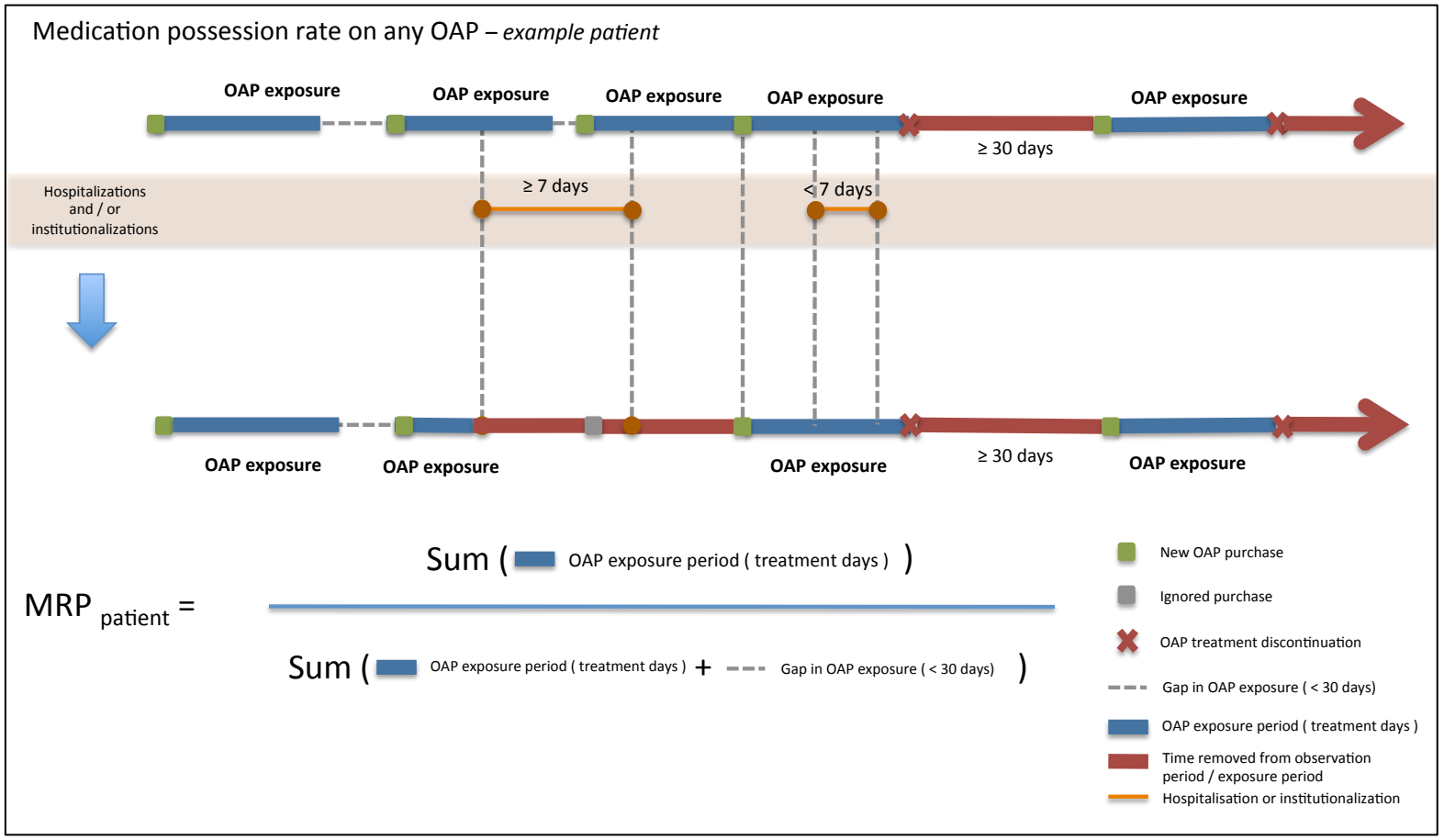

Figure 3 Example how to calculate OAP MPR

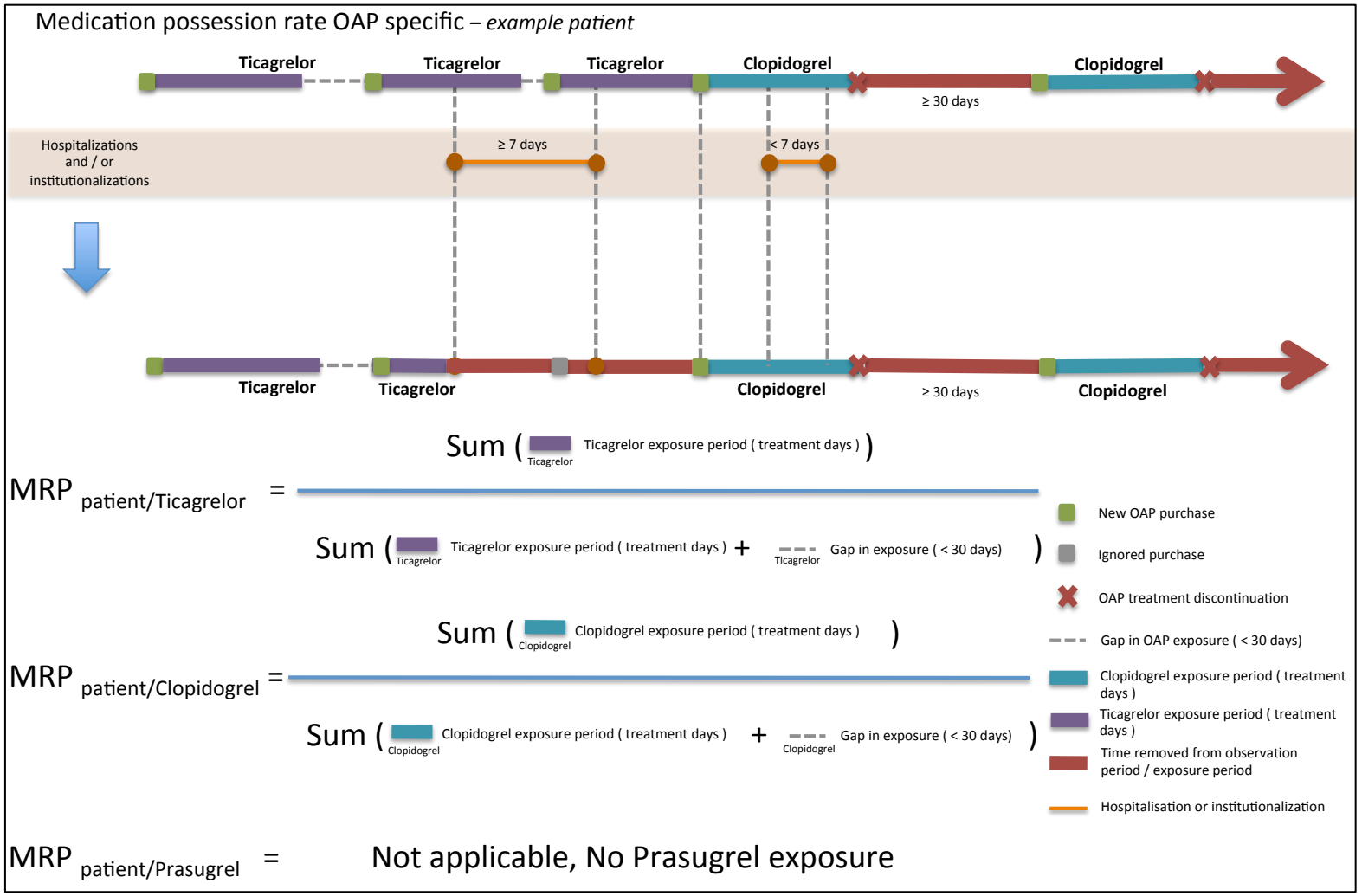

Figure 4 Example how to calculate MPR for a specific OAP

Table 6 Variable codes for cardiovascular comorbidities

	ICD-10	ATC	Special reimbursement code
Heart failure	I11.0, I13.0, I13.2, I50		201
Hypertension	I10	C02, C03, C07, C08, C09	205
Hyperlipidemia	E78	C10	211
Stroke total	I61-I64, G45		
Non-ischaemic stroke	I61, I62		
Ischaemic stroke	I63		
Transient ischemic attack (TIA)	G45		
Major bleedings	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		
Arrhythmia	I44-I49		207
Atrial fibrilaltion	I48		
Bleeding diathesis/coagulation disease	D66, D67, D68, D69		126, 129

