Ajmaline Testing and the Brugada Syndrome

Alessandro Rizzo, MD[a,c,1], Gianluca Borio, MD[a,c,1], Juan Sieira, MD, PhD[a,c], Sonia Van Dooren, PhD[b,c], Ingrid Overeinder, MD[a,c], Gezim Bala, MD, PhD[a,c], Gudrun Pappaert, RN[a,c], Riccardo Maj, MD[a,c], Thiago Guimarães Osório, MD[a,c], Muryo Terasawa, MD[a,c], Alessio Galli, MD[a,c], Federico Cecchini, MD[a,c], Vincenzo Miraglia, MD[a,c], Erwin Ströker, MD[a,c], Marc La Meir, MD, PhD[a,c], Pedro Brugada, MD, PhD, FHRS[a,c], Gian-Battista Chierchia, MD, PhD[a,c], and Carlo de Asmundis, MD, PhD, FHRS[a,c,*]

Brugada syndrome (BrS) diagnosis requires the presence of a typical type 1 ECG pattern. Owing to the spontaneous ECG variability, the real BrS prevalence in the general population remains unclear.

The aim of the present study was to evaluate the prevalence of positive ajmaline challenge for BrS in a cohort of consecutive patients who underwent electrophysiological evaluation for different clinical reasons. All consecutive patients from 2008 to 2019 who underwent ajmaline testing were prospectively included. A total of 2,456 patients underwent ajmaline testing, 742 (30.2%) in the context of familial screening for BrS. In non-familial screening group (1,714) ajmaline testing resulted positive in 186 (10.9%). Indications for ajmaline testing were: suspicious BrS ECG in 23 cases (12.4%), palpitations in 27 (14.5%), syncope in 71 (38.2%), presyncope in 7 (3.8%), family history of sudden cardiac death in 18 (9.7%), documented ventricular arrhythmias in 12 (6.5%), unexplained cardiac arrest in 4 (2.2%), atrial fibrillation in 16 (8.5%), brady-arrhythmias in 1 (0.5%), and cerebrovascular accidents in 7 (3.7%). Compared with the overall population, ajmaline testing positive patients were younger (42.8 ± 15.5 vs 48.9 ± 20.4; p <0.001) and more frequently male (65.1% vs 56.3%; p = 0.023). Implantable cardioverter defibrillator was implanted in 84 patients (45.2%). During a median follow-up of 42.4 months, 12 appropriate shocks and 13 implantable cardioverter defibrillator related complications were reported. In conclusion, the BrS was diagnosed in an unexpected high proportion of patients that underwent ajmaline testing for a variety of cardiovascular symptoms. This can lead to an adequate counseling and clinical management in BrS patients. **(Am J Cardiol 2020;135:91−98)**

Brugada syndrome (BrS) is an inherited disease responsible for sudden cardiac death (SCD) in structurally normal hearts due to ventricular fibrillation (VF).[1,2] The diagnosis of BrS is based on characteristic electrocardiographic findings following 2013 and 2015 criteria.[2,3] Owing to this variability, the real prevalence of BrS in the general population remains unclear although it has been estimated to range between 0.05% and 0.2%.[4−7] In subjects without spontaneous type 1 ECG pattern, sodium channel blocker challenge (SCBC) is commonly used to unmask the ECG pattern[2,8] (Figure 1). Current available literature points out that patients with drug-induced BrS are at a lower risk for arrhythmic events,[9−11] however SCD can still happen, therefore risk stratification of BrS patients is of utmost importance. The positive outcome of drug-induced BrS might be limited only to asymptomatic patients. Subjects presenting with syncope or SCD have a worse prognosis irrespective of ECG pattern.[12] The aim of the present study was to evaluate the real burden of positive ajmaline testing in a cohort of consecutive patients who underwent electrophysiological (EP) evaluation for different clinical reasons and its impact on BrS patients clinical management.

Methods

Consecutive patients who underwent ajmaline testing and eventual electrophysiological study (EPS) in our institution, Universitair Ziekenhuis Brussels, Belgium, between October 2008 and October 2019 were prospectively included. The study has been approved by the Universitair Ziekenhuis Brussels ethics committee. Those patients tested in the context of family BrS screening were excluded. Reasons for the drug challenge were: palpitations, presyncope, syncope believed to be of arrhythmic origin, ECG pattern suggestive for BrS (type 2 and Brugada-like pattern),[13] ventricular arrhythmias (VA) (premature ventricular contractions [PVC], non-sustained ventricular tachycardia [NSVT] and hemodynamically tolerated ventricular tachycardia [VT]), family history of SCD, cerebrovascular accidents

[a]Heart Rhythm Management Center, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, Brussels, Belgium; [b]Centre for Medical Genetics Universitair Ziekenhuis Brussel - Vrije Universiteit Brussel, Brussels, Belgium; and [c]European Reference Networks Guard-Heart, Brussels, Belgium. Manuscript received June 17, 2020; revised manuscript received and accepted August 24, 2020.

[1]Alessandro Rizzo and Gianluca Borio contributed equally to the work as first authorsSee page 97 for disclosure information.

*Corresponding author: Tel: +3224776009; fax: +3224776851.

