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DIOGO FILIPE DE ALMEIDA FERREIRA FERNANDES

Adequation of the therapeutic profile, co-morbidities and personal habits of Brugada patients with ICD and its link to dysrhythmic events

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Resumo

Introdução: A síndrome de Brugada é uma doença hereditária associada a um aumento do risco de morte súbita com possível necessidade de colocação de cardioversor-desfibrilhador implantável (CDI) de forma a interromper os eventos disrítmicos. Os nossos objetivos foram identificar possíveis desencadeadores de terapias apropriadas do CDI em doentes com síndrome de Brugada e avaliar se o perfil terapêutico passado e atual é adequado à doença.

Métodos: Um total de 30 doentes com síndrome de Brugada submetidos a implantação de CDI e seguidos no Centro Hospitalar e Universitário de Coimbra (CHUC) participaram neste estudo. Foi recolhida informação acerca da história da sua doença, eventos cardíacos anteriores, comorbilidades, medicação atual e passada e atividade física. O follow-up médio foi de 5.8 ± 5.3 anos. O CDI foi interrogado e foram registados os eventos arrítmicos e as terapêuticas administradas. Por fim, comparámos a coorte que recebeu terapias apropriadas do CDI com os restantes doentes para tentar identificar eventuais ligações entre as diferentes variáveis clínicas e disritmias ventriculares potencialmente fatais.

Resultados: Mais de metade dos doentes (53.3%) tomou pelo menos um fármaco não recomendado e 16.7% receberam terapias apropriadas do CDI, com uma incidência anual a longo prazo de 4.0%/ano. Foi encontrada uma tendência para maior ocorrência de terapias apropriadas do CDI em doentes que tomaram fármacos não recomendados (85.7% vs 45.5%, p = 0.062). Nos doentes com diabetes *mellitus* tipo 2 a ocorrência de terapias apropriadas foi significativamente superior à dos não diabéticos (33.3% vs 0.0%, p = 0.006).

Discussão e Conclusão: Este estudo revelou que ainda não existe o devido conhecimento das restrições farmacológicas impostas pela doença. Um grande número de doentes tomou pelo menos um fármaco não recomendado e este grupo apresentava uma tendência para receber mais terapias apropriadas do CDI. A diabetes *mellitus* tipo 2 também parece estar associada a maior ocorrência de disritmias ventriculares.

Palavras-Chave

Síndrome de Brugada, Cardioversor Desfibrilhador Implantável, Arritmia Cardíaca, Arritmias Induzidas por Fármacos, Morte Súbita

Abstract

Introduction: Brugada Syndrome is a hereditary disease linked with an increased risk of sudden death that may require an implantable cardioverter-defibrillator (ICD) in order to halt the malignant arrhythmic events. Our objectives were to identify possible triggers for appropriate ICD therapies in patients with Brugada Syndrome, focusing on their past and current therapeutic profile.

Methods: Thirty patients with high-risk Brugada syndrome, with ICD implanted at the Coimbra Hospital and University Centre, were enrolled. Patients were questioned about their Brugada Syndrome history, previous cardiac events, comorbidities, present and past medication and physical activity. Patients were followed-up during 5.8 ± 5.3 years. The ICD was interrogated and arrhythmic events and device therapies were recorded. The cohort who received appropriate ICD therapies was compared with the remaining patients to determine the potential link between clinical variables and potentially fatal arrhythmic events.

Results: More than half of the patients (53.3%) took at least one non-recommended drug and 16.7% received appropriate ICD therapies, with a long-term rate of 4.0%/year. There was a tendency for more appropriate ICD therapies in patients who took unsafe drugs (85.7% versus 45.5%, $p = 0.062$). Additionally, type 2 diabetic patients had significantly more appropriate therapies than their counterparts (33.3% vs 0.0%, $p = 0.006$).

Discussion and Conclusion: This study revealed that the medical community is still unaware of the pharmacological restrictions imposed by Brugada Syndrome. Patients who took non-recommended drugs and patients with type 2 diabetes mellitus seem to have a higher risk of ventricular arrhythmic events.

