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Long-term prognosis of patients with an *SCN5A* loss-of-function variant and progressive cardiac conduction disorder or Brugada syndrome

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ABSTRACT

BACKGROUND The long-term prognosis of patients with a loss-of-function variant in the cardiac sodium channel gene *SCN5A* is unknown.

OBJECTIVE This study aimed to evaluate the long-term arrhythmic risk in patients with an *SCN5A* loss-of-function variant to identify predictors of arrhythmic events.

METHODS Probands and family members with (likely) pathogenic *SCN5A* loss-of-function variants were retrospectively included. Clinical and electrocardiographic data at baseline and last follow-up were collected. Patients with a history of cardiac arrest, sustained ventricular tachycardia, symptomatic or documented atrial tachy- or bradyarrhythmia, or arrhythmogenic syncope were categorized as symptomatic. Arrhythmic events at follow-up were defined as sudden death, aborted cardiac arrest, documented ventricular fibrillation, and/or sustained ventricular tachycardia.

RESULTS We included 615 patients (349 men, 242 probands, 157 with a spontaneous type 1 Brugada electrocardiogram, and 111 symptomatic at baseline). During a median follow-up of 9.5 (Q1,Q3 5.0–14.3) years, arrhythmic events occurred in 41 patients (6.7%), equating an overall event rate of 0.7%/y: 2.0%/y in symptomatic and 0.3%/y in asymptomatic patients. In the overall study population, symptoms at baseline, male sex, and QRS prolongation were identified as independent predictors of arrhythmic events. In asymptomatic patients, male sex and QRS prolongation were also identified as predictors. Asymptomatic women with QRS interval < 100 ms did not experience arrhythmic events at follow-up.

CONCLUSION Key predictors of arrhythmic risk in patients with an *SCN5A* loss-of-function variant, regardless of a Brugada syndrome diagnosis, are symptoms at baseline, male sex, and prolonged QRS interval. Our findings may enable more tailored management strategies in patients with an *SCN5A* loss-of-function variant based on their individual risk profiles.

KEYWORDS Brugada syndrome; *SCN5A*; Loss-of-function; $Na_v1.5$; Prognosis; Arrhythmic events

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Introduction

The *SCN5A* gene encodes the α-subunit of the cardiac sodium channel ($Na_v1.5$), which conducts the fast depolarizing sodium current (I_{Na}) in the heart. Pathogenic loss-of-function variants in *SCN5A* lead to I_{Na} decrease and can cause Brugada syndrome (BrS), progressive cardiac conduction disorder (PCCD), and more related phenotypes.[1] Commonly, a loss-of-function variant in *SCN5A* can be found when genetic testing is performed in a patient with an unexplained (aborted) cardiac arrest or syncope at rest or during sleep, particularly if accompanied by electrocardiographic (ECG) changes suggestive of BrS and/or PCCD. In addition, cascade screening has led to a growing number of (asymptomatic) carriers with an *SCN5A* loss-of-function variant, who may or may not display abnormalities on their resting ECGs. In BrS, *SCN5A* variant analysis may help in risk stratification, as patients with BrS and an *SCN5A* variant have been reported to have a higher risk of arrhythmic events than do patients without such a variant.[2] However, the long-term prognosis of carriers of an *SCN5A* loss-of-function variant, regardless of a BrS diagnosis, remains uncertain. While symptomatic patients may receive symptom-guided therapy according to expert consensus recommendations, current guidelines do not provide clear indications on how to manage asymptomatic patients with an *SCN5A* loss-of-function variant.[3] This has led to significant variability in their clinical management among cardiologists, even among those practicing in the same country. Treatment may vary from a conservative strategy restricted to periodic evaluation and behavioral recommendations to invasive approaches involving electrophysiology study (EPS) for risk stratification, prophylactic implantation of an implantable cardioverter-defibrillator (ICD), and occasionally even epicardial ablation of the Brugada substrate evoked by infusion of a sodium channel blocking agent.[4–6] In centers adopting a conservative approach, patients are routinely monitored every 1–3 years, which necessitates significant clinical resources and imposes a substantial psychosocial impact on both patients and their families.[7] On the contrary, invasive approaches may unnecessarily expose patients to risks of procedure-related complications while the necessity of these procedures may be questionable.[6] This study aimed to assess the arrhythmic risk in a large population of patients with an *SCN5A* loss-of-function variant, evaluated during a median follow-up of 9.5 (Q1,Q3 5.0–14.3) years. In addition, the study aimed to identify predictors of arrhythmic events at follow-up, with particular focus on asymptomatic patients.

