Risk of adverse cardiovascular outcomes and all-cause mortality associated with concomitant use of clopidogrel and proton pump inhibitors in elderly patients

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Clopidogrel – Drug–drug interaction – Elderly –
Medicare – Proton pump inhibitors

Abstract

Objective:
To examine the effect of concomitant use of clopidogrel and PPIs in a national sample of elderly Medicare beneficiaries (age ≥65 years).

Methods:
A nested case–control design was employed. A cohort of Medicare beneficiaries who initiated clopidogrel and did not have any gap of ≥30 days between clopidogrel fills between July 1, 2006 and December 31, 2008 was identified from a 5% national sample of Medicare claims data. Within this cohort, cases beneficiaries who experienced any major cardiovascular event [MCE] [acute myocardial infarction, stroke, coronary artery bypass graft, or percutaneous coronary intervention] or all-cause mortality and controls beneficiaries who did not experience any MCE or all-cause mortality] were identified from inpatient and outpatient claims. Cases and controls were matched on age and the time to first clopidogrel fill. Conditional logistic regression was performed on the matched sample to evaluate the association between concomitant use of clopidogrel and PPIs and adverse health outcomes (MCEs and all-cause mortality).

Results:
A total of 43,159 clopidogrel users were identified. Among them, 15,415 (35.7%) received clopidogrel and a PPI concomitantly at any time during the study period, 3502 (8.1%) experienced a MCE, 7306 (17.1%) died, and a total of 9908 (22.8%) experienced the primary composite outcome (any MCE or all-cause mortality) during follow-up. The odds ratio (OR) for the primary composite outcome was 1.26 (95% confidence interval [CI]: 1.18–1.35). Secondary analyses indicated that elderly patients using clopidogrel and a PPI concomitantly were more likely to experience all-cause mortality (OR: 1.40; 95% CI: 1.29–1.53) as compared to those receiving clopidogrel only, but not MCEs (OR: 1.06; 95% CI: 0.95–1.18).

Conclusions:
Concomitant use of clopidogrel and PPIs was associated with a slightly increased risk of all-cause mortality but not MCEs.

Introduction

Clopidogrel belongs to the class of anti-platelet agents and is indicated for prevention of arterial thromboembolism in patients with peripheral arterial diseases or patients with acute coronary syndrome (ACS) who are treated medically or
Concomitant use of clopidogrel and PPIs in the elderly

through coronary revascularization procedures\(^1,2\). With global sales of $9.1 billion (US dollars) in 2009, clopidogrel is the second best selling drug worldwide\(^3\).

Clopidogrel is highly effective in reducing atherothrombotic and ischemic events; however, its use is often associated with gastrointestinal complications including ulceration and bleeding\(^4\). Several professional organizations such as the American Heart Association and the American College of Gastroenterology have recommended that a proton pump inhibitor (PPI) should be used with anti-platelet therapy consisting of clopidogrel alone or clopidogrel and aspirin for gastrointestinal protection\(^5\). However, evidence from mechanistic studies has indicated that the anti-platelet effect of clopidogrel is reduced in the presence of PPIs because PPIs inhibit CYP2C19, an enzyme responsible for the conversion of clopidogrel to its active metabolite\(^6-8\). Moreover, several observational studies have shown that concomitant use of clopidogrel and PPIs increases the risk of adverse cardiovascular events\(^9-15\). In response to growing concerns over combined use of clopidogrel and PPIs, the US Food and Drug Administration (FDA) issued a public advisory in 2009 advising physicians to re-evaluate the need of PPI use in patients receiving clopidogrel and subsequently a ‘black box’ warning was added to all clopidogrel (Plavix\(^9\)) labels in 2011 advising physicians to avoid prescribing clopidogrel and PPIs, namely omeprazole and esomeprazole, simultaneously\(^16\). Similarly, the European Medicines Agency issued a public statement in 2009 discouraging the concomitant use of clopidogrel and PPIs unless absolutely necessary\(^17\). However, no consensus has been reached regarding the effect of concurrent use of clopidogrel and PPIs, as results from two randomized controlled trials and several observational studies have shown no association between concomitant use of clopidogrel and PPIs and adverse cardiovascular events\(^5,8,18-24\).

