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Use of prasugrel vs clopidogrel and outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention in contemporary clinical practice: Results from the PROMETHEUS study

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Background and objectives We sought to determine the frequency of use and association between prasugrel and outcomes in acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) in clinical practice.

Methods PROMETHEUS was a multicenter observational registry of acute coronary syndrome patients undergoing PCI from 8 centers in the United States that maintained a prospective PCI registry for patient outcomes. The primary end points were major adverse cardiovascular events at 90 days, a composite of all-cause death, nonfatal myocardial infarction, stroke, or unplanned revascularization. Major bleeding was defined as any bleeding requiring hospitalization or blood transfusion. Hazard ratios (HRs) were generated using multivariable Cox regression and stratified by the propensity to treat with prasugrel.

Results Of 19,914 patients (mean age 64.4 years, 32% female), 4,058 received prasugrel (20%) and 15,856 received clopidogrel (80%). Prasugrel-treated patients were younger with fewer comorbid risk factors compared with their counterparts receiving clopidogrel. At 90 days, there was a significant association between prasugrel use and lower major adverse cardiovascular event (5.7% vs 9.6%, HR 0.58, 95% CI 0.50-0.67, $P < .0001$) and bleeding (1.9% vs 2.9%, HR 0.65, 95% CI 0.51-0.83, $P < .001$). After propensity stratification, associations were attenuated and no longer significant for either outcome. Results remained consistent using different approaches to adjusting for potential confounders.

Conclusions In contemporary clinical practice, patients receiving prasugrel tend to have a lower-risk profile compared with those receiving clopidogrel. The lower ischemic and bleeding events associated with prasugrel use were no longer evident after accounting for these baseline differences. (*Am Heart J* 2017;188:73-81.)

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Dual antiplatelet therapy with aspirin and an inhibitor of the platelet P2Y₁₂ receptor is standard therapy for prevention of thrombotic complications after percutaneous coronary intervention (PCI).^{1,2} Significant genetic and pharmacodynamic variability exists in response to clopidogrel, and lower levels of platelet inhibition may be observed in some patients leading to increased risk for thrombotic events.³⁻⁵ This variability is overcome by prasugrel, which demonstrated superior efficacy over clopidogrel in the TRIal to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38.⁵⁻⁷ However, compared with clopidogrel, prasugrel is associated with higher rates of major

bleeding, particularly in elderly, low-body-weight patients, and those with prior stroke or transient ischemic attack.⁷

Despite these randomized results, the prospective observational Treatment With Adenosine Diphosphate (ADP) Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) study evaluating 12,000 myocardial infarction (MI) patients undergoing PCI in the United States did not demonstrate an association between prasugrel and lower major adverse cardiovascular event (MACE) compared with clopidogrel.^{8,9} In contrast, a retrospective analysis of acute coronary syndrome (ACS) patients undergoing PCI (ACS-PCI) in the Premier Healthcare Alliance claims database reported lower readmission rates for MI or bleeding with prasugrel compared with clopidogrel.^{10,11} Whether these divergent results reflect differences in underlying patient case-mix, methodological assumptions, or study design remains unclear. This issue is clinically relevant because the real-world application, and the putative benefit or harm, of therapeutic interventions may not always conform to the controlled settings of a randomized study. This has important implications for informing processes of care, quality, and outcomes. Accordingly, we sought to examine the overall use and effect of prasugrel compared with clopidogrel in a large and contemporary registry of unselected real-world ACS patients undergoing PCI.^{12,13}

Methods

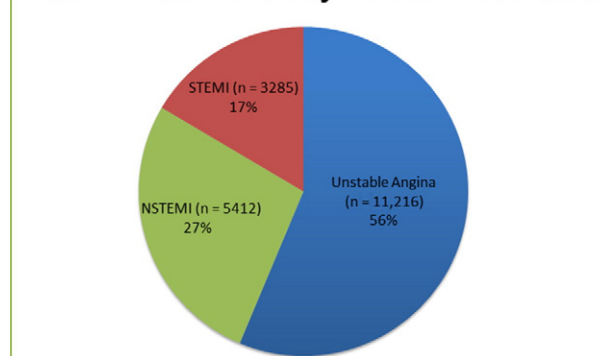
Population

PROMETHEUS was a retrospective cohort study including patients presenting with ACS managed with PCI from 8 academic medical centers in the United States between January 1, 2010 and June 30, 2013. The study period was selected based on the approval and availability of prasugrel in the US market in mid-2009, which allowed for initial uptake of the drug and the need for a minimum 90-day follow-up in this population. We included adult patients presenting across the entire spectrum of ACS undergoing PCI with stent implantation receiving either clopidogrel or prasugrel at the time of PCI. Patients receiving both agents in the periprocedural period were excluded.

