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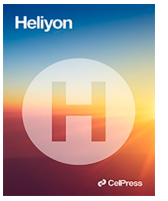

Research article

Functional and morphological improvement of significant non-culprit coronary artery stenosis by LDL-C reduction with a PCSK9 antibody: Rationale and design of the randomized FITTER trial

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A R T I C L E I N F O

Keywords:
Acute coronary syndrome (ACS)
Multivessel disease (MVD)
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Evolocumab

A B S T R A C T

Non-culprit coronary artery lesions are commonly present in patients presenting with an acute coronary syndrome (ACS). Additional stenting of non-culprit lesions in addition to the culprit lesion intends to prevent secondary events caused by these lesions. At the same time, multiple trials have demonstrated the potential of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in reducing plaque size and changing plaque composition of non-culprit lesions. Whether intensive low-density lipoprotein cholesterol (LDL-C) reduction with PCSK9 inhibitor evolocumab improves non-culprit vessel hemodynamics, reduces the risk of plaque rupture of important non-culprit lesions, and might obviate the need for additional stenting has not been investigated. The "Functional Improvement of non-infarcT related coronary artery stenosis by Extensive LDL-C Reduction with a PCSK9 Antibody" (FITTER) trial is a multi-center, randomized, double-blind, placebo-controlled clinical trial for patients presenting with ACS and multivessel disease (MVD). After treatment of the culprit lesion, fractional flow reserve (FFR) is performed in non-culprit vessels amenable for percutaneous coronary intervention (PCI). Coronary

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intervention in patients with hemodynamically important non-critical lesions (FFR: 0.67–0.85) is staged after baseline imaging using near-infrared spectroscopy (NIRS) and intravascular ultrasound (IVUS). Eligible patients are randomized and treated for 12 weeks with either evolocumab or placebo, in addition to high-intensity statin therapy. Follow-up angiography with repeat FFR and IVUS-NIRS is scheduled at 12 weeks. Staged PCI is performed at the operator's discretion.

The FITTER trial is the first study to evaluate the effect of maximal LDL-C reduction by the PCSK9 inhibitor evolocumab on invasively measured FFR, plaque size, and plaque composition in hemodynamically important non-culprit lesions, during a treatment period of just 12 weeks after an ACS. Currently, all patients have been included (August 2023) and data analysis is ongoing. *Trial registration number:* clinicaltrials.gov NCT04141579.

Abbreviations and acronyms

ACS	Acute coronary syndrome
ANCOVA	Analysis of covariance
CCS	Chronic coronary syndrome
EEM	External elastic membrane
FFR	Fractional flow reserve
FITTER	Functional improvement of non-infarct related coronary artery stenosis by extensive LDL-C reduction with a PCSK9 antibody
HIST	High-intensity statin therapy
IMP	Investigational medical product
IRA	Infarct-related artery
IVUS	Intravascular ultrasound
LCBI	Lipid core burden index
$LCBI_{total}$	LCBI over the total length of the region of interest
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiac events
$MaxLCBI_{4mm}$	Maximum lipid core burden index within a 4 mm segment
MI	Myocardial infarction
MLA	Minimum lumen area
MVD	Multivessel disease
NIRS	Near-infrared spectroscopy
NSTEMI	Non-ST-elevation myocardial infarction
OCT	Optical coherence tomography
PAV	Percent atheroma volume
PB	Plaque burden
PCI	Percutaneous intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PV	Plaque volume
STEMI	ST-elevation myocardial infarction
TAV	Total atheroma volume
UAP	Unstable angina pectoris

