Clinical Study Report Synopsis

Drug Substance	*B01AC04, Clopidogrel* *B01AC22, Prasugrel* *B01AC24, Ticagrelor*
Study Code	D5130N00010
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Drug Utilisation study in new users of ticagrelor, clopidogrel and prasugrel in national Swedish registries

Study dates:	Retrospective observational cohort study covering the period June 2011- December 2013
Phase of development:	Therapeutic use
Principal Investigator:	
Sponsor's Responsible Medical Officer:	

Study centre(s)

Sweden

Objectives

- To provide a detailed description of patients who are prescribed ticagrelor for the first time and to compare them with patients who are prescribed clopidogrel and prasugrel for the first time, and to estimate potential off-label use of ticagrelor.
- To ascertain incident cases and estimate the crude incidence rates for selected safety outcomes among new users in the three cohorts of ticagrelor, clopidogrel and prasugrel.

Study design

A retrospective cohort study using the Swedish national health registers.

The Swedish national health registers are maintained by the National Board of Health and Welfare (NBHW) and include the National Patient Register (NPR), which includes all diagnoses recorded in Swedish hospitals both in inpatient care and in hospital based ambulatory (outpatient) care and the prescribed drug register (PDR), which comprises all purchases of prescribed drugs at pharmacies (dispensed drugs). These registries are linked with the Total Population Register, which is maintained by Statistics Sweden and includes information on dates of emigration and death.

Identification of study subjects

All patients aged 20 to 84 years on the date of the initial prescription of ticagrelor, clopidogrel, or prasugrel within the study period, June 1, 2011 to December 31, 2012, were included in the study. The study inclusion period started the first month after ticagrelor market introduction in Sweden. In order to capture usual clinical practice no exclusion criteria was applied.

Study Cohorts

Three cohorts were identified according to use of the three drugs of interest: Incident users of ticagrelor, clopidogrel, or prasugrel. Patients were considered incident users on the date they were dispensed the specific drug of interest for the first time during the study period (index date) as long as they had not received that specific P2Y12 antagonist (ticagrelor, clopidogrel, or prasugrel) within one year prior to the index date. The index date for entry to a drug cohort was the date of the first qualifying incident prescription for that drug. Patients could be in more than one incident use cohort at different times if they were prescribed more than one of the P2Y12 receptor antagonists during the study period.

At the index date study subjects were further categorized according to previous P2Y12 antagonist exposure into “naïve” and “non-naïve” patients. “Naïve” patients were those without a previous P2Y12 antagonist prescription (different from the index study drug) recorded within one year before the index date. “Non-naïve” patients were those with one or more P2Y12 antagonist prescriptions (different from the index study drug) recorded within one year prior to the index date. Patients could be naïve for a particular drug and later

designated non-naïve for that drug if they went switched back and forth among the P2Y12 types within the study period.

During the study period, 49,332 unique P2Y12 receptor antagonist users were identified, with 42,319 contributing to the clopidogrel cohort (41,693 naïve and 626 non-naive), 1,428 contributing to the prasugrel cohort (991 naïve and 437 non-naive), and 6,945 contributing to the ticagrelor cohort (6,186 naïve and 759 non-naive).

Medication Use and Safety Outcomes

Study medication use during the follow-up period was classified into three categories:

- The current use period was defined as all continuous person-time while on the study medication up to the discontinuation date. The discontinuation date was defined as the date of the last prescription plus the days of supply of that prescription plus a 30 day grace period.
- The discontinuation period was defined as all person-time in the period immediately after the end of the current use period up to 90 days after the discontinuation date.
- The past use was all person-time accumulating after the discontinuation use period (discontinuation date + 90 days) and extending until the end of follow-up as long as no refill of the study drug occurred during this time.

Safety outcomes were determined from the patient register using ICD-10 code for diagnoses and NCSP codes for procedures for the following inpatient conditions:

- Intracranial bleeding,
- Gastrointestinal bleeding,
- Respiratory bleedings,
- Other bleeding: Episode of bleeding other than intracranial, gastrointestinal or respiratory bleeding.
- Pacemaker insertion,
- Brady-arrhythmia confirmed with ECG
- Cardiac arrest
- Heart failure
- Acute renal failure
- Acute liver injury

Safety outcomes were determined for the following outpatient conditions:

- Dyspnoea
- Syncope
- Gout.

Data collection and analysis

Patients using P2Y12 receptor antagonist users were identified from the prescribed drug register (PDR) which contains information on all drugs prescribed in Sweden that are

dispensed to patients outside hospitals The PDR includes patient demographic information, drugs by ATC codes, dates and settings of the dispensing, and the department specialty of the prescribing physician. Relevant co-medications for the P2Y12 antagonist users was also identified from the PDR.

