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Long-term clinical outcomes of patients with drug-induced type 1 Brugada electrocardiographic pattern: A nationwide cohort registry study ⓔ

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ABSTRACT

BACKGROUND There are limited real-world data on the extended prognosis of patients with drug-induced type 1 Brugada electrocardiogram (ECG).

OBJECTIVE We assessed the clinical outcomes and predictors of life-threatening arrhythmias in patients with drug-induced type 1 Brugada ECG.

METHODS This multicenter retrospective study, conducted at 21 Italian and Swiss hospitals from July 1997 to May 2021, included consecutive patients with drug-induced type 1 ECG. The primary outcome, a composite of appropriate ICD therapies and sudden cardiac death, was assessed along with the clinical predictors of these events.

RESULTS A total of 606 patients (mean age 49.7 ± 14.7 years; 423 [69.8%] men) were followed for a median of 60.3 months (interquartile range 23.0–122.4 months). Nineteen patients (3.1%) experienced life-threatening arrhythmias, with a median annual event rate of 0.5% over 5 years and 0.25% over 10 years. The *SCN5A* mutation was the only predictor of the primary outcome (hazard ratio 4.54; $P = .002$), whereas a trend was observed for unexplained syncope (hazard ratio 3.85; $P = .05$). In patients who were asymptomatic at presentation, the median annual rate of life-threatening arrhythmias is 0.24% over 5 years and increases to 1.2% if they have inducible ventricular fibrillation during programmed ventricular stimulation.

CONCLUSION In patients with drug-induced type 1 Brugada ECG, the annual risk of life-threatening arrhythmias is low, with the *SCN5A* mutation as the only independent predictor. Unexplained syncope correlated with worse clinical outcomes. Ventricular

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fibrillation inducibility at programmed ventricular stimulation significantly increases the median annual rate of life-threatening arrhythmias from 0.24% to 1.2% over 5 years.

Introduction

A type 1 Brugada electrocardiographic (ECG) pattern induced by fever or sodium channel–blocking drugs is generally considered diagnostic for Brugada syndrome (BrS) in patients with no other heart disease. BrS is a hereditary cardiac ion channelopathy, predisposing to sudden cardiac death (SCD) in patients with a structurally normal heart.[1] Despite ongoing discussion on risk stratification,[2–4] there are limited real-world data on the long-term prognosis of patients with drug-induced type 1 Brugada ECG, and SCD risk predictors are still lacking for this subgroup.[5–7] Therefore, we aimed to characterize the clinical outcomes of patients with drug-induced type 1 Brugada ECG and to identify clinical parameters correlating with life-threatening arrhythmias in this population.

Methods

Patients and design

We considered 662 eligible consecutive patients with drug-induced type 1 Brugada ECG followed at 21 tertiary referral hospitals throughout the Italian and Swiss territories. All patients were diagnosed from July 1997 to May 2021. Follow-up was censored in December 2022. Patients with an ejection fraction of <35% (n = 5), patients diagnosed after malignant arrhythmias (n = 4), patients who did not attend their scheduled follow-up visit immediately after diagnosis (n = 29), and patients with incomplete data (n = 13) or withdrawn consent (n = 2) were excluded. A total of 606 patients with drug-induced type 1 Brugada ECG were finally included. The diagnosis of drug-induced type 1 ECG was established when a type 1 ECG pattern was revealed after a challenge test with flecainide (2 mg/kg over 10 minutes) or ajmaline (1 mg/kg over 5 minutes). The test was considered positive if a coved type 1 ECG ($\geq$2 mm) was documented in at least 1 of the right precordial leads (V_1 and V_2) placed at the second, third, or fourth intercostal spaces. *Family history of SCD* was defined as a history of sudden cardiac or unexplained death at <40 years of age in a family member. *Family history of BrS* was defined as the presence of BrS in a first- or second-degree relative. We categorized unexplained syncope as at least 1 syncope not

Abbreviations
BrS: Brugada syndrome
ECG: electrocardiographic
ICD: implantable cardioverter-defibrillator
IQR: interquartile range
PPV: positive predictive value
PVS: programmed ventricular stimulation
NPV: negative predictive value
SCD: sudden cardiac death
VF: ventricular fibrillation

distinctly attributed to vasovagal origin. Our programmed ventricular stimulation (PVS) protocol consisted of double and triple extrastimuli during basic pacing at 2 sites (right ventricular apex and right ventricular outflow tract) and 2 drives (600 and 400 ms). The coupling interval of the extrastimuli was decreased in 10-ms steps until reaching chamber refractoriness or a minimal coupling interval of 200 ms. The stimulation protocol was discontinued if ventricular fibrillation (VF) or sustained (30-second)/syncopal polymorphic ventricular tachycardia was induced. For patients receiving an implantable cardioverter-defibrillator (ICD), we collected the following data: date of implantation, ICD type (single-chamber, dual-chamber, or subcutaneous ICD), number of ICD replacement procedures, and ICD therapies, including antitachycardia pacing and shock (either appropriate or not). The study is in accordance with the Declaration of Helsinki and its later amendments and was approved by the local ethics committee. All patients provided informed consent to participate in the study.

