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Prasugrel versus ticagrelor in patients with myocardial infarction undergoing percutaneous coronary intervention

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ABSTRACT

Objective The comparative efficacy and safety of prasugrel and ticagrelor in patients with myocardial infarction (MI) treated with percutaneous coronary intervention (PCI) remain unclear. We aimed to investigate the association of treatment with clinical outcomes.

Methods In the SWEDEHEART (Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies) registry, all patients with MI treated with PCI and discharged on prasugrel or ticagrelor from 2010 to 2016 were included. Outcomes were 1-year major adverse cardiac and cerebrovascular events (MACCE, death, MI or stroke), individual components and bleeding. Multivariable adjustment, inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were used to adjust for confounders.

Results We included 37 990 patients, 2073 in the prasugrel group and 35 917 in the ticagrelor group. Patients in the prasugrel group were younger, more often admitted with ST elevation MI and more likely to have diabetes. Six to twelve months after discharge, 20% of patients in each group discontinued the P2Y12 receptor inhibitor they received at discharge. The risk for MACCE did not significantly differ between prasugrel-treated and ticagrelor-treated patients (adjusted HR 1.03, 95% CI 0.86 to 1.24). We found no significant difference in the adjusted risk for death, recurrent MI or stroke alone between the two treatments. There was no significant difference in the risk for bleeding with prasugrel versus ticagrelor (2.5% vs 3.2%, adjusted HR 0.92, 95% CI 0.69 to 1.22). IPTW and PSM analyses confirmed the results.

Conclusion In patients with MI treated with PCI, prasugrel and ticagrelor were associated with similar efficacy and safety during 1-year follow-up.

INTRODUCTION

Dual antiplatelet therapy (DAPT), with aspirin and a P2Y12 receptor inhibitor, is the main antithrombotic treatment in patients with acute coronary syndrome (ACS). Ticagrelor and prasugrel have proven superior to clopidogrel in reducing the risk

of major adverse cardiac events, but at the expense of a higher bleeding rate.^{1,2}

Prasugrel is a third-generation thienopyridine, binding irreversibly to the P2Y12 receptors.³ Ticagrelor binds reversibly to P2Y12 receptors, without hepatic metabolism.⁴ Both drugs provide a more prompt, potent and predictable platelet inhibitory effect than clopidogrel.^{5,6} However, there are differences between the two drugs in side effect profile, number of daily doses during maintenance treatment and interactions.

Two randomised controlled trials (RCTs) have compared the efficacy and safety of ticagrelor versus prasugrel in patients with an ACS treated with percutaneous coronary intervention (PCI) showing conflicting results. The PRAGUE-18 trial (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) reported comparable efficacy and safety between the two agents.⁷ In contrast, the recent ISAR-REACT 5 trial (Intra-coronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) showed superiority of prasugrel over ticagrelor in terms of reduced risk for myocardial infarction (MI).⁸ Observational, real-life comparisons between ticagrelor and prasugrel have reported contradictory results.^{9–13}

Based on large RCTs,^{1,2} ticagrelor (in all patients with ACS) and prasugrel (in PCI-treated patients with ACS) have received a class 1 recommendation in the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology clinical practice guidelines.^{14,15} However, in the most recent ESC guidelines for management of patients with an ACS presenting without persistent ST segment elevation MI, based on the result of the ISAR-REACT 5 trial, prasugrel is recommended in preference to ticagrelor in patients proceeding to PCI.¹⁶

The aim of this study was to compare clinical outcomes, including both ischaemic and bleeding events, in real-world patients with acute MI undergoing PCI and receiving ticagrelor or prasugrel at discharge.

METHODS

Study population and data sources

This was a retrospective analysis of prospectively collected data using the SWEDEHEART (Swedish

Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies) registry. From January 2010 to December 2016, all patients with acute MI treated with PCI during the index hospitalisation and discharged with DAPT including aspirin and either prasugrel or ticagrelor were identified and included in the study. Patients on oral anticoagulants at discharge were excluded. To avoid double counting of events, only the first hospitalisation for MI during the study period was selected (online supplemental figure S1). Complete follow-up was available until 31 December 2017.