Most previous research on concomitant use of clopidogrel and PPIs has focused on general patient populations. A better understanding of the effects of the potential drug–drug interaction between clopidogrel and PPIs focusing on the elderly is important for several reasons. First, the effect of concomitant use of clopidogrel and PPIs is likely to be different in older adults, as older adults are more likely to experience cardiovascular events\(^25\) and they are also more susceptible to clopidogrel–PPI interactions\(^26\). Elderly patients might be more likely to be influenced by the clopidogrel–PPI interaction possibly due to their reduced liver function, which reduces metabolism of clopidogrel to its active metabolite\(^27\). When a PPI is co-administered with clopidogrel in the elderly, clopidogrel’s anti-platelet effect could be further reduced. Second, elderly patients on anti-platelet drugs are more likely to have gastrointestinal bleeding as compared to those younger than 50 years of age\(^28\) and physicians often prescribe PPIs to these patients to provide gastrointestinal protection\(^29\) because PPIs have been found to be the most effective agent in preventing gastrointestinal bleeding related to anti-platelet therapy\(^30\). Research on the concomitant use of clopidogrel and PPIs focusing on the elderly population has been limited. This lack of information is concerning because the effect of concomitant use of clopidogrel and PPIs in the elderly cannot be simply extrapolated from studies involving younger people. A few observational studies have evaluated the effect of clopidogrel–PPI interaction in the elderly population and results from these studies are likely to be inadequate to inform evidence-based prescribing because these studies only included patients within restricted geographic areas\(^31,32\).

In a randomized clinical study, Bhatt et al. examined the incidence of adverse gastrointestinal events and adverse cardiovascular events among elderly patients on dual clopidogrel and aspirin therapy receiving either omeprazole or placebo, and they did not find apparent cardiovascular interaction between clopidogrel and omeprazole\(^18\). While this randomized controlled study provides useful information about the clopidogrel–PPI interaction among elderly patients, only the interaction between clopidogrel and omeprazole and not other PPIs was evaluated in the study. To provide further insights into the real-world association between concomitant use of clopidogrel and PPIs and adverse outcomes in the elderly population, we conducted a nested case–control study involving a national sample of elderly patients using the 5% sample of Medicare administrative claims data.

Patients and methods

Setting

The study used a nested case–control design for the analysis of Medicare beneficiaries with age ≥65 years who initiated and continued to receive clopidogrel therapy with or without a PPI between July 1, 2006 and December 31, 2008. The study was approved by the University of Mississippi Institutional Review Board and the data were accessed only after execution of a data use agreement with the Centers for Medicare and Medicaid Services (CMS).

Data source

The 2006–2008 5% national sample of Medicare administrative claims database was used for this study. Records for healthcare services offered to Medicare beneficiaries in various settings such as inpatient, outpatient, and skilled nursing facilities were available through the Medicare claims database. The database also included records for prescription drugs dispensed under Medicare Part D.
Beneficiary demographic and enrollment information was available through the Medicare Beneficiary Summary file. All claims were linked through an encrypted unique common beneficiary identification number.

**Study population**

The cohort used for this study consisted of Medicare beneficiaries who: (1) were ≥65 years of age as of January 1, 2006; (2) had continuous Medicare part A coverage and at least 1 month of Part B coverage from January 1, 2006 to December 31, 2008 or until death, whichever occurred first; and (3) had initiated clopidogrel therapy and did not have any gap of 30 days or more between clopidogrel fills between July 1, 2006 and December 31, 2008, since previous literature suggests that a gap of 30 days or more between prescription fills should be considered as non-persistence with therapy. Clopidogrel fills were identified from the Medicare Part D drug event file using the National Drug Codes for clopidogrel. Only incident users of clopidogrel, that is, beneficiaries who had no clopidogrel claims between January 1 and June 30, 2006 (i.e., the baseline period), were included in the study. Beneficiaries enrolled in Medicare health maintenance organizations for any part of the study period were also excluded since no medical claims were available for these beneficiaries in our dataset.

