Non-Interventional Study Report

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A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA

Prepared for AstraZeneca Nordic Baltic by EPID Research

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACE	angiotensin-converting enzyme
ACS	acute cororary syndrome
ASA	acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical
CABG	coronary artery bypass grafting
CCI	Charlson Comorbidity Index
DAPT	dual antiplatelet treatment
DDD	defined daily doses
HILMO	Finnish Hospital Care Register
ICD-10	International classification of diseases, 10th revision
ID	patient identification number
MI	myocardial infarction
MPR	medication possession rate
NCSP	NOMESCO classification for surgical procedures (see NOMESCO)
NOMESCO	Nordic Medico-Statistical Committee
NSTEMI	non-STEMI (see STEMI)
PCI	percutaneous coronary intervention
PPI	proton pump inhibitor
SAP	Statistical Analysis Plan
SID	study IDs (see ID)
STEMI	ST elevation MI (see MI)
THL	The National Institute for Health and Welfare

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STUDY REPORT SUMMARY (ABSTRACT)

A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA

Rationale and objectives: Myocardial infarction (MI) affects about 5000 patients in Finland per year. Almost 20% of them die within one year after the event. Dual antiplatelet treatment with low dose acetylsalicylic acid and oral antiplatelet (OAP) is recommended for patients with acute coronary syndromes. New OAPs have recently been introduced in the market in the Nordic countries. How these multiple OAP treatment options are used in real life clinical practice is not well established. The aims of this study were to characterize OAP and non-OAP treated patients, and describe duration, discontinuation rates, switch patterns and medication possession rates of OAP treatments.

Methods: This was a retrospective observational database linkage study using data from different nationwide registers in Finland. The cohort consisted of patients hospitalized for unstable angina pectoris or acute MI alive at discharge in 2009-2013. The patients were classified as clopidogrel, prasugrel or ticagrelor (OAP) users or non-OAP treated based on their drug purchases within seven days after the hospital discharge.

Results: The study cohort consisted of 54 754 patients. The most common reason for inclusion was non-ST elevation MI (NSTEMI, 39%). The OAP-treated patients were invasively treated in 78% and non-OAP-treated in 33% of the cases. In total, 49% of the patients were OAP-treated and 90% of them made the first OAP purchase within one day after the discharge. The patients were older (mean 76 years) in the non-OAP-treated group compared with OAP-treated patients (mean 68 years), and they also had more underlying diseases such as hypertension. The mean follow-up time in the study was 2.2 years and the most common cause of death during the follow-up was chronic ischemic heart disease.

The treatment persistence in ticagrelor and prasugrel groups showed a clear discontinuation trend at one year after OAP initiation. For clopidogrel the discontinuations occurred also at 1, 3 and 6 months. On the other hand, in the clopidogrel group there were more patients receiving more than 12 months of the treatment. Of the index events STEMI was associated with highest treatment persistence, and during the first year the persistence was slightly higher in invasively-treated patients. The persistence decreased along the age and was slightly higher in men than in women. There were no differences in the discontinuation rates during the study period associated with cohort entry years.

The mean medication possession rate (MPR) in the OAP treated population was 99%. The number of switches between OAPs or from no treatment to treatment was low. Statins were initiated to 92% and beta-blockers to 90% of the OAP users without these medications at baseline.

Conclusions: The OAP users showed good compliance with immediate initiation and extremely high MPR of their medication. Their treatment followed the clinical practice guidelines in terms of using the OAP for 12 months and having statin and beta-blocker in the regimen. The proportion of non-OAP users was, however, high and under-treatment then present.

