



LJMU Research Online

Olier, I, Sirker, A, Hildick-Smith, DJR, Kinnaird, T, Ludman, P, de Belder, MA, Baumbach, A, Byrne, J, Rashid, M, Curzen, N, Mamas, MA and British Cardiovascular Intervention Society and the National Ins,

Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention.

<http://researchonline.ljmu.ac.uk/9243/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

Olier, I, Sirker, A, Hildick-Smith, DJR, Kinnaird, T, Ludman, P, de Belder, MA, Baumbach, A, Byrne, J, Rashid, M, Curzen, N, Mamas, MA and British Cardiovascular Intervention Society and the National Ins, (2018) Association of different antiplatelet therapies with mortality after primary

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

Prasugrel, Ticagrelor and Clopidogrel in primary percutaneous coronary intervention: a comparative analysis

Brief title: Prasugrel, Ticagrelor and Clopidogrel in primary PCI

Ivan Olier*, PhD^{1,2}; Alex Sirker*, MA MB BChir PhD³; Dave Hildick-Smith, MD⁴; Tim Kinnaird, MD^{1,5}; Peter Ludman, MD⁶; Mark A. de Belder, MD⁷; Andreas Baumbach, MD⁸; Jonathan Byrne, MD⁹; Muhammad Rashid, MBBS^{1,10}; Nick Curzen, PhD¹¹; Mamas A. Mamas BM BCh, MA, DPhil^{1,10} on behalf of the British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research

1. Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute of Primary Care and Health Sciences, Keele University, Stoke-on-Trent, UK.
2. School of Computing, Mathematics and Digital Technology, Manchester Metropolitan University, UK
3. The Heart Hospital, University College London Hospitals, London, UK
4. Sussex Cardiac Centre, Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom
5. Department of Cardiology, University Hospital of Wales, Cardiff, UK
6. Queen Elizabeth Hospital, Birmingham, UK
7. The James Cook University Hospital, Middlesbrough, UK
8. Barts Heart Centre, Queen Mary University, London, UK
9. Kings College Hospital, London, UK
10. Academic Department of Cardiology, Royal Stoke Hospital, University Hospital North Midlands, Stoke-on-Trent, UK.
11. University Hospital Southampton and Faculty of Medicine, University of Southampton, UK

* These authors contributed equally to the manuscript.

Corresponding Author:

Mamas A. Mamas

Professor of Cardiology / Honorary Consultant Cardiologist

Keele Cardiovascular Research Group,

University of Keele

Stoke-on-Trent, United Kingdom

Email: masmamas1@yahoo.co.uk

Phone: +441782671621

Fax: +441782674467

Word count: 2986

Abstract

Objectives: Prasugrel and ticagrelor both reduce ischaemic endpoints in high-risk acute coronary syndromes, compared to clopidogrel. However, comparative outcomes of these two newer drugs in the context of primary PCI for ST elevation MI (STEMI) remains unclear. We sought to examine this question using the British Cardiovascular Interventional Society national database in patients undergoing primary PCI for STEMI.

Methods: Data from January 2007 to December 2014 was used to compare use of P₂Y₁₂ antiplatelet drugs in primary PCI in > 89,000 patients. Statistical modeling, involving propensity matching, multivariable logistic regression (MLR) and proportional hazards modeling, was used to study the association of different antiplatelet drug use with all-cause mortality.

Results: In our main MLR analysis, prasugrel was associated with significantly lower mortality than clopidogrel at both 30-days (OR 0.87 95% CI 0.78-0.97, p=0.014) and 1-year (OR 0.89 95% CI 0.82-0.97, P=0.011) post PCI. Ticagrelor was not associated with any significant differences in mortality compared to clopidogrel at either 30-days (OR 1.07 95%CI 0.95-1.21, P=0.237) or 1-year (OR 1.058 95%CI 0.96-1.16, P=0.247). Finally, ticagrelor was associated with significantly higher mortality than prasugrel at both time points (30-days, OR 1.22 95%CI 1.03-1.44, P=0.020; 1-year OR 1.19 95% CI 1.04-1.35, P=0.01).

Conclusions: In a cohort of over 89,000 patients undergoing primary PCI for STEMI in the UK, prasugrel is associated with a lower 30-day and 1-year mortality than clopidogrel and ticagrelor. Given that an adequately powered comparative randomised trial is unlikely to be performed, these data may have implications for routine care.

Keywords

Prasugrel; Ticagrelor; Clopidogrel; Antiplatelet Drugs; Primary PCI

Key Messages

What is already known about this subject?

Both prasugrel and ticagrelor have been shown to have clinical outcome benefit in large RCTs of heterogeneous populations with ACS. However, there have been no head-to-head adequately randomised comparisons of clinical outcomes for prasugrel versus ticagrelor in PPCI.

What does this study add?

We observe that prasugrel was associated with significantly lower mortality than clopidogrel at both 30-days and 1-year post PCI whilst ticagrelor was not associated with any significant differences compared to clopidogrel at these timepoints. Ticagrelor is associated with significantly higher mortality in PPCI than prasugrel at both time points.

How this might impact on clinical practice?

Our findings regarding the use of different P2Y12 antiplatelet agents in STEMI and their association with mortality is a timely and important contribution to the literature and one that may influence practice as best currently available evidence in the absence of a more definitive randomised controlled trial.

Introduction

Dual antiplatelet therapy using aspirin plus P₂Y₁₂ inhibitor agents such as clopidogrel in percutaneous coronary intervention (PCI) have improved clinical outcomes, with reductions in stent thrombosis and improved ischaemic outcomes^{1 2}. However, there are important limitations with the use of clopidogrel. Genetic variability in the enzymatic activation of clopidogrel is associated with functional ‘hypo’-responders to this drug, with individuals at increased risk of adverse ischaemic events³. The relatively slow onset of action, even with high dose loading regimens⁴, may be disadvantageous in the emergency setting of primary PCI for ST elevation myocardial infarction (STEMI). Such limitations stimulated the drive for novel P₂Y₁₂ inhibitors, including prasugrel and ticagrelor, offering faster onset and more potent inhibition of platelet activity. Both prasugrel and ticagrelor have been shown to have clinical outcome benefit in large randomised trials in a variety of acute coronary syndromes (ACS)^{5 6} albeit at increased risk of non-CABG related major bleeding. Use of these novel agents in the United Kingdom has been targeted in real world practice to those contexts where ischaemic risks are greatest, such as in primary PCI. It is notable that the *post hoc* analyses of both PLATO and TRITON TIMI 18 failed to show a statistically significant benefit for ticagrelor or prasugrel over clopidogrel in the primary PCI subgroups of their heterogeneous ACS populations^{7 8} and in fact only 68% of the TRITON TIMI 18 STEMI cohort underwent primary PCI⁹.

Although prasugrel and ticagrelor are both ADP-receptor antagonists, there are a number of differences between them, including their pharmacodynamics, drug interactions and side effect profile¹⁰. Switching between the two agents produces demonstrable changes in platelet function^{10 11}. The landmark ACS trials (PLATO and TRITON) also found important differences in outcomes with these two drugs^{5 7}. However, outcomes from these landmark trials cannot be directly compared due to important differences in study populations, study design and inclusion / exclusion criteria¹².

There has been no head-to-head randomised comparison of clinical outcomes for prasugrel versus ticagrelor until the recently presented PRAGUE-18 trial in STEMI and highest-risk NSTEMI-ACS¹³ in which no significant differences were observed in either the 7-day composite efficacy (primary) endpoint or the 30-day key safety endpoint. However, this trial was prematurely stopped after interim analysis and a severe statistical under-powering to address the planned aim. A trial of adequate power for a head to head comparison between prasugrel versus ticagrelor would probably require a sample size approaching 15,000 patients¹⁴, with implications for the ISAR REACT 5 RCT aimed at addressing this question¹⁵.

In the context of (a) limited data regarding comparative outcomes associated with ticagrelor and prasugrel use and (b) the unlikelihood of an adequately powered randomized trial to compare them in the future, our aim was to use the national British Cardiovascular Intervention Society (BCIS) PCI registry to explore outcomes associated with different P₂Y₁₂ antiplatelet agents in a large real world national cohort that captures >99% of PCI cases performed in the United Kingdom.

Methods

Study design and data collection

This is a retrospective analysis of prospectively collected national data for all patients undergoing primary PCI in England and Wales from January 2007 to December 2014. BCIS records information on PCI practice in the UK with data collection managed by the National Institute of Cardiovascular Outcomes Research (NICOR)¹⁶⁻¹⁹. The BCIS database contains 113 clinical, procedural and outcome variables with more than 80,000 new records added each year. Using the Medical Research Information Services, we tracked the life status of patients using their NHS number, a unique identifier for any person registered within the NHS. All the data were collected as part of a national audit and were anonymised; therefore, institutional review board approval was not required for this study.

