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ORIGINAL RESEARCH ARTICLE

An International Multicenter Cohort Study on β-Blockers for the Treatment of Symptomatic Children With Catecholaminergic Polymorphic Ventricular Tachycardia

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BACKGROUND: Symptomatic children with catecholaminergic polymorphic ventricular tachycardia (CPVT) are at risk for recurrent arrhythmic events. β-Blockers decrease this risk, but studies comparing individual β-blockers in sizeable cohorts are lacking. We aimed to assess the association between risk for arrhythmic events and type of β-blocker in a large cohort of symptomatic children with CPVT.

METHODS: From 2 international registries of patients with CPVT, *RYR2* variant–carrying symptomatic children (defined as syncope or sudden cardiac arrest before β-blocker initiation and age at start of β-blocker therapy <18 years), treated with a β-blocker were included. Cox regression analyses with time-dependent covariates for β-blockers and potential confounders were used to assess the hazard ratio (HR). The primary outcome was the first occurrence of sudden cardiac death, sudden cardiac arrest, appropriate implantable cardioverter-defibrillator shock, or syncope. The secondary outcome was the first occurrence of any of the primary outcomes except syncope.

RESULTS: We included 329 patients (median age at diagnosis, 12 [interquartile range, 7–15] years, 35% females). Ninety-nine (30.1%) patients experienced the primary outcome and 74 (22.5%) experienced the secondary outcome during a median follow-up of 6.7 (interquartile range, 2.8–12.5) years. Two-hundred sixteen patients (66.0%) used a nonselective β-blocker (predominantly nadolol [n=140] or propranolol [n=70]) and 111 (33.7%) used a β1-selective β-blocker (predominantly atenolol [n=51], metoprolol [n=33], or bisoprolol [n=19]) as initial β-blocker. Baseline characteristics did not differ. The HRs for both the primary and secondary outcomes were higher for β1-selective compared with nonselective β-blockers (HR, 2.04

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[95% CI, 1.31–3.17]; and HR, 1.99 [95% CI, 1.20–3.30], respectively). When assessed separately, the HR for the primary outcome was higher for atenolol (HR, 2.68 [95% CI, 1.44–4.99]), bisoprolol (HR, 3.24 [95% CI, 1.47–7.18]), and metoprolol (HR, 2.18 [95% CI, 1.08–4.40]) compared with nadolol, but did not differ from propranolol. The HR of the secondary outcome was only higher in atenolol compared with nadolol (HR, 2.68 [95% CI, 1.30–5.55]).

CONCLUSIONS: β1-selective β-blockers were associated with a significantly higher risk for arrhythmic events in symptomatic children with CPVT compared with nonselective β-blockers, specifically nadolol. Nadolol, or propranolol if nadolol is unavailable, should be the preferred β-blocker for treating symptomatic children with CPVT.

Key Words: atenolol ■ child ■ death, sudden, cardiac ■ metoprolol ■ nadolol ■ polymorphic catecholergic ventricular tachycardia ■ propranolol

Clinical Perspective

What Is New?

- β1-selective β-blockers are associated with a higher risk for arrhythmic events, defined as syncope, appropriate implantable cardioverter defibrillator shock, sudden cardiac arrest, or sudden cardiac death, in symptomatic children with catecholaminergic polymorphic ventricular tachycardia compared with nonselective β-blockers.
- This difference in nonselective versus β1-selective β-blockers was driven by a significantly lower risk for arrhythmic events in patients treated with nadolol compared with metoprolol, bisoprolol, and atenolol.

What Are the Clinical Implications?

- Symptomatic children with catecholaminergic polymorphic ventricular tachycardia should preferably be treated with nadolol or another nonselective β-blocker, such as propranolol, should nadolol be unavailable.
- Nadolol, which is not universally available, should become and continue to be available in all countries for the treatment of these patients.

Nonstandard Abbreviations and Acronyms

CPVT	catecholaminergic polymorphic ventricular tachycardia
ICD	implantable cardioverter defibrillator
LCSD	left cardiac sympathetic denervation
LHR	likelihood ratio test
VA	ventricular arrhythmias

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited cardiac arrhythmia syndrome in which bidirectional or polymorphic ventricular arrhythmias (VAs) induced by exercise or emotional stress can trigger syncope, sudden cardiac arrest (SCA), or sudden cardiac death. CPVT is diagnosed in patients with a structurally normal heart and resting ECG and otherwise unexplained exercise- or catecholamine-induced bidirectional or polymorphic ventricular tachycardia or ventricular fibrillation.[1]

The mainstay of therapy to prevent arrhythmic events in patients with CPVT is a β-blocker.[1] Overall, β-blockers are associated with a reduced risk for arrhythmic events.[2] Nonetheless, a significant proportion of the patients who have CPVT treated with a β-blocker still experience breakthrough arrhythmic events during follow-up.[3,4] Previously symptomatic young patients are at particularly high-risk for the recurrence of arrhythmic events.[2] Nonadherence to therapy at the time of an arrhythmic event might contribute to this suboptimal effect of β-blockers.[4–6] In addition, the occurrence of arrhythmic events might also be related to a difference in efficacy between specific types of β-blockers,[2,7] as observed in patients with congenital long-QT syndrome.[8,9] In patients with breakthrough events despite β-blocker therapy, additional treatment with flecainide or left cardiac sympathetic denervation (LCSD) is indicated.[10–12]

Results from several small studies have suggested that nadolol, a nonselective β-blocker, may be superior to other types of β-blocker, in particular, β1-selective β-blockers, in the treatment of patients with CPVT.[2,7] However, this evidence is limited because of the small size of these cohorts. In addition, nadolol is currently unavailable in many countries. Therefore, there is a compelling need for a large-cohort study comparing the efficacy of the different types of β-blocker in patients with CPVT.[1,13] Here, data from 2 large international multicenter CPVT patient registries were used to evaluate the association of nonselective versus β1-selective β-blockers and of specific β-blockers with arrhythmic event rates in a high-risk CPVT population of symptomatic children.

