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CLINICAL RESEARCH
Genetics

Catecholaminergic polymorphic ventricular tachycardia mediated by ryanodine receptor 2: a validated risk stratification

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Abstract

Background and Aims Patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) are at risk for potentially life-threatening arrhythmic events (AEs) even while treated with β-blockers. The aim was to develop a model for individualized prediction of AEs in patients with *RYR2*-mediated CPVT on β-blocker monotherapy.

Methods The derivation and independent validation cohorts included 743 and 129 patients, respectively. AEs were defined as arrhythmic syncope, appropriate implantable cardioverter–defibrillator shock, sudden cardiac arrest (SCA), and sudden cardiac death. Near-fatal or fatal AEs (nf/fAEs) included all AEs except for arrhythmic syncope. Prediction models using Cox regression were developed and internally and externally validated.

Results A total of 102 (13.7%) patients in the derivation cohort and 24 (18.6%) patients in the validation cohort experienced ≥1 AE over a median follow-up of 5.1 [interquartile range (IQR), 7.7] and 2.4 (IQR, 4.4) years, respectively. Predictors of AE were arrhythmic syncope or SCA prior to diagnosis and age at β-blocker initiation. In the derivation and validation cohorts, the optimism-corrected C-indices of the models for AE were 0.67 [95% confidence interval (CI) 0.62–0.72] and 0.59 (95% CI 0.48–0.71), respectively. For nf/fAEs, ventricular arrhythmia severity before β-blocker initiation was a fourth independent predictor, and C-indices of the models in the derivation and validation cohorts were 0.74 (95% CI 0.68–0.80) and 0.60 (95% CI 0.47–0.72), respectively. In the derivation cohort, calibration slopes were 1.00 (95% CI 0.59–1.41) for AE and 1.00 (95% CI 0.69–1.32) for nf/fAE.

Conclusions These externally validated risk prediction models using clinical parameters accurately distinguished CPVT patients on β-blocker monotherapy at low and high risk for future AEs while treated with β-blockers. These models provide guidance for implementation of clinical management therapies to prevent AEs in patients with CPVT.

Structured Graphical abstract

Key Question

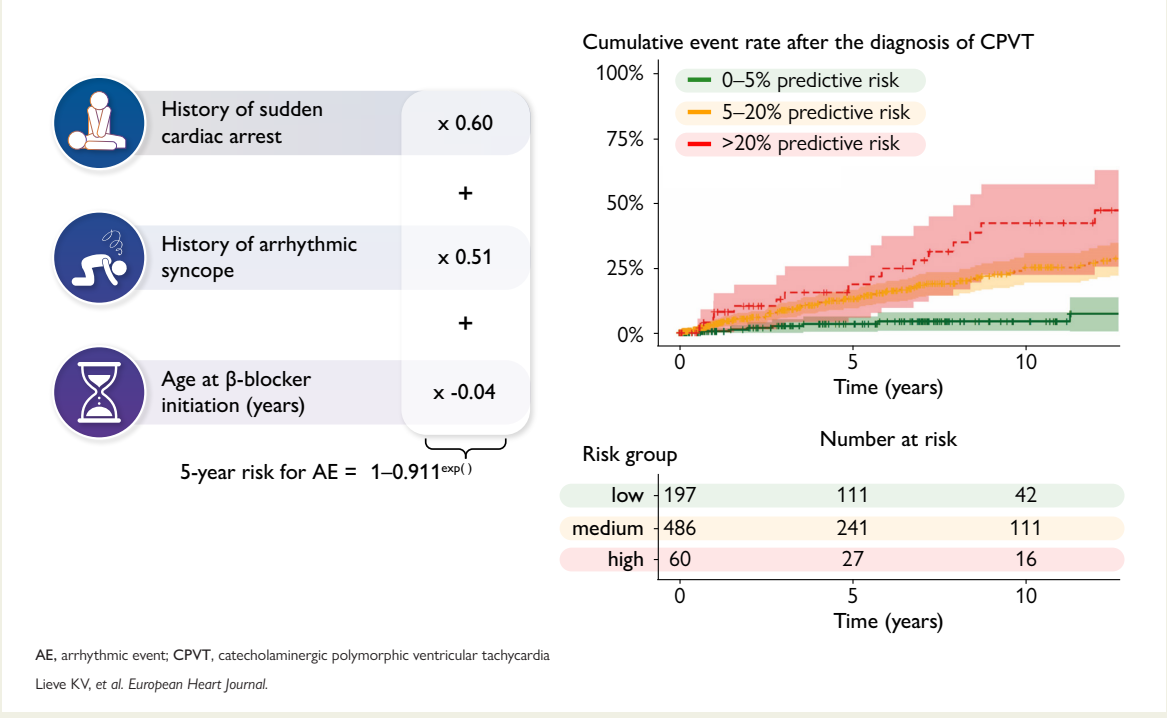
How should clinicians assess the risk of arrhythmic events (AEs) in patients with genetically-confirmed, *RYR2*-mediated catecholaminergic polymorphic ventricular tachycardia (CPVT) who are treated with β-blockers?

Key Finding

Three readily available clinical parameters were included in a novel CPVT risk prediction model: history of sudden cardiac arrest or arrhythmic syncope and age at β-blocker initiation. The model made it possible to accurately classify patients as low, intermediate, or high risk.

Take Home Message

This newly derived risk calculator for prediction has the potential to guide patient management after the diagnosis of CPVT.



AE, arrhythmic event; CPVT, catecholaminergic polymorphic ventricular tachycardia

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AE, arrhythmic event; CPVT, catecholaminergic polymorphic ventricular tachycardia

Keywords Catecholaminergic polymorphic ventricular tachycardia • β-Blockers • Risk stratification • Sudden cardiac death • Ventricular arrhythmias

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an uncommon genetic arrhythmia syndrome characterized by exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients without significant resting ECG abnormalities and structural cardiac abnormalities.[1] Patients typically present at a young age with syncope or sudden cardiac arrest (SCA) triggered by emotion or exercise.[2] Timely recognition is of vital importance since CPVT is an important cause of sudden cardiac death (SCD) in young adults with a normal autopsy.[3,4] Therapy with β-blockers has been the cornerstone of medical therapy for decades. At present, most patients with CPVT are treated with β-blocker monotherapy. Guidelines recommend adding flecainide or performing left cardiac sympathetic denervation (LCSD) in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional ventricular ectopy, while on β-blockers at the highest tolerated dose.[5]

Due to the rarity of the disease, limited data are available to predict which CPVT patient will have an arrhythmic event (AE) after the diagnosis is made and β-blocker therapy is initiated,[6–9] and risk stratification is poorly defined. Identifying predictors for AEs in patients treated with β-blocker monotherapy is important in decision-making about initiation of second-line add-on therapies, in particular flecainide[10] and LCSD.[11,12]

The objective of this study was to develop and validate a model including clinical and genetic characteristics for individualized prediction of post-diagnosis AEs in patients with genetically confirmed, *RYR2*-mediated CPVT who are treated with β-blockers.

