Risk of Rehospitalization for Patients Using Clopidogrel With a Proton Pump Inhibitor

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Background: Recent pharmacodynamic and retrospective clinical analyses have suggested that proton pump inhibitors (PPIs) may modify the antiplatelet effects of clopidogrel bisulfate.

Methods: We conducted a retrospective cohort study of persons enrolled in a multistate health insurance plan with commercial and Medicare clients to evaluate adverse clinical outcomes in patients using clopidogrel plus a PPI compared with clopidogrel alone. Patients who were discharged from the hospital after myocardial infarction (MI) or coronary stent placement and treated with clopidogrel plus a PPI (n = 1033) were matched 1:1 (using propensity scoring) with patients with similar cardiovascular risk factors treated with clopidogrel alone. Rehospitalizations for MI or coronary stent placement were evaluated for up to 360 days. A subanalysis was conducted to study the impact of pantoprazole sodium, the most used PPI.

Results: Patients who received clopidogrel plus a PPI had a 93% higher risk of rehospitalization for MI (adjusted hazard ratio, 1.93; 95% confidence interval, 1.05-3.54; $P = .03$) and a 64% higher risk of rehospitalization for MI or coronary stent placement (1.64; 1.16-2.32; $P = .005$) than did patients receiving clopidogrel alone. Increased risk of rehospitalization for MI or coronary stent placement was also observed for the subgroup of patients receiving clopidogrel plus pantoprazole (adjusted hazard ratio, 1.91; 95% confidence interval, 1.19-3.06; $P = .008$).

Conclusions: Patients who received clopidogrel plus a PPI had a significantly higher risk of rehospitalization for MI or coronary stent placement than did patients receiving clopidogrel alone. Prospective clinical trials and laboratory analyses of biochemical interactions are warranted to further evaluate the potential impact of PPIs on the efficacy of clopidogrel.

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ALTHOUGH PROTON PUMP INhibitor (PPI) medications are widely used to reduce the risk of gastrointestinal bleeding in patients receiving clopidogrel bisulfate, results of recent pharmacodynamic studies[1,2] have indicated that using a PPI with clopidogrel may reduce the efficacy of clopidogrel. In the Omeprazole Clopidogrel Aspirin study,[2] patients undergoing coronary stent placement receiving clopidogrel and aspirin combined with omeprazole had a higher platelet reactivity index value at the end of the 7-day treatment period than did patients taking clopidogrel and aspirin with placebo (51.4% vs 39.8%, $P < .001$). The investigators theorized that the reduced action of clopidogrel may be due to competitive metabolic effects of the PPIs on CYP2C19, one of the isoenzyme determinants of the pharmacodynamic response to clopidogrel.

Several retrospective evaluations have been conducted to gain a better understanding of whether the findings from this physiologic study translate to adverse clinical outcomes. A subanalysis of data from the Clopidogrel for Reduction of Events During Observation trial found that clopidogrel therapy reduced adverse events to a similar degree regardless of PPI use. Irrespective of clopidogrel use, patients treated with PPIs had higher baseline risk and worse cardiovascular outcomes than did patients not receiving PPIs.[3] In contrast, retrospective studies[4-7] have suggested higher rates of acute cardiovascular events in patients taking clopidogrel with PPIs vs patients taking clopidogrel alone. A retrospective cohort study[6] of patients taking clopidogrel who were discharged from Veterans Affairs hospitals with acute coronary syndrome found that periods of use of PPIs were associated with increased risk of death or rehospitaliza-

tion for acute coronary syndrome (adjusted hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.10-1.46). These past retrospective analyses were limited by the fact that patients receiving PPIs had a greater number of cardiovascular risk factors and comorbidities compared with patients using clopidogrel alone. Although the results were adjusted for differences in cardiovascular risk factors, this statistical adjustment may not have been adequate to control for unmeasured baseline differences between the 2 treatment groups. In addition, previous studies involved limited patient populations (ie, commercial insurance–only, elderly-only, and Veterans Affairs populations).

