

Individual Proton Pump Inhibitors and Outcomes in Patients With Coronary Artery Disease on Dual Antiplatelet Therapy: A Systematic Review

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Background—Observational studies evaluating the possible interaction between proton pump inhibitors (PPIs) and clopidogrel have shown mixed results. We conducted a systematic review comparing the safety of individual PPIs in patients with coronary artery disease taking clopidogrel.

Methods and Results—Studies performed from January 1995 to December 2013 were screened for inclusion. Data were extracted, and study quality was graded for 34 potential studies. For those studies in which follow-up period, outcomes, and multivariable adjustment were comparable, meta-analysis was performed. The adjusted odds or hazard ratios for the composite of cardiovascular or all-cause death, myocardial infarction, and stroke at 1 year were reported in 6 observational studies with data on individual PPIs. Random-effects meta-analyses of the 6 studies revealed an increased risk for adverse cardiovascular events for those taking pantoprazole (hazard ratio 1.38; 95% CI 1.12–1.70), lansoprazole (hazard ratio 1.29; 95% CI 1.09–1.52), or esomeprazole (hazard ratio 1.27; 95% CI 1.02–1.58) compared with patients on no PPI. This association was not significant for omeprazole (hazard ratio 1.16; 95% CI 0.93–1.44). Sensitivity analyses for the coronary artery disease population (acute coronary syndrome versus mixed) and exclusion of a single study due to heterogeneity of reported results did not have significant influence on the effect estimates for any PPIs.

Conclusions—Several frequently used PPIs previously thought to be safe for concomitant use with clopidogrel were associated with greater risk of adverse cardiovascular events. Although the data are observational, they highlight the need for randomized controlled trials to evaluate the safety of concomitant PPI and clopidogrel use in patients with coronary artery disease. (*J Am Heart Assoc.* 2015;4:e002245 doi: 10.1161/JAHA.115.002245)

Key Words: adverse cardiovascular outcomes • clopidogrel • coronary artery disease • medication interaction • proton pump inhibitor

In patients with acute coronary syndromes (ACS), dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor improves cardiovascular (CV) outcomes and is recommended by national guidelines for 1 year after initial hospitalization.^{1,2} Clopidogrel, now available in generic form, remains the most widely used P2Y12 inhibitor taken by post-

ACS outpatients. Clopidogrel is a prodrug that depends on cytochrome P450, or CYP, liver enzymes to metabolize it into active form. Due to the increased risk of gastrointestinal (GI) bleeding associated with clopidogrel and DAPT, many post-ACS patients are also started on a proton pump inhibitor (PPI) or H₂ receptor antagonist. PPI medications (the most frequently prescribed drugs to reduce the risk of GI bleeding) also interact with the CYP liver enzymes and thus may inhibit the conversion of clopidogrel to its active metabolite and potentially alter its efficacy. Several observational studies have been completed to evaluate possible medication interaction between PPI and DAPT and its association with CV outcomes.^{3–6} These studies have had mixed results, with some showing a potential interaction between clopidogrel and PPIs that is associated with worse CV outcomes and others showing no association with outcomes. Very few randomized data are available to answer this question, and a recently meta-analysis of this topic concluded that observational and randomized data on PPIs have divergent results.⁷

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Despite conflicting data and possible equipoise in the field, the US Food and Drug Administration issued a black box warning about the use of clopidogrel concomitant with PPI agents, specifically, omeprazole and esomeprazole, for which there is the most experience; in the case of omeprazole, data are from both observational and randomized, controlled studies. Uncertainty remains about extending this association to other PPIs because there seems to be variation in efficacy among drugs in this class. Each PPI has a differential effect on CYP metabolism and thus may have incongruous effects on clopidogrel metabolism and subsequent CV outcomes. Recent meta-analyses have grouped all PPIs together, likely for greater power, to evaluate the relationship among PPIs, clopidogrel, and CV outcomes⁸; however, based on pharmacology, there may be differential interactions between individual PPIs and clopidogrel. The aim of this study is to determine the relationship between individual PPI medications and adverse CV events in patients with both acute and stable coronary artery disease (CAD) taking clopidogrel.

