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Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome

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Context Prior mechanistic studies reported that omeprazole decreases the platelet inhibitory effects of clopidogrel, yet the clinical significance of these findings is not clear.

Objective To assess outcomes of patients taking clopidogrel with or without a proton pump inhibitor (PPI) after hospitalization for acute coronary syndrome (ACS).

Design, Setting, and Patients Retrospective cohort study of 8205 patients with ACS taking clopidogrel after discharge from 127 Veterans Affairs hospitals between October 1, 2003, and January 31, 2006. Vital status information was available for all patients through September 30, 2006.

Main Outcome Measures All-cause mortality or rehospitalization for ACS.

Results Of 8205 patients taking clopidogrel after discharge, 63.9% (n=5244) were prescribed PPI at discharge, during follow-up, or both and 36.1% (n=2961) were not prescribed PPI. Death or rehospitalization for ACS occurred in 20.8% (n=615) of patients taking clopidogrel without PPI and 29.8% (n=1561) of patients taking clopidogrel plus PPI. In multivariable analyses, use of clopidogrel plus PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without PPI (adjusted odds ratio [AOR], 1.25; 95% confidence interval [CI], 1.11-1.41). Among patients taking clopidogrel after hospital discharge and prescribed PPI at any point during follow-up (n=5244), periods of use of clopidogrel plus PPI (compared with periods of use of clopidogrel without PPI) were associated with a higher risk of death or rehospitalization for ACS (adjusted hazard ratio, 1.27; 95% CI, 1.10-1.46). In analyses of secondary outcomes, patients taking clopidogrel plus PPI had a higher risk of hospitalizations for recurrent ACS compared with patients taking clopidogrel without PPI (14.6% vs 6.9%; AOR, 1.86 [95% CI, 1.57-2.20]) and revascularization procedures (15.5% vs 11.9%; AOR, 1.49 [95% CI, 1.30-1.71]), but not for all-cause mortality (19.9% vs 16.6%; AOR, 0.91 [95% CI, 0.80-1.05]). The association between use of clopidogrel plus PPI and increased risk of adverse outcomes also was consistent using a nested case-control study design (AOR, 1.32; 95% CI, 1.14-1.54). In addition, use of PPI without clopidogrel was not associated with death or rehospitalization for ACS among patients not taking clopidogrel after hospital discharge (n=6450) (AOR, 0.98; 95% CI, 0.85-1.13).

Conclusion Concomitant use of clopidogrel and PPI after hospital discharge for ACS was associated with an increased risk of adverse outcomes than use of clopidogrel without PPI, suggesting that use of PPI may be associated with attenuation of benefits of clopidogrel after ACS.

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TREATMENT WITH CLOPIDOGREL in addition to aspirin reduces recurrent cardiovascular events following hospitalization for acute coronary syndrome (ACS) for patients treated either medically or with percutaneous coronary intervention.[1-3] Proton pump inhibitor (PPI) medications are often prescribed prophylactically with initiation of clopidogrel, with the goal of reducing the risk of gastrointestinal tract bleeding while taking dual-antiplatelet therapy. Recent mechanistic studies, however, suggest that PPIs may reduce the inhibitory effect of clopidogrel on platelet aggregation.[4,5] In addition, variations in platelet reactivity have been associated with adverse outcomes following stent implantation.[6,7] These investigations open the question of whether the efficacy of clopidogrel is influenced by concomitant use of PPI medication.

To date, there remains significant ongoing controversy regarding the clinical outcomes of patients taking clopidogrel and PPIs.[8] The US Food and Drug Administration recently released an early communication about a safety review of the potential interaction between these 2 types of medications.[9] However, there were insufficient data to make any recommendations, and the Food and Drug Administration highlighted the need for

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additional studies to evaluate the effectiveness of clopidogrel when used concurrently with PPIs.

To address this gap in knowledge, we evaluated the prevalence of use of clopidogrel plus PPI following hospital discharge for ACS in a national Veterans Affairs (VA) cohort and compared rates of all-cause mortality and rehospitalization for ACS, including myocardial infarction (MI) and unstable angina, between patients taking clopidogrel plus PPI vs clopidogrel without PPI. Based on prior mechanistic data, we hypothesized that use of clopidogrel plus PPI would be associated with higher adverse events compared with use of clopidogrel without PPI.