Methods

Study population

The derivation cohort was derived from the International CPVT Registry which was established in 2014 at Amsterdam UMC in collaboration with

31 centres across 20 countries. Patients were included in the Registry on the basis of previous expert consensus guidelines for the diagnosis of CPVT,[13] which are similar to current guidelines.[5] The Registry included patients in whom CPVT had been diagnosed between 1963 (clinical diagnosis of adrenergically-mediated polymorphic ventricular tachycardia) and 2023. When eligibility for inclusion was uncertain, cases were reviewed by members of the core team of investigators in Amsterdam to reach consensus. More details regarding design, data collection, and management are described in the Supplementary data online, Methods.

For the current study, we included patients with CPVT who were treated with β-blocker monotherapy and with variants in the *RYR2*-encoded cardiac ryanodine receptor that were classified as either a 'variant of uncertain significance' (VUS), 'likely pathogenic' variant, or 'pathogenic' variant according to the American College of Medical Genetics and Genomics (ACMG) criteria.[14] Genetic analysis was performed at the local institution or through commercial genetic testing platforms. Patients who harboured a VUS in *RYR2* had to have a phenotype compatible with CPVT, i.e. a progressive ventricular ectopy burden and complexity during exercise stress test (EST) or provocation tests. In addition, patients had to be <65 years old at diagnosis and had to have a follow-up period of at least 7 days. We excluded patients with a *RYR2* exon 3 deletion, because these variants have been associated with a complex phenotype including noncompaction cardiomyopathy,[15] patients with multiple likely pathogenic or pathogenic *RYR2* variants, and patients with a known *RYR2* loss-of-function variant associated with calcium release deficiency syndrome. In addition, patients with significant structural heart disease, defined as left ventricular ejection fraction <40% (unless this was due to a reversible cause such as a tachycardiomyopathy), (a history of) significant coronary artery stenosis, moderate to severe valvular stenosis or regurgitation (excluding tricuspid regurgitation), evidence of cardiomyopathy, or congenital heart disease with significant haemodynamic consequences, were excluded.

The external validation cohort involved patients meeting similar inclusion and exclusion criteria from the International Pediatric CPVT Registry.[2,8] The International Pediatric CPVT Registry was established in 2015 and is an international multicentre registry of paediatric patients diagnosed with CPVT <19 years of age and included patients from 33 centres, affiliated with the Pediatric and Congenital Electrophysiology Society, at the time of this study.

This study conformed to the Declaration of Helsinki. Data were collected in accordance with regulations set forth by local institutional review boards. At all participating centres institutional review board approval and informed consent were obtained if needed for this type of research. From the present study comprising 743 patients in the derivation cohort and 129 patients in the validation cohort, some have been reported in previously published studies.[2,7,8,10,16–18]

Clinical endpoints and follow-up

We defined two primary composite endpoints: (1) AEs and (2) near-fatal or fatal AEs (nf/fAEs). AEs were defined as (presumed) arrhythmic syncope, appropriate implantable cardioverter–defibrillator (ICD) shock, SCA, and SCD. The nf/fAEs included all AEs except for syncope. Definitions are detailed in Supplementary data online, *Table S1*.

Follow-up time was calculated for each patient as the time between the date of β-blocker therapy initiation to the date of their first AE or nf/fAE on β-blocker monotherapy, date of non-CPVT-related death, date of last contact, or the date at which a new CPVT-related therapy was initiated (i.e. flecainide or LCSD), whichever occurred first.

Statistical analysis

All statistical analyses were performed using R version 4.2.3 (The R Project for Statistical Computing). To determine a normal distribution, continuous variables were visually inspected using a histogram and tested for normal distribution using the Wilk–Shapiro test. Continuous variables were expressed as mean (standard deviation) or median [interquartile range (IQR)], where appropriate. Categorical variables were expressed as count and percentage. A two-sided *P* value of <.05 was considered statistically significant.

Missing data were reviewed and assumed to be missing at random. Values for missing predictors were imputed using multiple imputation techniques based on chained equations using the MICE package.[19–21] All pre-specified predictor variables, outcome variables, and the estimate of the cumulative hazard function were included in the multiple imputation model.[22,23] In addition, the mean heart rate on Holter monitoring without antiarrhythmic drugs, pre-exercise test heart rate on the EST without antiarrhythmic drugs, and resting heart rate on a resting ECG with antiarrhythmic drugs were included to impute the baseline heart rate without antiarrhythmic drugs. A total of 100 imputed datasets were generated, and the estimates were combined using Rubin's rules.[24]

Annual event rates were calculated by dividing the total number of AEs and nf/fAEs by the total number of person-years. The cumulative probability of a first AE and nf/fAE during follow-up was determined with the life-table method of Kaplan–Meier, and results were compared with the log-rank test.

Model development

Clinical risk factors for AEs and nf/fAEs identified in previously published CPVT patient cohorts and predictor variables that seemed plausible from a clinical point of view and/or that have been identified in risk models in other inherited cardiac disorders were considered as candidate predictor variables.[2,6–8,25–27] Variables considered were age at which β-blockers were initiated, sex, SCA prior to β-blocker initiation, (presumed) arrhythmic syncope prior to β-blocker initiation (for endpoint AE), (presumed) arrhythmic syncope prior to or after β-blocker initiation (for endpoint nf/fAE, time dependent variable), presence of ventricular couplets or non-sustained VT during EST or Holter prior to β-blocker initiation, family history of SCD, presence of an early repolarization pattern at the first resting ECG, resting heart rate adjusted for age and sex prior to β-blocker initiation, and *RYR2* variant classification, inheritance pattern, and location. Coding and definitions of predictor variables are provided in Supplementary data online, *Table S2*.