Methods

A systematic review was performed to evaluate the current literature and to collect and synthesize available data. This analysis was part of a broader systematic review assessing the effectiveness and safety of antiplatelet and anticoagulant medications used to treat patients with unstable angina and non-ST-segment elevation myocardial infarction (MI).⁹ The broader systemic review was funded from the Agency for Healthcare Research and Quality. The National Library of Medicine medical subject headings keyword nomenclature was used. The search areas for inclusion in this study were PubMed, Embase, and the Cochrane Database of Systematic Reviews from January 1, 1995, to December 30, 2013. The gray literature areas of research, including registries, conference abstracts, and completed studies, were also searched for relevant articles to include in our analysis (ClinicalTrials.gov, World Health Organization, International Clinical Trials Registry Platform Search Portal, ProQuest Conference Papers index).

Study Population

Study designs included were cohort (prospective and retrospective), case-control, and cross-sectional. There were very few randomized controlled trials for data, and the inclusion of their data would not have been reasonable for statistical and conceptual reasons. Studies were included if they were English-language studies comparing the concomitant use of clopidogrel and PPIs in the postdischarge treatment of patients with ACS or those undergoing percutaneous coronary intervention for CV outcomes and follow-up for at least

1 year. The studies must also have analyzed individual PPIs separately, including but not limited to omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole. Studies were excluded if they did not provide outcomes analyses for individual PPIs or if they had follow-up for <12 months or if they did not provide multivariable modeling with adjusted odds ratios (ORs) or hazard ratios (HRs). Outcomes of interest included the composite CV outcomes of CV and/or all-cause mortality, nonfatal MI, stroke, rehospitalization, and revascularization.

Study Selection

The studies were graded on the quality of data provided. Articles were independently reviewed by 2 investigators (C.M. and J.W.), and a third investigator served as an arbitrator in cases of disagreement (R.D.). Studies were included based on the aforementioned inclusion criteria and then were examined for data abstraction.

Statistical Methods

Data abstraction

Data abstraction forms and evidence tables were created to collect and summarize source data. The tables contained information on the study population, the individual PPI agents included in the study, outcomes measured, time of follow-up, and unadjusted and adjusted point estimates. The data were initially abstracted by a single investigator, with review for completeness and errors performed by a second investigator.

Data synthesis

The primary literature was summarized by abstraction of ORs and HRs reported by the authors. We expected that the relationship between omeprazole and adverse CV events could be confounded by multiple factors, many of which were risk factors for both GI bleeding risk and CV risk. These included age, sex, weight, renal function, and other medical comorbidities including previous GI bleeding. These factors were typically incorporated into multivariable logistic regression or propensity modeling for the studies that we included in our analyses. If available, we evaluated each study for the inclusion of information on the use of appropriate concomitant secondary prevention medications for CAD.

Both unadjusted and adjusted ORs and HRs were initially considered for the analysis. Random-effects modeling was used. Meta-analyses of direct comparison were performed if outcomes and follow-up periods were found to be comparable. An assessment of publication bias by constructing a funnel plot of samples, plotting study sample size versus

reported ORs or HRs (log scale), was planned if the number of studies were sufficient (ie >10). Sensitivity analyses were performed including tests for possible heterogeneous effects (Q statistic) if only ACS patients were included versus a mixed (stable and ACS) population. If any 1 study was found to have disparate results, a “one-out” sensitivity analysis was performed to determine whether there was any significant change in the results. All statistical analyses of the aggregate, deidentified data were performed by the Duke Clinical Research Institute using Comprehensive Meta-Analysis version 2 (Biostat).

Results

On searching the literature, 36 potential studies were initially identified for further evaluation. After application of the aforementioned exclusion criteria (Figure 1), 2 studies were excluded as duplicates, and 4 randomized controlled trials were excluded. In addition, 24 studies were excluded after being found to lack data on 1-year follow-up and outcomes for individual PPIs. The final study sample included 6 observational studies, 5 of good quality and 1 of fair quality, that included >41 000 patients^{4–6,10–12} (Table 1). In the specified studies within our sample, data on outcomes were available for omeprazole, esomeprazole,

pantoprazole, lansoprazole, and rabeprazole. Due to data constraints, rabeprazole was excluded from further analyses because insufficient data were available to synthesize. We also found that the use of concomitant medications was excellent (>75%) including aspirin, beta blockers, and statins and more variable use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in studies that reported these data (all studies except that by Kreutz et al¹⁰).

