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An International Multi-Center Cohort Study on β-blockers for the Treatment of Symptomatic Children with Catecholaminergic Polymorphic Ventricular Tachycardia

Running title: *Peltenburg et al.; Efficacy of individual beta-blockers in CPVT*

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Abstract

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

Methods: From two international registries of patients with CPVT, *RYR2* variant-carrying symptomatic children (defined as syncope or sudden cardiac arrest prior to BB initiation and age at start of BB therapy <18 years), treated with a BB were included. Cox-regression analyses with time-dependent covariates for BB 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 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 non-selective BB (predominantly nadolol [n=140] or propranolol [n=70]) and 111 (33.7%) used a β1-selective BB (predominantly atenolol [n=51], metoprolol [n=33], or bisoprolol [n=19]) as initial BB. Baseline characteristics did not differ. The HR for both the primary and secondary outcomes were higher for β1-selective compared with non-selective BBs (HR, 2.04 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: B1-selective BBs were associated with a significantly higher risk for arrhythmic events in symptomatic children with CPVT compared with non-selective BBs, specifically nadolol. Nadolol, or propranolol if nadolol is unavailable, should be the preferred BB for treating symptomatic children with CPVT.

Key words: Polymorphic catecholergic ventricular tachycardia; nadolol; propranolol; metoprolol; atenolol; sudden cardiac death; child

Clinical Perspective

What is new?

- B1-selective beta-blockers are associated with a higher risk for arrhythmic events – defined as syncope, appropriate ICD shock, sudden cardiac arrest, or sudden cardiac death – in symptomatic children with catecholaminergic polymorphic ventricular tachycardia compared with non-selective beta-blockers.
- This difference in non-selective versus β1-selective beta-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 non-selective beta-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.

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited cardiac arrhythmia syndrome in which ventricular tachyarrhythmias induced by exercise or emotional stress can trigger syncope, sudden cardiac arrest (SCA), or sudden cardiac death (SCD). 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 (VT) or ventricular fibrillation.[1]

The mainstay of therapy to prevent arrhythmic events in patients with CPVT is a beta-blocker (BB).[1] Overall, BBs are associated with a reduced risk for arrhythmic events.[2] Nonetheless, a significant proportion of the CPVT patients treated with a BB 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] Non-adherence to therapy at the time of an arrhythmic event might contribute to this suboptimal effect of BBs.[4-6] In addition, the occurrence of arrhythmic events might also be related to a difference in efficacy between specific types of BBs[2, 7], as observed in patients with congenital long-QT syndrome.[8, 9] In patients with breakthrough events despite BB 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 non-selective BB, may be superior to other types of BB – particularly β1-selective BBs – in the treatment of patients with CPVT.[2, 7] However, this evidence is limited due to 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 BB in patients with CPVT.[1, 13] Here, data from two large international multicenter CPVT patient registries was used to evaluate the association of non-selective versus β1-selective BBs and of

specific BBs 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 (PACES) Pediatric CPVT Registry who received treatment with a BB were enrolled. The International CPVT Registry is a multicenter observational registry established in April 2014 that includes CPVT patients diagnosed based on expert consensus.[14] As of December 1, 2020, a total of 1361 CPVT patients from 30 centers had been included in this Registry. The PACES Pediatric CPVT registry is an international multicenter registry of CPVT children diagnosed prior to 19 years of age and their first-degree relatives.[4] From March 2015 until December 2020, 156 CPVT patients from 27 centers have been 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 was obtained if needed for this type of research.

In CPVT patients, 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 prior to initiation of BB, whose age at initiation of BB therapy was <18 years were included in the study cohort. In addition, only patients who either had a variant of unknown significance (VUS) 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* VUS carriers were only included if a definite CPVT phenotype was present.