To further examine the potential for adverse clinical outcomes with combined clopidogrel and PPI therapy, we conducted a retrospective claims data analysis to measure the rate of rehospitalization in patients treated with clopidogrel and a PPI after coronary stent placement or after myocardial infarction (MI) compared with patients treated with clopidogrel alone. This study differs from previously conducted studies because we used propensity scoring to match patients according to their baseline cardiovascular risk factors in an effort to obtain more comparable patients across treatment groups. In addition, we used a more diverse patient population of commercial and Medicare members of a managed care organization. We hypothesized that patients taking clopidogrel plus a PPI would have a higher risk of rehospitalization for MI or a coronary stent procedure than would patients with similar baseline cardiovascular risk factors taking clopidogrel alone.

METHODS

This was a retrospective cohort study using electronic pharmacy and medical claims from commercial and Medicare members enrolled in a health insurance plan based in the western United States with annual membership of 1.9 to 2.1 million covered lives. The study was reviewed by an external institutional review board (Independent Review Consulting, Inc, Corte Madera, California) and received a determination that the research did not involve human subjects because limited data sets without patient identifiers were used for the analysis.

Patients 18 through 84 years of age were eligible for evaluation if they had filled a prescription for clopidogrel during the identification period (January 1, 2004, through December 31, 2006) and had an inpatient hospitalization with a primary diagnosis code for acute MI (*International Classification of Diseases, Ninth Revision,* diagnostic code 410.xx)[8] or a procedure code for coronary stent placement during the 30 days before the identification (index) date. Codes used to identify coronary stent placement procedures were *International Classification of Diseases, Ninth Revision,* procedure codes 36.06 and 36.07; *Current Procedural Terminology* codes 92980 and 92981[9]; and Healthcare Common Procedural Coding System codes G0290 and G0291.[10] Patients were also required to be continuously enrolled in the health plan during the 180 days before the index date (preperiod). Patients were excluded from the analysis if during the preperiod they filled a prescription for clopidogrel or had a diagnosis code representing renal disease, renal failure, liver failure, abnormality of secretion of gastrin, gastroesophageal reflux disease, *Helicobacter pylori*, or gastric, duodenal, peptic, or gastrojejunal ulcer.

Additional criteria were applied to identify 2 study cohorts (clopidogrel alone and clopidogrel plus a PPI) based on patients' PPI prescription fill records during the 90 days before and after the index date. The clopidogrel alone cohort consisted of patients who did not fill a prescription for a PPI during the 90 days before or the 90 days after the index date. Patients were identified for the clopidogrel plus PPI group if they filled a prescription for a PPI with an overlapping day's supply with the index date and they had at least 1 refill of the PPI during the 90 days after the index date.

Patients in the clopidogrel alone cohort were matched 1:1 with patients in the clopidogrel plus PPI cohort using the propensity scoring method.[11] Propensity scoring matching is a method for correcting for potential selection bias by balancing covariates between 2 groups of patients.[12] A propensity score, which represents the likelihood of receiving clopidogrel plus a PPI, was determined for each patient using logistic regression analysis. Patients were matched based on their propensity score. Covariates included in the propensity scoring model were age, sex, health plan type (Medicare vs commercial), geographical state, Charlson comorbidity index score[13] (calculated during the preperiod using the method described by Deyo et al[14]), preperiod hospitalization for a coronary stent procedure, and preperiod hospitalization, emergency department visit, or 2 or more outpatient claims for MI, other ischemic heart disease (including angina, ischemic heart disease, and atherosclerosis), stroke, other cerebrovascular disease, heart failure, hypertension, and diabetes mellitus. Patients without an identified match were excluded from the analysis. Only 8 patients in the clopidogrel plus PPI group were excluded owing to failure to find a match.