Omeprazole

Six observational studies including 10 201 patients assessed the effect of omeprazole when added to DAPT in both stable CAD and postdischarge ACS patients for the composite end point of CV or all-cause mortality, nonfatal MI, and stroke at 1 year.^{4–6,10–12} The result was an estimated HR of 1.16 (95% CI 0.93–1.44) (Figure 2A). There was evidence of extreme heterogeneity (Q value 28.70 for 5 *df*, *P*<0.001). The *I*² value was 82.58.

Pantoprazole

Six observational studies including 15 620 patients assessed the effect of pantoprazole when added to DAPT in both stable CAD and postdischarge ACS patients for the composite end point of CV or all-cause mortality, nonfatal MI, and stroke at 1 year.^{4–6,10–12} The result was an estimated HR of 1.38 (95% CI 1.12–1.70) (Figure 2B). There was evidence of extreme heterogeneity (Q value 36.50 for 5 *df*, *P*<0.001). The *I*² value was 86.30.

Lansoprazole

Five observational studies assessed the effect of lansoprazole when added to DAPT in 4681 stable and post-ACS CAD patients for the composite end point of CV or all-cause mortality, nonfatal MI, and stroke at 1 year.^{4–6,10,11} The result was an estimated HR of 1.29 (95% CI 1.09–1.52) (Figure 2C). There was no evidence of significant heterogeneity (Q value 5.89 for 4 *df*, *P*=0.208). The *I*² value was 32.07.

Esomeprazole

Six observational studies including 11 200 patients assessed the effect of esomeprazole when added to DAPT in both stable CAD and postdischarge ACS patients for the composite end point of CV or all-cause mortality, nonfatal MI, and stroke at 1 year.^{4–6,10–12} The result was an estimated HR of 1.27 (95% CI 1.02–1.58) (Figure 2D). There was evidence of extreme heterogeneity (Q value 27.28 for 5 *df*, *P*<0.001). The *I*² value was 81.67.

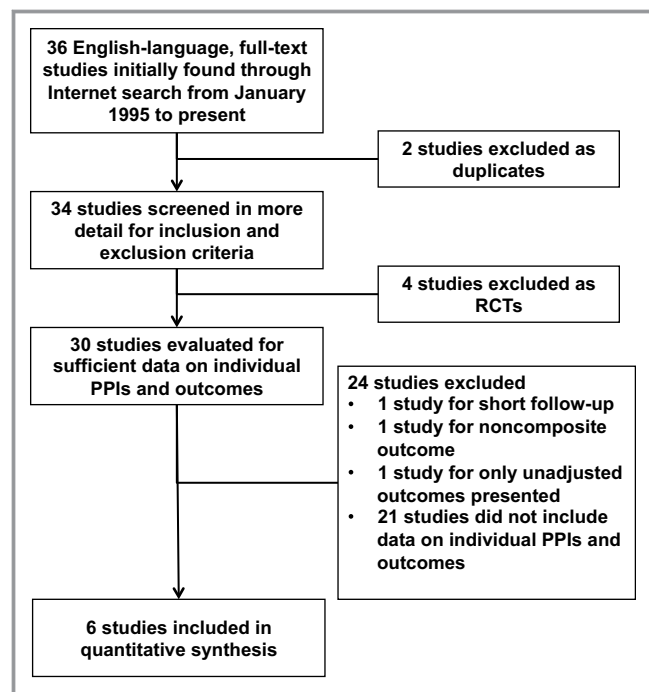


Figure 1. Study selection sample flow diagram depicting the results of our literature search and resulting exclusion of studies from quantitative analyses. PPIs indicates proton pump inhibitors; RCT, randomized controlled trial

