

STATE-OF-THE-ART REVIEW

Brugada Syndrome as a Major Cause of Sudden Cardiac Death in Asians



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ABSTRACT

Brugada syndrome (BrS) is one of the main inherited arrhythmia syndromes causing ventricular fibrillation (VF) and sudden cardiac death in young to middle-aged men, especially in Asians. The diagnosis of BrS is based on spontaneous or drug-provoked type 1 Brugada electrocardiogram. The current reliable therapy for BrS patients with VF history is the implantation of an implantable cardioverter-defibrillator. As for BrS patients without VF history, how asymptomatic BrS patients should effectively be treated is still uncertain because risk stratification of the BrS is still inadequate. Various parameters and combinations of several parameters have been reported for risk stratification of BrS. The *SCN5A* gene is believed to be the only gene that is responsible for BrS, and it has been reported to be useful for risk stratification. This review focuses on risk stratification of BrS patients, and focuses specifically on BrS patients of Asian descent. (JACC: Asia 2022;2:412–421) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Sudden cardiac death (SCD) is a leading problem worldwide. Globally, the incidence of SCD per 100,000 people per year was estimated to be 34.4 in Europe, 53.1 people in North America, 59.4 people in Asia, and 49.7 people in Australia (Figure 1A).¹ In other reports, the incidence of SCD per 100,000 people per year in Asia has been reported as 37 in Japan,² 41 in China,³ 38 in Thailand,⁴ and 43 in the Philippines⁵ (Figure 1B). Moreover, the POST SCD (Postmortem Systematic Investigation of SCD) Study in 2018 reported that the incidence ratios for the World Health Organization SCD including sudden arrhythmic death (SAD) were more than 2- and 3-fold higher in men vs women, and highest in black people, lowest in Hispanics, and intermediate in Asians and white people (Figure 2).⁶

As for SCD survival rate, Berdowski et al¹ reported that the survival rate to discharge was reported to be 7.6% in Europe, 6.8% in North America, 3.0% in Asia, and 9.7% in Australia. According to a report by the

Fire and Disaster Management Agency of Japan's Ministry of Internal Affairs and Communications in 2020, the 1-month survival rate was 55.9% and the rehabilitation rate was 48.2% in SCD patients using bystander cardiopulmonary resuscitation and automated external defibrillator, whereas the 1-month survival rate was 9.0% and the rehabilitation rate was 4.5% in those without. Bystander cardiopulmonary resuscitation and automated external defibrillator use are effective but currently insufficient worldwide.⁷ According to data from the Pan-Asian Resuscitation Outcomes Study between 2011 and 2016, the national Utstein (bystander witnessed, shockable rhythm) 30-day survival-to-discharge rate was 11.6%–23.1% in Singapore.⁸ This was related to the implementation of a 5-year national plan for prehospital emergency care, which consisted of both community, prehospital community policies, and implementation measures.⁸

