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THE EFFECT OF INTERACTION BETWEEN CLOPIDOGREL AND PROTON PUMP INHIBITORS ON ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Abstract

Study Objective—This study examined the effect of clopidogrel and proton pump inhibitors (PPIs) interaction on subsequent acute coronary syndrome (ACS)-related inpatient and emergency room (ER) visits.

Design—Population based, retrospective cohort study.

Data Source—IMS LifeLink Health Plan administrative claims database containing a large nationally dispersed group of commercially insured subjects between 2001 and 2008.

Patients—Subjects age ≥ 18 years with a diagnosis of ACS and at least one clopidogrel prescription within 90 days after the diagnosis were included. Exposed group was defined as having overlapping clopidogrel-PPI prescriptions. Subjects were followed from their first clopidogrel prescription until they experienced an adverse cardiovascular event (re-hospitalization or errors visit due to ACS), were disenrolled or reached the end of study period.

Measurements and Main Results—The clopidogrel plus PPIs group was matched 1:1 with the clopidogrel alone group using the propensity scoring method. Exposure to overlapping clopidogrel-PPI prescriptions was modeled as a time dependent covariate. Cox hazards regression was used to estimate the risk of an adverse cardiovascular event for those having overlapping clopidogrel-PPI prescriptions versus those having clopidogrel alone. Propensity score matching resulted in 2,674 patient pairs. The mean age was 61.30 years with a mean follow-up of 268 days and 70.04% were male. Clopidogrel use co-medicated with PPIs was associated with a significantly increased risk of cardiovascular adverse events (HR=1.438; 95% CI, 1.237-1.671), as compared to clopidogrel use not co-medicated with PPIs.

Conclusion—Concurrent use of clopidogrel plus PPIs was associated with a significant increase in risk of adverse cardiovascular events for ACS patients.

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Keywords

Clopidogrel; Proton; Pump; Inhibitors; Interaction; Cardiovascular; Adverse; Events; Outcomes; Acute; Coronary; Syndrome

INTRODUCTION

Coronary heart disease is the leading cause of death in the United States accounting for approximately 425,000 deaths in 2006.¹ The American College of Cardiology/American Heart Association guidelines recommend the use of antiplatelet therapy for the prevention of cardiovascular events.² Clopidogrel, an antiplatelet agent, is prescribed to patients who have had a recent heart attack, a recent stroke, established peripheral arterial disease or acute coronary syndrome (ACS).³⁻⁵ Clopidogrel can cause bleeding in the stomach and hence proton pump inhibitors (PPIs) are often prescribed in combination with this drug to reduce the risk of gastrointestinal bleeding.^{6, 7}

The US Food and Drug Administration (FDA) issued a warning in November 2009 stating that the co-medication of clopidogrel and omeprazole should be avoided based on the study results from the drug manufacturers. Like omeprazole, other drugs such as esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, and fluvoxamine may diminish the effect of clopidogrel by inhibiting the drug metabolizing enzyme CYP2C19 which is responsible for the conversion of clopidogrel to its active metabolite form.⁸⁻¹⁰ Significant controversy still exists regarding the clinical outcomes of patients with a co-medication of clopidogrel and PPIs. Several observational studies report the presence of a significant interaction between these drugs.¹¹⁻¹⁷ However, others have claimed that this drug interaction has no major clinical impact.¹⁸⁻²³ The aim of this study was to investigate the effect of clopidogrel plus PPI use on adverse cardiovascular events in a large nationally dispersed group of commercially insured population in the US. Specifically, we examined the effect of an interaction between clopidogrel and PPIs on adverse cardiovascular events which were defined as inpatient hospitalization or ER visits for myocardial infarction (MI), percutaneous coronary intervention (PCI) or intermediate coronary syndrome (ICS) in patients with ACS. This study adds to the existing research by utilizing a more robust methodology of modeling the drug interaction exposure as a time dependent covariate and a longer study period than the previous studies.