Table 1. Study Characteristics

Study; Population; Quality	Total Sample Size* PPI vs No PPI Samples	PPIs, n (%)	Outcomes/Time Period	Number of Outcomes	Covariates for Adjusted OR/HR
Kreutz, 2010 ¹⁰ ; general PCI population; good	Total: 16 690 PPI: 6828 No PPI: 9862	Omeprazole, 2307 (34%) Pantoprazole, 1653 (24%) Lansoprazole, 785 (11%) Esomeprazole, 3257 (48%)	Composite 1-year CV mortality, nonfatal MI, stroke, revascularization	Total: 3476; No PPI: 1766; PPI: 1710	Age, sex, hospitalization, stent, DM, HTN, CHF, CRI, HL, Meds
Ray, 2010 ⁵ ; mixed PCI population; good	Total: 20 596 PPI: 7226 No PPI: 8995	Omeprazole, 683 (9%) Pantoprazole, 4708 (62%) Lansoprazole Esomeprazole Rabeprazole	Composite 1-year CV mortality, nonfatal MI, stroke, sudden cardiac death	Total: 1041; No PPI: 580; PPI: 461	Age, sex, health insurance, CABG, PCI, meds, CHF, stroke, PAD
Simon, 2011 ¹¹ ; FAST-MI, all MI population; good	Total: 2744 PPI: 1449 No PPI: 900	Omeprazole, 993 (69%) Pantoprazole, 99 (7%) Lansoprazole, 46 (3%) Esomeprazole, 311 (22%)	Composite 1-year total mortality, nonfatal MI, stroke	Total: 225; No PPI: 100; PPI: 125	GRACE score, sex, smoking, HL, HTN, DM
Van Boxel, 2010 ¹² ; mixed CAD population; fair	Total: 18 139 PPI: 5734 No PPI: 12 405	Omeprazole, 1826 (32%) Pantoprazole, 2618 (46%) Esomeprazole, 1092 (19%) Rabeprazole, 133 (2%)	Composite 1-year total mortality, nonfatal MI, stroke, UA	Total: 1584 No PPI: 830; PPI: 754	Age, Gender, Meds, CHF, MI, CVD, COPD, CRI, DM, PUD
Charlot, 2010 ⁶ ; all MI population; good	Total: 56 406 PPI: 6753 No PPI: 17 949	Omeprazole, 2717 (17%) Pantoprazole, 4698 (30%) Lansoprazole, 2798 (18%) Esomeprazole, 5316 (34%)	Composite 1-year CV mortality, nonfatal MI, stroke	Total: 2564; No PPI: 1506; PPI: 1058	Age, gender, income, shock, DM, PUD, PCI, pulmonary edema, CVD, cancer, arrhythmia, CRI, ARF, meds
O'Donoghue 2009 ⁴ ; TRITON-TIMI 38, ACS population; good	Total: 13 608 PPI: 4529 No PPI: 9079	Omeprazole, 1675 (37%) Pantoprazole, 1844 (41%) Lansoprazole, 441 (10%) Esomeprazole, 613 (14%)	Composite 1-year CV mortality, MI, stroke	Total: 781; No PPI: 526; PPI: 255	Age, sex, ethnicity, HTN, HL, DM, Tob, index event, previous MI, CABG, CVD, PAD, CrCl, DES, Meds, BMI, Hgb, BP, heart rate

ACS indicates acute coronary syndromes; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRI, chronic renal insufficiency; CV, cardiovascular; CVD, cerebrovascular disease; DES, drug eluting stent; DM, diabetes mellitus; Hgb, hemoglobin; HR, hazard ratio; HTN, hypertension; meds, concomitant medications; MI, myocardial infarction; OR, odds ratio; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PUD, peptic ulcer disease; UA, unstable angina.

*For each study, the sample size shown is for patients also taking clopidogrel.

Sensitivity Analyses

Given the heterogeneity present in our results, we performed several sensitivity analyses. To explore potential heterogeneity within the study sample, we divided studies into groups: ACS-only versus mixed or stable CAD populations. As seen in Table 2, there were no significant changes to the resultant summary HRs (with wider CIs) in either the ACS-only or mixed population groups for any of the individual PPIs.

