The American Journal of Cardiology 244 (2025) 9–17

Contents lists available at ScienceDirect

The American Journal of Cardiology

journal homepage: www.elsevier.com/locate/ajc

Brugada Syndrome in Sports Cardiology: An Expert Opinion Statement of the Italian Society of Sports Cardiology (SICSport)

Antonio Scarà, MD[a,b], Luigi Sciarra[b*], Antonio Dello Russo[c], Elena Cavarretta[d,e], Zefferino Palamà, MD[f], Alessandro Zorzi[g], Francesco Brancati[h,i], Paolo Compagnucci, PhD[c], Michela Casella[c], Valeria Novelli, PhD[j], Giampiero Patrizi, MD[k], Pietro Delise, MD[l,m]

[a] San Carlo di Nancy Hospital – GVM, Rome, Italy
[b] MESVA Department, University of L'Aquila, L'Aquila, Italy
[c] Cardiology and Arrhythmology Clinic, Marche University Hospital, Ancona, Italy
[d] Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy
[e] Advanced Cardiovascular Therapies Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[f] Villa Verde Hospital, Taranto, Italy
[g] Cardiovascular Disease Department, University of Padua, Padua, Italy
[h] Human Genetics, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[i] San Raffaele Roma IRCCS, Rome, Italy
[j] IRCCS Monzino Cardiac Center, Milan, Italy
[k] Department of Cardiology, B. Ramazzini Hospital, Ausl Modena, Carpi, Italy
[l] Medical Center, Mestre, Italy
[m] Medical Center, Conegliano Veneto, Italy

ARTICLE INFO

Article History:
Received 2 January 2025
Revised 4 February 2025
Accepted 20 February 2025

Keywords:
Brugada syndrome
sports cardiology
risk stratification
ventricular arrhythmias
competitive sports eligibility

ABSTRACT

Brugada syndrome (BrS) is a genetic disorder marked by a characteristic electrocardiogram (ECG) pattern of ST-segment elevation and T-wave inversion in right precordial leads, which is associated with an increased risk of ventricular fibrillation in the absence of structural heart disease. Despite advancements in understanding its epidemiology, pathophysiology, and treatment, there is considerable variability in how sports cardiologists approach BrS. This expert opinion by the Italian Society of Sports Cardiology (SICSPORT) aim to review the current definition, diagnosis, epidemiology, genetics, risk stratification, and treatment of BrS and provide guidance for sport eligibility provides guidance for sports doctors and cardiologists in assessing competitive sports eligibility in athletes with BrS. A multiparametric approach to diagnosis and risk stratification is recommended, noting that the presence of a Brugada ECG pattern (BrP) does not confirm a BrS diagnosis. The risk of sudden cardiac death (SCD) is low in asymptomatic individuals with type 1 BrP, especially those with a drug-induced pattern. Pharmacological testing is not required for type 2 or 3 patterns without other risk factors. Low-risk individuals do not require therapy, while intermediate or high-risk patients may need pharmacological treatment, ICD implantation, or ablation. Asymptomatic individuals with type 2 or 3 BrP, no family history of SCD, and no other risk factors may be eligible for competitive sports, as well as asymptomatic type 1 BrP without risk factors and negative electrophysiological study. Conversely, sports eligibility should be denied in patients with BrS who have a history of syncope or cardiac arrest (high-risk subjects), regardless of ICD presence.

Introduction

Brugada syndrome (Brs) is characterized by a typical electrocardiogram (ECG) pattern of coved ST-segment elevation with T-wave inversion in right precordial leads and an increased risk of ventricular fibrillation typically occurring during sleep, in the absence of overt signs of structural heart disease.[1] Although the association between right bundle branch block, ST-segment elevation, and sudden cardiac death (SCD) was described by the Brugada brothers in 1992 and named after their observation,[2] Andrea Nava and coworkers in Padua had already recognized the main clinical features of the disease in 1989.[3] Nowadays, BrS is regarded as 1 of the most common causes of SCD in the young, with higher prevalence in young to middle-aged males.

*Corresponding author.
E-mail address: luigi.sciarra@univaq.it (L. Sciarra).

https://doi.org/10.1016/j.amjcard.2025.02.031

Over the last 35 years, significant progresses have been made in understanding the epidemiology, pathophysiology, clinical characteristics, risk stratification, and treatment of BrS.[1] In particular, step forwards have been made[4] in a better definition of the diagnostic criteria and how the possible therapeutic options have evolved during recent years. Regarding diagnosis, the Shangai BrS score (a clinical instrument including clinical/family history and genetic information in addition to the ECG repolarization pattern) has been introduced to avoid overdiagnosis of BrS in subjects with isolated sodium channel blocker-induced ECG pattern (BrP).[5] Regarding treatment options, catheter ablation of the right ventricular outflow tract epicardium was recently demonstrated to safely and effectively suppress ventricular fibrillation (VF) recurrences[6] and should be offered to BrS patients with recurrent VF episodes according to the 2022 European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias.[7]

Despite these considerable advances, management of BrS patients in sports cardiology remain controversial, especially the safe prescription of physical exercise and the competitive sports eligibility, which have been scarcely investigated.[8] There are relevant differences concerning competitive sports eligibility being the 2020 ESC guidelines on sports cardiology[9] more "permissive", and the 2023 Italian sports cardiology guidelines (COCIS protocols)[10] more restrictive. In this expert opinion statement of the Italian Society of Sports Cardiology (SICSPORT), we aim to provide a comprehensive review of the current definition, diagnosis (including the indications for and pitfalls of sodium channel blocker challenge), epidemiology, genetics, risk stratification (including recommendations for electrophysiology study), treatment of BrS (including indications for defibrillator implantation and catheter ablation), and finally, the sports cardiology perspective to streamline decisions regarding competitive sports eligibility in patients affected by BrS.

Brugada Patterns and Brugada Syndrome in Athletes

The Brugada ECG pattern is characterised by ST elevation in leads V1-V3 with an incomplete right-bundle-branch block appearance. This pattern may be constantly present or intermittent. In some cases, it can appear as response to some drugs as the IC antiarrhythmic drugs or during fever.[11-13] Three different kind of the Brugada ECG patterns have been described (Figure 1)[11-13]:

Type 1: ST elevation with at least 2 mm J-point elevation and a gradually descending ST segment followed by a negative T-wave.

Type 2: at least 2 mm J-point elevation and at least 1 mm ST elevation with a positive or biphasic T-wave.

Type 3: less than 2 mm J-point elevation and less than 1 mm ST elevation.

A first fundamental key-point, especially in long-limbed subjects, is represented by the distinction of incomplete right-bundle branch block from possible type 2 or 3 Brugada pattern. In these cases, the right interpretation of the surface electrocardiogram, in association with correct positioning of the precordial electrodes, can resolve most doubts (e.g., by measuring the β angle).[13]

In asymptomatic subjects, the finding of a Brugada ECG pattern is not equivalent to diagnosing the syndrome. BrS is characterized not only by the electrocardiographic pattern, but also by malignant arrhythmias and/or the risk of SCD.

