

ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents

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Abbreviation List

ACS = acute coronary syndromes
ADP = adenosine diphosphate
CI = confidence interval
CV = cardiovascular
GI = gastrointestinal
HR = hazard ratio
H2RA = histamine H ₂ receptor antagonist
MI = myocardial infarction
NNH = number-needed-to-harm
NSAID = nonsteroidal anti-inflammatory drug
OR = odds ratio
PCI = percutaneous coronary intervention
PPI = proton pump inhibitor
RCT = randomized clinical trial

RR = relative risk

VASP = vasodilator-stimulated phosphoprotein

Preamble

This expert consensus document was developed by the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA). Expert consensus documents inform practitioners, payers, and other interested parties of the opinion of ACCF and document cosponsors concerning evolving areas of clinical practice or medical technologies. Expert consensus documents cover topics for which the evidence base, experience with technology, or clinical practice is not considered sufficiently well developed to be evaluated by the formal ACCF/AHA Practice Guidelines process. Often, the topic is the subject of considerable ongoing investigation. Thus, the reader should view the expert consensus document as the best attempt of the ACCF and document cosponsors to inform clinical practice in areas where rigorous evidence may not yet be available.

To avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current healthcare-related relationships and those existing 12 months before initiation of the writing effort. The ACCF Task Force on Clinical Expert Consensus Documents (CECD) reviews these disclosures to determine which companies make products (on market or in development) that pertain to the document under development. Based on this information, a writing committee is formed to include a majority of members with no relevant relationships with industry (RWI), led by a chair with no relevant RWI. Authors with relevant RWI are not permitted to draft or vote on text or recommendations pertaining to their RWI. RWI are reviewed on all conference calls and updated as changes occur. Author and peer reviewer RWI pertinent to this document are disclosed in Appendixes 1 and 2, respectively. Additionally, to ensure complete transparency, authors' comprehensive disclosure information—including RWI not pertinent to this document—is available online. Disclosure information for the ACCF Task Force on CECD is also available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx, as well as the ACCF disclosure policy for document development at www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

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1. Introduction

The potential benefits of antiplatelet therapy for atherosclerotic cardiovascular (CV) disease have been amply demonstrated over the past 2 decades, especially with regard to the

role of thienopyridine drugs in preventing stent thrombosis. However, antiplatelet agents increase the risk of bleeding associated with mucosal breaks in the upper and lower gastrointestinal (GI) tract. Rational use of thienopyridines is based on weighing their risks against their benefits. The magnitude of the risks may vary among patients, based on their history and clinical characteristics, as may the magnitude of the benefits.

An earlier Expert Consensus Document, "Reducing the GI Risks of Antiplatelet and NSAID Use," recommended the use of a proton pump inhibitor (PPI) in patients with risk factors for upper GI bleeding treated with dual antiplatelet therapy.¹ Since its publication, evidence of a potential adverse drug interaction between PPIs and thienopyridines has emerged.² Many recent investigations of this potential adverse interaction have been performed, using a variety of research designs. It has been difficult for practitioners to assimilate this flood of information and to develop optimal treatment strategies for managing patients who might benefit from antiplatelet therapy, yet who might suffer from GI bleeding. The purpose of this document is to review critically the recent developments in this area, provide provisional guidance for clinical management, and highlight areas of future research necessary to address current knowledge gaps.