This was defined as bigeminal ventricular premature beats (VPBs) or more complex ventricular arrhythmias (VA) in index patients, and isolated VPBs or more complex VA 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 SCD, SCA, appropriate implantable cardioverter-defibrillator (ICD) shock, or syncope of (presumed) cardiac origin after the initiation of BB therapy. The secondary outcome was a composite outcome of the first occurrence of a (near-)fatal arrhythmic event, defined as SCD, SCA, or appropriate ICD shock.

Survival time was calculated for each patient from the date of the initiation of the first BB 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 BB 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 non-normal distributions. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using an independent samples t-test, Wilcoxon rank-sum test, one-way ANOVA, or Kruskal Wallis test, as appropriate. BB was treated as a time-dependent covariate in the main analysis, to account for patients switching between BBs or stopping BB. To describe the baseline characteristics, patients were grouped based on the first type of BB they received.

The most commonly prescribed BBs (atenolol, bisoprolol, metoprolol, propranolol, and nadolol) were described separately. Other uncommonly prescribed BBs (acebutolol, carvedilol, labetalol, carteolol, alprenolol, betaxolol, and sotalol) were grouped as one. We defined a daily dosage below 1.0 mg/kg in atenolol, metoprolol, and nadolol, 0.13 mg/kg in bisoprolol, and 2.0 mg/kg in propranolol as a cut-off for adequate therapy.[10,13] Non-adherence at the time of the arrhythmic event was defined by the discretion of the local investigator, mainly by asking the patients whether or not they took their medication according to the prescription prior to the event.

Kaplan-Meier analyses were used to evaluate differences in the occurrence of the primary and secondary outcomes between non-selective and β1-selective BBs and all individual BBs separately. Nadolol, propranolol, carvedilol, labetalol, carteolol, alprenolol, and sotalol were considered as non-selective BBs and atenolol, bisoprolol, metoprolol, betaxolol and acebutolol as β1-selective BBs.[18] For the analyses of individual BBs the most commonly prescribed BBs were assessed separately and the uncommonly prescribed BBs were grouped as one, as described above. Cox regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI), and to adjust for potential confounders. The likelihood ratio test (LHR) was used to evaluate statistical significance of the overall models and the chi-squared tests involving the parameter estimates and standard errors were used to evaluate statistical significance of separate categories. In all analyses, BB was treated as a time-dependent covariate. Thus, patients were counted in the BB group of the specific BB 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 ten 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 upon reasonable request. One author (PJP) 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 and forty patients (42.6%) were initially treated with nadolol, 70 (21.3%) with propranolol, 51 (15.5%) with atenolol, 33 (10.0 %) with metoprolol, 19 (5.8%) with bisoprolol, and 16 (4.9%) patients used other, rarely prescribed BBs, such as acebutolol and carvedilol. Two hundred and eighteen patients (66.3%) were consistently treated with one BB type, while 95 (28.9%) switched to another BB, and 16 (4.8%) switched twice or three times. Baseline characteristics were similar between all types of BBs (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 SCD (N=4; 4.0%). Arrhythmic events occurred mostly during exercise (N=54/78; 69.2%) or emotion (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 nine patients had an appropriate ICD shock, three had a SCA, and two 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 BB, flecainide and LCSD. Thirty-six (36.4%) patients had an ICD at the time of arrhythmic event. Only flecainide and presence of an ICD were included in the multivariable analyses for both the primary and secondary outcome (Supplemental Table 1). B1-selective BBs were associated with a higher risk of the primary outcome during follow-up as compared with non-selective BBs (Figure 2, p=0.001). Following adjustment for flecainide and presence of an ICD, patients using β1-selective BBs had a higher risk for the primary outcome compared with non-selective BBs (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 amongst specific types of BB (Figure 3, LHR, p=0.003). The risk for an arrhythmic event in patients treated with atenolol, bisoprolol and metoprolol was higher compared with patients treated with nadolol (Table 2) following 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). When 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 BBs also had a higher risk for near-fatal arrhythmic events compared with patients treated with non-selective BBs (Figure 4; LHR, p=0.005). The difference in risk for the occurrence of near-fatal arrhythmic events between β1-selective BBs and non-selective BBs 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 BB 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 when compared 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 BB types at the time of arrhythmic event and near-fatal arrhythmic event (p=0.084 and p=0.446, respectively; Table 3). Of the 306 patients with available information on side-effects, 63 (20.6%) experienced side-effects from their BB treatment. Information regarding non-adherence 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 non-adherence. The proportion of non-adherent patients was similar in the individual BB 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 BBs was independently associated with a higher risk for arrhythmic events and near-fatal arrhythmic events compared with non-selective BBs. This association was most evident for nadolol.