AMENDMENT HISTORY

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
11 Jun 2015	MI definition in inclusion criteria changed from ICD-10 I21-I24 to ICD-10 I21.	Amendment decided among investigators because only STEMI (ICD-10 I21.0-121.3), NSTEMI (I21.4) and unspecified acute MI (I21.9) were considered as acute MIs. ICDs I22-I24 were few in the source data.
11 Jun 2015	Inclusion period changer from 01 Jan 2009 - 31 Dec 2013 to 01 Jan 2009 - 15 Dec 2013.	Amendment decided among investigators because originally not all patients had possibility to become a user within 7 days.
11 Jun 2015	Age under 18 at hospital admission for acute coronary syndrome named as an exclusion criterion. (Originally no exclusion criteria were listed.)	Amendment decided among investigators based on the preliminary results showing some newborns to be including in the study population.
12 May 2015	Cardiovascular morbidity during follow-up associated with OAP medication discontinuation or prolongation for any OAP together or for each study OAP separately, mentioned in the study protocol v. 2.0 chapter 8.7, will not be described.	Considered to be safety analysis (and this is a descriptive drug utilization study) by EPID study team.
12 May 2015	OAP reuptake after discontinuation mentioned in study protocol version 2.0 dated 03 July 2014 “In case of a restart of OAP treatment after a > 30 days treatment gap the data will be analysed separately from the original treatment period.” was left out form the analyses.	This decision was made in order to avoid multiple index dates in one patient by EPID study team.
12 May 2015	Definitions for treatment discontinuation/duration developed after study protocol version 2.0 dated 03 July 2014. - Treatment gaps up to 30 days are included as treatment time in a continuous treatment period with no gap in the exposure.	Clarification and changes were made based on a desicion by EPID study team.

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
12 May 2015	Definitions for calculating medication possession period developed after study protocol version 2.0 dated 03 July 2014. - If a hospitalisation or an institutionalization of more than 7 days occurs, time between the admission and the next drug purchase is removed from the medication possession period, and treatment days resulting from the remaining tablets from the previous purchase are removed from number of treatment days. - Drug purchases occurring during hospitalizations or institutionalization of more than 7 days are ignored.	Clarification and changes were needed to calculate MPS as exact as possible. The decision was made by EPID study team.
09 Sep 2014	The concomitant medication not only at baseline but also after the index date was decided to be described.	Amendment decided among investigators.
09 Sep 2014	Treatment prolongation was defined as a treatment duration exceeding 12 months from the first OAP initiation. This was decided to be described by the baseline characteristics, prior comorbidities and concomitant medication use.	Amendment decided among investigators.

All the analysis mentioned in the SAP version 2.1 dated 22 Jun 2015 were performed and the conformable result tables are available in Appendix 2.

MILESTONES

Date	Milestone
Jan 2014	Signing Study Agreement
Mar 2014	Study Protocol version 1.0
	Ethics committee application sent.
	Study permit applications sent
Apr 2014	ENCePP registration accepted
May 2014	Conditional approval received from Ethics Committee
	Recruitment of the medical steering members completed
Jul 2014	Study Protocol version 2.0
	Final Ethics Committee approval
Sep 2014	Data permit approval process completed
	Data requests sent
Dec 2014	Statistical Analysis Plan version 1.0
	Register notification sent to the Data ombudsman
May 2015	Data collection completed
	Statistical Analysis Plan version 2.0
Jun 2015	Statistical Analysis Plan version 2.1
Jul 2015	Analysis dataset ready
Aug 2015	Analyses completed

1. BACKGROUND AND RATIONALE

1.1 Background

The prevalence of coronary artery disease is more than 50 000 patients in Finland with almost 70 000 attacks per year [1]. According to the PERFECT study performed by the National Institute for Health and Welfare (THL) the incidence of new myocardial infarction (MI) cases was 269 per 100 000 inhabitants in Finland during the years 2008-2010. MI affected then nearly 5000 new patients every year. Of these patients 6.7% died within 7 days and 19% within one year from the MI. Up to 40% of the MI patients were treated with percutaneous coronary intervention (PCI). [2] Acute MIs can be divided into three categories according to ST segment elevation: ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unspecified MIs. Corresponding ICD-10 code groups are I21.0-I21.3, I21.4 and I21.9, respectively.

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. Recurrent ischemic events are still quite frequent after MI, while sudden cardiac death is less common [4]. However, the incidence of these events has declined over time that supports the notion that contemporary treatments effectively improve outcomes after MI.

