Patient characteristics and safety outcomes in new users of ticagrelor and clopidogrel—An observational cohort study in Sweden

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Abstract

Purpose: We aimed to describe characteristics of new users of ticagrelor or clopidogrel following a recent coronary event, and to compare incidences of selected safety outcomes.

Methods: This observational cohort study used data from national Swedish registers. Patients first dispensed ticagrelor or clopidogrel (June 2011–December 2013) were identified from the Prescribed Drug Register and followed until censoring or 31 December 2014. Cohorts were restricted to patients with a recent coronary event-related hospital contact identified in the Patient Register.

Results: The study included 45 987 unique, naïve users of ticagrelor (73% men; mean age 66 years) or clopidogrel (69% men; mean age 69 years). Corresponding to indication, diagnoses before initiation were acute coronary syndrome (93%), myocardial infarction (76%), and percutaneous coronary intervention (69%). The most common medications used in the year before initiation of study therapy were antithrombotic agents (clopidogrel 62%, ticagrelor 43%), mainly low-dose acetylsalicylic acid. Ticagrelor users had a higher incidence (per 1000 person-years) of respiratory bleeding (24.6 [95% confidence interval (CI): 22.1–27.3]; vs clopidogrel users: 14.4 [13.1–15.8]) and dyspnea (25.9 [23.3–28.7]; vs clopidogrel users: 16.8 [15.4–18.4]). Epistaxis accounted for 83–93% of respiratory bleeds. Adjusted analyses found increased risks of gout and acute renal failure with ticagrelor.

Conclusions: Clopidogrel users were older with a higher prevalence of concomitant medications than ticagrelor users. Our study showed increased incidences of dyspnea and respiratory bleeding (mainly epistaxis) among current ticagrelor users compared with clopidogrel users, and increased risks of gout and acute renal failure after adjustment.

Keywords
clopidogrel, cohort study, patient characteristics, safety, ticagrelor

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1 | INTRODUCTION

Antagonists of the platelet adenosine diphosphate P2Y_{12} receptor have become a standard treatment in the management of patients with acute coronary syndrome (ACS). Current practice guidelines recommend dual antiplatelet therapy with acetylsalicylic acid (ASA) and a P2Y_{12} receptor antagonist in patients with or without ST-segment elevation, regardless of revascularization strategy.\(^1\)–\(^4\) Wide inter- and intraindividual variability in the extent of platelet inhibition has been shown following treatment with the P2Y_{12} receptor antagonist clopidogrel,\(^5\)\(^,\)\(^6\) a limitation likely to have important clinical implications. Antiplatelet agents with the potential to overcome this clinical challenge have therefore been developed. Ticagrelor, a reversible and direct-acting antagonist of the P2Y_{12} receptor, has demonstrated improved platelet inhibition over that achieved with clopidogrel,\(^7\)\(^,\)\(^8\) and was shown to be superior to clopidogrel for the prevention of vascular events in a large randomized trial of patients with ACS, the Study of PLATelet Inhibition and Patient Outcomes (PLATO).\(^9\) Consistency between randomized trial results and real-world data was shown in a study based on a national Swedish quality register.\(^10\),\(^11\)

As the latest entrant in its class, ticagrelor might have initially been prescribed to patients deemed less likely to achieve adequate inhibition of platelet aggregation with other antiplatelet drugs, or to individuals with a particular cardiovascular comorbidity pattern. If this were the case, differences in patient characteristics due to channeling\(^12\) would hamper direct comparisons of ticagrelor with other antiplatelet agents in early studies of safety outcomes. Improved knowledge of the ticagrelor patient population in terms of comorbidities and concomitant medication use would thus be helpful when interpreting data from sources such as adverse event reporting systems, and would provide information on ticagrelor treatment patterns in clinical practice.

A post-authorization safety study (PASS)\(^13\) of ticagrelor was initiated in 2011 as part of the European Union Risk Management Plan of an approved medicinal product. The goal of the PASS was to assess patient characteristics, drug utilization patterns, and incidence of selected outcomes in new users of P2Y_{12} receptor antagonists. Predefined outcomes were selected based on the results of PLATO and other information available at the time of the PASS. Adverse event rates observed with ticagrelor in PLATO raised no major safety concerns.\(^9\) As would be expected for an antiplatelet drug, bleeding was the primary safety issue. Dyspnea was also commonly reported with ticagrelor, leading to discontinuation of the drug by 1% of patients. Serum creatinine and uric acid levels increased slightly more during treatment with ticagrelor than with clopidogrel; however, this was not associated with a rise in clinically meaningful adverse renal outcomes. Ticagrelor was shown to increase the frequency of Holter-detected ventricular pauses, but with no increase in clinically relevant events.\(^9\) A few cases of severe hepatotoxicity potentially related to clopidogrel treatment had been reported in the literature,\(^14\) leading to an evaluation of hepatotoxicity potential with ticagrelor as part of the PASS. At the time, there was also limited knowledge of treating patients with renal impairment with ticagrelor.

