Prediction and Prevention of Sudden Death in the Brugada Syndrome

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Sudden cardiac death (SCD) secondary to sudden cardiac arrest (SCA) is a leading cause of death in the United States, claiming over a quarter million lives annually, and is directly responsible for 50% of all cardiovascular mortality. Brugada Syndrome (BrS) is an arrhythmogenic cardiovascular channelopathy that predisposes asymptomatic patients who have no identified disease to a high-risk of SCD/SCA as their first cardiac event/disease manifestation. Limited progress has been made in risk prediction of SCA and SCD, with the greatest challenge being the ability to identify the small high-risk subgroups concealed within the larger general population. In conclusion, accurate identification of high-risk asymptomatic BrS patients (through multiparametric risk scores composed of reliable and validated unambiguous clinical variables and biomarkers) may hold utility in improving current SCD prediction algorithms, and the appropriate primary prevention therapy may prove valuable in reducing risk of sudden death for this patient population. This systematic review aims to comprehensively summarize qualitative evidence that explore proposed clinical, electrocardiographic, electrophysiological, and genetic markers for risk stratification of patients with BrS phenotype, and to discuss the best available contemporary evidence regarding therapeutic approach. **(Am J Cardiol 2019;124:1797−1802)**

Brugada syndrome (BrS) is an arrhythmogenic cardiac channelopathy that predisposes asymptomatic patients without underlying structural heart disease to sudden cardiac arrest (SCA). Despite the absence of any identifiable anatomic abnormalities, a genetic defect resulting in abnormal function of a sodium channel critical for normal cardiac depolarization and repolarization predisposes to sudden cardiac death (SCD) as the first manifestation of the channelopathy.[1,2] Diagnostic criteria have been established for BrS[1,3] and prognostic value has been demonstrated for independent predictors of clinical outcome.[3] Implantation of an implantable cardioverter-defibrillator (ICD) for primary or secondary prevention of SCA reduces the risk of death for high-risk BrS patients (Table 1).[1-4] With 25% of all SCDs manifesting as the first symptomatic cardiac event, risk stratification and ICD placement has clinical utility by prevention of SCD in BrS patients. Indications for primary prevention ICD implantation in patients with BrS have been developed based on multiple risk stratification studies.[5,6] The objectives of our present study are to systematically review contemporary literature for qualitative evidence (1) in support of the establishment of validated prognostic risk factors for future arrhythmic events in all BrS patients and (2) to identify effective management strategies and therapeutic interventions which unequivocally prevent sudden death in this patient population.

Definition of BrS

BrS is characterized by type 1 coved ST-segment elevation in 1 or more right precordial leads positioned in the second, third, or fourth intercostal space that may exist spontaneously or through pharmacological provocation with a sodium channel blocking agent (ajmaline, flecainide, pilsicainde, or procainamide).[3] Signs and symptoms associated with BrS include syncope, VT/VF, aborted SCD, palpitations, nocturnal agonal respiration, and chest discomfort that often present during vagotonic periods, rest, sleep, or when febrile, but rarely during exercise.[3]

BrS is an autosomal dominant hereditary arrhythmogenic cardiovascular condition with incomplete penetrance.[2] The SCN5A gene, which encodes for the α subunit of the cardiac sodium channel, has been most commonly implicated in the development of BrS. Within the SCN5A gene, at least 80 distinct mutations have been identified and associated with BrS.[5,7] These SCN5A mutations cause a loss of function that manifest as a variety of irregularities in sodium channel activity.[7] However, SCN5A mutations have been identified in only 20% to 30% of BrS patients that have undergone genetic testing.[1] Additional gene mutations, approximately 20 to date, affecting sodium, calcium, and potassium channels, have been linked to BrS and identified in approximately 5% of BrS patients.[2] Recent findings suggest the majority of BrS cases are sporadic rather than familial.[2] Several studies have failed to identify a correlation between genotype and phenotypic expression in terms of overall prognosis and the risk of adverse cardiac events.[1,4,5]

A Brief History of BrS

In 1992, the Brugada brothers presented data on 8 patients with recurrent aborted SCD unattributable to any known disease. The first manifestation of cardiac disease for 7 of the 8