Dual antiplatelet treatment (DAPT) with low dose acetylsalicylic acid (ASA) and oral antiplatelet (OAP) is recommended for patients with acute coronary syndromes (ACS) whether treated invasively or non-invasively. Guidelines recommend DAPT inhibition to be maintained up to over 12 months unless contraindications are present, such as a high risk of bleeding [5,6].

1.2 Rationale

New OAPs have recently been introduced in the market for treatment of ACS patients in the Nordic countries Denmark, Finland, Norway and Sweden. How the multiple OAP treatment options are used in real life clinical practice is not known regarding:

- Patient selection for different OAP treatments and no OAP treatment
- Persistence of OAP treatments
- Switch pattern of OAP treatments
- Patient adherence to OAP treatments

Parallel studies have been conducted in Sweden, Norway and Denmark therefore it will be feasible to compare the results from four Nordic countries in near future.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objectives

1. To characterize and describe patients treated with OAP vs. non-OAP treated patients
2. To characterize and describe different OAP treatment patterns
3. To characterize and describe switch patterns of OAP treatments
4. To characterize and describe discontinuation rates of OAP treatments
5. To characterize and describe medication possession rate of OAP treatments

3. METHODOLOGY

3.1 Study Design

This was a retrospective observational database linkage cohort study using patient level data from different nationwide registers in Finland.

3.1.1 Data Sources

Original register sources used in the study and the relative register holders are presented in Table 1.

Table 1. 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 Special reimbursement statuses Place of domicile **
Causes of Death Registry	Statistics Finland	Time and causes of death
* Information on cancers will only be obtained through HILMO and not through the Finnish cancer registry ** For taking moving abroad during the follow-up period into account.		

3.1.2 Data Permit Process

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) was requested to cover the nationwide study. The approval was conditional until the study group gave further clarifications to the application. The first criterion was to name medical experts for the study group. Study protocol version 2.0 was written according to the clarification requests and the ethical approval was then received. The journal number for this approval was 131/13/03/00/14.

Data permits were applied from each registry holder separately. The approval journal numbers were:

- 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

3.1.3 Data Linkage and Management

Patients hospitalised for unstable angina pectoris or myocardial infarction and discharged from hospital between 01 Jan 2009 and 31 Dec 2013 were identified by The National Institute for Health and Welfare (THL). THL then converted the patient identification numbers (IDs) to study IDs (SIDs) and send the IDs and the SIDs to other register holders: Social Insurance Institution and Statistics Finland. All the three register holders then mined the study data based on the variable lists presented in the Annex 2 in study protocol version 2.0 and sent the raw data to EPID Research without IDs (including SIDs only).

R language [7] was used for data management and creating the analysis database, and in statistical analysis for creating tabulations and graphics as well as in all statistical modelling.

3.2 Study Population

Finnish adult patients hospitalized for unstable angina pectoris or acute MI alive at discharge in 2009-2013. The study cohort of 54 754 patients was formed according to inclusion and exclusion criteria from a source population of 64 530 patients (see Figure 5).

Population definitions

The OAP treated populations were defined as follows:

- OAP treated patients: ACS patients initiated with one of the study OAPs within 7 days after the index date.
    - Clopidogrel treated patients: ACS patients initiated on clopidogrel within 7 days after index date.
    - Prasugrel treated patients: ACS patients initiated on prasugrel within 7 days after index date.
    - Ticagrelor treated patients: ACS patients initiated on ticagrelor within 7 days after index date.

The non-OAP treated population is defined as follows:

- ACS population dispatched without any OAP within 7 days after the index date.

3.2.1 Definitions Related to Index Event

ACS Event

In this study ACS event referred to the any diagnosis of unstable angina pectoris (ICD-10: I20.0) or MI (ICD-10: I21) in hospital data.

Index event date

The date of the first registered admission to hospital for ACS with a discharge date between 01 January 2009 and 15 December 2013.

Index date

The discharge date after the first registered admission to hospital for ACS between 01 January 2009 and 15 December 2013 was called index date.

If a transfer between two hospitals happened on the same day, that day was not counted as an index date but the hospitalization due to the index event continued. The index date was then the one at actual discharge.

