PENELOPE-CTRL:

Real life lipid management compared to protocolized implementation of the current Dutch- and ESC-guidelines in very high-risk CV-patients

PROTOCOL TITLE Real life lipid management compared to protocolized implementation of the current Dutch- and ESC-guidelines in very high-risk CV-patients

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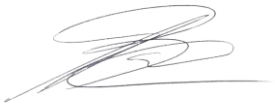
Study centres	***Aim: 13 sites***
Sponsor	***Clinical Operations WCN (COW)***
Subsidising party	***Sanofi-Aventis Netherlands B.V.***

PROTOCOL SIGN-OFF SHEET

Name	Signature	Date
Sponsor or legal representative: ***Clinical Operations WCN (WCN: Dutch Network for Cardiovascular Research)*** ***Drs. A. Schut (Board Member)*** *Moreelsepark 1* *3511 EP Utrecht*		**25JAN2023**
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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACS	**Acute coronary syndrome**
ASCVD	**Atherosclerotic cardiovascular disease**
CFS	**Clinical Frailty Score**
CVE	**Cardiovascular event**
CVRM	**Cardiovascular Risk Management**
ESC	**European Society of Cardiology**
LDL-C	**Low density lipoprotein cholesterol**
LLT	**Lipid Lowering Therapy**
NSTEMI	**Non-ST-Elevation Myocardial Infarction**
PCSK9-i	**Proprotein convertase subtilisin/kexin type 9 inhibitors**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
STEMI	**ST-Elevation Myocardial Infarction**
T2DM	**Type 2 Diabetes Mellitus**
WCN	**Werkgroep Cardiologische centra Nederland**
WMO	**Medical Research Involving Human Subjects Act (in Dutch, Wet Medisch-wetenschappelijk Onderzoek met mensen)**

2. ABSTRACT

Rationale: Guideline recommended evidence-based clinical care correlates with improved patient outcomes. In real life care, however, adherence to guideline recommendations remains suboptimal. In real life, patients may receive suboptimal treatment and as a result treatment targets are not always met. To support and improve secondary prevention for cardiovascular disease, PENELOPE and PENELOPE-CTRL are designed to support guideline implementation on lipid management and provide valuable feedback to care-givers on real world data.

The recent PENELOPE study was designed to determine the effect of a protocolized, Dutch-, and European Society of Cardiology (ESC) guidelines based strategy of stepwise intensified lipid management in patients at very high risk for Acute coronary syndrome (ACS). In PENELOPE 22 Dutch non-academic hospitals, members of the WCN investigator network, implemented a protocol guided guideline approach in a consecutive cohort of very high-risk patients admitted for ACS over the period 01-01-2019 to 31-08-2020. Lipid values and medication strategy are collected at baseline (index ACS), and after three months and one year post ACS, in order to establish the percentage of patients on target Low density lipoprotein cholesterol (LDL-C).

The current PENELOPE-CTRL study on the other hand, is designed to serve as a contemporary control cohort for PENELOPE. PENELOPE-CTRL is a retrospective observational study, creating a contemporary snapshot of real-life lipid management for secondary prevention in very high-risk patients. PENELOPE-CTRL will collect data in similar hospitals who did not participate in the PENELOPE trial.

To allow comparison of these two strategies, protocol guided versus real life implementation of the cholesterol treatment guidelines, both cohorts include similar patients, and similar data will be collected (e.g., lipid lowering drugs, lipid panels) . Analysis will be done at similar time points. Comparing the real-life data from PENELOPE-CTRL with the data from the PENELOPE study will quantify the effect of a strategy of protocolized guideline-based lipid management with regards to the incidence of target LDL-C levels in very high-risk patients, 3 months and one year after hospitalisation with a myocardial infarction.

Objective: To measure real life lipid lowering therapy (LLT) and resulting LDL-C levels in very high-risk patients. PENELOPE-CTRL will be used as a control cohort versus protocolized (PENELOPE study) implementation of the Dutch and ESC guidelines.

Study design: Retrospective cohort study.

Study population: Patients with a history of **Atherosclerotic cardiovascular disease** (ASCVD) and/or type 2 diabetes (T2DM), admitted for a type I ST-elevation myocardial infarct (STEMI) or non-STEMI. Patients <18 years or >70 years of age will be excluded.
In PENELOPE patients over 70 were included based on a frailty index. As this parameter cannot be determined retrospectively, patients over 70 will be excluded from the CTRL cohort, as well as from the comparative analysis for the two cohorts.

