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ECTOPIC trial: The efficacy of flEcainide Compared To metOprolol in reducing Premature ventrIcular Contractions: A randomized open-label crossover study in pediatric patients

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ABSTRACT

BACKGROUND Frequent premature ventricular contractions (PVCs) in children are usually considered benign. Symptoms and left ventricular dysfunction are indications for treatment with antiarrhythmic drugs.

OBJECTIVE This study aimed to evaluate the efficacy of flecainide vs metoprolol in reducing PVCs in children.

METHODS A randomized open-label crossover trial was conducted of children with a PVC burden of >15% on Holter monitoring successively treated with metoprolol and flecainide, or vice versa, with a drug-free interval of at least 2 weeks. Holter measurements were repeated before and after the start of the antiarrhythmic drug.

RESULTS Sixty patients were screened; 19 patients could be included. Median age was 13.9 years (interquartile range, 5.5 years). Mean baseline PVC burden was 21.7% (n = 18; SD ± 14.0) before the start of flecainide and 21.2% (n = 17; SD ± 11.5) before the start of metoprolol. In a mixed model analysis, the estimated mean reduction in PVC burden was 10.6 percentage points (95% CI, 5.8–15.3) for flecainide and 2.4 percentage points (95% CI,2.7–7.5) for metoprolol, with a significant difference of 8.2 percentage points (95% CI, 0.86–15.46; $P = .031$). Exploratory analysis revealed that 9 of 18 patients treated with flecainide and 1 of 17 patients treated with metoprolol had a reduction to a PVC burden below 5%. No discriminating factors between flecainide responders and nonresponders were found; the mean plasma level was not significantly different (0.34 mg/L vs 0.52 mg/L; $P = .277$).

CONCLUSION In children with frequent PVCs, flecainide led to a significantly greater reduction of PVC burden compared with metoprolol. Flecainide was effective in only a subgroup of patients, which appears to be unrelated to the plasma level.

KEYWORDS Premature ventricular contraction; Reduction; Antiarrhythmic drug; Flecainide; Metoprolol; Children; Randomized; Crossover

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Introduction

Frequent idiopathic premature ventricular contractions (PVCs) and idiopathic ventricular tachycardia (VT) in children and young adults are rare, especially in the first decade of life.[1] In older children and young adults, the incidence increases,[2] although exact numbers are unknown because most patients are asymptomatic. Frequent idiopathic PVCs have been considered benign in all age groups.[1] However, during the past decade, frequent

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PVCs have emerged as a cause of PVC-induced cardiomyopathy with left ventricular (LV) dysfunction in adults.[3,4] In children with frequent PVCs, decreased shortening fraction or PVC-induced cardiomyopathy has also been reported in smaller series,[5–10] reversible after treatment of PVCs.[11]

Current guidelines recommend antiarrhythmic drug (AAD) therapy or catheter ablation for treatment of children and adults with symptomatic idiopathic PVCs and nonsustained VT.[12,13] In AAD guidelines for adult patients, nondihydropyridine calcium channel blockers and flecainide are advised next to beta blockers.[13] In the pediatric age group, beta blockers are usually considered first-line treatment of symptomatic patients or patients with LV dysfunction.[14] However, especially in the pediatric population, data on the effect of AAD on frequent PVCs and VTs are scarce. In 2021, we published a systematic review of typically small case series on the effect of AADs on PVCs, combined with the results of our retrospective study of 35 children treated with AADs for frequent PVCs with or without asymptomatic VT.[15] In that study, flecainide seemed to be the only effective AAD compared with sotalol, beta blocker, and verapamil. To further investigate the effect of beta blockers compared with flecainide in reducing the PVC burden, we performed a randomized crossover trial of children.

Methods

Study design

The efficacy of flEcainide Compared To metOprolol in reducing Premature ventrIcular Contractions trial (ECTOPIC trial) is an open-label, prospective, randomized, multicenter, crossover trial in a tertiary care setting. Patients were screened in multiple centers in The Netherlands and referred to the Leiden University Medical Center in Leiden or the Erasmus Medical Center in Rotterdam for inclusion in the study. Patients received both flecainide and metoprolol in a consecutive way and were randomized to start with flecainide or metoprolol. Patients and physicians were not blinded to the medication used.

