

Brugada syndrome: new concepts and algorithms in management (RCD code: V-1A.1)

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Abstract

Clinical manifestation of Brugada syndrome (BrS) mainly results from polymorphic ventricular arrhythmias and includes sudden cardiac arrest (SCA). The Brugada sign, besides being present in true BrS, may result from different causes. Moreover, electrocardiogram findings in some clinical situations may resemble the BrS electrocardiographic pattern. Thus, differential diagnosis is crucial in the proper management of patients suspected of having BrS. Lifestyle modifications and close follow-up with or without pharmacologic treatment and/or implantable cardioverter-defibrillator placement constitute the most common approach to managing BrS patients. However, the role of ablation in BrS treatment is increasing. Due to diagnostic and therapeutic difficulties, the management of BrS is often challenging. This review provides new concepts and algorithms in the diagnostics and treatment of patients suspected of having BrS. JRCO 2017; 3 (5): 151–160

Key words: Brugada syndrome, diagnostics, treatment, algorithms

Introduction

Sudden cardiac arrest (SCA) may be a manifestation of both cardiac and non-cardiac causes. It requires prompt recognition and cardiopulmonary resuscitation with subsequent advanced cardiac life support [1]. Management of conscious patients after aborted SCA with suspected acute coronary syndrome (ACS), depending on electrocardiographic (ECG) presentation, is based on ST-segment elevation myocardial infarction (STEMI) guidelines with immediate coronary invasive strategy or should be treated as high-risk non-ST-segment elevation ACS with rapid (<2 hours) coronary invasive strategy. Comatose patients with a STEMI ECG should be transferred directly to the catheterization laboratory, while others should have obvious non-coronary causes excluded before proceeding with coronary angiography [1]. Further diagnostic processes, if no specific cause of SCA is identified, should include Brugada syndrome (BrS) assessment.

Diagnostic algorithms of BrS depend on the patient's clinical characteristics and are based on clinical history and specific ECG abnormalities (Figure 1–2). The current criteria of BrS diagnosis

and tests which may unmask the BrS ECG pattern have been previously described in detail [2,3]. Indications and contraindications for drug challenge, to unmask the BrS ECG pattern, should be considered before sodium-channel blocker administration. Table 1 shows selected indications and potential contraindications for ajmaline drug challenge.

Utility of cardiac imaging in BrS

Medical imaging of cardiac structures is important in BrS management. It is mainly used in forming a differential diagnosis, to exclude cardiac structural and vascular abnormalities, cardiomyopathies, and other causes of ECG changes [4–7]. However, there are studies describing structural heart changes which could be implicated in BrS. Some interesting results come from studies of BrS patients involving magnetic resonance imaging (MRI). Their findings are summarized in Table 2. In patients with the *SCN5A* mutation, morphologic and functional changes are observed in cardiovascular MRI, including larger right ventricular (RV) vol-

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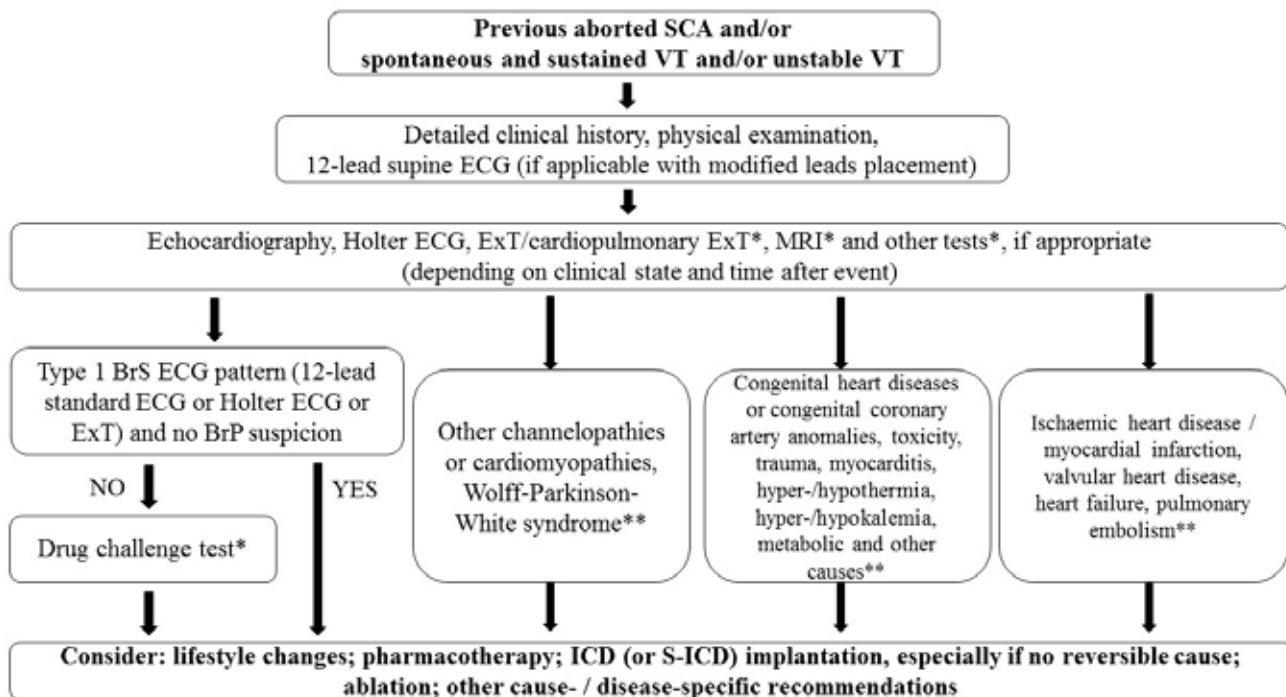