1.1. Summary of Findings and Consensus Recommendations

1. Clopidogrel reduces major CV events compared with placebo or aspirin.
2. Dual antiplatelet therapy with clopidogrel and aspirin, compared with aspirin alone, reduces major CV events in patients with established ischemic heart disease, and it reduces coronary stent thrombosis but is not routinely recommended for patients with prior ischemic stroke because of the risk of bleeding.
3. Clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding.
4. Patients with prior GI bleeding are at highest risk for recurrent bleeding on antiplatelet therapy. Other clinical characteristics that increase the risk of GI bleeding include advanced age; concurrent use of anticoagulants, steroids, or nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin; and *Helicobacter pylori* infection. The risk of GI bleeding increases as the number of risk factors increases.
5. Use of a PPI or histamine H₂ receptor antagonist (H2RA) reduces the risk of upper GI bleeding compared with no therapy. PPIs reduce upper GI bleeding to a greater degree than do H2RAs.
6. PPIs are recommended to reduce GI bleeding among patients with a history of upper GI bleeding. PPIs are appropriate in patients with multiple risk factors for GI bleeding who require antiplatelet therapy.
7. Routine use of either a PPI or an H2RA is not recommended for patients at lower risk of upper GI bleeding, who have much less potential to benefit from prophylactic therapy.
8. Clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both CV and GI complications.
9. Pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. The strongest evidence for an interaction is between omeprazole and clopidogrel. It is not established that changes in these surrogate endpoints translate into clinically meaningful differences.
10. Observational studies and a single randomized clinical trial (RCT) have shown inconsistent effects on CV outcomes of concomitant use of thienopyridines and PPIs. A clinically important interaction cannot be excluded, particularly in certain subgroups, such as poor metabolizers of clopidogrel.
11. The role of either pharmacogenomic testing or platelet function testing in managing therapy with thienopyridines and PPIs has not yet been established.

2. Role of Thienopyridines in CV Disease

Thienopyridine therapy has been evaluated as an alternative to or in addition to aspirin treatment ("dual antiplatelet therapy") to reduce CV events. The absolute risk reduction from thienopyridines is greater in patients at higher CV risk, particularly those with acute coronary syndromes (ACS) or patients who have had a coronary stent implanted.

In patients with ACS without ST-segment elevation, dual antiplatelet therapy with clopidogrel plus aspirin reduced the risk of cardiac death, myocardial infarction (MI), or stroke from 11.4% to 9.3%, compared with aspirin alone, irrespective of whether patients were revascularized or treated medically³ but increased major bleeding from 2.7% to 3.7%. In patients with ST-segment elevation MI treated with fibrinolytics, the addition of clopidogrel to aspirin reduced major CV events over 30 days from 10.9% to 9.1% but increased major bleeding from 1.7% to 1.9%.^{4,5}

Dual antiplatelet therapy with aspirin and clopidogrel reduces stent thrombosis following percutaneous coronary intervention (PCI).⁶ Patients who are implanted with a bare-metal stent are recommended to receive at least 1 month of clopidogrel, and patients receiving a drug-eluting stent are recommended to receive dual therapy for at least 12 months. In patients with atrial fibrillation who are unable to take vitamin-K antagonists, adding clopidogrel to aspirin reduced the rate of major vascular events (7.6% to 6.8%) and stroke (3.3% to 2.4%) compared with aspirin alone but with a greater risk of bleeding—2.0% per year.⁷

In patients with established atherosclerotic CV disease, clopidogrel alone reduced (5.8% to 5.3%) the combined risk of major CV events, ischemic stroke, MI, and vascular death compared with aspirin alone⁸ and led to less GI bleeding (2.7% to 2.0%). Clopidogrel is recommended as an alternative agent for patients with CV disease unable to take aspirin.^{9–12}

In the primary prevention setting, dual antiplatelet therapy with clopidogrel plus aspirin did not significantly reduce major CV events compared with aspirin alone (6.8% versus 7.3%) but increased severe bleeding (1.3% to 1.7%).¹³ Pa-

tients with recent ischemic stroke or transient ischemic attack treated with clopidogrel plus aspirin had an insignificant reduction in major CV events (16.7% to 15.7%) compared with aspirin alone and experienced more life-threatening hemorrhages (1.3% to 2.6%).¹⁴

Prasugrel is a new thienopyridine derivative with a rapid onset and consistent inhibition of platelet aggregation. In patients with ACS and planned PCI, prasugrel reduced major CV events from 12.1% to 9.9% compared with clopidogrel but increased major bleeding from 1.8% to 2.4% and fatal bleeding from 0.1% to 0.4%.¹⁵