The primary objective of this study was to compare the effectiveness of a treatment strategy initiating prasugrel relative to clopidogrel at the time of PCI in a usual care environment from academic centers in the United States. The selected academic centers maintain institutional databases prospectively recording baseline and procedural characteristics and clinical outcomes for PCI patients, irrespective of clinical presentation. The participating centers ran a query in their PCI database to identify all patients presenting with ACS who received

Figure 1

PROMETHEUS Cohort by Clinical Presentation



Frequency of clinical presentation in PROMETHEUS cohort. Pie chart displays the overall frequency and number of patients presenting with unstable angina, NSTEMI, and STEMI in the PROMETHEUS cohort.

prasugrel or clopidogrel during the study period. The data elements that were abstracted conform to the definitions used in the NCDR CathPCI registry. Follow-up was performed at each participating center by trained research personnel via telephone call, in-person visit, or medical record review and occurred either at regular intervals or during standard of care post-PCI clinical visits. All sites confirmed that relevant baseline and follow-up data on clinical end points up to 1 year were collected in each respective database using a prestudy feasibility questionnaire.

To facilitate data extraction, the study investigators first developed a prespecified extraction list of relevant baseline and outcome variables. This list was then disseminated to each individual site as a platform to extract the corresponding elements from the database at each participating center. After extraction, data were validated, examined for completeness and quality by the Data Coordinating Center at Mount Sinai, and aggregated to form one unified data set upon which all analyses were performed. Study sponsors (Daiichi Sankyo and Eli Lilly) had no access to patient-level data. Details of the study organization, participating centers, and investigators are shown in the Supplementary Appendix (Tables S1 and S2).

End points and definitions

The prespecified primary end point was *MACEs* defined as a composite of all-cause death, MI, stroke, or unplanned coronary revascularization at 90 days from index hospital PCI. In part, this time point was chosen because it was not possible to monitor drug compliance after hospital discharge and we assumed that the adherence rate would be high, whereas the switching rate would be low ($\leq 10\%$) at 90 days vs a later time interval (ie, 1 year). In addition, based on prior analyses from the TRITON-TIMI 38 trial, the therapeutic effect of

Table I. Baseline clinical characteristics by treatment group

	Prasugrel (n = 4058)	Clopidogrel (n = 15,856)	P
Age, y	58.7 ± 10.3	65.8 ± 12.3	<.0001
Female sex, n (%)	989 (24.4)	5315 (33.5)	<.0001
African American, n (%)	253 (6.2)	1872 (11.8)	<.0001
BMI (kg/m ²)	30.7 ± 6.2	29.7 ± 6.2	<.0001
Diabetes, n (%)	1382 (34.1)	6198 (39.1)	<.0001
Diabetes on insulin, n (%)	394 (9.7)	2140 (13.5)	<.0001
Hypertension, n (%)	2915 (71.8)	13,466 (84.9)	<.0001
Dyslipidemia, n (%)	3220 (79.3)	13,469 (84.9)	<.0001
Smoking, n (%)	1175 (29.0)	3831 (24.2)	<.0001
Prior MI, n (%)	833 (20.5)	5130 (32.4)	<.0001
Prior PCI, n (%)	788 (19.4)	4250 (26.8)	<.0001
Prior CABG, n (%)	359 (8.8)	3074 (19.4)	<.0001
Prior CVD	188 (4.6)	2197 (13.9)	<.0001
Prior CHF, n (%)	567 (14.0)	3684 (23.2)	<.0001
Prior PAD, n (%)	291 (7.2)	2140 (13.5)	<.0001
CKD, n (%)	619 (15.3)	4994 (31.5)	<.0001
Anemia, n (%)	339 (8.4)	2553 (16.1)	<.0001
CAD presentation, n (%)			
STEMI	773 (19.0)	2512 (15.8)	<.0001
NSTEMI	1159 (28.6)	4253 (26.8)	.03
Unstable angina	2126 (52.4)	9090 (57.3)	<.0001

Abbreviations: CHF, congestive heart failure; PAD, peripheral artery disease; CKD, chronic kidney disease.

prasugrel is largely evident within 90 days.¹⁴ The secondary end points included individual components of MACE, as well as MACE and its components at 1 year. Exploratory analyses were also performed for the composite outcome of all-cause death, MI, or stroke at 90 days and 1 year. The primary safety end point was *major bleeding*, defined as any clinically overt hemorrhage requiring hospitalization or blood transfusion.