Outcome events

The primary outcome event was a composite of appropriate ICD therapies (including appropriate ICD shock and antitachycardia pacing) and SCD. The secondary end point was all-cause mortality.

Statistical analysis

Categorical data are expressed as number (percentage), whereas continuous variables are expressed as either median (interquartile range [IQR]) or mean $\pm$ SD on the basis of their distribution as assessed by both the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Between-group differences for categorical variables were assessed using the χ^2 test because the sample size was >50 subjects, with the application of Yates correction, where appropriate. Either parametric Student *t* test or nonparametric Mann-Whitney *U* test and Wilcoxon test were instead used to compare continuous variables according to their distribution. Univariate and multivariate Cox regression models (stepwise method) were used to assess potential factors associated with the primary outcome event in the overall population. The multivariate model was computed on all covariates with a *P* value of <.10 by the univariate analysis. A subgroup analysis was performed for asymptomatic and symptomatic patients. The asymptomatic group included patients completely asymptomatic and those with vasovagal syncope; the symptomatic group included patients with syncope suspected to be of arrhythmic origin and those with unexplained syncope. Kaplan-Meier analyses were performed to assess the risk of primary outcome events for both

asymptomatic and symptomatic patients stratified according to PVS (positive, negative, not performed), and comparisons were performed using the log-rank test. We also computed the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PVS in predicting the primary outcome events in both symptomatic and asymptomatic subgroups. For all tests, a P value of <.05 was considered statistically significant. All analyses were performed using RStudio software (RStudio, Boston, MA).

Results

Overall population

We included 606 patients with drug-induced type 1 Brugada ECG (mean age 49.7 ± 14.7 years; 69.8% men) followed at our referral centers for a median follow-up duration of 60.3 months (IQR 23– 122.4 months). During the observation period, 19 patients (3.1%) experienced primary outcome events, which occurred over a median follow-up duration of 36 months (IQR 12.0–61.3 months). Notably, among these patients, 18 reported an appropriate ICD therapy for VF and 1 patient died suddenly (Online Supplemental Table 1). The median annual event rate was 0.5% (IQR 0.30%–0.5%) over 5 years and 0.25% (IQR 0.17%–0.46%) over 10 years. The overall mortality was 1.3% with no significant difference between patients with and without symptoms at presentation. Patients who developed ventricular arrhythmias during follow-up more likely reported unexplained syncope, inducible VF, and SCN5A mutation at presentation; moreover, they less frequently reported family history of BrS (Table 1).

In multivariable Cox regression analysis (Table 2), the presence of the SCN5A mutation at genetic testing was the only clinical variable independently associated with the primary outcome (hazard ratio 4.54; 95% confidence interval 1.30–15.90; P = .002) whereas a trend was observed for

unexplained syncope (hazard ratio 3.85; 95% confidence interval 0.99–14.95; P = .05).

Furthermore, the SCN5A mutation (97.5%), unexplained syncope (98.1%), and PVS positivity (98.4%) showed notably high NPVs. Eight of 606 patients (1.3%) died during follow-up: 1 patient (0.16%) who experienced an ICD shock eventually died of cancer and 7 patients (1.14%) (P = .13) who never developed ventricular arrhythmias died of various causes, including cancer (n = 2), vehicle crash (n = 2), traumatic work accident (n = 1), coronavirus disease 2019 (n = 1), or myocardial infarction (n = 1).