Figure 1. Algorithm of diagnosis and treatment of patients after aborted cardiac arrest or spontaneous and sustained ventricular tachycardia (VT) or unstable VT, suspected for Brugada syndrome (BrS). * Consider potential contraindications; ** Follow appropriate clinical practice guidelines. BrP – Brugada phenocopy; BrS – Brugada syndrome; ECG – electrocardiogram; ExT – exercise testing; ICD – implantable cardioverter-defibrillator; MRI – magnetic resonance imaging; SCA – sudden cardiac arrest; S-ICD – subcutaneous implantable cardioverter-defibrillator; VT – ventricular tachycardia

umes and lower RV ejection fraction. This may indicate a more severe phenotype in this group of patients in comparison to those without the *SCN5A* mutation or controls [8]. These findings are in line with those of Catalano et al., who observed that in their group of BrS patients, 33% presented with the spontaneous type 1 BrS ECG pattern and 30% with an identified *SCN5A* mutation [9]. Importantly, they compared BrS patients with sex-, body surface area-, and age-matched controls [9]. However, other authors have demonstrated that late-gadolinium-enhancement (LGE) does not appear in BrS patients and that wall motion abnormalities seen in these patients are also found in healthy controls [10]. Furthermore, they did not find any differences in RV dimensions and ejection fraction (EF) between BrS patients and healthy controls [10]. Interestingly, using the two-dimensional strain technique, mild RV function abnormalities were observed in BrS patients [11].

Risk assessment in Brugada syndrome

Predicting potential future arrhythmias in BrS patients is of utmost importance. Assessment of ventricular arrhythmias and sudden cardiac death (SCD) risk can help to guide patient management. BrS patients who survived cardiac arrest have a 13.5% per year incidence of an arrhythmic event, defined as sustained ventricular tachycardia (VT) / ventricular fibrillation (VF), ap-

propriate implantable cardioverter-defibrillator (ICD) therapy, or sudden death. BrS patients with syncope have an arrhythmic event risk of 3.2% per year, while the risk in asymptomatic BrS patients is 1% per year [12].

Fauchier et al., in their meta-analysis of 2743 BrS patients with and without previous cardiac arrest (13 studies, 2104 patients underwent programmed ventricular stimulation [PVS], 1789 patients available for subgroup analysis), concluded that VT/VF inducibility in an electrophysiological study (EPS) may identify an increased risk of subsequent events in asymptomatic patients and in patients with unexplained syncope [12]. In 2 registries, France, Italy, Netherlands, Germany (FINGER), including 1029 patients and PROgrammed ELEctrical stimUlation preDICTive valuE (PRELUDE), including 308 patients, VT/VF inducibility failed to identify high risk patients [13, 14]. In a recent pooled analysis performed by Stroubek et al. [15], among patients without prior SCA who underwent PVS (8 studies, 527 of 1312 patients induced into arrhythmias with up to triple extrastimuli testing), arrhythmia (sustained or hemodynamically significant polymorphic VT/VF) induction with up to triple extrastimuli was associated with a 2.7-fold increased risk of arrhythmia (SCA or high-voltage defibrillator therapy for polymorphic VT/VF) during follow-up. The risk of arrhythmia was the highest among patients induced with single or double extrastimuli [15]. As Sieira and Brugada have mentioned, discrepancies concerning PVS importance may be due to different study protocols [16]. EPS may be especially important in patients with intermediate risk, such as