Table 7 Variable codes for other comorbidities than cardiovascular comorbidities

	ICD-10	ATC	Special reimbursement code
Diabetes mellitus	E10-E14	A10	103
Chronic renal dysfunction	I15.0, I15.1, N03, N04, N05, N11, N18, Q60, Q61, Z49.1, Z99.2		137, 138
Moderate and severe liver disease	K71-K719, K721, K730-K768, R18		
Chronic obstructive pulmonary disease (COPD)	J44		
Dementia/Alzheimer's disease	F00-F03, G30		
Cancer	C00-C99		117 (leukemia)

Mortality during follow-up

Data on time and causes (ICD-10 codes) of deaths were received from the Causes of Death Registry. Based on the data the most common causes of death as well as cardiovascular causes of death (listed in Table 8) were described for the main cohort.

Table 8 Variables for cardiovascular causes of death

	ICD-10
Heart failure	I11.0, I13.0, I13.2, I50
Hypertension	I10
Hyperlipidemia	E78
Stroke total	I61-I64, G45
Non-ischaemic stroke	I61, I62
Ischaemic stroke	I63
Transient ischemic attack (TIA)	G45
Major bleedings	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
Arrhythmia	I44-I49
Atrial fibrilaltion	I48
Bleeding diathesis/coagulation disease	D66, D67, D68, D69

Miscellaneous

Other exploratory variables are listed in Table 9 and Table 10.

Table 9 Categories for other exploratory variables

	Description
Type of hospital	Local hospital, Central hospital, University hospital
CCI*	0, 1, 2, 3-5, 6-9, ≥10
Calendar year	2009, 2010, 2011, 2012, 2013

Hospital region	Ahvenanmaa, Etelä-Karjala, Etelä-Pohjanmaa, Etelä-Savo, Helsinki and Uusimaa, Helsinki and Uusimaa, Itä-Savo, Kainuu, Kanta-Häme, Keski-Pohjanmaa, Keski-Suomi, Kymenlaakso, Länsi-Pohja, Lappi, Päijät-Häme, Pirkanmaa, Pohjois-Karjala, Pohjois-Pohjanmaa, Pohjois-Savo, Satakunta, Vaasa, Varsinais-Suomi
* Charlson Comorbidity Index (CCI) weights in Table 10	

Table 10 Charlson Comorbidity Index [9] scores for different medical conditions with relative ICD-10 codes (modified from Quan et al. 2005 [10])

Condition	Score *	ICD-10 code **
Myocardial infarction	1	I21.x, I22.x, I25.2
Congestive heart failure	1	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	1	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	1	F00.x, F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	1	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Rheumatic disease	1	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	1	K25.x-K28.x
Mild liver disease	1	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	1	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	2	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Hemiplegia or paraplegia	2	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0- G83.4, G83.9
Renal disease	2	I12.0, I13.1, N03.2- N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0- Z49.2, Z94.0, Z99.2

Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	2	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x- C97.x
Moderate or severe liver disease	3	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	6	C77.x-C80.x
AIDS/HIV	6	B20.x-B22.x, B24.x

* 1 point will be added to the total score for each decade above the age of 40.

** The dot following with x is considered to include also the code without the dot (e.g. I21.x includes also I21)

5. STATISTICAL ANALYSIS

5.1 Statistical Methods – General Aspects

Raw data sanity checks

Multiple sanity checks were performed on the raw data received from the different register holders. Sanity check summaries were produced including the number of missing values, potential inconsistencies, variable description and variable structure for each dataset.

Modifications to raw data and missing data values

Information on the exact date of birth for the study patients was not included in the hospital care raw data; only the month and the year of birth were specified. When calculating the age at hospital discharge for the study patients the day of birth was set to the 15th of the corresponding month and year.

The place of residence data received from the prescription register only included information on the year of moving abroad. The date of emigration was set to the first of January of the corresponding year.

The prescriptions raw data received form the prescription register contained some records with missing information on the DDDs. When applicable, the package identification (Vnr) numbers were used to complete the missing information, otherwise the purchase was ignored (none of the OAP purchases were ignored after applying this process). Recorded purchases with missing or zero number of purchased packages were also ignored.

Formation of the study cohort

Hospital care data, drug prescription data, causes of death data and place of residence data were combined and used in the formation of the study cohort. Patients dying during the hospital stay related to the index ACS event and patients moving abroad during the cohort entry year were excluded from the study cohort. Also, one patient with an OAP prescription dying at the date of purchase was excluded since the OAP treatment duration for this patient is null.

Formation of the study groups

The prescription data was used to define the different study groups based on the type of OAP treatment within 7 days after index date as described in section 3.2.

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.

Grouping of quantitative variables

Age at index date was grouped into the following categories:
18-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85 and over.

Number of (previous) ACS events, number of (previous) ACS related invasive treatments, and total number of drugs were grouped into the following categories:
0, 1, 2, 3, 4 and 5 and over.

Charlson Comorbidity Index (CCI) was grouped into the following categories:
0, 1, 2, 3-5, 6-9 and 10 and over.

Time to OAP initiation for the OAP treated patients was grouped into the following categories:
0 (at index date), 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days.

Time to OAP initiation after 7 days from index date (days) for the non-OAP treated was grouped into the following categories:
1-7 days, 8-15 days, 16-30 days, 31-60 days, 61-120 days, 121-180 days, 181-270 days, and over 270 days.

Treatment duration was grouped into the following categories:
<90 days, ≥ 90 and <180 days, ≥ 180 and <270 days, ≥ 360.

Time to treatment switch was grouped into the following categories:1-15 days, 16-30 days, 31-60 days, 61-120 days, 121-180 days, 181-270 days and over 270 days.

Time to treatment switch with less than 30 days on original treatment was grouped into the following categories:
1-2 days, 3-4 days, 5-6 days, 7-13 days, 14-20 days and 21-30 days.

5.1.1 Primary Objectives: Calculation of Epidemiological Measures of Interest

Study populations characterization

When describing the study populations, all continuous variables were described with the number of observations, mean, standard deviation, range, median, first and third quartile. All categorical variables were summarized with relative frequencies.

The description of the index ACS event was presented for each of the study groups separately and included; the type of index ACS event, invasive treatments related to index

ACS event, the time spent in hospital type of hospital at index event and at discharge, hospital region at index event and at discharge and the cohort entry year.

The description of the study population at index date was presented for each of the study groups separately and included; age at index date, sex, previous ACS events, previous invasive treatments, prior comorbidities and baseline medication use. Prior comorbidities, ACS events and invasive treatments were searched in a 5 years history period prior to the index event date. Baseline medications were searched in a 4 months history period and included only on-going medication at index date based on the purchased amount.