Subgroup analysis

Asymptomatic group

A total of 410 patients (67.7%) had no history of unexplained syncope at presentation. Among them, 369 patients (60.9%) were completely asymptomatic and 41 (6.8%) had a history of vagal syncope. Of these 410 patients, 241 (58.8%) underwent PVS (Online Supplemental Table 2). Over a median follow-up duration of 50.5 months (IQR 21.4–116.0 months), 8 patients (2.0%) reported appropriate ICD therapy; no patient died suddenly (Figure 1). The median time to ICD therapy was 13 months (IQR 7.5–45.5 months). The median annual event rate was 0.24% (IQR 0.0%–0.25%) over 5 years and 0.12% (IQR 0.0%–0.25%) over 10 years. In univariate Cox analysis, only SCN5A mutation was a clinical predictor for primary outcome events (Online Supplemental Table 3). Of the 8 patients who reported appropriate ICD therapy during follow-up, 6 underwent PVS and all showed inducible VF. The Kaplan-Meier analysis showed a significantly different risk of primary outcome events between asymptomatic patients stratified according to PVS (log-rank, P = .0001) (Figure 2A). In the asymptomatic group, PVS served as a predictor for primary outcome events with a sensitivity of 100%, a specificity of 74%, a PPV of 9%, and an NPV of 100%.

Table 1 Baseline characteristics of the overall study population divided according to the clinical outcome

Characteristic	Overall population (n = 606)	Primary outcome event group (n = 19)	No primary outcome event group (n = 587)	P
Male sex	423 (69.8)	13 (68.4)	410 (69.8)	.890
Age (y)	49.7 ± 14.7	48.6 ± 12.6	49.7 ± 14.7	.740
Family history of BrS	156 (25.7)	1 (5.3)	155 (26.4)	.04
Family history of SCD	197 (32.5)	5 (26.3)	192 (32.7)	.540
History of AF	43 (7.1)	3 (15.8)	38 (6.8)	.190
Sinus rhythm	590 (97.4)	18 (94.7)	572 (97.4)	.430
Left ventricular ejection fraction (%)	60 (60.0–61.0)	60 (56.3–60.0)	60 (60.0–61.0)	.420
Unexplained syncope not vasovagal syncope	196 (32.3)	11 (57.9)	185 (31.5)	.016
Vasovagal syncope	41 (6.8)	0 (0)	41 (7.0)	.235
PVS positivity	133/389 (34.2)	10/14 (71.4)	123/375 (32.8)	.003
SCN5A mutation	55/258 (21.3)	5/10 (50.0)	50/248 (20.2)	.027
ICD recipients	265 (43.7)	18 (94.7)	247 (42.1)	<.001
Follow-up duration (mo)	60.3 (23.0–122.4)	143 (105.3–165.3)	59.7 (23.0–119.0)	<.001
Time to event (mo)	–	36 (12–61.3)	–	–
Overall mortality	8 (1.3)	1 (5.3)	7 (1.2)	.126

Values are presented as mean ± SD, median (interquartile range), or n (%).
AF = atrial fibrillation; BrS = Brugada syndrome; ICD = implantable cardioverter-defibrillator; PVS = programmed ventricular stimulation; SCD = sudden cardiac death.

Table 2 Univariable and multivariable Cox regression models for the primary outcome in the study population

Parameter	Univariable analysis				Multivariable analysis			
	HR	95% CI		P	HR	95% CI		P
Age	0.98	0.95	1.02	.33				
Sex								
Male (reference)	1							
Female	1.18	0.45	3.11	.74				
Family history of SCD	0.71	0.25	1.97	.50				
Family history of BrS	0.32	0.04	2.4	.27				
History of unexplained syncope not vasovagal syncope	2.50	1.01	6.20	.049	3.85	0.99	14.95	.052
PVS positivity	3.76	1.17	12.06	.026				
SCN5A mutation	4.88	1.39	17.07	.013	4.54	1.30	15.90	.002
History of AF	1.79	0.51	6.30	.36				

AF = atrial fibrillation; BrS = Brugada syndrome; CI = confidence interval; HR = hazard ratio; PVS = programmed ventricular stimulation; SCD = sudden cardiac death.

Symptomatic group

A total of 196 patients (32.3%) had a history of unexplained syncope; in 182 patients (92.8%), syncope was considered to be suspected arrhythmic origin for the lack of prodromes or atypical presentation. One hundred forty-eight of these patients (75.5%) underwent PVS (Online Supplemental Table 4). Over a median follow-up duration of 78.5 months (IQR 30.4–136.5 months), 10 patients (5.1%) experienced appropriate ICD therapy for VF; 1 patient (0.5%) died suddenly (Figure 1). The median time to ICD therapy was 47.0 months (IQR 28.5–58.5 months). The median annual event rate was 0.52% (IQR 0.51%–1.05%) over 5 years and 0.52% (IQR 0.18%–0.53%) over 10 years. In univariable Cox analysis, there were no clinical predictors for primary outcome events (Online Supplemental Table 5). Of the 19 patients who reported appropriate ICD therapy during follow-up, 14 underwent PVS and 10 showed inducible VF. The Kaplan-Meier analysis did not show a significantly different risk of primary outcome events between symptomatic patients stratified according to PVS (log-rank, P = .983) (Figure 2B). In the symptomatic group, PVS served as a predictor for primary outcome events with a sensitivity of 50%, a specificity of 55.7%, a PPV of 6.1%, and an NPV of 95.1%.

