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Outcomes of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia Treated With β-Blockers

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Supplemental content

IMPORTANCE Patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) may experience life-threatening arrhythmic events (LTAEs) despite β-blocker treatment. Further complicating management, the role of implantable cardioverter defibrillator (ICD) in CPVT is debated.

OBJECTIVE To investigate the long-term outcomes of patients with *RYR2* CPVT treated with β-blockers only and the cost to benefit ratio of ICD.

DESIGN, SETTINGS, AND PARTICIPANTS This prospective cohort study conducted from January 1988 to October 2020 with a mean (SD) follow-up of 9.4 (7.5) years included patients who were referred to the Molecular Cardiology Clinics of ICS Maugeri Hospital, Pavia, Italy. Participants included consecutive patients with CPVT who were carriers of a pathogenic or likely pathogenic *RYR2* variant with long-term clinical follow-up.

EXPOSURES Treatment with selective and nonselective β-blocker only and ICD implant when indicated.

MAIN OUTCOME AND MEASURES The main outcome was the occurrence of the first LTAE while taking a β-blocker. LTAE was defined as a composite of 3 hard end points: sudden cardiac death, aborted cardiac arrest, and hemodynamically nontolerated ventricular tachycardia.

RESULTS The cohort included 216 patients with *RYR2* CPVT (121 of 216 female [55%], median [IQR] age 14, [9-30] years). During a mean (SD) follow-up of 9.4 (7.5) years taking β-blockers only, 28 of 216 patients (13%) experienced an LTAE (annual rate, 1.9%; 95% CI, 1.3-2.7). In multivariable analysis, experiencing either an LTAE (hazard ratio [HR], 3.3; 95% CI, 1.2-8.9; $P = .02$) or syncope before diagnosis (HR, 4.5; 95% CI, 1.8-11.1; $P = .001$) and carrying a C-terminal domain variant (HR, 18.1; 95% CI, 4.1-80.8; $P < .001$) were associated with an increased LTAE risk during β-blocker therapy only. The risk of LTAE among those taking selective β-blockers vs nadolol was increased 6-fold (HR, 5.8; 95% CI, 2.1-16.3; $P = .001$). Conversely, no significant difference was present between propranolol and nadolol (HR, 1.8; 95% CI, 0.4-7.3; $P = .44$). An ICD was implanted in 79 of 216 patients (37%) who were followed up for a mean (SD) of 8.6 (6.3) years. At the occurrence of LTAE, ICD carriers were more likely to survive (18 of 18 [100%]) than non-ICD carriers (6 of 10 [60%]; $P = .01$).

CONCLUSIONS AND RELEVANCE In this cohort study, selective β-blockers were associated with a higher risk of LTAE as compared with nadolol. Independently from treatment, LTAE and syncope before diagnosis and C-terminal domain variants identified patients at higher risk of β-blocker failure, and the ICD was associated with reduced mortality in high-risk patients with CPVT.

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disease characterized by fatal emotion- or exercise-induced ventricular arrhythmias.[1] In most patients, CPVT is secondary to variants in the *RYR2* gene, encoding for cardiac ryanodine receptor,[2] a crucial protein for electromechanical coupling in the heart. Findings from resting electrocardiogram (ECG) are unremarkable, resulting in diagnostic delays, thus exposing young patients to the risk of sudden cardiac death (SCD). Twenty years after identification of *RYR2* as the leading cause of CPVT,[2,3] management of patients remains challenging. β-Blockers are the centerpiece of treatment,[4] but critical issues persist. First, an unexpectedly high proportion of patients experience breakthrough events despite β-blocker therapy.[5] Second, procurement issues with nadolol,[6] the β-blocker of choice for patients with CPVT, call for an appraisal of the role of alternative β-blockers. Importantly, these issues assume relevance in the absence of evidence that other treatments (ie, flecainide or left cardiac sympathetic denervation [LCSD]) confer adequate protection against LTAE and in the light of recent data[7] that questioned the utility of implantable cardioverter defibrillator (ICD).[4] The aims of our study were to evaluate the role of selective vs nonselective β-blocker in LTAE reduction, to identify genetic and clinical risk factors for breakthrough LTAE with β-blockers treatment only, and to determine if patients with CPVT benefit from the use of an ICD.

Key Points

Question Which factors are associated with the outcome of patients with *RYR2* catecholaminergic polymorphic ventricular tachycardia during β-blocker treatment?

Findings In this cohort study including 216 patients with *RYR2* catecholaminergic polymorphic ventricular tachycardia, symptoms prior to diagnosis, C-terminal domain *RYR2* variants, and selective β-blockers were associated with an increased risk of β-blocker failure, while the implantable cardioverter defibrillator was associated with a survival benefit in patients experiencing life-threatening arrhythmic events during β-blocker treatment.