Relevant clinical data for the identified P2Y12 receptor antagonist users were obtained from the National Patient Register (NPR). The personal identification number (PIN) unique to all Swedish citizens was used to link patients in the PDR who had used P2Y12 antagonists to NPR. The NPR contains ICD-10 coded data from all hospital admissions in Sweden from 1997 to present. At each discharge, information is collected about primary and secondary diagnoses, procedure codes, hospitals and wards of admission, and dates of admission and discharge.

Summary of results

Descriptive data

Among naïve users, the proportions of males (64%) were higher than the proportion of females (36%). The extremes were seen for clopidogrel (highest proportion women) and prasugrel (lowest proportion women). The age distribution was about the same for all study drugs with few young (less than 1% for 20-35 years and 13% or less for 35-50 years), more middle aged (28% to 44% for 50-65 years) and old (34% to 37% for 65-75 years). There was more variation in the oldest group; about 30% of ticagrelor and clopidogrel patients were in this category, while only 5% of prasugrel patients were this old. Non-naïve users included a higher proportion of males (73%) and age categories were even similar across the three drugs.

The co-morbidity pattern among naïve ticagrelor and prasugrel users were generally similar but naïve clopidogrel users showed less cardiovascular disease (MI/ACS/CABG/PCI 54% vs. ticagrelor 99% and prasugrel 96%) and more cerebrovascular disease (34% vs. ticagrelor 4 % and prasugrel 4 % (Table 1). Non-naïve users showed no substantial differences in comorbidity patterns across the three drugs.

The pattern of co-medication, within 1 year prior to index date, for naïve users of ticagrelor and clopidogrel was similar, but naïve prasugrel users showed less use of antithrombotic agents (35% vs. clopidogrel 56% and ticagrelor 48%), lipid modifying agents (35% vs. clopidogrel 47% and ticagrelor 44%) and beta blocking agents (36% vs. clopidogrel 43% and ticagrelor 45%). Concomitant use of low dose aspirin either before and/or within 30 days after the index date was lower in naïve clopidogrel users (76% vs ticagrelor 98% and 97% prasugrel 97%, respectively).

Table 1: Comorbidity within 1 year of index date among naïve users

Comorbidity	Clopidogrel	Prasugrel	Ticagrelor	Total
N	**41 693 (100%)**	**991 (100%)**	**6 186 (100%)**	**48 846 (100%)**
Cardiovascular Disease				
MI, ACS, PCI and/or CABG	22 388 (54%)	951 (96%)	6 110 (99%)	29 425 (60%)
MI	16 165 (39%)	871 (88%)	5 421 (88%)	22 437 (46%)

Comorbidity	**Clopidogrel**	**Prasugrel**	**Ticagrelor**	**Total**
N	**41 693 (100%)**	**991 (100%)**	**6 186 (100%)**	**48 846 (100%)**
MI (NSTEMI)	7 841 (19%)	159 (16%)	2 476 (40%)	10 466 (21%)
MI (STEMI)	3 450 (8%)	604 (61%)	2 313 (37%)	6 361 (13%)
MI (unspecified.)	4 874 (12%)	108 (11%)	632 (10%)	5 610 (11%)
ACS	20 593 (49%)	936 (94%)	6 014 (97%)	27 521 (56%)
PCI	14 191 (34%)	906 (91%)	5 236 (85%)	20 312 (42%)
CABG	534 (1%)	6 (1%)	89 (1%)	627 (1%)
Cardiac Arrest	259 (1%)	30 (3%)	121 (2%)	410 (1%)
Heart Failure	3 800 (9%)	94 (9%)	658 (11%)	4 549 (9%)
Peripheral Vascular Disease	3 275 (8%)	23 (2%)	226 (4%)	3 524 (7%)
Atrial fibrillation and flutter	3 474 (8%)	38 (4%)	303 (5%)	3 815 (8%)
Brady-arrhythmias	597 (1%)	19 (2%)	108 (2%)	724 (1%)
Pacemaker Insertion	938 (2%)	10 (1%)	101 (2%)	1 049 (2%)
Cerebrovascular Disease	14 071 (34%)	36 (4%)	227 (4%)	14 333 (29%)
Stroke	7 766 (19%)	14 (1%)	69 (1%)	7 848 (16%)
Bleeding				
Intracranial Bleeding	299 (1%)	7 (1%)	15 (0%)	321 (1%)
GI Bleeding	531 (1%)	5 (1%)	34 (1%)	570 (1%)
Respiratory Bleeding	246 (1%)	4 (0%)	29 (0%)	279 (1%)
Other Bleeding	719 (2%)	5 (1%)	100 (2%)	822 (2%)
Other Comorbidities				
Diabetes without complications	7 718 (19%)	189 (19%)	1 225 (20%)	9 125 (19%)
Diabetes with complications	2 277 (5%)	44 (4%)	249 (4%)	2 565 (5%)
Acute Renal Failure	188 (0%)	1 (0%)	20 (0%)	209 (0%)
Chronic Renal Disease	1 446 (3%)	14 (1%)	122 (2%)	1 581 (3%)
Dyspnoea	649 (2%)	14 (1%)	75 (1%)	737 (2%)
COPD	3 315 (8%)	70 (7%)	461 (7%)	3 840 (8%)
Syncope	604 (1%)	5 (1%)	49 (1%)	658 (1%)
Gout	399 (1%)	7 (1%)	44 (1%)	450 (1%)
Dementia	665 (2%)	0 (0%)	42 (1%)	707 (1%)
Peptic Ulcer Disease	380 (1%)	7 (1%)	20 (0%)	406 (1%)
Acute Liver Injury	4 (0%)	0 (0%)	0 (0%)	4 (0%)
Mild Liver Disease	284 (1%)	4 (0%)	34 (1%)	322 (1%)
Moderate/Severe Liver Disease	138 (0%)	1 (0%)	10 (0%)	149 (0%)
Cancer	2 492 (6%)	31 (3%)	315 (5%)	2 838 (6%)
Metastasis	247 (1%)	2 (0%)	17 (0%)	266 (1%)