The present study was an extension of the original PASS. Its purpose was to describe the characteristics of patients in whom ticagrelor or clopidogrel treatment was initiated for the first time following a recent coronary event, to assess comorbidities and concomitant medication use and to compare incidences of selected safety outcomes. It was limited to patients with a likely indication of a coronary event and had a longer study period than the original PASS. It also included adjusted analyses.

2 | METHODS

2.1 | Data sources

Data were obtained from the national registers maintained by the Swedish National Board of Health and Welfare and Statistics. Individual patient data were linked between registers by a unique personal identification number. The Prescribed Drug Register (PDR)\(^15\) contains data for all purchases of prescribed drugs at pharmacies by patients outside hospitals, including personal identification number, date of purchase, anatomical therapeutic chemical (ATC) code, and amount dispensed in defined daily doses,\(^16\) and the department specialty of the prescribing physician. The National Patient Register (NPR)\(^17\) includes all diagnoses and surgical procedures recorded in Swedish hospitals, in both inpatient and hospital-based ambulatory care, using International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes for diagnoses and Nordic...
Medico-Statistical Committee Classification of Surgical Procedures (NCSP) codes for procedures. Information on dates of emigration and deaths for all patients was retrieved from the Total Population Register.

2.2 | Study design and cohorts

A cohort study was performed using data for patients taking P2Y₁₂ receptor antagonists identified from the PDR.

All P2Y₁₂ receptor antagonist naïve incident clopidogrel and ticagrelor users aged 20–84 years were included at their first dispensing (index date) during the study period (1 June 2011–31 December 2013) (Figure 1). Incident users were defined as those who had not received the study drug during the year prior to the index date and naïve users as those without a previous prescription for any P2Y₁₂ receptor antagonist during this year. Prasugrel users were excluded because of low numbers. Furthermore, patients who had immigrated within 6 months of the index date were excluded to guarantee database coverage. In order to capture usual clinical practice no other exclusion criteria were applied.

Cohorts were subsequently restricted to patients for whom the likely indication was a coronary event, corresponding to the on-label indications for ticagrelor and clopidogrel at the time of the study (Figure 1). Diagnoses and procedures from the NPR used as proxies for the indication were myocardial infarction (MI; ICD-10 codes I21, I22, and I25.2), ACS (ICD-10 codes I20, I21, and I22), percutaneous coronary intervention (PCI; NCSP code FNG), and coronary artery bypass graft (CABG; NCSP codes FNA, FNB, FNC, FND, and FNE), occurring in the year before the index date (for details of ICD-10 and NCSP codes see Table S1). The use of patient register data for diagnoses has shown acceptable validity.17–20 All individuals were followed up from the index date until one of the following events occurred: a selected outcome, the patient’s 85th birthday, emigration, death, or 31 December 2014. For each outcome of interest a separate follow-up was performed. Patients with a history of the specific study outcome before the index date in each respective follow-up were excluded. Two cohorts were identified: ticagrelor initiators and clopidogrel initiators; patients could contribute data to both cohorts if separate treatment episodes occurred.

2.3 | Exposure

To analyze time-dependent exposure, allowing for investigation of decaying and/or persisting drug effects, study medication use was classified into three categories: (1) “current use”—patients contributed person-time to this category while they were being treated with the study medication, with an extended grace period of 30 days after the end of supply (based on defined daily doses); (2) “recent use”—patients contributed person-time to this category from 31 days after treatment with the last study drug dispensing would have ended (assuming full adherence) up to a maximum of 90 days; and (3) “past use”—patients contributed person-time to this category from the end of the recent use category until the end of follow-up, provided no refill of the study drug prescription occurred during this time (Figure 2). Each new dispensing ended the ongoing exposure and started a new current use of the dispensed drug.

The first continuous use period was defined as starting at the index date and ending at the first gap in drug supply (i.e., the start of the first recent use period) or the end of follow-up, whichever came first. Note that the first continuous use period included a grace period of 30 days as defined above, and was right censored at the end of the study.