METHODS

Study Population

In this observational cohort study, patients from the International CPVT Registry and the Pediatric and Congenital Electrophysiology Society Pediatric CPVT Registry who received treatment with a β-blocker were enrolled. The International CPVT Registry is a multicenter observational registry established in April 2014 that includes patients with

CPVT diagnosed on the basis of expert consensus.[14] As of December 1, 2020, a total of 1361 patients with CPVT from 30 centers had been included in this registry. The Pediatric and Congenital Electrophysiology Society Pediatric CPVT Registry is an international multicenter registry of CPVT children diagnosed before 19 years of age and their first-degree relatives.[4] From March 2015 until December 2020, 156 patients with CPVT from 27 centers were included in this registry. Both registries were initiated as retrospective cohort studies, but follow-up information has been collected prospectively. At all participating centers institutional review board approval and informed consent were obtained if needed for this type of research.

In patients with CPVT, age and the presence of symptoms before diagnosis are important predictors of future arrhythmic events.[2] Therefore, only symptomatic children, defined as syncope with or without seizures and SCA before the initiation of β-blockers, whose age at initiation of β-blocker therapy was <18 years were included in the study cohort. In addition, only patients who either had a variant of unknown significance or a (likely) pathogenic variant in the *RYR2* gene that encodes the cardiac ryanodine receptor (RyR2) according to the American College of Medical Genetics and Genomics guideline for the interpretation of variants were included.[15] *RYR2* variant of unknown significance carriers were only included if a definite CPVT phenotype was present. This was defined as bigeminal ventricular premature beats or more complex VAs in index patients, and isolated ventricular premature beats or more complex VAs in family members on exercise stress test, epinephrine challenge test, or Holter monitoring.[1]

We excluded patients with significant cardiac comorbidities. Patients with a *RYR2* exon 3 deletion,[16] a *RYR2* loss-of-function variant,[17] or a second (likely) pathogenic variant in *RYR2* or the gene encoding cardiac calsequestrin (*CASQ2*) were also excluded.

Outcomes

The primary outcome was a composite outcome of the first occurrence of an arrhythmic event, defined as sudden cardiac death, SCA, appropriate implantable cardioverter-defibrillator (ICD) shock, or syncope of (presumed) cardiac origin after the initiation of β-blocker therapy. The secondary outcome was a composite outcome of the first occurrence of a (near-)fatal arrhythmic event, defined as sudden cardiac death, SCA, or appropriate ICD shock.

Survival time was calculated for each patient from the date of the initiation of the first β-blocker to the date of the occurrence of the primary or secondary outcome or the date of the last clinical encounter, whichever occurred first. The median follow-up duration was calculated as the time from initiation of the first β-blocker until death or the date of last contact.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables are expressed as mean with standard deviation (SD) for normal distributions and median with interquartile range (IQR) for nonnormal distributions. Categorical variables were compared by using the Pearson χ^2 test or Fisher exact test, as appropriate. Continuous variables were compared by using an independent sample *t* test, Wilcoxon rank-sum test, 1-way ANOVA, or Kruskal-Wallis test, as appropriate. β-Blockers were treated as a time-dependent covariate in the main analysis to account for patients switching between β-blockers or stopping β-blockers. To describe the baseline characteristics, patients were grouped based on the first type of β-blocker they received. The most commonly prescribed β-blockers (atenolol, bisoprolol, metoprolol, propranolol, and nadolol) were described separately. Other uncommonly prescribed β-blockers (acebutolol, carvedilol, labetalol, carteolol, alprenolol, betaxolol, and sotalol) were grouped as one. We defined a daily dosage of 1.0 mg/kg in atenolol, metoprolol, and nadolol, 0.13 mg/kg in bisoprolol, and 2.0 mg/kg in propranolol as a cutoff for adequate therapy.[10,13] Nonadherence at the time of the arrhythmic event was defined by the discretion of the local investigator, mainly by asking the patients whether they took their medication according to the prescription before the event.

Kaplan-Meier analyses were used to evaluate differences in the occurrence of the primary and secondary outcomes between nonselective and β1-selective β-blockers and all individual β-blockers separately. Nadolol, propranolol, carvedilol, labetalol, carteolol, alprenolol, and sotalol were considered as nonselective β-blockers, and atenolol, bisoprolol, metoprolol, betaxolol and acebutolol as β1-selective β-blockers.[18] For the analyses of individual β-blockers, the most commonly prescribed β-blockers were assessed separately and the uncommonly prescribed β-blockers were grouped as one, as described earlier. Cox regression models were used to calculate hazard ratios (HRs) and 95% CIs, and to adjust for potential confounders. The likelihood ratio test (LHR) was used to evaluate statistical significance of the overall models, and the χ^2 tests involving the parameter estimates and standard errors were used to evaluate statistical significance of separate categories. In all analyses, β-blockers were treated as a time-dependent covariate. Thus, patients were counted in the β-blocker group of the specific β-blocker they used at that time during follow-up. Possible confounders at baseline (age, sex) and time-dependent covariates of treatment with flecainide, LCSD, and the presence of an ICD at baseline or during follow-up were assessed. Thus, flecainide, LCSD, or the presence of an ICD were only assessed for the actual duration of that therapy during follow-up. All covariates that were associated with the outcome in univariable analysis with a *P* value <0.20 were included in the final multivariable Cox regression model. To prevent overfitting of the model, a minimum number of 10 events per covariate was deemed necessary. Frailty terms were used to correct for familial association and the proportional hazards assumption was checked using Schoenfeld residuals. A *P* value <0.05 was considered to indicate statistical significance. All analyses were performed using R version 3.6.1. (R Project for Statistical Computing, Vienna, Austria). Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author. The program code for the statistical analysis will be made available for the purpose of reproducing the results on reasonable request. One author (P.J.P.) had full access to the data of both registries and takes responsibility for the integrity and data analysis. All authors have read and agree to the article as written.

RESULTS

Characteristics of the Patients

A total of 329 symptomatic children with CPVT were included (Figure 1). One hundred forty patients (42.6%) were initially treated with nadolol, 70 (21.3%) with propranolol, 51 (15.5%) with atenolol, 33 (10.0%) with metoprolol, and 19 (5.8%) with bisoprolol; 16 (4.9%) patients used other, rarely prescribed β-blockers, such as acebutolol and carvedilol. Two hundred eighteen patients (66.3%) were consistently treated with 1 β-blocker type, whereas 95 (28.9%) switched to another β-blocker, and 16 (4.8%) switched 2 or 3 times. Baseline characteristics were similar among all types of β-blockers (Table 1). At baseline, 20 (6.1%) patients used flecainide, and 23 (7.0%) had an ICD.