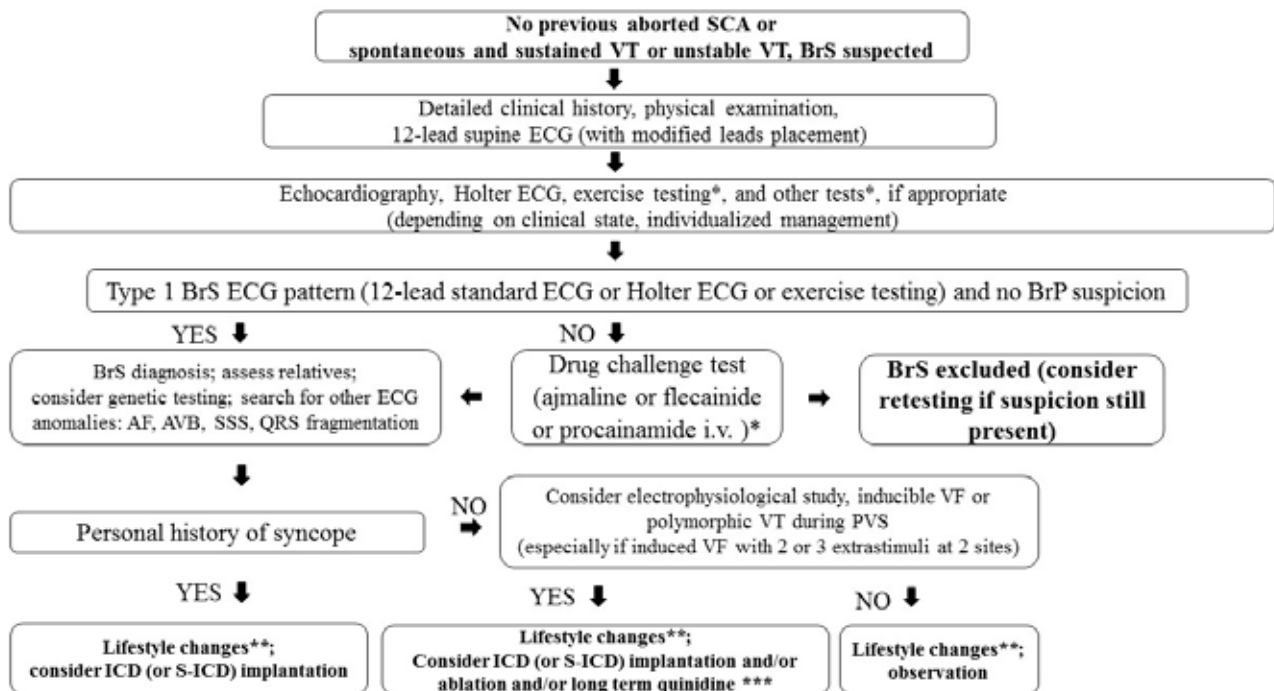


Figure 2. Algorithm of diagnosis and treatment of patients without aborted cardiac arrest or spontaneous and sustained ventricular tachycardia (VT) or unstable VT, suspected for Brugada syndrome (BrS). * Consider potential contraindications; ** Avoid large meals, alcohol; instant fever treatment with antipyretics; assess relatives; consider genetic testing (including family members), other details are described in the main text; *** Especially if VF/polymorphic VT were initially induced in PVS and efficacy of the treatment was found (no VF/polymorphic VT induction on treatment) or if pharmacotherapy is patient's preferred method of treatment. AF – atrial fibrillation; AVB – atrioventricular block; PVS – programmed ventricular stimulation; SSS – sick sinus syndrome; VF – ventricular fibrillation; for other abbreviations see the description of Figure 1

those who are asymptomatic (without a history of syncope), but who have a spontaneous BrS ECG pattern [17]. Current European Society of Cardiology (ESC) guidelines state that ICD placement may be considered in BrS patients in whom VF was induced during PVS with 2 or 3 extrastimuli at two sites [18].

A spontaneous type 1 ECG pattern and history of syncope are prognostic for future arrhythmias, and therefore, patients with such clinical characteristics should be considered as high-risk patients [13, 14, 17, 18]. On the other hand, low-risk patients are defined as silent mutation carriers or those who have a diagnostic ECG only after provocation challenge [17].

Prognostic information in BrS may be gained from a simple 12-lead ECG. Studies suggest that BrS with coexistence of early repolarization syndrome (ERS) is associated with a higher risk of arrhythmic events. In a study involving 127 patients with ICD, Kim et al. demonstrated that BrS patients with inferolateral ERS and ERS with right precordial J-waves had a significantly lower shock-free survival than the remainder (32% vs. 72%; $p < 0.0001$) [19], whereas Antzelevitch et al. linked the highest risk (5-fold increase) of ventricular arrhythmias to an early repolarization pattern in inferior, lateral, and right precordial leads [20]. Other ECG abnormalities such as QRS fragmentation, prolonged QRS duration, T peak-T end interval (transmural dispersion of repolarization), presence of wide S wave in lead I, and prominent R wave in aVR are associated with an elevated risk of arrhythmias [20, 21]. Moreover, in

a prospective cohort study of young patients with BrS, it was shown that the presence of first degree atrioventricular block (AVB), atrial arrhythmias, sick sinus node disease, and spontaneous type 1 BrS ECG pattern were indicators of future ventricular arrhythmias [22]. Taking into account the high incidence of different cardiac rhythm abnormalities in BrS, including atrial fibrillation, the most common atrial arrhythmia in BrS (incidence ranging from 6% to 53%), active screening and timely introduction of proper management is appropriate in this group of patients [23–25]. However, it is important to note that increased focus on AVB as a cause of symptoms in patients with BrS may lead to unnecessary invasive diagnostic tests with possible complications [26].

Morphologic changes in cardiac structure also appear to possess prognostic utility in BrS patients. In a multivariate analysis, Rudic et al. showed that reduced right ventricular ejection fraction (RVEF) and increased right ventricular end-diastolic volume index (RVEDVi) were associated with a history of syncope or aborted SCA at the time of BrS diagnosis [8].

Interestingly, hormonal influence may contribute to gender-related differences in the prevalence of BrS and may also account for a worse prognosis in male patients [27, 28].