Matched patients were followed up from the identification date until the first occurrence of 1 of the following: (1) patient disenrolled from the health plan; (2) patient reached the end of the 360-day follow-up period; (3) patient discontinued clopidogrel use (defined as a gap of ≥30 days past the end of the supply date for the last prescription for clopidogrel); (4) patient in the clopidogrel plus PPI group discontinued PPI therapy (defined as a gap of ≥30 days past the end of the supply date for the last prescription for a PPI); (5) patient in the clopidogrel alone group filled a prescription for a PPI; or (6) patient experienced a rehospitalization event. Two different rehospitalization event definitions were examined: (1) a hospitalization with a primary diagnosis code of acute MI and (2) a hospitalization with a primary diagnosis code of acute MI or a procedure code for coronary stent placement.

A subanalysis was conducted to determine whether there was a differential effect on risk for pantoprazole sodium, the most used PPI in this population. Patients in the clopidogrel plus PPI group who were using pantoprazole on the index date were compared with their matched pairs from the clopidogrel alone group. Patients were followed up until the first occurrence of any of the events included in the main analysis or until a patient in the clopidogrel plus pantoprazole group filled a prescription for a PPI other than pantoprazole.

Means were compared using paired *t* tests, and percentages were compared using the McNemar test for binary variables and the Bowker test for variables with more than 2 categories. Cox proportional hazards regression analysis stratified on matched pairs was conducted to estimate the relative risk of rehospitalization for patients receiving clopidogrel plus PPI vs patients receiving clopidogrel alone. Separate regression analyses were conducted for the outcome of MI hospitalization and for the outcome of MI or coronary stent procedure hospitalization. Baseline statistically significant differences in demographic and clinical characteristics between the cohorts were adjusted for in the proportional hazards regression analysis. For each regression analysis, the Wald proportionality test was used to verify that the data were consistent with the proportional hazards assumption. All com-

Table 1. Baseline Demographic and Clinical Characteristics of Patients Receiving PPI and Matched Controls