Follow-Up and Outcomes

During a median follow-up duration of 6.7 years (IQR, 2.8–12.5), 99 patients (30.1%) experienced an arrhythmic event and 74 (22.5%) experienced a near-fatal arrhythmic event. Appropriate ICD shock was the most frequent arrhythmic event (n=40; 40.4%), followed by syncope (n=38; 38.3%), SCA (n=17; 17.2%), and sudden cardiac death (n=4; 4.0%). Arrhythmic events occurred mostly during exercise (n=54/78; 69.2%) or emotional stress (n=13/78; 16.7%). Median age at the first arrhythmic event and first near-fatal arrhythmic event was 15.5 (IQR, 12.4–18.2) years and 16.2 (IQR, 13.0–20.1) years, respectively. Of the 38 patients who had syncope as their first arrhythmic event during follow-up, 14 (36.8%) experienced a near-fatal arrhythmic event during a median subsequent follow-up duration of 5.2 (IQR, 2.4–9.3) years, of whom 9 patients had an appropriate ICD shock, 3 had a SCA, and 2 died suddenly. At the time of the arrhythmic event, 21 (21.2%) patients received combination therapy with flecainide, 3 (3.0%) patients underwent LCSD, and 2 (2.0%) received combination therapy of β-blocker, flecainide, and LCSD. Thirty-six (36.4%) patients had an ICD at the time of the

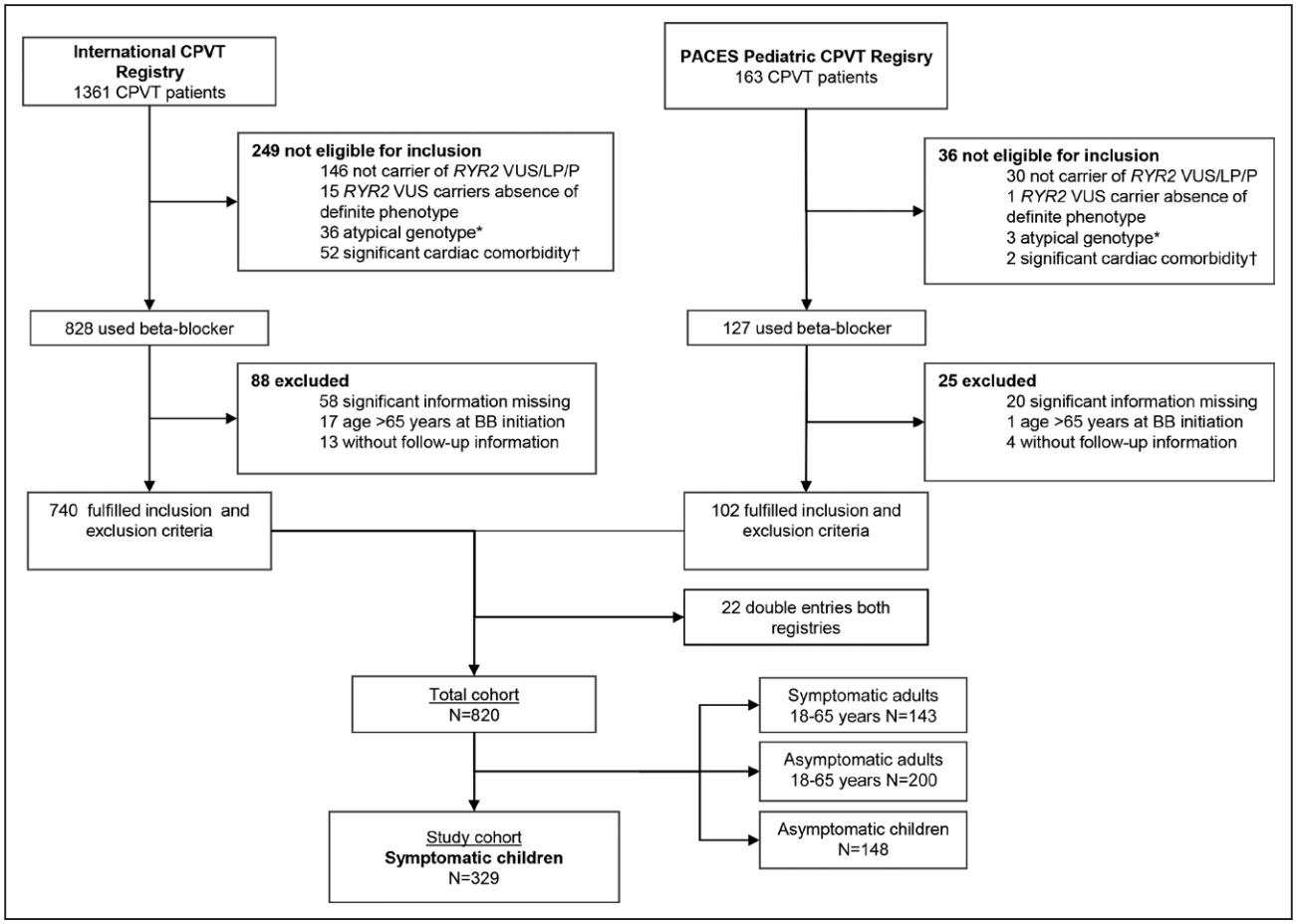

Figure 1. Flowchart of study participants.

*Defined as a *RYR2* exon 3 variant, a *RYR2* loss-of-function variant and a second (likely) pathogenic variant in the *RYR2* or *CASQ2* gene. Five of the 36 patients with an atypical genotype of the International CPVT Registry were accidentally excluded because they were inappropriately coded as having an atypical genotype. This is a random sample. †Defined as cardiomyopathy (unless attributable to an obvious reversible cause), a history of significant coronary artery disease, or a history of moderate or severe aortic, pulmonary, or mitral valve stenosis or regurgitation. BB indicates β-blocker; *CASQ2*, calsequestrin; CPVT, catecholaminergic polymorphic ventricular tachycardia; LP, likely pathogenic variant; P, pathogenic variant; PACES, Pediatric and Congenital Electrophysiology Society; *RYR2,* ryanodine receptor; and VUS, variant of uncertain significance.