E-mail addresses: carlodeasmundis@me.com; carlo.deasmundis@uzbrussel.be (C. de Asmundis).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.08.024

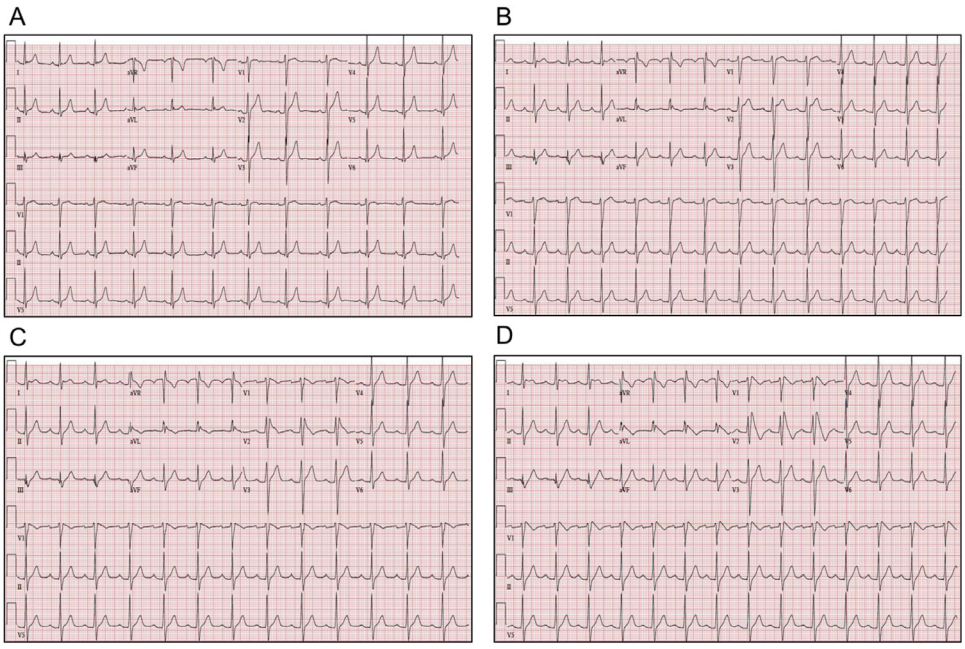

Figure 1. Positive ajmaline challenge. Normal baseline ECG (*A*) with a progressive conversion (*B,C*) to Brugada syndrome type 1 pattern (*D*) during ajmaline infusion. (*A*) Baseline ECG, (*B*) ajmaline 0.5 mg/kg, (*C*) ajmaline 0.7 mg/kg, (*D*) ajmaline 1 mg/kg.

(CVA), atrial fibrillation (AF) without structural heart disease, unexplained cardiac arrest (UCA) and suspected bradyarrhythmia. Indication for ajmaline testing in the context of UCA was defined as documented VF in absence of coronary artery disease, cardiomyopathy observed on transthoracic echocardiography and magnetic resonance imaging (MRI) or an ECG-based diagnosis (e.g., long QT syndrome). A family history of SCD was established when the index case was younger than 50 years of age or, at an older age, in the context of other features suggestive of an inherited arrhythmia.[14] Data were reviewed by 2 physicians blinded to the clinical information of the patients. Patients referred to our center for a second opinion on previously diagnosed BrS were not included in the study.

Ajmaline (1 mg/kg) was administered intravenously over a 5 minutes period to unmask the diagnostic ECG pattern of BrS in case of non-diagnostic baseline ECG. The test was considered positive if type 1 ECG pattern was documented in ≥1 precordial leads (V1-V3) at the fourth, third, or second intercostal space. The infusion was stopped when criteria for a positive test were reached. The test was prematurely terminated (<1 mg/kg without a type 1 ECG) for either excessive QRS widening (>140%) or induction of ventricular couplets, high degree atrio-ventricular block, ventricular tachycardia, or recurrent isolated PVC. In cases of premature termination, the test was considered inconclusive for BrS and ruled out from the study.

EPS included basal measurements of conduction intervals and programmed ventricular stimulation. The protocol used a single site of stimulation (right ventricular apex), 3 basic pacing cycles (600, 500, and 430 ms), adding 1, 2, and 3 ventricular premature beats down to a minimum of 200 ms. A patient was considered inducible if sustained VA lasting more than 30 seconds or requiring emergency intervention was induced (Figure 2). Programmed ventricular stimulation was performed before ajmaline administration. In case of a positive VT induction test, considered the risk of sustained arrhythmias, ajmaline testing was performed the following day.

Clinical follow-up of patients consisted of physical examination and ECG performed at least every 6 months in case of device therapy patients and every 2 years elsewise. Follow-up of ICDs was performed at 1 and 3 months after implantation and thereafter every 6 months. All available electrograms of appropriate and inappropriate shocks were analysed by at least 2 investigators independently. Appropriate therapies were defined as shocks or anti-tachycardia pacing delivered for VT or VF and inappropriate therapies were defined as those delivered in the absence of VA. Device related complications were defined as inappropriate shocks and/or lead failures (fracture, dislogment). The risk stratification score model proposed by our group[15] was then retrospectively applied to all the patients.

Data analysis was performed by means of SPSS 20.0 (Armonk, New York: IBM Corp). Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as percentages. Comparison between groups was made by means of Student's *t* test for unpaired data. Chi-square test was performed for nominal data. Logistic regression analysis was used to analyze predictors of positive result for ajmaline testing (binary variables). Arrhythmic events were defined as SCD, aborted SCD and appropriate ICD therapies. Survival analysis was performed by means of Kaplan Meyer curves and difference between groups expressed with Log Rank test. A p-value less than 0.05 was considered statistically significant.