Statistical analysis

Patients were grouped according to prasugrel or clopidogrel treatment at the time of PCI, defined as receipt of medication 24 hours before and during the PCI procedure in accordance with NCDR definitions. Baseline clinical and procedural characteristics were compared between the prasugrel and clopidogrel groups using the Student *t* test and χ^2 test and for continuous and categorical variables, respectively. The cumulative incidence of adverse events was calculated as a Kaplan-Meier estimate of time to first event, and comparisons between groups were performed using the log-rank test. Two-tailed *P* values <.05 were considered significant. Statistical analyses were performed using SAS version 9.3 (Cary, NC) and Stata version 12.1 (College Station, TX).

Multivariable and propensity adjustment

To evaluate the associations between treatment group (prasugrel vs clopidogrel) and the primary outcome, hazard ratios (HRs) were generated using Cox proportional hazards regression stratified by the propensity to

receive prasugrel. Propensity scores were calculated using a multivariable logistic regression model with the dependent outcome as treatment with prasugrel (vs clopidogrel). The propensity model was generated in an iterative fashion using the method of Rosenbaum and Rubin.¹⁵ In addition to age and sex, this model included all baseline covariates demonstrating significant differences (*P* < .05) between groups and additional variables that may be plausibly related to either the outcome or exposure. The final propensity model included the following main effects: center, coronary artery disease (CAD) presentation, diabetes, age, age squared, bivalirudin, smoking, gender, African American race, hypertension, family history of CAD, prior PCI, prior coronary artery bypass surgery (CABG), prior peripheral arterial disease, prior congestive heart failure, prior cerebrovascular disease (CVD), stent length, stent diameter, glycoprotein IIb/IIIa inhibitor use, hypercholesterolemia, prior MI, estimated glomerular filtration rate, stent type, body mass index (BMI), hemoglobin, and the following interaction terms: center * procedural glycoprotein IIb/IIIa inhibitor use, BMI * hemoglobin, prior CVD * prior PCI, and prior CVD * prior CABG. The overall *c* statistic for the propensity model was 0.81.

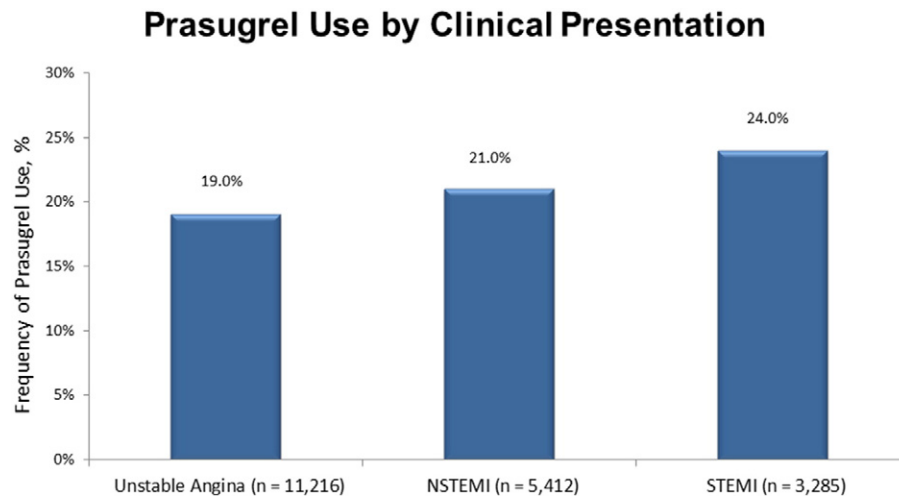
From this propensity model, each observation was assigned a predicted probability for prasugrel treatment. The distribution of propensity scores for the entire cohort and each treatment group was visually examined. Mutually exclusive strata (n = 10) were then generated based on the propensity scores for the entire cohort, a process that was blinded to any outcome data to avoid bias in selection. The number of strata and their respective cut-points were based on fulfilling previously established criteria and adequate balance in baseline covariates.^{15,16}

The adjusted associations between treatment groups and the primary MACE outcome at 90 days were calculated using Cox proportional hazards regression with propensity stratification as the primary method of analysis. In addition to treatment (prasugrel vs clopidogrel) and study center, covariates were included to account for residual imbalances between groups and/or to adjust for important variables related to the outcome of interest.