1. Introduction

Ischemic heart disease is the leading cause of morbidity and mortality worldwide and accounts for more than nine million deaths annually [1,2]. Acute coronary events are often caused by disruption of atherosclerotic plaque, the so-called culprit lesion [3,4]. Culprit lesions are generally treated with percutaneous intervention (PCI). Frequently, other non-culprit or bystander plaques are present. In patients with ST-elevation myocardial infarction (STEMI), PCI is the recommended guideline therapy for these non-culprit lesions. In non-ST-elevation myocardial infarction (NSTEMI), the benefit of PCI is less well established, but various trials are ongoing [5,6]. PCI of non-culprit lesions can prevent residual ischemia-related angina or non-culprit plaque rupture causing recurrent acute events [7]. Several studies identified lesions at risk for plaque rupture (high-risk lesions) based on intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and optical coherence tomography (OCT) images [8–12]. The presence of a high plaque burden (PB) or a small minimum lumen area (MLA) on IVUS, high lipid core burden index (LCBI) on NIRS, and a large lipid pool with thin fibrous cap on OCT are all acknowledged predictors of non-culprit major adverse cardiac events (MACE) [8–12].

Medical therapy with intensive low-density lipoprotein cholesterol (LDL-C) lowering drugs ameliorates plaque size and composition. Multiple trials have demonstrated that high-intensity statin therapy (HIST) induces plaque regression and decreases LCBI on IVUS- and NIRS imaging [13–16]. The addition of PCSK9 inhibitors, which lowers circulatory LDL-C even further, have shown to reduce plaque volume (PV) and to decrease LCBI in studies with a follow-up of at least 50 weeks [17–19]. Most studies included patients with non-culprit lesions of $\leq$ 50% visual obstruction. The full potential of intensive lipid-lowering therapy on more severe stenosis is unknown and might demonstrate effects even faster after treatment initiation. Furthermore, it is unclear whether the reduction in PV improves coronary conductance and is reflected by an increase in fractional flow reserve (FFR). There may be an optimal time window to improve function, PV, and composition of non-culprit lesions by powerful lowering of plasma LDL-C during the first weeks after an acute coronary syndrome (ACS). Hence, immediate maximal lipid-lowering therapy might reduce the need for

additional interventions of non-culprit lesions. The primary aim of the "Functional Improvement of non-infarcT related coronary artery stenosis by Extensive LDL-C Reduction with a PCSK9 Antibody" (FITTER) trial is to evaluate the effect of maximal LDL-C reduction by evolocumab compared to placebo in addition to HIST on non-culprit vessel hemodynamics and plaque composition, in patients with ACS and multivessel disease (MVD).

2. Methods

2.1. Primary objectives

The primary objectives of this trial are to evaluate the effect of maximal LDL-C reduction by evolocumab in addition to HIST, initiated immediately after invasive ACS treatment, on functional impairment and lipid core burden of important non-infarct related artery (non-IRA) lesions, measured by FFR and NIRS, in patients presenting with ACS and MVD. Secondary objectives are to evaluate the effect of maximal LDL-C reduction by evolocumab in addition to HIST on plaque characteristics of non-IRA lesions, measured by IVUS, in patients presenting with ACS and MVD. Finally, the relationship between PV, baseline lipid core burden, and changes in functional impairment of non-IRA lesions will be investigated.

2.2. Study design

The FITTER trial (clinicaltrials.gov NCT04141579) is an investigator-initiated, multicenter, double-blind, placebo-controlled, randomized clinical study, conducted in full accordance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, and Johannesburg), with ICH-GCP and with the laws and regulations of the Netherlands. Ethical approval was given by the Dutch Ethical Review Board (METC Oost Nederland, file number: 2019–5787, first approval: January 2020). All seven participating centers are situated in the Netherlands. A total of 150 patients will be included in this study.

Patients who are hospitalized with ACS, including STEMI, NSTEMI, or unstable angina pectoris (UAP), will be screened for enrollment. When eligible, full written consent for the entire study will be obtained before the index angiography. In emergency cases (STEMI, NSTEMI with refractory symptoms) oral consent for the additional measurements (FFR and IVUS-NIRS) will be obtained during coronary angiography, and full written consent will be signed after the index angiography and before randomization.

A detailed overview of the general inclusion and exclusion criteria is presented in Table 1. In short, patients are eligible if the following criteria are met.