Type of ACS index event

All hospitalizations between the index event date and index date were used to identify the type of ACS event. If more than one ACS diagnosis was registered the following order of priority was used:

- STEMI
- NSTEMI
- Unspecified acute MI
- Unstable angina pectoris

Time spent in hospital

Time spent in hospital was defined as the time difference between the index event date and the index date. If a transfer between two hospitals happened on the same day, it was not counted as a new hospitalization.

Observation Period

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

OAP initiation

A patient is defined to receive OAP for unstable angina pectoris or MI if a ticagrelor, clopidogrel or prasugrel prescription is filled within 7 days after index date.

For patients on one of the study OAPs within three months prior to the index date, the two closest OAP purchases within 3 months before and after the index date were compared, and if the purchases in question were of the same OAP, the patient was considered as an OAP-user at index date even without a purchase within 7 days after the discharge.

Baseline medication

Baseline medication use was searched for 120 days prior to index event date. Only on-going medication was taken into account. I.e. drug exposure in defined daily doses (DDDs) had to cover the index event date.

Baseline co-morbidities

Co-morbidity events were searched 5 years prior to index event date.

The above-mentioned definitions related to the index event are explained also in Figure 1.

3.3 Inclusion Criteria

Study population consisted of patients discharged alive from Finnish hospitals following admission for unstable angina pectoris (ICD-10: I20.0) or myocardial infarction (ICD-10: I21) between 01 Jan 2009 and 15 Dec 2013.

3.4 Exclusion Criteria

Age less than 18 years at hospital discharge for acute coronary syndrome.

One patient with an OAP prescription within 7 days after discharge was excluded from the cohort, as the treatment duration was 0 days meaning a death the same day of first OAP purchase date.

