Advances in treatment of pediatric arrhythmias

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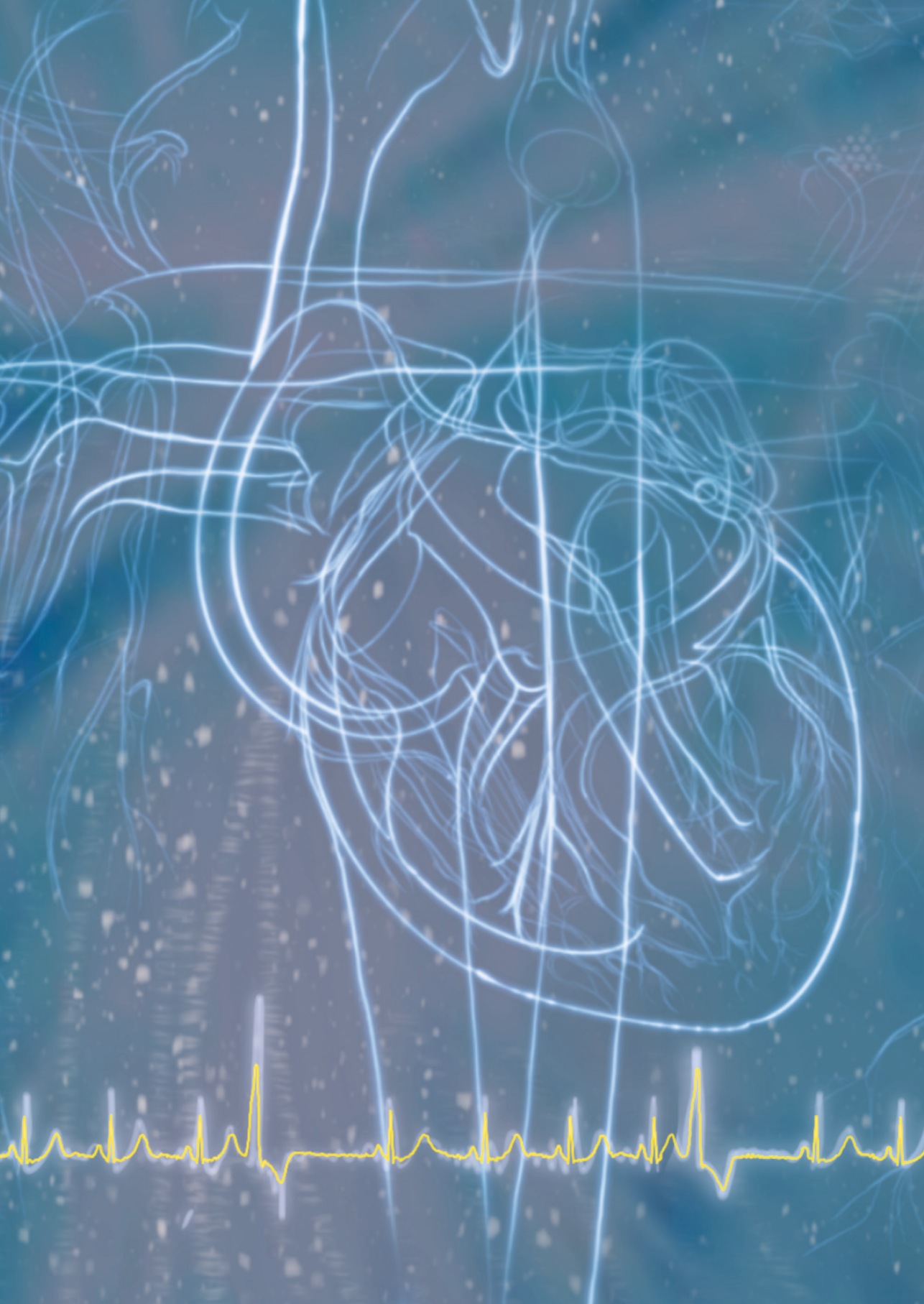

7 CHAPTER

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

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.

