Efficacy of Diltiazem to improve coronary microvascular dysfunction: A randomized clinical trial

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This study has been transitioned to CTIS with ID 2024-512030-15-00 check the CTIS register for the current data. Our primary objective is to assess the effect of diltiazem on coronary microvascular function as assessed by coronary reactivity testing...

Ethical review	Approved WMO
Status	Completed
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON49283

Source
ToetsingOnline

Brief title
EDIT-CMD

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Coronary Microvascular Dysfunction; Microvascular angina

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Abbott

Intervention

Keyword: Coronary Microvascular Dysfunction, Coronary Reactivity Test, Diltiazem, Treatment

Outcome measures

Primary outcome

The proportion of patients having a successful treatment with diltiazem,

defined as normalization of at least one abnormal parameter A normal IMR is

specified as IMR < 25, a normal CFR being a CFR > 2 and a normal acetylcholine

test is specified as one without ECG abnormalities and without signs of spasm

at the same acetylcholine dose used at baseline.

Secondary outcome

Change in the different parameters of the CRT (change in IMR, CFR,

acetylcholine test parameters and absolute coronary blood flow).

Study description

Background summary

Up to 40% of patients undergoing a coronary angiogram for symptoms/signs of ischemia do not have obstructive coronary artery disease (CAD). In about half of them the mechanism underlying cardiac ischemia is coronary microvascular dysfunction (CMD). In CMD, myocardial ischemia is caused by impaired endothelial and/or non-endothelial coronary vasoreactivity resulting in the coronary microvasculature not dilating properly or becoming vasospastic. Recently published diagnostic criteria state that to confirm the diagnosis, CMD patients should either have an impaired coronary flow reserve (CFR), increased microvascular resistance (IMR) or have evidence of microvascular spasms. Hence, invasive coronary reactivity testing (CRT) is considered the reference standard for a definitive diagnosis of CMD.

Patients with microvascular angina often have continuing episodes of chest pain leading to frequent first aid visits and hospital re-admissions with associated high health care costs. Moreover, CMD is associated with a worsened

cardiovascular prognosis. Therefore, adequate treatment is paramount. However, current treatment options are based on a limited number of small studies, most of which were not placebo-controlled. Based on prior studies and our clinical experience we believe diltiazem, a calcium channel blocker (CCB) could improve coronary microvascular function in patients with CMD.

Study objective

This study has been transitioned to CTIS with ID 2024-512030-15-00 check the CTIS register for the current data.

Our primary objective is to assess the effect of diltiazem on coronary microvascular function as assessed by coronary reactivity testing in symptomatic patients with CMD.

Study design

This is a clinical multicenter randomized with 1:1 ratio, double-blind, placebo-controlled study. Patients with chronic angina in the absence of obstructive CAD will be screened for study enrollment. Eligible patients will be asked for informed consent at the screening visit. Within 4 weeks after screening they will undergo coronary reactivity testing consisting of assessment of coronary flow reserve (CFR), index of microcirculatory resistance (IMR) and acetylcholine testing. If this shows either a CFR <= 2.0, an IMR >= 25 and/or abnormal acetylcholine testing indicating coronary spasm, the patient will continue in the intervention arm and will be randomized to either diltiazem or placebo treatment for 6 weeks. After 6 weeks, a coronary reactivity test with the assessment of CFR, IMR and spasm will be repeated and the diltiazem/placebo treatment will be discontinued. Follow-up will be obtained after 6 weeks of treatment, and 1 year and 5 years after treatment discontinuation.
If the coronary reactivity testing at baseline shows no signs of vascular dysfunction, patients will enter in the registration arm of the study (after informed consent). These patients will not receive any intervention. Follow-up will be obtained after 1 year and 5 years. Written informed consent is also required for enrollment in the registration arm.

Intervention

After establishing an abnormal coronary vascular function, 6 weeks treatment with either diltiazem 120-360 mg or placebo will be initiated in a double-blind fashion. Every two weeks dose titration will be performed if possible, under the guidance of patient tolerance (dizziness, leg edema, etc.), blood pressure and heart rate.

Study burden and risks

The extensive experience with diltiazem and the favourable safety profile in combination with the short duration of treatment make the risk low for participants. While the first coronary angiography with assessment of coronary function is clinically indicated in these patients, the second CRT is only in relation with study participation. Several reports show that CRT is a safe procedure with serious complication rates (death, myocardial infaction, etc.) ranging from 0 to 0.7%. We believe it is essential to investigate the effect of diltiazem on coronary function to justify its use in CMD patients.

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

1. Patients above the age of 18.
2. Patients with chronic angina, defined as symptoms of angina at least 2 times

a week despite medical therapy for the last 3 months.
3. No signs of obstructive coronary artery disease (CAD), documented within 5 years* before inclusion by one of the following modalities:
a. Coronary angiography: patients with non-obstructive (< 50% stenosis) coronary arteries are eligible, or patients with intermediate stenosis (between 50 and 70%) with documented FFR > 0.80 or iFR > 0.89 on angiogram.
b. Coronary computed tomography angiography (CCTA) with finding of non-obstructive coronary arteries
4. Baseline coronary reactivity testing with at least one of the following:
a. CFR <= 2.0
b. IMR >= 25
c. Abnormal acetylcholine test defined as the presence of (recognizable) angina, ischemic ECG abnormalities with or without epicardial spasm.
5. Signed written informed consent

Exclusion criteria

1. Other cause of angina deemed highly likely by the treating physician.
2. Active use of calcium channel blockers or any use of calcium channel blockers in the previous two weeks or known intolerance for non-dihydropyridine calcium channel blockers.
3. Left ventricular ejection fraction < 50%.
4. Recent PCI within the past 3 months.
5. Patients with history of coronary artery bypass grafting (CABG).
6. Surgically uncorrected significant congenital or valvular heart disease, cardiomyopathy or myocarditis.
7. Significant renal impairment (eGFR < 30).
8. Significant hepatic impairment (history or cirrhosis or abnormal serum ALT or AST 3-fold greater than the upper limit of normal).
9. Pregnant women or women of child bearing potential who are planning to become pregnant within the next 3 months.
10. Prior non-cardiac illness with an estimated life expectancy < 1 year.
11. Contra-indication to coronary reactivity testing:
a. Contraindication or known hypersensitivity to adenosine.
b. Contraindication or known hypersensitivity to acetylcholine.
c. Ongoing dipyridamole treatment.
12. Contra-indication for treatment with CCB: second or third degree AV block, sinus node dysfunction, and/or bradycardia (heart rate < 50 beats/minute) and/or potentially dangerous interaction due to the use of another CYP3A4 substrate in the opinion of the investigator.
13. Symptomatic hypotension or systolic BP < 100 mmHg at screening visit on 2 consecutive measurements.
14. History of hospitalization for asthma and/or current use of >= 2 types of pulmonary medications for asthma and/or severe COPD with FEV1 < 50% of predicted.

15. Participation in another clinical study with an IMP during the last month prior to enrollment.
16. Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study.
17. Unable to give informed consent (i.e. due to language barrier).

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:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-10-2019
Enrollment:	107
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diltiazem HCl Apotex retard MGA 120mg
Generic name:	diltiazemhydrochloride compound
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EU-CTR	CTIS2024-512030-15-00

Register	ID
EudraCT	EUCTR2018-003518-41-NL
CCMO	NL67497.091.19