ACS related events and interventions recorded in the hospital care data within 30 days after index date were searched and described for the OAP-treated patients and non-OAP treated patients. In addition, hospital care data, special reimbursement data and prescriptions data, between the index event date and 30 days after index date, were searched for cardiovascular and other comorbidities as defined in Table 6 and Table 7, respectively.

Changes in concomitant drugs use up to 120 days after index date were described for all study groups. This included the proportion of patients with discontinuations and initiations for each of the concomitant drugs of interest (see Table 4 and Table 5). This approach, by design, implies that end of follow-up within 120 days after index date is accounted as a discontinuation (if prior use) or a non-initiation (if no prior use). Therefore, a similar analysis was performed including only patients with at least 120 days of follow-up.

Patients with an OAP treatment duration exceeding 12 months (1 month = 30 days) from index date were described at the baseline by their characteristics, prior comorbidities and baseline medication use.

Among the patients dying during the study period, the proportions of patients by most common causes of death, ACS causes of death and cardiovascular causes of death were described. A stratified analysis by gender was also performed. The main causes of death were searched by ICD-10 codes in the causes of death data.

OAP treatment patterns

The time to initiate OAP treatment for the OAP treated groups was summarized with relative frequencies, mean, standard deviation, median, first and third quartile. Similarly, for patients with no OAP purchase within 7 days after index date, the time to initiate OAP treatment after 7 days from index date was summarized.

The proportion of patients covered by time from OAP initiation was presented with step curves describing 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 groups.

The proportion of patients completing 3, 6, 9 and 12 months of OAP treatment were presented in contingency tables including the following results:

- Patients surviving more than 12 months after OAP initiation
    - Proportion completing 12 months treatment.

  - Proportion completing 9 months treatment.
  - Proportion completing 6 months treatment.
  - Proportion completing 3 months treatment.

- Patients surviving more than 9 months after OAP initiation
  - Proportion completing 9 months treatment.
  - Proportion completing 6 months treatment.
  - Proportion completing 3 months treatment.

- Patients surviving more than 6 months after OAP initiation
  - Proportion completing 6 months treatment.
  - Proportion completing 3 months treatment.

- Patients surviving more than 3 months after OAP initiation
  - Proportion completing 3 months treatment.

Results were reported for all the OAP treated groups, and were stratified by type of index ACS event, invasive treatments related to index ACS event, gender, age group, time spent in hospital, type of hospital, calendar year, the Charlson's comorbidity index, comorbidities and co-medications.

Treatment switch

The first OAP treatment switch was described by reporting the number of patients switching to another OAP than the original OAP treatment. If a switch occurred after a gap exceeding 30 days in OAP exposure it was not reported. A similar analysis was done for patients with less than 30 days on original treatment and for patients with at least 360 days of follow-up. Stratification by time to switch was also performed and the time to switch was described with the mean, standard deviation, range, median, first and third quartile.

Treatment discontinuation

OAP discontinuation incidence rates with 95% confidence intervals within 12 months after index day were presented for each of the OAP treated groups. The treatment discontinuation risk time started at the date of first OAP purchase after index date and ended at first treatment discontinuation or end of follow-up.

OAP persistence after OAP initiation was presented in Kaplan-Meier plots showing the proportion of patients continuing OAP treatment versus days from OAP initiation.

OAP persistence was presented for a number of subgroups defined by: type of OAP treatment within 7 days after index date, type of index ACS event, invasive treatment related to index ACS event, type of invasive treatment related to index ACS event, gender, age group, time spent in hospital, type of hospital, calendar year, the Charlson's comorbidity index, co-morbidities and co-medications.

Medication possession rates

MPR and OAP specific MPR as defined in section 4.2 were described with the mean, standard deviation, median, first and third quartile. Stratified analyses by age groups and gender were also reported for the MPR.

5.2 Bias

5.2.1 Methods to Minimize Bias

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.

5.2.2 Adjustment for Multiple Comparisons

Not applicable as no real between-group comparisons were made.

5.3 Sample Size

At the beginning of the study, the study size was estimated to be about 25 000 myocardial infarction cases (and up to 300 000 hospitalizations due to any type of cardiac attacks). At the end of the study, the cohort included about 55 000 patients fulfilling the inclusion criteria.

5.4 Data Quality

In general the HILMO data quality is high; more than 95% of discharges can be identified from this nationwide register [11]. Primary care data and hospital clinical data (weight, laboratory samples, blood pressure etc.) were not available for this study, thus proper baseline characterization could not be estimated.

Coverage of the Prescription Register containing reimbursement information of all permanent residents of Finland is about 97%. Missing data includes relatively inexpensive packages and over the counter medications that are not reimbursed. Thus fully reliable information on ASA use was not available. DAPT treatment was then defined as OAP use only. For ASA use without OAP we could not make any estimations.

Medications used during hospitalizations were not available. The hospitalizations and institutionalizations were, however, taken into account in the exposure definitions by setting rules for continuous treatment and gaps in the analyses.

6. RESULTS

6.1 Study Participation

Numbers of the patients forming the study population are shown in Figure 5. The actual study cohort consisted of 54 754 ACS patients. In this population the mean follow-up time was 2.16 years (+/- sd 1.45 years). Patients with less than one year of follow-up represented 28% of the study population. The proportion of patients with less than one year of follow-up was considerably higher in the ticagrelor and prasugrel groups (69.32% and 38.50%, respectively). The yearly incidence of ACS was slightly decreasing through the study period (from 22% to 18% in 2009-2013).

