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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%),

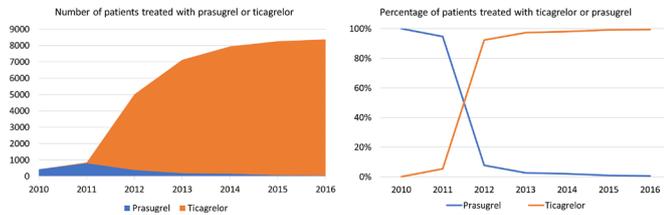


Figure 1 Temporal changes in the utilisation of prasugrel and ticagrelor during the study period.

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

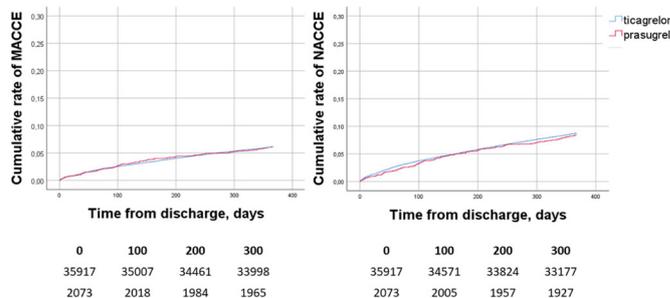


Figure 2 Cumulative rate of adverse events stratified by treatment. Kaplan-Meier curves present the cumulative rates of major adverse cardiac and cerebrovascular events (MACCE) and net adverse cardiac and cerebrovascular events (NACCE), stratified by treatment.

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

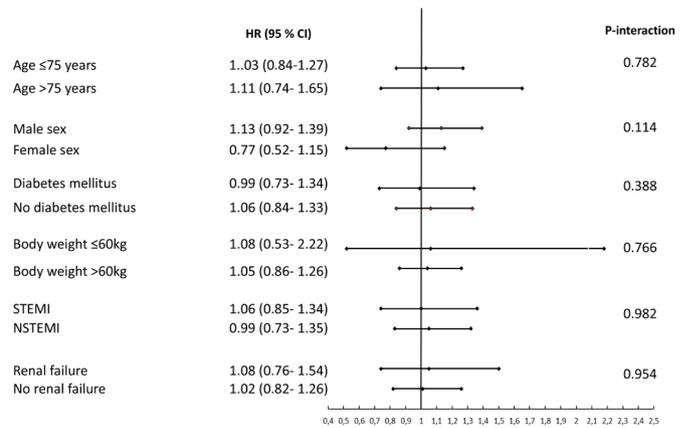


Figure 3 Subgroup analysis. Renal failure was defined as estimated glomerular filtration rate under 60 mL/min/1.72 m². NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

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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Supplement

D. Venetsanos, E. Träff, D. Erlinge et al. **Prasugrel versus Ticagrelor in myocardial infarction patients undergoing percutaneous coronary intervention**

Figure S1. Flow chart

Appendix:

Outcome definition

Statistical analysis

Table S1. Missing values

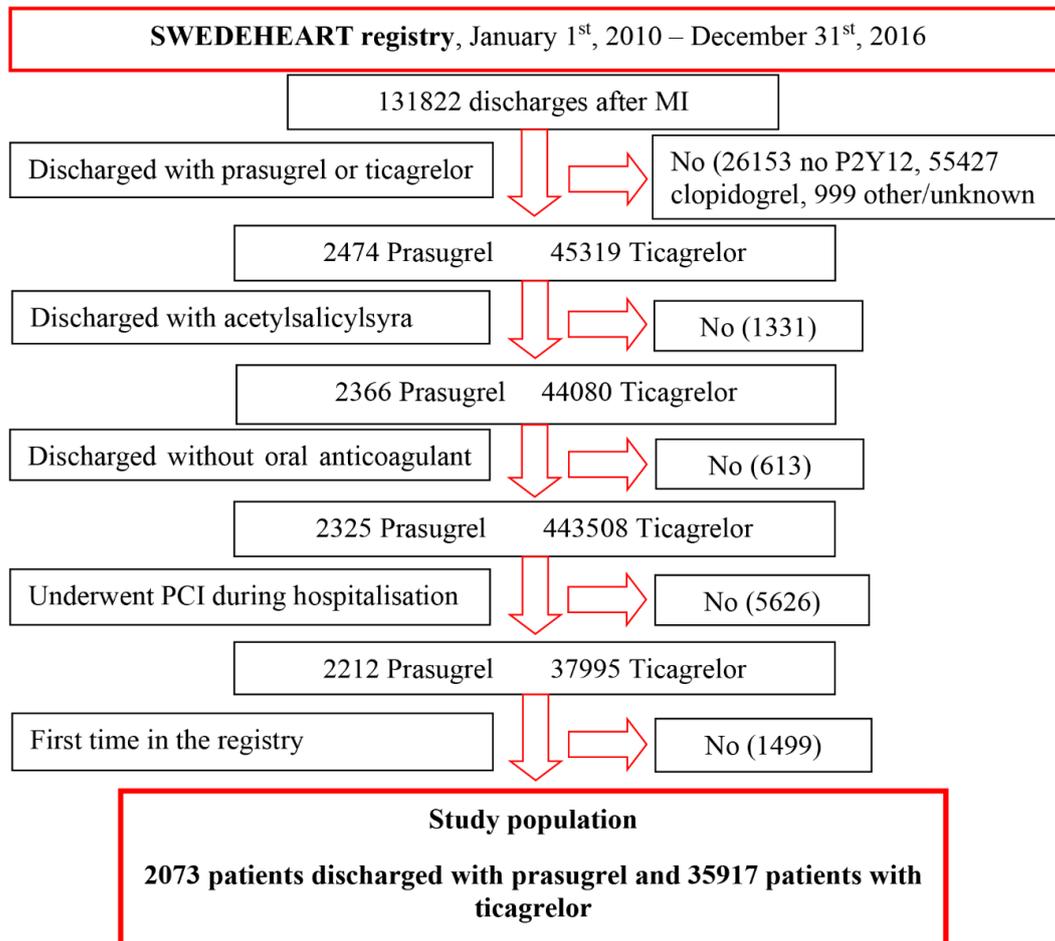
Table S2. P2Y12 receptor inhibitors and acetylsalicylic acid dispensed prescriptions during follow-up (6 to 12 months, from discharge)