The following sensitivity analyses for the primary MACE outcome were also performed: multivariable adjustment, propensity matching,¹⁷ and inverse probability weighting (IPW).¹⁸ A sensitivity analysis was also performed for the primary MACE outcome by defining treatment groups as only those patients receiving the same medication at the time of PCI and at discharge and restricted to those with out-of-hospital MACE (as-treated analysis).

Results

The study sample included 19,914 ACS-PCI patients. The mean age of the study population was 64.4 ±

Figure 2

Frequency of prasugrel use by clinical presentation. Bar graph depicts the frequency of prasugrel use according to clinical presentation.

12.3 years and 32% were women. Of this cohort, 20% ($n = 4,058$) received prasugrel and 80% (15,856) received clopidogrel at the time of PCI. The distribution by clinical presentation in the overall cohort is shown in Figure 1. Unstable angina ($n = 11,216$; 56%) was the most common presentation, followed by non-ST-elevation MI (NSTEMI) ($n = 5,412$; 27%) with ST-elevation MI (STEMI) least common ($n = 3,285$; 17%). Prasugrel use varied across the 8 sites from a minimum of 5% to a maximum of 38%. Loss to follow-up at 90 days and 1 year was 8.4% and 17.1%, respectively.

The baseline differences between patients receiving prasugrel and clopidogrel are shown in Table I. Prasugrel-treated patients were younger and more often male compared with those receiving clopidogrel. The frequency of comorbid conditions including diabetes, prior MI, prior CVD, chronic kidney disease, and anemia was higher among clopidogrel-treated patients. Prasugrel was more often used in patients with STEMI or NSTEMI, whereas clopidogrel was used more often in the United States. As shown in Figure 2, the frequency of prasugrel use increased with the severity of clinical presentation with a maximum of 24% among those presenting with STEMI.

Table II shows the procedural differences between the 2 groups. Angiographically, patients receiving prasugrel had a lower frequency of left main stem disease, fewer complex lesions (American College of Cardiology/American Heart Association type B2/C) and fewer lesions with moderate/severe calcification. In contrast, prasugrel-treated patients received longer stents with a greater diameter, whereas patients receiving clopidogrel were more likely to have bare-metal stents. Patients on prasugrel also received less bivalirudin but more glycoprotein IIb/IIIa inhibitors for procedural antithrombotic therapy. Figure 3 displays the frequency of prasugrel use

as a function of several established clinical or angiographic thrombotic risk factors (diabetes mellitus, troponin (+) ACS, stent diameter < 3.0 mm, or prior MI). Although prasugrel was used in more than 20% of patients with none or one such risk factor, use was paradoxically lowest (13.4%) among those with 4 thrombotic risk factors.

Unadjusted MACE rates at 90 days were 5.7% and 9.6% among those receiving prasugrel and clopidogrel, respectively (Table III and Figure 4; $P < .001$). Associations were attenuated and no longer statistically significant after adjusting for the propensity to receive prasugrel (HR 0.89, 95% CI 0.76-1.05, $P = .16$). The adjusted point estimates were concordant using different analytic methods (propensity matching, IPW, and covariate adjustment, respectively). Inverse probability weighting gave a less precise estimate, likely due to undue influence of a few patients with very large weights. Associations for most other end points at 90 days followed a similar pattern, with large and significant unadjusted reductions attenuating to more modest differences after adjustment.

At 365 days, reductions in MACE associated with prasugrel use were slightly larger in magnitude compared with those observed at 90 days (Table III and Figure 4) and remained significant after propensity stratification (HR for MACE 0.86, 95% CI 0.77-0.96). In contrast, no significant differences were observed between groups for both MI and bleeding at 365 days.