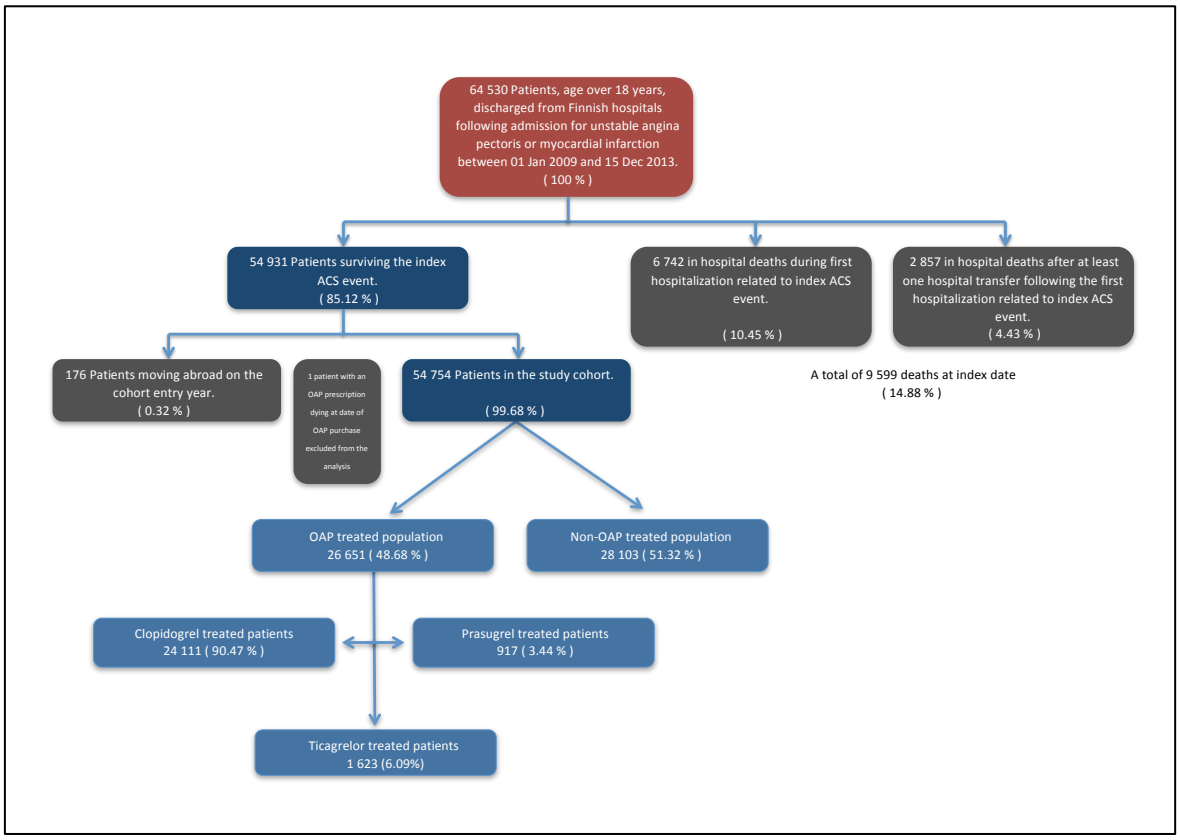

Figure 5 Population flowchart

6.2 Main Results

6.2.1 Characterization of patients

The most common reason for the index ACS hospitalization was NSTEMI (39%). STEMI and unstable angina pectoris were the reason for hospitalization in 27% and 20% of the cases, respectively. In prasugrel group STEMI was present in 81% of the cases (Table 1 in Annex 2). In most of the cases the study patients did not have ACS events in the patient history but the index event was the first, the proportion being > 90% in all study groups (Table 2 in Annex 2).

Of the cohort of 54 754 ACS patient included in the study, 49% (N=26 651) were treated with OAPs while 51% (N=28 103) formed a non-OAP-treated group (Figure 5). Of the OAP treated patients 91% (N = 24 111) received clopidogrel within 7 days after the discharge; 6.1% of the patients formed the ticagrelor group and 3.4% the prasugrel group. No previous OAP treatment had been in use in 96% of the cases. As many as 90% of the OAP-treated patients made the first OAP purchase within one day after the discharge (Table 3 in Annex 2).

The OAP-treated patients were invasively treated in 78% of the cases (Table 1 in Annex 2). Mostly they went through coronary angiography and/or PCI, in 65% and 63% of the cases, respectively. Having at least one intervention was most common among prasugrel-treated patients (90%). Of non-OAP-treated-patients 67% had conservative treatment. In the total ACS patient cohort CABG was reported in 7.3% only.

The mean time spent in hospital was longer in non-OAP-treated group (17 days) vs. in OAP-treated group (7 days) (Table 1 in Annex 2). This calculation included consecutive hospitalizations with no outpatient days in between. At the index event 77% of the patients were hospitalized in university or central hospitals (the two higher hospital types in Finland), and at final discharge 40% of the patients were treated in other (e.g. local) hospitals.

The patients were older (mean 76 years) in the non-OAP-treated group compared with OAP-treated patients (mean 68 years), people in the prasugrel group being the youngest (mean 60 years) (Table 2 in Annex 2). Sex differences were smaller in the non-OAP-treated group (53% men) compared to the OAP-treated (68% men). This was again highlighted in the prasugrel group: 78% of these patients were men.

At baseline hypertension and/or hyperlipidemia were present in 69% and 48%, respectively, of the OAP-treated patients; the respective prevalence values in the non-OAP-treated group were 83% and 53% (Table 2 in Annex 2). Other cardiovascular comorbidities such as arrhythmia, atrial fibrillation, heart failure and stroke were less common in the population at baseline. Of other baseline comorbidities diabetes mellitus was present in 28% of the non-OAP-treated and in 22% of the OAP-treated patients.

The proportion of patients with register entry for heart failure doubled from 4.4% to 8.9% in OAP-treated population when observing the first month after the index event compared to the medical history (Tables 2 and 6 in Annex 2), hypertension and hyperlipidemia increased by 30 percentage points. Within 30 days after the discharge 4.0% of the OAP-treated and 5.6% of the non-OAP-treated patients experienced a new ACS event (Table 5 in Annex 2).

For those patients who died during the study period the most common causes of death were chronic ischemic heart disease (32%) and myocardial infarction (STEMI and NSTEMI) (23%) (Table 10 in Annex 2). This analysis was performed independently from the OAP treatment.

Concomitant medication

The mean number of drugs at baseline was 2.3 for the whole cohort. That varied from 1.3 in prasugrel group to 2.6 in non-OAP group (Table 2 in Annex 2). The most common

baseline medications were statins and beta-blockers that were used by 25% and 24% of the patients in the OAP group and by 28% and 30% of the patients in the non-OAP-group (Table 2 in Annex 2). Also use of ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrate and antidiabetic drugs were common at baseline (16-19% of OAP patients; 17-24% of non-OAP patients). The baseline medication in clopidogrel treated patients followed the one of pooled OAP group; the patients receiving prasugrel or ticagrelor had fewer drugs at baseline.

When concerning initiation of new concomitant drugs within 120 days after the index day statins were initiated to 92%, beta-blockers to 90% and ACE inhibitors to 49% of those OAP-treated patients who were not users of these drugs at baseline (Table 8 in Annex 2). Again, the figures for clopidogrel were similar than for the whole OAP group. The initiation rates of these drugs in prasugrel and ticagrelor groups were higher, and in non-OAP group lower, mirroring the situation in baseline. Of the most common drugs at baseline medication calcium channel blockers were withdrawn most frequently within the 120 days after index date (Table 8 in Annex 2).

At baseline 31% of the patients in the OAP group were using medication causing drug-drug interactions with the OAPs (Table 5). In the clopidogrel group the proportion was 32%, 25% in the ticagrelor group and 22% in prasugrel group (Table 2 in Annex 2). Of these patients only 14-27% withdrew the use of potentially harmful combination within 120 days after the index date (Table 8 in Annex 2). On the other hand, 54-73% of the patients not receiving the interactive drugs at baseline initiated at least one during the same time period.

The results for the potential drug-drug interaction treatment periods in OAP treated patients (any time during the follow-up) are presented in Table 11. Of the drugs increasing the bleeding risk warfarin was the most commonly purchased during the OAP exposures. Simvastatin was used in 42% of the patients using ticagrelor.

Table 11 Number of clopidogrel, prasugrel and ticagrelor treated patients any time during follow-up who made purchases of interactive drugs during the OAP exposure. The results in grey boxes are extrapolated to be relevant by the interaction mechanism even if the pairs were not presented in the SFINX interaction database [8] sited online on 18 Jun 2014

	IA class	result	IA class	result	IA class	result
IA drug	**CLOPIDOGREL**		**PRASUGREL**		**TICAGRELOR**	
INCREASING, DYNAMIC						
Warfarin	C3	3436 (12.09%)		62 (5.11%)		77 (3.93%)
Ibuprofen	C0	1811 (6.37%)	C0	52 (4.28%)	C0	80 (4.08%)
Tramadol	C0	1505 (5.30%)	C0	44 (3.62%)	C0	69 (3.52%)
Citalopram	C0	871 (3.06%)		20 (1.65%)	C2	26 (1.33%)
Escitalopram	C0	661 (2.33%)	C0	22 (1.81%)	C2	35 (1.79%)
Diclofenac	C0	659 (2.32%)	C0	26 (2.14%)	C0	33 (1.68%)
Etoricoxib	C0	574 (2.02%)	C0	14 (1.15%)	C0	21 (1.07%)
Naproxen	C3	418 (1.47%)	C0	12 (0.99%)	C0	24 (1.23%)
Meloxicam	C0	314 (1.10%)	C0	2 (0.16%)	C0	7 (0.36%)