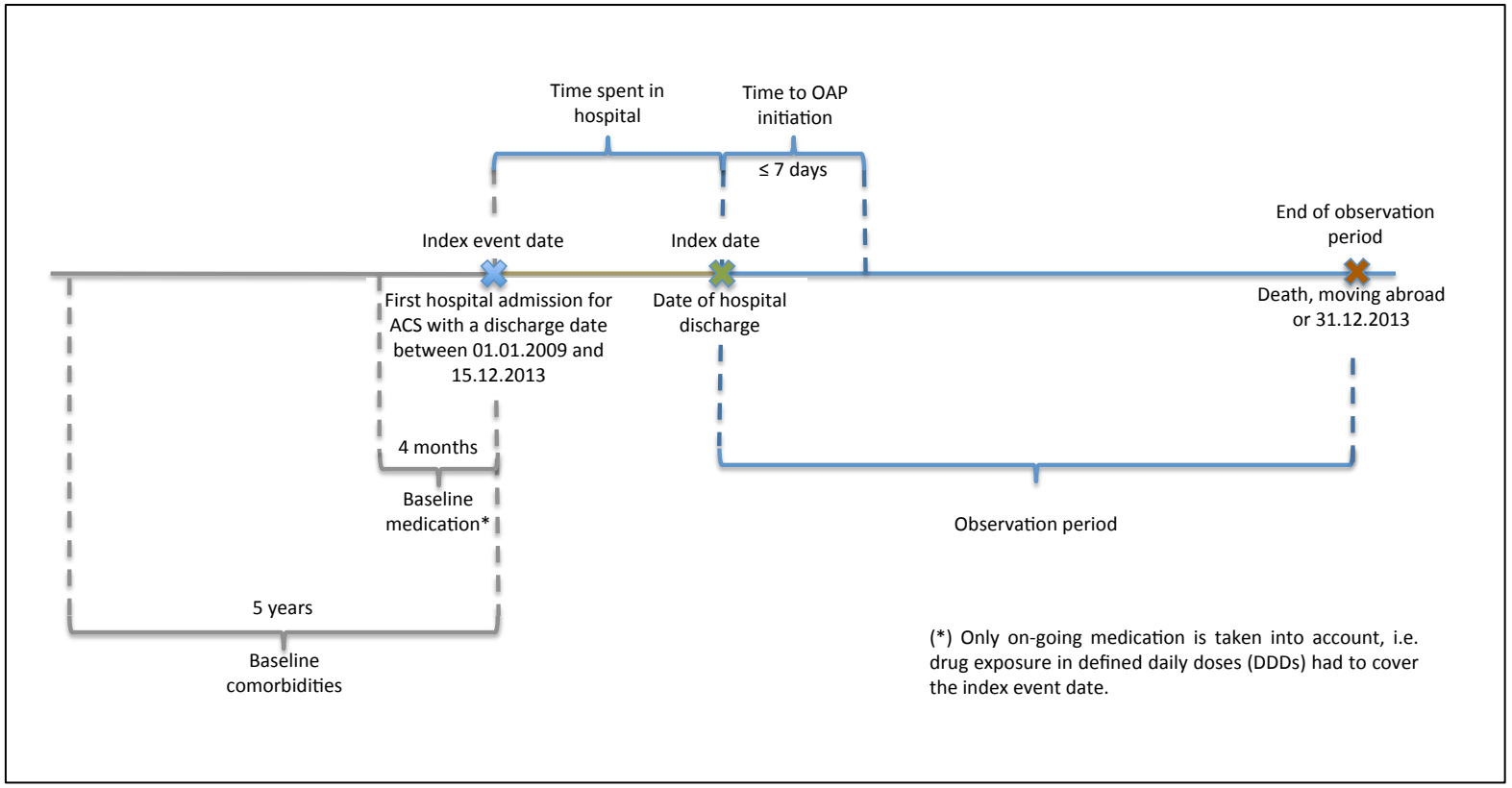


Figure 1 Definitions related to the index event date

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

Operational definitions developed during the study are listed in the chapter Amendment History.

Demographic variables used in this study were age at index date in years (<50, 50-64, 65-69, 70-74, 75-79, 80-84, 85+) and sex (male, female).

ACS index events and interventions related to the ACS event were identified in the hospitalization data and divided into groups by ICD-10 and NCSP codes, respectively. These codes are listed in and Table 3, respectively.

Table 2 ACS events and their ICD-10 codes

	ICD-10
Total ACS	I20.0, I21
Angina pectoris	I20.0
ST elevation MI	I21.0-I21.3
Non-ST elevation MI	I21.4
Unspecified acute MI	I21.9

Table 3 ACS-related interventions

	NCSP code
Any surgical operation of coronary arteries	FN
Coronary angiography	FN1CC, FN1BC, FN1AC
Coronary artery bypass grafting (CABG)	FNA-FNE
Percutaneous coronary intervention (PCI)	FN1AT, FN1BT, FN1YT, FNF, FNG, FN1ST,FN1XT

Abbreviation: NCSP; NOMESCO classification for surgical procedures

4.1 Exposure

The prescription database searches were based on Anatomical Therapeutic Chemical (ATC) codes. OAPs of interest were ticagrelor (ATC code B01AC24), clopidogrel (B01AC04) and prasugrel (B01AC22). Ticagrelor has been on the Finnish market since 2010 but the reimbursement status was given in 2012. For prasugrel we got data since

2010 and for clopidogrel for the whole study period since for it the marketing authorization was given already in 1998.

For 33 patients who purchased two different OAPs at the same day within 7 days after index date, the initial OAP was set to be the one with shortest exposure period followed by a switch to the one with the longer exposure period. We did assume simultaneous use of two OAPs for the overlapping time at the beginning.

In addition to ATC codes we received data about:

- Purchase dates
- Vnr numbers (identifying the packages)
- Package sizes
- Number of packages
- Total amount purchased in defined daily doses (DDD)

The duration of the OAP medication was based on the number of purchased tablets since after the initiation dose (given in hospital) 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).

The concomitant medication drug use (see Table 4) was defined as a purchase within 120 days after index date.

Number of potential drug-drug interaction treatment periods in OAP treated patients was measured by purchases of the drugs listed in Table 5 during the OAP treatment periods. An example case of this is presented in Figure 2.