Duration of treatment and presence of indication (potential off-label use)

The median duration of the first continuous use period for naïve ticagrelor users was 10.5 months with interquartile range 4.6-13.0 months. In total 2,552 (41.3%) of naïve ticagrelor users had a duration of 12 months and above. The majority (72.8%) of these had duration less

than 14 months. Among all naïve ticagrelor users, 88.8% had an estimated first continuous use duration of treatment less than 14 months.

The median duration of the first continuous use period for naïve clopidogrel users was 11.0 (interquartile range 4.3-14.4) months and 12.0 (interquartile range 7.0-13.3) months for naïve prasugrel users. In total 19,585 (47%) of naïve clopidogrel users and 480 (48%) of naïve prasugrel users had a duration of 12 months or above.

There were no diagnosis of MI, ACS, PCI or CABG recorded within the year before index date for 1% and 3% of naïve and non-naïve ticagrelor users respectively. Among naïve clopidogrel and prasugrel users there were no diagnosis of MI, ACS, PCI or CABG recorded within the year before index date in 46% and 4%, respectively.

Outcomes

Crude incidence rates of the selected outcomes in naïve users of clopidogrel, prasugrel and ticagrelor are provided in Table 2 below. There was no clear difference in incidence rates of intracranial, GI, and other bleeding across the different P2Y2 receptor antagonists. Incidence rates of respiratory bleeding in naïve prasugrel and ticagrelor users are higher than in naïve clopidogrel users. Crude incidence rates of heart failure among current users of prasugrel and ticagrelor were also higher than in current users of clopidogrel. In an analysis among patients with a history of MI/ACS, which is used as a proxy for treatment indication, the incidence rates of heart failure were comparable across current users of the drugs with IR (95% CI) per 1,000 person-years clopidogrel 23.2 (21.2-25.3), prasugrel 28.2 (18.4-41.3) and ticagrelor 24.9 (20.8-29.6) (Table 4). Incidence rates of respiratory bleeding remained higher in naïve prasugrel and ticagrelor users than in clopidogrel users in the stratified analysis (Table 3).

In the analysis of all naïve P2Y12 receptor antagonists the incidence rate of dyspnoea among current users of ticagrelor 26.2 (22.1-30.9) was higher than in current users of clopidogrel 12.0 (11.0-13.0) and prasugrel 9.1 (4.1-17.2) (Table 2). In an analysis among patients with a history of MI/ACS, the incidence rate of dyspnoea remained higher in current users of ticagrelor 26.3 (22.1-31.0) vs. current users of clopidogrel 15.8 (14.2-17.6) and prasugrel 9.4 (4.3-17.8) (Table 3). A similar pattern was observed in the analysis among patients with a history of MI and/or COPD, showing a higher incidence rate of dyspnoea in current users of ticagrelor 26.8 (22.4-31.8) vs. current users of clopidogrel 17.7 (15.8-19.7) and prasugrel 8.8 (3.8-17.3).