The Cox proportional hazards models were used to identify both univariable and multivariable predictors of AEs (including arrhythmic syncope) and nf/fAEs (excluding arrhythmic syncope) while on β-blocker monotherapy. We assessed the linearity assumption of the Cox regression model for each quantitative predictor by (1) inspecting Martingale residual plots against the continuous covariates, (2) comparing a linear fit with a non-linear fit using restricted cubic splines with three knots in a likelihood ratio test, and (3) categorizing variables into quintiles and evaluating the log hazard ratio across quintiles. The proportional hazards assumption required by the Cox model was investigated using Schoenfeld residuals.[28] A minimum of 10 events (AEs and nf/fAEs) per co-variate were required to prevent overfitting.[29] Characteristics with a $P < .2$ at univariable analysis for AEs and nf/fAEs were first entered as candidate variables in a multivariable Cox proportional hazards regression analysis. The final multivariable prediction models were selected using a backward-elimination algorithm, based on Akaike information criterion (i.e. alpha = 0.157), in 200 bootstrap samples. Variables selected in >60% of bootstrap samples[30] were included in the prediction models. Model development steps were performed in all 100 imputed datasets. Regression coefficients and (robust) standard errors were averaged using Rubin's rules over all imputed datasets to obtain the final models. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated. In all models, robust standard errors were computed to account for family clustering in the data.[31] Discrimination of the models was assessed with the Harrell's concordance index (C-index) and calibration with a regression model and calibration plot.[32] We performed sensitivity analyses removing patients with incomplete data, patients with *RYR2* founder variants, patients with a VUS, and patients with a SCA prior to diagnosis from analyses to assess the robustness of the models.

Internal validation was performed following Harrell's resampling validation strategy.[32] In short, per imputation set, 200 bootstrap samples were created in which the optimism of the C-statistic was estimated by

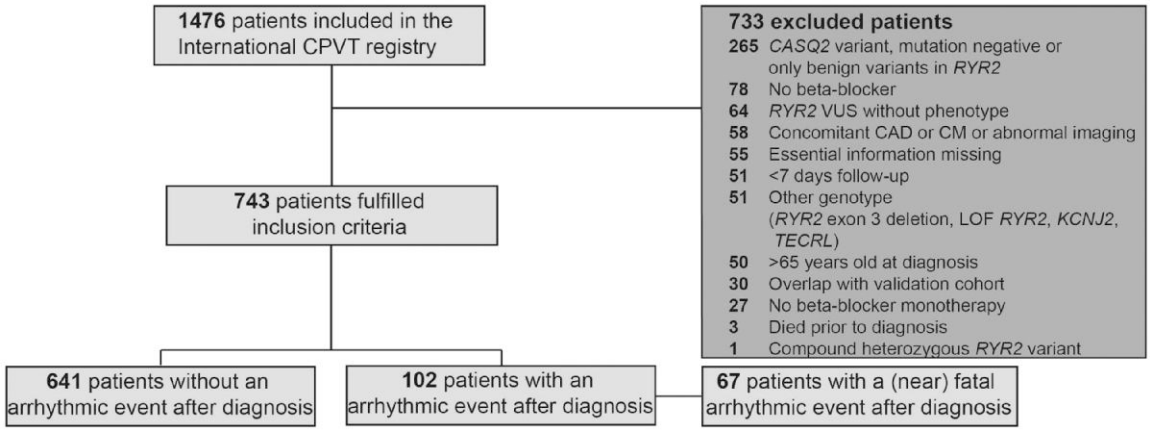

Figure 1 Study flowchart. CAD, coronary artery disease; CM, cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; LOF, loss of function; VUS, variant of uncertain significance

calculating the decrease in performance of the models in the bootstrap sample compared with the original performance. The resulting 200 optimism estimates were then averaged. Finally, these optimism estimates per imputation set were averaged over the 100 imputation sets.

A scoring system of the occurrence of the outcomes was developed from the prediction model, based on the sum of the points corresponding to each variable. The number of points for each variable identified in the model was attributed after identification of a common denominator across regression coefficients (i.e. the smallest beta in the multivariable models).

We validated our models in an external independent cohort. Similar to the original derivation cohort, missing data were considered to be missing at random and was imputed using multiple imputation techniques based on chained equations. Using the clinical scores for AE and nf/fAE from the derivation cohort, individuals in both cohorts were assigned to low (<5%), medium (5%–20%), or high (>20%) 5-year risk AE and nf/fAE groups. These groups were defined by consensus. Kaplan–Meier survival curves were created for the risk groups and compared using the log-rank test. AE and nf/fAE rates at 5 years were calculated. Regression analyses were performed with the use of the Cox proportional hazards model, estimating HRs and 95% CIs. The C-index was calculated to measure the discrimination between patients with a low, medium, and high risk of AEs and nf/fAEs.

Results

Characteristics of the derivation cohort

Of the 1476 patients in the International CPVT Registry, 743 patients (50.3%) from 367 families met the inclusion criteria of the study (*Figure 1*), and 23 families consisted of at least five individuals. Median age at initiation of β-blocker therapy was 16.0 years (IQR, 25), 406 patients (54.6%) were female, and 316 patients (42.5%) were probands (*Table 1*). At baseline, 331/735 patients (45.0%) were asymptomatic, 276/735 (37.6%) had experienced at least one (presumed) arrhythmic syncope, and 128/735 (17.4%) had experienced a SCA. The main initial β-blockers prescribed were nadolol (N = 211; 28.4%), bisoprolol (N = 174; 23.4%), metoprolol (N = 134; 18.0%), propranolol (N = 100; 13.5%), and atenolol (N = 90; 12.1%) (*Table 2*).

Outcomes of the derivation cohort

Patients were followed for a median duration of 5.1 years (IQR, 7.7), representing a total of 4846 patient-years. Follow-up was censored in 254 patients (34.2%) due to treatment intensification beyond β-blocker monotherapy, non-CPVT-related death in 9 patients (1.2%), and end of clinical follow-up in the absence of any AE on β-blocker monotherapy in 108 patients (14.5%).

During follow-up, 102 patients (13.7%) experienced an AE, corresponding to an annual event rate of 2.1% (95% CI 1.7–2.5). The cumulative AE incidence was 10.8% (95% CI 8.1–13.4) at 5 years (*Figure 2A*). Annual AE rates were 3.2% (95% CI 2.8–3.6) in patients who were symptomatic prior to β-blocker initiation and 0.7% (95% CI −0.4–1.7) in previously asymptomatic patients. At the time of the first AE, 30 (29.4%) patients used nadolol, 20 (19.6%) used propranolol, and 52 (51.0%) used a β1-selective β-blocker.

