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Antiplatelet drug selection in PCI to vein grafts in patients with acute coronary syndrome and adverse clinical outcomes: Insights from the British Cardiovascular Intervention Society Database

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Abstract

Objective

This study aims to evaluate outcomes associated with different P2Y12 agents in Saphenous Vein graft (SVG) percutaneous coronary intervention (PCI).

Background

SVG PCI is associated with greater risks of ischemic complications, compared to native coronary PCI. Outcomes associated with the use of potent P2Y12 blocking drugs, Prasugrel and Ticagrelor, in SVG PCI are unknown.

Methods

Patients included in the study underwent SVG PCI in the United Kingdom between 2007-2014 for acute coronary syndrome and were grouped by P2Y12 antiplatelet use. In-hospital major adverse cardiac events, major bleeding and 30-day and 1-year mortality were examined. Multiple imputations with chained equations to impute missing data were used. Adjustment for baseline imbalances was performed using i) multiple logistic regression (MLR) and (separately) ii) propensity score matching (PSM).

Results

Data was analyzed from 8,119 patients and most cases were treated with Clopidogrel (n=7,401), followed by Ticagrelor (n=497) and Prasugrel (n=221). In both MLR and PSM models, there was no significant evidence to suggest that either Prasugrel or Ticagrelor was associated with significantly lower 30-day mortality compared to Clopidogrel. The odds ratios reported from the multivariable analysis were 1.22 (95%CI: 0.60-2.51) for Prasugrel vs Clopidogrel and 0.48 (95%CI: 0.20-1.16) for Ticagrelor vs Clopidogrel. No significant differences were seen for in-hospital ischemic or bleeding events.

Conclusions

Our real world national study provides no clear evidence to indicate that use of potent P2Y12 blockers in SVG PCI is associated with improved clinical outcomes.

Introduction

Percutaneous coronary intervention (PCI) to saphenous vein grafts (SVG) is associated with increased risks, both acutely (particularly no-reflow) and longer-term vessel failure, compared to native coronary intervention.[1] These relate to differences in pathology – beyond the first year after bypass surgery, the predominant mechanism of SVG stenosis is atherosclerotic but characterized by more diffuse disease, greater foam cell and inflammatory cell components and less well-developed fibrous caps than in native coronary disease.[2] Such features render SVG lesions more prone to distal embolization during PCI and, in acute presentations, more often associated with a heavy thrombus burden.[3] SVG intervention represents an important component of the recent DAPT score for predicting future ischemic risk.[4] Hence peri-procedural myocardial ischemia and infarction are major concerns, notwithstanding use of strategies to reduce these, such as embolic protection devices[5,6] and/or vasoactive drugs.[7]

The role of potent platelet inhibition in ameliorating these problems is not clear. For example, intravenous glycoprotein IIb/IIIa inhibitor (GPI) use has not been associated with same benefits in SVG PCI as seen in native coronary intervention,[8] except possibly when used in conjunction with embolic protection.[9] More recently, the potent selective P2Y12 agents, Ticagrelor and Prasugrel, have become available and show a reduction in ischemic endpoints following PCI for acute coronary syndromes (ACS), compared to Clopidogrel.[10,11] There was also a reduction in all-cause mortality with Ticagrelor in this setting. This has led to increasing use of these agents in PCI settings associated with higher ischemic risk. Outside their role in PCI, potent P2Y12 blockade is also seen to improve graft patency following coronary artery bypass graft (CABG) surgery.[12] However, there are little data regarding possible benefits of potent P2Y12 inhibitor use in the specific setting of SVG PCI for ACS. The data cited above in relation to GPIs caution against extrapolation

from non-SVG studies. In the PLATO study, the outcomes in post-CABG patients with Ticagrelor use did not appear to differ from the overall study findings[13] – however this was a post-hoc analysis in which the usual caveats regarding potentially unbalanced comparison groups apply. Additionally, outcomes in that paper were not separated based on whether PCI was undertaken in a bypass graft or native vessel, further limiting interpretation. No equivalent subgroup evaluation is available for Prasugrel from TRITON-TIMI 38.

