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Efficacy of Flecainide in the Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia:

A Randomized Clinical Trial

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Abstract

IMPORTANCE—Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal genetic arrhythmia syndrome characterized by polymorphic ventricular tachycardia with physical or emotional stress, for which current therapy with β-blockers is incompletely effective. Flecainide acetate directly suppresses sarcoplasmic reticulum calcium release—the cellular mechanism responsible for triggering ventricular arrhythmias in CPVT—but has never been assessed prospectively.

OBJECTIVE—To determine whether flecainide dosed to therapeutic levels and added to β-blocker therapy is superior to β-blocker therapy alone for the prevention of exercise-induced arrhythmias in CPVT.

DESIGN, SETTING, AND PARTICIPANTS—This investigator-initiated, multicenter, single-blind, placebo-controlled crossover clinical trial was conducted from December 19, 2011, through December 29, 2015, with a midtrial protocol change at 10 US sites. Patients with a clinical diagnosis of CPVT and an implantable cardioverter-defibrillator underwent a baseline exercise test while receiving maximally tolerated β-blocker therapy that was continued throughout the trial. Patients were then randomized to treatment A (flecainide or placebo) for 3 months, followed by exercise testing. After a 1-week washout period, patients crossed over to treatment B (placebo or flecainide) for 3 months, followed by exercise testing.

INTERVENTIONS—Patients received oral flecainide or placebo twice daily, with the dosage guided by trough serum levels.

MAIN OUTCOMES AND MEASURES—The primary end point of ventricular arrhythmias during exercise was compared between the flecainide and placebo arms. Exercise tests were scored on an ordinal scale of worst ventricular arrhythmia observed (0 indicates no ectopy; 1, isolated premature ventricular beats; 2, bigeminy; 3, couplets; and 4, nonsustained ventricular tachycardia).

RESULTS—Of 14 patients (7 males and 7 females; median age, 16 years [interquartile range, 15.0–22.5 years]) randomized, 13 completed the study. The median baseline exercise test score was 3.0 (range, 0–4), with no difference noted between the baseline and placebo (median, 2.5; range, 0–4) exercise scores. The median ventricular arrhythmia score during exercise was significantly reduced by flecainide (0 [range, 0–2] vs 2.5 [range, 0–4] for placebo; $P < .01$), with complete suppression observed in 11 of 13 patients (85%). Overall and serious adverse events did not differ between the flecainide and placebo arms.

CONCLUSIONS AND RELEVANCE—In this randomized clinical trial of patients with CPVT, flecainide plus β-blocker significantly reduced ventricular ectopy during exercise compared with placebo plus β-blocker and β-blocker alone.

TRIAL REGISTRATION—clinicaltrials.gov Identifier: NCT01117454

Catecholaminergic polymorphic ventricular tachycardia (CPVT), a rare genetic arrhythmia syndrome, is characterized by polymorphic ventricular tachycardia with physical or emotional stress in patients with a structurally normal heart.[1] It can be a particularly lethal channelopathy, resulting in symptom onset during childhood and cardiac arrest as a frequent presentation.[2] Mutations in the genes encoding the cardiac ryanodine receptor 2 calcium release channel (*RYR2* [OMIM 180902]) or cardiac calsequestrin (*CASQ2* [OMIM 114251]) are implicated in approximately 60% of cases.[3,4] These proteins regulate intracellular calcium homeostasis in myocytes, and disruptions resulting in excessive sarcoplasmic reticulum calcium release are arrhythmogenic.[5] The recommended first-line therapy for CPVT consists of β-blockers,[6] but recurrent events are common despite β-blocker therapy, especially in children, and rates of near-fatal and fatal events remain unacceptably high.[7] The implantable cardioverter defibrillator (ICD) can be useful in patients at high risk of CPVT events, but ICD shocks can trigger catecholamine release, resulting in arrhythmic storm, multiple shocks, and death.[8,9] Left cardiac sympathetic denervation is a promising option for severely affected patients with syncope despite optimal medical therapy, but it is limited to specialized centers.[10,11] To date, randomized clinical trials have not been performed in CPVT and are exceptional in cardiac channelopathy research, as stated in the most recent international expert consensus statement: “randomized and/or blinded studies do not exist in this field”.[6(p1193)]