The SWEDEHEART is a nationwide registry including nearly all patients admitted to hospital due to symptoms suggestive of an ACS and all patients undergoing coronary catheterisation or heart surgery in Sweden (<http://www.ucl.uu.se/swedeheart/>). The registry collects around 110 variables for all patients admitted to hospital and around 250 variables for patients undergoing PCI. For this study, we used the individual 12-digit Swedish identification number to merge data from the SWEDEHEART registry with the National Board of Health and Welfare's Cause of Death Register, the National Patient Register (NPR) and the Swedish Prescribed Drug Register (SPDR) for information on vital status, medical history/readmissions and dispensed prescriptions. The NPR provides discharge diagnoses, according to the International Classification of Diseases codes (ICD), for all patients admitted to a hospital in Sweden since 1987. The SPDR provides information, according to the Anatomical Therapeutic Chemicals classification, on all prescriptions dispensed from Swedish pharmacies from July 2005. The SWEDEHEART registry is regularly monitored, with over 95% agreement between registered information and the patients' records.¹⁷ Patients are informed about their participation in the registry and the possibility to opt out.

Exposure

Patients were considered exposed to either ticagrelor or prasugrel based on discharge medication registered in the SWEDEHEART registry. To assess long-term compliance to prescribed P2Y12 receptor inhibitor and aspirin, data on dispensed prescriptions for P2Y12 receptor inhibitors and aspirin were collected between 6 and 12 months of follow-up. A patient was considered to be on treatment with ticagrelor or prasugrel respectively during follow-up if they had picked up a 3-month prescription, dispensed 6–12 months after discharge.

Outcome definitions

The primary outcome was major adverse cardiac and cerebrovascular events (MACCE), including all-cause mortality, MI or stroke, over 1 year after hospital discharge. Secondary outcomes were 1-year net adverse cardiac and cerebrovascular events (NACCE), defined as MACCE or any major bleeding, and the individual components of NACCE. MI was defined as rehospitalisation, identified by ICD codes I21 and I22 in accordance with international guidelines. Stroke was defined as rehospitalisation identified by ICD codes I60, I61, I62, I63 or I64. Major bleeding was defined as rehospitalisation for a cerebral, gastrointestinal or urogenital bleeding or bleeding from the respiratory tract, identified by ICD codes (Appendix: outcome definition section in the online supplemental file). External validations of diagnoses in the patient registry have shown good concordance with individual patients' medical records.^{18 19}

Statistical analysis

Patients were followed up to 1 year or until the time of an event. Cumulative event rates were estimated by the Kaplan-Meier method.

To compare the efficacy and safety outcomes of prasugrel versus ticagrelor, Cox proportional hazard models were used to calculate HR and 95% CI. In the unadjusted model, treatment was the only explanatory variable. To adjust for the non-randomised selection of treatment, multivariable Cox regression models were constructed including treatment and 35 additional covariates (Appendix: statistical analysis section in the online supplemental file). In a sensitivity analysis, calendar year was included in the model. The assumption of proportional hazard was reviewed using log-minus-log survival plots and by a formal test based on Schoenfeld residuals and was met. A two-sided *p* value <0.05 was considered statistically significant.

In a second analysis, using the same covariates, we used logistic regression to calculate the individual propensity score (PS), reflecting the individual's probability to be treated with prasugrel. Based on the individual PS, we calculated the stabilised inverse probability of treatment weights (IPTW). Covariate balance between the treatment groups before and after IPTW weighting was assessed using the mean absolute standardised differences, with differences less than 10% indicating good balance. IPTW Cox regression models were constructed including only treatment as covariate. Furthermore, based on the individual PS, we performed a 1:1 nearest neighbour matching without replacement, and a calliper width of 0.02, resulting in a propensity matched cohort. Covariate balance in the PS matched (PSM) cohort was assessed using the mean absolute standardised differences as above. Cox regression models were constructed in the matched cohort, including only treatment as covariate.

Finally, subgroup analyses were performed by including interaction terms in the multivariable Cox regression models. Subgroups included age (≤ 75 years vs > 75 years), sex, weight (≤ 60 kg vs > 60 kg), diabetes, renal failure (defined as estimated glomerular filtration rate < 60 mL/min/1.72 m²) and infarct type (ST segment elevation myocardial infarction (STEMI) vs non-ST segment elevation myocardial infarction (NSTEMI)).