Given the paucity of evidence to guide practice with potent antiplatelet drugs in SVG PCI, we undertook an analysis using the UK British Cardiovascular Interventional Society PCI database. Our aim was to explore outcomes associated with the use of the newer antiplatelet agents Prasugrel or Ticagrelor in the setting of SVG PCI for ACS.

Methods

Study design and data collection

The BCIS database records information on PCI procedures in the UK and the data collection is managed by the National Institute of Cardiovascular Outcomes Research (NICOR).[14,15,16] A retrospective analysis was performed of all participants with PCI to vein grafts and receipt of dual antiplatelet therapy from England and Wales between January 2007 and December 2014. Participants were tracked via the patient's National Health Service (NHS) number, a unique identifier for any person registered within the NHS in England and Wales, for mortality and adverse in-hospital outcomes.

Variables, exposures and outcomes

Data on participants' demographics (age, sex, body mass index and smoking status) and comorbidities (diabetes, hypertension, hypercholesterolemia, previous myocardial infarction, previous stroke, peripheral vascular disease, renal disease, valvular heart disease) were collected. Additional information was collected on previous CABG, previous PCI, radial access, cardiogenic shock, circulatory support, receipt of ventilation, diagnosis, glycoprotein IIb/IIIa inhibitor use, warfarin, thrombolysis, embolic protection device, PCI to non-vein graft vessel, use of drug eluting stent and year of PCI procedure. The primary exposure variable was Clopidogrel, Prasugrel and Ticagrelor and the outcome variables were 30-day and 1 year mortality, and in-hospital major adverse cardiovascular events (defined by in-hospital death, in-hospital Non-Q wave and Q wave myocardial infarction, re-infarction, emergency CABG and re-intervention PCI).

Statistical methods

Statistical analysis was performed on Stata v14 (Stata Corp., Texas, USA). Participants with missing data for 30-day mortality, antiplatelet therapy, CABG and patients

who did not have PCI to vein graft were excluded. A flow diagram of participant inclusion is shown in Figure 1. Descriptive statistics of included variables were presented as mean ± standard deviation for continuous data and percentages for categorical data according to antiplatelet therapy (Clopidogrel, Prasugrel or Ticagrelor). The clinical characteristics of the three groups were compared using ANOVA or Chi-squared tests for continuous or categorical variables respectively. Multiple imputations by chained equations were performed using *mi impute chained* function in Stata to generate 10 complete datasets. The imputed variables were age, sex, smoking, body mass index, diabetes, hypertension, hypercholesterolemia, previous myocardial infarction, previous stroke, peripheral vascular disease, renal failure, valvular heart disease, previous PCI, access site, cardiogenic shock, receipt of ventilation, glycoprotein IIb/IIIa inhibitor use, warfarin use, thrombolysis, embolic protection device use, PCI to non-veingraft vessels, drug eluting stent use, diagnosis and year of PCI procedure. The outcomes were included in the imputation model (mortality at 30-days and 1-year, in-hospital major adverse cardiovascular events and in-hospital bleeding), but we did not predict the outcome since that makes no difference.[17] The extent of missing data is presented in Supplementary Table 1. The imputed datasets were used to perform multiple logistic regressions to identify independent predictors of Clopidogrel, Prasugrel and Ticagrelor use. Multiple logistic regressions were also used to identify how antiplatelet therapy affects risk of 30-day and 1-year mortality, in-hospital MACE and in-hospital bleeding. In addition, propensity score matching methods were used to estimate adjusted risk estimates (using all covariates) for all pairwise antiplatelet group comparisons (Prasugrel vs Clopidogrel, Ticagrelor vs Clopidogrel, Ticagrelor vs Prasugrel). This was performed using the *teffects psmatch* function in Stata to estimate the average treatment effects while accounting for baseline differences across the groups. Estimates were aggregated across the 10 imputed datasets using Rubin's rules.[18] Using the standard setting for matching, a

minimum of one neighbor was matched for all observations. Tolerance for the overlap assumption was set to 10^{-5}.