Study parameters: Cardiovascular medical history and risk profile, baseline characteristics (including index event, lipid panels, baseline medication and LLT); and follow up data on LLT and lipid panels during the year post ACS

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: None, retrospective data collection.

3. INTRODUCTION AND RATIONALE

One of the main underlying causes of atherosclerotic cardiovascular disease is the retention of LDL-C and other cholesterol containing lipoproteins within the arterial wall. There is an approximately linear relationship between the absolute reduction in LDL-C and the proportional reductions in the incidence of coronary and major vascular events.[1] Clinical trials have clearly shown that the lower the achieved LDL-C values, the lower the risk of future cardiovascular events. Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition.[2, 3] For secondary prevention in very-high-risk patients the 2016 ESC Guidelines for the management of dyslipidaemia recommended an LDL-C reduction to <1.8 mmol/l.[1] in the 2019 ESC Guidelines this was narrowed down even further to <50% from baseline and an LDL-C goal of <1.4 mmol/L.[4] If the LDL-C goal is not achieved 4 - 6 weeks after the cardiovascular event (CVE) despite maximal tolerated statin therapy, ezetimibe should be added first, followed by Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-i). [3] The Dutch Cardiovascular Risk Management (CVRM) guideline (in the period PENELOPE was performed) recommends an LDL-C goal of at least <1.8 mmol/L for very high-risk CV-patients.

Adherence to treatment guidelines is a predictor of fewer CV hospitalizations. In real life care, however, compliance to guidelines for secondary prevention of cardiovascular disease, can be improved according to recent European and Swedish national studies. [5-8] A strategy of protocolized, Dutch- and ESC-guideline based stepwise approach in lipid lowering therapy (LLT) to reach target LDL-C in very high-risk patients was studied in the PENELOPE study. Protocolized LLT consisted of 3 steps, with LDL-C levels measured ≥4 weeks after each step:

- Step 1: if at baseline LDL-C >1.8 mmol/L, then a high intensity statin (HIST), defined as atorvastatin ≥40 mg OD or rosuvastatin ≥20 mg OD, had to be initiated.
- Step 2: if ≥4 weeks after step (1) LDL-C >1.8 mmol/L, then ezetimibe 10 mg OD had to be initiated.
- Step 3: if ≥4 weeks after step (2) LDL-C >1.8 mmol/L alirocumab had to be initiated following pre-specified criteria:
    - if LDL-C 1.8-2.6 mmol/L, addition and dosing of alirocumab was left at the investigator's discretion
    - if LDL-C 2.6-3.6 mmol/L, alirocumab 75 mg or 150 mg Q2W had to be initiated (dosing at the investigator's discretion)
    - if LDL-C >3.6 mmol/L, alirocumab 150 mg Q2W had to be initiated.

PENELOPE was designed to demonstrate feasibility and efficacy of guideline-based protocolized LLT in the Netherlands.
PENELOPE-CTRL is designed to document real life LLT and resulting LDL-C target attainment in the Netherlands.
Comparison of PENELOPE and PENELOPE-CTRL will demonstrate whether the strategy of protocolized guideline based LLT results in a higher incidence of target LDL-C levels in secondary prevention at set time points, and quantify this difference.

4. OBJECTIVES

Primary Objective:

To compare real life LLT and reaching target LDL-C levels in very high-risk patients versus protocolized (PENELOPE study) implementation of the current Dutch and ESC guidelines.

5. STUDY DESIGN

PENELOPE-CTRL is designed as a retrospective cohort study with its enrolment-period coinciding with the inclusion period of PENELOPE, i.e. January 1st, 2019 until August 31st, 2020.

6. STUDY POPULATION

a. POPULATION

All patients fulfilling the in- and exclusion criteria in the participating centres will be included in the PENELOPE-CTRL cohort (Registry). Participating sites are part of the WCN research network and have not participated in PENELOPE. These are all non-academic cardiovascular research centres, providing regional cardiovascular hospital care with a regional CVRM function. All sites are using the same standard operating procedures for clinical research.
Inclusion criteria are identical to the Penelope trial, with the exception of the introduction of a maximum age of 70 years in PENELOPE-CTRL. (Table 1) In PENELOPE, patients >70 years of age were required to have a clinical frailty score (CFS) ≤3. As retrospective electronic medical records data do not allow for accurate determination of the CFS, all patients >70 years will be excluded in PENELOPE-CTRL. For the comparative analysis the CTRL population will be compared to the Penelope patients ≤ 70 years old (N=663).Furthermore, only patients who were alive at discharge will be registered.