Discussion

The main findings of the present study are the following: the median annual rate of life-threatening arrhythmias in patients with drug-induced type 1 Brugada ECG is 0.5% over 5 years and 0.25% over 10 years. In the overall population, the SCN5A mutation at genetic testing is the only independent
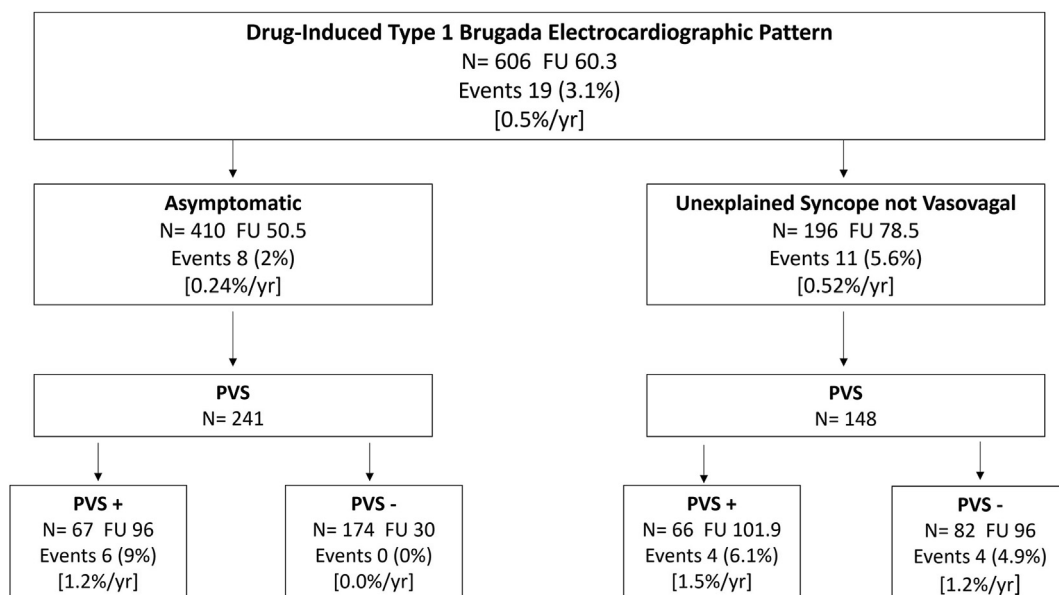
Figure 1
Median annual event rates over 5 years, first stratified according to the presence of symptoms and then according to PVS. FU = follow-up; PVS = programmed ventricular stimulation.
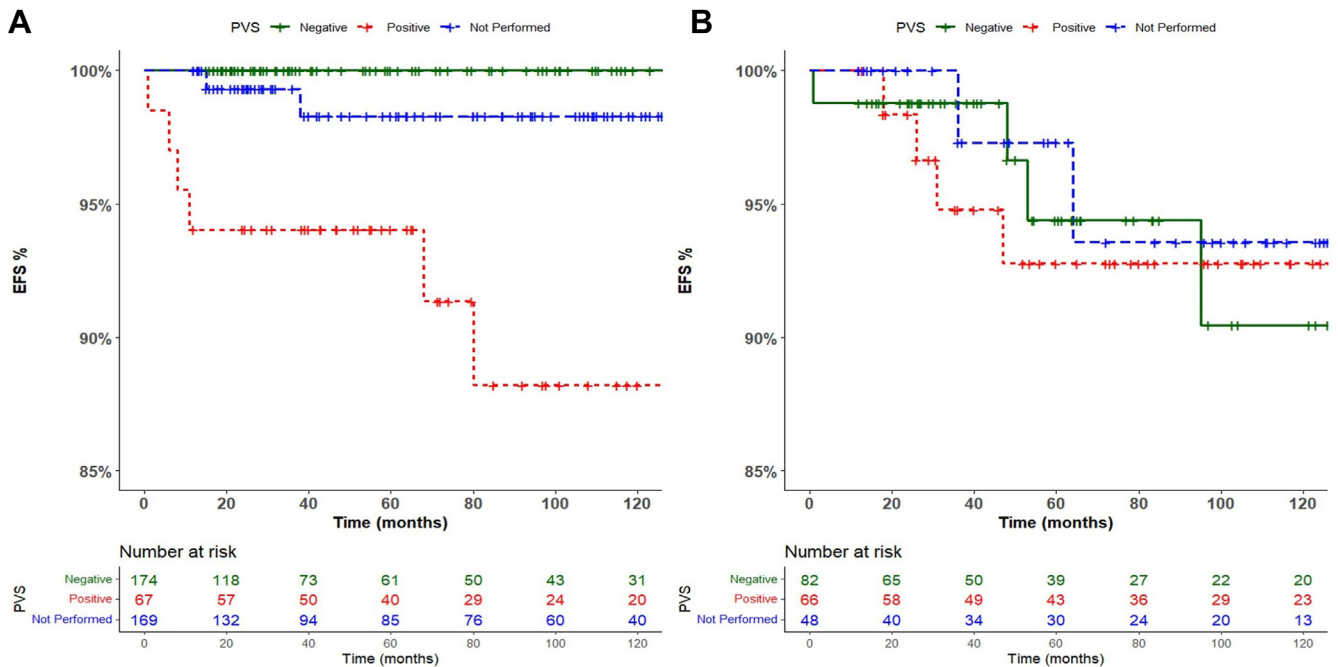
Figure 2
Kaplan-Meier curves comparing the survival from primary outcome events at 10 years in (**A**) asymptomatic and (**B**) symptomatic patients stratified according to PVS.
EFS = event-free survival; PVS = programmed ventricular stimulation.