Table S3. Covariate balance between treatment groups, presented as standardised difference (SD), before and after weighting for inverse propensity score weights

Table S4. Propensity matched population

Table S5. One-year outcomes before and after multivariable Cox regression, including calendar year

Figure S2: Distribution of propensity score before (a) and after (b) inverse probability weighting

Figure S1. Flow chart

Appendix

Outcome definition

Major bleeding was defined as any rehospitalisation for a cerebral, gastrointestinal or urogenital bleeding or bleeding from the respiratory tract, identified by using the following International Classification of Diseases codes: I60, I61, I62, D629, D500, H356, H431, H450, H922, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, N421, N938, N939, N950, R041, R042, R048, R049, R210, R319, T810, N501A.

Statistical analysis

Covariates that were included in multivariable analysis and in individual propensity score calculation were selected based on investigators clinical experience. The following covariates were included: age, gender, smoking status, history of diabetes mellitus, hypertension, hyperlipidemia, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous coronary artery by-pass grafting, previous stroke, previous congestive heart failure, known renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, previous cancer, a history of bleeding, cardiopulmonary resuscitation before admission, Killip class >1, anaemia on admission, estimated glomerular filtration rate <60 ml/min/1.72m² on admission, treatment with aspirin on arrival, P2Y12 receptor inhibitors on arrival, statins on arrival, multivessel disease, PCI with stent, PCI-access site, use of continuous positive airway pressure, administration of inotropic agents, iv diuretics during the index hospitalisation, medication at discharge including beta blockers, statins, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretics and antidiabetic treatment (no, po drugs or insulin) and MI type (ST segment elevation MI vs non-ST segment elevation MI).

Based on the individual PS, we calculated the stabilised inverse probability of treatment weights (IPTW). To obtain a similar number in the two treatment arms after inverse probability weighting, the weights were stabilized. Stabilization (multiplying the weight by the probability of being exposed for those exposed and the probability of being unexposed for those unexposed), results in a pseudo-population with similar percentage of patients exposed/un-exposed in each level of the covariates as the overall percentage in the study population. Stabilization does not affect the point estimates but reduces the variability of the weights.

Goodness of fit of the logistic regression, used to calculate the individual propensity score was assessed using Hosmer-Lemeshow test (0.11). The c-index was 0.73. Plots of PS after weighting for IPTW showed an

excellence balance between the two treatment groups. Finally, in a sensitivity analysis, truncation of PS score at 1st centile was performed and similar results were obtained (data not shown).

All 5 imputed data bases were used in the IPTW cox regression and multivariable cox regressions models to obtain the 5 completed data estimates of coefficients.

