Unmet LDL-C target in very high risk cardiovascular patients

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To assess the prevalence of LDL-C >1.8 mMol/L in a subgroup of very high risk patients with ASCVD, who remain at a very high-residual risk for ACS, despite treatment with high-intensity statins in combination with ezetimibe. This...

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

Summary

ID

NL-OMON21157

Source
Nationaal Trial Register

Brief title
PENELOPE

Condition

- Coronary artery disorders

Health condition
Hyperlipidaemia/high cholesterol post myocardial infarction

Research involving
Human

Sponsors and support

Primary sponsor:	WCN
Secondary sponsors:	Sanofi
Source(s) of monetary or material Support:	Sanofi

Intervention

- Other intervention

Explanation

Outcome measures

Primary outcome
Study endpoint:

- Proportion of patients with LDL-C >1.8 mMol/L during stepwise incremental lipid modifying therapy with respectively a statin, statin + ezetimibe.

Secondary outcome
Study parameters:

- Medical history: ASCVD; T2DM; developing allergies or intolerances to alirocumab, ezetimibe or statins

- LDL-C plasma levels at each consecutive step

- Optional: non-HDL plasma levels at each consecutive step

- Prescription preference for atorvastatin or rosuvastatin to achieve "high intensity statin therapy" (HIST)

- % of patients that tolerates sustained HIST on atorvastatin or on rosuvastatin

- % of patients that does NOT tolerate HIST with atorvastatin, but does tolerate HIST when switching to rosuvastatin

- % of patients that does NOT tolerate HIST with rosuvastatin, but does tolerate HIST when switching to atorvastatin

- % of patients that reaches target LDL ≤1.8 mMol/l while NOT on HIST

- % of patients that compared to baseline achieves 50% LDL reduction ([1] patients not on HIST; [2] patients on HIST; [3] patients on HIST + ezetimibe; [4] patients on HIST + ezetimibe + alirocumab)

- % of patients that compared to baseline achieves 50% LDL reduction AND LDL >1.8 OR LDL ≤1.8 (patient-groups 1-4)

- non-HDL-C levels in patients with LDL ≤1.8 mMol/l and in patients with LDL >1.8 mMol/l, with or without alirocumab

- Non-HDL-C levels in patients with LDL ≤1.8 mMol/l ánd triglycerides >2 mMol/l, with or without alirocumab

- Prescription preference when atorvastatin 1dd40mg does not meet the LDL-target

- Creatinine kinase in patients with statin intolerance

- % of patients with an LDL ≤1.8 mMol/l after one year on HIST

- % of patients with an LDL ≤1.8 mMol/l after one year on HIST + ezetimibe

- % of patients with an LDL ≤1.8 mMol/l after one year on HIST + ezetimibe + alirocumab

Components of the TIMI Risk Score for Secondary Prevention (TRS 2_P):

- CHF, hypertension, age (≥75 yr), diabetes, prior stroke, prior CABG, peripheral artery disease, eGFR <60, smoking

Study description

Background summary
Hyperlipidaemia is one of the important risk factors in developing cardiovascular disease. LDL-C of <1.8 mMol/L or a reduction of at least 50% is recommended for very high risk patients. Different classes of lipid- modifying drugs are available. In patients with hypercholesterolaemia or combined hyperlipidaemia, statin mono-therapy is first choice therapy. In a large proportion of patients on statin mono-therapy, however, therapeutical target LDL-C levels are not reached, and ezetimibe should be added. If target LDL-C levels are unmet despite statin-ezetimibe combination therapy, a PCSK9 inhibitor (PCSK9-i) may be added.

In real world care, the proportion of patients with atherosclerotic cardiovascular disease (ASCVD) not reaching target LDL-C levels despite consecutive therapy with statin mono-therapy, statin + ezetimibe or statin + ezetimibe + PCSK9-i is unknown.

In the Netherlands and many other European countries, reimbursement of the PCSK9-i is restricted to a subgroup of “very high risk patients” not reaching target LDL-C levels despite

statin-ezetimibe combi-therapy.

In the present study, the prevalence of very high risk patients with ASCVD who remain at very high-residual risk for an acute coronary syndrome (ACS), defined as an LDL-C >1.8 mmMol/L (or non-HDL >2.6 mMol/l) will be analysed by a prospective, stepwise implementation of high intensity statin mono-therapy, followed by high intensity statin + ezetimibe combination-therapy if LDL-C still >1.8 mMol/L after 4 weeks of statin mono-therapy. Lipid levels will be measured 4 weeks after initiation of each step. A subset of patients whose LDL-C remains >1.8 mMol/L despite this intervention, will be treated with the PCSK9 inhibitor Alirocumab, 75 or 150 mg, and the efficacy of this therapy will be measured by lipid levels after 4 weeks of therapy.