Meaning In this study, findings suggest that clinical, genetic, and therapeutic factors may help in identifying patients at increased arrhythmic risk despite β-blocker treatment, and implantable cardioverter defibrillator was associated with reduced mortality in high-risk patients with catecholaminergic polymorphic ventricular tachycardia.

Methods

Study Design and Cohort Composition

This was a longitudinal cohort study of patients with *RYR2* CPVT who were treated with β-blockers, referred to our attention between January 1988 and October 2020 (eTable 1 in the Supplement). CPVT was diagnosed according to the 2015 European Society of Cardiology Guidelines.[4] Clinical information acquired since the first visit was prospectively filed in our TRIAD registry and included demographic data, personal and family history, arrhythmic events, electrocardiographic features, and therapies. The study conformed to the principles of the Declaration of Helsinki. The study protocol was approved by the ethics committee of the IRCCS ICS Maugeri, Pavia, Italy. All patients or their legal guardians provided written informed consent to grant access to their clinical and genetic data for investigational purposes. No one received compensation or was offered any incentive for participating in this study.

Genetic Analysis

Genetic analysis on the *RYR2* gene was performed in probands either by Sanger sequencing (ABI PRISM 330; Thermo Fisher) or next-generation sequencing (Ion Torrent Personal Genome Machine; Thermo Fisher) depending on the enrollment year. Variants were evaluated by 2 expert laboratories (IRCCS, ICS Maugeri, Pavia, Italy, and Health in Code, A Coruña, Spain) and interpreted according to current criteria.[8] Only variants adjudicated as pathogenic or likely pathogenic by both laboratories were included (eTable 2 in the Supplement). Carriers of known loss-of-function *RYR2* variant,[9] and those with variants associated with other channelopathies were excluded. Cascade screening was offered to family members following the identification of a causative variant in the proband.

For the topological characterization of missense *RYR2* variants, we defined their location according to the cryoelectron microscope–resolved atomic map of the channel[10] (eMethods 2 in the Supplement). To identify domains overrepresented in patients with CPVT relative to control individuals (CPVT-enriched domains), we compared the distribution of the 83 missense variants found in our cohort with the distribution of 1913 rare (allele frequency < 0.01%) missense variants obtained from the Genome Aggregation Database (gnomAD), using a published methodology.[11,12]

Study End Points

The end point was the occurrence of the first life-threatening arrhythmic event (LTAE, composite of SCD, aborted cardiac arrest, or hemodynamically nontolerated ventricular tachycardia [VT][13]; eMethods 1 in the Supplement) while taking β-blocker therapy only. The follow-up for each patient was calculated from β-blocker therapy initiation to the occurrence of the study end point, death from nonarrhythmic cause, the date of last visit, or the initiation of other treatments (ie, other antiarrhythmics or LCSD), whichever occurred first. All the analyses performed refer to patients treated exclusively with β-blockers; patients who initiated other antiarrhythmic treatments or underwent LCSD were censured from the analyses.

Statistical Analysis

Statistical analysis was performed from April until August 2021 using R Software (version 3.6.0; The R Foundation for Statistical Computing). Data distribution was assessed using the 1-sided Kolmogorov-Smirnov test. Continuous data were reported as median and IQR and were compared using appropriate nonparametric tests. Categorical data were reported with frequencies and relative percentages and were compared using the χ^2 test or the Fisher exact test. Bonferroni correction was

Table 1. Demographic, Clinical, and Electrocardiographic Characteristics of the Study Population

Characteristic	No. (%)
Demographic	
Probands	120 (56)
Sex	
Female	121 (56)
Male	95 (44)
Age at therapy start, median (IQR), y	14 (9-30)
0-10	64 (30)
11-20	78 (36)
21-40	37 (17)
>40	37 (17)
Arrhythmic symptoms prior to therapy	
LTAE	40 (19)
Syncope	101 (47)
Age at first arrhythmic symptom, median (IQR), y	11 (8-15)
Therapeutic delay, median (IQR), y	2 (0.4-5.7)
Electrocardiographic features, median (IQR)[a]	
HR, beats per minute	63 (54-80)
PR, ms	140 (120-153)
QRS, ms	80 (80-90)
QTc interval, ms	396 (379-418)
U wave, No./total No.	85/194 (44)
Arrhythmic features, No./total No.[b]	
VT	106/177 (60)
VTns	77/106 (73)
VTs	29/106 (27)
Bidirectional morphology	59/106 (56)
Type of β-blocker at the initiation of treatment	
Nadolol	110 (51)
Propranolol	30 (14)
Selective	57 (26)
Other β-blockers	19 (9)

Abbreviations: HR, heart rate; LTAE, life-threatening arrhythmic event; VT, ventricular tachycardia; VTns, nonsustained ventricular tachycardia.