Table 1. Baseline Characteristics

Characteristics	Atenolol (n=51)	Bisoprolol (n=19)	Metoprolol (n=33)	Nadolol (n=140)	Propranolol (n=70)	Other (n=16)	*P* value
Median age at diagnosis (interquartile range)	12 (9–15)	11 (9–14)	13 (10–15)	13 (9–15)	12 (8–14)	10 (8–14)	0.750
Median age at initiation β-blocker therapy (interquartile range)	11 (8–15)	10 (9–15)	13 (9–15)	12 (9–15)	10 (8–14)	10 (8–13)	0.447
Female, n (%)	22 (43.1)	9 (47.4)	14 (42.4)	62 (44.3)	37 (52.9)	6 (37.5)	0.808
Probands, n (%)	47 (92.2)	15 (83.3)	27 (81.8)	123 (87.9)	62 (88.6)	16 (94.1)	0.854
Family members with sudden cardiac death <40 y of age, n (%)	9 (20.9)	1 (7.7)	8 (40.0)	31 (22.1)	16 (22.9)	1 (7.7)	0.312
Worst symptom before diagnosis							
Syncope with or without seizures, n (%)	19 (37.3)	3 (15.8)	16 (48.5)	49 (34.3)	25 (35.7)	5 (35.3)	0.320
Sudden cardiac arrest, n (%)	32 (62.7)	16 (84.2)	17 (51.5)	91 (65.0)	45 (64.3)	11 (58.8)	
Age at first symptom ± SD	9.0±3.9	9.8±3.0	9.0±4.2	9.4±3.4	8.0±3.5	8.4±2.8	0.163
Reason of first presentation							
Cardiac symptoms, n (%)	46 (90.2)	14 (73.7)	31 (93.9)	119 (85.0)	63 (90.0)	14 (87.5)	0.373
Family screening, n (%)	4 (7.8)	2 (11.1)	2 (6.1)	13 (9.3)	3 (4.3)	0 (0.0)	
RYR2 variant classification							
Pathogenic, n (%)	19 (37.3)	9 (47.4)	11 (33.3)	67 (47.9)	28 (40.0)	5 (31.2)	0.276
Likely pathogenic, n (%)	17 (33.3)	2 (10.5)	9 (27.3)	36 (25.7)	26 (37.1)	7 (43.8)	
Uncertain significance, n (%)	15 (29.4)	8 (42.1)	13 (39.4)	37 (26.4)	16 (22.9)	5 (31.2)	
Flecainide at baseline, n (%)	2 (3.9)	0 (0.0)	5 (15.2)	11 (7.9)	1 (1.4)	1 (5.9)	0.080
Implantable cardiac defibrillator at baseline, n (%)	3 (5.9)	0 (0.0)	1 (3.0)	14 (10.0)	4 (5.7)	1 (5.9)	0.245
Left cardiac sympathetic denervation at baseline, n (%)	0	0	0	0	0	0	NA

arrhythmic event. Only flecainide and the presence of an ICD were included in the multivariable analyses for both the primary and secondary outcome (Table S1).

β1-selective β-blockers were associated with a higher risk of the primary outcome during follow-up compared with nonselective β-blockers (Figure 2; *P*=0.001). After adjustment for flecainide and the presence of an ICD, patients using β1-selective β-blockers had a higher risk for the primary outcome than patients using nonselective β-blockers (HR, 2.04 [95% CI, 1.31–3.17]; *P*=0.002; LHR, *P*<0.001). In line with this result, arrhythmic event rates differed significantly among specific types of β-blocker (Figure 3; LHR, *P*=0.003). The risk for an arrhythmic event in patients treated with atenolol, bisoprolol, and metoprolol was higher than in patients treated with nadolol (Table 2) after multivariable adjustment. Propranolol was not associated with an increased incidence of arrhythmic events compared with nadolol (HR, 1.72 [95% CI, 0.98–3.03]; *P*=0.061). Compared with patients treated with propranolol, there was no difference in the risk of arrhythmic events for patients treated with atenolol, bisoprolol, or metoprolol.

Patients who were treated with β1-selective β-blockers also had a higher risk for near-fatal arrhythmic events than patients treated with nonselective β-blockers (Figure 4; LHR, *P*=0.005). The difference in risk for the occurrence of near-fatal arrhythmic events between β1-selective β-blockers and nonselective β-blockers remained statistically significant in the multivariable model (HR, 1.99 [95% CI, 1.20–3.30]; *P*=0.008; LHR, *P*<0.001). The risk for near-fatal arrhythmic events when stratified per individual β-blocker compared with nadolol also differed significantly (Figure 5; LHR, *P*=0.024). However, in the multivariable model, only patients treated with atenolol had a significantly higher risk for the occurrence of near-fatal arrhythmic events compared with patients treated with nadolol (HR, 2.68 [95% CI, 1.30–5.55]; *P*=0.008; Table 2). Similar to the analyses for the primary outcome, there was no significant association of the risk for near-fatal arrhythmic events of atenolol in comparison with propranolol.

Daily Dosage and Adherence

In 293 (67.7%) of 433 treatment periods, information on the maximum prescribed daily dose per kilogram body weight was available. The proportion of suboptimal treatment episodes ranged from 19.2% in metoprolol to 53.8% in bisoprolol (Table 3). At the time of arrhythmic event, daily dosage was suboptimal in 24 patients (24.2%). The proportion of children on a suboptimal daily dosage at the time of arrhythmic event ranged from 9.1% in those treated with metoprolol to 44.4% in those treated with bisoprolol. These proportions were similar at the time of near-fatal arrhythmic event and did not differ significantly between the β-blocker types at the time of arrhythmic event and near-fatal arrhythmic event (*P*=0.084 and *P*=0.446, respectively; Table 3). Of the