Characteristic	Patients Identified Before Matching		Patients in the Final Matched Cohorts		
	Clopidogrel Plus PPI (n=1041)	Clopidogrel Alone (n=6008)	Clopidogrel Plus PPI (n=1033)	Clopidogrel Alone (n=1033)	*P* Value[a]
Age, mean (SD), y	69.2 (10.9)	68.7 (10.8)	69.2 (10.9)	68.9 (11.0)	.47
Male sex, No. (%)	590 (56.7)	3932 (65.4)	588 (56.9)	573 (55.5)	.40
Medicare health plan, No. (%)	671 (64.5)	3952 (65.8)	663 (64.2)	650 (62.9)	.48
Geographical state, No. (%)					
California	764 (73.4)	4058 (67.5)	757 (73.3)	790 (76.5)	
Texas	155 (14.9)	1043 (17.4)	154 (14.9)	149 (14.4)	
Oklahoma	57 (5.5)	360 (6.0)	57 (5.5)	42 (4.1)	.24
Washington	37 (3.6)	343 (5.7)	37 (3.6)	33 (3.2)	
Oregon	28 (2.7)	204 (3.4)	28 (2.7)	19 (1.8)	
Charlson comorbidity index score, No. (%)					
0	114 (11.0)	947 (15.8)	114 (11.0)	133 (12.9)	
1	304 (29.2)	2051 (34.1)	304 (29.4)	327 (31.7)	
2	254 (24.4)	1394 (23.2)	254 (24.6)	261 (25.3)	.04
≥3	369 (35.5)	1616 (26.9)	361 (35.0)	312 (30.2)	
Mean (SD)	2.31 (1.85)	1.90 (1.66)	2.28 (1.81)	2.13 (1.85)	
Preperiod history of hospitalization, No. (%)					
Coronary stent procedure	829 (79.6)	5134 (85.5)	825 (79.9)	827 (80.1)	.90
Myocardial infarction	560 (53.8)	2803 (46.7)	554 (53.6)	546 (52.9)	.66
Other ischemic heart disease	520 (50.0)	3438 (57.2)	518 (50.1)	533 (51.6)	.42
Stroke	6 (0.6)	17 (0.3)	4 (0.4)	8 (0.8)	.25
Other cerebrovascular disease	10 (1.0)	35 (0.6)	9 (0.9)	8 (0.8)	.81
Heart failure	27 (2.6)	161 (2.7)	27 (2.6)	18 (1.7)	.17
Hypertension	10 (1.0)	60 (1.0)	10 (1.0)	5 (0.5)	.20
Diabetes mellitus	8 (0.8)	32 (0.5)	8 (0.8)	7 (0.7)	.80
Preperiod history of emergency department visit, No. (%)					
Myocardial infarction	265 (25.5)	1274 (21.2)	260 (25.2)	262 (25.4)	.91
Other ischemic heart disease	120 (11.5)	681 (11.3)	120 (11.6)	122 (11.8)	.88
Stroke	5 (0.5)	14 (0.2)	3 (0.3)	6 (0.6)	.32
Other cerebrovascular disease	9 (0.9)	37 (0.6)	9 (0.9)	8 (0.8)	.80
Heart failure	39 (3.8)	170 (2.8)	38 (3.7)	31 (3.0)	.38
Hypertension	12 (1.2)	38 (0.6)	11 (1.1)	9 (0.9)	.65
Diabetes mellitus	9 (0.9)	19 (0.3)	6 (0.6)	3 (0.3)	.26
Preperiod history of 2 outpatient claims, No. (%)					
Myocardial infarction	82 (7.9)	303 (5.0)	81 (7.8)	75 (7.3)	.60
Other ischemic heart disease	296 (28.4)	2040 (34.0)	294 (28.5)	286 (27.7)	.63
Stroke	4 (0.4)	5 (0.1)	1 (0.1)	4 (0.4)	.18
Other cerebrovascular disease	35 (3.4)	134 (2.2)	31 (3.0)	32 (3.1)	.90
Heart failure	67 (6.4)	294 (4.9)	66 (6.4)	57 (5.5)	.39
Hypertension	349 (33.5)	1960 (32.6)	344 (33.3)	321 (31.1)	.23
Diabetes mellitus	213 (20.5)	1145 (19.1)	208 (20.1)	205 (19.9)	.86

Abbreviation: PPI, proton pump inhibitor.
[a] *P* values for the comparison between the final matched clopidogrel plus PPI and clopidogrel alone cohorts.

parisons were 2-sided and were performed at an α level of .05 to be considered significant. Data extraction and analyses were conducted using a commercial software package (SAS version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

A total of 6008 patients met the criteria for the clopidogrel alone group, and 1041 patients met the criteria for the clopidogrel plus PPI group (**Table 1**). The *C* statistic for the propensity score model was 0.61. Only 8 patients (<1%) in the clopidogrel plus PPI group were eliminated through matching, resulting in 1033 patients in each matched cohort. After eliminating the 4975 clopidogrel alone patients who were not matched with a clopidogrel plus PPI patient, the final clopidogrel alone population had a lower percentage of male patients (55.5% vs 65.5%), a different geographical distribution, and a higher mean Charlson comorbidity index score (2.13 vs 1.90) vs the clopidogrel alone patients identified before matching. The final matched clopidogrel plus PPI and clopidogrel alone cohorts were similar in terms of demographics and preperiod cardiovascular medical history; however, the distribution of the Charlson comorbidity index scores was different between the groups (*P*=.04), with a higher mean score in the clopidogrel plus PPI group. Mean participant age was 69.1 years, and 56.2% of patients were male.

In the clopidogrel plus PPI cohort, the number (and percentage) of patients using each PPI medication on the index date was 659 (63.8%) for pantoprazole, 159 (15.4%) for rabeprazole sodium, 86 (8.3%) for omeprazole, 83 (8.0%) for lansoprazole, and 46 (4.5%) for esomeprazole magnesium.

