Pharmacoepidemiological study protocol ER-9502

Risk of subsequent cardiovascular events in patients discharged after myocardial infarction - PERSEUS

Authors: Tuire Prami, Houssem Khanfir

Protocol number: ER-9502

Sponsor: AstraZeneca Nordic Baltic

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Study Information

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Marketing authorization holder	AstraZeneca Nordic Baltic is representing Brilique (ticagrelor) with the indication under consideration.
Research question and objectives	To describe the risk development and risk factors of subsequent cardiovascular events in patients discharged from hospital after myocardial infarction.
Country of study	Finland
Author	Tuire Prami, Houssem Khanfir

Marketing authorisation holder

Marketing authorization holder(s)	AstraZeneca Nordic Baltic SE-151 85 Södertälje Sweden
AstraZeneca protocol reference	D1843R00244
MAH contact person	Anna Deleskog, Pål Hasvold

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1 List of abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
ASA	Acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical
CABG	coronary-artery bypass grafting
CAD	Coronary atherosclerotic disease
CI	Confidence interval
DAPT	Dual antiplatelet treatment
DDD	Defined daily dose
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HR	Hazard ratio
ICD-10	10th revision of international classification of diseases
ID	Patient identification number
LMWH	Low molecular weight heparin
MI	Myocardial infarction
NCSP	NOMESCO classification for surgical procedures
NOAC	Novel oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
NSTEMI	Non-ST elevation myocardial infarction
OAP	Oral antiplatelet
PCI	Percutaneous coronary intervention
SAP	Statistical analysis plan
SID	Study identification number
STEMI	ST elevation myocardial infarction
THL	National Institute for Health and Welfare
TIA	Transient ischemic attack

2 Responsible parties

Sponsor: AstraZeneca Nordic Baltic

Study conduct: EPID Research Oy, Metsänneidonkuja 12, FI-02130 Espoo, Finland

Principal investigator: Tuire Prami (Ph.D.), EPID Research

Co-investigators: Pasi Korhonen (Ph.D., Adj. prof.), EPID Research

Fabian Hoti (Ph.D.), EPID Research

Sponsor project lead: Anna Deleskog (Project Lead), AstraZeneca Nordic Baltic

Pål Hasvold (Medical Evidence Scientific Lead), AstraZeneca Nordic Baltic

Scientific committee (also referred to as Steering committee):

Tuire Prami (Ph.D.), EPID Research

Juhani Airaksinen (MD, PhD, Prof.), Turku University Hospital

Eeva Reissell (MD, PhD), National institute for Health and Welfare

Ville Kytö (MD, PhD, Adj. prof.), Turku University Hospital

Anna Deleskog (Project Lead), AstraZeneca Nordic Baltic

Pål Hasvold (Medical Evidence Scientific Lead), AstraZeneca Nordic Baltic

3 Abstract

Title: Risk of subsequent cardiovascular events in patients discharged after myocardial infarction - PERSEUS

Rationale and background: Myocardial infarction affects about 5000 patients in Finland per year. Almost 20% of them die within one year after the event. Among the Nordic countries, cardiovascular death rates are the highest in Finland. Current guidelines advise to treat myocardial infarction patients with 12-month dual antiplatelet treatment. An ongoing PEGASUS-TIMI 54 clinical study aims to survey the advantages of longer use of ticagrelor and acetylsalicylic acid in secondary prevention.

Research question and objectives: The aim of the present study is to describe the risk development and risk factors of subsequent cardiovascular events in patients discharged from hospital after myocardial infarction. The study questions focus on patients surviving more than one year without subsequent myocardial infarction or stroke and on patients with known additional risk factors. Pre-specified subgroup analyses in populations mimicking the PEGASUS-TIMI 54 study population in a real-life setting will be performed to enable comparison of real-life and randomised study settings.

Study design: Retrospective observational database linkage cohort study

Study setting and population: Patients discharged from hospital following admission for myocardial infarction in 2009-2012, and alive 7 days after the discharge. The patients will be followed-up until death, moving abroad, or the end of year 2013, whichever occurs first. Patients surviving more than one year after the discharge without a subsequent myocardial infarction or stroke will be surveyed with special interest. Primary endpoints are myocardial infarction, stroke, cardiovascular mortality and overall mortality.

Data sources: Finnish Hospital Care Register (HILMO) and Social HILMO maintained by the National Institute for Health and Welfare, Prescription Register maintained by the Social Insurance Institution, and Causes of Death Registry maintained by Statistics Finland

Study size: Based on unpublished results from an on-going study by Prami *et al.* the study population size is estimated to be 44 000 patients.

Data analysis: The risk development for the endpoints of interest will be presented using Kaplan-Meier estimates. The analysis will be performed for each of the study populations and stratified by age, gender and patient risk level. Adjusted hazard ratio estimates with 95% confidence intervals and P-values will also be presented.

4 Amendments and updates

None, this is the first version of the protocol.

5 Milestones

Milestone	Planned date
Start of data permit process	04/2015
Registration in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) e-register	04/2015
End of data permit process	09/2015
Start and end of data collection	09/2015
Start of data analysis	09/2015
End of data analysis	12/2015
Start of study reporting process	12/2015
Final report of study results	01/2016
Start of scientific reporting process	01/2016

6 Rationale and background

The incidence of new myocardial infarctions (MI) was 269 per 100 000 inhabitants in Finland during the years 2008-2010 [1]. Every year MI affected nearly 5000 new patients of which 6.7% died within 7 days and 19% within one year from the MI. Based on the World Health Organization (WHO) data from 2011, coronary heart disease death rate was 237 per 100 000 inhabitants in Finland [2]. This means that Finland was ranked 28th on the list with best results from San Marino, France and Portugal.

MIs resulting from atherosclerotic plaque rupture with subsequent thrombosis lead to complete or near complete occlusion of an epicardial coronary artery [3]. Minimization of the mechanical obstruction from thrombus is the main goal of therapy in ST elevation myocardial infarction (STEMI). Recurrent ischemic events are still quite frequent after MI, while sudden cardiac death is less common [4]. Known risk factors have been associated with deaths after acute coronary syndrome hospitalizations [5]. Invasive treatment with angiography after acute MI has been shown to decrease the risk of death and recurrent MI [6]. This finding was in association with use of secondary preventive medication. Efficient oral antiplatelet (OAP) treatment, however, increases the bleeding rate [7].

Currently the local clinical guidelines advise to treat both STEMI and non-ST elevation myocardial infarction (NSTEMI) patients with an OAP (clopidogrel, prasugrel or ticagrelor) for 12 months together with acetylsalicylic acid (ASA) [8,9]. The OAP treatment maybe longer in case of ASA insufficiency [8] or shorter if the patient has increased bleeding risk [9].

A large, international, randomised clinical outcomes study PEGASUS-TIMI 54 [10] is currently conducted by AstraZeneca to determine the clinical efficacy and safety of long-term dual antiplatelet therapy (DAPT) with ticagrelor in combination with ASA compared to aspirin as monotherapy in patients with recent MI and additional atherothrombotic risk. The study aims to determine whether the DAPT treatment with ticagrelor and ASA reduces the risk of secondary cardiovascular events among patients with an MI within 1-3 years prior study start and additional atherothrombotic risks compared to ASA as monotherapy. The median follow-up time in PEGASUS study is anticipated to be over two years.

