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An international multicenter cohort study on implantable cardioverter-defibrillators for the treatment of symptomatic children with catecholaminergic polymorphic ventricular tachycardia

Avani Lamba, BS,[1] Thomas M. Roston, MD, PhD,[1,2] Puck J. Peltenburg, MD,[3,4,41] Dania Kallas, MS,[1] Sonia Franciosi, PhD,[1] Krystien V.V. Lieve, MD, MSc,[3,41] Prince J. Kannankeril, MD,[5] Minoru Horie, MD, PhD,[6] Seiko Ohno, MD, PhD,[6,7] Ramon Brugada, MD,[8] Takeshi Aiba, MD,[9] Peter Fischbach, MD,[10] Linda Knight, MS, CGC,[10] Jan Till, MBBS, BS, MD,[11] Sit-Yee Kwok, MBChB,[12] Vincent Probst, MD,[13,41] David Backhoff, MD,[14,41] Martin J. LaPage, MD, MS,[15] Anjan S. Batra, MD, MBA,[16] Fabrizio Drago, MD,[17,41] Kristina Haugaa, MD, PhD,[18,41] Andrew D. Krahn, MD,[2] Tomas Robyns, MD,[19,41] Heikki Swan, MD,[20,41] Terezia Tavacova, MD,[21,41] Christian van der Werf, MD, PhD,[3,41] Joseph Atallah, MD, CM, MS,[22] Martin Borggrefe, MD,[23] Boris Rudic, MD,[23] Georgia Sarquella-Brugada, MD, PhD,[24,41] Ehud Chorin, MD, PhD,[25] Allison Hill, MD,[26] Janneke Kammeraad, MD, PhD,[27,41] Anna Kamp, MD, MPH,[28] Ian Law, MD,[29] James Perry, MD,[30] Jason D. Roberts, MD, MAS,[31] Svjetlana Tisma-Dupanovic, MD,[32] Christopher Semsarian, MBBS, PhD, MPH,[33] Jonathan R. Skinner, MD,[34] Jacob Tfelt-Hansen, MD, DMSc,[35,41] Isabelle Denjoy, MD,[36,41] Antoine Leenhardt, MD,[36,41] Peter J. Schwartz, MD,[37] Michael J. Ackerman, MD, PhD,[38] Nico A. Blom, MD, PhD,[4,39,41] Arthur A.M. Wilde, MD, PhD,[3,40,41] Shubhayan Sanatani, MD[1,40]

ABSTRACT

BACKGROUND Catecholaminergic polymorphic ventricular tachycardia (CPVT) may cause sudden cardiac death (SCD) despite medical therapy. Therefore, implantable cardioverter-defibrillators (ICDs) are commonly advised. However, there is limited data on the outcomes of ICD use in children.

OBJECTIVE The purpose of this study was to compare the risk of arrhythmic events in pediatric patients with CPVT with and without an ICD.

From the [1]BC Children's Hospital, Division of Cardiology, Department of Pediatrics, The University of British Columbia, Vancouver, British Columbia, Canada, [2]Center for Cardiovascular Innovation, Division of Cardiology, The University of British Columbia, Vancouver, Canada, [3]Amsterdam UMC, University of Amsterdam, Heart Centre, Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, the Netherlands, [4]Department of Pediatric Cardiology, Amsterdam UMC, University of Amsterdam, Emma Children's Hospital, Amsterdam, The Netherlands, [5]Department of Pediatrics, Monroe Carell Jr Children's Hospital at Vanderbilt, Vanderbilt University Medical Centre, Nashville, Tennessee, [6]Department of Cardiovascular Medicine, Shiga University of Medical Science, Otsu, Japan, [7]Department of Bioscience and Genetics, National Cerebral and Cardiovascular Centre, National Cerebral and Cardiovascular Centre, Suita, Japan, [8]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; Cardiovascular Genetics Center, Institut d'Investigació Biomèdica Girona (IDIBGI), University of Girona, Girona, Spain; Medical Science Department, School of Medicine, University of Girona, Girona, Spain; Cardiology Service, Hospital Josep Trueta, Girona, Spain, [9]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Centre, Suita, Japan, [10]Sibley Heart Center, Children's Healthcare of Atlanta, Atlanta, Georgia, [11]Department of Cardiology, Royal Brompton Hospital, London, UK, [12]Hong Kong Children's Hospital, Hong Kong, SAR China, [13]Université de Nantes, CHU Nantes, CNRS, INSERM, l'institut du thorax, Nantes, France, [14]University of Gottingen, Gottingen, Germany, [15]University of Michigan, Ann Arbor, Michigan, [16]Division of Cardiology, Department of Pediatrics, Irvine and Children's Hospital of Orange County, University of California, Orange, California, [17]Pediatric Cardiology and Cardiac Arrhythmias Unit, Department of Pediatric Cardiology and Cardiac Surgery, Bambino Gesù Children's Hospital, IRCCS, Palidoro-Rome, Italy, [18]ProCardio Center for Innovation, Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; and Department of Cardiology, Karolinska University Hospital, and Department of Medicine, Huddinge, Karolinska Institute, Stockholm, Sweden, [19]Department of Cardiovascular Diseases, University Hospitals Leuven, Belgium; Department of Cardiovascular Sciences,

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METHODS We compared the risk of SCD in patients with *RYR2* (ryanodine receptor 2) variants and phenotype-positive symptomatic CPVT patients with and without an ICD who were younger than 19 years and had no history of sudden cardiac arrest at phenotype diagnosis. The primary outcome was SCD; secondary outcomes were composite end points of SCD, sudden cardiac arrest, or appropriate ICD shocks with or without arrhythmic syncope.