Results

Figure 1 displays the numbers of cases eligible for analysis during the study period and reasons for case exclusion. A total of 8,119 patients comprised our main study cohort. Their baseline clinical data, year of PCI procedure, details of adjunctive therapy and unadjusted clinical outcomes are shown in Table 1, grouped by the P2Y12 antiplatelet agent used. The cohort that was treated with Clopidogrel (n=7,401) was numerically much larger than either the cohort that was treated with Ticagrelor (n=497) or Prasugrel (n=221). Clopidogrel use in SVG PCI was seen to decline after 2010, as demonstrated graphically in Figure 2. Over this time, there has been an increase in Ticagrelor use year-on-year, whilst Prasugrel use in this setting has remained stable since 2011.

Despite the marked difference in overall group sizes, the mean age and gender distribution was similar across groups. It is noteworthy that patient age range, body mass index and the frequency of previous CVA were similar between the different P2Y12 groups. Some important differences between the characteristics of the groups also merit specific mention. The predominant use of Prasugel was in the setting of STEMI whilst for Ticagrelor, use in NSTEMI/UA was most frequent. There was a higher proportion of radial access use in the patients receiving more potent P2Y12 blockers, which might be a time (i.e. year of treatment)-dependent effect. Greater use of embolic protection devices was seen with Ticagrelor, whilst use of adjunctive GPI was highest with Prasugrel. Table 2, showing predictors of P2Y12 antiplatelet choice from multivariable analysis, indicates those which appear to be independently associated with their use. Whilst younger age appears as a predictor for both Prasugrel and Ticagrelor use, the odds ratio of around 1 indicates a very small effect size, as seen from the raw data in Figure 1.

Unadjusted data (Table 1) demonstrate a higher 30-day mortality associated with Prasugrel use compared to the other 2 agents, which was also observed for 1-year mortality.

Recorded in-hospital MACE and major bleeding are very similar across groups. Given the marked differences in composition / clinical characteristics of the groups (as noted above), we undertook multivariable analysis. Tables 3 and 4 illustrate clinical outcomes when adjustment was made by use of multivariable analysis (MVA) and by propensity score matching (PSM), respectively. In the MVA, we observed a large effect estimate for lower 30-day mortality with Ticagrelor use, compared to Clopidogrel, although this did not reach statistical significance. No other significant differences for early mortality or in-hospital complications were noted from MVA. The matching success for our propensity score model is shown in Supplementary Table 2. As shown in Table 4, there was no difference in outcomes comparing antiplatelet drugs.

Discussion

Vein graft PCI represents a distinct subset, for which patient outcomes remain inferior to those seen in native coronary disease. Hence a search for approaches to improve outcomes for patients with vein graft disease is important. Where practical, treatment of native disease in the territory of the diseased graft (rather than the graft itself) is now the preferred option. However, this is not always straightforward, particularly if this native coronary contains a complex chronic total occlusion or has diffuse severe disease. So SVG PCI will continue to be the favoured revascularization option in a proportion of cases, and therefore defining an optimal anti-ischemic strategy in such cases remains important. There is currently a lack of trial evidence or observational data on the effect of potent specific P2Y12 receptor inhibition in SVG PCI.

Key findings of this work and possible explanations

SVG PCI represented a small proportion (approximately 2%) of overall PCI activity within the UK and the majority of such cases were undertaken in the setting of ACS with use of potent P2Y12 blockade (with Prasugrel or Ticagrelor) predominantly in such ACS cases. One unanticipated finding from our work was noted in relation to the demographics of patients receiving Prasugrel. In TRITON TIMI 38, subgroup analyses indicated worse outcomes in Prasugrel-treated patients with previous CVA, and neutral findings in those of age>75 years or with body weight <60kg, leading to specific precautions for these cohorts in the marketing authorization.[19] Nevertheless, in real-world practice, the Prasugrel group appeared similar with respect to these clinical variables to the other groups. One can only speculate as to the reasons involved but the high proportion of STEMI cases in the Prasugrel group might have led to clinical decisions prioritizing rapidity of onset of action with Prasugrel (in this most acute of settings) above the known increased bleeding risks.