Table 4 ATC codes for the study drugs other than OAPs

Drug or drug group	ATC code
ARB	C09C, C09D
ACE inhibitor	C09A, C09B
Nitrate	C01
Beta-blocker	C07
Calcium channel blocker	C08
Antidiabetic drug	A10
Insulin	A10A
Oral antidiabetic	A10B
H_2-receptor antagonist	A02BA
Prostaglandin	A02BB

Proton pump inhibitor	A02BC
Combinations for eradication of Helicobacter pylori	A02BD
Other drugs for peptic ulcer and GORD	A02BX
Statin	C10AA
Fibrate	C10AB
NSAID	M01A (excluding glucosamine M01AX05)
SSRI	N06AB
Warfarin	B01AA03
Direct thrombin inhibitor	B01AE
Direct factor Xa inhibitor	B01AF
Other antithrombotic agent	B01AX
Drugs causing interactions with OAP	See Table 5

Abbreviations: ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme; GORD, gastro-oesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor

Table 5 Drugs potentially causing C and D drug-drug interactions with clopidogrel, prasugrel and ticagrelor in the SFINX interaction database [8] sited online on 18 Jun 2014

IA drug	ATC code
Aceclofenac	M01AB16
Acemetacin	M01AB11
Acetylsalicylic acid	A01AD05, B01AC06, N02BA01, M01BA03, B01AC56, N02BA51, N02BA71, C10BX02, C10BX05, C10BX01, C10BX04
Amiodarone	C01BD01
Atazanavir	J05AE08
Bupropion	N06AX12
Carbamazepine	N03AF01
Celecoxib	L01XX33, M01AH01
Ciclosporin	L04AD01
Cimetidine	A02BA01, A02BA51

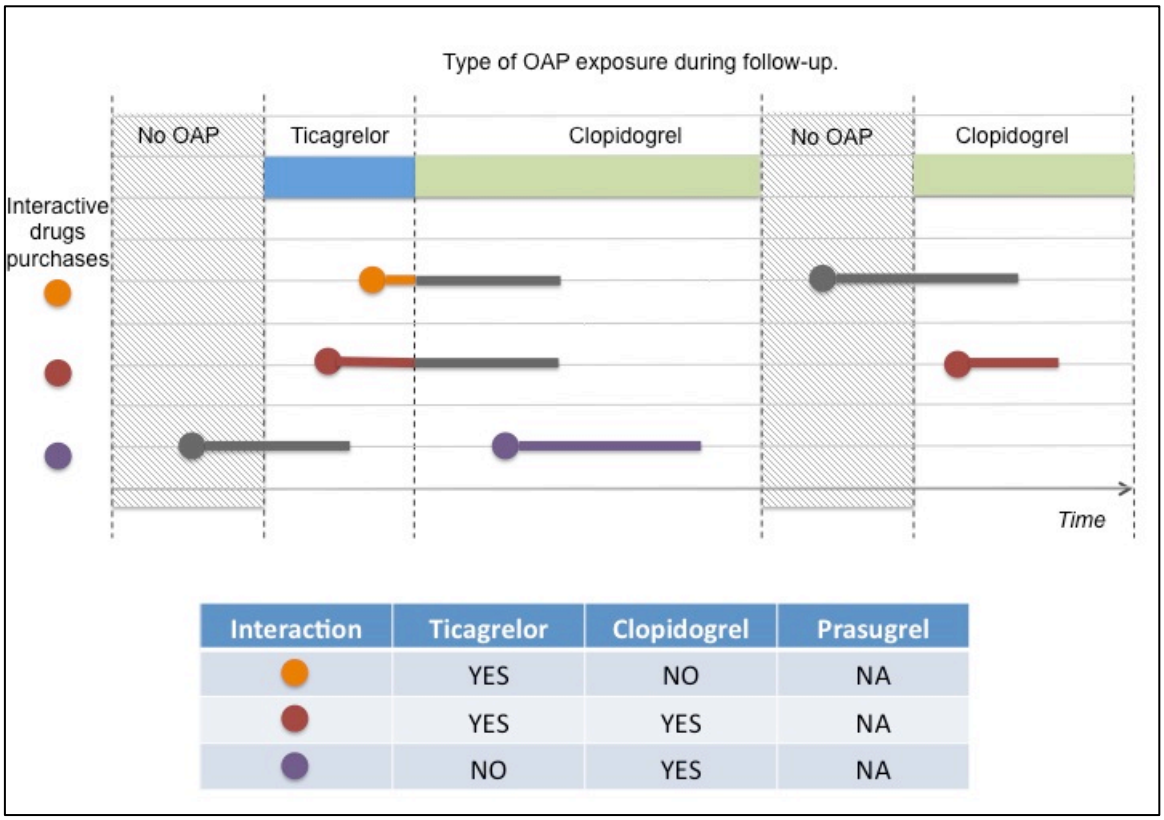
Citalopram	N06AB04
Clarithromycin	J01FA09, A02BD06, A02BD07, A02BD05, A02BD04
Clomipramine	N06AA04
Crizonib	L01XE16
Cyclophosphamide	L01AA01
Dabigatran	B01AE07
Darunavir	J05AE10
Dexibuprofen	M01AE14
Dexketoprofen	M01AE17
Diclofenac	M01AB05, M01AB55
Digoxin	C01AA05
Ditiazem	C08DB01
Duloxetine	N06AX21
Efavirenz	J05AG03, J05AR06, J05AR11
Enzalutamide	L02BB04
Erythromycin	J01FA01
Escitalopram	N06AB10
Esomeprazole	B01AC56, A02BC05, A02BD06, M01AE52
Etodolac	M01AB08
Etoricoxib	M01AH05
Fluconazole	J02AC01
Fluoxetine	N06AB03, N06CA03
Flurbiprofen	M01AE09, R02AX01
Flurbiprofen (topical)	S01BC04, M02AA19
Fluvoxamine	N06AB08
Fosamprenavir	J05AE07
Ibuprofen	C01EB16, M01AE01, M01AE51