Keywords

Brugada Syndrome, Implantable Cardioverter-Defibrillator, Cardiac Arrhythmia, Drug-induced Arrhythmias, Sudden Death

Abbreviations list

ATP	Antitachycardia Pacing
BMI	Body Mass Index
BrS	Brugada Syndrome
DM	Diabetes Mellitus
ECG	Electrocardiogram
FH	Family history
IPAQ	International Physical Activity Questionnaire
METS	Metabolic equivalents
PVT	Polymorph Ventricular Tachycardia
SD	Sudden Death
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

Introduction

Brugada Syndrome (BrS) is a hereditary disease described for the first time in 1992 characterized by an increased risk of ventricular arrhythmias and sudden death (SD) in patients without structural heart disease.[1–9]

Recent studies estimate a global prevalence of 1 to 5 per 10.000 people.[1–5,10,11] In Southeast Asia and Japan the disease is considered endemic, having a prevalence as high as 10 to 12 per 10.000 people.[1–5,7,10,12,13] However, since a great number of patients are asymptomatic and, as a result, undiagnosed, these numbers may be even higher.[3] Furthermore, BrS is more prevalent in men.[1,5,7,13] Nowadays, BrS is regarded has one of the main causes of sudden death in otherwise healthy individuals with structurally normal hearts, especially in patients under 40 years old.[1,4,5,14]

In most cases the disease has an autosomal dominant mode of transmission with variable penetrance[1–5,7,8,11–14] and more than 20 genes have been identified.[14] Mutation of SCN5A, a gene encoding an α subunit of the cardiac sodium channel, is present in about 20% of the patients.[1,3–5,7,11–13] It is believed that genetic mutations occurring in this gene cause ionic unbalances which form the basis for the symptoms and changes observed in BrS.[1,3–5,7,11–13]

Syncope is the most common form of presentation.[1–5,7,8,11,14] Other possible symptoms are sudden death,[2–5,8,9,12,14] aborted sudden death,[2,3,5,7,11,14] ventricular fibrillation (VF),[2–7,14] polymorph ventricular tachycardia (PVT),[2–6,14] nocturnal agonal respiration[2–7,11] or supraventricular arrhythmias with palpitations or dizinness,[1–5,7,8,11] usually in men[1,3–5,7,10–12] sleeping or resting[2–5,7,10,11,13] with ages between 30 and 50 years old.[1,3,4,7,10,11,13] Nevertheless, most patients are asymptomatic at the time of diagnosis,[1–5,11] being identified by chance or during genetic screening of first degree relatives.

A HRS/EHRA/APHRS consensus in 2013 states that diagnosis is made through a pathognomonic electrocardiogram (ECG), either spontaneous or induced with a Class I

antiarrhythmic drug.[7] Other electrocardiographic signs may support the diagnosis and improve risk stratification, such as early repolarization pattern[1,6,11,12,14–16] (J wave, present in 10% of the patients)[11], aVR sign[1,3,12,14,16], intraventricular conduction delay[1,4,5,11,12,14,16] and increased QTc interval.[3] Patients with BrS also have a greater risk of developing atrial fibrillation,[1–4,6,7,11,13,14] with some studies describing an incidence of 15 to 30%.[3,4,6,11] Following diagnosis it is necessary to stratify the risk of cardiac events and, consequently, identify the ones with indication for an implantable cardioverter-defibrillator (ICD).[1,3–5,10,11,17,18] This is the only proven effective therapeutic strategy for the prevention of sudden cardiac death in BrS patients.[1,3–5,10,11,17] However, these patients are vulnerable to inappropriate shocks and may require multiple device replacements during their life,[7,19] leading to a lower quality of life.

Furthermore, BrS patients must adopt certain behaviors that diminish the probability of arrhythmic events such as avoiding certain drugs,[5,7,10,11,13,20,21] as the ones listed at www.brugadadrugs.org,[20,21] avoid cannabis[13] and cocaine[4,5,12,13] consumption, excessive alcohol,[4,5,10,12,13,22] high carbohydrate intake[5,10] and very hot baths.[5] These patients must maintain a healthy and active lifestyle while respecting the restrictions imposed by their disease.[13] Vigorous exercise has also been linked with ventricular arrhythmias and an increase in ST abnormalities.[23]

Given that BrS is one of the main causes of sudden cardiac death in young patients and that there are many factors that may contribute to arrhythmic events, it is of the utmost importance to investigate if medications and lifestyle are responsible for complications during long-term follow-up.

Consequently, the objectives of this study were to identify possible triggers for appropriate ICD therapies in BrS patients and evaluate the past and current medication impact on this channelopathy.

Methods

Study design and Patient selection

The study employed a retrospective observational design.