The number of missing values in covariates included in the multivariable analyses is presented in online supplemental table S1. Missing values at random were assumed and multiple missing values imputations were performed, generating five data sets. All covariates included in the multivariable analyses, treatment and calendar year were included in the model. Statistical analysis was performed using SPSS V.23.0 and STATA V.15.0 software.

Patient and public involvement

It was not possible to involve patients or the public in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS

The study population consisted of 37 990 patients, 2073 in the prasugrel group and 35 917 in the ticagrelor group. The use of prasugrel and ticagrelor increased over time, initially with prasugrel, later with ticagrelor (figure 1).

The baseline and clinical characteristics are presented in tables 1 and 2. Briefly, patients in the prasugrel group were younger (62 years vs 66 years), more likely to be male (79% vs 73%) and more often presented with STEMI (73% vs 46%). Prasugrel-treated patients were more likely to have a history of diabetes mellitus (24% vs 21%) and previous MI (24% vs 18%),

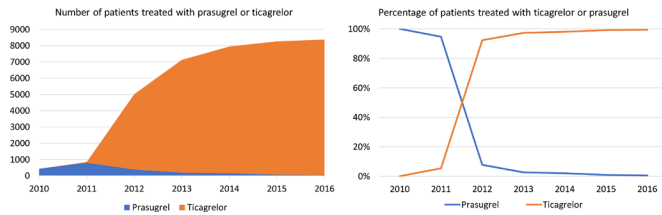


Figure 1 Temporal changes in the utilisation of prasugrel and ticagrelor during the study period.

but less likely to have a history of hypertension (49% vs 52%) or a previous stroke (4% vs 6%).

Periprocedural management during PCI and medications at discharge are presented in table 3. Radial access was less often used (66% vs 81%) and multivessel disease was more often present (52% vs 50%) in the prasugrel group compared with the ticagrelor group. Preloading with a P2Y12 receptor inhibitor before arrival to the cath laboratory was a common strategy in both groups (90% vs 87%), but clopidogrel was used for this purpose more often in the prasugrel group. Inotropic agents and intravenous diuretics during the index hospitalisation were more often administered in the prasugrel group than in the ticagrelor group. At discharge, patients in the prasugrel group were more likely to receive ACE inhibitor/angiotensin receptor blocker

Table 1 Baseline characteristics

| | Prasugrel | Ticagrelor | P value |
|---------------------------------------|-------------|---------------|---------|
| Patients, n | 2073 | 35917 | |
| Demographics | | | |
| Age, mean±SD | 62.2 (10.2) | 66.5 (11.2) | <0.001 |
| ≥71 years | 434 (25.6) | 13 511 (37.6) | <0.001 |
| ≥75 years | 156 (7.5) | 8069 (22.5) | <0.001 |
| Weight, kg, mean±SD | 85.5 (15.8) | 82.4 (15.8) | <0.001 |
| Weight ≤60 kg | 78 (3.9) | 2513 (7.1) | <0.001 |
| Female sex | 435 (21.0) | 9657 (26.9) | <0.001 |
| Medical history | | | |
| Smoking | | | <0.001 |
| Never smoker | 644 (32.1) | 13 150 (37.6) | |
| Previous smoker | 715 (35.6) | 12 464 (35.7) | |
| Current smoker | 648 (32.3) | 9338 (26.7) | |
| Previous MI | 488 (23.5) | 6524 (18.2) | <0.001 |
| History of diabetes mellitus | 500 (24.2) | 7674 (21.4) | 0.003 |
| History of hypertension | 1006 (48.8) | 18 544 (51.8) | 0.008 |
| History of hyperlipidaemia | 616 (29.9) | 8858 (25.0) | <0.001 |
| Previous PCI | 457 (22.1) | 5363 (15.0) | <0.001 |
| Previous CABG | 114 (5.5) | 2002 (5.6) | 0.885 |
| Previous stroke | 90 (4.3) | 2139 (6.0) | 0.002 |
| History of CHF | 88 (4.5) | 1348 (3.8) | 0.136 |
| History of renal failure, on dialysis | 11 (0.5) | 119 (0.3) | 0.131 |
| History of COPD | 88 (4.2) | 1914 (5.3) | 0.032 |
| History of PAD | 71 (3.4) | 1184 (3.3) | 0.750 |
| History of dementia | 2 (0.1) | 86 (0.2) | 0.188 |
| History of cancer* | 28 (1.4) | 750 (2.1) | 0.021 |
| Previous bleeding | 63 (3.0) | 1321 (3.7) | 0.131 |

Results are presented as numbers and percentages unless otherwise indicated.