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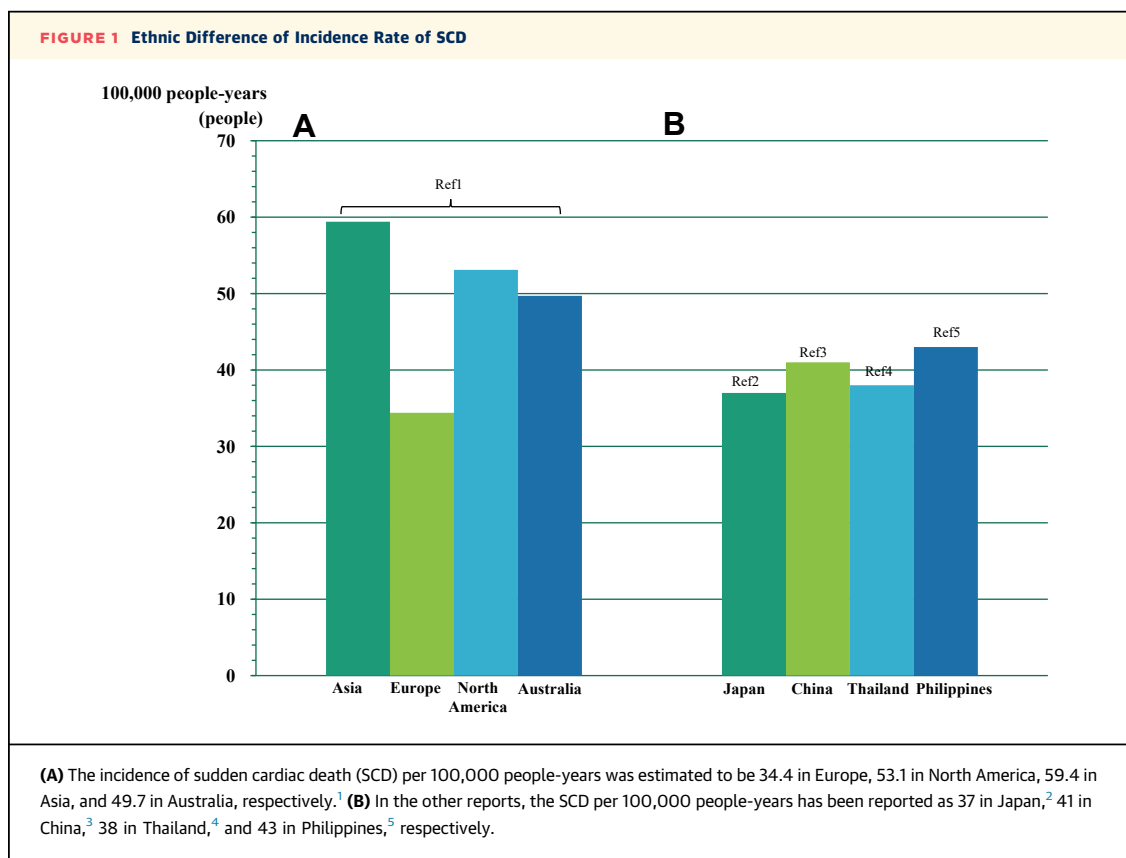
Detecting and intervening in the diseases that cause SCD at an early stage are also important. As for causes of SCD listed in the 2020 Asia Pacific Heart Rhythm Society/Heart Rhythm Society (APHRS/HRS) expert consensus statement on the investigation of SCD,⁷ the most common SCD cause in young people younger than 35 years are inherited heart diseases, including inherited arrhythmia syndromes. Coronary artery disease is the most common SCD cause from 35 years of age, but inherited arrhythmia syndromes also continue to be a common SCD cause up until 50 years of age.⁷ According to the POST SCD Study,⁶ the rate of SAD among all the SCD was highest in Asians (61.9%) and lowest in black people (44.6%) (Figure 2). In Japan, the Hisayama study (1962-2009) was reported in 2013 as only the autopsy data. This study demonstrated that the most common cause of SCD was coronary artery diseases, but the rate was <30%.⁹ In the autopsy data of Chinese adults, unexplained sudden death was a major cause and accounted for 22.5% of victims younger than 35 years of age.¹⁰ According to data of 289 SCD victims in Hong Kong, 35% of the deaths were caused by coronary artery disease, 40% of the deaths were caused by structural heart diseases, and 25% of the deaths were unexplained.

