Elimination of ventricular premature beats and ventricular tachycardia with catheter ablation versus optimal anti-arrhythmic drug treatment

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Primary Objective: The aim of this study is to compare efficacy of antiarrhythmic drugs (sotalol or combination of flecainide and verapamil) and catheter ablation in reducing VPB/VT burden in patients with symptomatic idiopathic VPB/VTs.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON48860

Source
ToetsingOnline

Brief title
ECTOPIA

Condition

- Cardiac arrhythmias

Synonym
Premature ventricular beats, ventricular extrasystole

Research involving
Human

Sponsors and support

Primary sponsor: Maatschap Cardiologie Zwolle

Source(s) of monetary or material Support: Maatschap Cardiologie Zwolle

Intervention

Keyword: - Anti-arrhythmic drugs, - catheter ablation, - Premature ventricular beats

Outcome measures

Primary outcome

Primary objective: Compare efficacy in VPB/VT burden reduction in patients with frequent idiopathic VPB/VT after 3 months treatment with two different antiarrhythmic drug regimens (sotalol or combination of flecainide and verapamil) and primary catheter ablation of VPB/VT substrate.

Secondary outcome

Secondary objectives:

1. To explore the influence of different modulating factors on VPB/VT burden and response to treatment measured with percentage VPB/VT burden reduction and change in QOL scores

- Sympathetic drive, assessed by positive HR-VPB correlation, i.e. correlation between hourly VPB density and hourly HR during 24 hours ambulatory Holter monitoring

- Gender differences in VPB/VT burden and response to different treatment modalities.

- Effect of hormonal changes in women, i.e. explore the effect of estrogen depletion by comparing VPB/VT burden and response to different treatment modalities in pre- and postmenopausal women.

2. To evaluate safety of investigational treatments, assessing:

- The rate of adverse events related to catheter ablation (especially in the

subgroup of VPB/VTs of non-

RVOT origins)

- The rate of pro-arrhythmic effects of treatment with sotalol or combination

of flecainide and verapamil.

- The rate of VPB/VT-induced CMP in our study population by early detection of

subtle changes in left

ventricular function with the use of global longitudinal strain (GLS)

Study description

Background summary

Frequent ventricular premature beats (VPB) and ventricular tachycardia (VT) in healthy subjects without structural heart disease is considered benign. However, it may cause invalidating symptoms or VPB/VT induced cardiomyopathy (CMP). First choice therapy for reduction of VPB/VT burden is preferably beta-blockers or non-dihydropyridine calcium channel blockers (verapamil or diltiazem). However, effective reduction of VPB/VTs can be established in only 10-20% of patients using these drugs. Next step is class I and III anti-arrhythmic drugs (AADs), but they are known for their potential severe side effects, especially amiodarone is associated with potentially severe side effects. Class Ic AAD (e.g. propafenone, flecainide) are effective in reducing VPB/VT burden with 80% in 50-74% and are relatively well tolerated. Catheter ablation is highly effective with a VPB/VT burden reduction of >90% in 80-90% of patients. Current guidelines recommend catheter ablation in patients with VPB/VT from right ventricular outflow tract (RVOT) origin in case of symptoms, failure of AAD or decline in left ventricular function. (Class I, level of evidence B).

There is only one randomized trial comparing catheter ablation and AAD in patients with *idiopathic* VPB/VT and structural normal hearts. In that study, catheter ablation (80.6%) was superior in efficacy compared to AADs (11.4%). However, treatment with AADs in this study was not randomized, using propafenone and metoprolol in a 3:1 ratio and only patients with RVOT VPB/VTs

were included. In conclusion, comparison of different AADs versus catheter ablation in reduction of benign VPB/VTs has not been fully elucidated. We therefore propose a three group randomized trial comparing Class III and Class Ic AADs with catheter ablation in a 1:1:1 ratio. We hypothesise that flecainide (combined with verapamil) has similar efficacy compared to catheter in suppressing VPB/VTs and that sotalol is inferior in efficacy to both therapies.

The underlying mechanisms of VPB/VTs are considered a combination of triggered activity and enhanced abnormal automaticity. Increased VPB/VT burden depends on several factors; e.g. age, hormones and sleep apnea. The role of the autonomic nervous system, in particular sympathovagal imbalance, plays an important role in these patients. In patients with sympathetic overdrive, VPB/VT burden increases during higher heart rates (HR), i.e. positive HR dependency of ventricular ectopy. Relationship between effectiveness of different AADs and HR was previously described in small studies with heterogeneous populations. In the current study, we will use a cross-over design to study the effect of AADs and HR dependency of VPB/VTs. The collected data will enable us to study the role of the autonomic nervous system and explore the potential underlying electrophysiological mechanisms of VPB/VTs. It is known that enhanced VPB/VT burden is more often seen in females. Another objective of the current study is to delineate the effect of gender on treatment efficacy and quality of life (QOL). In addition, we will study differences in VPB/VT burden and treatment efficacy in pre-and postmenopausal women. Finally, this study will assess safety and efficacy of long-term treatment with flecainide and verapamil compared with catheter ablation, especially in the subgroup of patients with non RVOT VPB/VT foci that are anatomically challenging for catheter ablation, e.g. aortic cusp or mitral annulus.