METHODS

Data for this study were collected as part of the Cardiac Care Follow-up Clinical Study, which uses national data from the Veterans Health Administration (VHA) external peer review program for quality monitoring for a variety of medical conditions and procedures, including acute MI and unstable angina. Beginning in 2003, the records of all patients discharged from any VHA hospital with acute MI or unstable angina were manually abstracted using standard reporting forms as part of a national VA cardiac care initiative. Additional details of the study methods have been previously published.[10,11]

Patient Population

This was a retrospective cohort study of all patients with acute MI or unstable angina as documented by standard electrocardiographic criteria, elevated troponin levels, and other clinical evidence, discharged from any 1 of 127 VHA medical centers between October 1, 2003, and January 31, 2006, and prescribed clopidogrel at hospital discharge. During this period, 8790 patients with ACS were prescribed clopidogrel at hospital discharge based on chart documentation. Of these patients, 8205 patients (93.3%) filled a prescription for clopidogrel through the VA outpatient pharmacy.

Clopidogrel and PPI Use

Use of clopidogrel and PPI medications were based on pharmacy refill data, which records the date dispensed and the number of days supplied for each dispensed medication. Clopidogrel and PPI medications were considered available and taken if there was a prescription for the medication that covered the date of follow-up based on the dispense date and the number of days supplied.[10,11] In the primary analysis, we allowed a 7-day gap between prescription refills before a patient was considered to have discontinued the medication. In secondary analysis, we increased the gap to 14 days between prescription refills to categorize a patient as discontinuing a medication. The findings were consistent with the primary results and are not further reported.

Outcome

The primary outcome was the combined end point of all-cause mortality or rehospitalization for ACS (MI or unstable angina) following index hospital discharge for ACS. Secondary outcomes included (1) rehospitalization for ACS; (2) revascularization procedures, percutaneous coronary intervention, or coronary artery bypass graft surgery; and (3) all-cause mortality following index ACS hospitalization. The VA vital status file was used to assess the mortality outcome.[12,13] This file has 98.3% sensitivity and 97.6% exact agreement with dates when compared with the National Death Index.[12]

The ACS outcome was based on chart review consistent with the patient inclusion criteria using standard electrocardiographic criteria, elevated troponin levels, and/or other clinical evidence. Revascularization procedures were based on *International Classification of Diseases, Ninth Revision (ICD-9)* and Current Procedural Terminology codes for percutaneous coronary intervention or coronary artery bypass graft surgery performed within the VHA. Vital status information was available for all patients through September 30, 2006.

Statistical Methods

The primary analytic cohort consisted of patients taking clopidogrel at hospital discharge with or without a prescription for PPI medication at any point in time (ie, at hospital discharge or during follow-up) (n=8205). Baseline characteristics, ACS presentation, and treatment (including coronary revascularization), and unadjusted death or ACS outcomes were compared between patients prescribed clopidogrel with or without PPI. Multivariable logistic regression, adjusting for all variables in TABLE 1 (demographics, comorbidities, ACS presentation and treatment) assessed the association between taking PPI and adverse outcomes among patients taking clopidogrel after hospital discharge.

To further account for potential confounding × indication for PPI use, secondary analyses were performed that restricted the cohort to patients prescribed PPI at hospital discharge or during follow-up (n=5244).[14] Baseline characteristics, ACS presentation factors, and hospital treatment were compared between patients prescribed PPI at hospital discharge vs during follow-up. A time-varying analysis was used in which patients could have different categories of medication use over time: clopidogrel plus PPI, clopidogrel without PPI, PPI without clopidogrel, or no use of clopidogrel or PPI. This approach allowed comparison of the incidence of adverse events during periods of use of clopidogrel plus PPI vs use of clopidogrel without PPI. Survival time was measured from hospital discharge and censored at the end of follow-up. Unadjusted cumulative death and ACS rates were compared for the different categories of medication use during follow-up using the Aalen cumulative hazard method.[15] Multivariable Cox proportional hazard models evaluated the association between medication use as a time-varying covariate and outcomes. These models adjusted for all of the variables in Table 1 and the proportional hazards assumption was confirmed by the Schoenfeld residual test.[16]