The changing pattern of antiplatelet use for SVG PCI over the study period is noteworthy. The increasing use of more potent P2Y12 agents is likely explained by an extrapolation of favourable findings from landmark trials in ACS, in the absence of any direct positive or negative data for the specific context of SVG intervention. More interesting however is the fairly stable pattern of Prasugrel uptake, in contrast to the steadily increasing use of Ticagrelor. Possible influencing factors here include more favourable evidence with Ticagrelor in terms of all-cause mortality reduction, and its apparent advantages over Prasugrel in specific settings such as medically managed ACS[10,13,20] and in specific groups such as the elderly.[21] These considerations might have influenced individual institutions' decisions in opting to switch to one or other P2Y12 blocker in high-risk ACS, and hence also (as a consequence) in the SVG PCI subset of these patients.

We observed higher use of radial access and of embolic protection devices with potent P2Y12 blockers that may have favoured better outcomes with these agents in unadjusted analyses, although this effect was mitigated in the adjusted analyses once differences in baseline covariates were made. The markedly higher use of GPI seen with Prasugrel likely reflected the high proportion of STEMI cases in that group, where onset of antiplatelet action is most rapidly required. As noted earlier, the benefit of GPI in the setting of SVG PCI is equivocal (although its adverse impact on risk of bleeding is not).

Following multivariable analysis, we observed no significant differences for the potent P2Y12 blockers over Clopidogrel in SVG PCI for a number of clinically important endpoints. There are various potential explanations for this finding. Firstly, the pathophysiology of vein graft disease may lead to downstream debris during PCI that differs significantly in composition from that encountered with native coronary atheroma. Friable, foam-cell rich plaque might constitute the bulk of such debris and this could explain the lack of effect seen with both GPI and (in our present work) with potent oral P2Y12 blockers.

A second possibility is that a benefit with Ticagrelor or Prasugrel over Clopidogrel might actually exist but our study was underpowered to detect this, given i) the relatively low patient numbers in the potent P2Y12 groups and ii) the modest event rates across all groups. This possibility is difficult to exclude fully and would require significantly larger numbers to clarify, although it is unlikely that an adequately powered randomised trial would ever be undertaken to investigate this. Furthermore, any clinical benefit with potent P2Y12 agents in SVG PCI may not be sufficient to be seen as a survival advantage but might produce a reduction in recurrent myocardial infarction or MACE. Such an effect would not be detected outside the index hospital admission in our present work. A third possibility for our present findings is that an anti-ischemic benefit exists with potent P2Y12 blockers but that any mortality benefit is offset by adverse effects from later (post-discharge) major bleeding. This is plausible, given the demographics of the potent P2Y12 groups, which contain subgroups known to be at higher risk of bleeding problems. Clarification of this issue would require more information about cause of death, and capture of ischemic and bleeding events post discharge which is not currently available in the BCIS dataset.

Limitations

There are certain limitations in this work that apply to all observational and registry-based research. Most importantly, such studies cannot determine cause and effect and hence only associations can be identified. Additionally, conclusions drawn from these associations may be influenced by confounders that will not be 'visible' on the dataset (unmeasured confounding). These reflect variables which are not captured but which are related to both (non-blinded) treatment allocation and to outcome. Among these are factors such as frailty and non-cardiovascular co-morbidity.[22,23] However, in this particular work, clinical assessment of frailty or multi-morbidity would be expected to lead to use of Ticagrelor or

Prasugrel in 'less frail' / multi-morbid patients overall, and hence any confounding in this regard should favour outcomes in the potent P2Y12 groups. Hence, it is unlikely that neutral effects on outcome found with these agents in our study are attributable to being disadvantaged by frailty as an unrecorded confounder. In addition, we did not have information on the age of the graft at time of PCI. While our analysis suggests no difference in outcomes for patients depending on choice of antiplatelet therapy, there may still be a difference depending on treatment but we are not able to detect it in the current study due to small sample size.

Another recognized limitation is that robust outcome tracking is currently available only for mortality. Clinical advantages with more potent antiplatelet agents may exist but may not be sufficient to appear as a mortality signal. In-hospital MACE and bleeding rates were available but a reliance on retrospective documentation at a centre-level (rather than by robust linkage) is likely to contribute to low recorded event rates for these endpoints. Furthermore, out of hospital MACE and bleeding events are not captured on our dataset, unless fatal. Nevertheless despite such limitations, our study provides important new data around outcomes associated with newer P2Y12 agents in SVG PCI as there is unlikely to be an adequately powered RCT comparing outcomes for hard clinical endpoints and so should be considered best available evidence currently available.

