Functional Improvement of non-infarcT relaTed coronary artery stenosis by Extensive LDL-C Reduction with a PCSK9 Antibody.

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Primary objectives1A. To evaluate the effect of maximal LDL-C reduction by Evolocumab on top of high intensity lipid-lowering therapy , initiated immediately after invasive ACS treatment on functional impairment of non-infarct related artery (non-...

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

Summary

ID

NL-OMON52478

Source
ToetsingOnline

Brief title
FITTER

Condition

- Coronary artery disorders

Synonym
coronary artery disease (CAD)

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Amgen,Infraredx Inc.,Subsidie van bedrijf; Amgen B.V. en InfraRedx Inc.

Intervention

Keyword: ACS, FFR, Multi Vessel Disease (MVD), PSCK9

Outcome measures

Primary outcome

1A. The primary physiological study endpoint is the change in FFR from baseline

to follow-up

in non-IRA lesions.

1B. The primary invasive imaging endpoint is the change in lipid core burden

index at the

4mm maximal segment (MaxLCBI4mm) from baseline to follow-up of the non-IRA as

performed in sites capable of Near-InfraRed Spectroscopy (NIRS).

Secondary outcome

Secondary endpoints:

1. The change in percent atheroma volume (PAV, mm3)

2. The change in normalized total atheroma volume (TAV, mm3)

3. The change in maximum plaque burden (%)

4. The change in minimum luminal area (MLA, mm2)

Exploratory endpoints

1. The correlation between achieved on-treatment LDL-C and the change in FFR, the change in LCBI, and the change in PAV.
2. The correlation between baseline NIRS derived MaxLCBI4mm and change in FFR of the non-IRA.
3. The correlation between change in IVUS-derived plaque characteristics and change in FFR of the non-IRA
4. Change of microvascular resistance as measured by CFR and IMR

The immunological side study will investigate the relation between LDL-C reduction and reduction of pro-inflammatory monocyte phenotypes.

Clinical endpoints will be tabulated and listed in the final study report; among which percentage of lesions with a FFR >0.80 at follow-up and patient-oriented composite endpoint (POCE): composite of all-cause death, any stroke, any MI and any revascularization, unplanned ischemia driven PCI of the target lesion, any unplanned ischemia driven PCI in the total study population.

Study description

Background summary

In a large number of patients presenting with acute coronary syndrome (ACS) multivessel disease is identified. Optimal treatment approach for bystander lesions in non-infarct related arteries (non-IRA*s) has not been well established. Some RCT*s favor preventive complete revascularization over deferred PCI. Background medical treatment wasn*t optimal in these studies, however, which could have caused bias. Revascularization of lesions in the non-IRA can be guided by fractional flow reserve (FFR). In this study we want to investigate the effect of maximal LDL-C reduction by Evolocumab and HIST compared to placebo on functional impairment of non-IRA lesions, measured by FFR, and we want to evaluate the change in Near-InfraRed Spectroscopy (NIRS) derived lipid core burden index at the 4mm maximal segment (MaxLCBI4mm) from baseline to follow-up in the non-IRA. Secondly, we want to evaluate the change in plaque characteristics, measured by IVUS, and change in microvascular circulation. We will investigate correlations between on treatment LDL-C, LCBI, and plaque characteristics, with non-culprit FFR. Finally the study will investigate the relation between LDL-C reduction and change in pro-inflammatory monocyte phenotypes.

Study objective

Primary objectives
1A. To evaluate the effect of maximal LDL-C reduction by Evolocumab on top of high
intensity lipid-lowering therapy , initiated immediately after invasive ACS treatment on
functional impairment of non-infarct related artery (non-IRA) lesions, measured by FFR, in
patients presenting with MVD-ACS.
1B. To evaluate the effect of maximal LDL-C reduction by Evolocumab on top of high
intensity lipid-lowering therapy, initiated immediately after invasive ACS treatment on the lipid
core burden of non-infarct related artery (non-IRA) lesions, measured by NIRS, in patients
presenting with MVD-ACS.