Results for the exploratory outcome of death, MI, or stroke demonstrate significant reductions associated with prasugrel use at 90 and 365 days using propensity stratification and covariate adjustment. In contrast, results were nonsignificantly different for this outcome using IPW (Table III).

Table II. Baseline procedural characteristics by treatment group

	Prasugrel (n = 4058)	Clopidogrel (n = 15,856)	P
Multivessel disease, n (%)	1672 (41.2)	6724 (42.4)	.17
PCI vessel			
Left main, n (%)	84 (2.1)	583 (3.7)	<.0001
LAD, n (%)	1972 (48.6)	6923 (43.7)	<.0001
Circumflex, n (%)	1100 (27.1)	4794 (30.2)	<.0001
RCA, n (%)	1430 (35.2)	5367 (33.9)	.097
B2/C type lesion, n (%)	2848 (70.2)	10,758 (67.8)	<.0001
Moderate to severe calcification, n (%)	422 (10.4)	2349 (14.8)	<.0001
Bifurcation lesion, n (%)	446 (11.0)	1676 (10.6)	.38
Total stent length, mm	31.4 ± 20.2	30.50 ± 20.9	.016
Minimum stent diameter, mm	3.01 ± 0.49	2.96 ± 0.50	<.0001
At least 1 first-generation DES, n (%)	297 (7.3)	2495 (15.7)	<.0001
At least 1 second-generation DES, n (%)	3283 (80.9)	10,278 (64.8)	<.0001
At least 1 BMS, n (%)	569 (14.0)	3926 (24.8)	<.0001
Procedural anticoagulation			
Bivalirudin, n (%)	2743 (67.6)	11,726 (74.0)	<.0001
GPIIb/IIIa inhibitor, n (%)	1178 (29.0)	3388 (21.4)	<.0001
LMWH, n (%)	38 (0.9)	169 (1.1)	.77

Abbreviations: LAD, Left anterior descending artery; RCA, right coronary artery; DES, drug-eluting stent; BMS, bare-metal stent; GPIIb/IIIa, glycoprotein IIb/IIIa; LMWH, low-molecular-weight heparin.

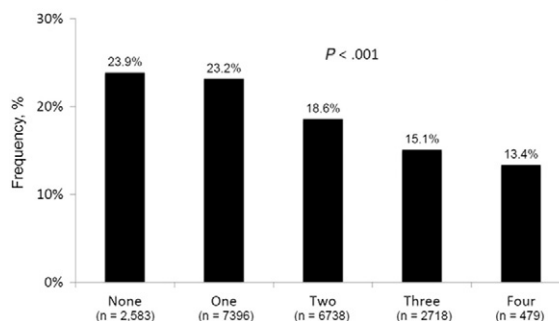
Supplementary Table III shows the results after including those patients receiving the same medication at the time of PCI and at hospital discharge (as-treated analysis). These results demonstrate comparable results to those obtained in the overall population with unadjusted reductions in risk associated with prasugrel use diminishing upon adjustment.

Discussion

Salient findings from this report of prasugrel use in contemporary clinical practice include the following: (i) use of prasugrel was relatively uncommon in an ACS-PCI setting despite evidence from clinical trials, although use increased among those with troponin positive syndromes; (ii) patients receiving prasugrel were younger and highly selected with fewer comorbidities compared with their counterparts receiving clopidogrel and the decision to use prasugrel appears to be strongly influenced by the warnings in the US product insert; (iii) unadjusted risks for both ischemic and bleeding complications were substantially lower among those receiving prasugrel compared with clopidogrel; and (iv) differences in adverse events were attenuated and no longer significant at 90 days after adjusting for baseline imbalances between groups. Taken together, the current findings represent the first cohort study using real-world

Figure 3

Frequency of prasugrel use by number of thrombotic risk factors



Frequency of prasugrel use by number of thrombotic risk factors. Thrombotic risk factors include presentation with troponin (+) syndrome, diabetes mellitus, prior MI, or stent diameter <3.0 mm. Vertical bars display the frequency of prasugrel use according to the total number of thrombotic risk factors among patients.

data from academic medical centers across the United States to study the use and outcome of prasugrel as compared with clopidogrel in patients across the entire ACS clinical spectrum undergoing PCI.