The aim of the present study is to describe the risk development and risk factors of subsequent cardiovascular events in patients discharged from hospital after myocardial infarction. The main focus is on patients surviving more than one year without subsequent myocardial infarction or stroke. Special interest is also focused on patients with known additional risk factors.

A similar study is on-going in parallel in Sweden (i.e. the HELICON study) [11] and under planning in Norway and Denmark, which makes between-country comparison possible. The study setting aims to mimic the PEGASUS-TIMI 54 study [10] in order to make the comparison of real-life data study and the randomized clinical trial possible.

7 Research questions and objectives

The objective of this study is to describe the risk development and risk factors of subsequent cardiovascular events in patients discharged from hospital after myocardial infarction. We study all patients alive one week after the discharge, and because the mortality is high during the first year, the main focus is in patients surviving without subsequent myocardial infarction or stroke more than one year. Subgroups of patients surviving more than two or three years without subsequent events will be evaluated. Patients with known additional risk factors form a subgroup. Of these high risk patients a subgroup mimicking the HELICON study [11] and another subgroup mimicking the PEGASUS-TIMI 54 study [10] population are analysed in order to make the comparison of a real-life-setting study and a randomized clinical trial possible. (See chapter 8.2.2 for more details about study groups.)

7.1 Primary objectives

a) To assess MI, stroke, cardiovascular mortality and overall mortality rates for the following populations:

   1) Patients hospitalized for MI and alive 7 days after the discharge (Group 1)

   2) A subgroup of patients from Group 1 who survived without a subsequent MI or stroke 12, 24 and 36 months after the first MI during the study period (Group 2)

   3) A subgroup of high risk patients from Group 2 who survived without a subsequent MI or stroke 12, 24 and 36 months after the first MI during the study period (Group 3)

   4) A subgroup of patients from Group 3 mimicking the HELICON [11] study population in a real-life setting (Group 4)

   5) A subgroup of patients from Group 4 mimicking the PEGASUS-TIMI 54 [10] study population in a real-life setting (Group 5)

   (See chapter 8.2.2 for more details about study groups.)

b) To assess the association of risk between different cardiovascular risk factors and the incidence of MI, stroke, cardiovascular mortality and overall mortality.

c) To describe patient demographics, clinical characteristics and drug treatment in all study groups.

7.2 Secondary objectives

d) To assess the rate of other cardiovascular events in study groups 1, 2, 3, 4 and 5.

e) To assess the rate of major organ specific bleedings in study groups 1, 2, 3, 4 and 5.

f) To describe the prevalence of increased bleeding risks in study groups 1, 2, 3, 4 and 5.

7.3 Exploratory objectives

g) To describe the distribution of sub-events for MI, stroke, cardiovascular mortality and overall mortality as follows:
   - MI: STEMI, NSTEMI
   - Stroke: Haemorrhagic stroke, ischemic stroke, other stroke
   - Cardiovascular mortality: MI mortality, STEMI mortality, NSTEMI mortality, overall stroke mortality, haemorrhagic stroke mortality, ischemic stroke mortality, other stroke mortality, other cardiovascular mortality (heart failure, atrial fibrillation, unstable angina pectoris)
   - Overall mortality: Cause specific mortality (most common causes of death)

8 Research methods

8.1 Study design

This is a retrospective observational database linkage cohort study using patient level data from different nationwide registers in Finland. The primary endpoints are MI, stroke, cardiovascular mortality and overall mortality.

8.2 Population and setting

Study population consists of patients discharged from Finnish hospitals following admission for myocardial infarction (the 10th revision of international classification of diseases (ICD-10) codes I21-I22) between 01

Jan 2009 and 31 Dec 2012, and alive 7 days after the discharge. The discharge day is called index date. The patients are followed-up from the index date until death, moving abroad or the end of year 2013. Medical disease history is evaluated from five years before the index date and medication history from one year before the index date. These history periods are fixed to be of same length for all patients. The study setting is presented in Figure 1.

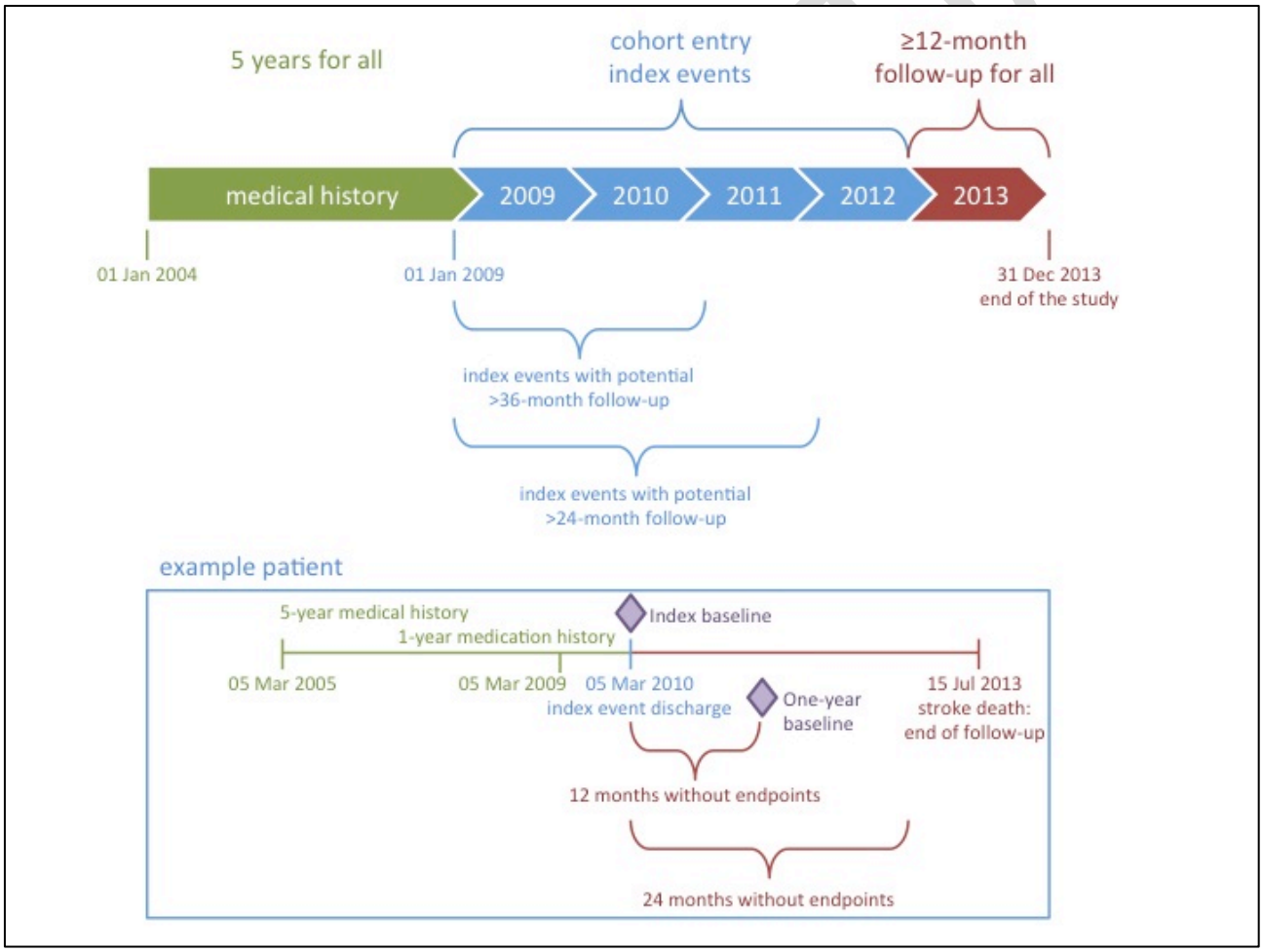
8.2.1 Definitions

Index date: The date of discharge from hospital following admission for myocardial infarction (ICD-10 codes I21-I22) between 01 Jan 2009 and 31 Dec 2012.