To further explore the effect of a possible outlier study, we repeated the entire analysis excluding the study by Simon et al due to the use of ORs and the small sample size (Figure 3A and 3B). As seen in Figure 3, there were no significant changes for the summary HR estimates for any of the individual PPIs or for the overall PPI effect estimate. Finally, given that the number of studies included in the quantitative analyses was substantially <10, publication bias analyses were not pursued because the power of those tests

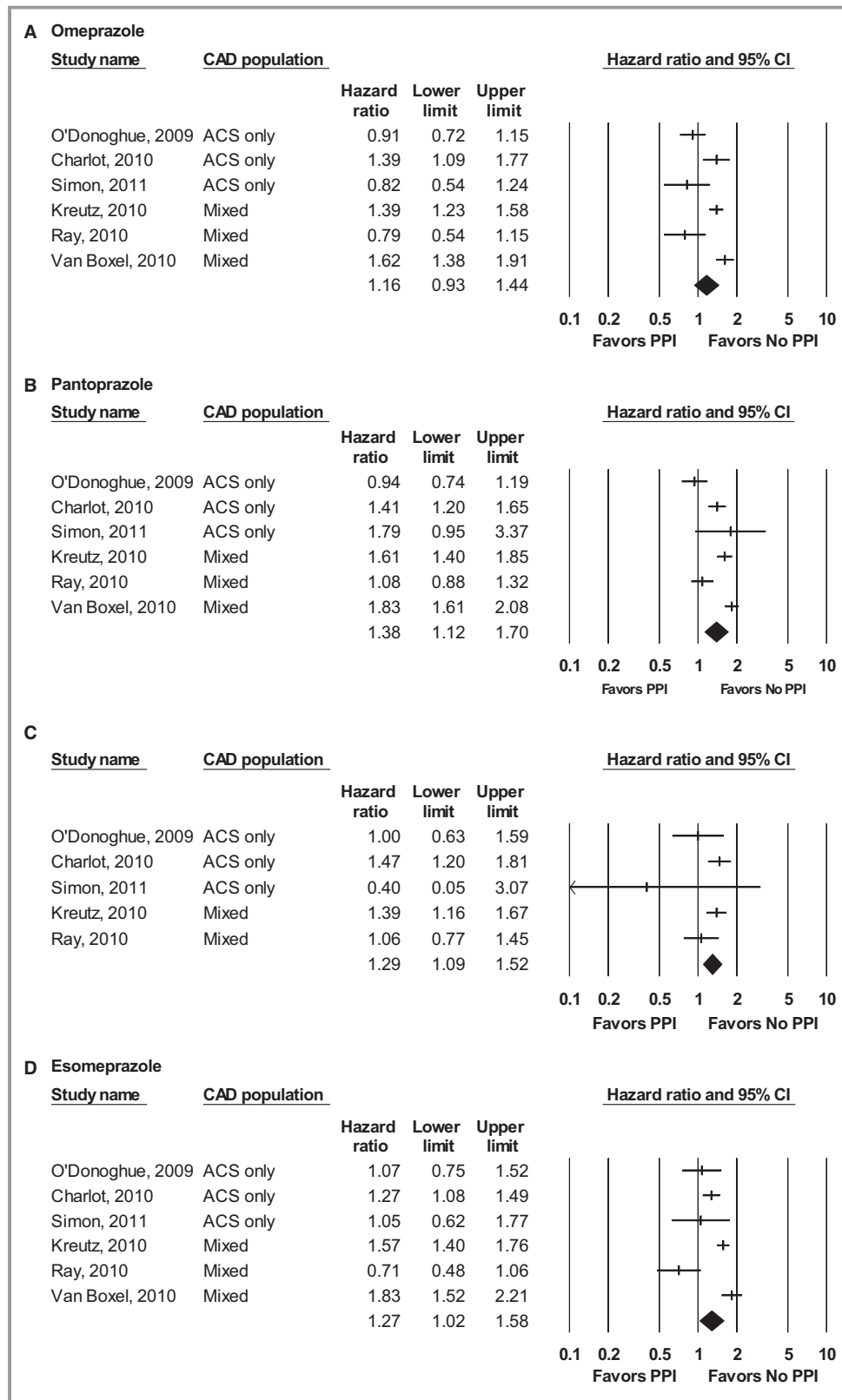


Figure 2. Results of individual PPI meta-analyses across included studies: (A) omeprazole, (B) pantoprazole, (C) lansoprazole, (D) esomeprazole. ACS indicates acute coronary syndromes; CAD, coronary artery disease; PPI, proton pump inhibitor.