To further assess the robustness of our findings, a series of sensitivity analyses was performed among patients taking clopidogrel after hospital discharge and prescribed PPI at any point in time. First, because patients with a history of gastrointestinal tract bleeding may be associated with both PPI use and adverse outcomes, patients with a history of gastrointestinal tract bleeding prior to the index hospitalization were excluded (n=414). Second, because bleeding events also may be associated with PPI use and adverse outcomes, patients with any bleeding events during the index hospitalization or after hospital discharge were excluded (n=1288). Third, patients who filled a H_2-antagonist prescription at anytime during follow-up were excluded because presence of these medications may indicate more severe gastrointestinal tract disease and higher rates of adverse outcomes (n=1547). Fourth, the clustering of patients within hospitals was accounted for in the Cox models.[17]

Next, to confirm the findings of the primary cohort analysis, a nested case-control study was performed to assess the association between medication use and outcomes among patients who were prescribed clopidogrel plus PPI at hospital discharge or during follow-up. When a death or ACS event occurred (1561 cases), 10 controls with the same duration of follow-up and without an event were matched with a case. Medication use with clopidogrel plus PPI, clopidogrel without PPI, PPI without clopidogrel, or neither of these medications at the time of an event was compared between cases and controls.[18] Conditional multivariable logistic regression assessed the association between medication use and outcomes, adjusting for all variables in Table 1.

In addition, the association between use of clopidogrel plus PPI compared with use of clopidogrel without PPI was assessed for the individual secondary outcomes of rehospitalization for ACS, revascularization procedures, and mortality. Moreover, among patients prescribed a PPI medication at some point, the dose of PPI medication prescribed and the duration of concomitant use of clopidogrel and PPI was examined to determine whether the intensity of treatment was associated with

Table 1. Baseline Characteristics of Patients Taking Clopidogrel After Hospital Discharge[a]

	Clopidogrel Without PPI (n = 2961)	Clopidogrel With PPI (n = 5244)	*P* Value	Clopidogrel With PPI		*P* Value
				During Follow-up (n = 1953)	At Discharge (n = 3291)	
Age, mean (SD), y	65.7 (11.7)	67.7 (11.4)	<.001	67.4 (11.4)	67.8 (11.3)	.21
Male sex	2928 (98.9)	5162 (98.4)	.10	1921 (98.4)	3241 (98.5)	.74
Diabetes	1126 (38.0)	2386 (45.5)	<.001	900 (46.1)	1486 (45.1)	.51
Prior myocardial infarction	594 (20.1)	1383 (26.4)	<.001	517 (26.5)	866 (26.3)	.90
PCI within last 6 mo	209 (7.1)	395 (7.5)	.59	148 (7.6)	247 (7.5)	.92
CABG surgery	587 (19.8)	1377 (26.3)	<.001	503 (25.8)	874 (26.6)	.52
Heart failure	477 (16.1)	1372 (26.2)	<.001	498 (25.5)	874 (26.6)	.40
Cerebrovascular disease	225 (7.6)	478 (9.1)	.02	195 (10.0)	283 (8.6)	.09
Peripheral vascular disease	481 (16.2)	1345 (25.6)	<.001	483 (24.7)	862 (26.2)	.24
Prior clopidogrel use	519 (17.5)	1379 (26.3)	<.001	474 (24.3)	905 (27.5)	.01
Cancer	166 (5.6)	382 (7.3)	<.01	135 (6.9)	247 (7.5)	.42
COPD	503 (17.0)	1346 (25.7)	<.001	454 (23.2)	892 (27.1)	.002
Renal disease	294 (9.9)	914 (17.4)	<.001	323 (16.5)	591 (18.0)	.19
Liver disease	70 (2.4)	181 (3.5)	<.01	64 (3.3)	117 (3.6)	.59
Dementia	301 (10.2)	726 (13.8)	<.001	261 (13.4)	465 (14.1)	.44
TIMI risk score, mean (SD)	2.8 (1.2)	2.9 (1.2)	<.001	2.9 (1.2)	2.9 (1.3)	.79
LVEF <40%	719 (24.3)	1395 (26.6)	.02	535 (27.4)	860 (26.1)	.32
ACS presentation						
STEMI	644 (21.7)	876 (16.7)	<.001	331 (16.9)	545 (16.6)	.43
NSTEMI	2036 (68.8)	3696 (70.5)		1358 (69.5)	2338 (71.0)	
PCI performed	1644 (55.5)	2427 (46.3)	<.001	902 (46.2)	1525 (46.3)	.91
CABG performed	75 (2.5)	137 (2.6)	.83	44 (2.3)	93 (2.8)	.21
Discharge medications						
Aspirin	2700 (91.2)	4687 (89.4)	.01	1736 (88.9)	2951 (89.7)	.57
β-Blocker	2747 (92.8)	4892 (93.3)	.64	1818 (93.1)	3074 (93.4)	.21
ACE inhibitor	2340 (79.0)	4114 (78.4)	.09	1531 (78.4)	2583 (78.5)	.84
Statin	2825 (95.4)	5031 (95.9)	.25	1875 (96.0)	3156 (95.9)	.85