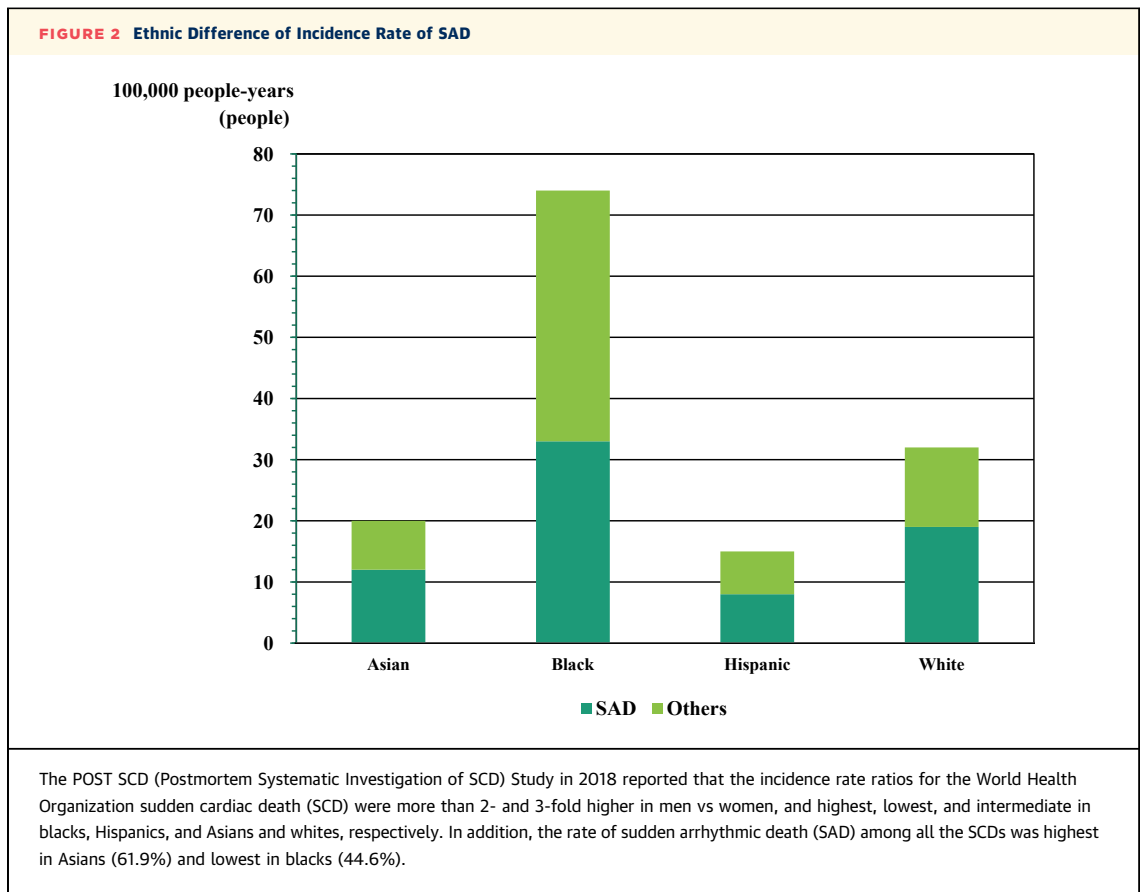
Among the unexplained cases, 85% had negative autopsy, suggesting SAD.¹¹

According to data reported by Nowbar et al¹² in 2019, based on an analysis of data from health organizations, the mortality rate from ischemic heart disease worldwide is 57.4 per 100,000 population in Japan, 140 in Turkey, 80.2 in France, 184.9 in the United States, and 260.9 in the United Kingdom. Lower mortality rates associated with ischemic heart disease were noted in Asia compared with Europe and the United States.¹² Therefore, the role of inherited arrhythmia syndromes in SCD is particularly important in Asia.¹³ The main inherited arrhythmia syndromes are Brugada syndrome (BrS), long-QT syndrome, short-QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. Among them, BrS is one of the major cause of SCD in young to middle-aged men and it is the most common cause in some Asian countries.^{14,15} According to the 2005-2015 All-Japan Utstein Registry data, the 18- to 39-year-old male group showed a higher rate of SCD events at midnight to early morning compared with that of other age groups.¹⁶ This may reflect a BrS characteristic, which is that BrS is

ABBREVIATIONS AND ACRONYMS

- APHRS** = Asia Pacific Heart Rhythm Society
- BrS** = Brugada syndrome
- ECG** = electrocardiogram
- HRS** = Heart Rhythm Society
- ICD** = implantable cardioverter-defibrillator
- SAD** = sudden arrhythmic death
- SCD** = sudden cardiac death
- VF** = ventricular fibrillation





more common in men and is more likely to cause sudden death at night or at rest. Thus, this review article specifically focuses on BrS under the theme of inherited arrhythmia syndromes in Asia.

BrS EPIDEMIOLOGY AND DIAGNOSIS

BrS is one of the inherited arrhythmia syndromes, is characterized by a type 1 Brugada electrocardiogram (ECG) pattern of ST-segment elevation in the right precordial leads, and has a high SCD risk caused by ventricular fibrillation (VF).¹⁷ BrS is 8-10 times more prevalent in males than in females¹⁸ and typically manifests during adulthood at a mean age of 45 years.¹⁹

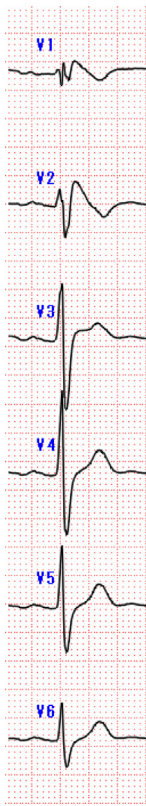
BrS can be diagnosed in patients with ST-segment elevation with type 1 morphology, characterized by ST-segment elevation ≥ 2 mm in at least one lead in the right precordial leads V_1 , V_2 , positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after administration of sodium channel blockers after HRS/European Heart Rhythm Association/APHRS expert consensus statement (Figure 3).^{15,19,20} Prevalence of BrS is much higher in Asian countries, especially Thailand, Philippines, and Japan.²¹ The estimated prevalence of

BrS ranges from 0.02%-0.1% in Europe and from 0.1%-0.25% in Asia.^{22,23} According to a meta-analysis in 2018, the global BrS pool prevalence is 0.5 per 1,000. Southeast Asians show the highest prevalence (3.7 per 1,000), and North Africans the lowest (0 per 1,000). The prevalence of Asians is 9 times more often than in Caucasians, and 36 times more common than Hispanics.²⁴ Thus, BrS is a disease of much concern, especially in Asia.