Outcomes

Our outcomes were mortality at 30 days and one year, In-hospital major bleeding complication and Major Adverse Cardiovascular Events (MACE), Bleeding complications were defined as a composite of reported gastrointestinal bleed, intracerebral bleed, retroperitoneal hematoma, tamponade, blood or platelet transfusion, or an arterial access site complication requiring intervention^{16 20 21}, whilst a composite of in-hospital mortality, re-infarction and revascularization (emergency coronary artery bypass graft or re-intervention PCI) constituted MACE^{18 20}.

Study aim

The primary aim of this study was to investigate the association between the use of a particular antiplatelet drug (clopidogrel, prasugrel and ticagrelor) and 30-day and 1-year mortality.

Statistical analysis

Patient exclusion criteria

The data presented relate to all reported Primary PCI procedures undertaken in patients in England and Wales between January 1, 2007, and December 31, 2014. Procedures were excluded if outcome data, age, or gender were missing from the dataset.

Descriptive statistics

For basic analyses of demographics, procedural details and unadjusted outcomes, continuous variables were evaluated as median and interquartile range (IQR), whilst categorical variables were reported using frequencies and proportions (in percentages). Medians, IQRs, frequencies and percentages quoted for unadjusted data refer to numbers within the cohort where data were available. Chi-squared tests were used to assess the significance of differences in proportions between groups for categorical variables. Kruskal-Wallis rank sum test was used for continuous variables. All statistical tests were two-tailed and an alpha of 5% (for significance) was used throughout.

Multiple imputations for missing data

Multiple imputation methods were used in order to reduce potential bias created by missing data²². To this aim, we used the *mice* R package, version 2.25²³ which is freely available on the The Comprehensive R Archive Network (CRAN) repository (<https://cran.r-project.org>). Chained equations were used to impute data for all variables with missing values to generate 10 dataset instances for use in the analyses.

Multivariate statistical modelling

Multivariate logistic regression models were performed over the multiple imputed dataset instances in order to elucidate associations, in the form of odd ratios, between antiplatelet drug selection and adverse outcomes. We also used multivariate Cox regression models to estimate hazard ratios between antiplatelet and survival time outcome censored to 1 year. In order to control for potential confounding, all models were adjusted for the following covariates: age, gender, smoking status, diabetes, history of peripheral vascular disease (PVD), hypertension, hypercholesterolemia, history of renal disease, previous coronary artery bypass graft (CABG), previous myocardial infarction (MI), previous stroke, previous PCI, left ventricular ejection

fraction (LVEF), pre-procedural TIMI flow score, access site, vascular closure device (VCD) use, stent type, vessel attempted, cardiogenic shock (CS), intra-aortic balloon pump (IABP) use, ventilatory support, thrombectomy, glycoprotein IIb/IIIa inhibitors (GPI) use, bivalirudin use, and year of procedure.

Propensity score matching

A sensitivity analysis was performed using propensity score matching. The method was implemented in three separated logistic regression models (prasugrel vs clopidogrel, ticagrelor vs clopidogrel, and ticagrelor vs prasugrel) over the multiple imputed dataset instances using the aforementioned variables as explanatories and the antiplatelet drug use as the outcome. We used the *MatchIt* R package, version 2.4-21²⁴, to estimate the propensity scores and to form the new matched dataset instances according to them. As initial settings, we used the nearest-neighbor matching method and no procedures were discarded. Depending on the type of outcome, binary or survival time, conditional logistic or Cox regression models were performed, respectively, over the matched dataset instances.

Results

A total of 125,424 primary PCI procedures were undertaken on patients in England and Wales between 2007 and 2014 of which 89,067 (71.0 %) were included in the descriptive analyses and statistical modeling. Figure 1 displays a detailed flowchart for procedure inclusion/exclusion criteria, the commonest reasons being that antiplatelet agent was unknown in 34,265 procedures (27.42%).

Figure 2 provides details on antiplatelet agent in primary PCI use at primary care trusts (PCTs, England) and local health boards (LHBs, Wales) levels. This figure shows differences in use across England and Wales over time, ticagrelor mainly being prescribed in northern England and in some parts of the London area, whilst prasugrel seems to be favored in west England and some LHBs in Wales.

Table 1 presents baseline patient demographics, procedural details, pharmacology and outcomes for the three antiplatelet groups. Supplementary Table S1a gives details of missing value levels presented in the data and Supplementary Table S1b patient demographics, procedural details, pharmacology and outcomes for patients where antiplatelet regime was

missing. Results of statistical tests included in Table 1 illustrate significant differences amongst the groups. For instance, patients from the clopidogrel group were older and more likely to be female, and to have a history of peripheral vascular disease, hypertension, hypercholesterolemia, renal disease, coronary artery bypass graft, myocardial infarction, stroke, or PCI. Patients prescribed with prasugrel are younger, more likely to be male and current smokers, and less likely to be diabetics, whilst patients in the ticagrelor group were more likely to be non-smokers.

Differences in procedural characteristics between the 3 groups were also observed, with procedures within the clopidogrel group less likely to be undertaken through the radial route, more likely to have multivessel PCI and present with cardiogenic shock and to require the use of intra-aortic balloon pump, although less likely to receive thrombectomy. Procedures within the prasugrel group were more likely to have patients with TIMI 0 flow, but less likely to require ventilatory support, whilst drug eluting stents were more likely to be used within the ticagrelor group. In addition, the use of bivalirudin is considerably less frequent within the clopidogrel group whilst glycoprotein IIb/IIIa inhibitors are less likely used within the ticagrelor group.

Crude mortality at both 30 days and 1 year were highest in patients treated with clopidogrel (6.5% and 10.2% respectively); $P < 0.0001$ and lowest in patients treated with prasugrel (3.6% and 5.9%); $P < 0.0001$ (ticagrelor 5.5% and 8.5%); $P < 0.0001$. Similarly, in-hospital MACE was significantly lower in the prasugrel group (3.2%) compared to either the group receiving clopidogrel (4.9%) or ticagrelor (4.8%); $P < 0.0001$, whilst crude in-hospital bleeding rates were higher in the clopidogrel group (1.5%) compared to either prasugrel (0.7%) or ticagrelor (0.6%); $P < 0.0001$.

Table 2 shows the results of fitting multivariate logistic regression models to the original multiple imputed datasets. Compared with clopidogrel, prasugrel was associated with a lower risk of mortality at both 30 days (OR 0.87 95% CI 0.78-0.97, $P = 0.014$) and 1 year (OR 0.89 95% CI 0.82-0.97, $P = 0.011$). prasugrel was also associated with decreased in-hospital major bleeding (OR 0.73 95% CI 0.59-0.91, $P = 0.005$) although no significant differences in in-hospital MACE were observed (OR 0.94 95% CI 0.84-1.06, $P = 0.30$). In contrast, no significant differences in either 30-day (OR 1.07 95% CI 0.95-1.21, $P = 0.24$) or 1-year mortality (OR 1.06 95% CI 0.96-1.16, $P = 0.25$) were observed between patients receiving ticagrelor compared to those receiving clopidogrel. Finally, ticagrelor was associated with an increased risk of 30-day (OR 1.22, 95% CI 1.03-1.44, $P = 0.020$) and 1-year (OR 1.19 95% CI 1.04-1.35) mortality compared to the prasugrel group. A similar increased risk of in-hospital MACE (OR 1.25, 95%

CI 1.06-1.47, $P=0.008$) was observed associated with the use of ticagrelor compared with prasugrel although no significant differences in in-hospital major bleeding were observed.

Figure 3 displays the Kaplan-Meier estimates of the survivor function for the 3 cohorts, and adjusted for the same set of covariates used before. Survival analyses were performed using multivariate Cox regressions in which the survival time outcome was censored at 1 year. Table 3 summarizes the results, which shows associations between antiplatelet use and mortality. prasugrel was associated with a no significant difference in mortality compared to clopidogrel (HR 0.94 95% CI 0.87-1.01, $P=0.084$), whilst use of ticagrelor was associated with a significant increased mortality risk (HR 1.10 95% CI 1.02-1.19, $P=0.019$). Patients treated with ticagrelor also had a significantly greater risk of mortality than those patients receiving prasugrel (HR 1.13 95% CI 1.01-1.27, $P=0.030$).

