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ORIGINAL RESEARCH

International Multicenter Cohort Study on Beta-Blocker–Free Treatment Strategies for Catecholaminergic Polymorphic Ventricular Tachycardia Patients

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ABSTRACT

BACKGROUND Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, potentially life-threatening genetic heart disease. Nonselective beta-blockers (BBs) are highly effective in reducing CPVT-triggered arrhythmic events. However, some patients suffer from unacceptable BB side effects and might require strategies without a BB.

OBJECTIVES This study sought to review the spectrum of and outcomes associated with BB-free treatment configurations in patients with CPVT enrolled in the International CPVT Registry.

METHODS From the Registry, patients with *RYR2* variant-positive CPVT treated with a BB-free strategy for ≥6 months were included. Two treatment groups were defined: patients classified as very low risk and treated with intentional nontherapy (INT) and patients who needed to be treated but did not tolerate BBs and were treated with 3 different strategies.

RESULTS Overall, 100 of 1,017 patients (10%) were on a BB-free treatment strategy. There were 73 patients (33 female [42%]) in the INT group. In patients 66 (90%), INT was pursued after low-risk assessment in asymptomatic patients and absent or negligible stress test phenotype. Twenty-seven patients (22 female,81%) were treated using 3 different BB-free treatment strategies (flecainide monotherapy, n = 21; left cardiac sympathetic denervation monotherapy, n = 2; flecainide + left cardiac sympathetic denervation, n = 4). In total, 25 patients (93%) were previously treated with BBs. During a median follow-up of 6 years (interquartile range, 3-9 years), 2 patients (2%) had a CPVT-associated event.

CONCLUSIONS Although nonselective BBs remain the cornerstone treatment for CPVT, 10% of patients with CPVT required a BB-free treatment strategy. After careful risk assessment, safe and effective BB-free treatment strategies can be configured. (JACC Clin Electrophysiol. 2024;■:■–■) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BB = beta-blocker

BCE = breakthrough cardiac event

CPVT = catecholaminergic polymorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

INT = intentional nontherapy

LCSD = left cardiac sympathetic denervation

LQTS = long QT syndrome

PVC = premature ventricular contraction

VA = ventricular arrhythmia

VT = ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic arrhythmia disorder in which bidirectional or polymorphic ventricular arrhythmias (VAs) induced by exercise or emotional stress can trigger syncope, sudden cardiac arrest, or sudden cardiac death in young and otherwise healthy patients.[1] According to the recent guidelines, treatment and sudden cardiac death prevention in individuals with CPVT should be guided by presence of a culprit variant in the disease-causing genes, symptomatic status, and the presence of ectopy on the stress test.[2] However, genetic cardiology experts must take other factors into consideration, including age, the degree of ectopy on the stress test, response and adherence to therapy, psychosocial factors, and quality of life.

Beta-blockers (BBs, particularly nadolol or propranolol) are the mainstay therapies to prevent arrhythmic events in patients with CPVT, although a certain subset of patients may require adjuvant/combination therapy with flecainide and/or left cardiac sympathetic denervation (LCSD).[2,3] Nonselective BBs significantly reduce cardiac events in patients with CPVT.[2,4,5] Therefore, international guidelines recommend universal BB therapy as the first-line management strategy for patients diagnosed with CPVT, as well as their genotype-positive family members, even in the absence of documented exercise or stress-induced VAs.[2] However, a recent study showed that 15% of patients with CPVT were not adherent to CPVT medications and had a significantly higher concerns about the quality of life-interfering effects of their medications.[6] In long QT syndrome (LQTS), a similar, but more common channelopathy, some patients may not tolerate BBs owing to side effects, such as fatigue, dizziness, and sleep disturbance; in those cases, BB-free strategies have been implemented successfully.[7-9] Moreover, in a small subset of LQTS patients, after careful clinical assessment and risk stratification, intentional nontherapy (INT) with adherence to preventative measures only (ie, avoidance of QT-prolonging drugs, attention to fluid and electrolyte status, and fever reduction) can be implemented safely as a bona fide alternative treatment option.[9] After the success of BB-free treatment strategies in LQTS, it is important to consider whether a subset of patients with CPVT, who are not amenable to BBs either owing to side effects or from an efficacy standpoint, could benefit from BB-free treatment strategies. Herein, we review the spectrum of and outcomes associated with BB-free treatment configurations in patients with CPVT from the International CPVT Registry.