Epidemiology

The worldwide incidence of BrS is estimated around 0.05%, while Brugada pattern (BrP) is more common, ranging from 0.12 to 0.8%, with age- and sex-related incomplete penetrance and variable expressivity.[14] Ethnic and sex differences in the prevalence of BrS exist. A meta-analysis of 28 articles with a total population of 369,068 individuals reported the highest prevalence in Asian subjects (1.8 per 1,000 (95% CI, 1.0-2.6) in particular South East Asia subjects (3.7 per 1,000, 95% CI, 0.7-6.7).[15] Thailand showed the highest pooled prevalence of 6.8 per 1,000 (95% CI: 0.5-13.2), which was 14 times higher than the worldwide prevalence,[15] as reported also by Rattanawong et al.[16] in a population of healthy young to middle age individuals, both for BrS (0.41%; 95% CI, 0.21-0.78) and Type 2/3 BrP (0.86%; 95% CI, 0.58%-1.38%). The pooled prevalence of BrS in Caucasian subjects was 0.2 per 1,000 (95% CI, 0.0-0.3), 9 times less frequent than in Asian subjects and it increases with age, in fact in a study of 47,000 Austrian males was only 0.002%.[17] The lowest prevalence was reported in Australian subjects 0.002 per 1,000 (95% CI, 0.0-0.1) and in subjects from North Africa (0 per 1,000).[15] The pooled prevalence of Type 2/3 BrP was as higher as 6.1 per 1,000 (95% CI, 5.0-7.1),[15] with a similar trend based on ethnicity: 8.3 per 1,000 (95% CI, 6.1-10.5) in Asian, 6.9 per 1,000 (95% CI, 4.7-9.2) in Caucasian, and 0.07 per 1,000 (95% CI, 0.0-0.1) in Hispanic subjects. Both the BrS and BrP are more prevalent in males 0.6, 95% CI, 0.2-1.0 and 10.5, 95% CI, 7.5-13.5, respectively, than in females 0.1, 95% CI, 0.0-0.2 and 3.7, 95% CI, 2.1-5.3, respectively.[15] It is important to distinguish between the BrS and the phenocopies[18]. Several metabolic conditions (for example hyperkalemia, hyponatremia, hypercalcemia), ischaemic injuries (isolated right ventricular infarction, inferior myocardial infarction), myocardial/pericardial inflammatory disease, external mechanical compression (due to pectus excavatum, mediastinal masses) can produce a BrP.[18]

The presence of a Type 2/3 BrP is not diagnostic alone for BrS and it has been described as highly prevalent as 12% in the athletic population, especially in endurance athletes, partially linked to the extreme exercise-induced right ventricular (RV) enlargement.[19] Common features for BrP and early repolarization are the male prevalence, vagal influence and normalization with quinidine. Moreover, improper recording of the ECG with high pass filtering and high placement of the precordial lead can cause a *rSr'* pattern, but not a baseline Type 1 BrP, in athletes and in the general population.[20] Misplaced leads can generate the need of additional exams and unnecessary sport restriction, especially in tall endurance athletes.

Genetic testing in BRUGADA syndrome

Genetic testing for Brugada syndrome (BrS) is currently recommended in subjects with (1) spontaneous or (2) pharmacologically induced type I pattern, in association with clinical features (such as polymorphic ventricular tachycardia, ventricular fibrillation, arrhythmic syncope) or family history, to support the diagnosis.1 It should be requested by a cardiologist or a physician with specific knowledge in BrS, particularly after excluding phenocopies and known confounding factors.[21]

Genetic testing aims to confirm the clinical-instrumental diagnosis of BrS and to identify at risk family members by extending the molecular analysis for the specific pathogenic variant identified (cascade screening). Nevertheless, this test, also because of the low diagnostic yield, has a limited value for risk stratification, which mainly remains based on clinical-anamnestic-instrumental characterization.[7]

Currently, the SCN5A gene, which encodes for the α subunit of the sodium channel NaV1.5, is the main BrS gene analyzed in a clinical diagnostic setting, with a detection rate for pathogenic or likely pathogenic variants not exceeding 21%.[22,23] At the same time, however, also many variants of uncertain significance, even in the SCN5A gene alone, are identified because of high allelic heterogeneity. Therefore, to obtain reliable reports it is advisable to refer to laboratories with high research expertise and particular experience for this specific test.[24,25] Recent studies have indeed demonstrated how a good interpretation of the variants, supported by functional studies, can lead to

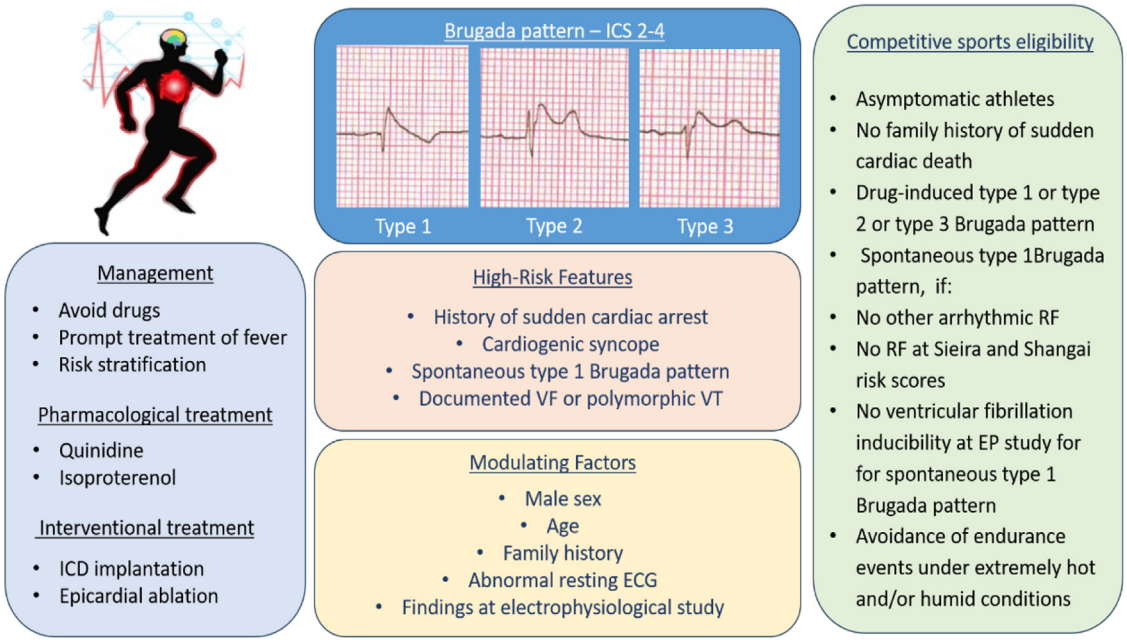

Figure 1. Graphical abstract: Management of Brugada syndrome in sports cardiology, sports eligibility and risk stratification. ECG = electrocardiogram; EP = electrophysiological study; ICD = implantable cardiac defibrillator; ICS = intercostal space; RF = risk factors; VF = ventricular fibrillation; VT = ventricular tachycardia. *Image of athlete courtesy of* FreeDigitalPhotos.net.

a significant contribution to the genetic diagnosis by identifying patients with increased risk of ventricular arrhythmias.[26] Over the years, other minor disease-genes have been associated to BrS, but to date the lack of clear scientific evidence (functional studies, population data and segregation analyses) suggests their analysis only in research rather than clinical settings.[23,27] In some cases, such as CACNA1C gene encoding the Cav1.2 calcium channel, BrS may be associated with other features such as short-QT, warranting appropriate genetic testing.[28,29] Other genes are very rarely implicated, despite a high rate of variants of uncertain significance emerging at genetic testing, making it difficult to interpret at clinical level or for risk stratification.[24] This is 1 of the reasons why genetic testing indication should be established as part of a genetic counseling, sharing in advance appropriateness and genetic testing strategy with the referral cardiologist.

The European Society of Human Genetics (ESHG) recommends performing genetic testing in highly specialized laboratories, in which the interpretation of the genetic data is performed by experts in that specific discipline. Furthermore, genetic testing must be part of a process that includes genetic counseling.[30] Objectives of this counseling are the explanation of the limits of the test and the different results that can be obtained (detection of a pathogenic variant, absence of clinically actionable variants, identification of a variant of uncertain significance), as well as clarifying that a negative result does not rule out the condition. Laboratory test results should be ideally linked to a letter written by a geneticist, which combine with the report (of which it is an integral part), allows the above messages to be explained in an understandable and explanatory way. This approach allows to clarify, for example, the risk of transmission of the variant to the family members and discuss the limits of genome interpretation in case of a variant of uncertain significance, which isn't clinically actionable and requires re-evaluation over time. On the contrary, the laboratory report must contain a detailed description of methods and full-blown information regarding the sensitivity of the test, the coverage (if NGS based), which genes were sequenced (both for NGS and Sanger sequencing or other techniques) and if other techniques have been used for the identification of deletions/duplications, if indicated.