A sensitivity analysis was performed by fitting conditional logistic and Cox regressions over 10 propensity score matched dataset instances (Supplementary Table S2 that provides an overview of the propensity score matched datasets and Table 4) and in general the findings were materially similar, namely use of prasugrel was associated with a lower risk of mortality compared with ticagrelor, although no significant differences in mortality were demonstrated associated with the use of ticagrelor (compared to clopidogrel). Furthermore, prasugrel use was independently associated with a lower risk of mortality compared to ticagralor. Three further sensitivity analyses were performed using, firstly, a restricted dataset containing procedures undertaken since 2010, only, when all three antiplatelet drugs were available in the UK; and, secondly, a dataset which extends the prasugrel and ticagrelor group definitions to allow inclusion of procedures in which patients were prescribed clopidogrel as well as prasugrel, and clopidogrel as well as ticagrelor (presumably reflecting pre-treatment with clopidogrel prior to prescription of either ticagrelor or prasugrel that was observed in 1.8% of cases), respectively. Finally, a third sensitivity analysis was undertaken by including the patients in whom the anti-platelet status was unknown. Results from these analyses are presented in the supplementary material (supplementary Table S3-S5).

Discussion

Rationale for the present study

Both prasugrel and ticagralor are associated with lower rates of ischaemic end points compared to clopidogrel in large randomised trials that included a heterogeneous population of ACS patients. However, two important questions that relate directly to clinical practice remain unclear. Firstly, whether the newer agents are significantly better than clopidogrel in a primary

PCI population and secondly, the relative benefits of these 2 novel agents compared to each other.

With a specific focus on STEMI, the landmark RCTs came to different conclusions in their relevant *posthoc* subgroup analyses. In the PLATO subgroup of patients treated with primary PCI within 12 hours for STEMI²⁵, ticagrelor did not show a significant reduction in the primary efficacy endpoint versus clopidogrel, nor did it reduce cardiovascular death (in contrast to the overall study population). The possible reasons for this are various but include the smaller cohort size (around 4000 patients) compared to over 70,000 patients included in our analysis. Similarly, the TRITON subgroup who underwent primary PCI (with around 2300 patients) also demonstrated no significant reduction in the primary endpoint with prasugrel compared to clopidogrel⁹. We therefore attempted to evaluate the relative benefits of Prasugrel versus ticagrelor in primary PCI from a large observational registry and the present analysis provides the first comparative evaluation between prasugrel and ticagrelor in the “real world” from a national perspective.

Interpreting key findings of our study

Association of P2Y12 antagonist and clinical outcomes

Certain baseline demographics are noteworthy when considering the association of oral antiplatelet agents and mortality in the present work. For example, radial access was far more frequently employed in patients receiving ticagrelor and prasugrel than in those receiving clopidogrel. The reasons behind this are not immediately clear but may be partly time-dependent, since radial use in the UK progressively increased over the study period (2009-2014)¹⁷ and a greater proportion of the clopidogrel cases were undertaken in the earlier part of this period compared to the other 2 agents. Given the relationship between radial access and reduced major bleeding and mortality in STEMI^{21 26 27} this would favour outcomes in groups who received prasugrel and ticagrelor. Furthermore, the group who received clopidogrel had a higher incidence of adverse risk factors for outcome, for example, evidence of cardiogenic shock at presentation and a history of previous stroke. Hence, it was not surprising to find that unadjusted (raw) data indicated both novel potent antiplatelets were associated with a significant mortality advantage over clopidogrel.

After multivariate adjustment for differences in baseline co-variables, the significant mortality impact of the newer agents (each compared to clopidogrel) was found to persist for prasugrel but not ticagrelor. The mortality finding for prasugrel versus clopidogrel in our main adjusted analyses is interesting, since a reduction in the primary endpoint (of cardiovascular death,

myocardial infarction, or stroke) at 15 months was also observed in the TRITON STEMI subgroup who underwent PCI (with around 3000 patients) with prasugrel compared to clopidogrel (HR 0.79, 95% CI 0.65 - 0.97; $p = 0.022$)⁹, although not in the primary PCI subgroup (HR 0.89, 95% CI 0.69-1.13). The primary PCI subgroup in TRITON was much smaller in size than ours (2340 versus over 70,000 cases), – hence it may simply be that the much larger population in our registry allowed a mortality effect too small to detect in the RCT to be demonstrated. Another pertinent factor arises from the likely pattern of use of prasugrel in our study versus that in TRITON. Given the real-world setting of our study, it is likely that prescribing guidance for prasugrel was largely followed and hence groups with neutral or adverse effect with prasugrel from TRITON were underrepresented in our study’s prasugrel group (as seen from patient age and history of stroke in Table 1). This too may have contributed to a larger advantage of prasugrel over clopidogrel in our work, compared to the landmark RCT. For the comparison of prasugrel versus ticagrelor, our mortality findings at both early (30 days) and later (1 year) time points favoured prasugrel in the main analysis. Although there are potential unadjusted confounders or selection bias inherent in a study such as this, the differences described here may well reflect a genuine difference in clinical effect, rather than related to confounders or selection bias. Compliance may be a factor, since prasugrel is a once daily medication whereas ticagrelor has a b.d. regimen for use, and this may predispose to better adherence to prasugrel prescriptions. Another possible influence on compliance is the differing side effect profiles – for example, dyspnea sometimes noted with ticagrelor (but not prasugrel) might be a reason underlying non-compliance or unplanned switching to another agent, again potentially impacting on outcomes. Differences in pharmacodynamics between prasugrel and ticagrelor in patients presenting with STEMI may contribute to our findings²⁸. For example, in one randomized study 2 h post loading dose ticagrelor achieved 12% platelet inhibition compared to 48% with prasugrel. Furthermore, the mean time to achieve platelet reactivity <240 units (using Accumetrics verifyNow) was 3 ± 2 h with prasugrel compared to 5 ± 4 h in patients treated with ticagrelor²⁸. In a further analysis of 16,000 patients ACS managed with PCI treated with either prasugrel or ticagrelor, both MACE (HR 0.80, 95% CI 0.64–0.98, $P = 0.03$) and net adverse clinical events NACE (HR 0.78 95% CI 0.64–0.94, $P = 0.009$) were significantly lower in the prasugrel groups compared to ticagrelor in a propensity score matched cohort²⁹. Similarly, a recent network meta-analysis of 37 studies including 88,402 patients that sought to compare the clinical efficacy and safety of P₂Y₁₂ inhibitors in patients with STEMI undergoing primary PCI demonstrated that prasugrel was associated with reduced risk of 30-day mortality (OR 0.69, 95% CI 0.56-0.84) and 30-day MACE (OR 0.69, 95% CI

0.56-0.84), but not cardiovascular mortality (OR 0.74, 95% CI 0.43-1.25) or major bleeding (OR 0.76 95% CI 0.57-1.05)³⁰.

Nevertheless, in keeping with all observational studies, the potential for undetected or unquantified confounders exists. An important limitation, specific to this work, relates to the recording of P2Y12 blocker choice on the registry database at the time of the primary PCI procedure. Hence, it is not possible to detect cases where there may have been premature drug discontinuation or substitution of the initially selected agent later in the clinical course e.g. due to side effects or whether the antiplatelet agent was given pre- or post-procedure. Thirdly, we acknowledge that there is likely to be selection bias, in that newer antiplatelet agents are more likely to be prescribed to less sick, younger patients that may drive some of our observations, although it is unlikely that such a mechanism would explain the differences in outcomes that we report between the 2 newer (prasugrel and ticagrelor) agents. Finally, our secondary endpoints (in hospital major bleeding and in-hospital MACE) are based on retrospective recording (by operators or other team members) of these complications and are not externally validated. This is in contrast to the highly robust mortality tracking, derived from linkage of the PCI registry to the national UK mortality database. Hence the conclusions drawn from these secondary endpoints are acknowledged to be less robust than our mortality outcomes.

Conclusions

In a cohort of just over 89,000 patients undergoing primary PCI for STEMI in clinical practice in the UK, prasugrel is associated with a lower 30 day and 1 year mortality than clopidogrel and ticagrelor. Give that it is unlikely that an adequately powered randomized trial will be undertaken to compare them in the future, these data may have implications for routine clinical care.

Funding sources

Unrestricted educational grant from Daiichi Sankyo to MAM, although the company had no role in the design of study, preparation of manuscript or access to the contents of the manuscript prior to submission.