Potential mechanisms of differences between BBs

In CPVT, VA are induced during periods of increased adrenergic stress, such as exercise or emotional stress. BBs act by inhibiting adrenergic stimulation of β-adrenergic receptors in the myocardium, lungs and blood vessels. Our finding that non-selective BBs, specifically nadolol, were associated with a lower risk of arrhythmic events aligns with previous studies involving much smaller cohorts of CPVT patients.[2, 7] Furthermore, in patients with the congenital long-QT syndrome, the most common inherited cardiac arrhythmia syndrome, a similar benefit of non-selective BBs has been described.[8, 9]

Theoretically, the observed difference in BB efficacy might be associated with non-adherence and the prescribed daily dosage. Non-adherence is a well-known concern in the treatment of patients with inherited cardiac arrhythmia syndromes.[5] In this cohort 30 (38.7%) patients were non-adherent at the time of their arrhythmic event and 24 (24.2%) patients were taking a suboptimal dose of BB at the time of their arrhythmic event. BBs vary in elimination half-life, with a half-life of 20-24 hours for oral nadolol compared with 3-6 hours for propranolol, 9-12 hours for bisoprolol, 6-7 hours for atenolol, and 3-7 hours for metoprolol. This is also dependent on the type of formulation. Since patients may be protected longer on a BB 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 BBs. Interestingly, the survival curves for both the arrhythmic events and near-fatal arrhythmic events showed that the rate of events increased after 3-4 years of follow-up, especially in the group of β1-selective beta-blockers. This resembles a pubertal age of ~14 to 15 years old in all BB groups. During puberty, non-adherence 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 non-adherence and suboptimal dosages might be related to the observed difference in efficacy between BBs. However, there was no association between suboptimal dosage and non-adherence with BB type at the time of an arrhythmic event or near-fatal arrhythmic event in this cohort, but adherence data was unavailable in a considerable proportion of patients to draw meaningful conclusions.

Differences in the pharmacokinetic characteristics between the individual BBs may also contribute to these findings. Firstly, the inter-individual pharmacokinetic variability is especially high for metoprolol and propranolol.[20] This could be associated with lipophilicity and hydrophilicity of BBs and therefore the respective hepatic and renal elimination. Lipophilic BBs, 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 non-adherence and subsequently a higher risk for events, as described above. Besides that, hydrophilic BBs – such as atenolol and nadolol – generally show a lower pharmacokinetic variability.[20] BBs 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 similar plasma concentration compared with “slow” metabolizers. Additionally, food induces changes in the bioavailability. Food enhances the bioavailability of

metoprolol and propranolol, while 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 BB as is shown in these results.

Furthermore, BBs 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] VA in CPVT are triggered by delayed after-depolarizations 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 VA. A blockade of the peak sodium current might reduce the risk for delayed after-depolarizations to result in action potentials. Carvedilol and nebivolol are the only BBs 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 due to the small number of patients treated with these BBs.