Table S1. Missing values

Baseline characteristics	N missing	Clinical characteristics on arrival	N missing	Percutaneous Coronary Intervention	N missing
Age, years	0	CPR outside hospital	425	Access site- radial artery	127
Body weight	472	Thrombolysis before admission	233	Multivessel disease	208
Sex	0	Atrial Fibrillation on arrival	313	PCI with stent	158
Smoking	1031	Heart rate	208	Medication during PCI	
Previous MI	0	Systolic blood pressure	208	Aspirin	0
History of Diabetes Mellitus	0	Killip Class	596	P2Y12 receptor inhibitors	0
History of Hypertension	130	Laboratory data index		Unfractionated heparin	14
History of Hyperlipidaemia	443	Estimated GFR	1649	GP IIb/IIIa receptor inhibitor	23
Previous PCI	137	Anaemia	2220	During the index hospitalisation	
Previous CABG	0	Crusade bleeding score	2874	CPAP	31
Previous stroke	0	Medication on arrival		New onset AF	12
History of CHF	977	Oral Anticoagulant	422	Iv diuretics	25
History of Renal failure - on dialysis	0	Aspirin	431	Inotropic drug	29
History of COPD	0	P2Y12 receptor inhibitors	427	LMWH /fondaparinux	60
History of PAD	0	Statins	443	Medication at discharge	
History of Dementia	0	Beta blockers	567	Aspirin	0
History of Cancer	0	ACE-I/ARB	503	Beta blockers	3
Previous Bleeding	0	Anti-Diabetic medications	376	ACE-I/ARB	0
Clinical characteristics on arrival		Diuretics	504	Statins	2
Infarct type	4			Anti-diabetic medications	1
Abbreviations (in order of appearance): MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Infarct type, ST segment elevation myocardial infarction or non ST segment elevation myocardial infarction; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CPAP, continuous positive airway pressure;					

Table S2. P2Y12 receptor inhibitors and acetylsalicylic acid dispensed prescriptions during follow-up (6 to 12 months, from discharge)

Patients, n 37990	Dispensed prescriptions 6-12 months after the index procedure			
	No or other	Ticagrelor	Prasugrel	Clopidogrel
Ticagrelor group	4048 (11.3)	28838 (80.3)	282 (0.8)	2749 (7.7)
Prasugrel group	232 (11.2)	59 (2.8)	1647 (79.5)	135 (6.5)
Among patients who survived the first year after discharge				
Ticagrelor group	3223 (9.2)	28646 (82.2)	281 (0.8)	2711 (7.8)
Prasugrel group	190 (9.4)	59 (2.9)	1641 (81.0)	135 (6.7)
	Acetylsalicylic acid			
	Yes		No	
Ticagrelor group	33412 (93.0)		2505 (7.0)	
Prasugrel group	1945 (93.8)		128 (6.2)	

Table S3. Covariate balance between treatment groups, presented as mean standardised difference (MSD), before and after weighting for inverse probability of treatment weights

	Before IPTW			After IPTW		
	Prasugrel	Ticagrelor	MSD	Prasugrel	Ticagrelor	MSD
Age, mean	62.2	66.5	39.5	65.4	66.2	7.8
Female sex	0.21	0.27	13.9	0.27	0.27	0.0
Previous/current smokers	0.68	0.62	11.2	0.62	0.63	1.1
Previous MI	0.24	0.18	13.3	0.21	0.18	5.3
History of Diabetes Mellitus	0.24	0.21	6.6	0.24	0.22	4.4
History of Hypertension	0.49	0.52	5.9	0.53	0.52	2.0
History of Hyperlipidaemia	0.30	0.25	10.7	0.27	0.25	4.7
Previous PCI	0.22	0.15	18.1	0.18	0.16	6.4
Previous CABG	0.05	0.06	0.3	0.06	0.06	0.6
Previous stroke	0.04	0.06	3.1	0.08	0.06	9.3
History of CHF	0.04	0.04	3.1	0.05	0.04	3.0
History of renal failure	0.02	0.02	0.6	0.02	0.02	3.0
History of COPD	0.04	0.05	5.1	0.05	0.05	0.8
History of PAD	0.03	0.03	0.7	0.03	0.03	0.5
History of Cancer	0.01	0.02	5.7	0.02	0.02	3.8
Previous Bleeding	0.03	0.04	3.5	0.04	0.04	2.8
Killip Class II-IV	0.05	0.05	0.1	0.05	0.05	2.1
CPR outside hospital	0.03	0.02	7.1	0.03	0.02	8.0
Estimated GFR ≤ 60 ml/min/1.73 ²	0.13	0.16	8.4	0.16	0.16	0.1
Anaemia	0.21	0.20	2.1	0.20	0.20	0.1
Aspirin on arrival	0.30	0.28	4.6	0.31	0.29	5.1
P2Y12 on arrival	0.10	0.04	24.9	0.04	0.04	1.5
Statins on arrival	0.30	0.25	10.5	0.28	0.26	4.4
Multivessel disease	0.52	0.49	5.0	0.52	0.50	4.0
PCI with stent	0.93	0.93	1.7	0.93	0.93	1.3
Radial access site	0.66	0.81	34.9	0.81	0.80	1.1
CPAP during hospitalisation	0.02	0.03	0.3	0.03	0.03	1.8
Inotropic drugs	0.05	0.03	13.1	0.03	0.03	2.0
Beta blocker at discharge	0.92	0.91	4.5	0.91	0.91	2.1
ACE-I/ARB at discharge	0.89	0.86	8.1	0.85	0.86	4.8
Statin at discharge	0.98	0.97	0.9	0.97	0.97	2.5
Anti-diabetic medication at discharge	0.20	0.17	7.3	0.20	0.18	4.5
Diuretics at discharge	0.18	0.16	4.3	0.17	0.16	2.2
Infarct Type-STEMI	0.73	0.46	56.1	0.50	0.48	3.9
Figures present proportion, if not otherwise stated. Abbreviations (in order of appearance): SD, standardised difference; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; CPAP,						