Contributions:

MAM, IO and AS designed the study; acquired, and interpreted data and drafted the first draft of manuscript; IO analyzed the data. MAM and IO agree to be the guarantors who are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. NC, TK, PL, JB, MR, DHS, MAB, and AB made substantial contributions to the design of the work, critically revised the report

REFERENCES

- 1 Schomig A, Neumann FJ, Kastrati A, *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**: 1084-9.
- 2 Bertrand ME, Rupprecht HJ, Urban P, *et al.* Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : The clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**: 624-9.
- 3 Gawaz M, Geisler T. Coronary artery disease: Platelet activity: An obstacle for successful PCI. *Nat Rev Cardiol.* 2009;**6**: 391-2.
- 4 Hochholzer W, Trenk D, Frundi D, *et al.* Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005;**111**: 2560-4.
- 5 Wallentin L, Becker RC, Budaj A, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**: 1045-57.
- 6 Wiviott SD, Braunwald E, McCabe CH, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**: 2001-15.
- 7 Montalescot G, Wiviott SD, Braunwald E, *et al.* Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. 2009;**373**: 723-31.
- 8 Steg PG, James S, Harrington RA, *et al.* Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A platelet inhibition and patient outcomes (PLATO) trial subgroup analysis. *Circulation* 2010;**122**: 2131-41.
- 9 Udell JA, Braunwald E, Antman EM, *et al.* Prasugrel versus clopidogrel in patients with ST-segment elevation myocardial infarction according to timing of percutaneous coronary intervention: A TRITON-TIMI 38 subgroup analysis (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in myocardial infarction 38). 2014;**7**: 604-12.

- 10 Khan N, Cox AR, Cotton JM. Pharmacokinetics and pharmacodynamics of oral P2Y₁₂ inhibitors during the acute phase of a myocardial infarction: A systematic review. *Thromb Res* 2016;**143**: 141-8.
- 11 Angiolillo DJ, Curzen N, Gurbel P, *et al.* Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in patients with stable coronary artery disease: Results of the SWAP-2 study (switching anti platelet-2). *J Am Coll Cardiol* 2014;**63**: 1500-9.
- 12 Husted S, Boersma E. Case study: Ticagrelor in PLATO and prasugrel in TRITON-TIMI 38 and TRILOGY-ACS trials in patients with acute coronary syndromes. *Am J Ther* 2016;**23**: e1876-89.
- 13 Motovska Z, Hlinomaz O, Miklik R, *et al.* Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: Multicenter randomized PRAGUE-18 study. *Circulation* 2016;**134**: 1603-12.
- 14 Wendling P. PRAGUE-18: Prasugrel, ticagrelor equal in STEMI, but questions remain. medscape. aug 30, 2016. <http://www.medscape.com/viewarticle/868142> accessed on **24 March 2016**.
- 15 Schulz S, Angiolillo DJ, Antoniucci D, *et al.* Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy—design and rationale of the iNtracoronary stenting and antithrombotic regimen: Rapid early action for coronary treatment (ISAR-REACT) 5 trial. 2014;**7**: 91-100.
- 16 Mamas MA, Anderson SG, Carr M, *et al.* Baseline bleeding risk and arterial access site practice in relation to procedural outcomes after percutaneous coronary intervention. *J Am Coll Cardiol* 2014;**64**: 1554-64.
- 17 Mamas MA, Nolan J, de Belder MA, *et al.* Changes in arterial access site and association with mortality in the united kingdom: Observations from a national percutaneous coronary intervention database. *Circulation* 2016;**133**: 1655-67.
- 18 Sirker A, Mamas M, Robinson D, *et al.* Bivalirudin, glycoprotein inhibitor, and heparin use and association with outcomes of primary percutaneous coronary intervention in the united kingdom. *Eur Heart J* 2016;**37**: 1312-20.
- 19 Ludman PF, British Cardiovascular Intervention Society. British cardiovascular intervention society registry for audit and quality assessment of percutaneous coronary interventions in the united kingdom. *Heart* 2011;**97**: 1293-7.
- 20 Kwok CS, Kontopantelis E, Kunadian V, *et al.* Effect of access site, gender, and indication on clinical outcomes after percutaneous coronary intervention: Insights from the british cardiovascular intervention society (BCIS). *Am Heart J* 2015;**170**: 164,172. e5.
- 21 Mamas MA, Ratib K, Routledge H, *et al.* Influence of arterial access site selection on outcomes in primary percutaneous coronary intervention: Are the results of randomized trials achievable in clinical practice? *JACC Cardiovasc Interv* 2013;**6**: 698-706.

- 22 Rubin DB. Multiple imputation for nonresponse in surveys. 1987, New York: J. NY Wiley.
- 23 Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. 2011;**45** (3).
- 24 Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *Journal of Statistical Software*. 2011; **14**:1-28.
- 25 Velders MA, Abtan J, Angiolillo DJ, *et al*. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. *Heart* 2016;**102**: 617-25.
- 26 Mamas MA, Ratib K, Routledge H, *et al*. Influence of access site selection on PCI-related adverse events in patients with STEMI: Meta-analysis of randomised controlled trials. *Heart* 2012;**98**: 303-11.
- 27 Mehta SR, Jolly SS, Cairns J, *et al*. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol* 2012;**60**: 2490-9.
- 28 Alexopoulos D, Xanthopoulou I, Gkizas V, *et al*. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012;**5**: 797-804.
- 29 Larmore C, Effron MB, Molife C, *et al*. “Real-World” comparison of prasugrel with ticagrelor in patients with acute coronary syndrome treated with percutaneous coronary intervention in the united states. 2015;.
- 30 Rafique AM, Nayyar P, Wang TY, *et al*. Optimal P2Y 12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. 2016;**9**: 1036-46.

List of Figures and Tables

Figure 1. Flowchart for procedure inclusion/exclusion.

Figure 2. Changes in use of antiplatelet drugs in Primary Care Trusts in England and Local Health Boards in Wales.

Figure 3. Kaplan-Meier curves for the propensity score matched datasets. Confidence intervals are represented by colored shades.

Table 1: Baseline patient demographics, procedural details, pharmacology, and outcomes.

	Clopidogrel (58,248)	Prasugrel (17,714)	Ticagrelor (13,105)	P-value†	P-value‡
Age	64.0 (54.0 - 75.0)	61.0 (52.0 - 69.0)	63.0 (53.0 - 72.0)	< 0.0001	< 0.0001
Gender (Male)	42,821 (73.5%)	13,739 (77.6%)	9,721 (74.2%)	< 0.0001	< 0.0001
Smoking status				< 0.0001	< 0.0001
Never	16,934 (32.3%)	4,797 (29.6%)	4,545 (37.6%)		
Ex-smoker	15,465 (29.5%)	4,021 (24.8%)	2,742 (22.7%)		
Current	20,033 (38.2%)	7,384 (45.6%)	4,785 (39.6%)		
Diabetes	8,233 (14.8%)	2,315 (13.4%)	1,927 (15.0%)	< 0.0001	< 0.0001
History of peripheral vascular disease	2,024 (3.6%)	416 (2.5%)	332 (2.7%)	< 0.0001	0.21
Hypertension	25,022 (44.9%)	6,363 (37.5%)	4,986 (40.5%)	< 0.0001	< 0.0001
Hypercholesterolemia	23,246 (41.7%)	6,850 (40.4%)	4,630 (37.6%)	< 0.0001	< 0.0001
History of renal disease	478 (0.9%)	67 (0.4%)	42 (0.3%)	< 0.0001	0.34
History of coronary artery bypass graft	1,866 (4.7%)	356 (2.5%)	367 (4.2%)	< 0.0001	< 0.0001
History myocardial infarction	7,603 (14.0%)	1,866 (10.7%)	1,472 (12.3%)	< 0.0001	< 0.0001
History of stroke	2,368 (4.2%)	322 (1.9%)	411 (3.3%)	< 0.0001	< 0.0001
History of percutaneous coronary intervention	5,642 (9.9%)	1,458 (8.3%)	1,120 (8.7%)	< 0.0001	0.22
Left ventricular ejection fraction				< 0.0001	< 0.0001
Good (>50%)	10,098 (52.1%)	2,764 (55.8%)	1,978 (51.1%)		
Moderate (30%-50%)	7,117 (36.7%)	1,763 (35.6%)	1,532 (39.6%)		
Poor (<30%)	2,181 (11.2%)	427 (8.6%)	363 (9.4%)		
TIMI flow				< 0.0001	< 0.0001
TIMI 0	35,718 (69.2%)	12,239 (75.8%)	8,140 (71.6%)		
TIMI 1	4,660 (9.0%)	1,057 (6.5%)	964 (8.5%)		
TIMI 2	5,031 (9.8%)	1,502 (9.3%)	1,101 (9.7%)		
TIMI 3	6,189 (12.0%)	1,341 (8.3%)	1,161 (10.2%)		
Access site (Radial)	26,514 (47.1%)	12,692 (74.9%)	9,765 (78.3%)	< 0.0001	< 0.0001
Stent				< 0.0001	< 0.0001
None	4,422 (8.0%)	1,050 (6.1%)	773 (6.1%)		
Bare metal	19,479 (35.2%)	4,217 (24.5%)	1,503 (11.9%)		
Drug eluting	31,492 (56.9%)	11,974 (69.5%)	10,381 (82.0%)		
Vessel attempted				< 0.0001	< 0.0001
Venous or arterial graft	803 (1.4%)	259 (1.5%)	143 (1.1%)		
Left main stem artery	411 (0.7%)	67 (0.4%)	230 (1.8%)		
Left anterior descending artery	22,858 (39.5%)	6,905 (39.2%)	4,974 (38.2%)		
Left circumflex artery	7,216 (12.5%)	2,186 (12.4%)	1,839 (14.1%)		
Right coronary artery	22,915 (39.6%)	7,269 (41.2%)	5,147 (39.5%)		
Multiple	3,671 (6.3%)	937 (5.3%)	700 (5.4%)		
Cardiogenic shock	4,155 (7.2%)	988 (5.6%)	812 (6.2%)	< 0.0001	0.020
Intra-aortic balloon pump use	2,832 (5.1%)	567 (3.4%)	421 (3.4%)	< 0.0001	0.77
Ventilatory support	1,891 (3.5%)	425 (2.5%)	392 (3.4%)	< 0.0001	< 0.0001
Thrombectomy	25,933 (46.6%)	8,583 (51.0%)	6,518 (52.7%)	< 0.0001	0.005
Bivalirudin use	5,095 (8.7%)	5,697 (32.2%)	2,963 (22.6%)	< 0.0001	< 0.0001
Glycoprotein IIb/IIIa inhibitors use	30,258 (53.7%)	7,672 (44.5%)	4,294 (34.8%)	< 0.0001	< 0.0001
Year				< 0.0001	< 0.0001
2007	3,448 (5.9%)	0 (0.0%)	0 (0.0%)		
2008	5,467 (9.4%)	0 (0.0%)	0 (0.0%)		
2009	8,134 (14.0%)	42 (0.2%)	0 (0.0%)		
2010	9,491 (16.3%)	1,649 (9.3%)	4 (0.0%)		
2011	9,204 (15.8%)	4,383 (24.7%)	15 (0.1%)		
2012	8,528 (14.6%)	5,049 (28.5%)	1,601 (12.2%)		
2013	7,408 (12.7%)	3,594 (20.3%)	4,870 (37.2%)		