METHODS

Design Overview

This is a retrospective cohort study utilizing a 10% sample of IMS LifeLink Health Plan Claims Database from years 2001 to 2008. The LifeLink Health Plan Claims Database is comprised of commercial health plan information obtained from approximately 98 health care plans across the United States for 61 million unique patients. Approximately 11% of the population in the database had Medicare or Medicaid at some point in time during their enrollment period. It is representative of the national, commercially insured population in terms of age and gender with average member enrollment duration of 2.5 years. This study was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Patient Population

We identified ACS patients having an emergency visit or hospitalization with an ICD-9-CM code for ACS (410.xx [acute myocardial infarction] or 411.1x [intermediate coronary

syndrome]) or a CPT-4 procedure code (92980, 92981, 92973, 92982, 92984, 92995, 92996, 33510-33514, 33516, 33533-33536, 33545, 33572 [coronary artery bypass graft, repair of damaged heart septum, coronary endarterectomy, coronary stent placement, percutaneous coronary thrombectomy, coronary artery dilation balloon, remove heart vessel plaque]) between January 1, 2001 to December 31, 2008. The study population consisted of new users of clopidogrel of age 18 years or above. A new user was operationally defined as a subject having his/her first prescription within 90 days after the diagnosis of ACS and with no clopidogrel use during the 180 days prior to the ACS diagnosis. The index date was defined as the date of the first prescription of clopidogrel (Figure 1). The baseline period was defined as 180 days before the index date. Further, those patients who had an ACS diagnosis during the 180 days period prior to index date were excluded. The follow up period began with the start of the first prescription of clopidogrel and continued until the occurrence of an adverse cardiovascular event (defined below), disenrollment from the plan, discontinuation of clopidogrel, or the end of study period. In case of a discontinuation of clopidogrel, the patient was followed for a maximum period of 30 days after discontinuing.

Exposure to PPIs

The exposure of interest was the use of any of the PPIs, identified as omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole dispensed at any point after the diagnosis of ACS during the study period. As the co-medication exposure for a patient can occur intermittently during the follow up, overlapping clopidogrel-PPIs use was modeled as a time dependent covariate. Specifically, exposure to overlapping clopidogrel-PPIs was calculated for each day of the follow up based on the prescription fill dates and days of supply to estimate the “run-out” date of each prescription. The variable “exposure” could take a value of 1 or 0 for each day of the follow up period depending on the patient exposure or non-exposure to overlapping clopidogrel-PPIs prescriptions during the follow up. In this way, all the clopidogrel-PPIs overlapping days at various intervals were accounted for in the analysis. This time dependent approach is for defining drug exposure only and does not affect how the outcome event is identified. Using overlapping clopidogrel-PPIs time intervals as a time dependent covariate reduces exposure misclassification and gives precise risk estimates that preserves the temporal relationship between exposure and outcome.²⁴

Adverse Cardiovascular Events

Adverse cardiovascular events were defined as any occurrence of rehospitalization or ER visit for MI, PCI or ICS in patients with ACS during the follow up period, identified using the ICD-9 codes and CPT codes as listed previously.

Covariates

Various factors that could affect the outcome were identified by reviewing relevant literature.^{11-22, 25} Only those variables which could be measured directly or had a proxy measure were included. These variables were measured over the baseline period and are included in Table 1.

Statistical Analysis

Descriptive statistics (means, standard deviations, percentages) were reported and Chi-square tests or t-tests were used to analyze the differences at baseline between the group using clopidogrel alone versus the group using clopidogrel plus PPIs. These baseline comparisons were performed both for the unmatched and the matched samples. Matching was performed using propensity scores to balance the distribution of observed confounders across the two groups, thus reducing the possibility of selection bias caused by observed baseline differences between patients who would receive PPIs versus those who would

not.²⁶ Patients who had at least one day exposure to clopidogrel-PPIs co-medication during the follow-up period were matched 1 to 1 within calipers using greedy matching algorithm.

Finally, we estimated the hazards of adverse cardiovascular events associated with concomitant use of clopidogrel and PPIs as compared with the use of clopidogrel alone. In order to do this we estimated three different Cox regression models, all with the time dependent parameter for the overlapping exposure. The first model used the unmatched sample and was not unadjusted for any covariates. The second one also used the unmatched sample but adjusted for the baseline variables. The final model used the propensity score matched sample.