Sixty-seven patients (9.0%) experienced a nf/fAE during follow-up, corresponding to an annual event rate of 1.3% (95% CI 0.8–1.8). The cumulative nf/fAE incidence was 5.9% (95% CI 3.9%–7.9) at 5 years (*Figure 2B*). Annual nf/fAE rates were 2.7% (95% CI 2.2–3.1) in patients who were symptomatic prior to β-blocker initiation and 0.3% (95% CI 0.0–1.7) in previously asymptomatic patients.

Risk score model development and internal validation

The proportion of missing data for the eight initial predictors ranged from 0% to 50% (*Table 1*). The clinical variables that were selected after stepwise backward selection are presented in *Table 3* for AE and *Table 4* for nf/fAE.

For individual patients, the 5-year risk of an AE can be calculated with the following formula: P (AE at 5 years) = $1–0.911^{exp\ (LP)}$, where linear predictor (LP) for AE can be calculated by LP = (0.60*SCA) + (0.51*syncope) + (−0.04*age at β-blocker initiation). For nfAE, the 5-year risk of an nfAE can be calculated with P (nfAE at 5 years) = $1–0.939^{exp(LP)}$ and LP for nfAE can be calculated by LP = (1.17*SCA) + (0.66*syncope) + (0.07*couplet or non-sustained VT on baseline EST or Holter) + (−0.03*age at β-blocker initiation).

Using the clinical scores from *Tables 3* and *4*, patients could be assigned to a 5-year risk category for AE and nf/fAE, respectively. For AE, scores ≤−29 indicated a low risk (<5%), scores between −28 and 8 a medium risk (5%–20%), and scores >8 a high risk (>20%) (*Table 3*). For nf/fAE, scores ≤−1 indicated a low risk (<5%), scores

Table 1 Baseline characteristics of the unimputed data of the patients in the derivation cohorts

Variable	All patients (N = 743)	Symptomatic patients (N = 404)	Asymptomatic patients (N = 331)	*P* value*
Proband status, no. (%)	316 (42.5)	295 (73.0)	20 (6.0)	<.001
Female sex, no. (%)	406 (54.6)	223 (55.2)	179 (54.1)	.819
Median age at worst symptom, year (interquartile range)	NA	12.0 (8.0–16.0)[a]	NA	NA
Worst symptom before diagnosis, no./total no. (%)				
Asymptomatic	331/735 (45.0)	NA	331 (100.0)	NA
(Presumed) arrhythmic syncope	276/735 (37.6)	276 (68.3)	NA	
Sudden cardiac arrest	128/735 (17.4)	128 (31.7)	NA	
Median age at initiation of β-blocker therapy, year (interquartile range)	16.0 (10–35)	14.0 (10–22)	26.0 (12–44)	<.001
Family history of SCD in a first degree relative <40 years, no./total no. (%)	169/684 (24.7)	76/374 (20.3)	90/302 (29.8)	.006
Age- and sex adjusted percentage of median resting heart rate, mean (SD)	98.4 (23.0)[b]	94.1 (25.2)[c]	101.3 (21.1)[d]	<.001
Early repolarization, no./total no. (%)	47/472 (10.0)	32/254 (12.6)	12/212 (5.7)	.017
Worst ventricular arrhythmia without antiarrhythmic drugs, no./total no. (%)				<.001
None	140/592 (23.6)	43/300 (14.3)	96/288 (33.3)	
Isolated PVCs	75/592 (12.7)	26/300 (8.7)	49/288 (17.0)	
Bigeminal PVCs	79/592 (13.3)	41/300 (13.7)	37/288 (12.8)	
Couplet	102/592 (17.2)	48/300 (16.0)	53/288 (18.4)	
Non-sustained ventricular tachycardia	196/592 (33.1)	142/300 (47.3)	53/288 (18.4)	
RYR2 variant classification, no. (%)				<.001
Pathogenic	403 (54.2)	193 (47.8)	206 (62.2)	
Likely pathogenic	190 (25.6)	112 (27.7)	76 (23.0)	
Variant of uncertain significance	150 (20.1)	99 (24.5)	49 (14.8)	

Total number of patients for a given variable detailed in case of missing data.
NA, not applicable; PVC, premature ventricular complex; RYR2, ryanodine receptor 2; SCD, sudden cardiac death; SD, standard deviation.
**P* value for comparison of symptomatic and asymptomatic cases of the development cohort calculated with linear or logistic regression with Generalized Estimating Equations (GEE) correction for relatedness (working correlation structure: exchangeable).
[a]Data available for 364 patients.
[b]Data available for 371 patients.
[c]Data available for 148 patients.
[d]Data available for 221 patients.

between 0 and 53 a medium risk (5%–20%), and scores >53 a high risk (>20%) (*Table 4*).

With an optimism-corrected (0.83%) C-index of 0.67 (95% CI 0.62–0.72) for AE, and an optimism-corrected (0.7%) C-index of 0.74 (95% CI 0.68–0.80) for nf/fAE, these models had a moderate and good ability to discriminate between patients who experienced an AE or nf/fAE and patients who remained asymptomatic during follow-up, respectively. Internal validation with bootstrapping revealed calibration slopes of 1.00 (95% CI 0.59–1.41) for AE and 1.00 (95% CI 0.69–1.32) for nf/fAE (see Supplementary data online, *Figures S1A* and *S1B*).

Next, the location of the variant within the topology of the *RYR2*-encoded ryanodine receptor/calcium release channel was explored as a possible predictor. In a univariable analysis, variants located in the central domain were associated with a higher incidence of AEs (HR 1.9; 95% CI 1.0–3.5) and nf/fAEs (HR 2.2; 95% CI 1.0–4.6) as compared with variants located in other regions. In addition, *de novo* variants were associated with a higher incidence of nf/fAEs (HR 2.2; 95% CI 1.1–4.3). However, in the multivariable models, adding the *RYR2* variant's location or inheritance pattern did not improve the models for either endpoint (see Supplementary data online, *Table S3*).

Patients with predicted 5-year risk of AE <5% (N = 197) had a 5-year observed AE incidence of 3.4% (95% CI 0.5–6.4) (*Figure 3A*). Patients with a predicted 5-year risk between 5% and 20% (N = 486) had a 5-year observed AE incidence of 12.9% (95% CI 9.4–16.4).