Table 2 Crude incidence rates (per 1,000 person-years) of selected safety outcomes in naïve current users of clopidogrel, prasugrel and ticagrelor

	Clopidogrel		Prasugrel		Ticagrelor	
Outcomes	**N**	**Incidence rate (95% CI) per 1,000 person-years**	**N**	**Incidence rate (95% CI) per 1,000 person-years**	**N**	**Incidence rate (95% CI) per 1,000 person-years**
Intracranial bleeding	217	4.9 (4.3-5.6)	2	2.0 (0.2-7.2)	23	4.2 (2.6-6.3)
GI bleeding	540	12.4 (11.4-13.5)	24	24.4 (15.6-36.3)	78	14.3 (11.3-17.8)
Respiratory bleeding	405	9.3 (8.4-10.2)	18	18.3 (10.8-28.9)	132	24.3 (20.4-28.9)
Other bleeding	381	8.7 (7.9-9.6)	9	9.1 (4.2-17.3)	53	9.7 (7.3-12.7)
Pacemaker insertion	161	3.7 (3.1-4.3)	7	7.1 (2.8-14.6)	35	6.4 (4.5-8.9)
Brady-arrhythmias	151	3.4 (2.9-4.0)	3	3.0 (0.6-8.8)	25	4.6 (2.9-6.7)
Cardiac arrest	84	1.9 (1.5-2.4)	2	2.0 (0.2-7.3)	12	2.2 (1.1-3.8)
Heart failure	627	14.7 (13.6-15.9)	26	27.3 (17.8-40.0)	133	25.3 (21.2-30.0)
Acute renal failure	89	2.0 (1.6-2.5)	1	1.0 (0.0-5.6)	17	3.1 (1.8-4.9)
Acute liver injury	2	0.0 (0.0-0.2)	0		0	
Dyspnoea	522	12.0 (11.0-13.0)	9	9.1 (4.1-17.2)	142	26.2 (22.1-30.9)
Syncope	431	9.9 (9.0-10.9)	5	5.0 (1.6-11.7)	54	9.9 (7.4-12.9)
Gout	85	1.9 (1.5-2.4)	0		12	2.2 (1.1-3.8)

Table 3 Crude incidence rates (per 1,000 person-years) of selected safety outcomes in naïve current users of clopidogrel, prasugrel and ticagrelor with history of MI/ACS

	Clopidogrel		Prasugrel		Ticagrelor	
Outcomes	**N**	**Incidence rate (95% CI) per 1,000 person-years**	**N**	**Incidence rate (95% CI) per 1,000 person-years**	**N**	**Incidence rate (95% CI) per 1,000 person-years**
Intracranial bleeding	111	4.9 (4.1-5.9)	2	2.1 (0.3-7.5)	23	4.2 (2.7-6.4)
GI bleeding	356	16.0 (14.4-17.7)	22	23.1 (14.5-35.0)	77	14.3 (11.3-17.9)
Respiratory bleeding	279	12.5 (11.1-14.0)	18	18.9 (11.2-29.9)	128	24.0 (20.0-28.5)
Other bleeding	185	8.3 (7.1-9.6)	7	7.3 (2.9-15.0)	52	9.7 (7.2-12.7)
Pacemaker insertion	133	6.0 (5.0-7.1)	6	6.2 (2.3-13.6)	35	6.5 (4.5-9.0)
Brady-arrhythmias	101	4.5 (3.7-5.5)	3	3.1 (0.6-9.1)	25	4.6 (3.0-6.8)

	Clopidogrel		**Prasugrel**		**Ticagrelor**	
Cardiac arrest	72	3.2 (2.5-4.0)	2	2.1 (0.3-7.5)	11	2.0 (1.0-3.6)
Heart failure	493	23.2 (21.2-25.3)	26	28.2 (18.4-41.3)	129	24.9 (20.8-29.6)
Acute renal failure	51	2.3 (1.7-3.0)	1	1.0 (0.0-5.8)	17	3.1 (1.8-5.0)
Acute liver injury	1	0.0 (0.0-0.2)	0		0	
Dyspnoea	352	15.8 (14.2-17.6)	9	9.4 (4.3-17.8)	140	26.3 (22.1-31.0)
Syncope	254	11.4 (10.0-12.9)	5	5.2 (1.7-12.1)	53	9.9 (7.4-12.9)
Gout	57	2.5 (1.9-3.3)	0		12	2.2 (1.1-3.9)