Venlafaxin	C0	237 (0.83%)	C0	11 (0.91%)	C0	8 (0.41%)
Duloxetine	C0	212 (0.75%)	C0	10 (0.82%)	C0	10 (0.51%)
Sertraline	C0	142 (0.50%)	C0	4 (0.33%)	C2	12 (0.61%)
Ketoprofen	C0	141 (0.50%)	C0	2 (0.16%)	C0	7 (0.36%)
Fluoxetine	C0	88 (0.31%)	C0	3 (0.25%)	C2	5 (0.26%)
Celecoxib	C1*	76 (0.27%)*	C0	1 (0.08%)	C0	3 (0.15%)
Indometacin	C0	63 (0.22%)	C0	1 (0.08%)	C0	0 (0.00%)
Paroxetine	C0	63 (0.22%)	C0	2 (0.16%)	C2	3 (0.15%)
Dabigatran		30 (0.11%)		3 (0.25%)	C0	1 (0.05%)
Etodolac	C0	30 (0.11%)		0 (0.00%)	C0	0 (0.00%)
Clomipramine	C0	17 (0.06%)	C0	2 (0.16%)	C0	1 (0.05%)
Nabumetone	C0	13 (0.05%)	C0	0 (0.00%)	C0	0 (0.00%)
Fluvoxamine	C0 *	11 (0.04%) *	C0	1 (0.08%)	C0	0 (0.00%)
Tolfenamic acid	C0	7 (0.02%)	C0	2 (0.16%)	C0	0 (0.00%)
Mefenamic acid	C0	4 (0.01%)	C0	0 (0.00%)	C0	0 (0.00%)
Milnacipran	C0	4 (0.01%)	C0	0 (0.00%)	C0	0 (0.00%)
DECREASING, KINETIC						
Esomeprazole	D4	1904 (6.70%)				
Omeprazole	D4	1806 (6.35%)				
Fluconazole	C0	266 (0.94%)				
Morphine	C3	18 (0.06%)				
Fluvoxamine	C0	11 (0.04%)				
Carbamazepine					D0	5 (0.26%)
Phenytoin					D0	1 (0.05%)
INCREASING, KINETIC						
Esomeprazole			C0	49 (4.04%)		
Amiodarone					C0	16 (0.82%)
Ditiazem					C3	8 (0.41%)
Clarithromycin					D0	7 (0.36%)
Ciclosporin					C0	2 (0.10%)
Erythromycin					D0	1 (0.05%)
Verapamil					D0	1 (0.05%)
OTHER, KINETIC						
Simvastatin					C3	818 (41.76%)
Celecoxib	C1	76 (0.27%)				
Bupropion	C3	41 (0.14%)				
Digoxin					C3	8 (0.41%)
Abbreviation: IA, interaction * Listed also under kinetic interactions						

6.2.2 OAP treatment switches

Of those prasugrel and ticagrelor-treated patients who switched the original treatment to another OAP (not discontinuing OAP treatment) >99% switched to clopidogrel (Table 165 in Annex 2). The number of switches was, however, quite low. Also the most of those patients who started the OAP treatment after no use of any OAP become clopidogrel users. If clopidogrel was changed to another OAP prasugrel was more common option than ticagrelor. (The last do not take into account the fact that ticagrelor has not been on the

market as long as prasugrel.) Time to switch results are presented in chapter 4.2 in Annex 2.

6.2.3 Discontinuation rates of OAP treatments

The treatment persistence of all OAPs is shown in Figure 6. Ticagrelor and prasugrel follow the same trend: clear drop in use at one year after OAP initiation. For clopidogrel use there were persistence drops also at 1, 3 and 6 months. For clopidogrel there have been also longer treatment periods than 12 months. The persistence decreased along the age (Figure 7) and was slightly higher in men than in women before the common drop after day 360 (Figure 8). When observing ticagrelor only the best persistent was in age group 55-59 years and there was no sex-related difference (see 5.5.2 and 5.5.3 in Annex 2). There were no between-year differences in the persistence during the study period (Figure 9: clopidogrel representing the first of the calendar years alone).