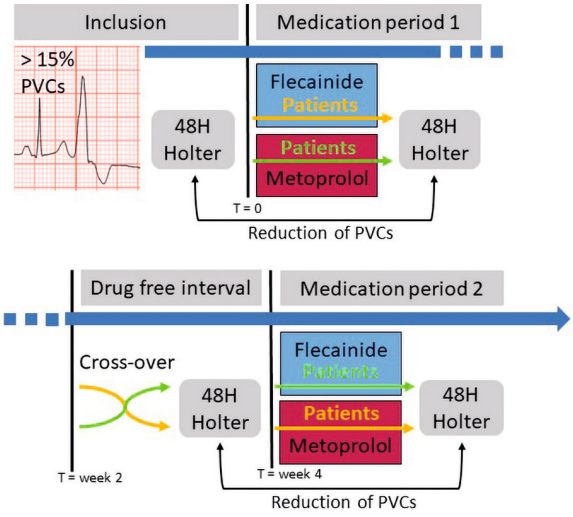
Results

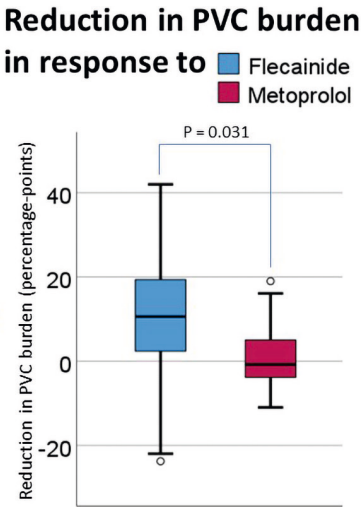
Sixty patients were screened; 19 patients could be included. Median age was 13.9 years (interquartile range, 5.5 years).Mean baseline PVC burden was 21.7% (n 5 18; SD6 14.0) before the start of flecainide and 21.2% (n5 17; SD 6 11.5) before the start of metoprolol. In a mixed model analysis, the estimated 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; P5.031). 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 non-responders were found; the mean plasma level was not significantly different (0.34 mg/L vs 0.52 mg/L; P 5 .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.

GRAPHICAL ABSTRACT





INTRODUCTION

Frequent idiopathic premature ventricular contractions (PVCs) and idiopathic ventricular tachycardia (VTs) 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, since most patients are asymptomatic. Frequent idiopathic PVCs have been considered benign in all age groups.[1] However, over the past decade frequent PVCs have emerged as cause of PVC induced cardiomyopathy with left ventricular (LV) dysfunction in adults.[3,4] In children with frequent PVCs, decreased shortening fraction (SF) or PVC induced cardiomyopathy has also been reported in smaller series,[5-10] reversible after treatment of PVCs.[11]

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

Patients needed to full-fill the inclusion criteria: age ≥ 1 year and < 18 years, structurally normal heart confirmed by echocardiography, PVC-burden > 15% on two different 24-hour Holter-recordings, with or without idiopathic VT. The cut-off of > 15% was chosen to only include patients with a significant amount of PVCs, there is no cut-off 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, psychomotor mental retardation.

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 two weeks, written informed consent was obtained from the patient and/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 CONSORT guidelines. The ECTOPIC trial was registered in the Dutch Trial Register on 06-02-2017 number 26689.

Study protocol

Baseline characteristics were collected, including sex, age, height, weight, date of diagnosis and presence of symptoms. Baseline testing consisted of 12-lead ECG, echocardiography, 48-hour Holter-recording, exercise test (≥7 years of age, <7 years analysis of Holter during exercise), baseline NT-pro-BNP. This was followed by the first medication period consisting of oral dosage of flecainide controlled release (4 mg/kg/day) or metoprolol controlled release (2 mg/kg/day) for at least 5 days to allow plasma levels to reach a steady state. After 5 days 12-lead ECG, echocardiography, 48-hour Holter-recordings were repeated and flecainide plasma levels measured if applicable. If the response to medication on Holter was less than 5 percentage-points reduction in PVC-burden, the dosage of flecainide or metoprolol was increased for another 5 days to 6 mg/kg/day or 3 mg/kg/day respectively. Subsequently, measurements were repeated, and plasma levels of flecainide measured if applicable. The medication was stopped both in the patients that did or did not had 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 side-effects. The most effective medication was used to perform a cardiac MRI 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.