Ticagrelor, a novel, reversible, direct-acting P2Y₁₂ receptor blocker (not yet approved for use in the United States) reduced the primary endpoint of vascular death, MI, or stroke from 11.7% to 9.8% compared with clopidogrel, with no significant difference in major bleeding (11.6% versus 11.2%) but with an increased risk of noncoronary artery bypass graft major bleeding (3.8% to 4.5%).¹⁶

For patients with ischemic stroke or transient ischemic attack, antiplatelet therapy with aspirin, clopidogrel, or the combination of dipyridamole and aspirin is recommended to prevent recurrent stroke, but the combination of clopidogrel and aspirin is not recommended,¹⁷ and prasugrel is contraindicated.¹⁵

3. Risk of GI Bleeding and Related Mortality Associated With Clopidogrel Alone or in Combination

GI bleeding among patients receiving antiplatelet therapy can develop from many different lesions and anatomic sites. Upper GI bleeding may be due to esophagitis¹⁸ or peptic ulcer disease related to *H. pylori* infection, or aspirin, or other NSAIDs.¹⁹ These mucosal breaks are aggravated by the antiplatelet effects of thienopyridines, promoting bleeding. Bleeding from other GI sites is also exacerbated by antiplatelet therapy.^{20–27}

Several risk factors for GI bleeding in the setting of antiplatelet therapy have been reported consistently. A history of bleeding or other complications of peptic ulcer disease is the strongest risk factor for subsequent upper GI bleeding.²⁸ Advanced age also significantly increases the absolute risk of upper GI bleeding. Use of anticoagulants, steroids, or NSAIDs has also been shown to be consistent predictors for GI bleeding, as has *H. pylori* infection.^{29–35} The relative risk (RR) of GI bleeding increases with the number of adverse risk factors present in an individual patient.³⁶

The risk of GI bleeding associated with thienopyridines has been assessed in several case-control studies (Online Table 1) and in RCTs with prospectively assessed GI bleeding safety endpoints (Online Table 2). In head-to-head randomized trials of aspirin and clopidogrel, the risk of GI bleeding was higher in patients treated with aspirin (Online Table 2), although the absolute risk difference was small.

Dual antiplatelet therapy with clopidogrel and aspirin increased the risk of GI bleeding by 2- to 3-fold compared with aspirin alone in randomized trials (Online Table 2), but the absolute risk increase was in the range of 0.6% to 2.0%. Two RCTs^{3,7} provide specific data on GI bleeding risk

associated with dual antiplatelet therapy, demonstrating an RR of 1.78 (95% confidence interval [CI]: 1.25 to 2.54; number needed to harm [NNH] of 130) and 1.96 (95% CI: 1.46 to 2.63; NNH of 167). There are fewer data on the risk of GI bleeding in routine practice among patients who are less selected and not as closely monitored as patients in clinical trials. In a cohort of Tennessee Medicaid patients treated with clopidogrel, the rate of upper GI bleeding was 1.2% per year.³⁶

There are few data on the mortality attributable to GI bleeding in patients on clopidogrel alone or on dual antiplatelet therapy. In studies of varying duration and design, the case fatality rates for GI bleeding associated with dual antiplatelet therapy have been low (0% to 0.3%).^{3,29–31} Nevertheless, the RR for death from a GI bleed has been estimated at 2.5,³⁷ and GI bleeding appears to be a significant predictor of death, even after adjustment for CV morbidity, age, sex, diabetes, PCI status, and concomitant therapy.^{37,38}

4. Strategies to Prevent Thienopyridine-Related Upper GI Bleeding

Thienopyridines do not cause ulcers or erosions of the digestive tract,³⁹ but their antiplatelet effects may promote bleeding at the site of preexisting lesions caused by the use of aspirin or NSAIDs, or infection with *H. pylori*.⁴⁰ Upper GI bleeding in the setting of thienopyridine use may be reduced by suppressing gastric acid production, thereby promoting healing of peptic ulcers and mucosal erosions, as well as by stabilizing thrombi.⁴¹ Acid production can be suppressed either by H2RAs or by PPIs; the efficacy of each has been examined to prevent GI bleeding related to antiplatelet use.