Follow-up: Each patient is followed from the index date to death, moving abroad or the end of year 2013 whichever occurs first. For a particular endpoint the follow-up ends at the time of the endpoint, death, moving abroad or the end of year 2013 whichever occurs first.

Subsequent MI: Any hospitalization for myocardial infarction (ICD-10 codes I21-I22) after index date.

Figure 1: Study setting



8.2.2 Study groups

Group 1:

Patients who were hospitalized for MI (ICD-10 I21-I22) between 01 Jan 2009 and 31 Dec 2012 and alive 7 days after the discharge

- All the patients included in the study belong to this group starting from their index date.

Group 2:

A subgroup of patients from Group 1 who were hospitalized for MI (ICD-10 I21-I22) between 01 Jan 2009 and 31 Dec 2012 and alive 7 days after the discharge

with no subsequent MI or stroke during the following 12 months after the index date.

- The membership of this group can start at one year after the index date.

Group 3:

A subgroup of patients from Group 2 who were hospitalized for MI (ICD-10 I21-I22) between 01 Jan 2009 and 31 Dec 2012 and alive 7 days after the discharge

with no subsequent MI or stroke during the following 12 months after the index date, and

with at least one additional risk factor at one year baseline check.

- Additional risk factor means at least one of the following: age ≥65 years, diabetes mellitus on medication, or ≥1 MIs, multivessel coronary atherosclerotic disease (CAD), chronic renal dysfunction or ischemic stroke in the history (during the fixed 5 years history period before one year baseline).
- The membership of this group can start at one year after the index date.

Group 4:

A subgroup of patients from Group 3 who were hospitalized for MI (ICD-10 I21-I22) between 01 Jan 2009 and 31 Dec 2012 and alive 7 days after the discharge

with no subsequent MI or stroke during the following 12 months after the index date, and

with at least one additional risk factor at one year baseline check, and

with no chronic use of anticoagulation.

- Additional risk factor means at least one of the following: age ≥65 years, diabetes mellitus on medication, or ≥1 MIs, multivessel CAD, chronic renal dysfunction or ischemic stroke in the history (during the fixed 5 years history period before one year baseline).
- Anticoagulation medication here means warfarin, novel oral anticoagulants (NOACs) and low molecular weight heparins (LMWHs).
- Chronic use of anticoagulation means warfarin/NOAC/LMWH use for ≥3 months, which is still ongoing at one-year baseline.
- The membership of this group can start at one year after the index date.
- This patient group is mimicking the HELICON [11] study population.

Group 5:

A subgroup of patients from Group 4 who were hospitalized for MI (ICD-10 I21-I22) between 01 Jan 2009 and 31 Dec 2012 and alive 7 days after the discharge

with no subsequent MI or stroke during the following 12 months after the index date, and

with at least one additional risk factor at one year baseline check, and

age ≥50 years at one year baseline check, and

with no chronic use of anticoagulation at one year baseline check, and

without any of PEGASUS exclusion criteria at one year baseline check.

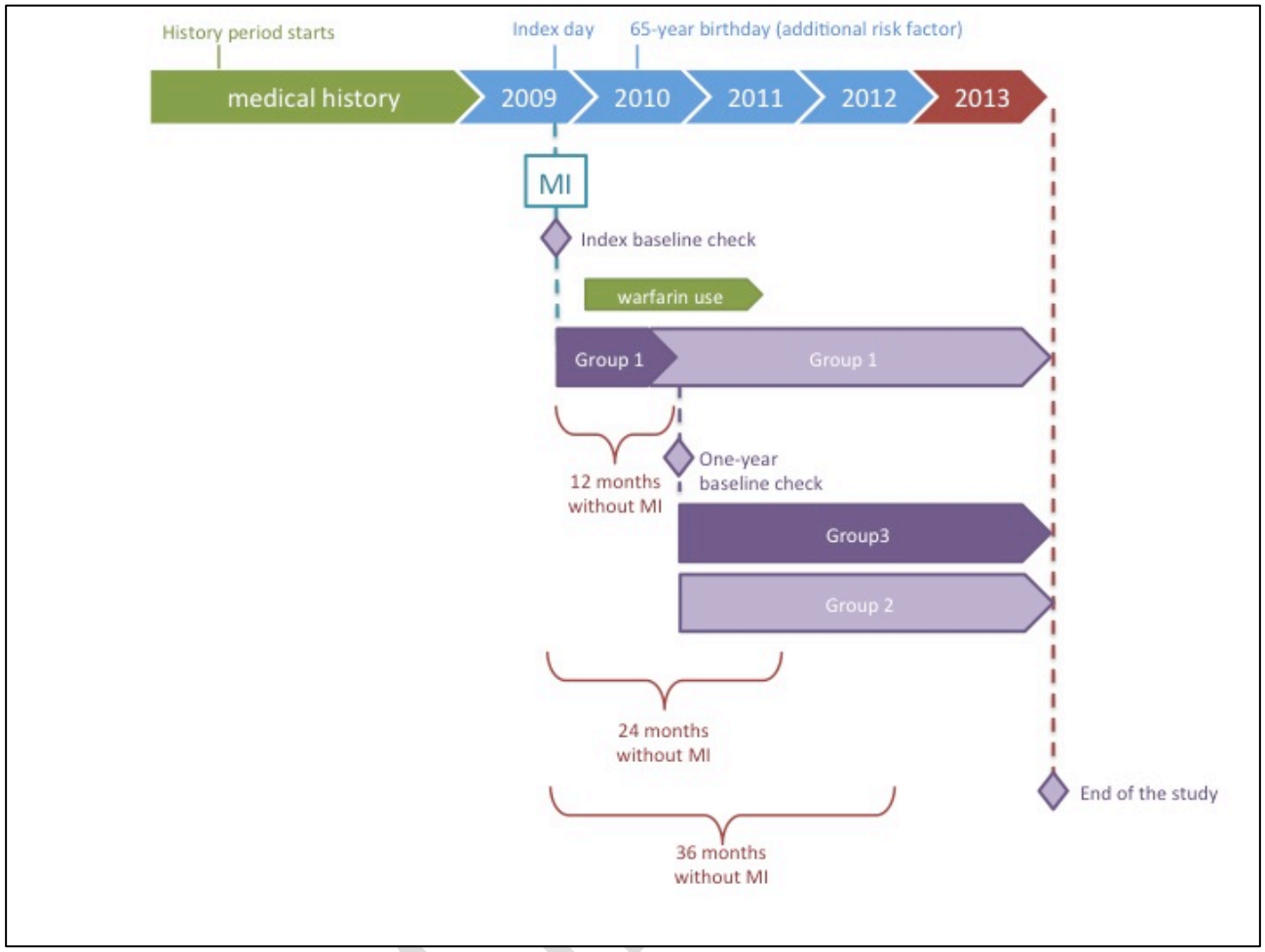
- Additional risk factor means at least one of the following: age ≥65 years, diabetes mellitus on medication, or ≥1 MIs, multivessel CAD or chronic renal dysfunction in the history (fixed 5 years history period before one year baseline).
- Anticoagulation medication here means warfarin, NOACs and LMWHs.
- Chronic use of anticoagulation means warfarin/NOAC/LMWH use for ≥3 months, which is still ongoing at one-year baseline.
- PEGASUS exclusion criteria at one year baseline check date are:
  - Use of OAPs
  - Bleeding disorder
  - Increased bleeding risk
  - History of ischemic stroke (during the fixed 5 years history period before one year baseline)
  - History of coronary-artery bypass grafting (CABG) (during the fixed 5 years history period before one year baseline)
  - Severe liver disease
  - Severe renal failure
- The membership of this group can start at one year after the index date.
- This patient group is mimicking the PEGASUS-TIMI 54 [10] study population.