The autonomic nervous system (ANS) is involved in arrhythmogenesis in BrS [29], and it should be noted that vasovagal syncope may occur and influence SCD risk stratification [29, 30]. Clinical history and laboratory data may be helpful in establishing a diagno-

Table 1. Selected indications and potential contraindications for ajmaline challenge [65–68]**Selected indications for ajmaline challenge**

- * Suspected Brugada phenocopy
- * Type 2 BrS ECG pattern
- * Persons with other factors indicating strong BrS suspicion and non-diagnostic baseline ECG (e.g. unexplained syncope or SCA or concealed BrS genetic mutation or family history of BrS/SCA)

Selected potential contraindications for ajmaline challenge

- * Use of class I antiarrhythmic agent
- * History of myocardial infarction
- * Atrioventricular block (second- / third-degree), bifascicular block or LBBB
- * Breastfeeding, pregnancy

LBBB – left bundle branch block; for other abbreviations see the description of Figure 1.

sis. Moreover, head-up tilt test can be used to investigate a patient's susceptibility to vasovagal syncope [31].

Another test which may have important clinical implications in patients with BrS is exercise testing (ExT). Makimoto et al. report an augmentation of ST-segment elevation ≥ 0.05 mV in leads V1 to V3 in the early recovery phase of treadmill ExT when compared with baseline in 37% of BrS patients. This phenomenon was absent in healthy controls [32]. The presence of ExT-induced augmentation of ST-segment elevation in right precordial leads in early recovery was an independent predictor for cardiac events [32]. Subramanian et al. assessed the usefulness of ExT to predict major arrhythmic events (MAE, i.e. SCD or resuscitated VF) in asymptomatic patients with a type 1 Brugada ECG [33]. Independent predictors of MAE included an increase in S wave upslope duration ratio $>30\%$ at peak exercise, J point elevation augmentation in lead aVR >2 mm in late recovery, and delayed heart rate recovery in late recovery [33]. This study did not confirm the results of Makimoto et al., and did not show that augmented ST-segment elevation in precordial leads is an independent predictor of MAE during follow-up. This result was probably due to the small sample size and limited number of events [33]. It is worth noting that type 1 BrS ECG changes may appear during exercise in patients without BrS, and other causes of the BrS ECG pattern should be considered. In a recently reported case, the BrS ECG pattern was likely induced by ischemia (Brugada phenocopy) [34]. ExT and cardiopulmonary exercise testing may provide information on exercise safety and may reveal or augment the BrS ECG pattern [29, 35, 36]. The specific role of these tests in the management of BrS patients requires further studies.

Treatment of patients with BrS

Lifestyle modifications

The first step in BrS treatment is the introduction of lifestyle modifications (Figure 1 and Figure 2). Appropriate measures include avoidance of certain medications (listed on www.brugadadrugs.org), large meals (especially rich in carbohydrates), excessive alcohol intake, and hyperthermia, which necessitates immediate fever treatment with antipyretics [18, 37].

Participation in sports activities is a potential risk in BrS patients, as it may be associated with syncope and ventricular arrhythmias

[38]. Therefore, assessing the eligibility of BrS patients for or disqualifying them from different kinds of physical activity is still a matter of concern. Exercise is not a typical trigger of VF in BrS, and most episodes of sudden death occur at rest and at night [39]. It is postulated that increased vagal activity resulting from chronic athletic conditioning, predisposes BrS patients to arrhythmias at rest or during recovery from high-intensity exercise, often together with elevated body temperature in the latter [40]. This is in line with the 2005 ESC recommendation to restrict patients with a definitive diagnosis of BrS from competitive sports [41]. In 2015, the American Heart Association (AHA) and American College of Cardiology (ACC) published a statement regarding the eligibility for and disqualification from competitive sports for athletes with cardiac channelopathies in which the authors were clearly less restrictive regarding asymptomatic and optimally treated patients [42]. Detailed ESC, AHA and ACC recommendations are shown in Table 3. The low level of evidence in these recommendations is a reflection of poor clinical data concerning the problem [43]. In a systematic literature review, Masrur et al. report only 18 articles concerning BrS and exercise, including 16 case reports and 2 larger studies about exercise testing in BrS patients [38]. No exercise-related sudden death was reported in the above mentioned review, however, a recent case report of SCA during training in a competitive football player without previous BrS diagnosis was described [44].

ECS recommendations from 2005 permit patients after ICD placement to participate in low-moderate dynamic and low static sports (IA, B), except those with risk of bodily collision, once several conditions are met. These conditions include lack of malignant VTs, normal cardiac function at least 6 months after ICD placement or the last ICD intervention, and that the underlying cardiac condition is not in itself a contraindication for competitive sports [41]. The AHA and ACC statement permits participation in sports classified as IA for athletes with an ICD if they are free of episodes of ventricular flutter or VF requiring device therapy for 3 months (Class IIa; Level of Evidence C). Authors of this statement also note that participation in sports with higher peak static and dynamic components than class IA may be considered if the athlete is free of episodes of ventricular flutter or VF requiring device therapy for 3 months (Table 3) [45].