METHODS

STUDY POPULATION. This study was conducted using data from the International CPVT Registry. Appropriate research ethics board approval and informed consent have been obtained for all participating centers. The International CPVT registry is a multicenter observational registry established in April 2014 that includes patients diagnosed with CPVT on the basis of expert consensus.[1,10] In this study, patients were included if they met the following criteria: 1) presence of a pathogenic/likely pathogenic variant in *RYR2,* or a variant graded by a

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Demographics of Patients With CPVT on INT

Demographics	
Total patients on INT	73
Female	33 (42)
Age at INT initiation, y	9 (4-40)
Age subgroups, y	
0-6	31 (43)
7-20	17 (23)
>20	25 (34)
Diagnosis by cascade screening	71 (97)
Symptomatic before diagnosis	0 (0)
Absence of complex arrhythmia on stress test/Holter[a]	70 (96)
BCE during INT	1 (1)
Follow-up, y	6 (3-9)
Reason for INT	
Very low risk for BCEs	60 (82)
Patient preference and low risk stratification	6 (8)
BB intolerance	3 (4)
Unknown	4 (5)

Values are n (%) or median (IQR). [a]Holter was used for children (<6 years old).
BB = beta-blockers; BCE = breakthrough cardiac events; CPVT = catecholaminergic polymorphic ventricular tachycardia; INT = intentional nontherapy.

genetic test company as a variant of uncertain significance in *RYR2* but in a patient or in a family member with a clinically established CPVT phenotype, defined as the presence of complex VA on the stress test or with cardiac events (ie, a phenotype-enhanced variant upgrade); and 2) treated with a BB-free treatment strategy for a minimum of 6 months after diagnosis and evaluation by their genetic cardiologist or arrhythmia specialist.

The included patients were divided into 2 groups. Group 1 consisted of low-risk patients defined based on the absence of symptoms, absence of phenotype on exercise stress test, and extreme of age at diagnosis. The absence of a CPVT phenotype on the stress test was defined as the absence of complex arrhythmias, such as bigeminy premature ventricular contractions (PVCs), couplet PVCs, or nonsustained VT/sustained VT during exercise, which represents an ectopy score as previously described as 0 (no ventricular ectopy) or 1 (isolated PVC [<10 min]).[11] For young children (<6 years old) or for those who were unable to undergo an exercise stress test, a 24-hour Holter monitor was used to discern any complex arrhythmias. Of note, it is important that children engage in some form of exercise or physical activity while wearing the Holter monitor to increase the likelihood of detecting arrhythmias. Moreover, because sentinel events are most likely to occur during the first 2 decades of life (mean age, 7-9 years) and are rarely the cause of sudden infant death syndrome, the low-risk patients were divided into 3 age subgroups for further evaluation[12-15]: ages 0 to 6 years, 7 to 20 years, and >20 years. Therefore, the extreme of age were defined as <7 or >20 years old. In this cohort, patients did not take any CPVT-directed medications and were monitored with periodic electrocardiograms and exercise tests. Group 2 included patients who needed to be treated but did not tolerate or did not want to be on BBs. Three alternative treatment strategies were used for group 2: flecainide monotherapy, LCSD monotherapy, and dual therapy of flecainide and LCSD.

Patients were excluded if they had significant cardiac comorbidities, a deletion in exon 3 of *RYR2*, a known loss-of-function variant in *RYR2*, a second (likely) pathogenic variant in *RYR2*, or a variant in *CASQ2*-encoded calsequestrin. Additionally, patients who had a variant of uncertain significance in *RYR2* but lacked a compelling CPVT phenotype were excluded.

