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Contemporary Perspectives on J-Wave Syndromes: An Expert Consensus Statement

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ABSTRACT

J-wave syndromes (JWS)—comprising Brugada syndrome (BrS) and early repolarization syndrome (ERS)—are important causes of malignant ventricular arrhythmias and sudden cardiac death in patients whose hearts appear structurally normal. Since the 2016 consensus, advances in genetics, pathophysiology, and therapy have redefined both understanding and management. BrS, once viewed as a purely electrical disorder, is now recognized along a microstructural–electrical continuum, with sodium-channel dysfunction and subtle epicardial fibrosis of the right ventricular outflow tract as key contributors. Likewise, ERS—historically considered benign—carries significant risk when inferolateral J-waves coexist with arrhythmic events. Genetically, SCN5A remains the sole gene with definitive disease association, while polygenic susceptibility materially modulates risk, underscoring complex inheritance. Risk stratification remains challenging: patients with prior cardiac arrest or arrhythmic syncope are highest risk, whereas asymptomatic individuals warrant multiparametric assessment integrating clinical features, ECG markers, electrophysiologic studies, and genetics. For decades, treatment centered on implantable cardioverter-defibrillators and quinidine, both limited by availability, tolerance, and device complications. More recently, epicardial substrate ablation has emerged as a transformative therapy, with large registries and randomized trials demonstrating durable suppression of ventricular fibrillation and acceptable safety. This APHRS-organized international consensus updates and extends the 2016 Expert Consensus and the 2022 ESC Guidelines, providing contemporary diagnostic frameworks, pragmatic risk-stratification tools, and treatment algorithms for BrS and ERS. It emphasizes JWS as a microstructural–electrical disease spectrum and elevates substrate ablation as a major therapeutic advance, while outlining priorities for genetics, risk-stratification and treatment algorithms.

Abbreviations: BrS, Brugada syndrome; CMR, cardiac magnetic resonance; ER, Early repolarization; fQRS, fragmented QRS; GWAS, genome-wide association study; ILR, implantable loop recorder; JWS, J-wave syndromes; LV, left ventricle/left ventricular; PES, programmed electrical stimulation; PRS, polygenic risk score; PVCs, Premature ventricular contractions; RV, right ventricle/right ventricular; RVOT, Right ventricular outflow tract; RVOT, right ventricular outflow tract; VT/VF, Ventricular tachycardia/ Ventricular fibrillation.

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1 | Introduction

Over three decades ago, Pedro and Joseph Brugada unveiled a clinical entity now recognized for its distinctive electrocardiogram (ECG) patterns, the type 1 Brugada ECG pattern, characterized by J-wave augmentation and coved-type ST elevation in the right precordial leads, hallmarks linked to malignant ventricular arrhythmias and sudden cardiac death (SCD) [1] in victims without overt structural heart disease and thought to be a primary electrical disorder. This condition quickly became known as Brugada syndrome (BrS) in the medical community. Interestingly, the prominent J-wave with right precordial ST-elevation, along with malignant ventricular arrhythmias, had been described earlier, but the focus of this study was on associated distinct structural abnormalities in their study patients [2]. This has led to a belief that the cases described by Martini et al. and the Brugada brothers represent different phenomena.

However, despite initial theories positioning the syndrome as primarily an electrical disturbance, subsequent research has definitively linked BrS to structural anomalies in the right ventricular outflow tract (RVOT) [3–6]. Although use of the term ‘Brugada syndrome’ has been contentious [2], there is now an emerging consensus that BrS encompasses a complex interplay between electrical abnormalities of ionic currents and subtle

structural myopathic changes, challenging and expanding our understanding of this enigmatic condition [7].

Parallel to this, the early repolarization (ER) ECG pattern has been acknowledged by ECG scholars for its commonality among younger populations and considered a benign variant. However, subsequent focused research has identified a specific ER pattern, featuring distinct J-wave augmentation patterns in the inferolateral leads, as a significant marker for an increased risk of ventricular fibrillation (VF) and SCD [8, 9], like those seen in BrS. The recognition of the inferolateral ER pattern as a potential indicator of sudden death in individuals without structural heart disease—coined as early repolarization syndrome (ERS)—has prompted a reevaluation of its clinical significance. Furthermore, the co-occurrence of Brugada and ER patterns (Figure 1) in a notable subset of patients has highlighted the interconnected nature of these conditions, merging them under the broader categorization of J-Wave syndrome (JWS) [10].

Following the 2016 consensus on JWS [11] remarkable strides have been made in elucidating the pathophysiological mechanisms, genetic factors, and treatment modalities associated with JWS. Acknowledging these advances, the Asia Pacific Heart Rhythm Society (APHRS) convened leading world experts, including representatives from the Asian Pacific Heart Rhythm

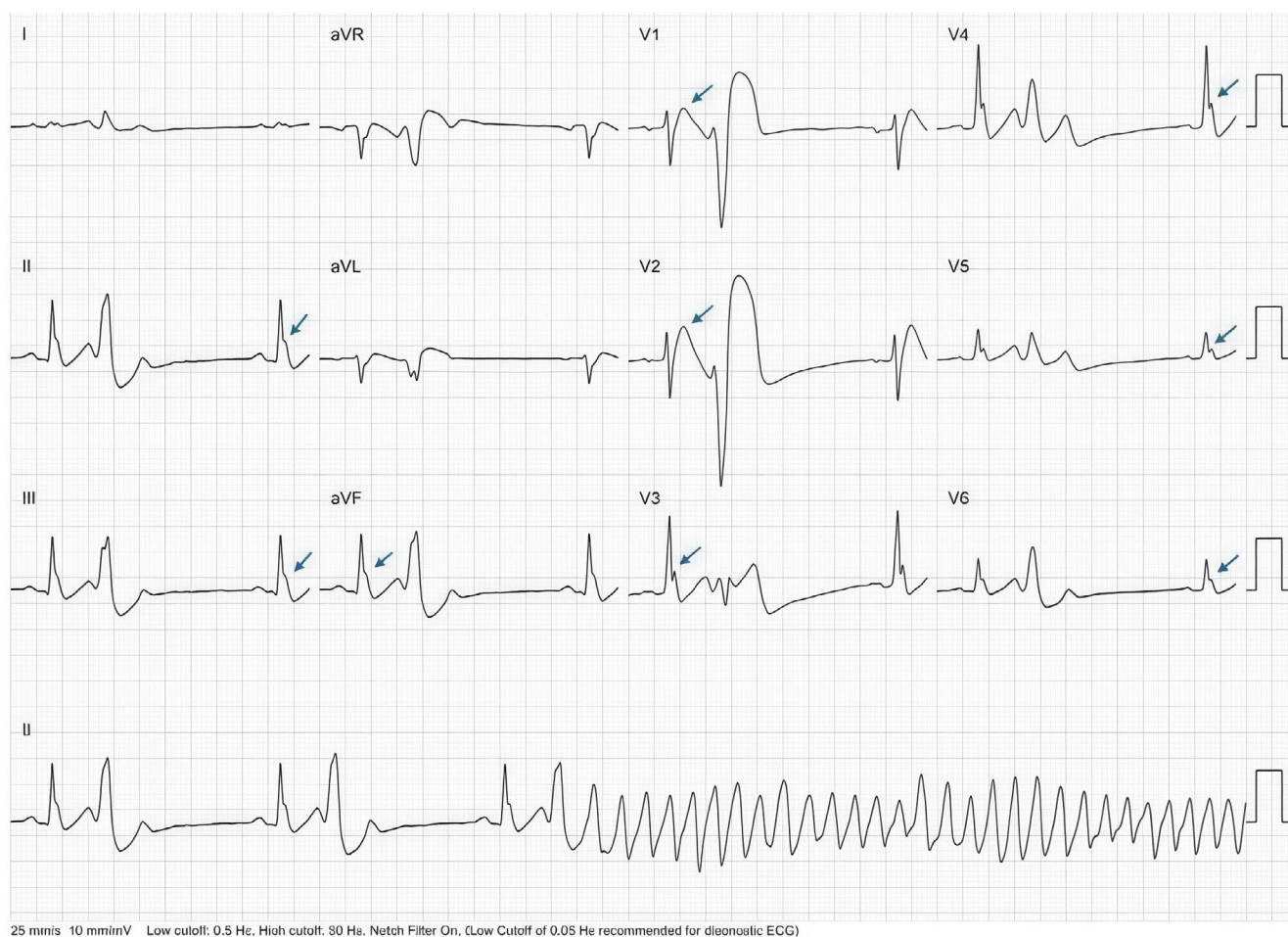


FIGURE 1 | A 12 lead ECG of a JWS patient with VF storm who had a combined Type 1 Brugada ECG pattern and Early repolarization pattern characterized by J-wave augmentation in both inferior and all precordial leads (arrows). Bigeminy PVCs were frequent from the right ventricle and triggered VF.

Society, in Hua-Hin, Thailand, in 2019. The objective of this conference was to integrate contemporary genetic insights, uncover novel mechanistic understanding, and showcase therapeutic breakthroughs. This consensus report aims to bolster the expertise of healthcare professionals in JWS, facilitating more accurate diagnoses and improved patient management strategies. This concerted effort to bridge research and clinical practice seeks to elevate the standard of care in the intriguing and complex realm of JWS, promising to make a significant impact on patient outcomes in this evolving field. This APHRS-led consensus was initiated at an in-person expert meeting in Hua Hin, Thailand (2019) with participation from experts across the globe. Draft statements were developed by topic working groups and underwent two rounds of blinded voting by all coauthors. Statements with $\geq 80\%$ agreement were retained and translated into advice statements, diagnostic scores, and management algorithms (Data S1–S4). All authors reviewed and approved the final document.

1.1 | J-Wave Syndrome Diagnosis

BrS and ERS collectively embody JWS, sharing a unified pathophysiological framework yet recognized as two distinct entities within the JWS spectrum [3, 11]. A cohesive pathophysiological model for these syndromes illuminates not only the common electrocardiographic characteristics and arrhythmic mechanisms but also encompasses clinically observed phenomena such as genetic predispositions, pharmacological responses, circadian rhythms, and variations attributable to age and sex; and, lastly but importantly, it also encompasses the (electrocardiographic) differences between the ERS and BrS (Figure 2).

The cornerstone for diagnosing BrS remains the identification of the type 1 electrocardiographic pattern, initially complemented by specific clinical features [12, 13]. Nevertheless, the 2013 HRS/EHRS/APHRS guidelines moderated these criteria, inadvertently leading to a rise in overdiagnoses [14]. To mitigate this issue, a refined classification system introduced in 2016 integrated clinical observations, the ECG marker, and genetic information into a comprehensive point score [11]. This scoring system differentiates between sodium-channel blocker-induced and spontaneous type 1 Brugada patterns. Importantly, only the spontaneous Brugada ECG presentation unequivocally establishes a BrS diagnosis, whereas the induced Brugada pattern requires supplementary criteria for confirmation (Table 1), leading to an international consensus statement on when to undertake sodium channel blocker challenge [15]. Genetic test results have modest influence.

Similarly, the diagnostic approach for ERS involves identifying a specific ER pattern, characterized by an end-of-QRS notch or J-wave augmentation (> 0.1 mV) on the downslope of a prominent R wave, with or without ST elevation in at least two of the inferolateral leads. Following the precedent set by the BrS diagnostic criteria, the methodology for diagnosing ERS has evolved to include clinical observations and genetic data, culminating in the development of a scoring system to accurately diagnose ERS (Table 2).

Since its introduction, the scoring system from the 2016 Expert Consensus has received widespread acceptance, and the latest ESC guidelines [16] largely endorse this diagnostic framework accepting that updates would be required over time. This manuscript will not give detailed intricacies of this scoring system

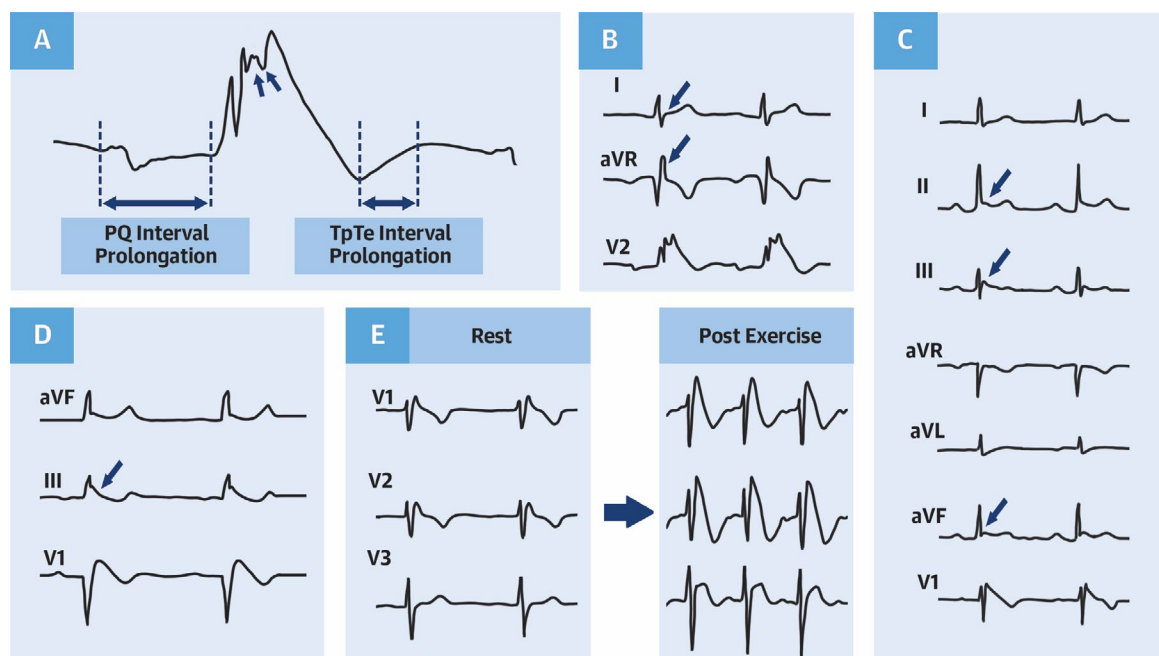


FIGURE 2 | Various ECG risk markers. (A) The ECG (lead V2) shows type 1 ECG, PQ prolongation (235 ms), fragmented QRS (arrow heads) and long TpTe interval (105 ms). (B) Large S wave in lead I and aVR sign. Wide and deep S wave is observed in lead I and tall R wave is observed in lead aVR. (C) Inferolateral early repolarization. J waves are observed in inferior leads. (D) Peripheral type 1 ECG. Coved-type ST elevation appears in lead III and right precordial leads during antiarrhythmic drug test. J wave also appears in lead aVF. (E) ST augmentation after exercise test. ECG converted to a significant type 1 ECG after exercise.

TABLE 1 | Modified Shanghai scoring system for the diagnosis of BrS.

Criteria	Points
I. ECG (at least 1 ECG criterium is required for diagnosis)	
Only award points once for the highest score within this category.	
Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
Sodium-channel blocker-induced Brugada type I ECG pattern at nominal or high leads	2
II. Clinical history	
Only award points once for highest score within this category	
Unexplained cardiac arrest or documented VF/polymorphic VT	3
Nocturnal agonal respirations	2
Suspected arrhythmic syncope	2
Syncope of unclear mechanism/unclear etiology	1
III. Family history (first or second degree relative)	
Only award points once for the highest score within this category	
Definite BrS	2
Suspicious SCD (fever, nocturnal, Brugada aggravating drugs)	1
Unexplained SCD <45 years with negative autopsy	0.5
IV. Genetic test result	
Pathogenic or likely pathogenic genetic variant in SCN5A	0.5

Note: Score: > 3.5 points required for probable/definite Brugada syndrome (BrS); 2–3 points for possible BrS; < 2 points is considered nondiagnostic.

because they are thoroughly described in the 2016 consensus publication [11].

1.2 | Pathophysiology of J-Wave Syndromes

Two primary pathophysiological mechanisms have been proposed to explain the electrocardiographic and arrhythmogenic characteristics common to the syndromes constituting JWS [17]. The first, known as the repolarization hypothesis, attributes these characteristics to heterogeneity in repolarization, specifically to regionally accentuated differences in the density of the transient outward current. This discrepancy can result in a pronounced phase 1 repolarization, potentially leading to the loss of the action potential's dome and significant regional variations in action potential duration and subsequent spontaneous of a premature beat in the myocardium with the short action potential [10, 18]. The second

mechanism, the conduction abnormality hypothesis, posits that conduction delays or failures—stemming from structural tissue abnormalities—are the primary culprits [5]. These mechanisms have sparked scholarly debate; we approach this dichotomy of mechanistic divisions as a scientific challenge and posit that the mechanisms should be viewed as complementary and conceivably coexisting phenomena that merit further investigation.