Study objective
To assess the prevalence of LDL-C >1.8 mMol/L in a subgroup of very high risk patients with ASCVD, who remain at a very high-residual risk for ACS, despite treatment with high-intensity statins in combination with ezetimibe. This subgroup of very high risk patients is defined as patients with a history of ASCVD and/or diabetes mellitus type II (T2DM), and a new type I ST elevation or non-ST elevation myocardial infarction ([N]STEMI).

Study design
A prospective, open label, stepwise cohort study of consecutive patients admitted for type I STEMI or NSTEMI, characterized by a rise and/or fall of troponin with at least one value above the 99th percentile upper reference limit, and a history of ASCVD and/ or T2DM.

Patients with an LDL-C≤1.8 mMol/L at baseline will be registered, but not included in the study. All patients with an LDL-C>1.8 mMol/L, with or without therapy with statins and/or ezetimibe at baseline, will be treated with high-intensity statin therapy (i.e., atorvastatin ≥40 mg or rosuvastatin ≥20 mg or the maximum tolerated dose of a statin) for a period of 4 weeks. Lower statin doses are acceptable for patients with a valid reason for not using high intensity doses (advanced age and high frailty score, low body weight, drug-drug interaction). Patients with known statin-attributed muscle symptoms or who develop statin-attributed muscle symptoms during the study will be treated following the therapeutic flow-chart for management of patients with statin-associated muscle symptoms of the EAS Consensus Panel.

After 4 weeks, lipids are measured. If LDL-C >1.8 mMol/L, ezetimibe 10 mg is added on top of statin therapy. Patients with documented statin intolerance to at least three different statins, as defined by the EAS Consensus Panel, will be treated with 10 mg ezetimibe mono-therapy. Four weeks later lipids are measured, and if LDL-C >1.8 mMol/L, alirocumab will be added on top of current treatment with a statin and ezetimibe, in accordance with the following dosing-schedule:

• if 1.8<LDL-C<2.6 mMol/L, at the investigator’s discretion no alirocumab, or alirocumab 75 mg, or alirocumab 150 mg will be added

• if 2.6≤LDL-C<3.6 mMol/L, at the investigator’s discretion alirocumab 75 mg or alirocumab 150 mg will be added

• if LDL-C≥3.6 mMol/L, alirocumab 150 mg will be added

Two weeks after the second dose of alirocumab, lipids are measured.

Intervention
Patients are treated according to cholesterol treatment guidelines, with a step-wise approach (HIST, + ezetimibe, HIST+ ezetimibe + PCSK9-i The choice of PCSK9 inhibitor is directed by the protocol. When a PCSK-9 inhibitor needs to be prescibed, alirocumab is the drug of choice

Study burden and risks
There are no additional risks or burden for study participants.

The burden for the patient is limited to the drawing of blood samples (at 4, 8 and 12 weeks and 12 months), all of which are standard of care. For this study no extra visits or physical examinations are required.

Contacts

Public
Werkgroep Cardiologische centra Nederland
Astrid Schut
Moreelsepark 1
3511 EP
Utrecht
Netherlands

+3130 223 9937
Scientific
Werkgroep Cardiologische centra Nederland
Astrid Schut
Moreelsepark 1
3511 EP
Utrecht
Netherlands

+3130 223 9937

Eligibility criteria

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

Inclusion criteria

-Admission because of type I (N)STEMI, and

-History of ASCVD (i.e., cerebrovascular disease (Transient ischemic attack, cerebral infarction, amaurosis fugax, retinal infarction), Coronary artery disease (unstable Angina pectoris, MI, ACS, coronary revascularization (coronary angioplasty or surgical procedure for coronary bypass)), Peripheral artery disease (Symptomatic and documented obstruction of an distal extremity artery or surgical operation (percutaneous transluminal angioplasty, bypass or amputation), and/or a history of T2DM.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in

this study:

- Age <18 years

- Age >70 years ánd a Clinical Frailty Score >3.

- To measure the frailty score, the validated Dutch translation of the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale will be used (table 2)

- Pregnancy and lactating women

- Known intolerance for alirocumab

- Active PCSK9-i therapy

- Participation in lipid modifying drug trials

- Life expectancy <1 yr.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2019
Enrollment:	1000
Type:	Actual

IPD sharing statement

Plan to share IPD: No

Ethics review

Approved WMO Date:	11-09-2019
Application type:	First submission
Review commission:	Medical Research Ethics Committees United (MEC-U) Postbus 2500 3430 EM Nieuwegein 088 320 8784 info@mec-u.nl

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
NTR-new	NL7556
Other	NL66879.100.18

Study results