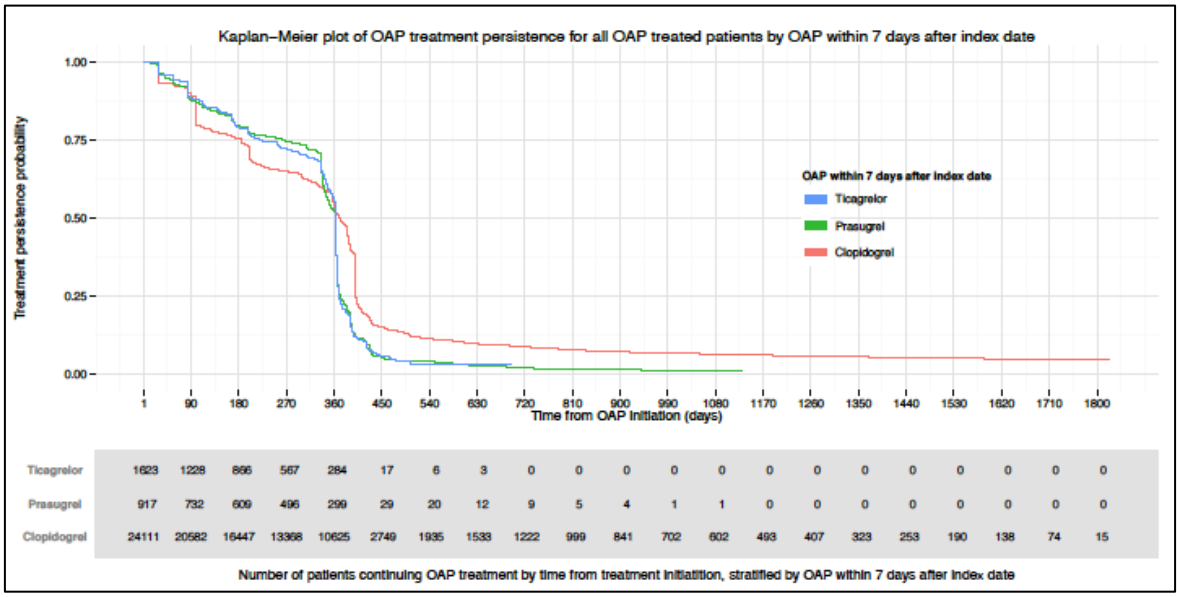

Figure 6 Treatment persistence stratified by OAP within 7 days after index date

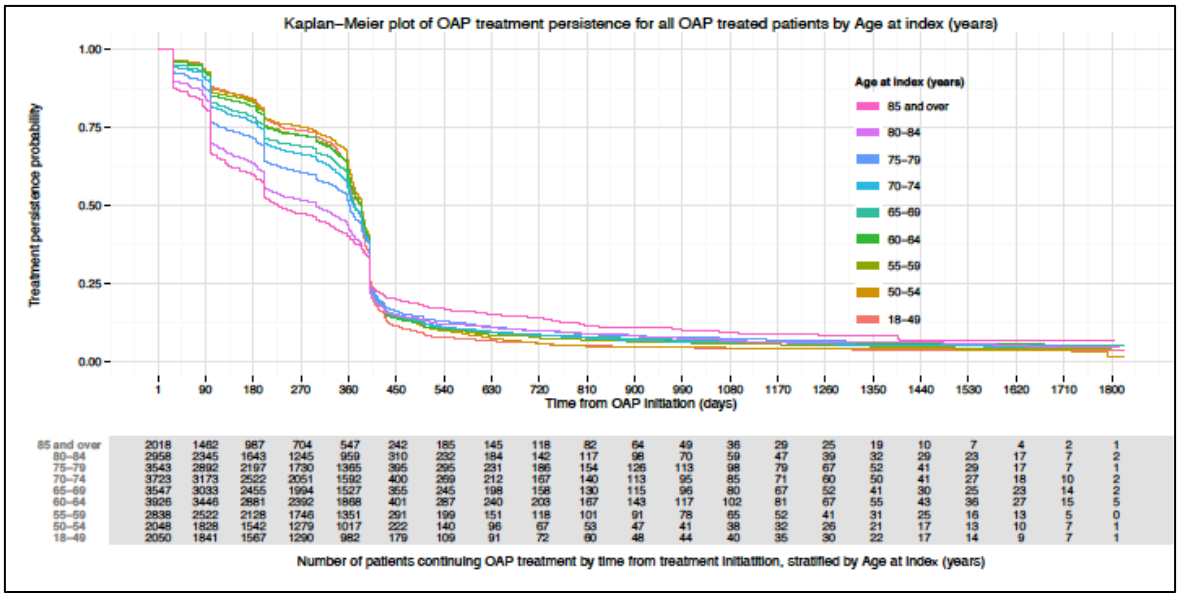

Figure 7 Treatment persistence stratified by age at index date

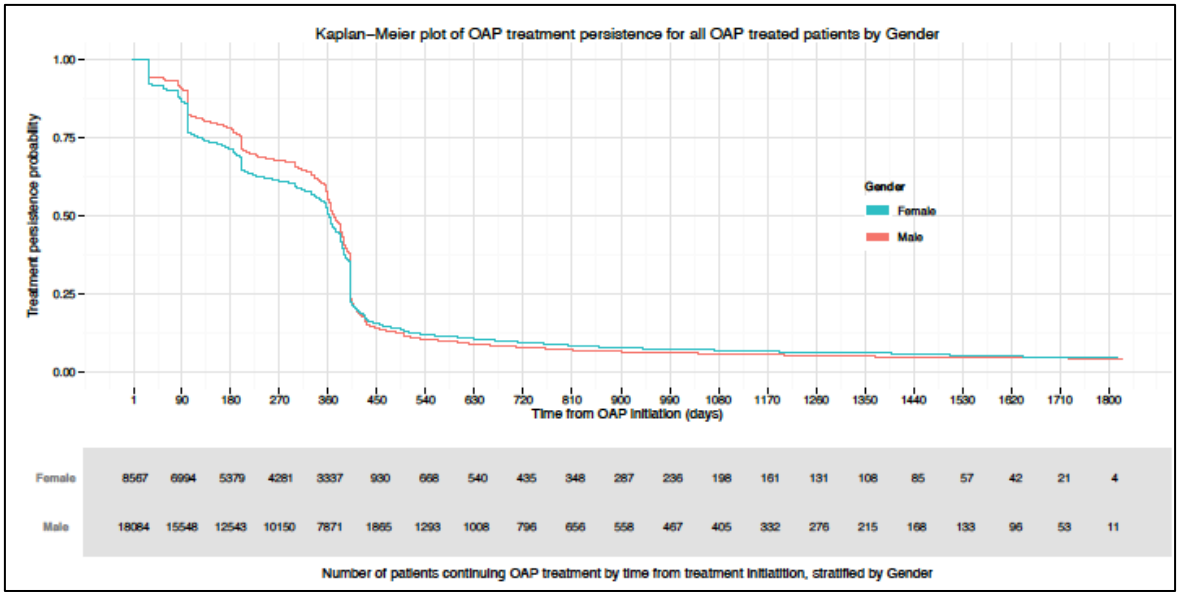

Figure 8 Treatment persistence stratified by sex

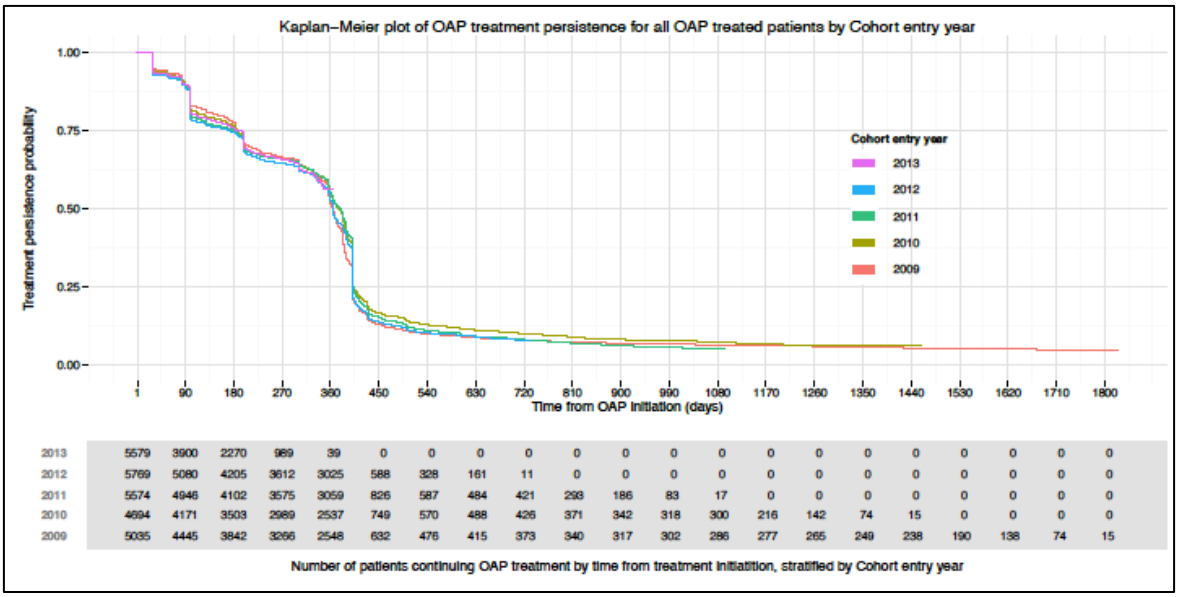

Figure 9 Treatment persistence stratified by cohort entry year

The Kaplan-Meier persistence curves stratified by the type of ACS events had the same pattern, the one for STEMI associated with the highest treatment persistence (Figure 10). The persistence was slightly higher during the first year in those patients with invasive treatment for the ACS but on the other hand patients without operations related to ACS remained on the OAPs slightly longer (Figure 11). This did not change when observing the three OAPs separately (see 5.3.4, 5.4.4 and 5.5.4 in Annex 2).