In the TRITON-TIMI 38 randomized trial, prasugrel reduced ischemic events by 19%, albeit at an excess cost of bleeding, among ACS patients undergoing PCI.⁷ Consistent with these randomized data, our results show lower 90-day and 1-year MACE rates with prasugrel before and after adjustment, although adjusted differences at 90 days were modest and not statistically significant. The magnitude and direction of benefit was largely consistent across the different analytic approaches.

There are several possibilities that might reconcile the divergent results between earlier randomized trial data and our observational findings. First, the proportion of patients who might be expected to derive the largest benefit at 90 days from potent platelet inhibition (ie, STEMI) comprised only 17% of the PROMETHEUS cohort, whereas 26% of patients enrolled in TRITON-TIMI 38 presented with STEMI.^{7,19,20}

Second, it is possible that the relatively low-risk patients selected to receive prasugrel in a real-world setting may not derive or even require the same degree of therapeutic protection compared with those enrolled in randomized trials (ie, risk/treatment paradox).^{21,22} Indeed, the frequency of many clinical risk factors that are associated with substantial thrombotic risk, including diabetes mellitus, prior MI, and small stent diameter were substantially lower among those treated with prasugrel

Table III. Crude event rates, and unadjusted and adjusted associations for adverse events

	Treatment group*		HRs (95% CI)			
	Prasugrel (n = 4058)	Clopidogrel (n = 15,856)	Unadjusted	Propensity stratified†	IPW	Covariate adjusted
90 d						
MACE, primary end point, n (%)	216 (5.7)	1415 (9.6)	0.58 (0.50-0.67)	0.89 (0.76-1.05)	0.94 (0.76-1.16)	0.94 (0.80-1.09)
Death, MI, or stroke, n (%)	101 (2.7)	1000 (6.8)	0.39 (0.31-0.47)	0.75 (0.60-0.94)	0.82 (0.61-1.11)	0.77 (0.61-0.96)
Death, n (%)	23 (0.6)	408 (2.8)	0.21 (0.10-0.30)	0.62 (0.40-0.99)	0.52 (0.3-0.94)	0.68 (0.44-1.05)
MI, n (%)	74 (1.9)	562 (3.8)	0.51 (0.40-0.64)	0.84 (0.64-1.11)	1.1 (0.76-1.55)	0.84 (0.65-1.10)
Unplanned revascularization, n (%)	138 (3.7)	586 (4.1)	0.89 (0.75-1.08)	1.06 (0.86-1.31)	1.21 (0.92-1.58)	1.05 (0.85-1.28)
Bleeding, n (%)	75 (1.9)	442 (2.9)	0.65 (0.51-0.83)	1.03 (0.78-1.36)	1.01 (0.69-1.48)	1.03 (0.79-1.35)
365 d						
MACE, n (%)	433 (12.1)	2866 (20.6)	0.56 (0.50-0.62)	0.86 (0.77-0.96)	0.91 (0.79-1.06)	0.85 (0.76-0.95)
Death, MI, or stroke, n (%)	199 (5.6)	1778 (12.8)	0.42 (0.36-0.48)	0.83 (0.71-0.98)	0.89 (0.72-1.10)	0.80 (0.68-0.94)
Death, n (%)	62 (1.8)	901 (6.6)	0.26 (0.20-0.33)	0.69 (0.52-0.91)	0.63 (0.43-0.91)	0.67 (0.51-0.87)
MI, n (%)	122 (3.3)	855 (6.1)	0.54 (0.44-0.65)	0.90 (0.72-1.11)	1.13 (0.86-1.49)	0.86 (0.70-1.06)
Unplanned revascularization, n (%)	300 (8.5)	1507 (11.5)	0.74 (0.65-0.84)	0.92 (0.80-1.06)	1.00 (0.84-1.20)	0.88 (0.77-1.01)
Bleeding, n (%)	112 (3.1)	664 (4.7)	0.64 (0.52-0.78)	0.97 (0.78-1.22)	0.86 (0.63-1.18)	0.96 (0.77-1.19)

* Event rates calculated as Kaplan-Meier estimates at different time points.