RESULTS The study included 235 patients, 73 with an ICD (31.1%) and 162 without an ICD (68.9%). Over a median follow-up of 8.0 years (interquartile range 4.3–13.4 years), SCD occurred in 7 patients (3.0%), of whom 4 (57.1%) were noncompliant with medications and none had an ICD. Patients with ICD had a higher risk of both secondary composite outcomes (without syncope: hazard ratio 5.85; 95% confidence interval 3.40–10.09; $P < .0001$; with syncope: hazard ratio 2.55; 95% confidence interval 1.50–4.34; $P = .0005$). Thirty-one patients with ICD (42.5%) experienced appropriate shocks, 18 (24.7%) inappropriate shocks, and 21 (28.8%) device-related complications.

CONCLUSION SCD events occurred only in patients without an ICD and mostly in those not on optimal medical therapy. Patients with an ICD had a high risk of appropriate and inappropriate shocks, which may be reduced with appropriate device programming. Severe ICD complications were common, and risks vs benefits of ICDs need to be considered.

KEYWORDS Ventricular tachycardia; Sudden cardiac death; Catecholaminergic polymorphic ventricular tachycardia; Inherited arrhythmia; Ryanodine receptor; Implantable cardioverter-defibrillator

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited arrhythmia syndrome that can cause sudden cardiac death (SCD) and is defined by adrenergic-induced bidirectional and/or polymorphic ventricular tachycardia (VT) during emotional or physical stress.[1,2] CPVT is often associated with a young age at presentation, with median symptom onset in late childhood and early adolescence.[3,4] β-blockers, particularly nonselective agents, are first-line therapy.[1,5] Flecainide and left cardiac sympathetic denervation (LCSD) are effective adjunctive options that can be combined with β-blockers.[6,7] However, arrhythmic events despite combination therapy of a β-blocker and flecainide have been described in ∼10% of pediatric patients.[4] Current practice guidelines recommend that an implantable cardioverter-defibrillator (ICD) should be inserted in patients with prior sudden cardiac arrest (SCA) or ventricular arrhythmias and/or cardiac events despite combination therapy with a β-blocker and flecainide.[8,9] While patients with CPVT have been reported to have high rates of appropriate shocks,[10,11] this approach remains controversial because ICDs for CPVT are also associated with a reduced quality of life, frequent reinterventions for generator and lead issues, and traumatic repetitive shocks, both appropriate and inappropriate.[10–12] In addition, reports of death due to and despite ICDs have been reported previously.[12–14] In this study, we compare the risk of life-threatening arrhythmic events in symptomatic children with CPVT with and without an ICD.

Methods

Study population

This retrospective study comprises patients from 2 international multicenter registries: the International Pediatric CPVT Registry (based in Vancouver, Canada) and the International CPVT Registry (based in Amsterdam, The Netherlands) established in 2015 and 2014, respectively.[4,14] The International Pediatric CPVT Registry enrolls patients with CPVT diagnosed before 19 years of age and their first-degree relatives; as of December

University of Leuven, Leuven, Belgium, [20]Heart and Lung Centre, Helsinki University Hospital and Helsinki University, Helsinki, Finland, [21]Department of Pediatric Cardiology, Children's Heart Centre, Second Faculty of Medicine, Charles University in Prague, Motol University Hospital, Prague, Czech Republic, [22]Cardiology, Faculty of Medicine & Dentistry - Pediatrics Dept., Stollery Children's Hospital, Edmonton, Canada, [23]Department of Medicine, University Medical Center Mannheim, Mannheim, Germany; German Center for Cardiovascular Research (DZHK), Partner Site Heidelberg, Mannheim, Germany, [24]Pediatric Arrhythmias, Inherited Cardiac Diseases and Sudden Death Unit, Hospital Sant Joan de Déu, Spain; Medical Science Department, School of Medicine, Universitat de Girona, Girona, Spain, [25]Department of Cardiology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [26]Children's Hospital Los Angeles, Los Angeles, California, [27]Department of Pediatric Cardiology, Erasmus MC - Sophia, Rotterdam, The Netherlands, [28]Nationwide Children's Hospital, Columbus, Ohio, [29]University of Iowa Stead Family Children's Hospital, Iowa City, Iowa, [30]Rady Children's Hospital, San Diego, California, [31]Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, Western University, London, Ontario, Canada; Population Health Research Institute, Hamilton Health Sciences, and McMaster University, Hamilton, Ontario, Canada, [32]Nemours Children's Clinic, Orlando, Florida, [33]Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, The University of Sydney, Sydney, Australia; Faculty of Medicine and Health, The University of Sydney, Sydney, Australia, [34]Cardiac Inherited Disease Group New Zealand, Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand; Department of Paediatrics Child and Youth Health, The University of Auckland, Auckland, New Zealand, [35]Department of Cardiology, Rigshospitalet, Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [36]Service de Cardiologie et CNMR Maladies Cardiaques Héréditaires Rares, Hôpital Bichat, APHP, Université de Paris Cité, Paris, France, [37]Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin, Milan, Italy, [38]Departments of Cardiovascular Medicine, Pediatric and Adolescent Medicine, and Molecular Pharmacology & Experimental Therapeutics; Division of Heart Rhythm Services and Pediatric Cardiology, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota, and [39]Department of Pediatric Cardiology, Willem-Alexander Children's Hospital, Leiden University Medical Centre, Leiden, The Netherlands.

[40]Drs Wilde and Sanatani contributed equally to this work.

[41]Member of the European Reference Network for rare, low prevalence and complex diseases of the heart: ERN GUARD-Heart.