predictor of life-threatening clinical events, including appropriate ICD therapy and SCD. The prevalence of unexplained syncope is high and seems to be associated with worse clinical outcomes. In patients who are asymptomatic at presentation, the median annual rate of life-threatening arrhythmias is 0.24% over 5 years; this rate increases to 1.2% in those who exhibit inducible VF during PVS.

In a recent meta-analysis by Rattanawong et al,[8] including 4099 patients with BrS (57.6% with drug-induced type 1 BrS ECG) sourced from 18 studies, with a mean follow-up duration of 4.5 years, the annual incidence of major arrhythmic events was 0.21% in those with drug-induced type 1 Brugada and no history of life-threatening arrhythmias. Our results showed a median annual rate of life-threatening arrhythmias of 0.5% over 5 years of follow-up but higher than previously reported.

Detection of an *SCN5A* gene mutation ranges from 11% to 28% in probands with BrS[9,10]; however, these percentages refer to cohorts that include both patients with spontaneous BrS and those with drug-induced BrS. We described a prevalence of *SCN5A* mutations of 20% at genetic testing in patients with drug-induced type 1 Brugada ECG; moreover, the *SCN5A* mutation was the only independent predictor of life-threatening arrhythmias in our study population. Our data confirm in this large cohort of patients with drug-induced type 1 Brugada ECG the results of a recent meta-analysis including 1780 patients with BrS from 17 studies; Chen et al[11] showed that the presence of *SCN5A* mutations was associated with an elevated risk of major arrhythmic events in both Asian and Caucasian populations. The association between the *SCN5A* mutation and worse prognosis may be related to the more pronounced electrophysiological

abnormalities, such as a larger epicardial arrhythmogenic substrate and more prolonged abnormal electrograms.[12–14]

Among the overall population, approximately one-third of patients had a history of unexplained syncope (not suggestive of vasovagal syncope), which correlated with worse clinical outcomes. As in previous studies,[15,16] 57.9% of those patients in our study who developed life-threatening arrhythmias during follow-up originally presented with syncope that was not thought to represent vagal syncope at their initial clinical evaluation. The clinical presentation of syncope may be not sufficient for distinguishing neurally mediated from arrhythmic syncope. Indeed, specific triggers and typical prodromes may be present in both forms of syncope in patients with channelopathies and may often precede nonarrhythmic syncope.[17,18] A careful comprehensive evaluation, including head-up tilt testing and PVS, aiming to exclude the correlation between arrhythmic events and clinical symptoms should be considered in the patient-centered care of subjects with drug-induced type 1 Brugada ECG.