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
[a]Values are expressed as number (percentage) unless otherwise indicated.

Table 2. Adverse Outcomes Following Hospital Discharge for Acute Coronary Syndrome (ACS)

Outcome	No. (%) of Events: Clopidogrel Without PPI (n = 2961)	No. (%) of Events: Clopidogrel With PPI (n = 5244)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Primary outcome				
Death or rehospitalization for ACS	615 (20.8)	1561 (29.8)	1.62 (1.45-1.80)	1.25 (1.11-1.41)
Secondary outcome				
Rehospitalization for ACS	205 (6.9)	764 (14.6)	2.29 (1.95-2.69)	1.86 (1.57-2.20)
Revascularization procedures	353 (11.9)	815 (15.5)	1.36 (1.19-1.55)	1.49 (1.30-1.71)
Death (all-cause)	493 (16.6)	1042 (19.9)	1.24 (1.10-1.40)	0.91 (0.80-1.05)

Abbreviations: CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitors.
[a]Adjusted for all variables in Table 1 except male sex.

adverse outcomes. For PPI dosing, omeprazole and rabeprazole were focused on because these were the 2 most commonly prescribed PPI medications and their dosage ranges were similar. In addition, among patients prescribed PPI, the association between the specific PPI medication and adverse outcomes was assessed.

To determine if use of PPI without clopidogrel was associated with adverse outcomes, cardiovascular events were also compared between patients with and without a PPI prescription who were not taking clopidogrel after hospital discharge. Demonstration of a lack of an association between PPI use and adverse outcomes in patients not taking clopidogrel would further support the conclusion that an interaction between PPI and clopidogrel is associated with adverse outcomes, rather than use of PPI itself. This analysis included 6450 patients with ACS, of whom 80.0% (n=5163) were prescribed PPI at hospital discharge or during follow-up and 20.0% (n=1287) were not prescribed PPI.

Based on the sample size of 8205 patients taking clopidogrel after discharge with or without PPI, the minimum detectable odds ratio (OR) with 80% power in a 2-sided test and an α level of .05 (based on an exposure prevalence of approximately 60% and event rate in the nonexposure group of 20%) was 1.17. Statistical analyses were conducted using Stata software version 10.0 (StataCorp, College Station, Texas). A waiver of informed consent was obtained for the Cardiac Care Follow-up Clinical Study, which was approved by the University of Washington Human Subjects Committee and the Colorado Multiple Institutional Review Board.