[a] Data from 194 of 216 patients (90%) with an electrocardiogram available.

[b] Data from 177 of 216 patients (82%) with an arrhythmic assessment prior to therapy.

applied to account for multiple comparisons. To quantify the risk of experiencing an LTAE while receiving β-blockers only, we used a Kaplan-Meier estimator of LTAE-free survival function with follow-up during β-blocker treatment as a timescale, and the approach proposed by Snapinn et al[14] to fit an extended standard Kaplan-Meier estimate stratified by time-varying type of principal β-blockers used.

Multivariable Cox proportional hazards model was used to evaluate the associations of history of LTAE before diagnosis of CPVT, occurrence of unexplained syncope before diagnosis of CPVT, variants in CPVT-enriched domains, and type of β-blocker therapy with the risk of experiencing an LTAE during β-blocker treatment. The type of β-blocker used was considered a time-dependent covariate to account for patients who switched or stopped β-blocker therapy. The use of propranolol and selective β-blockers (metoprolol, atenolol, bisoprolol, and nebivolol) was compared with nadolol, which is accepted as standard of care.[6] Periods without therapy were defined as time-lags of 1 week or more during which patients interrupted treatment and were excluded from the analysis. A robust sandwich estimator for the covariance matrix of the Cox regression coefficients was used to adjust for clustering caused by inclusion of members of the same family. A 2-sided *P* value less than .05 was considered significant.

Results

Cohort Composition

The study included 216 patients with RYR2 CPVT (121 of 216 female [55%], median [IQR] age 14, [9-30] years). Specifically, they were 120 probands (66 female patients [55%], median [IQR] age at diagnosis, 14.0 [10.0-20.5] years) and their 96 family members (55 female family members [57%]; median [IQR] age at diagnosis 18.0 [6.8-44.7] years). Interestingly, in 36 of 78 of probands (46%) the *RYR2* variant was likely de novo.

Baseline Characteristics

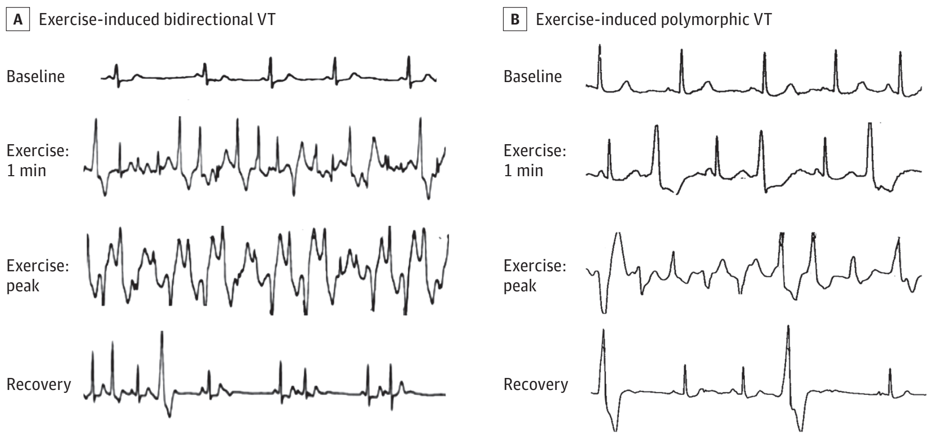
Table 1 summarizes baseline characteristics of the study population. Prior to diagnosis and initiation of treatment, 119 of 216 patients (55%) experienced CPVT-related arrhythmic symptoms, occurring at a median (IQR) age of 11.0 (7.5-15.4) years; 40 of 216 patients (19%) had survived an LTAE (24 [60%] female; median [IQR] age, 15.3 [11.1-25.1] years); and 101 of 216 patients (47%) had experienced an unexplained syncope. Importantly, 22 of 101 patients (22%) who had experienced a syncope also experienced an LTAE prior to the diagnosis of CPVT and starting treatment, with a median (IQR) lag between the syncope and the occurrence of LTAE of 1.8 (1.0-5.7) years.

All patients presented with a normal ECG (Table 1). Of the 177 of 216 patients (82%) for whom an arrhythmic evaluation prior to β-blocker therapy was available, 106 (60%) had a documentation of catecholamine-induced VT. In 59 of 106 patients (56%), bidirectional VT was documented (**Figure 1**A), while in the remaining 47 of 119 cases (44%), only polymorphic VT (Figure 1B) was recorded.