**Cases and controls**

In this study, our primary end point was a composite outcome of any major cardiovascular event (MCE) or all-cause mortality. MCEs considered in this study were acute myocardial infarction (AMI), stroke, receiving coronary artery bypass grafting (CABG) surgery, or receiving percutaneous coronary intervention (PCI). For patients experiencing more than one adverse event, the first occurrence of any of these events was deemed as the index event. Within the cohort of clopidogrel users, we defined cases as patients who experienced an index event between the date of the first prescription claim for clopidogrel and December 31, 2008. The date that a beneficiary experienced the index event was designated as the index date for cases. Cases were identified using the International Classification for Diseases, version 9, Clinical Modification (ICD9-CM) diagnosis and procedure codes and the CMS Common Procedure Coding System (HCPCS) codes from Medicare inpatient and outpatient claims data (Appendix 1). CABG was identified based on the primary and secondary procedure codes associated with the inpatient records. Since PCI may be performed as an outpatient procedure with a patient being discharged on the same day, we used primary and secondary procedure codes associated with inpatient and outpatient claims to identify PCI. We identified AMI based on the approach proposed by Kiyota et al. (2004), which has been found to have a high positive predictive value. For the identification of stroke, we used the algorithm suggested by Reker et al. (2001). Both AMI and stroke were identified using Medicare inpatient claims. All-cause mortality was determined using information from the Medicare Beneficiary Summary file. For each case, we selected one control from the cohort who did not experience a MCE or all-cause mortality; cases and their corresponding controls were matched on age (±5 years) and time to cohort entry (±7 days). Time to cohort entry was determined as the time between the start of the study period, July 1, 2006, and the date of the first clopidogrel fill. The index date for each control was set as the index date of the corresponding case to which it was matched (i.e., the date on which a MCE or all-cause mortality occurred).

**Clopidogrel and PPI use**

Information about use of clopidogrel and PPIs for each patient was obtained from the Medicare Part D drug event file. The PPIs considered in this study included omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole. Concomitant use of clopidogrel and PPIs in cases and controls was determined based on whether or not the beneficiary possessed the two drugs simultaneously between July 1, 2006 and the index date. Possession of the drugs was determined on a daily basis using the prescription fill date and the days’ supply field for each prescription. Early fills were taken into account by carrying forward the days of overlap between prescription fills. Concomitant use of clopidogrel and PPIs was considered as a dichotomous variable. Beneficiaries who possessed clopidogrel and a PPI together for one or more days between July 1, 2006 and the index date were considered as concomitant users of clopidogrel and PPIs, whereas those who did not possess the two drugs simultaneously were considered as clopidogrel only users.