	Clopidogrel (58,248)	Prasugrel (17,714)	Ticagrelor (13,105)	P-value†	P-value‡
2014	6,568 (11.3%)	2,997 (16.9%)	6,615 (50.5%)		
Bleeding	843 (1.5%)	121 (0.7%)	76 (0.6%)	< 0.0001	0.30
Major adverse cardiovascular event	2,783 (4.9%)	545 (3.2%)	616 (4.8%)	< 0.0001	< 0.0001
30 days mortality	3,534 (6.4%)	622 (3.6%)	689 (5.5%)	< 0.0001	< 0.0001
1 year mortality	5,656 (10.2%)	999 (5.9%)	1,075 (8.5%)	< 0.0001	< 0.0001

†Resulting tests when comparing the three groups. ‡Resulting tests when comparing Ticagrelor vs Prasugrel only.

Table 2: Results of multivariate logistic regression models. Odd ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 multiple imputed dataset instances.

Outcome	Cohort	Odd ratio (95% CI)	P-value
Bleeding	Prasugrel vs Clopidogrel	0.732 (0.588-0.910)	0.005
	Ticagrelor vs Clopidogrel	0.648 (0.493-0.852)	0.002
	Ticagrelor vs Prasugrel	0.866 (0.600-1.249)	0.441
MACE	Prasugrel vs Clopidogrel	0.940 (0.837-1.056)	0.296
	Ticagrelor vs Clopidogrel	1.171 (1.037-1.323)	0.011
	Ticagrelor vs Prasugrel	1.249 (1.059-1.472)	0.008
30 days mortality	Prasugrel vs Clopidogrel	0.870 (0.777-0.973)	0.014
	Ticagrelor vs Clopidogrel	1.074 (0.954-1.208)	0.237
	Ticagrelor vs Prasugrel	1.216 (1.031-1.435)	0.020
1 year mortality	Prasugrel vs Clopidogrel	0.891 (0.815-0.974)	0.011
	Ticagrelor vs Clopidogrel	1.058 (0.962-1.163)	0.247
	Ticagrelor vs Prasugrel	1.188 (1.042-1.354)	0.010

Table 3: Results of multivariate Cox regression models with survival time censored at 1 year. Hazard ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 multiple imputed dataset instances.

Cohort	Hazard ratio (95% CI)	P-value
Prasugrel vs Clopidogrel	0.935 (0.866-1.009)	0.084
Ticagrelor vs Clopidogrel	1.099 (1.016-1.189)	0.019
Ticagrelor vs Prasugrel	1.133 (1.012-1.267)	0.030

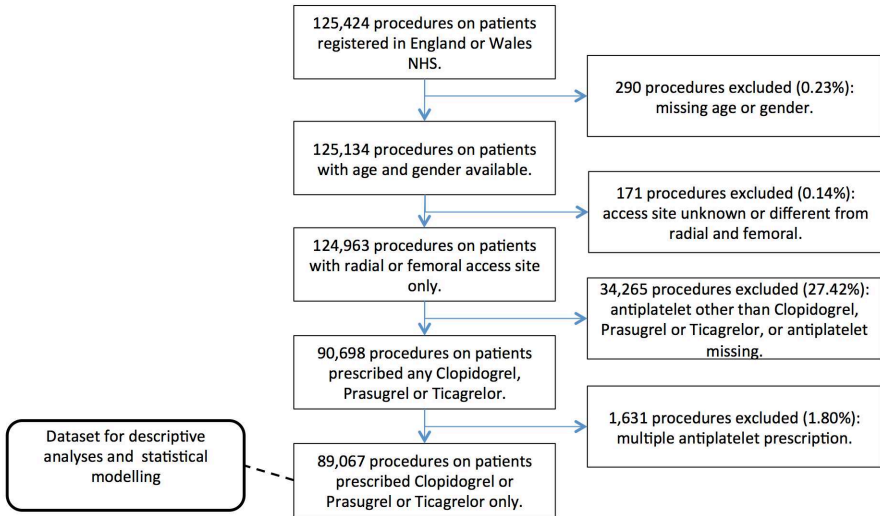
Table 4: Sensitivity analysis 1

(a) Results of conditional logistic regression models. Odd ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

Outcome	Cohort	Odd ratio (95% CI)	P-value
Bleeding	Prasugrel vs Clopidogrel	0.737 (0.511-0.961)	0.031
	Ticagrelor vs Clopidogrel	0.682 (0.464-1.005)	0.053
	Ticagrelor vs Prasugrel	0.949 (0.515-1.748)	0.863
MACE	Prasugrel vs Clopidogrel	0.964 (0.814-1.141)	0.669
	Ticagrelor vs Clopidogrel	1.219 (1.015-1.463)	0.034
	Ticagrelor vs Prasugrel	1.309 (1.059-1.619)	0.013
30 days mortality	Prasugrel vs Clopidogrel	0.860 (0.738-0.998)	0.042
	Ticagrelor vs Clopidogrel	1.099 (0.942-1.282)	0.229
	Ticagrelor vs Prasugrel	1.281 (1.053-1.557)	0.013
1 year mortality	Prasugrel vs Clopidogrel	0.855 (0.755-0.968)	0.014
	Ticagrelor vs Clopidogrel	1.082 (0.959-1.220)	0.201
	Ticagrelor vs Prasugrel	1.250 (1.075-1.454)	0.004

(b) Results of Cox regression models with survival time censored at 1 year. Hazard ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

Cohort	Hazard ratio (95% CI)	P-value
Prasugrel vs Clopidogrel	0.871 (0.774-0.981)	0.023
Ticagrelor vs Clopidogrel	1.099 (0.971-1.243)	0.133
Ticagrelor vs Prasugrel	1.258 (1.085-1.458)	0.002