Data abstracted from the International CPVT Registry included clinical characteristics, demographics, treatment strategies, and general outcomes including breakthrough cardiac events (BCEs) defined as arrhythmic syncope/seizure, appropriate implantable cardioverter-defibrillator (ICD) shock, sudden cardiac arrest or sudden cardiac death.

STATISTICAL ANALYSES. All continuous variables were presented as mean ± SD or median and interquartile range (IQR). All categorical variables were presented as frequencies and percentages.

RESULTS

Among 1,071 *RYR2* variant-positive patients who met inclusion criteria, 100 patients (10%) were managed without BB therapy for ≥6 months (53 females [53%]; median age at BB-free therapy initiation, 18 years [IQR: 6-42 years]). The results will be described in 2 parts: patients on INT (group 1 [n = 73]) (Table 1) and patients who received CPVT1-directed therapies but without a BB (group 2 [n = 27]) (Table 2).

INT (GROUP 1). In total, 73 patients (73%) were intentionally not treated (INT). There were 33 females (42%) and the median age at INT initiation was 9 years old (IQR: 4-40 years) with a median follow-up on INT of 6 years (IQR: 3-9 years). To recall, as defined for inclusion in group 1, all patients were asymptomatic before INT initiation and in 71 patients (97%) the CPVT diagnosis was made via family-specific variant testing (ie, cascade screening) (Table 1).

TABLE 2 Demographics of Patients With CPVT and a BB-free Alternative Treatment Strategy

Demographics	
Total	27
Female	22 (81)
Age when the BB-free therapy started, y	29 (20-43)
ICD implanted	8 (30)
Time on BB-free therapy, y	8 ± 4
Treated with BB before	25 (93)
Symptomatic before diagnosis	13 (48)
BCE on BB-free therapy	1 (4)
Follow-up, y	7 (2-10)
Treatment strategies	
Flecainide monotherapy	21 (78)
LCSD monotherapy	2 (7)
LCSD + flecainide	4 (15)
Reason for BB-free treatment	
BB intolerance	16 (59)
Fatigue	14
Cold sensation	1
Asthma worsening	1
BB intolerance + nonadherence	2 (7)
Unknown	9 (33)

Values are n (%), median (IQR) or mean ± SD.

ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; other abbreviations as in Table 1.

After careful clinical evaluation, 60 patients (82%) were classified as very low risk for CPVT-mediated cardiac events and were managed as INT. In 6 patients (8%), INT was started because of patient preference and low-risk designation. Three patients (4%) had been treated previously with BBs. However, owing to BB intolerance and low-risk status, the treatment was changed to INT (Table 1). In 4 patients (5%), no clear documentation for INT could be ascertained on retrospective chart review.

Overall, 70 patients (96%) showed no phenotype during the stress test or Holter monitoring. Of note, 3 patients (4%) showed ventricular bigeminy or PVC couplets on the stress test. However, 2 of these 3 patients were diagnosed when they were >70 years of age and the third patient was 27 years old, but showed unacceptable BB side effects. None of the patients in group 1 had an ICD.

There were 31 patients (43%) between 0 and 6 years of age, 17 patients (23%) between 7 and 20 years, and 25 patients (34%) >20 years of age (Table 1). Of note, all patients on INT were kept on regular electrocardiographic/ exercise stress test surveillance.

From a genotype standpoint, the most prevalent variant in the *RYR2* gene among this group was p.Arg420Trp, identified in 24 patients (33%). The genotypes of these individuals are detailed in Supplemental Table 1.

During a median follow-up of 6 years (IQR: 3-9 years), 1 patient (1%) experienced a probable CPVT1-associated cardiac event. The patient was a 21-year-old woman who had exertional syncope with spontaneous recovery after 3 years on INT. Subsequently, BB therapy was started. Moreover, despite the absence of a sentinel event, BB therapy was restarted in 2 additional patients (3%) during follow-up owing to the occurrence of complex VAs on their follow-up stress tests and per patient/parent request in 2 patients (3%). The considerations for INT on patients with CPVT are illustrated in the **Central Illustration**.