Differences between the groups are listed in Table 1. An example of a patient who represents Group 1 from index date onwards and subsequently both Groups 2 and Group 3 from one year after the index date is presented in Figure 2. The contribution of the follow-up time of this example patient into the various groups is illustrated with light purple bars.

Table 1: Differences between the study groups in patient characteristics

Study group	Meets inclusion criteria	No MI or stroke 1 year after index day	Additional risk factor	No chronic anticoagulation	≥50 years	Meets Pegasus exclusion criteria
Group 1	✔					
Group 2	✔	✔				
Group 3	✔	✔	✔			
Group 4	✔	✔	✔	✔		
Group 5	✔	✔	✔	✔	✔	✔

Figure 2. An example of a patient representing Group 3 at one year after the index date



8.3 Variables

Table 2: Baseline variables of patient characteristics evaluated at index date

Variable name	Descriptions	Categories
Age	Age at index date	<18, 18-49, 50-64, 65-69, 70-74,75-79,80-84, ≥85
Gender		Male/Female
Type of index MI	ICD-10 I21.0-I21.3, I21.4, I21.9	STEMI/NSTEMI
Interventions associated with index event	NOMESCO classification for surgical procedures (NCSP) codes beginning with FN (defined based on the data)	Yes/No
Type of hospital	Type of hospital	Local hospital, central hospital, university hospital

Year of the index date	Calendar year of the index date	2009, 2010, 2011, 2012
Number of MIs in the history *	ICD-10 I21-I22	0, 1, 2, 3-4, ≥5 (defined based on the data)
History of arrhythmia *	ICD-10 I44-I49	Yes/No
Hypertension *	ICD-10 I10	Yes/No
Hyperlipidemia *	ICD-10 E78	Yes/No
Stroke (total) *	ICD-10 I61-64	Yes/No
Haemorrhagic stroke *	ICD-10 I61-I62	Yes/No
Ischemic stroke *	ICD-10 I63	Yes/No
Other stroke (not sub-classified)*	ICD-10 I64	Yes/No
Transient ischemic attack (TIA) *	ICD-10 G45	Yes/No
MI complications *	ICD-10 I23	Yes/No
Other acute ischaemic heart diseases *	ICD-10 I24	Yes/No
Heart failure *	ICD-10 I50	Yes/No
Atrial fibrillation *	ICD-10 I48	Yes/No
Unstable angina pectoris *	ICD-10 I20.0	Yes/No
Major bleedings *	ICD-10 D62, D68.3, I60, J94.2, K22.1, K22.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K63.1, K63.3, K92.0-K92.2, R04, R31, S06.4-S06.6	Yes/No
Bleeding disorder *	ICD-10 D66, D67, D68, D69	Yes/No
Prior cardiovascular interventions *	NCSP codes beginning with FN	Yes/No
Diabetes *	ICD-10 E10-E14	Yes/No
Chronic renal dysfunction *	ICD-10 I15.0, I15.1, N03, N04, N05, N11, N18, Q60, Q61	Yes/No
Chronic obstructive pulmonary disease *	ICD-10 J44	Yes/No
Dementia/Alzheimer's disease *	ICD-10 F00-F03, G30	Yes/No
Cancer diagnose *	ICD-10 C00-C99	Yes/No
Warfarin use	Anatomical Therapeutic Chemical (ATC) code	Yes/No

	B01AA03	
NOAC use	ATC B01AE, B01AF, B01AX02 , B01AX03, B01AX06	Yes/No
LMWH use	ATC B01AB04, B01AB05	Yes/No
Clopidogrel use	ATC B01AC04	Yes/No
Prasugrel use	ATC B01AC22	Yes/No
Ticagrelor use	ATC B01AC24	Yes/No
Nitrate use	ATC C01	Yes/No
Angiotensin-converting enzyme (ACE) inhibitor use	ATC C09A, C09B	Yes/No
Angiotensin II receptor blocker (ARB) use	ATC C09C, C09D	Yes/No
Beta-blocker use	ATC C07	Yes/No
Calcium channel blocker use	ATC C08	Yes/No
Statin use	ATC C10AA	Yes/No
Fibrate use	ATC C10AB	Yes/No
Insulin use	ATC A10A	Yes/No
Oral antidiabetic use	ATC A10B	Yes/No
Proton pump inhibitor use	ATC A02BC	Yes/No
Nonsteroidal anti-inflammatory drug (NSAID) use	ATC M01A (excluding glucosamine M01AX05)	Yes/No
Selective serotonin reuptake inhibitor use	ATC N06AB	Yes/No
Drugs causing interactions with OAPs	See separate table in Annex 4	Yes/No

* History for comorbidities is evaluated based on the 5-year period before index date.

Table 3: Primary outcome variables (time to first event)

Variable name	**Descriptions**
MI	ICD-10 I21-I22
Stroke (total)	ICD-10 I61-64
Cardiovascular mortality	Death due to ICD-10 I21-I22, I61-64, I50, I48, I20.0
Composite end-point	Deaths due to MI, stroke or cardiovascular mortality causes specified above

Overall mortality	Death from any cause

Table 4: Secondary outcome variables (time to first event)

Variable name	**Descriptions**
Heart failure	ICD-10 I50
Atrial fibrillation	ICD-10 I48
Unstable angina pectoris	ICD-10 I20.0
Major bleedings	ICD-10 D62, D68.3, I60, J94.2, K22.1, K22.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K63.1, K63.3, K92.0-K92.2, R04, R31, S06.4-S06.6

Table 5: Exploratory variables (time of event)

Variable name	**Descriptions**
STEMI	ICD-10 I21.0-I21.3
NSTEMI	ICD-10 I21.4, I21.9
Haemorrhagic stroke	ICD-10 I61-I62
Ischemic stroke	ICD-10 I63
Other stroke (not sub-classified)	ICD-10 I64
MI mortality	Death due to ICD-10 I21-I22
STEMI mortality	Death due to ICD-10 I21.0-I21.3
NSTEMI mortality	Death due to ICD-10 I21.4, I21.9
Haemorrhagic stroke mortality	Death due to ICD-10 I61-I62
Ischemic stroke mortality	Death due to ICD-10 I63
Other stroke (not sub-classified) mortality	Death due to ICD-10 I64
Other cardiovascular mortality (heart failure, atrial fibrillation, unstable angina pectoris)	Death due to ICD-10 I50, I48, I20.0
Cause specific mortality	Most common causes of death: ICD-10 codes (based on the data)

Table 6: Covariates measured at the time of outcome and at the one-year baseline.