BrS PROGNOSIS AND RISK STRATIFICATION

Kamakura et al²⁵ reported that family history of SCD at younger than 45 years of age and coexistence of early repolarization pattern in inferolateral leads, in addition to Brugada ECG, were independent predictors of fatal arrhythmic events in a Japanese cohort, although spontaneous type 1 ECG and inducibility of VF by the electrophysiological study were not reliable parameters. Another Japanese cohort, including 460 BrS patients with type 1 ECG, reported that VF events were observed in 27 of 84 patients (32%, 8.4%/y) with a history of VF, 8 of 109 patients with a history of syncope alone (7%, 1.7%/y), and 3 of 267 asymptomatic patients (1%, 0.3%/y).²⁶ Similarly, in the European registry (FINGER [France, Italy,

FIGURE 3 Type1 BrS ECG



Type 1 Brugada type electrocardiograms (ECGs), whether spontaneous or after sodium channel blockers provocation, are characterized by a coved type ST-segment elevation ≥ 2 mm in at least one lead located in the right precordial leads V₁, V₂, positioned in the second, third, or fourth intercostal space. BrS = Brugada syndrome.

Netherlands, Germany] Brugada syndrome registry), VF events were reported to be 7.7%/y in those with a history of VF, 1.9%/y in those with only syncope, and 0.5%/y in asymptomatic BrS patients.²⁷ A recent meta-analysis from Asia reported that a SCD history in family members younger than 40 years of age held a significant increase in the risk of major arrhythmic events.²⁸ Moreover, SCD risk stratification in BrS has not been completely explained and is still controversial (Table 1). Many previous studies, including 2 large European BrS registries (FINGER and PRELUDE [PProgrammed ELectrical stimUlation preDICTive Value]), reported that a syncope history was significantly associated with VF events.^{25,27,29-31} Predicting the risk by a single parameter is difficult, although various parameters for risk stratification have been reported. We reported a novel logistic model using previously reported noninvasive risk factors for VF in

patients with BrS (a combination of the history of syncope, r-J interval in V₁, QRS duration in V₆, and T_{peak} to T_{end} dispersion), and it was useful for assessing risk stratification in routine clinical practice.³² The Shanghai score^{33,34} and Sciera score,³⁵ which are both diagnostic scores consisting of a combination of multiple factors, have been devised for VF risk stratification in BrS.

Shanghai Score is a risk stratification scoring system that integrates ECG, clinical history, family history, and genetic test, with a score of 3.5 or higher as probable/definite BrS. A notable point of the Shanghai score is that the spontaneous type 1 ECG is assigned the highest point (3.5 points) among other parameters, making spontaneous type 1 ECG the main focus of the scoring system, whereas a drug-induced type 1 Brugada ECG (type 2 or 3 Brugada ECG at baseline) is assigned 2 points.³³ Kawada et al³³ validated the appropriateness of the Shanghai Score System for diagnosis of 393 Japanese BrS patients. They reported that an increase in score was associated with an increase in the frequency of ventricular tachycardia/VF events, and that VF events did not occur in any BrS patients with a score of <3.5 .³⁴ The results of this study suggested the credibility of the Shanghai score and showed that a rigorous diagnosis of BrS was important.

However, Probst et al³⁶ recently reported that these risk scores were inadequate for stratifying the risk of arrhythmic events in intermediate-risk patients. According to Japanese guidelines,³⁷ BrS patients with a VF history or aborted cardiac arrest, in addition to type 1 ECG, have been indicated for implantable cardioverter-defibrillator (ICD) implantation as Class I indication. An ICD is recommended as Class IIa indication if arrhythmogenic syncope is found in patients with type 1 ECG. In addition, an unexplained syncope, induction of VF by a single or 2 consecutive extracardiac stimulations,³⁸ family history of sudden death,^{25,28} and SCN5A mutation³⁹ are all considered mild to moderate risk.