Recently, important studies are underway to try to fill the diagnostic gaps of single gene or multigene panels testing in BrS. An example are the genome-wide studies exploring the polygenic bases of BrS and highlighting the usefulness of the polygenic risk score (PRS) as a support tool for the clinical characterization and management of the disease, although not yet in a diagnostic setting.[31]

Risk stratification and appropriateness of 1C test in sports cardiology

The risk of SCD in asymptomatic subjects with type 1 pattern is low, particularly in subjects with drug-induced type 1 pattern.[32,33] Malignant arrhythmias in BrS typically appear at rest during phases of bradycardia. In athletes' setting, it is possible to assume that an enhanced vagal reaction during recovery or predominant vagal tone[34] at rest may increase the susceptibility to develop arrhythmias during recovery or at rest. However, there are no reports directly linking exercise or sports with Brugada patterns and the demonstration of this correlation remains anecdotal or supposed[35] and not proved by prospective studies.

For example, in asymptomatic subjects with drug-induced type 1 (without family history, etc.) the risk of SCD is virtual.[33-37] The same applies to subjects with spontaneous type 1, asymptomatic, without other risk factors and negative electrophysiological study.[38]

It is necessary to pay attention to a correct prescription of the test in asymptomatic athletes and without other risk factors, in order to avoid excessively protective disqualifying attitudes. It therefore follows that in Sports Cardiology, but also in daily clinical practice, the indication for sodium channel testing must be extremely stringent in the following cases:[7,39]

(1) Subjects with type 2 or 3 pattern and family history of SCD.
(2) Subjects with type 2 or 3 patterns and syncope suspected of an arrhythmic cause.

Pharmacological testing is not indicated extensively in all cases with type 2 or 3 patterns or in doubtful cases in the absence of a family history of SCD and syncope.[40]

In risk stratification, particularly useful in subjects with Brugada type 2 or 3 pattern is the search during the variations of the circadian rhythm, through the positioning of 12-lead ECG Holter monitoring with modified position (Figure 2).[41]

Additionally, several groups have studied the possible role of exercise testing for risk stratification: an association has been described between premature ventricular contractions (PVC) (in parallel with ST augmentation) during the early recovery phase of treadmill exercise testing (1.5 to 3 minutes) and future occurrence of ventricular fibrillation.[42] Other authors related S wave upslope duration at peak exercise, J point elevation in AVR more than 2mm during late recovery and delayed heart rate recovery with future arrhythmic events.[43] However those evidences are related to retrospective studies and for these reasons prospective validation of these models is required.

Recently 2 different scores have been proposed for risk stratification in BrS: Sieira and Shanghai Score [44,45] (see Tables 1 and 2). Both scores combine a series of information (ECG pattern, personal and family history, etc) to identify 3 different risk categories (low-risk, high-risk and doubtful risk). However, some differences can be found between these risk stratification scores; for example Sieira score includes electrophysiological study results (2 points in case of ventricular vulnerability), while Shanghai score concerns more detailed questions about family history and attributes a minimal value to genetic test positivity.

Table 1
The risk score according to Sieira et al.[44]

Scoring factors
Spontaneous type 1 ECG pattern = 1
Sudden death family history = 1
Syncope = 2
Sinus node dysfunction = 3
EPS inducibility = 2
Cardiac arrest = 4
Risk grading:
Low risk 1
High risk >4
Doubtful risk (grey zone) 2-4

Several scoring factors, with different relative weight, can be combined to estimate individual risk in subject with Brugada syndrome. EPS = electrophysiological study.

Treatment: role of drugs, ICD implantation and cardiac ablation

Treatment of Brugada patients is a very complex issue, at present. First, it is important to remark that a large number of subjects, which show a low arrhythmic risk, need no pharmacological nor other therapies. The crucial points in this low-risk population are: (1) to avoid drugs that may induce ST-segment elevation in right precordial leads

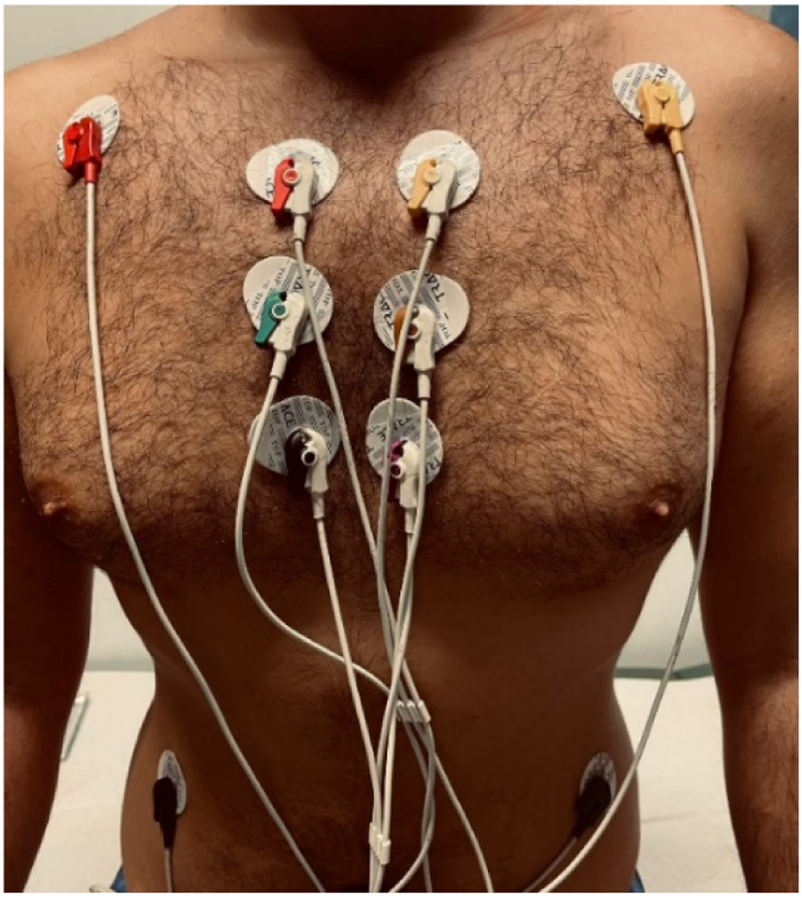

Figure 2. Position of a 12 leads ambulatory ECG in an athlete with suspected Brugada pattern. All 6 precordial leads are positioned in the right and left parasternal lines. V1-V2 leads are applied in the 2nd intercostal space. The following couples V3-V4 and V5-V6 are positioned moving down of 1 and 2 spaces (respectively in the 3rd and 4th intercostal space). This configuration maximizes the possibility to disclose the dynamic appearance of a type 1 Brugada ECG pattern.

(http://www.brugadadrugs.org), (2) to avoid cocaine, cannabis, and excessive alcohol intake, (3) to treat of fever with antipyretic drugs.[7]

Moving from this statement, any consideration about drugs, ICD implantation or cardiac ablation must be deserved to intermediate or high-risk subjects.