Results

A total of 2,456 patients underwent ajmaline testing and EPS between October 2008 and October 2019 in our center (Figure 3). Ajmaline testing was performed in the context

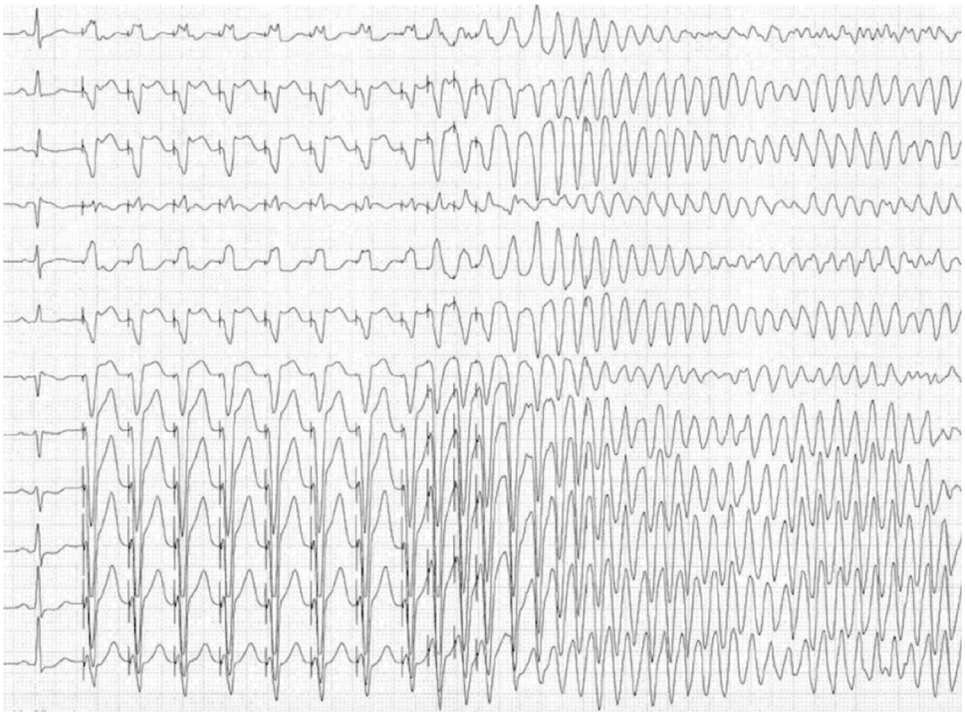

Figure 2. Electrophysiological study in a patient with positive ajmaline challenge. Ventricular fibrillation induction during electrophysiological study (performed with a decapolar catheter Biotronik ViaCath NG 10/S/2-6-2 mm and a quadripolar catheter Boston Scientific Viking 6F) with 8 basic pacing cycles of 430 ms and 3 premature extrabeats (250 ms).

of familial screening for BrS in 742 (30.2%) patients and for other reasons in 1714 (69.8%). Baseline and EPS patients characteristics are shown in Table 1. Ajmaline testing was positive in 186 patients (10.9%); the rate of positive ajmaline was not significantly different over the years analyzed ($p = 0.225$) and ranged from a minimum of 5.0% in 2013 to a maximum of 14.9% in 2016. Baseline characteristics and indications of patients with positive and negative ajmaline testing are displayed in Table 2 and Figure 4. During ajmaline testing 2 patients experienced VT and VF that required direct current (DC) shock to restore the sinus rhythm and 2 patients had major allergic reaction solved without complications. In patients with a negative ajmaline testing, 13 (0.9%) had VT/VF induction, 40 (2.6%) NSVT or 52 PVC (3.4%), 73 (4.8%) presented advanced conduction disease requiring a pacemaker implantation, 103 (6.7%) were diagnosed with reflex syncope, 52 (3.4%) typical atrio-ventricular nodal reentrant tachycardia (AVNRT), 31 (2%) atrial flutter, 193 (12.6%) atrial fibrillation, 27 (1.8%) premature atrial contraction and 944 (61.8%) had a negative EPS.

Compared with the overall population, ajmaline testing positive patients were younger (42.8 ± 15.5 vs 48.9 ± 20.4; $p < 0.001$) and more frequently male (65.1% vs 56.3%;

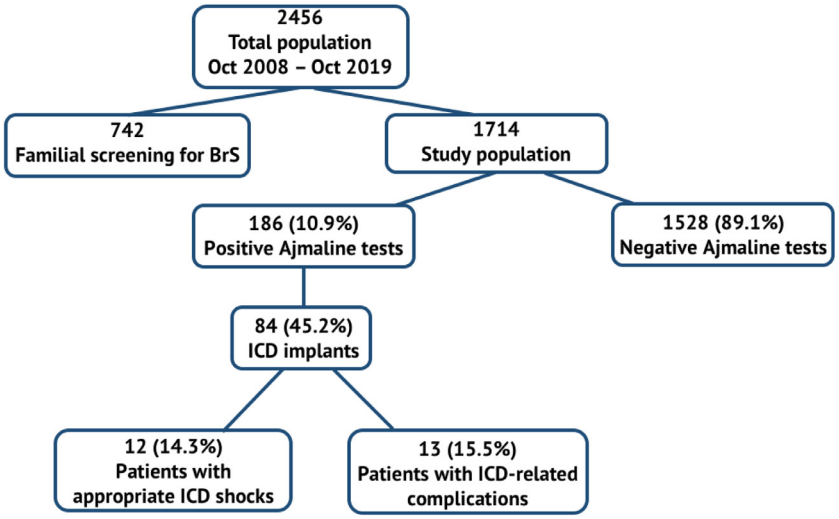

Figure 3. Flowchart of patients underwent ajmaline testing. BrS = Brugada syndrome; ICD = Implantable cardioverter defibrillator.