Abbreviations

BrS: Brugada syndrome

ECG: electrocardiogram/electrocardiographic

EPS: electrophysiology study

ICD: implantable cardioverter-defibrillator

I_{Na}: sodium current

PCCD: progressive cardiac conduction disorder

SCBT: sodium channel blocker testing

SCD: sudden cardiac death

VF: ventricular fibrillation

VT: ventricular tachycardia

Methods

Study population

Consecutive patients who had undergone genetic testing in the Amsterdam University Medical Centers or the Centre Hospitalier Universitaire de Nantes between January 1996 and December 2022 and a pathogenic/likely pathogenic loss-of-function variant (ie, a class 4 or 5 variant according to the American College of Medical Genetics and Genomics classification[8]) in *SCN5A* was found were retrospectively included. A pathogenic/likely pathogenic variant was considered as a loss-of-function variant if (1) it was associated with BrS and/or PCCD in patients or (2) it was predicted to lead to haploinsufficiency, or (3) in the case of missense variants, functional evidence for loss-of-function effects was available. *SCN5A* variants in patients with long QT syndrome and/or with functional evidence for gain-of-function (or both gain-of-function and loss-of-function) effects were not included.[9] Patients were categorized as symptomatic at baseline (ie, at the time of genetic diagnosis) if they presented with or had a history of (1) aborted cardiac arrest, (2) symptomatic or sustained ventricular tachycardia (VT), (3) symptomatic and documented atrial tachy- or bradyarrhythmia, or (4) arrhythmogenic syncope. The research reported in this article adhered to the Helsinki Declaration as revised in 2013 and was approved by institutional medical ethics committees. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Genetic analysis of SCN5A

The methods and materials used for the genetic analysis of *SCN5A* have been described in the Online Supplement.

Management of patients

Baseline

Upon first clinical evaluation, patients with an *SCN5A* loss-of-function variant were all provided with behavioral recommendations, including avoidance of specific drugs and prompt treatment of fever.[10] Symptomatic patients were treated according to expert consensus recommendations available at the time of evaluation.[3,11–13] Sodium channel blocker testing (SCBT) and EPS for risk stratification were performed according to the clinical judgment of the treating physician and available institutional protocols at the time of diagnosis.

Follow-up

All patients underwent regular outpatient reevaluation every 1–3 years with reassessment of symptoms, family history, comorbidities, and medication use. Patients with pacemaker or ICD were followed at the pacemaker/ICD clinic every 6–12 months. As long as patients remained asymptomatic, no therapy was initiated.

Clinical data collection

Baseline data collected retrospectively from electronic health records included sex, age, indication for cardiac evaluation,

symptoms, family history of sudden cardiac death (SCD), data from SCBT and EPS (if performed), whether a device was implanted, and follow-up duration. Family history was considered positive for SCD in the case of (aborted) SCD during fever, during sleep, or while using BrS-aggravating drugs or in the case of unexplained SCD at the age of <45 years with a negative autopsy. Twelve-lead ECGs recorded at baseline and (if available) at follow-up were analyzed. The BrS ECG pattern was assessed according to the first consensus report criteria and subsequent updates and considered as type 1 if showing a coved-type ST-segment elevation of ≥2 mm followed by a negative T wave in ≥1 right-precordial leads, including recordings from the second and third intercostal spaces.[11–13] PCCD was defined as PQ interval > 200 ms, QRS interval > 120 ms, and/or sinus node dysfunction (ie, atrial standstill, symptomatic bradyarrhythmia, or sinus arrest of >3 seconds) without a BrS ECG pattern. Patients were considered to have an arrhythmic event during follow-up in the event of occurrence of sudden unexplained death, aborted cardiac arrest, documented ventricular fibrillation (VF), sustained VT, or appropriate ICD intervention for VT or VF.

Statistical analysis

Continuous variables were presented as mean ± SD or as median with first and third quartiles (Q1,Q3) on the basis of their distribution assessed using the Shapiro-Wilk test and were compared using the paired *t* test, Wilcoxon signed rank test, or Mann-Whitney *U* test, as appropriate. Categorical data were presented in number (percentage) and were compared using the χ^2 test, Fisher exact test, or McNemar test, as appropriate. Arrhythmic events were counted as the number of patients with an arrhythmic event. The arrhythmic event rate per year was used to compare the events between groups; statistical significance of the difference between 2 rates was expressed by rate ratio (RR), and the *P* value was calculated using the z test. Uni- and multivariable Cox proportional hazards regression models were used to assess whether variables at baseline were associated with the occurrence of arrhythmic events at follow-up. Covariates with a *P* value of <.20 after univariable analysis were assessed with the multivariable Cox proportional hazards regression analysis with and without backward selection and expressed as *P* values or hazard ratios (HRs). Analysis was corrected for family relatedness using a generalized estimation equations model for numerical and categorical data and a mixed effect Cox regression model for survival analysis. Survival curves and associated cumulative hazard curves were plotted using the Kaplan-Meier method and comparison between groups was performed using the log-rank test. A *P* value of <.05 was considered as statistically significant. All analyses were performed using IBM SPPS Statistics 28.0 (Armonk, NY) or RStudio 4.3.2 (Boston, MA).