Identification of CPVT-Enriched *RYR2* Domains

To identify mutational hotspots, we compared the distribution of 83 *RYR2* missense variants that were identified in the probands (eTable 2 in the Supplement) with 1913 rare *RYR2* variants in control individuals (eTable 3 in the Supplement). We found that the following were CPVT-enriched domains (see eMethods 2 in the Supplement): HD1 domain (residues 2110-2679; odds ratio [OR], 3.1; 95% CI, 1.8-5.1; *P* < .001), central domain (residues 3636-4030; OR, 4.0; 95% CI, 2.2-7.3; *P* < .001), U-motif domain (residues 4091-4207; OR, 10.0; 95% CI, 4.5-22.4; *P* < .001), S2 domain (residues 4570-4594; OR, 9.4; 95% CI, 1.8-49.3; *P* = .001), S6 domain (residues 4836-4888; OR, 15.8; 95% CI, 2.6-95.4; *P* < .001), and C-terminal domain (CTD) (residues 4889-4969; OR, 9.6; 95% CI, 3.0-31.4; *P* < .001; **Figure 2**; eFigure and eTable 3 in the Supplement).

Figure 1. Typical Electrocardiographic Manifestations of *RYR2* Catecholaminergic Polymorphic Ventricular Tachycardia (VT)



Example of ventricular arrhythmias elicited by exercise in 2 different patients (1 male, 1 female) with 2 different missense *RYR2* variants (p.M4728A and p.R4822L). Findings of the basal electrocardiogram are normal, but exercise progressively induces the appearance of ventricular arrhythmias with increasing complexity. Ventricular arrhythmias usually start as isolated premature ventricular complexes, organizing into bigeminy and couplets (exercise 1 minute), followed by the appearance of VT with a bidirectional (A) or polymorphic (B) morphology. The interruption of exercise leads to the gradual resolution of arrhythmias in the inverse order of appearance (recovery 1 minute).

Outcome During β-Blocker Treatment

All patients received β-blockers only (Table 1) and were followed up for a mean (SD) of 9.4 (7.5) years. Of them, 28 of 216 patients (13%) experienced an LTAE during β-blocker therapy only, corresponding to annual rate of LTAE of 1.9% (95% CI, 1.3%-2.7%). Relevantly, 12 of 28 (43%) had already survived an LTAE prior to diagnosis and in the absence of therapy, while the remaining 16 (57%) experienced their first LTAE during treatment with β-blocker. As shown in **Figure 3**A, the cumulative probability of experiencing an LTAE while treated with β-blocker therapy only was 2.4% (95% CI, 0.3%-4.5%), 9.3% (95% CI, 4.8%-13.6%), and 20.8% (95% CI, 12.9%-28.0%) at 1, 5, and 10 years of follow-up, respectively.

Of the 28 individuals who experienced an LTAE while taking β-blockers only, 18 (64%) had an ICD when the LTAE occurred and all survived. Of the remaining 10 patients who were not carriers of an ICD, 4 (40%) died suddenly (eTable 4 in the Supplement), 4 (40%) were rescued by external defibrillation, while 2 patients (20%) experienced a hemodynamically unstable fast polymorphic VT, which terminated spontaneously. Overall, the probability that an LTAE resulted in a fatal outcome was higher in patients without an ICD (4 of 10 [40%] died) as compared with patients with an ICD implanted (0 of 18 died; $P = .01$). A total of 7 of 24 patients (29%) surviving a first LTAE had multiple LTAEs during their life (median [IQR], 3 [2-7]).