Conclusions

Our study of real world SVG PCI from the UK national registry shows no benefit in 30-day mortality, 1-year mortality or in-hospital complications for the newer, more potent, oral P2Y12 antiplatelet agents over Clopidogrel.

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Contributorship statement:

MAM conceptualized the study. CSK/EK performed the analyses. AS drafted the paper and all authors contributed in the writing of the paper.

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None.

Conflict of interest disclosure

The authors have no conflicts of interest to declare.

Figure Legends

Figure 1: Flow diagram of PCI procedures in England and Wales

Figure 2: Antiplatelet use among patients with PCI to vein graft according to year

Table 1: Participant characteristics

Table 2: Multivariable predictors of antiplatelet use

Table 3: Odds of adverse outcome

Table 4: Propensity score match analysis

List of Supplementary material

Supplementary Table 1: Missing data table

Supplementary Table 2: Matching success diagnostics for propensity model

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systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes 2017;3:20-36.

Table 1: Participant characteristics

Variable	Clopidogrel (n=7,401)	Prasugrel (n=221)	Prasugrel vs clopidogrel p-value	Ticagrelor (n=497)	Ticagrelor vs clopidogrel p-value
Age	71±9	69±9	<0.001	70±9	0.13
Male sex	6,221 (84%)	189 (86%)	0.60	420 (85%)	0.71
Body mass index	28±5	29±4	0.21	29±5	0.077
Current or ex-smoker	730 (11%)	38 (19%)	<0.001	66 (14%)	0.048
Diabetes	2,513 (35%)	65 (30%)	0.12	190 (39%)	0.10
Hypertension	5,230 (73%)	150 (72%)	0.71	355 (75%)	0.40
Hypercholesterolemia	5,307 (74%)	152 (73%)	0.60	315 (67%)	<0.001
Previous myocardial infarction	4,960 (74%)	162 (76%)	0.51	318 (71%)	0.31
Previous stroke	597 (8%)	13 (6%)	0.28	40 (9%)	0.92
Peripheral vascular disease	929 (13%)	23 (11%)	0.41	59 (13%)	0.77
Renal disease	143 (2%)	4 (2%)	0.90	1 (0.2%)	0.005
Valvular heart disease	202 (3%)	5 (2%)	0.72	13 (3%)	0.92
Previous PCI	2,959 (41%)	100 (46%)	0.12	186 (38%)	0.20
Radial access	1,578 (22%)	64 (29%)	0.007	204 (42%)	<0.001
Cardiogenic shock	138 (2%)	8 (4%)	0.071	12 (2%)	0.43
Circulatory support	158 (2%)	12 (6%)	0.001	6 (1%)	0.17
Receipt of ventilation	83 (1%)	4 (2%)	0.40	11 (2%)	0.036
Diagnosis NSTEMI/UA STEMI	 6,151 (88%) 809 (12%)	 68 (32%) 146 (68%)	<0.001	 371 (76%) 118 (24%)	<0.001
Glyoprotein IIb/IIIa inhibitor (GPI) use	2,043 (30%)	93 (45%)	<0.001	123 (27%)	0.20
Warfarin	121 (2%)	2 (0.9%)	0.32	4 (0.8%)	0.097
Thrombolysis	163 (3%)	3 (2%)	0.35	1 (0.3%)	0.005
Embolic protection device	1,397 (20%)	31 (15%)	0.052	109 (23%)	0.090
Non-graft PCI	1,232 (17%)	34 (15%)	0.62	60 (12%)	0.008
Drug eluting stent	4,810 (65%)	155 (70%)	0.11	417 (84%)	<0.001
Year 2007 2008 2009 2010 2011 2012 2013 2014	 785 (11%) 974 (13%) 1,095 (15%) 1,139 (15%) 966 (13%) 941 (13%) 835 (11%) 666 (9%)	 0 (0%) 1 (0.5%) 2 (0.9%) 22 (10%) 53 (24%) 56 (25%) 46 (21%) 41 (19%)	<0.001	 0 (0%) 0 (0%) 0 (0%) 1 (0.2%) 2 (0.4%) 61 (12%) 171 (34%) 262 (53%)	<0.001
Mortality at 30 days	207 (3%)	13 (6%)	0.007	8 (2%)	0.12
Mortality at 1 year	581 (9%)	23 (13%)	0.052	16 (7%)	0.33
In-hospital MACE	176 (2%)	8 (4%)	0.24	12 (2%)	0.97