*Any cancer diagnosis in the last 3 years.

CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Table 2 Clinical characteristics and medications on arrival

| | Prasugrel | Ticagrelor | P value |
|---|-------------|---------------|---------|
| Patients, n | 2073 | 35 917 | |
| Diagnosis | | | |
| STEMI | 1508 (72.8) | 16 619 (46.3) | <0.001 |
| NSTEMI | 563 (27.2) | 19 296 (53.7) | |
| Clinical characteristics on arrival | | | |
| CPR outside hospital | 66 (3.2) | 759 (2.1) | 0.001 |
| Thrombolysis before admission | 128 (6.2) | 189 (0.5) | <0.001 |
| Atrial fibrillation on arrival | 42 (2.0) | 797 (2.2) | 0.570 |
| Heart rate, pulse/min, mean±SD | 76 (19) | 78 (19) | 0.003 |
| Systolic blood pressure, mm Hg, mean±SD | 144 (28) | 150 (29) | <0.001 |
| Killip class II–IV | 105 (5.2) | 1815 (5.1) | 0.924 |
| Laboratory data index | | | |
| Estimated GFR, mL/min/1.73 m ² | 84 (24) | 81 (24) | <0.001 |
| ≤60 mL/min/1.73 m ² | 265 (13.2) | 5577 (16.3) | <0.001 |
| Anaemia | 418 (20.8) | 6753 (20.0) | 0.369 |
| Crusade bleeding score, median (25th–75th percentile) | 20 (14–27) | 21 (16–29) | <0.001 |
| Medication on arrival | | | |
| Oral anticoagulant | 9 (0.4) | 127 (0.4) | 0.246 |
| Aspirin | 620 (30.1) | 9925 (28.0) | 0.034 |
| P2Y12 receptor inhibitor | | | |
| Clopidogrel | 164 (8.0) | 767 (2.2) | <0.001 |
| Ticagrelor | 31 (1.5) | 503 (1.4) | |
| Prasugrel | 5 (0.2) | 2 (0.0) | |
| Beta blocker | 609 (29.7) | 9600 (27.1) | 0.010 |
| ACE-I/ARB | 734 (35.8) | 11 677 (33.0) | 0.008 |
| Antidiabetic medication | | | |
| Oral | 166 (8.1) | 2736 (7.7) | 0.010 |
| Insulin | 209 (10.1) | 2955 (8.3) | |
| Statin | 616 (29.9) | 8858 (25.0) | <0.001 |
| Diuretic | 264 (12.9) | 4795 (13.5) | 0.400 |

Results are presented as numbers and percentages unless otherwise indicated. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; CPR, cardiopulmonary resuscitation; GFR, glomerular filtration rate; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

and antidiabetic drugs compared with patients in the ticagrelor group.

There was no difference in long-term adherence: 80.3% in the ticagrelor group vs 79.5% in the prasugrel group ($p=0.35$) were adherent to the P2Y12 receptor inhibitor prescribed at discharge (online supplemental table S2).

IPTW weighting and PSM cohort

IPTW weighting resulted in excellent covariate balance between the prasugrel group and the ticagrelor group (online supplemental table S3). Propensity matching resulted in a population of 4142 patients, 2071 in each group, well balanced in all covariates included in the PS calculation (online supplemental table S4).