Role of drugs

Quinidine is the most investigated antiarrhythmic drug (AAD) in Brugada syndrome (BrS). Quinidine has been historically classified among the class I (membrane stabilizing), AAD within the Vaughan Williams classification, because it blocks the rapid sodium channel (INa) in the activated state with a high relative blocking potency. However, this kind of classification can be misleading, since numerous other cardiac channels and receptors are blocked by quinidine (Ito, IK1, IKr and IKs), well explaining its potential usage in different clinical settings, but also its potential for pro-arrhythmic effects.[46]

Several small studies showed a potential efficacy of quinidine in the secondary prevention of ventricular arrhythmias (VA) in Brugada syndrome. These studies enrolled patients with previous cardiac arrest, already implanted with an ICD, proving the ability of the drug to prevent or significantly reduce arrhythmic events.[47–50]

Quinidine has been also evaluated as a possible prophylactic choice for asymptomatic patients, with spontaneous coved type ECG and VA induction at electrophysiological study (EPS).[50–54] Indirect evidence of its value was given by the prevention of a second VF inducibility when a VA was inducible at basal EPS. However, the low incidence of spontaneous arrhythmic events in this kind of group does not allow to definitely proving its efficacy; on the other hand, quinidine therapy presents a relatively high incidence of minor side effects (usually diarrhoea) that can lead to drug discontinuation. Finally the possible pro-arrhythmic effect (torsade de pointes) should always weighted before to start drug administration.[55]

Following these small evidences and according to 2022 ESC guidelines, quinidine should be considered in patients with BrS who should receive an ICD but have a contraindication, decline, or have recurrent ICD shocks (class IIa; level of evidence C).[7]

Additionally, it appear reasonable to use quinidine as pharmacological option in BrS, to prevent atrial fibrillation recurrences, the alternative being represented by catheter ablation.[56]

Another drug with possible antiarrhythmic effect in Brugada syndrome has been reported: isoproterenol. The efficacy of isoproterenol infusion in the suppression of electrical storms in BsS was well evaluated[57,58] and its use in this context is supported by the most recent ESC guidelines (class IIa; level of evidence C).[7]

Implantable cardioverter defibrillator implantation

The Implantable cardioverter defibrillator (ICD) is the most effective therapy for prevention of sudden cardiac death (SCD). However, the survival benefits guaranteed by ICD therapy may be paralleled[59] by a significant incidence over time of lead-related complications or inappropriate discharges, especially in young subjects and athletes, which may increase long-term morbidity and mortality.[60]

Patients with aborted cardiac arrest or documented spontaneous sustained VT (secondary prevention) are clearly at high risk for SCD and for them an ICD indication is clear (class I - level of evidence C).[61]

The difficulty concerns the “grey zone” composed of asymptomatic patients with a spontaneous type 1 ECG pattern. Their risk appears quite low and quantifiable between 0.5% and 1% per year[62]; however, a relatively low annual risk may implicate, especially for young subjects, a relatively high risk over time. For these patients current ESC guidelines suggest that an ICD implantation should be considered in case of an arrhythmic syncope (class IIa – level of evidence C); moreover, ICD implantation may be considered in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extrastimuli (class IIb – level of evidence C).[7] In this latter case, however, it appear reasonable to involve the patient in a shared decision-making process, as decisive evidence is currently lacking.

Table 2
The Shanghai risk score.[45]

ECG pattern (V1-V3 in II-IV intercostal space)
Spontaneous type 1 ECG pattern = 3.5
Type 1 ECG pattern during fever = 3
Drug induced type 1 ECG pattern = 2
Clinical history
Cardiac arrest = 3
Nocturnal agonal breathing = 2
Syncope for suspected arrhythmia = 2
Syncope for doubtful mechanism = 1
AF/atrial flutter occurring before 30 years = 0.5
Family history (I and II degree relatives)
Confirmed Brugada syndrome = 2
Cardiac arrest in suspected Brugada syndrome = 1
Sudden death before 45 years = 0.5
Genetic test
Positive genetic test = 0.5
Risk grading:
Low risk <4
High risk >6.5
Doubtful risk (grey zone) 4-6.5

Several scoring factors, with different relative weight, can be combined to estimate individual risk in subject with Brugada syndrome. AF = atrial fibrillation.

Because the first objective of ICD therapy consists in the prevention of SCD, without exposing the patients to potentially lethal complications, all efforts should directed to implant the safer device, reducing the risk of electrode and device-related side effects. The present availability of subcutaneous ICD (S-ICD) that guarantees protection from SCD while minimizing the risks of intravascular lead infection or failure offers an advisable alternative to the traditional ICD in young patients with BrS (when cardiac stimulation is not required).[63]

Cardiac ablation

Epicardial ablation of the arrhythmogenic substrate in the right ventricular outflow tract area has been proposed and was first performed by Nademanee and colleagues in 2011.[64] They treated 9 heavy symptomatic patients with recurrences of ICD interventions. After ablation of an area with abnormal low amplitude QRS voltages and late to very late (>200ms) fractionated activity, in 8 patients the ECG normalized, and recurrence of arrhythmic events was successfully prevented. For such critical patients this procedure may be useful and current ESC guidelines[7] remark its possible role (class IIA – level of evidence C).

Moreover, Pappone and colleagues extended this epicardial approach also to 135 asymptomatic patients. They described disappearance of the typical ECG pattern after the procedure and that it was no longer elicitable by ajmaline or flecainide exposure.[65] The exact role for epicardial ablation remains to be established. However, the weight of the potential complications (e.g., damage to the coronary arteries or cardiac tamponade) and the relatively low event rate in asymptomatic patients raises ethical questions about this prophylactic approach. Current ESC guidelines[7] strongly confirm this concept and, at present, this type of treatment in asymptomatic subjects should be discouraged (class III – level of evidence C).

Competitive sports eligibility of Brugada syndrome

The classification of sports based on cardiovascular involvement serves as crucial starting point for establishing eligibility criteria,

particularly in individuals with heart disease or abnormalities. This classification is based on the acute physiological responses of the heart and blood vessels to physical activity, the specific adjustments required by each sport or discipline, and the long-term adaptations that result from consistent exercise or training[9] (Table 3): group A includes sports where excellence is attributed to the athlete's technical skills, with moderate increases in heart rate (HR) and blood pressure (BP); group B (power sports) is characterized by anaerobic energy utilization, leading to brief BP spikes but only modest HR increases; group C encompasses sports that combine aerobic and anaerobic metabolism, leading to intermittent increases in preload (and/or after load) with intense periods of activity alternating with recovery phases; finally group D (endurance sports) is characterized by isotonic-dynamic muscular activity, predominantly powered by aerobic energy, which results in an increased cardiac output.

At variance with many other substrates of sudden cardiac death, ventricular arrhythmias in patients with Brugada syndrome do not typically occur during exercise but are instead favored by vagal stimulation. This justifies the more liberal approach of sports cardiology guidelines[9] regarding eligibility to competitive sports of patients with Brugada syndrome compared to other inherited cardiovascular diseases. However, it should be emphasized that this view is not shared by the entire medical community, as some believe that the neuroautonomic remodeling caused by prolonged training with heightened vagal activity may increase the propensity to ventricular fibrillation.

According to the 2020 ESC sports cardiology guidelines,[9] asymptomatic patients with either a drug-induced or spontaneous type 1 Brugada ECG participation in competitive sports may be considered, with the exception of activities associated with an increase in core temperature >39° (e.g., endurance events under extremely hot and/or humid conditions) (class IIB). In patients who received an ICD for secondary prevention, return to play may be considered after 3 months without events.

Similar to the ESC guidelines, also the 2015 AHA guidelines[66] suggest that asymptomatic patients with BrS (class IIA) or symptomatic patients after 3 months since the last event (class IIB) may participate in competitive sport respecting precautionary measures (avoidance of hyperthermia, avoidance of hyperthermia, availability of an automated external defibrillator…). Although both the AHA and ESC guidelines appear very permissive, it must be underlined that a class IIB recommendation implies that experts 'opinions and evidence were not unanimous. The 2024 HRS expert consensus statement[67] appears even more permissive on the topic: the focus is pointed just to the avoidance of arrhythmia triggers including sodium-channel blocking drugs, alcohol, and heavy meals (class IB) and aggressive treatment of fever (class IC with limited data) and avoidance of hyperthermia (IC for expert opinion) including taking precautions to prevent overheating particularly for prolonged endurance exercise in warm climates. Furthermore, the statement assesses that in athletes with inherited arrhythmia syndromes who have received a clinically indicated ICD, sports participation is reasonable: however is important to underline that, even in this case, the class IIA is combined with a level of evidence B that derives from nonrandomized studies.[68-69]

Approximately 35 years after its first publication in 1989, the Italian Society of Sports Cardiology and the Italian Federation of Sports Medicine (FMSI), in collaboration with other leading italian Cardiological Scientific Associations (ANCE – National association of Outpatient cardiology, ANMCO – National association of inpatient cardiology, SIC – Italian Society of cardiology), presented the 2023 version of the Cardiological Guidelines for competitive Sports eligibility.[10] This update included, for the first time, class of recommendations and levels of evidence, offering a comprehensive and detailed guide for the participation of athletes with heart disease in sports. This last version of COCIS,[10] in the evaluation of athletes with BrS, suggests a multiparametrical approach to risk stratification by using electrocardiographic risk factors (i.e., sinus node dysfunction, atrioventricular or intraventricular conduction delays, fragmented QRS, slurring or notching of the QRS in the infero-lateral leads without ST-segment elevation, disclosure of a type 1 pattern or increase in the degree of J-point elevation in the recovery phase of exercise testing) and score systems such as the Sieira[41] and Shangai[42] scores.