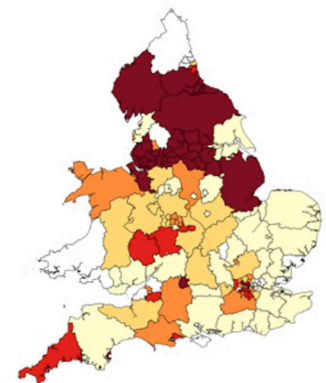
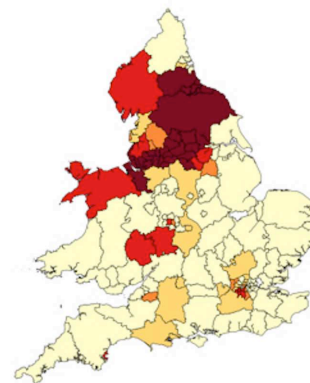
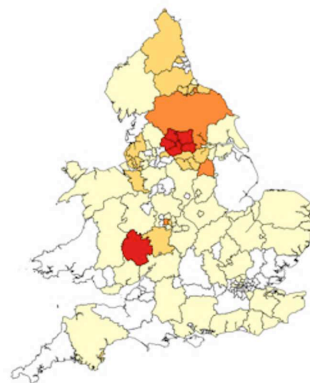
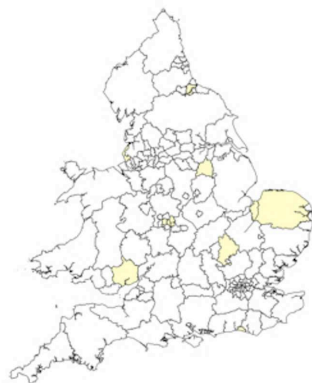
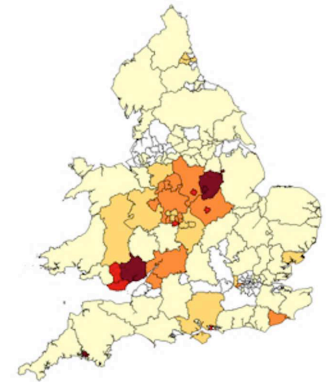
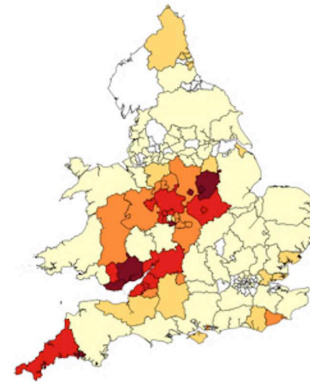
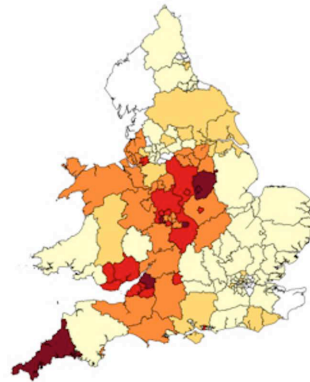
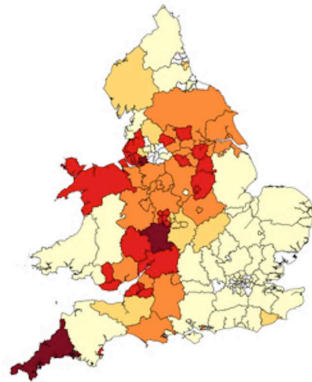
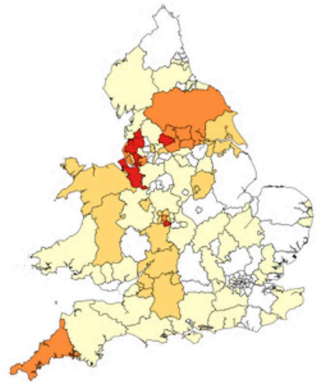
2010

2011

2012

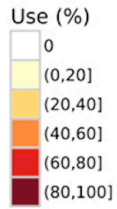
2013

2014

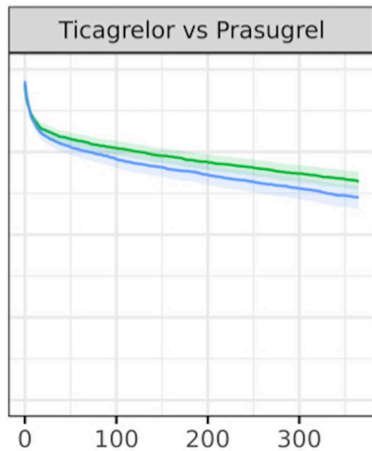
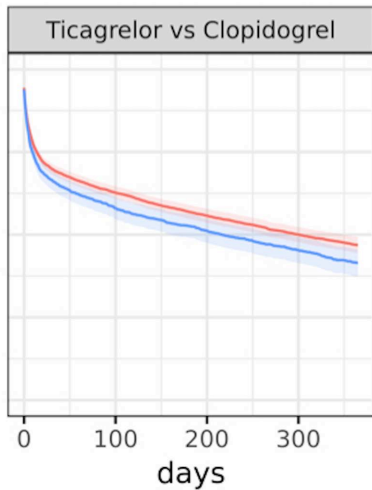
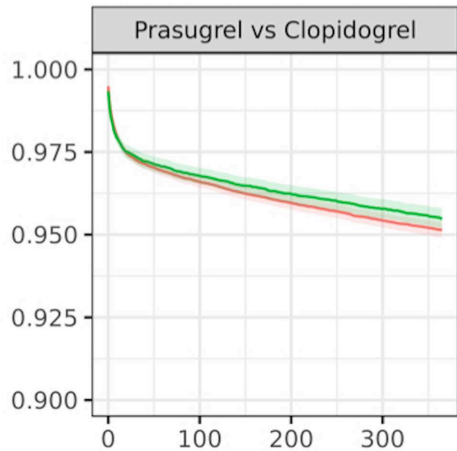


Prasugrel

Ticagrelor



Proportion Survival



Antiplatelet

— Clopidogrel

— Prasugrel

— Ticagrelor

Supplementary Table S1: Proportion of missing values presents in the original dataset

Variable	Included (%)	Missing (%)
Age	89067 (100.0)	0 (0.0)
Gender	89067 (100.0)	0 (0.0)
Smoking status	80706 (90.6)	8361 (9.4)
Diabetes	85706 (96.2)	3361 (3.8)
History of peripheral vascular disease	85046 (95.5)	4021 (4.5)
Hypertension	85046 (95.5)	4021 (4.5)
Hypercholesterolemia	85046 (95.5)	4021 (4.5)
History of renal disease	80681 (90.6)	8386 (9.4)
History of coronary artery bypass graft	62921 (70.6)	26146 (29.4)
History myocardial infarction	83847 (94.1)	5220 (5.9)
History of stroke	85046 (95.5)	4021 (4.5)
History of percutaneous coronary intervention	87548 (98.3)	1519 (1.7)
Left ventricular ejection fraction	28223 (31.7)	60844 (68.3)
TIMI flow	79103 (88.8)	9964 (11.2)
Access site	85730 (96.3)	3337 (3.7)
Stent	85291 (95.8)	3776 (4.2)
Vessel attempted	88530 (99.4)	537 (0.6)
Cardiogenic shock	88553 (99.4)	514 (0.6)
Intra-aortic balloon pump use	85013 (95.4)	4054 (4.6)
Ventilatory support	82589 (92.7)	6478 (7.3)
Thrombectomy	84846 (95.3)	4221 (4.7)
Bivalirudin use	89067 (100.0)	0 (0.0)
Glycoprotein IIb/IIIa inhibitors use	85914 (96.5)	3153 (3.5)
Year	89067 (100.0)	0 (0.0)
Bleeding	87055 (97.7)	2012 (2.3)
Major adverse cardiovascular event	87051 (97.7)	2016 (2.3)
30 days mortality	85076 (95.5)	3991 (4.5)
1 year mortality	85060 (95.5)	4007 (4.5)

Supplementary Table S2: Quality of matching of propensity score matched dataset instances.