Outcomes

The cumulative rate of MACCE over 1-year follow-up was 6.1% vs 6.1% (127 vs 2196 events) and the corresponding numbers for NACCE were 8.4% vs 8.7% (174 vs 3130 events) in prasugrel-treated and ticagrelor-treated patients, respectively (figure 2). The risk for MACCE or NACCE did not significantly differ between the two groups before or after adjustment (MACCE,

Table 3 In-hospital management and medications at discharge

| | Prasugrel | Ticagrelor | P value |
|--|-------------|---------------|---------|
| Patients, n | 2073 | 35 917 | |
| Percutaneous coronary intervention | | | |
| Access site—radial artery | 1359 (65.7) | 28 980 (81.0) | <0.001 |
| Multivessel disease | 1075 (52.1) | 17 669 (49.5) | 0.022 |
| PCI with stent | 1917 (92.7) | 3329 (93.1) | 0.491 |
| Medication before/during PCI* | | | |
| Aspirin | 2027 (97.7) | 35 255 (98.2) | 0.165 |
| P2Y12 receptor inhibitor, before PCI | 1871 (90.3) | 31 272 (87.1) | <0.001 |
| Clopidogrel | 1129 (54.5) | 3594 (10.0) | <0.001 |
| Ticagrelor | 159 (7.7) | 27 736 (77.2) | |
| Prasugrel | 632 (30.5) | 339 (0.9) | |
| P2Y12 receptor inhibitor, during PCI | 746 (36.0) | 5457 (15.2) | <0.001 |
| Clopidogrel | 49 (2.4) | 333 (0.9) | <0.001 |
| Ticagrelor | 22 (1.1) | 5255 (14.6) | |
| Prasugrel | 696 (33.6) | 101 (0.3) | |
| P2Y12 receptor inhibitors, before/during PCI | 2045 (98.6) | 35 000 (97.4) | <0.001 |
| Clopidogrel | 360 (27.0) | 1957 (5.4) | <0.001 |
| Ticagrelor | 176 (8.5) | 32 610 (90.8) | |
| Prasugrel | 1309 (63.1) | 433 (1.2) | |
| Unfractionated heparin | 1786 (86.2) | 33 409 (93.0) | <0.001 |
| Glycoprotein IIb/IIIa receptor inhibitor | 154 (7.4) | 2511 (7.0) | 0.448 |
| During the index hospitalisation | | | |
| CPAP | 51 (2.5) | 897 (2.5) | 0.914 |
| New-onset AF | 55 (2.7) | 874 (2.4) | 0.531 |
| Intravenous diuretic | 310 (15.0) | 4127 (11.5) | <0.001 |
| Inotropic drug | 105 (5.1) | 917 (2.6) | <0.001 |
| LMWH/fondaparinux | 744 (35.9) | 16 102 (47.1) | <0.001 |
| Medication at discharge | | | |
| Aspirin | 2073 (100) | 35 197 (100) | NA |
| Beta blocker | 1908 (92.0) | 32 608 (90.8) | 0.056 |
| ACE-I/ARB | 1844 (89.0) | 30 988 (86.3) | 0.001 |
| Statin | 2024 (97.6) | 35 015 (97.5) | 0.687 |
| Antidiabetic medication | | | |
| Oral | 182 (8.8) | 3047 (8.5) | 0.002 |
| Insulin | 225 (10.9) | 3123 (8.7) | |
| Diuretic | 366 (17.7) | 5765 (16.1) | 0.054 |

Results are presented as numbers and percentages unless otherwise indicated.

*Were administrated the last 24 hours before or during PCI.

ACE-I, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CPAP, continuous positive airway pressure; LMWH, low molecular weight heparin; NA, not applicable; PCI, percutaneous coronary intervention.

adjusted HR 1.03, 95% CI 0.86 to 1.24; NACCE, adjusted HR 1.03, 95% CI 0.88 to 1.20). Moreover, there were no significant differences between the two treatments, with IPTW analysis (MACCE, adjusted HR 1.11, 95% CI 0.87 to 1.40; NACCE, adjusted HR 1.12, 95% CI 0.91 to 1.37) or when the analysis was performed in the PSM cohort (MACCE, HR 1.04, 95% CI 0.81 to 1.33; NACCE, adjusted HR 1.02, 95% CI 0.83 to 1.27).