continuous positive airway pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, ST elevation myocardial infarction

Table S4. Propensity matched cohort

	Ticagrelor	Prasugrel	p-value
Number of patients	2071	2071	
Demographics			
Age, years, mean \pm SD	62.2 (11.0)	62.3 (10.1)	0.29
Female sex	434 (21.0)	435 (21.0)	0.97
Previous/current smoker	1389 (67.1)	1400 (67.5)	0.72
Medical History			
Previous MI	441 (21.3)	486 (23.5)	0.10
History of Diabetes Mellitus	455 (22.0)	500 (24.1)	0.10
History of Hypertension	1023 (49.4)	1012 (48.9)	0.73
History of Hyperlipidaemia	589 (28.4)	617 (29.8)	0.34
Previous PCI	434 (21.0)	456 (22.0)	0.41
Previous CABG	98 (4.7)	114 (5.5)	0.26
Previous stroke	89 (4.3)	90 (4.3)	0.94
History of CHF	80 (3.9)	93 (4.5)	0.31
History of COPD	100 (4.8)	88 (4.2)	0.37
History of PAD	59 (2.8)	71 (3.4)	0.29
History of Cancer*	27 (1.3)	28 (1.4)	0.89
Previous Bleeding	66 (3.2)	63 (3.0)	0.79
Clinical characteristics on arrival			
Killip Class II-IV	102 (4.9)	107 (5.2)	0.72
CPR outside hospital	77 (3.7)	68 (3.3)	0.45
Estimated GFR \leq 60 ml/min/1.73 ²	250 (12.1)	273 (13.2)	0.28
Anaemia	419 (20.2)	431 (20.8)	0.64
Crusade bleeding score	20 (14- 27)	20 (14- 27)	0.32
1-20	1082 (52.2)	1062 (51.3)	0.54
21-30	658 (31.8)	654 (31.6)	
31-40	229 (11.1)	232 (11.2)	
\geq 41	102 (4.9)	123 (5.9)	
Medications on arrival			
Aspirin	584 (28.2)	628 (30.3)	0.13
P2Y ₁₂ receptor inhibitors	176 (8.6)	203 (9.8)	0.17
Statins	595 (28.7)	620 (29.9)	0.39
Percutaneous Coronary Intervention			
Multivessel disease	1042 (50.3)	1076 (52.0)	0.29
PCI with stent	1939 (93.6)	1920 (92.7)	0.24
Transradial access	1383 (66.8)	1361 (65.7)	0.13
During the index hospitalisation			
CPAP	64 (3.1)	51 (2.5)	0.22
Inotropic drug	104 (5.0)	104 (5.0)	1.00
Medication at discharge			
Beta blockers	1915 (92.5)	1906 (92.0)	0.60
ACE-I/ARB	1836 (88.7)	1842 (88.9)	0.77
Statins	2013 (97.2)	2022 (97.6)	0.38
Anti-diabetic medications	375 (18.1)	407 (19.7)	0.20
Diuretics	343 (16.6)	366 (17.7)	0.34
Infarct type			
ST-segment elevation MI	1537 (74.2)	1507 (72.8)	0.29
Non-ST-segment elevation MI	534 (25.8)	564 (27.2)	
Results are presented as numbers and percentages unless otherwise indicated. Abbreviations (in order of appearance): SD, standard deviation; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; CPAP, continuous positive airway pressure; ACE-I, angiotensin-converting			

enzyme inhibitor; ARB, angiotensin receptor blocker; *Any cancer diagnosis the last 5 years; ** Were administrated 24 hours before or during PCI

Table S5. One-year outcomes before and after multivariable Cox regression, including calendar year