1. Patients with successful PCI of the IRA without complications related to the procedure (permanent no-reflow or perforation), and
2. At least one important non-IRA lesion with a FFR of 0.67–0.85, amenable for PCI.

Table 1
General inclusion- and exclusion criteria.

General inclusion criteria
Acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI) of the infarct-related artery (IRA)
Multivessel disease (MVD)
Fractional flow reserve (FFR) of the non-IRA lesion: 0.67–0.85
Age $\geq$18 years at screening
General 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 $\leq$ 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.

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; MVD, multivessel disease; FFR, fractional flow reserve; IRA, infarct-related artery; LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction; eGFR, estimated glomerular filtration rate.

Culprit lesions are treated conform international guidelines and local protocols. Lesions in the non-IRA with a visually estimated angiographic stenosis of > 30% will be considered for FFR measurement. Preferably, non-culprit FFR measurements are performed during the same procedure as the culprit PCI. However, if deemed unfeasible (unstable patients for example), non-culprit FFR measurements can be performed in a second staged procedure (during the same hospitalization). Patients with a FFR > 0.85 will be treated conservatively and are not included in the study. Although usually a cut-off of 0.80 is used to mark hemodynamically significant lesions, non-IRA lesions up to 0.85 are also considered of interest and eligible for the study. A threshold of 0.85 accounts for the intrinsic variability of single FFR measurements (standard deviation for repeated FFR measurements = 0.02, 2x standard deviation = 0.04) [20]. Furthermore, non-culprit coronary microvascular function can be impaired during the acute context of myocardial infarction, which may overestimate the FFR in the acute phase. After a few weeks, microvascular function returns to normal and the non-culprit FFR might slightly decline [21]. Consequently, patients with a non-IRA lesion FFR just above 0.80 might benefit from PCI when FFR would drop at follow-up. For safety purposes, non-IRA lesions with an FFR < 0.67 will be treated with PCI. This safety cut-off was maintained throughout the study, since a large patient-level meta-analysis of multiple FFR trials showed that FFR values below 0.67 most evidently identify those at risk of myocardial infarction (MI) or death [22]. These patients will not be included in the study. Patients with an out-of-range FFR measurement are labeled as screen failures. In centers with ability to perform IVUS-NIRS, imaging acquisition will be achieved after FFR measurement.

After the initial procedure, patients will be randomized in a 1:1 fashion into two groups (evolocumab or placebo) using a 2:4:6 random block randomization algorithm. Randomization is stratified per study site. Following eligibility screening, enrollment and randomization, total study duration for each individual patient is 12 weeks. A detailed study design overview is presented in the

