ORIGINAL RESEARCH

Impact of Proton Pump Inhibitor Use on the Comparative Effectiveness and Safety of Prasugrel Versus Clopidogrel: Insights From the Treatment With Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) Study

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***Background*—**Proton pump inhibitors (PPIs) reduce gastrointestinal bleeding events but may alter clopidogrel metabolism. We sought to understand the comparative effectiveness and safety of prasugrel versus clopidogrel in the context of proton pump inhibitor (PPI) use.

***Methods and Results*—**Using data on 11 955 acute myocardial infarction (MI) patients treated with percutaneous coronary intervention at 233 hospitals and enrolled in the TRANSLATE-ACS study, we compared whether discharge PPI use altered the association of 1-year adjusted risks of major adverse cardiovascular events (MACE; death, MI, stroke, or unplanned revascularization) and Global Use of Strategies To Open Occluded Arteries (GUSTO) moderate/severe bleeding between prasugrel- and clopidogrel-treated patients. Overall, 17% of prasugrel-treated and 19% of clopidogrel-treated patients received a PPI at hospital discharge. At 1 year, patients discharged on a PPI versus no PPI had higher risks of MACE (adjusted hazard ratio [HR] 1.38, 95% confidence interval [CI] 1.21-1.58) and GUSTO moderate/severe bleeding (adjusted HR 1.55, 95% CI 1.15-2.09). Risk of MACE was similar between prasugrel and clopidogrel regardless of PPI use (adjusted HR 0.88, 95% CI 0.62-1.26 with PPI, adjusted HR 1.07, 95% CI 0.90-1.28 without PPI, interaction P=0.31). Comparative bleeding risk associated with prasugrel versus clopidogrel use differed based on PPI use but did not reach statistical significance (adjusted HR 0.73, 95% CI 0.36-1.48 with PPI, adjusted HR 1.34, 95% CI 0.79-2.27 without PPI, interaction P=0.17).

***Conclusions*—**PPIs did not significantly affect the MACE and bleeding risk associated with prasugrel use, relative to clopidogrel.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01088503. **(*J Am Heart Assoc.* 2016;5: e003824 doi: 10.1161/JAHA.116.003824)**

Key Words: bleeding risk • clopidogrel • major adverse cardiovascular events • prasugrel • proton pump inhibitors

Treatment with aspirin and a $P2Y_{12}$ receptor inhibitor such as clopidogrel or prasugrel represents the mainstay of medical therapy following acute myocardial infarction (MI) for patients treated medically or with percutaneous coronary intervention (PCI).[1,2] Proton pump inhibitors (PPIs) are often prescribed to help reduce the risk of gastrointestinal bleeding for patients on dual antiplatelet therapy (DAPT), a strategy that has been supported by an expert consensus statement.[3]

Several studies have raised concerns that concomitant administration of a PPI with a $P2Y_{12}$ receptor inhibitor (particularly clopidogrel) can interfere with metabolism by competing with a liver enzyme, CYP2C19, leading to reduced

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/10/e003824/DC1/embed/inline-supplementary-material-1.pdf

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antiplatelet activity.[4,5] Novel and more potent $P2Y_{12}$ receptor inhibitors such as prasugrel are now used more frequently in clinical practice, yet there is limited information on the comparative effectiveness of prasugrel versus clopidogrel in the setting of PPI use.[6]

The Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) study was a prospective longitudinal observational study of patients in the United States who had either ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI) treated with PCI and a $P2Y_{12}$ receptor inhibitor. This analysis was designed to (1) describe the prevalence of PPI use at discharge among acute MI patients treated with either prasugrel or clopidogrel in contemporary practice and (2) compare the effectiveness and safety of prasugrel versus clopidogrel in the context of PPI use.

Methods

Study Population

The TRANSLATE-ACS study design has been previously described.[7] Briefly, STEMI and NSTEMI patients treated with PCI and a $P2Y_{12}$ receptor inhibitor during the index MI hospitalization were included in the study. Patients who were unable to provide written informed consent for longitudinal follow-up were excluded. Because the main intent of the study was to observe longitudinal antiplatelet therapy use in routine clinical practice, patients were excluded who were participating in another research study that specified use of either an investigational or approved $P2Y_{12}$ receptor inhibitor within the first 12 months post-MI.[7] TRANSLATE-ACS was an observational study, so all treatment decisions, including choice of antiplatelet therapy and PPI use, were left to the discretion of the individual treating physicians in accordance with practice guideline recommendations and local standards of care.