Results

Baseline characteristics

The study population consisted of 615 patients. The clinical characteristics at baseline are displayed in Table 1. Functional evidence for *SCN5A* loss of function was found for 58 of the 93 missense variants (62.4%), representing 335 patients (Online Supplemental Table 1). At baseline, 111 patients (18.0%) were symptomatic and 504 (82.0%) asymptomatic (Table 1). Compared with asymptomatic individuals, patients with symptoms at baseline were more often probands, displayed more often a spontaneous type 1 BrS ECG, had longer PQ and QRS intervals, and received more often an ICD or pacemaker (for details, see Online Supplemental Table 2).

Arrhythmic events during follow-up

During a median follow-up of 9.5 (Q1,Q3 5.0–14.3) years, arrhythmic events occurred in 41 patients (6.7%) (Table 2)

Table 1 Clinical characteristics of the study population (N = 615) at baseline

Baseline characteristic	Value
Male sex	349 (56.7)
Proband	242 (39.3)
Age (y)	36 ± 18.5
Genetic characteristics	
Compound heterozygous	5 (0.8)
Missense variant	414 (67.3)
Nonsense variant	201 (32.7)
Reason for genetic testing	
Cardiac arrest or syncope	79 (12.8)
Family screening	378 (61.5)
Abnormal ECG	158 (25.7)
Symptomatic	111 (18.0)
Aborted cardiac arrest	21 (18.9)
Sustained VT	8 (7.2)
Sustained atrial tachyarrhythmia and/or bradyarrhythmia	34 (30.6)
Arrhythmogenic syncope	48 (43.3)
Asymptomatic	504 (82.0)
SCD in the family	190 (30.9)
BrS ECG pattern*	381 (62.0)
PCCD	134 (21.8)
ECG characteristics	
Heart rate (beats/min)	68 (60–78)
PQ interval (ms)	192 ± 36.0
QRS interval (ms)	104 (94–116)
QTc interval (ms)	409 (390–428)
Spontaneous type 1 BrS ECG	157 (25.5)
Fragmented QRS	127 (20.7)
Early repolarization	43 (7.0)
SCBT	249 (40.5)
Drug-induced type 1 ECG	231 (92.8)
EPS	137 (22.3)
Inducible VT/VF during EPS	56 (40.9)
Device implantation	144 (23.4)
ICD	122 (84.7)
Pacemaker	22 (15.3)

Values are presented as mean ± SD, median (Q1,Q3), or n (%).
BrS = Brugada syndrome; ECG = electrocardiogram/electrocardiographic; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; PCCD = progressive cardiac conduction disorder; Q1,Q3 = first and third quartiles; QTc = QT interval corrected for heart rate using the Bazett formula; SCBT = sodium channel blocker testing; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.
*Either spontaneous or drug-induced.

Table 2 Arrhythmic events at follow-up

Variable	All patients (N = 615)	Symptomatic at baseline (n = 111)	Asymptomatic at baseline (n = 504)	P*
Follow-up duration (y)	9.5 (5.0–14.3)	11.8 (6.3–16.1)	9.1 (4.9–13.7)	<.001
Arrhythmic events	41 (6.7)	26 (23.4)	15 (3.0)	<.001
Sudden death or aborted cardiac arrest	4	0	4	
Appropriate ICD shock	25	18	7	
Ventricular arrhythmias	12	8	4	
Time till arrhythmic events (mo)	51 (15–130)	26 (12–96)	115 (18–144)	.100

Values are presented as median (Q1,Q3) or n (%).
ICD = implantable cardioverter-defibrillator; Q1,Q3 = first and third quartiles.
*Symptomatic vs asymptomatic.

with an annual event rate of 0.7%. The mean age at the time of arrhythmic event was 44 ± 16 years. The baseline characteristics of patients with or without an arrhythmic event at follow-up are presented in Online Supplemental Table 3. Compared with those without events at follow-up, patients with events were more often men (80.5% vs 55.1%; $P = .003$), probands (70.7% vs 37.1%; $P < .001$), and symptomatic at baseline (63.4% vs 14.8%; $P < .001$). Moreover, patients with events at follow-up had longer PQ intervals (202 ms vs 191 ms, respectively; $P = .049$), longer QRS intervals (115 ms vs 104 ms, respectively; $P < .001$), and more often a spontaneous type 1 BrS ECG (53.7% vs 23.5%, respectively; $P < .001$) than did patients without events.