4.1. Histamine H₂ Receptor Antagonists

The use of H2RAs can suppress gastric acid production by 37% to 68% over 24 hours,^{42,43} and standard doses have a modest protective effect in patients taking aspirin. In a randomized trial of 404 patients with peptic ulcers or esophagitis who were taking aspirin, fewer gastroduodenal ulcers developed over 12 weeks among patients assigned to famotidine (3.8%) than to placebo (23.5%; $P=0.0002$).¹⁸ In another study, however, H2RAs did not significantly protect clopidogrel users (RR: 0.83; 95% CI: 0.20 to 3.51).⁴⁴ No randomized trials have directly compared PPIs with H2RAs in patients with CV disease on antiplatelet therapy. However, observational data suggest PPIs may be more effective than H2RAs in preventing upper GI bleeding. In a cohort of 987 patients who were prescribed aspirin and clopidogrel, PPI use led to a greater reduction in upper GI bleeding (odds ratio [OR]: 0.04; 95% CI: 0.002 to 0.21) than H2RA use (OR: 0.43; 95% CI: 0.18 to 0.91).³⁰

4.2. Proton Pump Inhibitors

PPIs reduce gastric acid secretion for up to 36 hours.⁴⁵ Observational data suggest that PPIs reduce the risk of GI bleeding in patients on antiplatelet therapy. In 1 cohort study, the baseline clopidogrel-related gastroduodenal bleeding risk of 1.2% per year was reduced by 50% in patients prescribed a PPI.³⁶ In this same study, PPI use reduced the absolute risk of GI bleeding by 2.8% per year among patients with ≥ 3 risk factors for GI

