The efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention.
ATPCI study
An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years.

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The purpose of this study is to demonstrate the long term efficacy and safety of trimetazidine, when given in addition to other evidence-based cardiovascular therapies, in patients having had a recent PCI.The primary objectives are to demonstrate...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON38975

Source
ToetsingOnline

Brief title
ATPCI study

Condition

- Coronary artery disorders

Synonym
chest pain, spasm of the heart

Research involving
Human

Sponsors and support

Primary sponsor: Servier
Source(s) of monetary or material Support: Sponsor of the study: Institut de Recherches Internationales Servier (I.R.I.S.)

Intervention

Keyword: angina pectoris, double-blind, percutaneous Coronary Intervention, placebo-controlled

Outcome measures

Primary outcome

Superiority of trimetazidine over placebo on the time to first occurrence of an

event in the composite of:

- cardiac death;

- hospitalisation for a cardiac event;

- Recurrent or persistent angina leading to adding, switching or increasing the

dose of one of the evidence-based antianginal therapies;

- recurrent or persistent angina leading to performing a coronary angiography.

Secondary outcome

Superiority of trimetazidine over placebo on the time to first occurrence of an

event in the composite of:

- cardiac death;

- hospitalisation for a cardiac event;

- recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;

- recurrent or persistent angina leading to performing a coronary angiography;

- evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;

- evidence of ischemia (documented by Stress Imaging) leading to performing a coronary angiography.

Effect of trimetazidine, compared with that of placebo, on the following endpoints:

Components of the primary endpoint:

- cardiac death;

- hospitalisation for a cardiac event;

- recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;

- recurrent or persistent angina leading to performing a coronary angiography.

Other secondary endpoints:

- evidence of ischemia (documented by Stress Imaging) leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies;

- evidence of ischemia (documented by Stress Imaging) leading to performing a

coronary angiography;

- cardiac death or hospitalisation for a cardiac event;

- recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapies, or leading to performing a coronary angiography;

- all-cause mortality;

- hospitalisation for non-fatal MI;

- hospitalisation for fatal or non-fatal MI;

- hospitalisation for fatal or non-fatal MI or occurrence of cardiac death;

- hospitalisation for ischaemic chest pain;

- hospitalisation for heart failure;

- any coronary revascularization;

- repeat coronary revascularization in response to angina.

Other efficacy endpoints:

- CCS class of angina symptoms;

- number of angina episodes per week;

- number of doses of short-acting nitrates taken per week in response to angina;

- number of antianginal drugs taken by the patient;

- Seattle Angina Questionnaire scores (in countries where a validated translation is available).

- EQ-5D-3L Questionnaire scores;

- level of cardiac troponin (before each repeat PCI and between 6 and 24 hours

after).

Study description

Background summary

An ever increasing number of patients with angina are being treated by means of percutaneous coronary intervention (PCI). In spite of an initially technically successful PCI procedure a significant proportion of patients can either have residual angina or else can develop recurrent angina during the first year. In some studies, up to 30% of patients one year following PCI were found to be suffering from angina (Courage , Bari).

In June 2012, the European Medicine Agency (EMA) recognized the positive risk-ratio of trimetazidine as an add-on to first-line antianginal therapies in symptomatic patients with stable angina pectoris insufficiently controlled by, or intolerant to first-line antianginal treatments.

The aim of this study is to investigate the long-term efficacy and safety of trimetazidine when added to standard treatment following PCI. No anti-anginal treatment has currently been able to demonstrate a reduction in major cardiac events in patients with stable angina pectoris, but this goal is to be looked for as a first step when studying an anti-anginal treatment. Thus, the main efficacy criterion will be based on the occurrence of symptoms and cardiac events as compared to placebo. The assessment of long-term safety will also be a major objective, with particular attention to adverse events of interest such as neurological symptoms (including Parkinson*s syndrome), coagulation disorders, thrombocytopenia, agranulocytosis, falls, arterial hypotension, hepatic disorders, and serious skin disorders.

Study objective

The purpose of this study is to demonstrate the long term efficacy and safety of trimetazidine, when given in addition to other evidence-based cardiovascular therapies, in patients having had a recent PCI.

The primary objectives are to demonstrate the superiority of trimetazidine over placebo in preventing recurrence or exacerbation of angina pectoris and reducing cardiac events, and to document its safety by analysing the occurrence of serious adverse events.

The secondary objectives are to evaluate the effect of trimetazidine on the other efficacy endpoints, as well as the other safety parameters, clinical and

biological.

Study design

This is a phase III, international, multicentre, double-blind, placebo-controlled study randomised in 3 parallel and balanced groups:
trimetazidine 35mg b.i.d.,
trimetazidine 70 mg b.i.d.,
placebo.

This study will include 10 300 patients in about 54 countries and about 800 centres.