	Prasugrel	Ticagrelor	
Patients, n	2073	35917	
	Events, n (%)		HR (95% CI)
MACCE			
Crude	127 (6.1)	2196 (6.1)	1.00 (0.84- 1.20)
MV analysis including calendar year			1.08 (0.89- 1.32)
NACCE			
Crude	174 (8.4)	3130 (8.7)	0.96 (0.82- 1.12)
MV analysis including calendar year			1.07 (0.90- 1.27)
All-cause mortality			
Crude	48 (2.3)	1056 (2.9)	0.79 (0.59- 1.05)
MV analysis including calendar year			0.95 (0.69- 1.30)
Myocardial infarction			
Crude	85 (4.1)	1123 (3.2)	1.32 (1.06- 1.64)
MV analysis including calendar year			1.15 (0.90- 1.48)
Stroke			
Crude	18 (0.9)	385 (1.1)	0.81 (0.50- 1.30)
MV analysis including calendar year			0.84 (0.50- 1.40)
Major bleeding			
Crude	51 (2.5)	1124 (3.2)	0.78 (0.59- 1.03)
MV analysis including calendar year			0.98 (0.72- 1.33)
Major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, myocardial infarction, or stroke (ischemic and haemorrhagic); Net adverse cardiac and cerebrovascular events (NACCE) including MACCE and major bleeding during follow up. Hazard ratios (HR) with 95% confidence intervals were derived from Cox regression analysis. In the unadjusted model (crude) only treatment was included as covariate. In the multivariable model (MV) 34 additional covariates and calendar year were included.			

Supplement

D. Venetsanos, E. Träff, D. Erlinge et al. **Prasugrel versus Ticagrelor in myocardial infarction patients undergoing percutaneous coronary intervention**

Figure S1. Flow chart

Appendix:

Outcome definition

Statistical analysis

Table S1. Missing values

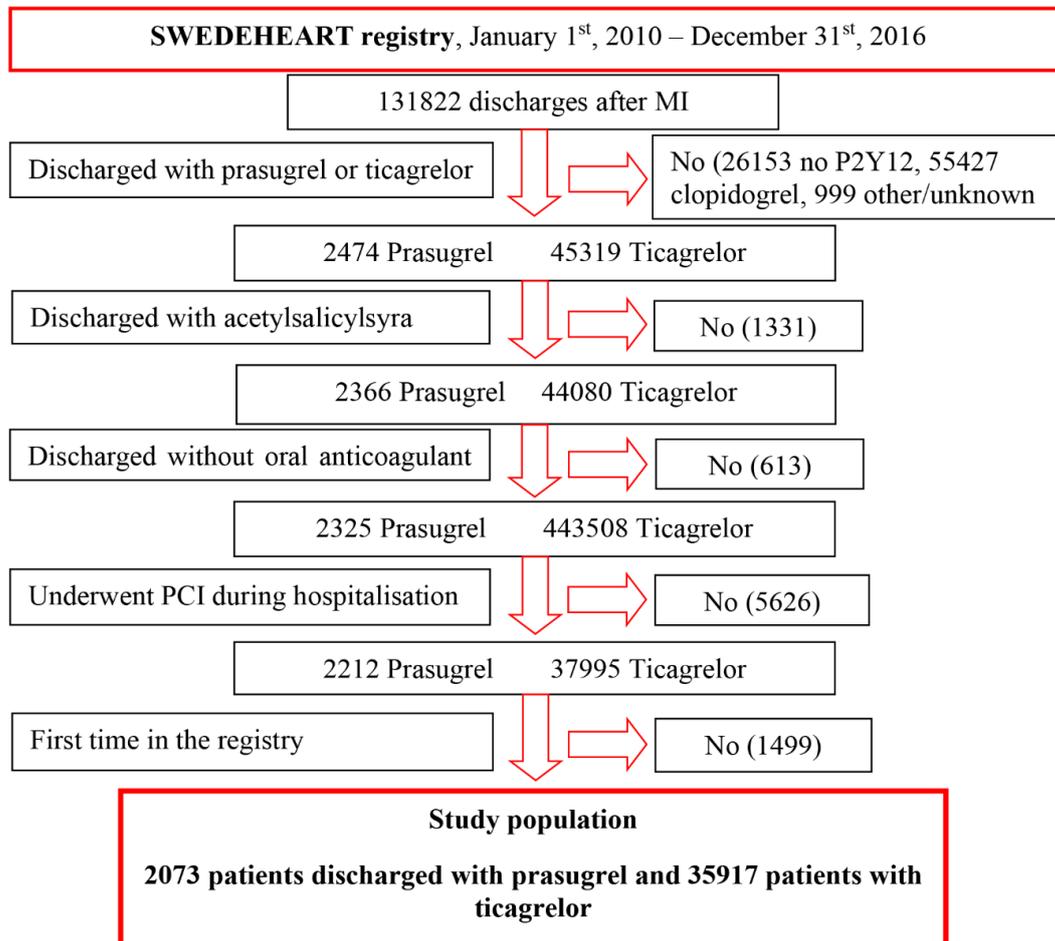
Table S2. P2Y₁₂ receptor inhibitors and acetylsalicylic acid dispensed prescriptions during follow-up (6 to 12 months, from discharge)