Table 2. Sensitivity Analyses based upon CAD Population for Individual PPIs

Drug	CAD Population	Studies (n)	Effect Size (95% CI)	P Value for Heterogeneity
Omeprazole	ACS only	3	1.04 (0.76–1.41)	0.31
	Mixed	3	1.28 (0.97–1.71)	
Pantoprazole	ACS only	3	1.29 (0.89–1.77)	0.45
	Mixed	3	1.49 (1.14–1.95)	
Lansoprazole	ACS only	3	1.26 (0.91–1.74)	0.96
	Mixed	2	1.24 (0.92–1.68)	
Esomeprazole	ACS only	3	1.15 (0.83–1.60)	0.57
	Mixed	3	1.37 (1.01–1.85)	

ACS indicates acute coronary syndromes; CAD, coronary artery disease.

is not great enough to provide accurate estimates of bias with small sample sizes.^{13,14}

Discussion

In a systematic review of observational data available for the association of individual PPIs with adverse cardiac outcomes in CAD patients on clopidogrel, several PPIs previously assumed to be safe were found to have an association with harm. Omeprazole did not have a statistically significant association with adverse CV events, independent of CAD status (ACS versus stable CAD), whereas pantoprazole, lansoprazole, and esomeprazole were all significantly associated with adverse CV outcomes. There remains a need for

randomized controlled trials or patient-level meta-analyses to evaluate the safety of individual PPIs for concomitant use with clopidogrel in patients with CAD.

Although an abundance of observational data from individual studies shows a relationship between PPIs (as a group) and adverse CV outcomes, there are several plausible explanations for those findings. The most compelling argument remains that PPI use is a marker for high risk rather than a cause of poor CV outcomes. This is well illustrated by several studies of both clopidogrel and newer generation P2Y₁₂ antagonists. Goodman et al evaluated the effect of PPIs on adverse CV events in post-ACS patients taking either ticagrelor or clopidogrel in the PLATO trial.¹⁵ An important distinction is that although ticagrelor blocks the P2Y₁₂ receptor, it is an active compound and thus, unlike clopidogrel, does not require metabolism by the CYP 2C19 system for activation. As such, there is no pharmacokinetic mechanism for interaction between PPIs and ticagrelor. The authors showed that patients taking PPIs or other non-PPI GI drugs had significantly higher rates of adverse CV events in both the clopidogrel and ticagrelor treatment groups. Using landmark analyses for the start of PPIs either at the time of randomization or subsequently during the trial (day 2, 4, 9, 30, 60, 90, or 180), PPIs were only independently associated with adverse cardiac events if patients started them prior to or at randomization. These authors concluded that the most reasonable explanation for these findings was that PPI use served as a marker of patients at high risk for CV events and that the association of events with PPIs for patients on clopidogrel and ticagrelor was heavily confounded. Dunn et al came to a similar conclusion in analyzing the results of the CREDO trial for patients with and without the use of PPIs.¹⁶

Alternative mechanisms have been proposed to explain the association of PPIs with adverse CV events. In a large-scale pharmacovigilance study, Shah et al examined the use of PPIs in an unselected group of patients to evaluate the association of PPIs with CV events and mortality. In their study, regardless

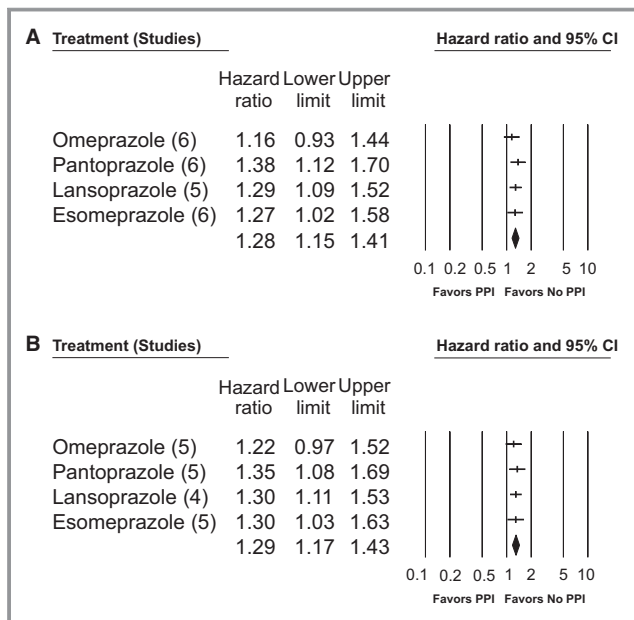


Figure 3. Sensitivity analyses of overall PPI effect (A) with and (B) without the study by Simon et al.¹¹ PPI indicates proton pump inhibitor.

