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Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest

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Aims	In patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), implantable cardioverter-defibrillator (ICD) shocks are sometimes ineffective and may even trigger fatal electrical storms. We assessed the efficacy and complications of ICDs placed in patients with CPVT who presented with a sentinel event of sudden cardiac arrest (SCA) while undiagnosed and therefore untreated.
Methods and results	We analysed 136 patients who presented with SCA and in whom CPVT was diagnosed subsequently, leading to the initiation of guideline-directed therapy, including β-blockers, flecainide, and/or left cardiac sympathetic denervation. An ICD was implanted in 79 patients (58.1%). The primary outcome of the study was sudden cardiac death (SCD). The secondary outcomes were composite outcomes of SCD, SCA, appropriate ICD shocks, and syncope. After a median follow-up of 4.8 years, SCD had occurred in three patients (3.8%) with an ICD and none of the patients without an ICD ($P = 0.1$). SCD, SCA, or appropriate ICD shocks occurred in 37 patients (46.8%) with an ICD and 9 patients (15.8%) without an ICD ($P < 0.0001$). Inappropriate ICD shocks occurred in 19 patients (24.7%) and other device-related complications in 22 patients (28.9%).
Conclusion	In previously undiagnosed patients with CPVT who presented with SCA, an ICD was not associated with improved survival. Instead, the ICD was associated with both a high rate of appropriate ICD shocks and inappropriate ICD shocks along with other device-related complications. Strict adherence to guideline-directed therapy without an ICD may provide adequate protection in these patients without all the potential disadvantages of an ICD.
Keywords	Catecholaminergic polymorphic ventricular tachycardia • Implantable cardioverter-defibrillator • Secondary prevention • Sudden cardiac arrest • Sudden cardiac death

Introduction

Survivors of sudden cardiac arrest (SCA) due to non-reversible cardiac diseases are at increased risk of recurrent and potentially fatal arrhythmic events. Accordingly, implantable cardioverter-defibrillators (ICDs) are generally a Class I indication in these patients to reduce the risk of sudden cardiac death (SCD).[1,2]

In patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), however, this may be different. This inherited arrhythmia syndrome is characterized by adrenergically mediated ventricular arrhythmias, including bidirectional or polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) in individuals with a normal resting ECG and no structural heart disease.[3] In the current North American and European guidelines, an ICD is a Class I recommendation for CPVT patients presenting with SCA,[1,2,4] even when CPVT had not been diagnosed previously and the patient was therefore untreated. However, in patients with CPVT, ICD shocks are sometimes ineffective and potentially proarrhythmic.[5–8] Fatal electrical storms, initiated by both appropriate and, more disturbingly, following inappropriate ICD shocks, have been reported.[9–11] Therefore, the risk–benefit of ICD therapy in patients with CPVT requires further evaluation.

Here, we studied patients with previously undiagnosed and untreated CPVT who presented with SCA as their sentinel event, with an emphasis on the efficacy and complications of ICDs during follow-up.

Methods

Study population

The study population comprised 136 patients from the International CPVT Registry, a multicentre retrospective observational registry established in 2014. In all centres, institutional review board approval was obtained for this type of study.

All patients included in the International CPVT Registry met current phenotypic and/or genotypic diagnostic criteria for CPVT.[4] CPVT was diagnosed based on phenotype in the presence of a structurally normal heart, normal resting ECG, and unexplained exercise- or catecholamine-induced bidirectional or polymorphic ventricular premature beats or VT. In patients >40 years of age, coronary artery disease had to be ruled out. CPVT was diagnosed based on genotype in the presence of a pathogenic variant in the CPVT-associated genes, in particular *RYR2* (heterozygous) and *CASQ2* (homozygous or compound heterozygous). When eligibility for inclusion was uncertain, cases were reviewed by members of the core team of investigators at the Amsterdam UMC, Amsterdam, the Netherlands, to reach consensus.