Univariable analysis in the overall study population identified symptoms at baseline (HR 8.33; 95% confidence interval [CI] 4.29–16.10; $P < .001$), proband status (HR 3.42; 95% CI 1.74–6.76; $P < .001$), male sex (HR 3.16; 95% CI 1.45–6.85; $P = .004$), spontaneous type 1 BrS ECG (HR 2.97; 95% CI 1.60–5.50; $P < .001$), and QRS interval (HR 1.03; 95% CI 1.02–1.04; $P < .001$) as predictors of arrhythmic events at follow-up (Table 3). Multivariable Cox proportional hazards regression analysis identified symptoms at baseline (HR 6.78; 95% CI 3.30–13.95; $P < .001$), male sex (HR 2.84; 95% CI 1.14–7.03; $P = .024$), and QRS interval (HR 1.03; 95% CI 1.01–1.05; $P < .001$) as independent predictors of arrhythmic events at follow-up (Table 3). Kaplan-Meier analysis showed a significantly higher risk of events at follow-up for patients with vs those without symptoms at baseline ($P < .001$) (Figure 1A), for men vs women ($P = .002$) (Figure 1B), and for patients with prolonged QRS interval vs those without (>120 ms vs 100–120 ms vs <100 ms; $P < .001$) (Figure 1C).

Arrhythmic events during follow-up in patients with or without symptoms at baseline

During follow-up, 26 arrhythmic events occurred in patients with symptoms at baseline (23.4%) and 15 occurred in patients without symptoms at baseline (3.0%) ($P < .001$). The annual event rate was 2.0% in symptomatic and 0.3% in asymptomatic patients (RR 6.1; 95% CI 3.2–11.7; $P < .001$). The mean age at the time of arrhythmic event was 41 ± 16 years in symptomatic and 51 ± 15 years in asymptomatic patients ($P = .058$). The follow-up duration was longer in patients

Table 3 Uni- and multivariable analyses for the occurrence of arrhythmic events at follow-up in the overall study population

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	P	HR (95% CI)	P
Age at presentation	1.01 (0.99–1.03)	.357		
Male sex	3.16 (1.45–6.85)	.004	2.84 (1.14–7.03)	.024
Proband	3.42 (1.74–6.76)	<.001	1.31 (0.57–2.98)	.520
Nonsense variant	1.85 (0.97–3.55)	.064	1.42 (0.70–2.87)	.330
Symptomatic	8.33 (4.29–16.10)	<.001	6.78 (3.30–13.95)	<.001
SCD in the family	0.44 (0.20–0.96)	.038	0.61 (0.27–1.40)	.250
Heart rate	1.00 (0.98–1.02)	.970		
PQ interval	1.01 (1.00–1.01)	.233		
QRS interval	1.03 (1.02–1.04)	<.001	1.03 (1.01–1.05)	<.001
QTc interval	1.01 (1.00–1.01)	.140	1.00 (0.99–1.01)	.600
Spontaneous type 1 BrS ECG	2.97 (1.60–5.50)	<.001	1.65 (0.78–3.49)	.190
Fragmented QRS	1.19 (0.58–2.42)	.640		
Early repolarization	1.36 (0.48–3.90)	.560		
Inducible VT/VF during EPS	0.77 (0.30–2.05)	.610		

BrS = Brugada syndrome; CI = confidence interval; ECG = electrocardiogram; EPS = electrophysiology study; HR = hazard ratio; QTc = QT interval corrected for heart rate using the Bazett formula; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