2.4 | Covariates

Comorbidities related to the indication of clopidogrel and ticagrelor were included: coronary events (MI, ACS) and coronary interventions, atrial fibrillation and flutter, and stroke (Table S1). Further additions were comorbidities corresponding to the 13 selected safety outcomes (see below) and additional disease groups specified by Charlson et al.,21,22 with modified definitions for chronic obstructive pulmonary disease, moderate or severe liver disease, and acquired immune deficiency syndrome/human immunodeficiency virus infection (Table S2).
Use of the following concomitant medications was investigated: antidiabetic agents (ATC code A10), antithrombotic agents (B01), cardiac therapy (C01), antihypertensives (C02), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08), agents acting on the renin–angiotensin system (C09), lipid-modifying agents (C10), oral steroids (H02), and non-steroidal anti-inflammatory drugs (M01A) (Table 1).

In all covariate definitions, a time window of 1 year before the index date was used.

### 2.5 | Outcomes

The 13 selected safety outcomes were intracranial bleeding, gastrointestinal bleeding, respiratory bleeding, other bleeding, pacemaker insertion, bradyarrhythmias, cardiac arrest, heart failure, acute renal failure, acute liver injury, dyspnea, syncope, and gout. Diagnoses were identified from the NPR using ICD-10 codes (Table S3) from main diagnoses from inpatient and outpatient care.

### 2.6 | Statistical analysis

Numbers and proportions were used to describe categorical variables, and means with standard deviations and/or medians with interquartile ranges were used to describe continuous variables. Ticagrelor and clopidogrel cohorts were described in terms of age and sex distribution, and prevalence of concomitant treatments and recorded comorbidities.

Crude incidences (with 95% confidence intervals [CIs]) were estimated as the ratio of the number of cases with the outcome of interest divided by the number of person-years among users of the study drug grouped by exposure category (current, recent, or past use). An analysis comparing ticagrelor and clopidogrel was also carried out for the selected safety outcomes using Cox regression, adjusting for sex, age, income, education, use of concomitant medication (ASA, cardiac therapy, diuretics, beta blocking agents, agents acting on the renin–angiotensin system, and lipid-modifying agents), heart failure, PCI, ACS, stroke, atrial fibrillation, MI, and cerebrovascular disease. This analysis was not specified in the original PASS protocol.

### 3 | RESULTS

In total, 45,987 unique naïve users of ticagrelor or clopidogrel were included in this study, with 30,492 contributing to the clopidogrel cohort and 15,607 contributing to the ticagrelor cohort (i.e., 112 patients contributed to both cohorts) (Figure 1).

### 3.1 | Patient characteristics

The majority of the naïve ticagrelor or clopidogrel users were men (71%), and the mean age was 68 years (Table 1). Clopidogrel users were, on average, older than ticagrelor users. Corresponding to the inclusion criteria, nearly all patients (98–99%) had a previous MI or ACS diagnosis. Overall, the comorbidities and interventions related to the indication were ACS (93%), MI (76%), and PCI (69%); CABG was less common (3%). Patients taking clopidogrel had a lower prevalence of previous MI, ACS, and PCI than those taking ticagrelor, when analyzed separately (Table 1). In terms of comorbidities corresponding to outcomes and Charlson comorbidities in the previous year, clopidogrel users had a higher prevalence of heart failure and cerebrovascular disease than ticagrelor users.

Overall, 56% ($n = 25,627$) of patients had a history of antithrombotic agent use; most of them (91% [23,299/25,627]) took low-
**TABLE 1**  Baseline characteristics: sex, age, concomitant medications, and comorbidities during the 1 year before the index date