In this study, we included all patients who presented with a sentinel event of SCA (definition detailed in the Supplementary material online, Supplementary Methods), were diagnosed with CPVT based on the aforementioned phenotypic and/or genotypic diagnostic criteria, and survived to hospital discharge with preserved neurologic function. Patients had to be treatment naïve and guideline-directed therapy, including β-blockers, flecainide, left cardiac sympathetic denervation (LCSD), and/or an ICD,[1,2,4] had to have been initiated after the sentinel SCA. The study population included (mainly historical) cases in which CPVT was not diagnosed initially, but at least one of the aforementioned guideline-directed therapies was initiated after the sentinel SCA, and CPVT was later diagnosed during follow-up. All patients had to have a follow-up period of at least 6 months after the SCA (unless an outcome event occurred within 6 months).

Standardized forms in a custom online database were used to collect patient data, including baseline characteristics, results of cardiac and genetic evaluation, therapy, and arrhythmic events during follow-up (see the Supplementary material online, Supplementary Methods).

Outcomes

The primary outcome was SCD in patients with vs. without an ICD. The secondary outcomes included (i) a composite outcome of SCD, SCA, and appropriate ICD shocks and (ii) a composite outcome of SCD, SCA, appropriate ICD shocks, and syncope in CPVT patients with an ICD vs. without an ICD. SCD, SCA, appropriate ICD shock, and syncope were defined according to current recommendations (see the Supplementary material online, Supplementary Methods).[1,2,12]

Follow-up time for the primary analyses was calculated for each patient as the date of their sentinel SCA to the date of an outcome event, date of ICD implant in patients in whom no ICD was implanted at baseline, date of ICD explant in patients in whom an ICD was implanted at baseline, or date of last contact, whichever occurred first.

Statistical analysis

Continuous variables were compared with the use of the Wilcoxon rank sum test and are reported as median with interquartile ranges (IQRs). Categorical variables were compared with the use of the Fisher's exact test and Pearson's χ^2 test and are reported as frequencies and percentages. Incidence rates were computed by dividing the number of patients experiencing the primary and secondary outcomes by the total number of person-years. We used the Kaplan–Meier method to provide survival estimates with 95% confidence intervals (CIs), which were assessed with a log-rank test. Relative risks or risk differences at 4-year follow-up were calculated by dichotomizing all patients with a minimal follow-up of 4 years by whether or not an event had occurred within this follow-up period. In addition, hazard ratios with 95% CIs and P-values from univariable and multivariable (corrected for age at baseline) Cox regression analyses and from corresponding Wald statistics have been provided. An interaction term was added to the Cox proportional hazards model to investigate the interaction between age as a continuous variable and the presence of an ICD. P-values of <0.05 were considered to indicate statistical significance. All analyses were performed with the use of SPSS Statistics software, version 24 (IBM Corporation, Armonk, NY, USA). All graphs were compiled with the use of R version 3.4.3 (R Project for Statistical Computing, Vienna, Austria).

Results

Characteristics of the patients

A total of 136 patients with a sentinel event of SCA between 1983 and June 2017, who were subsequently diagnosed with and treated for CPVT, were included in the study (Figure 1 and Table 1). Median age at time of the SCA was 14.0 years (IQR 9.0–20.8) and 112 patients (82.4%) presented in or after the year 2000.

One hundred and twenty-nine patients (94.9%) were treated with β-blockers. Thirty-nine patients (28.7%) were treated with flecainide and 10 patients (7.4%) underwent LCSD at baseline or during follow-up.

An ICD was implanted immediately after the sentinel SCA in 79 patients (58.1%). Fifty-seven patients (41.9%) did not receive an ICD, mainly because these patients were considered well protected with medication only and due to concerns regarding the possible proarrhythmic effects of the ICD (Supplementary material online, Table S1).

Patients in whom an ICD was implanted were older [median age 16.0 years (IQR 12.0–26.0)] than patients in whom no ICD was implanted [median age 11.0 years (IQR 7.5–14.0)] (P < 0.001). ICDs were relatively more often implanted in patients from North America (21/28 patients; 75.0%) and Oceania (Australia and New Zealand; 9/9 patients; 100%) than in patients from Europe (45/79 patients; 57.0%) and Asia (4/20 patients, 20.0%).