b. INCLUSION CRITERIA

- Age >18 and ≤70 years
- Alive at hospital discharge after admission for (N)STEMI between 1-1-2019 and 31-08-2020

- Planned for follow-up at a participating PENELOPE CTRL site
- History of T2DM and/or history of ASCVD defined as either one of:
    - cerebrovascular disease/ event: transient ischemic attack, cerebral infarction, amaurosis fugax, retinal infarction
    - Coronary artery disease/ event: unstable angina pectoris, MI, ACS, coronary revascularization (coronary angioplasty or surgical procedure for coronary bypass)
    - Peripheral artery disease (symptomatic and documented obstruction of a distal extremity artery or surgical intervention (percutaneous transluminal angioplasty, bypass or amputation)

Table 1. Inclusion criteria PENELOPE and PENELOPE CTRL, and PENELOPE analysis population

	PENELOPE	PENELOPE (cohort compared to CTRL)	PENELOPE CTRL
Age	≥18 years, ≤70 years	≥18 years, ≤70 years	≥18 years, ≤70 years
	>70 years and CFR≤3	-	-
history of ASCVD	✓	✓	✓
T2DM	✓	✓	✓
admission for (N)STEMI	✓	✓	✓

c. EXCLUSION CRITERIA

- Pregnant and lactating women

Participation in lipid modifying drug trials up to two years after index CVE.

d. PATIENT SELECTION

All eligible patients will be identified for data capture in the participating PENELOPE CTRL centers by the local team of the PI. Eligible patients will be pre-identified from local electronic health records using text-mining (CT-cue) on the in- and exclusion criteria. A local member of the study team will confirm eligibility based on the detailed structured and non-structured local electronic health record data. A feasibility query in participating centres shows a cohort of 700-1200 candidates.

7. DATA COLLECTION

The following data will be collected from the local electronic health record starting at admission up to 18 months:

- Baseline characteristics including at least age at admission, index event, medical history and cardiovascular risk factors
- Lipid lowering medication, including start and stop dates, (perceived) cause of interruption or intolerance, and dosage
- Lipid panels: all available total cholesterol, LDL, HDL, and TG values will be collected
- Clinical course, including death, myocardial infarction, stroke and (urgent) revascularisation and co-medication

8. STUDY OUTCOMES

a. PRIMARY STUDY OUTCOME

The primary outcome is defined as the cumulative incidence of patients reaching the LDL-C target level (≤ 1.8 mmol/L) after admission for a type I (N)STEMI with oral lipid lowering medication only, compared to the designated PENELOPE cohort.

Further details on handling of missing or out of window values collected form regular care will be detailed in the endpoint charter, used for endpoint adjudication.

After analysis of the PENELOPE CTRL data the CTRL cohort will be compared to the original PENELOPE cohort.

b. SECONDARY STUDY OUTCOMES

a) Mean time of reaching the primary outcome, compared to the designated PENELOPE cohort.

b) Cumulative incidence of patients reaching the LDL-C target level (≤ 1.8 mmol/L) within 90 days after admission for a type I (N)STEMI with oral lipid lowering medication only. This outcome will be estimated with two analysis:

   - only including patients reaching (at least once) LDL-C target within 90 days (without using LDL-C measurements after this window) and
   - additionally including the first available LDL-C measurement (at least 14 days) after the last modification in oral lipid lowering therapy within 90 days after baseline (even if this measurement is after 90 days). This way CTRL mimics the original PENELOPE dataset, where LDL measurement 4-6 weeks after a drug regimen change was mandatory to establish the treatment effect, and this measurement also includes the effect of the last drug regimen change within 90 days.

c) Cumulative incidence of patients reaching other LDL-C target levels (e.g. ≤ 1.4 mmol/L and 50% LDL-C reduction compared to baseline) and mean LDL-C levels with only oral medication after admission for a type I (N)STEMI, compared to the designated PENELOPE cohort.
d) Cumulative incidence of reaching LDL-C target levels (≤ 1.8 mmol/L, ≤ 1.4 mmol/L and 50% LDL-C reduction) compared to baseline) and mean LDL-C levels with any lipid lowering drugs (so including the effects of PCSK9i), compared to the designated PENELOPE cohort.
e) Cumulative incidence of patients reaching LDL-C target levels with only (i) high-intensive statin (compared to cum. effect after STEP 1 in PENELOPE) or (ii) high-intensive statin and/or ezetimibe (compared to cum. effect after STEP 2 in PENELOPE).

c. STUDY PROCEDURES

As PENELOPE-Control is a retrospective cohort registration there are no study procedures.

d. Randomisation, blinding and treatment allocation

Not applicable.

e. Withdrawal of individual subjects

Not applicable.

f. Premature termination of the study

Not applicable.