| Variable                                      | Clopidogrel (n = 30492) | Ticagrelor (n = 15607) | Total population (N = 46 987) |
|-----------------------------------------------|-------------------------|------------------------|--------------------------------|
| **Sex**                                       |                         |                        |                                |
| Men                                           | 21 122 (69)             | 11 409 (73)            | 32 447 (71)                    |
| **Age (years)**                               |                         |                        |                                |
| 20–35                                         | 46 (<1)                 | 47 (<1)                | 93 (<1)                        |
| 35–50                                         | 1440 (5)                | 1161 (7)               | 2595 (6)                       |
| 50–65                                         | 8488 (28)               | 5570 (36)              | 14 020 (30)                    |
| 65–75                                         | 10 940 (36)             | 5518 (35)              | 16 419 (36)                    |
| 75–84                                         | 9578 (31)               | 3311 (21)              | 12 860 (28)                    |
| **Mean (SD)**                                 | 69 (10.0)               | 66 (10.3)              | 68 (10.2)                      |
| **Median (IQR)**                              | 70 (62–77)              | 67 (59–74)             | 69 (61–76)                     |
| **Comorbidities related to indication**        |                         |                        |                                |
| PCI                                           | 18 771 (62)             | 13 082 (84)            | 31 772 (69)                    |
| CABG                                          | 791 (3)                 | 371 (2)                | 1161 (3)                       |
| ACS                                           | 27 646 (91)             | 15 367 (98)            | 42907 (93)                     |
| MI                                            | 21 263 (70)             | 13 616 (87)            | 34 879 (76)                    |
| NSTEMI                                         | 10 158 (33)             | 6416 (41)              | 16 526 (36)                    |
| STEMI                                          | 4200 (14)               | 5429 (35)              | 9616 (21)                      |
| **Unspecified**                               | 6905 (23)               | 1771 (11)              | 8634 (19)                      |
| MI and/or ACS                                 | 29 793 (98)             | 15 465 (99)            | 45 147 (98)                    |
| **Other cardiovascular comorbidities**         |                         |                        |                                |
| Stroke                                        | 1622 (5)                | 165 (1)                | 1784 (4)                       |
| Atrial fibrillation and flutter               | 3905 (13)               | 819 (5)                | 4714 (10)                      |
| **Concomitant medications (ATC codes)**       |                         |                        |                                |
| Antidiabetic agents (A10)                     | 6577 (22)               | 2706 (17)              | 9249 (20)                      |
| Antithrombotic agents (B01)                   | 18 998 (62)             | 6722 (43)              | 25 627 (56)                    |
| Vitamin K antagonists (B01AA)                 | 2464 (8)                | 294 (2)                | 2751 (6)                       |
| Low-dose ASA (B01AC06)                        | 17 006 (56)             | 6382 (41)              | 23 399 (51)                    |
| Cardiac therapy (C01)                         | 12 083 (40)             | 3959 (25)              | 15 984 (35)                    |
| Digitalis glycosides (C01AA)                  | 696 (2)                 | 94 (1)                 | 785 (2)                        |
| Anti hypertensives (C02)                      | 473 (2)                 | 184 (1)                | 655 (1)                        |
| Diuretics (C03)                               | 8531 (28)               | 3025 (19)              | 11 522 (25)                    |
| Beta blocking agents (C07)                    | 16 564 (54)             | 6325 (41)              | 22 808 (50)                    |
| Calcium channel blockers (C08)                | 8534 (28)               | 3523 (23)              | 12 020 (26)                    |
| Agents acting on the renin–angiotensin system (C09) | 15 535 (51) | 6833 (44) | 22 291 (48) |
| Lipid-modifying agents (C10)a                 | 16 048 (53)             | 6108 (39)              | 22 071 (48)                    |
| Simvastatin (C10AA01, C10BA02)                | 11 992 (39)             | 4155 (27)              | 16 098 (35)                    |
| Oral steroids (H02)                           | 3528 (12)               | 1491 (10)              | 5004 (11)                      |
| NSAIDs (M01A)                                 | 6315 (21)               | 3167 (20)              | 9467 (21)                      |
| CYP3A4 strong inducersb                       | 370 (1)                 | 115 (1)                | 484 (1)                        |
| CYP3A4 strong inhibitorsc                     | 229 (1)                 | 61 (<1)                | 290 (1)                        |
| **Comorbidities corresponding to outcomes**   |                         |                        |                                |
| Intracranial bleeding                         | 130 (<1)                | 36 (<1)                | 166 (<1)                       |
| Gastrointestinal bleeding                     | 423 (1)                 | 90 (1)                 | 512 (1)                        |
| Respiratory bleeding                          | 219 (1)                 | 80 (1)                 | 298 (1)                        |
| Other bleeding                                | 591 (2)                 | 245 (2)                | 830 (2)                        |
| Pacemaker insertion                           | 1034 (3)                | 281 (2)                | 1308 (3)                       |
| Bradycardiac rhythm                           | 643 (2)                 | 278 (2)                | 917 (2)                        |
| Cardiac arrest                                | 335 (1)                 | 292 (2)                | 627 (1)                        |
| Heart failured                                | 4519 (15)               | 1580 (10)              | 6084 (13)                      |

(Continues)
dose ASA in the year before the index date. Other common concomitant medications were beta-blocking agents, agents acting on the renin–angiotensin system, and lipid-modifying agents (Table 1). The clopidogrel cohort had a numerically higher proportion of use of these concomitant medications than the ticagrelor cohort (51%–62% vs. 39%–44%, respectively).

### 3.2 Crude incidences of safety outcomes

Figure 3 shows the observed incidences of safety outcomes according to current, recent, and past use. Event counts and person time are shown in Table 2 and Table S4. The observed incidences of bleeding among current users of either drug were numerically higher for gastrointestinal and respiratory bleeding than for intracranial and other bleeding. Ticagrelor was associated with a higher estimated incidence of respiratory bleeding (24.6 per 1000 person-years [95% CI: 22.1–27.4]) than clopidogrel (14.4 per 1000 person-years [95% CI: 13.1–15.8]). For both drugs, epistaxis was the main type of respiratory bleeding, accounting for 83%–93% of cases, depending on the drug and type of use (clopidogrel or ticagrelor, and current, recent, or past use).