Patients with an ICD were more often treated with metoprolol and bisoprolol, whereas nadolol and propranolol were more often initiated in patients without an ICD (Table 1). There were no significant differences in the proportion of patients treated with flecainide or LCSD.
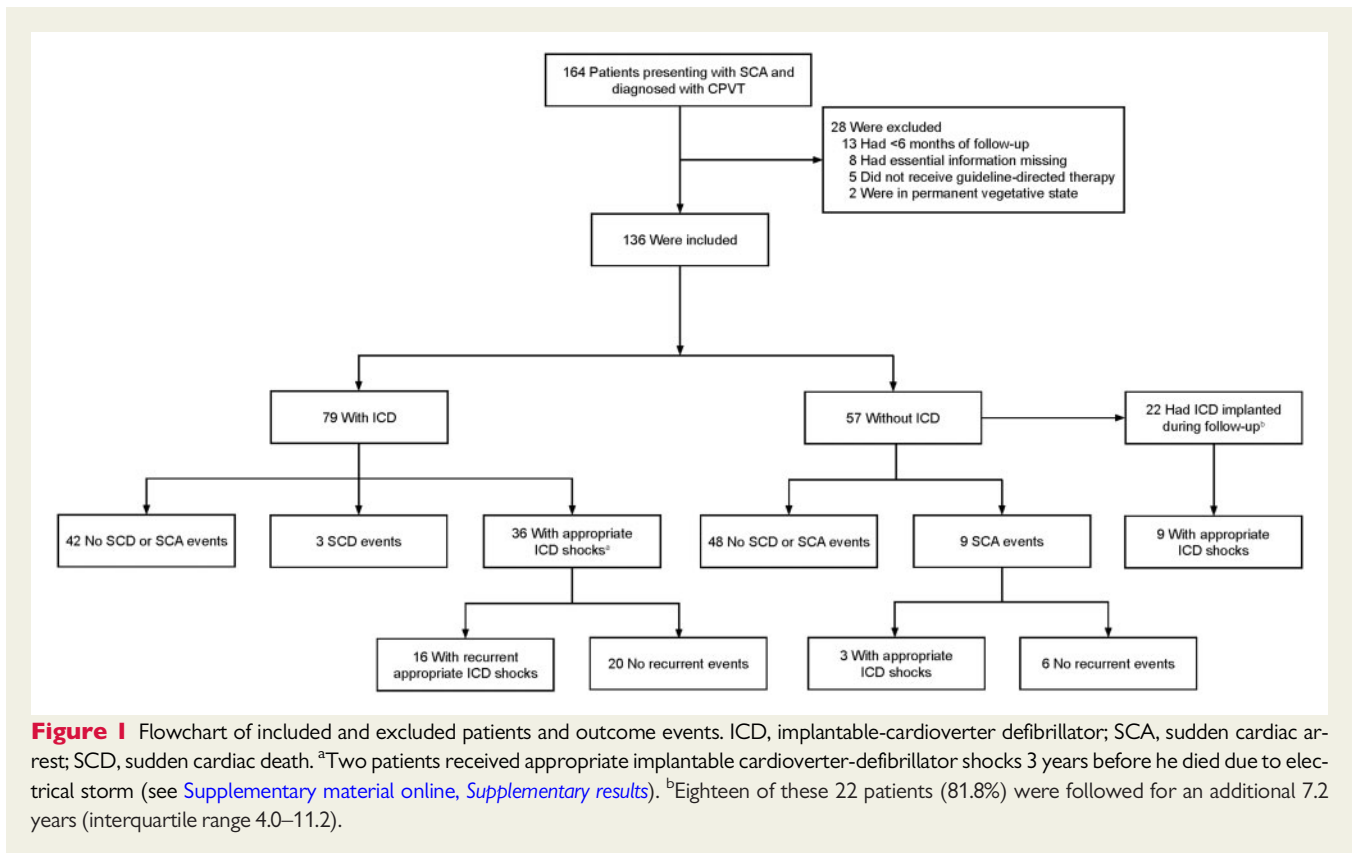
Follow-up and outcomes

After a median follow-up of 4.8 years (IQR 2.5–10.5), SCD had occurred in three patients (3.8%) with an ICD (0.6 events per 100 person-years) and in none of the patients without an ICD (0; P = 0.1 by the log-rank test; Figure 2A and Table 2). At 4 years, SCD event rates were 1.3% (95% CI 0.0–4.0%) in patients with an ICD and 0% in patients without an ICD. The risk difference at 4 years was 2.0%. A detailed description of the three patients with an ICD who died during follow-up is provided in the Supplementary material online, Supplementary Results. None of the patients died due to other causes.