**Covariates**

Covariates included in the study were baseline demographics (gender, and race), presence of end stage renal disease (ESRD), dual eligibility status, presence of important cardiovascular comorbidities (angina, chronic obstructive pulmonary disease [COPD], congestive heart failure, diabetes, hypertension, hyperlipidemia, and peripheral arterial disease), previous use of dialysis, and history of gastrointestinal disorders (including gastrointestinal bleeding, duodenal or gastric ulcer, gastroesophageal reflux disease, and erosive esophagitis), AMI, stroke, CABG, and PCI. Race was divided into three categories: white, black, and others. Presence of ESRD and dual
elibility were both considered as dichotomous variables. Presence of cardiovascular comorbidities, history of gastrointestinal disorders, previous use of dialysis, history of AMI, stroke, CABG, and PCI were determined based on the inpatient and outpatient claims at baseline (January 1 – June 30, 2006). In addition, we adjusted for the use of classes of medications which may affect the antiplatelet effect of clopidogrel including other CYP2C19 inhibitors (chloramphenicol, cimetidine, felbamate, fluoxetine, fluvoxamine, ketoconazole, moedafinil, and oxcarbazepine), CYP3A4 inhibitors (amiodarone, diltiazem, verapamil, voriconazole, fluconazole, nicardipine, and nifedipine), and sulfonylureas during the study period (July 1, 2006 – December 31, 2008)\textsuperscript{37}. We also adjusted for the use of drugs which have the potential to reduce the likelihood of adverse cardiovascular events such as angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, acetylsalicylic acid, β-adrenergic antagonists, calcium-channel antagonists, digoxin, spironolactone, statins, and diuretics during the study period\textsuperscript{31}. 

**Statistical analysis**

In the bivariate analyses, the chi-square test was used for the comparison of categorical variables whereas Student’s t-test was used for the comparison of continuous variables between cases and controls. Frequencies and percentages were reported for categorical variables, whereas means and standard deviations were reported for continuous variables. In the multivariable analysis, conditional logistic regression was performed on matched cases and controls to determine the association between concomitant clopidogrel use and PPI use and the occurrence of any MCE or all-cause mortality. The covariates listed earlier were adjusted for in the conditional logistic regression model. Odds ratios (OR) and 95% confidence intervals (CIs) were computed. In addition, we conducted a set of secondary analyses to test the robustness of our primary findings. Firstly, we evaluated the association between concomitant use of clopidogrel and PPIs and the occurrence of each individual adverse outcome (AMI, stroke, CABG, PCI, and all-cause mortality). Secondly, we computed the odds of experiencing any MCE or all-cause mortality. All analyses were performed using Statistical Analysis System (SAS) version 9.2 (SAS Institute Inc., Cary, NC, USA). The greedy algorithm was used for matching cases and controls. The SAS procedure PROC LOGISTIC with the STRATA statement was used for conditional logistic regressions.

**Results**

We identified 43,159 Medicare beneficiaries as incident clopidogrel users. Of these beneficiaries, 15,415 (35.7%) used clopidogrel and a PPI concomitantly at any time during the study period; 3502 (8.1%) experienced a MCE, 7306 (17.1%) died, and a total of 9908 (23.0%) experienced an adverse outcome (a MCE or all-cause mortality) during follow-up. The majority of the beneficiaries were female (61.5%) and white (84.0%). The mean age of the cohort was 76.8 years. Detailed patient demographic and clinical characteristics are presented in Table 1. Baseline demographic and comorbidity characteristics of the matched cases and controls are also presented in Table 1. For example, cases were more likely than controls to be males (39.5% vs. 33.8%, \(p<0.001\)) and blacks (8.9% vs. 7.9%, \(p<0.001\)). A greater percentage of cases had diabetes (32.6% vs. 29.4%, \(p<0.001\)), COPD (17.5% vs. 12.8%, \(p<0.001\)), and congestive heart failure (20.7% vs. 12.5%, \(p<0.001\)) than controls. A greater percentage of controls had hypertension (68.8% vs. 61.8%, \(p<0.001\)), hyperlipidemia (52.7% vs. 40.7%, \(p<0.001\)), esophageal reflux disease (13.2% vs. 11.0%, \(p<0.001\)) than controls. In terms of medication use, a greater percentage of cases were users of CYP3A4 inhibitors (5.2% vs. 4.5%, \(p=0.037\)), angiotensin-converting enzyme inhibitors (51.7% vs. 46.7%, \(p<0.001\)), β-adrenergic antagonists (74.0% vs. 68.6%, \(p<0.001\)), and sulfonylureas (18.3% vs. 15.3%, \(p<0.001\)) than controls. Controls were more likely to be users of angiotensin receptor antagonists (22.5% vs. 19.9%, \(p<0.001\)) and statins (67.3% vs. 60.3%, \(p<0.001\)) as compared to cases. 