Table 1
Baseline and EPS characteristics of cohort of patients underwent ajmaline testing between October 2008 and October 2019 in our center

Variable	Overall n patients= 1714
Men	981 (57.3%)
Age (years)	48.2 ± 20.0
Heart rate (bpm)	71.3 ± 15.1
PR (ms)	164.6 ± 49.5
QRS (ms)	99.9 ± 23.8
QTc (ms)	413.7 ± 40.4
AH (ms)	92.5 ± 35.1
HV (ms)	45.4 ± 23.1
RWCL (ms)	428.7 ± 108.7
AWCL (ms)	399.4 ± 135
cSNRT (ms)	365 ± 262.3
ΔHV (ms)	21.7 ± 32.5

AWCL = anterograde Wenckebach cycle length; cSNRT = corrected sinus node recovery time; ΔHV = HV after ajmaline infusion- baseline HV; RWCL = retrograde Wenckebach cycle length.

p = 0.023). ECG and EPS data were comparable except for a slightly longer baseline QRS duration in BrS patients (104.3 ± 23.8 vs 99.3 ± 23.8; p = 0.008) and an inducible sustained VT of VF during EPS 7/186 (3.8% vs 0.3%; p <0,001); Table 2. Follow-up was available in 172 patients (92.5%). Median follow-up was 42.4 months (interquartile range: 9.2 to 86.6). 159 (85.5%) patients who underwent genetic testing and at least 1 gene mutation could be identified in 43 of them (27%), in 4 cases double mutations. The most common genetic alteration was on *SCN5A* gene in 26 (60.5%) cases. The other mutations were *SCN10A* (2 patients, 5%), *SCN4A* (3 patients, 7%), *ANK2* (3 patients, 7%), *AKAP9* (4 patients, 9%), *KCNQ1* (3 patients, 7%); *CACNA1C, GPD1L* in 1 patient (2%). At baseline 16 (8.6%) patients presented with a history of AF and during FU we documented 22 (11.8%) new onset AF. Two patients died due to cancer related complications.

Implantable cardioverter defibrillator (ICD) was placed in 84 patients (45.2%) with a mean risk score of 2.1 ± 1.3, significantly higher compared with non-ICD recipients (0.5 ± 0.8; p <0,001). Reasons for ICD implantation were syncope in 71 patients (84%), sustained induced VA in 7 (8.3%), UCA 4 (4.7%) and sustained VA during SCBC in 2 (2.3%). During FU 12 patients (14.3%) experienced 1 or more appropriate shocks (Figure 5). ICD related complications were observed in 13 patients (15.5%), 8 lead failures (either atrial or ventricular), and 5 inappropriate shocks due to fast heart rate AF. Three patients (2%) without ICD presented at least 1 episode of NSVT. Right ventricle outflow tract epicardial ablation was performed in 11 (5.9%) patients; cryobaloon pulmonary vein isolation in 13 (7%), 3 (1.6%) AVNRT, and 2 (1.1%) cavo-tricuspid isthmus blocks. A total of

Table 2
Comparison of baseline, electrophysiological study characteristics and indications of patients with positive and negative ajmaline testing

Variable	Positive ajmaline testing patients = 186	Negative ajmaline testing patients = 1528	p value
Men	121 (65.1%)	859 (56.4%)	0.028*
Age (years)	42.7 ± 15.5	48.9 ± 20.4	<0.001*
Heart rate (bpm)	70.8 ± 13.2	71.4 ± 15.4	0.610
Hypertension	16 (8.6%)	146 (9.6%)	0.901
LVEF (%)	61.2 ± 5.2	59.7 ± 4.4	0.870
Diabetes mellitus	4 (2.2%)	15 (1%)	0.143
eGFR, ml/min/1.73 m^2	85.2 ± 10.2	83.2 ± 15.4	0.456
PR (ms)	163 ± 27.8	164.9 ± 52.2	<0.634
QRS (ms)	104.3 ± 23.8	99.3 ± 23.8	0.008*
QTc (ms)	410.3 ± 35.6	414.3 ± 41.1	0.161
AH (ms)	92.4 ± 24.1	92.6 ± 36.4	0.959
HV (ms)	44± 8.7	45.5 ± 24.4	0.140
RWCL (ms)	445.6 ± 116.4	426.7 ± 107.8	0.207
AWCL (ms)	386.8 ± 88.4	409.9 ± 139.3	0.156
cSNRT (ms)	363.3 ± 212.8	365.5 ± 268.1	0.937
ΔHV (ms)	26.1 ± 12.5	21.4 ± 33.3	0.066
Syncope	71 (38.2%)	651 (42.6%)	0.159
Palpitations	27 (14.5%)	280 (18.3%)	0.061
Presyncope	7 (3.8%)	152 (10%)	0.156
Bradyarrhytmia	1 (0.5%)	89 (5.8%)	<0.001*
AF	16 (8.6%)	146 (9.6%)	0.900
VA	12 (6.5%)	85 (5.6%)	0.138
Family history SCD	18 (9.7%)	51 (3.3%)	<0.001*
Suspected ECG	23 (12.4%)	37 (2.4%)	<0.001*
CVA	7 (3.8%)	22 (1.4%)	0.055
UCA	4 (2.2%)	15 (1%)	0.143
Inducibility of VA in EPS	7 (3.8%)	5 (0.3%)	<0.001*

AF = atrial fibrillation; AWCL = anterograde Wenckebach cycle length; cSNRT = corrected sinus node recovery time; CVA = cerebrovascular accidents; eGFR = estimated glomerular filtration rate; EPS = electrophysiological study; ΔHV = HV after ajmaline infusion- baseline HV; LVEF = left ventricular ejection fraction; RWCL = retrograde Wenckebach cycle length; SCD = sudden cardiac death; UCA = unexplained cardiac arrest; VA = ventricular arrhythmias.