The composite outcome of either SCD, SCA, or appropriate ICD shocks occurred in 37 patients (46.8%) with an ICD (9.7 events per 100 person-years) compared to 9 patients (15.8%) without an ICD (2.3 events per 100 person-years; P < 0.0001 by the log-rank test; Figure 2B and Table 2). Four-year event rates were 39.0% (95% CI 26.3–49.4%) in patients with an ICD and 6.2% (95% CI 0.0–12.8%) in patients without an ICD, and the relative risk at 4 years was 5.0 (95% CI 1.7–15.4). The hazard ratio for SCD, SCA, or appropriate ICD shocks in patients with an ICD, as compared to patients without an ICD, was 5.89 (95% CI 2.66–13.04; P < 0.0001 by multivariable Cox regression).

Regarding those 9/57 patients (15.8%) without an ICD who experienced at least one recurrent SCA after diagnosis and treatment, two of the events occurred in the 1980s. In addition, three events were associated with definite or probable medication non-adherence. Among the six adherent patients, four events occurred in patients on β-blocker monotherapy (metoprolol 0.7 mg/kg/day, propranolol 3 mg/kg/day, and nadolol 160 mg/day and atenolol 50 mg/day in patients with unknown body weight), one event in a patient treated with low-dose bisoprolol (0.1 mg/kg/day) combined with flecainide (6 mg/kg/day), and one event in a possible non-adherent patient treated with nadolol (2.6 mg/kg/day) combined with flecainide (3.3 mg/kg/day).

Appropriate ICD shocks occurred in 36 patients (45.6%) with an ICD. Of these, five patients did not have drug therapy and four events

Figure 1 Flowchart of included and excluded patients and outcome events. ICD, implantable-cardioverter defibrillator; SCA, sudden cardiac arrest; SCD, sudden cardiac death. [a]Two patients received appropriate implantable cardioverter-defibrillator shocks 3 years before he died due to electrical storm (see Supplementary material online, *Supplementary results*). [b]Eighteen of these 22 patients (81.8%) were followed for an additional 7.2 years (interquartile range 4.0–11.2).

were associated with definite or probable medication non-adherence. The type and programming of ICDs did not differ between patients who did and did not receive appropriate ICD shocks (Supplementary material online, *Table S2*).

Syncope occurred as the first or only recurrent event during follow-up in one patient (1.3%) with an ICD and in eight patients (14.0%) without an ICD. The composite outcome of SCD, SCA, appropriate ICD shocks, or syncope occurred in 38 patients (48.1%) with an ICD (10.1 events per 100 person-years) and 17 patients (29.8%) without an ICD (4.7 events per 100 person-years, $P = 0.014$ by the log-rank test, *Figure* 2C and *Table 2*). At 4 years, this endpoint had occurred in 41.9% (95% CI 29.0–52.5%) of patients with an ICD and in 14.1% (95% CI 3.7–23.3%) of patients without an ICD. The relative risk at 4 years was 2.5 (95% CI 1.3–5.2). The hazard ratio for SCD, SCA, or syncope in patients with an ICD, as compared to patients without an ICD, was 2.99 (95% CI 1.59–5.64; $P = 0.001$ by multivariable Cox regression).

Subgroup analysis

We hypothesized that the risk of SCD, SCA, or appropriate ICD shocks might be different between young children and adolescents or adults, because younger age at diagnosis has been associated with an increased risk of arrhythmic events in symptomatic and asymptomatic patients with CPVT,[13] and medication non-adherence may be more prevalent among young children. Indeed, the hazard ratio for SCD, SCA, or appropriate ICD shocks in patients with an ICD, as compared to patients without an ICD, was 12.75 (95% CI 3.53–46.08; $P < 0.0001$ by Cox regression) in children <14 years of age

($n = 64$, including 25 with an ICD), and 3.93 (95% CI 0.92–16.82; $P = 0.065$ by Cox regression) in patients ≥14 years of age ($n = 72$, including 54 with an ICD). There was no interaction between age and the presence of an ICD.

Recurrent outcome events

Among the 36 patients with an ICD who received an appropriate shock, 16 (44.4%) received ≥1 recurrent appropriate shocks during an additional follow-up of 2.9 years (IQR 0.8–6.7) after the 1st shock. Of these, seven patients received one additional shock, six patients received two to four additional shocks, and three patients received 8–14 additional shocks. Two of these patients died.