Variable name	Descriptions	Categories
Warfarin use	ATC B01AA03	Yes/No
NOAC use	ATC B01AE, B01AF, B01AX02 , B01AX03, B01AX06	Yes/No
LMWH use	ATC B01AB04, B01AB05	Yes/No
Clopidogrel use	ATC B01AC04	Yes/No
Prasugrel use	ATC B01AC22	Yes/No
Ticagrelor use	ATC B01AC24	Yes/No
Nitrate use	ATC C01	Yes/No
ACE inhibitor use	ATC C09A, C09B	Yes/No
ARB use	ATC C09C, C09D	Yes/No
Beta-blocker use	ATC C07	Yes/No
Calcium channel blocker use	ATC C08	Yes/No
Statin use	ATC C10AA	Yes/No
Fibrate use	ATC C10AB	Yes/No
Insulin use	ATC A10A	Yes/No
Oral antidiabetic use	ATC A10B	Yes/No
Proton pump inhibitor use	ATC A02BC	Yes/No
NSAID use	ATC M01A (excluding glucosamine M01AX05)	Yes/No
Selective serotonin reuptake inhibitor use	ATC N06AB	Yes/No
Drugs causing interactions with OAPs	See separate table in Annex 4	Yes/No
Interventions during the follow-up	FN interventions (based on the data)	Yes/No
MI complications during the follow-up	ICD-10 I23	Yes/No
Other acute ischaemic heart diseases during the follow-up	ICD-10 I24	Yes/No
TIA during the follow-up	ICD-10 G45	Yes/No
Calendar year		2009, 2010, 2011, 2012, 2013

Table 7: Additional risk factors for characterisation of patients in Groups 3, 4 and 5

Variable name	Descriptions	Categories
Age ≥65 years	Age at one year baseline	Yes/No
Diabetes mellitus on medication	A least one antidiabetic drug treatment (ATC A10) ongoing at one year baseline	Yes/No
≥1 MIs	ICD-10 I21-I22 during the fixed 5 years history period before one year baseline	Yes/No
Multivessel CAD	I25.1 during the fixed 5 years history period before one year baseline	Yes/No
Chronic renal dysfunction	ICD-10 I15.0, I15.1, N03, N04, N05, N11, N18, Q60, Q61 during the fixed 5 years history period before one year baseline	Yes/No
Ischemic stroke	ICD-10 I63 during the fixed 5 years history period before one year baseline	Yes/No
Number of additional risk factors	Number of additional risk factors as a count evaluated from the fixed 5 years history period before one year baseline	0, 1, 2, 3-4, ≥5 (defined based on the data)

Table 8: Exclusion criteria used for defining Group 4 and Group 5

Variable name	Descriptions	Categories
Anticoagulation medication	ATC B01AA03, B01AE, B01AF, B01AX02, B01AX03, B01AX06, B01AB04, B01AB05	Yes/No
Use of OAPs	ATC B01AC04, B01AC22, B01AC22	Yes/No
Bleeding disorder	ICD-10 D66, D67, D68, D69	Yes/No
Increased bleeding risk	History (fixed 5 years) of intracranial bleeding, central nervous system tumor or intracranial vascular abnormality; GI bleeding within 60 days	Yes/No
History of ischemic stroke	ICD-10 I63 during fixed 5 years history period before one year baseline	Yes/No
History of coronary-artery bypass grafting	Interventions FNC or FND during fixed 5 years history period before one year baseline	Yes/No
Severe liver disease	ICD-10 K70.4, K71, K72, K73, K74, K76, K77, P78	Yes/No
Renal failure requiring dialysis	ICD-10 Z49, Z99.2	Yes/No

8.4 Data sources

Source registers used in the study and the relative register holders are presented in Table 9.

Table 9. Registers used in the study with the register holders and relevant register contents

Register	Register holder	Content
Finnish Hospital Care Register (HILMO)	National Institute for Health and Welfare	Diagnoses (incl. cancers *) Interventions Hospitalization periods
Social HILMO	National Institute for Health and Welfare	Institutionalization (other than hospitalization) periods
Prescription Register	Social Insurance Institution	Drug purchases Reimbursement statuses Place of domicile **
Causes of Death Registry	Statistics Finland	Time and causes of death

* The study will not include separate cancer registry

** For taking moving abroad during the follow-up period into account.

The variables related to different registers are listed in Annex 2.

Data permit process and data linkage:

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover the nationwide study. Data permits will be requested from each registry holder based on the study protocol and ethical approval. If the ethical approval is not received, EPID Research will not proceed with the permit process, and the study cannot be continued. Neither can the study be continued if any one of the register holders does not grant a permission to use the specific registry data.

The present PERSEUS study is a substudy from ER-9468 AZ THALIA study (A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA). In the THALIA study, the National Institute for Health and Welfare (THL) identified Finnish patients with unstable angina pectoris or myocardial infarction between 01 Jan 2009 and 31 Dec 2013. THL then converted the patient identification numbers (IDs) to study IDs (SIDs) and sent the IDs and the SIDs to Social Insurance Institution and Statistics Finland. The THALIA study population was formed, and the follow-up and history data requested as mentioned in Annex 3.

The study permit numbers for the THALIA study are as follows:

- National Institute for Health and Welfare: THL/522/5.05.00/2014
- Social Insurance Institution: Kela 21/522/2014
- Statistics Finland: TK-53-532-14

The present study is possible to be performed by using the existing data from the THALIA study. Thus there is no need for data extraction by the original register holders. EPID Research will be the register holder for the new, formed study database, and will also take the responsibility of destroying the data after the study.

8.5 Study size

Based on unpublished results from an on-going study by Prami *et al.* (A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA) the study population would consist of 44 000 patients with MI from 01 Jan 2009 to 31 Dec 2012.

8.6 Data management

R language (www.r-project.org, read 26 Jan 2015) will be used in data management for creating the analysis database and in statistical analysis for creating tabulations and graphics as well as in all statistical modeling. R language is described in more detail in report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.r-project.org/doc/R-FDA.pdf, read 26 Jan 2015. Full audit trail starting from raw data obtained from register holders and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses is kept for inspection for five years after publication of results. The study may be inspected by the sponsor's independent representative(s), scientific committee, or by the competent authorities.

All study data and supporting documents will be retained for five years after the end of the study and then destroyed. As the register holder of the study register, EPID Research is in charge of archiving and deleting the data. Secure archives will be maintained for the orderly storage and retrieval of all study related material. An index shall be prepared to identify the archived contents and their locations. Access to the archives will be controlled and limited to authorised personnel only.

Access to the study data cannot be given to any third parties, neither the study data can be used to other purposes than prescribed in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

8.7 Data analysis plan

A separate statistical analysis plan (SAP) including detailed statistical analysis outputs will be produced by EPID research before undertaking the analysis.