† Propensity stratification is the prespecified primary method of adjustment. It is based on dividing the patient population into 10 strata based on the distribution of patient propensity score.

compared with clopidogrel. Moreover, although prasugrel use increased by clinical severity, only 24% of STEMI patients received this agent. Such selected use of prasugrel is consistent with the results of the prospective TRANSLATE-ACS registry, which also showed a similar imbalance in underlying risk factors among MI patients treated with prasugrel compared with clopidogrel.⁸ Clearly, further study is needed to explore the determinants of clinical decision making at the time of PCI because our results, similar to TRANSLATE-ACS, suggest that a more potent treatment is being used in patients with a lower likelihood to derive meaningful benefit.^{8,23} Whether or not recalibrating the intensity of antiplatelet pharmacotherapy to more closely approximate a patient's inherent thrombotic risk is a hypothesis that warrants further study.²⁴

In exploratory analyses, we observed a significant 25% reduction in the composite occurrence of all-cause death, MI, or stroke at 90 days associated with prasugrel use, a magnitude of benefit virtually identical to that observed in TRITON-TIMI 38 using a similar outcome and time point. Nevertheless, the magnitude and direction of effect for the individual components that drove this composite end point varied substantially, with important implications for interpreting and comparing such results across studies. More specifically, in TRITON-TIMI 38, prasugrel use led to significant reductions in MI, not death, whereas in PROMETHEUS, adjusted reductions in MI at 90 and 365 days were nonsignificant. In contrast, we observed significant reductions in all-cause mortality associated with prasugrel use in both unadjusted and adjusted analyses. Hence, contrasting effects on individual end points across studies yielded similar estimates for a

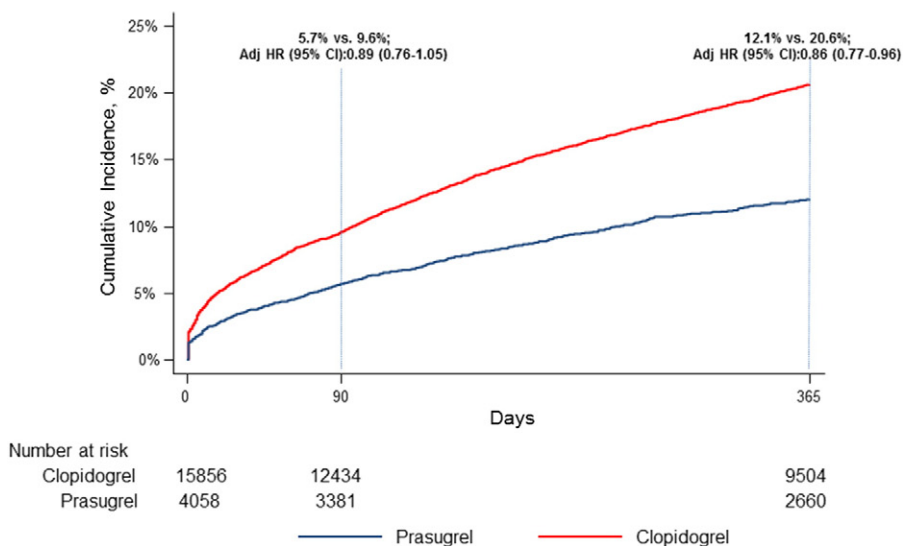
composite outcome that included those very components.

The reductions in death observed in PROMETHEUS may be attributable to selection bias, coupled with a modest reduction in ischemic events without concordant excess bleeding risk. With respect to the former, it is possible that residual or unmeasured confounding strongly influenced the mortality point estimates because prasugrel-treated patients were much healthier compared with those receiving clopidogrel. In support of the latter, it is plausible that a modest reduction in MACE risk in the absence of bleeding harm may confer a mortality advantage. This hypothesis remains speculative, however, because the reductions in MI and MACE were numerically lower compared with mortality and without statistical significance. As a result, it is unlikely that similar findings to ours will be duplicated, because the associations with death were observed absent a concordant reduction in other ischemic events.