ESC sport cardiology guidelines[9] and 2024 HRS expert consensus statement[67] illustrate a shared decision-making approach to return to play: from this perspective, the athlete should be provided with the most comprehensive information about his medical condition and the potential risks of returning to sports. Additionally, the physician should also share any uncertainties due to the lack of scientific evidence. Based on this understanding, the athlete can then decide whether or not to resume sports activities. This approach, reasonable in many aspects in those countries having a more liberal approach to competitive sport practice, is, however, not sharable by COCIS 2024 guidelines[10]: the Italian legislative framework, since 1982, requires medical certification for participation in competitive sports. This situation, implying potential medical liability in the event of adverse occurrences related to competitive sports, necessitates a more cautious approach when evaluating competitive sports eligibility, especially when strong scientific evidence are lacking.

In line with these concepts, considering the absence of certainties derived from randomized trials, and principally based on expert consensus and limited data, the Italian guidelines recommend (Table 4) to grant eligibility (class IC) in asymptomatic athletes with negative family history of premature sudden death, drug-induced type 1 ECG and no other arrhythmic or electrocardiographic risk factors. The same applies to athletes with asymptomatic spontaneous type 1 ECG

Table 3
classification of sports activities based on cardiovascular involvement (adapted from COCIS 2024[10])

	Group A (Skill)	Group B (Power)	Group C (Mixed)	Group D (Endurance)
Heart rate	+/++	++	++/+++	+++
Blood pressure	+	+++	++	++
Cardiac output	+	++	++	+++
Cardiac remodelling	-	+	++	+++

Table 4
Italian recommendations for cardiovascular eligibility to competitive sports (COCIS) in cases of Brugada syndrome

	CLASS	LoE
Eligibility may be granted: • in asymptomatic subjects with ECG pattern type 2 or 3, in the absence of family history of sudden death and other risk factors • In asymptomatic subject with ECG pattern type 1, without risk factors and negative EPS	I	C
Eligibility may be granted in asymptomatic subject with spontaneous ECG pattern type 1 and low risk (no family history for sudden death and/or Brugada syndrome, etc..) Eligibility should be denied in subject with doubtful/high risk score, but some individual exceptions can be evaluated in High Qualified Medical Centers	II	C
Eligibility must be denied in Brugada subject with suspected arrhythmic syncope or cardiac arrest and type 1 ECG pattern (spontaneous or drug induced). ICD implantation (when indicated) does not allow revising eligibility criteria.	III	B

LOE = level of evidence; ICD = implantable cardioverter defibrillator.

pattern, no other risk factors and negative electrophysiological study for ventricular fibrillation inducibility.

For asymptomatic patients with spontaneous type 1 pattern who had not undergone electrophysiological study, sports eligibility may still be granted (class IIC) provided no other risk factors listed in the Sieira and Shangai scores are present. In asymptomatic patients with risk factors, eligibility should normally not be granted with possible exceptions that should be considered on a case-by-case basis after evaluation in experienced centers (class IIC).

Finally, patients with Brugada syndrome and a history of syncope of possible arrhythmic origin or cardiac arrest sports eligibility should be denied, irrespective from the presence of an ICD (class IIIB).

Conclusion

The discovery of a Brugada ECG pattern in the setting of sports cardiology may sometimes open challenging questions. However, the finding of an isolated Brugada ECG pattern does not allow to diagnosing the syndrome. This latter condition results from the combination of the electrocardiographic pattern to malignant arrhythmias and/or risk factors of sudden death. The Sieira[44] and Shangai[45] scores appear very helpful to avoid overdiagnosis of BrS in subjects with an isolated ECG pattern, and to stratify arrhythmic risk.

The risk of sudden death in asymptomatic subjects with type 1 pattern is generally low, in particular in case of drug-induced type 1 pattern. Pharmacological testing to induce type 1 ECG is not extensively indicated in all cases with type 2 or 3 patterns, in the absence of other risk factors. The largest number of "Brugada" subjects, which show a low arrhythmic risk, need no specific therapies. For this reason, any consideration regarding drugs, ICD implantation or cardiac ablation must reserve to intermediate or high-risk subjects.

Competitive sports eligibility may be granted in asymptomatic subjects with ECG pattern type 2 or 3, in the absence of family history of sudden death and other risk factors. The same can be applied in case of asymptomatic subject with ECG pattern type 1, without risk factors and negative electrophysiological study, given its high negative predictive value. On the other side, in patients with BrS and a history of syncope or survived from aborted sudden death, sports eligibility should be denied, irrespective from the presence of an implantable cardiac defibrillator (according to the Italian law). Doubtful cases (grey zones) should be referred to High Qualified Medical Centres for an individual and thorough evaluation of arrhythmic risk and subsequent decision about eligibility.

Invasive therapies, such as epicardial ablations, should be limited to highly symptomatic subjects, or aborted sudden death survivors; ablation is not indicated merely to obtain eligibility.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Antonio Scarà: Writing – original draft, Project administration, Conceptualization. **Luigi Sciarra:** Writing – review & editing. **Antonio Dello Russo:** Writing – review & editing. **Elena Cavarretta:** Writing – original draft. **Zefferino Palamà:** Writing – original draft. **Alessandro Zorzi:** Writing – review & editing, Writing – original draft. **Francesco Brancati:** Writing – review & editing. **Paolo Compagnucci:** Writing – original draft. **Michela Casella:** Writing – review & editing. **Valeria Novelli:** Writing – original draft. **Giampiero Patrizi:** Visualization. **Pietro Delise:** Supervision.

References

1 Krahn AD, Behr ER, Hamilton R, Probst V, Laksman Z, Han HC. Brugada Syndrome. JACC Clin Electrophysiol 2022;8(3):386–405. https://doi.org/10.1016/j.jacep.2021.12.001.

2 Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20(6):1391–6. https://doi.org/10.1016/0735-1097(92)90253-j.

3 Martini B, Nava A, Thiene G, Buja GF, Canciani B, Scognamiglio R, Daliento L, Dalla Volta S. Ventricular fibrillation without apparent heart disease: description of six cases. Am Heart J 1989;118(6):1203–9. https://doi.org/10.1016/0002-8703(89)90011-2.

4 Cutler MJ, Eckhardt LL, Kaufman ES, Arbelo E, Behr ER, Brugada P, Cerrone M, Crotti L, deAsmundis C, Gollob MH, Horie M, Huang DT, Krahn AD, London B, Lubitz SA, Mackall JA, Nademanee K, Perez MV, Probst V, Roden DM, Sacher F, Sarquella-Brugada G, Scheinman MM, Shimizu W, Shoemaker B, Sy RW, Watanabe A, Wilde AAM. Clinical management of Brugada syndrome: commentary from the experts. Circ Arrhythm Electrophysiol 2024;17(1):e012072. https://doi.org/10.1161/CIRCEP.123.012072.

5 Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AA. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. Heart Rhythm 2016;13(10):e295–324. https://doi.org/10.1016/j.hrthm.2016.05.024.