Observation period

The observation period is defined as the time from the index date to the date of death, 31 December 2013 or moving abroad, whichever occurs first.

For a particular endpoint the follow-up ends at the time of the endpoint, death, moving abroad or the end of year 2013 whichever occurs first.

Baseline co-morbidities

Baseline co-morbidities including previous interventions (Table 2) evaluated at the index date will be defined using all available data from the 5-year medical history period prior to index date.

Similarly, co-morbidities including previous interventions evaluated at the one-year baseline (Table 6) will defined using all available data from the 5-year medical history period prior to the baseline check date.

Baseline medication

The baseline medication (Table 2) use at index date will be defined using data from the 1-year medication history period prior to index date. Medications must be on going at the time of the index date.

Similarly, the medications evaluated at the one-year baseline (Table 6) will be defined using data from the 1-year medication history period prior to the baseline check date. The drug exposure must reach the baseline check day to be called on going.

For the antithrombotic drugs the duration of exposure will be reported during the previous year as well (even if not on going at the check date).

Drug exposure

For OAP medication, drug exposure is based on the number of tablets. The daily dosing is uniform for all patients: 2 tablets of ticagrelor (90 mg), 1 tablet of clopidogrel (75 mg) and 1 tablet of prasugrel (5 mg or 10 mg but not varying).

For other drugs, drug exposure starts at date of purchase. The duration of the exposure period is defined by the total amount purchased divided by the defined daily dose (DDDs) with the following adjustments:

- Treatment gaps up to 30 days are included as treatment time in a continuous treatment period.
- If a gap in drug exposure occurs during a hospitalization period and the drug exposure continues after discharge the gap is ignored.
- If the start of a gap in drug exposure occurs at time of institutionalization it is assumed that drug exposure continues during institutionalization.

Chronic use of anticoagulants in Group 4 and 5 definition means warfarin/NOAC/LMWH use for ≥3 months, which is still ongoing at the one-year baseline date (one year after the index date). The specific ATC codes for each medication are given below:

- warfarin ATC B01AA03
- NOACs: B01AE, B01AF
    - The following ATCs will be also taken into account due to ATC changes in groups B01AE and B01AF during the study period:
        - B01AX02 (desirudin)
        - B01AX03 (lepirudin)
        - B01AX06 (rivaroxaban)
- LMWHs: B01AB04, B01AB05

Multiple MI records

Multiple MI diagnoses in the hospital data following the index MI within a fixed time period are considered as one event. The time period will be defined in the SAP.

Missing data

If a variable is totally missing it is excluded from the analysis. If a variable is missing for only some of the patients a missing data category is added and used in the analysis.

8.7.1 Analysis of primary objectives

Objective a: Rates assessment for the primary outcomes

For Group 1, Kaplan-Meier estimates will be used to evaluate the survival rates during the first year following index date for the endpoints defined in Table 3. The analysis will be stratified by age, gender and other potential cardiovascular risk factors. The analysis will be described in detail in the SAP.

For Group 2-5, Kaplan-Meier estimates will be used to evaluate the survival rates:

- Between the one-year baseline check date and the end of study
- During the first year following the one-year baseline check
- During the second year following the one-year baseline check
- Two years after the one-year baseline check date and end of follow-up

for the endpoints defined in Table 3. The analysis will be stratified by age, gender and other potential cardiovascular risk factors. The analysis will be described in detail in the SAP.

Incidence rates with 95% confidence intervals (CIs) stratified by patients demographics, OAP use, bleeding disorder, increased bleeding risk, previous stroke, previous CABG, severe liver disease and severe renal failure will be estimated for the endpoints defined in Table 3 for all the study groups.

Objective b: Risk factors associated with the primary endpoints

Adjusted hazard ratio (HR) estimates with 95% CIs and P-values will be estimated separately for the outcomes defined in Table 3 using the conventional Cox's proportional hazards model adjusting for patients demographics, OAP use, bleeding disorder, increased bleeding risk, previous stroke, previous CABG, severe liver disease and severe renal failure, for all the study groups defined in section 8.2.2.

The proportional hazards assumption will be checked for the adjusting covariates, the checks will be performed by plotting the log (-log (survival)) vs. log (time) curves for the categories in each variable.

Objective c: Study population description

For the study groups defined in section 8.2.2 all continuous variables will be described using standard statistical measures, i.e. number of observations, mean, standard deviation, median, first and third quartile. All categorical variables will be summarized with number of observations and percentages in each category.

For the additional risk factors (Table 7), a separate table will be produced to describe the proportion of patients presenting each risk factor separately.

8.7.2 Analysis of secondary objectives

Objective d-e: Rates assessment for the secondary endpoints
For Group 1, Kaplan-Meier estimates will be used to evaluate the survival rates during the first year following index date for the endpoints defined in

Table 4. The analysis will be stratified by age, gender and other potential cardiovascular risk factors.

For Group 2-5, Kaplan-Meier estimates will be used to evaluate the survival rates:

- Between the one-year baseline check date and the end of study
- During the first year following the one-year baseline check
- During the second year following the one-year baseline check
- Two years after the one-year baseline check date and end of follow-up

for the endpoints defined in

Table 4. The analysis will be stratified by age, gender and other potential cardiovascular risk factors.
Incidence rates with 95% CIs stratified by patients demographics, OAP use, bleeding disorder, increased bleeding risk, previous stroke, previous CABG, severe liver disease and severe renal failure will be estimated for the endpoints defined in

Table 4 for all the study groups.

Objective f: prevalence of increased bleeding risks

The proportion of patients with increased bleeding risks i.e. a history (fixed 5 years) of intracranial bleeding, central nervous system tumour or intracranial vascular abnormality; GI bleeding within 60 days will be described at cohort entry date for Group 1 and at the one year baseline check date for Group 2, 3 and 4.

8.7.3 Analysis of exploratory objectives

Objective g: Distribution of sub-events

The cumulative proportion of patients with MI, stroke, cardiovascular mortality and overall mortality will be reported during the first 7 days, 30 days, 3 months, 6 months, 9 months, 12 months, 24 months and 36 months after index date.

Events will be sub-classified as follows:

- MI: STEMI, NSTEMI
- Stroke: Haemorrhagic stroke, ischemic stroke, other stroke (not sub-classified)
- Cardiovascular mortality: MI mortality, STEMI mortality, NSTEMI mortality, stroke mortality (total), haemorrhagic stroke mortality, ischemic stroke mortality, other stroke (not sub-classified) mortality, other cardiovascular mortality (heart failure, atrial fibrillation, unstable angina pectoris)
- Overall mortality: Cause specific mortality (most common causes of death).

8.7.4 Additional analysis

Attrition rate

The proportion of patients assigned to Group 4 and 5 at the one-year baseline check who are not fulfilling the inclusion criteria after that will be described over time starting from the one-year baseline check date until the end of study.

For Group 4, the proportion of patients with a chronic use of anticoagulants after the one-year baseline check will be presented over time starting from the one-year baseline check until the end of study.

For Group 5, the proportion of patients with a chronic use of anticoagulants and/or with at least one of the PEGASUS exclusion criteria after the one-year baseline check will be presented over time starting from the one-year baseline check until the end of study.