To assess the robustness of our findings, several sensitivity analyses were performed. First, two separate analyses were conducted by extending the “run-out” date of the interaction exposure time period by 7 and 30 days. This was done for two reasons. First, the clopidogrel-PPIs drug-drug interaction might exist after stopping the prescription use. Second, some patients might not adhere to the prescription and might continue to finish the prescription beyond the end date of the days’ supply of the prescription.

A second series of sensitivity analyses were performed by varying the exposure definition itself as described in the following: (1) The exposure was defined as the use of PPIs at any point during the 90 days before or 90 days after the index date with a minimum of 7 continuous days overlap with clopidogrel prescription, (2) The exposure was defined as the use of PPIs during the 90 days before the index date or at any point during the study period after the index date with at least one overlapping day with the clopidogrel prescription. Cox regression analyses were then conducted for both the unmatched and the propensity score matched samples.

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

We identified 12,841 patients diagnosed with ACS and with a clopidogrel prescription filled within 90 days after this ACS diagnosis between January 2001 and December 2008. Of these, 2,740 patients were excluded from the study as shown in Figure 2. The remaining 10,101 patients satisfied our inclusion and exclusion criteria.

There were significant baseline differences between clopidogrel users and clopidogrel plus PPI users in the pre-matched sample (Table 1). The average age was 60 ($\pm$ 11.2 standard deviation [SD]) years among the clopidogrel users and 62 ($\pm$ 11.7 SD) years among the clopidogrel plus PPI users and 76% of the clopidogrel users were male as compared to 69% of the clopidogrel plus PPIs users. Clopidogrel plus PPI users had more comorbidities, and used more cardiovascular medications in the baseline period than the clopidogrel alone group. After propensity score matching there were 2,674 pairs with no statistically significant differences in baseline characteristics.

The results of the Cox regression models for the unmatched unadjusted, unmatched adjusted, and the matched samples are presented in Table 2. All of the results indicated, to varying degrees, that the concomitant use of Clopidogrel and PPIs was associated with a statistically significant increased risk of adverse cardiovascular events.

Sensitivity Analyses

The results obtained after increasing the exposure period by adding 7 days to the days of supply were virtually identical to those reported above (Table 3). For example, the patients with overlapping exposure to clopidogrel plus PPIs in the propensity score matched sample were at a 41% increased hazard of a rehospitalization or ER visit due to ACS (HR: 1.409; 95% CI: 1.213-1.636) as compared to the clopidogrel alone group. Similar results were found when the exposure period was increased by adding 30 days to the supply days for patients on clopidogrel plus PPIs (Table 3).

When the exposure was defined as the use of PPIs at any point during the 90 days before or 90 days after the index date with a minimum of 7 continuous days overlap with clopidogrel prescription, the proportional hazards model showed a significant hazard of co-medication on ACS related rehospitalization or ER visit as compared to patients on clopidogrel alone (HR: 1.248, 95% CI: 1.094-1.425) in the unmatched sample. However, when the propensity score matched sample of 3,394 was analyzed, the effect of clopidogrel plus PPIs was non-significant (HR: 1.221, 95% CI: 0.984-1.517; $P=0.0702$). When the exposure definition was the use of PPIs, dispensed at 90 days before the index date or at any point during the study period after the index date with at least one overlapping day with the clopidogrel prescription, concomitant PPIs use with clopidogrel did not show any increase in the hazard for rehospitalization or ER visit due to ACS (Table 4). Finally, when a sensitivity analysis was performed by excluding from the outcome the patients having an ER only visit there was no change in the results, with hazard ratios remaining essentially the same (results not reported).