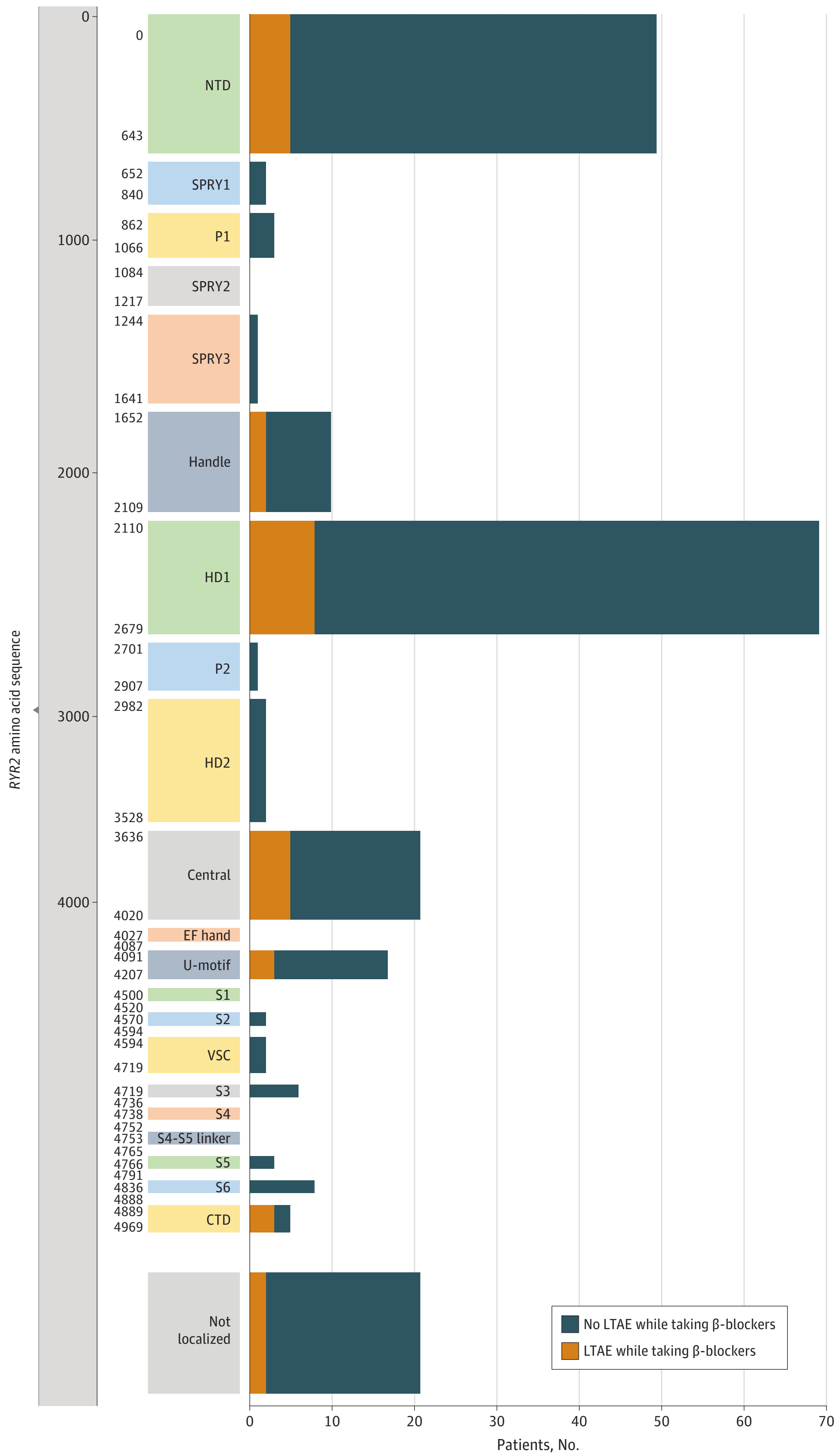
Factors Associated With the Occurrence of an LTAE During β-Blocker Treatment

Multivariable analysis (**Table 2**) demonstrated that history of LTAE before diagnosis (hazard ratio [HR], 3.3; 95% CI, 1.2-8.9; $P = .02$) and unexplained syncope before diagnosis (HR, 4.5; 95% CI, 1.8-11.1; $P = .001$), as well as C-terminal domain variants (HR, 18.1; 95% CI, 4.1-80.8; $P < .001$) were independent predictors for LTAE occurrence during β-blocker treatment only. Importantly, selective β-blockers (LTAE rate 4.0% per year; 95% CI, 2.2%-6.6%) were associated with a 6-fold increase of LTAE risk (HR, 5.8; 95% CI, 2.1-16.3; $P = .001$) as compared with nadolol (LTAE rate 0.8% per year; 95% CI, 0.3%-1.6%; Figure 3B). Conversely, propranolol (LTAE rate 2.1% per year; 95% CI, 0.4%-6.3%) use was not associated with a significant increase in risk as compared with nadolol (HR, 1.8; 95% CI, 0.4-7.3; $P = .44$; Figure 3B). C statistics confirmed that the model performed well (C statistic = 0.81; 95% CI, 0.72-0.91) and sensitivity analysis in probands confirmed the results of the multivariable analysis (eTable 5 in the Supplement).