Flecainide acetate is a class IC antiarrhythmic drug approved by the US Food and Drug Administration for use in children and adults for the prevention of documented ventricular arrhythmias judged by the physician to be life-threatening. In 2009, Watanabe et al[12] reported the unexpected finding that flecainide showed remarkable efficacy in suppressing sarcoplasmic reticulum calcium release, the cellular mechanism responsible for triggering ventricular ectopy in CPVT. Flecainide also inhibits delayed afterdepolarization–mediated triggered activity due to sodium channel block, an additional potential mechanism for efficacy in CPVT.[13] Flecainide prevented catecholamine-induced ventricular arrhythmias in a well-established mouse model of CPVT and was highly efficacious in 2 severely affected patients with drug-refractory CPVT.[12] In a retrospective open-label therapeutic trial, flecainide was associated with reduced exercise-induced arrhythmias in 22 of 29 patients with CPVT compared with a β-blocker alone.[14] Reduction of exercise-induced arrhythmias is a clinically relevant outcome because persistence of ventricular arrhythmias in the form of couplets or nonsustained ventricular tachycardia (NSVT) on exercise testing has been associated with subsequent cardiac events in CPVT.[15] To study the efficacy of flecainide added to conventional treatment with maximally tolerated β-blockers in the treatment of CPVT, we conducted a single-blind, placebo-controlled, randomized clinical crossover trial.

Methods

Trial Design and Protocol Change After Enrollment Started

We conducted a single-blind, multicenter, placebo-controlled, randomized clinical crossover study at 10 centers in the United States (Vanderbilt University Medical Center, Nashville, Tennessee; UCLA [University of California, Los Angeles], Medical Center; New York University Langone Medical Center, New York City, New York; Nationwide Children’s

Hospital, Columbus, Ohio; Children's Hospital of Orange County, Orange, California; MetroHealth Campus, Case Reserve Western University, Cleveland, Ohio; East Carolina University, Greenville, North Carolina; Primary Children's Hospital, University of Utah, Salt Lake City; Duke University Medical Center, Durham, North Carolina; and Cook Children's Healthcare, Fort Worth, Texas), with Vanderbilt University Medical Center as the coordinating center from December 19, 2011, through December 29, 2015, with a midtrial change in protocol and primary outcome due to low enrollment. The study was approved by the institutional review board at each participating center. All patients 18 years or older provided written informed consent; those younger than 18 years provided assent, and a parent or guardian provided written informed consent.

The initial study design was a single-blind (blinded participants) randomized crossover study in which each participant received flecainide or placebo (treatment A) for 18 months and, after a 1-week washout, crossed over to placebo or flecainide (treatment B) for 18 months. Exercise treadmill tests were performed at enrollment (baseline, using β-blocker therapy only), 3 months after treatment A, and 3 months after crossover to treatment B. The primary end point was VT or appropriate ICD therapy, and the secondary end point was the degree of ventricular arrhythmias induced on exercise testing. Adequate power for the primary end point required enrolling 60 subjects. In June 2015, after only 14 of the desired 60 participants were enrolled, and with approval from the funding source and the data and safety monitoring board (DSMB), we modified the study protocol to evaluate only the secondary end point (ventricular arrhythmias on exercise testing). At that point, participants who had completed the treatment A exercise test crossed over without the 18-month treatment duration. Similarly, participants discontinued treatment B after the 3-month exercise test was complete. The initial protocol, modified protocol, and statistical analysis plans are available in Supplement 1.