Table S3. Covariate balance between treatment groups, presented as standardised difference (SD), before and after weighting for inverse propensity score weights

Table S4. Propensity matched population

Table S5. One-year outcomes before and after multivariable Cox regression, including calendar year

Figure S2: Distribution of propensity score before (a) and after (b) inverse probability weighting

Figure S1. Flow chart

Appendix

Outcome definition

Major bleeding was defined as any rehospitalisation for a cerebral, gastrointestinal or urogenital bleeding or bleeding from the respiratory tract, identified by using the following International Classification of Diseases codes: I60, I61, I62, D629, D500, H356, H431, H450, H922, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, N421, N938, N939, N950, R041, R042, R048, R049, R210, R319, T810, N501A.

Statistical analysis

Covariates that were included in multivariable analysis and in individual propensity score calculation were selected based on investigators clinical experience. The following covariates were included: age, gender, smoking status, history of diabetes mellitus, hypertension, hyperlipidemia, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous coronary artery by-pass grafting, previous stroke, previous congestive heart failure, known renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, previous cancer, a history of bleeding, cardiopulmonary resuscitation before admission, Killip class >1, anaemia on admission, estimated glomerular filtration rate <60 ml/min/1.72m² on admission, treatment with aspirin on arrival, P2Y12 receptor inhibitors on arrival, statins on arrival, multivessel disease, PCI with stent, PCI-access site, use of continuous positive airway pressure, administration of inotropic agents, iv diuretics during the index hospitalisation, medication at discharge including beta blockers, statins, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretics and antidiabetic treatment (no, po drugs or insulin) and MI type (ST segment elevation MI vs non-ST segment elevation MI).

Based on the individual PS, we calculated the stabilised inverse probability of treatment weights (IPTW). To obtain a similar number in the two treatment arms after inverse probability weighting, the weights were stabilized. Stabilization (multiplying the weight by the probability of being exposed for those exposed and the probability of being unexposed for those unexposed), results in a pseudo-population with similar percentage of patients exposed/un-exposed in each level of the covariates as the overall percentage in the study population. Stabilization does not affect the point estimates but reduces the variability of the weights.

Goodness of fit of the logistic regression, used to calculate the individual propensity score was assessed using Hosmer-Lemeshow test (0.11). The c-index was 0.73. Plots of PS after weighting for IPTW showed an

excellence balance between the two treatment groups. Finally, in a sensitivity analysis, truncation of PS score at 1st centile was performed and similar results were obtained (data not shown).

All 5 imputed data bases were used in the IPTW cox regression and multivariable cox regressions models to obtain the 5 completed data estimates of coefficients.

Table S1. Missing values

Baseline characteristics	N missing	Clinical characteristics on arrival	N missing	Percutaneous Coronary Intervention	N missing
Age, years	0	CPR outside hospital	425	Access site- radial artery	127
Body weight	472	Thrombolysis before admission	233	Multivessel disease	208
Sex	0	Atrial Fibrillation on arrival	313	PCI with stent	158
Smoking	1031	Heart rate	208	Medication during PCI	
Previous MI	0	Systolic blood pressure	208	Aspirin	0
History of Diabetes Mellitus	0	Killip Class	596	P2Y12 receptor inhibitors	0
History of Hypertension	130	Laboratory data index		Unfractionated heparin	14
History of Hyperlipidaemia	443	Estimated GFR	1649	GP IIb/IIIa receptor inhibitor	23
Previous PCI	137	Anaemia	2220	During the index hospitalisation	
Previous CABG	0	Crusade bleeding score	2874	CPAP	31
Previous stroke	0	Medication on arrival		New onset AF	12
History of CHF	977	Oral Anticoagulant	422	Iv diuretics	25
History of Renal failure - on dialysis	0	Aspirin	431	Inotropic drug	29
History of COPD	0	P2Y12 receptor inhibitors	427	LMWH /fondaparinux	60
History of PAD	0	Statins	443	Medication at discharge	
History of Dementia	0	Beta blockers	567	Aspirin	0
History of Cancer	0	ACE-I/ARB	503	Beta blockers	3
Previous Bleeding	0	Anti-Diabetic medications	376	ACE-I/ARB	0
Clinical characteristics on arrival		Diuretics	504	Statins	2
Infarct type	4			Anti-diabetic medications	1
Abbreviations (in order of appearance): MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Infarct type, ST segment elevation myocardial infarction or non ST segment elevation myocardial infarction; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CPAP, continuous positive airway pressure;					