Between April 2010 and October 2012, 12 365 acute MI patients treated with PCI were enrolled in TRANSLATE-ACS. For the purpose of this analysis, we examined the 11 969 patients who were treated with either clopidogrel or prasugrel during the index hospitalization. We excluded patients who died in hospital (n=14). Our final study population included 11 955 acute MI patients discharged from 233 United States hospitals.

Data Collection and Study Endpoints

Baseline clinical characteristics, demographics, past medical history, in-hospital antiplatelet therapy or antithrombotic therapy use, laboratory studies, PCI data, and discharge medications were abstracted from the medical record or patient interviews into the TRANSLATE-ACS data collection form using standardized data elements and definitions aligned with those used by the National Cardiovascular Data Registry.[8] Limited platelet function and pharmacogenomic testing were performed in the TRANSLATE-ACS study.[9] Data were screened on entry, and only those data meeting predetermined criteria for completeness and accuracy were entered into the database for analysis.

Postdischarge study follow-up was conducted via centralized telephone interviews by trained personnel at the Duke Clinical Research Institute (Durham, NC). The primary outcomes of the study were postdischarge bleeding and major adverse cardiovascular events (MACE) during the 1-year period following the index MI hospitalization. MACE were defined as a composite of death, MI, unplanned revascularization, or stroke at 1 year. Bleeding was defined using Global Use of Strategies To Open Occluded Arteries (GUSTO) criteria; moderate/severe bleeding was defined as intracranial hemorrhage, bleeding that caused hemodynamic compromise requiring intervention, or bleeding that required a blood transfusion.[10] All MACE and bleeding events were independently adjudicated by study physicians via review of relevant medical records using protocol-specified endpoint definitions.

Statistical Methods

Patients were divided into 4 groups based on prasugrel versus clopidogrel treatment and PPI versus no PPI use at discharge[7]; we compared baseline and in-hospital characteristics among these groups. Categorical variables were summarized by count and percentages and compared using the Pearson chi-squared test or the Fisher exact test. Continuous variables were summarized by median (25th and 75th percentiles) and compared using Kruskal-Wallis tests. Unadjusted cumulative incidence of each outcome was compared between prasugrel- and clopidogrel-treated patients, with and without discharge PPI use. Inverse probability-weighted adjusted Cox proportional hazards modeling was used to compare risks of MACE and GUSTO moderate/severe bleeding. Propensity scores were calculated to estimate the likelihood of prasugrel versus clopidogrel treatment based on 56 demographic, clinical, and angiographic covariates, and propensity score models were fit separately by PPI group. The pre- and post-inverse probability-weighted balance of all the covariates among the different exposures was assessed using standardized differences showing good balance of covariates between groups (all standardized differences <0.10, Table S1).

TRANSLATE-ACS received approval by the Duke University Institutional Review Board, as well as by all the Institutional Review Boards of all participating sites. All subjects provided written informed consent. All statistical analyses were performed at the Duke Clinical Research Institute using SAS software version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Baseline Patient Characteristics

Among 11 955 acute MI patients, 3123 (26%) were treated with prasugrel. A similar proportion of prasugrel-treated patients (17%) and clopidogrel-treated patients (19%) were discharged on a PPI. Patients discharged on a PPI were older, more likely to be female, diagnosed with NSTEMI, and had a greater prevalence of comorbidities than patients discharged without a PPI (Table 1). The rate of prior gastrointestinal or genitourinary bleeding was 2.4% among patients discharged on a PPI compared with 0.8% among patients discharged without a PPI. Irrespective of discharge PPI use, patients who received prasugrel were more likely than clopidogrel-treated patients to be younger and male but less likely than clopidogrel-treated patients to have cardiovascular risk factors such as prior MI, prior revascularization, or prior stroke/transient ischemic attack (Table 1). The prevalence of diabetes mellitus was lower among prasugrel-treated patients than clopidogrel-treated patients in those discharged on a PPI (26% vs 35%, P=0.0002), but the prevalence of diabetes mellitus was not significantly different

Table 1. Baseline Characteristics Among Patients on Prasugrel Versus Clopidogrel, Stratified by PPI Versus No PPI at Discharge