All-cause mortality (cumulative rate 2.3% vs 2.9%) and stroke (cumulative rate 0.9% vs 1.1%) did not significantly differ between prasugrel-treated and ticagrelor-treated patients before or after adjustment, regardless of the statistical model used. Prasugrel was associated with a higher unadjusted risk for recurrent

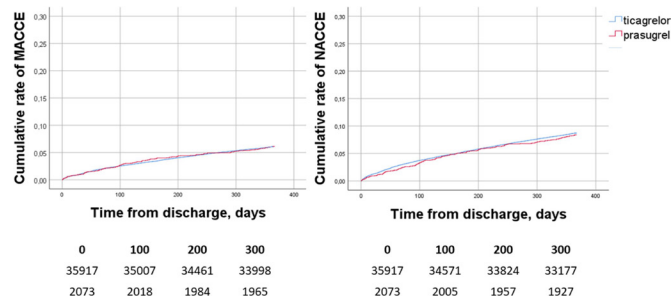


Figure 2 Cumulative rate of adverse events stratified by treatment. Kaplan-Meier curves present the cumulative rates of major adverse cardiac and cerebrovascular events (MACCE) and net adverse cardiac and cerebrovascular events (NACCE), stratified by treatment.

MI (cumulative rate 4.1% vs 3.2%, crude HR 1.32, 95% CI 1.06 to 1.64). However, no statistically significant difference remained after adjustment (adjusted HR 1.26, 95% CI 0.98 to 1.58). Similarly, we found no significant difference in the risk for all-cause mortality, stroke or recurrent MI using IPTW analyses or in the PSM cohort. The incidence of major bleeding (cumulative rate 2.5% vs 3.2%) did not significantly differ between prasugrel-treated and ticagrelor-treated patients (adjusted HR 0.92, 95% CI 0.69 to 1.22), regardless of the statistical model used (table 4).

Similar results were obtained when calendar year was included in the multivariate analyses (online supplemental table S5).

Subgroup analysis showed no significant interaction between treatment efficacy and safety and the selected subgroups (figure 3).

DISCUSSION

In this real-world observational study, we found no significant difference in a composite of death, MI or stroke at 1-year follow-up in patients with MI treated with PCI and discharged with prasugrel or ticagrelor. Moreover, there were no significant differences in the individual components of the composite outcome or bleeding complications. Adjusted analyses with IPTW weighting and PS matching confirmed our results.

Prasugrel and ticagrelor have been compared with clopidogrel in two large trials, the TRITON-TIMI trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) and the PLATO trial (Platelet Inhibition and Patient Outcomes), respectively, with similar treatment benefit compared with clopidogrel.^{1 2 20} From an indirect comparison, even if differences between the study populations should be acknowledged, these trials do not indicate any large differences in treatment efficacy between the two drugs.

There are two randomised head-to-head comparisons between prasugrel and ticagrelor with clinical outcomes. Both are substantially smaller than the previously mentioned trials for regulatory approval. The PRAGUE-18 trial showed no significant difference in the primary endpoint (cardiovascular death MI or stroke) at 12 months, among 1230 patients with STEMI or high-risk NSTEMI randomised to prasugrel or ticagrelor (HR 1.17, 95% CI 0.74 to 1.84).⁷ However, reimbursement matters led to a high incidence of switching to clopidogrel during follow-up, making the comparison very difficult. In contrast and contradicting its own hypothesis, the open-label ISAR-REACT 5 trial showed better outcome with prasugrel compared with ticagrelor.⁸ In 4018 patients with ACS, the primary endpoint,