From our primary analysis with conditional logistic regression performed on matched cases and controls, after extensive multivariable adjustment, we found that the estimated odds of experiencing the primary composite outcome (any MCE or all-cause mortality) were 26% higher for patients with concomitant use of clopidogrel conditions (such as cancer) also contribute to all-cause mortality. Most of these conditions have been taken into consideration in the calculation of CCI and previous research has shown that CCI is a significant predictor of all-cause mortality\textsuperscript{38}. Finally, we evaluated the association between concomitant use of clopidogrel and individual types of PPIs and the occurrence of the primary composite outcome of any MCE or all-cause mortality. All analyses
and a PPI as compared to patients who were taking clopidogrel only (OR: 1.26; 95% CI: 1.18–1.34, p < 0.001). In the secondary analyses, we found a significant effect of concomitant use of clopidogrel and a PPI on all-cause mortality (OR: 1.40; 95% CI: 1.29–1.53, p < 0.001), whereas the effects on individual cardiovascular events were not statistically significant (Table 2). The association between concomitant use of clopidogrel and PPIs and occurrence of any MCE was not statistically significant (OR: 1.06; 95% CI: 0.95–1.18, p = 0.305). In terms of association between concomitant use of clopidogrel and PPIs and all-cause mortality, the results on including CCI and cardiovascular comorbidities not included in the CCI calculation as covariates were similar to those obtained by including individual cardiovascular comorbidities as covariates (OR: 1.36; 95% CI: 1.25–1.47, p < 0.001). The results evaluating the effects of individual types of PPIs were similar to the results of our primary analysis (Table 3).

### Discussion

This study examined the risk of adverse outcomes associated with concomitant use of clopidogrel and PPIs in a national sample of elderly Medicare beneficiaries. To our knowledge, this is the first study evaluating the effect of clopidogrel–PPI interaction in the elderly population.
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Through a nested case–control design, we studied the association between concomitant use of clopidogrel and PPIs in patients with acute coronary syndromes or percutaneous coronary intervention (PCI) and found that concomitant use was associated with an increased risk of major cardiovascular events (OR: 1.27; 95% CI: 1.03–1.57) and revascularization (OR: 0.97; 95% CI: 0.84–1.70) compared to patients not using clopidogrel. These findings are consistent with the results of previous observational studies. However, the results of our study were not statistically significant in patients with acute myocardial infarction or death (OR: 1.22; 95% CI: 0.99–1.51) and were only marginally significant in patients with stroke (OR: 1.05; 95% CI: 0.86–1.28). The associations were also not statistically significant in patients taking other PPIs, except for pantoprazole (OR: 1.25; 95% CI: 1.16–1.34). These results suggest that the potential interaction between clopidogrel and PPIs may be more pronounced in elderly AMI patients who were prescribed clopidogrel within 3 days of discharge from a local hospital. They also found a significant association between readmission for AMI and current use of a PPI (most recent prescription fill for a PPI within 30 days before readmission for AMI or death) (OR: 1.27; 95% CI: 1.03–1.57). However, a significant association between readmission for AMI and PPI use was not observed by the authors in previous users of clopidogrel, who had their most recent prescription fill for a PPI 31–90 days before readmission for AMI or death, and in remote users of clopidogrel, who had their most recent prescription fill for a PPI 91–180 days before readmission for AMI or death.