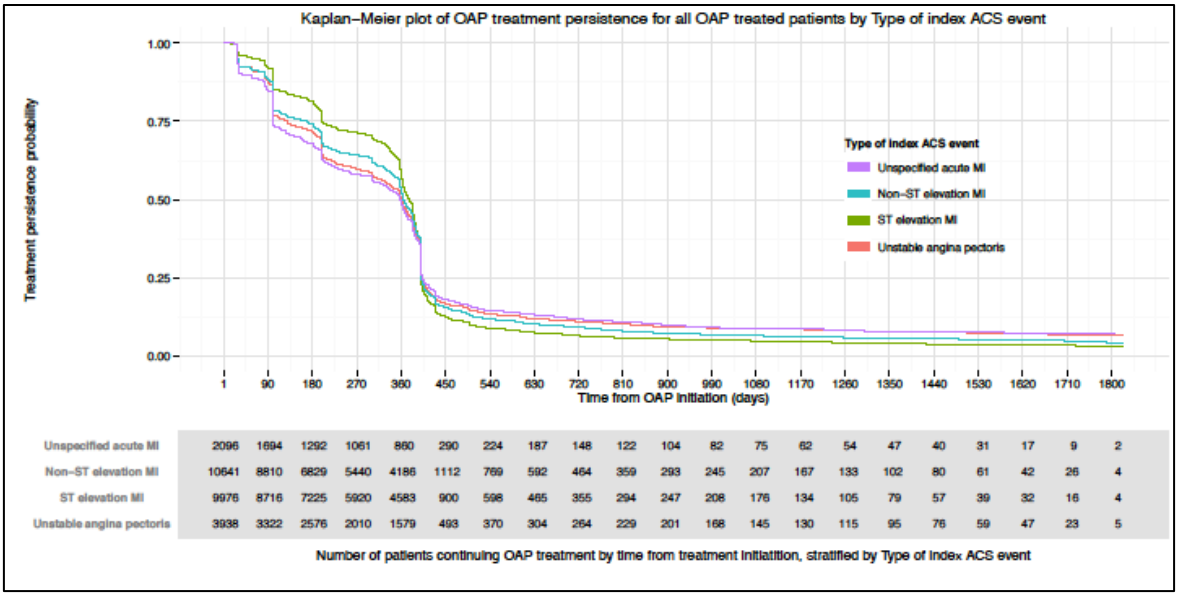

Figure 10 Treatment persistence stratified by type of index ACS event

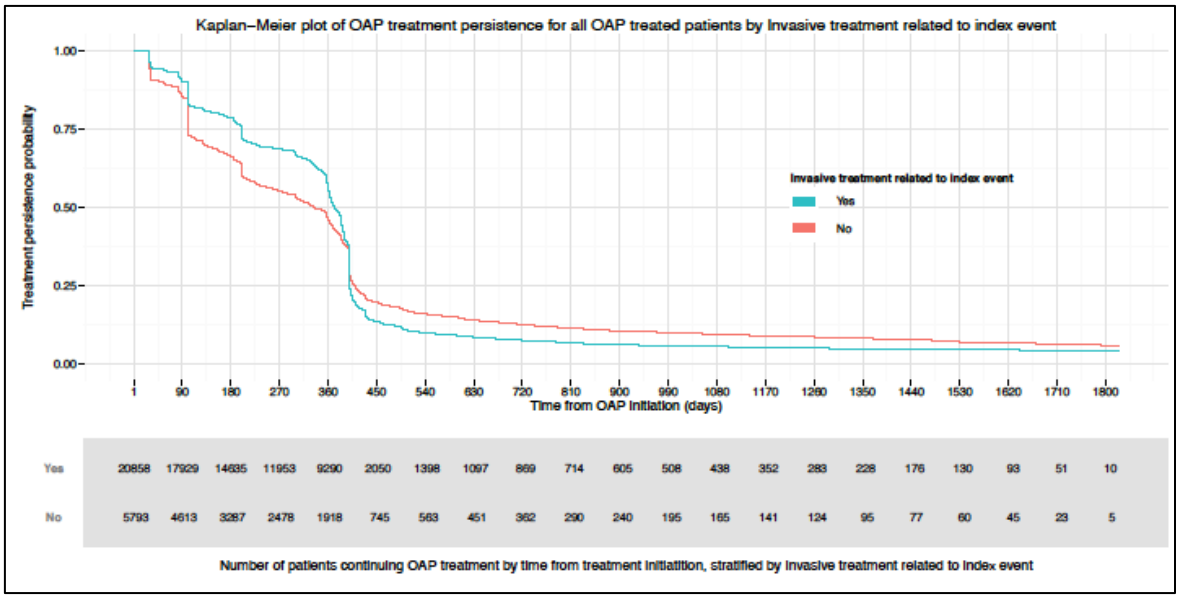

Figure 11 Treatment persistence stratified by invasive treatment related to index event

Of the cardiovascular comorbidities arrhythmia and atrial fibrillation – as well as dementia/Alzheimer's disease – decreased the OAP persistence (see 5.2.30, 5.2.31 and 5.2.37 in Annex 2). Slightly decreased Kaplan-Meier persistence curves were seen also for patients with prior heart failure, hypertension or stroke (see 5.2.22, 5.2.23 and 5.2.25 in Annex 2). Hyperlipidemia or diabetes mellitus in medical history as strata did not affect the OAP persistence (see 5.2.24 and 5.2.33 in Annex 2).

All the Kaplan-Meier plots presented in this chapter are found also in Annex 2.

6.2.4 Treatment duration and prolongation of OAPs

As seen in Figure 6 there is a clear drop in OAP use after one year. When observing those patients who survive more than 360 days after the index date, more than half of the OAP patients used the OAP medication ≥ 360 days (Table 13 in Annex 2). ACS event type or sex did not affect this (Table 14 and Table 27 in Annex 2), although 70% of these patients were men (Table 9 in Annex 2). The proportion of 18-64-year-old patients surviving more than 360 days and using OAP medication ≥ 360 days was ≥ 60%; only 42% of > 80-year-old patients had the same situation (Tables 18-26 in Annex 2). Mean age was 66 years (Table 9 in Annex 2).

Hypertension and hyperlipidemia were the most common baseline diseases also in the population completing ≥ 360 days OAP treatment (prevalences being 65% and 46%, respectively) (Table 9 in Annex 2) but these comorbidities did not affect the OAP treatment duration. Among the patients with atrial fibrillation and dementia/Alzheimer's disease and surviving more than 360 days after OAP initiation, the proportion who completed one year on an OAP was close to 30% (Table 93 and Table 105 in Annex 2). In patients with previous warfarin use this figure was 26% (N = 156) (Table 150 in Annex 2). Other specific drugs at baseline were not associated with changes in proportions of

patients fulfilling one year on OAP treatment and the use of them was similar as in the overall study cohort.

The treatment duration was slightly longer in those patients going through an invasive treatment related to the index event than in those with conservative treatment (Table 30 and Table 31 in Annex 2). The type of intervention did not cause remarkable changes in this (Tables 32-37 in Annex 2), neither did the status of previous ASC event nor previous intervention (Tables 56-73 in Annex 2). If the admission or discharge happened in a university hospital the proportion of patients receiving OAP treatment for more than 360 days was > 60% (Table 47 and Table 50 in Annex 2). In general longer stays at the hospital (> 20 days) decreased this proportion close to 40% (Table 41 and 42 in Annex 2).

6.2.5 OAP medication possession rates

The mean MPR in the OAP treated population was 99%. It was >98% in both men and women, and in all age groups (Table 173 in Annex 2). When observing different OAPs the MPRs for clopidogrel, ticagrelor and prasugrel were 99%, 98% and 97%, respectively (Table 174 in Annex 2).

7. SAFETY EVALUATION

Collection and reporting of adverse events were not applicable in this a descriptive drug utilization study using administrative data and statistics with no safety outcome analysis.

Planned analysis about 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, were not performed.

8. CONCLUSION & DISCUSSION

8.1 Discussion

This descriptive cohort study about OAP treatment patterns observed about 55 000 ACS patients of which 80% were hospitalized due to myocardial infarction and one fifth due to unstable angina pectoris in 2009-2013. The mean age in the cohort was 72 years and 60% of the patients were men. Half of the patients were non-OAP-users; the other half started OAP medication, clopidogrel in 90% of the cases, within 7 days after the discharge from the hospital. As a matter of fact, over 90% of the OAP-treated patients made the first OAP purchase within one day after the discharge.

Of both OAP and non-OAP-treated patients close to 40% entered the cohort due to NSTEMI, the most common index event in the prasugrel group was STEMI in 80% of the cases. In the whole cohort the index event was the first ACS in 93% of the patients. The index event was invasively treated in about 80% of the OAP patients, in 90% of the prasugrel patients but only in about 30% of the non-OAP treated patients.