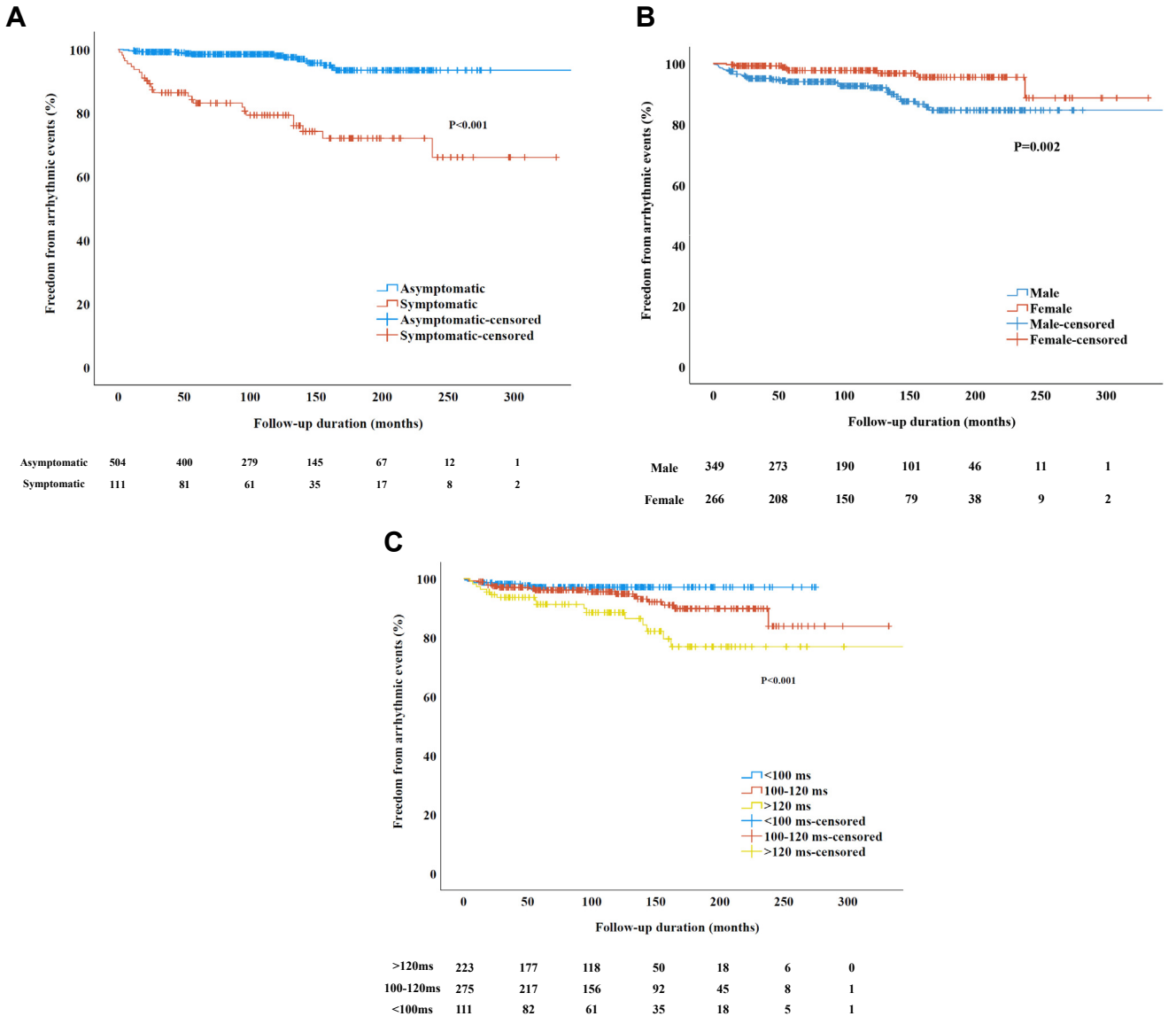

Figure 1
Kaplan-Meier curves comparing freedom from arrhythmic events at follow-up are shown (**A**) for patients with symptoms ("symptomatic") vs patients without symptoms ("asymptomatic") at baseline, (**B**) for men vs women, and (**C**) for patients with different QRS intervals, that is, QRS interval <100 ms vs QRS interval 100–120 ms vs QRS interval >120 ms.

with symptoms than in those without symptoms at baseline ($P < .001$). The time until arrhythmic event did not differ between the groups (Table 2).

As symptoms at baseline was an independent predictor of arrhythmic events during follow-up, we separately performed uni- and multivariable Cox proportional hazards regression analysis in patients without symptoms at baseline to find predictors for arrhythmic events in this subgroup. Univariable analysis identified male sex (HR 4.97; 95% CI 1.12–22.00; $P = .035$), spontaneous type 1 BrS ECG (HR 3.04; 95% CI 1.10–8.42; $P = .033$), longer QRS interval (HR 1.03; 95% CI 1.01–1.04; $P = .004$), and longer corrected QT interval (HR 1.01; 95% CI 1.00–1.02; $P = .009$) as predictors of events at follow-up. Multivariable analysis identified male sex (HR 5.44; 95% CI 1.17–25.38; $P = .031$) as an independent predictor of arrhythmic events (Online Supplemental Table 4). The backward selection method also identified longer QRS interval (HR 1.03; 95% CI 1.01–1.05; $P = .005$) as a predictor of arrhythmic events along with male sex (HR 5.27; 95% CI 1.15–24.09; $P = .032$).

Figure 2A compares annual event rates in 4 subgroups of patients without symptoms at baseline: men with QRS interval $\geq$ 100 ms (n = 197 patients; 0.59%/y), men with QRS interval < 100 ms (n = 85 patients; 0.27%/y), women with QRS interval $\geq$ 100 ms (n = 114 patients; 0.19%/y), and women with QRS interval < 100 ms (n = 107 patients; 0%/y). Figure 2B compares the cumulative hazard curves from the Kaplan-Meier survival functions in these 4 groups.