Inclusion and exclusion criteria

Patients needed to fulfill the inclusion criteria: age ≥1 year and <18 years, structurally normal heart confirmed by echocardiography, and PVC burden >15% on 2 different 24-hour Holter recordings, with or without idiopathic VT. The cutoff of >15% was chosen to include only patients with a significant amount of PVCs; there is no cutoff known for children above which PVCs should be treated. The exclusion criteria were age <1 year (because of the significant chance of spontaneous resolution of PVCs), structural cardiac defects, history of cardiac surgery, myocarditis, cardiomyopathies, inherited arrhythmia syndromes, verapamil-sensitive PVC/VT, and psychomotor mental retardation.

Abbreviations

AAD: antiarrhythmic drug

LV: left ventricular

PVC: premature ventricular contraction

VT: ventricular tachycardia

Informed consent and ethical approval

Patients and parents were informed about the study in person and provided with written patient information sheets. After a reflection period of 2 weeks, written informed consent was obtained from the patient or the parents, depending on the age of the child. Ethical approval was granted from the local and central ethical committee on research involving human subjects. The research reported in this paper adhered to the Helsinki Declaration as revised in 2013 and Consolidated Standards of Reporting Trials guidelines.

Study protocol

Baseline characteristics including sex, age, height, weight, date of diagnosis, and presence of symptoms were collected. Baseline testing consisted of 12-lead electrocardiography, echocardiography, 48-hour Holter recording, exercise test (≥7 years of age; <7 years, analysis of Holter recording during exercise), and baseline N-terminal pro–B-type natriuretic peptide level. This was followed by the first medication period consisting of oral dosage of flecainide controlled release (4 mg/kg per day) or metoprolol controlled release (2 mg/kg per day) for at least 5 days to allow plasma levels to reach a steady state. After 5 days, 12-lead electrocardiography, echocardiography, and 48-hour Holter recordings were repeated and flecainide plasma levels measured if applicable. If the response to medication on Holter monitoring was <5 percentage points reduction in PVC burden, the dosage of flecainide or metoprolol was increased for another 5 days to 6 mg/kg per day or 3 mg/kg per day, respectively. Subsequently, measurements were repeated, and plasma levels of flecainide were measured if applicable. The medication was stopped in both the patients who did and the patients who did not have a dosage increase. After an off-drug period of at least 2 weeks, baseline measurements were repeated before the second medication was initiated according to the same schedule (Figure 1). During patient visits, patients and parents were asked about their experience of adverse effects. The most effective medication was used to perform cardiac magnetic resonance imaging with delayed gadolinium enhancement to measure cardiac function and dimensions during sinus rhythm.

Outcome parameter

The primary outcome was defined as the percentage points reduction of the PVC burden on 48-hour Holter recording, based on the difference between the PVC burden at baseline and the measurement of the PVC burden after 5 days of treatment. The co-primary outcome was defined as the percentage points reduction of the PVC burden on 48-hour Holter recording, based on the difference between the PVC burden at baseline measurement and the measurement of the PVC burden with the highest dosage that was used.

Statistical methods

Data were expressed as counts with percentages, mean (standard deviation) in case of normal distribution, or median (interquartile range or min-max) in case of nonnormal distribution. Statistical analysis was performed with SPSS software version 29 (IBM, Armonk, NY).