Trial Participants

We recruited children and adults with a clinical diagnosis of CPVT and a functioning ICD in place from the 10 US centers. Inclusion criteria were a clinical diagnosis of CPVT based on reproducible polymorphic/bidirectional VT with exercise or ventricular ectopy during exercise testing, with a putative pathogenic *RYR2* (heterozygous) or *CASQ2* (homozygous) mutation; a functioning ICD in place; and a stable dosage of standard therapy defined as the maximal tolerated dosage of β-blocker. The dosage and choice of β-blocker were determined by the patients' physicians before trial entry and remained unchanged throughout the conduct of the trial. Patients were excluded if they were pregnant or planning to become pregnant during the study period, were younger than 5 years, were unable to perform treadmill exercise, had significant structural heart disease, were taking amiodarone hydrochloride, or had a known hypersensitivity to flecainide. Patients using flecainide before enrollment were eligible for the trial; these participants discontinued flecainide therapy at least 1 week before their baseline assessment. Documentation of the clinical diagnosis of CPVT (electrocardiographic [ECG] recordings of ventricular ectopy during exercise, genetic test reports) and absence of structural heart disease (cardiac imaging reports) was reviewed and confirmed by the coordinating center before randomization. Female patients had a negative pregnancy test result at the first study visit and at the crossover visit. The race and

ethnicity of each patient were recorded, in accordance with US National Institutes of Health policy and definitions.

Randomization and Blinding

Randomization of treatment order was performed at the coordinating center, and assignments were distributed to the participating sites at the time of enrollment. Participants were randomized in permuted blocks of 4. The study drug, flecainide acetate, was administered every 12 hours, with a starting dose of 100 mg/d (50 mg every 12 hours) and a maximum dose of 400 mg/d. Study drug and placebo were provided by a central pharmacy (US Compounding) and mailed directly to enrolled participants; flecainide and placebo were similar in appearance. Investigators were aware of treatment assignment, but participants were blinded.

Study Procedures

After enrollment (and a 1-week washout for participants who previously used flecainide), patients underwent a baseline exercise test during standard therapy with β-blocker alone. Patients then initiated treatment A (flecainide or placebo) in a blinded fashion. After 1 week, a trough flecainide level and ECG were obtained. For patients randomized to flecainide, the target serum level was 0.50 to 0.80 μg/mL. Patients with levels of less than 0.35 μg/mL had the dose doubled, and those with levels of 0.35 to 0.50 μg/mL increased the dosage by 50%, unless the maximum dosage had been achieved. Patients requiring a dose adjustment (and randomly chosen participants in the placebo arm) had a second serum sample and ECG obtained at 1 month. Any additional dose adjustments were made before the 3-month visit, with all patients taking their trough level–adjusted dosage for at least 20 consecutive days before the exercise test. Serum levels were obtained locally, and dosage adjustments were made by the coordinating center and central pharmacy after confirmation with the enrolling site investigator (P.J.K., J.P.M., M.C., S.G.P., N.J.K., P.S.R., A.S.B., E.S.K., D.L.F., E.V.S., S.P.E., R.J.K., M.P.C., and M.V.D.) that no adverse effects or significant widening of the QRS complex duration on ECG occurred. The dosage escalation continued until the trough flecainide level was greater than 0.50 μg/mL, the QRS width was greater than 120 milliseconds or prolonged by more than 50 milliseconds of the baseline QRS, or the maximum dosage was achieved. Adherence with the flecainide regimen was confirmed with serum levels obtained on the day of each exercise test.

Participants underwent initial exercise treadmill testing at baseline while receiving β-blockers only. After 3 months of treatment A, participants underwent exercise treadmill testing (exercise test A) and had a serum sample obtained for measurement of the flecainide level. Participants then discontinued treatment A, and after 1 week of standard therapy alone, started treatment B. Determination of flecainide dosage and levels was performed as described above. After 3 months of treatment B, another exercise test (exercise test B) was performed and a serum flecainide level was measured. Treatment B was discontinued after exercise test B, and the patient’s participation in the study was complete. Participants were then unblinded, and the decision to continue flecainide therapy was left to the discretion of the treating physician.