2022, a total of 245 CPVT (pediatric) patients from 27 centers have been enrolled in this registry. The International CPVT Registry enrolls pediatric and adult patients with CPVT; as of December 2022, a total of 1465 CPVT patients from 30 centers have been enrolled in this registry. Both registries include patients diagnosed with CPVT according to diagnostic criteria established by major practice guidelines.[8,9] All diagnoses were made by cardiologists at participating institutions. Institutional review board approval was obtained in accordance with the requirements at each participating center. The research reported in this article adhered to the Helsinki Declaration (as revised in 2013) guidelines.

We included patients with CPVT who were younger than 19 years and without a history of SCA at the date of their CPVT phenotype diagnosis (baseline). Since the presence of symptoms and the age at symptom onset are known to be important predictors of adverse arrhythmic outcomes in patients with CPVT,[4] we included only children with a CPVT phenotype and cardiac symptoms including syncope with or without seizures, near-syncope, palpitations, or documented VT. In addition, all included patients had a *RYR2* (ryanodine receptor 2) variant that was (likely) pathogenic (class 4–5) or of uncertain significance (class 3), determined according to the American College of Medical Genetics and Genomics criteria.[15] Patients with *RYR2* variants of unknown significance were included only if they did not have SCA before baseline, and a definite CPVT phenotype, defined as bigeminal ventricular premature beats or more complex VAs in probands and isolated ventricular premature beats or more complex VAs in family members on exercise stress test, epinephrine challenge test, or Holter monitoring.[5] Patients with significant cardiac comorbidities or hemodynamically significant heart disease, defined as cardiomyopathy, (a history of) significant coronary artery disease, or (a history of) moderate or severe aortic, pulmonary, or mitral valve stenosis or regurgitation, were excluded. In addition, we excluded patients with *RYR2* exon 3 deletion and known *RYR2* loss-of-function variants causing calcium release deficiency syndrome[16] as well as those with variants in other CPVT-related genes such as *CASQ2* (calsequestrin 2), *TECRL* (*trans*-2,3-enoyl-CoA reductase–like), *TRDN* (triadin), and *CALM1–3* (calmodulin 1–3), or those with a second (likely) pathogenic variant in the *RYR2* or *CASQ2* genes. Patients with <6 months of follow-up were also excluded unless they experienced an arrhythmic event within this period.

Abbreviations

CALM: calmodulin

CASQ2: calsequestrin 2

CPVT: catecholaminergic polymorphic ventricular tachycardia

ICD: implantable cardioverter-defibrillator

LCSD: left cardiac sympathetic denervation

RYR2: ryanodine receptor 2

SCA: sudden cardiac arrest

SCD: sudden cardiac death

VF: ventricular fibrillation

VT: ventricular tachycardia

Data collection and outcomes

Patient data for both registries were entered into REDCap, a secure web application.[17] We collected data on demographics, presenting symptom(s), clinical and genetic testing, treatments, and outcomes at baseline and during follow-up. Syncope must have been exertional in nature or occurred in the absence of prodromal symptoms suggestive of autonomic instability, indicating a presumed arrhythmic event. ICD-related outcomes such as appropriate and inappropriate shocks, electrical storm, and device-related complications were adjudicated by local investigators.

The primary outcome analyzed was the incidence of SCD in patients with and without ICD. Secondary outcomes were composite end points of (1) SCD, SCA, or appropriate ICD shocks and (2) SCD, SCA, appropriate ICD shocks, or arrhythmic syncope. Survival time was calculated for all patients from the date of their CPVT phenotype diagnosis to the date of the occurrence of the 2 secondary composite outcomes or the date of last follow-up entered in the registries, whichever occurred first. The median follow-up time for the primary analyses was calculated for patients with and without an ICD from the date of CPVT phenotype diagnosis to the date of SCD, or date of last registry contact, as appropriate. For 9 patients, an ICD was implanted before the date of CPVT phenotype diagnosis. For these patients, date of ICD implantation was used as the baseline for both survival and follow-up time calculations.

Statistical analysis

For comparison of clinical characteristics, continuous variables are reported as median with interquartile range for non-normal distributions and as mean ± SD for normal distributions and are compared using the Wilcoxon rank-sum test and the independent sample *t* test, respectively. Categorical data are reported as count and proportion and are compared using the Pearson χ^2 test or Fisher exact test, as appropriate.

ICD therapy, β-blockers, flecainide, and LCSD therapy were treated as time-dependent covariates to ensure that therapies were only considered in regression for the appropriate durations during follow-up. β-blocker variable had 3 levels: nonselective β-blocker, β1-selective β-blocker, and no β-blocker. Nadolol, propranolol, carvedilol, labetalol, carteolol, and alprenolol were considered nonselective β-blockers, and atenolol, bisoprolol, metoprolol, betaxolol, acebutolol, celiprolol, and kerlone were β1-selective β-blockers.[5] Cox regression models for the 2 secondary composite outcomes were used to calculate hazard ratios and 95% confidence intervals and to adjust for potential confounders. Cox regression was not conducted for the primary outcome (SCD) because the ICD group had no SCD event. The likelihood ratio test was used to evaluate the statistical significance of the overall models, and the χ^2 tests involving the parameter estimates and standard errors were used to evaluate the statistical significance of separate categories. Possible confounders (age at symptom onset, sex, and proband status) and time-dependent covariates of treatment with β-blockers, flecainide, and LCSD at baseline or during follow-up were assessed. All covariates that were associated with the outcome in univariable analysis with a *P* value of <.25 were included in

the final multivariable Cox regression model. Nested models were compared using the likelihood ratio test.