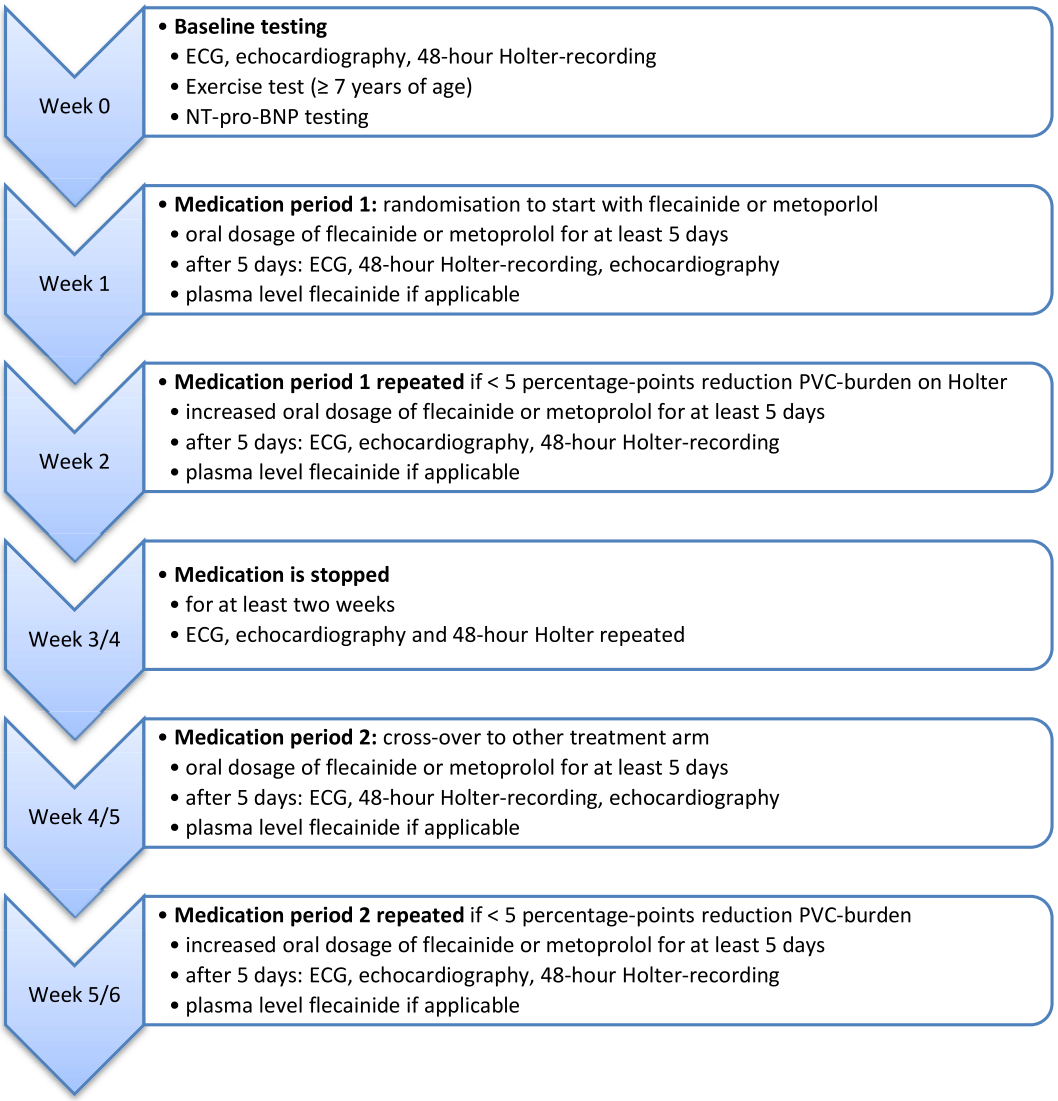

Figure 1
Study protocol. ECG = electrocardiography; NT-pro-BNP = N-terminal pro–B-type natriuretic peptide; PVC = premature ventricular contraction.

A statistical analysis plan was made before the study that described the use of a linear mixed model with therapy and period as fixed factors and a random intercept per patient for primary and co-primary end point analysis. The dependent variable in this model was the reduction in PVC burden (baseline minus PVC burden after medication). Baseline measurement was used as an additional covariate. This model allowed estimation of a possible period effect and of a therapy*period interaction. The estimated therapy effect marginalized during the 2 periods in this model was used to compare the primary study parameters.

During planning and design of the study, a sample size of 49 was calculated on the basis of the hypothesis that the reduction of PVCs by flecainide will be greater than the reduction of PVCs by metoprolol. A difference of 5.0 percentage points between the mean percentage of decrease of PVCs in the 2 groups was considered clinically relevant. A standard deviation of 12.2 was anticipated for the differences. The sample size calculation was based on a β error of 20% and an α level of .05. As this was an intrapatient design, the 2 observations for the 2 therapies were assumed to be correlated.

