letsas et al. 2008 [61]
Calò et al. 2016 [62]	**Prominent S wave in lead 1**	Leong et al. 2019 [51]
Babai Bigi et al. 2007 [63]	**Prominent R wave in lead aVR**	Junttila et al. 2008 [56] Maury et al. 2013 [58]
Maury et al. 2013 [58] Migliore et al. 2019 [64]	**AV conduction delay**	
Rollin et al. 2013 [65]	**Type 1 BrS morphology in peripheral leads**	

Abbreviations: SAECG, signal averaged electrocardiogram; AV, atrioventricular; BrS, Brugada syndrome.

reflex given the risk of malignant arrhythmia is generally low and device complication rates are high. For now, these patients are best served by close clinical follow-up and primary prevention ICD therapy is not recommended in this cohort [29,37,38].

Pharmacotherapy and Catheter Ablation in BrS

Non-device therapy is a useful adjunct for BrS patients with arrhythmic storm and recurrent shocks but does not replace the need for ICD in high risk patients. Quinidine has been used in patients with BrS and its proposed mechanism of action in BrS is via the inhibition of I_{to} [7]. The utility of electrophysiologically-guided quinidine therapy has been shown in both high risk and asymptomatic BrS patients in 2004 [41,42]. Non-randomised data has continued to support the use of quinidine therapy in managing arrhythmic storms. However, randomised data has failed to show benefit in asymptomatic patients [43,44] and no study has demonstrated a mortality benefit with quinidine [37], possibly due to low event rates. Moreover, the use of quinidine is not without issues such as drug-related adverse events (including pro-arrhythmia) and limited availability [45]. Current guidelines support the use of quinidine to treat electrical storms or in those who qualify for an ICD but have a contraindication or decline device therapy [37]. The use of quinidine in asymptomatic patients remains speculative although it is hoped that an ongoing multi-centre registry will provide data in this cohort [46].

Radiofrequency catheter ablation for BrS was initially performed via an *endo*cardial approach targeting triggers within the right ventricular outflow tract (RVOT) [16]. More recently, *epi*cardial substrate ablation, with or without intraprocedural drug provocation, has produced encouraging results including normalisation of the ECG morphology, reducing or eliminating VT inducibility and reduction in ventricular arrhythmias during short-term follow-up [17,47]. Catheter ablation may be considered in BrS patients with electrical storm and recurrent ventricular arrhythmias [37], but extending this recommendation to other patient cohorts (eg. prophylactic ablation) will required further data from larger studies with longer term follow-up.

Future Directions in BrS

The three decades following the original description of BrS has seen determined efforts to unravel the complex associations between the Brugada ECG changes and sudden death [2]. Competing hypotheses regarding the molecular mechanisms of BrS have been described and they may not be mutually exclusive. Looking beyond the BrS epithet may reveal of a cluster of diseases with a crossover of features both genetically and clinically including conduction disease, ventricular arrhythmias and minor structural changes. As a scientific community, we appear to be moving away from a view of BrS as a homogeneous disease to a more nuanced understanding of BrS as a heterogeneous entity with a broad

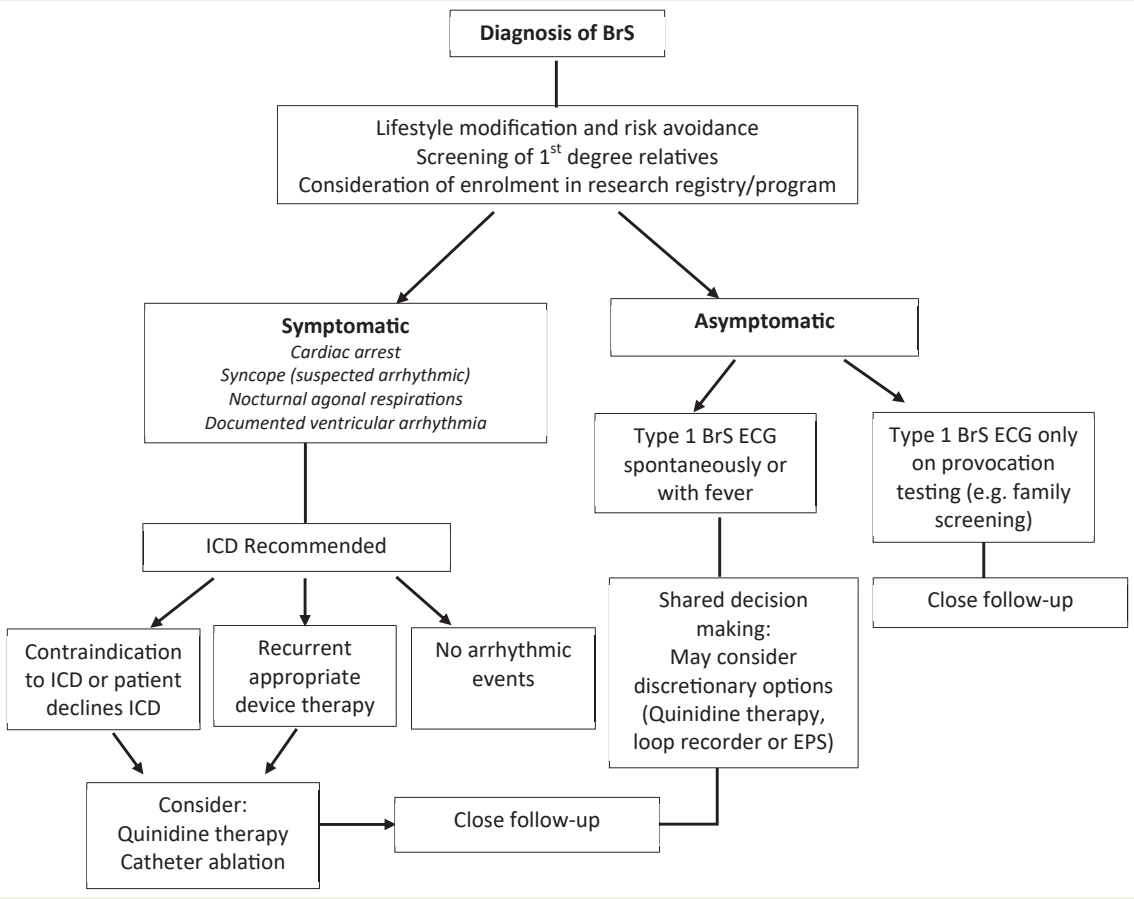

Figure 3 Proposed Paradigm for Management of Patients with BrS.
Abbreviations: BrS, Brugada syndrome; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; EPS, electrophysiology study.

spectrum of presentation and outcomes [18]. Brugada syndrome has provided an important lesson in the dynamic nature of our understanding of gene variant association with disease. Further focus on how variants, either alone or in combination, mechanistically cause or trigger events in BrS [22] will be key to ensuring the safe translation of genetic data to personalised clinical care.

As the mechanistic understanding of BrS improves and larger multi-centre clinical registries are developed, emerging markers of risk may be confirmed or refuted, giving clinicians increased guidance on the management of asymptomatic BrS patients [31]. Finally, improved non-device therapy for this largely young cohort is on the horizon, with encouraging results from catheter ablation in high risk cohorts with ICD protection. Further research is needed to assess the safety of catheter ablation as stand-alone therapy and also its role in patients who do not qualify for ICD therapy.

Disclosures

Nil.

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