The proportional hazards assumption was checked using the Schoenfeld test and residuals. The proportional hazards assumption was considered met if the *P* value was >.05 for the model. If the model *P* value was statistically significant, we used a step function to stratify for the risk factor that violated the proportional hazards assumption on the basis of the distribution of Schoenfeld residuals by time. The results of the Schoenfeld test are presented in Online Supplemental Tables 1–4. A *P* value of <.05 was considered statistically significant. All analyses were performed using R version 4.2.2. (R Project for Statistical Computing, Vienna, Austria).[18]

Results

Clinical characteristics of the study population

A total of 235 symptomatic patients with CPVT without a history of SCA at baseline were included (Figure 1), of whom 73 (31.1%) had an ICD implanted anytime between baseline or follow-up and 162 (68.9%) never had an ICD during the duration of the study. The mean age at CPVT phenotype diagnosis was 11.5 ± 3.8 years for the no ICD group and 11.7 ± 3.5 years for the ICD group (*P* = .690). A total of 230 patients (97.9%) were treated with β-blockers, 145 (60.9%) with flecainide, and 53 (22.6%) with LCSD at any time during follow-up. LCSD was more common in the ICD group (31.5%) compared with the no ICD group (18.5%) (*P* = .027). The clinical characteristics of both groups are presented in Table 1.

Clinical outcomes during follow-up

Over a median follow-up of 8.0 years (interquartile range 4.3–13.4 years), 7 patients (3.0%) experienced SCD, all of whom did not have an ICD at the time of SCD. Circumstances during SCD events in the 7 (3.0%) patients are reported in Table 2. Compliance at the time of SCD was known for 6 (85.7%) patients, of whom 4 (66.7%) were noncompliant with medications. This corresponds to an SCD event rate of 3 of 162 (1.9%; 0.23% per year) in patients without ICD among patients who were presumably compliant with medications. Only 2 (33.3%) patients were both compliant and adequately treated with medications during their SCD events. One (50.0%) of the latter 2 patients died in the hospital and could not be controlled with any therapy.

In the univariable model, ICDs were associated with a higher risk of secondary composite outcome excluding syncope compared with the no ICD group (Hazard Ratio 5.85; 95% CI 3.40–10.09; *P* < .0001) (Table 3). β-blocker, flecainide, and proband status were included in the multivariable analysis, and after adjustment, ICDs were still associated with a higher risk compared with the no ICD group (Hazard Ratio

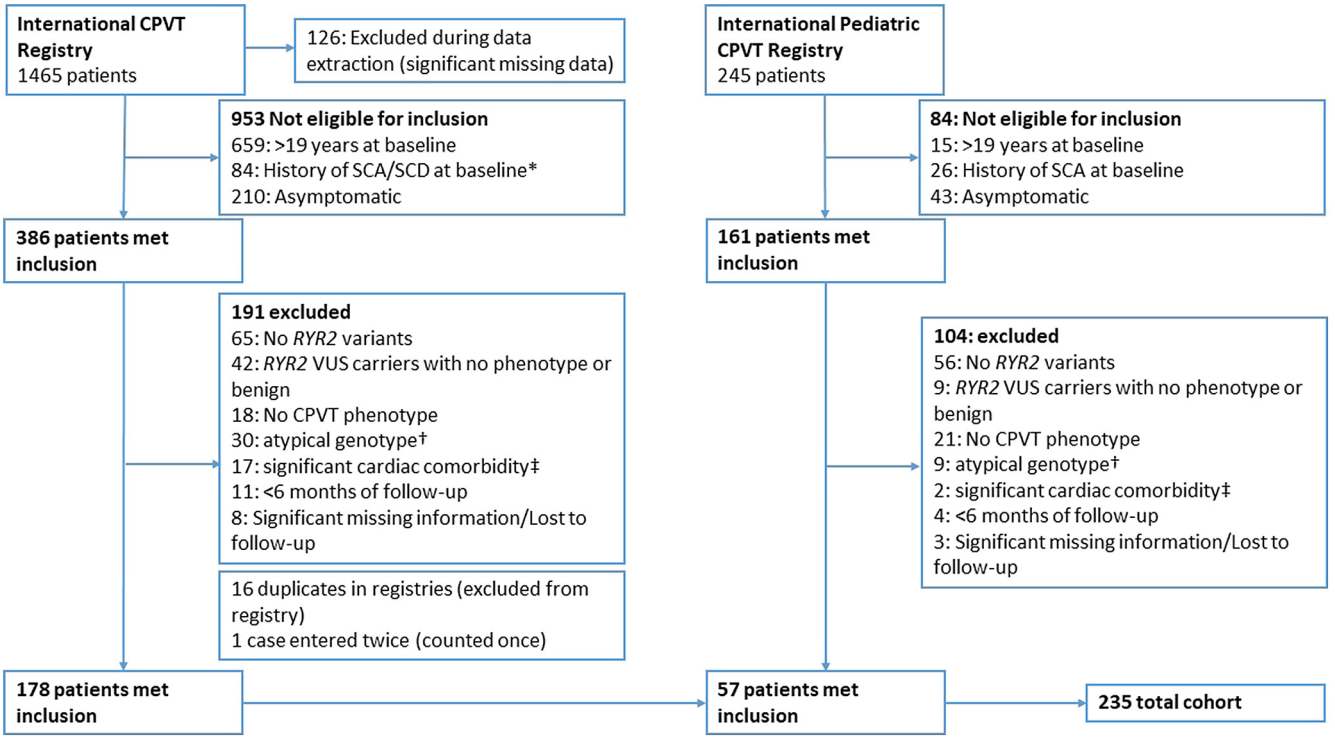

Figure 1
Flowchart depicting the study cohort selection process. *One patient experienced SCD before the diagnosis and was excluded. †Defined as *RYR2* exon 3 variants, a *RYR2* loss-of-function variant (CRDS), variants in other genes associated with CPVT such as *CALM1*, and a second (likely) pathogenic variant in the *RYR2* or *CASQ2* gene. ‡Defined as cardiomyopathy, a history of significant coronary artery disease, or a history of moderate or severe aortic, pulmonary, or mitral valve stenosis or regurgitation. Patients with <6 months of follow-up who experienced cardiac events (SCD, SCA, appropriate ICD shocks, or syncope) within this period were not excluded. *CALM1* = calmodulin 1; *CASQ2* = calsequestrin 2; CPVT = catecholaminergic polymorphic ventricular tachycardia; CRDS = calcium release deficiency syndrome; ICD = implantable cardioverter-defibrillator; *RYR2* = ryanodine receptor 2; SCA = sudden cardiac arrest; SCD = sudden cardiac death; VUS = variant of uncertain significance.