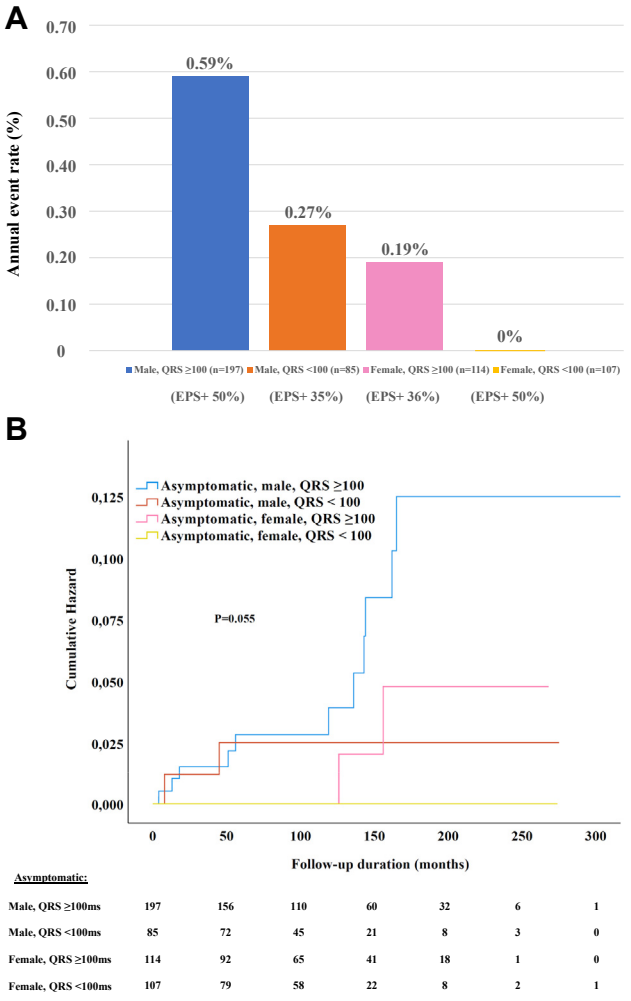

Figure 2
Arrhythmic events in subgroups of patients without symptoms at baseline. The (**A**) annual event rates and (**B**) cumulative hazard curves are shown for men and women who were asymptomatic at baseline and with QRS interval <100 ms or ≥100 ms. The percentages at the bottom of **A** represent the proportion of patients per subgroup with inducible ventricular tachycardia/ventricular fibrillation during the electrophysiology study (ie, electrophysiology study positive).

Value of EPS in risk stratification

EPS was performed in 137 patients. Of the 56 patients in whom VT/VF could be induced, 7 (12.5%) suffered from an arrhythmic event at follow-up, while of the 81 patients in whom no VT/VF was induced, 12 (14.8%) experienced an arrhythmic event ($P = .700$). VT/VF inducibility was not identified as a predictor of arrhythmic events at follow-up in the overall study population ($P = .610$) (Table 3) or in the subgroup without symptoms at baseline ($P = .280$) (Online Supplemental Table 4).

In addition, the proportion of patients with EPS-induced VT/VF was not different between the 4 subgroups of patients without symptoms at baseline: men with QRS interval ≥ 100 ms (28 of 56 patients who underwent EPS [50%]), men with QRS interval < 100 ms (7 of 20 patients [35%]), women with QRS interval ≥ 100 ms (5 of 14 patients [36%]), and women with QRS interval < 100 ms (4 of 8 patients [50%]) (Figure 2A).

Subgroup analysis in patients with a BrS ECG pattern

To evaluate the long-term arrhythmic risk in patients with an *SCN5A* loss-of-function variant *and* BrS, we performed a subgroup analysis in 381 patients with a documented type 1 BrS ECG pattern (157 spontaneous and 224 drug-induced). During a median follow-up of 10.7 (7.0–15.8) years, arrhythmic events occurred in 34 patients (8.9%) with an annual event rate of 0.8% (Online Supplemental Table 5). The annual event rate was 2.0% in symptomatic and 0.4% in asymptomatic patients with BrS *and* an *SCN5A* loss-of-function variant (RR 4.4; 95% CI 2.2–8.8; $P < .001$). Univariable analysis identified symptoms at baseline (HR 5.48; 95% CI 2.76–10.86; $P < .001$), male sex (HR 3.45; 95% CI 1.34–8.92; $P = .011$), nonsense variant (HR 2.26; 95% CI 1.15–4.44; $P = .019$), longer QRS interval (HR 1.05; 95% CI 1.03–1.06; $P < .001$), and spontaneous type 1 BrS ECG (HR 2.55; 95% CI 1.26–5.16; $P = .009$) as predictors of events during follow-up. Multivariable analysis identified symptoms at baseline (HR 5.27; 95% CI 2.58–10.77; $P < .001$), male sex (HR 3.18; 95% CI 1.14–8.89; $P = .027$), and longer QRS interval (HR 1.05; 95% CI 1.02–1.07; $P < .001$) as independent predictors of events (Online Supplemental Table 6).

Subgroup analysis in patients with PCCD

We also performed a subgroup analysis in patients with a PCCD phenotype. In total, 134 patients had PCCD (Table 1), in whom 5 arrhythmic events (3.7%) occurred during a median follow-up of 8.8 (4.0–12.8) years (Online Supplemental Table 7). The annual event rate was 1.4% in symptomatic patients and 0.1% in asymptomatic patients (RR 12.6; 95% CI 1.6–312.9; $P = .014$). Univariable analysis identified proband status (HR 21.47; 95% CI 2.39–192.79; $P = .006$), symptoms at baseline (HR 14.31 [1.59–128.65]; $P = .018$), longer QRS interval (HR 1.03; 95% CI 1.00–1.06; $P = .031$), and longer corrected QT interval (HR 1.03; 95% CI 1.01–1.05; $P = .003$) as predictors of events during follow-up in patients with PCCD. After multivariable analysis, none of these variables were identified as independent predictors of events (Online Supplemental Table 8).