The study was conducted at the Coimbra Hospital and University Centre (CHUC), in Coimbra. Patients with a diagnosis of BrS confirmed by two trained arrhythmologists and an ICD implanted in the time period between January 2004 and March 2017 were included (Figure 1). The mean follow-up time was 5.8 ± 5.3 years.

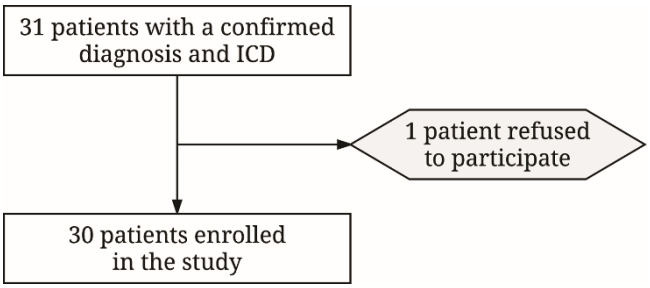

Figure 1 *- Patient Selection*

The study was conducted in accordance to the Declaration of Helsinki and was approved by Local Ethics Committee of the Coimbra Hospital and University Center. Each patient provided an informed consent to participate in the study.

Data collection

Patients were questioned about BrS history (date of diagnosis, reason of diagnosis, FH of sudden death), previous cardiac events (syncope and aborted sudden death), comorbidities (type 2 diabetes mellitus (DM), dyslipidemia, arterial hypertension, stroke, coronary heart disease, acute myocardial infarction and heart failure), present and past medication (including the drugs mentioned in www.brugadadrugs.org), personal habits (alcohol intake, cocaine and cannabis usage, carbohydrate intake, hot baths) and current lifestyle (physical activity, smoking). They were also asked to fill in the short form of the International Physical Activity Questionnaire (IPAQ).

Furthermore, the ICD was interrogated and arrhythmic events and device therapies were recorded and reviewed by two trained arrhythmologists.

Data analysis

The data were analyzed using IBM® SPSS® Statistics version 24.

First, we made a descriptive analysis of the different variables. We determined the mean and standard deviation of the continuous variables and the relative frequency of the qualitative variables.

A Mann-Whitney U test was used to compare quantitative variables between patients receiving appropriate ICD therapies and the ones who did not receive any appropriate ICD therapies. The Chi-squared test was employed to compare the same groups regarding qualitative variables. A p-value inferior to 0.05 was considered statistically significant.

Results

General description of the population

A total of 30 BrS patients with an ICD were studied. Twenty-three of them were male (76.7%) and 7 were female (23.3%). The mean age of the cohort was 55.2 ± 13.6 years old and the mean body mass index (BMI) was 25.8 ± 3.3 kg/m^2.

The demographic and clinical characteristics of the studied population are shown in Table 1.

Most patients studied had a spontaneous type 1 Brugada ECG (90.0%). Only 14 patients (46.7%) were submitted to genetic testing (Figure 2).

In terms of clinical history, 7 patients (23.3%) had history of cardiac arrest before the diagnosis and 19 (63.3%) referred past events of syncope. Fourteen patients (46.7%) had at least one confirmed case of sudden death in first degree relatives.

Regarding electrocardiographic patterns, one patient (3.3%) had early repolarization, 7 (23.3%) aVR sign, 11 (36.7%) intraventricular conduction defect and 4 (13.3%) documented persistent or paroxysmal atrial fibrillation. In this cohort, the mean QTc interval in DII was 407.7 ± 26.2 ms.

The most common co-morbidity was dyslipidemia (16 patients, 53.3%) followed by hypertension (10 patients, 33.3%). Concerning lifestyle, 11 patients (36.6%) were active or former smokers, 8 (26.7%) consumed alcohol frequently, 4 (13.3%) had a high carbohydrate intake and 1 (3.3%) admitted to taking very hot baths. The group of active and former smokers smoked on average 11.4 ± 9.1 pack-year. Regarding physical exercise the mean metabolic equivalents (METS) was 2575.8 ± 2430.8.