Table 2. Rehospitalization Rates and Risk of Rehospitalization in Patients Receiving PPI and Matched Controls

Characteristic	Clopidogrel Plus PPI (N=1033)	Clopidogrel Alone (N=1033)	Relative Risk for Clopidogrel Plus PPI vs Clopidogrel Alone			
			HR (95% CI)	*P* Value	Adjusted HR (95% CI)[a]	*P* Value
Hospital for myocardial infarction						
No. of patients with an event	36	22				
Total No. of person-years of follow-up	372.5	532.0	1.94 (1.06-3.54)	.03	1.93 (1.05-3.54)	.03
No. of events per 100 person-years	9.7	4.1				
Hospitalization for myocardial infarction or coronary stent procedure						
No. of patients with an event	97	72				
Total No. of person-years of follow-up	351.1	503.8	1.64 (1.16-2.31)	.005	1.64 (1.16-2.32)	.005
No. of events per 100 person-years	27.6	14.3				

Abbreviations: CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor.
[a] Adjusted for Charlson comorbidity index score.

Rehospitalization due to MI occurred at a rate of 9.7 events per 100 person-years for the clopidogrel plus PPI cohort compared with 4.1 events per 100 person-years in the clopidogrel alone cohort (adjusted HR, 1.93; 95% CI, 1.05-3.54, *P*=.03) (**Table 2**). Event rates were higher for the outcome of rehospitalization due to MI or a coronary stent procedure; the clopidogrel plus PPI cohort experienced 27.6 events per 100 person-years, and the clopidogrel alone cohort experienced 14.3 events per 100 person-years (adjusted HR, 1.64; 95% CI, 1.16-2.32; *P*=.005).

For the pantoprazole subanalysis, 659 patients receiving clopidogrel plus pantoprazole were compared with their matched pairs receiving clopidogrel alone (**Table 3**). Baseline characteristics were similar for the clopidogrel plus pantoprazole and clopidogrel alone groups except for the groups having a different distribution of geographical state locations (*P*=.03) and Charlson comorbidity index scores (*P*=.04). In addition, the clopidogrel plus pantoprazole group had a lower percentage of patients with a preperiod hospitalization for other ischemic heart disease (46.3% vs 52.4%, *P*=.008) and a higher percentage of patients with a preperiod history of 2 outpatient medical claims for heart failure (7.4% vs 4.6%, *P*=.02).

Rates of rehospitalization for MI and for MI or a coronary stent procedure were higher for the clopidogrel plus pantoprazole group compared with the clopidogrel alone group (**Table 4**). After adjusting for baseline differences between the clopidogrel plus pantoprazole and clopidogrel alone cohorts, there were not enough rehospitalization events for the outcome of rehospitalization for MI to show a significant difference between the 2 cohorts (adjusted HR, 2.18; 95% CI, 0.88-5.39; *P*=.09). However, for the outcome of rehospitalization for MI or coronary stent placement, patients receiving clopidogrel plus pantoprazole had a significantly higher risk than did patients receiving clopidogrel alone (adjusted HR, 1.91; 95% CI, 1.19-3.06; *P*=.008).

COMMENT

In this analysis of a large cohort of commercially insured and Medicare patients in the western United States, patients previously hospitalized for a coronary stent procedure or MI who were treated with clopidogrel plus a PPI had a significantly higher risk of rehospitalization than did patients treated with clopidogrel alone (a 93% higher risk of rehospitalization due to MI alone and a 64% higher risk of rehospitalization due to MI or a coronary stent procedure). Although the findings are consistent with several previous retrospective cohort studies[4-6] that noted a higher risk of adverse clinical events in patients treated with clopidogrel plus a PPI compared with patients treated with clopidogrel alone, this study adds to the literature because we used a more representative population (including women and patients older than 65 years) and we matched PPI users with patients with similar demographic and cardiovascular risk histories who were not taking a PPI.