Results

From September 2018 to December 2022, 60 patients were screened; 51 patients fulfilled the inclusion criteria, and 9 patients had another cardiac diagnosis after careful review or did not reach the threshold of 15% PVCs. Finally, 19 patients provided consent to participate in the study. These 19 patients contributed to 35 treatment periods and 70 Holter recordings that were used for the primary outcome analysis. The number of patients included was smaller than the calculated sample size. The inclusion in this investigator-initiated study was severely delayed because of the COVID pandemic and had

to be stopped because of limited personal and financial resources. Only after the end of the study was statistical analysis made at group level according to the predesigned statistical analysis plan.

Baseline characteristics

Baseline characteristics are presented in Table 1. The median age at diagnosis was 13.3 years, the youngest being 2.9 years; the median age at the start of the study was 13.9 years, the youngest being 7.9 years. Symptoms were present in 47% of the patients. Cardiac function on echocardiography and N-terminal pro–B-type natriuretic peptide levels were normal in all patients. Cardiac magnetic resonance imaging confirmed a structurally normal heart in all patients with no delayed enhancement.

Table 1 Baseline characteristics

No. of patients	N = 19
Sex, male	11 (58)
Weight, kg	54.9 (±19.0)
Length, cm	161.0 (±17.1)
Age at diagnosis, y	13.3 (2.9–17.8)
Age at start of study, y	13.9 (7.9–18.1)
Time between diagnosis and start of study, mo	6.1 (1.1–82.1)
Cardiac function, shortening fraction on echocardiography, %	36 (±5)
Cardiac function, 2D ejection fraction on echocardiography, %	56 (±7)
NT-pro-BNP, ng/L	43.97 (±50.60)
Heart rate at which PVCs are suppressed, beats/min	153 (±35)
Cardiac function, ejection fraction on MRI,[a] %	53 (±4)
Holter recording	
PVC burden, %	20.5 (±12.3)
Type of PVC	
Isolated PVC	17 (90)
Couplets	12 (63)
Triplets	7 (37)
Nonsustained VT	1 (5)
Bigeminy	14 (74)
Trigeminy	1 (5)
Electrocardiography	
R-R interval sinus beat, ms	920 (±212)
QTc sinus beat, ms	384 (±43)
QRS duration PVC, ms	121 (±21)
PVC axis	
Superior	2 (11)
Inferior	17 (89)
PVC morphology V_1	
RBBB	6 (32)
LBBB	13 (68)
Coupling interval PVC, ms	480 (±99)

Categorical variables are presented as n (%). Continuous variables are presented as mean (±SD) or median (min-max).
2D = 2-dimensional; LBBB = left bundle branch block; NT-pro-BNP = N-terminal pro–B-type natriuretic peptide; MRI = magnetic resonance imaging; PVC = premature ventricular contraction; RBBB = right bundle branch block; VT = ventricular tachycardia.
[a]Cardiac MRI performed after medication testing.

The mean PVC burden at the start of the study was 20.5% (SD ± 12.3; Table 1). PVCs were monomorphic in all patients: 12 had a left bundle branch block morphology and inferior axis; 5 had a right bundle branch block morphology with inferior axis; 1 with a left bundle branch block morphology and 1 with a right bundle branch block morphology had a superior axis.

Treatment outcome

The PVC burden at baseline was 21.7% (n = 18; SD ± 14.0) for patients before the start of flecainide and 21.2% (n = 17; SD ± 11.5) for patients before the start of metoprolol, combining medication periods 1 and 2 (Table 2). The estimated mean reduction in PVC burden after 5 days of the starting dose of medication was 10.6 percentage points (95% CI, 5.8–15.3) for flecainide and 2.4 percentage points (95% CI, −2.7 to 7.5) for metoprolol (Figure 2). In a mixed model analysis, this led to a significant difference in estimated mean reduction of the PVC burden of 8.2 percentage points (95% CI, 0.86–15.46; $P = .031$).