Table 1 Clinical characteristics of patients with CPVT with and without an ICD

Characteristic	No ICD (n = 162)	ICD (n = 73)	*P*
Mean age at baseline (y)	11.5 ± 3.8	11.7 ± 3.5	.690
Mean age at the first symptom (y)	10.2 ± 3.9	10.4 ± 3.7	.815
Female	78 (48.1)	31 (42.5)	.419
Proband	139 (85.8)	59 (80.8)	.332
Family member with SCD/SCA	39 (24.1)	18 (24.7)	.923
Worst symptom before diagnosis			
Syncope with seizures	37 (22.8)	14 (19.2)	.529
Syncope without seizures	115 (80.0)	55 (75.3)	.490
Other cardiac symptoms*	10 (6.2)	4 (5.5)	.835
RYR2 variant classification			
Pathogenic	109 (67.3)	48 (65.8)	.818
Likely pathogenic	10 (6.2)	2 (2.7)	.269
Uncertain significance	43 (26.5)	23 (31.5)	.433
Median age at ICD implantation (y)	NA	15 (11–18)	NA
At any time during follow-up			
β-blocker	159 (98.1)	71 (97.3)	.662
First β-blocker			
Atenolol	17 (10.5)	12 (16.4)	.200
Bisoprolol	15 (9.3)	7 (9.6)	.936
Metoprolol	13 (8.0)	6 (8.2)	.960
Nadolol	80 (49.4)	29 (39.7)	.170
Propranolol	23 (14.2)	15 (20.5)	.221
Other	11 (6.8)	2 (2.7)	.209
Most recent β-blocker			
Atenolol	4 (2.5)	4 (5.5)	.239
Bisoprolol	12 (7.4)	10 (13.7)	.125
Metoprolol	9 (5.6)	6 (8.2)	.440
Nadolol	108 (66.7)	41 (56.2)	.122
Propranolol	18 (11.1)	10 (13.7)	.571
Other	8 (4.9)	0 (0.0)	.061
Flecainide	98 (60.5)	45 (61.6)	.867
LCSD	30 (18.5)	23 (31.5)	.027

Values are presented as mean ± SD, median (interquartile range), or n (%).
CPVT = catecholaminergic polymorphic ventricular tachycardia; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; NA = not applicable; *RYR2* = ryanodine receptor 2; SCA = sudden cardiac arrest; SCD = sudden cardiac death.
*Other cardiac symptoms were near-syncope, palpitations, and documented ventricular tachycardia/ventricular arrhythmia.

5.93; 95% CI 3.38–10.40; $P < .0001$); however, both models fit the data equally well (likelihood ratio test, $P = .179$). We also fit stratified univariable and multivariable Cox models for this composite end point (Online Supplemental Table 2).

In the univariable model, ICDs were associated with a higher risk of secondary composite outcome including syncope compared with the no ICD group (Hazard Ratio 2.59; 95% CI 1.54–4.35; $P = .0003$). β-blocker, flecainide, and age at the first symptom were included as covariates in the multivariable analysis, and after adjustment, ICDs were still associated with a higher risk of this outcome compared with the no ICD group (Hazard Ratio 2.55; 95% CI 1.50–4.34; $P = .0005$, likelihood ratio test, $P = .007$) (Table 3).

Over a median follow-up of 6.1 years, 91 events occurred in patients with no ICD in place, of which 60 (65.9%) were (presumed) arrhythmic syncope, 24 (26.4%) were SCA, and 7 (7.7%) were SCD. Among patients with ICD during follow-up, 33 of 73 patients (45.2%) experienced a total of 98 cardiac events, of which 92 (93.9%) were appropriate shocks, 4 (4.1%) were (presumed) arrhythmic syncope, and 2 (2.0%) were SCA. Of the 92 patients who reported appropriate ICD shocks, 48 (52.2%) were on either nadolol or propranolol and 25 (27.2%) were on dual therapy with flecainide. Corrected daily dosage was available for 60 patients (64.5%), of whom 14 (23.3%) were on suboptimal therapy; and compliance at the time was known for 52 (56.5%), of whom 22 (42.3%) were noncompliant and 2 (3.6%) were not on therapy at the time of appropriate shock (Online Supplemental Table 5). A total of 22 inappropriate shocks occurred in 18 patients (24.7%); of those shocks, 8 (36.4%) were due to supraventricular arrhythmia, 7 (31.8%) due to unspecified ICD malfunction, 4 (18.2%) due to inappropriate sensing, and 3 (13.6%) due to electrical noise. Types and proportions of ICD-related complications in patients with ICD are presented in Table 4. A total of 5 patients (6.8%) experienced ICD storm. Overall, at least 1 inappropriate shock and/or major device-related complication occurred in 30 patients (40.5%) treated with an ICD. A total of 14 patients (19.2%) had their ICD implanted after an SCA event during follow-up, and 5 of these patients (35.7%) subsequently experienced an arrhythmic event. A total of 5 patients (6.8%) had their ICD deactivated/explanted during follow-up. Reasons for ICD explantation are presented in the Online Supplement.