A recent multicenter study (BRUGADA-RISK [A Primary Prevention Clinical Risk Score Model for Patients With Brugada Syndrome]), including 1,110 patients with BrS, identified that arrhythmia-related syncope, spontaneous type 1 Brugada ECG, early repolarization pattern, and type 1 Brugada ECG pattern in peripheral leads were associated with a higher risk of SCD.⁴⁰ BRUGADA-RISK estimated the risk of VF or SCD at 5 years in patients with BrS and the Brugada risk calculator was invented using these 4 parameters.⁴¹ Given the high prevalence of BrS in Asians, this simple Brugada risk calculator may contribute significantly to the prevention of

TABLE 1 Parameters for Risk Stratification of VF Events in BrS

	Brugada et al ³⁰	Eckardt et al ³¹	Kamakura et al ²⁵	FINGER ²⁷	PRELUDE ²⁹	Takagi et al ²⁶	Kawazoe et al ³²	Sieira et al ³⁵	Yamagata and Shimizu ³⁹	Kawada and Morita ^{33,34}	BRUGADA-RISK ³³	Rattanawong et al ²⁸
Year	2002	2005	2009	2010	2012	2007	2016	2017	2017	2018	2021	2021
N	334	212	330	1,029	308	430	143	400	415	393	1,110	3,386
Prior VF	a	a	a	a		a	a	a	a	a	a	
Syncope	a	a	b	a	a	a	a	a		a	a	
Spontaneous type1	a	a	b	a	a	b	b	a		a	a	
FH of SCD	b	b	a	b		b	b	a		a		^a Only age <40 y
VF inducibility	a	b	b	b	b	b	b	a				
Male		b	b	a			b					
SCN5A mutation									a	a		
Others							Logistic model	Sieira score		Shanghai score		Meta-analysis
						QRS duration in lead V ₂ >90 ms	Syncope			+Atrial fibrillation	+Early repolarization	
						Inferolateral J-wave	+r-J interval in V ₁				+Type 1 Brugada ECG pattern	
						Horizontal ST-segment morphology	+QRS duration in V ₆				In peripheral leads	
						After J-wave	+Tp-e dispersion					

^aRisk factors associated to events. ^bRisk factors not associated to events.
 BRS = Brugada syndrome; BRUGADA RISK = A Primary Prevention Clinical Risk Score Model for Patients With Brugada Syndrome; ECG = electrocardiogram; FH = family history; FINGER = France, Italy, Netherlands Germany registry; PRELUDE = PProgrammed Electrical stimUlation preDICTive Value); SCD = sudden cardiac death; VF = ventricular fibrillation.