Early investigations into BrS and, more recently, ERS, have identified structural abnormalities that lead to myocardial fiber separation. Corrado et al. assessed 16 family members displaying electrocardiographic features of BrS without apparent structural heart disease [19]. Post-mortem examinations of the probands following sudden cardiac death revealed myocardial atrophy and fatty replacement of the RV free wall, alongside sclerotic disruptions in the proximal right bundle branch. Similar myocardial abnormalities were reported in earlier case studies, including individuals with idiopathic VF, one of whom unequivocally fulfilled BrS criteria [2]. Additional studies, including those by Coronel et al. and Frustaci et al. documented cardiomyopathic changes or myocarditis in BrS patients, including some with pathogenic SCN5A variants [6, 20]. Nademanee et al. identified higher ventricular epicardial collagen content, indicative of fibrosis, and decreased connexin-43 (Cx43) signal in the RVOT in the hearts of six sudden arrhythmic death syndrome probands with a familial diagnosis of BrS, compared to controls [4]. The RVOT was most affected, concordant with epicardial biopsies from sites of abnormal late potentials in patients prior to surgical ablation [4]. This was backed up by a larger study indicating increased subtle interstitial and focal replacement fibrosis across the whole heart in BrS decedents, with greatest predilection for the RVOT and epicardium, regardless of the presence of a SCN5A variant [21]. Further studies documented fibrosis and inflammatory markers in BrS patients, correlating with electroanatomic mapping anomalies [3, 22]. Similar findings of myocardial fibrosis and its correlation with J-wave distribution on ECGs have been observed in ERS patients and VF survivors [23, 24].

These findings suggest that fibrosis causes a localized, branching myocardial network, creating conditions for current-to-load mismatch (source-sink mismatch) and activation block at branching points. This scenario, coupled with reduced I_{Na} , diminishes conduction reserve in the RVOT's epicardium in BrS and possibly in ERS [4, 5, 7, 25]. Pharmacologic provocation with ajmaline and/or programmed ventricular stimulation using premature beats can create localized conduction block at multiple sites, revealing variable patterns of blocks without being reactivated from the surrounding epicardial substrate sites, behaving like a mosaic of small independent substrates (with different properties) rather than a mass of tissue that is globally activated or blocked, behaving like a mosaic of small dependent substrates rather than a mass of tissue that is globally activated or blocked [26, 27]. The late activated myocardium may not be reactivated from the surrounding epicardial substrate sites leading to conduction failure.

Conduction safety at sites of tissue expansion, where source-sink mismatch takes place, is also modulated by other ionic

TABLE 2 | Proposed 'modified' Shanghai score system for diagnosis of early repolarization syndrome.

I. Clinical History
A. Unexplained cardiac arrest, documented VF or polymorphic VT 3
B. Suspected arrhythmic syncope 2
C. Syncope of unclear mechanism/unclear etiology 1
<i>*Only award points once for highest score within this category</i>
II. 12-Lead ECG
A. ER ≥ 0.2 mV in > 2 inferior and/or lateral ECG leads with horizontal/descending ST segment 2
B. Dynamic changes in J-point elevation (≥ 0.1 mV) in > 2 inferior and/or lateral ECG leads 1.5
C. ≥ 0.1 mV J-point elevation in at least 2 inferior and/or lateral ECG leads 1
<i>*Only award points once for highest score within this category</i>
III. Ambulatory ECG monitoring
A. Short coupled PVCs with R on ascending limb or peak of T wave 2
IV. Family History
A. Relative with definite ERS 2
B. ≥ 2 first-degree relatives with a II.A. ECG pattern 2
C. A first-degree relative with a II.A. ECG pattern 1
D. Unexplained sudden cardiac death < 45 years in a first/s-degree relative 0.5
<i>*Only award points once for highest score within this category</i>
SCORE (Requires at least one ECG finding)
≥ 5 points – Probable/Definite ERS
3–4.5 points—Possible ERS
< 3 points—Non-Diagnostic

currents than I_{Na} : a reduction in I_{to} or an increase in L-type calcium current can facilitate propagation across a tissue expansion [5, 28]. Conversely, an increase in I_{to} or a decrease in I_{Ca} can cause conduction block [28]. Of particular significance is the observation that patients with pathogenic SCN5A variants often exhibit larger VF substrates with subtle microstructural fibrosis involving both RV and left ventricular epicardium [29]. In rare cases, conduction block can be predominantly caused by localized functionally impaired conduction due to a unique specific SCN5A variant while microstructural fibrosis can be minimal [30].

RVOT is normally the last part of the heart to be activated. Thus, in BrS, the compromised tissue at the RVOT often fails to excite, resulting in a significant systolic intracellular electrotonic 'injury' current from activated to unexcited tissue. This in turn generates a monophasic extracellular potential, which is represented on the right precordial leads (or leads placed more cranially) of the ECG in the form of ST-elevation and a reduction of the depth of the negative T-wave, [22] manifesting as ST-elevation and reducing the depth of the negative T-wave on the right precordial ECG leads. The last activated site therefore is proximal to the unexcited region and temporally precedes the ST-elevation, marking the classic type 1 Brugada sign (Figure 2A).

Sodium channel blockade reduces I_{Na} thereby exacerbating conduction block at these branching sites, enhancing source-sink mismatch, underscoring the conduction abnormality hypothesis, and forming the provocation test basis to bring about the Brugada pattern [27]. This blockade also paves the way for re-entrant arrhythmias by inducing activation failure. Alternative activation pathways may allow delayed excitation of tissue beyond the block line, a phenomenon observed in ERS but not in the typical BrS setting where compromised tissue, usually in the RVOT, remains excitable but is not excited due to its position at the end of the normal activation pathway. Indeed, pre-excitation of the unexcited tissue by pacing resolves the ST-elevation in BrS patients [31].

In ERS, patients can be categorized into two groups [32]: (1) Those exhibiting depolarization/conduction abnormalities, and (2) Those without apparent depolarization abnormalities during endocardial and epicardial mapping. Most patients belong to the first group. However, in contrast to BrS, the sites of late activation in these ERS patients are often located in areas other than the RVOT, including the RV inferior, RV free wall, and left ventricular (LV) epicardium. Consequently, the initially unexcited tissue in these regions is activated with a delay through a secondary conduction pathway. This leads to a transient systolic intracellular electrotonic current flowing

from activated to unexcited tissue, generating a short-lived positive extracellular potential. This potential is represented as a J-wave on the relevant ECG leads [33]. In some instances, late-activated myocardium may also be evident as a fractionated QRS complex or a J-wave, characteristic of the ER pattern (Figure 2C,D). Interestingly, sodium channel blockers (SCBs) exacerbate the source-sink mismatch and may increase the J-wave amplitude in these ERS patients [32]. However, in some cases of ERS, these drugs also slow conduction elsewhere in the heart, leading to a delay in the secondary activation route. A similar variation in J wave behavior is demonstrated during exercise with a subset of patients showing persistence of the J wave with higher heart rates while in others the J wave is eliminated [34]. The J-waves may be obscured by the broadening QRS complex and effectively disappear [34, 35]. This underscores the complex interplay between myocardial structural integrity, electrical conduction, and the seemingly contradictory effects of pharmacological agents on the electrocardiographic phenotype associated with the ER pattern and the Brugada pattern.

For the second group of patients, who exhibit no late depolarization abnormalities or fractionated electrograms, the underlying electrophysiological mechanism of J-wave generation remains uncertain. It is probable that repolarization abnormalities play a significant role in the genesis of the J-wave within this group.

The occurrence of fractionated potentials and/or local J-waves in ERS/BrS patients resembles the fractionated potentials observed in infarcted myocardium [36, 37], caused by dyssynchronous activation of structurally compromised tissue. Similar structural alterations have been identified in the RVOT myocardium of BrS patients, elucidating the fractionated potentials observed during epicardial mapping [4, 6]. The relation between fractionated potentials and ST-segment changes may stem from two mechanisms. First, late activation contributes to pronounced local J-waves because the local notch in the epicardial action potential of late-activated tissue aligns with the action potential plateau phase in the rest of the heart, a mechanism predominantly observed in the ER pattern [23]. Second, ST-segment elevation can occur in late-activated tissue due to excitation failure from a current-to-load mismatch, with fractionated potentials preceding a monophasic potential that manifests as ST-elevation in extracellular electrograms [37]. Therefore, fractionated potentials are not required throughout the entire ST-elevation period. The J-wave evident in ECG leads—marked by slurring or notching at the QRS-complex's end—is likely the collective average of local, late, fractionated potentials. The significant observation that areas with abnormal fractionated electrograms co-localize with VF reentrant and focal and rotational activities sustained VF further supports the concept that these regions serve as VF substrates [27, 32]. Sites of VF drivers, identified through non-invasive electrocardiographic imaging mapping during VF, exhibit concordance with areas of abnormal late fractionated potentials in the RV epicardium [27, 32].

Recently, evidence has emerged that JWS may not necessarily adhere to a strict depolarization-repolarization dichotomy [38, 39]. A study of human hearts from two siblings with malignant, drug-refractory ERS, describes KV1.4/ I_{to} , slow-mediated endocardial repolarization abnormalities coexisting with

diffuse fibrosis. High-resolution ex vivo optical mapping, molecular profiling, and computational modeling demonstrate that a pause-dependent repolarization gradient in the endocardium of both right and left ventricles causes J-wave augmentation, Brugada ECG pattern, and VF trigger that may be perpetuated by the underlying microstructural fibrosis [39]. Although the increase in I_{to} may also facilitate conduction block [5, 28], this study [39] suggests that the two electrophysiological derangements underlying J-wave syndrome and its malignant ventricular arrhythmias may co-exist in some cases.

1.3 | Genetics of J-Wave Syndromes

The association of rare genetic variants within the coding region of *SCN5A*, which encodes the cardiac sodium channel NaV1.5, with BrS was first established in 1998 [40]. Approximately 20% of BrS patients have *SCN5A* variants that cause a loss of function in NaV1.5 [41]. Despite multiple genes being implicated in BrS over the years through candidate gene studies, a thorough evaluation using the ClinGen framework affirmed robust support only for *SCN5A*'s involvement, with the association of other genes remaining disputed [42, 43]. Consequently, the 2022 Expert Consensus Statement on Genetic Testing for Cardiac Diseases, endorsed by four major heart rhythm societies, advises screening solely for *SCN5A* variants (for exonic and splice site variants) and recommends against routine reporting of rare variants in genes with a disputed association with BrS [44].

Genetic testing for *SCN5A* variants is suggested for individuals presenting with a spontaneous type 1 ECG or a drug-induced type 1 ECG, particularly when supported by clinical features or family history. Following the identification of a pathogenic (P) or likely pathogenic (LP) variant in a proband, classified using American College of Medical Genetics criteria [45], genetic testing of relatives is advised. For variants of uncertain significance (VUS), targeted sequencing for co-segregation analysis in relatives may be considered [45]. This recommendation is underscored by findings that BrS patients with pathogenic *SCN5A* variants exhibit more pronounced conduction abnormalities [46] a larger arrhythmic substrate in the RVOT and RV epicardium, and poorer arrhythmic outcomes [13, 47–49].

Although initially considered a Mendelian disorder with autosomal dominant inheritance, BrS is now recognized for its complex genetic architecture with only 20% of probands of European ancestry and approximately 5%–10% of Asian ancestry hosting a pathogenic or likely pathogenic variant [46, 47]. This means that multiple genetic variants, with a wide spectrum of population frequency and effect size, in aggregate, contribute to risk. Indications of complex inheritance include the fact that many cases are sporadic and familial clustering is rare [50]; observation of low disease penetrance in families with *SCN5A* P/LP variants [51]; and the absence of familial *SCN5A* variants in some affected members [52]. The latter observation questions a simple causality of the *SCN5A* P/LP variants for BrS and suggests multicausality. Genome-wide association studies (GWAS) have further substantiated this, identifying common small-effect susceptibility variants (single nucleotide polymorphisms [SNPs]) and demonstrating that these common genetic variants in aggregate may

account up to 30% of inter-individual variability in disease risk [53, 54]. The largest GWAS studies thus far have been conducted in BrS cases (defined by occurrence of type 1 BrS ECG at baseline or after drug challenge) of European (2820 cases) and Japanese (940 cases) ancestry, between them identifying common variant association signals at 13 chromosomal loci [54, 55]. Cross-ancestry meta-analysis of these European and Japanese datasets led to the identification of an additional 6 loci. These studies, alongside data from a GWAS conducted on 154 Thai BrS patients [56], and association of selected SNPs in 190 BrS cases from Taiwan [53, 57] and 208 cases from Japan [53], point to a shared polygenic architecture of BrS susceptibility across ancestries, although differences in minor allele frequency of susceptibility variants exist between ancestries, and ancestry-specific susceptibility variants may still exist.

A polygenic risk score (PRS) analysis (assessing the aggregate effect of common variants) based on the 21 SNPs from the European ancestry GWAS uncovered a higher mean PRS in patients without a (likely) pathogenic variant in *SCN5A* compared to those with one [54]. Similarly, patients who displayed the type 1 BrS ECG at baseline had a higher mean PRS compared to those in whom the ECG was induced by sodium channel blockade (SCB) challenge [54]. These observations indicate that disease susceptibility in different individuals relies upon varying contributions of multiple factors, including both rare and common genetic variants and other factors such as exposure to sodium channel blockade (SCB).

In two exploratory studies, a PRS based on the early 3 BrS susceptibility SNPs [53] was associated with development of type 1 BrS ECG after SCB challenge [58] and with spontaneous and SCB-provoked phenotype in both genotype positive and negative members of *SCN5A* families [59]. While these findings await confirmation and extension to larger cohorts (including consideration of a larger number of relevant susceptibility variants), one can envision that *SCN5A* sequencing and SNP genotyping may be performed to assess pretest probability when considering drug testing in suspected BrS in the future. A study conducted in 2182 patients with BrS suggested an association of the same 3-SNP PRS with life-threatening arrhythmic events [60] although another study on 2367 patients did not find an association between a more extensive PRS, based on the 21 risk variants identified in the larger European ancestry GWAS, and cardiac events [54].

Although the prevalence of disease is much higher in the East (especially Southeast) Asia compared with regions of predominantly European ancestry, the presence of P/LP *SCN5A* variants is paradoxically remarkably lower in these regions [56, 61]. Studies conducted in recent years in Thai BrS cases point to a role for ancestry-specific low-frequency *SCN5A* genetic variation as a contributory factor. These variants include a functional missense variant and a non-coding variant affecting a regulatory element (RE5; which impacts negatively on the sodium channel density) in *SCN5A*, both of which have been shown to be significantly enriched in Thai BrS patients compared to ancestry-matched controls (Arg965Cys: 6.5% of BrS cases vs. 0.4% of controls; RE5 variant: 3.9% of cases vs. 0.06% of controls) [62].

The genetic landscape of BrS remains an area of active research. Future common variant GWAS in larger cohorts and

the application of whole exome or genome sequencing are anticipated to reveal additional susceptibility variants, enriching our understanding of the complex genetic architecture of BrS.

Family and population studies support to some extent the presence of a heritable component in risk for ERS [63, 64]. Furthermore, in families with a history of sudden cardiac death (SCD)—including both phenotype-positive survivors and autopsy-negative cases—ER is overrepresented [65–67].

Despite this evidence, strong genetic data identifying causal genes remain limited, though several genes have been linked to ERS. Currently, there is no official ClinGen consensus curation project for ERS.

SCN5A variants have been reported in 2%–10% of cases. Given that affected individuals exhibit conduction slowing, a loss-of-function mechanism is expected and has been demonstrated [68, 69]. Additionally, variants in potassium channel genes involved in the early phase of the action potential have been reported in patients with ERS. The first identified was the p.S422L variant in *KCNJ8*, which encodes the α -subunit of the ATP-sensitive potassium (KATP) channel, detected in unrelated patients with ERS [70–72]. However, this variant has too high a population frequency to cause by itself a rare monogenic disorder [73]. *KCNQ3*, which underlies the Ito current, has also been associated with ERS in isolated cases [74, 75]. Notably, GWAS conducted for ER pattern in the general population identified a signal at the *KCNQ3* locus [76]. This not only provides further support for the involvement of this gene but also suggests polygenic inheritance.

Other genes with potential associations to ERS include various calcium channel genes (both α -subunit and auxiliary subunits), *SCN10A* [44] and KV1.4-driven I_{to} , slow-mediated endocardial repolarization abnormalities [39].

1.4 | Risk Stratification

Risk stratification in BrS is crucial and must be differentiated between symptomatic and asymptomatic individuals, reflecting the significant disparity in the risk of VF and SCD. For symptomatic patients, the risk ranges from 3% to 15% [77, 78]. Conversely, asymptomatic patients have a much lower annual incidence of VF, approximately 0.4% [79]. Risk assessment utilizes a range of methods, including clinical features, genetic markers, ECG findings, and VF inducibility, instead of depending solely on a single factor (Table 3). As a result, scoring systems that incorporate multiple factors are recommended to assess the necessity of treatments such as implantable cardioverter-defibrillators (ICDs) to reduce the risk of sudden death, or pharmacological or ablation treatments to prevent VF. These factors encompass:

1. VF/cardiac arrest: Patients who have experienced VF or aborted cardiac arrest are at significant risk of recurrent VF and SCD with the annual incidence of VF events ranging from 7.7% to 14.2% [77, 80]. Therefore, ICD implantation is recommended for all patients with a history of VF, provided there are no contraindications [16].

TABLE 3 | Risk stratification in Brugada syndrome: key variables.