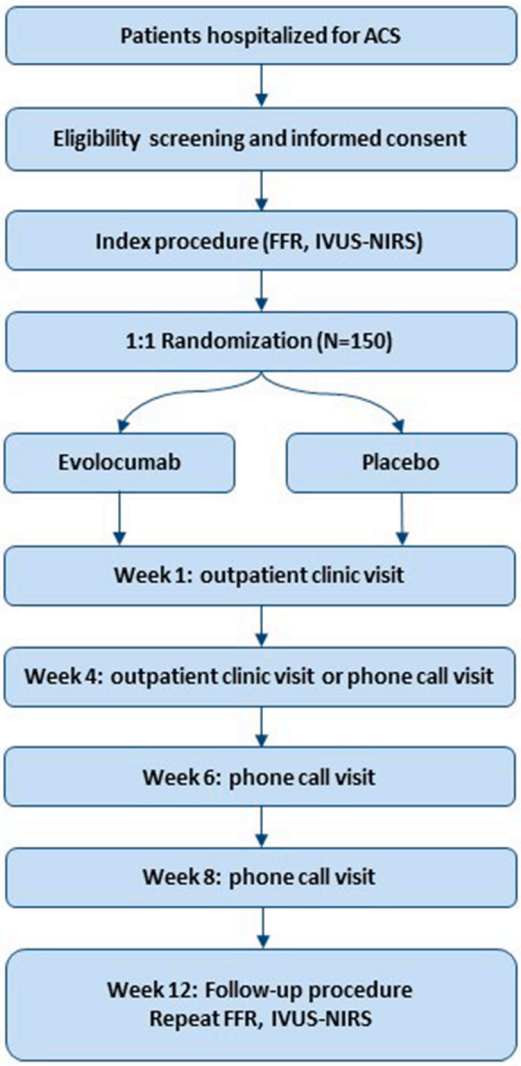

Fig. 1. Study flowchart.
Abbreviations: ACS, acute coronary syndrome; FFR, fractional flow reserve; IVUS, intravascular ultrasound; NIRS, near-infrared spectroscopy.

graphical abstract. Follow-up visits will occur at weeks 1, 4, 6, 8, and 12 (Fig. 1). First administration of the study drug (140 mg evolocumab or matching placebo) is performed in hospital, as soon as possible after inclusion. In total, six doses will be administered every two weeks by self-injection. If the patient is unable to administer the drug by self-injection, this will be done by trained research personnel on site. All participants will receive HIST as background therapy (atorvastatin $\geq$ 40 mg or equivalent). If during the study statin intolerance is suspected, patients are allowed to switch statin type (preferably to an equipotent regimen) or switch to a lower dose if a high-intensity statin regimen is not tolerated. The research team will be notified before adjusting the statin therapy. Patients, treating physicians, and research team are blinded for LDL-C measurements throughout the study. At week 12, the non-IRA lesions will be re-assessed with FFR and IVUS-NIRS. If at week 12 FFR measurement of the non-culprit vessel is $>$ 0.80, the non-culprit lesion is treated conservatively. Otherwise, if the non-culprit PCI $\leq$ 0.80, non-culprit PCI is at the operator's discretion.

2.3. Study endpoints

The primary endpoints of this trial are.

- The change in FFR from baseline to follow-up in non-IRA lesions (primary physiological endpoint), and
- The change in maximum lipid core burden index within a 4 mm segment ($maxLCBI_{4mm}$) from baseline to follow-up in the non-IRA (primary imaging endpoint).

The secondary endpoints of this trial are:
The change in IVUS-derived plaque characteristics of non-IRA lesions.

- Percent atheroma volume (PAV),
- Normalized total atheroma volume (TAV),
- Maximum plaque burden (PB), and
- Minimum lumen area (MLA).

A detailed list of all study endpoints is presented in Table 2.

2.4. Pressure wire measurements

FFR measurements are performed using a pressure wire, preferably PressureWire™ X Guidewire (Abbott Cardiovascular) or OmniWire™ (Philips). The FFR-wire is advanced distal to the non-culprit lesion of interest. The position of the FFR-wire will be captured. During follow-up procedure, this image is used to place the FFR-wire at the exact same location as the baseline measurement. FFR measurements are performed after administration of 100–200 μg intracoronary nitroglycerin. Hyperemia is achieved by an

Table 2
Summary of study endpoints.

Primary endpoints	1A The primary physiological study endpoint is the change in fractional flow reserve (FFR) from baseline to follow-up in non-infarct-related artery (IRA) lesions.
	1B The primary invasive imaging endpoint is the change in maximum lipid core burden index within a 4 mm segment ($maxLCBI_{4mm}$) from baseline to follow-up of the non-IRA as performed in sites capable of near-infrared spectroscopy (NIRS).
Secondary endpoints	Change in intravascular ultrasound (IVUS)-derived plaque characteristics of non-IRA lesions:
	2a The change in percent atheroma volume (PAV, %)
	2b The change in normalized total atheroma volume (TAV, mm^3)
	2c The change in maximum plaque burden (PB, %)
	2d The change in minimum lumen area (MLA, mm^2)
Exploratory endpoints	1. The correlation between achieved on-treatment low-density lipoprotein cholesterol (LDL-C) and the change in FFR, the change in lipid core burden index (LCBI), and the change in PAV.
	2. The correlation between baseline NIRS-derived $maxLCBI_{4mm}$ 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 function as measured by coronary flow reserve and index of microvascular resistance.
	5. Change in inflammatory phenotype of peripheral blood mononuclear cells and monocytes.
Safety clinical endpoints	Composite of patient-oriented composite endpoints (POCE):
	All-cause death
	Any stroke
	Any myocardial infarction
	Any revascularization (not mentioned: revascularization of study vessel at planned follow-up)
	Unplanned ischemia driven percutaneous coronary intervention (PCI) of target lesion
	Any unplanned ischemia driven PCI
Safety endpoints	Adverse events, serious adverse events