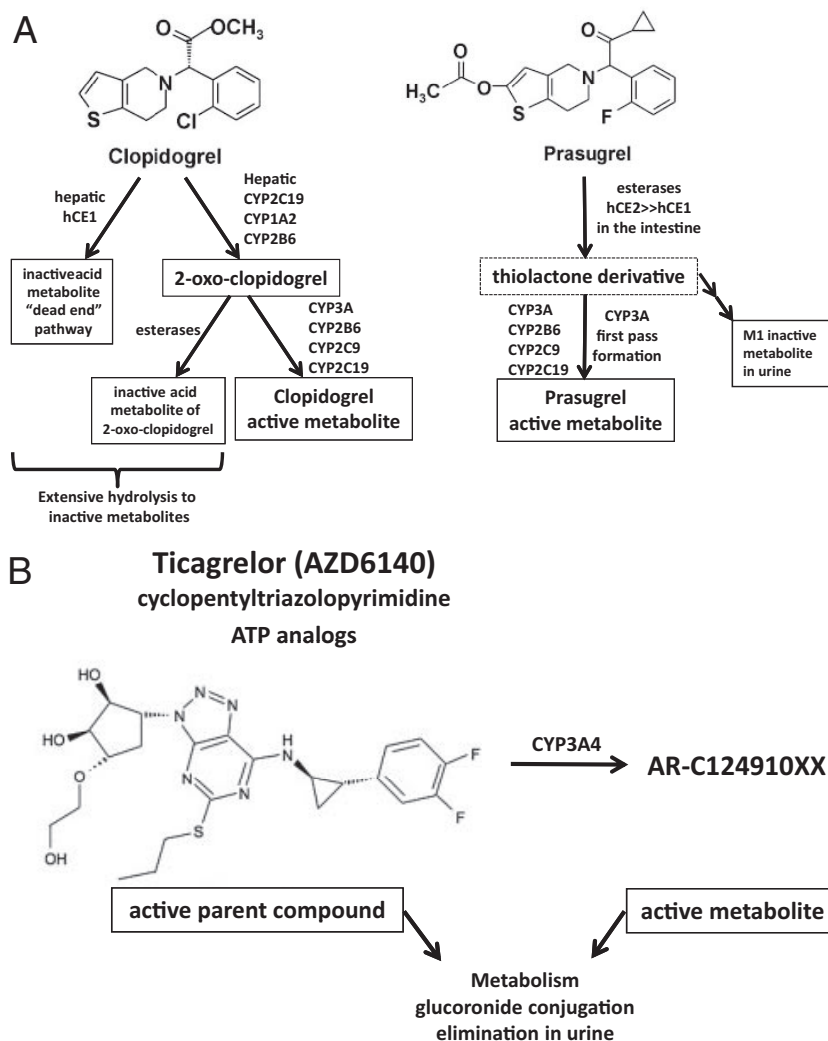


Figure 1. Thienopyridine Metabolism. (A) Clopidogrel and prasugrel; (B) ticagrelor. ATP indicates adenosine triphosphate; CYP, cytochrome P-450; and hCE1 and 2, human carboxylesterases 1 and 2.

bleeding. In a large case-control study comparing 2779 patients with endoscopically confirmed upper GI hemorrhage with 5532 controls, concomitant use of a PPI and a thienopyridine was associated with less upper GI bleeding (RR: 0.19; 95% CI: 0.07 to 0.49) than thienopyridine use alone.⁴⁴ Smaller cohort studies confirm similar risk reduction with concurrent PPI prescription.³¹ In the results of a recent randomized trial,⁴⁶ patients with CV disease taking enteric-coated aspirin who were randomized to receive clopidogrel plus omeprazole had fewer GI events (ie, a composite outcome of overt or occult bleeding, symptomatic gastroduodenal ulcer or erosion) than patients randomized to receive clopidogrel alone (hazard ratio [HR]: 0.34; 95% CI: 0.18 to 0.63).

5. Drug Metabolism: Thienopyridine, H2RA, and PPI

5.1. Thienopyridine Metabolism

Clopidogrel is a pro-drug converted in vivo to an active metabolite that irreversibly binds to the platelet adenosine diphosphate (ADP) P2Y₁₂ receptor, thereby inhibiting platelet aggregation. The bioavailability of the active metabolite is

determined by intestinal absorption, which may be influenced by an ABCB1 polymorphism, and by metabolism through the cytochrome P-450 pathway.⁴⁷ Clopidogrel is activated in a 2-step process (Figure 1A) mediated by oxidative biotransformation in the liver, in which CYP2C19 and CYP3A have particularly important roles (Figure 1A).^{48,49} The parent compound clopidogrel, and to a lesser extent 2-oxo-clopidogrel, are both substrates and inhibitors of CYP1A2, CYP2B6, and CYP2C19.⁵⁰ Clopidogrel and 2-oxo-clopidogrel are extensively hydrolyzed to inactive metabolites, potentially magnifying the effects of CYP2C19 inhibitors and polymorphisms.⁵¹ However, redundant pathways (Figure 1A) for activation of clopidogrel may mitigate the effect of inhibitors and reduced function polymorphisms of CYP450 isoenzymes in vitro.^{49,52}

Prasugrel is also a pro-drug that requires biotransformation to active metabolites by cytochrome P-450 enzymes, including CYP3A isoforms, CYP2B6, CYP2C9, and CYP2C19 (Figure 1A). Prasugrel is hydrolyzed to a thiolactone derivative in the intestine and then oxidized to its active metabolite in both the intestine and the liver (Figure 1A).^{51,53} Reduced-function

CYP2C19 alleles are not believed to have a clinically meaningful effect in prasugrel-treated patients.⁵⁴

Ticagrelor (AZD6140) is an orally active cyclopentyltriazolopyrimidine adenosine triphosphate analog that reversibly inhibits P2Y₁₂ platelet receptors (Figure 1B). Ticagrelor, which is not yet approved in the United States, is an active compound and is metabolized by CYP3A4 to an active metabolite.^{55,56} Ticagrelor and its active metabolite are both metabolized and glucuronidated in the liver before elimination in the urine. Genetic variations in CYP isoenzymes do not appear to affect metabolism of ticagrelor.