Trial Oversight

The US Food and Drug Administration reviewed the protocol and concluded that the study met all the requirements for exemption from Investigational New Drug regulations. The DSMB met before enrollment and then biannually through the conclusion of the trial. Per National Heart, Lung and Blood Institute (NHLBI) policy (updated in December 2014), NHLBI program staff participated as nonvoting members in DSMB meetings beginning in 2015.

End Points and Statistical Analysis

The original primary end point was VT or appropriate ICD therapy. In June 2015, after the protocol change, the primary end point was reduction in ventricular ectopy at the exercise test with comparison of flecainide and placebo. Exercise tests were analyzed and scored as previously described[14,16] on an ordinal scale of worst ventricular arrhythmia observed in which 0 indicates no ventricular ectopy; 1, isolated premature ventricular contractions (<10 per minute); 2, premature ventricular contractions in a bigeminal pattern (>10 per minute); 3, ventricular couplets (2 consecutive beats); and 4, nonsustained VT (≥3 consecutive beats).

In addition, the following exercise variables were compared: resting heart rate, peak sinus heart rate, exercise time, maximal workload achieved, and maximal number of ventricular ectopic beats during the worst 10-second period of exercise. Analysis of exercise tests was performed with the investigators blinded to treatment assignment. Throughout the trial, the incidence and severity of all adverse events were recorded. The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) was used to grade severity of adverse events. Adverse events with CTCAE grade 3 or higher were considered to be serious. The DSMB regularly reviewed adverse event data. Adverse events, serious adverse events, and likely drug-related adverse events were compared between the flecainide and placebo arms. Data are reported as medians and interquartile ranges or as numbers and percentages. All comparisons were evaluated using Wilcoxon signed rank test with continuity correction, with $P < .05$ indicating statistical significance. Data were analyzed using R software (version 3.2.2; https://www.r-project.org/). Interim analysis was not performed.

Results

Trial Population

A total of 14 participants (7 males and 7 females) were randomized. One participant randomized to placebo for treatment A withdrew from the study 3 months after the treatment A exercise test owing to pregnancy (she had a negative pregnancy test result at enrollment). This participant was excluded from the study cohort because she did not receive flecainide during the trial. One participant randomized to flecainide for treatment A withdrew before treatment B (placebo) exercise test. This participant was included in the study cohort but is excluded from the primary paired analysis comparing flecainide and placebo (Figure 1). Baseline characteristics of the study cohort (n = 13) are listed in Table 1. The cohort was young (median age, 16 years [interquartile range, 15.0–22.5 years]) and predominantly white and non-Hispanic. Putative pathogenic mutations were present in *RYR2* in 10 patients

and *CASQ2* in 1; 2 patients had negative genetic findings. Seven patients had a history of aborted cardiac arrest; in 4, it was their presenting symptom. All patients were using β-blockers, primarily nadolol, at maximally tolerated dosages. At the time of the protocol change, 3 participants had completed the full original protocol. Nine additional participants completed the original protocol timeline through the treatment B exercise test and discontinued treatment B a few months earlier than originally planned. Only 1 participant had not already crossed over to treatment B when the protocol change was made. That participant crossed over after 9 months of treatment A and then received treatment B for 3 months, followed by the treatment B exercise test.

Original Primary Outcome Before Protocol Change

Only 3 ICD therapies for VT (the originally intended primary outcome) were observed in 2 participants. One participant received an appropriate shock during each arm of the study, after 108 days in the flecainide arm and after 194 days in the placebo arm. At exercise testing, this participant had NSVT at baseline, bigeminy during flecainide treatment, and NSVT during placebo treatment. One participant randomized to placebo first had no ICD shocks during 18 months of the placebo treatment and had an appropriate shock after 284 days of flecainide treatment. At exercise testing, this participant had couplets at baseline, NSVT during placebo treatment, and bigeminy during flecainide treatment. In all 3 instances of ICD shocks, the participants did not seek medical attention until several weeks later, precluding assessment of compliance with a flecainide level at the time of ICD shock. Aside from these 3 episodes treated with an ICD shock, no episodes of sustained VT or inappropriate ICD shocks and no deaths occurred during the trial.