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Table 1
Summarized Recommendations for selected Brugada syndrome patients per the 2017 AHA/ACC/HRS's Guidelines[1]

BrS subgroup	Type 1 BrS ECG pattern	Benefit-to-risk	Class (strength) of recommendation	Recommendation
Asymptomatic	Spontaneous	Benefit ≥ Risk	Class IIb (Weak)	EPS with PVS using single and double extrastimuli
Asymptomatic	Induced[†]	Benefit >>> Risk	Class I (Strong) Is Recommended Is Indicated	Observation without therapy
Symptomatic[‡]	Spontaneous	Benefit >>> Risk	Class I (Strong) Is Recommended Is Indicated	ICD implantation*

* All recommendations related to ICDs require that meaningful survival of >1 year is expected; meaningful survival means that a patient has a reasonable quality of life and functional status.[1]

[†] Type 1 BrS ECG Pattern induced after provocative drug test with intravenous administration of Class I antiarrhythmic drugs in the presence or absence of types 2/3 ECG.[3]

[‡] Symptomatic, with respect to BrS, refers to patients who have experienced VAs (VT or resuscitated VF) or syncopal episodes presumed due to VA.[3]

patients was syncope without any prodrome. In 5 of these patients, their first syncopal event was followed by aborted SCD. The Brugada brothers found common electrocardiogram (ECG) features among these 8 patients previously mentioned. The common clinical and electrocardiographic features found among these 8 patients collectively defined a distinct syndrome with unknown origin, and termed BrS.[8]

Beginning with the first consensus report in 2002 and through more contemporary guideline documents,[7,9] diagnostic criteria, genotype-phenotype correlation, risk stratification, and management of BrS has continued to evolve. The 2013 HRS/EHRA/Asian Pacific Heart Rhythm Society expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes provides a more current definition for the definitive diagnosis of BrS: a spontaneous or drug-induced (using sodium channel blocking agents, such as ajmaline, flecainide, pilsicainde, or procainamide) type 1 ST-segment elevation ≥ 2 mm in at least 1 right precordial lead (V1 and V2).[3] This definition has since been maintained in the subsequent 2015 European Society of Cardiology (ESC) guidelines.[1,10] Although type 2 and type 3 ST-segment elevations (termed "saddleback" type) are not diagnostic of BrS, the drug-induced conversion of either to type 1 ECG morphology in combination with 1 or more of the aforementioned findings is considered diagnostic.[7] Contemporary studies recognize type 2 and type 3 ECG morphologies as normal ECG variants not associated with an elevated risk of SCD.[11]

The 2017 AHA/ACC/HRS Guideline for the Management of Patients with VAs and the Prevention of SCD does not update or specify the criteria used for the definitive diagnosis of BrS. Instead, Al-Khatib et al provide updated recommendations for BrS management based on the current state of knowledge of BrS (Figure 1).[1]

Methods

PubMed MEDLINE, OVID MEDLINE, the Cochrane Library, and Web of Science were systematically searched for all English language literature published January 1, 2008 through January 1, 2018 using the following terms: "BrS" and "prospective." Studies were screened for eligibility and included into our systematic review if the study was prospective, multicenter, published final results, enrolled a minimum of 50 patients, and had a mean follow-up period of at least 24 months. Of the database results screened, 14 publications were included and systematically reviewed herein.

For each citation meeting the eligibility criteria, 2 reviewers independently reviewed the full article, and consensus regarding inclusion and content was reached. Based on primary endpoint and data assessed, each article was stratified as contributing to risk stratification or therapeutic strategy for the prevention of SCD. For publications contributing to risk stratification, identified independent predictive risk factors have been tabulated (Table 2).

Results

Fourteen studies met inclusion criteria collectively containing a total of 4,341 enrolled subjects. Of the 14 studies, 13 provide data pertaining to risk stratification, while only 2 studies evaluate a potential therapeutic strategy. Independent risk factors shown to be predictive of future arrhythmic events have been tabulated for each study (Table 2). Other factors not denoted with an "X" in Table 2 were either evaluated and not shown to have predictive value or were not evaluated.