8.7.5 Sensitivity analyses

Adjusted HR estimates with 95% CIs and P-values will be estimated for the main outcomes using the conventional Cox's proportional hazards model adjusting for the covariates presented in Table 8 of section 0 as time dependent variables.

Analysis results for the primary objectives will be reported including only patients with a five-year MI clear history before the index MI.

8.8 Quality control

The study will be conducted as specified in this protocol. All revisions to the protocol must be approved by the sponsor, the principal investigator and the co-authors of the study. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to register holders.

The study protocol has been written by following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, ENCePP (www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_Rev3.pdf, read 26 Jan 2015). The protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (www.pharmacoepi.org/resources/guidelines_08027.cfm, read 26 Jan 2015).

The study protocol will be registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp, read 26 Jan 2015). Study results will also be published in ENCePP pages.

About storage of records and archiving of the statistical programming performed to generate the results, and possible audits, see section 8.6. Due to the study type (register study using administrative databases) on-site monitoring will not be performed.

8.9 Limitations of the research methods

Coverage of the Prescription Register containing reimbursement information about all permanent residents of Finland is about 97%. Missing data includes relatively inexpensive packages and over the counter medications that are not reimbursed. This leads to under-recording of e.g. ASA and NSAID use.

Medications used during hospitalizations are not available. However, based on the hospital care register the hospitalization periods can be taken into account to define gaps in the drug treatment periods. Also moving abroad or institutionalization during the follow-up period will be taken into account.

In clinical trials the drug treatment of interest is fixed, and if a patient changes from one treatment to another (as from placebo to clopidogrel in PEGASUS-TIMI 54 [10] study) the treatment modification is well controlled and documented. In our study the subgroups (including Group 5 mimicking PEGASUS) are defined at one year after the index day and membership of the groups does not change over time. Anticoagulation treatment (also part of the inclusion and exclusion criteria for Group 3-4) may, however, change. These types of sources of bias are taken into account in sensitivity analyses and group specific attrition analysis.

In our study patients enter the cohort at the time of the index MI during the study period and the study groups (including Group 5 mimicking PEGASUS) are defined at one year (fixed for all) after the index MI. In PEGASUS-TIMI 54 a patient is recruited to the study 1-3 years after an MI. To make the present study setting more comparable, in addition to one-year analysis, we run analyses in patients surviving 24 and 36 months without subsequent MIs.

Our study is based on nationwide administrative registers. Primary care data and hospital clinical data (weight, smoking, blood pressure etc.) are not available for this study, thus proper baseline risk cannot be estimated. In the PEGASUS-TIMI 54, the collection of baseline variables (e.g. body mass index) was more complete and of better quality. Of the inclusion criteria, the data quality is poor for multivessel CAD as there are no specific ICD-10 codes for different CAD types. Of the exclusion criteria for increased risk of bleeding in PEGASUS-TIMI 54, the variables “intracranial or spinal cord surgery within 5 years” and “major surgery within 30 days” are not available, as the data request is based on the data produced for THALIA study including the NCSP codes for coronary artery interventions only.

9 Protection of human subjects

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

EPID Research will receive pseudonymized data including SIDs only. EPID Research employees have undertaken professional secrecy and are aware of their concern with the Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the register holders). The study registers are formed on the basis of the Personal Data Act (523/1999) §12 and the data is handled as described in §14 therein.

The sponsor will not have access to the patient level data at any time and sponsor’s representation in the scientific committee does not repeal this principle.

The protocol will be subjected to Ethics Committee of Hospital District of Helsinki and Uusimaa for review and approval. Register notification of the forming study registers will be sent to the Office of the Data Protection Ombudsman.

10 Management and reporting of adverse events/adverse reactions

This study does not meet the criteria for adverse event reporting.

11 Plans for disseminating and communicating study results

The principal investigator together with the co-investigators will write a study report. This report will be delivered to the sponsor and members of the scientific committee.

An abstract of the study findings will be provided through the ENCePP e-register of studies within three months following the final study report. According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results. The abstract of the main results of the study will be published, whether positive or negative. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

Based on the study report, the principal investigator and co-investigators with co-authors (members of the scientific committee and possible other contributors approved by the scientific committee) will prepare (a) scientific manuscript(s) for academic publication. The scientific committee decides the publication forums.

The sponsor is entitled to view the final results prior to submission for publication. The sponsor also has the right to comment the results and interpretations thereof without unjustifiably delaying the publication. In this particular study the commenting time for the sponsor during the review rounds is agreed to be maximum of one month. Possible changes in the presentations must be based on scientific reasons only. The scientific committee is free not to take the comments of the sponsor into account. The principal investigator and the sponsor are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors, ICMJE. It is stated that each author should have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html, read 27 Jan 2015). The sponsor acknowledges that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to employees of the sponsor.

12 References

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13 Approvals

We have reviewed this study protocol (ER-9502 Version 1.0, dated 02 April 2015) and agree to its terms by signing it.

Principal investigator:

Signature Date

Tuire Prami
EPID Research, Metsänneidonkuja 12, FI-02130 Espoo

Medical experts of the scientific committee:

Signature Date

Juhani Airaksinen
Turku University Hospital, P.O. Box 52 FI-20521 Turku

Signature Date

Eeva Reissell
THL, P.O. Box 30 FI-00271 Helsinki

Signature Date

Ville Kytö
Turku University Hospital , P.O. Box 52 FI-20521 Turku

On behalf of the sponsor:

Signature Date

Susanne Skovgaard Nickelsen, MD VP Medical/Regularory AstraZeneca Nordic-Baltic
Medical Nordic-Baltic, AstraZeneca Nordic-Baltic, Arne Jacobsens Allé 13 DK-2300 Copenhagen S Denmark

Annex 1. List of stand alone documents

- ENCePP checklist for study protocols.

Annex 2. Variable lists according to data sources

The National Institute for Health and Welfare (THL)

The population identification will be based on THL data of patients with myocardial infarction (ICD-10: I21) between 01 Jan 2009 and 31 Dec 2012 in the HILMO register.

History and follow-up information (years 2004-2013) is also based on the HILMO register. The raw data includes:

- All diagnoses (ICD-10 codes and dates)
- Interventions with a NCSP code beginning with FN (and dates)
- Hospitalization periods (starting and stopping days)

For follow-up (years 2009-2013) the data from the Social HILMO register is used about

- Institutionalizations (starting and stopping days)

The above-mentioned data include the information about the patient (SID codes created by THL, age and gender) and the hospital.

The Social Insurance Institution

The data originating from the Social Insurance Institution includes information about

- Drug purchases from years 2008-2013 (including one year history)
- Reimbursements statuses from years 2004-2013 (including five years history)
- Place of domicile if abroad at the end of the years 2009-2013

Statistics Finland

For the identified population data about deaths will be used as follows:

- Date of death
- Causes of death (all levels)

Data sent to EPID Research includes SIDs only.

The present study is possible to be performed by using the existing data for the THALIA study (ER-9468: A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA). Thus there is no need for data extraction by the original register holders.

Annex 3. Data extraction and delivery in THALIA study

THL identified the population with unstable angina pectoris (ICD-10: I20.0) or myocardial infarction (ICD-10: I21-I24) between 01 Jan 2009 and 31 Dec 2013 in the HILMO register.