Patients with a predicted 5-year risk >20% (N = 60) had a 5-year observed AE rate of 18.5% (95% CI 6.7–30.2). The relative risks of the medium vs low and high vs low risk categories for AEs were 4.7 (95% CI 2.1–10.3; $P = .0002$) and 8.4 (95% CI 3.2–22.3; $P < .0001$), respectively.

Patients with predicted 5-year risk of nf/fAE <5% (N = 419) had a 5-year observed nf/fAE rate of 1.5% (95% CI 0.1–2.9) (*Figure 3B*). Patients with a predicted 5-year risk between 5% and 20% (N = 290) had a 5-year observed nf/fAE rate of 12.3% (95% CI 7.6–17.0). Patients with a predicted 5-year risk >20% (N = 34) had a 5-year observed nf/fAE rate of 10.8% (95% CI 0.0–22.5). The relative risks of the medium vs low and high vs low risk categories for nf/fAEs were 6.7 (95% CI 3.4–12.9; $P < .0001$) and 8.6 (95% CI 3.6–20.2; $P < .0001$), respectively.

Among the 331 patients who were asymptomatic at the baseline, 153 patients (46.2%) were categorized as low risk for the AE endpoint and 178 patients (53.8%) were categorized as intermediate risk. For the nf/fAE endpoint, 325 of the 331 asymptomatic patients (98.2%) were categorized as low risk (predicted 5-year nf/fAE risk <5%), and 6 patients (1.8%) were categorized as medium risk (predicted 5-year nf/fAE risk between 5% and 20%). None of the patients were categorized as high risk for AEs or nf/fAEs. Asymptomatic patients had a 5-year observed AE incidence of 3.8% (95% CI 1.3–6.3) and a 5-year observed nf/fAE incidence of 0.5% (95% CI, 0.0–1.5) (see Supplementary data online, *Figures S2A* and *S2B*).

Among the 404 patients who were symptomatic at the baseline, 40 patients (9.9%) were categorized as low risk for the AE endpoint, 304 patients (75.2%) were categorized as intermediate risk, and 60 patients (14.9%) were categorized as high risk. For the nf/fAE endpoint, 86 symptomatic patients (21.3%) were categorized as low risk, 284 patients (70.3%) were categorized as medium risk, and 34 of the patients (8.4%) were categorized as high risk. Symptomatic patients had a 5-year observed AE incidence of 17.0.% (95% CI 12.5–21.2) and a 5-year observed nf/fAE incidence of 10.6% (95% CI 7.0–14.2) (see Supplementary data online, *Figures S3A* and *S3B*).

Table 2 β-Blocker types and doses

β-Blocker type	All patients (N = 743)	Daily dose (mg/kg) median (interquartile range)
Nadolol, no. (%)	211 (28.4)	1.00 (0.76–1.62)
Bisoprolol, no. (%)	174 (23.4)	0.06 (0.04–0.10)
Metoprolol, no. (%)	134 (18.0)	0.97 (0.69–2.21)
Propranolol, no. (%)	100 (13.5)	1.72 (1.00–2.16)
Atenolol, no. (%)	90 (12.1)	1.06 (0.86–1.67)
Sotalol, no. (%)	10 (1.3)	2.79 (2.38–3.09)
Carvedilol, no. (%)	7 (0.9)	0.12 (0.90–0.43)
Acebutolol, no. (%)	4 (0.5)	3.39 (4.22–5.53)
Other, no. (%)	13 (1.7)	NA

NA, not applicable.

Sensitivity analyses

Next, we performed a sensitivity analysis in the 267 patients (35.9%) in whom all pre-specified predictors were used in analysis. The baseline characteristics of the complete cases are provided in Supplementary data online, *Table S4*. There were no major differences between the baseline characteristics of the complete cases and the imputed dataset. In this analysis, SCA, severe ventricular arrhythmias on baseline EST or Holter, and age at β-blocker initiation were selected for both endpoints (see Supplementary data online, *Table S5*).

To ensure our findings were not driven by two *RYR2* founder variants that were relatively over-represented in our cohort (p.R420W and p.G357S), we performed a sensitivity analysis excluding the 162 patients (21.8%) with either of these variants. Here, we found similar predictors compared with the main analysis including all patients, with the exception of the presence of severe ventricular arrhythmias on EST or Holter in the nf/fAE model. The differences in the coefficients of the models were modest (see Supplementary data online, *Table S6*).

Next, we excluded the 150 patients (20.2%) in whom a VUS in *RYR2* was identified from the analysis to assess the effects of a VUS designation on the risk stratification model. Here, the presence of severe

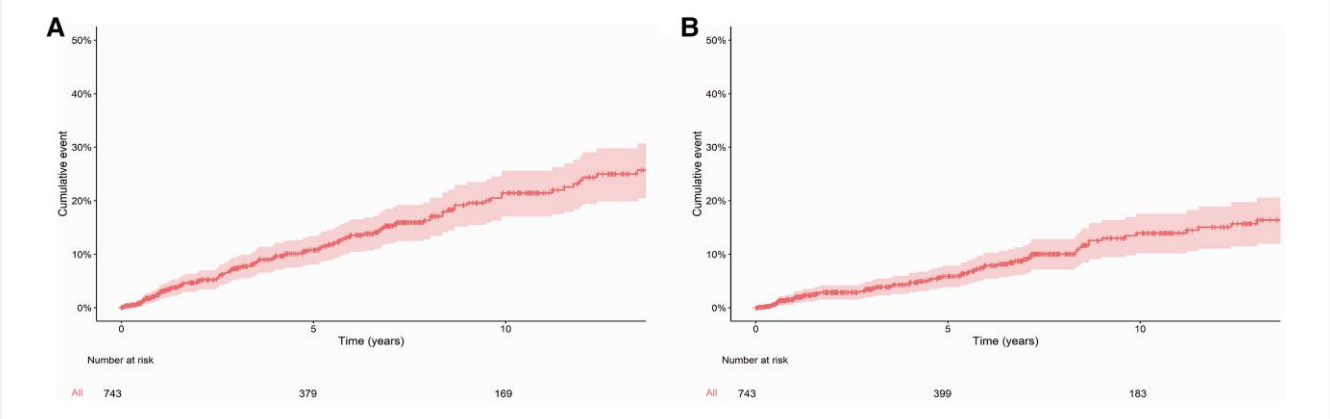

Figure 2 The cumulative event rate for arrhythmic events (panel *A*) and (near)-fatal arrhythmic events (panel *B*) with 95% confidence intervals (shaded area)