6 Nademanee K, Chung FP, Sacher F, Nogami A, Nakagawa H, Jiang C, Hocini M, Behr E, Veerakul G, Jan Smit J, Wilde AAM, Chen SA, Yamashiro K, Sakamoto Y, Morishima I, Das MK, Khongphatthanayothin A, Vardhanabhuti S, Haissaguerre M. Long-term outcomes of Brugada substrate ablation: A report from BRAVO (Brugada Ablation of VF Substrate Ongoing Multicenter Registry). Circulation 2023;147(21):1568–78. https://doi.org/10.1161/CIRCULATIONAHA.122.063367.

7 Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M. ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43(40):3997–4126. https://doi.org/10.1093/eurheartj/ehac262.

8 Mascia G, Arbelo E, Hernandez-Ojeda J, Solimene F, Brugada R, Brugada J. Brugada Syndrome and exercise practice: current knowledge, shortcomings and open questions. Int J Sports Med 2017;38(8):573–81. https://doi.org/10.1055/s-0043-107240.

9 Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M. ESC Scientific Document Group. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J 2021;42(1):17–96. https://doi.org/10.1093/eurheartj/ehaa605.

10 Zeppilli P, Biffi A, Cammarano M, Castelletti S, Cavarretta E, Cecchi F, Colivicchi F, Contursi M, Corrado D, D'Andrea A, Deferrari F, Delise P, Dello Russo A, Gabrielli D, Giada F, Indolfi C, Maestrini V, Mascia G, Mos L, Oliva F, Palamà Z, Palermi S, Palmieri V, Patrizi G, Pelliccia A, Perrone Filardi P, Porto I, Schwartz PJ, Scorcu M, Sollazzo F, Spampinato A, Verzeletti A, Zorzi A, D'Ascenzi F, Casasco M, Sciarra L. Italian Cardiological Guidelines (COCIS) for Competitive Sport Eligibility in athletes with heart disease: update 2024. Minerva Med 2024;115(5):533–64. https://doi.org/10.23736/S0026-4806.24.09519-3.

11 Tadros R, Tan HL, ESCAPE-NET InvestigatorsEl Mathari S, Kors JA, Postema PG, Lahrouchi N, Beekman L, Radivojkov-Blagojevic M, Amin AS, Meitinger T, Tanck MW, Wilde AA, Bezzina CR. Predicting cardiac electrical response to sodium-channel blockade and Brugada syndrome using polygenic risk scores. Eur Heart J 2019;40(37):3097–107. https://doi.org/10.1093/eurheartj/ehz435.

12 Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. Circulation 1998;97(5):457–60. https://doi.org/10.1161/01.cir.97.5.457.

13 Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105(1):73–8. https://doi.org/10.1161/hc0102.101354.

14 Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada Syndrome: JACC State-of-the-art review. J Am Coll Cardiol 2018;72(9):1046–59. https://doi.org/10.1016/j.jacc.2018.06.037.

15 Vutthikraivit W, Rattanawong P, Putthapiban P, Sukhumthammarat W, Vathesatogkit P, Ngarmukos T, Thakkinstian A. Worldwide prevalence of Brugada Syndrome: A systematic review and meta-analysis. Acta Cardiol Sin 2018;34(3):267–77. https://doi.org/10.6515/ACS.201805_34(3).20180302B.

16 Rattanawong P, Ngarmukos T, Chung EH, Vutthikraivit W, Putthapiban P, Sukhumthammarat W, Vathesatogkit P, Sritara P. Prevalence of brugada ECG pattern in Thailand from a population-based cohort study. J Am Coll Cardiol 2017;69(10):1355–6. https://doi.org/10.1016/j.jacc.2016.12.028.

17 Schukro C, Berger T, Stix G, Pezawas T, Kastner J, Hintringer F, Schmidinger H. Regional prevalence and clinical benefit of implantable cardioverter defibrillators in Brugada syndrome. Int J Cardiol 2010;144(2):191–4. https://doi.org/10.1016/j.ijcard.2009.03.136.

18 Baranchuk A, Nguyen T, Ryu MH, Femenía F, Zareba W, Wilde AA, Shimizu W, Brugada P, Pérez-Riera AR. Brugada phenocopy: new terminology and proposed classification. Ann Noninvasive Electrocardiol 2012;17(4):299–314. https://doi.org/10.1111/j.1542-474X.2012.00525.x.

19 Chung EH, McNeely 3rd DE, Gehi AK, Brickner T, Evans S, Pryski E, Waicus K, Stafford H, Mounsey JP, Schwartz JD, Huang S, Pursell I, Ciocca M. Brugada-type patterns are easily observed in high precordial lead ECGs in collegiate athletes. J Electrocardiol 2014;47(1):1–6. https://doi.org/10.1016/j.jelectrocard.2013.08.014.

20 Chung EH. Brugada ECG patterns in athletes. J Electrocardiol 2015;48(4):539-–43. https://doi.org/10.1016/j.jelectrocard.2015.05.001.

21 Wilde AAM, Semsarian C, Márquez MF, Shamloo AS, Ackerman MJ, Ashley EA, Sternick EB, Barajas-Martinez H, Behr ER, Bezzina CR, Breckpot J, Charron P, Chockalingam P, Crotti L, Gollob MH, Lubitz S, Makita N, Ohno S, Ortiz-Genga M, Sacilotto L, Schulze-Bahr E, Shimizu W, Sotoodehnia N, Tadros R, Ware JS, Winlaw DS, Kaufman ES, Document ReviewersAiba T, Bollmann A, Choi JI, Dalal A, Darrieux F, Giudicessi J, Guerchicoff M, Hong K, Krahn AD, MacIntyre C, Mackall JA, Mont L, Napolitano C, Ochoa JP, Peichl P, Pereira AC, Schwartz PJ, Skinner J, Stellbrink C, Tfelt-Hansen J, Deneke T. Developed in partnership with and endorsed by the European Heart Rhythm Association (EHRA), a branch of the European Society of Cardiology (ESC), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). 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. Europace 2022;24(8):1307–67. https://doi.org/10.1093/europace/euac030.

22 Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, Brugada P, Fressart V, Guerchicoff A, Harris-Kerr C, Kamakura S, Kyndt F, Koopmann TT, Miyamoto Y, Pfeiffer R, Pollevick GD, Probst V, Zumhagen S, Vatta M, Towbin JA, Shimizu W, Schulze-Bahr E, Antzelevitch C, Salisbury BA, Guicheney P, Wilde AA, Brugada R, Schott JJ, Ackerman MJ. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm 2010;7(1):33–46. https://doi.org/10.1016/j.hrthm.2009.09.069.

23 Pannone L, Bisignani A, Osei R, Gauthey A, Sorgente A, Monaco C, Della Rocca DG, Del Monte A, Strazdas A, Mojica J, Al Housari M, Miraglia V, Mouram S, Vetta G, Paparella G, Ramak R, Overeinder I, Bala G, Almorad A, Ströker E, Pappaert G, Sieira J, de Ravel T, La Meir M, Sarkozy A, Brugada P, Chierchia GB, Van Dooren S, de Asmundis C. Genetic testing in Brugada syndrome: A 30-year experience. Circ Arrhythm Electrophysiol 2024;17(4):e012374. https://doi.org/10.1161/CIRCEP.123.012374.

24 Ghouse J, Skov MW, Bigseth RS, Ahlberg G, Kanters JK, Olesen MS. Distinguishing pathogenic mutations from background genetic noise in cardiology: the use of large genome databases for genetic interpretation. Clin Genet 2018;93(3):459–66. https://doi.org/10.1111/cge.13066.

25 Glazer AM, Wada Y, Li B, Muhammad A, Kalash OR, O'Neill MJ, Shields T, Hall L, Short L, Blair MA, Kroncke BM, Capra JA, Roden DM. High-throughput reclassification of SCN5A variants. Am J Hum Genet 2020;107(1):111–23. https://doi.org/10.1016/j.ajhg.2020.05.015.