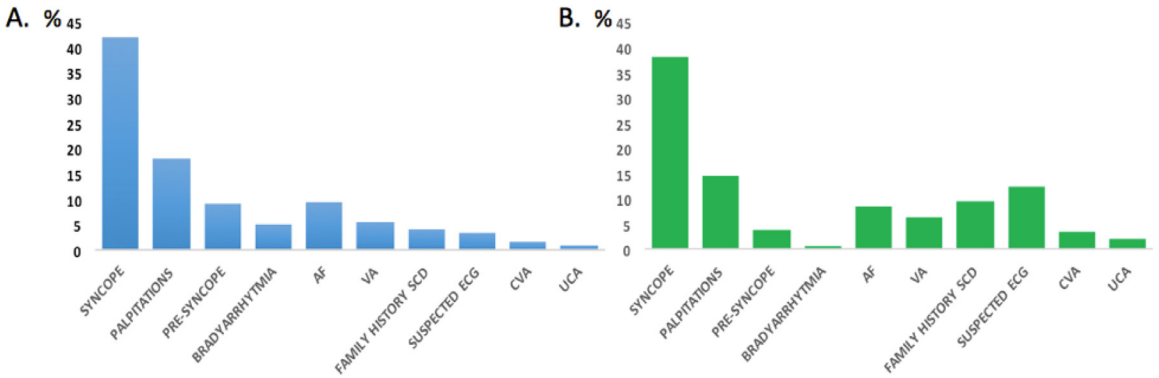

Figure 4. Overview of clinical indications for ajmaline challenge. (*A*) Clinical indication for ajmaline testing and EPS in overall population. (*B*) Clinical indication for ajmaline testing and EPS in probands. EPS = electrophysiological study; AF = atrial fibrillation without structural heart disease; SCD = sudden cardiac death; VA = ventricular arrhythmias; CVA = cerebrovascular accidents; UCA = unexplained cardiac arrest.

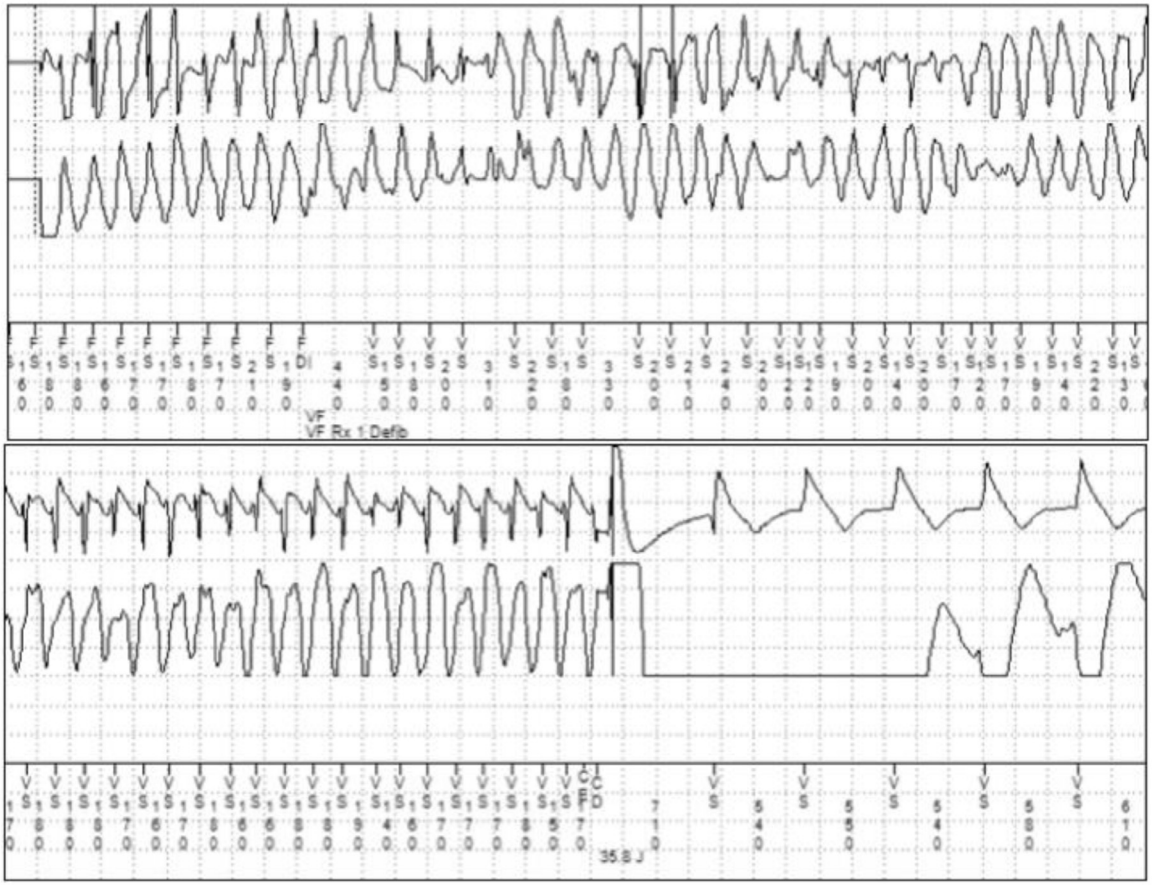

Figure 5. Appropriate ICD shock in a high risk Brugada syndrome patient. Episode of appropriate ICD shock delivered during ventricular fibrillation in a patient with positive ajmaline testing and previous syncope. ICD=Implantable cardioverter defibrillator.

40 (21.5%) patients were treated with β-blockers, 8 (4.3%) with amiodarone and 5 (2.7%) with quinidine.

Risk stratification score model[15] applied to our population showed 74 (39.8%) probands with score 0, 32 (17.2%) with score 1, 52 (28%) score 2, 17 (9.1%) score 3, 8 (4.3%) score 4, and 3 (1.6%) with score 5. Survival curves are shown in Figure 6.