Asymptomatic patients

In our study population, 67.7% of patients were asymptomatic at presentation. We included in this subgroup those with a history of typical vagal syncope because, in line with previous studies,[17,18] they exhibited a very low arrhythmic risk, comparable to that of completely asymptomatic patients. According to our findings, the median annual rate of life-threatening arrhythmias was 0.24% over 5 years, which increased to 1.2% in patients with inducible VF at PVS. PVS has been proposed as a method to enhance risk stratification of patients with BrS;

however, its role in risk stratification remains controversial, possibly because of the different patient populations (spontaneous and induced type 1 Brugada ECG) and the varying PVS protocols (double or triple extrastimuli) used across different studies. The most recent European guidelines[1] recommend to consider PVS for asymptomatic patients exhibiting a spontaneous type 1 Brugada ECG; however, no indication was provided for its use in those with drug-induced type 1 ECG. Our data suggest that PVS could be considered in asymptomatic patients with drug-induced type 1 Brugada ECG to improve SCD risk stratification.

Symptomatic patients

In our study population, 32.3% had a history of unexplained syncope not suggestive of vasovagal syncope. We included in this subgroup both patients with suspected arrhythmic syncope and those with unexplained syncope at comprehensive noninvasive evaluation since they showed a similar risk of arrhythmias.[19,20] According to our results, the median annual rate of life-threatening arrhythmias was 0.52% over 5 years and remained stable over 10 years. In this subgroup, VF inducibility at PVS did not significantly stratify the arrhythmic risk. Differently from a previous study that did not show ventricular events in patients with BrS and negative PVS,[21] our data suggest that a non-negligible residual risk remains in patients with unexplained syncope and negative PVS.

Clinical perspective

Based on these long-term follow-up data, our findings suggest that genetic testing for *SCN5A* mutations should be performed in all patients with drug-induced type 1 Brugada ECG to identify those at an increased risk of life-threatening arrhythmias. Moreover, PVS could be considered in asymptomatic patients with drug-induced type 1 Brugada ECG to improve SCD risk stratification, since patients with VF inducibility showed an increased annual risk of life-threatening arrhythmias. Finally, patients with unexplained syncope and negative PVS had a non-negligible residual arrhythmic risk in need of more careful monitoring.

Study limitations

First, the retrospective nature of the study did not permit the continuous monitoring of the overall study cohort, potentially resulting in the inclusion of patients experiencing intermittent spontaneous type 1 Brugada ECG. According to Gaita et al,[22] ∼10% of drug-induced type 1 ECGs develop a spontaneous type 1 ECG pattern during follow-up when evaluated with repeated 12-lead Holter recordings. In our study population, only 138 patients (22.8%) were followed with at least one 12-lead Holter yearly, and among them only, 3 patients showed an intermittent spontaneous type 1 Brugada ECG during a median follow-up duration of 84 months (IQR 66–114 months). Among the 19 patients who experienced the primary outcome event, the patient who died suddenly did not show spontaneous type 1 Brugada ECG at ECG evaluation, including 12-lead 24-hour Holter monitoring performed 2 months before the

event; the remaining 18 ICD recipients who reported appropriate ICD therapies did not show a spontaneous type 1 Brugada ECG at 12-lead ECG recordings performed 3 ± 1 months before the event or any changes in QRS morphology at the device-stored intracardiac electrograms. Second, patients who experienced the clinical events had a longer median follow-up duration than did those asymptomatic; however, the median time to clinical event was lower than the median follow-up time of the asymptomatic group, reducing the impact of the observation time on our results. Third, syncope is a prevalent symptom in the general population; hence, the reliance on historical data might have led to an overestimation of the arrhythmic pattern. Fourth, the retrospective nature of the analysis limited further evaluation of specific ECG abnormalities at baseline or during the drug provocative test and their potential evolution over time.[23,24] Lastly, despite being a multicenter study, only Italian centers and 1 Swiss center were encompassed in the analysis; consequently, the ability to extrapolate the findings to other ethnicities remains limited.

Conclusion

In a real-world setting of patients with drug-induced type 1 Brugada ECG, the annual risk of life-threatening arrhythmias is low, accounting for up to 0.5% at 5 years and 0.25% at 10 years but higher than previously reported. In unselected populations, the *SCN5A* mutation is the only indepedent predictor of life-threatening arrhythmias. Unexplained syncope correlates with worse clinical outcomes. The PVS positivity increases the annual risk of life-threatening arrhythmias over 5 years in asymptomatic patients with drug-induced type 1 Brugada ECG. A non-negligible residual arrhythmic risk remains in patients with unexplained syncope and negative PVS.

Appendix

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.01.015.

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