In the nine patients without an ICD who experienced an SCA during follow-up, an ICD was implanted and no medication change was made in four patients, the flecainide dose was increased and metoprolol was added in one patient, the propranolol dose was increased and flecainide was added in one patient, propranolol was changed to nadolol and LCSD was performed in one patient, an ICD was implanted and flecainide was added in one patient, and an ICD was implanted and LCSD was performed in one patient. During an additional follow-up of 5.3 years (IQR 1.4–21.3), three patients with an ICD received appropriate shocks, whereas no other events occurred in the other six patients.

Safety

Inappropriate ICD shocks occurred in 19 of 77 patients (24.7%; 95% CI 16.4–35.4%; unknown in two patients). In seven patients inappropriate shocks occurred due to supraventricular tachycardia, in three patients

Table I　Clinical characteristics

	Whole cohort (n = 136)	ICD (n = 79)	No ICD (n = 57)	P-value
Age at SCA (years)	14.0 (9.0–20.8)	16.0 (12.0–26.0)	11.0 (7.5–14.0)	<0.0001
0–10	44 (32.4)	16 (20.3)	28 (49.1)	<0.0001
11–20	58 (42.6)	33 (41.8)	25 (43.9)	
21–30	20 (14.7)	17 (21.5)	3 (5.3)	
31–40	7 (5.1)	6 (7.6)	1 (1.8)	
>40	7 (5.1)	7 (8.9)	0 (0.0)	
Female gender	75 (55.1)	46 (58.2)	29 (50.9)	0.485
Proband	123 (90.4)	73 (92.4)	50 (87.7)	0.389
Family history of SCD in first-degree relative <40 years[a]	9/123 (7.5)	5/71 (7.0)	4/49 (8.2)	1.000
Previous syncope	61 (44.9)	30 (38.0)	31 (54.4)	0.080
Genotype				
RYR2 variant	105/128 (82.0)	59/76 (77.6)	46/52 (88.5)	0.160
CASQ2 variant	4/58 (6.9)	4/27 (12.9)	0/27 (0.0)	0.116
Therapy				
β-Blocker	129 (94.9)	74 (93.7)	55 (96.5)	0.699
First β-blocker type				0.038
Nadolol	40/127 (31.5)	18/73 (24.7)	22/54 (40.7)	
Metoprolol	24/127 (18.9)	18/73 (24.7)	6/54 (11.1)	
Propranolol	25/127 (19.7)	12/73 (16.4)	13/54 (24.1)	
Atenolol	23/127 (18.1)	14/73 (19.2)	9/54 (16.7)	
Bisoprolol	12/127 (9.4)	10/73 (13.7)	2/54 (3.7)	
Other[b]	3/127 (2.4)	1/73 (1.4)	2/54 (3.7)	
Flecainide	39 (28.7)	20 (25.3)	19 (33.3)	0.340
LCSD	10 (7.4)	4 (5.1)	6 (10.5)	0.320

Values are median (interquartile range) or n (%). Total numbers are included when they differ from those in the overall study group.
[a]Only applicable in probands (data missing in three patients).
[b]Other β-blockers included sotalol (n = 2) and carvedilol (n = 1).
ICD, implantable-cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; SCA, sudden cardiac arrest; SCD, sudden cardiac death.

due to electrical noise, in three patients due to lead fracture, in two patients due to ICD malfunction, in two patients due to malsensing, and in two patients the reasons for inappropriate shocks were unknown.

Other device-related complications occurred in 22 of 76 patients (29.0%; 95% CI 20.0–40.0%; unknown in three patients), including three patients with two complications. These complications included lead malfunction or dislodgement in 12 patients, infection in five patients, cardiac perforation in two patients, failed sensing not leading to inappropriate shocks in two patients, Twiddler syndrome in one patient, migration of the pulse generator in one patient, depression due to multiple ICD shocks in one patient, and inappropriate antitachycardia pacing leading to VF which was terminated by an ICD shock in one patient.