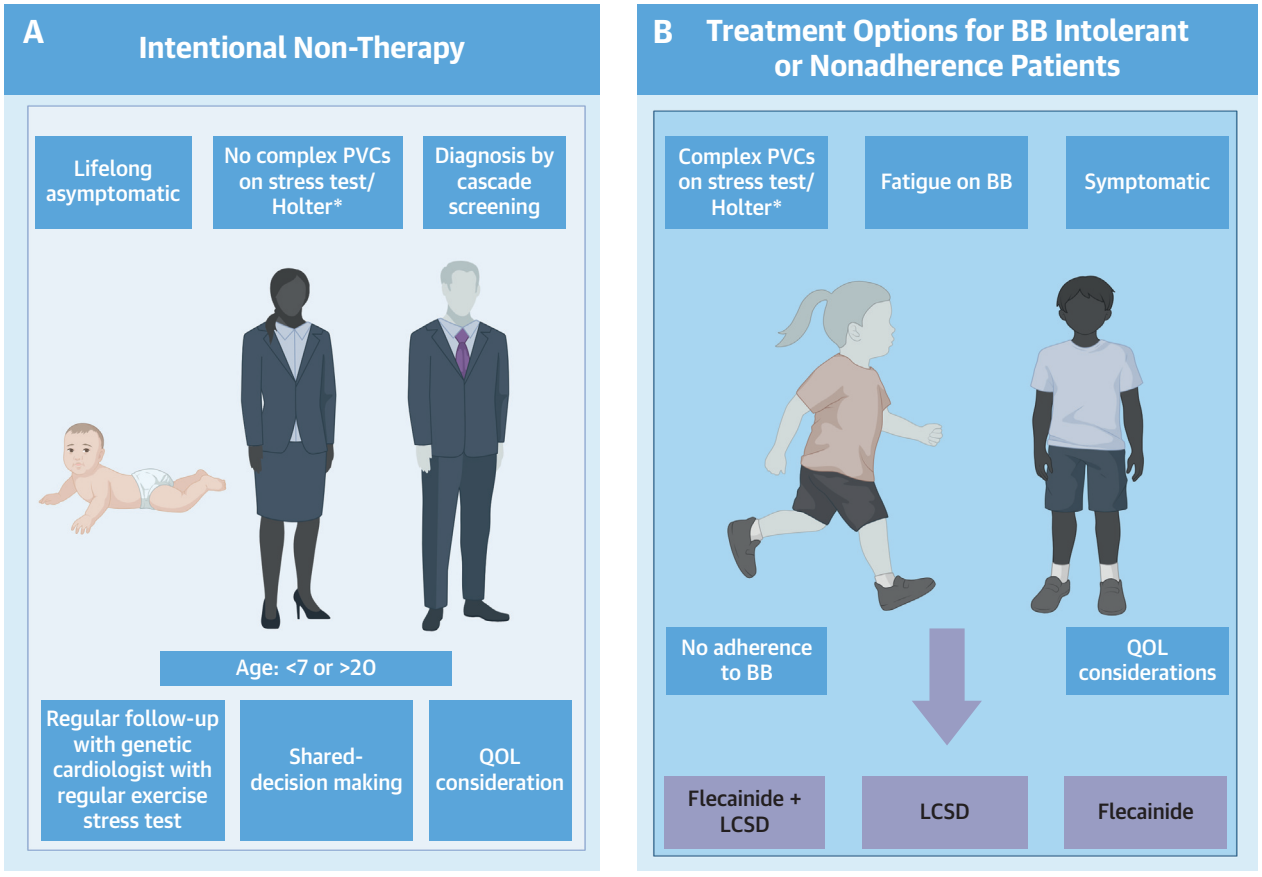
TREATMENTS WITHOUT BBs (GROUP 2). In total, 27 patients (27%; 22 female [81%]) were treated intentionally, but with a BB-free treatment strategy. The median age at BB-free treatment initiation for this subgroup was 29 years (IQR: 20-43 years), and in 17 patients (63%) the diagnose was made owing to a family history. Ten patients (37%) were probands. In total, 25 of the 27 patients (93%) had been treated with BB previously, 13 patients (48%) had a probably CPVT1-attributable cardiac event before their diagnosis, and 8 patients (30%) previously had an ICD implanted.