DISCUSSION

This study investigated the effect of interaction between clopidogrel and PPIs using a sample of 10,101 commercially insured patients with ACS from January 2001 through December 2008. We observed that the use of clopidogrel plus PPIs was associated with a 43% increased risk of rehospitalization or ER visit due to ACS compared to clopidogrel alone. More importantly, these findings were confirmed for all but one of the sensitivity analyses. Further, the findings are consistent with several previous studies which also noted an increased risk of adverse cardiovascular events associated with use of clopidogrel plus PPIs compared with clopidogrel alone.¹¹⁻¹⁷

This study is unique in several ways. First, we used a population that was geographically more diverse than those in previous studies, with substantial number of subjects in all four census regions of the US. Second, since our study period spanned 8 years (2001-2008), we could follow patients for a longer time period than the previous studies. For example, Ho et al had about 3 years, Stockl et al and Kreutz et al had 1 year period, and Rassen et al and Juurlink et al. had less than a year of study window.^{11-13, 17, 19} Finally, we used a more robust methodology of adjusting for time dependence of exposure which establishes stronger temporal linkages between the interaction and cardiovascular events which was not used in the previous studies.

Our study findings indicating a significant association between use of clopidogrel plus PPIs and risk of adverse cardiovascular event is consistent with the proposed mechanism that PPIs inhibit the enzymatic conversion of clopidogrel to its active form.⁹⁻¹¹ Theoretically, this could explain the adverse cardiovascular events such as MI, ICS or PCI associated with the concomitant use of clopidogrel plus PPIs which was observed in this study. Previous studies which assessed the platelet inhibition of clopidogrel in the presence of PPIs validate this mechanism.^{27, 28}

Although a few studies assessed the impact of PPIs on the platelet inhibitory effect of clopidogrel,²⁷⁻³⁰ studies examining clinical outcomes are inconsistent and conflicting. Several studies report conclusions similar to those of our study, indicating an increased risk of adverse cardiovascular events associated with concomitant use of clopidogrel plus PPIs.^{11-17, 31}

However, not all studies reported association between cardiovascular events and concomitant use of clopidogrel and PPIs. Bhatt et al, reporting data from the COGENT trial, found no increased risk of cardiovascular events in patients on clopidogrel plus omeprazole.³² Retrospective cohort studies by Ray et al and Rassen et al also found no association of adverse cardiovascular events and use of clopidogrel plus PPIs.^{19, 20} Interestingly, a cohort study in Denmark by Charlott et al included 24,702 patients with MI and concluded that PPIs use was associated with a 29% increased risk of adverse cardiovascular events regardless of clopidogrel use. This study did not find any evidence that concomitant use of clopidogrel plus PPIs was associated with increased risk of adverse cardiovascular events.²¹ Another study by Blackburn et al suggested that the use of acid-suppressing drugs like PPIs increased before the occurrence of ischemic events.³³ The authors reported that the use of PPIs was higher among the cases than the controls (4.0% [64/1612] vs 2.2% [179/8060], odd ratio 1.32, 95% CI 0.95-1.84, p=0.094).

A survey of these studies reveals that a lot of variability exists between the studies in terms of study design, patient population, outcomes measured and drug exposure definitions. For example, Ray et al and Rassen et al concluded no increased risk of adverse cardiovascular events associated with concomitant use of clopidogrel plus PPIs.^{19, 20} Although both studies tried to control for bias by calculating a propensity score and including it in the regression model as deciles, our study addressed selection bias caused by observed baseline differences by utilizing a more robust technique of propensity score matching using calipers.³⁴ These methodological differences could explain the differing outcomes between our study and these previous studies. Our study also provides advantages to previous studies that concluded increased risk of cardiovascular events associated with concomitant use of clopidogrel plus PPIs. For example, Ho et al investigated only the Veterans Affairs population and had a shorter observational period as compared with the current study (3 years vs. 8 years).¹³ The Juurlink et al study considered exposure only during the first 90 days post discharge whereas we modeled exposure to clopidogrel plus PPIs as a time dependent covariate.¹²

In order to reduce exposure misclassification, our study utilized a robust approach of defining exposure to PPIs as a time dependent covariate. The time dependent analysis approach does not assume that once a patient starts a medication it is continued indefinitely. This approach accounts for the stopping, switching and restarting of a PPI and thus reduces the temporal misclassification bias which may be prevalent in some of the previous studies. Sensitivity analyses were also performed in our study to test the robustness of our findings, including accounting for patient non-adherence behavior by increasing exposure to clopidogrel plus PPIs through adding 7 and 30 days to the “run-out” date of the interaction exposure time period.