RESULTS

Of 8205 patients with ACS taking clopidogrel after hospital discharge, 63.9% (n=5244) were prescribed PPI at discharge, during follow-up, or both and 36.1% (n=2961) were not prescribed PPI. Patients taking clopidogrel after hospital discharge and prescribed PPI at any point in time were older and had more comorbid conditions (Table 1). Median follow-up after hospital discharge was 521 days (interquartile range, 305-779 days). Death or rehospitalization for ACS occurred in 20.8% (n=615) of patients prescribed clopidogrel without PPI and 29.8% (n=1561) of patients prescribed clopidogrel plus PPI. In multivariable analysis, use of clopidogrel plus PPI at any point in time was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without PPI (adjusted OR [AOR], 1.25; 95% confidence interval [CI], 1.11-1.41) (TABLE 2).

For the secondary outcomes, the rates of recurrent hospitalization for ACS (14.6% [n=764] vs 6.9% [n=205]; $P<.001$), revascularization procedures (15.5 [n=815] vs 11.9 [n=353]; $P<.001$), and death (19.9% [n=1042] vs 16.6% [n=493]; $P<.001$) were higher among patients taking clopidogrel plus PPI compared with those taking clopidogrel without PPI. In multivariable analyses, use of clopidogrel plus PPI remained significantly associated with a higher risk for recurrent ACS (AOR, 1.86; 95% CI, 1.57-2.20) and revascularization procedures (AOR, 1.49; 95% CI, 1.30-1.71) compared with use of clopidogrel without PPI; however, there was no association between use of clopidogrel plus PPI and all-cause mortality (AOR, 0.91; 95% CI, 0.80-1.05) compared with use of clopidogrel without PPI.

In the analyses restricting the cohort to patients filling PPI medications at hospital discharge (n=3291) or during follow-up (n=1953), baseline characteristics were similar between these 2 patient groups (Table 1). The cumulative incidence rates of death or rehospitalization for ACS after 1080 days of follow-up for the different medication exposure groups were 0.62 for use of neither clopidogrel nor PPI, 0.55 for use of PPI without clopidogrel, 0.47 for clopidogrel plus PPI, and 0.33 for clopidogrel without PPI. In multivariable analyses with medication use as a time-varying covariate, periods of use of clopidogrel without PPI were associated with a significantly lower risk of adverse events compared with periods without use of either clopidogrel or PPI ($P<.001$). However, this association appeared to be attenuated when comparing periods of use of clopidogrel plus PPI use with periods without use of either clopidogrel or PPI (FIGURE). Periods of clopidogrel plus PPI use were associated with a higher risk of death or rehospitalization for ACS compared with periods

of use of clopidogrel without PPI (adjusted hazard ratio [AHR], 1.27; 95% CI, 1.10-1.46) (TABLE 3).

The association between use of clopidogrel plus PPI and a higher risk of an adverse outcome compared with use of clopidogrel without PPI remained significant in the analysis excluding patients with a history of gastrointestinal tract bleeding prior to index hospitalization for ACS (AHR, 1.30; 95% CI, 1.11-1.51), excluding patients with a bleeding event during the index hospitalization or follow-up (AHR, 1.23; 95% CI, 1.04-1.45), and excluding patients with any H_2-antagonist prescription during follow-up (AHR, 1.21; 95% CI, 1.02-1.44) (Table 3). The results also were consistent after adjusting for the clustering of patients within hospitals. In the nested case-control study analysis, use of clopidogrel plus PPI remained associated with higher odds of death or rehospitalization for ACS compared with use of clopidogrel without PPI (AOR, 1.32; 95% CI, 1.14-1.54).