Abbreviations: FFR, fractional flow reserve; IRA, infarct related artery; $maxLCBI_{4mm}$, maximum lipid core burden index within a 4 mm segment; NIRS, near-infrared spectroscopy; IVUS, intravascular ultrasound; PAV, percentage atheroma volume; TAV, normalized total atheroma volume; PB, plaque burden; MLA, minimum lumen area; LDL-C, low-density lipoprotein cholesterol; LCBI, lipid core burden index; POCE, composite of patient-oriented composite endpoints; PCI, percutaneous coronary intervention.

intracoronary bolus injection of 100–200 mcg adenosine or by infusion of 140 mcg/kg/min adenosine administered through a central or peripheral vein. Either intracoronary or intravenous adenosine administration can be chosen per discretion of the treating interventional cardiologist. Yet, the administration method must be the same for baseline and follow-up measurements. After the FFR measurement is performed, the drift is captured. If the drift is > 0.02, FFR measurement has to be repeated and drift will be measured again, until an acceptable drift is achieved (≤ 0.02 drift). If possible and available, index of microvascular resistance/coronary flow reserve measurements are performed with the PressureWire™ X and a continuous intravenous adenosine infusion.

2.5. Acquisition of IVUS-NIRS imaging and analysis

In centers capable of IVUS-NIRS imaging, the combined 50 MHz Dualpro TVC-MC10 IVUS-NIRS 3.2-F rapid exchange catheter (InfraReDx, Burlington, Massachusetts) is used for all procedures. The catheter is positioned beyond a distal landmark and within the same segments as the registered FFR wire position. Image acquisition is performed with a transducer rotation of 240 rpm after the administration of 100–200 μg intracoronary nitroglycerin, using a motorized catheter pullback at a speed of 0.5 mm/s. The NIRS spectra data are mapped and paired with corresponding cross-sectional IVUS frames, presented as a ring around the IVUS image. NIRS and IVUS images are analyzed offline by an independent core laboratory (Cardiovascular Research Institute (CVRI), Dublin, Ireland). The core laboratory personnel are blinded to all other patient data, outcome data, and the sequence of imaging (baseline or follow-up).

The arterial lumen and external elastic membrane (EEM) borders will be segmented. Pullbacks at baseline will be matched with the corresponding pullbacks at follow-up, based on the anatomical locations of readily visible IVUS-derived landmarks. Outcome parameters will be derived as follows:

- The lipid core burden index (LCBI) is computed as the fraction of valid pixels within the study region that exceed a lipid-core plaque probability of 0.6, multiplied by 1000. For each vessel, we will calculate the LCBI over the total length of the region of interest ($LCBI_{total}$) and also the $maxLCBI_{4mm}$.
- PAV will be calculated according to the following equation:
  - o $\Sigma(EEM_{area} - Lumen_{area})/\Sigma EEM_{area}$ x 100
- Normalized TAV will be calculated according to the following equation:
  - o $(EEM_{area} - Lumen_{area})$/number of Images in pullback $\times$ median number of images in cohort
- The maximum PB is defined as the highest single slice plaque burden within the region of interest:
  - o $(EEM_{area} - Lumen_{area})/EEM_{area}$ x 100
- The MLA is referred to as the smallest lumen area within the region of interest.

