



Q/ Does concurrent use of clopidogrel and PPIs increase CV risk in patients with ACS?

EVIDENCE-BASED ANSWER

A | No. Adding a proton pump inhibitor (PPI) in patients taking antiplatelet medications such as clopidogrel for acute coronary syndrome (ACS) doesn't increase the composite risk of cardiovascular (CV) events: CV

death, myocardial infarction (MI), and cerebrovascular accident (CVA) (strength of recommendation: **B**, randomized, controlled trial [RCT] and preponderance of posthoc analyses of large RCTs).

Evidence summary

A double-blind, double-dummy, placebo-controlled RCT comparing a combination of clopidogrel, aspirin, and omeprazole with clopidogrel, aspirin, and placebo found no increase in composite CV outcomes with the PPI (TABLE).¹ Using a PPI did, however, significantly reduce gastrointestinal (GI) bleeding (hazard ratio [HR] = 0.13; 95% confidence interval [CI], 0.03-0.56). Although several meta-analyses have been conducted, they all rely on this single RCT that directly addresses the question, plus post-hoc analyses of other RCTs.

Four of 5 analyses find little or no difference in CV outcomes with a PPI

Four of 5 posthoc analyses (which weren't themselves randomized) of RCTs found unclear or no differences in composite CV outcomes with concurrent use of a PPI and antiplatelet therapy, after multivariate adjustment for differences in populations taking or not taking a PPI.

Posthoc analysis of the largest study found worse CV outcomes for both clopidogrel and ticagrelor with concomitant PPI use.² However, patients on any GI drugs (PPI or non-PPI) had composite outcomes similar to patients on a PPI (PPI vs non-PPI GI treatment: HR = 0.98; 95% CI, 0.79-1.23), and

patients not taking GI drugs had fewer composite outcomes compared with patients on a PPI (clopidogrel vs no GI therapy: HR = 1.29; 95% CI, 1.12-1.49; ticagrelor vs no GI therapy: HR = 1.30; 95% CI, 1.14-1.49). Researchers postulated that because the rate of composite outcomes increased equally for patients on *any* GI drug, the higher rate of CV adverse events with a PPI might have been related to GI disease rather than PPI use.

A similar posthoc analysis found no differences with or without PPI use among patients with ACS undergoing planned percutaneous coronary intervention (PCI) and assigned to clopidogrel or prasugrel.³ Researchers performed multivariate adjustment for differences in age, gender, ethnicity, and initial presence of unstable angina/non-ST-elevation MI.

A smaller study also found no significant differences in composite CV outcomes in patients using PPIs.⁴ Patients did have higher rates of MI (HR = 0.62; 95% CI, 0.42-0.91), but they were more likely to be older and have a previous diagnosis of non-ST-elevation MI, higher incidence of previous coronary artery bypass graft surgery, and history of peptic ulcer disease.

The fourth posthoc analysis of an RCT found that concomitant PPI use (91% of pa-

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TABLE

CV outcomes in patients with ACS on antiplatelet medication with/without a PPI

Primary outcome					
Study type (duration in mo)	Total N (number taking PPI)	Design of trial	Composite outcome	Result, PPI vs no PPI	Comments
RCT (4-12) ¹	3761 (1876)	Clopidogrel + ASA + placebo vs clopidogrel + ASA + omeprazole	All-cause death, MI, coronary revascularization, or CVA	HR = 0.99; (95% CI, 0.68-1.44)	Only RCT that directly addressed whether adding a PPI affects CV outcomes
Posthoc analyses					
RCT (12) ²	18,624 (6539)	Clopidogrel or ticagrelor	CV death, MI, or CVA	Clopidogrel HR = 1.2 (95% CI, 1.04-1.38) Ticagrelor HR = 1.24 (95% CI, 1.07-1.45)	Patients taking GI drugs (either PPI or non-PPI) had similar composite outcomes; patients not taking GI drugs had outcomes similar to non-PPI patients
RCT (15) ³	13,608 (4529)	Clopidogrel or prasugrel	CV death, MI, or CVA	Clopidogrel HR = 0.94 (95% CI, 0.80-1.11) Prasugrel HR = 1 (95% CI, 0.84-1.2)	
RCT (17) ⁴	7243 (1666)	Clopidogrel or prasugrel	CV death, MI, or CVA	HR = 1.01 (95% CI, 0.85-1.19)	Outcome of MI alone differed significantly
RCT (6-24) ⁵	1970 (738)	6 or 24 mo of ASA + clopidogrel	All-cause death, MI, or CVA Bleeding	HR = 1.05 (95% CI, 0.79-1.4) HR = 0.996 (95% CI, 0.67-1.47)	
Open-label trial (6) ⁶	801 (109)	Drug-eluting (sirolimus or paclitaxel) vs bare metal stents, plus clopidogrel	Cardiac death, nonfatal MI, target vessel revascularization	30.3% with PPI vs 20.8% no PPI ($P = .03$) Death rate: 9.2% vs 7.4% ($P = .51$)	Patients taking PPI were more likely to be female and have GI disease, diabetes, or higher serum creatinine levels

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CI, confidence interval; CV, cardiovascular; CVA, cerebrovascular accident; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; PPI, proton pump inhibitor; RCT, randomized controlled trial.

tients on lansoprazole) didn't alter outcomes among patients undergoing PCI and receiving dual antiplatelet therapy with clopidogrel and aspirin.⁵ Researchers used a multivariate adjustment for differences in age, gender, and renal function and found no difference in outcomes during the 6-month or 24-month period. PPI prescription was at physician discretion. Researchers didn't assess for dose-dependent effects of PPI.

A fifth, flawed study finds more adverse events with PPIs

A posthoc analysis of a smaller, open-label trial found increased major adverse cardiac events with PPI use among patients taking clopidogrel after PCI.⁶ Researchers didn't adjust for differences in populations at baseline, however, and patients taking PPIs were more likely to be female or older and have diabetes, GI disease, or higher serum creatinine levels.

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Editor's takeaway

The best evidence (a large RCT) found that adding a PPI to antiplatelet therapy didn't alter CV outcomes in patients with ACS, but it did reduce GI bleeds. Hopefully this will give providers the confidence to use PPIs, if clinically indicated, in patients taking antiplatelet therapy with clopidogrel or prasugrel.

JFP

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