In total, a PVC reduction of <5 percentage points was achieved in 6 of 18 patients on a flecainide dosage of 4 mg/kg per day and in 9 of 17 patients on a metoprolol dosage of 2 mg/kg per day. According to the protocol, these patients received higher dosages of medication (6 mg/kg per day for flecainide and 3 mg/kg per day for metoprolol). After 5 days of the highest dosage, the estimated mean reduction in PVC burden was 12.3 percentage points (95% CI, 7.3–17.2) for flecainide and 4.8 percentage points (95% CI, −0.6 to 10.1) for metoprolol. The difference in the estimated mean reduction in PVC burden was 7.5 percentage points (95% CI, 0.20–14.76; $P = .044$) according to the mixed model analysis. The results of PVC reduction of the individual medication periods are presented in the Supplemental Material.

Three patients did not complete the second medication period. Two patients decided to discontinue the study after the first medication period (one because of malaise/confusion during flecainide treatment; another for reasons unrelated to the study after metoprolol treatment). A third patient who started with flecainide showed signs of Brugada characteristics on the electrocardiogram a week after an increased dosage of flecainide, without reduction of PVCs. The flecainide was stopped immediately. The patient was genetically tested, but no class IV/V variant associated with Brugada syndrome was found; electrocardiograms made during fever episodes did not reveal a Brugada pattern. In addition, both parents had no signs of Brugada syndrome on electrocardiography or during ajmaline testing. There were few adverse effects in other patients, none of which led to discontinuation of the study; 2 experienced fatigue during flecainide treatment, 3 experienced fatigue during metoprolol treatment, and 1 also experienced nightmares.

Response of individual patients

The response of individual patients to flecainide and metoprolol is presented in Figure 3, which shows a steep drop in

Table 2 Estimated marginal mean reduction and difference in mean reduction based on a linear mixed model with reduction in PVC burden as dependent variable; treatment and medication period as factors including their interaction; baseline PVC burden as covariate

	Flecainide	Metoprolol
No. of patients	18	17
PVC burden at baseline, %	21.7 (±14.0)	21.2 (±11.5)
Primary outcome parameter		
PVC burden after 5 days of *starting* dose of medication, %	11.2 (±12.3)	20.3 (±8.4)
Estimated mean reduction PVC burden, %-points	10.6 (5.8–15.3)	2.4 (−2.7 to 7.5)
Difference in estimated mean reduction PVC burden, %-points	8.2 (0.86–15.46); P = .031	
Co-primary outcome parameter		
PVC burden after 5 days of *highest* dose of medication, %	9.4 (±11.4)	18.3 (±11.8)
Estimated mean reduction PVC burden, %-points	12.3 (7.3–17.2)	4.8 (−0.6 to 10.1)
Difference in estimated mean reduction PVC burden, %-points	7.5 (0.20–14.76); P = .044	

Values are reported as mean (±SD) or mean (95% CI).
Abbreviations as in Table 1.

PVC burden to below 5% in response to flecainide in a subgroup of patients. When treated with the flecainide starting dose for 5 days (mean, 3.6 mg/kg per day; SD ± 0.9), 8 had a reduction to a burden below 5% PVCs. After increasing the dosage (mean, 5.3 mg/kg per day; SD ± 0.74), 1 additional patient responded to flecainide with a reduction to a PVC burden below 5%.

Further exploratory analysis showed that this subgroup of 9 patients who responded to flecainide (responders) had a mean plasma level of 0.34 mg/L (SD ± 0.22) compared with a mean of 0.52 mg/L (SD ± 0.37; $P = .277$) in the nonresponders. The overall mean level of flecainide was 0.43 mg/L (SD ± 0.29), with no correlation to the percentage points of PVC reduction in a linear regression analysis ($P = .183$). No factors discriminating between the responders and nonresponders were found (Table 3).

After 5 days of the starting dose of metoprolol (mean, 2.0 mg/kg per day; SD ± 0.2), none of the patients had a PVC reduction to a PVC burden below 5%. Increasing the metoprolol dosage (mean, 2.8 mg/kg per day; SD ± 0.2) resulted in 1 patient with a PVC burden below 5%. In further exploratory analysis, there was no correlation between the percentage points of PVC reduction in response to metoprolol and the mean heart rate at which the PVCs were suppressed during exercise ($P = .291$).