Primary Outcomes After Protocol Change

The median baseline exercise test score was 3 (range, 0–4), with 9 participants experiencing ventricular couplets or non-sustained VT despite maximally tolerated β-blocker therapy. The flecainide acetate dose ranged from 100 to 200 mg (median, 150 mg) twice daily with serum trough levels of 0.48 μg/mL (range, <0.10 to 0.86 μg/mL) on the day of the flecainide exercise test. Ventricular ectopy during exercise was significantly reduced by flecainide compared with placebo (exercise test score, 0 [range, 0–2] vs 2.5 [range, 0–4]; $P = .008$) in the 12 patients with data available and compared with β-blocker therapy alone (baseline; $P = .005$) in the 13 patients with data available (Table 2 and Figure 2). Two patients with NSVT with placebo had persistent bigeminy with flecainide (with levels of 0.44 and 0.48 μg/mL), and complete suppression was observed in 11 of 13 (85%). We found no significant difference between the baseline (median, 3.0; range, 0–4) and placebo (median, 2.5; range, 0–4) exercise scores ($P = .70$). All flecainide levels on the day of the placebo exercise test were less than 0.10 μg/mL. The maximal number of ectopic beats during the worst 10 seconds was also significantly reduced by flecainide (0 [range, 0–11] vs 10 [range, 0–17] by placebo; $P = .009$) in the 12 patients with data available. We found no difference in the maximal number of ectopic beats during 10 seconds between baseline and placebo (13 [range, 0–17] vs 10 [range, 0–17]; $P = .39$). Total exercise time, maximal workload achieved, and resting heart rate were not significantly affected by flecainide, but peak sinus rate was lower compared with the baseline and placebo exercise tests (eTable 1 in Supplement 2).

Adverse Events

Overall adverse events were frequent and did not differ significantly between the flecainide and placebo arms (mean, 1.6 events per patient with flecainide vs 1.1 events per patient with placebo; $P = .22$). Serious adverse events occurred with similar frequency between flecainide (2 events in 2 patients) and placebo (4 events in 2 patients) ($P = .42$), and none were likely to have been related to the study drug, as judged by the study team and DSMB (eTable 2 in Supplement 2). Adverse events likely related to the study drug were more common with flecainide ($P = .04$) and included blurry vision in 4 cases and 1 case each of light-headedness and fatigue. One case of diarrhea occurred during placebo treatment.

Discussion

This randomized placebo-controlled crossover study demonstrated that flecainide added to β-blocker therapy is superior to maximally tolerated β-blocker therapy alone in reducing exercise-induced ventricular arrhythmias in patients with CPVT. With combination therapy, no participant had couplets or NSVT during exercise testing. This finding is a clinically relevant reduction because couplets or NSVT during exercise testing have been associated with subsequent cardiac events in CPVT.[15] Previous studies[14,16] have demonstrated reductions in ventricular ectopy during exercise with flecainide, consistent with our results, but those were nonrandomized, open-label therapeutic trials without a true placebo arm. Furthermore, many of those patients were receiving suboptimal β-blocker therapy.[14] This study is, to our knowledge, the first randomized clinical trial in CPVT, demonstrating that randomized clinical trials are feasible in rare syndromes by using a statistically efficient crossover design.

The rationale for flecainide use for treatment of CPVT is supported by in vitro studies demonstrating that flecainide blocks RyR2 in lipid bilayers,[12] suppresses calcium waves in *CASQ2*-knockout myocytes,[17] abolishes delayed afterdepolarization–mediated triggered activity,[13] and reduces exercise-induced ventricular arrhythmias in *CASQ2* and *RYR2* mouse models.[12,13] The efficacy of flecainide in human patients with CPVT has been previously demonstrated in the following 3 retrospective cohorts: 29 predominantly *RYR2* mutation– positive patients,[14] 12 genotype-negative patients,[16] and 10 *CASQ2* homozygous mutation–positive patients.[18] A dose-dependent response has been suggested previously, with mean (SD) daily doses of 113 (39) mg in nonresponders,[14] 142 (78) mg in partial responders, and 150 (60) mg in those with complete suppression. This finding is further supported by our finding that a median dosage of 300 mg/d was required to achieve target trough drug levels. One could speculate that chronotropic incompetence from combination therapy with β-blocker plus flecainide would result in lower levels of exertion during exercise and thus a lower arrhythmia score. However, maximal workload achieved during each exercise test did not differ significantly, suggesting similar levels of effort across the 3 exercise tests.