Table S2. P2Y12 receptor inhibitors and acetylsalicylic acid dispensed prescriptions during follow-up (6 to 12 months, from discharge)

Patients, n 37990	Dispensed prescriptions 6-12 months after the index procedure			
	No or other	Ticagrelor	Prasugrel	Clopidogrel
Ticagrelor group	4048 (11.3)	28838 (80.3)	282 (0.8)	2749 (7.7)
Prasugrel group	232 (11.2)	59 (2.8)	1647 (79.5)	135 (6.5)
Among patients who survived the first year after discharge				
Ticagrelor group	3223 (9.2)	28646 (82.2)	281 (0.8)	2711 (7.8)
Prasugrel group	190 (9.4)	59 (2.9)	1641 (81.0)	135 (6.7)
Acetylsalicylic acid				
	Yes		No	
Ticagrelor group	33412 (93.0)		2505 (7.0)	
Prasugrel group	1945 (93.8)		128 (6.2)	

Table S3. Covariate balance between treatment groups, presented as mean standardised difference (MSD), before and after weighting for inverse probability of treatment weights

	Before IPTW			After IPTW		
	Prasugrel	Ticagrelor	MSD	Prasugrel	Ticagrelor	MSD
Age, mean	62.2	66.5	39.5	65.4	66.2	7.8
Female sex	0.21	0.27	13.9	0.27	0.27	0.0
Previous/current smokers	0.68	0.62	11.2	0.62	0.63	1.1
Previous MI	0.24	0.18	13.3	0.21	0.18	5.3
History of Diabetes Mellitus	0.24	0.21	6.6	0.24	0.22	4.4
History of Hypertension	0.49	0.52	5.9	0.53	0.52	2.0
History of Hyperlipidaemia	0.30	0.25	10.7	0.27	0.25	4.7
Previous PCI	0.22	0.15	18.1	0.18	0.16	6.4
Previous CABG	0.05	0.06	0.3	0.06	0.06	0.6
Previous stroke	0.04	0.06	3.1	0.08	0.06	9.3
History of CHF	0.04	0.04	3.1	0.05	0.04	3.0
History of renal failure	0.02	0.02	0.6	0.02	0.02	3.0
History of COPD	0.04	0.05	5.1	0.05	0.05	0.8
History of PAD	0.03	0.03	0.7	0.03	0.03	0.5
History of Cancer	0.01	0.02	5.7	0.02	0.02	3.8
Previous Bleeding	0.03	0.04	3.5	0.04	0.04	2.8
Killip Class II-IV	0.05	0.05	0.1	0.05	0.05	2.1
CPR outside hospital	0.03	0.02	7.1	0.03	0.02	8.0
Estimated GFR ≤ 60 ml/min/1.73 ²	0.13	0.16	8.4	0.16	0.16	0.1
Anaemia	0.21	0.20	2.1	0.20	0.20	0.1
Aspirin on arrival	0.30	0.28	4.6	0.31	0.29	5.1
P2Y12 on arrival	0.10	0.04	24.9	0.04	0.04	1.5
Statins on arrival	0.30	0.25	10.5	0.28	0.26	4.4
Multivessel disease	0.52	0.49	5.0	0.52	0.50	4.0
PCI with stent	0.93	0.93	1.7	0.93	0.93	1.3
Radial access site	0.66	0.81	34.9	0.81	0.80	1.1
CPAP during hospitalisation	0.02	0.03	0.3	0.03	0.03	1.8
Inotropic drugs	0.05	0.03	13.1	0.03	0.03	2.0
Beta blocker at discharge	0.92	0.91	4.5	0.91	0.91	2.1
ACE-I/ARB at discharge	0.89	0.86	8.1	0.85	0.86	4.8
Statin at discharge	0.98	0.97	0.9	0.97	0.97	2.5
Anti-diabetic medication at discharge	0.20	0.17	7.3	0.20	0.18	4.5
Diuretics at discharge	0.18	0.16	4.3	0.17	0.16	2.2
Infarct Type-STEMI	0.73	0.46	56.1	0.50	0.48	3.9
Figures present proportion, if not otherwise stated. Abbreviations (in order of appearance): SD, standardised difference; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; CPAP,						

continuous positive airway pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, ST elevation myocardial infarction