Other frequently used CV medications are also metabolized by the CYP450 system^{51,52} and may interact with thienopyridine metabolism. Of note are statins, which are metabolized by the CYP450 system,^{51,52} and aspirin, which induces CYP2C19.⁵⁷

5.2. H2RA Metabolism

The H2RAs currently available in the United States (cimetidine, ranitidine, famotidine, and nizatidine) vary in their ability to inhibit gastric acid secretion. Hepatic metabolism is the dominant elimination pathway for orally administered cimetidine (60%), ranitidine (73%), and famotidine (50% to 80%) but not nizatidine (22%).⁵⁸ Cimetidine may interact with drugs metabolized via the cytochrome P-450 pathway, as it inhibits CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4.^{59–61} Although cimetidine might decrease the biotransformation of clopidogrel by competitive inhibition of CYP2C19, there have been no controlled studies of this hypothesis. Ranitidine interacts weakly with cytochrome P-450,^{58,62,63} and famotidine and nizatidine do not bind to the cytochrome P-450 system and, therefore, have low potential to interact with clopidogrel.^{58,62}

5.3. PPI Metabolism

All PPIs used in the United States (omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole) are weak bases converted to their active forms in the acidic environment of active gastric parietal cells.⁶⁴ PPIs are metabolized by the hepatic cytochrome P-450 system, predominantly CYP2C19, and, to a lesser extent, CYP3A4.⁶⁵ The studies assessing the degree to which different PPIs interact with CYP2C19 have yielded inconsistent results, so no definitive conclusions can be drawn comparing the pharmacokinetics and potential for drug interaction of the various PPIs with clopidogrel and prasugrel.

6. Hypotheses Regarding the PPI-Antiplatelet Interaction

6.1. Reduced Biological Action of Clopidogrel Through Competitive Metabolic Effects of CYP2C19

Concomitant use of PPIs may competitively inhibit activation of clopidogrel by CYP2C19, thereby attenuating its antiplatelet effect. Coadministration of other CYP2C19-inhibiting drugs may further reduce the efficacy of clopidogrel and inhibition of platelet aggregation.⁶⁶ The reported interaction of clopidogrel and PPIs is consistent with a set of clinical pharmacokinetic findings referred to as high-risk pharmacokinetics.⁶⁶ The risk of drug inefficacy is greater when drug

concentrations depend on variable activity of a single metabolic pathway.

6.2. Reduced Biological Action of Clopidogrel Related to Genetic Polymorphisms

The potential for impaired antiplatelet activity is supported by data on the effect of natural variations in CYP2C19 activity, based on genetic polymorphisms. The CYP2C19*2, CYP2C19*3, and CYP2C19*4 alleles decrease active metabolite production compared with the most common CYP2C19 genotype. Individuals who are heterozygous for loss-of-function alleles are “intermediate metabolizers,” and those who are homozygous are “poor metabolizers.” CYP2C19 polymorphisms have been associated with reduced platelet inhibition and an increased rate of recurrent CV events.^{53,67,68} Reduced platelet inhibition may be overcome with higher clopidogrel doses,⁶⁹ but any increased CV efficacy from higher-dose treatment must be weighed against an increased risk of GI bleeding.⁷⁰