Nadolol has recently been shown to be superior to β1-selective β-blockers in suppressing ventricular arrhythmias during exercise testing in CPVT.[19] The previous retrospective studies[14,16,18] investigating the efficacy of flecainide have included cohorts where nadolol use was infrequent (5 of 29, 4 of 12, and 0 of 10 patients), and β1-selective β-blockers were

common in the 2 larger studies (19 of 29 and 6 of 12 patients).[14,16] Thus, in retrospect, many of those patients may not be receiving optimal β-blocker therapy for CPVT. Our cohort was predominantly treated with nadolol and at maximally tolerated dosages, but many were still at risk for cardiac events, as evidenced by couplets or NSVT on exercise testing. Our data demonstrate that flecainide prevents exercise-induced ventricular arrhythmias in those with significant ventricular ectopy despite optimal β-blocker therapy.

The care of patients with CPVT and other genetic arrhythmia syndromes is limited by the lack of a robust evidence base for nearly all therapies. In the most recent expert consensus statement on the diagnosis and management of inherited primary arrhythmia syndromes,[6] all recommendations are level of evidence C (expert opinion). On the basis of primarily the previous retrospective data,[14,16] flecainide is now listed as a class IIA recommendation in addition to β-blockers in patients with CPVT who experience recurrent syncope or polymorphic/bidirectional VT while using β-blockers. Flecainide appears to have been rapidly adopted into clinical practice because a recent publication (the largest published series to date) reported flecainide use in 23% of patients with CPVT.[2] One of the challenges to enrollment in the present trial was the relatively widespread use of flecainide in patients with difficult to control CPVT. Some of these patients and their clinicians were unwilling to discontinue flecainide therapy and be randomized to placebo, again based on results of retrospective open-label studies. We provided a higher level of evidence supporting flecainide use for treatment of CPVT and did not observe any proarrhythmia or worsening of ventricular arrhythmias during exercise. Overall and serious adverse events were no more frequent with flecainide compared with placebo. None of the serious adverse events (eTable 2 in Supplement 2) were related to study drug. Adverse events related to flecainide were mild.

Limitations

This study is limited by the small sample size, because we were unable to enroll enough patients to assess our originally intended primary end point (appropriate ICD therapies). Although with the statistically efficient crossover design we were adequately powered to detect a difference in exercise test scores, this outcome is still a surrogate. Study participants were blinded, but it was not possible to blind investigators, because flecainide use is apparent from QRS widening on the ECG. Reduction of exercise-induced arrhythmias is clinically relevant in the care of patients with CPVT[15] but may not have applicability in other conditions. All study patents were receiving maximally tolerated dosages of β-blockers at baseline, mostly nadolol, but 3 were using β1-selective β-blockers. Recently published data suggest that nadolol is superior to β1-selective β-blockers for suppression of ventricular arrhythmias during exercise testing in CPVT.[19] These 3 patients in our study who received β1-selective β-blockers might have a lower exercise score at baseline and with placebo with nadolol. Because the data regarding nadolol's superiority in reducing exercise-induced arrhythmias was published after completion of this trial, we did not change the medication of the 3 patients using β1-selective β-blockers to nadolol during the study period. We also did not formally assess adequacy of β-blocker dosage, which was determined before trial entry by treating physicians and remained constant throughout the clinical trial. Because all patients were using β-blockers throughout the trial, we do not have any data supporting

flecainide as monotherapy, which has been suggested for the rare patient who cannot tolerate any dose of β-blocker.[20] The protocol change could have had an effect on study participants that biased the results, although we cannot easily speculate in which direction the results would be biased.