The incidence of dyspnea per 1000 person-years was 25.9 (95% CI: 23.3–28.7) with current ticagrelor use, compared with 16.8 (95% CI: 24.0–22.4) with current clopidogrel use.

### Table 1 (Continued)

| Variable                        | Clopidogrel (n = 30,492) | Ticagrelor (n = 15,607) | Total population (N = 45,987) |
|---------------------------------|--------------------------|-------------------------|-------------------------------|
|                                 | n (%)                    | n (%)                   | n (%)                         |
| Acute renal failure             | 188 (1)                  | 50 (<1)                 | 238 (1)                       |
| Acute liver injury              | 2 (<1)                   | 0 (0)                   | 2 (<1)                        |
| Dyspnea                         | 682 (2)                  | 196 (1)                 | 878 (2)                       |
| Syncope                         | 415 (1)                  | 122 (1)                 | 536 (1)                       |
| Gout                            | 410 (1)                  | 133 (1)                 | 542 (1)                       |
| **Charlson comorbidities**      |                          |                         |                               |
| Peripheral vascular disease     | 1939 (6)                 | 558 (4)                 | 2487 (5)                      |
| Cerebrovascular disease         | 3430 (11)                | 527 (3)                 | 3948 (9)                      |
| Dementia                        | 450 (1)                  | 93 (1)                  | 542 (1)                       |
| COPD                            | 3036 (10)                | 1194 (8)                | 4215 (9)                      |
| Rheumatologic disease           | 1070 (4)                 | 438 (3)                 | 1506 (3)                      |
| Peptic ulcer disease            | 237 (1)                  | 42 (<1)                 | 279 (1)                       |
| Mild liver disease              | 222 (1)                  | 99 (1)                  | 321 (1)                       |
| Diabetes without complications  | 7037 (23)                | 3085 (20)               | 10,086 (22)                   |
| Diabetes with complications     | 1840 (6)                 | 625 (4)                 | 2448 (5)                      |
| Paraplegia                      | 360 (1)                  | 60 (<1)                 | 418 (1)                       |
| Renal disease                   | 1552 (5)                 | 392 (3)                 | 1939 (4)                      |
| Any malignancy                  | 2078 (7)                 | 781 (5)                 | 2855 (6)                      |
| Moderate/severe liver disease   | 35 (<1)                  | 4 (<1)                  | 39 (<1)                       |
| Metastatic solid tumor          | 198 (1)                  | 54 (<1)                 | 251 (1)                       |
| HIV infection                   | 17 (<1)                  | 7 (<1)                  | 24 (<1)                       |

**Note:** Percentages are calculated using the following total numbers of patients: clopidogrel, 30,492; ticagrelor, 15,607; total, 45,987.

**Abbreviations:** ACS, acute coronary syndrome; ASA, acetylsalicylic acid; ATC, anatomical therapeutic chemical; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CYP3A4, cytochrome P450 3A4; HIV, human immunodeficiency virus; IQR, interquartile range; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation MI.

**a**Simvastatin (C10AA01), lovastatin (C10AA02), pravastatin (C10AA03), fluvastatin (C10AA04), atorvastatin (C10AA05), rosuvastatin (C10AA07), pitavastatin (C10AA08), bezafibrate (C10AB02), gemfibrozil (C10AB04), fenofibrate (C10AB05), colesevelam (C10AC04), nicotinic acid (C10AD02), acipimox (C10AD06), nicotinic acid, combinations (C10AD52), omega-3 triglycerides including other esters and acids (C10AX06), ezetimibe (C10AX09), lomitapide (C10AX12), evolocumab (C10AX13), alirocumab (C10AX14), simvastatin and ezetimibe (C10BA02), atorvastatin and ezetimibe (C10BA05).

**b**Rifampicin (J04AB02), phenytoin (N03AB02), carbamazepine (N03AF01).

**c**Aprepitant (A04AD12), verapamil (C08DA01), selective calcium channel blockers with direct cardiac effects (C08DB), trandolapril and verapamil (C09BB10), erythromycin (J01FA01), ciprofloxacin (J01MA02), triazole derivatives (J02AC), protease inhibitors (J05AE), imatinib (L01XE01), ciprofloxacin (S02A1A5).