Table 1 *- Baseline demographical and clinical characteristics*

	Total (n=30)	
	Value	***Proportion (%)***
Heart rate (bpm)	71.7 ± 14.1	
Brugada Type		
Spontaneous type 1	27	90.0
Provoked type 1	3	10.0
Genetic test	14	46.7
Mutation detected (SC5NA)	3	21.4
Aborted sudden death	7	23.3
Syncope	19	63.3
FH of sudden death	14	46.7
ECG Data		
Early repolarization pattern	1	3.3
aVR sign	7	23.3
Intraventricular conduction defect	11	36.7
QTc interval in DII (ms)	407.7 ± 26.2	
Persistent/paroxysmal atrial fibrillation	4	13.3
Comorbidities		
Dyslipidemia	16	53.3
Type 2 DM	2	6.7
Hypertension	10	33.3
Stroke/Transient ischemic attack	1	3.3
Smoking		
Non-smoker	11	36.7
Active smoker	4	13.3
Former smoker	7	23.3
Unknown	8	26.7

Pack-year	11.4 ± 9.1	
Alcohol consumption	8	26.7
High carbohydrate intake	4	13.3
Very hot baths	1	3.3
Physical exercise (METS)	2575.8 ± 2430.8	
Sedentarism	12	40.0

BMI, body mass index; FH, family history; DM, diabetes mellitus; METS, metabolic equivalents

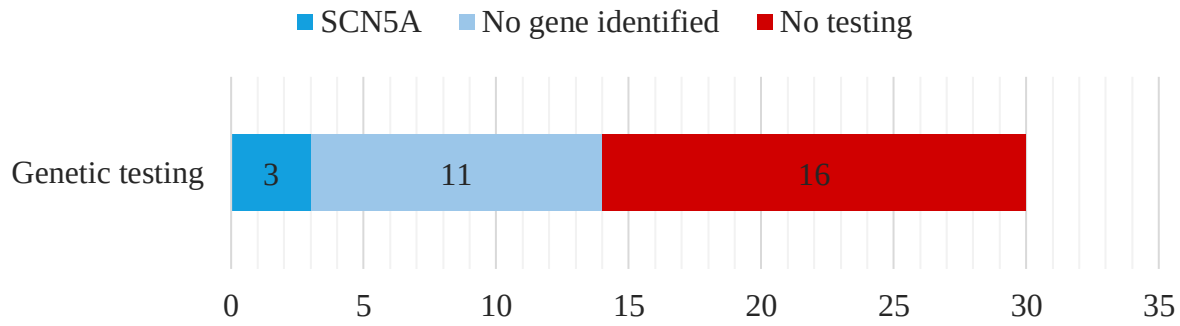

Figure 2 *- Genetic testing and results*

Therapeutic profile since diagnosis

Sixteen patients (53.3%) had taken at least one drug that is contraindicated or should be avoided since the diagnosis and 5 of them (16.7%) took a combination of them. The most prescribed non-recommended drug in the studied cohort was metoclopramide (6 patients, 20%: Figure 3).

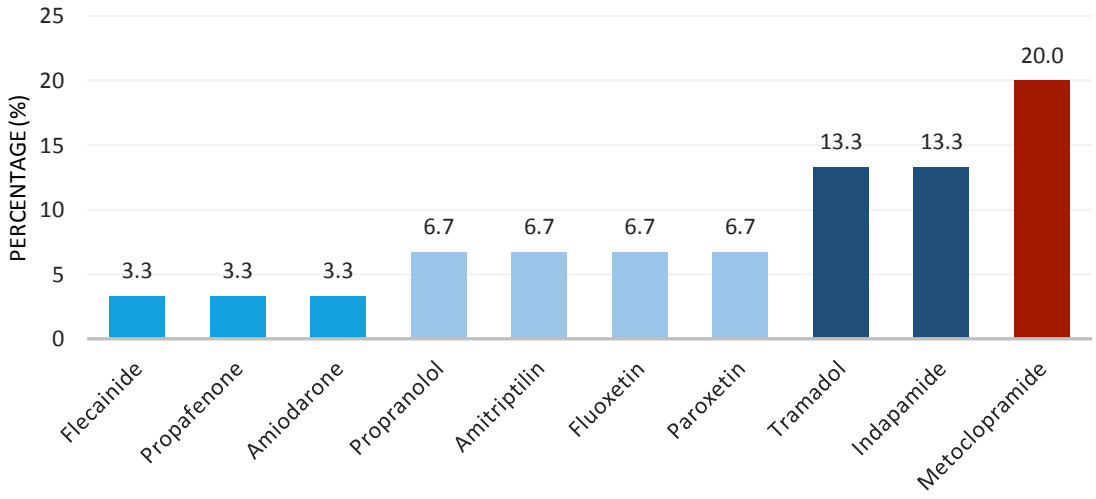

Figure 3 *- Non-recommended drugs taken*

Cardiac events and ICD therapies

Seven patients (23.3%) received ICD therapies during a mean follow-up of 5.8 ± 5.3 years (Table 2). Five patients (16.7%) had appropriate shocks and 2 (6.7%) antitachycardia pacing