Indinavir	J05AE02
Indometacin	C01EB03, M01AB01, M01AB51
Ipilimumab	L01XC11
Itraconazole	J02AC02
Kebuzone	M01AA06
Ketoconazol	J02AB02
Ketoprofen	M01AE03, M01AE53
Ketorolac	M01AB15
Lepirudin	B01AE02
Lopinavir	J05AR10
Lornoxicam	M01AC05
Lumiracoxib	M01AH06
Meclofenamic acid	M01AG04
Mefenamic acid	M01AG01
Meloxicam	M01AC06, M01AC56
Metamizole	N02BB02, N02BB52, N02BB72
Midazolam (per oral)	N05CD08
Milnacipran	N06AX17
Mitotane	L01XX23
Morphine	N02AA01, N02AG01, A07DA52, N02AA51
Nabumetone	M01AX01
Naproxen	M01AE02, M01AE52, M01AE56
Nelfinavir	J05AE04
Nifluminic acid	M01AX02
Nimesulide	M01AX17
Omeprazole	A02BC01, A02BD05, A02BD01
Parecoxib	M01AH04

Paroxetine	N06AB05
Phenobarbital	N03AA02
Phenylbutazone	M01AA01, M01BA01
Phenytoin	N03AB02, N03AB52
Piroxicam	M01AC01
Posaconazole	J02AC04
Primidone	N03AA03
Proglumetacin	M01AB14
Quinidine	C01BA01, C01BA51, C01BA71
Quinine	P01BC01, M09AA72
Rifampicin	J04AB02, J04AM02, J04AM05, J04AM06
Rifamycin	J04AB03
Ritonavir	J05AR10, J05AE03
Rofecoxib	M01AH02
Saquinavir	J05AE01
Sertraline	N06AB06
Sibutramine	A08AA10
Simvastatin	C10AA01, C10BX01, C10BA02, C10BA04, C10BX04, A10BH51
Sulindac	M01AB02
Telithromycin	J01FA15
Tenoxicam	M01AC02
Tiaprofenic acid	M01AE11
Tipranavir	J05AE09
Tolfenamic acid	M01AG02
Tramadol	N02AX02, N02AX52
Troleandomycin	J01FA08
Valdecoxib	M01AH03