	Prasugrel vs Clopidogrel				Prasugrel vs Clopidogrel			
	PPI at Discharge				No PPI at Discharge			
	Overall (n=2167)	n=531	n=1636	*P* Value	Overall (n=9788)	n=2592	n=7196	*P* Value
Demographics								
Age	63 (55-70)	60 (52-66)	64 (56-72)	<0.0001	59 (51-67)	56 (49-63)	60 (52-69)	<0.0001
Male	65.9	74.0	63.3	<0.0001	73.4	79.4	71.3	<0.0001
White race	89.4	90.2	89.2	0.76	87.6	87.7	87.6	0.77
Past medical history								
Prior MI	24.5	17.7	26.7	<0.0001	18.4	13.9	20.0	<0.0001
Prior CABG	14.8	8.9	16.7	<0.0001	8.1	4.8	9.3	<0.0001
Prior PCI	28.1	23.0	29.7	0.0002	20.2	16.8	21.4	<0.0001
Prior stroke/TIA	7.7	2.3	9.5	<0.0001	4.9	1.8	6.0	<0.0001
Prior HF	10.0	6.6	11.1	0.0003	5.1	2.3	6.1	<0.0001
Prior AF/flutter	7.1	5.5	7.6	0.10	4.2	2.4	4.8	<0.0001
Hypertension	76.1	71.0	77.8	0.0008	64.8	59.5	66.7	<0.0001
Diabetes mellitus	32.4	26.0	34.5	0.0002	25.2	24.3	25.5	0.19
Dyslipidemia	73.1	68.7	74.5	0.007	63.9	60.6	65.1	<0.0001
GI/GU bleeding w/in last 6 months	2.4	1.3	2.8	0.06	0.8	0.7	0.8	0.77
ACTION Bleeding risk Score	26 (22-31)	24 (20-29)	27 (23-32)	<0.0001	25 (21-29)	24 (20-28)	25 (21-29)	<0.0001
Chronic lung disease	15.9	12.8	16.9	0.02	8.5	5.3	9.6	<0.0001
Admission features								
STEMI	45.7	51.2	43.9	0.003	53.1	60.2	50.5	<0.0001
Cardiogenic shock	2.5	1.7	2.7	0.19	2.0	2.7	1.8	0.005
BMI, kg/m^2	30 (26-34)	30 (27-34)	30 (26-34)	0.04	29 (26-33)	30 (27-34)	29 (26-33)	<0.0001
Heart rate, beats/min	76 (66-89)	75 (65-88)	77 (66-89)	0.10	76 (65-89)	77 (66-90)	76 (65-88)	0.001
Systolic BP, mm Hg	139 (120-157)	140 (122-159)	138 (120-156)	0.15	140 (121-159)	141 (123-160)	139 (121-158)	0.007
Hemoglobin, g/dL	14 (12-15)	14 (13-15)	14 (12-15)	<0.0001	14 (13-16)	15 (14-16)	14 (13-15)	<0.0001
Creatinine clearance*	65 (48-84)	73 (58-91)	62 (46-82)	<0.0001	75 (58-93)	80 (65-96)	72 (55-92)	<0.0001

Values presented in percentages (%) or median (interquartile range). ACTION indicates Acute Coronary Treatment and Intervention Outcomes Network; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; GI/GU, gastrointestinal/genitourinary; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.
*Creatinine clearance (mg/min per 1.73 m^2) calculated by Cockroft-Gault formula.