of clopidogrel use, patients taking PPIs were at increased hazard for MI (HR 1.16; 95% CI 1.09–1.24) and a 2-fold high hazard for all-cause mortality (HR 2.00; 95% CI 1.07–3.78; $P=0.031$) compared with patients not taking PPIs.¹⁷ They did not find a similar association in patients on H2 receptor blocking agents. Although the exact mechanism by which PPIs would have this effect on a general population is unknown, the authors point to previous animal model studies indicating that PPI administration may be associated with decreased nitric oxide synthase activity, which is a known marker for vascular health and thrombosis. Although these findings are intriguing, they do not help elucidate the possible interaction between clopidogrel and PPIs. The most valid method to evaluate the relationship of PPIs and clopidogrel remains a randomized controlled trial.

At present, very little randomized controlled trial evidence is available to answer this question. Smaller randomized controlled trials have been performed with pantoprazole¹⁸ and omeprazole,¹⁹ evaluating platelet reactivity and function as end points. These studies showed that platelet reactivity is higher in patients on concomitant clopidogrel and omeprazole therapy compared with those on clopidogrel alone or those on clopidogrel and concomitant pantoprazole; however, none of these studies were large enough or adequately powered to study clinical outcomes. The COGENT trial was designed to evaluate the effect of omeprazole versus placebo on thrombotic and bleeding outcomes in patients prescribed DAPT with clopidogrel for at least 12 months.²⁰ The trial enrolled only patients who were expected to receive at least 12 months of DAPT (with clopidogrel) and were not currently taking PPIs, H2 receptor antagonists, or other antacid GI agents. Unfortunately, the trial was stopped prematurely due to slow enrollment and lack of funding, but with the limited sample size and follow-up available, patients taking omeprazole and DAPT versus those on DAPT alone had a similar risk of thrombotic events and a significantly decreased risk of GI bleeding. To date, these data represent the best available on the relationship between an individual PPI and adverse CV outcomes in patients with CAD. Despite these findings, the US Food and Drug Administration still issued a warning about the combination of omeprazole or esomeprazole with clopidogrel based on observational data.

When few randomized controlled trial data are available, researchers will often try to combine the best sources of data available to reach conclusions. Systematic reviews with meta-analysis enable researchers and clinicians to use the findings across multiple studies and to increase power to answer important clinical questions. The results of our systematic review are consistent with a previous randomized controlled study²⁰ indicating that omeprazole is not associated with adverse CV events in patients with CAD on concomitant

clopidogrel. For the remaining individual PPIs, including pantoprazole, lansoprazole, and esomeprazole, our observational results add to previous literature but are strictly hypothesis generating and point to the need for more randomized controlled trial evidence evaluating the efficacy and safety of these PPIs in patients with CAD on concomitant clopidogrel. There is currently no solid evidence to prompt the change of an individual PPI therapy to another to avoid interaction with clopidogrel. At this time, due to inconsistencies in the available data, consideration should be given to changing the guidelines to reflect this uncertainty.

Limitations

Our study had several limitations. Detailed data on drug regimen and duration and GI bleeding events were not available in all studies. There was variation in composite end point definition and covariates used in adjusted OR or HR, such as the use of all-cause versus CV mortality, which may have introduced some imprecision into our effect estimates. In addition, we performed meta-analysis combining HRs and ORs, which can be of questionable statistical validity if event rates are high. Event rates were uniformly $\leq 25\%$, and sensitivity analyses were performed excluding the study by Simon et al—the only study to use ORs—and found that results were very similar with or without those data. Moreover, individual end point results were not available, limiting our ability to use metaregression or indirect comparison methods. Finally, all data were based on observational studies that may be confounded by selection bias, in which sicker patients with more comorbidities are treated with a PPI and thus are at higher risk for adverse clinical outcomes.

Conclusions

Several frequently used PPIs previously thought to be safe for concomitant use with clopidogrel were associated with greater risk of adverse CV events. Although the data are observational, they highlight the need for randomized controlled trials or patient-level meta-analyses to evaluate the safety of concomitant PPI and clopidogrel use in patients with CAD.

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Disclosures

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