The extent of clopidogrel-PPIs interaction may also vary depending upon the population characteristics of the sample. Our study utilized a more demographically and geographically diverse and a more nationally representative population as compared to the previous studies which limited patient population to elderly only, Medicaid only, Medicare only, population from the western United States only, or Veterans Affairs population only.

The results of this study should be seen in the light of several limitations. This study had no information on cardiovascular risk factors like smoking, hypertension, serum lipid levels, blood pressure, race/ethnicity and treatment with glycoprotein IIb/IIIa inhibitors and heparins. These factors could have affected the physician's decision to prescribe clopidogrel for a longer or shorter duration of time. Also, smokers and those with upper gastrointestinal diseases would be more likely to receive PPIs; the resulting bias may cause overestimation of cardiovascular risk. Aspirin and omeprazole are available as nonprescription medications. The use of nonprescription medications cannot be ascertained in the claims database used for this study. This can result in exposure misclassification which in turn can bias the results towards null. Medication exposure determined from the prescription records cannot determine if patients adhered to the medications regimen.

Cardiovascular deaths could not be assessed in this database; this could probably lead to underestimation of the rate of occurrence of adverse cardiovascular events. Although propensity matching was successful in balancing the observed baseline differences between the clopidogrel plus PPIs group and the clopidogrel alone group, unobserved differences may still exist, which may lead to residual selection bias. In particular, we had no knowledge of the genotype of the patients. It is noted that patients with an absence of functional allele for CYP2C19 cannot effectively convert clopidogrel to its active form.³⁵ This could result in an increased risk of adverse cardiovascular events. The study did not account for PPIs dosing strength and the exposure to PPIs was studied as a class effect. Finally, it is possible that procedures including stents and coronary artery bypass graft may not be related to the clopidogrel-PPI drug interaction and may simply be elective procedures, given that coronary artery disease is a chronic progressive disease. However, in an administrative database there is no way of knowing whether these types of events were related to thrombosis from the drug interaction or were elective.

Other limitations of retrospective claims data such as incomplete claims, missing information and errors in coding also apply to this study. The data obtained from the administrative database was not validated with chart reviews. The effect of PPIs on the antiplatelet activity of clopidogrel can be measured by platelet aggregation tests; however, the clinical laboratory information is not available in administrative claims databases.

CONCLUSIONS

Conflicting and inconsistent evidence exists to describe the effect of co-medication of clopidogrel and PPIs on adverse cardiovascular events. Our data suggest that concomitant use of clopidogrel and PPIs was associated with an increased risk of adverse cardiovascular events such as MI, PCI or ICS in patients with prior ACS. These findings in addition to previous research that found an association with this interaction are tipping the balance of evidence that suggest PPIs may reduce the effectiveness of clopidogrel. Future research is needed to assess clopidogrel-PPIs drug-drug interaction in specific subgroups of patients based on their genotype. Until a large scale randomized study is conducted comparing clopidogrel use alone or in combination with a PPI that definitively demonstrates the safety of using this drug combination, clinicians should cautiously use these two drugs concomitantly weighing the GI benefits of PPIs against the cardiovascular risk and against the low risk of adverse GI events with clopidogrel (as gleaned from the landmark CURE trial) for each individual patient.

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Figure 1. Study Time Frame

dx= diagnosis

Index Date= First Prescription (Rx) of Clopidogrel within 90 days after ACS diagnosis

Baseline Period= 180 days prior to index date

Follow-up period= From Index date until the earliest of

- i. Event
- ii. Disenrollment of patient
- iii. End of study period
- iv. 30 days after discontinuation of Clopidogrel

Figure 2. Patient Selection Flowchart

Table 1
Baseline Descriptive Statistics Before and After Propensity Score Matching