Table 2. Selected studies concerning magnetic resonance imaging (MRI) in patients with Brugada syndrome (BrS)

Clinical study	Group	Findings
Rudic et al., 2016, [8]	81 consecutive genetically screened BrS patients, 30 healthy controls	* BrS patients with an <i>SCN5A</i> mutation (16 patients; 20%) had larger RV volumes and lower RVEF when compared to patients without a mutation or healthy controls. * RV end-diastolic volume, RV end-systolic, and left ventricular cardiac output have shown good predictive performance of an <i>SCN5A</i> mutation.
Veltmann et al., 2012, [69]	20 patients with drug (ajmaline) induced BrS ECG pattern, 10 patients with spontaneous type 1 BrS ECG pattern	* Maximal RVOT area was found most commonly in the 3rd intercostal space (n = 22), then in the 4th intercostal space (n = 5) and least commonly in the 2nd intercostal space (n=3). * Maximal ST-segment elevation coincided with maximal RVOT area in almost all of the patients (29 of 30 patients).
Tessa et al., 2012, [10]	29 with BrS type 1 ECG pattern, 29 healthy controls	* No difference in regard to left ventricular and RV dimensions and RVEF. * RV wall motion abnormalities found in 19 patients (65.5%) and in 22 healthy controls (75.9%) (the majority consisted of hypokinesia, mainly in the RV inferior wall). * None of the 24 studied patients showed LGE.
Papavassiliu et al., 2010, [70]	69 consecutive BrS patients, 30 healthy controls	* The RVOT area was enlarged and LVEF was reduced in BrS patients with a spontaneous type 1 ECG when compared to other BrS patients or controls. * Patients with a spontaneous type 1 BrS ECG pattern had lower RVEF and end-systolic volumes than healthy controls.
Catalano et al., 2009, [9]	30 consecutive BrS patients, 30 sex-, body surface area-, and age-matched controls	* BrS patients had higher incidence of mild RV wall motion abnormalities, reduced outflow tract ejection fraction and enlarged inflow tract diameter when compared with controls. * BrS patients had increased global RV end-systolic volume when compared with controls. * BrS patients did not differ in regard to outflow tract dimensions, global RV end-diastolic volume, left ventricular parameters, and atrial areas when compared with controls.
Papavassiliu et al., 2004, [71]	20 consecutive BrS patients, 20 age- and sex-matched healthy controls	* In BrS patients the RVOT area was enlarged, when compared to controls. * Trend towards larger right ventricular end-diastolic and end-systolic volumes and lower RVEF in BrS patients when compared with healthy controls. * No differences in left ventricular parameters between BrS patients and controls. * High intramyocardial T1 signal in some BrS patients (n = 4) but was not observed in controls.

LGE – late-gadolinium-enhancement; LVEF – left ventricular ejection fraction; RV – right ventricular; RVEF – right ventricular ejection fraction; RVOT – right ventricular outflow tract; for other abbreviations see the description of Figure 1 and Table 1.

Pharmacotherapy

There are some controversies regarding the medical treatment of BrS (Figure 1, Figure 2 and Table 4). Some authors state that BrS might be treated on a long-term basis with class 1A antiarrhythmic drugs [46]. Others claim that the utility of this treatment, in spite of its effectiveness, is often limited due to side-effects [16]. Belhassen et al. presented experience in the treatment of 96 patients with quinidine and disopyramide. Patients with inducible VF in PVS (n = 66) were given quinidine, while patients without inducible VF were not treated with medication [46]. To confirm the efficacy of the drug, 5 patients had additional PVS after quinidine treatment initialization. There were no recurrences of ventricular arrhythmias while on treatment, even in patients with previous arrhythmic storms. However, the incidence of side-effects requiring drug discontinuation was 38% (n = 23). These side-effects included: diarrhea (n = 11), thrombocytopenia (n = 4), fever (n = 2), allergic reaction, esophagitis, sinus node dysfunction, lupus erythematosus-like syndrome, hepatitis, hyperpigmentation, and marked weakness. None of the patients developed arrhythmia due to QT prolongation. The authors also point out non-compliance in patients as a noteworthy problem in such treatment [46]. In another study, patients with inducible VF or polymorphic VT were given quinidine. A second PVS was performed in patients with therapeutic level of the drug and if VF was non-inducible, the drug was

continued. In other cases, such as when VF was still inducible during PVS, and additional symptoms were present, an ICD was implanted [47]. Current ESC guidelines recommend quinidine in patients who have an indication for ICD implantation, but do not agree to such treatment, those who could benefit from an ICD but have a contraindication for such therapy, and in patients who require treatment due to supraventricular arrhythmias (class IIa indication) [18]. Quinidine or isoproterenol should be considered (class IIa indication) as treatment in the case of electric storm in BrS [18].

Implantable cardioverter-defibrillator placement

The main treatment strategy in symptomatic BrS patients involves ICD implantation. The randomized control trial – Defibrillator versus Beta-blockers for Unexplained death in Thailand (DEBUT), was the first study to show the benefits of ICD implantation vs beta-blocker (propranolol) administration in patients with BrS. In spite of recurrent VF, there were no fatal events in the ICD arm of the study, as compared to the propranolol arm [48]. However, while interpreting the results of this trial we should take into account that propranolol has sodium-channel-blocking properties [49]. Selected clinical studies concerning ICD treatment in BrS patients are listed in Table 4.