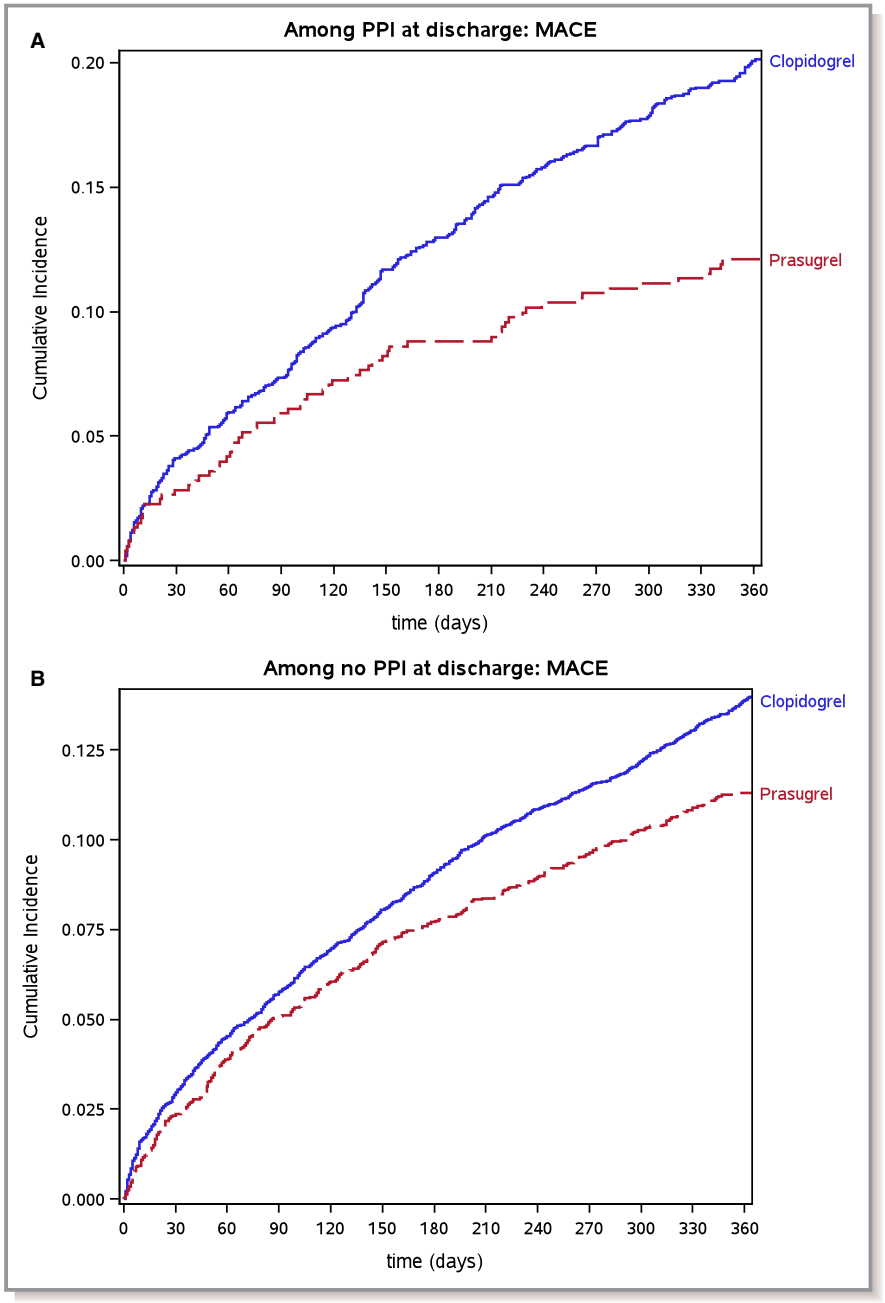

Figure 1. Unadjusted cumulative incidence of MACE. Unadjusted cumulative incidence of MACE among patients (A) on a PPI and (B) not on a PPI. MACE indicates major adverse cardiovascular event; PPI, proton pump inhibitor.

between prasugrel- and clopidogrel-treated patients who were discharged home without a PPI (24% vs 26%, P=0.19). Among patients discharged on triple antithrombotic therapy (n=606, 5.1%), 7.9% were discharged on a PPI compared to 4.4% who were not discharged on a PPI (P<0.0001). There was no significant difference in aspirin use at discharge and at 12 months among patients discharged on a PPI versus those who were not (discharge, 97.9% vs 98.3%, P<0.2; 12 months, 74.7% vs 72.8%, P=0.38).

PPI Use at Follow-Up

At 1 year postdischarge, PPI use overall was similar between patients discharged on prasugrel versus clopidogrel (16% vs 15%, P=0.38). Among patients discharged on a PPI, there was no significant difference in PPI use among patients discharged on prasugrel versus clopidogrel at 12 months (60% vs 61%, P=0.64). Similarly, among patients not discharged on a PPI, there was no significant difference in PPI use among patients

discharged on prasugrel versus clopidogrel at 12 months (5% vs 5%, *P*=0.55). There was no significant difference in adherence to either prasugrel or clopidogrel at 12 months between patients discharged on a PPI and those who were not discharged on a PPI (prasugrel, 74.7% vs 72.8%, *P*=0.38; clopidogrel, 84.1% vs 83.7%, *P*=0.74).

MACE and GUSTO Moderate/Severe Bleeding

At 1 year, the unadjusted MACE rate was higher among patients discharged on a PPI versus no PPI (18.2% vs 13.3%, *P*<0.0001). After multivariable adjustment, a higher risk of MACE persisted among patients discharged on a PPI (adjusted hazard ratio [HR] 1.38, 95% confidence interval [CI] 1.21-1.58). Similarly, higher unadjusted and adjusted risks of bleeding were observed for patients discharged on a PPI versus not (unadjusted 3.9% vs 2.3%, *P*<0.0001, adjusted HR 1.55, 95% CI 1.15-2.09).

Significant differences were observed in the unadjusted risk of MACE between the prasugrel and clopidogrel groups, irrespective of PPI use (Figure 1). Yet after risk adjustment, MACE risk was not significantly different between prasugrel and clopidogrel, and the relationship between $P2Y_{12}$ receptor inhibitor type and MACE was not altered by discharge PPI use (interaction *P*=0.31, Table 2).