**d**Modified Charlson comorbidities excluding MI and congestive heart failure (part of indication).
FIGURE 3  Safety outcomes: crude incidences with 95% confidence intervals
| Outcome                  | Cohort     | Current | Recent | Past |
|--------------------------|------------|---------|--------|------|
|                          | n          | Person-years | HR (95% CI) | n          | Person-years | HR (95% CI) | n          | Person-years | HR (95% CI) |
| Intracranial bleeding    | Clopidogrel| 142     | 30 285 | 1.08 (0.79–1.48) | 27        | 6803       | 0.80 (0.34–1.85) | 101        | 33 509       | 0.71 (0.43–1.18) |
|                          | Ticagrelor | 66      | 14 229 |                          | 8         | 3709       |                          | 21         | 10 095       |                          |
| GI bleeding              | Clopidogrel| 484     | 29 905 | 1.03 (0.87–1.21) | 52        | 6771       | 1.91 (1.22–3.00) | 215        | 33 296       | 0.87 (0.63–1.20) |
|                          | Ticagrelor | 237     | 14 103 |                          | 40        | 3695       |                          | 52         | 10 038       |                          |
| Respiratory bleeding     | Clopidogrel| 431     | 29 666 | 1.58 (1.36–1.84) | 45        | 6775       | 1.76 (1.07–2.88) | 182        | 33 281       | 0.82 (0.57–1.16) |
|                          | Ticagrelor | 345     | 14 012 |                          | 31        | 3695       |                          | 43         | 10 041       |                          |
| Other bleeding           | Clopidogrel| 306     | 29 960 | 1.02 (0.83–1.25) | 47        | 6757       | 0.82 (0.45–1.47) | 193        | 33 176       | 1.10 (0.80–1.50) |
|                          | Ticagrelor | 161     | 14 101 |                          | 17        | 3692       |                          | 58         | 10 017       |                          |
| Pacemaker insertion      | Clopidogrel| 196     | 29 938 | 1.04 (0.81–1.34) | 51        | 6722       | 1.38 (0.81–2.34) | 165        | 33 060       | 0.91 (0.63–1.31) |
|                          | Ticagrelor | 106     | 14 134 |                          | 34        | 3691       |                          | 42         | 10 039       |                          |
| Brady-arrhythmias        | Clopidogrel| 138     | 30 159 | 1.11 (0.80–1.53) | 24        | 6783       | 1.48 (0.68–3.22) | 118        | 33 393       | 0.67 (0.40–1.12) |
|                          | Ticagrelor | 62      | 14 183 |                          | 11        | 3700       |                          | 19         | 10 065       |                          |
| Cardiac arrest           | Clopidogrel| 91      | 30 315 | 0.83 (0.52–1.31) | 15        | 6805       | 0.74 (0.23–2.35) | 55         | 33 560       | 0.67 (0.32–1.41) |
|                          | Ticagrelor | 27      | 14 220 |                          | 4         | 3706       |                          | 9          | 10 098       |                          |
| Heart failure            | Clopidogrel| 721     | 28 204 | 1.01 (0.89–1.16) | 99        | 6364       | 0.97 (0.66–1.41) | 350        | 31 373       | 0.82 (0.64–1.06) |
|                          | Ticagrelor | 373     | 13 583 |                          | 44        | 3575       |                          | 82         | 9656         |                          |
| Acute renal failure      | Clopidogrel| 83      | 30 299 | 1.57 (1.04–2.38) | 16        | 6805       | 1.87 (1.05–3.43) | 75         | 33 533       | 0.80 (0.44–1.43) |
|                          | Ticagrelor | 40      | 14 224 |                          | 8         | 3709       |                          | 15         | 10 102       |                          |
| Acute liver injury       | Clopidogrel| 3       | 30 348 | 1.34 (0.19–9.25) | 1         | 6810       | 1.17 (0.03–44.50) | 0          | 33 596       | NA^c                     |
|                          | Ticagrelor | 2       | 14 248 |                          | 1         | 3712       |                          | 0          | 10 110       |                          |
| Dyspnea                  | Clopidogrel| 501     | 29 761 | 1.66 (1.44–1.93) | 100       | 6742       | 1.17 (0.81–1.68) | 355        | 33 066       | 0.95 (0.74–1.21) |
|                          | Ticagrelor | 362     | 13 992 |                          | 51        | 3684       |                          | 90         | 9996         |                          |
| Syncope                  | Clopidogrel| 333     | 29 797 | 1.10 (0.90–1.35) | 56        | 6873       | 1.22 (0.75–1.98) | 256        | 33 234       | 1.02 (0.77–1.37) |
|                          | Ticagrelor | 162     | 14 107 |                          | 29        | 3696       |                          | 67         | 10 042       |                          |
| Gout                     | Clopidogrel| 85      | 30 222 | 1.64 (1.11–2.44) | 19        | 6789       | 1.62 (0.76–3.45) | 95         | 33 422       | 1.14 (0.73–1.79) |
|                          | Ticagrelor | 46      | 14 204 |                          | 13        | 3705       |                          | 29         | 10 074       |                          |

Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NA, not applicable.