26 Ishikawa T, Kimoto H, Mishima H, Yamagata K, Ogata S, Aizawa Y, Hayashi K, Morita H, Nakajima T, Nakano Y, Nagase S, Murakoshi N, Kowase S, Ohkubo K, Aiba T, Morimoto S, Ohno S, Kamakura S, Nogami A, Takagi M, Karakachoff M, Dina C, Schott JJ, Yoshiura KI, Horie M, Shimizu W, Nishimura K, Kusano K, Makita N. Functionally validated SCN5A variants allow interpretation of pathogenicity and prediction of lethal events in Brugada syndrome. Eur Heart J 2021;42(29):2854–63. https://doi.org/10.1093/eurheartj/ehab254.

27 Hosseini SM, Kim R, Udupa S, Costain G, Jobling R, Liston E, Jamal SM, Szybowska M, Morel CF, Bowdin S, Garcia J, Care M, Sturm AC, Novelli V, Ackerman MJ, Ware JS, Hershberger RE, Wilde AAM, Gollob MH. National Institutes of Health Clinical Genome Resource Consortium. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for brugada syndrome. Circulation 2018;138(12):1195–205. https://doi.org/10.1161/CIRCULATIONAHA.118.035070.

28 Novelli V, Memmi M, Malovini A, Mazzanti A, Liu N, Yanfei R, Bongianino R, Denegri M, Monteforte N, Bloise R, Morini M, Napolitano C. Role of CACNA1C in Brugada syndrome: prevalence and phenotype of probands referred for genetic testing. Heart Rhythm 2022;19(5):798–806. https://doi.org/10.1016/j.hrthm.2021.12.032.

29 Burashnikov E, Pfeiffer R, Barajas-Martinez H, Delpón E, Hu D, Desai M, Borggrefe M, Häissaguerre M, Kanter R, Pollevick GD, Guerchicoff A, Laiño R, Marieb M, Nademanee K, Nam GB, Robles R, Schimpf R, Stapleton DD, Viskin S, Winters S, Wolpert C, Zimmern S, Veltmann C, Antzelevitch C. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. Heart Rhythm 2010;7(12):1872–82. https://doi.org/10.1016/j.hrthm.2010.08.026.

30 Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, Race V, Sistermans E, Sturm M, Weiss M, Yntema H, Bakker E, Scheffer H, Bauer P. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet 2016;24(10):1515. https://doi.org/10.1038/ejhg.2016.63.

31 Chevallier S, Forclaz A, Tenkorang J, Ahmad Y, Faouzi M, Graf D, Schlaepfer J, Pruvot E. New electrocardiographic criteria for discriminating between Brugada types 2 and 3 patterns and incomplete right bundle branch block. J Am Coll Cardiol 2011;58(22):2290–8. https://doi.org/10.1016/j.jacc.2011.08.039.

32 Sieira J, Ciconte G, Conte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, Saitoh Y, Casado-Arroyo R, Juliá J, La Meir M, Wellens F, Wauters K, Pappaert G, Brugada P. Long-term prognosis of drug-induced Brugada syndrome. Heart Rhythm 2017;14(10):1427–33. https://doi.org/10.1016/j.hrthm.2017.04.044.

33 Delise P, Probst V, Allocca G, Sitta N, Sciarra L, Brugada J, Kamakura S, Takagi M, Giustetto C, Calo L. Clinical outcome of patients with the Brugada type 1 electrocardiogram without prophylactic implantable cardioverter defibrillator in primary prevention: a cumulative analysis of seven large prospective studies. Europace 2018;20(FI1):f77–85. https://doi.org/10.1093/europace/eux226.

34 Smith ML, Hudson DL, Graitzer HM, Raven PB. Exercise training bradycardia: the role of autonomic balance. Med Sci Sports Exerc 1989;21(1):40–4. https://doi.org/10.1249/00005768-198902000-00008.

35 Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y, Hosoda S. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation 1997;95(9):2277–85. https://doi.org/10.1161/01.cir.95.9.2277.

36 Mascia G, Brugada J, Barca L, Benenati S, Della Bona R, Scarà A, Russo V, Arbelo E, Di Donna P, Porto I. Prognostic significance of electrophysiological study in drug-induced type-1 Brugada syndrome: a brief systematic review. J Cardiovasc Med (Hagerstown) 2024;25(11):775–80. https://doi.org/10.2459/JCM.0000000000001665.

37 Russo V, Caturano A, Migliore F, Guerra F, Francia P, Nesti M, Conte G, Perini AP, Mascia G, Albani S, Marchese P, Santobuono VE, Dendramis G, Rossi A, Attena E, Ghidini AO, Sciarra L, Palamà Z, Baldi E, Romeo E, D'Onofrio A, Nigro G. IBRYD Study Group. Long-term clinical outcomes of patients with drug-induced type 1 Brugada electrocardiographic pattern: A nationwide cohort registry study. Heart Rhythm 2024;21(5):555–61. https://doi.org/10.1016/j.hrthm.2024.01.015.

38 Sieira J, Conte G, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, Saitoh Y, Irfan G, Casado-Arroyo R, Juliá J, La Meir M, Wellens F, Wauters K, Van Malderen S, Pappaert G, Brugada P. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20 years experience. Circ Arrhythm Electrophysiol 2015;8(4):777–84. https://doi.org/10.1161/CIRCEP.114.002647.

39 Govindan M, Batchvarov VN, Raju H, Shanmugam N, Bizrah M, Bastiaenen R, Kiotsekoglou A, Camm J, Behr ER. Utility of high and standard right precordial leads during ajmaline testing for the diagnosis of Brugada syndrome. Heart 2010;96(23):1904–8. https://doi.org/10.1136/hrt.2010.201244.

40 Sciarra L, Moriya M, Robles AG, Sarubbi B. Type 2 Brugada pattern: more doubts than certainties. Minerva Cardiol Angiol 2021;69(4):426–8. https://doi.org/10.23736/S2724-5683.20.05471-7.

41 Matusik PT, Bijak P, Kaźnica-Wiatr M, Karpiński M, Matusik PS, Maziarz A, Podolec P, Lelakowski J. Twelve-lead ECG, Holter monitoring parameters, and genetic testing in Brugada syndrome: insights from analysis of multigenerational Family with a history of sudden cardiac arrest during physical activity. J Clin Med 2023;12(20):6581. https://doi.org/10.3390/jcm12206581.

42 Morita H, Asada ST, Miyamoto M, Morimoto Y, Kimura T, Mizuno T, Nakagawa K, Watanabe A, Nishii N, Ito H. Significance of exercise-related ventricular arrhythmias in patients with Brugada syndrome. J Am Heart Assoc 2020;9(23):e016907. https://doi.org/10.1161/JAHA.120.016907.

43 Subramanian M, Prabhu MA, Harikrishnan MS, Shekhar SS, Pai PG, Natarajan K. The utility of exercise testing in risk stratification of asymptomatic patients with type 1 brugada pattern. J Cardiovasc Electrophysiol 2017;28(6):677–83. https://doi.org/10.1111/jce.13205.

44 Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, Baltogiannis G, Di Giovanni G, Saitoh Y, Juliá J, Mugnai G, La Meir M, Wellens F, Czapla J, Pappaert G, de Asmundis C, Brugada P. A score model to predict risk of events in patients with Brugada Syndrome. Eur Heart J 2017;38(22):1756–63.

45 Kawada S, Morita H, Antzelevitch C, Morimoto Y, Nakagawa K, Watanabe A, Nishii N, Nakamura K, Ito H. Shanghai Score system for diagnosis of brugada syndrome: validation of the score system and system and reclassification of the patients. JACC Clin Electrophysiol 2018;4(6):724–30.

46 The Sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Circulation. 1991;84(4):1831–51. https://doi.org/10.1161/01.cir.84.4.1831.

47 Hermida JS, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P, Guicheney P, Di Fusco S, Rey JL, Cauchemez B, Leenhardt A. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol 2004;43(10):1853–60. https://doi.org/10.1016/j.jacc.2003.12.046.