For history and follow-up information (years 2004-2013) THL delivered the data from the HILMO register about

- All diagnoses (ICD-10 codes and dates)
- Interventions with a NCSP code beginning with FN (and dates)
- Hospitalization periods (starting and stopping days)

For follow-up (years 2009-2013) the data from the Social HILMO register about

- Institutionalizations (starting and stopping days)

The above-mentioned data included the information about the patient (SID codes created by THL, age and gender) and the hospital.

THL converted the patient IDs to SIDs and sent the ID – SID pairs to other register holders: Social Insurance Institution and Statistics Finland. The data sent to EPID Research included SIDs only.

For the population identified in THL the Social Insurance Institution shall deliver the data about

- Drug purchases from years 2008-2013 (including one year history)
    - ATCs (restricted list)
    - Purchase dates
    - VNR numbers
    - Package sizes
    - Number of packages
    - Total amount purchased in defined daily doses
- Reimbursements statuses from years 2004-2013 (including five years history)
    - Reimbursement decisions with reimbursement codes (restricted list) with ICD-10 codes
    - Starting and stopping dates
- Place of domicile if abroad at the end of the years 2009-2013

Data sent to EPID Research will include SIDs only.

For the population identified in THL Statistics Finland delivered the data about deaths:

- Date of death
- Causes of death (all levels)

Data sent to EPID Research will include SIDs only.

The study permit numbers for the THALIA study are as follows:

- National Institute for Health and Welfare: THL/522/5.05.00/2014
- Social Insurance Institution: Kela 21/522/2014
- Statistics Finland: TK-53-532-14

Annex 4 Drug-drug interactions of OAPs

Annex table 1: Class C and D drug-drug interactions of ticagrelor, clopidogrel and prasugrel listed in the SFINX interaction database [12] sited online on 18 Jun 2014

ATC1	ATC2	ATC3	ATC4	ATC5	ATC6	IA drug	TICAGRELOR	CLOPIDOGREL	PRASUGREL
M01AB16						aceclofenac	C0	C0	C0
M01AB11						acemetacin	C0	C0	C0
A01AD05	B01AC06	N02BA01	M01BA03	B01AC56	N02BA51	acetylsalicylic acid	C0		C3
N02BA71	C10BX02	C10BX05	C10BX01	C10BX04		*acetylsalicylic acid (cont.)*	*C0*		*C3*
C01BD01						amiodarone	C0		
J05AE08						atazanavir	D0		
N06AX12						bupropion		C3	
N03AF01						carbamazepine	D0		
L01XX33	M01AH01					celecoxib	C0	C1	C0
L04AD01						ciclosporin	C0		
A02BA01	A02BA51					cimetidine		D0	
N06AB04						citalopram	C2	C0	
J01FA09	A02BD06	A02BD07	A02BD05	A02BD04		clarithromycin	D0		
N06AA04						clomipramine	C0	C0	C0
L01XE16						crizonib	D0		
L01AA01						cyclophosphamide		C0	
B01AE07						dabigatran	C0		

J05AE10						darunavir	D0		
M01AE14						dexibuprofen	C0	C0	C0
M01AE17						dexketoprofen	C0	C0	C0
M01AB05	M01AB55					diclofenac	C0	C0	C0
C01AA05						digoxin	C3		
C08DB01						ditiazem	C3		
N06AX21						duloxetine	C0	C0	C0
J05AG03	J05AR06	J05AR11				efavirenz	D0		
L02BB04						enzalutamide	C0		
J01FA01						erythromycin	D0		
N06AB10						escitalopram	C2	C0	C0
B01AC56	A02BC05	A02BD06	M01AE52			esomeprazole		D4	C0
M01AB08						etodolac	C0	C0	
M01AH05						etoricoxib	C0	C0	C0
J02AC01						fluconazole		C0	
N06AB03	N06CA03					fluoxetine	C2	C0	C0
M01AE09	R02AX01					flurbiprofen	C0	C0	C0
S01BC04	M02AA19					flurbiprofen (topical)			C0
N06AB08						fluvoxamine	C0	C0	C0
J05AE07						fosamprenavir	D0		
C01EB16	M01AE01	M01AE51				ibuprofen	C0	C0	C0

J05AE02						indinavir	D0		
C01EB03	M01AB01	M01AB51				indometacin	C0	C0	C0
L01XC11						ipilimumab	C3	C3	C3
J02AC02						itraconazole	D0		
M01AA06						kebuzone	C0	C0	C0
J02AB02						ketoconazol	D3		
M01AE03	M01AE53					ketoprofen	C0	C0	C0
M01AB15						ketorolac	C0	C0	C0
B01AE02						lepirudin		C0	
J05AR10						lopinavir	D0		
M01AC05						lornoxicam	C0	C0	C0
M01AH06						lumiracoxib	C0	C0	C0
M01AG04						meclofenamic acid	C0	C0	C0
M01AG01						mefenamic acid	C0	C0	C0
M01AC06	M01AC56					meloxicam	C0	C0	C0
N02BB02	N02BB52	N02BB72				metamizole	C0	C0	C0
N05CD08						midazolam (per oral)	C3		
N06AX17						milnacipran	C0	C0	C0
L01XX23						mitotane	C0		
N02AA01	N02AG01	A07DA52	N02AA51			morphine		C3	
M01AX01						nabumetone	C0	C0	C0

M01AE02	M01AE52	M01AE56				naproxen	C0	C3	C0
J05AE04						nelfinavir	D0		
M01AX02						nifluminic acid	C0	C0	C0
M01AX17						nimesulide	C0	C0	C0
A02BC01	A02BD05	A02BD01				omeprazole		D4	
M01AH04						parecoxib	C0		C0
N06AB05						paroxetine	C2	C0	C0
N03AA02						phenobarbital	D0		
M01AA01	M01BA01					phenylbutazone	C0	C0	C0
N03AB02	N03AB52					phenytoin	D0		
M01AC01						piroxicam	C0	C0	C0
J02AC04						posaconazole	D0		
N03AA03						primidone	D0		
M01AB14						proglumetacin			C0
C01BA01	C01BA51	C01BA71				quinidine	C0		
P01BC01	M09AA72					quinine	C0		
J04AB02	J04AM02	J04AM05	J04AM06			rifampicin	D3		
J04AB03						rifamycin	D3		
J05AR10	J05AE03					ritonavir	D0		C3
M01AH02						rofecoxib	C0	C0	C0
J05AE01						saquinavir	D0		

N06AB06						sertraline	C2	C0	C0
A08AA10						sibutramine		D3	
C10AA01	C10BX01	C10BA02	C10BA04	C10BX04	A10BH51	simvastatin	C3		
M01AB02						sulindac	C0	C0	
J01FA15						telithromycin	D0		
M01AC02						tenoxicam	C0	C0	C0
M01AE11						tiaprofenic acid	C0	C0	C0
J05AE09						tipranavir	D0		
M01AG02						tolfenamic acid	C0	C0	C0
N02AX02	N02AX52					tramadol	C0	C0	C0
J01FA08						troleandomycin	D0		
M01AH03						valdecoxib	C0	C0	C0
N06AX16						venlafaxin	C0	C0	C0
C09BB10	C08DA01	C08DA51				verapamil	D0		
J02AC03						voriconazole	D0	C0	
B01AA03						warfarin		C3	