Conclusions

This prospective placebo-controlled randomized clinical trial demonstrates that flecainide, dosed to therapeutic trough levels, is highly efficacious in reducing ventricular arrhythmias associated with exercise in patients with CPVT and persistent exercise-induced ectopy despite a maximally tolerated β-blocker dose. No serious adverse events or proarrhythmias were related to flecainide. Long-term follow-up studies are required to ensure that cardiac events are reduced by flecainide plus optimal β-blocker therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Is flecainide acetate more effective than placebo when used in addition to maximally tolerated β-blocker therapy for the prevention of exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia?

Findings

This randomized clinical trial in 14 patients with catecholaminergic polymorphic ventricular tachycardia using maximally tolerated β-blockers demonstrated that ventricular arrhythmias during exercise were significantly reduced by flecainide, with complete suppression observed in 11 of 13 patients, compared with placebo. Overall and serious adverse events did not differ between the flecainide and placebo arms.

Meaning

Flecainide is efficacious in reducing ventricular arrhythmias associated with exercise in patients with catecholaminergic polymorphic ventricular tachycardia and persistent exercise-induced ectopy despite a maximally tolerated β-blocker dosage.

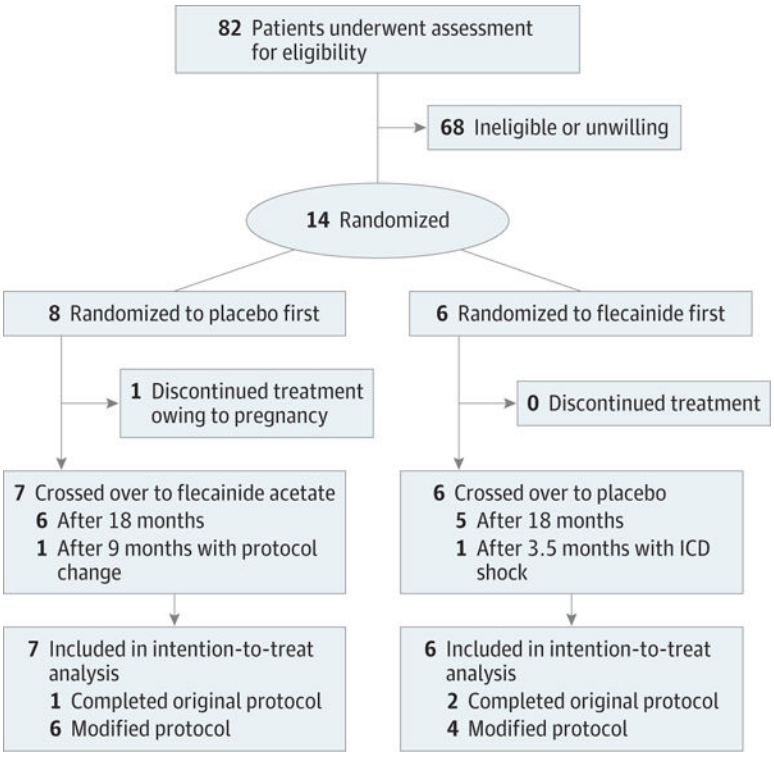

Figure 1. Study Flowchart

Participant flow is shown for a randomized clinical crossover trial of flecainide acetate for catecholaminergic polymorphic ventricular tachycardia.

ICD indicates implantable cardioverter defibrillator.