In-hospital bleeding	37 (0.5%)	1 (0.5%)	0.92	2 (0.4%)	0.76

PCI=percutaneous coronary intervention, NSTEMI=non-ST segment elevated myocardial infarction, UA=unstable angina, STEMI=ST-elevated myocardial infarction, MACE=major adverse cardiovascular events

Table 2: Multivariable predictors of antiplatelet use

A) Significant multivariable predictors of prasugrel use

Variable	Odds ratio (95% CI)	p-value
Age	0.97 (0.95-0.99)	<0.001
Previous PCI	1.39 (1.02-1.89)	0.037
Radial access	1.49 (1.06-2.09)	0.022
Circulatory support	278 (1.25-6.18)	0.012
Diagnosis compared to NSTEMI/UA STEMI	14.81 (10.55-20.77)	<0.001

NSTEMI=non-ST segment elevated myocardial infarction, UA=unstable angina, STEMI=ST-elevated myocardial infarction

B) Significant multivariable predictors of ticagrelor use

Variable	Odds ratio (95% CI)	p-value
Age	0.98 (0.96-0.99)	<0.001
Hypercholesterolemia	0.70 (0.55-0.89)	0.004
Renal disease	0.16 (0.03-0.90)	0.037
Radial access	1.66 (1.33-2.05)	<0.001
Diagnosis compared to NSTEMI/UA STEMI	2.12 (1.60-2.82)	<0.001
Embolic protection device	1.50 (1.15-1.96)	0.003
Drug eluting stent	1.64 (1.24-2.16)	<0.001

NSTEMI=non-ST segment elevated myocardial infarction, UA=unstable angina, STEMI=ST-elevated myocardial infarction

Table 3: Odds of adverse outcome

Analysis	n	Odds ratio (95% CI)	p-value
Multivariable 30 day mortality compared to Clopidogrel	7,930		
Prasugrel		1.22 (0.60-2.51)	0.58
Ticagrelor		0.48 (0.20-1.16)	0.10
Multivariable 1 year mortality compared to Clopidogrel	6,979		
Prasugrel		1.36 (0.81-2.28)	0.24
Ticagrelor		0.71 (0.39-1.30)	0.27
Multivariable in-hospital MACE compared to Clopidogrel	7,867		
Prasugrel		0.64 (0.27-1.50)	0.31
Ticagrelor		0.95 (0.45-2.01)	0.90
Multivariable in-hospital bleeding compared to Clopidogrel*	7,756		
Prasugrel		0.47 (0.05-4.06)	0.49
Ticagrelor		1.04 (0.21-5.07)	0.96

*Thrombolysis and warfarin omitted from this analysis because of varying sets.

Table 4: Propensity score match analysis with average treatment effects

Analysis	Group	Coefficient	95% CI		p-value
30 day mortality	Prasugrel vs Clopidogrel (n=7,444)	0.0430	-0.0354	0.1214	0.28
	Ticagrelor vs Clopidogrel (n=7,713)	-0.0099	-0.0376	0.0179	0.48
	Ticagrelor vs Prasugrel (n=703)	-0.0326	-0.0935	0.0283	0.28
1 year mortality	Prasugrel vs Clopidogrel (n=6,749)	0.1254	-0.0684	0.3192	0.20
	Ticagrelor vs Clopidogrel (n=6,803)	-0.0179	-0.0779	0.0421	0.56
	Ticagrelor vs Prasugrel (n=406)	-0.0741	-0.1489	0.0006	0.052
In-hospital MACE	Prasugrel vs Clopidogrel (n=7,383)	0.0002	-0.0394	0.398	0.99
	Ticagrelor vs Clopidogrel (n=7,652)	-0.0083	-0.0245	0.0079	0.31
	Ticagrelor vs Prasugrel (n=699)	0.0040	-0.0251	0.0331	0.79
In-hospital bleeding	Prasugrel vs Clopidogrel (n=7,381)	0.0132	-0.0246	0.0511	0.49
	Ticagrelor vs Clopidogrel (n=7,650)	0.0004	-0.0085	0.0094	0.93
	Ticagrelor vs Prasugrel (n=699)	-0.0016	-0.0168	0.0137	0.84