Study limitations

Due to the retrospective nature of this cohort study, it is unavoidably subjected to risk of bias. By performing intensive data-checks and retrieval of missing data, the risk of information bias was made as low as possible. However, some data were unavailable, possibly influencing these results. Firstly, the presence of couplets or nonsustained VT on the exercise stress test at baseline could not be corrected for. These complex VA are associated with a worse outcome[2], but an exercise stress test before initiation of BB was available in only 59 (17.9%) of the patients. This also prevented us from performing meaningful analyses on the effect of BB on VA on exercise stress test in this cohort. Furthermore, data on the daily dose and non-

adherence at the time of arrhythmic event were missing in a significant proportion of patients. In the entire study population without arrhythmic event, information on non-adherence was unavailable. Secondly, the number of patients in some of the BB subgroups is very small, potentially affecting the findings. Lastly, data regarding the prescribed beta-blocker formulation and the number of daily intakes was unavailable.

Clinical implications

We conclude that β1-selective BBs are associated with a higher risk for arrhythmic events and near-fatal arrhythmic events in symptomatic children with CPVT. When BBs 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 non-randomized observational study, making it impossible to establish causal effects between BB treatment and outcomes. However, in the absence of a prospective randomized trial on this topic and the perspective thereof, we believe nadolol should be the preferred initial BB 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 BBs in terms of a lower risk for arrhythmic events, we would recommend remaining with a non-selective BB, such as propranolol, in situations where nadolol is either unavailable or not tolerated. Furthermore, the rate of non-adherence and suboptimal dosages at the time of an event in this population is high. Clinicians should be aware of this in order to appropriately treat and counsel their patients. Future studies should focus on the lower-risk CPVT populations – asymptomatic children and adults – and reasons for non-adherence to further improve BB treatment, particularly in high-risk CPVT patients.

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Supplemental Materials

Supplemental Table 1

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Table 1. Baseline Characteristics

	Atenolol (N=51)	**Bisoprolol (N=19)**	**Metoprolol (N=33)**	**Nadolol (N=140)**	**Propranolol (N=70)**	**Other (N=16)**	***P***
Median age at diagnosis [IQR]	12 [9-15]	11 [9-14]	13 [10-15]	13 [9-15]	12 [8-14]	10 [8-14]	0.750
Median age at initiation BB therapy [IQR]	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 SCD <40 years 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
SCA, 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
ICD at baseline, n (%)	3 (5.9)	0 (0.0)	1 (3.0)	14 (10.0)	4 (5.7)	1 (5.9)	0.245
LCSD at baseline, n (%)	0	0	0	0	0	0	NA

*Defined as syncope with or without seizures or sudden cardiac arrest. BB indicates beta-blocker; ICD, implantable cardiac defibrillator; IQR, interquartile range; LCSD, left cardiac sympathetic denervation; SCA, sudden cardiac arrest; SCD, sudden cardiac death, SD, standard deviation.

Table 2. Multivariate Cox Proportional Model of Individual Beta-blockers in Symptomatic Children

	Primary endpoint		**Secondary endpoint**	
	Hazard Ratio (95% CI)	***P***	**Hazard Ratio (95% CI)**	***P***
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*

*_P_-value of the Log-likelihood ratio test. AE indicates arrhythmic event; CI; Confidence Interval; nfAE, (near-)fatal arrhythmic event. Reference group is nadolol and therefore no hazard ratio nor _P_-value for nadolol is reported in this table.

Table 3. Maximum Daily Dosage Per Beta-blocker Group

	Atenolol	**Bisoprolol**	**Metoprolol**	**Nadolol**	**Propranolol**	**Complete cohort**	***P***
Median daily dosage in mg/kg [IQR] 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 AE (% 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 nfAE (% 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 since patients could be included in multiple groups.
AE indicates arrhythmic event; IQR, interquartile range; nfAE, (near-)fatal arrhythmic event.

Figure Legends

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 as they were inappropriately coded as having an atypical genotype. This is a random sample. †Defined as cardiomyopathy (unless due 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. *CASQ2* indicates calsequestrin; *LP*, likely pathogenic variant; *P*, pathogenic variant; *RYR2*, ryanodine receptor; VUS, variant of uncertain significance.

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

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

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

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