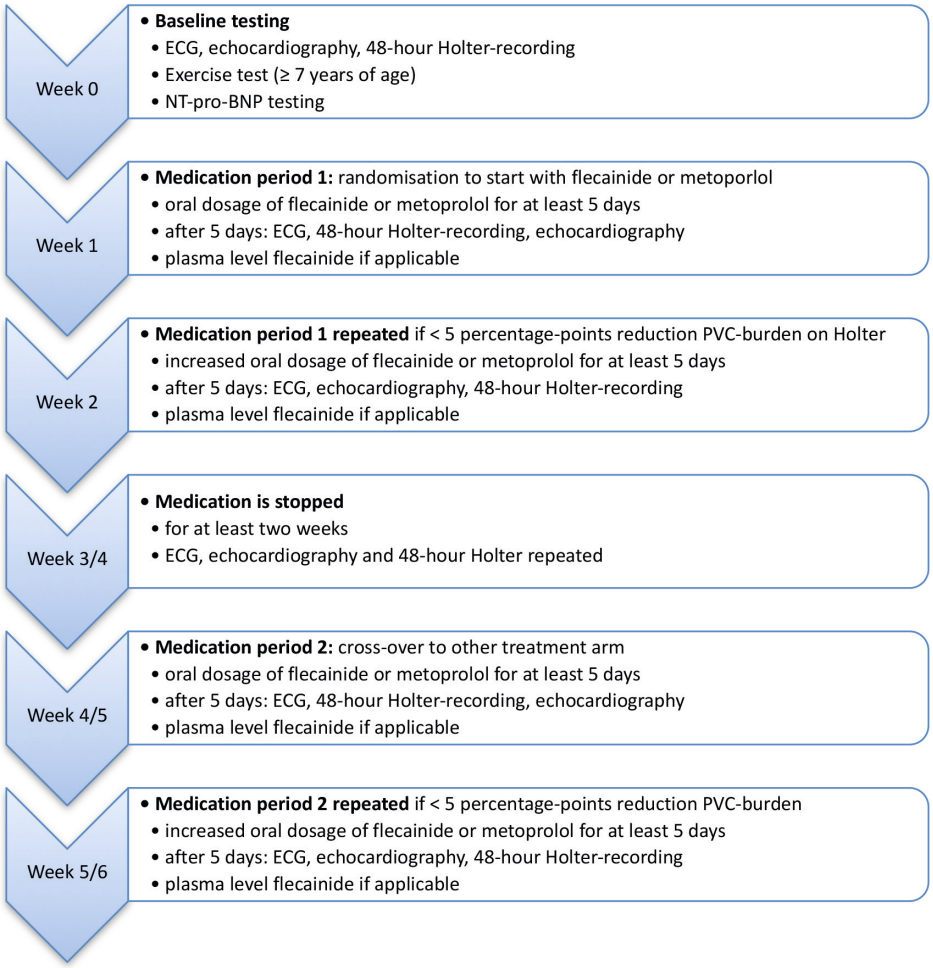


Figure 1: Study protocol

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 non-normal distribution. Statistical analysis was performed using the IBM SPSS software version 29.

A statistical analysis plan was made prior to the study, which described the use of a linear mixed models with therapy and period as fixed factors and a random intercept per patient for primary and co-primary endpoint analysis. The dependent variable in this model was the reduction in PVC-burden (baseline minus PVC-burden after medication). Baseline measurement was used as additional co-variate. This model allowed estimation of a possible period-effect and of a therapy*period interaction. The estimated therapy effect marginalized over the two 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, based on 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 two groups, was considered as clinically relevant. A standard deviation of 12.2 was anticipated for the differences. The sample size calculation was based on a beta-error of 20% and an alpha-level of 0.05. As this was an intra-patient design, the two observations for the two therapies were assumed to be correlated.