With a large percentage (63.8%) of patients using pantoprazole in the clopidogrel plus PPI group, this study contributes additional information because a previously published retrospective cohort study[6] evaluated a population where omeprazole was the predominant PPI used. The finding that patients receiving pantoprazole with clopidogrel had a significantly higher risk of rehospitalization for MI or coronary stent placement than did those receiving clopidogel alone suggests that the potential interaction between PPIs and clopidogrel is not specific to omeprazole. Although these results may seem to contradict a population-based nested case-control study that did not find an association between use of pantoprazole and loss of beneficial effects of clopidogrel,[7] this other study may have had too small of a sample of events (46 cases) among pantoprazole users to detect differences between cases and controls. In addition, because cases and controls were matched for the overall study population, the subpopulation of pantoprazole users was not necessarily equally matched with controls.

The present findings regarding pantoprazole also raise questions about the potential mechanism of a drug-drug interaction between PPIs and clopidogrel. Laboratory studies have suggested that pantoprazole may have less potential to interact with clopidogrel than do other PPIs. A study[15] evaluating the inhibitory effects of PPIs on cytochrome P450 activity found that pantoprazole has lower inhibition potency on CYP2C19 than do lansoprazole, omeprazole, and esomeprazole. Furthermore, a

Table 3. Baseline Demographic and Clinical Characteristics of Patients Receiving Pantoprazole and Matched Controls

Characteristic	Clopidogrel Plus Pantoprazole (n=659)	Clopidogrel Alone (n=659)	*P* Value
Age, mean (SD), y	69.6 (11.0)	69.2 (10.8)	.43
Male sex, No. (%)	367 (55.7)	362 (54.9)	.73
Medicare health plan, No. (%)	440 (66.8)	421 (63.9)	.21
Geographical state, No. (%)			
California	481 (73.0)	509 (77.2)	
Texas	94 (14.3)	103 (15.6)	
Oklahoma	39 (5.9)	22 (3.3)	.03
Washington	23 (3.5)	17 (2.6)	
Oregon	22 (3.3)	8 (1.2)	
Charlson comorbidity index score, No. (%)			
0	62 (9.4)	80 (12.1)	
1	182 (27.6)	200 (30.4)	
2	175 (26.6)	160 (24.3)	.04
≥3	240 (36.4)	219 (33.2)	
Mean (SD)	2.40 (1.86)	2.23 (1.92)	
Preperiod history of hospitalization, No. (%)			
Coronary stent procedure	521 (79.1)	523 (79.4)	.88
Myocardial infarction	380 (57.7)	353 (53.6)	.06
Other ischemic heart disease	305 (46.3)	345 (52.4)	.008
Stroke	2 (0.3)	6 (0.9)	.16
Other cerebrovascular disease	6 (0.9)	6 (0.9)	>.99
Heart failure	16 (2.4)	8 (1.2)	.09
Hypertension	9 (1.4)	4 (0.6)	.17
Diabetes mellitus	5 (0.8)	6 (0.9)	.76
Preperiod history of emergency department visit, No. (%)			
Myocardial infarction	171 (26.0)	162 (24.6)	.50
Other ischemic heart disease	76 (11.5)	82 (12.4)	.58
Stroke	1 (0.2)	4 (0.6)	.18
Other cerebrovascular disease	7 (1.1)	4 (0.6)	.32
Heart failure	26 (4.0)	18 (2.7)	.19
Hypertension	7 (1.1)	7 (1.1)	>.99
Diabetes mellitus	5 (0.8)	3 (0.5)	.41
Preperiod history of 2 outpatient claims, No. (%)			
Myocardial infarction	58 (8.8)	49 (7.4)	.34
Other ischemic heart disease	172 (26.1)	170 (25.8)	.88
Stroke	1 (0.2)	4 (0.6)	.18
Other cerebrovascular disease	20 (3.0)	22 (3.3)	.75
Heart failure	49 (7.4)	30 (4.6)	.02
Hypertension	218 (33.1)	203 (30.8)	.32
Diabetes mellitus	128 (19.4)	133 (20.2)	.72