Secondary objectives
2A. To evaluate the effect of maximal LDL-C reduction by Evolocumab on top of high intensity
lipid-lowering therapy, initiated immediately after invasive ACS treatment on plaque
characteristics of non-infarct related artery (non-IRA) lesions, measured by

IVUS, in patients
presenting with MVD-ACS.
2B. To evaluate the relation between baseline lipid core burden and changes in functional
impairment of non-IRA lesions during treatment by Evolocumab on top of high intensity lipid-lowering therapy.
2C. To evaluate the effect of maximal LDL-C reduction by Evolocumab on top of high intensity
lipid-lowering therapy, initiated immediately after invasive ACS treatment on microvascular
circulation in patients presenting with MVD-ACS.
2D. To investigate the relationship between LDL-C reduction post-ACS and change in pro-inflammatory monocyte phenotypes.

Hypotheses
1A. Addition of PCSK-9 inhibitors to treatment post-ACS will lead to significant reduction of
functional impairment of a non-IRA lesion in patients with MVD-ACS.
1B. Addition of PCSK-9 inhibitors to treatment post-ACS will lead to significant reduction of
lipid core burden of a non-IRA lesion in patients with MVD-ACS.
2A. Addition of PCSK-9 inhibitors to treatment post-ACS will lead to significant plaque
reduction in a non-IRA lesion in patients with MVD-ACS.
2B. Change in functional impairment will be more pronounced in patients with higher
baseline lipid core burden
2C: Addition of PCSK-9 inhibitors to treatment post-ACS will lead to significant amelioration
of the microvascular circulation in patients with MVD-ACS.
2D. LDL-C lowering attenuates the pro-inflammatory myeloid cell reprogramming by ACS.

Study design

This is a multi-center, randomized, double blind, placebo controlled clinical trial.

Intervention

The patients will be randomised 1:1 to (A), one group will recieve 140mg Evolocumab every two weeks (Q2W) for 12 weeks, using personal injectors; (B) the other group will receive placebo. All participants will receive high intensity statin therapy (HIST) as background therapy (Atorvastatin 40mg or equivalent).

Study burden and risks

After inclusion, all patiënts have to undergo staged FFR + NIRS, meaning they will undergo invasive strategy for a second time, and if needed additional stenting of significant lesions, with the asocciated periprocedural risks (eg. death, stroke, MI, vascular complications), however these risks are quite small (<2% major complications).

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

- ACS with PCI of infarct related artery
- Multivessel Disease (MVD)

- FFR of non-IRA lesion: 0.67 - 0.85
- Age >= 18 years at screening

Exclusion criteria

- Refusal or inability to provide informed consent
- Prior coronary artery bypass graft
- Known left ventricular ejection fraction (LVEF) < 30%
- Untreated functional left main stem stenosis (FFR <= 0.80)
- Contra-indication for antithrombotic therapy according to ESC guidelines
- Non-IRA stenosis not amenable for PCI treatment (operator*s decision)
- Complicated IRA treatment, with one or more of the following:
- Extravasation
- Permanent no re-flow after IRA treatment (TIMI flow 0-1)
- Inability to implant a stent
- Known severe cardiac valve dysfunction that will require surgery in the follow-up period.
- Severe kidney disease defined as an eGFR < 30 ml/min.
- Known severe liver disease defined as Child-Pugh score of 10-15.
- Female subject is pregnant, breastfeeding or planning to become pregnant or planning to breastfeed during treatment and for an additional 15 weeks after the last dose of investigational product. Females of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Female subjects of childbearing potential unwilling to use 1 acceptable method of effective contraception during treatment and for an additional 15 weeks after the last dose of investigational product.
- Female subject who has not used an acceptable method(s) of birth control for at least 1 month prior to screening, unless the female subject is sterilized or postmenopausal.

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-11-2020
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Repatha or placebo
Generic name:	Evolocumab or placebo

Ethics review

Approved WMO Date:	16-10-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2020
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2024
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
EudraCT	EUCTR2019-002578-29-NL
ClinicalTrials.gov	NCT04141579
CCMO	NL71538.091.19