Table 3 Univariable and multivariable Cox regression analysis of risk factors for arrhythmic event

Predictors of arrhythmic event	Univariable model			Multivariable model (final model)			Clinical score
	HR	95% confidence interval	*P* value	HR	95% confidence interval	*P* value	
Female sex	0.9	(0.6–1.4)	.723	Not included in the final model			
Sudden cardiac arrest	2.4	(1.4–3.9)	.001	1.8	(1.1–2.9)	.012	15
Syncope	2.1	(1.3–3.4)	.002	1.7	(1.1–2.6)	.023	13
Severe ventricular arrhythmias on baseline Holter or exercise stress test	1.4	(0.9–2.0)	.121	Not included in the final model			
Age at start β-blockers (per year increase)	0.96	(0.94–0.98)	<.001	0.96	(0.94–0.98)	<.001	−1
Early repolarization	1.2	(0.6–2.6)	.591	Not included in the final model			
Resting heart rate (per 10% decrease)	0.99	(0.98–1.0)	.385	Not included in the final model			
Family history of sudden cardiac death <40 years	0.7	(0.4–1.1)	.097	Not included in the final model			

Table 4 Univariable and multivariable Cox regression analysis of risk factors for near-fatal/fatal arrhythmic event

Predictors of near-fatal/fatal arrhythmic event	Univariable model			Multivariable model			Clinical score
	HR	95% CI	*P* value	HR	95% CI	*P* value	
Female sex	0.8	(0.5–1.3)	.386	Not included in the final model			
Sudden cardiac arrest	4.1	(2.3–7.3)	<.001	3.2	(1.8–5.7)	<.001	43
Syncope	2.6	(1.4–4.7)	.002	1.9	(1.1–3.4)	.021	25
Severe ventricular arrhythmias on baseline Holter or exercise stress test	1.4	(0.9–2.3)	.175	1.1	(0.6–2.0)	.820	3
Age at start β-blockers (per year increase)	0.96	(0.94–0.98)	.001	0.97	(0.95–1.0)	.022	−1
Early repolarization	0.6	(0.2–2.0)	.439	Not included in the final model			
Resting heart rate (per 10% decrease)	1.0	(0.98–1.0)	.878	Not included in the final model			
Family history of sudden cardiac death <40 years	0.9	(0.5–1.5)	.712	Not included in the final model			

ventricular arrhythmias on EST or Holter was not selected as a predictor in both models, but the differences in the coefficient for the remaining predictors were modest (see Supplementary data online, *Table S7*).

Finally, we excluded 128 patients (17.2%) with a SCA prior to diagnosis to assess the effects of patients with a lower-risk profile on the risk stratification model. In the AE model, syncope and the resting heart rate were selected as predictors. In the nf/fAE model, syncope and the presence of severe ventricular arrhythmias on EST or Holter were selected as predictors (see Supplementary data online, *Table S8*).

External validation

Baseline characteristics of the external validation cohort, consisting of 129 patients from 110 families, are presented in Supplementary data online, *Table S9*. The patients in the validation cohort were younger and the proportion of probands and symptomatic patients was higher as compared with the derivation cohort. All of the 129 patients had complete data on the predictors of AE and nfAE identified in the derivation cohort. During a median follow-up duration of 2.4 years (IQR, 4.3), 24 patients (18.6%) experienced an AE during 422.9 patients-years, corresponding to an annual event rate of 5.7% (95% CI 4.8–6.5). Fourteen patients (10.8%) experienced a nf/fAE during 434.6 patient-years, corresponding to an annual event rate of 3.2% (95% CI 2.2–4.2).

Patients with predicted 5-year risk of AE <5% (N = 11) had a 5-year observed AE incidence of 0.0% (95% CI 0.0–0.0) (see Supplementary data online, *Figure S4A*). Patient with a predicted 5-year AE risk between 5% and 20% (N = 75) had a 5-year observed incidence of 22.5% (95%

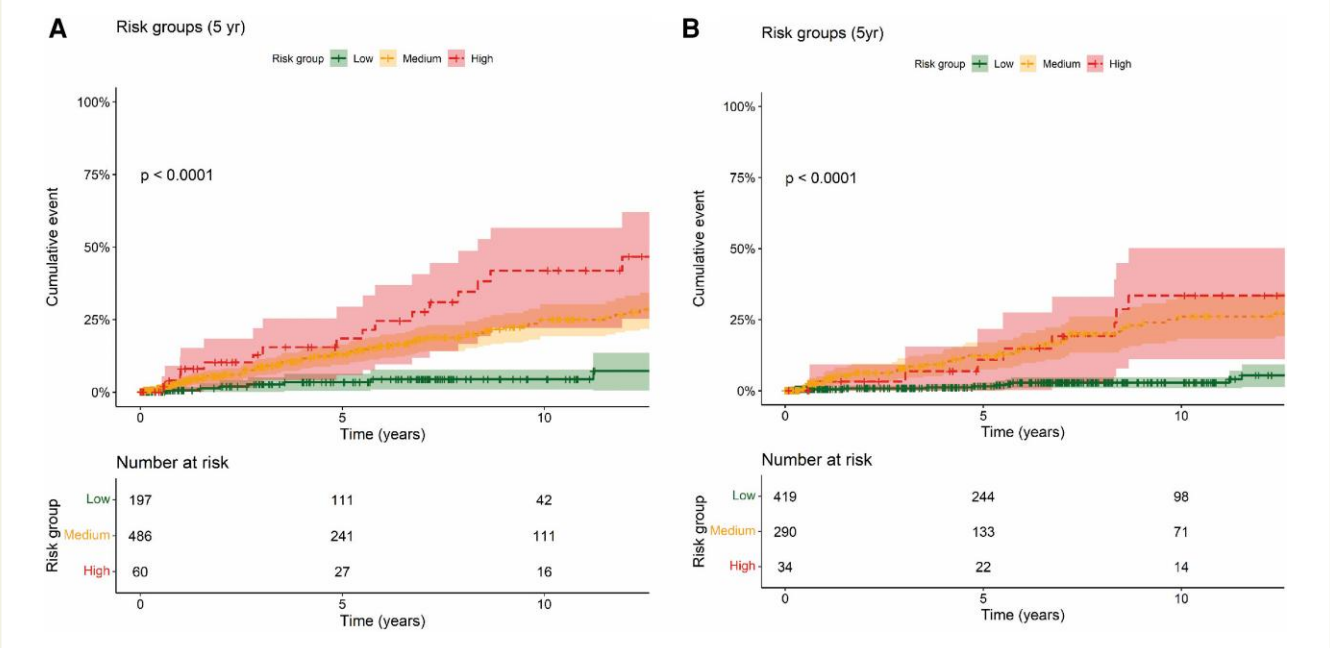

Figure 3 Cumulative event rates for arrhythmic events (panel *A*) and (near)-fatal arrhythmic events (panel *B*) in patients with a low- (<5% predicted 5-year risk), medium- (5–20% predicted 5-year risk), and high-risk score (>20% predicted 5-year risk) with 95% confidence intervals (shaded area)