The best characterized and most common loss-of-function polymorphism is the CYP2C19*2 allele (53), which is carried by 51% to 55% of Asians, 33% to 40% of African Americans, 24% to 30% of Caucasians, and 18% of Mexican Americans.^{53,71–75} The antiplatelet effect of clopidogrel varies directly with the number of loss-of-function alleles; 2 copies are associated with a 65% reduction in clopidogrel antiplatelet efficacy and 1 copy with a 47% reduction.^{71–75} The genetic variation in CYP2C19 is associated with up to a 50% greater risk of adverse clinical outcomes, including CV death, MI, or stroke, and a 3-fold increased risk of stent thrombosis in patients receiving clopidogrel.^{53,72} However, the CYP2C19*2 variant appears to account for only 12% of variation in platelet aggregability in response to ADP; and other factors, such as diabetes, obesity, and acute ischemia,⁷⁶ likely contribute much more to variability in platelet response.^{72,73,77}

7. Evidence-Based Review: PPI and Clopidogrel/Thienopyridine Pharmacokinetic and Pharmacodynamic Effect

Platelet function tests serve as surrogate markers for the clinical effectiveness of antiplatelet drugs. The standard platelet function test is aggregometry, which measures ADP-stimulated platelet aggregation in whole blood or platelet-rich plasma. A more recent test quantifies phosphorylation of vasodilator-stimulated phosphoprotein (VASP) in whole blood and appears to be a more specific measure of clopidogrel-mediated inhibition of platelet aggregation. The newest test, the Verify Now P2Y₁₂ assay, is similar to VASP. It has not been established that changes in these surrogate endpoints translate into clinically meaningful differences.

Among 162 healthy subjects, carriers of at least 1 reduced-function CYP2C19 allele had significantly less inhibition of platelet aggregation on standard aggregometry in response to clopidogrel than did noncarriers.⁵³ The ultrarapid metabolizer genotypes had the greatest platelet inhibition from clopidogrel, and the poor metabolizer genotypes had the least platelet inhibition.

The influence of omeprazole on the antiplatelet effects of clopidogrel was assessed in a double-blind trial⁷⁸ of 124 patients after coronary stenting treated with aspirin and

clopidogrel. Patients randomized to omeprazole for 7 days had significantly less platelet inhibition, as measured by the VASP method, than patients randomized to placebo. In another study of 104 patients given a higher maintenance dose of 150 mg clopidogrel after coronary stenting,⁷⁹ patients randomized to omeprazole had significantly less platelet inhibition on the VASP assay than patients randomized to pantoprazole, with 44% clopidogrel nonresponders in the omeprazole group compared with 23% in the pantoprazole group ($P=0.04$). In the PRINCIPLE-TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis In Myocardial Infarction 44) trial, patients undergoing PCI taking a PPI had significantly less platelet inhibition with clopidogrel than those not on a PPI, whereas patients taking prasugrel as well as a PPI had a trend toward reduced-platelet inhibition.⁸⁰

In randomized trials that used *ex vivo* platelet assays as surrogate clinical endpoints, patients treated with omeprazole demonstrated impaired clopidogrel response,^{78,79} even when a high antiplatelet dose was used. Studies of other PPIs have not demonstrated this effect,^{79,81} but these studies were conducted in different populations using different study designs. Few direct head-to-head comparison studies have been reported. The ongoing SPICE (Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects) trial (NCT00930670) will directly compare the effects of commonly prescribed PPIs (ie, omeprazole, pantoprazole, esomeprazole) and a H2RA (ranitidine) on *ex vivo* platelet aggregation among 320 post-PCI patients who require dual antiplatelet therapy. Secondary outcomes include assessment of clopidogrel resistance, prevalence of CYP2C19*2 polymorphism and its effect on PPI and antiplatelet activity, all-cause mortality, MI, revascularization, stroke, and GI bleeding at 1 year.⁸²

8. PPI and Clopidogrel/Prasugrel Clinical Efficacy

8.1. Do PPIs Decrease Clinical Efficacy of Clopidogrel or Prasugrel?

Observational studies of different populations, sizes, and degree of methodologic rigor have examined whether patients prescribed a PPI plus clopidogrel have an increased risk of CV events compared with patients prescribed clopidogrel alone (Online Table 3). The results are mixed: several studies have shown small but significant associations between PPI use and CV events, but others show no significant association. The magnitude of the treatment effect in positive studies has been modest, with risk ratios <2.0 . Whether differences in study results are because of differences in confounding factors between study groups cannot be determined. In observational studies, PPIs may be selectively prescribed to higher-risk patients, potentially biasing the estimated CV risk.³⁶ Small, yet significant, differences in common, clinically important events would, however, represent an important public health issue.