Regarding the effect of the concomitant use of clopidogrel and PPIs in elderly patients with acute myocardial infarction or death, the results were statistically significant across all types of PPIs. The significant interaction between clopidogrel and PPIs was associated with an increased but not statistically significant risk of myocardial infarction or death (OR: 1.22; 95% CI: 0.99–1.51) and revascularization (OR: 0.97; 95% CI: 0.84–1.70) were also found to be non-significant in this study. In a Canadian study, Juurlink et al. (2009) studied elderly AMI patients who were prescribed clopidogrel within 3 days of discharge from a local hospital. They found a significant association between readmission for AMI and current use of a PPI (most recent prescription fill for a PPI within 30 days before readmission for AMI or death) (OR: 1.27; 95% CI: 1.03–1.57). However, a significant association between readmission for AMI and PPI use was not observed by the authors in previous users of clopidogrel, who had their most recent prescription fill for a PPI 31–90 days before readmission for AMI or death, and in remote users of clopidogrel, who had their most recent prescription fill for a PPI 91–180 days before readmission for AMI or death.

As far as the effect of the clopidogrel–PPI interaction in the general population is concerned, some observational studies have found an increased risk of cardiovascular events, whereas others have found no statistically significant effect. Since these studies consisted of patient populations that included younger individuals, direct comparison of findings from our study with these studies was not possible.

Regarding the effect of concomitant use of clopidogrel and PPIs in elderly patients with acute myocardial infarction or death, the results were statistically significant across all types of PPIs. The significant interaction between clopidogrel and PPIs was a little unexpected, given that previous mechanistic studies and observational studies evaluating the potency of PPIs in CYP2C19 inhibition showed that

### Table 2. Association between concomitant use of clopidogrel and proton pump inhibitors and adverse health outcomes.

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Odds ratioa</th>
<th>95% confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MCE or all-cause mortalityb</td>
<td>1.26</td>
<td>1.18–1.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Individual adverse outcomeb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>0.85</td>
<td>0.59–1.23</td>
<td>0.391</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.05</td>
<td>0.86–1.28</td>
<td>0.609</td>
</tr>
<tr>
<td>CABG</td>
<td>0.82</td>
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<td>0.356</td>
</tr>
<tr>
<td>PCI</td>
<td>1.11</td>
<td>0.94–1.31</td>
<td>0.227</td>
</tr>
<tr>
<td>All-cause mortality</td>
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</tr>
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</table>

aAdjusted for all patient characteristics (covariates) in Table 1 except for age, time to cohort entry, and Charlson comorbidity index.

bObtained from conditional logistic regressions performed on cases and controls matched on age (±5 years) and time to cohort entry.

### Table 3. Association between concomitant use of clopidogrel and individual types of proton pump inhibitors and major adverse cardiovascular events or all-cause mortalityc.

<table>
<thead>
<tr>
<th>Proton pump inhibitor</th>
<th>Odds ratioa</th>
<th>95% confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>1.23</td>
<td>1.14–1.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>1.17</td>
<td>1.09–1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lanzoprazole</td>
<td>1.18</td>
<td>1.09–1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>1.20</td>
<td>1.12–1.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>1.25</td>
<td>1.16–1.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

aAdjusted for all patient characteristics (covariates) in Table 1 except for age, time to cohort entry, and Charlson comorbidity index.

bObtained from conditional logistic regressions performed on cases and controls matched on age (±5 years) and time to cohort entry (±7 days).

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Using a national sample, elderly patients on clopidogrel therapy have an increased tendency to gastrointestinal bleeding and hence need effective medications such as PPIs for gastrointestinal protection. On the other hand, they may be more prone to be affected by a potential clopidogrel–PPI interaction. Although a previous randomized controlled study has examined the potential interaction between clopidogrel and omeprazole in an elderly population, this study adds to the literature by determining the real-world effect of the clopidogrel–PPI interaction in this vulnerable population.