The unadjusted risk of GUSTO moderate/severe bleeding was significantly lower among prasugrel- versus clopidogrel-treated patients, regardless of discharge PPI status (Figure 2); however, after risk adjustment, prasugrel was no longer associated with lower GUSTO moderate/severe bleeding risk when compared with clopidogrel in both PPI- and non–PPI-treated patients (adjusted HR 0.73, 95% CI 0.36-1.48 with PPI, adjusted HR 1.34, 95% CI 0.79-2.27 without PPI). The HR estimate changed direction, but the interaction *P*-value did not reach statistical significance (interaction *P*=0.17, Table 2).

Table 2. Comparative Effectiveness of Prasugrel Versus Clopidogrel for MACE and GUSTO Moderate/Severe Bleeding

	Cumulative Incidence		Adjusted HR (95% CI)	*P* Value for Interaction
MACE	Prasugrel	Clopidogrel		0.31
PPI	12.1%	20.2%	0.88 (0.62-1.26)	
No PPI	11.3%	14.0%	1.07 (0.90-1.28)	
GUSTO moderate/severe bleeding	Prasugrel	Clopidogrel		0.17
PPI	1.9%	4.6%	0.73 (0.36-1.48)	
No PPI	1.7%	2.5%	1.34 (0.79-2.27)	

CI indicates confidence interval; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; MACE, major adverse cardiovascular event; PPI, proton pump inhibitor.

Discussion

This large observational study compared the effectiveness and safety of prasugrel versus clopidogrel with and without concomitant administration of PPI among a large population of acute MI patients who underwent PCI. Our study has several notable findings. First, PPIs were prescribed in fewer than 1 in 5 post-MI patients in routine clinical practice. PPI prescription was typically reserved for those who were older, had a greater prevalence of medical comorbidities, and were more likely to present with NSTEMI. Second, even after multivariable adjustment, patients prescribed PPI use at discharge were associated with higher 1-year risks of MACE and GUSTO moderate/severe bleeding than those discharged without a PPI. Finally, the adjusted risk of MACE and GUSTO moderate/severe bleeding was not significantly different between prasugrel- and clopidogrel-treated patients, irrespective of PPI use.

An expert consensus statement has provided recommendations regarding the use of PPIs in the setting of DAPT based on the increased risk of bleeding, particularly gastrointestinal bleeding events.[3] Nevertheless, concerns that PPIs can lead to decreased antiplatelet effects when coadministered with clopidogrel have diminished enthusiasm for routine PPI use in the setting of DAPT.[11] Several studies have analyzed the pharmacokinetic and pharmacodynamic interaction of PPIs and $P2Y_{12}$ receptor inhibitors, including clopidogrel and prasugrel. Sibbing et al demonstrated a significant influence on platelet response to clopidogrel for the PPI omeprazole but not for pantoprazole or esomeprazole. Patients under concomitant treatment with clopidogrel and omeprazole demonstrated 30% higher values of adenosine diphosphate–induced platelet aggregation, presumably due to the dependence of CYP2C19 isoenzyme for the metabolism of both clopidogrel and omeprazole.[12] Similar results were demonstrated in the Omeprazole Clopidogrel Aspirin (OCLA) study in which omeprazole coadministration with clopidogrel led to a 30% increase in platelet function parameters.[13]

To date, many outcomes-based studies evaluating the interaction between PPIs and $P2Y_{12}$ receptor inhibitors have been nonrandomized, focused predominantly on clopidogrel, and have led to equivocal conclusions as to the effectiveness and safety of $P2Y_{12}$ receptor inhibitors when used concomitantly with PPIs. In a retrospective cohort of Veterans Affairs patients with acute coronary syndrome, Ho et al demonstrated that concomitant administration of clopidogrel and a PPI was associated with a 25% increase in all-cause mortality