QRS interval during follow-up

Since longer QRS interval at baseline was identified as an independent predictor of arrhythmic events, we studied whether QRS prolonged more significantly in patients with arrhythmic events at follow-up. To do this, we compared baseline ECGs with ECGs recorded at the last follow-up visit. Twelve-lead ECGs at the last follow-up visit were available for 305 patients. The median time difference between the first and the last ECG was 6.9 (3.8–10.9) years. The change in QRS interval during follow-up was not different between patients with (n = 12) and without (n = 293) arrhythmic events at follow-up ($P = 0.295$) (Online Supplemental Table 9). In patients with arrhythmic events at follow-up, the median QRS interval at baseline and follow-up was 133 (112–142) and 130 (116–173) ms, respectively ($P = .099$). In patients without

arrhythmic events at follow-up, the median QRS interval at baseline and follow-up was 108 (97–120) and 112 (100–123) ms, respectively ($P < .001$).

Subgroup analysis based on the type of SCN5A variant and functional evidence for loss of function

Since functional evidence for loss of function effects was available only for 58 of 93 missense variants (62.4%), we compared patients carrying variants with predicted haploinsufficiency *and* missense variants with evidence for loss of function effects (as 1 group) with patients carrying missense variants without evidence for loss of function effects. We did not find any differences in arrhythmic event rates between the 2 groups, neither in the overall study cohort (Online Supplemental Table 10) nor after excluding patients with PCCD (Online Supplemental Table 11).

Discussion

This study evaluated the long-term arrhythmic risk in 615 patients with a loss-of-function variant in *SCN5A*, including 111 symptomatic and 504 asymptomatic patients at the time of genetic diagnosis, and revealed several key findings with significant clinical implications.

Arrhythmic risk and predictors of arrhythmic events in the overall study population

During a median follow-up of 9.5 years, we observed a 6.7% incidence of arrhythmic events in the study population, equating to an annual event rate of 0.7%. Symptomatic patients at baseline exhibited a significantly higher annual event rate (2.0%) than did asymptomatic patients (0.3%), emphasizing the importance of symptom status as a primary risk stratifier. Univariable analysis identified symptoms at baseline, proband status, male sex, spontaneous type 1 BrS ECG, and QRS interval as predictors of arrhythmic events. However, multivariable analysis identified symptom status at baseline, male sex, and QRS interval as independent predictors. The association of male sex with higher arrhythmic risk aligns with previous studies, indicating sex-specific differences in BrS phenotypic expression and arrhythmic susceptibility.[14] Identification of QRS prolongation as a predictor of arrhythmic events suggests that intraventricular conduction delay reflects a substrate prone to arrhythmias and supports earlier observations of its prognostic value in inherited arrhythmia syndromes.[15,16]

Interestingly, while in our study population patients with arrhythmic events at follow-up were more often probands, had longer PQ intervals, and displayed more often a spontaneous type 1 BrS ECG (Online Supplemental Table 3), these parameters were not identified as independent predictors of arrhythmic events. In contrast to our results, proband status and spontaneous type 1 BrS ECG are well-recognized risk factors for arrhythmic events in BrS.[17,18] With regard to proband status, this may be because of the composition of our study population, with most probands (163 of 242 [67.4%]) being asymptomatic at baseline. With regard to spontaneous type 1 BrS ECGs, it may be possible that it less well represents arrhythmic risk in patients with an *SCN5A* loss-of-function variant than in patients with BrS, because *SCN5A* loss-of-function variants cause conduction delay in the whole heart and not only in the right ventricular outflow tract. Consequently, QRS prolongation may better represent arrhythmic risk in these patients than ST-segment elevation in the right precordial leads. This notion is supported by the identification of QRS prolongation as opposed to a spontaneous type 1 BrS ECG as an independent predictor of arrhythmic events at follow-up in our study population.

Our subgroup analysis in patients with a documented type 1 BrS ECG pattern showed a comparable event rate (0.8%/y) as in the overall study population (0.7%/y). Moreover, QRS prolongation (along with symptoms and male sex) was identified as an independent predictor of arrhythmic events in this subgroup. This supports the importance of QRS prolongation as a predictor of arrhythmic events in patients with an *SCN5A* loss-of-function variant, regardless of the presence of type 1 BrS ECG pattern.

Of note, the arrhythmic event rate in patients with BrS and an *SCN5A* loss-of-function variant was lower in our study than in previous reports.[2,19,20] However, this may be explained by differences in baseline characteristics between the study cohorts, including more probands,[19] more patients with a spontaneous type 1 BrS ECG, and more patients with symptoms at baseline in earlier studies than in our study.[19,20] These characteristics have been associated with a worse prognosis in BrS[2] and may at least partially explain the differences in arrhythmic event rates between our study and previous reports.