Through a nested case–control design, we studied the association between concomitant use of clopidogrel and PPIs and the risk of experiencing a MCE or all-cause mortality using the 5% national sample of Medicare beneficiaries. We found that the risk of experiencing this composite outcome was 26% higher among elderly Medicare beneficiaries using clopidogrel and a PPI concomitantly as compared to beneficiaries using clopidogrel only. Results from our secondary analyses indicate that concomitant use of clopidogrel and PPIs is associated with significantly increased risk for all-cause mortality, but not for MCEs. The significant association between concomitant clopidogrel and PPI use and occurrence of all-cause mortality held even after controlling for CCI in the secondary analysis. These results suggest that all-cause mortality was the major contributor to our primary finding of statistically significant association between concomitant use of clopidogrel and PPI and adverse health outcomes. These results are somewhat consistent with the findings from two previous studies focusing on the elderly population. Rassen et al. (2009) evaluated the clopidogrel–PPI interaction in low-income patients enrolled in three health insurance programs in British Columbia, New Jersey, and Pennsylvania. They studied patients aged ≥65 years who were hospitalized for ACS or PCI between 2001 and 2005. They found that concomitant use of clopidogrel and PPIs was associated with an increased but not statistically significant risk of myocardial infarction or death (OR: 1.22; 95% CI: 0.99–1.51). The associations between concurrent clopidogrel and PPI use and occurrence of individual outcomes of death (OR: 1.20; 95% CI: 0.84–1.70) and revascularization (OR: 0.97; 95% CI: 0.79–1.21) were also found to be non-significant in this study. In a Canadian study, Juurlink et al. (2009) studied elderly AMI patients who were prescribed clopidogrel within 3 days of discharge from a local hospital. They found a significant association between readmission for AMI and current use of a PPI (most recent prescription fill for a PPI within 30 days before readmission for AMI or death) (OR: 1.27; 95% CI: 1.03–1.57). However, a significant association between readmission for AMI and PPI use was not observed by the authors in previous users of clopidogrel, who had their most recent prescription fill for a PPI 31–90 days before readmission for AMI or death, and in remote users of clopidogrel, who had their most recent prescription fill for a PPI 91–180 days before readmission for AMI or death.
pantoprazole had the least inhibitory potency\(^39\)–\(^44\). Significant interaction between clopidogrel and pantoprazole was also observed in studies by Kreutz et al.\(^11\) and Stockl et al.\(^45\), suggesting that a different mechanism may be associated with the interaction between clopidogrel and PPIs. Results concerning the clopidogrel–pantoprazole interaction in studies focusing on elderly adults have been inconsistent. While Rassen et al.\(^32\) observed no difference in rate ratios for adverse outcomes in pantoprazole and other PPI users, Juurlink et al.\(^31\) found that current pantoprazole users were less likely to experience adverse outcomes compared to other PPI users. Future efforts are needed to further explore the mechanism underlying the interaction between clopidogrel and PPIs.

Our study has a number of strengths. To our knowledge, this is the only study evaluating the effect of concomitant use of clopidogrel and PPIs in older adults using a national sample. Second, we have included all clopidogrel users in the study unlike other studies which have concentrated on a specific set of users such as individuals hospitalized for ACS or PCI\(^32\) or AMI\(^31\). We believe this broad-based patient inclusion makes findings from our study more generalizable. Furthermore, we have taken utmost care to eliminate many sources of confounding in our study. For example, we have adjusted for the presence of major cardiovascular comorbidities such as hypertension, diabetes, and congestive heart failure, which usually lead to adverse cardiovascular events. We also adjusted for the use of medications which may potentially affect clopidogrel’s anti-platelet effect. Additionally, we included CCI as a covariate in our analysis to determine the effect of clopidogrel–PPI interaction on all-cause mortality.