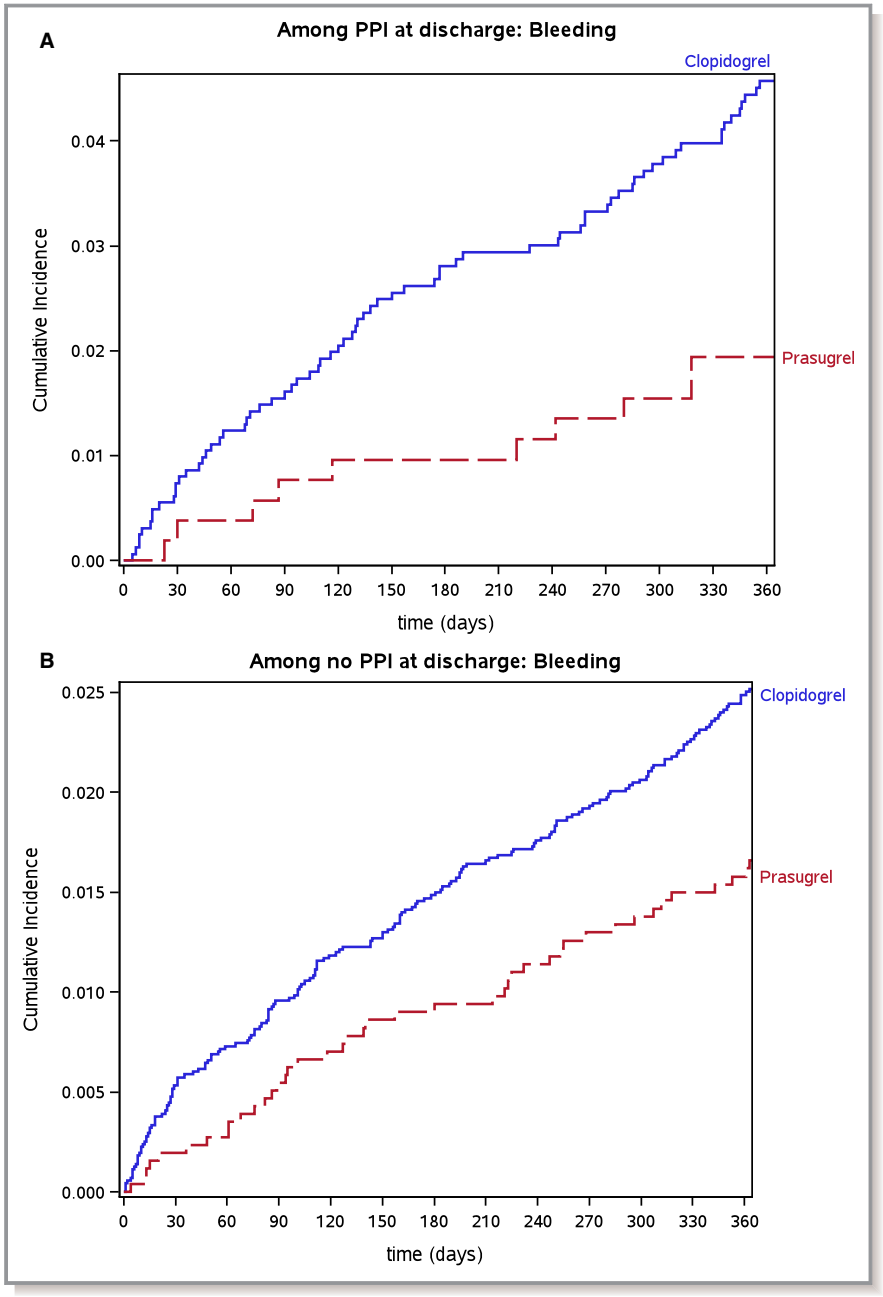

Figure 2. Unadjusted cumulative incidence of GUSTO moderate/severe bleeding. Unadjusted cumulative incidence of GUSTO moderate/severe bleeding among patients (A) on a PPI and (B) not on a PPI. GUSTO indicates Global Use of Strategies to Open Occluded Arteries; PPI, proton pump inhibitor.

or rehospitalization related to acute coronary syndrome.[4] In the randomized Clopidogrel and the Optimization of Gastrointestinal Events (COGENT-1) trial, patients on clopidogrel who were randomized to receive concomitant omeprazole had a substantially lower risk of gastrointestinal bleeding compared to placebo; however, this study was terminated prematurely because there was no apparent interaction between clopidogrel and omeprazole from the perspective of adverse cardiovascular endpoints.[14]

Our study demonstrates that in a large contemporary population of acute MI patients treated with PCI and DAPT, fewer than 1 in 5 patients were discharged home on a PPI. Our population was comprised of an older and more medically complex group of patients. This PPI use pattern suggests that providers are selectively prescribing PPIs and most likely prescribing them to patients at higher risk of bleeding in accordance with more recent recommendations.[3] Despite extensive adjustment for measured covariates, patients who

were discharged on a PPI had a significantly higher risk of MACE and GUSTO moderate/severe bleeding compared with those not discharged on a PPI.