^aThe model was adjusted for sex, age, income, education, acetylsalicylic acid use, cardiac therapy, diuretic use, beta blocking agent use, use of agents acting on the renin–angiotensin system, use of lipid-modifying agents, heart failure, percutaneous coronary intervention, acute coronary syndrome, stroke, atrial fibrillation, myocardial infarction, and cerebrovascular disease.

^bStatistically significant, p < 0.05.

^cNo events observed.
Cl: 15.4–18.4) with current clopidogrel use. The incidence of heart failure per 1000 person-years was similar for the two groups (current use—ticagrelor 27.5 [95% CI: 24.7–30.4], clopidogrel 25.6 [95% CI: 23.7–27.5]; past use—ticagrelor 8.5 [95% CI: 6.8–10.5], clopidogrel 11.2 [95% CI: 10.0–12.4]).

For clopidogrel, incidences of all outcomes except pacemaker insertion, acute liver injury, and gout showed a declining pattern when moving from current to recent to past use (Figure 3). For ticagrelor, all outcomes except other bleeding, pacemaker insertion, acute liver injury, and gout showed a declining incidence pattern moving from current to recent to past use.

### 3.3 Survival analysis of safety outcomes

Comparison of the current use of ticagrelor and clopidogrel showed a statistically significantly increased risk of respiratory bleeding, dyspnea, acute liver failure, and gout with ticagrelor (Table 2). When considering recent use, there were significantly increased risks of gastrointestinal and respiratory bleeding with ticagrelor compared with clopidogrel. No significant differences in risks between the two agents were observed with past use.

### 4 DISCUSSION

This observational cohort study used data from national Swedish registers to assess comorbidities, concomitant medication use, and incidences of selected safety outcomes in patients in whom ticagrelor or clopidogrel treatment was initiated for the first time following a recent coronary event. The study is an extension of the ticagrelor PASS initiated in 2011. The study population and predefined outcomes were based on approved drug indications and data available at the time. Prescribing patterns of ticagrelor and clopidogrel are likely to have changed in the years since the study. European guidelines published during the study period recommend ticagrelor over clopidogrel for patients with ACS, as do current European and US guidelines. European and US guidelines recommend extension of dual antiplatelet therapy (DAPT) with ticagrelor 60 mg in high-risk patients with a history of MI who have tolerated 12 months of DAPT and who are not at heightened bleeding risk.

As could be expected in a population with cardiovascular disease, the age distribution of ticagrelor and clopidogrel users was skewed towards older age, with a higher proportion of men than women. Not all patients had a recorded MI and/or ACS diagnosis, and some were thus included because of the coronary intervention procedure (PCI or CABG) only. The absence of a diagnosis code of coronary disease may be explained by the use of data from the NPR, which does not cover primary care, although the ACS definition used in this study includes angina pectoris diagnoses in inpatient and outpatient specialized care. At the time the study was conducted clopidogrel had a broader indication than ticagrelor, including stroke, peripheral artery disease, and prevention of thromboembolic events in atrial fibrillation. During the study both drugs were recommended for use in combination with low-dose ASA, but this differed by indication for clopidogrel. Concomitant medications used in this study were dominated by anti-thrombotic agents, low-dose ASA, beta blocking agents, agents acting on the renin–angiotensin system, and lipid-modifying agents for both study drugs. For clopidogrel, these concomitant medications were purchased by about 50%–60% of users within 1 year before the index date; for ticagrelor, these proportions were around 40%–45%.

When considering safety outcomes, we found a declining pattern in the crude incidence of heart failure over current, recent, and past use for both clopidogrel and ticagrelor, and incidences were similar for the two drugs. The crude incidence of dyspnea was higher during current use of ticagrelor than with current use of clopidogrel, and adjusted analyses showed an increased risk of dyspnea with ticagrelor compared with clopidogrel for current use. Dyspnea is a well-known adverse event that was commonly reported in patients receiving ticagrelor in PLATO. Ticagrelor-related dyspnea in PLATO was mostly transient, mild, or moderate in intensity. No differences in pulmonary function parameters were observed between the ticagrelor and clopidogrel groups in the PLATO pulmonary function sub-study.

Our study found no clear difference in the crude incidence of intracranial bleeding, gastrointestinal bleeding, and other bleeding between clopidogrel and ticagrelor groups. The crude incidence of respiratory bleeding was higher with ticagrelor than with clopidogrel. Respiratory bleeding was dominated by epistaxis (between 83–93%) for both drugs and for all periods of use. Adjusted analyses found an increased risk of respiratory bleeding (mostly epistaxis) with ticagrelor compared with clopidogrel for current and recent use.