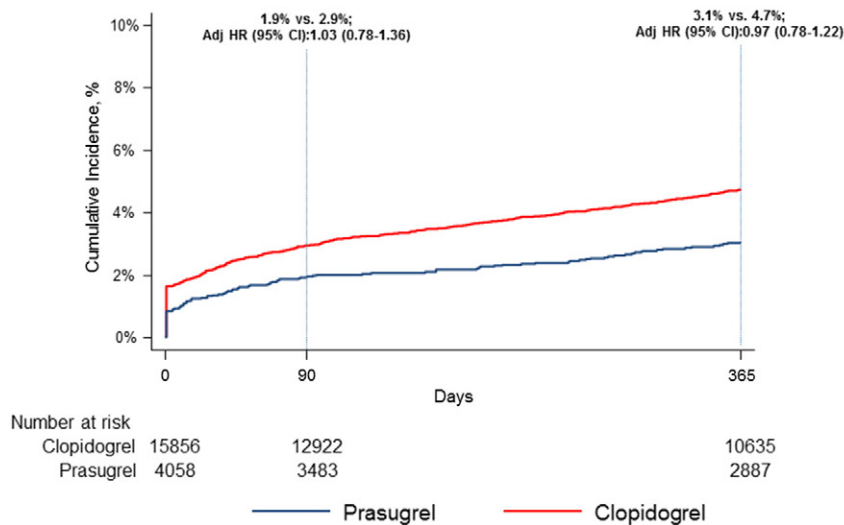
Unadjusted bleeding rates were also significantly lower among prasugrel- vs clopidogrel-treated patients in our study, findings that are consistent with TRANSLATE-ACS and are most likely attributable to the lower-risk profile of patients selected to receive prasugrel.⁸ At 1 year, the absolute differences in bleeding rates in favor of prasugrel in our study and TRANSLATE-ACS were 1.7% and 1.0%, respectively.⁸ This suggests that prasugrel-treated patients in PROMETHEUS were somewhat healthier and at lower risk for bleeding compared with their counterparts in the TRANSLATE-ACS study, further supporting the inclusion of a more selected cohort unlikely to manifest overt bleeding risk. After adjustment, however, HRs for bleeding were not significantly different between groups.

Figure 4

A
Cumulative MACE at 90 Days and One Year by Treatment Group



B
Cumulative Bleeding at 90 Days and One Year by Treatment Group



Cumulative MACEs and bleeding by treatment group. Kaplan-Meier curves displaying the cumulative rate of MACEs (composite of all-cause death, MI, stroke, or unplanned coronary revascularization—**A**) and bleeding (**B**) by treatment group at 90 and 365 days.

Differences in patient populations, bleeding ascertainment, and/or selection bias may account for the inconsistent results between studies. For example, we relied on bleeding-related hospitalizations as our safety end point, whereas bleeding was prospectively ascertained and adjudicated in TRANSLATE-ACS. Therefore, underreporting of bleeding may have biased our results to the null. Alternatively, real-world selection for prasugrel

use may be largely driven by factors that correlate with bleeding propensity rather than ischemic risk, resulting in the treatment for patients both unlikely to manifest overt harm but also not experience any meaningful benefit.²⁵

Limitations

Among the important limitations of our study was the observational retrospective design, thereby precluding

causal inferences. Although we used several statistical methods to account for the substantial imbalances between treatment groups, we cannot exclude the possibility of residual or unmeasured confounders influencing our estimates. However, our findings were consistent in both direction and magnitude across the different adjustment techniques. In the absence of standard prospective data collection that was uniform across study centers, we may have underestimated the rates of some clinical events. Detailed data on medication adherence, an important determinant of risk after PCI, were not available across centers. Although we used an early time point of 90 days for our primary analysis, we were unable to account for therapeutic crossover and/or compliance in the follow-up period after hospital discharge. In addition, granular information on timing of medication administration relative to diagnostic angiography and PCI was not available. Although ticagrelor was approved for use in July 2011, which coincides with the inclusion period for our study, we directed each center to only provide data on patients treated with either clopidogrel or prasugrel in accordance with the study aims and objectives. Although we may have excluded certain patients treated with ticagrelor in the latter 2 years of the study period, administrative data describing national trends in P2Y₁₂ inhibitor use during this time frame are largely consistent with our results in that clopidogrel was the most commonly used drug followed by prasugrel with ticagrelor used least frequently.^{26,27}

Conclusions

In a large, real-world cohort of ACS patients undergoing PCI at medical centers across the United States, we observed that prasugrel is used infrequently and in much lower-risk patients compared with those receiving clopidogrel. Large reductions in risk for both ischemic and bleeding complications associated with prasugrel use were no longer apparent after considering baseline differences between groups. Recalibrating “real-world” use of prasugrel to better approximate a patient's ischemic risk may yield a more appreciable therapeutic benefit, a hypothesis that warrants further study.

Appendix. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ahj.2017.02.013>.

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