Table S4. Propensity matched cohort

	Ticagrelor	Prasugrel	p-value
Number of patients	2071	2071	
Demographics			
Age, years, mean \pm SD	62.2 (11.0)	62.3 (10.1)	0.29
Female sex	434 (21.0)	435 (21.0)	0.97
Previous/current smoker	1389 (67.1)	1400 (67.5)	0.72
Medical History			
Previous MI	441 (21.3)	486 (23.5)	0.10
History of Diabetes Mellitus	455 (22.0)	500 (24.1)	0.10
History of Hypertension	1023 (49.4)	1012 (48.9)	0.73
History of Hyperlipidaemia	589 (28.4)	617 (29.8)	0.34
Previous PCI	434 (21.0)	456 (22.0)	0.41
Previous CABG	98 (4.7)	114 (5.5)	0.26
Previous stroke	89 (4.3)	90 (4.3)	0.94
History of CHF	80 (3.9)	93 (4.5)	0.31
History of COPD	100 (4.8)	88 (4.2)	0.37
History of PAD	59 (2.8)	71 (3.4)	0.29
History of Cancer*	27 (1.3)	28 (1.4)	0.89
Previous Bleeding	66 (3.2)	63 (3.0)	0.79
Clinical characteristics on arrival			
Killip Class II-IV	102 (4.9)	107 (5.2)	0.72
CPR outside hospital	77 (3.7)	68 (3.3)	0.45
Estimated GFR \leq 60 ml/min/1.73 ²	250 (12.1)	273 (13.2)	0.28
Anaemia	419 (20.2)	431 (20.8)	0.64
Crusade bleeding score	20 (14- 27)	20 (14- 27)	0.32
1-20	1082 (52.2)	1062 (51.3)	0.54
21-30	658 (31.8)	654 (31.6)	
31-40	229 (11.1)	232 (11.2)	
\geq 41	102 (4.9)	123 (5.9)	
Medications on arrival			
Aspirin	584 (28.2)	628 (30.3)	0.13
P2Y12 receptor inhibitors	176 (8.6)	203 (9.8)	0.17
Statins	595 (28.7)	620 (29.9)	0.39
Percutaneous Coronary Intervention			
Multivessel disease	1042 (50.3)	1076 (52.0)	0.29
PCI with stent	1939 (93.6)	1920 (92.7)	0.24
Transradial access	1383 (66.8)	1361 (65.7)	0.13
During the index hospitalisation			
CPAP	64 (3.1)	51 (2.5)	0.22
Inotropic drug	104 (5.0)	104 (5.0)	1.00
Medication at discharge			
Beta blockers	1915 (92.5)	1906 (92.0)	0.60
ACE-I/ARB	1836 (88.7)	1842 (88.9)	0.77
Statins	2013 (97.2)	2022 (97.6)	0.38
Anti-diabetic medications	375 (18.1)	407 (19.7)	0.20
Diuretics	343 (16.6)	366 (17.7)	0.34
Infarct type			
ST-segment elevation MI	1537 (74.2)	1507 (72.8)	0.29
Non-ST-segment elevation MI	534 (25.8)	564 (27.2)	
Results are presented as numbers and percentages unless otherwise indicated. Abbreviations (in order of appearance): SD, standard deviation; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; CPR, cardiopulmonary resuscitation; GFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; CPAP, continuous positive airway pressure; ACE-I, angiotensin-converting			

enzyme inhibitor; ARB, angiotensin receptor blocker; *Any cancer diagnosis the last 5 years; ** Were administrated 24 hours before or during PCI

Table S5. One-year outcomes before and after multivariable Cox regression, including calendar year

	Prasugrel	Ticagrelor	
Patients, n	2073	35917	
	Events, n (%)		HR (95% CI)
MACCE			
Crude	127 (6.1)	2196 (6.1)	1.00 (0.84- 1.20)
MV analysis including calendar year			1.08 (0.89- 1.32)
NACCE			
Crude	174 (8.4)	3130 (8.7)	0.96 (0.82- 1.12)
MV analysis including calendar year			1.07 (0.90- 1.27)
All-cause mortality			
Crude	48 (2.3)	1056 (2.9)	0.79 (0.59- 1.05)
MV analysis including calendar year			0.95 (0.69- 1.30)
Myocardial infarction			
Crude	85 (4.1)	1123 (3.2)	1.32 (1.06- 1.64)
MV analysis including calendar year			1.15 (0.90- 1.48)
Stroke			
Crude	18 (0.9)	385 (1.1)	0.81 (0.50- 1.30)
MV analysis including calendar year			0.84 (0.50- 1.40)
Major bleeding			
Crude	51 (2.5)	1124 (3.2)	0.78 (0.59- 1.03)
MV analysis including calendar year			0.98 (0.72- 1.33)
Major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, myocardial infarction, or stroke (ischemic and haemorrhagic); Net adverse cardiac and cerebrovascular events (NACCE) including MACCE and major bleeding during follow up. Hazard ratios (HR) with 95% confidence intervals were derived from Cox regression analysis. In the unadjusted model (crude) only treatment was included as covariate. In the multivariable model (MV) 34 additional covariates and calendar year were included.			