Variables	Prasugrel vs Clopidogrel (332,000)		Ticagrelor vs Clopidogrel (245,200)		Ticagrelor vs Prasugrel (245,200)	
	Cases	Controls	Cases	Controls	Cases	Controls
Age	61.0 (52.0 - 69.0)	60.0 (51.0 - 70.0)	63.0 (54.0 - 73.0)	63.0 (53.0 - 74.0)	63.0 (54.0 - 73.0)	62.0 (54.0 - 70.0)
Gender	128,640 (77.5%)	128,389 (77.3%)	90,830 (74.1%)	91,135 (74.3%)	90,830 (74.1%)	93,169 (76.0%)
Smoking status						
Never	49,881 (30.0%)	50,619 (30.5%)	46,674 (38.1%)	46,669 (38.1%)	46,674 (38.1%)	41,797 (34.1%)
Ex-smoker	41,608 (25.1%)	41,617 (25.1%)	28,173 (23.0%)	28,304 (23.1%)	28,173 (23.0%)	29,476 (24.0%)
Current	74,511 (44.9%)	73,764 (44.4%)	47,753 (39.0%)	47,627 (38.8%)	47,753 (39.0%)	51,327 (41.9%)
Diabetes	22,194 (13.4%)	21,936 (13.2%)	18,426 (15.0%)	18,125 (14.8%)	18,426 (15.0%)	17,548 (14.3%)
History of peripheral vascular disease	4,124 (2.5%)	4,194 (2.5%)	3,366 (2.7%)	3,309 (2.7%)	3,366 (2.7%)	3,152 (2.6%)
Hypertension	62,496 (37.6%)	62,800 (37.8%)	49,750 (40.6%)	49,795 (40.6%)	49,750 (40.6%)	47,949 (39.1%)
Hypercholesterolemia	67,499 (40.7%)	66,468 (40.0%)	46,162 (37.7%)	45,450 (37.1%)	46,162 (37.7%)	46,907 (38.3%)
History of renal disease	758 (0.5%)	865 (0.5%)	441 (0.4%)	439 (0.4%)	441 (0.4%)	445 (0.4%)
History of coronary artery bypass graft	4,859 (2.9%)	4,754 (2.9%)	4,622 (3.8%)	4,299 (3.5%)	4,622 (3.8%)	3,542 (2.9%)
History myocardial infarction	17,872 (10.8%)	18,166 (10.9%)	14,857 (12.1%)	14,577 (11.9%)	14,857 (12.1%)	14,059 (11.5%)
History of stroke	3,174 (1.9%)	3,580 (2.2%)	4,238 (3.5%)	4,174 (3.4%)	4,238 (3.5%)	2,882 (2.4%)
History of percutaneous coronary intervention	13,906 (8.4%)	14,066 (8.5%)	10,551 (8.6%)	10,261 (8.4%)	10,551 (8.6%)	10,631 (8.7%)
Left ventricular ejection fraction						
Good (>50%)	96,820 (58.3%)	96,743 (58.3%)	63,299 (51.6%)	64,015 (52.2%)	63,299 (51.6%)	67,129 (54.8%)
Moderate (30%-50%)	57,276 (34.5%)	57,414 (34.6%)	49,250 (40.2%)	48,725 (39.7%)	49,250 (40.2%)	46,066 (37.6%)
Poor (<30%)	11,904 (7.2%)	11,843 (7.1%)	10,051 (8.2%)	9,860 (8.0%)	10,051 (8.2%)	9,405 (7.7%)
TIMI flow						
TIMI 0	125,587 (75.7%)	125,253 (75.5%)	87,725 (71.6%)	88,039 (71.8%)	87,725 (71.6%)	90,144 (73.5%)
TIMI 1	10,994 (6.6%)	11,153 (6.7%)	10,311 (8.4%)	10,430 (8.5%)	10,311 (8.4%)	9,044 (7.4%)
TIMI 2	15,494 (9.3%)	15,496 (9.3%)	11,912 (9.7%)	11,721 (9.6%)	11,912 (9.7%)	11,823 (9.6%)
TIMI 3	13,925 (8.4%)	14,098 (8.5%)	12,652 (10.3%)	12,410 (10.1%)	12,652 (10.3%)	11,589 (9.5%)
Access site	124,145 (74.8%)	120,273 (72.5%)	96,558 (78.8%)	96,188 (78.5%)	96,558 (78.8%)	94,875 (77.4%)
Stent						
None	10,068 (6.1%)	10,181 (6.1%)	7,616 (6.2%)	7,594 (6.2%)	7,616 (6.2%)	7,617 (6.2%)
Bare metal	39,943 (24.1%)	39,273 (23.7%)	14,527 (11.8%)	14,868 (12.1%)	14,527 (11.8%)	15,601 (12.7%)
Drug eluting	115,989 (69.9%)	116,546 (70.2%)	100,457 (81.9%)	100,138 (81.7%)	100,457 (81.9%)	99,382 (81.1%)
Vessel attempted						
Venous or arterial graft	2,478 (1.5%)	2,370 (1.4%)	1,266 (1.0%)	1,271 (1.0%)	1,266 (1.0%)	1,460 (1.2%)

Variables	Prasugrel vs Clopidogrel (332,000)		Ticagrelor vs Clopidogrel (245,200)		Ticagrelor vs Prasugrel (245,200)	
	Cases	Controls	Cases	Controls	Cases	Controls
Left main stem artery	603 (0.4%)	639 (0.4%)	2,075 (1.7%)	1,767 (1.4%)	2,075 (1.7%)	603 (0.5%)
Left anterior descending artery	64,846 (39.1%)	64,875 (39.1%)	47,018 (38.4%)	47,148 (38.5%)	47,018 (38.4%)	48,171 (39.3%)
Left circumflex artery	20,628 (12.4%)	20,589 (12.4%)	17,507 (14.3%)	17,124 (14.0%)	17,507 (14.3%)	16,316 (13.3%)
Right coronary artery	68,704 (41.4%)	68,625 (41.3%)	48,246 (39.4%)	48,760 (39.8%)	48,246 (39.4%)	49,443 (40.3%)
Multiple	8,741 (5.3%)	8,902 (5.4%)	6,488 (5.3%)	6,530 (5.3%)	6,488 (5.3%)	6,607 (5.4%)
Cardiogenic shock	9,190 (5.5%)	9,259 (5.6%)	7,735 (6.3%)	7,815 (6.4%)	7,735 (6.3%)	7,069 (5.8%)
Intra-aortic balloon pump use	5,441 (3.3%)	5,451 (3.3%)	4,153 (3.4%)	4,201 (3.4%)	4,153 (3.4%)	3,963 (3.2%)
Ventilatory support	4,103 (2.5%)	4,192 (2.5%)	4,134 (3.4%)	4,043 (3.3%)	4,134 (3.4%)	3,556 (2.9%)
Thrombectomy	83,788 (50.5%)	84,718 (51.0%)	64,526 (52.6%)	62,955 (51.3%)	64,526 (52.6%)	63,383 (51.7%)
Bivalirudin use	53,630 (32.3%)	39,284 (23.7%)	28,970 (23.6%)	25,869 (21.1%)	28,970 (23.6%)	32,494 (26.5%)
Glycoprotein IIb/IIIa inhibitors use	74,041 (44.6%)	76,067 (45.8%)	41,926 (34.2%)	42,247 (34.5%)	41,926 (34.2%)	46,800 (38.2%)

Supplementary Table S3: Sensitivity analysis 2 – Dataset restricted to years 2010 to 2014, only.

(a) Results of logistic regression models. Odd ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

Outcome	Cohort	Odd ratio (95% CI)	P-value
Bleeding	Prasugrel vs Clopidogrel	0.689 (0.535-0.888)	0.004
	Ticagrelor vs Clopidogrel	0.587 (0.433-0.795)	<0.001
	Ticagrelor vs Prasugrel	0.958 (0.696-1.321)	0.795
MACE	Prasugrel vs Clopidogrel	0.882 (0.778-1.000)	0.051
	Ticagrelor vs Clopidogrel	0.976 (0.865-1.101)	0.694
	Ticagrelor vs Prasugrel	1.400 (1.233-1.589)	<0.001
30 days mortality	Prasugrel vs Clopidogrel	0.813 (0.721-0.917)	<0.001
	Ticagrelor vs Clopidogrel	0.900 (0.805-1.005)	0.062
	Ticagrelor vs Prasugrel	1.404 (1.247-1.581)	<0.001
1 year mortality	Prasugrel vs Clopidogrel	0.814 (0.735-0.902)	<0.001
	Ticagrelor vs Clopidogrel	0.906 (0.825-0.995)	0.039
	Ticagrelor vs Prasugrel	1.381 (1.254-1.520)	<0.001

(b) Results of Cox regression models with survival time censored at 1 year. Hazard ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

Cohort	Hazard ratio (95% CI)	P-value
Prasugrel vs Clopidogrel	0.820 (0.742-0.905)	<0.001
Ticagrelor vs Clopidogrel	0.914 (0.835-0.999)	0.047
Ticagrelor vs Prasugrel	1.386 (1.264-1.521)	<0.001

Supplementary Table S4: Sensitivity analysis 3 – Dataset Including procedures undertaken in patients with multiple antiplatelets[§].