RESULTS

From September 2018 to December 2022 60 patients were screened. Fifty-one patients fulfilled the inclusion criterion, nine 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, which 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, statistical analysis was made at group level according to the pre-designed 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 NT-pro-BNP levels were normal in all patients. Cardiac MRI confirmed a structural normal heart in all patients with no delayed enhancement.

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 LBBB-morphology and inferior axis; 5 had a RBBB-morphology with inferior axis; one with a LBBB-morphology and one with a RBBB-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) before the start of metoprolol, combining medication period 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 – 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 of 0.86 – 15.46, P = 0.031).

Table 1: Baseline characteristics

Number of patients	**N = 19**
Sex (male), number (%)	11 (58)
Weight (kg), mean (SD)	54.9 (± 19.0)
Length (cm), mean (SD)	161.0 (± 17.1)
Age at diagnosis (years), median (min-max)	13.3 (2.9-17.8)
Age at start of study (years), median (min-max)	13.9 (7.9-18.1)
Time between diagnosis – start of study (months), median (min-max)	6.1 (1.1-82.1)
Cardiac function, shortening fraction on echo (%), mean (SD)	36 (± 5)
Cardiac function, 2D ejection fraction on echo (%), mean (SD)	56 (± 7)
NT-pro-BNP (ng/L), mean (SD)	43.97 (± 50.60)
Heart-rate at which the PVCs are suppressed (beats/min), mean (SD)	153 (± 35)
Cardiac function, ejection fraction on MRI (%), mean (SD)†	53 (± 4)
Holter	
PVC-burden (%), mean (SD)	20.5 (± 12.3)
Type of PVC, number (%)	
- Isolated PVC	17 (90)
- Couplets	12 (63)
- Triplets	7 (37)
- Non-sustained VT	1 (5)
- Bigeminy	14 (74)
- Trigeminy	1 (5)
ECG	
RR-interval sinus beat (ms), mean (SD)	920 (± 212)
QTc sinus beat (ms), mean (SD)	384 (± 43)
QRS-duration PVC (ms), mean (SD)	121 (± 21)
PVC-axis, number (%)	
- Superior	2 (11)
- Inferior	17 (89)
PVC-morphology V1, number (%)	
- RBBB	6 (32)
- LBBB	13 (68)
Coupling-interval PVC (ms), mean (SD)	480 (± 99)

† Cardiac MRI performed after medication testing

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 co-variate.

	Flecainide	Metoprolol
Number of patients (#)	18	17
PVC-burden at baseline (%), mean (SD)	21.7 (± 14.0)	21.2 (± 11.5)
Primary outcome parameter		
PVC-burden after 5 days of *starting* dose of medication (%), mean (SD)	11.2 (± 12.3)	20.3 (± 8.4)
Estimated mean reduction PVC-burden (%-points), mean (95% CI)	10.6 (5.8 – 15.3)	2.4 (-2.7 – 7.5)
Difference in estimated mean reduction PVC-burden (%-points), mean (95% CI)	8.2 (0.86 – 15.46) P = 0.031	
Co-primary outcome parameter		
PVC-burden after 5 days of *highest* dose of medication (%), mean (SD)	9.4 (± 11.4)	18.3 (± 11.8)
Estimated mean reduction PVC-burden (%-points), mean (95% CI)	12.3 (7.3 – 17.2)	4.8 (-0.6 – 10.1)
Difference in estimated mean reduction PVC-burden (%-points), mean (95% CI)	7.5 (0.20 – 14.76) P = 0.044	

In total 6/18 patients had a PVC reduction of less than 5 percentage-points on a flecainide dosage of 4 mg/kg/day and 9/17 patients on a metoprolol dosage of 2 mg/kg/day respectively. According to the protocol, these patients received higher dosages of medication (6 mg/kg/day for flecainide and 3 mg/kg/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 – 10.1) for metoprolol. The difference in the estimated mean reduction in PVC-burden was 7.5 percentage-points (95% CI of 0.20 – 14.76, P = 0.044), according to the mixed model analysis. The results of PVC reduction of the individual medication periods are presented in the supplementary 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 ECG 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; ECGs made during fever episodes did not reveal a Brugada pattern. In addition, both parents had no signs of Brugada on ECG or during ajmaline testing. There were few side effects in other patients, none of which let to discontinuation of the study; two experienced fatigue during flecainide treatment; three experienced fatigue during metoprolol treatment, one experienced also nightmares.