Discussion

This study is the first prospective randomized crossover study to evaluate the effect of AADs on frequent PVCs in children with a structurally and functionally normal heart. We could demonstrate that flecainide (4 mg/kg per day) significantly reduced the PVC burden on 48-hour Holter recording, with an estimated mean reduction of 10.6 percentage points, compared with the estimated mean reduction of only 2.4 percentage points by metoprolol (2 mg/kg per day). This

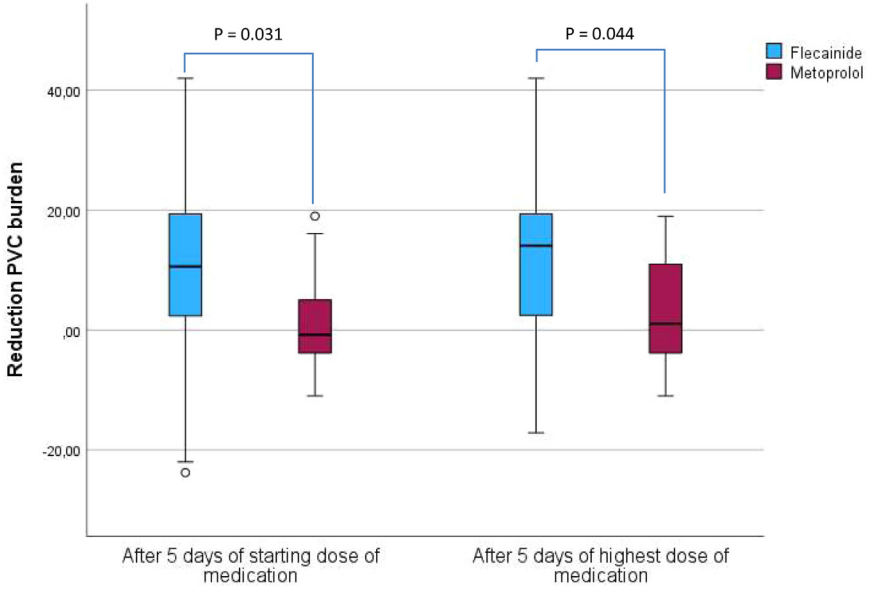

Figure 2
Estimated mean reduction in premature ventricular contraction (PVC) burden per medication: mean PVC burden at baseline minus mean PVC burden after starting dose of medication (*left*) and highest dose of medication (*right*); boxplot with the *black line* representing the median.