(a) Results of logistic regression models. Odd ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

Outcome	Cohort	Odd ratio (95% CI)	P-value
Bleeding	Prasugrel vs Clopidogrel	0.636 (0.481-0.842)	0.002
	Ticagrelor vs Clopidogrel	0.552 (0.404-0.754)	<0.001
	Ticagrelor vs Prasugrel	0.933 (0.668-1.301)	0.681
MACE	Prasugrel vs Clopidogrel	0.892 (0.778-1.022)	0.099
	Ticagrelor vs Clopidogrel	0.992 (0.880-1.119)	0.898
	Ticagrelor vs Prasugrel	1.418 (1.246-1.614)	<0.001
30 days mortality	Prasugrel vs Clopidogrel	0.833 (0.733-0.947)	0.005
	Ticagrelor vs Clopidogrel	0.925 (0.826-1.036)	0.178
	Ticagrelor vs Prasugrel	1.418 (1.256-1.601)	<0.001
1 year mortality	Prasugrel vs Clopidogrel	0.823 (0.742-0.912)	<0.001
	Ticagrelor vs Clopidogrel	0.936 (0.853-1.026)	0.158
	Ticagrelor vs Prasugrel	1.402 (1.270-1.548)	<0.001

(b) Results of Cox regression models with survival time censored at 1 year. Hazard ratios, confidence intervals (in brackets), and p-values represent the pooled results over 10 propensity score matched dataset instances.

Cohort	Hazard ratio (95% CI)	P-value
Prasugrel vs Clopidogrel	0.828 (0.750-0.915)	<0.001
Ticagrelor vs Clopidogrel	0.941 (0.862-1.028)	0.178
Ticagrelor vs Prasugrel	1.406 (1.279-1.546)	<0.001

[§] Patients prescribed both prasugrel and clopidogrel, and ticagrelor and clopidogrel were included in prasugrel and ticagrelor groups, respectively.

Supplementary Table S5: Baseline patient demographics, procedural details, pharmacology, and outcomes including unknown antiplatelet prescription.

	Clopidogrel (58,248)	Prasugrel (17,714)	Ticagrelor (13,105)	Unknown (27,344)	P-value
Age	64.4 (±13.4)	60.6 (±11.7)	63.0 (±12.9)	62.9 (±13.1)	< 0.0001
Gender (Male)	42,821 (73.5%)	13,739 (77.6%)	9,721 (74.2%)	20,261 (74.1%)	< 0.0001
Smoking status					< 0.0001
Never	16,934 (32.3%)	4,797 (29.6%)	4,545 (37.6%)	8,835 (36.9%)	
Ex-smoker	15,465 (29.5%)	4,021 (24.8%)	2,742 (22.7%)	5,821 (24.3%)	
Current	20,033 (38.2%)	7,384 (45.6%)	4,785 (39.6%)	9,312 (38.9%)	
Diabetes	8,233 (14.8%)	2,315 (13.4%)	1,927 (15.0%)	3,296 (12.8%)	< 0.0001
History of peripheral vascular disease	2,024 (3.6%)	416 (2.5%)	332 (2.7%)	896 (3.4%)	< 0.0001
Hypertension	25,022 (44.9%)	6,363 (37.5%)	4,986 (40.5%)	9,682 (37.1%)	< 0.0001
Hypercholesterolemia	23,246 (41.7%)	6,850 (40.4%)	4,630 (37.6%)	9,370 (35.9%)	< 0.0001
History of renal disease	478 (0.9%)	67 (0.4%)	42 (0.3%)	211 (0.8%)	< 0.0001
History of coronary artery bypass graft	1,866 (4.7%)	356 (2.5%)	367 (4.2%)	1,052 (5.3%)	< 0.0001
History myocardial infarction	7,603 (14.0%)	1,866 (10.7%)	1,472 (12.3%)	2,881 (12.0%)	< 0.0001

History of stroke	2,368 (4.2%)	322 (1.9%)	411 (3.3%)	972 (3.7%)	< 0.0001
History of percutaneous coronary intervention	5,642 (9.9%)	1,458 (8.3%)	1,120 (8.7%)	2,124 (8.2%)	< 0.0001
Left ventricular ejection fraction					< 0.0001
Good (>50%)	10,098 (52.1%)	2,764 (55.8%)	1,978 (51.1%)	3,400 (43.6%)	
Moderate (30%-50%)	7,117 (36.7%)	1,763 (35.6%)	1,532 (39.6%)	3,493 (44.8%)	
Poor (<30%)	2,181 (11.2%)	427 (8.6%)	363 (9.4%)	910 (11.7%)	
TIMI flow					< 0.0001
TIMI 0	35,718 (69.2%)	12,239 (75.8%)	8,140 (71.6%)	14,182 (74.1%)	
TIMI 1	4,660 (9.0%)	1,057 (6.5%)	964 (8.5%)	1,175 (6.1%)	
TIMI 2	5,031 (9.8%)	1,502 (9.3%)	1,101 (9.7%)	1,670 (8.7%)	
TIMI 3	6,189 (12.0%)	1,341 (8.3%)	1,161 (10.2%)	2,106 (11.0%)	
Access site (Radial)	26,514 (47.1%)	12,692 (74.9%)	9,765 (78.3%)	14,375 (54.7%)	< 0.0001
Stent					< 0.0001
None	4,422 (8.0%)	1,050 (6.1%)	773 (6.1%)	1,784 (7.2%)	
Bare metal	19,479 (35.2%)	4,217 (24.5%)	1,503 (11.9%)	5,996 (24.1%)	
Drug eluting	31,492 (56.9%)	11,974 (69.5%)	10,381 (82.0%)	17,111 (68.7%)	
Vessel attempted					< 0.0001
Venous or arterial graft	803 (1.4%)	259 (1.5%)	143 (1.1%)	512 (1.9%)	
Left main stem artery	411 (0.7%)	67 (0.4%)	230 (1.8%)	380 (1.4%)	
Left anterior descending artery	22,858 (39.5%)	6,905 (39.2%)	4,974 (38.2%)	10,585 (39.1%)	
Left circumflex artery	7,216 (12.5%)	2,186 (12.4%)	1,839 (14.1%)	3,247 (12.0%)	
Right coronary artery	22,915 (39.6%)	7,269 (41.2%)	5,147 (39.5%)	10,598 (39.1%)	
Multiple	3,671 (6.3%)	937 (5.3%)	700 (5.4%)	1,767 (6.5%)	
Cardiogenic shock	4,155 (7.2%)	988 (5.6%)	812 (6.2%)	2,553 (9.5%)	< 0.0001
Intra-aortic balloon pump use	2,832 (5.1%)	567 (3.4%)	421 (3.4%)	1,433 (5.6%)	< 0.0001
Ventilatory support	1,891 (3.5%)	425 (2.5%)	392 (3.4%)	1,726 (8.4%)	< 0.0001
Thrombectomy	25,933 (46.6%)	8,583 (51.0%)	6,518 (52.7%)	13,118 (51.3%)	< 0.0001
Bivalirudin use	5,095 (8.7%)	5,697 (32.2%)	2,963 (22.6%)	996 (3.6%)	< 0.0001
Glycoprotein IIb/IIIa inhibitors use	30,258 (53.7%)	7,672 (44.5%)	4,294 (34.8%)	14,172 (54.5%)	< 0.0001
Year					< 0.0001
2007	3,448 (5.9%)	0 (0.0%)	0 (0.0%)	915 (3.3%)	
2008	5,467 (9.4%)	0 (0.0%)	0 (0.0%)	1,694 (6.2%)	
2009	8,134 (14.0%)	42 (0.2%)	0 (0.0%)	2,859 (10.5%)	
2010	9,491 (16.3%)	1,649 (9.3%)	4 (0.0%)	3,744 (13.7%)	
2011	9,204 (15.8%)	4,383 (24.7%)	15 (0.1%)	4,415 (16.1%)	
2012	8,528 (14.6%)	5,049 (28.5%)	1,601 (12.2%)	5,037 (18.4%)	
2013	7,408 (12.7%)	3,594 (20.3%)	4,870 (37.2%)	4,420 (16.2%)	
2014	6,568 (11.3%)	2,997 (16.9%)	6,615 (50.5%)	4,260 (15.6%)	
Bleeding	843 (1.5%)	121 (0.7%)	76 (0.6%)	315 (1.2%)	< 0.0001
Major adverse cardiovascular event	2,783 (4.9%)	545 (3.2%)	616 (4.8%)	1,410 (5.3%)	< 0.0001
30 days mortality	3,534 (6.4%)	622 (3.6%)	689 (5.5%)	1,931 (7.5%)	< 0.0001
1 year mortality	5,656 (10.2%)	999 (5.9%)	1,075 (8.5%)	2,788 (10.8%)	< 0.0001