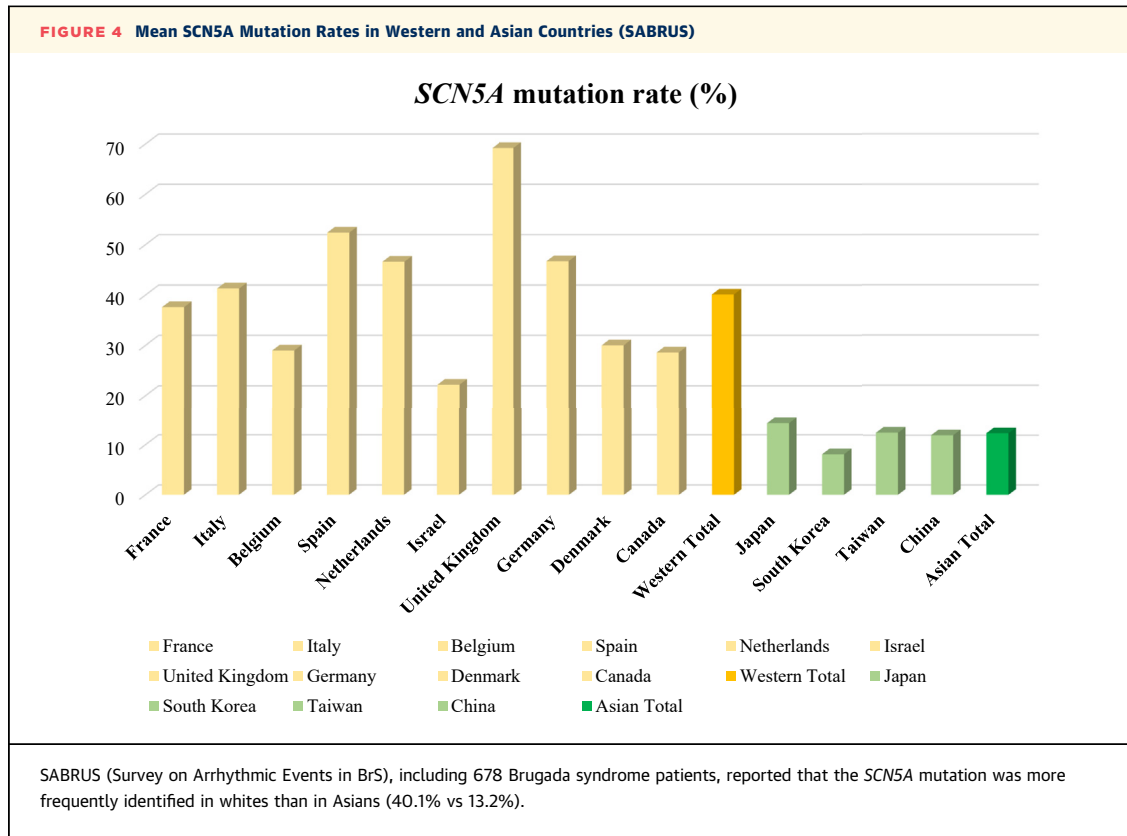
sudden death in family members of BrS patients. Milman et al⁴² investigated the ethnic differences of clinical characteristics and arrhythmic events between Western and Asian patients with BrS. They suggested that Asian BrS patients present almost exclusively as male adults and more often have aborted cardiac arrest and spontaneous type 1 ECG than white BrS patients. On the other hand, white BrS patients have a higher rate of family history of SCD and *SCN5A* mutation than Asian BrS patients. Moreover, the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) revealed that a shorter time-to-first appropriate ICD therapy was observed in Asian BrS patients.⁴³ In consideration of the racial differences in the characteristics of BrS, the validation of the Brugada risk calculator in Asian BrS patients would be required as a multicenter study.

GENETICS

The *SCN5A* gene, which codes for cardiac voltage-gated sodium channels, recently has been agreed on as the only reliable gene causing BrS.⁴⁴ The *SCN5A* gene accounts for the vast majority of patients with BrS in whom the mutation was identified. The Survey on Arrhythmic Events in BrS including 678 BrS patients reported that the *SCN5A* mutation was more

frequently identified in whites than in Asians (40.1% vs 13.2%) (Figure 4).⁴² Many other susceptibility genes have been reported, but their frequencies were rare and their association with the Brugada phenotype is currently limited.^{45,46} A recent evidence-based review of genes also concluded that only the *SCN5A* gene is classified as having definitive evidence as a cause for BrS (Table 2).⁴⁷

Predictive values of *SCN5A* mutations for VF events have been controversial for a long time. *SCN5A* mutations were reported not to be associated with VF events in European BrS cohorts.²⁷ However, a recent study in Europe reported contrary evidence that patients harboring *SCN5A* mutations exhibit more pronounced epicardial electrical abnormalities as an arrhythmogenic substrate and have a more aggressive clinical presentation.⁴⁸ The current Japanese multicenter prospective registry, including 415 probands with BrS, demonstrated that probands carrying *SCN5A* mutations had more conduction abnormalities on ECG and have a higher risk for cardiac events than probands without *SCN5A* mutations.⁴⁰ A large number of *SCN5A* variants have been reported to underlie BrS, but only a few missense variants had available functional data.⁴⁹ The in silico assessment of channel function does not always reflect BrS phenotype and risk stratification.⁵⁰ Most recently, Ishikawa⁵¹ reported that functionally