A comprehensive family screening was achieved in 124 patients (66.7%; mean of 4.7 $\pm$ 3.7 per proband) for a total of 602 FM screened. Among them at least in positive FM was identified in 89 cases (71.8%) with 240 new positive BrS family members diagnosed.

Discussion

The main finding of the present study is the high burden of the BrS diagnosis after a drug challenge test (10.9%) in a selected population of consecutive patients who underwent

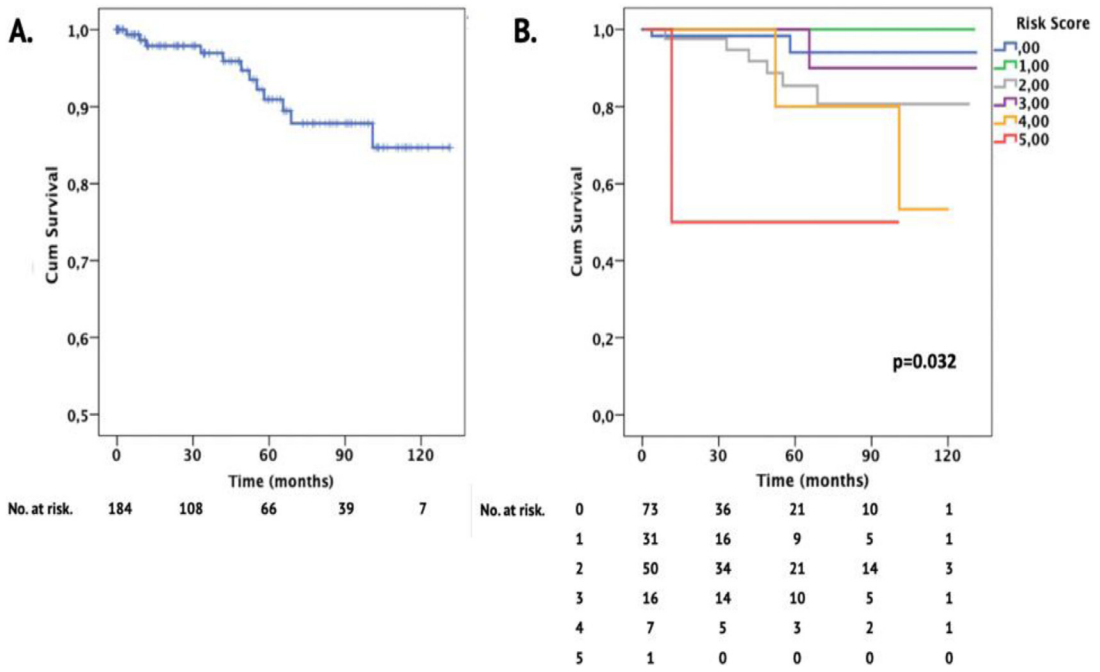

Figure 6. Cumulative major adverse cardiac event survival curves. (*A*) Cumulative major adverse cardiac event survival in the overall population. (*B*) Cumulative major adverse cardiac event survival with Sieira J. et al[15] risk stratification score that includes ECG pattern, early familial sudden cardiac death antecedents, inducible electrophysiological study, presentation as syncope or as aborted sudden cardiac death, sinus node dysfuncion and has a predictive performance of 0.82. A score greater than 2 confers a 5-year event probability of 9.2%.

EP examination. Of note, only a minority of patients (12.4%) presented with baseline ECG suspicious for Brugada syndrome. Such a high positive test rate is striking, given the fact that BrS is classically considered to be a rare disease.[2,16–20]

The true burden of BrS is still nowadays difficult to establish due to the unknown real prevalence in general population and the dynamic variability of the ECG pattern in affected patients.[2,4] Nonetheless, the prevalence of BrS is believed to range from 1 in 5,000 to 1 in 2,000 and the incidence of BrS pattern type 1 on ECG has ranged from 0.12% to 0.8% in several studies.[16–20] BrS has been considered responsible for 4% to 12% of all SCD, up to 20% in patients with structurally normal heart and it is 8 to 10 times more prevalent in men than women.[21] ECG in BrS characteristically shows considerable dynamic variability as it is known to be augmented by vagal tone,[22] whereas exercise and catecholamine infusion tend to reduce ECG manifestation.[23] According to the most recent guidelines,[2] BrS diagnosis can be established on the basis of a specific ECG pattern solely. Some concerns exist that this could result in overdiagnosis of the syndrome, particularly in patients displaying a type 1 ECG pattern only after SCBC, in absence of a clinical and/or familial suggestive history.[24] The latter aspect still represents a matter of debate in the scientific community[16] as it has been questioned the real specificity of SCBC. Induction of a type 1 ECG pattern was also observed in other conditions, such as 27% of patients with AVNRT,[25] 18% of patients with myotonic dystrophy,[19,26] and 16% with arrhythmogenic right ventricular cardiomyopathy.[27,28] The high burden of drug-induced BrS found in the present study could be related to the selected population enrolled, mainly symptomatic for tachyarrhythmias, syncope/presyncope or UCA. However, we do not believe that the high diagnostic yield of the ajmaline test in the context of our study is due to a lack of specificity or other reasons that could lead to an overdiagnosis of BrS. The BrS population identified is comparable to currently described BrS patient cohorts,[9] in particular regarding the familial clustering (71.8% of probands with 1 or more positive FM), the burden of positive genetic testing (27%) and the incidence of VA (14.2% of patients receiving appropriate ICD shock in ICD recipients and 6.5% in the overall population).[9]

Moreover, despite BrS diagnosis remains a matter of debate and ICD placement is indicated only in selected high-risk patients,[2,11–29] a positive SCBC can surely be crucial in further clinical management. In particular avoiding administration of potentially pro-arrhythmic drugs (class I antiarrhythmic drugs frequently used in patients with palpitations, alpha adrenergic blockers, Ca^{2+} channel blockers, etc.), aggressive treatment of all febrile episodes and avoiding hypokalemia, large carbohydrate meals or very hot baths. Therefore, one of the major consequences of this study, is that ajmaline testing could lead to an adequate counseling and management in BrS patients and their families.