Risk stratification

Of the articles matching inclusion criteria, a total of 7 studies[4,12–17] identify the utility of syncope of arrhythmic origin as an independent risk factor of future arrhythmic events. A single study[18] finds the highest risk for future cardiac events included those with a spontaneous type 1 ECG and a minimum of 2 risk factors, specifically family history of SCD, syncope, and electrophysiology study (EPS) inducibility. An additional study[19] finds syncope, or aborted SCD, combined with multiple electrical abnormalities, including, but not limited to, a spontaneous type 1 ECG and atrial fibrillation, to have the great risk of future cardiac events and as an indication for ICD implantation. Five studies[4,12–14,16] find a history of aborted SCD/SCA to be predictive of future arrhythmic events. One study[19] finds aborted SCD combined with multiple electrical abnormalities to be predictive of future cardiac events and an indication for ICD implantation.

Three studies[4,15,17] identify the presence of a spontaneous type 1 ECG at baseline as an independent risk factor for future arrhythmic events in BrS patients. Two studies[18,19]

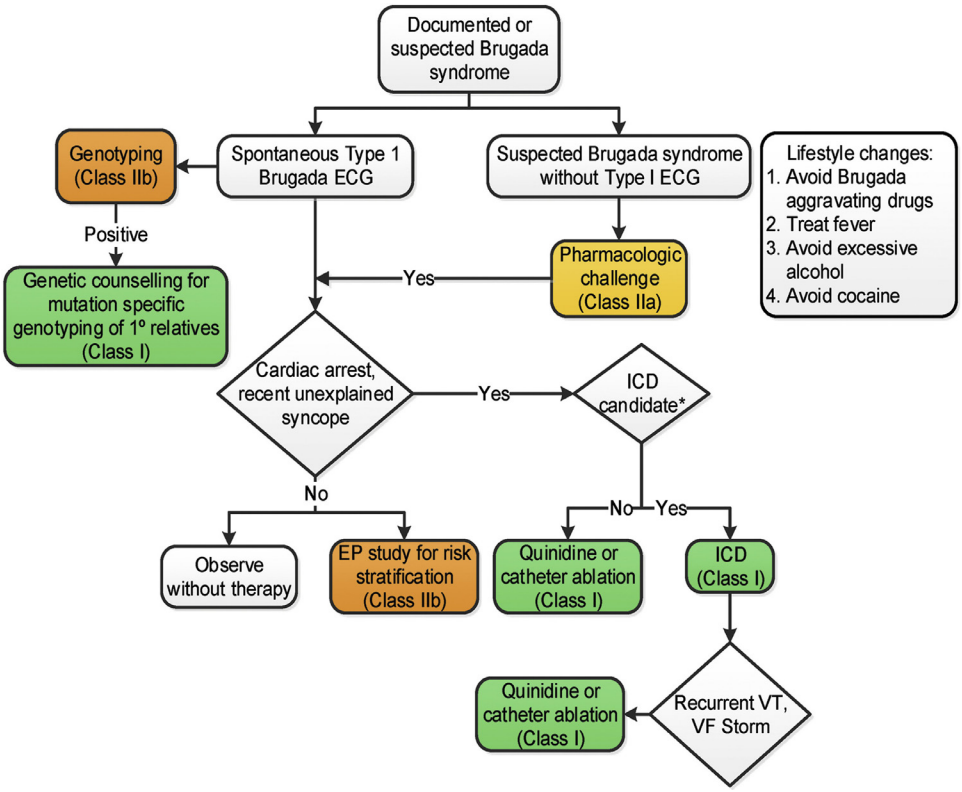

Figure 1. Prevention of sudden cardiac death in Brugada syndrome patients. Reproduced with permission from Elsevier.[1]

identify the predictive value of a spontaneous type 1 ECG when combined with additional specific risk factors, as described previously. One study[20] identifies a family history of SCD to be an independent risk factor for the recurrence of cardiac events. As described previously, a single study[18] finds the highest risk for future cardiac events included those with a spontaneous type 1 ECG and a minimum of 2 risk factors, specifically family history of SCD, syncope, and EPS inducibility.