Prasugrel is a more potent $P2Y_{12}$ receptor inhibitor with superior efficacy in reducing cardiovascular events when compared with clopidogrel, but its use is associated with increased bleeding.[2] To date, there are limited studies comparing the effectiveness and safety of prasugrel in the setting of PPI use with respect to adverse cardiovascular outcomes and bleeding. A secondary analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) demonstrated that although PPIs attenuated the platelet inhibitory effect of clopidogrel, PPI use was not associated with greater risk of cardiovascular death, MI, or stroke for patients treated with either prasugrel or clopidogrel.[2,6,15] In a post-hoc analysis of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial, Nicolau et al demonstrated that among acute coronary syndrome patients medically managed without revascularization, the use of PPIs did not result in a differential antiplatelet response between prasugrel and clopidogrel for the primary composite endpoint of cardiovascular death, MI, or stroke.[16]

Our study adds to existing literature by comparing outcomes between prasugrel- and clopidogrel-treated patients with and without concomitant PPI use in routine clinical practice among patients who underwent PCI. Once prescribed at discharge, PPIs are likely to be continued long-term, regardless of $P2Y_{12}$ receptor inhibitor type. We observed that prasugrel- and clopidogrel-treated patients had a similar adjusted risk of MACE, and this relationship was preserved irrespective of PPI use. These results suggest that the effectiveness of prasugrel and clopidogrel was not altered by PPI use in routine clinical practice.

From a bleeding perspective, prasugrel use was not associated with significantly different risk-adjusted GUSTO moderate/severe bleeding at 1 year compared with patients treated with clopidogrel. Nonetheless, the comparative bleeding risk associated with prasugrel versus clopidogrel appeared to differ based on PPI use (HR point estimate changed direction), but this difference did not reach statistical significance because HRs and the interaction term were not significant. This nonstatistical difference trend should be validated in future studies. Although our results do not favor the selection of any specific $P2Y_{12}$ receptor inhibitor in the setting of PPI use, the increased bleeding risk associated with higher-potency $P2Y_{12}$ receptor inhibitors compared with clopidogrel may be mitigated by judicious PPI use. Patients discharged on a PPI are at higher risk of MACE and bleeding despite adjustment of known confounders, which suggests that these patients have comorbidity profiles different from those not discharged on a PPI. Knowledge of this comorbidity profile, including a greater proclivity toward bleeding, may alter therapeutic decision making and/or vigilance for bleeding. Furthermore, this profile may explain the trends in bleeding outcomes seen in our analysis.

Several limitations need to be acknowledged in the interpretation of these data. First, this is a secondary analysis of TRANSLATE-ACS examining PPI subgroups; the primary analysis of TRANSLATE-ACS did not show overall effectiveness of prasugrel versus clopidogrel in routine clinical practice. Second, the $P2Y_{12}$ receptor inhibitor and the PPI were not selected in a randomized fashion and were left to the discretion of the treating physician. Third, indication for PPI treatment was not captured in the data collection form; therefore, despite rigorous multivariable adjustment, there remains the potential for residual unmeasured confounding. Fourth, because only 18% of the overall population was discharged on a PPI, this study is underpowered for comparisons between prasugrel and clopidogrel in the PPI-treated group. Finally, individual PPI types have variable interactions with the cytochrome P450 system, but the association of individual PPI types with outcomes could not be studied in this population.[17,18]

In conclusion, PPIs were used selectively in fewer than 20% of patients in this contemporary observational study of acute MI patients treated with PCI and either clopidogrel or prasugrel. PPIs were prescribed to patients with increased comorbid illness. Despite multivariable adjustment, significantly higher rates of 1-year MACE and GUSTO moderate/severe bleeding persisted among patients discharged on a PPI. The use of PPIs did not significantly affect the comparative effectiveness or bleeding risk of prasugrel versus clopidogrel. Our results support current recommendations regarding PPI use with DAPT.

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Disclosures

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Dr Zettler reports shareholding with Eli Lilly & Company. Dr Baker reports being an employee of Daiichi Sankyo, Inc. Dr Messenger reports no relevant disclosures. Dr Faries reports being a full-time employee of Eli Lilly and Company; minor shareholder in Eli Lilly and Company. Dr Effron reports employment from Eli Lilly and Company; shareholding with Lilly, USA. Dr Cohen reports research grant support from Eli Lilly, Daiichi Sankyo, Astra Zeneca; consulting fees from Eli Lilly and Astra Zeneca; and speaking honoraria from Eli Lilly and Astra Zeneca. Dr Wang reports research funding from AstraZeneca, Gilead, Lilly, The Medicines Company, and Canyon Pharmaceuticals (all significant); educational activities or lectures (generates money for Duke) for AstraZeneca (modest); consulting (including CME) for Medco (modest) and American College of Cardiology (significant). The remaining authors have no disclosures to report.