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Clopidogrel plus PPIs (N=2958)	Clopidogrel Alone (N=7143)	P-value	Clopidogrel plus PPIs (N=2674)	Clopidogrel Alone (N=2674)	P-value
Age, mean (SD)	61.53	59.63	11.2	61.27	61.33	11.7
Male, n (%)	2034	5450	76.3	1871	1875	70.1
Region, n (%)						
East	710	1273	17.8	621	647	24.2
Midwest	1180	3182	44.5	1080	1071	40.0
South	823	2013	28.2	747	732	27.4
West	245	675	9.4	226	224	8.4
Charlson Comorbidity Index, n (%)						
0	1003	3044	42.6	945	905	33.8
1	788	1968	27.5	707	734	27.4
2	552	1098	15.4	498	507	18.9
>=3	615	1033	14.5	524	528	19.7
Mean, SD	1.51	1.16	1.4	1.45	1.46	1.6
Baseline Conditions, n (%)						
Ulcer	65	36	0.5	30	32	1.2
Gastritis	187	117	1.6	111	98	3.7
GERD	757	502	7.0	503	477	17.8
Obesity	208	447	6.3	183	176	6.6
Diabetes Mellitus	857	1884	26.4	779	766	28.6
Congestive Heart Failure	489	969	13.6	437	431	16.1
Cerebrovascular Disease	290	596	8.3	262	244	9.1
Baseline Medications, n (%)						
ACE	732	1529	21.4	647	678	25.4
Anticoagulants	163	274	3.8	142	142	5.3
COX2	243	277	3.9	187	190	7.1
HMGCoA	1180	2367	33.1	1046	1069	39.9

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Clopidogrel plus PPIs (N=2958)	Clopidogrel Alone (N=7143)	P-value	Clopidogrel plus PPIs (N=2674)	Clopidogrel Alone (N=2674)	P-value
NSAIDs	672	1047	14.7	554	564	21.1
Antiarrhythmic	43	90	1.3	35	36	1.3
Anticonvulsant	241	325	4.5	183	203	7.5
Antidepressant	622	891	12.5	515	519	19.4
AntiDiabetic	658	1358	19.0	594	600	22.4
AntiHypertensive	1346	2793	39.1	1192	1212	45.3
Benzodiazepine	364	457	6.4	292	283	10.6
BetaBlockers	1103	2269	31.8	978	1003	37.5
Bronchodilator	408	633	8.9	342	352	13.2
Calcium Channel Blockers	571	1052	14.7	492	478	17.8
Diuretics	685	1280	17.9	603	620	23.2
Insulin	222	422	5.9	202	207	7.7
Corticosteroids	342	571	7.9	291	297	11.1
Antipsychotic	61	60	0.8	44	46	1.7
Analgesic-Opioid	788	1328	18.6	647	677	25.3
Antihistamine	289	365	5.1	225	216	8.1
Antianginal	680	1317	18.4	608	588	21.9
Glucocorticosteroids	339	567	7.9	289	294	10.9
Antacid	0	5	0.0	0	0	0
Vasodilator	23	50	0.7	21	24	0.9
ADHD	2	2	0.0	1	2	0.1
Index Hospitalization Diagnosis, n (%)						
MI	1232	3210	44.9	1128	1110	41.5
Non-stenting revascularization *	127	270	3.8	117	110	4.1
ICS	755	1569	21.9	656	667	24.9
Stents	844	2094	29.3	773	787	29.4
Use of PPIs during Baseline Period, n (%)						
Follow Up In Days, mean (SD)	1206	50	0.7	1009	46	1.7
	308.54	226.37	283.0	309.31	227.38	276.6