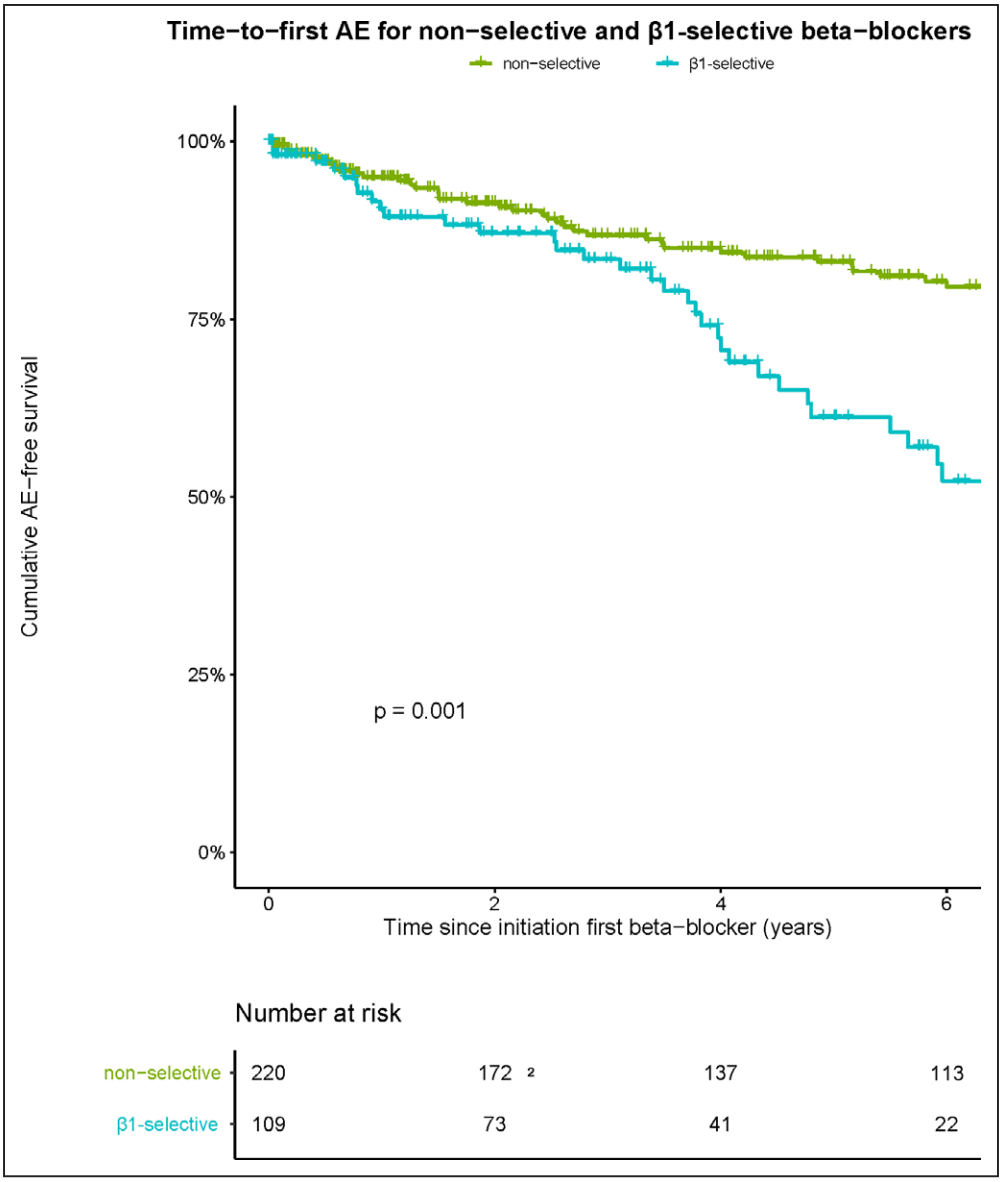

Figure 2. Kaplan-Meier curve showing the occurrence of AE in symptomatic children using nonselective versus β1-selective β-blockers.
AE indicates arrhythmic event.

306 patients with available information on side effects, 63 (20.6%) experienced side effects from their β-blocker treatment. Information regarding nonadherence to medical therapy at the time of the arrhythmic event was available in 72 (72.7%) patients. In 30 (38.7%) patients the arrhythmic event was definitely or probably associated with nonadherence. The proportion of nonadherent patients was similar in the individual β-blocker types at the time of arrhythmic event (*P*=0.363) and near-fatal arrhythmic event (*P*=0.598).

DISCUSSION

In this large cohort of symptomatic children with CPVT, treatment with β1-selective β-blockers was independently associated with a higher risk for arrhythmic events and near-fatal arrhythmic events compared with nonselective β-blockers. This association was most evident for nadolol.

Potential Mechanisms of Differences Between β-Blockers

In CPVT, VAs are induced during periods of increased adrenergic stress, such as exercise or emotional stress. β-Blockers act by inhibiting adrenergic stimulation of β-adrenergic receptors in the myocardium, lungs, and blood vessels. Our finding that nonselective β-blockers, specifically nadolol, were associated with a lower risk of arrhythmic events aligns with previous studies involving much smaller cohorts of patients with CPVT.[2,7] Furthermore, in

