Extra energy for hearts with a genetic defect: ENERGY trial

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Main objective: to measure the effect of trimetazidine on myocardial external efficiency in asymptomatic MYH7, MYBPC3 or TNNT2 mutation carriers Secondary objectives: to study the effect of trimetazidine on diastolic function, left ventricle and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON52384

Source
ToetsingOnline

Brief title
ENERGY

Condition

- Myocardial disorders

Synonym
Abnormally thick heart muscle disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMW Programma Translationeel Onderzoek: Beurs Jolanda van der Velden

Intervention

Keyword: Cardiomyopathy, Hypertrophic, Therapy, Trimetazidine

Outcome measures

Primary outcome

The difference in mean myocardial energy efficiency after two months of treatment with trimetazidine compared to placebo

Secondary outcome

To study the effect of trimetazidine on: • diastolic function: echocardiography to measure E, A, E/A, E*, E/E* in cm/s • left ventricle and left atrial volume parameters: end-diastolic volume, end-systolic volume, ejection fraction, left ventricular mass, left atrial volume • exercise capacity: duration of exercise, workload • and electrophysiological properties of the heart: ECG to measure PR, QRS, QT interval, ST elevation/depression, heart rate

Study description

Background summary

Hypertrophic cardiomyopathy (HCM) is the most frequent and lethal genetic heart disease. It is caused by mutations in sarcomeric proteins, the building blocks of the heart. Individuals are at high-risk for ventricular arrhythmias and sudden cardiac death, or develop cardiomyopathy at a young age. The current treatment options are insufficient to prevent the disease. In the ENERGY trial we will investigate if metabolic therapy with trimetazidine reverses the reduced myocardial efficiency in asymptomatic mutation carriers. This trial is based on our preclinical and clinical studies, which revealed that 1) mutant proteins cause an energetic deficiency of the heart and 2) this energetic deficit is already observed in human mutation carriers without cardiomyopathy. The mutation-induced energy deficiency of the heart causes hypertrophy and dysfunction of the heart. Approach: We will treat asymptomatic mutation carriers with trimetazidine or placebo and measure cardiac efficiency at baseline and after 2 months of treatment. Impact: Our study will establish if

energy deficiency represents a novel HCM drug target before onset of cardiac hypertrophy. This phase II clinical trial builds proof for a multicenter phase III clinical trial to study if metabolic therapy prevents cardiac hypertrophy, acute cardiac arrest and development of cardiomyopathy in asymptomatic mutation carriers.

Study objective

Main objective: to measure the effect of trimetazidine on myocardial external efficiency in asymptomatic MYH7, MYBPC3 or TNNT2 mutation carriers Secondary objectives: to study the effect of trimetazidine on diastolic function, left ventricle and left atrial volume parameters, exercise capacity, and electrophysiological properties of the heart

Study design

randomized, double blind, placebo-controlled trial

Intervention

Trimetazidine 20mg three times daily, or placebo 20mg three times daily

Study burden and risks

Burden associated with participation:
Patients will be asked to visit the hospital 5 times. After the first visit, subjects will receive information about the study and will be given time (>48 hours) to decide if they want to participate.
Approximately two days after the first visit, subjects will be called to ask if they want to participate in the study. If yes, an appointment will be made for the second visit. During this visit informed consent will be signed and a subjects will undergo an echo, ECG and venapunction to determine whether the subject is eligible to participate in the trial (see 3.3 exclusion criteria).
On visits 3 and 5, subjects will visit the VUmc to undergo PET- and MRI-investigations in supine position for a maximum of 1.5 hours per investigation. To minimize the burden of travelling, both procedures will be carried out on the same day. For intravenous administration of the contrast-agent Gadolinium-DTPA (Dotarem©), a venflon will be inserted in the vena brachialis. An ECG, echo, and exercise test and a survey will also be taken. From the intravenous line, vials of blood will be drawn for research purposes.
On visit 4 a research nurse will perform a clinical check-up, echo, ecg and venapunction.
Risk associated with participation:
Trimetazidine is a drug with mild and reversible side-effects. We estimate minimal health risk by participation in this study.
Patients with renal failure (glomerular filtration rate (GFR) < 30 ml/min) will

be excluded to avoid development of Gadolinium-DTPA induced nephrogenic systhemic fibrosis (NSF).
The total radiation dose for study participants is 6 mSv, falls in the risk category IIb and represents low risk. The range of 1 to 10 mSv corresponds with a maximum risk of one in ten thousand, and is of the same order of magnitude as the annual natural background radiation in some parts of the world. (Netherlands commission on radiation dosimetry, 9 september 2015).which is well below the threshold of 10 mSv for negligible risk.
Group relatedness:
This study will be done in MYH7, MYBPC3 and TNNT2 mutation carriers as previous research showed these mutation carriers have an energetic defect of >20% difference in myocardial energy efficiency compared to healthy controls. To reveal a 15% beneficial effect of trimetazidine on MEE, taking into account a standard deviation of 15% based on our previous studies of MEE in HCM mutation carriers, a number of 20 carriers should be included in each group (with metabolic therapy or placebo) to reach a power of 80%
Benefit:
This study aims to find a preventive treatment for HCM, which currently does not exist.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Carrier of HCM associated genetic mutation in the gene encoding for Myosin Heavy Chain 7 (MYH7), Myosin Binding Protein C3 (MYBPC3) or cardiac muscle Troponin T (TNNT2)
18 - 65 years

Exclusion criteria

Cardiovascular disease (in particular HCM defined by maximum wall thickness >15mm), Parkinson disease or parkinsonian symptoms, Renal insufficiency GFR <60 ml/min, Any absolute or relative contra-indication for MRI (i.e. pacemaker and claustrophobia), pregnancy, diabetes mellitus, chronic use of systemic medication (except oral contraception)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-03-2019

Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vastarel
Generic name:	Trimetazidine

Ethics review

Approved WMO Date:	21-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2018-000029-29-NL
CCMO	NL64662.029.18

Study results

Date completed:	07-03-2023

Actual enrolment:	40