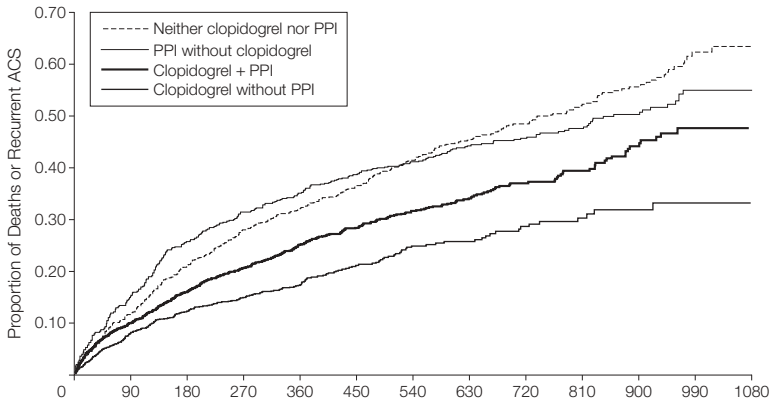
Among patients prescribed PPI at hospital discharge or during follow-up, 59.7% (n=3132) were prescribed omeprazole, 2.9% (n=151) were prescribed rabeprazole, 0.4% (n=22) were prescribed lansoprazole, 0.2% (n=15) were prescribed pantoprazole, and 36.7% (n=1924) were prescribed more than 1 type of PPI during follow-up. For patients prescribed omeprazole or rabeprazole, the mean (SD) dose daily was 26.5 (10.7) mg and the median dose was 20 mg (interquartile range, 20-33.3 mg). There was no obvious dose-response relationship between PPI dose and adverse outcomes (OR, 1.00; 95% CI, 0.99-1.01 for each 1-mg increment), with recognition of low variability in the dose range. However, each 10% increase in the proportion of time taking clopidogrel plus PPI during follow-up was associated with a higher risk of death or rehospitalization for ACS (OR, 1.07; 95% CI, 1.05-1.09). In evaluating individual PPI agents, there was a consistent association between omeprazole (OR, 1.24; 95% CI, 1.08-1.41) and rabeprazole (OR, 2.83; 95% CI, 1.96-4.09) with adverse outcomes. The association among the other PPIs (ie, lansoprazole and pantoprazole) was not explored given the small numbers of patients taking these medications.

Finally, whether a prescription for PPI was associated with an increased risk of death or rehospitalization for ACS among patients not taking clopidogrel after hospital discharge (n=6450) was examined. When patients were not taking clopidogrel after hospital discharge, a prescription for PPI was not associated with death or rehospitalization for ACS (AOR, 0.98; 95% CI, 0.85-1.13), supporting the hypothesis that the interaction of PPI and clopidogrel, rather than PPI itself, was associated with increased adverse outcomes.

COMMENT

To our knowledge, this is the first study to compare outcomes of patients taking clopidogrel without PPI with pa-

Figure. Cumulative Risk of All-Cause Mortality and Recurrent Acute Coronary Syndrome (ACS) Among Patients Taking Clopidogrel After Hospital Discharge for ACS and Prescribed a Proton Pump Inhibitor (PPI) at Hospital Discharge or During Follow-up (n=5244)



No. at risk							
Neither clopidogrel nor PPI	1223	1688	1531	1127	751	391	180
PPI without clopidogrel	1093	1223	1210	921	585	310	155
Clopidogrel without PPI	2425	1878	1179	620	362	147	78
Clopidogrel + PPI	3931	2490	1577	891	494	214	102

The number at risk indicates the number of individuals at risk for each period during the 90-day interval with medication use as the time-varying covariate. Because medication use is assessed as a time-varying covariate, the number of individuals at risk in each interval can increase over time as patients change categories of medication use.

Table 3. Risk of Death or Rehospitalization While Taking Clopidogrel and a Proton Pump Inhibitor (PPI) Following Hospital Discharge for Acute Coronary Syndrome

	No. of Patients	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Use of clopidogrel with PPI after hospital discharge or during follow-up[b]	5244	1.35 (1.18-1.56)	1.27 (1.10-1.46)
No history of gastrointestinal tract bleeding	4830	1.38 (1.19-1.61)	1.30 (1.11-1.51)
No gastrointestinal tract bleeding during index hospitalization or follow-up	3956	1.32 (1.13-1.56)	1.23 (1.04-1.45)
No H_2-antagonist prescription	3697	1.30 (1.09-1.54)	1.21 (1.02-1.44)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for all variables in Table 1 except male sex.
[b] Compared with periods of use of clopidogrel without PPI.

tients taking clopidogrel plus PPI in a national cohort of patients with ACS. We found that PPI medications were frequently prescribed with clopidogrel following hospitalization for ACS, and concomitant use of clopidogrel and PPI was associated with a higher risk of adverse outcomes than use of clopidogrel without PPI. The findings were consistent in various sensitivity analyses and using a nested case-control study method. In contrast, among patients who were not taking clopidogrel after hospital discharge, PPI use was not associated with adverse outcomes. These findings, coupled with prior mechanistic studies, suggest that concomitant use of clopidogrel and PPI may be associated with an attenuation of the benefits of clopidogrel after hospitalization for ACS.