Several limitations of our study need to be addressed. Due to limitations of the data source, we could not identify from our cohort, beneficiaries who were poor metabolizers of clopidogrel due to genetic polymorphisms of the cytochrome P450 enzyme CYP2C19. Poor clopidogrel metabolizers may be more likely to experience adverse cardiovascular outcomes or mortality. Using Medicare administrative claims data, we were also unable to identify over-the-counter use of PPI medications (omeprazole and lansoprazole). It is possible that clopidogrel only users would be more likely to have purchased over-the-counter PPIs than those who have received prescription PPIs. Similarly, we were unable to account for the over-the-counter use of aspirin, which is generally used with clopidogrel to treat peripheral arterial diseases or ACS because aspirin is often available over the counter. In addition, although we have tried to minimize confounding by indication through controlling for history of gastrointestinal disorders (including gastrointestinal bleeding, duodenal or gastric ulcer, gastroesophageal reflux disease, and erosive esophagitis) in our analyses, there may be other sources of confounding by indication which are not captured by our data such as uncoded diagnoses of gastrointestinal disorders or a physician’s impression that a given patient is at an increased risk for gastrointestinal problems. Furthermore, in our analyses, we could not account for unmeasured factors such as smoking, blood pressure level, serum cholesterol level, and family history of cardiovascular disease, which are likely to affect cardiovascular outcomes. We used Medicare beneficiaries’ prescription drug filling data to identify medication uses. Though the beneficiaries possessed the medications, we were not able to verify whether they actually took them. Nonetheless, previous research has shown that filling a prescription is usually consistent with taking the drug\(^46\). Finally, causes of death were not available from our data therefore all-cause mortality, and not cardiovascular mortality, was used as an outcome measure in our study.

### Conclusion

We found a slightly increased risk of experiencing any MCE or all-cause mortality in elderly adults using clopidogrel and PPIs concomitantly. These results were consistent across all PPIs. The associations between concomitant clopidogrel and PPI use and occurrence of MCEs, considered individually or as a group, were not statistically significant, while the odds of all-cause mortality were higher in elderly concomitant users of clopidogrel and PPIs. Since the reasons of death were unidentifiable from our data, considering the fact that all-cause mortality can occur due to non-cardiovascular reasons, the results for the association between concomitant clopidogrel and PPI use and all-cause mortality might have been biased away from the null in spite of controlling for CCI in the secondary analyses. Therefore, findings from this study do not present conclusive evidence to suggest avoiding PPIs in elderly patients on anti-platelet therapy with clopidogrel. Conservatively, other gastrointestinal protecting agents such as histamine-2-receptor antagonists could be considered\(^47\).

### Transparency

**Declaration of funding**

This study was sponsored by the Centers for Medicare and Medicaid Services (CMS).

**Declaration of financial/other relationships**

R.K.M., Y.Y., M.V.D., J.P.B., M.W.S., B.F.B., and K.D.N. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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Appendix 1. ICD9-CM and HCPCS codes used to identify cardiovascular outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICD-9-CM codes</th>
<th>HCPCS codes</th>
</tr>
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<tbody>
<tr>
<td>AMI</td>
<td>410.X0 and 410.X1&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Stroke</td>
<td>primary diagnosis code of 430.xx–434.xx, 436.xx, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91 or primary diagnosis code of V57.xx and any secondary diagnosis code of 342.xx, 430.xx, 431.xx, 432.xx, 433.xx, 434.xx, 435.xx, 436.xx, 437.xx or 438.xx or primary diagnosis code of 433.xx or 435.xx and any secondary diagnosis code of 342.xx, 430.xx, 431.xx, 432.xx, 434.xx, or 436.xx&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>36.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33510–33514, 33516, 33533–33536, 33517–33519 33521–33523, S2205–S2209</td>
</tr>
<tr>
<td>PCI</td>
<td>36.01, 36.02, 36.05, 00.66, 36.06, 36.07&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92982, 92984, 92995, 92996, 92980, 92981, 92973–92975, 92978, 92979, 90290, 90291, C1753</td>
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</table>

<sup>a</sup>ICD9-CM diagnosis codes.
<sup>b</sup>ICD9-CM procedure codes.
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; AMI = acute myocardial infarction; ICD9-CM = International Classification for Diseases version 9 Clinical Modification; HCPCS = Centers for Medicare and Medicaid Services Common Procedure Coding System.