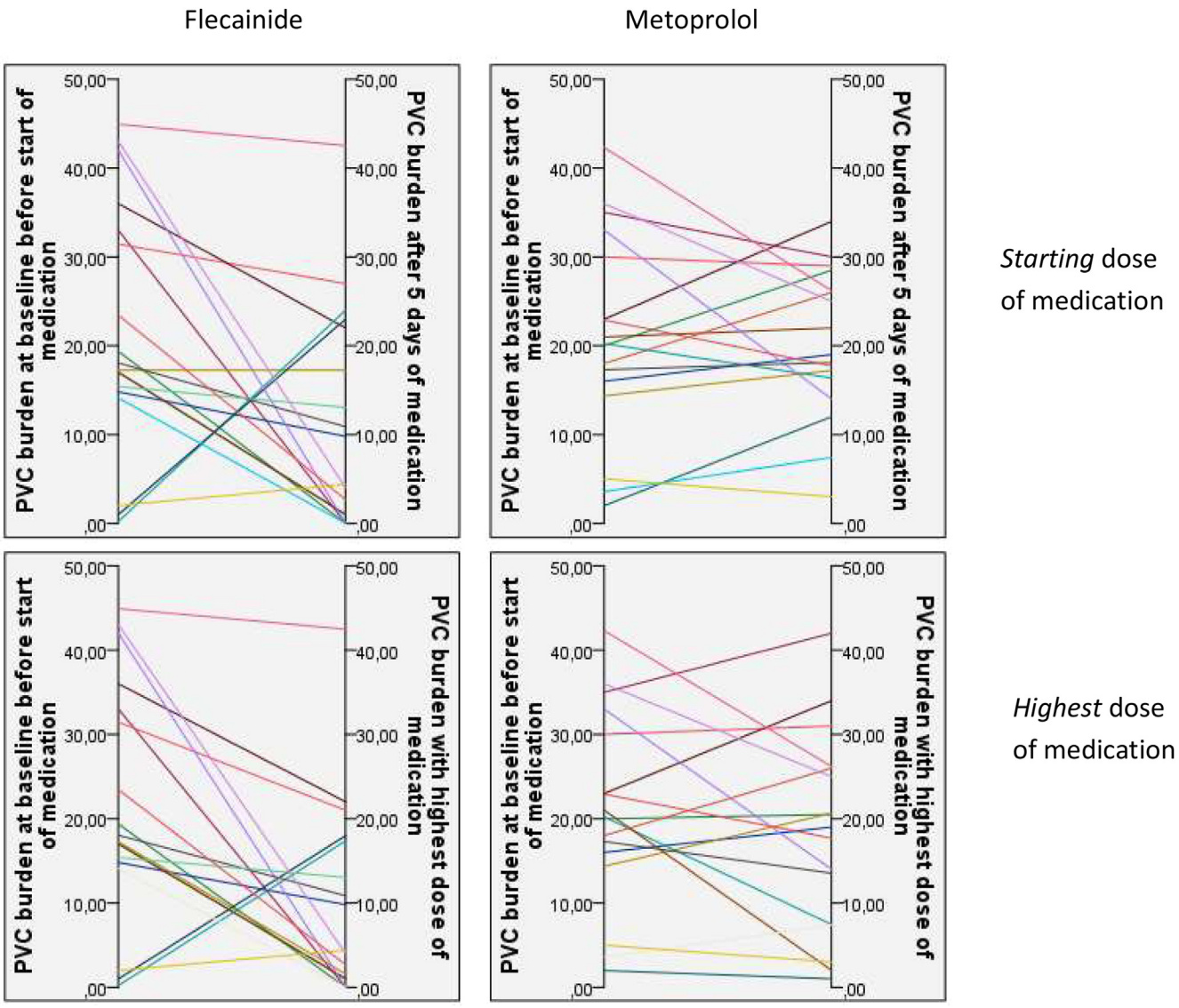

Figure 3
Response of individual patients to flecainide (*left*) and metoprolol (*right*) after 5 days of starting dose of medication (*top*) and highest dose of medication (*bottom*). Each *colored line* represents 1 patient.

difference in the estimated mean reduction between flecainide and metoprolol of 8.2 percentage points is significant. Of note, flecainide led to almost complete suppression of PVCs in half of the patients without the need of a high flecainide dosage or plasma level.

Current guidelines for children with frequent PVCs recommend AADs in case of symptoms or LV dysfunction, with beta blockers as first-line therapy,[12,16] which is in concurrence with older studies in adult patients that report beta blockers to be effective in treating PVCs.[17] In severe symptomatic cases, flecainide is advised, eventually followed by ablation.

Most pediatric series are small and mostly describe the effect of AADs in VT, of which the effect varies widely.[18–21] Kakavand and associates[6] are the only investigators to report on the effect of AADs in frequent PVCs of >5% in a retrospective study and showed in 19 patients that both beta blockers and flecainide may be effective.

In 2021, we published a retrospective series of 35 children evaluating the efficacy of AADs in PVCs in children and a review of the literature.[15] In that study, we found the efficacy of the 4 classes of AADs in reducing the burden of PVCs to be limited; the overall mean reduction was 4.4 percentage points. Only flecainide had a significant mean reduction of 13.8 percentage points, contrary to beta blockers, which reduced the PVC burden by a mean of 1.7 percentage points. This corresponds to the effect of flecainide and metoprolol found in this randomized study.