Key variables	Relatively risk
Age	VF typically manifests post-adolescence to age 70, peaking at 40–50 years. Risk decreases after 70, with VF events rare before 16 years
Sex	Males exhibit a higher risk than females, attributed to testosterone's effects on cardiac currents. Women show lower symptomatic rates and VF occurrences
Family History	While some studies suggest its predictive value, most do not support family history as a reliable risk factor
SCN5A variant	Present in ~20% of BrS cases, associated with conduction issues and a higher risk of VF, especially in variants affecting the pore region
ECG Markers	Type 1 ECG, particularly spontaneous occurrences, indicate higher VF risk. Other markers include PQ interval prolongation, wide QRS, fragmented QRS, aVR sign, large S wave in lead I, and peripheral type 1 ECG
Na channel Blocker	Helps diagnose BrS; however, its prognostic value, especially in asymptomatic patients, remains limited
SAEG	Late potentials recorded in the RVOT area suggest a higher risk of VF
PES	Controversial in predicting VF, with some studies showing its predictive value, especially when VF is inducible by ≤ 2 stimuli

2. Syncope: Syncope in BrS may be a manifestation of self-terminating VF or VT. About 20% of individuals who suffer sudden death have had a history of syncope [81]. The annual event rate for BrS patients with syncope is between 1.9% and 2.2%, with an HR for the presence of syncope ranging from 1.48 to 3.7 [78, 82–85]. The lower event rate and HR for syncope (in comparison with VF/CA) may be attributable to the inclusion of individuals with non-arrhythmic syncope, such as reflex neurogenic syncope, in the study cohort [86]. Further, a minority of patients with syncope may show symptomatic bradyarrhythmia as the cause [87, 88]. Since the prognosis for non-arrhythmic syncope is similar to that of asymptomatic patients, integrating the event rate of the non-arrhythmogenic syncope population with that of their arrhythmogenic counterparts is expected to be lower than that of patients with prior VF [84, 85]. Therefore, identifying syncope caused by ventricular arrhythmias, which typically has an abrupt onset without preceding symptoms, is critical [84, 85]. Syncope occurring in the

supine position or at night, including nocturnal agonal respiration, may be of arrhythmic origin. Conversely, prodromes likely unrelated to arrhythmias include blurred vision, nausea, vomiting, facial pallor, light-headedness (relative risk 0.4), and sweating. Arrhythmic syncope can be precipitated by various factors, including environmental or emotional stress, and may present with convulsions, abnormal respiration, or urinary incontinence. In suspected cases, the annual VF event rate is 5.5% [89]. Thus, identifying patients with high-risk syncope is vital in preventing SCD.

Table 3 lists other key risk variables besides symptoms:

3. Age and sex: Brugada-type ECG patterns and the onset of VF typically emerge after adolescence, linked to testosterone levels [90, 91]. Initial VF episodes most commonly occur between ages 16–70 years, especially around 40–50 years. The likelihood of initial or recurrent VF declines in individuals over age 70 [92–94], with a VF event rate reported at 0.3%/year for those >60 years old [95]. Despite the rarity of VF in the elderly, secondary prevention remains essential. First VF events before age 16 years are uncommon, occurring in only 4% of patients, with a higher percentage of females at this young age [92]. The Brugada-type ECG is also rare in children and tends to manifest post-puberty [96]. A SCN5A P/LP variant is prevalent in 21%–71% of young cases [97, 98]. VF event rates stand at 2.1% among the young, rising to 4.5%/year in symptomatic individuals and decreasing in asymptomatic patients (0%) [98]. Early studies already demonstrated a male predominance in BrS, with the male-to-female ratio being higher in Asians (9:1) than in Caucasians (7:3) [99]. This predominance is attributed to testosterone's effect on enhancing the cardiac transient outward current [90, 91]. Women tend to be less symptomatic, with an annual event rate of 0.25%–0.7%, and the HR for VF in males is between 2.9 and 4.5 [100–102]. Before puberty, females tend to be more likely to be symptomatic [90, 92, 103]. Additionally, adult women have a lower frequency of spontaneous type 1 ECG and induced VF compared to men [99–102]. In women, risk factors for VF are not very different from men, including being a proband (HR, 10.2), having survived a cardiac arrest (HR, 25.4–69.4), experiencing syncope (HR, 6.8), having spontaneous type 1 ECG (HR, 2.7), sinus node dysfunction (HR, 9.1), fQRS (HR, 20.2), a wide QRS complex (>120 ms; HR, 4.7), and VF induced by programmed stimulation (HR, 5.3) [100–102].
4. Family history of SCD: The predictive value of a family history of SCD for cardiac events remains unclear, with few studies highlighting its utility and most studies finding no significant association [78, 84, 104, 105]. Specifically, a history of sudden death in young first-degree relatives (<35 years of age) does not reliably predict the occurrence of VF events [104].
5. SCN5A variant: Pathogenic loss-of-function SCN5A variants are present in approximately 20% of BrS cases. Patients with these variants often exhibit conduction disturbances, and the severity of the sodium channel

dysfunction correlates with the severity of the clinical course. *SCN5A* variants are more commonly found in younger patients [106, 107]. In approximately the first 20 years after the first description of this association, the presence of an *SCN5A* variant was not considered a risk factor [108, 109]. Later studies, however, demonstrated a clear role for pathogenic *SCN5A* variants in risk prediction [46, 47, 110, 111]. In contrast to the earlier studies, functional data were added and more stringent variant calling criteria were applied [110]. It seems likely that earlier studies were diluted by the inclusion of apparently pathogenic variants, however, without functional abnormalities [112].

6. ECG markers:

1.4.1 | Spontaneous Type 1 ECG Pattern

While various ECG markers have been proposed to identify high-risk patients, the spontaneous type 1 Brugada ECG pattern, which is often detected at leads V1–V2 located in the upper intercostal spaces, is unanimously accepted as a high-risk ECG marker associated with an increased risk for VF [113–115]. Previous studies have consistently described that the risk of VF is higher in patients with spontaneous type 1 ECG than in those with non-type 1 or drug-induced type 1 ECG [114, 115]. Studies including both symptomatic and asymptomatic patients showed that the hazard risk of spontaneous type 1 ECG for VF events is 1.8–6.6 and that the annual rate of VF events is 2.3%–2.9% for patients with spontaneous type 1 ECG and 0.4%–1.2% for patients with non-type 1 ECG [77, 78, 82, 84, 85, 98, 105]. In asymptomatic patients, the hazard risk for VF with spontaneous type 1 ECG is between 2.0 and 5.3, and the rate of VF events is 0.8%/year for patients with spontaneous type 1% and 0.4%/year for those without [83, 116]. It is noteworthy to recognize that asymptomatic individuals with spontaneous type 1 ECG have 0.05% prevalence in the general population, but this figure rises to 0.2% in Southeast Asia, compared to 0%–0.07% in Europe and North America [117]. Thus, detecting high-risk asymptomatic patients with spontaneous type 1 ECG is of paramount importance. The recent study by Gaita et al. found that 1.5% of arrhythmic events occurred in the overall asymptomatic population, corresponding to an event rate of 0.2% per year [47]. The event rate was 0.4% per year in patients with spontaneous type-1 ECG and 0.03% per year in those with drug-induced type-1 ECG ($p < 0.001$) [79].

Lastly, although non-type 1 ECG is generally considered less risky than spontaneous type 1 ECG, patients who have experienced an aborted cardiac arrest without a spontaneous type 1 ECG often face early recurrence of VF, similar to patients with spontaneous type 1 ECG and VF [82]. Indeed, antemortem ECGs from sudden cardiac deaths with familial evidence of BrS are more likely to be normal than those showing the type 1 pattern [81]. Also, the appearance of type 1 ECG may vary spontaneously, showing fluctuations in the ECG type and ST level. These spontaneous ECG fluctuations or alterations have been recognized as a significant risk factor for VF events [80, 118]. Further, 12 lead ambulatory monitoring of the high precordial ECG leads can diagnose dynamic type 1 patterns in patients

with only a prior provoked ECG pattern, and who remain at elevated risk [119].

1.4.2 | PQ Interval Prolongation

Some studies have identified a correlation between PQ interval prolongation (Figure 2A) and an increased risk of VF events, with odds ratios (OR) ranging from 2.41 to 11.5 [120, 121] and an HR of 3.84 [122]. However, other research has not confirmed the prognostic significance of PQ prolongation [83, 123]. The reported cutoff values for PQ interval prolongation vary, typically set at 170 ms or 200 ms [98, 120, 121]. PQ interval prolongation is frequently observed in patients with *SCN5A* variants [107] and the presence of a P/LP *SCN5A* variant has been associated with elevated risk [47, 110].

1.4.3 | QRS Widening and Bundle Branch Block

The definition of a “wide QRS complex” varies, with thresholds set at > 90 ms [124], > 105 ms [83], and > 120 ms [123, 125] in different studies. The risk associated with a wide QRS complex for VF events is reported to increase three- to fourfold [83, 123–125].

A right bundle branch block (RBBB) pattern is also observed in patients with BrS. A complete RBBB can either mask or enhance the type 1 ST-elevation characteristic of the syndrome [126–128]. While the prognostic significance of complete RBBB remains unclear, it may indicate a higher risk in symptomatic patients, with an HR of 3.2 [129].

1.4.4 | Fragmented QRS (fQRS)

fQRS is identified by the presence of multiple spikes within a QRS complex (Figure 2A). It indicates delayed activation of separated myocardial fibers associated with injured myocardium and suggests the potential presence of a substrate for lethal arrhythmias. The settings of the ECG filter are crucial for detecting fQRS; specifically, the low pass filter should be set at ≥ 100 Hz to prevent masking of small spikes and ensure accurate evaluation of fQRS [130].

Several definitions of fQRS in BrS focus on abnormal conduction in the RVOT region. Abnormal fragmentation within the QRS complex is defined as:

- ≥ 4 spikes in 1 lead or ≥ 8 spikes across leads V1–V3 [130].
- ≥ 2 spikes within the QRS complex in leads V1–V3 [77].
- A QRS complex with > 2 positive spikes within the QRS complex in 2 contiguous leads [131].

Abnormal potentials on the epicardial myocardium can also appear in the inferolateral region of the RV [132]; hence, fQRS may also manifest in the limb and left lateral leads. The general definition of fQRS across all ECG leads is a QRS complex with > 2 positive spikes within the QRS complex in 2 contiguous leads [133].

fQRS more frequently occurs in high-risk patients and can predict the occurrence of VF in both symptomatic and asymptomatic patients. The HR of fQRS has been reported to be:

- 4.1–5.2 for overall patients [125, 133, 134].
- 4.9 for patients without documented VF [77].
- 8.2 for patients with syncope [83].
- 5.9–7.4 for asymptomatic patients [83, 135].

Using the fQRS feature across all ECG leads increases its sensitivity and negative predictive value, compared to using fQRS definitions limited to the right precordial leads [133].

1.4.5 | aVR Sign and Large S Wave in Lead I

The aVR sign and large S wave in lead I represent an abnormal electrical axis of the QRS complex (Figure 2B). The aVR sign is defined as R wave ≥ 0.3 mV or R/q ≥ 0.75 in lead aVR and this sign is frequently observed in high-risk patients (odds ratio for VF: 4.8) [136, 137]. A significant S wave (≥ 0.1 mV and/or ≥ 40 ms) in lead I has also been reported to be an independent risk marker, and HR for VF is 39.1 [138]. However, some studies failed to show the significance of these signs for predicting VF [83, 123, 127], and further studies are required to confirm these observations.

1.4.6 | Type 1 ECG in Peripheral Leads

Coved-type ECG changes can also manifest in peripheral leads, such as limb or left lateral leads (Figure 2D). These changes are observed in approximately 9%–10% of patients, whether with spontaneous or drug-induced type 1 ECG [139, 140]. Patients displaying a peripheral type 1 ECG often have SCN5A P/LP variants and exhibit induced VF, tall J-waves, and bradycardia. Notably, the presence of peripheral type 1 ECG is associated with an increased risk of malignant arrhythmic events, with an OR for VF estimated at 4.6 [140].

1.4.7 | Inferolateral ER and J-Wave

ER with J-wave augmentation is observed in 11%–21% of patients with BrS [83, 134, 141, 142] and its presence signifies a considerable risk for VF, particularly in high-risk patients who have previously experienced VF or an electrical storm, with incidence rates ranging from 32% to 36% [143, 144]. Inferolateral ER serves as an independent predictor of VF, sudden death, and electrical storms, with an HR between 3.3 and 4.9 [82, 83, 125, 142, 144]. The risk escalates notably in patients with a persistent J-wave (HR, 4.88) [145] and in those with a J-wave accompanied by horizontal ST segments (HR, 11.0) [141].

1.4.8 | QT and T_{peak}-T_{end} Intervals

Although ST-T abnormalities may reflect conduction failure in BrS patients, they typically also indicate repolarization

issues, and several parameters associated with the QT-T interval are noteworthy: the QT interval, the TpTe interval, TpTe dispersion, and the ratio of the TpTe to QT interval (TpTe/QT) (Figure 2A). The TpTe interval denotes dispersion of repolarization, and its prolongation suggests the presence of action potential heterogeneity, which allegedly can lead to functional reentry (phase 2 reentry) [10], although it also may be secondary to conduction delay. In BrS patients, these QT interval indices are notably increased, especially among high-risk groups [83, 146–149]. The threshold for the TpTe interval is set at ≥ 95 –100 ms. The risk associated with a prolonged TpTe interval for VF includes an OR of 1.1–9.6 [147–149] and an HR of 5.7 in asymptomatic patients and 7.1 in symptomatic patients [83]. However, a comprehensive study involving 448 BrS patients did not demonstrate the prognostic significance of the TpTe interval [150].

1.4.9 | Sinus Node Dysfunction (SND)

SND is observed in 1.1%–1.7% of BrS patients, with a higher prevalence in pediatric cases (6.7%–9.0%) [97, 98, 103], which hypothetically is related to the presence of pathogenic SCN5A variants (but this has not been convincingly demonstrated). Sino-atrial conduction disturbances are implicated in causing SND in BrS [151]. SND is linked to VF events, with an HR of 5.0 in the overall patient population [84] and 3.3 in younger patients [103].

1.4.10 | Exercise Test

VF is generally not observed during exercise in BrS patients. However, the fluctuations in autonomic nerve activities during and after an exercise test can induce various ECG changes [152–154]. These changes include ST-elevation augmentation in the early recovery phase (Figure 2E), QRS widening [153, 155], delayed heart rate recovery [154], and arrhythmias. Specifically, augmentation of ST-elevation was observed in 37% of BrS patients within 2–3 min of the post-exercise recovery phase [152]. These ECG changes are linked to VF events during follow-up in both symptomatic and asymptomatic patients, with an HR for VF of 3.17. This response is thought to be due to sympathetic withdrawal and parasympathetic rebound during the recovery phase, as well as an increase in body temperature and heart rate resulting from exercise [156].

1.4.11 | SCB Challenge

Although the SCB test has been utilized to unmask Brugada ECG pattern and latent epicardial substrates that promote VF during the epicardial ablation procedure, its prognostic value in BrS patients is limited [11, 14, 15]. In addition, the specificity of the test is not optimal [15, 157]. Asymptomatic patients with drug-induced type 1 ECG generally follow a relatively benign clinical course compared to those with spontaneous type 1 ECG. Patients whose ECG does not convert to a type 1 pattern following the SCB test have a very favorable prognosis compared to those with SCB-induced type 1 ECG [77, 78]. SCB-induced type 1 ECG is linked to atrial arrhythmias and

sudden death in children [158]. A study involving both spontaneous and SCB-induced type 1 ECG revealed that an ST level ≥ 0.3 mV after SCB administration (HR, 2.8) and SCB-induced ventricular tachyarrhythmias (HR, 3.6) are associated with VF events. In asymptomatic patients, an ST level ≥ 0.3 mV after SCB administration (HR, 1.7) and drug-induced ventricular tachyarrhythmias (HR, 15.6) are also predictors of ventricular tachycardia (VT)/VF events [159]. The incidence and prognostic value of drug-induced arrhythmias can be influenced by the type of SCB used, such as ajmaline, procainamide, flecainide, and pilsicainide [160–162].

1.4.12 | Signal-Averaged Electrogram

A signal-averaged electrogram records microvolt-level late potentials from a surface ECG [48, 163], which are frequently recorded in patients with VF or aborted cardiac arrest, with an OR of 8.5 [48]. In patients with BrS, late potentials are usually recorded in the RVOT area and represent epicardial delayed potentials [164].

1.4.13 | Programmed Electrical Stimulation (PES)

The prognostic significance of PES in predicting future VF, especially in asymptomatic patients (with a type 1 pattern) and those without previous VF episodes, remains a topic of debate [165, 166]. Some studies have demonstrated that VF induced during PES could predict future VF events, highlighting its potential usefulness as a prognostic tool [79, 84, 116, 135, 165, 167, 168]. However, other research has failed to demonstrate its effectiveness [77, 78, 82, 105, 169], showing conflicting results that could be attributed to variations in study designs, patient populations (symptomatic versus asymptomatic), and electrophysiological study protocols.

For instance, the FINGER registry, which included a large cohort of 1029 patients, did not demonstrate the utility of PES in predicting fatal arrhythmic events, with a *p*-value of 0.05 in the Kaplan–Meier curves assessing prognosis based on PES results [78]. This suggests that the predictive value of PES might be limited, especially since new-onset VF in asymptomatic patients is relatively low, indicating that large sample sizes and long-term follow-up are necessary for more definitive conclusions.