Discussion

In this study cohort, SCD events exclusively occurred in those without ICD. However, noncompliance with guideline-directed therapy was common in these patients. Patients with ICD had a high risk of experiencing appropriate shocks. At least 1 inappropriate shock and/or major device-related complication occurred in 40% of patients treated with an ICD. Collectively, these data demonstrate that ICD decision making in the setting of CPVT is highly complex, and while there is a potential for a lifesaving benefit, a potential risk of serious complications also exists.

The primary outcome of SCD alone did not occur in those who had ICD, and consequently regression models could not be constructed because of the absence of SCD events. A recent large single-center study similarly reported that none of their patients with ICD, but 4 patients without ICD (treated with only β-blockers), experienced SCD.[19] However, a paradoxical finding in our cohort was the observation that ICD recipients had a higher risk of meeting the secondary composite outcomes—this was driven by the appropriate shock (42.5% patients, over a median follow-up of 6.2 years) component of the outcome, which was an end point that could not be met by the non-ICD cohort. A prior study of SCA survivors, not previously on medical therapy, showed a similar increased risk of arrhythmic events in patients with ICD compared with patients without ICD driven by a very high appropriate shock rate (46% over 5 years).[14]

Consequently, the next rational step is to focus on why ICD shocks occur so frequently in patients with CPVT. One of the

Table 2 Circumstances during events in 7 patients who experienced SCD (primary outcome)

Patient no.	Circumstance during the event	Age at the event (y)	Proband status	*RYR2* variant classification	Medications/therapies during the event (daily dosage)	Compliance
1	The patient was found unresponsive after sports training. The patients forgot to take medications on the day of the event	17	Proband	VUS	Metoprolol (0.86 mg/kg)	Noncompliant
2	The event occurred immediately after the patient left work. The patient was stressed immediately before the event. The patient discontinued taking medications ∼13 mo before the event	36	Proband	Pathogenic	None	Noncompliant
3	The event occurred at home while at rest. The patient was an avid sports player. Compliance at the time of the event is unknown; however, the patient had a history of being difficult to instruct regarding medications	16	Proband	Pathogenic	Propranolol (1.59 mg/kg)	Unknown
4	The event occurred during sports training. The patient had discontinued taking flecainide before the event	22	Proband	Pathogenic	Nadolol (2 mg/kg); flecainide (2.5 mg/kg)	Noncompliant
5	The patient experienced severe ventricular arrhythmias during the hospital stay before the event. Verapamil boluses were tried during VT episodes without success. Before initiating oral propranolol, the patient was treated with esmolol intravenous therapy and labetalol intravenous therapy. During hospitalization, the patient was under sedation with pentobarbital. LCSD was clinically ineffective, and ventricular arrhythmia persisted. Right-sided CSD was planned 6 dafter LCSD; however, the patient died before planned RCSD	8	Proband	Pathogenic	Propranolol (dosage unknown); flecainide (2.4 mg/kg). LCSD performed 5 d before death to manage VT. Extent of denervation not known	Compliant
6	The event occurred during sports training. The patient had not been taking medications as prescribed. The patient previously had an ICD; however, the ICD was explanted 7 mo before the event	18	Proband	VUS	Nadolol (0.25 mg/kg); propafenone (2.8 mg/kg). LCSD (complete denervation) performed 8 y before death to manage VT	Noncompliant
7	The patient was found unresponsive after an emotionally stressful event. The patient had a history of being compliant with medications	27	Nonproband	Pathogenic	Nadolol (1.27 mg/kg); flecainide (1.59 mg/kg)	Probably compliant

CSD = cardiac sympathetic denervation; LCSD = left cardiac sympathetic denervation; RCSD = right cardiac sympathetic denervation; *RyR2* = ryanodine receptor 2; SCD = sudden cardiac death; VT = ventricular tachycardia; VUS = variant of uncertain significance.

Table 3 Cox model output for secondary outcomes

	Univariable analysis		Multivariable analysis	
Outcome	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
SCD, SCA, or appropriate ICD shock	5.85 (3.40–10.09)	<.0001	5.93 (3.38–10.40)	<.0001
SCD, SCA, appropriate shock, or syncope	2.59 (1.54–4.35)	.0003	2.55 (1.50–4.34)	.0005

CI = confidence interval; ICD = implantable cardioverter-defibrillator; SCA = sudden cardiac arrest; SCD = sudden cardiac death.

main reasons probably relates to device programming algorithms. Traditional ICD settings may deliver early shocks for hemodynamically stable polymorphic or bidirectional VT that would have otherwise been self-limiting. In one of the original descriptions of pediatric CPVT, Leenhardt et al[2] stated that "children very quickly learned how to avoid the stress that might trigger the lightheadedness." This common observation in CPVT may indicate that patients are aware that most of their arrhythmias will subside upon immediate rest, which thus potentially leads to the avoidance of syncope. However, standard ICD programming may not factor in the predictable response of patients with CPVT to symptoms. Any future study examining the risks and benefits of ICD use in CPVT must prospectively use a CPVT-specific programming algorithm that minimizes and delays the delivery of shocks. In addition, it is possible that these patients were prone to having recurrent and incessant VT events and as such ICDs were implanted by treating physicians as prophylactic therapy to prevent potential SCA/SCD events. Some appropriate shocks may have also potentially prevented VT events that would have otherwise precipitated to SCA/SCD. However, it is also important to consider that appropriate shocks are not always synonymous or surrogates for cardiac arrest.[14] Interestingly, the majority of these appropriate shocks occurred within the first 6 months of implantation (Figure 2). This may be attributed to treatment alterations and/or programming readjustment early on post–ICD implantation. In addition, only half of the patients were on either nadolol or propranolol during their appropriate shock events. For those in whom dosage and compliance information was available, almost half were noncompliant with medications and a quarter were on suboptimal therapy during their events (Online Supplemental Table 5). Since 1 group cannot experience this end point and appropriate shocks likely overestimate the true life-threatening arrhythmia event rate, it may seem logical to exclude appropriate shocks from the outcomes. However, this could potentially lead to an underreporting of syncope or even SCA in the ICD group, since shocks may abort VAs before loss of consciousness. Therefore, unfortunately, there is no design or method that can completely resolve this issue.