Implantable cardioverter-defibrillator implantation and explantation during follow-up

In 22 of 57 patients (38.6%) in whom no ICD was implanted after the initial SCA, an ICD was implanted after a median follow-up of 4.6 (IQR 1.6–12.4) years without an ICD. Indications for subsequent ICD implantation were mainly SCA or syncope during follow-up (Supplementary material online, Table S3). Between their sentinel event of SCA and their eventual ICD implantation, all 22 patients were treated with β-blockers (including atenolol in six patients, propranolol in six patients, nadolol in seven patients, metoprolol in two patients, and sotalol in one patient), three patients with flecainide, and one patient with LCSD. Eighteen of these 22 patients were followed for an additional 7.2 years (IQR 4.0–11.2). Nine patients (45.0%) received at least one appropriate shock and none of the patients died.

During follow-up, the ICD was explanted in 3 of 79 patients (3.8%). In two patients, the ICD was explanted when the initial diagnosis was revised to CPVT during follow-up and the ICD was considered potentially proarrhythmic, including the patient who suffered from depression after multiple shocks. In one patient, a subcutaneous ICD was explanted twice because of severe infections and it was decided not to implant a transvenous ICD.

Discussion

In this largest observational study of previously undiagnosed and untreated patients with CPVT who had presented with a sentinel event
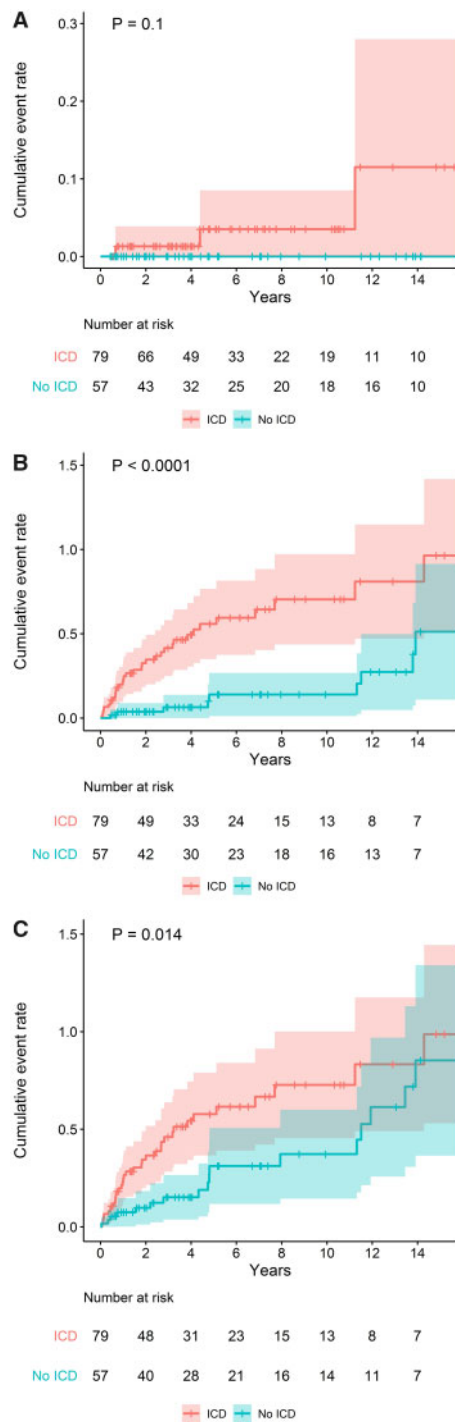
Figure 2 Time-to-event curves for sudden cardiac death and for combinations of sudden cardiac death, sudden cardiac arrest, appropriate implantable cardioverter-defibrillator shocks, and syncope. Kaplan–Meier survival curves and corresponding 95% confidence intervals in patients with an implantable cardioverter-defibrillator (green) and without an implantable cardioverter-defibrillator (red). (*A*) Sudden cardiac death. (*B*) Sudden cardiac death, sudden cardiac arrest, and appropriate implantable cardioverter-defibrillator shock. (*C*) Sudden cardiac death, sudden cardiac arrest, appropriate implantable cardioverter-defibrillator shock, and syncope.

of SCA to date, implantation of an ICD was not associated with a reduction of SCD as compared with patients who did not receive an ICD despite the global guidelines-based Class I recommendation for its use (*Take home figure*).[1,2,4] Instead, the ICD was associated with a high rate of (i) appropriate ICD shocks, which were not associated with a survival benefit, (ii) inappropriate ICD shocks, and (iii) numerous other device-related complications. The incidence of appropriate ICD shocks was significantly higher than the combined incidence of both SCA and syncope in patients without an ICD, suggesting that a significant number of ventricular tachyarrhythmia episodes that led to appropriate ICD shocks would not have resulted in either SCD or SCA requiring external defibrillation or even a syncope in the absence of an ICD.