Table 4 One-year outcomes

| | Prasugrel | Ticagrelor | |
|------------------------------|---------------|------------|---------------------|
| Patients, n | 2073 | 35917 | |
| | Events, n (%) | | HR (95% CI) |
| MACCE | | | |
| Crude | 127 (6.1) | 2196 (6.1) | 1.00 (0.84 to 1.20) |
| MV analysis | | | 1.03 (0.86 to 1.24) |
| IPTW weighting | | | 1.11 (0.87 to 1.40) |
| PSM cohort* | 127 (6.1) | 122 (5.9) | 1.04 (0.81 to 1.33) |
| NACCE | | | |
| Crude | 174 (8.4) | 3130 (8.7) | 0.96 (0.82 to 1.12) |
| MV analysis | | | 1.03 (0.88 to 1.20) |
| IPTW weighting | | | 1.12 (0.91 to 1.37) |
| PSM cohort* | 174 (8.4) | 169 (8.2) | 1.02 (0.83 to 1.27) |
| All-cause mortality | | | |
| Crude | 48 (2.3) | 1056 (2.9) | 0.79 (0.59 to 1.05) |
| MV analysis | | | 0.89 (0.67 to 1.20) |
| IPTW weighting | | | 1.04 (0.69 to 1.56) |
| PSM cohort* | 48 (2.3) | 59 (2.8) | 0.81 (0.55 to 1.19) |
| Myocardial infarction | | | |
| Crude | 85 (4.1) | 1123 (3.2) | 1.32 (1.06 to 1.64) |
| MV analysis | | | 1.26 (0.98 to 1.58) |
| IPTW weighting | | | 1.26 (0.95 to 1.67) |
| PSM cohort* | 85 (4.1) | 66 (3.2) | 1.26 (0.91 to 1.77) |
| Stroke | | | |
| Crude | 18 (0.9) | 385 (1.1) | 0.81 (0.50 to 1.30) |
| MV analysis | | | 0.94 (0.58 to 1.53) |
| IPTW weighting | | | 0.93 (0.52 to 1.67) |
| PSM cohort* | 18 (0.9) | 14 (0.7) | 1.28 (0.64 to 2.58) |
| Major bleeding | | | |
| Crude | 51 (2.5) | 1124 (3.2) | 0.78 (0.59 to 1.03) |
| MV analysis | | | 0.92 (0.69 to 1.22) |
| IPTW weighting | | | 1.02 (0.72 to 1.47) |
| PSM cohort* | 51 (2.5) | 51 (2.5) | 0.99 (0.67 to 1.46) |

MACCE including all-cause death, myocardial infarction or stroke (ischaemic and haemorrhagic); NACCE including MACCE and major bleeding during follow-up. HR with 95% CI was derived from Cox regression analysis.

In the unadjusted model (crude) only treatment was included as covariate. In the multivariable model 34 additional covariates were included. Using the same covariates, the individual propensity score, reflecting the probability to be treated with prasugrel, and propensity score weights (IPTW) were calculated. IPTW Cox regression models were constructed.

*Propensity matching resulted in a population of 4142 patients (PSM cohort), 2071 in each group.

IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events; MV, multivariable model; NACCE, net adverse cardiac and cerebrovascular events; PSM, propensity score matched.

death, MI or stroke occurred in 9.3% in the ticagrelor group and 6.9% in the prasugrel group (HR 1.36, 95% CI 1.09 to 1.70, $p=0.006$) at 1 year. The observed difference was mainly driven by a higher incidence of MI in the ticagrelor group. There are several differences between the ISAR-REACT 5 trial and both previous and present analyses which may, at least partly, explain the differences in outcomes. The ISAR-REACT 5 trial was a comparison between two treatment strategies with, in addition to difference in drug treatment, different loading dose strategies (with preloading significantly more often in ticagrelor-treated patients). Also, almost 20% of the randomised patients were discharged without the study treatment, and at 1-year follow-up another 15.2% of patients assigned to ticagrelor and 12.5% of patients assigned to prasugrel had stopped their treatment

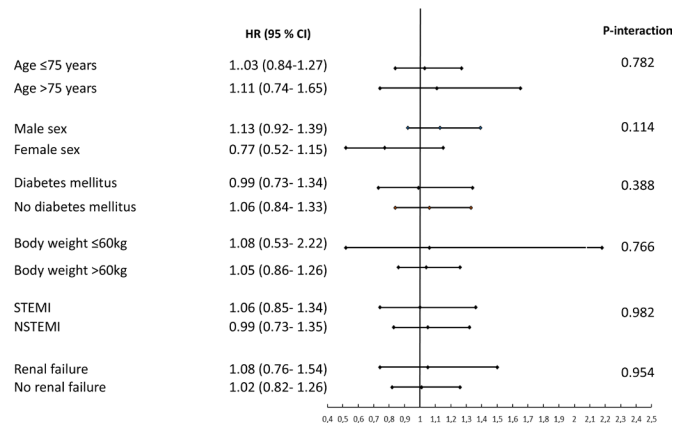


Figure 3 Subgroup analysis. Renal failure was defined as estimated glomerular filtration rate under 60 mL/min/1.72 m². NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

prematurely ($p=0.003$). In the present study, preloading was a common practice in both groups. Furthermore, since patients were allocated based on discharge medication, the study did not include in-hospital outcomes. Finally, all patients included in the present analysis were discharged with either prasugrel or ticagrelor, and a similar rate (about 80% in both groups) continued over the study period with the P2Y₁₂ receptor inhibitor they received at discharge.