MACE=major adverse cardiovascular events

Figure 1

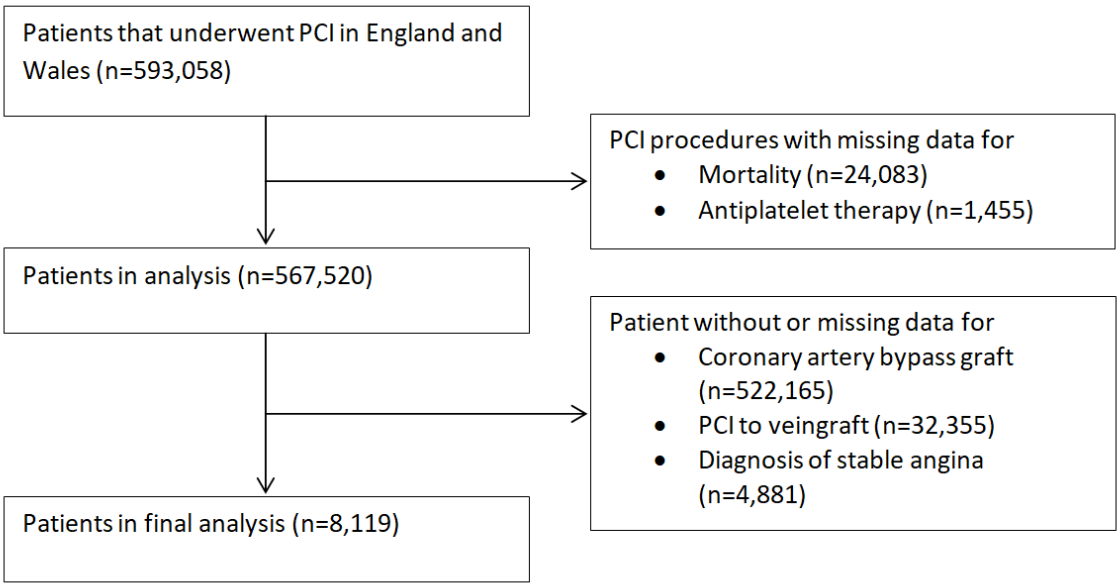
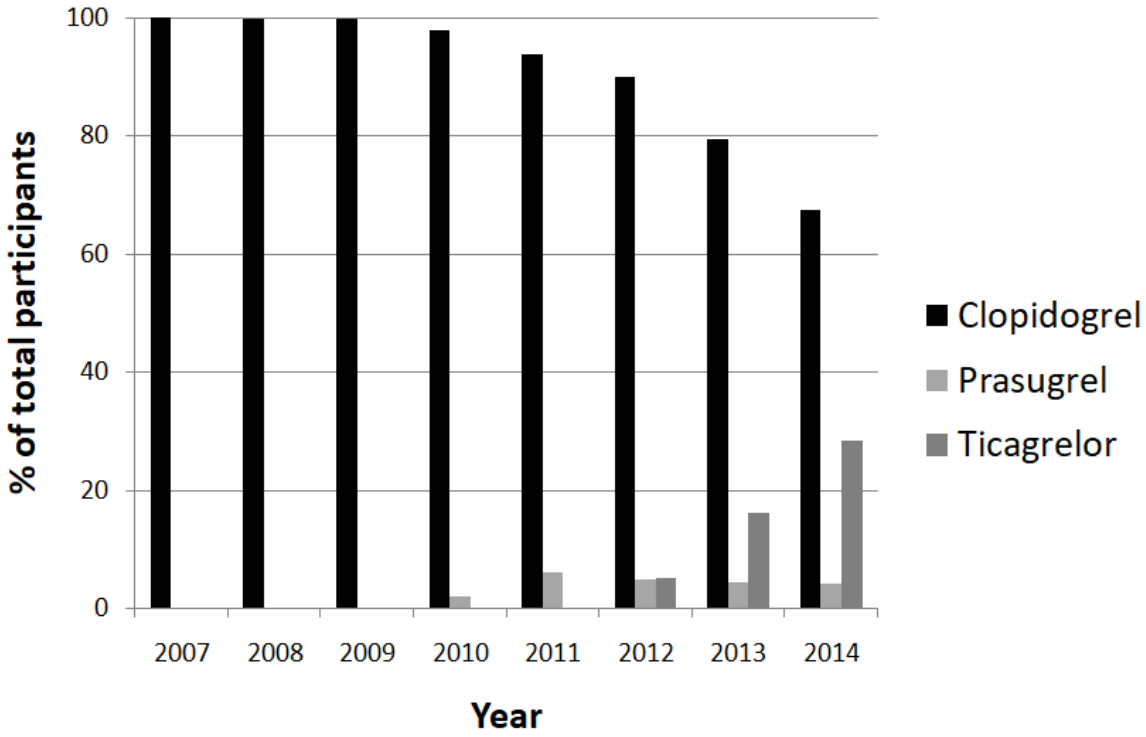