SCBC is routinely used as part of an EPS performed in a bradycardia diagnosis workup.[30] In our study, the most frequent indication for ajmaline testing was syncope (42.1%) with a prevalence of syncope in probands of 38.2% (Figure 4). Nevertheless, the indication for the test was non-bradycardia related symptoms in a significant proportion of our population: symptomatic palpitations (14.5% in probands) and AF (9.5%). The frequent correlation between atrial fibrillation or CVA and BrS was furthermore

confirmed from our data.[31,32] Given the important dynamic variability of BrS pattern the use of SCBC as a routine tool in EPS protocol could be important.

SCBC has prognostic value in patients with BrS. Available literature points out that asymptomatic patients with drug-induced BrS are at a lower risk for arrhythmic events.[9,12] We present one of the biggest cumulative person-year populations of drug-induced BrS reported up to date. Our study supports a more benign course of drug-induced BrS, particularly amongst asymptomatic patients, with a low risk score; however the rate of arrhythmic events at FU is not negligible.

ICD placement is the most accepted therapy for preventing SCD in high-risk BrS patients[2] but long-term complications of ICD can significantly increase health burden and decrease quality of life, particularly in young patients.[33] Current guidelines recommend ICD placement in patients with aborted SCD (class Ia), syncope (class IIa), and ventricular arrhythmia inducibility during programmed stimulation study (class IIb).[2] In our study, ICD was implanted in 84 probands (45.2%) with a mean risk score[15] of 2.1 $\pm$ 1.3, significantly higher compared with non-ICD recipients (0.5 $\pm$ 0.8; p <0.001) and 12 (14.3%) appropriate shocks were delivered from the device. ICD related complications were observed in 13 patients including 8 lead fractures and 5 inappropriate shocks. As displayed in the survival curves (Figure 6) probands with a low risk score (0 or 1 points) had lower major adverse cardiac event rate compared with the others with a higher risk score (4 or 5 points). Even though in the present study a risk score model was applied retrospectively these results highlight the importance of a clinical score for risk stratification of the patients even in drug induced BrS pattern.

Although the study included all consecutive ajmaline tests performed for palpitations, presyncope, syncope, tachyarrhythmias, ECG pattern suggestive for BrS, UCA/SCD in a real-life setting, it suffers from some limitations. Only ajmaline was used in this study. Applicability of results to less potent sodium channel blockers used to diagnose BrS is uncertain. Prolonged ECG were not performed routinely during follow-up, therefore transient type I ECG pattern might be underestimated.

In conclusion, the BrS is diagnosed in an unexpected high proportion of patients that undergo SCBC for a variety of cardiovascular symptoms. SCBC can be crucial in the clinical management and counseling of these patients and their families. Given the important dynamic variability of BrS pattern the use of SCBC as a routine tool in EPS protocol could be useful. Large outcome studies are needed to assess the clinical gain of ajmaline testing in evaluation of patients who underwent electrophysiological evaluation.

Authors contribution

Alessandro Rizzo: Conceptualization, Project administration, Writing- Original draft preparation, Writing - Review & Editing, **Gianluca Borio**: Conceptualization, Writing- Original draft preparation, Formal analysis, **Juan Sieira**, Conceptualization, Writing- Original draft preparation, **Sonia Van Dooren**, Validation, **Ingrid Overeinder**, Validation**, Gezim Bala**, Investigation, **Gudrun Pappaert**, Resources, **Riccardo Maj**, Conceptualization, **Thiago Guimarães Osório**, Conceptualization, **Muryo Terasawa,** Data curation, **Alessio Galli**, Data curation, **Federico Cecchini**, Data curation, **Vincenzo Miraglia**, Data curation, **Erwin Ströker**, Conceptualization, **Marc La Meir**, Conceptualization, **Pedro Brugada**, Conceptualization, Supervision, **Gian-Battista Chierchia**, Conceptualization, Project administration, **Carlo de Asmundis**, Conceptualization, Writing- Original draft preparation, Supervision.

Disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Carlo de Asmundis, Gian Battista Chierchia and Pedro brugada receive compensation for teaching purposes and proctoring from AF solutions, Medtronic, Abbott, Biotronik, Atricure and research grants on behalf of the center from Biotronik, Medtronic, St Jude Medical Abbot, Livanova, Boston Scientific Biosense Webster.

1. 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* 1992:1391–1396. 20.
2. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ. Task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *European Heart J* 2015;36:2793–2867.
3. 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, Document Reviewers, Ackerman M, Belhassen B, Estes NA 3rd, Fatkin D, Kalman J, Kaufman E, Kirchhof P, Schulze-Bahr E, Wolpert C, Vohra J, Refaat M, Etheridge SP, Campbell RM, Martin ET, Quek SC, Heart Rhythm Society; European Heart Rhythm Association; Asia Pacific Heart Rhythm Society. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;15:1389–1406.
4. Gallagher MM, Forleo GB, Behr ER, Magliano G, De Luca L, Morgia V, De Liberato F, Romeo F. Prevalence and significance of Brugada-type ECG in 12,012 apparently healthy European subjects. *Int J Cardiol* 2008;130:44–48.
5. Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T, Satomi K, Suyama K, Aihara N, Kurita T, Kamakura S, Shimizu W. Augmented ST segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. *J Am Coll Cardiol* 2010;56:1576–1584.
6. Keller DI, Rougier JS, Kucera JP, Benammar N, Fressart V, Guicheney P, Madle A, Fromer M, Schläpfer J, Abriel H. Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. *Cardiovasc Res* 2005;67:510–519.
7. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: 1 report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;111:659–670.
8. Bébarová M, Matejovic P, Pásek M. Effect of ajmaline on transient outward current in rat ventricular myocytes. *Gen Physiol Biophys* 2005;24:27–45.
9. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre

M, Mabo P, Le Marec H, Wolpert C, Wilde A. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada syndrome registry. *Circulation* 2010;121:635–643.
10. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol* 2012;59:37–45.
11. Letsas KP, Liu T, Shao Q Letsas KP, Liu T, Shao Q, Korantzopoulos P, Giannopoulos G, Vlachos K, Georgopoulos S, Trikas A, Efremidis M, Deftereos S, Sideris A. Meta-analysis on risk stratification of asymptomatic individuals with the Brugada phenotype. *Am J Cardiol* 2015;116:98–103.
12. 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;14:1427–1433.
13. Bayés de Luna A, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, Lambiase P, Riera AP, Garcia-Niebla J, Pastore C, Oreto G, McKenna W, Zareba W, Brugada R, Brugada P. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. *J Electrocardiol* 2012;45:433–442.
14. Tadros R, Nannenberg EA, Lieve KV, Škorić-Milosavljević D, Lahrouchi N, Lekanne Deprez RH, Vendrik J, Reckman YJ, Postema PG, Amin AS, Bezzina CR, Wilde A, Tan HL. Yield and pitfalls of ajmaline testing in the evaluation of unexplained cardiac arrest and sudden unexplained death: single-center experience with 482 families. *J Am Coll Cardiol* 2017;3:1400–1408.
15. 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. *European Heart J* 2017;38:1756–1763.
16. Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AA. Everybody has Brugada syndrome until proven otherwise? *Heart Rhythm* 2015;12:1595–1598.
17. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, Aydin M, Pfeiffer R, Burashnikov E, Wu Y, Antzelevitch C. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. *Heart Rhythm* 2015;12:1584–1594.
18. Meregalli PG, Ruijter JM, Hofman N, Bezzina CR, Wilde AA, Tan HL. Diagnostic value of flecainide testing in unmasking SCN5A-related Brugada syndrome. *J Cardiovasc Electrophysiol* 2006;17:857–864.
19. Maury P, Audoubert M, Cintas P, Rollin A, Duparc A, Mondoly P, Chiriac AM, Acket B, Zhao X, Pasquié JL, Cardin C, Delay M, Sadron M, Carrié D, Galinier M, Davy JM, Arne-Bès MC, Raczka F. Prevalence of type 1 Brugada ECG pattern after administration of Class 1C drugs in patients with type 1 myotonic dystrophy: Myotonic dystrophy as a part of the Brugada syndrome. *Heart Rhythm* 2014;11:1721–1727.
20. Peters S, Trummel M, Denecke S, Koehler B. Results of ajmaline testing in patients with arrhythmogenic right ventricular dysplasiacardiomyopathy. *Int J Cardiol* 2004;95:207–210.
21. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome. *J Am Coll Cardiol* 2018;72:1046–1059.
22. Mizumaki K, Fujiki A, Nishida K Sakabe M, Tsuneda T, Sugao M, Iwamoto J, Nagasawa H, Inoue H. Bradycardia-dependent ECG changes in Brugada syndrome. *Circ J* 2006;70:896–901.
23. Amin AS, de Groot EA, Ruijter JM, Wilde AA, Tan HL, et al. Exercise-induced ECG changes in Brugada syndrome. *Circ Arrhythm Electrophysiol* 2009;2:531–539.
24. 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. *J Arrhythm* 2016;32:315–339.
25. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, Aydin M, Pfeiffer R, Burashnikov E, Wu Y, Antzelevitch C. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. *Heart Rhythm* 2015;12:1584–1594.
26. Korantzopoulos P, Bechlioulis A, Lakkas L, Naka KK. Brugada syndrome in a young patient with type 1 myotonic dystrophy requiring an implantable cardioverter defibrillator for primary prevention: a case report. *Eur Heart J Case Rep* 2019;3:086.
27. Corrado D, Zorzi A, Cerrone M, Rigato I, Mongillo M, Bauce B, Delmar M. Relationship between arrhythmogenic right ventricular cardiomyopathy and Brugada syndrome: new insights from molecular biology and clinical implications. *Circ Arrhythm Electrophysiol* 2016;9:e003631.
28. Peters S. Early and late manifestation of Brugada syndrome ECG in arrhythmogenic cardiomyopathy. *Int J Cardiol* 2016;220:260–261.
29. Sieira J, Brugada P. Management of Brugada syndrome 2016: should all high risk patients receive an ICD? All high-risk patients should receive an implantable cardiac defibrillator. *Circ Arrhythm Electrophysiol* 2016;9:e004195.
30. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martín A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk GJ, ESC Scientific Document Group. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;39:1883–1948.
31. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. *J Am Coll Cardiol* 2008;51:1149–1153.
32. de Asmundis C, Mugnai G, Chierchia GB, Sieira J, Ströker E, Conte G, Rodriguez-Mañero M, Pappaert G, Van Dooren S, De Regibus V, La Meir M, Brugada P. Abnormally high risk of stroke in Brugada syndrome. *J Cardiovasc Med* 2020;2:59–65.
33. Sherrid MV, Daubert JP. Risks and challenges of implantable cardioverter-defibrillators in young adults. *Prog Cardiovasc Dis* 2008;51:237–263.