Defining the Role of the ICD in Patients With CPVT

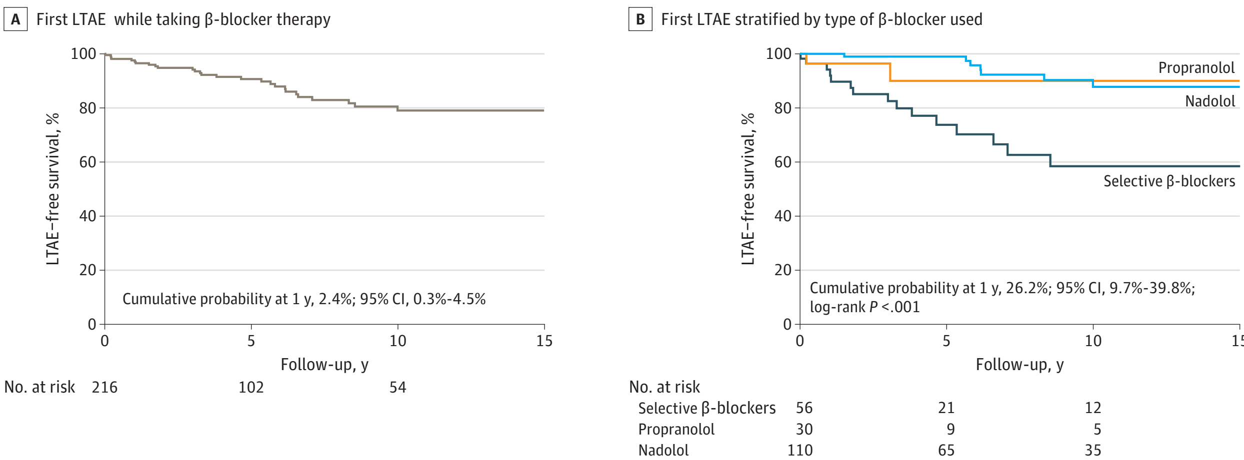
Globally, 79 of 216 patients (37%) received an ICD (46 of 79 patients [58%] female; median [IQR] age at implant, 16.0 [13.1-28.4] years), with 33 of 79 patients (42%) being implanted in secondary prevention of SCD. Over a median (IQR) 7.5 (3.7-12.6) years of follow-up, 21 of 79 patients (27%) experienced an LTAE that triggered an appropriate ICD shock (LTAE rate 4.1% per year; 95% CI, 2.5%-6.3%). ICD successfully terminated the LTAE in 18 of 21 cases (86%). Overall, all 15 episodes of VF were successfully interrupted, while only 3 of 6 episodes (50%) of hemodynamically unstable, polymorphic fast VT were terminated ($P < .001$). Furthermore, complications requiring surgical revision occurred in 14 of 79 patients (17%) (2.6% per year; 95% CI, 1.4%-4.3%), while 12 patients (15%) (2.0% per year; 95% CI, 1.1%-3.6%) experienced inappropriate shocks (eTable 6 in the Supplement). Importantly, no inappropriate shock triggered an LTAE, and overall, the benefit of ICD implant outweighed the harm (eTable 7 in the Supplement).

Figure 2. Distribution of Patients With and Without Life-Threatening Arrhythmic Events (LTAEs) During β-Blocker Treatment Only According to the Location of *RYR2* Variants on the Amino Acid Sequence



The figure represents the amino acid sequence of *RYR2* protein, divided into the different domains identified by Dhindwal et al.[10] The length of each domain is proportional to the number of amino acids that compose the domain. Amino acids that are not localized to any domain are grouped and represented separately on the right-hand side. Columns above each *RYR2* domain represent the number of patients with variants localized in that specific domain. Blue shows the proportion of patients without LTAE during β-blocker treatment, while orange shows the proportion of patients with LTAE during β-blocker treatment only. As shown by the multivariable analysis, patients with variants in the C-terminal domain (CTD; amino acids 4889-4969) were at increased risk of experiencing an LTAE during β-blocker treatment only.

Figure 3. Clinical Course of Patients With *RYR2* Catecholaminergic Polymorphic Ventricular Tachycardia During β-Blocker Therapy Only



A, Kaplan-Meier estimate of cumulative survival free from the first life-threatening arrhythmic events (LTAEs) in β-blocker therapy only shows the cumulative probability of experiencing a first catecholaminergic polymorphic ventricular tachycardia while taking β-blocker therapy was 2.4% (95% CI, 0.3%-4.5%), 9.3% (95% CI, 4.8%-13.6%), and 20.8% (95% CI, 12.9%-28.0%) at 1, 5, and 10 years of follow-up, respectively. B, Kaplan-Meier estimate of cumulative survival free from the first LTAE stratified by time-varying type of principal β-blocker used demonstrates that the cumulative probability of experiencing a first LTAE while taking β-blocker therapy only was 26.2% (95% CI, 9.7%-39.8%), 10.0% (95% CI, 0.0%-22.9%), and 1.0% (95% CI, 0%-3.0%) at 5 years of follow-up for selective β-blockers, propranolol, and nadolol, respectively.