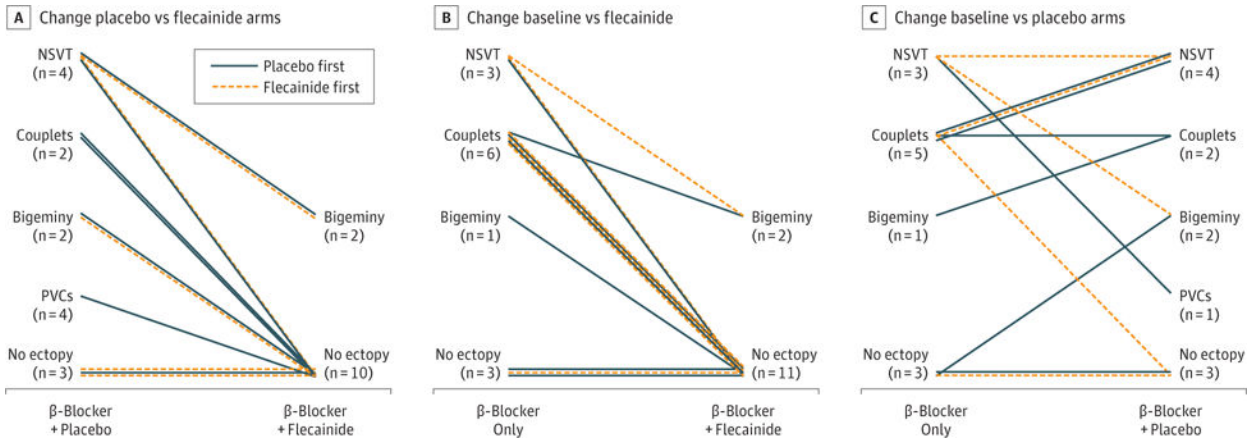

Figure 2. Efficacy of Flecainide in Reducing Ventricular Arrhythmias During Exercise in Catecholaminergic Polymorphic Ventricular Tachycardia

A, Change in arrhythmia score for each patient between the placebo and flecainide acetate arms for the 12 patients with available data ($P = .008$).

B, Change in arrhythmia score for each patient between baseline (β-blocker only) vs flecainide arm for the 13 patients with available data ($P = .005$).

C, Change in arrhythmia score for each patient between baseline (β-blocker only) vs placebo arm for the 12 patients with available data ($P = .70$). NSVT indicates nonsustained ventricular tachycardia; PVC, premature ventricular contractions.

Table 1

Baseline Characteristics of the Study Cohort

Characteristic	Patient Data (n = 13)[a]
Age, median (IQR), y	16 (15.0–22.5)
Male	7 (54)
White	12 (92)
Hispanic	1 (8)
Putative pathogenic mutation	11 (85)
RYR2	10 (77)
CASQ2	1 (8)
Weight, median (IQR), kg	74.5 (54–86)
Height, median (IQR), cm	168 (157–180)
β-Blocker use[b]	13 (100)
Nadolol	9 (69)
Atenolol	2 (15)
Metoprolol succinate	1 (8)
Propranolol hydrochloride	1 (8)
Exercise score at baseline[c]	
0	3 (23)
1	0 (0)
2	1 (8)
3	6 (46)
4	3 (23)

Abbreviations: *CASQ2*, cardiac calsequestrin gene; IQR, interquartile range; *RYR2*, ryanodine receptor 2 calcium release channel gene.

[a]Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b]β-Blocker use was unchanged throughout the trial. For nadolol, median daily dose was 80 mg; for atenolol, median daily dose was 112 mg; for metoprolol succinate, daily dose was 50 mg; and for propranolol hydrochloride, daily dose was 240 mg.

[c]Scores are for β-blocker treatment alone, with 0 indicating no ectopy; 1, isolated premature ventricular contractions; 2, bigeminy; 3, couplets; and 4, nonsustained ventricular tachycardia.

Table 2

Proportions of Patients With Each Ventricular Arrhythmia Score

	No. (%) of Patients[a]		
Ventricular Arrhythmia	**β-Blocker Alone**	**β-Blocker + Flecainide Acetate**	**β-Blocker + Placebo**
NSVT	3 (23)	0	4 (33)
Couplets	6 (46)	0	2 (17)
Bigeminy	1 (8)	2 (17)	2 (17)
PVCs	0	0	1 (8)
No ectopy	3 (23)	10 (83)	3 (25)

Abbreviations: NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contractions.

[a] $P = .005$, baseline compared with flecainide arm; $P = .008$, flecainide vs placebo arms; and $P = .70$, baseline compared with placebo arms.