Earlier meta-analyses had failed to establish the significance of PES in prognosis prediction [109, 170]. However, more recent meta-analyses and pooled data analyses have shown that VF induction by PES is associated with future VF events [171, 172], with HRs ranging from 2.7 to 13.6 in studies affirming the utility of PES [116, 167, 172–174]. Additionally, specific subgroups of patients have been examined, with HR for VF induction by a single or double extra-stimulus ranging from 3.03 to 5.7 [135, 173], which significantly increased to 12.4 when focusing on induction by a single extra-stimulus [174]. Moreover, VF induction by PES has been linked to future arrhythmic events in both asymptomatic patients (HR, 3.6–13.6) [79, 116, 135, 172] and patients who have experienced syncope (HR, 3.3) [171, 175]. Although the controversy over the significance of VF inducibility by PES has not been completely resolved, the elimination of VF inducibility

during an epicardial ablation procedure is considered crucial for preventing VF recurrence [132, 176, 177].

1.4.14 | Combination of Risk Factors for Risk Stratification

A combination of risk factors can predict the occurrence of ventricular arrhythmias more effectively. Early studies had already established that high-risk patients can often be identified by a combination of a spontaneous type 1 ECG and a history of syncope [74]. Several comprehensive studies that include various other symptoms—such as aborted cardiac arrest, syncope, and asymptomatic cases—have shown that previous symptoms (aborted cardiac arrest and syncope) are significant predictors of future events, with HRs ranging from 3.7 to 28.9 [11, 84, 125, 178]. However, determining the indication for ICD implantation in asymptomatic patients based on a single risk marker remains challenging (see management).

Previous studies have addressed combinations of other risk factors and there is no consensus on which factors should be combined for effective risk stratification. Risk factors that have been considered in combination include male gender [84], proband status [84], family history of sudden death [10, 84, 105, 179], inducibility by PES [10, 84, 135, 180] spontaneous type 1 ECG [84, 180, 181], ER [125, 134], fQRS [125, 134, 135, 180], the r-J interval in lead V2 [178], QRS interval in leads V2 or V5 [178, 180], TpTe interval and its dispersion [135, 178], SND [84], deep S-wave in lead I [182], peripheral type 1 ECG [183], and late potentials in a signal-averaged electrogram [182]. These factors collectively suggest that patients with multiple risk factors have a higher risk for VF and score systems have been proposed to stratify patients according to risk [10, 84] but their values in predicting asymptomatic patients are limited.

Recently, Rattanawong et al. carried out a meta-analysis of an extensive review of the existing literature, which included a pooled analysis of 67 risk-stratifying studies involving 7358 patients with Brugada Syndrome (BrS) [184]. Their analysis encompassed both symptomatic (37%) and asymptomatic (63%) patients, as well as those with either a spontaneous (70%) or drug-induced type 1 ECG pattern. From these data, the investigators developed a new risk score—Predicting Arrhythmic eventT (PAT)—based on the risk factors identified in the meta-analysis. Notably, to focus on predicting the first arrhythmic event, patients with a history of such events were excluded from the scoring process. The PAT score, comprising nine factors (seven of which are derived from the ECG), was validated in a relatively small internal and external cohort. It demonstrated a sensitivity of 95.5% and a specificity of 89.1% in predicting the first major arrhythmic event in the overall cohort of patients with BrS. The PAT score outperformed the currently used score proposed by Sieira et al. [84] and Shanghai scores. While Rattanawong et al.'s study has promise, one must exercise caution before fully embracing this scoring system because studies to validate it are warranted.

In summary, while aborted cardiac arrest and arrhythmic syncope are definite risk factors, the evaluation of multiple risk

factors is crucial, particularly in the risk stratification of asymptomatic patients.

1.5 | Management and Therapeutic Options

For the first two decades after its description, management of symptomatic JWS was essentially limited to two modalities—implantable cardioverter-defibrillators (ICDs) and quinidine—both with important limitations. Over the past decade, catheter ablation aimed at eliminating VF substrates has emerged and is now increasingly used in symptomatic BrS. This development has yielded two large observational series with long-term follow-up and two randomized trials supporting ablation efficacy in symptomatic BrS. Accordingly, a contemporary treatment algorithm that integrates patient selection, investigative testing, and therapeutic choice for both symptomatic and asymptomatic JWS is essential (see Figures 3–5 and discussion below).

1.5.1 | Pharmacological Therapy

Quinidine represents the foremost drug for long-term pharmacological treatment of both BrS and ERS. As a Class 1a anti-arrhythmic drug, quinidine blocks the transient outward potassium current (I_{to}), a mechanism believed to counteract BrS by enhancing depolarization reserve [5, 117]. The efficacy of quinidine has been supported by various observational studies [185–187], although a definitive positive effect could not be

established in the only randomized study due to the absence of events during its 18-month crossover phases. Notably, the only arrhythmic events recorded were in the control group [188]. Quinidine is associated with dose-dependent side effects, primarily gastrointestinal, leading to discontinuation by many patients [188, 189]. However, quinidine-induced diarrhea may be effectively managed with cholestyramine, allowing continued treatment [187, 190]. A notable challenge is quinidine's limited availability in many countries [191].

Other therapeutic options such as denopamine, cilostazol, and bepridil show promise but are currently only available mainly in Japan and a very few countries. Despite limited availability, each drug has demonstrated effectiveness in case studies [190].

1.5.2 | ICD Therapy

ICD therapy is the only treatment conclusively proven to abort SCD in high-risk JWS patients [11, 14, 16]. There is unanimous support for ICD implantation for secondary prevention in patients who have survived a resuscitated SCD or VF episode [11, 16]. Likewise, there is consensus on the necessity of ICDs for primary prevention in patients with a history of cardiogenic syncope and a spontaneous type 1 ECG pattern, highlighting their high-risk status [11, 14, 16].

The management of asymptomatic patients, especially those whose type 1 ECG pattern is only apparent after administration

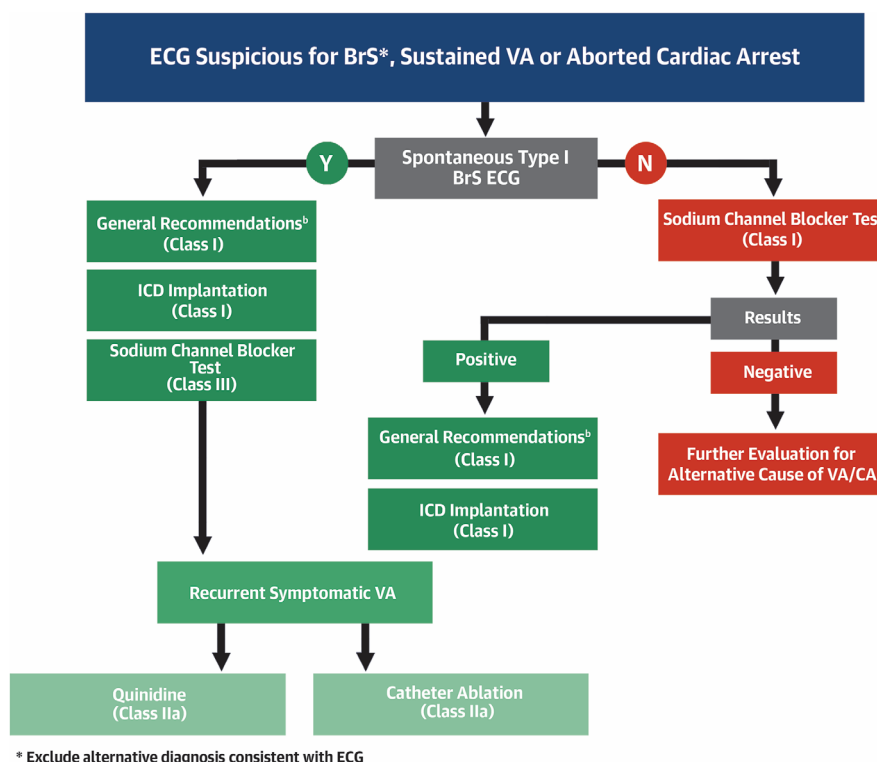


FIGURE 3 | Modified from 2022 European Society Guidelines [16] algorithm for the management of patients who develop VT/VF or survived CA and are suspicious of BrS. BrS, Brugada syndrome; CA, cardiac arrest; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; N, No; VA, ventricular arrhythmia; Y, Yes. ^bGeneral recommendations: Avoidance of drugs that may induce ST-segmentation elevation in right precordial leads <http://www.brugadadrugs.org>, avoidance of cocaine and excessive alcohol intake, treatment of fever with antipyretic drugs.

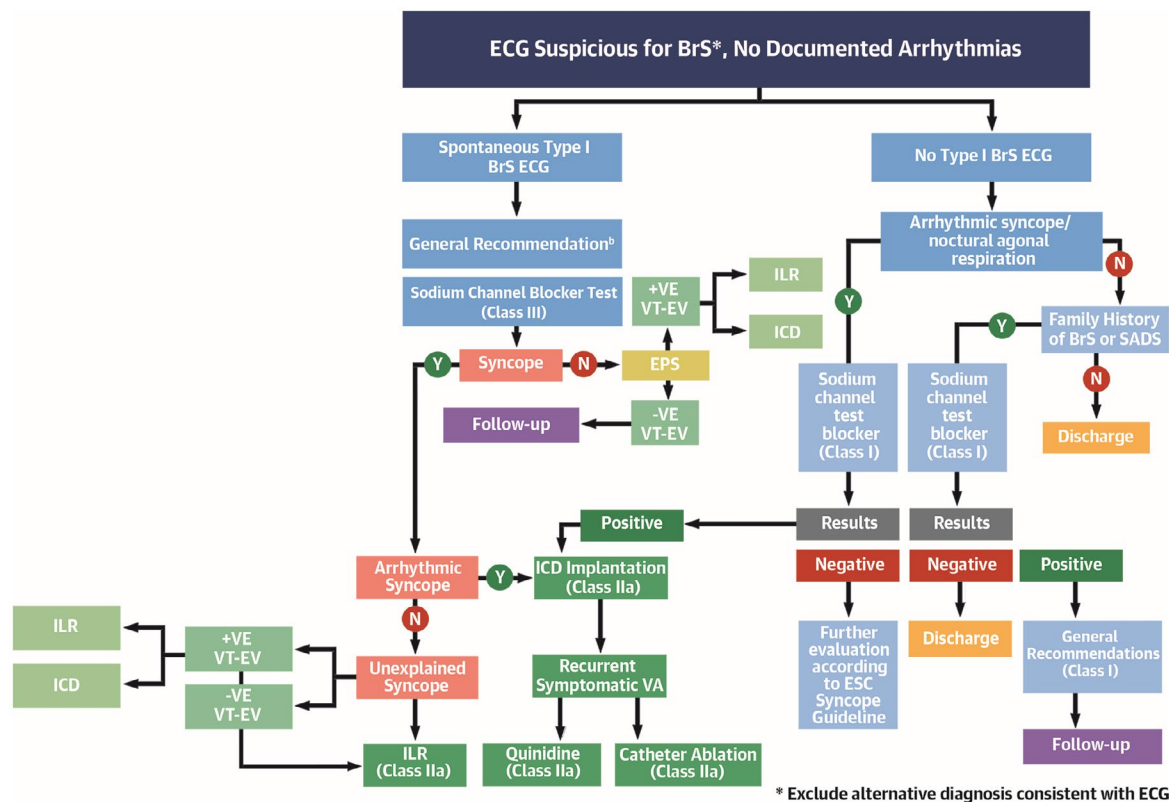


FIGURE 4 | Modified from 2022 European Society Guidelines [16] algorithm for the management of asymptomatic patients who have no documented arrhythmias and are suspicious of BrS. +VE, positive VT/VF induction (≤ 2 extra ventricular stimuli); -VE, Negative VT/VF induction; BrS, Brugada syndrome; CA, cardiac arrest; ECG, electrocardiogram; EPS, Electrophysiologic study; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; N, No; VA, ventricular arrhythmia; Y, Yes.

of an SCB, remains contentious. This group is considered low-risk, and the general recommendation is against routine ICD implantation, favoring regular follow-up and specific precautionary measures instead [10, 16, 192]. As discussed earlier, the approach to identify high-risk asymptomatic patients with spontaneous type 1 ECG patterns for ICD treatment is less clear, reflecting varied opinions on disease severity and the mixed outcomes of different studies. Appropriate risk stratification may play a critical role in identifying asymptomatic BrS patients at high risk of sudden death who may benefit from ICD or ablation treatment (see Figures 3 and 4). A strategy should rely on multiple risk factors rather than a single parameter (see above), using several scoring models developed to aid decision-making regarding ICD implantation in high-risk cases [184].

Recent analyses of BrS patients without a history of sudden cardiac arrest and based on prospective, observational studies involving programmed electrical stimulation suggest that inducible arrhythmias—elicited with up to two ventricular premature beats—are predictive of future ventricular events [171–174]. This method, in current guidelines a class IIb indication [16], could also be beneficial in evaluating patients with unknown syncope.

The annual rate of appropriate ICD interventions in BrS patients ranges from 2.2% to 3.7%. This statistic is significant for a predominantly young and healthy population with a life expectancy exceeding 30years [193–198]. Nonetheless, the long-term

management of ICD therapy must carefully consider the relatively high complication rates associated with the device [193–201]. These complications, which occur in 20%–30% of cases over a follow-up period of 21–47 months, include inappropriate shocks from sinus tachycardia, supraventricular arrhythmias, T-wave oversensing, and lead dysfunction. Adjusting ICD settings to include a single VF zone with a high cutoff limit (> 210 – 220 bpm) and extending detection times can minimize unnecessary interventions for self-terminating arrhythmias [202–204]. Additional preventive measures involve restricting competitive and recreational activities that could damage the lead. Subcutaneous ICDs offer a viable alternative for individuals not requiring pacing, although concerns remain about inappropriate sensing due to the variability in QRS and T-wave morphology typical of BrS [205, 206].

While ICD therapy is pivotal in preventing SCD in BrS and ERS patients, it intervenes only after the onset of VF. Challenges with ICDs include frequent shocks from recurrent VT/VF episodes and device- or lead-related complications, as highlighted in studies by Miyazaki et al. [200], and Olde Nordkamp et al. [205]. Some patients suffer, despite quinidine therapy, from VF storms requiring urgent interventions with isoproterenol infusion and deep sedation or hypothermia (not consistent in ERS) [34]. Unfortunately, these measures are not always successful, with some patients having persistent VF or multiple ICD shocks, impacting their quality of life significantly. In severe cases, cardiac transplantation may become necessary.

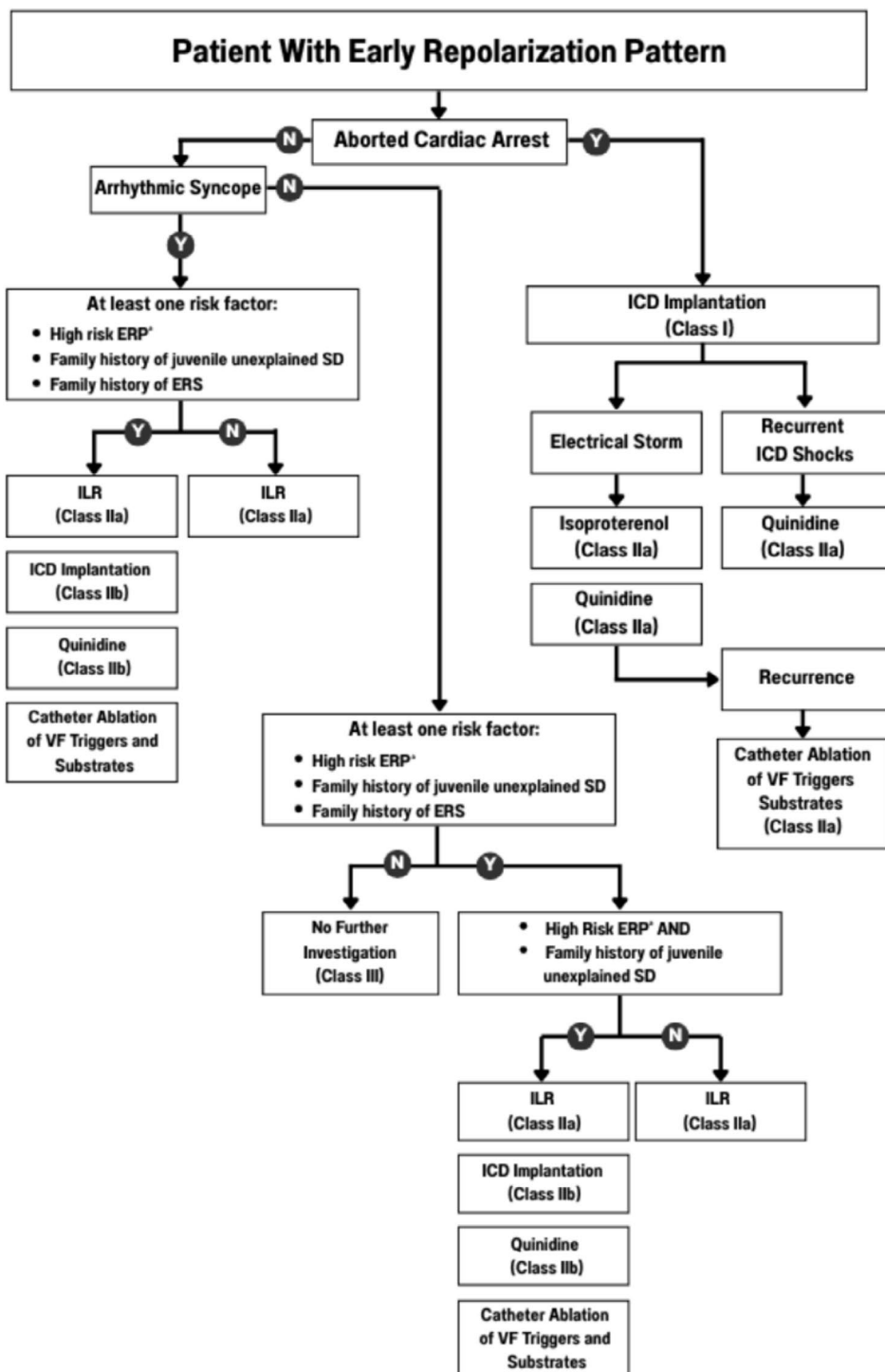


FIGURE 5 | Management of patients with early repolarization pattern/syndrome, modified from 2022 European Society Guidelines [16]. ERP, early repolarization pattern; ERS, early repolarization syndrome; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; N, No; PVC, premature ventricular complex; SD, sudden death; Y, Yes. ERP^a, high risk features: J waves 0.2 mm, dynamic changes in ST morphology.