The utility of EPS inducibility in the risk stratification of BrS is supported by 3 studies.[12,17,19] A single study finds sustained VA induced during EPS to have predictive value only in its earlier cohort of BrS patients.[21] This discrepancy may be attributed to the 54% of patients in the latter group who presented with a history of aborted SCD and opted to undergo ICD implantation without EPS study, which can be compared to only 10% in the earlier group.[21] Although another study[18] finds the highest risk for future cardiac events included those with a spontaneous type 1 ECG and a minimum of 2 risk factors, specifically family history of SCD, syncope, and EPS inducibility. The remaining risk factors in Table 2 include atrial fibrillation as well as additional electrical markers. Each of these risk factors have been recognized by isolated studies[15,16,20,22,23] for their utility in identification of BrS patients at risk of future arrhythmic events.

Therapeutic strategies

In one of the largest and longest follow-ups of BrS patients with ICDs,[14] the 5-year rate of appropriate shock was approximately 6% in asymptomatic patients, that is, those who have not had cardiac arrest or syncope. In contrast, the 5-year rate of appropriate shock was approximately 11% in patients presenting with syncope (without any clear extracardiac cause) and 48% in patients who had ICD placement for secondary prevention due to aborted SCD. In a mean follow-up of approximately 5 years, the total mortality in patients presenting with aborted SCA was zero, 1.6% in those presenting with syncope, and 2.4% in those receiving primary prevention ICD in the absence of syncope or cardiac arrest.[14] Although an appropriate shock rate of up to 48% at 5 years has been reported in the literature, the 5-year rate of inappropriate shock was 23% in this study population. Major complications require surgical intervention (e.g., lead fracture or infection), while minor complications are handled noninvasively without associated adverse patient outcomes. In this patient population, major complications, excluding inappropriate shocks, included lead failure (occurring in 15.9% of patients) and lead or device infection (in 2.4%). Other complications (occurring in 6.3% of patients) included, but were not limited to, lead dislodgement, pocket hematoma, pericardial effusion, and severe depression.[14]

Other therapeutic strategies have included pharmacologic therapy. The QUIDAM study explore the use of hydroquinidine in high-risk BrS patients.[24] Due to a premature termination of the study, attributable to hydroquinidine-related adverse effects, primarily gastrointestinal in nature, the QUIDAM study was unsuccessful in demonstrating the efficacy and safety of hydroquinidine in high-risk BrS patients.[24] The high incidence of adverse effects associated with quinidine use and its lack of availability on a global level[25] impact its usefulness as a treatment.[7]

Table 2
Independent predictive risk factors for future cardiac events categorized by study

	Giustetto et al	Benito et al	Probst et al	Sacher et al	Delise et al	Priori et al‡	2013 Takagi et al	2018 Takagi et al	Gonzalez Corcia et al	Casado-Arroyo et al	Kamakura et al	Calo et al	Gray et al
Syncope	X	X	X#	X#	X†	X	X	X§	X††				
Aborted SCD/SCA	X	X	X#	X#			X¶		X††				
Spontaneous type 1 ECG			X#		X†	X		X§	X††				
Family history SCD					X†						X		
EPS inducibility	X				X†			X§,‖	X**	X*			
Atrial fibrillation									X††			X	
Duration of the S-wave ≥40 ms in lead I												X	
QRS interval in lead V_2 > 90 ms							X						
J wave in inferolateral leads ± horizontal ST elevation							X						
ECG presence of early repolarization											X		
Ventricular effective refractory period <200 ms						X							
QRS fragmentation						X							
Temporal burden of type 1 ST-segment elevation													X

* Sustained VA induced during EPS was found to have predictive value in the early group only (which included both prospectively and retrospectively enrolled patients).

† Highest risk for future cardiac events included those with a spontaneous type 1 ECG and a minimum of 2 risk factors, specifically family history of SCD, syncope, and EPS inducibility.

‡ Study enrollment included patients without a history of aborted SCD.

§ Predictive value of this risk factor was determined by univariate analysis (multivariate analysis was not performed).

‖ PES inducibility by a single ventricular extra-stimulus is the specific stimulation protocol shown to be predictive of future cardiac events in BrS patients without previous SCA.

¶ Both VF and aborted SCD have predictive value.

These risk factors have been identified through both retrospectively and prospectively enrolled patients.

** Authors do not specify this study as either single-center or multicenter.

†† Using a risk model in young patients, indication for an ICD included either aborted SCD or syncope with multiple electrical abnormalities, such as spontaneous type 1 ECG or atrial fibrillation.