2.6. Statistical analysis and power calculation of the primary endpoints

The study was originally designed with a single primary endpoint (the change in FFR, physiological endpoint) with a powered secondary endpoint (the change in $maxLCBI_{4mm}$, imaging endpoint, representing plaque composition, indicative of plaque rupture risk). During the execution of the study, the importance of plaque composition as a predictor of non-culprit MACE and as a target for PCSK9 inhibitors was further recognized in contemporary publications [8,18]. Therefore, prior to unblinding and prior to knowledge of any study result, the powered secondary endpoint was upgraded to a second primary endpoint in an official amendment to the study protocol. The study will be considered positive in the presence of a statistically significant difference in at least one primary endpoint. Both primary endpoints will be tested independently. To maintain the overall familywise error rate at 0.05, we will use a Hochberg correction. In short, if the largest p-value is < 0.05, both null hypotheses are rejected; if the largest p-value is ≥ 0.05, the smaller p-value is compared with alpha $= 0.025$; and if the second p-value is < 0.025, the null hypothesis corresponding to that primary outcome variable will be rejected. The p-values for the secondary endpoints will only be interpreted (i.e., the subsequent null hypotheses can only be rejected), if at least one of the null hypotheses of both primary endpoints is rejected. The secondary endpoints will be tested using a hierarchical procedure.

2.7. Power analysis of the primary hemodynamic parameter

Incorporating results from the YELLOW trial [15], we expect FFR levels to be 0.73 ± 0.1 at baseline and 0.78 ± 0.1 and 0.75 ± 0.1 at follow-up in the intervention and control group, respectively. Based on ANCOVA, at a two-sided alpha level of 0.05, a total sample size of 127 would result in 80% power to detect this difference. We assume a correlation of 0.8 between FFR at baseline and FFR at follow-up, based on previous FFR studies [23]. To compensate for dropouts of about 15%, a total of 150 patients should be included at baseline.

2.8. Power analysis of the primary imaging parameter

Based on results from the YELLOW trial [15] and the incremental effect of evolocumab on LDL-C [17,24], we assume a reduction of 42.49 ± 20.7 and 28.33 ± 20.7 mean percentage change in $maxLCBI_{4mm}$ in the intervention and control group, respectively. We assume a correlation of 0.6 between $maxLCBI_{4mm}$ at baseline and $maxLCBI_{4mm}$ at follow-up regarding previous NIRS studies [25]. Based on ANCOVA, at a two-sided alpha level of 0.025 and to compensate for dropouts of about 20%, a total of 84 patients should be included at baseline to reach 90% power.

2.9. Patient and public involvement in the research

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Discussion

The FITTER trial will evaluate the effect of maximal LDL-C reduction on functional impairment, PV, and plaque composition in important non-IRA lesions of patients presenting with ACS and MVD. Complete revascularization of all patients with ACS and MVD during first hospitalization continues to be disputed [26–28]. Although several studies demonstrated an advantage of complete revascularization in STEMI patients, the timing of the intervention of non-culprit lesions is still unclear [29–33]. Especially for patients with NSTEMI, data is scarce [27]. Although the BIOVASC trial [34] recently established non-inferiority of immediate complete revascularization in all ACS patients compared to staged revascularization, current international ACS guidelines do not discourage staging of PCI for non-culprit lesions [27]. Therefore, initial treatment of the culprit lesion by PCI with a "cooling down" period and staged PCI of non-culprit stenoses remains a feasible alternative that is widely applied in routine clinical practice. The FFR determines the functional severity of coronary stenoses. IVUS-NIRS allows the characterization of plaque size, composition, and lipid content, thereby identifying those plaques that pose a significant risk of causing recurrent ACS. Therefore, the FITTER trial obtains a complete picture of physiological importance and anatomical risk of non-IRA lesions and evaluates the potential effect of short-term PCSK9 inhibition on these lesions.