Table 3. European Society of Cardiology (ESC) recommendations for competitive sports participation in athletes with cardiovascular disease and American Heart Association (AHA) and American College of Cardiology (ACC) scientific statement on eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities, including patients with Brugada syndrome and patients after implantable-cardioverter defibrillator placement [41, 42, 45]. Data are cited

Recommendations	Class of Recommendations and Level of Evidence
Patients with Brugada syndrome according to ESC (2005)	
Criteria for eligibility: positive Brugada syndrome Recommendation: no competitive sports	–
Patients with Brugada syndrome according to AHA and ACC (2015)	
For athletes with a suspected/diagnosed cardiac channelopathy, a comprehensive evaluation by a heart rhythm specialist or genetic cardiologist with sufficient experience and expertise with these disorders is recommended	Class I; Level of Evidence C
It is recommended that symptomatic athletes with any suspected or diagnosed cardiac channelopathy be restricted from all competitive sports until a comprehensive evaluation has been completed, the athlete and his or her family are well informed, a treatment program has been implemented, and the athlete has been asymptomatic on therapy for 3 months	Class I; Level of Evidence C
It is reasonable for an asymptomatic athlete with genotype-positive/phenotype-negative (i.e., concealed channelopathy) BrS to participate in all competitive sports with appropriate precautionary measures, including avoidance of drugs that exacerbate the BrS in affected athletes (http://www.brugadadrugs.org), electrolyte/hydration replenishment and avoidance of dehydration, avoidance or treatment of hyperthermia from febrile illnesses or training-related heat exhaustion or heat stroke for athletes with BrS, acquisition of a personal automatic external defibrillator as part of the athlete's personal sports safety gear, and establishment of an emergency action plan with the appropriate school or team officials	Class IIa; Level of Evidence C
Competitive sports participation may be considered for an athlete with either previously symptomatic or electrocardiographically evident BrS assuming appropriate precautionary measures and disease specific treatments are in place and that the athlete has been asymptomatic on treatment for at least 3 months	Class IIb; Level of Evidence C
Patients after ICD placement according to ESC (2005)	
Criteria for eligibility: no malignant VTs, normal cardiac function, at least 6 months after the implantation, or the last ICD intervention Recommendation: low-moderate dynamic and low static sports (I A,B), except those with risk of bodily collision	–
Patients after ICD placement according to AHA and ACC (2015)	
Participation in sports classified as IA for athletes with an ICD is reasonable if they are free of episodes of ventricular flutter or ventricular fibrillation requiring device therapy for 3 months	Class IIa; Level of Evidence C
Participation in sports with higher peak static and dynamic components than class IA may be considered if the athlete is free of episodes of ventricular flutter or ventricular fibrillation requiring device therapy for 3 months. The decision regarding athletic participation should be made with consideration of, and counseling of, the athlete regarding the higher likelihood of appropriate and inappropriate shocks and the potential for device-related trauma in high-impact sports	Class IIb; Level of Evidence C
ACC – American College of Cardiology; AHA – American Heart Association; ESC – European Society of Cardiology; for other abbreviations see the description of Figure 1.	

Despite its high clinical effectiveness, ICD treatment may result in reduced quality of life and may be associated with possible complications. Adverse events related to ICD treatment aside from peri-procedural complications, include inappropriate shocks, lead failures, and ICD infections. Considering the majority of patients are young at the time of BrS diagnosis, the possibility of life-time complications resulting from ICD therapy is high. In a meta-analysis of 63 studies comprising 4916 patients with inherited arrhythmia syndromes, inappropriate shocks occurred in 20% of patients, 22% of patients experienced ICD-related complications, and there was a 0.5% ICD-related mortality (0.08% per year) [50]. Similar data was obtained by Miyazaki et al. in a study of 41 patients with BrS. During a median follow-up of 76 months, 37% of patients experienced 21 adverse events, including a 20% rate (11 events in 8 patients) of device-related complications, and 24% of patients (n = 10)

had at least one inappropriate shock [51]. In a study by Sacher et al, 378 patients with a type 1 Brugada ECG pattern had an ICD implanted. During a mean follow-up of over 6 years, most appropriate device therapies were experienced by SCA survivors (48%). Among patients with appropriate device therapy, 19% had previous syncope and 12% were previously (at the time of implantation) asymptomatic [52]. Additionally, the complication rate was high and reached 37% for inappropriate shocks and 29% for lead failure [52]. Similar conclusions were reached by Conte et al. who studied 176 patients with BrS in whom an ICD was implanted. During a mean follow-up period of 83.8 ± 57.3 months, appropriate ICD shocks occurred in 15.9% of patients, while 18.7% of patients had inappropriate shocks. Moreover, 15.9% of patients experienced device-related complications, which consisted of lead fracture, lead dislocation, pulse generator migration, and device infections. Aborted SCD and

Table 4. Selected studies concerning Brugada syndrome (BrS) treatment. Pharmacotherapy, implantable-cardioverter defibrillator use and performance of ablation in BrS patients