Noteworthy results from ineligible publications based on inclusion criteria

The overall lack of current literature on the treatment of BrS matching this review's inclusion criteria highlights a significant knowledge gap in the short- and long-term care of this patient population. The QUIDAM study is the single inclusion criteria-matching publication evaluating alternative therapeutic strategies to the ICD. Although ICD implantation as secondary prevention has been established as the standard of care for high-risk BrS patients,[3,5,7] promising alternatives, including pharmacological intervention using class 1A antiarrhythmic agents, minimally invasive procedures focusing on substrate radiofrequency ablation, and subcutaneous-ICD (S-ICD) implantation, continue to be evaluated in smaller and/or single-center studies. Current guidelines include a Class I recommend for quinidine or catheter ablation exclusively in patients who are not candidates for an ICD or have recurrent VT, or VF storm with a previously placed ICD.[1]

Discussion

Although there has been considerable progress in refinement of risk stratification for SCD in BrS patients, the options for therapy for prevention of SCD remain limited.[7] Based on the available current data, the ICD remains the only proven effective treatment for improving survival. No clinical trials assessing the efficacy of alternative therapies, including quinidine and ablation, have been completed.

ICDs have been established for their effectiveness in prolonging patient survival in multiple patient populations with prospective randomized trials.[26,27] Observational studies[5,6] have established the role of ICDs in the treatment of the BrS. The benefit of ICDs in primary and secondary prevention of SCD needs to be weighed against the risks of device therapy. A recent meta-analysis found that 21% (3.9% per year) of ICD-implanted BrS patients experienced inappropriate shock(s), while 21% (3.4% per year) experienced complications during follow-up as compared to 10% to14% in the general population.[28] One single-center prospective study[29] with a long follow-up period finds 8.7% of ICD-implanted patients experienced inappropriate shocks and 20.2% experienced ICD-related complications. These findings indicate ICD implantation is an effective intervention for high-risk patients but carries a risk of device-related complications.[29]

The multiple studies we have systematically evaluated provide robust evidence that aborted SCD/SCA, syncope, and a spontaneous type 1 ECG are independent markers of

increased arrhythmic risk. ICD implantation is indicated in BrS patients with these risk factors. In the absence of other prognostic indicators, a family history of SCD is generally not considered a sufficient indication for ICD therapy. Although controversy of the role of EPS inducibility remains, many experts perform EPS in select BrS patients as a means of further stratifying a patient's risk. A lack of consistency among EPS protocols utilized across enrollment centers may influence the inconsistent prognostic utility of this modality.[17] Isolated studies[15,16,20,22,23] identify additional ECG characteristics as well as atrial fibrillation as independent markers of future cardiac events, however, they have not been consistently shown to be predictive. As such, these factors are generally not considered to increase the risk of SCA/SCD in BrS patients, and ICD implantation is not indicated.

ICD implantation is recommended in patients with a spontaneous type 1 ECG in conjunction with a history of cardiac arrest, sustained VA, or syncope.[1] A family history of SCD, drug-induced type 1 ECG patterns, and EPS inducibility, are not recognized as independent risk factors of cardiac events. BrS patients, including those not indicated for ICD implantation, should be notified of, and avoid, potential triggers of VF and SCA, including fever, cocaine use, excessive alcohol use, psychotropic medications, and anesthetic agents.[1]

The most recent ESC guideline document[10] recommends ICD implantation for BrS patients with a history of aborted SCA or documented spontaneous sustained VT. ICD implantation should be considered in BrS patients with a spontaneous type 1 ECG in conjunction with a history of syncope (Class IIa indication). ICD placement may be appropriate in selected BrS patients who develop VF during EPS with 2 or 3 extrastimuli at 2 sites (Class IIb indication).[10]

Evidence from contemporary observational studies, included herein, generally align with both US-based and European-based recommendations for the risk stratification and treatment of BrS patients. Risk stratification has the capacity to guide the management and treatment of BrS patients, and thereby reduce the occurrence of SCD. Future research to refine risk stratification for primary prevention of SCD in BrS patients is needed to maximize the ratio of sudden death/total mortality.

Disclosures

The authors have no conflicts of interest to disclose.

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