9. DATA SAFETY MONITORING BOARD

Not applicable.

10. STATISTICAL ANALYSIS

The primary analysis consists of a comparison of outcomes between de PENELOPE CTRL and the original PENELOPE intention to treat population. Baseline characteristics of the cohorts will be presented. To assess for potential remaining imbalances between the cohorts a t-test and Chi-squared test will be used for continuous and dichotomous variables, respectively.
In case of imbalance in patient characteristics between the cohorts, a step-wise approach will be used to correct for this.

- First, a propensity score is derived to asses for membership of trial. Second, a propensity score is derived on the baseline criteria.
- If the distribution of the propensity scores is dissimilar between PENELOPE CTRL and PENELOPE adjustment for differences in propensity function is done in two methods.
    - First, logistic regression analysis with propensity score as co-variate.
    - Second, stratified analysis with deciles of the propensity score.

Percentages are converted to Odds Ratio to allow for multivariable analysis. Missing values are reported and appropriately imputed in the statistical models.
Statistical analysis will be formalised in the SAP, as well as the statistical methods to be used for endpoint analysis. For comparison between the PENELOPE and PENELOPE CTRL cohort, the same additional exclusion criteria were applied: ‘known intolerance for alirocumab’ and ‘active PCSK9-I therapy at baseline’. Life expectancy <1 year was omitted as this could not be determined reliably from the medical records retrospectively. For the primary outcome and secondary outcomes b, c and e (investigating the effects of oral LLT), patients will be excluded as soon as they start using PCSK9i.

11. SAFETY REPORTING

PENELOPE CTRL is a retrospective Registry cohort, collecting data from routine clinical care. Therefore safety reporting to IRB or RA is not applicable, and is the responsibility of the caregiver as part of routine clinical care.

12. ETHICAL CONSIDERATIONS

a. Regulation statement

In the Netherlands, there is no regulation for non-interventional studies like the Medical Research Involving Human Subjects Act (WMO) for interventional studies. In the absence of a regulation, a

framework of standards (Normenkader) has been put in place to ensure non-interventional studies are properly conducted. These standards aim to provide a framework for those who initiate the study, for those who assess the legitimacy of the study and those who conduct the study. PENELOPE-CRTL will be conducted in accordance with these standards. PENELOPE- CTRL will be used as a control cohort for PENELOPE. PENELOPE is evaluated as a "WMO-obligated" protocol, requiring informed consent. PENELOPE-CTRL is submitted in the DCRF route as a pharma funded investigator initiated nWMO cohort, and evaluated by the MEC-U who also was the central ethic committee for PENELOPE.

b. Recruitment and consent

Retrospective data will be used in this analysis and therefore recruitment and consent are not applicable. Informed Consent has been waived by the MEC_U under the condition that all participating centres have a local opt-out for use of data on the website. This will be documented in the Green Light process before start of data collection.

c. Benefits and risks assessment, group relatedness

Not applicable.

d. Compensation for injury

Not applicable.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

e. Handling and storage of data and documents

The principal investigator of a study centre is responsible for data capture in CASTOR (eCRF), in which they have access to data of their centre only through personalised accounts. All data are captured in a coded manner, using fake initials and only age at admission, to avoid identification. The key that links patient study ID to EMR records is kept within the hospital by the investigator and his team. After data base lock, the PI will receive a digital copy of the data entered for his site. All details related to data recording, data handling and data review will be documented in a Data Management Plan.

The principal investigator has the option to outsource the data entry to a centralised person assigned by WCN, if preferred. This professional is kept by professional secrecy and will receive a named account for restricted EMR access.

Study documentation will be kept for 15 years after study closure.

f. Monitoring and Quality Assurance

There will be no monitoring in this retrospective data analysis.

All WCN sites are well trained, have a valid ICH-GCP certificate and use WCN site SOP's.

A Clinical Study Report (CSR) will be sent to all study centres within 10 months following the study's final data transfer.

g. Amendments

Amendments are changes made to the research after a favourable advice from the nWMO advisory committee has been obtained. All amendments to this protocol will be notified to the nWMO advisory committee.

h. Annual Progress Report

Not applicable.

i. Temporary halt and (prematurely) End of Study Report

Not applicable.

j. Public disclosure and publication policy

Results of this study will be published in a peer reviewed medical journal and can be used in future discussions with the Dutch Health Authorities and the Health Insurance Companies.

14. REFERENCES

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