CI 10.7–34.3). Patients with a predicted 5-year AE risk >20% (N = 43) had a 5-year observed incidence of 34.4% (95% CI, 14.6–54.2). The relative risks of the medium vs low and high vs low risk categories for AEs were 3.9 (95% CI 0.5–504.7; *P* = .25) and 4.2 (95% CI 1.5–550.8; *P* = .23), respectively. The optimism-corrected C-index for the AE model was 0.59 (95% CI 0.48–0.71).

Patients with predicted 5-year risk of nf/fAE <5% (N = 35) had a 5-year observed nf/fAE incidence of 0.0% (95% CI 0.0–0.0) (see Supplementary data online, *Figure S4B*). Patient with a predicted 5-year risk between 5% and 20% (N = 64) had a 5-year observed nf/fAE incidence of 17.8% (95% CI 4.8–30.7). Patients with a predicted 5-year risk >20% (N = 30) had a 5-year observed nf/fAE incidence of 15.1% (95% CI −2.0–32.2). The relative risks of the medium vs low and high vs low risk categories for nf/fAEs were 4.2 (95% CI 0.9–40.6; *P* = .07) and 2.4 (95% CI 0.4–25.8; *P* = .37), respectively. The optimism-corrected C-index for the nf/fAE model was 0.60 (95% CI 0.47–0.72).

Discussion

We developed and performed an internal and external validation of the first prediction model to generate individualized risk estimates for AEs and nf/fAEs in patients with *RYR2*-mediated CPVT treated with β-blockers. These models accurately distinguished patients who had incident AEs and nf/fAEs during follow-up from those who remained event-free, using non-invasive parameters that are readily available to the clinician. The risk stratification models showed that patients who were symptomatic prior to diagnosis, who were young when β-blocker therapy was initiated and had severe ventricular arrhythmias at the baseline were at the highest risk of experiencing AEs and nf/fAEs during follow-up (*Structured Graphical Abstract*). We observed that predicted and observed risks were concordant.

Predictors of arrhythmic events

We developed risk stratification models in patients treated with β-blockers in order to quantify the risk of AE and nf/fAE on the basis of several readily available clinical characteristics: age at initiation of β-blocker therapy, history of a (presumed) arrhythmic syncope or SCA prior to β-blocker initiation, and the presence of severe significant ventricular arrhythmias, defined as couplets or non-sustained VT, on the EST or Holter at baseline before initiation of antiarrhythmic drugs.

Hitherto, four studies have assessed predictors of AEs in patients with CPVT.[6–9] These relatively small studies, including up to 216 patients, identified younger age at diagnosis, syncope or SCA prior to diagnosis, and proband status as predictors for AEs. We were able to confirm these findings and, importantly, to develop and validate two models for individualized prediction in a significantly larger cohort.

Couplets or non-sustained VT on the last EST prior to an AE have been associated with AEs,[6] but this variable has not been investigated previously in a multivariable analysis. Here, we found that the presence of couplets and non-sustained VTs at the baseline was a modest predictor of nf/fAE. The modest association of ventricular arrhythmias at baseline with adverse outcomes has multiple potential explanations. First, a proportion of the patients in our registry were diagnosed with CPVT at a young age through cascade screening and may not yet have developed a CPVT phenotype with ventricular arrhythmias, as assessed by EST or Holter, prior to initiating β-blocker therapy. Second, patients with more complex ventricular arrhythmias may have been prescribed higher doses of β-blockers and other therapies (e.g. flecainide and LCSD) protecting them from AEs and nf/fAEs. Third, we recently showed that the repeatability of the most complex ventricular arrhythmia on the EST in patients with CPVT is moderate.[33] This indicates that some patients with complex ventricular arrhythmias on other ESTs might coincidentally not have shown these arrhythmias on the baseline test that was included in our analyses.

The baseline EST without AAD may provide other valuable prognostic information apart from the complexity of the ventricular arrhythmias. Larger heart rate recovery following exercise[34] and early onset of VA on the EST[35] have both been associated with AEs at follow-up. This demonstrates the prognostic relevance of the EST. However these two variables have not been investigated in a multivariable analysis.

Early repolarization has been associated with an increased risk of SCD in the general population and in patients with Brugada syndrome and congenital long QT syndrome.[36–38] In addition, one study reported that early repolarization was associated with symptoms prior to diagnosis in patients with CPVT.[25] Our study showed that early repolarization is not a significant predictor of CPVT-triggered AEs during follow-up. C-terminal-localizing *RYR2* variants have been associated with a higher incidence of non-sustained VT on the initial EST[18] and AEs.[8] In addition, probands have been found to be more likely to have *de novo* variants, most often located in the C-terminus of *RYR2*, and these probands harbouring *de novo RYR2* variants showed an earlier onset of symptoms than those with assured familial inheritance.[39] In univariate analysis, we found that variants located in the central domain and *de novo* variants were indeed associated with a higher incidence of AEs and nf/fAEs and nf/fAEs, respectively. However, patients with variants located in the central domain and *de novo* variants also had a more severe phenotype at baseline resulting in a higher clinical risk score, and therefore the *RYR2* variant location and inheritance did not have an incremental value in their individualized risk estimates. It is, however, unknown whether the current risk stratification models also apply to genotype-negative patients with CPVT.

Clinical utility

This study adds important data to consider in formulating guidelines for tailoring treatment strategies in patients with CPVT. Currently, guidelines advocate treating every patient who is clinically diagnosed with CPVT with β-blocker therapy (preferably nadolol or propranolol),[17] in addition to restriction of exercise, based on the presence of ventricular arrhythmias (Class I recommendation).[5] In addition, guidelines recommend considering β-blocker therapy in every genotype-positive patient regardless of the presence of ventricular arrhythmias (class IIa recommendation).[5] Treatment intensification with either flecainide, LCSD, or both is recommended in the setting of persistent polymorphic or bidirectional VT or recurrent AEs.