Venlafaxin	N06AX16
Verapamil	C09BB10, C08DA01, C08DA51
Voriconazole	J02AC03
Warfarin	B01AA03

Abbreviation: IA, interaction



Interaction	Ticagrelor	Clopidogrel	Prasugrel
●	YES	NO	NA
●	YES	YES	NA
●	NO	YES	NA

Figure 2 Example how to calculate drug-drug interactions for particular OAPs

4.2 Outcome Definitions and Variables

Outcomes of interest were defined as follows:

Treatment switch

Treatment switch was defined as a purchase of another OAP than the initial OAP, or as a later initiation of an OAP (switch from no-treatment to treatment) when no OAP is registered within 7 days after index date.

The exposure period of the new OAP was considered to start immediately at the time of purchase of the new OAP, thus the possible remaining tablets of the old OAP were considered not to be used any longer.

Treatment duration

Treatment duration was defined as number of treatment days (= 1 tablet per day for clopidogrel and prasugrel; 2 tablets per day for ticagrelor) based on tablet purchases during the observation period (from index day to the last day of medication).

Treatment gaps up to 30 days were included as treatment time in a continuous treatment period with no gap in the exposure. This rule was valid also in case of a gap between two different OAPs.

If a gap in drug exposure occurred during a hospitalization period and the drug exposure continued within 30 days after discharge, the gap was ignored.

If the start of a gap in drug exposure occurred at time of an institutionalization, it was assumed that drug exposure continued during the institutionalization.

Treatment prolongation

Treatment prolongation was defined as a treatment duration exceeding 12 months from the first OAP initiation. Treatment here referred to the use of any of the study OAPs regardless of switches.

Treatment discontinuation

Treatment discontinuation was defined as a treatment gap of at least 30 days after the last day on OAP (calculated from number of tablets after the last purchase).

If a gap in drug exposure occurred during a hospitalization period and the drug exposure continued within 30 days after discharge, the gap was ignored.

If the start of a gap in drug exposure occurred at time of an institutionalization, it was assumed that drug exposure continued during the institutionalization.

Medication possession rate

Medication possession rate (MPR) on any of the study OAPs for each patient is defined as number of treatment days on any of the study OAPs (= 1 tablet per day for clopidogrel and prasugrel; 2 tablets per day for ticagrelor) based on tablets purchased during the medication possession period (from index day to the last day of medication) divided by the number of days in the medication possession period * 100 (Figure 3).

OAP specific MPR for each patient is defined as number of treatment days on one of the study OAPs (= 1 tablet per day for clopidogrel and prasugrel; 2 tablets per day for ticagrelor) based on tablets purchased during the OAP specific medication possession periods (all exposure periods on a specific OAP starting after index date) divided by the number of days in the OAP specific medication possession period * 100 (Figure 4).

If a hospitalization or an institutionalization of more than 7 days occurs, time between the admission and the next drug purchase is removed from the medication possession period, and treatment days resulting from the remaining tablets from the previous purchase are removed from number of treatment days.

Drug purchases occurring during hospitalizations or institutionalization of more than 7 days are ignored.

Proportion of patients covered

Proportion of patients covered is defined as the number of patients having on-going OAP medication at any time (having filled at least a prescription of one of the study OAPs after hospitalization for ACS event) divided by the number of patients alive within different OAP treated populations.

Time to treatment initiation

Time to treatment initiation is defined as the number of days elapsed between the index day and the initiation of one of the study OAPs.

Time to switch

Time to switch is defined as the treatment duration of the initial OAP before a switch to any other OAP than the original treatment.

Patients initiating the OAP treatment later than within 7 days after index date are considered as switchers from no treatment to OAP treatment. For these originally non-OAP-treated patients the time to switch is calculated starting from 7 days after index date.

4.3 Other Variables and Covariates

Baseline comorbidities

Comorbidity within 5 years prior to index event date was searched by ICD-10 codes, ATC codes and special reimbursement statuses. Cardiovascular comorbidities and other comorbidities of interest are listed in Table 6 and Table 7, respectively.