BB intolerance with or without nonadherence was the main reason for alternative treatments in 18 patients (67%). The main reason for BB intolerance was fatigue in 14 patients (67%) (Table 2). In 9 patients (33%), no specific rationale for treatment without a BB was documented clearly on retrospective review.

There were 3 BB-free treatment configurations used: 21 patients (78%) were treated with flecainide as monotherapy, 2 patients (7%) with LCSD monotherapy, and 4 patients (15%) with dual therapy of flecainide and LCSD. There was no increase in arrhythmias during the exercise stress test after starting BB-free therapy. Initially, 9 patients (33%) presented with complex arrhythmias, such as bigeminy or couplets. During the BB-free follow-up, only 3 patients (11%) exhibited couplets or bigeminy during the stress test. Notably, all 3 of these patients had similar exercise test results before beginning the BB-free strategies. From a genotype standpoint, the most prevalent variant in the *RYR2* gene in group 2 was again p.Arg420Trp, identified in 6/27 patients (22%). The genotypes of the patients in group 2 are detailed in Supplemental Table 2.

Over a median of 7 years (IQR: 2-10) with a BB-free treatment strategy in place, only a 24-year-old woman (1 of 27 patients [5%], p.R420Q), had an appropriate ICD shock during exercise while on

CENTRAL ILLUSTRATION **Considerations for Beta-Blocker-Free Treatment in CPVT**



Neves R, et al. JACC Clin Electrophysiol. 2024;■(■):■-■.

(A) Considerations for intentional nontherapy in CPVT. (B) Considerations for various therapeutic strategies for BB intolerant or nonadherence patients in CPVT. *Holter should be used for children <6 years old. Figure created with BioRender.com. BB = beta blocker; BCE = breakthrough cardiac event; CPVT = catecholaminergic polymorphic ventricular tachycardia; LCSD = left cardiac sympathetic denervation; PVC = premature ventricular contraction; QOL = quality of life.

flecainide (50 mg 2 times a day) monotherapy for 1 year. After this BCE, the patient had her dose of flecainide was increased to 200 mg 2 times a day. Moreover, a BB was added in 1 asymptomatic patient after 2 years on flecainide monotherapy owing to patient preference. The considerations for alternative treatments for patients with CPVT are illustrated in the **Central Illustration**.

In this cohort of patients with CPVT treated without BBs, a shared decision-making approach was used regarding return-to-play or continuation as an athlete in his or her sport of choice. This decision followed a meticulous risk assessment, ensuring no complex ventricular ectopy was present on stress tests. A total of 10 patients (10%) continued participating in sports after their diagnosis and treatment (INT [n = 6], flecainide monotherapy [n = 3], and LCSD + flecainide [n = 1]). The primary sports classification according to the Bethesda guidelines was most commonly IIC (n = 5), followed by IC (n = 3), IIA (n = 1), and IB (n = 1). Importantly, each athlete was required to have his or her own personal automatic external defibrillator as a part of their personal emergency action plan. Notably, there was no BCE among these 10 CPVT1 athletes during follow-up while participating in sports.

DISCUSSION

CPVT is a potentially fatal genetic arrhythmia syndrome. The mainstay therapy for CPVT is primarily BB therapy, preferably either nadolol or propranolol,

which is effective in controlling arrhythmias in the majority of patients.[2,5] However, BBs can cause a variety of side effects and are not well-tolerated in some patients, thereby affecting compliance as well as quality of life. This phenomenon has been demonstrated previously in the context of LQTS, where 44% of patients on BB therapy (nadolol or propranolol) reported considerable side effects.[16] Moreover, a recent study from an international cohort of patients with CPVT showed that 15% of patients with CPVT were nonadherent on BBs with high concerns about the CPVT medication.[6] Although treatment for patients with CPVT is primarily focused on risk reduction, it is important to consider the patient's quality of life during treatment discussions when the side effects of BBs are not acceptable.