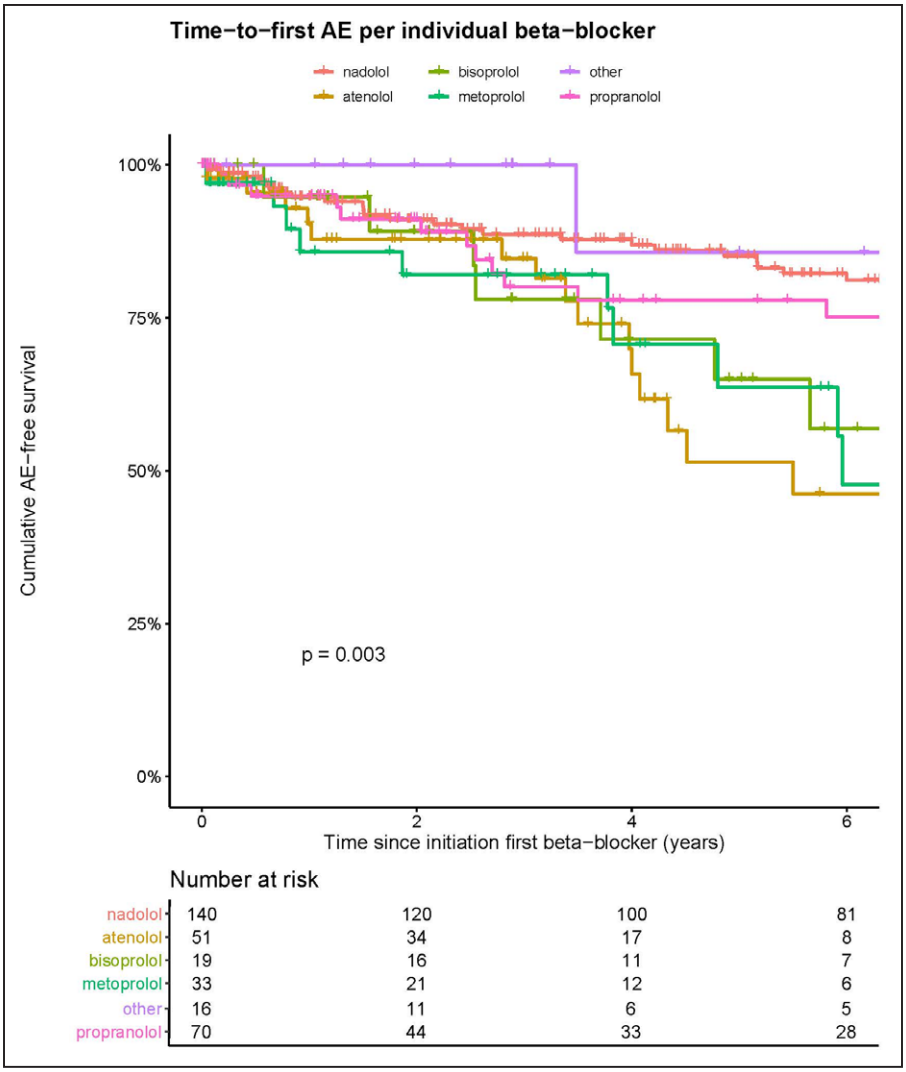

Figure 3. Kaplan-Meier curve showing the occurrence of AE in symptomatic children using different types of β-blockers.
Other β-blockers are rarely prescribed β-blockers (acebutolol, carvedilol, labetalol, carteolol, alprenolol, betaxolol, and sotalol) and are grouped as one. AE indicates arrhythmic event.

patients with the congenital long-QT syndrome, the most common inherited cardiac arrhythmia syndrome, a similar benefit of nonselective β-blockers has been described.[8,9]

Theoretically, the observed difference in β-blocker efficacy might be associated with nonadherence and the prescribed daily dosage. Nonadherence is a well-known concern in the treatment of patients with inher-

Table 2. Multivariate Cox Proportional Model of Individual β-Blockers in Symptomatic Children

	Primary end point		Secondary end point	
β-Blockers	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Nadolol	Reference		Reference	
Atenolol	2.68 (1.44–4.99)	0.002	2.68 (1.30–5.55)	0.008
Bisoprolol	3.24 (1.47–7.18)	0.004	2.54 (0.93–6.91)	0.068
Metoprolol	2.18 (1.08–4.40)	0.031	1.86 (0.86–4.03)	0.115
Propranolol	1.72 (0.98–3.02)	0.061	1.39 (0.69–2.78)	0.355
Other	2.89 (1.44–5.79)	0.003	2.05 (0.46–9.41)	0.356
Overall		<0.001*		<0.001*

Reference group is nadolol and therefore no hazard ratio or *P* value for nadolol is reported in this table.
**P* value of the Log-likelihood ratio test.

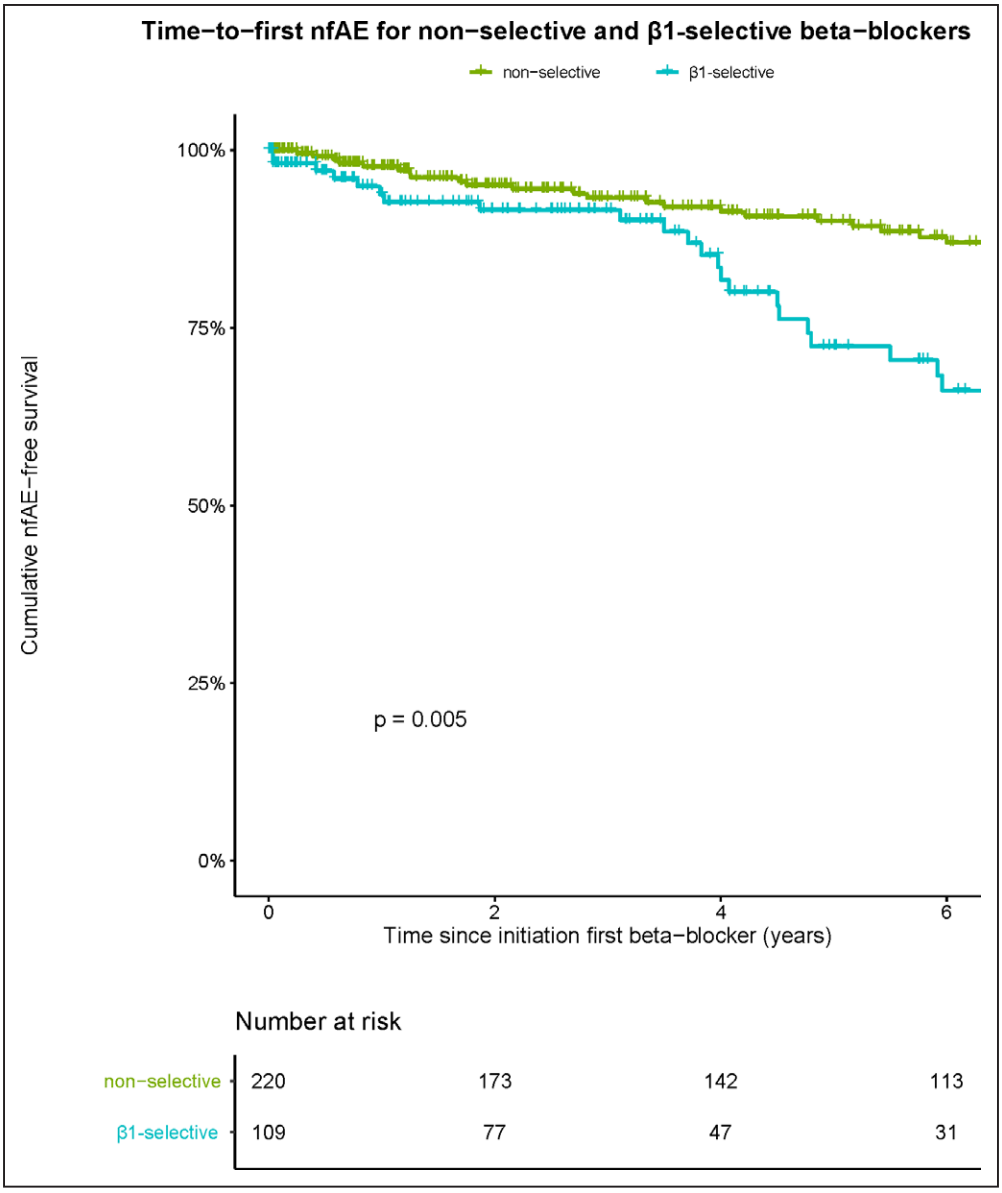

Figure 4. Kaplan-Meier curve showing the occurrence of nfAE in symptomatic children using nonselective versus β1-selective β-blockers.
nfAE indicates (near-)fatal arrhythmic event.