The results of this pediatric study are in line with more recent trials in adults in which the beta blocker carvedilol and class 1C AADs were compared.[22,23] In the study by Hwang and coworkers,[22] the PVC burden was reduced 5.6 (±9.3) percentage points by carvedilol and 10.6 (±12.1) percentage points by flecainide ($P = .023$). During the setup of this study, we hypothesized that carvedilol might be superior

Table 3 Analysis of differences between responders and nonresponders to flecainide

	Flecainide responders	Flecainide nonresponders	*P* value
No. of patients	9	9	
Age at diagnosis, y	13.1 (7.8–17.8)	11.5 (2.9–16.9)	.769
PVC burden at baseline, %	22.7 (±12.8)	18.7 (±12.8)	.766
PVC axis inferior	8/9 (89)	8/9 (89)	1
PVC morphology V_1 LBBB	5/9 (56)	7/9 (78)	.317
QRS duration PVC, ms	128 (±16)	110 (±25)	.186
Coupling interval of PVC, ms	473 (±94)	488 (±113)	.647
QTc sinus beat, ms	401 (±43)	398 (±55)	.607
Heart rate at which PVCs are suppressed during exercise, beats/min	158 (±39)	153 (±29)	.067

Categorical variables are presented as n (%). Continuous variables are presented as mean (±SD) or median (min-max).
Abbreviations as in Table 1.

in reducing PVCs compared with other beta blockers because of its direct inhibitory effect on store overload-induced calcium release, which is the proposed mechanism causing delayed afterdepolarization, triggered activity, and finally PVCs. However, it was concluded that there is no difference between the effect of carvedilol and the effect of other beta blockers reported in prior series.[24,25]

In another study by Hamon and colleagues[23] involving an adult cohort, the authors stated that beta blockers may even have a negative effect on the burden of PVCs in subgroups of patients because PVCs often decrease at higher heart rates. Therefore, lowering the heart rate by beta blockers may increase PVC burden.[26] This is in line with the effect on PVC burden of metoprolol and carvedilol in a study by Turan and colleagues.[27] They reported a reduction of 0.6 and 2.0 percentage points for metoprolol and carvedilol, respectively, with a poor or even increased response of the PVC burden in 88% of the patients. Consequently, it might be expected that in patients who still have PVCs at higher heart rates, metoprolol would have more effect. However, in this study, we found no correlation between the heart rate at which the PVCs are suppressed during exercise and the effect of metoprolol on the PVC burden.

The effect of flecainide on PVC burden has been recognized in adults and is confirmed in children in our study. In addition, our data suggest that flecainide is especially effective in a subgroup of patients with an effect that is not dose related: we did not find a correlation between the reduction in PVC burden and the flecainide levels; and the group of responders to flecainide had a lower flecainide level compared with the group of nonresponders, and increasing the dose had little effect on the PVC burden in the nonresponders.

PVCs are thought to be caused by different underlying mechanisms, like delayed afterdepolarizations inducing triggered activity[22] or automaticity resulting in parasystole.[28,29] Class 1C AADs are known to be able to reduce triggered activity,[30] which might explain why flecainide seems to work only in a subgroup of patients. In explorative analyses, we were not able to establish factors discriminating between the responders and the nonresponders based on PVC characteristics, such as coupling interval and PVC morphology, to localize the focus of the PVCs. This needs to be explored in additional larger studies.

The results of this study led us to change the way we treat children with frequent PVCs. Our current practice is to start treatment only in case of symptoms or LV dysfunction, with flecainide being the first-line therapy.

Limitations

The number of patients included in this prospective randomized crossover trial is small because of external factors. However, because the difference in effect of flecainide vs metoprolol was higher than we expected, we were still able to reach statistical significance in this smaller group of patients.

It is well known in the natural history of PVCs that the PVC burden can vary. In this study, we compensated for this factor by randomizing the patients to start with metoprolol or flecainide and by performing the measurements in a short time frame of a few weeks.

Conclusion

In children with frequent PVCs, flecainide reduces the PVC burden significantly better than metoprolol. Metoprolol has minimal effect on the PVC burden. Flecainide was effective in a subgroup of patients, which appeared to be unrelated to the plasma level. Flecainide may be considered the first line of treatment in symptomatic children with frequent PVCs and a structurally normal heart. Future studies should focus on possible identifying factors of response to AAD treatment.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.07.111.

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