(ATP). The long-term rate of appropriate ICD therapies was 4.0%/year (2.9%/year for appropriate shocks and 1.1%/year for ATP). There were 2 cases (6.7%) of inappropriate shocks due to atrial fibrillation.

Table 2 *- Cardiac events and ICD therapies*

	Total (n=30)	
	Value	***Proportion (%)***
Appropriate shocks	5	16.7
ATP	2	6.7
Type of arrhythmia treated		
VT	4	13.3
VF	3	10.0
Inappropriate shocks	2	6.7

ATP, antitachycardia pacing; VT, Ventricular tachycardia; VF, Ventricular fibrillation

Comparison between patients with and without appropriate ICD therapies

There were no statistically significant differences between the population who received appropriate ICD therapies and the one who did not regarding age, BMI, physical activity (METS) and QTc duration.

The Chi-squared test results are shown in Table 3. Patients with appropriate ICD therapies during follow-up tended to be more frequently treated with non-recommended drugs than patients without ICD therapies (85.7% versus 45.5%, p = 0.062). Additionally, patients with type 2 DM showed a significantly higher proportion of adequate ICD therapies during follow-up (33.3% versus 0.0%, p = 0.006).

Table 3 *- Relationship between appropriate ICD therapies and the different variables*

	Adequate ICD therapies		***p-value***
	Yes (n = 7)	***No (n = 23)***	
Gender			
Male/Female (%)	57.1/42.9	82.6/17.4	0.163
Mutation detected (%)	25.0	25.0	1.000
Early repolarization pattern (%)	0.0	4.8	0.557
aVR sign (%)	14.3	28.6	0.639
Intraventricular conduction defect (%)	14.3	47.6	0.118
Persistent/paroxysmal atrial fibrillation (%)	0.0	20.0	0.200
Syncope (%)	57.1	68.2	0.593

Aborted Sudden death (%)	28.6	22.7	0.753
FH of Sudden death (%)	42.9	55.0	0.580
Sedentarism (%)	75.0	50.0	0.364
Dyslipidemia (%)	100.0	60.0	0.121
Type 2 DM (%)	33.3	0.0	0.006
Hypertension (%)	60.0	33.3	0.271
Stroke/Transient ischemic attack (%)	0.0	4.8	0.557
Smoking (%)			
Active smoker	20.0	17.6	0.871
Former smoker	40.0	29.4	
Non-smoker	40.0	52.9	
Alcohol consumption (%)	40.0	37.5	0.920
High carbohydrate intake (%)	25.0	18.8	0.780
Very hot baths (%)	0.0	6.3	0.608
Non-recommended drugs (%)	85.7	45.5	0.062

Discussion

The main findings of this study are: 1) a large proportion of high-risk BrS patients took at least one unsafe drug in any moment after the ICD implantation, 2) patients who took at least one non-recommended drug had a higher tendency for adequate ICD therapies and 3) type 2 DM was associated with a higher rate of appropriate ICD therapies.

Sample characteristics

The cohort of patients studied was mainly male (76.7%), which goes in accordance with other international studies regarding the prevalence of the disease.[1,5,7,13] Only 21.0% of the patients submitted to genetic test had an identifiable mutation, all in the SCN5A gene, a number similar to the one demonstrated by other studies.[1,3–5,7,11–13]

Family history (FH) of sudden death and syncope[1–5,7,8,11,14] remain two of the most important clues for the diagnosis, being present respectively in 46.7% and 63.3% of the patients. Both the early repolarization pattern (3.3%) and atrial fibrillation (13.3%) were less frequent in the studied cohort than demonstrated in previous studies, which may be justified by the small size of the sample. Consequently, these results demonstrate that almost all patients have a background of familial sudden death or syncope that may provide an important clue to an early diagnosis and lead to a successful prevention of SD in young patients. As a result, programs

should be developed to ensure a correct study and follow-up of patients (and their first-degree relatives as well) likely to have the disease.