Investigational medicinal product (IMP) will be given in addition to routine post-PCI treatment which includes secondary prevention therapy, as per current guidelines, with or without regular antianginal therapy as decided by the investigator according to his/her normal practice or specific requirements of local/national guidelines and the patient*s clinical condition. Following the PCI and prior to randomisation regular antianginal therapy may be withdrawn or prescribed at the discretion of the investigator. However, regular antianginal therapy should not be changed (either drug or dose) following randomisation of the patient except for clinical reasons. The reasons for change must be detailed in the eCRF. Whatever the reason, all changes (i.e. addition, switch of antianginal therapy or increase of the dose) will be adjudicated.

The IMP will be allocated by centralised randomisation at the inclusion visit, with stratification by both country and by type of presentation (i.e. planned procedure for stable angina or urgent procedure following an acute/unstable presentation).

The estimated duration of the recruitment period is 24 months. The minimum follow-up duration for the last included patients will be 24 months. It is expected that the first included patients will be followed for 48 months (estimated mean follow-up duration of 36 months). Depending on the number of observed events, the follow-up duration may be prolonged up to 5 years.

All randomised patients should continue the study procedures and should attend the scheduled follow-up visits until the study end, even after the occurrence of an efficacy pre-specified event and after IMP withdrawal.

The patients will be selected as soon after PCI as possible, but preferably not on the actual day of the procedure. The Selection Visit (ASSE) should ideally be performed during the hospitalisation for the PCI, or shortly after discharge. With regards to angina, patients can be selected regardless of their symptomatic status post PCI (i.e. whether they are free from angina or not), and regardless of their CCS class.

Intervention

Trimetazidine MR 35mg and placebo will be provided in the form of tablets with an identical appearance for all treatment groups.

No investigational medicinal product (IMP: trimetazidine or placebo) will be given to patients during the period between selection and inclusion. From inclusion onwards, all patients will receive a fixed regimen of two tablets to be taken at mealtimes in the morning and evening:
- 2 tablets of placebo twice daily, or
- 1 tablet of trimetazidine and 1 tablet of placebo twice daily, or
- 2 tablets of trimetazidine twice daily.

Study burden and risks

- Common risks (affects 1 to 10 users in 100): dizziness, headache, abdominal pain, diarrhoea, indigestion, feeling sick, vomiting, rash, itching, hives and feeling of weakness.
- Rare risks (affects 1 to 10 users in 10 000): fast or irregular heartbeats (also called palpitations), extra heartbeats, faster heartbeat, fall in blood pressure on standing-up which causes dizziness, light headedness or fainting, malaise (generally feeling unwell), fall, flushing.
- Unknown risks (frequency cannot be estimated from the available data): extrapyramidal symptoms (unusual movements, including trembling and shaking of the hands and fingers, twisting movements of the body, shuffling walk and stiffness of the arms and legs), usually reversible after treatment discontinuation. Sleep disorders (difficulty in sleeping, drowsiness), constipation, serious generalised red skin rash with blistering, swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing. Severe reduction in number of white blood cells which makes infections more likely, reduction in blood platelets, which increases risk of bleeding or bruising. A liver disease (nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine).

Contacts

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Women or men >= 21 years old and < 85 years old of any ethnic origin.
Patients presenting a single or multivessel coronary artery disease and having undergone PCI treating at least one stenosis to either a native coronary artery or a coronary graft where the PCI was:
- indicated because of angina pectoris occurring either in the context of stable angina (elective PCI) or in the context of an acute presentation such as unstable angina/NSTEMI, but excluding STEMI;
- achieved by stent implantation or by other acceptable interventional means;
- successful as planned by the operator and with no further revascularization (either percutaneous or surgical) planned;
- uncomplicated such that the patient's discharge was not, or will not be, delayed because of a cardiac or cerebrovascular problem

Exclusion criteria

- Severe uncontrolled rythm disturbances including paroxysmal VT and SVT;- Known severe aortic or mitral valve disease;
- Clinical signs and/or symptoms of heart failure corresponding to NYHA class IV;
- Hypertrophic obstructive cardiomyopathy or other forms of left ventricular outflow tract obstruction;
- Active myocarditis, pericarditis or endocarditis;

- Hystory of agranulocytosis, severe thrombocytopenia or severe coagulation disorder;
- History of pulmonary embolism within preceding 6 months;
- Known severe uncontrolled arterial hypertension;
- Known chronic severe or moderate renal failure, with sCrCl < 60 mL/min or eGFR<60 mL/min/1.73m²;
- Current or previous movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremor, gait instability of central origin

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	200
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Vastarel MR 35 mg
Generic name:	Trimetazidine Dihydrochloride

Ethics review

Approved WMO

Date:	04-10-2013

Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-11-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2010-022134-89-NL
CCMO	NL46320.008.13
Other	U1111-1145-1743 (WHO Universal Trial Number, UTN)