Table 2. Factors Associated With the Occurrence of First LTAE During β-Blocker Therapy According to Multivariable Cox Regression in 216 Patients With *RYR2*-Related CPVT[a]

Factor	No. of patients	No. of events per person-year	Rate per 100 person-years (95% CI)	HR (95% CI)	*P* value
Episode of life-threatening arrhythmias before diagnosis					
No	176	16/1225	1.3 (0.7-2.1)	1 [Reference]	NA
Yes	40	12/262	4.6 (2.4-8.0)	3.3 (1.2-8.9)	.02
Episode of unexplained syncope before diagnosis					
No	115	5/814	0.6 (0.2-1.4)	1 [Reference]	NA
Yes	101	23/674	3.4 (2.2-5.1)	4.5 (1.8-11.1)	.001
Variant location					
Not CPVT-enriched domains	94	9/495	1.8 (0.8-3.5)	1 [Reference]	NA
HD1 domain	71	8/621	1.3 (0.6-2.5)	1.0 (0.3-3.0)	.97
Central domain	20	5/128	3.9 (1.3-9.1)	1.6 (0.5-5.4)	.47
U-motif domain	16	3/102	2.9 (0.6-8.6)	2.1 (0.6-7.1)	.22
S2 domain	2	0/14	0 (0-26.3)	NA	NA
S6 domain	8	0/105	0 (0-3.5)	NA	NA
C-terminal domain	5	3/23	13.0 (2.7-38.1)	18.1 (4.1-80.8)	<.001
Therapy (time-dependent)[b]					
Nadolol[c]	NA	7/880	0.8 (0.3-1.6)	1 [Reference]	NA
Propranolol[d]	NA	3/140	2.1 (0.4-6.3)	1.8 (0.4-7.3)	.44
Selective[e]	NA	15/358	4.2 (2.3-6.9)	5.8 (2.1-16.3)	.001

Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; HR, hazard ratio; LTAE, life-threatening arrhythmic event; NA, not applicable.

[a] The outcome is the occurrence of a first life-threatening arrhythmic event (LTAE) during β-blocker therapy only.

[b] Additionally in other β-blockers: 3 events in 109 person-years of observation.

[c] The daily dosage (median [IQR]) of nadolol was 1.0 (0.7-1.2) mg/kg.

[d] The daily dosage (median [IQR]) of propranolol was 2.0 (1.4-3.2) mg/kg.

[e] The most used drugs were atenolol and metoprolol, at median (IQR) daily dosage of 0.9 (0.6-2.0) mg/kg and 1.4 (1.0-2.3) mg/kg, respectively.

Discussion

CPVT is a potentially fatal genetic arrhythmia syndrome, but 20 years after the identification of *RYR2* as the main causative gene,[2,15] an important delay between the first clinical manifestation and the diagnosis persists. In our cohort of 216 patients with *RYR2* CPVT who were followed up prospectively, half of patients who were not diagnosed after an unexplained syncope also experienced an LTAE before CPVT was recognized. Moreover, despite β-blocker therapy, approximately 15% of patients experienced LTAEs. The challenge for the clinician is, therefore, 2-fold: first, to timely diagnose a patient and start β-blocker therapy, and then, to identify patients at a high risk of β-blocker failure.

Not All β-Blockers Are Equally Protective in Patients With CPVT

Nadolol, a powerful β-blocker with a long half-life, is preferred by the experts in the field. Although it reduces the arrhythmic burden in patients with CPVT,[16] we observed that 25% of LTAEs in patients treated with β-blockers only occurred in nadolol. Furthermore, owing to its limited availability in many countries worldwide,[6] a clinical need for an evidence-based appraisal of alternative β-blockers exists.

Our data demonstrated that commonly used selective β-blockers are associated with a particularly high risk of LTAE (4.0% per year) in patients with CPVT, and they may be used only in case of nonselective β-blocker intolerance or unavailability. Conversely, our data suggest that propranolol might be an alternative to nadolol, where the latter is unavailable. A word of caution must be spent on the dosing regimen of standard-release propranolol (3-4 administrations daily), which might favor poor adherence. In some countries, long-acting formulation of propranolol is available but since both the area under the plasma concentration-time curve and the peak concentration are significantly lower than following identical doses of standard-release propranolol,[17] it should not be considered a simple milligram-for-milligram substitute for standard-release propranolol,[18] and higher doses of long-acting propranolol may need to be used.

Clinical Factors Associated With β-Blocker Failure

We provide factors identifying patients at increased LTAE risk during β-blocker therapy. Specifically, patients with CPVT-related symptoms before diagnosis (LTAE or an unexplained syncope) should be regarded at high risk for β-blocker failure.