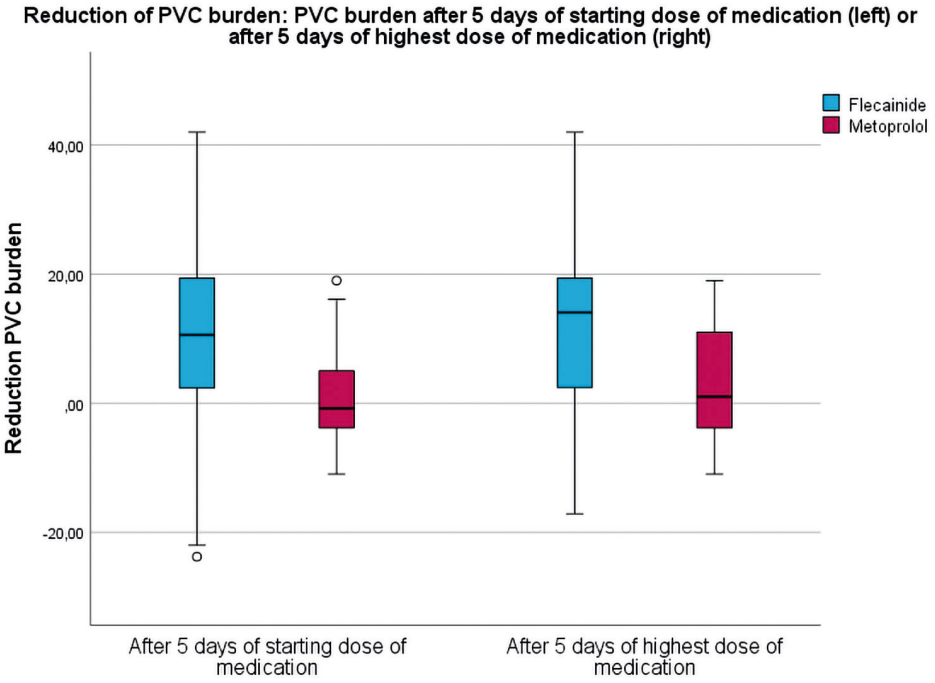


Figure 2: Estimated mean reduction in PVC-burden per medication: mean PVC-burden at baseline minus mean PVC-burden after starting dose of medication (left panel) and highest dose of medication (right panel); boxplot with the black line representing the median.

Table 3: Analysis of differences between responders and non-responders of flecainide.

	Flecainide responders	Flecainide non-responders	P-value
Number of patients (#)	9	9	
Age at diagnosis (years), median (min-max)	13.1 (7.8-17.8)	11.5 (2.9-16.9)	0.769
PVC-burden at baseline (%), mean (SD)	22.7 (SD±12.8)	18.7 (SD±12.8)	0.766
PVC-axis inferior, number (%)	8/9 (89)	8/9 (89)	1.000
PVC-morphology V1 LBBB, number (%)	5/9 (56)	7/9 (78)	0.317
QRS-duration PVC (ms), mean (SD)	128 (SD±16)	110 (SD±25)	0.186
Coupling-interval of PVC (ms), mean (SD)	473 (SD±94)	488 (SD±113)	0.647
QTc sinus beat (ms), mean (SD)	401 (SD±43)	398 (SD±55)	0.607
Heart-rate at which the PVCs are suppressed during exercise (beats/min), mean (SD)	158 (SD±39)	153 (SD±29)	0.067

Response of individual patients

The response of individual patients to flecainide and metoprolol is presented in figure 3, which shows a steep drop in 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/day, SD ± 0.9), 8 had a reduction to a burden below 5% PVCs. After increasing the dosage (mean 5.3 mg/kg/day SD ± 0.74) one additional patient responded to flecainide with a reduction to a PVC-burden below 5%.