Mechanistic and translational studies suggest a biological mechanism supporting the findings of this outcomes study. Prior platelet studies have demonstrated that PPIs reduce the antiplatelet effects of clopidogrel.[4,5] These medications share common metabolic pathways mediated by cytochrome P450 isoenzymes (ie, CYP2C19) in the liver.[19] Gilard et al[4] demonstrated that patients taking PPI following percutaneous coronary intervention and treatment with clopidogrel had less platelet inhibition compared with non-PPI users. These investigators randomized patients who were receiving dual-antiplatelet therapy to omeprazole or placebo following stent implantation and also found less platelet inhibition among patients randomized to omeprazole.[5]

In our study, we found a significant association between treatment with clopidogrel and PPI and the primary combined outcome of all-cause mortality and rehospitalization for ACS. In a sensitivity analysis of the secondary outcomes, it appears that this increased risk is primarily due to recurrent hospitalization for ACS, which is consistent with the hypothesized mechanism of a relatively prothrombotic state due to inhibition of the antiplatelet activity of clopidogrel by PPI medications. Approximately 60% of the patients that took PPI medications in this study were prescribed omeprazole, and there was a strong association between use of clopidogrel and omeprazole and adverse outcomes, directly supporting the platelet studies. While we found similar results with rabeprazole, the sample size was small and future studies should further assess whether this potential interaction occurs with rabeprazole as well as other PPI medications. We did not find a dose-response relationship between PPI medications and adverse outcomes, but this may be due to the small degree of variance in the prescribed PPI doses or that the usual prescribed doses of PPI medications fully inhibit the CYP2C19-mediated generation of the active clopidogrel metabolite. In contrast, we found that longer duration of treatment with clopidogrel plus PPI was associated with adverse outcomes, suggesting that time receiving the combination treatment is important. It is not known whether evidence for a similar interaction will be seen with other thienopyridine medications or how long it takes for the inhibitory effect of PPI medications to wear off once therapy is stopped. Future studies of platelet activity should explore these issues, which can then be addressed in subsequent clinical studies evaluating patient outcomes.

Additionally, several studies have demonstrated that a CYP2C19 gene polymorphism is associated with higher platelet aggregability, greater clopidogrel nonresponse, and an increased risk of cardiovascular events, which is similar to the antiplatelet inhibitory effects of PPIs on clopidogrel.[20-24] Both high platelet-activity levels and clopidogrel nonresponse have been associated with increased risk of adverse events following stent implantation.[6,7] Thus, prior studies suggest the hypothesis that an attenuation of the antiplatelet effects of clopidogrel by omeprazole could lead to adverse clinical outcomes by lessening the efficacy of clopidogrel. Our study takes the next step by providing epidemiological evidence consistent with an attenuation of the platelet inhibitory effects of clopidogrel by PPI medications in a national cohort of patients with ACS.

The results of this study, along with preliminary data reported by Aubert et al[25] that suggested an increased risk of nonfatal cardiovascular events with clopidogrel plus PPI highlight the need for additional investigation, ideally randomized controlled trials, to determine whether use of clopidogrel plus PPI is causally associated with increased risk of adverse outcomes compared with use of clopidogrel without PPI. In the meantime, however, this study raises some concern about concomitant use of PPI medications and clopidogrel following hospitalization for ACS. While the risk estimates associated with clopidogrel plus PPI vs clopidogrel without PPI were modest, the absolute number of adverse events attributable to this potential drug interaction is considerable when extrapolated to a population level, given how frequently PPI medications are prescribed to patients receiving dual-antiplatelet therapy. However, this epidemiological study cannot confirm a causal relationship, and cannot address the individual patient benefits of PPI therapy with clopidogrel after hospitalization for ACS. Pending additional evidence, however, the results of this study may suggest that PPIs should be used for patients with a clear indication for the medication, such as a history of gastrointestinal tract bleeding, consistent with current guideline recommendations, rather than routine prophylactic prescription.[3] Alternative gastrointestinal tract medication regimens also may be considered until additional data regarding concomitant use of PPI and clopidogrel becomes available.