Clinical study	Group	Intervention	Follow-up	Effects
Pharmacotherapy				
Belhassen et al., 2015, [46]	96 BrS patients	Quinidine or disopyramide administered to VF inducible patients	Mean of 113.3 ± 71.5 months	* No arrhythmic events associated with QT prolongation while on therapy; * In 38% of patients on quinidine therapy, side effects occurred.
Bouzeaman et al., 2014, [47]	44 BrS patients	Hydroquinidine in asymptomatic BrS patients with inducible VF	Mean of 6.6 ± 3 years	* 23% (n = 10) of patients had positive PVS under hydroquinidine and 20% (n = 9) of patients received an ICD (one patient refused ICD); * 77% (n = 34) of patients were non-inducible during PVS and were maintained on hydroquinidine; * 12% (n = 4) of non-inducible patients received an ICD during follow-up; * 1.04% of the overall annual rate of arrhythmic events, no difference resulting from PVS under hydroquinidine; * Among non-inducible patients, 24% (n = 8) experienced mild-to-moderate drug intolerance without drug discontinuation, while 9% (n = 3) discontinued the drug due to intolerance; * Among patients after ICD placement, 31% (n=4) had device-related complications, while 38% (n=5) experienced inappropriate shocks.
Shinohara et al., 2014, [72]	7 patients (5 with BrS, 2 with ERS)	Bepridil + cilostazol in patients with ICD and recurrent VF	Combined follow up of 375 months	* 6 patients free from VF; * 1 patient with VF at cilostazol discontinuation.
Belhassen et al., 2004, [73]	25 BrS patients	Quinidine bisulfate administration in patients with inducible VF in EPS	Mean of 56 ± 67 (6 to 219) months	* In 88% (n = 22) of patients, quinidine prevented VF induction, in this group 36% (n = 8) of patients had side effects which disappeared after drug discontinuation; * No arrhythmias in follow-up.
Implantable cardioverter-defibrillator				
Olde Nordkamp et al., 2016, [50]	4916 patients (1037 BrS patients)	Meta-analysis	Mean of 51 ± 38 months	* In 21% (n = 214/1037) of patients with BrS, inappropriate ICD shocks were observed; * In 21% (n = 161/753) of BrS patients, ICD-related complications occurred; * In 0.5% (n=21/4388) of patients ICD-related mortality occurred.
Conte et al., 2015, [53]	176 BrS patients	ICD implantation	Mean of 83.8 ± 57.3 months	* 17% (n=30) of patients had sustained VA; * 15.9% (n=28) of patients had appropriate ICD shocks; * 4.5% (n=8) of patients died; * Aborted SCD and VA inducibility on EPS were found to be predictors of appropriate shock; * 13.6% (n=24) of patients were asymptomatic before ICD placement and later had VF; * 18.7% (n=33) of patients had inappropriate ICD shocks; * 15.9% (n=28) of patients had device-related complications.
Sacher et al., 2013 [52]	378 BrS patients	ICD implantation	Mean of 77 ± 42 months	* Ventricular arrhythmia was observed in 48% of patients with previous SCD, 19% of patients with previous syncope, and in 12% of asymptomatic patients; * Rate of inappropriate shock was 37%, while lead failure rate was 29%; * 2% of patients died.
Miyazaki et al., 2013 [51]	41 BrS patients	ICD implantation	Median of 76 months	* 12% (n=5) of patients had appropriate ICD shock (12 patients with ICD received appropriate ICD discharges); * 20% (n=8) of patients had device-related complications; * 24% (n=10) of patients had inappropriate shock.
Nademanee et al., 2003 [48]	86 SUDS survivors and probable SUDS survivors (54 with ECG abnormalities such as RBBB and ST elevation at precordial lead, V1 to V3)	ICD implantation vs propranolol	Maximum of 3 years after randomization	* 18% (n=7/39) of patients died in the beta-blocker group and 0 in the ICD group; * Annual event rates were 10% in the beta-blocker group and 20% in the ICD group; * Study discontinued by Data Safety Monitoring Board.
Hai et al., 2015, [57]	21 patients (6 BrS)	S-ICD implantation	Mean of 107.2 ± 81.3 days	* No inappropriate shocks or device-related complications; * In 28.6% (n=6) of patients, wound complications and in 1 patient, appropriate ICD therapy were observed.

Ablation				
Brugada et al., 2015, [64]	14 BrS patients	BrS and implanted ICD – epicardial ablation guided by flecainide	Median of 5 (3.8–5.3) months	* Elimination of the substrate, also after flecainide administration; * Lack of ventricular arrhythmia inducibility; * Elimination of Brugada pattern in ECG; * 1 patient with post ablation pericarditis.
Nademanee et al., 2011, [62]	9 BrS patients	BrS and recurrent VF episodes, epicardial ablation in the RVOT region	Mean of 20 ± 6 months	* Elimination of Brugada pattern in ECG (reappeared in only 1 patient); * VF non-inducible (in 7 of 9 patients); * No VF recurrence off medication in a follow-up (except 1 patient on amiodarone).
Haïssaguerre et al., 2003, [59]	3 BrS patients (7 total)	Ablation of PVC in LQTS and BrS patients with ICD and recurrent VF and numerous PVC	Mean of 17 ± 17 months (in BrS 7 ± 6 months)	* No recurrent VF in follow-up; * 1 patient with late recurrence of PVC.