1.5.3 | Ablation Treatment for BrS

The pursuit of effective prevention of VF in BrS patients has led to the exploration of catheter ablation as a potential treatment. Early efforts, particularly by the Bordeaux group [207], focused on endocardial mapping and ablating VF triggers in symptomatic patients. However, the rarity of spontaneous VF-triggering premature ventricular contractions made this approach less

feasible, shifting the focus towards identifying and ablating specific substrate sites [132].

Advances in ablation technology and techniques, such as the Sosa technique for pericardial access, advanced electroanatomical mapping, and specialized ablation catheters for epicardial use, have facilitated comprehensive mapping of both the endocardium and epicardium in BrS patients. This led to the

identification of substrate sites, mainly in the RVOT epicardium, characterized by low voltage fractionated late potentials. Radiofrequency ablation of these sites has proven effective in normalizing ECG patterns and preventing VF occurrences [208].

As discussed in the pathophysiology section, arrhythmogenic substrate in BrS patients is predominantly in RVOT. However, approximately 30% of these patients also show substrate presence in the inferior RV epicardium, and a small fraction (about 2%) in the posterolateral LV epicardium [32, 209]. Those patients with detectable substrates in both the RV inferior and LV epicardium often exhibit simultaneous ER abnormalities on ECG.

Some epicardial BrS substrates remain concealed and require SCBs like ajmaline, pilsicainide, and flecainide for detection [27, 176, 210]. SCBs typically reveal these concealed sites, enlarging the substrate area [27, 176, 211, 212]. Notably, a comprehensive study by Pappone et al. showed that ablation, following detailed endo-epicardial mapping and ajmaline administration, normalized ECG patterns in 98.5% of patients and prevented VF during follow-up, emphasizing the procedure's dynamic nature and its ability to address extensive abnormal areas in severely symptomatic patients [211, 212]. Therefore, using a SCB is crucial for uncovering all substrate sites, thereby allowing more effective ablation and significantly improved outcomes.

Following the initial findings, several centers worldwide have adopted catheter ablation for BrS, confirming the presence of arrhythmogenic substrates in the RV epicardium and the procedure's safety and efficacy in preventing VF recurrences. Large cohort studies and registries, including those by the Pappone group [213], and the Brugada Ablation of VF Substrate Ongoing Multicenter (BRAVO) registry, have consistently supported these findings [209].

The BRAVO registry enrolled 159 highly symptomatic BrS patients (median age 42 years, male) undergoing substrate ablation for recurrent VF episodes [209]. Post-ablation outcomes were excellent, with a 95% VF-free survival rate over 5 years. Multivariable analysis identified ECG normalization (type-1 Brugada pattern) post-ablation—both with and without sodium-channel blockade—as the sole significant predictor of a VF-free outcome (HR, 0.078; 95% CI, 0.008–0.753; $p=0.0274$). Importantly, no arrhythmic or cardiac deaths occurred, though hemopericardium was noted in four patients (2.5%), confirming the procedure's safety and long-term effectiveness.

More recently, in early 2025, two randomized controlled trials (RCTs) provided further compelling evidence supporting substrate ablation in BrS. The Brugada Syndrome Ablation for the Prevention of VF Episodes (BRAVE) trial, a prospective, multicenter study, randomized symptomatic BrS patients with implantable cardioverter-defibrillators (ICD) into ablation versus control groups [214]. Ablation targeted electroanatomically mapped arrhythmogenic areas primarily at the RV epicardium. After 3 years, the ablation group experienced significantly fewer VF events (HR = 0.288; $p=0.0184$) after the first ablation session, prompting The Data Safety Monitoring Board to early terminate the trial after interim analysis. Among all ablation recipients, including crossovers and registry participants, 83% were VF-free following a single procedure, rising to 90% with repeat ablation.

Ablation-related complications were minimal, with one hemopericardium without long-term consequences.

The second trial by Pappone et al. was a prospective, single-center, open-label study randomizing patients with previous cardiac arrest or ICD therapies in a 2:1 ratio to either epicardial ablation or no ablation [215]. The primary endpoint was freedom from VF recurrence, and secondary outcomes included procedural and ICD-related complications and quality-of-life assessments. Following premature termination due to clear superiority, 40 patients (83% male, median age 44 years) had been randomized. After a median follow-up of 4 ± 1.7 years, VF-free survival was significantly higher in the ablation group (96%) compared to the control group (50%). The single VF recurrence in the ablation group involved a subsequent successful ablation from the endocardial RVOT. No unexplained or arrhythmic deaths occurred; however, pericarditis with pericardial effusion occurred in two patients post-ablation, with one requiring pericardiocentesis. Notably, ICD-related complications, including inappropriate shocks and lead extractions, were unexpectedly high (33%) in both groups. Additionally, quality-of-life measures favored the ablation group significantly. Collectively, these two RCTs strongly corroborate earlier observational studies and advocate for epicardial ablation as a frontline therapy for recurrent VF in BrS patients, particularly in regions where alternative therapies such as quinidine are unavailable or poorly tolerated.

Based on the discussion above, Figure 3 illustrates the treatment algorithm for BrS patients who have survived an episode of sustained VT/VF or aborted cardiac arrest.

1.5.4 | Ablation Treatment for Early Repolarization Syndrome (Figure 5)

ERS is now widely recognized as part of JWS. Historically, ERS treatment options were limited to pharmacologic interventions—quinidine for long-term prevention of recurrent VF and isoproterenol for acute treatment of ICD storm from frequent VF episodes—and ICD implantation for sudden death prophylaxis in patients experiencing life-threatening ventricular tachyarrhythmias, like the treatment approach for BrS [10, 16].

A recent multicenter study has highlighted catheter ablation as a promising therapeutic approach [32]. In this study two distinct ERS phenotypes were identified: (1) Group 1, with late depolarization abnormalities predominantly at the RV epicardium ($n=40$); and (2) Group 2, with no depolarization abnormalities ($n=11$) [32]. One patient was not mapped in detail due to a VF storm. Group 1 was further divided into two subgroups: Group 1A consisted of 33 ERS patients with a Brugada ECG pattern, and Group 1B consisted of 7 ERS patients without a Brugada ECG pattern. The study reported that areas of late depolarization coincided with VF driver areas. For Group 1, the major substrate sites were the anterior RVOT/RV epicardium and the RV inferior epicardium. In Group 2, in which substrates were not detected, the Purkinje network emerged as the primary underlying VF trigger. Ablations were performed on 43 patients: 33 in Group 1 underwent VF substrate ablation only, and 5 underwent ablation of both VF substrates and triggers (mean 1.4 ± 0.6 sessions). Additionally, 5 patients in Group 2 and 1 without

group classification underwent Purkinje VF trigger ablation only (mean 1.2 ± 0.4 sessions). The ablations were successful in significantly reducing VF recurrences ($p < 0.0001$). After a follow-up period of 31 ± 26 months, 39 patients (91%) experienced no VF recurrences.

These findings underscore the importance of late depolarization abnormalities, especially in the RV epicardium, and the critical role of the Purkinje network, particularly in the inferoposterior septal areas of the left ventricle, as primary VF triggers [27]. This evidence positions catheter ablation as an effective therapeutic modality for ERS, significantly expanding treatment options beyond traditional.

1.6 | Future Directions

Over the past three decades, understanding of JWS has advanced substantially. Recent work demonstrates that subclinical structural abnormalities—particularly epicardial and subepicardial fibrosis of the right ventricular (RV) wall—are common in JWS [4, 5]. This recognition broadens the earlier view of JWS as a purely ion-channel disorder. While ion-channel dysfunction remains crucial, structural remodeling now appears to be a major disease component, raising key unanswered questions: What initiates these structural changes? Which genetic and environmental factors modulate them? Can we detect such abnormalities before life-threatening arrhythmias occur? And how might we implement effective prevention?

Emerging data also implicate autoimmune mechanisms, notably anti-Nav1.5 autoantibodies that markedly reduce I_{Na} in approximately 90% of BrS patients irrespective of genotype [216]. Rigorous validation of this autoimmune hypothesis is a priority and could yield non-invasive biomarkers and targeted interventions that forestall maladaptive structural change.

In parallel with research on ion-channel dysfunction in JWS, several seminal genetic studies have revealed that polygenic variants [53, 54, 56, 57], particularly those that adversely affect sodium channel encoding and regulatory variants in the intron region, can significantly reduce I_{Na} , leading to severe conduction abnormalities in the fibrotic areas of the RVOT/RV and ultimately causing ventricular fibrillation (VF) [62]. As a result, more studies are required to further elucidate the complex genetic architecture of JWS. The identification of both rare pathogenic variants and high polygenic risk variants associated with VF occurrence will be pivotal in identifying high-risk patients for primary prevention strategies.

Subtle sub-epicardial myopathic changes in BrS have been challenging to detect with conventional imaging modalities such as echocardiography and MRI. Although recent studies using specialized echocardiographic techniques have identified abnormalities in the RV—including RV dilatation, reduced RV ejection fraction, delayed contraction of the RV outflow tract, and abnormal strain values—these findings remain controversial regarding their specificity and reproducibility [217–219]. With the anticipated improved resolution of the imaging modalities, it is to be expected that a structural arrhythmogenic substrate will be detected in some of the patients [220]. Indeed, advances

in high-resolution body surface electrocardiographic mapping, ultra-high field MRI, molecular imaging, and integrated multimodal approaches show significant promise. Future research and clinical validation in these areas are essential for improving the diagnosis and management of patients with BrS.

Historically, ICD implantation and quinidine therapy have been the primary treatments for patients with J-wave syndrome (JWS). Recently, catheter ablation has emerged as an effective alternative for preventing ventricular fibrillation (VF) recurrences, suggesting the possibility of using ablation as a stand-alone or primary therapy. Therefore, developing precise and reliable risk stratification tools to accurately identify high-risk asymptomatic JWS patients is crucial, as they could potentially be protected by ablation alone without the need for ICD implantation.

Integrating advanced non-invasive diagnostic modalities and AI-driven risk-scoring systems could significantly improve patient selection and preventive strategies. Although effective prevention of catastrophic events in JWS patients appears increasingly attainable, several critical questions remain:

1. Can comprehensive substrate ablation safely replace ICD implantation as first-line therapy if all arrhythmogenic substrates are eliminated?
2. Should asymptomatic Brugada syndrome (BrS) patients be considered for prophylactic ablation?
3. Could extensive substrate ablation increase the risk of scar-related reentrant ventricular tachycardia (VT) or negatively impact right ventricular (RV) function?

Future randomized clinical trials are essential to answer these important clinical questions.

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Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

1. P. Brugada and J. Brugada, "Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome. A Multicenter Report," *Journal of the American College of Cardiology* 20, no. 6 (1992): 1391–1396.
2. B. Martini, A. Nava, G. Thiene, et al., "Ventricular Fibrillation Without Apparent Heart Disease: Description of Six Cases," *American Heart Journal* 118, no. 6 (1989): 1203–1209.
3. C. Miles, B. J. Boukens, C. Scrocco, et al., "Subepicardial Cardiomyopathy: A Disease Underlying J-Wave Syndromes and Idiopathic Ventricular Fibrillation," *Circulation* 147, no. 21 (2023): 1622–1633.
4. K. Nademanee, H. Raju, S. V. de Noronha, et al., "Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome," *Journal of the American College of Cardiology* 66, no. 18 (2015): 1976–1986.
5. M. G. Hoogendijk, M. Potse, A. Vinet, J. M. de Bakker, and R. Coronel, "ST Segment Elevation by Current-To-Load Mismatch: An Experimental and Computational Study," *Heart Rhythm* 8, no. 1 (2011): 111–118.
6. R. Coronel, S. Casini, T. T. Koopmann, et al., "Right Ventricular Fibrosis and Conduction Delay in a Patient With Clinical Signs of Brugada Syndrome: A Combined Electrophysiological, Genetic, Histopathologic, and Computational Study," *Circulation* 112, no. 18 (2005): 2769–2777.
7. E. R. Behr, Y. Ben-Haim, M. J. Ackerman, A. D. Krahn, and A. A. Wilde, "Brugada Syndrome and Reduced Right Ventricular Outflow Tract Conduction Reserve: A Final Common Pathway?," *European Heart Journal* 42, no. 11 (2021): 1073–1081.
8. M. Haissaguerre, N. Derval, F. Sacher, et al., "Sudden Cardiac Arrest Associated With Early Repolarization," *New England Journal of Medicine* 358, no. 19 (2008): 2016–2023.
9. J. T. Tikkanen, O. Anttonen, M. J. Junttila, et al., "Long-Term Outcome Associated With Early Repolarization on Electrocardiography," *New England Journal of Medicine* 361, no. 26 (2009): 2529–2537.
10. C. Antzelevitch and G. X. Yan, "J Wave Syndromes," *Heart Rhythm* 7, no. 4 (2010): 549–558.
11. C. Antzelevitch, G. X. Yan, M. J. Ackerman, et al., "J-Wave Syndromes Expert Consensus Conference Report: Emerging Concepts and Gaps in Knowledge," *Heart Rhythm* 13, no. 10 (2016): e295–e324.
12. A. A. Wilde, C. Antzelevitch, M. Borggrefe, et al., "Proposed Diagnostic Criteria for the Brugada Syndrome: Consensus Report," *Circulation* 106, no. 19 (2002): 2514–2519.
13. C. Antzelevitch, P. Brugada, M. Borggrefe, et al., "Brugada Syndrome: Report of the Second Consensus Conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association," *Circulation* 111, no. 5 (2005): 659–670.
14. S. G. Priori, A. A. Wilde, M. Horie, et al., "HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients With Inherited Primary Arrhythmia Syndromes: Document Endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013," *Heart Rhythm* 10, no. 12 (2013): 1932–1963.
15. E. R. Behr, B. G. Winkel, B. Ensam, et al., "The Diagnostic Role of Pharmacological Provocation Testing in Cardiac Electrophysiology: A Clinical Consensus Statement of the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC, the ESC Working Group on Cardiovascular Pharmacotherapy, the Association of European Paediatric and Congenital Cardiology (AEPC), the Paediatric and Congenital Electrophysiology Society (PACES), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society