Asymptomatic patients and risk stratification

While the risk of arrhythmic events in asymptomatic patients was numerically low (0.3%/y), it is clinically relevant because of the young age and long life-expectancy of these patients and because the first symptom may be sudden death or aborted cardiac arrest (as was the case in 4 patients in this study who were not protected by an ICD). Therefore, risk stratification remains extremely important. Multivariable analysis identified male sex and QRS interval as independent predictors of arrhythmic events in asymptomatic patients. Accordingly, men with prolonged QRS had the highest risk of arrhythmic events at follow-up while women with normal QRS interval were at lowest risk (Figure 2). In fact, no arrhythmic events occurred during follow-up in asymptomatic women with normal QRS interval.

Implication for clinical management

Our findings may aid in managing patients with *SCN5A* loss-of-function variants through a more nuanced approach, by taking into consideration individual risk factors such as symptom status, sex, and QRS interval, thereby optimizing the use of resources while minimizing unnecessary interventions. For patients with symptoms at the time of diagnosis, our results underscore the necessity for more aggressive management. For example, in men with an *SCN5A* loss-of-function variant, arrhythmogenic syncope, and prolonged QRS additional

diagnostic tests, such as repeated Holter recordings or implantation of an implantable loop recorder, should be considered and prophylactic ICD implantation may be considered. Conversely, asymptomatic patients might be managed conservatively with lifestyle modifications and periodic evaluations with varying intervals (eg, every 1–5 years) depending on their sex and QRS interval (<100 ms or ≥100 ms). Asymptomatic women with QRS interval < 100 ms are at the lowest risk of arrhythmic events and should not undergo invasive risk stratification or therapeutic procedures.

Importantly, induction of VT/VF during EPS was not identified as a predictor of arrhythmic events in our study, which contrasts with previous findings in asymptomatic patients with a BrS ECG pattern.[21] This may be due to the low number of patients who had undergone EPS in our study or because patients who underwent EPS were not at high risk of arrhythmic events as initially assumed, thereby rendering the higher risk of false-positive findings. However, the performance of EPS in asymptomatic patients was not better in those with high-risk features (men with QRS interval ≥ 100 ms) than in those without risk features (women with QRS interval < 100 ms). These findings highlight the need for better risk stratification tools in asymptomatic men with an *SCN5A* loss-of-function variant, especially those with QRS interval ≥ 100 ms.

Limitations

Our study has several limitations, including its retrospective design and potential selection bias, given that only patients from 2 tertiary referral centers were included. In addition, the reliance on electronic health records for data collection may have introduced information bias. In this regard, because of the well-known fluctuations of the BrS ECG pattern, we may have underestimated the presence of a spontaneous type 1 BrS ECG during follow-up. Although in a subset of patients, of whom ECGs at the last follow-up visit were evaluated, we did not find a higher incidence of spontaneous type 1 BrS ECGs in patients with vs those without arhythmic events at follow-up, we cannot exclude the presence of a spontaneous type 1 BrS ECG before the occurrence of the arrhythmic event. Furthermore, patients with PCCD did not undergo systematic SCBT, which may also contribute to missing patients who could actually have BrS. Moreover, the heterogeneity in follow-up duration and the evolution of management strategies over the study period may have affected the findings. In addition, the risk of arrhythmic events may have been underestimated in symptomatic patients as we did not take into consideration the effect of therapeutic interventions in this group during follow-up.

Finally, functional evidence for loss of function (I_{Na} reduction) was available for 62.4% of missense variants, and some of the variants have been previously associated with pleiotropy or overlap phenotypes.[22] Nevertheless, we did not include patients with long QT syndrome and *SCN5A* variants with functional evidence for gain of function (or both gain of function and loss of function). In addition, missense variants without functional evidence available were included only if they were associated with BrS and/or PCCD or were predicted to lead to haploinsufficiency. However, importantly, comparing variants with predicted haploinsufficiency *and* missense variants with functional evidence for loss of function effects vs missense variants without evidence for loss-of-function effects, did not show a significant difference in arrhythmic event rates. Moreover, type of *SCN5A* variant (missense or nonsense) was not identified as a predictor of arrhythmic events in the study population, suggesting similar effects of the different variant types on phenotypic expressivity and disease severity.

Conclusion

This study provides insights into the long-term arrhythmic risk in patients with *SCN5A* loss-of-function variants, with an annual event rate of 2.0%/y in patients with symptoms at the time of diagnosis and an annual event rate of 0.3% in asymptomatic patients. Symptom status, male sex, and prolonged QRS are key predictors of arrhythmic events, suggesting that these factors may guide risk stratification and management decisions. While symptomatic patients, particularly men with prolonged QRS, warrant a more aggressive approach, a tailored and more nuanced approach for asymptomatic patients, based on their individual risk profiles, should be followed. In particular, women with normal QRS interval can be reassured and reevaluated with long intervals.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.10.057.

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