EPS- electrophysiological study; ERS – early repolarization syndrome; LQTS – long QT syndrome; PVC – premature ventricular contractions; RVOT – right ventricular outflow tract; SCD – sudden cardiac death; SUDS – sudden unexplained death syndrome; VA- ventricular arrhythmia; for other abbreviations see the description of Figure 1 and 2.

sustained VT/VF inducibility on EPS were independent predictors of appropriate shock occurrence [53].

Some uncertainties about ICD implantation in BrS may partially be solved by the wider use and longer follow-up of subcutaneous ICD (S-ICD), which are believed to be associated with lower infection risk and fewer severe device-related complications. In a pooled analysis of 2 studies, Investigational Device Exemption (IDE) and the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry, involving 882 patients with a 3-year follow up, inappropriate shocks occurred in 13.1% of patients and device-related complications in 11.1% of patients without electrode failures or infections [54–56]. Limited data exists on the use of S-ICD in BrS patients. In an Asian study involving 21 patients who underwent S-ICD implantation, 28.6% of them were BrS patients. During the follow-up (107.2 ± 81.3 days) there were no inappropriate shocks or severe device-related complications. However, the authors noted wound-related complications in 8 (38.1%) patients [57]. The lower rate of device-related complications, together with a rare need for cardiac pacing in BrS, may make S-ICD a reasonable alternative in the ICD treatment of BrS. Cautious ECG assessment is crucial to qualifying eligible patients for this treatment and there are already reports of a high percentage of inappropriate sensing in BrS patients upon development of the type 1 ECG morphology [16, 58].

Currently, ICD placement in asymptomatic BrS patients is questionable. Based on available data, in our opinion, in asymptomatic patients with only a drug-induced BrS ECG pattern lacking other apparent risk factors (including significant ventricular arrhythmias), ICD treatment is not recommended. Asymptomatic patients with a spontaneous type 1 BrS ECG pattern may benefit from detailed SCD risk assessment. ESC guidelines recommend ICD implantation in aborted SCA survivors and in BrS patients who have documented spontaneous sustained VT (class I recommendations) [18]. Moreover, ICD implantation should be considered in patients with a spontaneous type 1 BrS ECG pattern and history of syncope (class IIa recommendations) and may be considered in those with positive PVS (defined as VF induced by 2 or 3 extrastimuli at 2 sites, class IIb recommendations) [18].

Ablation

Ablation of arrhythmogenic substrate has been effective in selected groups of patients with BrS. Over ten years ago, endocardial radiofrequency ablation of frequent ventricular ectopy (localized by mapping the earliest endocardial activity) triggering polymorphic VT or VF was found to be a possible method of treatment in BrS patients. The majority of these originated from the right ventricular outflow tract (RVOT) region, a well-established pathologic area in BrS patients [59, 74]. However, in BrS, premature ventricular contractions (PVC) are usually infrequent, and therefore, the difficulty in documenting VT/VF-triggering PVCs makes this an impractical approach for general use [60]. Shah et al. performed endocardial ablation of the septal and anterolateral RVOT under pace mapping guidance in a BrS patient after recurrent episodes of VF without clinical ectopy during EPS. Previously, PVCs initiating VF of a left bundle branch morphology with inferior axis and QRS transition in V4 were observed [61].

In a group of 9 BrS patients with recurrent VF episodes and inducible VF, epicardial ablation in the anterior RVOT region (where exclusive presence of abnormal low voltage, prolonged duration, and fractionated late potentials were identified) allowed normalization of the BrS ECG pattern (in 89% of patients) and made VF non-inducible (in 78% of patients) [62]. The authors did not rely on only low voltage areas in substrate identification, which could be affected by confounding factors such as tissue contact, pericardial fat, and fluid accumulation [63]. The study group expanded to over 50 patients in whom the authors were able to eliminate the Brugada ECG pattern without VF recurrence in a median follow-up of 3 years [63]. In a study involving 14 BrS patients with ICD, Brugada et al. performed epicardial contact mapping (after endocardial mapping) and ablation of a substrate which consisted of RV abnormal electrograms (amplitude <1.5 mV or wide duration >80 ms), multiple >3 or delayed components, beyond the QRS complex end) in low-voltage areas (<1.5 mV) during sinus rhythm, after flecainide administration [64]. After the ablation, remapping confirmed elimination of the substrate (disappearance of abnormal electrograms and low-voltage areas replaced by dense scar areas of bipolar signal amplitude of <0.5 mV), also after flecainide administration. There

was lack of ventricular arrhythmia inducibility after the procedure. Moreover, ECG showed elimination of the Brugada pattern, and remained normal after the median follow-up of 5 months, even after flecainide administration [64]. These promising findings require further investigation before widespread introduction into clinical practice. Current ESC guidelines recommend catheter ablation (class IIb recommendations) in BrS patients with a history of electrical storm or repeated appropriate ICD shocks [18].

Conclusions

BrS represents an important and complex clinical entity. Management of BrS patients is challenging, but based on proper differential diagnostics, risk stratification, and suitable clinical treatment, the risk of potential complications and SCD may be substantially minimized. Lifestyle modifications should be implemented in all BrS patients, while BrS-specific pharmacotherapy, ICD placement and/or ablation should only be reserved for selected groups of patients.

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