Importantly, flecainide and LCSD are extremely effective for patients with CPVT.[3,11,12,17-19] Also, transposing lessons learned in LQTS, it is important to consider whether there is a subgroup of patients with CPVT that can safely be treated as INT owing to an ascertained low risk of cardiac event. Although risk stratification has been challenging in CPVT, the risk: benefit ratio in our patients supported INT. In this study for the approximately 10% of patients for whom BB was not the best option, we evaluated 4 BB-free treatment options: INT, flecainide monotherapy, LCSD monotherapy, and dual therapy with flecainide and LCSD.

CONSIDERATIONS FOR INT IN CPVT. In this group of highly selected patients characterized by asymptomatic status and absence of complex arrhythmias during exercise stress test, we show for the first time in this multicenter international study that an INT strategy can indeed be used safely with excellent outcomes. It must be noted that nearly all of these patients were identified through cascade screening, therein representing a low-risk, asymptomatic subset of subsequently identified patients with CPVT. In addition to the phenotype, the genotype also has a role when deciding to pursue with INT for these patients. For example, this cohort has an overrepresentation of the well-described p.R420W-RYR2 variant, which has been associated with a low penetrance (approximately 25%) and mild disease expression.[20,21]

Although CPVT can manifest at any time, sentinel events are most likely to occur during the first 2 decades of life and are uncommon after 40 years of age.[12] Moreover, CPVT is rarely the cause of sudden infant death syndrome, with a mean age of presentation at 7-9 years.[13-15] Therefore, patients who were: 1) diagnosed by cascade screening; 2) outside of the age group at increased risk for cardiac events (ie, young children or those >20 years old); and 3) lacked a CPVT phenotype on stress testing, INT can be a treatment option following careful risk stratification by a genetic cardiologist expert and using the principles of shared decision-making. Although 23% of the patients on INT are in the 7 to 20 age group, the genetic cardiologist experts contributing to this article suggest that these cases are highly specific. There also seems to be an over-representation of the p.R420W variant (41%) in this group. As such, INT should not be considered a general option for this age group. Rather, BB-free options should be considered for infants and older patients, often diagnosed through cascade screening and lacking a phenotype.

In this group of patients with CPVT, treated without any medication or intervention, periodic exercise test surveillance remains extremely important, and CPVT therapy must be initiated or r-initiated if complex VAs on the exercise test or Holter monitoring occurs during follow-up or if a sentinel event occurs. The electrocardiographic surveillance may differ among institutions. As a reference at Mayo Clinic, where 30% of the patients on INT within this cohort were evaluated and treated, infants and young children (<6 years old) undergo electrocardiographic surveillance using a Holter monitor every 6 months, and once the child is able to perform a stress test (around 6 years of age), exercise test surveillance is performed annually. CPVT therapy is started in the presence of complex VA (bigeminy, couplets, nonsustained VT on Holter, or stress test). Moreover, families are recommended to have an automatic external defibrillator as a part of family safety gear. To date with this approach, there have been no tragedies. In fact, the initiation of CPVT1-directed medical therapy has never been required owing to a sentinel event between their annual evaluations at Mayo Clinic in pre-asymptomatically tested individuals.

As such, INT should only be pursued after careful clinical evaluation, shared decision-making, and appropriate patient selection after a detailed clinical risk assessment by a genetic cardiologist expert. Patient education is of paramount importance. Furthermore, patients must be counseled on communicating with the team about any potential sentinel event in the setting of INT. Last, although

INT may be an appropriate consideration for improved quality of life and patient's desire in low-risk patients owing to the prevalence of BB side effects, it should never be viewed as an alternative to BBs or more advanced therapies in phenotype-positive, symptomatic high-risk patients. In fact, it must be emphasized that the vast majority of our patients (90%) remain under standard, guideline-directed BB therapy.[2]