Sedentarism, dyslipidemia, hypertension, smoking and alcoholism remain some of the most frequent problems in modern society and major contributors to a shorter lifespan. As such, it is important to emphasize that BrS patients may have multiple comorbidities that continue to require medical treatment after the diagnosis. However, their treatment must always take into consideration the pharmacological restrictions that this disease requires.[20,21] Regarding physical exercise, a great number of patients had little or no physical activity, indicating that efforts should be made to promote a healthy and active lifestyle, avoiding nevertheless vigorous exercise.[13]

Therapeutic profile

Many drugs have been reported to induce potentially fatal arrhythmias in BrS patients. In this study, more than half of the patients had taken at least one drug that is contraindicated or should be avoided in BrS, with several patients taking multiple drugs. Metoclopramide was the most incorrectly prescribed drug followed by tramadol and indapamide. Other identified drugs were antidepressants such as amitriptiline, paroxetin and fluoxetin, and antiarrhytmic drugs (namely propranolol, amiodarone, propafenone and flecainide). Since these drugs are responsible for an increased risk for developing VF and ventricular tachycardia (VT)[20,21], it is possible that a large portion of the medical community is still unaware of the restrictions imposed by this disease. Accordingly, it is crucial to educate the medical community about the existence of a written document from www.brugadadrugs.org enumerating all non-recommended drugs, make certain that it is given to the patients and ensure that the patients adhere to its contents.

The rate of appropriate ICD therapies was 4.0%/year (2.9%/year for appropriate shocks and 1.1%/year for ATP). Patients with appropriate ICD therapies had a tendency to be more frequently treated with non-recommended drugs than patients without appropriate ICD

therapies. Furthermore, research of other drugs and herbal medicines potentially unsafe or with a negative impact in the disease must continue.

Electrophysiological effects of the most taken non-recommended drugs

The various non-recommended drugs taken by this cohort have different electrophysiological effects, some of which are yet to be truly understood.

Metoclopramide, the most wrongly prescribed drug, has a class IIb recommendation and should be preferably avoided.[20,21] Its arrhythmogenic mechanism involves cardiac sodium channels, but the exact mode of action is still unknown.[24]

Indapamide and tramadol were the second most frequently used non-recommended drugs. Both are considered preferably avoided drugs with a class IIb recommendation.[20,21] Indapamide's electrophysiological effect derives both from the induction of hypokalemia (enhances the Ito current and sustaining polymorphic VT and VF) and hyponatremia (possibly resulting in a reduction of the INa currents, inducing type 1 Brugada pattern),[25] whereas tramadol is known to block sodium-channels *in vitro*.[26,27]

Type 2 DM and arrhythmic risk in Brugada syndrome

The effect of type 2 DM in BrS has yet to be determined. Nevertheless, previous studies found that DM is linked with an increased risk of ventricular arrhythmias.[28–30] Its proposed mechanisms are an abnormal ventricular repolarization[28] and sympathetic overstimulation as a result of autonomic neuropathy[28,30] and hypoglycemia.[28,29] Furthermore, DM has been consistently associated with ischemic heart disease and acute myocardial infarction, two conditions that facilitate ventricular arrhythmias.[31] Our study revealed no association between appropriate ICD therapies and acute myocardial infarction or coronary artery disease syndrome, potential confounding variables.

In our study patients with type 2 DM presented a significantly higher proportion of appropriate ICD therapies than their counterparts. However, the arrhythmogenic potential of DM in Brugada syndrome needs to be confirmed in further studies.

Limitations

One of the major limitations of this study was the sample size, mainly due to the fact that BrS is a rare disease[1–5,10,11] and that only a fraction of the patients require an ICD.[1,3–5,10,11,17,18] Furthermore, the study was unicentric and retrospective and as a result, other factors that may influence ICD therapies such as emotions, psychological states and daily activities were not taken into consideration.

Conclusion

Our data revealed that most high-risk BrS patients took at least one non-recommended drug. These patients had a higher tendency to have appropriate ICD therapies. Further efforts are necessary to raise awareness in the medical community and in patients about unsafe drugs and arrhythmic triggers that must be avoided.

Furthermore, type 2 DM was associated with a higher rate of appropriate ICD therapies. Nevertheless, studies with larger cohorts are necessary to assess the real dimension of the problem and to determine if type 2 DM is an independent predictor of arrhythmic events in BrS.

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