Study objective

Primary Objective: The aim of this study is to compare efficacy of antiarrhythmic drugs (sotalol or combination of flecainide and verapamil) and catheter ablation in reducing VPB/VT burden in patients with symptomatic idiopathic VPB/VTs.

Study design

Prospective, randomized, multicenter trial

Intervention

Patients will be randomized in a 1:1:1 fashion into one of the following three arms after completion of the consent procedure and baseline assessment:

(A) sotalol (n=60) = maximal tolerated dose, starting dose (and minimum dose) 80 mg BID. Maximal dose of 320 mg/day

(B) flecainide (n=60) = maximal tolerated dose, starting dose (and minimum dose) 100 mg/day (slow release), Maximal dose of 200 mg, in combination with: verapamil = 120 mg BID
(C) catheter ablation (n= 60)

Study burden and risks

The potential clinical benefit for patients in the AAD arms could be that they will not be restrained from any of the potentially highly effective treatment strategies of this trial, since a cross-over is performed between two AADs and catheter ablation will also be offered after 6 months. In standard care, especially combination of flecainide and verapamil, is not a conventional combination in most centers. This study will provide access to this therapy in a safe setting with close monitoring. For patients in the catheter ablation group (especially patients with non-RVOT VPB/VTs) a highly successful therapy (80-90%) treatment will be available as a primary treatment. Catheter ablation of VPB/VT of RVOT origin is a validated and safe therapy in patients with symptomatic drug refractory VPB/VTs with a very low amount of major complications (<1%, consisting of rare case of RVOT rupture) and minor complications (<3%, consisting of right bundle branch block, CVA, damage to coronary arteries, groin haematoma, pericardial effusion) .Ablation of non-RVOT VPB/VT origins (e.g. left ventricular outflow tract, aortic cusp or aortomitral continuity) with more anatomically challenging approach are also associated with low complication rate. However, available evidence is based on small registry studies from highly experienced ablation centres like ours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Patients willing and capable to provide written informed consent
- Patients with frequent symptomatic VPB/VT and/or nonsustained VTs with a burden of * 5% AND
-Absence of structural heart disease AND
-Absence of underlying cardiac ischemia AND
-Patient is considered an acceptable candidate for catheter ablation treatment with a
dominant morphology of VPB/VT origin judged by the treating physician.
-For those already undergoing treatment, all antiarrhythmic drugs including digitalis must be discontinued during a 2- week washout period before entry to the study

Exclusion criteria

-Age >75 years
- Previous catheter ablation therapy for VPB/VT
-Patients with sustained ventricular tachycardia or cardiac channelopathies (e.g. CPVT, long- or short QT syndrome, Brugada syndrome)
-WPW syndrome
- Use of medication with risk of QTc prolongation (e.g. antidepressant, antiemetic), except for study medication sotalol.
- Left ventricular dysfunction (LV ejection fraction <55%)
-Estimated glomerular filtration rate < 50 ml/min/1.73 m2
-Hepatic impairment defined by a total bilirubin * 2 times the upper limit (ULN) of normal ALAT or ASAT * 3 times ULN at screening.
-Untreated hypo- or hyperthyroidism or electrolyte imbalance
- Untreated obstructive sleep apnea

-Patients with history of myocardial infarction or bypass surgery
- More than grade 1/3 valvular regurgitation and/or significant valve stenosis (moderate or severe)
- Contraindication for any of the antiarrhythmic drugs used in this study
- Enrolment in another trial
- Woman currently pregnant or breastfeeding or not using reliable contraceptive measures during fertile age
- Mental or physical inability to participate in the study
-Life expectancy * 12 months

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-02-2019
Enrollment:	180
Type:	Actual

Medical products/devices used

Generic name:	Catheter ablation
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	flecainide
Generic name:	Flecainide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	sotalol

Generic name:	Sotalol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	verapamil
Generic name:	Verapamil
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-08-2018
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-11-2018
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	29-06-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001518-13-NL
ClinicalTrials.gov	NCT03845010
CCMO	NL65761.075.18