Table 4 Number and proportions of ICD-related events and complications in 73 patients with ICD

Variable	No. of events	No. of patients (%)
Appropriate ICD shocks*	92	31 (42.5)
Inappropriate ICD shocks*	22	18 (24.7)
Electrical noise	3	3 (16.7)
Supraventricular tachycardia	8	8 (44.4)
Inappropriate sensing	4	2 (11.1)
ICD malfunction	7	7 (38.9)
Complications	NA	21 (28.2)
Lead fracture/dislodgment	NA	11 (15.1)
ICD storm	NA	5 (6.8)
Generator dysfunction	NA	2 (2.7)
ICD-related infection	NA	2 (2.7)
Other†	NA	1 (1.4)

ICD = implantable-cardioverter defibrillator; NA = not applicable.
*Shocks, both appropriate and inappropriate, are counted only once if multiple occurred within 24 h.
†Patient had left-sided pneumothorax after ICD implantation.

Medication adherence may explain the outcomes of this study, and noncompliance could be a contributor to increased cardiac events. Therapeutic compliance at the time of SCD was known for 6 of 7 patients (85.7%), of whom at least 4 (66.7%) were noncompliant. In addition, in 3 patients, the β-blocker dosage was lower than that usually suggested in the literature (patients 1, 3 and 6; daily dosage cutoff for adequate therapy was considered as follows: nadolol 1.0 mg/kg, metoprolol 1.0 mg/kg, and propranolol 2.0 mg/kg).[5] Of the 2 patients who were probably compliant, 1 experienced severe VAs in the hospital despite exhaustive medical therapy, including LCSD, which proved to be ineffective. One patient had their ICD explanted less than a year before their death after elective replacement indicator, after which they were managed solely on medications. In the large single-center study that reported similar findings, it was unclear whether patients without ICD who experienced SCD were on adequate medical therapy and compliant at the time of event.[19] Given these findings, we believe that optimal antiarrhythmic therapy without ICD implantation in a fully adherent patient with CPVT likely results in a very low risk of SCD. Our data suggest that a nonselective β-blocker was associated with lower cardiac risk compared with a β1-selective β-blocker (Table 5). Thus, adding flecainide and/or LCSD to nonselective β-blockers is effective and should ideally be used before implanting an ICD.[6,7]

There are other considerations regarding ICD therapies in CPVT. It has been shown in 2 important studies that shocks for polymorphic VT and bidirectional VT are generally ineffective and may trigger more severe arrhythmias.[10,11] In rare cases, arrhythmic death has also been described after exhaustive ICD therapy for incessant VT/ventricular fibrillation (VF),[20] and both inappropriate and appropriate shocks have been implicated in fatal electrical storm.[3,21] This is particularly concerning when considering that 24.7% of the ICD cohort in the

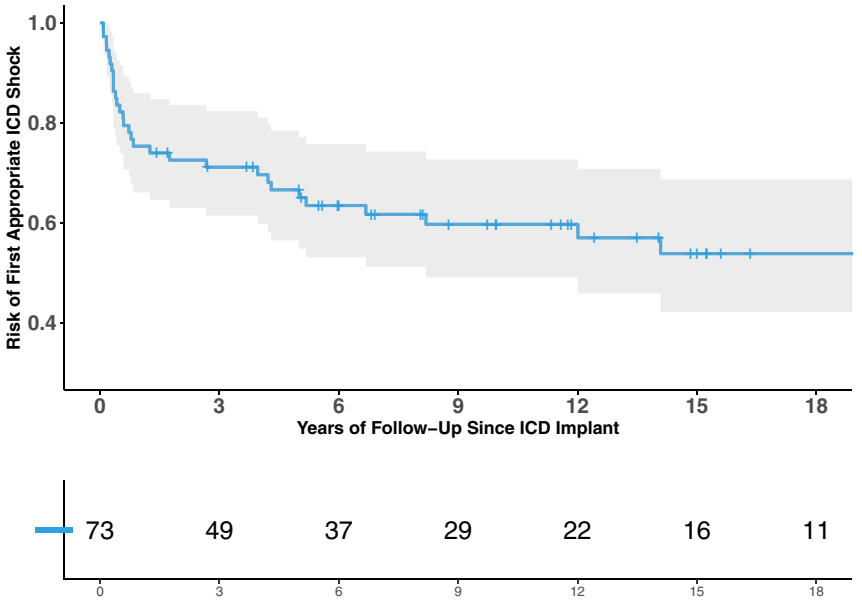

Figure 2
Risk of the first appropriate ICD shock in 73 patients with ICD. Risk-free survival was calculated from the date of ICD implantation and censored at the date of the first appropriate shock. ICD = implantable cardioverter-defibrillator.

present study had at least 1 inappropriate shock—most of which occurred because of supraventricular tachycardia (36.4%), consistent with previous CPVT ICD studies that reported either supraventricular tachycardia (36.8%) or, specifically, atrial tachycardia (36%) as major contributors to inappropriate shocks.[10,14] In addition, antitachycardia pacing appears ineffective for this disease and could potentiate the degeneration of stable VT into fatal VF.[10,11] In contrast, shocks for VF are largely successful.[10,11] Despite these challenges, CPVT-specific device programming that incorporates longer detection times, shorter detection cycle lengths, and eliminates antitachycardia pacing may help prioritize shocks for VF while minimizing therapies for stable polymorphic VT and bidirectional VT.[11,12] While the present study could not assess the efficacy and safety of this approach, it remains a promising option that could beneficially shift the risk-to-benefit ratio. Notably, a minority of patients with ICD had LCSD, which may be a promising adjunctive therapy in patients with ICD. Particularly in patients who reported recurrent ICD shocks, LCSD has shown to dramatically reduce the yearly shock rate (93% reduction in shock rate in a large study comprising patients with CPVT).[7]