ited cardiac arrhythmia syndromes.[5] In this cohort, 30 (38.7%) patients were nonadherent at the time of their arrhythmic event and 24 (24.2%) patients were taking a suboptimal dose of β-blocker at the time of their arrhythmic event. β-Blockers vary in elimination half-life, with a half-life of 20 to 24 hours for oral nadolol compared with 3 to 6 hours for propranolol, 9 to 12 hours for bisoprolol, 6 to 7 hours for atenolol, and 3 to 7 hours for metoprolol. This is also dependent on the type of formulation. Because patients may be protected longer on a β-blocker with a longer half-life compared with a shorter half-life, a missed dose of nadolol might be less risky compared with a missed dose of other types of β-blockers.The survival curves for both the arrhythmic events and near-fatal arrhythmic events showed that the rate of events increased after 3 to 4 years of follow-up, especially in the group of β1-selective β-blockers. This resembles a pubertal age of ≈14 to 15 years in all β-blocker groups. During puberty, nonadherence might play a particularly important role[5,19] and growth spurts might induce a suboptimal daily dosage for body weight. This supports the hypothesis that both nonadherence and suboptimal dosages might be related to the observed difference in efficacy between β-blockers. However, there was no association between suboptimal dosage and nonadherence with β-blocker type at the time of an arrhythmic event or near-fatal arrhythmic event in this cohort, but adherence data were unavailable in a considerable proportion of patients to draw meaningful conclusions.

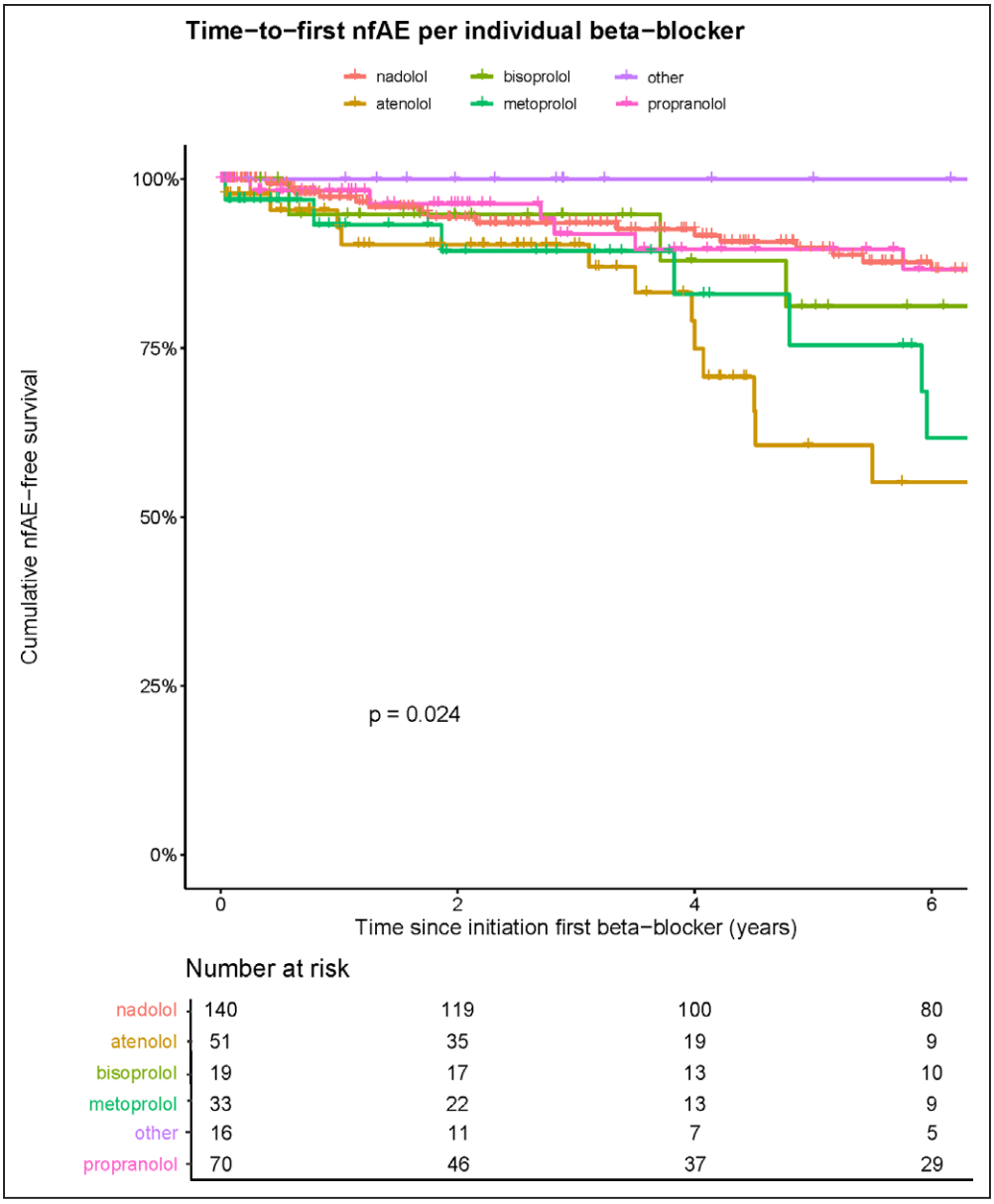

Figure 5. Kaplan-Meier curve showing the occurrence of nfAE in symptomatic children using different types of β-blockers. Other β-blockers are rarely prescribed β-blockers (acebutolol, carvedilol, labetalol, carteolol, alprenolol, betaxolol, and sotalol) and are grouped as one. nfAE indicates (near-)fatal arrhythmic event.