Patients that underwent PCI in England and Wales (n=593,058)
PCI procedures with missing data for
Mortality (n=24,083)
Antiplatelet therapy (n=1,455)
Patients in analysis (n=567,520)
Patient without or missing data for
Coronary artery bypass graft (n=522,165)
PCI to veingraft (n=32,355)
Diagnosis of stable angina (n=4,881)
Patients in final analysis (n=8,119)

Figure 2


100
80
60
40
20
0
% of total participants
2007
2008
2009
2010
2011
2012
2013
2014
Year
Clopidogrel
Prasugrel
Ticagrelor

Supplementary Table 1: Missing data table

Variable	Available	Missing	% Missing
Age	8,116	3	0.04%
Sex	8,102	17	0.2%
Body mass index	4,686	3,433	42%
Current smoker	7,174	945	12%
Diabetes	7,841	278	3.4%
Hypertension	7,819	300	3.7%
Hypercholesterolemia	7,817	302	3.7%
Previous myocardial infarction	7,392	727	9.0%
Previous stroke	7,785	334	4.1%
Peripheral vascular disease	7,783	336	4.1%
Renal disease	7,518	601	7.4%
Valvular heart disease	7,784	335	4.1%
Previous PCI	7,953	166	2.0%
Radial access	7,956	163	2.0%
Cardiogenic shock	7,933	186	2.3%
Circulatory support	7,689	430	5.3%
Receipt of ventilation	7,276	843	10.4%
Diagnosis	7,663	456	5.6%
Glyoprotein IIb/IIIa inhibitor use	7,586	533	6.6%
Antiplatelet	8,119	0	0%
Warfarin	7,129	990	12%
Thrombolysis	6,916	1,203	15%
Embolic protection device	7,618	501	6.2%
Non-graft PCI	8,119	0	0%
Drug eluting stent	8,119	0	0%
Year	8,119	0	0%

PCI=percutaneous coronary intervention.

Supplementary Table 2: Matching success diagnostics for propensity model

Comparison	Group	Mean (SD)	Median (IQR)
Prasugrel vs Clopidogrel	Case	0.9708 (0.0555)	0.9900 (0.9814-0.9937)
	Control	0.9708 (0.0554)	0.9897 (0.9814-0.9937)
	Abs(Case-Control)	0.0003 (0.0008)	0.00014 (0.00005-0.00030)
Ticagrelor vs Clopidogrel	Case	0.9370 (0.0561)	0.9231 (0.9528-0.9740)
	Control	0.9369 (0.0560)	0.9527 (0.9231-0.9745)
	Abs(Case-Control)	0.0003 (0.0012)	0.00013 (0.00004-0.00030)
Ticagrelor vs Prasugrel	Case	0.3087 (0.2263)	0.2065 (0.1221-0.5056)
	Control	0.3076 (0.2233)	0.2077 (0.1224-0.5055)
	Abs(Case-Control)	0.0031 (0.0107)	0.0011 (0.0004-0.0025)