- (APHRS), and the Latin American Heart Rhythm Society (LAHRS)," *Europace* 27, no. 4 (2025): euaf067, <https://doi.org/10.1093/europace/euaf067>.
16. K. Zeppenfeld, J. Tfelt-Hansen, M. de Riva, et al., "2022 ESC Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death," *European Heart Journal* 43, no. 40 (2022): 3997–4126.
 17. A. A. Wilde, P. G. Postema, J. M. di Diego, et al., "The Pathophysiological Mechanism Underlying Brugada Syndrome: Depolarization Versus Repolarization," *Journal of Molecular and Cellular Cardiology* 49, no. 4 (2010): 543–553.
 18. T. Aiba, W. Shimizu, I. Hidaka, et al., "Cellular Basis for Trigger and Maintenance of Ventricular Fibrillation in the Brugada Syndrome Model: High-Resolution Optical Mapping Study," *Journal of the American College of Cardiology* 47, no. 10 (2006): 2074–2085.
 19. D. Corrado, A. Nava, G. Buja, et al., "Familial Cardiomyopathy Underlies Syndrome of Right Bundle Branch Block, ST Segment Elevation and Sudden Death," *Journal of the American College of Cardiology* 27, no. 2 (1996): 443–448.
 20. A. Frustaci, S. G. Priori, M. Pieroni, et al., "Cardiac Histological Substrate in Patients With Clinical Phenotype of Brugada Syndrome," *Circulation* 112, no. 24 (2005): 3680–3687.
 21. C. Miles, A. Asimaki, I. C. Ster, et al., "Biventricular Myocardial Fibrosis and Sudden Death in Patients With Brugada Syndrome," *Journal of the American College of Cardiology* 78, no. 15 (2021): 1511–1521.
 22. M. Pieroni, P. Notarstefano, A. Oliva, et al., "Electroanatomic and Pathologic Right Ventricular Outflow Tract Abnormalities in Patients With Brugada Syndrome," *Journal of the American College of Cardiology* 72, no. 22 (2018): 2747–2757.
 23. B. J. Boukens, V. Benjacholas, S. van Amersfoort, et al., "Structurally Abnormal Myocardium Underlies Ventricular Fibrillation Storms in a Patient Diagnosed With the Early Repolarization Pattern," *JACC. Clinical Electrophysiology* 6, no. 11 (2020): 1395–1404.
 24. N. K. Y. Funabashi, "J Wave Reaching to Equal or More Than 2 or 3 LV Inferior Leads May Predict the Presence of Organized Fibrotic Myocardium or Fat Change in Survivors of Ventricular Fibrillation," *European Heart Journal* 43, no. 1 (2022): ehab849.037.
 25. P. G. Meregalli, A. A. Wilde, and H. L. Tan, "Pathophysiological Mechanisms of Brugada Syndrome: Depolarization Disorder, Repolarization Disorder, or More?," *Cardiovascular Research* 67, no. 3 (2005): 367–378.
 26. M. Haissaguerre, K. Nademanee, F. Sacher, et al., "Multisite Conduction Block in the Epicardial Substrate of Brugada Syndrome," *Heart Rhythm* 19, no. 3 (2022): 417–426.
 27. K. Nademanee, G. Veerakul, A. Nogami, et al., "Mechanism of the Effects of Sodium Channel Blockade on the Arrhythmogenic Substrate of Brugada Syndrome," *Heart Rhythm* 19, no. 3 (2022): 407–416.
 28. S. Rohr and K. Jp, "Involvement of the Calcium Inward Current in Cardiac Impulse Propagation: Induction of Unidirectional Block by Nifedipine and Reverse by Bay K 8644," *Biophysical Journal* 72 (1997): 13.
 29. G. Cheniti, M. Haissaguerre, C. Dina, et al., "Left Ventricular Abnormal Substrate in Brugada Syndrome," *JACC. Clinical Electrophysiology* 9, no. 10 (2023): 2041–2051.
 30. E. Renard, R. D. Walton, D. Benoist, et al., "Functional Epicardial Conduction Disturbances due to a SCN5A Variant Associated With Brugada Syndrome," *JACC. Clinical Electrophysiology* 9, no. 8 Pt 1 (2023): 1248–1261.
 31. J. N. ten Sande, R. Coronel, C. E. Conrath, et al., "ST-Segment Elevation and Fractionated Electrograms in Brugada Syndrome Patients Arise From the Same Structurally Abnormal Subepicardial RVOT Area but Have a Different Mechanism," *Circulation. Arrhythmia and Electrophysiology* 8, no. 6 (2015): 1382–1392.
 32. K. Nademanee, M. Haissaguerre, M. Hocini, et al., "Mapping and Ablation of Ventricular Fibrillation Associated With Early Repolarization Syndrome," *Circulation* 140, no. 18 (2019): 1477–1490.
 33. B. J. Boukens, M. Potse, and R. Coronel, "Fibrosis and Conduction Abnormalities as Basis for Overlap for Overlap of Brugada and Early Repolarization Syndrome," *International Journal of Molecular Sciences* 22 (2021): 1570, <https://doi.org/10.3390/ijms22041>.
 34. R. Bastiaenen, H. Raju, S. Sharma, et al., "Characterization of Early Repolarization During Ajmaline Provocation and Exercise Tolerance Testing," *Heart Rhythm* 10, no. 2 (2013): 247–254.
 35. V. M. Meijborg, M. Potse, C. E. Conrath, C. N. Belterman, J. M. de Bakker, and R. Coronel, "Reduced Sodium Current in the Lateral Ventricular Wall Induces Inferolateral J-Waves," *Frontiers in Physiology* 7 (2016): 365.
 36. J. M. de Bakker and F. H. Wittkamp, "The Pathophysiologic Basis of Fractionated and Complex Electrograms and the Impact of Recording Techniques on Their Detection and Interpretation," *Circulation. Arrhythmia and Electrophysiology* 3, no. 2 (2010): 204–213.
 37. T. Kawara, R. Derksen, J. R. de Groot, et al., "Activation Delay After Premature Stimulation in Chronically Diseased Human Myocardium Relates to the Architecture of Interstitial Fibrosis," *Circulation* 104, no. 25 (2001): 3069–3075.
 38. B. J. Boukens and R. Coronel, "Delayed Activation due to Early Repolarization: A Combination of Hypotheses," *JACC. Clinical Electrophysiology* 9, no. 8 Pt 1 (2023): 1262–1264.
 39. R. D. Walton, E. Renard, M. Haissaguerre, and D. Benoist, "Endocardial Ito Overexpression and Fibrotic Remodeling Underlying Pause-Dependent Early Repolarization in Humans," *JACC. Clinical Electrophysiology* (2026), in press, <https://doi.org/10.1016/j.jacep.2026.01.022>.
 40. Q. Chen, G. E. Kirsch, D. Zhang, et al., "Genetic Basis and Molecular Mechanism for Idiopathic Ventricular Fibrillation," *Nature* 392, no. 6673 (1998): 293–296.
 41. S. Le Scouarnec, M. Karakachoff, J. B. Gourraud, et al., "Testing the Burden of Rare Variation in Arrhythmia-Susceptibility Genes Provides New Insights Into Molecular Diagnosis for Brugada Syndrome," *Human Molecular Genetics* 24, no. 10 (2015): 2757–2763.
 42. S. M. Hosseini, R. Kim, S. Udupa, et al., "Reappraisal of Reported Genes for Sudden Arrhythmic Death: Evidence-Based Evaluation of Gene Validity for Brugada Syndrome," *Circulation* 138, no. 12 (2018): 1195–1205.
 43. N. T. Strande, E. R. Riggs, A. H. Buchanan, et al., "Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource," *American Journal of Human Genetics* 100, no. 6 (2017): 895–906.
 44. A. A. M. Wilde, C. Semsarian, M. F. Marquez, et al., "European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases," *Heart Rhythm* 19, no. 7 (2022): e1–e60.
 45. S. Richards, N. Aziz, S. Bale, et al., "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology," *Genetics in Medicine* 17, no. 5 (2015): 405–424.
 46. K. Yamagata, M. Horie, T. Aiba, et al., "Genotype-Phenotype Correlation of SCN5A Mutation for the Clinical and Electrocardiographic Characteristics of Proband With Brugada

- Syndrome: A Japanese Multicenter Registry," *Circulation* 135, no. 23 (2017): 2255–2270.
47. G. Cicconte, M. M. Monasky, V. Santinelli, et al., "Brugada Syndrome Genetics Is Associated With Phenotype Severity," *European Heart Journal* 42, no. 11 (2021): 1082–1090.
 48. T. Ikeda, H. Sakurada, K. Sakabe, et al., "Assessment of Noninvasive Markers in Identifying Patients at Risk in the Brugada Syndrome: Insight Into Risk Stratification," *Journal of the American College of Cardiology* 37, no. 6 (2001): 1628–1634.
 49. P. Rattanawong, J. Chenbhanich, P. Mekraksakit, et al., "SCN5A Mutation Status Increases the Risk of Major Arrhythmic Events in Asian Populations With Brugada Syndrome: Systematic Review and Meta-Analysis," *Annals of Noninvasive Electrocardiology* 24, no. 1 (2019): e12589.
 50. E. Schulze-Bahr, L. Eckardt, G. Breithardt, et al., "Sodium Channel Gene (SCN5A) Mutations in 44 Index Patients With Brugada Syndrome: Different Incidences in Familial and Sporadic Disease," *Human Mutation* 21, no. 6 (2003): 651–652.
 51. S. G. Priori, C. Napolitano, M. Gasparini, et al., "Clinical-And-Genetic-Heterogeneity-Of-Right-Bundle-Branch-Block-And-ST-Segment-Elevation-Syndrome: A Prospective Evaluation of 52 Families," *Circulation* 102 (2000): 6.
 52. V. Probst, A. A. Wilde, J. Barc, et al., "SCN5A Mutations and the Role of Genetic Background in the Pathophysiology of Brugada Syndrome," *Circulation. Cardiovascular Genetics* 2, no. 6 (2009): 552–557.
 53. C. R. Bezzina, R. Pazoki, A. Bardai, et al., "Genome-Wide Association Study Identifies a Susceptibility Locus at 21q21 for Ventricular Fibrillation in Acute Myocardial Infarction," *Nature Genetics* 42, no. 8 (2010): 688–691.
 54. J. Barc, R. Tadros, C. Glinge, et al., "Genome-Wide Association Analyses Identify New Brugada Syndrome Risk Loci and Highlight a New Mechanism of Sodium Channel Regulation in Disease Susceptibility," *Nature Genetics* 54, no. 3 (2022): 232–239.
 55. T. Ishikawa, T. Masuda, T. Hachiya, et al., "Brugada Syndrome in Japan and Europe: A Genome-Wide Association Study Reveals Shared Genetic Architecture and New Risk Loci," *European Heart Journal* 45, no. 26 (2024): 2320–2332.
 56. P. Makarawate, C. Glinge, A. Khongphatthanayothin, et al., "Common and Rare Susceptibility Genetic Variants Predisposing to Brugada Syndrome in Thailand," *Heart Rhythm* 17, no. 12 (2020): 2145–2153.
 57. J. M. Jimmy Juang, Y. B. Liu, C. Y. Julius Chen, et al., "Validation and Disease Risk Assessment of Previously Reported Genome-Wide Genetic Variants Associated With Brugada Syndrome: SADS-TW BrS Registry," *Circulation: Genomic and Precision Medicine* 13, no. 4 (2020): e002797.
 58. R. Tadros, H. L. Tan, E.-N. Investigators, et al., "Predicting Cardiac Electrical Response to Sodium-Channel Blockade and Brugada Syndrome Using Polygenic Risk Scores," *European Heart Journal* 40, no. 37 (2019): 3097–3107.
 59. Y. D. Wijeyeratne, M. W. Tanck, Y. Mizusawa, et al., "SCN5A Mutation Type and a Genetic Risk Score Associate Variably With Brugada Syndrome Phenotype in SCN5A Families," *Circulation: Genomic and Precision Medicine* 13, no. 6 (2020): e002911.
 60. D. Kukavica, A. Trancuccio, A. Mazzanti, et al., "Nonmodifiable Risk Factors Predict Outcomes in Brugada Syndrome," *Journal of the American College of Cardiology* 84, no. 21 (2024): 2087–2098.
 61. E. M. J. Marsman, P. G. Postema, and C. A. Remme, "Brugada Syndrome: Update and Future Perspectives," *Heart* 108, no. 9 (2022): 668–675.
 62. R. Walsh, J. Mauleekoonphairoj, I. Mengarelli, and F. M. Bosada, "A Rare-Non-Coding Enhancer Variant in SCN5A Contributes to the High Prevalence of Brugada Syndrome in Thailand," *Circulation* 151, no. 1 (2025): 31–444.
 63. R. Bastiaenen, I. M. Nolte, P. B. Munroe, et al., "The Narrow-Sense and Common Single Nucleotide Polymorphism Heritability of Early Repolarization," *International Journal of Cardiology* 279 (2019): 135–140.
 64. W. Reinhard, B. M. Kaess, R. Debiec, et al., "Heritability of Early Repolarization: A Population-Based Study," *Circulation. Cardiovascular Genetics* 4, no. 2 (2011): 134–138.
 65. S. Honarbakhsh, N. Srinivasan, C. Kirkby, et al., "Medium-Term Outcomes of Idiopathic Ventricular Fibrillation Survivors and Family Screening: A Multicentre Experience," *Europace* 19, no. 11 (2017): 1874–1880.
 66. G. Mellor, C. P. Nelson, C. Robb, et al., "The Prevalence and Significance of the Early Repolarization Pattern in Sudden Arrhythmic Death Syndrome Families," *Circulation. Arrhythmia and Electrophysiology* 9, no. 6 (2016): e003960, <https://doi.org/10.1161/CIRCEP.116.003960>.
 67. L. M. Nunn, J. Bhar-Amato, M. D. Lowe, et al., "Prevalence of J-Point Elevation in Sudden Arrhythmic Death Syndrome Families," *Journal of the American College of Cardiology* 58, no. 3 (2011): 286–290.
 68. H. Watanabe, A. Nogami, K. Ohkubo, et al., "Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization," *Circulation. Arrhythmia and Electrophysiology* 4, no. 6 (2011): 874–881.
 69. Z. H. Zhang, H. Barajas-Martinez, H. Xia, et al., "Distinct Features of Probands With Early Repolarization and Brugada Syndromes Carrying SCN5A Pathogenic Variants," *Journal of the American College of Cardiology* 78, no. 16 (2021): 1603–1617.
 70. H. Barajas-Martinez, D. Hu, T. Ferrer, et al., "Molecular Genetic and Functional Association of Brugada and Early Repolarization Syndromes With S422L Missense Mutation in KCNJ8," *Heart Rhythm* 9, no. 4 (2012): 548–555.
 71. M. Haissaguerre, S. Chatel, F. Sacher, et al., "Ventricular Fibrillation With Prominent Early Repolarization Associated With a Rare Variant of KCNJ8/KATP Channel," *Journal of Cardiovascular Electrophysiology* 20, no. 1 (2009): 93–98.
 72. A. Medeiros-Domingo, B. H. Tan, L. Crotti, et al., "Gain-Of-Function Mutation S422L in the KCNJ8-Encoded Cardiac K(ATP) Channel Kir6.1 as a Pathogenic Substrate for J-Wave Syndromes," *Heart Rhythm* 7, no. 10 (2010): 1466–1471.
 73. K. R. Veeramah, T. M. Karafet, D. Wolf, R. A. Samson, and M. F. Hammer, "The KCNJ8-S422L Variant Previously Associated With J-Wave Syndromes Is Found at an Increased Frequency in Ashkenazi Jews," *European Journal of Human Genetics* 22, no. 1 (2014): 94–98.
 74. S. Chauveau, A. Janin, M. Till, E. Morel, P. Chevalier, and G. Millat, "Early Repolarization Syndrome Caused by de Novo Duplication of KCND3 Detected by Next-Generation Sequencing," *Heart Rhythm Case Rep* 3, no. 12 (2017): 574–578.
 75. K. Takayama, S. Ohno, W. G. Ding, et al., "A de Novo Gain-Of-Function KCND3 Mutation in Early Repolarization Syndrome," *Heart Rhythm* 16, no. 11 (2019): 1698–1706.
 76. A. Teumer, T. Trenkwalder, T. Kessler, et al., "KCND3 Potassium Channel Gene Variant Confers Susceptibility to Electrocardiographic Early Repolarization Pattern," *JCI Insight* 4, no. 23 (2019): e131156, <https://doi.org/10.1172/jci.insight.131156>.
 77. S. G. Priori, M. Gasparini, C. Napolitano, et al., "Risk Stratification in Brugada Syndrome: Results of the PRELUDE (PROgrammed ELEctrical stimUlation preDICTive valuE) Registry," *Journal of the American College of Cardiology* 59, no. 1 (2012): 37–45.
 78. V. Probst, C. Veltmann, L. Eckardt, et al., "Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome: Results From the