Early registry studies of non-culprit vessels like PROSPECT and AtheroRemo identified plaque burden and MLA as important predictors of clinical cardiovascular events [12,35]. The hazard ratios (HR) for MACE in the PROSPECT study were 5.03 (95% CI, 2.51 to 10.11; $p < 0.001$) for a PB > 70%, and 3.21 (95% CI, 1.61 to 6.42; $p = 0.001$) for a MLA ≤ 4 mm^2, respectively [12]. However, in the AtheroRemo, which evaluated hard endpoints such as recurrent ACS and death, the HR for PB was lower (2.9; 95% CI, 1.60 to 5.25; $p < 0.001$) and even non-significant for MLA (1.23; 95% CI, 0.67 to 2.26; $p = 0.50$) [35]. The additional importance of lipid content of non-culprit lesions on top of plaque burden and MLA was demonstrated by the LRP and PROSPECT II [8,10]. The PROSPECT II trial recruited patients with a recent MI [8]. Three-vessel IVUS-NIRS imaging was performed after PCI of all flow-limiting lesions. After a median follow-up of 3.7 years, the adjusted odds ratios for non-culprit MACE in patients with lesions with a maxLCBI$_{4mm} \geq 324.7$, PB $\geq 70\%$, or MLA ≤ 4.0 mm^2 were 3.80 (95% CI, 1.87 to 7.70; $p = 0.0002$), 5.37 (95% CI, 2.42 to 11.89; $p < 0.0001$), and 1.85 (95% CI, 0.95 to 3.61; $p = 0.072$), respectively [8]. Lesion-level risk of MACE for patients with lesions with a maxLCBI$_{4mm} \geq 324.7$ and PB $\geq$ 70% was 7% (95% CI, 4.0–10.0). The beneficial effects of statins and PCSK9 inhibitors on IVUS-NIRS- and OCT-derived plaque characteristics of mild bystander lesions have been established in multiple studies [13–18]. The GLAGOV trial demonstrated that the addition of evolocumab compared to placebo resulted in a greater decrease of PAV on serial IVUS imaging after 78 weeks (difference, −1.0%; 95% CI, −1.8% to −0.64%; $p < 0.001$) [17]. More recently, the PACMAN-AMI trial showed similar results with alirocumab in addition to HIST on PAV in patients presenting with ACS (difference, −1.21%; 95% CI, −1.78% to −0.65%; $p < 0.001$) [18]. Moreover, the maxLCBI$_{4mm}$ declined more in the alirocumab group compared with placebo group (difference, −41.24; 95% CI, −70.71 to −11.77; $p = 0.006$). Lastly, mean fibrous cap thickness, which was measured by OCT, increased more in the alirocumab group compared to placebo (difference, 29.65 μm; 95% CI, 11.75 to 47.55]; $p = 0.001$) [18]. Likewise, the HUYGENS trial evaluated the effect of evolocumab compared to placebo for 52 weeks on serial OCT and IVUS. The evolocumab group demonstrated a greater increase in minimum fibrous cap thickness (+42.7 vs. +21.5 μm; $p = 0.015$), greater decrease maximum lipid arc (−57.5° vs. −31.4°; $p = 0.04$) and greater regression of PAV (−2.29% ± 0.47% vs. −0.61% ± 0.46%; $p = 0.009$) [19]. Patients included in the PACMAN-AMI and HUYGENS trials were statin-naive ACS patients, unlike in the GLAGOV trial, where CCS patients were already on statin therapy. The greater regression in PAV observed in PACMAN-AMI and HUYGENS reflect the combined effect of PCSK9 inhibitor therapy and newly initiated statin therapy. However, these trials included non-target lesions with no more than ≤ 50% lumen obstruction by visual assessment. The FITTER trial evaluates the effect of the PCSK9 inhibitor evolocumab on PV and plaque morphology within vessels with important non-IRA lesion that have a FFR of 0.67–0.85. These lesions could not only demonstrate a higher PV, but conceivably also a higher lipid load. The HUYGENS and PACMAN-AMI studies observed a greater decline in PAV than the GLAGOV study, in part due to newly initiated statin therapy, but possibly also due to a higher PAV at baseline [17–19]. Therefore, a higher degree of atheroma regression is expected in the FITTER trial. Yet, it is unclear whether this positive effect on plaque anatomy translates into improved coronary hemodynamics. The FFR is the current gold standard to determine the hemodynamic severity of a coronary stenosis [36]. The FITTER trial is the first multicenter randomized controlled study that assesses the impact of aggressive lipid-lowering therapy on invasively measured FFR. Significant improvement of hemodynamically relevant non-culprit lesions could improve an initial strategy and might identify those plaques that do not require an additional non-culprit PCI and stent placement for remaining ischemia. A potential reduction in LBCI, measured with IVUS-NIRS, might suggests a lower residual risk for spontaneous or periprocedural (i.e., during staged PCI) coronary events. Furthermore, additional insights will be obtained into the relationship between aggressive lipid-lowering and maxLCBI$_{4mm}$. Although not powered for demonstrating clinical events, the study will provide information about the safety of performing FFR-guided staged procedures for important non-culprit coronary lesions with a FFR at baseline of 0.67–0.85.