SCA occurred in nine patients without an ICD. Three events were associated with definite or probable medication non-adherence, which is a well-known contributor to arrhythmic events in CPVT[8] and underscores the importance of encouraging medication adherence. Three events occurred in patients who were treated with monotherapy with a β-blocker other than nadolol, which is thought to be most effective β-blocker in patients with CPVT.[13–15] Some of these events could possibly have been prevented by medication adherence and nadolol combined with flecainide[16,17] and/or LCSD[18,19]. Indeed, further escalation of these recommended therapies was associated with a favourable long-term prognosis in these patients.

Forty-five percent of the patients with an ICD received at least one appropriate shock, but this was not associated with a reduction of SCD as compared with patients without an ICD. Previous studies have shown a moderate efficacy of appropriate ICD shocks in patients with CPVT.[5–8] Roses-Noguer et al.[5] studied 13 CPVT patients with an ICD and found that only 20 of 63 appropriate ICD shocks (32%) were effective in terminating the ventricular tachyarrhythmia. Shocks delivered to VF were effective in 83% of episodes, whereas shocks delivered to VT were effective in only 3% of episodes. Miyake et al.[6] reported on 24 CPVT patients with an ICD. Ten of these patients experienced a total of 75 appropriate shocks, of which 43 (57%) demonstrated successful primary termination. All successful appropriate shocks were for VF. In both studies, none of the patients died. In a large series of children with CPVT, an ICD was implanted in 121 children, of whom 67 (55%) had a history of SCA.[8] Among the patients with an ICD, electrical storm occurred in 18 patients (18.2%) and death occurred in three patients (2%), including one fatality due to electrical storm.

Collectively, these data suggest that CPVT patients may have recurrent VTs which cannot successfully be terminated by ICD shocks, but do not degenerate into VF and therefore do not impact on survival. On the other hand, appropriate or inappropriate shocks may trigger or maintain electrical storm, which may be fatal,[8–11] as was probably the case in at least two patients in our study. In other words, this Class I recommended intervention (the ICD) conferred no demonstrable survival benefit but only device-related co-morbidities including death where the ICD itself could be concluded to be the direct and proximate cause of the patient's death.

The other non-lethal side effects associated with an ICD in our study were substantial. Inappropriate ICD shocks occurred in 24.7% of the patients and other device-related complications in 28.9%. This is consistent with a meta-analysis on the harm of ICDs in patients with inherited cardiac diseases, in which the number of inappropriate
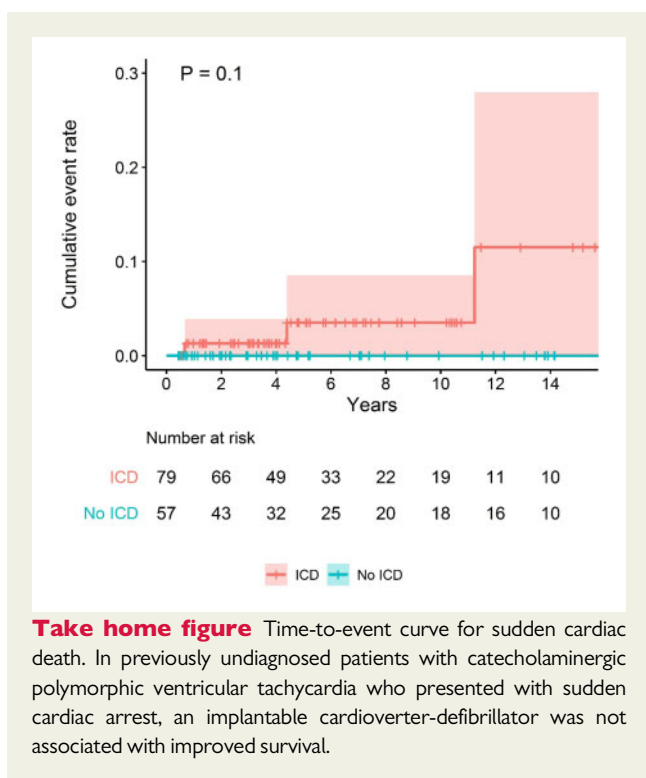
Table 2 Primary and secondary outcomes