Table 4. Rehospitalization Rates and Risk of Rehospitalization in Patients Receiving Pantoprazole and Matched Controls

Characteristic	Clopidogrel Plus Pantoprazole (N=659)	Clopidogrel Alone (N=659)	Relative Risk for Clopidogrel Plus Pantoprazole vs Clopidogrel Alone			
			HR (95% CI)	*P* Value	Adjusted HR (95% CI)[a]	*P* Value
Hospital for myocardial infarction						
No. of patients with an event	23	15				
Total No. of person-years of follow-up	209.0	335.5	2.10 (0.99-4.46)	.05	2.18 (0.88-5.39)	.09
No. of events per 100 person-years	11.0	4.5				
Hospitalization for myocardial infarction or coronary stent procedure						
No. of patients with an event	66	45				
Total No. of person-years of follow-up	195.4	318.8	1.90 (1.23-2.94)	.004	1.91 (1.19-3.06)	.008
No. of events per 100 person-years	33.8	14.1				

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for Charlson comorbidity index score, geographical state, preperiod hospitalization for other ischemic heart disease, and preperiod history of 2 outpatient medical claims for heart failure.

mechanistic study measuring the platelet reactivity index for patients taking clopidogrel with pantoprazole, esomeprazole, or no PPI found that use of pantoprazole or esomeprazole was not associated with impaired response to clopidogrel.[16] Because the pantoprazole results from this clinical outcomes study differ from previous laboratory and mechanistic study results, additional research is necessary to evaluate the potential mechanism of the PPI-clopidogrel interaction and the specific effects of individual PPI medications on the efficacy of clopidogrel.

As support for a potential drug-drug interaction between PPIs and clopidogrel emerges, so does the question of which types of patients may benefit or have risks from adding PPI therapy when they are receiving clopidogrel. The Society for Cardiovascular Angiography and Interventions recently issued a statement recommending that health care providers who are treating patients with dual antiplatelet therapy after coronary stent placement consider prescribing a histaminergic blocker or antacids instead of a PPI.[17] Furthermore, the European Medicines Evaluations Agency (EMEA) has recommended that the product information for clopidogrel-containing medicines be amended to discourage concomitant use of PPIs and clopidogrel-containing medicines unless absolutely necessary. According to the EMEA, further information is needed regarding the inhibition of clopidogrel metabolism by other medicines and the implications of genetic variation (eg, poor metabolizers of CYP2C19) in the ability to fully convert clopidogrel to its active form, regardless of interactions with other medicines.[18]

Although recent recommendations from the Society for Cardiovascular Angiography and Interventions and the EMEA discourage the concomitant use of PPIs with clopidogrel, there is limited research evaluating gastrointestinal outcomes associated with not prescribing a PPI or switching patients who are receiving clopidogrel after coronary stent placement to a histaminergic blocker or antacids instead of a PPI. We conducted a post hoc analysis to better understand the risk of gastrointestinal bleeding in this study. Although we had excluded patients with previous claims history of gastrointestinal bleeding or reflux disease from the study cohorts, patients receiving clopidogrel plus PPIs had a higher risk of hospitalization for gastrointestinal bleeding than did patients receiving clopidogrel alone (8.1 vs 1.5 events per 100 person-years; adjusted HR, 9.78; 95% CI, 2.51-38.10; $P=.001$). This finding likely reflects the fact that patients at higher risk for gastrointestinal bleeding are prescribed PPIs. Limitations in the database (eg, unable to account for the use of aspirin or nonprescription nonsteroidal anti-inflammatory medications) prevent us from evaluating the differential effect of PPI use on gastrointestinal bleeding in this cohort of persons matched on cardiovascular risk factors.