Our models help clinicians to identify patients at increased risk of AEs and nf/fAEs while treated with β-blockers. The developed risk models should compel direct CPVT-directed treatment intensification beyond β-blocker monotherapy. Specifically, among patients with an intermediate or high-risk prediction, mostly patients who presented with syncope or SCA, immediate combination therapy with β-blockers and flecainide,[10] β-blockers, flecainide and LCSD,[11,12] or LCSD and flecainide (if β-blockers are not tolerated)[40] should now be considered the standard of care. Importantly, ICDs have been associated with significant harm in patients with CPVT,[41] and a survival benefit has not been shown.[16] Therefore, these risk stratification models are not intended to inform ICD insertion. If an ICD was inserted in the past, the previously mentioned combination therapies or triple therapy should also be recommended.

Limitations

We included patients with a *RYR2* VUS, likely pathogenic, or pathogenic variant as categorized by the ACMG criteria,[14] because excluding the CPVT cases with a VUS may introduce bias. The pathogenicity of a *RYR2* VUS is, by definition, uncertain. Furthermore, the ACMG criteria have not been validated for all specific genetic disorders. Guidicessi *et al.* showed that the 2015 ACMG variant calling guideline may be too stringent for *RYR2* variants for various reasons.[42] First, the ACMG criteria are heavily weighted on the necessity of functional studies, while only few *RYR2* variants have been characterized functionally. Second, due to the large size of the *RYR2*-encoded ryanodine receptor, the odds of identifying novel variants are high. Without significant co-segregation including both paternity and maternity confirmed (non-)carriership, upgrading an ultra-rare variant to likely pathogenic or pathogenic status is challenging with the current ACMG paradigm. However, by including the power of the phenotype, for most patients with a robust clinical diagnosis of CPVT, an identified and genetic test company graded VUS is almost certainly eligible for a phenotype-enhanced variant promotion to likely pathogenic variant status,[42] hence the inclusion of VUS in this study design. We can, however, not exclude the possibility that some patients with a loss-of-function *RYR2* variant causing calcium release deficiency syndrome were included, as not all variants have been functionally assessed and these patients also show some degree of exercise-induced ventricular ectopy.

A limitation of this study is that not all baseline variables were available for all patients given the partially retrospective nature of the registries. We used predictors that are readily available at the baseline to estimate the risk of AEs and nf/fAEs during follow-up in order to make the risk stratification models as accessible as possible. Although this method provides clinicians with an easy tool to assess risk, these parameters may change during follow-up. For example, young asymptomatic children who are diagnosed through cascade screening may not display a CPVT phenotype at the first evaluation but may develop a CPVT phenotype over time, which may increase their risk of AEs. Also, type and intensity of β-blocker treatment are important when predicting future AEs as therapeutic choices likely impact prognosis and these variables may change over time resulting in a different risk profile. Monitoring PVCs and ventricular arrhythmias during exercise may provide valuable information, especially in assessing the intensity of β-blocker treatment. However, our group has shown the repeatability of the most complex ventricular arrhythmia on the EST in patients with CPVT is moderate.[33] The optimism-corrected C-indices for both risk stratification models in the external validation cohort were low to modest. This is most probably due to the differences in the derivation and validation cohort. The derivation cohort contained both paediatric and adult patients, of whom 45% were asymptomatic at the baseline. The validation cohort was derived from a paediatric registry, of whom only 23% were asymptomatic at the baseline. For some analyses, there were only a small number of events, and a sparse-data bias may be applicable. Finally, our study is subject to potential model misspecification bias, including bias due to omitted predictors, which represents an important limitation to be considered when interpreting the results.

Future options for improving the risk stratification model could be to incorporate genetic data into the risk model, particularly through the inclusion of a polygenic risk score, which could potentially capture the cumulative effect of multiple genetic variants on disease risk. Also the baseline EST could potentially contain more independent risk predictors, such as heart rate recovery,[34] early onset ventricular arrhythmias,[35] which could improve the performance of the models. Finally, adding a dynamic aspect to risk prediction by using data of clinical reassessment of the patients on beta-blocker monotherapy, as recently shown for congenital long QT syndrome,[43] could improve risk prediction.

Conclusion

Based on the largest cohort of patients with *RYR2*-mediated CPVT reported to date, this is the first study to develop risk stratification

models in patients treated with β-blocker monotherapy. Age at initiation of β-blocker therapy, symptoms prior to diagnosis, and severity of the ventricular arrhythmias at baseline EST before initiation of antiarrhythmic drugs were predictors of CPVT-triggered AEs during follow-up. Our study shows that it is possible to accurately classify patients as low, intermediate, or high risk. This newly derived CPVT risk calculator can guide the tailoring of patient-specific therapies and treatment intensification for these patients.

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Supplementary Data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Dr. Van der Werf is a medical consultant for Cardurion Pharmaceuticals and Solid Biosciences Inc. Dr. Giudicessi has an equity interest in Pfizer, GlaxoSmith Kline, and Viatris. Dr. Kammeraad received a research grant from Medtronic (SET-ICD study). Dr. Yap is a consultant for Boston Scientific and Johnson & Johnson and has received research grants from Medtronic, Biotronik, and Boston Scientific. Dr. Zorio received a research grant from Pfizer (AFEDI study) and has served as medical consultant for Alnylam, Bristol-Meyer-Squibbs, Pfizer, and Sanofi-Genzyme. Dr. Ackerman is a consultant for Abbott, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Illumina, Invitae, Medtronic, Solid Biosciences Inc., and UpToDate. Dr. Ackerman and Mayo Clinic are/were involved in an equity/IP/royalty relationship with AliveCor, Anumana, ARMGO Pharma, Pfizer, and Thryv Therapeutics. Dr. Leenhardt serves as Expert Witness (modest) of Sanofi and Expert Witness (modest) of Mylan. Dr. Wilde serves as an unpaid consultant and is a member of the scientific advisory board of Thryv Therapeutics. However, none of these entities were involved in this study in any way. The other authors report no conflicts.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available to maintain patient confidentiality but are available from the corresponding author on reasonable request and after the agreement of all the co-authors.

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Ethical Approval

Data were collected in accordance with regulations set forth by local institutional review boards. At all participating centres institutional review board approval and informed consent were obtained if needed for this type of research.

Pre-registered Clinical Trial Number

None supplied.

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