ICD complications occurred in 28.8% of the cohort, an observation consistent with previous pediatric (33%) and adult (28.9%) CPVT cohort studies.[10,14] A previous ICD study comprising a diverse cohort (with congenital heart disease,

Table 5 Univariable analysis of potential confounders

		Secondary composite end point (without syncope)		Secondary composite end point (with syncope)	
Covariate		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
β-blocker*	Nonselective β-blocker	Reference	Reference	Reference	Reference
	β1-Selective β-blocker	1.63 (0.89–2.99)	.117	1.95 (1.19–3.22)	.009
	No β-blocker	0.57 (0.20–1.62)	.293	0.71 (0.32–1.58)	.405
Flecainide†		1.50 (0.84–2.68)	.17	0–2 y:2.52 (1.27–4.99)	.008
				2–8 y:0.92 (0.39–2.14)	.840
				>8 y:1.04 (0.29–3.81)	.949
LCSD therapy		0.85 (0.34–2.17)	.742	0.79 (0.34–1.85)	.592
Proband status		2.06 (0.88–4.85)	.096	1.44 (0.76–2.74)	.262
Female‡		0.73 (0.42–1.27)	.262	0.80 (0.51–1.26)	.332
Age at the first symptom		0.96 (0.89–1.03)	.275	0.95 (0.89–1.01)	.116

Significance level: $P < .25$.
CI = confidence interval; LCSD = left cardiac sympathetic denervation.
*β-blocker variable has 3 levels, with nonselective β-blocker being the reference group.
†Stratified in the multivariable composite outcome model with syncope due to violation of the proportional hazards assumption. Strata determined by the distribution of Schoenfeld residuals by time.
‡Males are the reference group.

cardiomyopathy, and channelopathies) reported no significant differences in the frequency of ICD complications between their pediatric and adult populations (2.3% vs 2.6%; $P = .3$).[22] There was heterogeneity in studies regarding the definition of ICD-related complications; however, mechanical complications (including lead dislodgments and malfunction) and infection were commonly reported.[23,24] One recent systematic review of randomized controlled trial studies of adults reported an overall pooled ICD complication rate of 4.4% per year.[21] It is challenging to compare ICD storm rates because this complication is infrequently reported in ICD complication studies, but also because various definitions have been used to describe an ICD storm.[21,25] The incidence of storms has been reported to be between 4% and 60% in previous studies of varying lengths of follow-up, with primary prevention ICDs being associated with lower rates of storm compared with secondary prevention devices; however, the rate is similar for both ischemic and nonischemic disease.[26]

In conclusion, nonselective β-blockers should be considered first-line therapy for all patients with CPVT, followed by flecainide. ICDs may be considered in patients who have recurrent breakthrough arrhythmic events despite use of guideline-directed therapy and may prove lifesaving in these cases. In addition, ICDs may be considered a prophylactic therapeutic option in patients who despite being at high risk of experiencing arrhythmic events are routinely noncompliant with medications. The decision to implant an ICD should be weighed against the potential risks of severe ICD-related complications and recurrent shocks. Despite these findings, the decision to implant an ICD in a patient who is nonadherent to medical therapy or still has significant arrhythmias despite optimization of nadolol, flecainide, and LCSD remains a challenging one. Viewpoints on these data may differ depending on the values and preferences of patients and their physicians. This study cannot address whether preservation of quality of life takes precedence over a low but meaningful risk of SCD in pediatric CPVT.

Limitations

The study was inherently limited by its retrospective multicenter design. Furthermore, we did not have access to device programming data, which in a young, otherwise healthy cohort is a significant contributor to the adjudication of appropriate shocks, and medication adherence was not always known throughout follow-up. Shock appropriateness was determined by the site investigators who were electrophysiologists. The secondary composite outcomes included several different components to capture meaningful outcomes; however, the no ICD group could not experience the appropriate shock outcome. In addition, the high appropriate shock rate within the first 6 months of ICD implantation inflated the overall appropriate shock event rate. Finally, there may be indication bias with regard to outcomes in patients with ICD and unmeasured confounders, particularly differences in arrhythmia severity on exercise stress test between the 2 groups, may potentially indicate that the ICD group is more severely affected than the no ICD group.

Conclusion

SCD events were infrequent in the entire cohort and occurred only in the no ICD group. However, this was predominantly in those who were noncompliant or not on optimal medical therapy. Patients with ICD were at a high risk of experiencing appropriate shocks. Severe ICD-related complications, including ICD storm(s) and inappropriate shocks related to supraventricular tachycardia, were common. These findings present opportunities for improving ICD programming targeted toward CPVT to improve patient outcomes. ICDs may be considered as second line prophylactic therapy in patients who experience breakthrough, recurrent and incessant events despite adhering to guideline-directed therapy or in patients who are routinely noncompliant with medications. This decision should be carefully weighed against the potential for severe ICD-related complications.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.04.006

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Address reprint requests and correspondence: Dr Shubhayan Sanatani, BC Children's Hospital, Division of Cardiology, Department of Pediatrics, The University of British Columbia, 1F9-4480 Oak St, Vancouver, British Columbia, Canada V6H 3V4. E-mail address: ssanatani@cw.bc.ca

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