48 Márquez MF, Bonny A, Hernández-Castillo E, De Sisti A, Gómez-Flores J, Nava S, Hidden-Lucet F, Iturralde P, Cárdenas M, Tonet J. Long-term efficacy of low doses of quinidine on malignant arrhythmias in Brugada syndrome with an implantable cardioverter-defibrillator: a case series and literature review. Heart Rhythm 2012;9(12):1995–2000. https://doi.org/10.1016/j.hrthm.2012.08.027.

49 Anguera I, García-Alberola A, Dallaglio P, Toquero J, Pérez L, Martínez JG, Peinado R, Rubín JM, Brugada J, Cequier A. Shock reduction with long-term quinidine in patients with Brugada syndrome and malignant ventricular arrhythmia episodes. J Am Coll Cardiol 2016;67(13):1653–4. https://doi.org/10.1016/j.jacc.2016.01.042.

50 Belhassen B, Glick A, Viskin S. Excellent long-term reproducibility of the electrophysiologic efficacy of quinidine in patients with idiopathic ventricular fibrillation and Brugada syndrome. Pacing Clin Electrophysiol 2009;32(3):294–301. https://doi.org/10.1111/j.1540-8159.2008.02235.x.

51 Bouzeman A, Traulle S, Messali A, Extramiana F, Denjoy I, Narayanan K, Marijon E, Hermida JS, Leenhardt A. Long-term follow-up of asymptomatic Brugada patients with inducible ventricular fibrillation under hydroquinidine. Europace 2014;16(4):572–7. https://doi.org/10.1093/europace/eut279.

52 Malhi N, Cheung CC, Deif B, Roberts JD, Gula LJ, Green MS, Pang B, Sultan O, Konieczny KM, Angaran P, Dorian P, Lashevsky I, Healey JS, Alak A, Tadros R, Andorin A, Steinberg C, Ayala-Paredes F, Simpson CS, Atallah J, Krahn AD. Challenge

and impact of Quinidine access in sudden death syndromes: A national experience. JACC Clin Electrophysiol 2019;5(3):376–82. https://doi.org/10.1016/j.jacep.2018.10.007.
53 Andorin A, Gourraud JB, Mansourati J, Fouchard S, le Marec H, Maury P, Mabo P, Hermida JS, Deharo JC, Delasalle B, Esnault S, Sadoul N, Davy JM, Leenhardt A, Klug D, Defaye P, Babuty D, Sacher F, Probst V. The QUIDAM study: hydroquinidine therapy for the management of Brugada syndrome patients at high arrhythmic risk. Heart Rhythm 2017;14(8):1147–54. https://doi.org/10.1016/j.hrthm.2017.04.019.
54 Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada Syndrome: thirty-three-year experience using electrophysiologically guided therapy with class 1A antiarrhythmic drugs. Circ Arrhythm Electrophysiol 2015;8(6):1393–402. https://doi.org/10.1161/CIRCEP.115.003109.
55 Mazzanti A, Tenuta E, Marino M, Pagan E, Morini M, Memmi M, Colombi B, Tibollo B, Frassoni S, Curcio A, Raimondo C, Maltret A, Monteforte N, Bloise R, Napolitano C, Bellazzi R, Bagnardi V, Priori SG. Efficacy and limitations of quinidine in patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2019;12:e007143. https://doi.org/10.1161/CIRCEP.118.007143.
56 Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, Giachino D, Bianchi F, Barbonaglia L, Ferraro A. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. Heart Rhythm 2014;11(2):259–65. https://doi.org/10.1016/j.hrthm.2013.10.043.
57 Watanabe A, Fukushima Kusano K, Morita H, Miura D, Sumida W, Hiramatsu S, Banba K, Nishii N, Nagase S, Nakamura K, Sakuragi S, Ohe T. Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. Eur Heart J 2006;27(13):1579–83. https://doi.org/10.1093/eurheartj/ehl060.
58 Ohgo T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Ohe T, Shimizu W. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Heart Rhythm 2007;4(6):695–700. https://doi.org/10.1016/j.hrthm.2007.02.014.
59 Schwartz PJ, Ackerman MJ, Antzelevitch C, Bezzina CR, Borggrefe M, Cuneo BF, Wilde AAM. Inherited cardiac arrhythmias. Nat Rev Dis Primers 2020;6(1):58. https://doi.org/10.1038/s41572-020-0188-7.
60 Conte G, Sieira J, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, La Meir M, Wellens F, Czapla J, Wauters K, Levinstein M, Saitoh Y, Irfan G, Julià J, Pappaert G, Brugada P. Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience. J Am Coll Cardiol 2015;65(9):879–88. https://doi.org/10.1016/j.jacc.2014.12.031.
61 Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. 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 2013;10(12):1932–63. https://doi.org/10.1016/j.hrthm.2013.05.014.
62 Marsman EMJ, Postema PG, Remme CA. Brugada syndrome: update and future perspectives. Heart 2022;108(9):668–75. https://doi.org/10.1136/heartjnl-2020-318258.
63 Knops RE, Olde Nordkamp LRA, Delnoy PHM, Boersma LVA, Kuschyk J, El-Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kääb S, Mittal S, Quast ABE, Smeding L, van der Stuijt W, de Weger A, de Wilde KC, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke FALE, Burke MC, de Jong JSSG, Wright DJ, Tijssen JGP, Wilde AAM. PRAETORIAN investigators. Subcutaneous or transvenous defibrillator therapy. N Engl J Med. 2020;383(6):526–36. https://doi.org/10.1056/NEJMoa1915932.
64 Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, Likittanasombat K, Bhuripanyo K, Ngarmukos T. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011;123(12):1270–9. https://doi.org/10.1161/CIRCULATIONAHA.110.972612.
65 Pappone C, Brugada J, Vicedomini G, Ciconte G, Manguso F, Saviano M, Vitale R, Cuko A, Giannelli L, Calovic Z, Conti M, Pozzi P, Natalizia A, Crisà S, Borrelli V, Brugada R, Sarquella-Brugada G, Guazzi M, Frigiola A, Menicanti L, Santinelli V. Electrical substrate elimination in 135 consecutive patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017;10(5):e005053. https://doi.org/10.1161/CIRCEP.117.005053.
66 Ackerman MJ, Zipes DP, Kovacs RJ, Maron BJ. American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with Cardiovascular abnormalities: Task Force 10: the Cardiac channelopathies: A scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015;132(22):e326–9. https://doi.org/10.1161/CIR.0000000000000246.
67 Lampert R, Chung EH, Ackerman MJ, Arroyo AR, Darden D, Deo R, Dolan J, Etheridge SP, Gray BR, Harmon KG, James CA, Kim JH, Krahn AD, La Gerche A, Link MS, MacIntyre C, Mont L, Salerno JC, Shah MJ. 2024 HRS expert consensus statement on arrhythmias in the athlete: evaluation, treatment, and return to play. Heart Rhythm 2024;21(10):e151–252. https://doi.org/10.1016/j.hrthm.2024.05.018.
68 Heidbuchel H, Willems R, Jordaens L, Olshansky B, Carre F, Lozano IF, Wilhelm M, Müssigbrodt A, Huybrechts W, Morgan J, Anfinsen OG, Prior D, Mont L, Mairesse GH, Boveda S, Duru F, Kautzner J, Viskin S, Geelen P, Cygankiewicz I, Hoffmann E, Vandenberghe K, Cannom D, Lampert R. Intensive recreational athletes in the prospective multinational ICD Sports Safety Registry: results from the European cohort. Eur J Prev Cardiol 2019;26(7):764–75. https://doi.org/10.1177/2047487319834852.
69 Saarel EV, Law I, Berul CI, Ackerman MJ, Kanter RJ, Sanatani S, Cohen MI, Berger S, Fischbach PS, Burton DA, Dziura J, Brandt C, Simone L, Li F, Olshansky B, Cannom DS, Lampert RJ. Safety of sports for young patients with implantable cardioverter-defibrillators: long-term results of the multinational ICD sports Registry. Circ Arrhythm Electrophysiol 2018;11(11):e006305. https://doi.org/10.1161/CIRCEP.118.006305.