There have been prior concerns of drug interactions involving clopidogrel. Specifically, mechanistic studies reported that atorvastatin attenuates the platelet inhibitory effects of clopidogrel likely due to common metabolic pathways.[26-29] However, subsequent epidemiological studies did not find differences in outcomes between pa-

tients prescribed clopidogrel with or without atorvastatin.[28,29] One potential limitation of the clopidogrel-atorvastatin epidemiological studies is that medication use was assessed at only 1 point in time and this can result in misclassification bias. In contrast, the current study included detailed pharmacy dispensing data to assess medication use over time. The assessment of medication use with a time-varying method does not assume that once a patient starts the medication it is continued indefinitely, and accounts for stops and restarts of the medication, reducing the likelihood of misclassification bias.[30] In addition, medication use based on pharmacy records has been correlated with a broad range of patient outcomes, and has been shown to be more accurate than patient self-report.[31-33] The current study also accounted for patient adherence behavior by allowing gaps between prescription refills of up to 14 days.[14]

There are important considerations in interpreting the results of this study. Since June 2003, the PPI omeprazole has been available over-the-counter and we were unable to determine over-the-counter use.[34] However, it is unlikely that many VA patients would pay out of pocket for such an over-the-counter medication that is available to them under the VA pharmacy benefits plan. Moreover, we would expect such use to occur more frequently in the group using clopidogrel without PPI, causing our results to be biased toward the null (ie, to be more conservative). Our cohort consisted primarily of male veterans and should be replicated in other cohorts. However, this was a real-world cohort from the largest integrated health care delivery system in the United States. Cause-specific mortality data were not available from VA data sources. Future studies should assess whether patients taking clopidogrel plus PPI have an increased risk of cardiovascular-related mortality to further support the mechanistic platelet studies and results of this study. Also, data on recurrent ACS or revascularization events outside the VHA were not available unless patients were transferred to a VA hospital. However, it is anticipated that recurrent hospitalizations or procedures outside the VA would tend to bias the results toward the null. Next, follow-up for our study ended in 2006, however, neither clopidogrel nor the PPI medications that we evaluated have changed since that time and there is no a priori reason to hypothesize that the association would change over time.

In addition, there are inherent limitations with an observational study design, and we cannot conclude causality or exclude unmeasured confounding as a contributor to the observed association. For example, (1) a prescription for PPI may be a marker of more severe comorbid conditions that may be associated with adverse outcomes; (2) patients receiving PPI may have more epigastric or atypical chest pain leading to a PPI prescription; or (3) PPI medications may have a negative inotropic effect on the myocardium.[35] However, we performed a series of sensitivity analyses, including restriction of the cohort to only those patients who had a PPI prescription at hospital discharge or during follow-up to reduce the potential medication indication bias, and adjusted for a wide range of potential confounders. Further, a PPI prescription without clopidogrel was not associated with adverse outcomes. Thus, the results of this study support the hypothesis of an inhibitory effect of PPI medications on clopidogrel.

In conclusion, this study found that concomitant use of clopidogrel and PPI after rehospitalization for ACS is associated with a higher risk of adverse outcomes compared with clopidogrel use without PPI. These findings, coupled with prior mechanistic studies, suggest that concomitant PPI use may attenuate the benefits of clopidogrel use after ACS. Pending further studies to confirm these results and prospectively assess cardiovascular outcomes for patients taking clopidogrel plus PPI vs clopidogrel without PPI, the results of this study may suggest that PPIs should be used for patients with a clear indication for the medication, rather than routine prophylactic prescription.

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