- FINGER Brugada Syndrome Registry," *Circulation* 121, no. 5 (2010): 635–643.
79. F. Gaita, N. Cerrato, C. Giustetto, et al., "Asymptomatic Patients With Brugada ECG Pattern: Long-Term Prognosis From a Large Prospective Study," *Circulation* 148, no. 20 (2023): 1543–1555.
80. Y. Take, H. Morita, N. Toh, et al., "Identification of High-Risk Syncope Related to Ventricular Fibrillation in Patients With Brugada Syndrome," *Heart Rhythm* 9, no. 5 (2012): 752–759.
81. H. Raju, M. Papadakis, M. Govindan, et al., "Low Prevalence of Risk Markers in Cases of Sudden Death due to Brugada Syndrome Relevance to Risk Stratification in Brugada Syndrome," *Journal of the American College of Cardiology* 57, no. 23 (2011): 2340–2345.
82. S. Kamakura, T. Ohe, K. Nakazawa, et al., "Long-Term Prognosis of Probands With Brugada-Pattern ST-Elevation in Leads V1–V3," *Circulation. Arrhythmia and Electrophysiology* 2, no. 5 (2009): 495–503.
83. H. Morita, A. Watanabe, S. Kawada, et al., "Identification of Electrocardiographic Risk Markers for the Initial and Recurrent Episodes of Ventricular Fibrillation in Patients With Brugada Syndrome," *Journal of Cardiovascular Electrophysiology* 29, no. 1 (2018): 107–114.
84. J. Sieira, G. Conte, G. Ciconte, et al., "A Score Model to Predict Risk of Events in Patients With Brugada Syndrome," *European Heart Journal* 38, no. 22 (2017): 1756–1763.
85. R. Casado-Arroyo, P. Berne, J. Y. Rao, et al., "Long-Term Trends in Newly Diagnosed Brugada Syndrome: Implications for Risk Stratification," *Journal of the American College of Cardiology* 68, no. 6 (2016): 614–623.
86. W. K. Shen, R. S. Sheldon, D. G. Benditt, et al., "2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society," *Journal of the American College of Cardiology* 70, no. 5 (2017): 620–663.
87. M. Bergonti, F. Sacher, E. Arbelo, et al., "Implantable Loop Recorders in Patients With Brugada Syndrome: The BruLoop Study," *European Heart Journal* 45, no. 14 (2024): 1255–1265.
88. C. Scrocco, Y. Ben-Haim, B. Devine, et al., "Role of Subcutaneous Implantable Loop Recorder for the Diagnosis of Arrhythmias in Brugada Syndrome: A United Kingdom Single-Center Experience," *Heart Rhythm* 19, no. 1 (2022): 70–78.
89. F. Sacher, F. Arsac, S. B. Wilton, et al., "Syncope in Brugada Syndrome Patients: Prevalence, Characteristics, and Outcome," *Heart Rhythm* 9, no. 8 (2012): 1272–1279.
90. W. Shimizu, K. Matsuo, Y. Kokubo, et al., "Sex Hormone and Gender Difference—Role of Testosterone on Male Predominance in Brugada Syndrome," *Journal of Cardiovascular Electrophysiology* 18, no. 4 (2007): 415–421.
91. K. Matsuo, M. Akahoshi, S. Seto, and K. Yano, "Disappearance of the Brugada-Type Electrocardiogram After Surgical Castration: A Role for Testosterone and an Explanation for the Male Preponderance," *Pacing and Clinical Electrophysiology* 26, no. 7 Pt 1 (2003): 1551–1553.
92. A. Milman, A. Andorin, J. B. Gourraud, et al., "Age of First Arrhythmic Event in Brugada Syndrome: Data From the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 Patients," *Circulation. Arrhythmia and Electrophysiology* 10, no. 12 (2017): e005222, <https://doi.org/10.1161/CIRCEP.117.005222>.
93. G. Conte, C. Dea, J. Sieira, et al., "Clinical Characteristics, Management, and Prognosis of Elderly Patients With Brugada Syndrome," *Journal of Cardiovascular Electrophysiology* 25, no. 5 (2014): 514–519.
94. T. Kamakura, M. Wada, I. Nakajima, et al., "Evaluation of the Necessity for Cardioverter-Defibrillator Implantation in Elderly Patients With Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 8, no. 4 (2015): 785–791.
95. M. Minier, V. Probst, P. Berthome, et al., "Age at Diagnosis of Brugada Syndrome: Influence on Clinical Characteristics and Risk of Arrhythmia," *Heart Rhythm* 17, no. 5 Pt A (2020): 743–749.
96. G. Conte, C. de Asmundis, G. Ciconte, et al., "Follow-up From Childhood to Adulthood of Individuals With Family History of Brugada Syndrome and Normal Electrocardiograms," *Journal of the American Medical Association* 312, no. 19 (2014): 2039–2041.
97. V. Probst, I. Denjoy, P. G. Meregalli, et al., "Clinical Aspects and Prognosis of Brugada Syndrome in Children," *Circulation* 115, no. 15 (2007): 2042–2048.
98. M. C. Gonzalez Corcia, J. Sieira, A. Sarkozy, et al., "Brugada Syndrome in the Young: An Assessment of Risk Factors Predicting Future Events," *Europace* 19, no. 11 (2017): 1864–1873.
99. A. Milman, J. B. Gourraud, A. Andorin, et al., "Gender Differences in Patients With Brugada Syndrome and Arrhythmic Events: Data From a Survey on Arrhythmic Events in 678 Patients," *Heart Rhythm* 15, no. 10 (2018): 1457–1465.
100. P. Berthome, R. Tixier, J. Briand, et al., "Clinical Presentation and Follow-Up of Women Affected by Brugada Syndrome," *Heart Rhythm* 16, no. 2 (2019): 260–267.
101. B. Benito, A. Sarkozy, L. Mont, et al., "Gender Differences in Clinical Manifestations of Brugada Syndrome," *Journal of the American College of Cardiology* 52, no. 19 (2008): 1567–1573.
102. J. Sieira, G. Conte, G. Ciconte, et al., "Clinical Characterisation and Long-Term Prognosis of Women With Brugada Syndrome," *Heart* 102, no. 6 (2016): 452–458.
103. Y. Michowitz, A. Milman, A. Andorin, et al., "Characterization and Management of Arrhythmic Events in Young Patients With Brugada Syndrome," *Journal of the American College of Cardiology* 73, no. 14 (2019): 1756–1765.
104. A. Sarkozy, A. Sorgente, T. Boussy, et al., "The Value of a Family History of Sudden Death in Patients With Diagnostic Type I Brugada ECG Pattern," *European Heart Journal* 32, no. 17 (2011): 2153–2160.
105. P. Delise, G. Allocca, E. Marras, et al., "Risk Stratification in Individuals With the Brugada Type 1 ECG Pattern Without Previous Cardiac Arrest: Usefulness of a Combined Clinical and Electrophysiologic Approach," *European Heart Journal* 32, no. 2 (2011): 169–176.
106. P. G. Meregalli, H. L. Tan, V. Probst, et al., "Type of SCN5A Mutation Determines Clinical Severity and Degree of Conduction Slowing in Loss-Of-Function Sodium Channelopathies," *Heart Rhythm* 6, no. 3 (2009): 341–348.
107. J. P. Smits, L. Eckardt, V. Probst, et al., "Genotype-Phenotype Relationship in Brugada Syndrome: Electrocardiographic Features Differentiate SCN5A-Related Patients From Non-SCN5A-Related Patients," *Journal of the American College of Cardiology* 40, no. 2 (2002): 350–356.
108. A. Adler, R. Rosso, E. Chorin, O. Havakuk, C. Antzelevitch, and S. Viskin, "Risk Stratification in Brugada Syndrome: Clinical Characteristics, Electrocardiographic Parameters, and Auxiliary Testing," *Heart Rhythm* 13, no. 1 (2016): 299–310.
109. A. K. Gehi, T. D. Duong, L. D. Metz, J. A. Gomes, and D. Mehta, "Risk Stratification of Individuals With the Brugada Electrocardiogram: A Meta-Analysis," *Journal of Cardiovascular Electrophysiology* 17, no. 6 (2006): 577–583.
110. T. Ishikawa, H. Kimoto, H. Mishima, et al., "Functionally Validated SCN5A Variants Allow Interpretation of Pathogenicity and Prediction of Lethal Events in Brugada Syndrome," *European Heart Journal* 42, no. 29 (2021): 2854–2863.

111. V. Santinelli, G. Ciconte, F. Manguso, et al., "High-Risk Brugada Syndrome: Factors Associated With Arrhythmia Recurrence and Benefits of Epicardial Ablation in Addition to Implantable Cardioverter Defibrillator Implantation," *Europace* 26, no. 1 (2024): euae019, <https://doi.org/10.1093/europace/euae019>.
112. A. A. M. Wilde and C. I. Wu, "Does Function Trump Bioinformatics in Brugada Syndrome-Associated SCN5A Mutation Calling? Patients, Computers, and Patches," *European Heart Journal* 42, no. 29 (2021): 2864–2865.
113. K. Miyamoto, M. Yokokawa, K. Tanaka, et al., "Diagnostic and Prognostic Value of a Type 1 Brugada Electrocardiogram at Higher (Third or Second) V1 to V2 Recording in Men With Brugada Syndrome," *American Journal of Cardiology* 99, no. 1 (2007): 53–57.
114. J. Brugada, R. Brugada, and P. Brugada, "Determinants of Sudden Cardiac Death in Individuals With the Electrocardiographic Pattern of Brugada Syndrome and no Previous Cardiac Arrest," *Circulation* 108, no. 25 (2003): 3092–3096.
115. S. G. Priori, C. Napolitano, M. Gasparini, et al., "Natural History of Brugada Syndrome: Insights for Risk Stratification and Management," *Circulation* 105, no. 11 (2002): 1342–1347.
116. J. Sieira, G. Ciconte, G. Conte, et al., "Asymptomatic Brugada Syndrome: Clinical Characterization and Long-Term Prognosis," *Circulation. Arrhythmia and Electrophysiology* 8, no. 5 (2015): 1144–1150.
117. Y. Mizusawa and A. A. Wilde, "Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 5, no. 3 (2012): 606–616.
118. S. Richter, A. Sarkozy, C. Veltmann, et al., "Variability of the Diagnostic ECG Pattern in an ICD Patient Population With Brugada Syndrome," *Journal of Cardiovascular Electrophysiology* 20, no. 1 (2009): 69–75.
119. C. Scrocco, Y. Ben-Haim, B. Ensam, et al., "The Role for Ambulatory Electrocardiogram Monitoring in the Diagnosis and Prognostication of Brugada Syndrome: A Sub-Study of the Rare Arrhythmia Syndrome Evaluation (RASE) Brugada Study," *Europace* 26, no. 5 (2024): euae091, <https://doi.org/10.1093/europace/euae091>.
120. A. Miyamoto, H. Hayashi, T. Makiyama, et al., "Risk Determinants in Individuals With a Spontaneous Type 1 Brugada ECG," *Circulation Journal* 75, no. 4 (2011): 844–851.
121. P. Maury, A. Rollin, F. Sacher, et al., "Prevalence and Prognostic Role of Various Conduction Disturbances in Patients With the Brugada Syndrome," *American Journal of Cardiology* 112, no. 9 (2013): 1384–1389.
122. F. Migliore, M. Testolina, A. Zorzi, et al., "First-Degree Atrioventricular Block on Basal Electrocardiogram Predicts Future Arrhythmic Events in Patients With Brugada Syndrome: A Long-Term Follow-Up Study From the Veneto Region of Northeastern Italy," *Europace* 21, no. 2 (2019): 322–331.
123. M. J. Junttila, P. Brugada, K. Hong, et al., "Differences in 12-Lead Electrocardiogram Between Symptomatic and Asymptomatic Brugada Syndrome Patients," *Journal of Cardiovascular Electrophysiology* 19, no. 4 (2008): 380–383.
124. M. Takagi, Y. Yokoyama, K. Aonuma, N. Aihara, M. Hiraoka, and Japan Idiopathic Ventricular Fibrillation Study I, "Clinical Characteristics and Risk Stratification in Symptomatic and Asymptomatic Patients With Brugada Syndrome: Multicenter Study in Japan," *Journal of Cardiovascular Electrophysiology* 18, no. 12 (2007): 1244–1251.
125. K. Tokioka, K. F. Kusano, H. Morita, et al., "Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome: Combination of Depolarization and Repolarization Abnormalities," *Journal of the American College of Cardiology* 63, no. 20 (2014): 2131–2138.
126. Y. Aizawa, S. Takatsuki, M. Sano, et al., "Brugada Syndrome Behind Complete Right Bundle-Branch Block," *Circulation* 128, no. 10 (2013): 1048–1054.
127. S. Rolf, W. Haverkamp, and L. Eckardt, "True Right Bundle Branch Block Masking the Typical ECG in Brugada Syndrome," *Pacing and Clinical Electrophysiology* 28, no. 3 (2005): 258–259.
128. K. Nakagawa, S. Nagase, H. Morita, et al., "Impact of Premature Activation of the Right Ventricle With Programmed Stimulation in Brugada Syndrome," *Journal of Cardiovascular Electrophysiology* 29, no. 1 (2018): 71–78.
129. T. Wada, S. Nagase, H. Morita, et al., "Incidence and Clinical Significance of Brugada Syndrome Masked by Complete Right Bundle-Branch Block," *Circulation Journal* 79, no. 12 (2015): 2568–2575.
130. H. Morita, K. F. Kusano, D. Miura, et al., "Fragmented QRS as a Marker of Conduction Abnormality and a Predictor of Prognosis of Brugada Syndrome," *Circulation* 118, no. 17 (2008): 1697–1704.
131. M. Subramanian, M. A. Prabhu, M. Rai, et al., "A Novel Prediction Model for Risk Stratification in Patients With a Type 1 Brugada ECG Pattern," *Journal of Electrocardiology* 55 (2019): 65–71.
132. K. Nademanee, M. Hocini, and M. Haissaguerre, "Epicardial Substrate Ablation for Brugada Syndrome," *Heart Rhythm* 14, no. 3 (2017): 457–461.
133. H. Morita, A. Watanabe, Y. Morimoto, et al., "Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 10, no. 3 (2017): e004765, <https://doi.org/10.1061/CIRCEP.116.004765>.
134. G. Conte, C. de Asmundis, J. Sieira, et al., "Prevalence and Clinical Impact of Early Repolarization Pattern and QRS-Fragmentation in High-Risk Patients With Brugada Syndrome," *Circulation Journal* 80, no. 10 (2016): 2109–2116.
135. S. Asada, H. Morita, A. Watanabe, et al., "Indication and Prognostic Significance of Programmed Ventricular Stimulation in Asymptomatic Patients With Brugada Syndrome," *Europace* 22, no. 6 (2020): 972–979.
136. M. A. Babai Bigi, A. Aslani, and S. Shahrzad, "aVR Sign as a Risk Factor for Life-Threatening Arrhythmic Events in Patients With Brugada Syndrome," *Heart Rhythm* 4, no. 8 (2007): 1009–1012.
137. A. A. Y. Ragab, C. A. Houck, L. van der Does, et al., "Usefulness of the R-Wave Sign as a Predictor for Ventricular Tachyarrhythmia in Patients With Brugada Syndrome," *American Journal of Cardiology* 120, no. 3 (2017): 428–434.
138. L. Calo, C. Giustetto, A. Martino, et al., "A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome: The S-Wave in Lead I," *Journal of the American College of Cardiology* 67, no. 12 (2016): 1427–1440.
139. V. N. Batchvarov, M. Govindan, A. J. Camm, and E. R. Behr, "Brugada-Like Changes in the Peripheral Leads During Diagnostic Ajmaline Test in Patients With Suspected Brugada Syndrome," *Pacing and Clinical Electrophysiology* 32, no. 6 (2009): 695–703.
140. A. Rollin, F. Sacher, J. B. Gourraud, et al., "Prevalence, Characteristics, and Prognosis Role of Type 1 ST Elevation in the Peripheral ECG Leads in Patients With Brugada Syndrome," *Heart Rhythm* 10, no. 7 (2013): 1012–1018.
141. M. Takagi, K. Aonuma, Y. Sekiguchi, et al., "The Prognostic Value of Early Repolarization (J Wave) and ST-Segment Morphology After J Wave in Brugada Syndrome: Multicenter Study in Japan," *Heart Rhythm* 10, no. 4 (2013): 533–539.
142. S. Georgopoulos, K. P. Letsas, T. Liu, et al., "A Meta-Analysis on the Prognostic Significance of Inferolateral Early Repolarization Pattern in Brugada Syndrome," *Europace* 20, no. 1 (2018): 134–139.