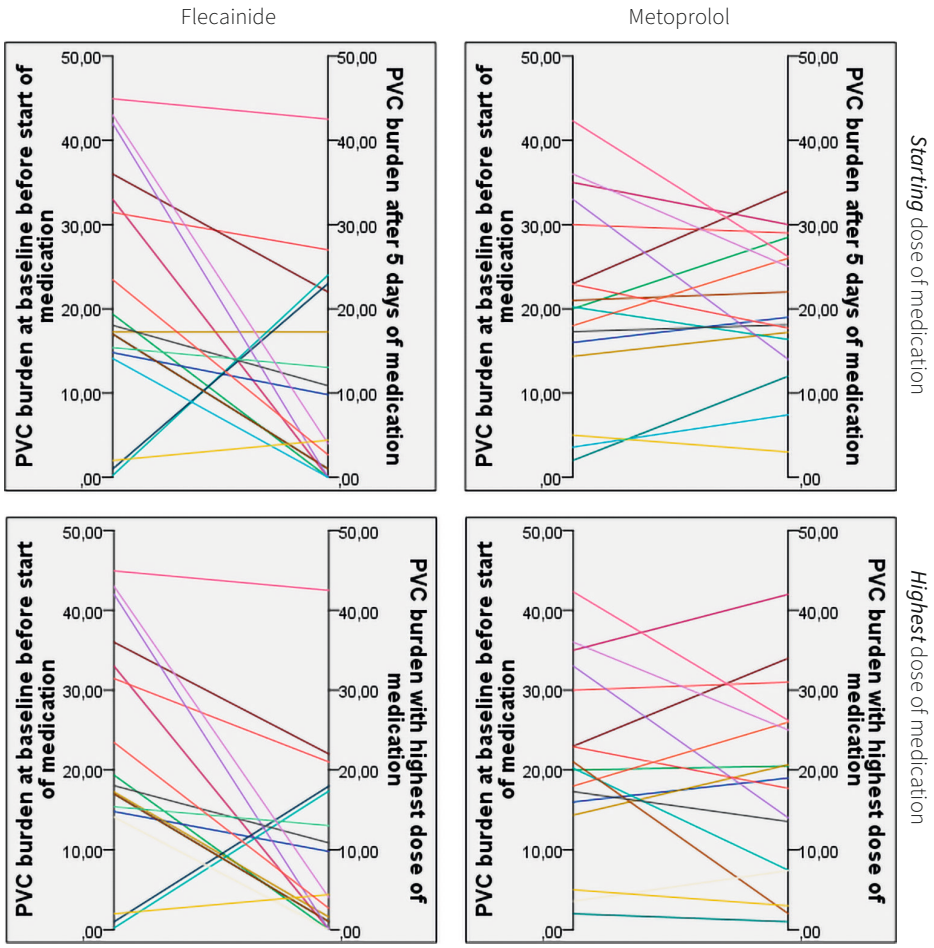


Figure 3: Response of individual patients to flecainide (left side) and metoprolol (right side) after 5 days of starting dose of medication (top) and highest dose of medication (bottom). Each colored line represents one patient.

Further exploratory analysis showed that this subgroup of nine patients that responded to flecainide (responders) had a mean plasma level of 0.34 mg/L (SD ± 0.22), compared to a mean of 0.52 mg/L (SD ± 0.37, P = 0.277) in the non-responders. The overall mean level

of flecainide was 0.43 mg/L (SD ± 0.29), with no correlation to the percentage-points PVC reduction in a linear regression analysis (P = 0.183). No discriminating factors between the responders and non-responders were found (Table 3).

After 5 days of starting dose of metoprolol (mean 2.0 mg/kg/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/day SD ± 0.2) resulted in one 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 = 0.291).