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Supplemental Material

Table S1. Standardized Difference between Prasugrel and Clopidogrel Patients by PPI Strata

Variable	Among PPI: SD		Among No PPI: SD	
	Before Weighting	After Weighting	Before Weighting	After Weighting
Age	-0.48	-0.08	-0.46	-0.03
Age ≥75 years	-0.49	-0.06	-0.43	-0.02
History of a-fib/flutter	-0.09	0.10	-0.13	-0.03
BMI	0.07	0.08	0.00	-0.01
BMS vs. other	-0.25	-0.09	-0.12	0.02
Chronic lung disease	-0.11	0.03	-0.17	0.02
Creatinine clearance	0.39	0.03	0.28	-0.01
Culprit lesion: bifurcation	0.11	0.05	0.03	-0.02
Culprit lesion in graft	-0.16	-0.09	-0.11	0.01
Dialysis	-0.16	-0.04	-0.07	0.01
EF	-0.03	-0.00	-0.03	0.00
DES vs. other	0.23	0.04	0.13	-0.03
Diabetes	-0.19	0.03	-0.03	0.04
Duke CAD index	-0.13	-0.01	-0.08	0.01
Dyslipidemia	-0.14	0.04	-0.10	0.02
Employed	0.38	0.03	0.31	0.01
EQ-5D VAS	0.14	0.04	0.02	-0.01
EQ-5D index U.S. weights	0.16	0.01	0.11	-0.03
Femoral access	-0.06	-0.06	-0.06	-0.01
GI/GU bleeding w/in last 6 months	-0.10	0.01	-0.01	0.04
Government vs. private insurance	-0.23	-0.00	-0.19	0.03
Hispanic	0.06	0.02	0.06	0.01
Heart rate	-0.09	-0.02	0.07	0.02
High school graduate	0.15	-0.02	0.10	-0.02
Hypertension	-0.17	0.01	-0.16	0.02
Number of lesions treated	-0.01	0.04	-0.05	-0.02
Left main disease (≥50%)	-0.10	0.00	-0.11	0.02
Married	0.20	-0.00	0.07	-0.02
Household income, per 5000 increase	0.19	0.04	0.10	-0.02
Home ADP	0.17	-0.05	0.15	-0.03
Home anticoagulation	-0.15	0.11	-0.19	-0.06
Home aspirin	-0.17	-0.04	-0.16	0.03
None/non-U.S. vs. private insurance	0.12	0.00	0.07	-0.01
Number of diseased vessels	-0.21	-0.03	-0.13	0.02
Pre-procedural hemoglobin (g/dL)	0.41	0.03	0.29	-0.01
HF w/in 2 weeks	-0.25	0.04	-0.15	0.04
Prior CABG	-0.24	-0.00	-0.18	0.01
Cardiac arrest w/in 24 hours	0.02	-0.02	0.06	-0.00
Cardiogenic shock w/in 24 hours	-0.07	-0.02	0.06	0.02

Prior CVD	-0.40	-0.04	-0.23	0.05
Prior HF	-0.16	0.02	-0.19	0.04
Prior MI	-0.22	-0.02	-0.16	0.04
History of PAD	-0.27	-0.06	-0.17	0.04
Prior PCI	-0.15	0.03	-0.12	0.06
Prior stroke or TIA	-0.31	-0.06	-0.22	0.03
Procedure success	0.09	-0.01	0.02	-0.02
Black race	-0.11	-0.00	-0.05	0.00
Other race	0.16	0.04	0.09	0.00
Current/recent smoker	0.08	0.02	0.06	0.00
Systolic BP	0.06	-0.01	0.06	0.02
Total lesion length	0.01	0.00	-0.00	0.00
Transfer in	-0.27	-0.07	-0.32	0.01
Troponin ratio over ULN	-0.09	-0.05	-0.00	-0.01
Weight <60 kg	-0.16	-0.06	-0.15	0.00
Male	0.23	-0.01	0.19	-0.02
STEMI	0.15	0.00	0.19	-0.01

ADP indicates adenosine diphosphate; BMI, body mass index; BMS, bare metal stent; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cerebrovascular disease; DES, drug-eluting stent; EF, ejection fraction; EQ-5D, EuroQOL five dimension; GI/GU, gastrointestinal/genitourinary; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; ULN, upper limit of normal; U.S., United States; VAS, visual analogue scale