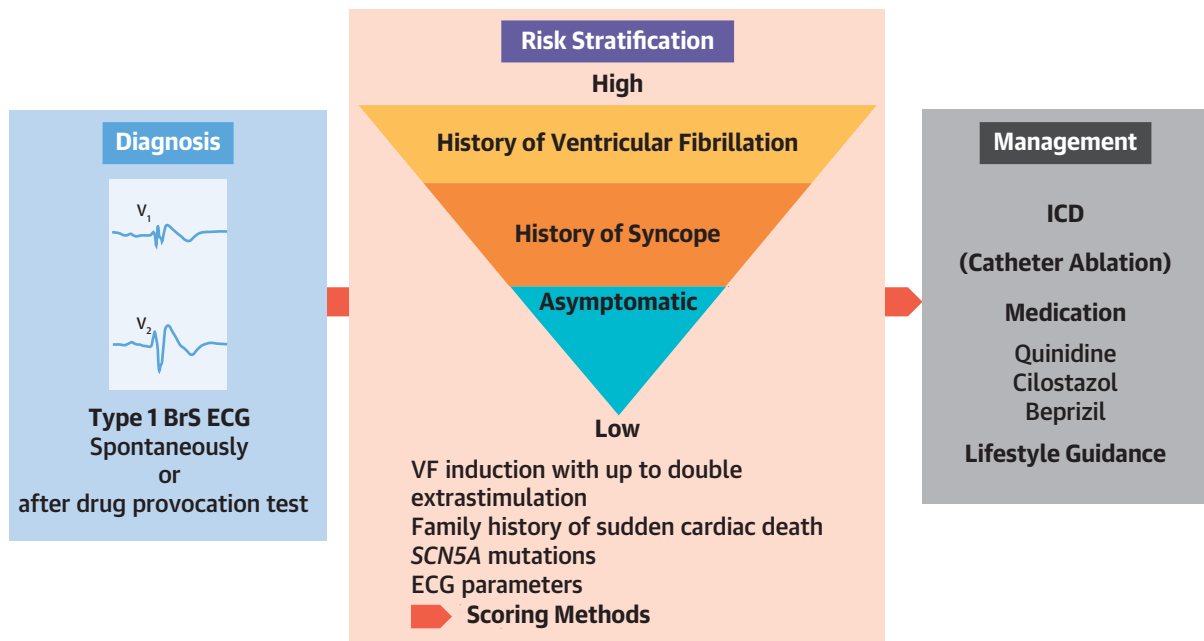


proved loss-of-function *SCN5A* mutations were a significant predictor for subsequent VF events in a similar Japanese BrS registry. In a genome-wide association study, 3 single-nucleotide variation (SNV) (formerly SNP) were reported to be associated with BrS.⁵² The result in replication was confirmed and the *HEY2* SNV was reported to be an useful prognostic marker for Japanese BrS.⁵³ Genetic diagnosis is currently difficult because genes responsible for BrS have not been completely elucidated. However, the accumulation of many studies has made it possible to use *SCN5A* mutations as one of the risk stratifications. BrS biomarkers have also been investigated and α -cardiac actin, α -skeletal actin, keratin, and connexin-43 were reported to be useful for BrS risk stratification, although not enough consensus was noted.⁵⁴ Overlapping between BrS and arrhythmogenic right ventricular cardiomyopathy has long been debated. In 2020, Scheirlynck et al⁵⁵ reported that dilation of the right ventricular outflow, in addition to type 1 ECG, exacerbated the occurrence of arrhythmic events in patients with BrS. They suggested that BrS is not just a primary electrical disease but also overlapping phenotypes of ion channelopathy and structural abnormalities through the disruption of

TABLE 2 Genes Associated With BrS

Name	Gene	Protein	Prevalence
BrS1	<i>SCN5A</i>	α -Subunit Nav1.5 sodium channel	20%-25%
BrS2	<i>GPD1L</i>	Glycerol-3-phosphate dehydrogenase 1-like	Rare
BrS3	<i>CACNA1C</i>	α -Subunit α 1C Cav1.2 calcium channel	1%-2%
BrS4	<i>CACNB2b</i>	β -Subunit Cav β 2b calcium channel	1%-2%
BrS5	<i>SCN1b</i>	β -Subunit Nav β 1 sodium channel	Rare
BrS6	<i>KCNE3</i>	β -Subunit MiRP2 potassium channel	Rare
BrS7	<i>SCN3b</i>	β -Subunit Nav β 3 sodium channel	Rare
BrS8	<i>HCN4</i>	Hyperpolarization-activated cyclic nucleotide-gated channel 4	Rare
BrS9	<i>KCND3</i>	α -Subunit KV4.3 potassium channel	Rare
BrS10	<i>KCNJ8</i>	α -Subunit KIR6.1 potassium channel	Rare
BrS11	<i>CACNA2D1</i>	δ -Subunit Cav α 2 δ 1 calcium channel	Rare
BrS12	<i>KCNE5</i>	β -Subunit potassium channel	Rare
BrS13	<i>RANGRF</i>	RAN guanine nucleotide release factor	Rare
BrS14	<i>KCND2</i>	α -Subunit KV4.2 potassium channel	Rare
BrS15	<i>TRPM4</i>	Calcium-activated nonselective ion channel	Rare
BrS16	<i>SCN2B</i>	β -subunit Nav β 2 sodium channel	Rare
BrS17	<i>PKP2</i>	Plakophilin 2	Rare
BrS18	<i>ABCC9</i>	ATP-sensitive potassium channels	Rare
BrS19	<i>SLMAP</i>	Sarcolemma-associated protein	Rare
BrS20	<i>KCNH2</i>	α -Subunit of HERG potassium channel	Rare
BrS21	<i>SCN10A</i>	α -Subunit Nav1.8 sodium channel	1%-16%
BrS22	<i>FGF12</i>	Fibroblast growth factor 12	Rare
BrS23	<i>SEMA3A</i>	Semaphorin family protein	Rare

ATP = adenosine triphosphate; other abbreviation as in Table 1.