4. Summary

The FITTER trial is an investigator-initiated, multicenter, double-blind, placebo-controlled, randomized trial enrolling 150 patients to evaluate the effect of 12 weeks of maximal LDL-C reduction by the PCSK9 inhibitor evolocumab in addition to optimal medical therapy on FFR and IVUS-NIRS-derived plaque characteristics of important non-culprit lesions in patients presenting with ACS and

MVD.

5. Strengths and limitations of this study

This study investigates the potential of pharmacological therapy for improving bystander lesions in patients treated with PCI of the culprit lesion in acute coronary syndrome, a frequently encountered problem with high costs. This trial is a multicenter, placebo-controlled, double-blind randomized study, which minimizes the risk of bias and will give an outcome with high validity and reproducibility. The study is independently monitored on study flow and imaging outcome parameters are independently analyzed by a central core laboratory.

Although this study is adequately powered to detect a difference in primary and secondary outcomes, 150 is still a relatively small number of patients. Therefore, slight differences might not be detected. The study is not powered to detect differences in clinical outcomes, a larger follow-up study with more patients will be needed to assess this.

Data statement

No research data is available in this design paper.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Robert-Jan M van Geuns reports financial support and equipment, drugs, or supplies were provided by Amgen Inc. Robert-Jan M van Geuns reports financial support and equipment, drugs, or supplies were provided by Infraredx Inc. Robert-Jan M van Geuns reports financial support was provided by HealthHolland. Pieter C Smits reports a relationship with Abbott Vascular Inc that includes: funding grants and speaking and lecture fees. Pieter C Smits reports a relationship with Shanghai MicroPort Medical Group Co Ltd that includes: funding grants and speaking and lecture fees. Pieter C Smits reports a relationship with SMT that includes: funding grants and speaking and lecture fees. Pieter C Smits reports a relationship with Terumo Medical Corporation that includes: speaking and lecture fees. Robert A Byrne reports a relationship with Abbott Vascular Inc that includes: funding grants. Robert A Byrne reports a relationship with Biosensors that includes: funding grants. Robert A Byrne reports a relationship with Boston Scientific Corporation that includes: funding grants. Robert A Byrne reports a relationship with Translumina GmbH that includes: funding grants. Niels van Royen reports a relationship with BIOTRONIK Inc that includes: funding grants. Niels van Royen reports a relationship with Abbott Vascular Inc that includes: funding grants and speaking and lecture fees. Niels van Royen reports a relationship with Medtronic Inc that includes: funding grants. Niels van Royen reports a relationship with Philips that includes: funding grants. Niels van Royen reports a relationship with Rainmed that includes: speaking and lecture fees. Niels van Royen reports a relationship with Shanghai MicroPort Medical Group Co Ltd that includes: speaking and lecture fees. Niels van Royen reports a relationship with Bayer AG that includes: speaking and lecture fees. Robert-Jan M van Geuns reports a relationship with Abbott Vascular Inc that includes: speaking and lecture fees. Robert-Jan M van Geuns reports a relationship with AstraZeneca that includes: funding grants and speaking and lecture fees. Robert-Jan M van

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