DISCUSSION

This study is the first prospective randomized cross-over study, to evaluate the effect of AADs on frequent PVCs in children with a structural and functional normal heart. We could demonstrate that flecainide (4 mg/kg/day) significantly reduced the PVC-burden on 48-hour Holter-recording, with an estimated mean reduction of 10.6 percentage-points, compared to the estimated mean reduction of only 2.4 percentage-points by metoprolol (2 mg/kg/day). This 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 AAD in case of symptoms and/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 AAD in ventricular tachycardia, of which the effect varies widely.[18-21] Kakavand et al. are the only authors that report on the effect of AAD in frequent PVC of > 5% in a retrospective study and showed in 19 patients that both beta-blockers and flecainide may be effective.[6]

In 2021 we have published a retrospective series of 35 children evaluating the efficacy of AAD in PVCs in children and a review of the literature.[15] In this study we have found that the efficacy of the four classes of AADs in reducing the burden of PVCs was 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 with the effect of flecainide and metoprolol found in the present randomized study.

The results of this pediatric study are in line with more recent trial in adults, in which the beta-blocker carvedilol and Class-1C AAD were compared.[22,23] In the study by Hwang et

al., the PVC-burden was reduced 5.6 (± 9.3) percentage-points by carvedilol and 10.6 (± 12.1) percentage-points by flecainide (P = 0.023). During the setup of this study, the authors hypothesized that carvedilol might be superior in reducing PVCs compared to other beta-blockers due to its direct inhibitory effect on store overload-induced calcium release, which is the proposed mechanisms causing delayed afterdepolarization, triggered activity and finally PVCs. However, they concluded that there was 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 et al. (2019) 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, since 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 et al. [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 our present 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 suggests that flecainide is especially effective in a subgroup of patients with an effect that is not dose related: 1) we did not find a correlation between the reduction in PVC-burden and the flecainide levels; 2) the group of responders to flecainide had a lower flecainide level compared to the group of non-responders and increasing the dose had little effect on the PVC-burden in the non-responders.

PVCs are thought to be caused by different underlying mechanisms, like (delayed) after depolarizations inducing triggered activity[22] or automaticity resulting in parasystole.[28,29] Class-1C AAD are known to be able to reduce triggered activity,[30] which might explain why flecainide only seems to work in a subgroup of patients. In explorative analyses we were not able to establish discriminating factors between the responders and the non-responders, 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 let us to change the way we treat children with frequent PVCs. Our current practice is to start treatment only in case of symptoms and/or LV dysfunction, with flecainide being the first-line therapy.

Limitations

The number of patients included in this prospective randomized cross-over trial is small, due to external factors. However, since 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.

Conclusions

In children with frequent PVCs flecainide reduces the PVC-burden significantly better, as compared to metoprolol. Metoprolol has minimal effect on the PVC-burden. Flecainide was very 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 PVC and a structural normal heart. Future studies should focus at possible identifying factors of response to AAD treatment.

Acknowledgements

Ms Elsmere Visser-Solognier for her enormous efforts in planning and organizing all patient visits, and accurate data management.

SUPPLEMENTARY MATERIAL

Reduction of mean PVC per medication period

	Medication period 1		**Medication period 2**	
	Flecainide	Metoprolol	Flecainide	Metoprolol
Number of patients (#)	8	11	10	6
PVC-burden baseline (%), mean (SD)	16.6 (SD ± 12.9)	23.4 (SD ± 11.6)	25.7 (SD ± 14.2)	17.1 (SD ± 11.2)
PVC-burden after 5 days of *starting* dosage (%), mean (SD)	6.9 (SD ± 8.2)	23.9 (SD ± 6.8)	14.7 (SD ± 14.3)	13.7 (SD ± 7.1)
Reduction in PVC-burden (%-points), mean (SD)	9.8 (SD ± 18.7)	-0.6 (SD ± 8.9)	10.9 (SD ± 17.8)	3.4 (SD ± 8.2)
PVC-burden after 5 days of *highest* dosage (%), mean (SD)	6.2 (SD ±6.8)	23.0 (SD ± 11.5)	11.9 (SD ± 13.8)	9.6 (SD ± 6.4)
Reduction in PVC-burden (%-points), mean (SD)	10.4 (SD ± 17.4)	0.4 (SD ± 9.1)	13.8 (SD ± 15.7)	7.5 (SD ±9.4)

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