With the results of this study and other recent studies noting possible reduced efficacy of clopidogrel when used concomitantly with PPIs, the recommendations from the Society for Cardiovascular Angiography and Interventions and the EMEA to discourage concomitant use of PPIs and clopidogrel unless absolutely necessary seem prudent. However, until more research is conducted on cardiovascular and gastrointestinal outcomes for different patient subpopulations (eg, individuals with a high risk or a history of gastrointestinal bleeding, poor metabolizers of CYP2C19), individual patient characteristics will also need to be considered to determine whether potential benefits of PPIs in preventing gastrointestinal bleeding in patients receiving antiplatelet therapy outweigh the risks of a potentially reduced effect of clopidogrel.

There were several potential limitations to this analysis. Although we matched patients in each group on potential cardiovascular risk factors in the electronic claims database, information on important cardiovascular risk factors, such as race/ethnicity, family history of MI, obesity, and smoking status, were not evaluated. Furthermore, matching may not have accounted for additional unobservable factors that may have influenced physician prescribing of a PPI medication. Because insurance claims databases do not contain reliable death information, cardiovascular deaths were not assessed, and the results probably underestimate the rate of occurrence of MI.

Because aspirin is not billed through the pharmacy claims system, it was not possible to control for aspirin use between the 2 study groups. The effect of unknown use of aspirin could bias the findings because higher-risk patients treated with aspirin plus clopidogrel may be more likely to be treated with a PPI than were patients treated with clopidogrel alone. On the other hand, patients receiving both aspirin and clopidogrel would be expected to have a lower rate of events than would patients receiving only clopidogrel, which would bias the results toward a lower risk of events in patients taking PPIs. However, it is likely that most patients evaluated in this study would have been treated with dual antiplatelet therapy because the combination of clopidogrel and aspirin is recommended treatment after a coronary stent procedure or MI.[19-21]

Because we could not account for nonprescription use of PPI medications, it is possible that some patients in the clopidogrel alone group received nonprescription PPIs. However, the use of over-the-counter PPIs in the clopidogrel alone group would not be expected to alter the overall study conclusions because this potential bias is toward the null (ie, likely to be more conservative).

Type of coronary stent placement is another factor that could affect the study outcomes. Because recent studies have reported higher numbers of late-stent thrombosis with drug-eluting stents compared with bare-metal stents,[22] we conducted a post hoc analysis to measure whether the cohorts in this analysis were balanced in terms of proportion of patients with a drug-eluting stent. During the 30 days before the first prescription fill of clopidogrel, the percentage of patients with a hospitalization with a procedure code for a drug-eluting stent was similar for patients receiving clopidogrel alone vs patients receiving clopidogrel plus a PPI (70.9% vs 72.4%, $P=.40$, for the main analysis; and 69.5% vs 71.8%, $P=.33$, for the pantoprazole subanalysis). These findings should alleviate concerns about potential differences in type of stent between the 2 groups.

To ensure that patients were exposed to clopidogrel at the time of the study, we started following up patients from their first known exposure to clopidogrel (ie, first outpatient prescription for clopidogrel after a coronary stent procedure or MI). However, because patients likely start clopidogrel therapy when they are in the hospital recovering from their initial event, we cannot rule out the possibility that there were different MI or revascularization rates for the clopidogrel alone and clopidogrel plus PPI groups before the first clopidogrel outpatient prescription.

Because of these limitations and other limitations inherent to retrospective claims analyses (eg, confounding bias, incomplete claims, and errors in diagnosis coding), further evaluation through prospective, randomized, controlled clinical trials is necessary to be able to make definite conclusions regarding the causality of increased adverse clinical outcomes using clopidogrel with a PPI. Pragmatic trials may be one lower-cost way to address this important clinical issue. Furthermore, laboratory analyses of biochemical interactions of these drugs may result in a better understanding of their effect on clinical care.

In conclusion, this study provides additional information supporting a potentially higher risk of adverse clinical outcomes in patients receiving clopidogrel with a PPI. These findings highlight the need for additional prospective randomized clinical studies to further evaluate clinical outcomes associated with a potential drug-drug interaction between clopidogrel and PPIs.

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