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Clopidogrel plus PPIs (N=2958)	Clopidogrel Alone (N=7143)	P-value	Clopidogrel plus PPIs (N=2674)	Clopidogrel Alone (N=2674)	P-value
Time On Clopidogrel In Days, mean (SD)	303.64	330.5	273.0	304.32	333.1	267.0
Time On Clopidogrel Plus PPIs, mean (SD)	177.67	248.8		174.7	247.7	
Time On PPIs Alone in Days, mean (SD)	28.68	33.6	4.4	27.09	33.2	6.0
Type of PPIs Distribution, n (%)						
Esomeprazole	684	23.1		597	22.3	
Lansoprazole	522	17.6		478	17.9	
Omeprazole	803	27.1		727	27.2	
Pantoprazole	763	25.8		708	26.5	
Rabeprazole	186	6.3		164	6.1	
Time to Filling of Clopidogrel, n (%)						
Within 3 days	1664	56.2	64.5	1509	56.4	61.7
Within 4-5 days	532	17.9	15.9	484	18.1	15.4
Within 6-7 days	228	7.7	6.1	200	7.5	6.7
Within 8-15 days	250	8.4	6.3	231	8.6	7.3
Within 16-30 days	144	4.9	3.2	130	4.9	3.9
30 < days	140	4.7	3.8	120	4.5	5.0
Type of Event Distribution, n (%)						
MI	196	46.9	50.7	172	46.9	48.4
Non-stenting revascularization*	13	3.1	1.9	10	2.7	2.7
ICS	104	24.9	20.5	87	23.8	21.6
Stents	105	25.1	26.7	97	26.5	27.0
Event Rate	418	14.1	12.7	366	13.7	12.6
Censor Rate	2540	85.9	87.3	2308	86.3	87.4

SD: Standard deviation, MI: Myocardial infarction; ICS: Intermediate coronary intervention, PPI: Proton Pump Inhibitor

* Includes angioplasty and coronary artery bypass graft

Table 2
Relative Risk of Adverse Cardiovascular Outcomes following Hospital Discharge in
Patients on Clopidogrel plus Proton Pump Inhibitors Versus Clopidogrel Alone
(Reference Group)

Sample	Hazard Ratio	95% Confidence Interval	
Full sample, unadjusted (N=10,101)	1.298	1.146	1.471
Full sample, adjusted (N=10,101)	1.277 ^a	1.119	1.458
Propensity score matched sample (N=5,348)	1.438	1.237	1.671

^aHazard ratio adjusted for covariates mentioned in Table 1

Table 3
Relative Risk of Adverse Cardiovascular Outcomes following Hospital Discharge in
Patients on Clopidogrel plus Proton Pump Inhibitors Versus Clopidogrel Alone
Sensitivity Analyses of Extending the Exposure Period of the Interaction

Exposure Extended 7 Days to the Run-Out Date of Interaction			
Sample	Hazard Ratio	95% Confidence Interval	
Full sample, unadjusted (N=10,101)	1.272	1.125	1.439
Full sample, adjusted (N=10,101)	1.249 ^a	1.095	1.424
Propensity score matched sample (N=5,348)	1.409	1.213	1.636
Exposure Extended 30 Days to the Run-Out Date of Interaction			
Sample	Hazard Ratio	95% Confidence Interval	
Full sample, unadjusted (N=10,101)	1.292	1.146	1.457
Full sample, adjusted (N=10,101)	1.273 ^b	1.119	1.447
Propensity score matched sample (N=5,348)	1.452	1.252	1.685

^a Hazard ratio adjusted for covariates mentioned in Table 1 for 7 days added to run-out date of interaction

^b Hazard ratio adjusted for covariates mentioned in Table 1 for 30 days added to run-out date of interaction

Table 4
Relative Risk of Adverse Cardiovascular Outcomes following Hospital Discharge in Patients on Clopidogrel plus Proton Pump Inhibitors Versus Clopidogrel Alone
Sensitivity Analyses by Modifying the Exposure Definition

Exposure of interest is the use of proton pump inhibitors, defined as omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole, dispensed at any point 90 days before or 90 days after the index date with a minimum of 7 days overlap with a clopidogrel prescription

Sample	Hazard Ratio	95% Confidence Interval	
Full sample, unadjusted (N=10,101)	1.248	1.094	1.425
Propensity score matched sample (N= 3,394)	1.221	0.984	1.517

Exposure of interest is the use of proton pump inhibitors, defined as omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole dispensed at 90 days before the index date or any point during the study period after the index date with at least one overlapping day with the clopidogrel a prescription

Sample	Hazard Ratio	95% Confidence Interval	
Full sample, unadjusted (N=10,101)	0.954	0.849	1.071
Propensity score matched sample (N=5,348)	0.840	0.703	1.002

CI: Confidence Interval