Akin to other hereditary arrhythmogenic diseases, such as Brugada syndrome,[19] or long QT syndrome (LQTS),[20] survivors of LTAE have a poorer outcome at follow-up, with recurrence rate during β-blocker therapy of 5.8% per year. Importantly, survivors of LTAE in CPVT have a significantly higher recurrence rate than LTAE survivors with LQTS (2.0% per year).[20]

At variance with previous evidence,[5] our data highlight how important syncope is in CPVT, both for diagnosis and prognosis. Exercise- or emotion-induced syncope is frequently the first symptom of CPVT, and in one-fifth of patients is a harbinger of an avoidable LTAE: half of patients who experienced an LTAE before diagnosis had experienced a syncope 2 years prior. More importantly, we demonstrate that syncope is also a useful factor associated with β-blocker therapy failure. In light of this evidence, awareness about exercise- or emotion-related syncope as an ominous clue of a potentially lethal genetic condition should be raised not only among cardiologists but especially among emergency medicine specialists, pediatricians, and general practitioners. Prompt referral to an expert tertiary center would reduce the diagnostic delay but, in our cohort, would have prevented half of cardiac arrests prior to diagnosis.

Genotype Factors

The *RYR2* gene is one of the largest human genes and the attribution of a pathogenic role to a rare variant is challenging,[21] given the high rate of rare but benign variants: it is estimated that 3.2% of healthy control individuals carry them.[22] Our data suggest that CPVT-causing variants are not randomly distributed, but cluster in functionally relevant domains.[23] Identification of these hotspots is important when dealing with a rare variant, aiding in distinguishing causative variants from background noise.

In analogy with what we identified in patients with LQTS, we demonstrate that genetic substrate modulates β-blocker therapy response.[24] Crucially, we showed that patients with *RYR2* variants affecting the C-terminal domain (CTD, amino acids 4889-4969) were at higher risk of β-blocker failure, independently of clinical presentation and β-blocker type used (Figure 2). CTD is highly conserved[25] and plays a fundamental role in the channel function. Functional studies on skeletal isoform (*RYR1*) have identified that 3 activating ligands (Ca^{2+}, ATP, and caffeine) bind to different interdomain interfaces of the CTD,[26] suggesting a pivotal role in the channel gating. Recent data reinforced this hypothesis, demonstrating that *RYR2* variants affecting the CTD alter electrostatic interactions critical for the maintenance of the channel's closed state, resulting in a reduced threshold for arrhythmogenic spontaneous Ca^{2+} release.[23]

ICD in CPVT

Malignancy of CPVT has led to the proposal for other treatments, such as flecainide and LCSD. However, survival data on flecainide are missing, while LCSD is burdened by arrhythmic recurrences in one-third of patients.[27] ICD has represented the bastion of protection against LTAE for patients with CPVT. Accordingly, we found that ICD confers a significant survival benefit in patients with CPVT treated with β-blocker. Our observation sharply departs from the data by Van der Werf et al,[7] who failed in identifying such a benefit in survivors of cardiac arrest with CPVT. In their cohort, over approximately 5 years of follow-up, SCD occurred in 3 of 79 patients (4%) with an ICD. However, the authors do not provide compelling evidence to define whether an ICD-induced proarrhythmic event caused the death, as in one case no information on medication was available; in the second, the patient was treated with combination of drugs, including verapamil and amiodarone, which may be pro-arrhythmic in their own right, or as suggested by authors themselves raised the defibrillation threshold; while in the third patient, sudden death occurred but the ICD was not interrogated. Naturally, the choice of ICD should be carefully weighted, as complications requiring surgical revision occurred in 17% of patients, but this notwithstanding, in our experience, the benefits of ICD implant still outweigh the harms, especially in survivors of LTAE, and we advocate for its continued use in high-risk patients with CPVT.

Limitations

A prospective cohort study focusing on β-blocker therapy only is subject to the inherent limitations of such an analysis. Previous randomized clinical trials were unable to recruit enough patients for the assessment of a clinically relevant end point,[28] supporting the view that nonrandomized data may represent the best source of evidence for relatively rare conditions such as CPVT.

Conclusions

In this cohort study of patients with *RYR2*-related CPVT, selective β-blockers were associated with a higher risk of LTAE as compared with nadolol. Patients who have survived an LTAE and/or experienced an unexplained syncope prior to diagnosis, as well as carriers of variants located in the CTD of *RYR2*, were at higher risk of β-blocker failure. ICD was associated with reduced mortality in patients with high-risk CPVT.

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