ALTERNATIVE TREATMENTS FOR PATIENTS WITH UNACCEPTABLE BB SIDE EFFECTS. The combination of flecainide and BBs decreases ventricular ectopy during exercise with subsequent decrease in cardiac events in patients with CPVT.[11,19,22,23] The use of flecainide as monotherapy has been described previously in patients who experienced BB side effects and is suggested to be a safe and effective strategy in the management of patients with CPVT.[24,25] Flecainide is generally well-tolerated and associated with a trend toward increased heart rates and exercise capacity, because it exerts a lesser effect on sinus rate during exercise.[24] Herein, we showed the use of flecainide as monotherapy in a small fraction of the entire International CPVT Registry (only 2%) with excellent outcomes. In addition, LCSD has been used in patients with CPVT since 2008, with subsequent multicenter studies showing a significant long-term decrease in cardiac events.[17,18,26] LCSD is indicated as a treatment intensification option for patients with recurrent syncopal events, sustained VT, or appropriate ICD shocks despite receiving BB therapy.[2] Moreover, BCEs can occur owing to a single missed dose of BBs.[3] Thus, for patients with CPVT who are not protected adequately on BBs, either owing to recurrent BCEs despite adherence or owing to nonadherence, treatment with LCSD should be considered either as monotherapy or as adjunct therapy.

Herein, we showed 3 BB-free treatment combinations for patients with CPVT who do not tolerate or do not want to be on BBs. Among these 27 patients treated with flecainide, a LCSD or dual therapy with flecainide and LCSD, there was only 1 nonfatal sentinel event. Although large case series or clinical trials are needed to determine the true efficacy of these BB-free treatment paradigms for CPVT, such trials are likely to never occur. Accordingly, they should be discussed with patients when BBs therapy is not tolerated. Of note, a general recommendation among the genetic cardiologist experts in this study is that for higher risk, previously symptomatic patients who are intolerant to BBs, dual therapy with the combination of flecainide and LCSD is considered a preferable option.

The guidelines recommend that patients with CPVT should avoid competitive sports, strenuous exercise, and exposure to stressful environments.[2] However, recent studies suggest that the risk may be acceptable for well-treated and well-informed athletes after their diagnosis of CPVT.[27] In this cohort of patients with CPVT treated without BB, patients were allowed to participate in their sports after a shared decision-making approach, after a careful risk assessment that showed no complex ventricular ectopy on stress tests. It is crucial that families and patients be well-informed about the treatment, the importance of adherence to treatment, and that they are reminded to bring along their personal automatic external defibrillator.

STUDY LIMITATIONS. Owing to its retrospective nature, this study has several limitations. First, the number of patients in some of the treatment subgroups is relatively small. However, this series includes more patients on INT than many of the earlier series describing CPVT. Second, owing to the multicenter nature of these data, not all information was collected uniformly or available, and the indications for certain treatment strategies and decisions were not documented clearly to enable precise ascertainment on retrospective review. Variations in the quality of collected data from various centers and its resultant effect on conclusions was limited by performing a thorough data check and retrieval of any missing data.

CONCLUSIONS

The results of our study suggest that a strategy of INT may be used safely in carefully selected, low-risk patients with CPVT1. It is important to caution that this data is primarily from a young population (<7 years old), and the follow-up is not long. All CPVT1-directed treatment strategies including INT need to be carefully considered and discussed with the patient and family. For symptomatic or asymptomatic patients with a positive CPVT1 stress test who do not tolerate their BB therapy, an alternative BB-free treatment strategy (flecainide monotherapy, LCSD monotherapy, or combination therapy with both flecainide and LCSD) should be implemented instead of INT.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although nonselective BBs remain the cornerstone treatment for CPVT, a subset of patients may require a BB-free treatment approach. After meticulous risk assessment, safe and efficacious BB-free treatment strategies can be tailored to individual patients.

TRANSLATIONAL OUTLOOK: Future studies involving large case series are necessary to ascertain the true efficacy of BB-free treatment paradigms for CPVT. These studies will provide valuable insights into the optimal management of patients with CPVT who are unable to tolerate BBs.

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KEY WORDS Beta-blockers, CPVT, side effects

APPENDIX For supplemental tables, please see the online version of this article.