CENTRAL ILLUSTRATION Brugada Syndrome

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This illustration shows the flow from diagnosis to treatment of Brugada Syndrome (BrS). BrS is diagnosed with a spontaneously type 1 Brugada electrocardiogram (ECG) or type 1 Brugada ECG after provocative drug test. Ventricular fibrillation (VF) induction with up to double extra stimulation, family history of sudden cardiac death, *SCN5A* mutations, and ECG parameters are helpful for risk stratification. Recently, the scoring method, which combines several risks, is also used. In cases of secondary prevention, implantable cardioverter-defibrillator (ICD) is indicated, and in asymptomatic cases, oral administration of quinidine is performed depending on risk stratification in addition to lifestyle guidance.

the voltage-gated sodium channel cytoskeleton/desmosome pathway.⁵⁵

THERAPY

The only proven and effective treatment strategy to prevent sudden death in cases of BrS is ICD. Moreover, ICD implantation is a Class I indication for BrS patients with spontaneous type 1 BrS ECG and a history of VF. ICD implantation is indicated for Class IIa in BrS patients with type 1 ECG who have a history of arrhythmogenic syncope.¹⁵ According to Japanese guidelines,^{37,56} ICD implantation is indicated for Class IIb if VF is induced by a single or 2 consecutive extraventricular stimulations in asymptomatic BrS patients combined with other clinical findings, other abnormal ECG findings, or *SCN5A* gene mutations. The HRS/European Heart Rhythm Association/APHRs expert consensus statement also indicates that VF

induction by electrophysiological examination is Class IIb.¹⁵

The most effective drug to prevent VF development in BrS patients is quinidine, which suppresses Ito.⁵⁷ In Japan, the multichannel blocker, beprizil, is used to prevent VF in BrS. It has been reported that beprizil prevented VF in BrS patients by suppressing multiple K channels including Ito and up-regulating Na channels.⁵⁸ Nademanee et al⁵⁹ reported that electrical epicardial substrate ablation in the right ventricular outflow tract in BrS patients can prevent VF inducibility in a high-risk population. Epicardial ablation was effective because an arrhythmogenic substrate in a wide area on the epicardial side of the right ventricle can be observed in most patients. Ablation therapy for BrS patients is currently indicated as a Class IIb indication by Japanese guidelines and is performed to save lives in high-risk BrS patients with repeated VF and VF storm cases.^{15,38} The

HIGHLIGHTS

- SCD is a leading problem worldwide and early detection of diseases causing SCD is important.
- The rate of sudden arrhythmic death is highest in Asians and BrS is one of the main SCD causes in Asians.
- This review focuses on the epidemiology, diagnosis, prognosis, risk stratification, genetics, and therapy of BrS based on currently available evidence including ethnic differences.
- Clarification of the pathophysiology and risk stratification of BrS is still insufficient. With the current guidelines alone, handling BrS cases in clinical practice is difficult, and further clinical and basic explanation is required in the future.

level of evidence for the guideline may increase in the future as more information on BrS ablation cases in Asia is accumulated.

CONCLUSIONS

We reviewed the racial differences in the prevalence and the causes of SCD. Asians have a lower frequency of SCD than blacks, however, Asians have a higher mortality rate from sudden lethal arrhythmias.

Among them, BrS is one of the most important causes of SCD in Asians. We show the flow from diagnosis to treatment of BrS in the **Central Illustration**. The risk stratification of BrS has long been investigated, and multifactorial combinations are becoming mainstream. Because of the racial differences in the characteristics of BrS, the validation of various risk factors for stratification will be necessary in Asian BrS patients. Although genetic background of BrS has not been fully understood, *SCN5A* mutations may help stratify the risk of BrS. Because BrS may not be a monogenic disease, further research including multigene risk assessments and omics will be required in the future to reduce SCD in Asians.

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