	ICD (n = 79)	No ICD (n = 57)	Univariable analysis		Multivariable analysis[a]	
			Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
SCD	3 (3.8)	—	NA[b]	NA[b]	NA[b]	NA[b]
SCD, SCA, or appropriate ICD shock	37 (46.8)	9 (15.8)	3.91 (1.87–8.15)	<0.0001	5.89 (2.66–13.04)	<0.001
SCD, SCA, appropriate ICD shock, or syncope	38 (48.1)	17 (29.8)	2.03 (1.14–3.61)	0.003	2.99 (1.59–5.64)	0.001

Values are n (%) unless otherwise indicated.
[a]Corrected for age at baseline.
[b]Cox regression model could not be constructed, because no SCD events occurred in patients without an ICD.
ICD, implantable-cardioverter defibrillator; NA, not applicable; SCA, sudden cardiac arrest; SCD, sudden cardiac death.

Take home figure Time-to-event curve for sudden cardiac death. In previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia who presented with sudden cardiac arrest, an implantable cardioverter-defibrillator was not associated with improved survival.

shocks and other device-related complications was highest in patients with CPVT.[20] In three patients, the ICD was explanted, including one in whom recurrent shocks led to device-related distress and anxiety. In a recent study on psychosocial implications of living with CPVT, young patients with an ICD reported significantly worse device-related distress and shock anxiety than older patients with an ICD.[21]

Supraventricular arrhythmias have previously been reported in 5–26% of patients with CPVT.[22,23] In CPVT patients with an ICD, aggressive treatment of supraventricular arrhythmias with medication or catheter ablation is very important to reduce the risk of inappropriate ICD shocks which can trigger an electrical storm.[10] Indeed, in seven patients an inappropriate ICD shock was caused by a supraventricular arrhythmia. In addition, all three patients who died were known to have either atrial fibrillation or atrial flutter and this

triggered the fatal electrical storm in at least one of them. One may consider an even more stringent policy as to ICD implantation in patients with documented supraventricular arrhythmias.

This was a non-randomized, retrospective, observational study. A prospective randomized trial on this topic will be difficult to execute, because CPVT is a rare condition, only a minority of the patients with CPVT present with SCA (~13% of the patients in the International CPVT Registry), and the incidence of SCD, which would be the most appropriate primary endpoint, is low.

Our study presented some limitations inherent to this kind of clinical retrospective research, including retrospective data extraction. Some potentially important data were unknown in a substantial number of patients. In addition, some differences existed between the patients with and without an ICD. Most importantly, patients who did not receive an ICD were significantly younger. Younger age at diagnosis has been associated with an increased risk of arrhythmic events in symptomatic and asymptomatic patients with CPVT,[13] indicating a possible elevated risk of outcome events in the patients in whom no ICD was implanted. Indeed, the increased incidences of SCD and SCA in patients with an ICD as compared with those without an ICD were most pronounced in children <14 years of age. Finally, we cannot rule out that some ICD shocks were wrongfully classified as appropriate in the patients with a single chamber ICD.

In conclusion, among patients who presented with SCA prior to diagnosis of and treatment for CPVT, the ICD did not confer a survival benefit (Take home figure) but only ICD-associated co-morbidities including device-attributable death. In patients in whom an ICD was implanted directly after the SCA, we observed three cases of SCD, including two due to electrical storm, as well as high rates of appropriate and inappropriate ICD shocks and other ICD-related complications. Strict adherence to guideline-based therapy including β-blockers, flecainide, and LCSD without an ICD may provide adequate protection for secondary prevention of SCD without exposing the patient to the potential harm of ICDs in patients with CPVT. This option as well as the utmost importance of medication adherence should be discussed with these young patients and/or their parents. Contrary to the current guidelines that stipulate an ICD as a Class I recommendation for patients with CPVT who experienced SCA, it may be as reasonable to forego an ICD and instead proceed with triple therapy comprised of nadolol, flecainide, and LCSD.

Supplementary material

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