Most of the OAP-treated patients went through coronary angiography and/or PCI. In this study group only 2.0% were treated with CABG. In non-OAP-treated patients CABG was performed in 12% of the cases but the number for CABG still seems low. This issue may

need further observation e.g. at regional level. There may be differences in registration of the interventions in the patient data.

The most common baseline comorbidities in the study population were hypertension (76% of the population), hyperlipidemia (50%) and diabetes mellitus (25%). The morbidity was somewhat more frequent in the non-OAP-treated group than in the OAP-treated group. The baseline prevalences of hypertension, arrhythmia, atrial fibrillation and heart failure, mentioning examples of the most common diseases, were about ten percentage points higher in non-OAP-treated group than in OPA-treated population.

The proportion of patients with hypertension and hyperlipidemia increased by 30 percentage points, and heart failure doubled, within the first month after the index event compared to the medical history. These figures are not telling about the incidence or increased prevalence but tell how many had register entries related to these comorbidities during a quite short follow-up time. We consider these numbers reliable, but more careful calculations among the new cases could be performed to report the incidence. The reported proportion of diabetic patients decreased in this analysis, which may be due to the practice that during the first month after the ACS diabetes has not been at the focus. It is, however, congenial that the proportion of patients with major bleedings after the ACS event was low: 2.3% in the non-OAP-treated group and only 0.7% in the OAP-treated patients (Table 6 in Annex 2).

The treatment persistence shown in Figure 6 indicates clearly that the use of ticagrelor and prasugrel are similar with a clear discontinuation trend after 12 months. For clopidogrel there are drops also at 1, 3 and 6, but not so clearly at 9 months. This did not change along the study years (5.3.11 in Annex 2). The package size explain why there are certain delays in clopidogrel drops compared to calculated months: Almost 70% of the clopidogrel purchases were made with 100 pill packages and the one-year drop in the Kaplan-Mayer curve was at 400 days. On the other hand in 70% of the prasugrel and ticagrelor cases their regimen multiplied 28 pills and the one-year drops of prasugrel and ticagrelor were closer to 364 days (13 times 28).

For clopidogrel there was more often also longer treatment periods than 12 months, when comparing with prasugrel and ticagrelor for which the drop after one year approaches zero (Figure 6). Especially those patients with history of clopidogrel did not quit the treatment within one year (5.3.39 in Annex 2). The patients staying on the clopidogrel the longest were over 85 years old (5.3.2 in Annex 2). There may be an explanation that these patients spent longer times in the hospitals: By definition, in our study the OAP treatment was not considered discontinued even with long gaps in purchases if a patient was treated in a hospital. In general, studying patients older than 85 years as a separate group would give additional information about OAP treatment patterns.

The persistence in the patients with invasive treatment for the ACS was somewhat higher when comparing to non-operated patients (Figure 11). The drops at 1, 3, 6 and 12 had the same trend in both invasively and non-invasively treatments. The patients without operations related to ACS remained, however, on the OAPs slightly longer. This may be again due to older people and their long hospitalizations in this proportion of patients. The shape of these curves equal to ones of coronary angiography and PCI analysed separately. (5.2.4 and 5.2.6 in Annex 2). Arrhythmia, atrial fibrillation and dementia/Alzheimer's

disease at baseline decreased the persistence, slightly also for patients with prior heart failure, hypertension or stroke.

The number of switches was low; only 384 patients receiving one OAP within 7 days after the index day changed the OAP to another without a gap of 30 day (when the situation would have been considered as discontinuation). About 4000 patients who did not receive any OAP within 7 days after the index day became clopidogrel users during the follow-up, 1400 of them within less than 30 days after the follow-up start (Table 165 and Table 166 in Annex 2). Of those patients receiving originally clopidogrel but changing the OAP, 65% (N = 100) switched to prasugrel and 35% (N = 53) to ticagrelor. When considering these numbers, one should take into account that both prasugrel and ticagrelor came on the market during the study period ticagrelor being the latter.

The quality of the nationwide hospital data is reported to be high [11] and in the case of the three OAP also the exposure definition can be considered highly reliable. In rare cases in pharmacoepidemiological studies using prescription data we can define the exposure by counting tablets. As for clopidogrel, prasugrel and ticagrelor the dosing in tablets per day is fixed, the treated and un-treated periods for each patient were easy to detect. We also were able to calculate MPRs for each OAP treated patients.

The mean MPR in the study was excellent: 99%. No between-sex or age differences were found in MPRs. Among different OAPs the MPR of clopidogrel was the best, but all three drugs had that within 97-99%. As the median MPR was 100% (based on the purchases) more than half of the patients used one OAP DDD per day (Table 173 in Annex 2). At least the high MPR, early initiation and regular purchases tell about good compliance.

Even though the OAP exposure periods were clear, only few time-dependent analyses were done. The aim of this study was not to study safety-related endpoints and because of this no drug specific analyses were performed. Then e.g. the mortality rates were presented in the whole cohort only. There is an on-going spin-off study, PERSEUS, that will concentrate on hard outcomes as well.

The amount of OAP-treated patients having drugs causing interactions with OAP at their regimen at baseline was 31% (32% for clopidogrel, 25% for ticagrelor and 21% for prasugrel) (Table 2 in Annex 2). For non-OAP-treated patients this was even higher: 39%. In this group the use of warfarin at baseline was 7.7% (clopidogrel 3.4%, ticagrelor 1.1% and prasugrel 0.6%) but also the use of proton pump inhibitors (PPI) was most common: 18% (clopidogrel 13%, ticagrelor 13% and prasugrel 11%). Only 14% of the clopidogrel-treated patients receiving interactive drugs at baseline withdrawn the co-medication within 120 days after the index date (Table 8 in Annex 2). In ticagrelor and prasugrel groups this proportion was over 20%, but also in non-OAP-treated population 12% discontinued this type of medication. On the other hand, in the OAP-treated population 72% (73% for clopidogrel, 54% for ticagrelor and 68% for prasugrel) of those who did not use an interaction drug at baseline started one within 120 days after the index date (Table 8 in Annex 2). Among them warfarin was started in 8.4% of the OAP-patients, but the initiation in the non-OAP-group was more than double as common. Initiation rates for PPIs were ≥ 30% in each group. With a closer look at the concomitant medication during any time of the OAP treatment warfarin was the most commonly purchased interactive drug during the OAP exposures. Of potential interactions increasing the risk of bleedings

also the use of SSRIs and serotonergic tramadol was considerably high. Also the use of NSAIDs was notable even though these drugs can be purchased over the counter and our data is based on reimbursed prescriptions only.

8.2 Conclusion

This descriptive cohort study observed in about 55 000 ACS patients of which 80% were suffering from MI. Half of these patients became OAP users, and over 90% of them made the first OAP purchase within one day after the discharge. Also the MPR during the follow-up was ideal. According to the guidelines there was a clear drop at one year in the persistence curves and almost all OAP users had also a statin and beta-blocker in their regimen. The proportion of non-OAP users was, however, high and the treatment of ACSs nationwide was not that well in control. This study did not observe outcomes thus no strong clinical conclusions can be done neither in OAP or non-OAP treated populations.

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10. ANNEXES

Annex 1: List of Stand-alone Documents

- Study Protocol version 1.0 dated 18 March 2014
- Study Protocol version 2.0 dated 03 July 2014
- Statistical Analysis Plan version 1.0 dated 09 December 2014
- Statistical Analysis Plan version 2.0 dated 12 May 2015
- Statistical Analysis Plan version 2.1 dated 22 June 2015

Annex 2: Study Results