In support of this analysis, some previous observational studies showed similar efficacy with ticagrelor and prasugrel.¹⁰⁻¹³ In a report from USA on more than 13 000 Medicare patients treated with PCI, including a PSM analysis (756 in each group), there was no difference in mortality between the two treatments.¹¹ Larmore *et al*⁹ reported a modest benefit associated with prasugrel in patients with ACS compared with ticagrelor over short-time, but not medium-time (90 days), follow-up. The present analysis included a higher risk population and assessed 1-year outcomes, which may be especially important in patients with MI. Contrasting our results, Olier *et al*²¹ reported that prasugrel was associated with lower risk for in-hospital major adverse cardiovascular events and 1-year mortality, compared with ticagrelor. The study included primary PCI-treated patients with STEMI only. The authors proposed lower patient adherence to ticagrelor (possibly due to side effects and the two-times-per-day maintenance regimen) and differences in pharmacodynamic properties between the drugs as explanations to the observed difference. However, supportive data on long-term adherence to prescriptions were not provided and previous studies have shown similar pharmacodynamic properties between the two drugs in the setting of STEMI.⁶ There are several potential explanations to the differences between the study by Olier *et al*²¹ and the present data. All patients with MI treated with PCI and ticagrelor or prasugrel were included in our study; hence, patients were older with more risk factors in the present population. Furthermore, we adjusted for differences in guidelines-recommended, evidence-based medications prescribed at discharge. Finally, we found similar long-term adherence to prasugrel and ticagrelor during follow-up (difference in adherence to ticagrelor between the two studies may be of importance) and similar risk for MI, stroke and bleeding complications between the groups, which further support an equivalent risk for death with prasugrel and ticagrelor.

Also supporting our results, a recent network meta-analysis comparing all three oral P2Y12 inhibitors indicated no difference in all-cause mortality, MI, stroke or bleeding complications between prasugrel and ticagrelor.²²

In our study treatment allocation was based on discharge medication. In the TRITON trial almost half of the events occurred during the first 3 days.¹ Therefore, the observed MACCE rate in our study is higher than in previous randomised trials, reflecting a real-life population.

Limitations

There are some important limitations to our analysis. First, this was an observational real-world study with its inherent limitations such as the non-randomised treatment selection. Despite adequate statistical methods to adjust for differences in patients' characteristics, residual confounders cannot be excluded. Second, given the similarity in effect between ticagrelor and prasugrel, compared with clopidogrel in the PLATO trial and the TRITON trial, respectively, the relatively small prasugrel-treated population in the present analysis increases the risk for a type II error. However, the point estimates and CI do not indicate any large differences between the groups. Third, we did not adjudicate outcome events. However, validation of the administrative data used in the analysis has been performed, with good agreement between registry data and patients' medical records.¹⁸ Fourth, in this analysis treatment allocation was based on discharge medication, and consequently in-hospital events were not counted. This could make comparisons with previous studies more difficult. However, in both the PLATO and TRITON trials, most of the separation of the event rates occurred after the acute phase. Hence, potential differences in effect in the postdischarge period should be of importance for the patient. Finally, use of ticagrelor increased over time, while use of prasugrel decreased, which may be a potential problem in the comparison. However, adding calendar year to the model did not change the result. Taken together we believe it is unlikely that year of inclusion had a major impact on the result.

CONCLUSION

In this national real-world study including patients with MI treated with PCI, prasugrel and ticagrelor were associated with equivalent risk for MACCE, a composite of death, MI or

stroke, and NACCE, including bleeding complications, at 1-year follow-up.

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Key messages

What is already known on this subject?

- In patients with myocardial infarction (MI) undergoing percutaneous coronary intervention (PCI), prasugrel and ticagrelor have proven to be superior to clopidogrel.
- The comparative efficacy and safety of prasugrel and ticagrelor remain unknown.

What might this study add?

- We found no significant difference in the risk for death, recurrent MI or stroke between the two treatments.
- There was no significant difference in the risk of bleeding with prasugrel versus ticagrelor.

How might this impact on clinical practice?

- In patients with MI treated with PCI, prasugrel and ticagrelor appear associated with similar efficacy and safety during 1-year follow-up.

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