Our results demonstrated that crude incidences of pacemaker insertion, bradycardias, cardiac arrest, acute renal failure, acute liver injury, syncope, and gout in current users of ticagrelor were comparable to those in current users of clopidogrel. When comparing current use of ticagrelor with clopidogrel, adjusted analysis found an increased risk of acute renal failure and gout. Gout, dyspnea and respiratory bleedings are clinical events that are obvious. On the other hand, hyperuricemia or renal function need to be monitored if there is a suspicion of an elevated risk of gout or renal failure. Potential mechanisms for an increased risk of renal failure and dyspnea might be a drug interaction between angiotensin receptor blockers and ticagrelor. Moreover, ticagrelor is metabolized through the kidneys, which may influence renal function and the uptake/secretion of uric acid leading to gout. For the treating physician, the observed safety signals may be considered before deciding between ticagrelor and clopidogrel in patients with elevated risk for these outcomes. Randomized trials imply no need for update of clinical guidelines, for example, in PLATO, the slight increase in serum levels of creatinine and uric acid for ticagrelor as compared with clopidogrel resolved after the end of treatment. Reports of gout did not differ between treatment groups in PLATO. In two other large randomized trials, gout occurred more commonly with ticagrelor than with placebo, but
there was no noticeable difference between ticagrelor and placebo in rates of renal adverse events or renal impairment.\textsuperscript{33,34} Future observational research on antiplatelet agents should include longer follow-up and more patients and focus on a wide range of adverse events. The research should be planned to be able to confirm or refute the findings of the current study.

4.1 | Strengths and limitations

The major strength of this study is the use of Swedish national registers, covering the total population and allowing inclusion of all patients taking ticagrelor and clopidogrel in Sweden, mirroring actual clinical use of the drugs. No exclusion criteria other than at least 0.5 years of database coverage prior to initiation of study drug treatment were applied.

A limitation is that the diagnoses covered only hospital care: although both inpatient and outpatient data were included, diagnoses from primary care were absent from this study. In addition, we could only assess the use of P2Y\textsubscript{12} receptor antagonists and concomitant medications in the outpatient setting because the PDR holds only community pharmacy dispensing data; patients administered P2Y\textsubscript{12} receptor antagonists or concomitant medications in hospital alone were not captured. The indication for therapy is not captured in the data employed, so a medical history of MI, ACS, PCI, or CABG was used as a proxy for indication. Also, when comparing a new drug, ticagrelor, to an established drug, clopidogrel, differences between the two study cohorts may affect the results. To illustrate any differences, we estimated hazard ratios for all bleeding events also in subgroups by age, renal function, diabetes and multiple comorbidities (see Table S5). Furthermore, the exact date of treatment discontinuation was not known, and the duration of therapy was estimated based on the amount of drug dispensed due to non-available information on prescribed dose. The defined daily dose was in this study chosen for calculation of treatment duration since on average it is correct, with few patients deviating from the once/twice daily recommendation. Also, adherence was unknown, but we believe that it does not differ between the two study drugs. Moreover, treatment episodes continuing beyond the end of follow-up were cut short. Finally, residual confounding may occur in the adjusted analyses presented.

5 | CONCLUSIONS

Patients taking clopidogrel were older and had a higher prevalence of concomitant medication use than those taking ticagrelor. Our study showed an elevated risk of dyspnea for current ticagrelor users compared with clopidogrel users. We also found an elevated risk of respiratory bleeding (mainly epistaxis) with current and recent use of ticagrelor. Furthermore, the results of adjusted analyses suggest a higher risk of gout and acute renal failure among current ticagrelor users compared with clopidogrel users.

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CONFLICT OF INTEREST

M.L. is an employee of the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations), including AstraZeneca, for performance of drug safety and drug utilization studies. M.A. was an employee at the Centre for Pharmacoepidemiology, Karolinska Institutet at the time the study was conducted. Morten Andersen reports grants from AstraZeneca, Novartis, Pfizer, Janssen, H. Lundbeck & Mertz, and the Novo Nordisk Foundation (NNF15SA0018404) outside the submitted work, and personal fees from Atrium and the Danish Pharmaceutical Industry Association for leading and teaching pharmacoepidemiology courses.

ETHICS STATEMENT

The study was approved by the Ethical Review Board at Karolinska Institutet, Stockholm (reference number 2013/1:11).

AUTHOR CONTRIBUTIONS

Marie Linder made substantial contributions to the conception and design of the study, the acquisition of data, and the interpretation of data, as well as carrying out the statistical analysis and drafting the paper. Morten Andersen contributed to the design of the study, the interpretation of the results, and writing and revision of the paper. Both authors have given final approval for the article to be published and agree to be accountable for all aspects of the work.

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