143. Y. Kaneko, M. Horie, S. Niwano, et al., "Electrical Storm in Patients With Brugada Syndrome Is Associated With Early Repolarization," *Circulation. Arrhythmia and Electrophysiology* 7, no. 6 (2014): 1122–1128.
144. T. Kamakura, T. Shinohara, K. Yodogawa, et al., "Long-Term Prognosis of Patients with J-Wave Syndrome," *Heart* 106, no. 4 (2020): 299–306.
145. H. Kawata, H. Morita, Y. Yamada, et al., "Prognostic Significance of Early Repolarization in Inferolateral Leads in Brugada Patients With Documented Ventricular Fibrillation: A Novel Risk Factor for Brugada Syndrome With Ventricular Fibrillation," *Heart Rhythm* 10, no. 8 (2013): 1161–1168.
146. J. Castro Hevia, C. Antzelevitch, F. Tornes Barzaga, et al., "Tpeak-Tend and Tpeak-Tend Dispersion as Risk Factors for Ventricular Tachycardia/Ventricular Fibrillation in Patients With the Brugada Syndrome," *Journal of the American College of Cardiology* 47, no. 9 (2006): 1828.
147. G. Tse, M. Gong, C. K. H. Li, et al., "T(Peak)-T(End), T(Peak)-T(End)/QT Ratio and T(peak)-T(end) Dispersion for Risk Stratification in Brugada Syndrome: A Systematic Review and Meta-Analysis," *Journal of the American College of Cardiology* 34, no. 6 (2018): 587–597.
148. P. Maury, F. Sacher, J. B. Gourraud, et al., "Increased Tpeak-Tend Interval is Highly and Independently Related to Arrhythmic Events in Brugada Syndrome," *Journal of Arrhythmia* 12, no. 12 (2015): 2469–2476.
149. S. Zumhagen, E. M. Zeidler, B. Stallmeyer, M. Ernsting, L. Eckardt, and E. Schulze-Bahr, "Tpeak-Tend Interval and Tpeak-Tend/QT Ratio in Patients With Brugada Syndrome," *Europace* 18, no. 12 (2016): 1866–1872.
150. G. Mugnai, B. Hunuk, J. Hernandez-Ojeda, et al., "Role of Electrocardiographic Tpeak-Tend for the Prediction of Ventricular Arrhythmic Events in the Brugada Syndrome," *Heart Rhythm* 120, no. 8 (2017): 1332–1337.
151. H. Morita, K. Fukushima-Kusano, S. Nagase, et al., "Sinus Node Function in Patients With Brugada-Type ECG," *American Journal of Cardiology* 68, no. 5 (2004): 473–476.
152. H. Makimoto, E. Nakagawa, H. Takaki, et al., "Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients With Brugada Syndrome," *Circulation Journal* 56, no. 19 (2010): 1576–1584.
153. A. S. Amin, E. A. de Groot, J. M. Ruijter, A. A. Wilde, and H. L. Tan, "Exercise-Induced ECG Changes in Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 2, no. 5 (2009): 531–539.
154. M. Subramanian, M. A. Prabhu, M. S. Harikrishnan, S. S. Shekhar, P. G. Pai, and K. Natarajan, "The Utility of Exercise Testing in Risk Stratification of Asymptomatic Patients With Type 1 Brugada Pattern," *Journal of the American College of Cardiology* 28, no. 6 (2017): 677–683.
155. P. Chakraborty, M. Rahimi, A. M. Suszko, et al., "Exercise-Induced QRS Prolongation in Brugada Syndrome: Implications for Improving Disease Phenotyping and Diagnosis," *Journal of Cardiovascular Electrophysiology* 10, no. 8 (2024): 1813–1824.
156. G. Mascia, E. Arbelo, J. Hernandez-Ojeda, F. Solimene, R. Brugada, and J. Brugada, "Brugada Syndrome and Exercise Practice: Current Knowledge, Shortcomings and Open Questions," *JACC. Clinical Electrophysiology* 38, no. 8 (2017): e2.
157. A. A. M. Wilde, A. S. Amin, H. Morita, and R. Tadros, "Use, Misuse, and Pitfalls of the Drug Challenge Test in the Diagnosis of the Brugada Syndrome," *European Heart Journal* 44, no. 27 (2023): 2427–2439.
158. G. Conte, W. Dewals, J. Sieira, et al., "Drug-Induced Brugada Syndrome in Children: Clinical Features, Device-Based Management, and Long-Term Follow-Up," *Journal of the American College of Cardiology* 63, no. 21 (2014): 2272–2279.
159. A. Ueoka, H. Morita, A. Watanabe, et al., "Prognostic Significance of the Sodium Channel Blocker Test in Patients With Brugada Syndrome," *Journal of the American Heart Association* 7, no. 10 (2018): e008617, <https://doi.org/10.1161/JAHA.118.008617>.
160. G. Conte, J. Sieira, A. Sarkozy, et al., "Life-Threatening Ventricular Arrhythmias During Ajmaline Challenge in Patients With Brugada Syndrome: Incidence, Clinical Features, and Prognosis," *International Journal of Sports Medicine* 10, no. 12 (2013): 1869–1874.
161. C. C. Cheung, G. Mellor, M. W. Deyell, et al., "Comparison of Ajmaline and Procainamide Provocation Tests in the Diagnosis of Brugada Syndrome," *JACC. Clinical Electrophysiology* 5, no. 4 (2019): 504–512.
162. M. Gasparini, S. G. Priori, M. Mantica, et al., "Flecainide Test in Brugada Syndrome: A Reproducible but Risky Tool," *Pacing and Clinical Electrophysiology* 26, no. 1P2 (2003): 338–341.
163. K. Yoshioka, M. Amino, W. Zareba, et al., "Identification of High-Risk Brugada Syndrome Patients by Combined Analysis of Late Potential and T-Wave Amplitude Variability on Ambulatory Electrocardiograms," *Circulation Journal* 77, no. 3 (2013): 610–618.
164. K. Hisamatsu, K. F. Kusano, H. Morita, et al., "Relationships Between Depolarization Abnormality and Repolarization Abnormality in Patients With Brugada Syndrome: Using Body Surface Signal-Averaged Electrocardiography and Body Surface Maps," *Journal of Cardiovascular Electrophysiology* 15, no. 8 (2004): 870–876.
165. J. Brugada, R. Brugada, and P. Brugada, "Electrophysiologic Testing Predicts Events in Brugada Syndrome Patients," *Heart Rhythm* 8, no. 10 (2011): 1595–1597.
166. A. A. Wilde and S. Viskin, "EP Testing Does Not Predict Cardiac Events in Brugada Syndrome," *Heart Rhythm* 8, no. 10 (2011): 1598–1600.
167. J. Sieira, G. Conte, G. Cicconte, et al., "Prognostic Value of Programmed Electrical Stimulation in Brugada Syndrome: 20 Years Experience," *Circulation. Arrhythmia and Electrophysiology* 8, no. 4 (2015): 777–784.
168. C. Giustetto, S. Drago, P. G. Demarchi, et al., "Risk Stratification of the Patients With Brugada Type Electrocardiogram: A Community-Based Prospective Study," *Europace* 11, no. 4 (2009): 507–513.
169. M. Kanda, W. Shimizu, K. Matsuo, et al., "Electrophysiologic Characteristics and Implications of Induced Ventricular Fibrillation in Symptomatic Patients With Brugada Syndrome," *Journal of the American College of Cardiology* 39, no. 11 (2002): 1799–1805.
170. M. Paul, J. Gerss, E. Schulze-Bahr, et al., "Role of Programmed Ventricular Stimulation in Patients With Brugada Syndrome: A Meta-Analysis of Worldwide Published Data," *European Heart Journal* 28, no. 17 (2007): 2126–2133.
171. L. Fauchier, M. A. Isorni, N. Clementy, B. Pierre, E. Simeon, and D. Babuty, "Prognostic Value of Programmed Ventricular Stimulation in Brugada Syndrome According to Clinical Presentation: An Updated Meta-Analysis of Worldwide Published Data," *International Journal of Cardiology* 168, no. 3 (2013): 3027–3029.
172. J. Sroubek, V. Probst, A. Mazzanti, et al., "Programmed Ventricular Stimulation for Risk Stratification in the Brugada Syndrome: A Pooled Analysis," *Circulation* 133, no. 7 (2016): 622–630.
173. H. Makimoto, S. Kamakura, N. Aihara, et al., "Clinical Impact of the Number of Extrastimuli in Programmed Electrical Stimulation in Patients With Brugada Type 1 Electrocardiogram," *Heart Rhythm* 9, no. 2 (2012): 242–248.
174. M. Takagi, Y. Sekiguchi, Y. Yokoyama, et al., "The Prognostic Impact of Single Extra-Stimulus on Programmed Ventricular Stimulation in Brugada Patients Without Previous Cardiac Arrest: Multi-Centre Study in Japan," *Europace* 20, no. 7 (2018): 1194–1200.

175. C. Giustetto, N. Cerrato, E. Ruffino, et al., "Etiological Diagnosis, Prognostic Significance and Role of Electrophysiological Study in Patients With Brugada ECG and Syncope," *International Journal of Cardiology* 241 (2017): 188–193.
176. J. Brugada, C. Pappone, A. Berruezo, et al., "Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation," *Circulation. Arrhythmia and Electrophysiology* 8, no. 6 (2015): 1373–1381.
177. F. P. Chung, S. B. Raharjo, Y. J. Lin, et al., "A Novel Method to Enhance Phenotype, Epicardial Functional Substrates, and Ventricular Tachyarrhythmias in Brugada Syndrome," *Heart Rhythm* 14, no. 4 (2017): 508–517.
178. H. Kawazoe, Y. Nakano, H. Ochi, et al., "Risk Stratification of Ventricular Fibrillation in Brugada Syndrome Using Noninvasive Scoring Methods," *Heart Rhythm* 13, no. 10 (2016): 1947–1954.
179. S. Kawada, H. Morita, C. Antzelevitch, et al., "Shanghai Score System for Diagnosis of Brugada Syndrome: Validation of the Score System and System and Reclassification of the Patients," *JACC. Clinical Electrophysiology* 4, no. 6 (2018): 724–730.
180. K. P. Letsas, G. Bazoukis, M. Efremidis, et al., "Clinical Characteristics and Long-Term Clinical Course of Patients With Brugada Syndrome Without Previous Cardiac Arrest: A Multiparametric Risk Stratification Approach," *Europace* 21, no. 12 (2019): 1911–1918.
181. H. Okamura and H. Morita, "Risk Stratification in Patients With Brugada Syndrome Without Previous Cardiac Arrest – Prognostic Value of Combined Risk Factors," *Circulation Journal* 79, no. 2 (2015): 310–317.
182. K. M. W. Leong, F. S. Ng, S. Jones, et al., "Prevalence of Spontaneous Type I ECG Pattern, Syncope, and Other Risk Markers in Sudden Cardiac Arrest Survivors With Brugada Syndrome," *Pacing and Clinical Electrophysiology* 42, no. 2 (2019): 257–264.
183. A. Deliniere, A. Baranchuk, J. Gai, et al., "Prediction of Ventricular Arrhythmias in Patients With a Spontaneous Brugada Type 1 Pattern: The Key Is in the Electrocardiogram," *Europace* 21, no. 9 (2019): 1400–1409.
184. P. Rattanawong, N. Mattanapojanat, C. Mead-Harvey, et al., "Predicting Arrhythmic Event Score in Brugada Syndrome: Worldwide Pooled Analysis With Internal and External Validation," *Heart Rhythm* 20, no. 10 (2023): 1358–1367.
185. B. Belhassen, "A 25-Year Control of Idiopathic Ventricular Fibrillation With Electrophysiologic-Guided Antiarrhythmic Drug Therapy," *Heart Rhythm* 1, no. 3 (2004): 352–354.
186. I. Anguera, A. Garcia-Alberola, P. Dallaglio, et al., "Shock Reduction With Long-Term Quinidine in Patients With Brugada Syndrome and Malignant Ventricular Arrhythmia Episodes," *Journal of the American College of Cardiology* 67, no. 13 (2016): 1653–1654.
187. B. Belhassen, A. Glick, and S. Viskin, "Efficacy of Quinidine in High-Risk Patients With Brugada Syndrome," *Circulation* 110, no. 13 (2004): 1731–1737.
188. A. Andorin, J. B. Gourraud, J. Mansourati, et al., "The QUIDAM Study: Hydroquinidine Therapy for the Management of Brugada Syndrome Patients at High Arrhythmic Risk," *Heart Rhythm* 14, no. 8 (2017): 1147–1154.
189. A. Mazzanti, E. Tenuta, M. Marino, et al., "Efficacy and Limitations of Quinidine in Patients With Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 12, no. 5 (2019): e007143, <https://doi.org/10.1161/CIRCEP.118.007143>.
190. T. Ohgo, H. Okamura, T. Noda, et al., "Acute and Chronic Management in Patients With Brugada Syndrome Associated With Electrical Storm of Ventricular Fibrillation," *Heart Rhythm* 4, no. 6 (2007): 695–700.
191. S. Viskin, A. A. Wilde, M. E. Guevara-Valdivia, et al., "Quinidine, a Life-Saving Medication for Brugada Syndrome, Is Inaccessible in Many Countries," *Journal of the American College of Cardiology* 61, no. 23 (2013): 2383–2387.
192. B. Belhassen, "Management of Brugada Syndrome 2016: Should All High Risk Patients Receive an ICD? Alternatives to Implantable Cardiac Defibrillator Therapy for Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 9, no. 11 (2016): e004185, <https://doi.org/10.1061/CIRCEP.116.004185>.
193. G. Conte, J. Sieira, G. Ciconte, et al., "Implantable Cardioverter-Defibrillator Therapy in Brugada Syndrome: A 20-Year Single-Center Experience," *Journal of the American College of Cardiology* 65, no. 9 (2015): 879–888.
194. A. Dereci, S. C. Yap, and A. F. L. Schinkel, "Meta-Analysis of Clinical Outcome After Implantable Cardioverter-Defibrillator Implantation in Patients With Brugada Syndrome," *JACC. Clinical Electrophysiology* 5, no. 2 (2019): 141–148.
195. J. Hernandez-Ojeda, E. Arbelo, R. Borrás, et al., "Patients With Brugada Syndrome and Implanted Cardioverter-Defibrillators: Long-Term Follow-Up," *Journal of the American College of Cardiology* 70, no. 16 (2017): 1991–2002.
196. F. Sacher, V. Probst, Y. Iesaka, et al., "Outcome After Implantation of a Cardioverter-Defibrillator in Patients With Brugada Syndrome: A Multicenter Study," *Circulation* 114, no. 22 (2006): 2317–2324.
197. F. Sacher, V. Probst, P. Maury, et al., "Outcome After Implantation of a Cardioverter-Defibrillator in Patients With Brugada Syndrome: A Multicenter Study-Part 2," *Circulation* 128, no. 16 (2013): 1739–1747.
198. A. Sarkozy, T. Boussy, G. Kourgiannides, et al., "Long-Term Follow-Up of Primary Prophylactic Implantable Cardioverter-Defibrillator Therapy in Brugada Syndrome," *European Heart Journal* 28, no. 3 (2007): 334–344.
199. "Epicardial Ablation in Brugada Syndrome in the Prevention of Sudden Cardiac Death. A Randomized Prospective Follow-Up Study [Internet]," (2017), <https://clinicaltrials.gov/study/NCT03294278>.
200. S. Miyazaki, T. Uchiyama, Y. Komatsu, et al., "Long-Term Complications of Implantable Defibrillator Therapy in Brugada Syndrome," *American Journal of Cardiology* 111, no. 10 (2013): 1448–1451.
201. R. Rosso, A. Glick, M. Glikson, et al., "Outcome After Implantation of Cardioverter Defibrillator [Corrected] in Patients With Brugada Syndrome: A Multicenter Israeli Study (ISRABRU)," *Israel Medical Association Journal* 10, no. 6 (2008): 435–439.
202. D. D. Spragg and R. D. Berger, "How to Avoid Inappropriate Shocks," *Heart Rhythm* 5, no. 5 (2008): 762–765.
203. A. J. Moss, C. Schuger, C. A. Beck, et al., "Reduction in Inappropriate Therapy and Mortality Through ICD Programming," *New England Journal of Medicine* 367, no. 24 (2012): 2275–2283.
204. M. S. Wathen, P. J. DeGroot, M. O. Sweeney, et al., "Prospective Randomized Multicenter Trial of Empirical Antitachycardia Pacing Versus Shocks for Spontaneous Rapid Ventricular Tachycardia in Patients With Implantable Cardioverter-Defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) Trial Results," *Circulation* 110, no. 17 (2004): 2591–2596.
205. L. R. A. Olde Nordkamp, G. Conte, B. Rosenmoller, et al., "Brugada Syndrome and the Subcutaneous Implantable Cardioverter-Defibrillator," *Journal of the American College of Cardiology* 68, no. 6 (2016): 665.
206. N. Miwa, Y. Nagata, T. Yamaguchi, et al., "Effect of Diurnal Variations in the QRS Complex and T Waves on the Eligibility for Subcutaneous Implantable Cardioverter-Defibrillators," *Heart Rhythm* 16, no. 6 (2019): 913–920.
207. M. Haissaguerre, F. Extramiana, M. Hocini, et al., "Mapping and Ablation of Ventricular Fibrillation Associated With Long-QT and Brugada Syndromes," *Circulation* 108, no. 8 (2003): 925–928.

208. K. Nademanee, G. Veerakul, P. Chandanamattha, et al., "Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium," *Circulation* 123, no. 12 (2011): 1270–1279.
209. K. Nademanee, F. P. Chung, F. Sacher, et al., "Long-Term Outcomes of Brugada Substrate Ablation: A Report From BRAVO (Brugada Ablation of VF Substrate Ongoing Multicenter Registry)," *Circulation* 147, no. 21 (2023): 1568–1578.
210. K. Nademanee, "Radiofrequency Ablation in Brugada Syndrome," *Heart Rhythm* 18, no. 10 (2021): 1805–1806.
211. C. Pappone, J. Brugada, G. Vicedomini, et al., "Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome," *Circulation. Arrhythmia and Electrophysiology* 10, no. 5 (2017): e005053.
212. C. Pappone, G. Ciconte, F. Manguso, et al., "Assessing the Malignant Ventricular Arrhythmic Substrate in Patients With Brugada Syndrome," *Journal of the American College of Cardiology* 71, no. 15 (2018): 1631–1646.
213. V. Santinelli, G. Ciconte, F. Manguso, et al., "High-Risk Brugada Syndrome: Factors Associated With Arrhythmia Recurrence and Benefits of Epicardial Ablation in Addition to Implantable Cardioverter Defibrillator Implantation," *Europace* 26, no. 1 (2024): euae019.
214. K. Nademanee, W. Wongcharoen, N. Chimparlee, et al., "Brugada Syndrome Ablation for the Prevention of Ventricular Fibrillation Episodes (BRAVE)," *Heart Rhythm* 22 (2025): 1975–1983.
215. C. Pappone, G. Ciconte, G. Vicedomini, et al., "Epicardial Ablation in High-Risk Brugada Syndrome to Prevent Ventricular Fibrillation: Results From a Randomized Clinical Trial," *Europace* 27 (2025): 27(5).
216. A. Tarantino, G. Ciconte, D. Melgari, et al., "NaV1.5 Autoantibodies in Brugada Syndrome: Pathogenetic Implications," *European Heart Journal* 45, no. 40 (2024): 4336–4348.
217. R. Bastiaenen, A. T. Cox, S. Castelletti, et al., "Late Gadolinium Enhancement in Brugada Syndrome: A Marker for Subtle Underlying Cardiomyopathy?," *Heart Rhythm* 14, no. 4 (2017): 583–589.
218. C. Pappone, V. Santinelli, V. Mecarocci, et al., "Brugada Syndrome: New Insights From Cardiac Magnetic Resonance and Electroanatomical Imaging," *Circulation. Arrhythmia and Electrophysiology* 14, no. 11 (2021): e010004.
219. F. Trevisan, M. Bertini, C. Balla, et al., "Type 1 Brugada Pattern Is Associated With Echocardiography-Detected Delayed Right Ventricular Outflow Tract Contraction," *Journal of the American College of Cardiology* 77, no. 22 (2021): 2865–2867.
220. B. J. Boukens, K. Nademanee, and R. Coronel, "Reply: J-Wave Syndromes: Where's the Scar?," *JACC. Clinical Electrophysiology* 6, no. 14 (2020): 1863–1864.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** joa370284-sup-0001-DataS1.pdf. **Data S2:** joa370284-sup-0002-DataS2.pdf. **Data S3:** joa370284-sup-0003-DataS3.pdf. **Data S4:** joa370284-sup-0004-DataS4.pdf.