Differences in the pharmacokinetic characteristics between the individual β-blockers may also contribute to these findings. First, the interindividual pharmacokinetic variability is especially high for metoprolol and propranolol.[20] This could be associated with lipophilicity and hydrophilicity of β-blockers and therefore the respective hepatic and renal elimination. Lipophilic β-blockers, such as metoprolol and propranolol, can pass the blood-brain barrier and might therefore be more likely to induce central nervous system–related side effects.[21] This could potentially result in nonadherence and subsequently a higher risk for events, as described earlier. Besides that, hydrophilic β-blockers, such as atenolol and nadolol, in general, show a lower pharmacokinetic variability.[20] β-Blockers with a high variability, including metoprolol and propranolol, are primarily metabolized in the liver and therefore mediated by the cytochrome p450 2D6 (CYP2D6) enzyme. Genetic variants in this enzyme are associated with increased or decreased metabolism.[22] Fast metabolizers will need higher dosages of the same drug to obtain a plasma concentration similar to slow metabolizers. In addition, food induces changes in the bioavailability. Food enhances the bioavailability of metoprolol and propranolol, whereas it reduces the bioavailability of atenolol.[23–25] Nadolol has a low pharmacokinetic variation,[20] which may explain the apparent benefit of nadolol over the other types of β-blocker as is shown in these results.

Table 3. Maximum Daily Dosage per β-Blocker Group

Daily dosage	Atenolol	Bisoprolol	Metoprolol	Nadolol	Propranolol	Complete cohort	*P* value
Median daily dosage in mg/kg (interquartile range) of all treatment episodes (n=293 [43.7%] of 670 treatment episodes)	1.0 (0.8–1.5)	0.11 (0.05–0.19)	1.7 (1.0–2.8)	1.1 (0.8–1.6)	2.0 (1.4–2.8)	–	–
Suboptimal daily dose (% of treatment episodes with a known dosage) (n=293 [43.7%] of 670 treatment episodes))	14 (35.0)	14 (53.8)	5 (19.2)	56 (36.8)	17 (34.7)	66 (20.1)	NA*
Suboptimal daily dose at time of arrhythmic event (% of total number of events in group, total n=99)	5 (29.4)	4 (44.4)	1 (9.1)	10 (28.6)	4 (20.0)	24 (24.2)	0.084
Suboptimal daily dose at the time of (near-)fatal arrhythmic event (% of total number of events in group, total n=74)	4 (28.6)	2 (33.3)	4 (44.4)	8 (28.6)	3 (23.1)	17 (23.0)	0.445

*No statistical analyses were performed because this applied to treatment episodes rather than patients because patients could be included in multiple groups.

Furthermore, β-blockers have various pharmacodynamic effects, for example, on cardiac ion channels. Propranolol affects both the peak and late sodium current, whereas nadolol solely blocks the peak sodium current and metoprolol has no effect on these currents.[26] VAs in CPVT are triggered by delayed afterdepolarizations caused by elevated diastolic intracellular calcium levels secondary to spontaneous calcium release from the sarcoplasmic reticulum. The calcium overload is removed by the sodium-calcium exchanger in the cell membrane, causing an inward sodium flux. Delayed after depolarizations of sufficient amplitude can trigger an action potential and induce VAs. A blockade of the peak sodium current might reduce the risk for delayed afterdepolarizations to result in action potentials. Carvedilol and nebivolol are the only β-blockers that directly suppress calcium leakage from the sarcoplasmic reticulum by interacting with the RyR2 channel.[27,28] However, the efficacy of carvedilol and nevibolol could not be assessed in this cohort because of the small number of patients treated with these β-blockers.

Study Limitations

Because the retrospective nature of this cohort study, it is unavoidably subjected to the risk of bias. The risk of information bias was made as low as possible by performing intensive data checks and retrieval of missing data. However, some data were unavailable, possibly influencing these results. First, the presence of couplets or nonsustained ventricular tachycardia on the exercise stress test at baseline could not be corrected for. These complex VAs are associated with a worse outcome,[2] but an exercise stress test before initiation of β-blocker was available in only 59 (17.9%) of the patients. This also prevented us from performing meaningful analyses on the effect of β-blockers on VAs on the exercise stress test in this cohort. Furthermore, data on the daily dose and nonadherence at the time of arrhythmic event were missing in a significant proportion of patients. In the entire study population without arrhythmic event, information on nonadherence was unavailable. Second, the number of patients in some of the β-blocker subgroups was very small, potentially affecting the findings. Last, data regarding the prescribed β-blocker formulation and the number of daily intakes was unavailable.

Clinical Implications

We conclude that β1-selective β-blockers are associated with a higher risk for arrhythmic events and near-fatal arrhythmic events in symptomatic children with CPVT. When β-blockers were assessed separately, the association of a higher risk for arrhythmic events was evident with atenolol, bisoprolol, and metoprolol compared with nadolol. This was a nonrandomized observational study, making it impossible to establish causal effects between β-blocker treatment and outcomes. However, in the absence of a prospective randomized trial on this topic and the perspective thereof, we believe that nadolol should be the preferred initial β-blocker for treatment of this population. Therefore, we deem it necessary that nadolol is made available and continues to be available in all countries. Even though propranolol did not reach statistical significance over β1-selective β-blockers in terms of a lower risk for arrhythmic events, we would recommend remaining with a nonselective β-blocker, such as propranolol, in situations where nadolol is either unavailable or not tolerated. Furthermore, the rate of nonadherence and suboptimal dosages at the time of an event in this population is high. Clinicians should be aware of this to treat and counsel their patients appropriately. Future studies should focus on the lower-risk CPVT populations, asymptomatic children and adults, and reasons for nonadherence to further improve β-blocker treatment, in particular, in high-risk patients with CPVT.

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Disclosures

Dr Ackerman is a consultant to ARMGO Pharma and Invitae. Dr Leenhardt serves as: Sanofi; Expert Witness (modest) Mylan: Expert Witness (modest). Dr Giudicessi has an equity interest in Pfizer, GlaxoSmith Kline, and Viatris. Dr Kammeraad received a research grant from Medtronic (SET-ICD study). The other authors report no conflicts.

Supplemental Material

Table S1

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