The effect of PPIs on clinical efficacy has been evaluated retrospectively in nonrandomized cohorts within randomized trials. In a study of 13 608 patients randomized to either clopidogrel or prasugrel after PCI, use of PPI did not

affect the outcome of a composite of CV death, MI, or stroke, either among clopidogrel-assigned patients (adjusted HR: 0.94; 95% CI: 0.80 to 1.11) or among the prasugrel-assigned patients (HR: 1.00; 95% CI: 0.84 to 1.20).⁸⁰ In this study, there was no difference among the PPIs used, including omeprazole ($n=1675$), lansoprazole ($n=441$), esomeprazole ($n=613$), and pantoprazole ($n=1844$). The results were similar among those with a reduced-function CYP2C19 allele. In the CREDO (Clopidogrel for Reduction of Events During Observation) trial, PPI use was associated with an increased rate of CV events whether or not the patient was treated with clopidogrel.⁸³ The evidence from these studies and observational comparisons is inconclusive regarding the clinical effects of concomitant use of a PPI and a thienopyridine.

8.2. Randomized Clinical Trials

Only 1 RCT has examined the potential interaction between clopidogrel and PPIs with CV events as the outcome. In a double-blind, placebo-controlled trial,⁴⁶ 3761 patients with either ACS or PCI were randomized to a fixed-dose combination of clopidogrel and omeprazole (75/20 mg) or clopidogrel alone. All patients received aspirin. The data from this trial revealed no significant difference in a composite CV endpoint (MI, stroke, coronary artery bypass graft, PCI, CV death) for patients on the fixed-dose combination compared with clopidogrel alone (HR: 0.99; 95% CI: 0.68 to 1.44), but fewer GI adverse events (HR: 0.34; 95% CI: 0.18 to 0.63). However, the study was halted short of its planned enrollment and duration; and the number of CV events was low (55 versus 54 CV events). Consequently, the confidence limits for CV events are broad and do not exclude a clinically important increase in risk of up to 44%.

8.3. Does the Choice of PPI Matter?

Pharmacokinetic studies *in vitro* have suggested that all PPIs inhibit CYP2C19 to varying degrees, but the relative magnitude of inhibition varies by specific PPI and laboratory assay used. Pharmacodynamic studies using ADP-stimulated platelet aggregation in patients treated with clopidogrel suggest a variable inhibitory effect of different PPIs,^{80,84,85} but few head-to-head comparison studies have been performed.

In the combined analysis of 2 trials of clopidogrel and prasugrel, the rate of CV death, MI, or stroke was similar for all PPIs and no different than the rate in patients not taking a PPI.⁸⁰ A nested case-control study of patients receiving clopidogrel after MI suggested pantoprazole may increase the risk of rehospitalization for MI or PCI compared with other PPIs.⁸⁶ However, a retrospective cohort study of 20 596 patients showed no effect of any PPI on the frequency of CV events among patients taking clopidogrel, with similar HRs for esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole.³⁶ Other observational studies of patients taking clopidogrel have suggested that the risk of CV events is similar for all PPIs.^{45,87,88}

Thus, although pharmacokinetic and pharmacodynamic data suggest varying inhibition by different PPIs of the enzyme systems necessary to convert clopidogrel to its active form, there is no good evidence that these differences on surrogate markers translate into meaningful differences in clinical outcomes. No

prospective trials directly compare the clinical events of different PPIs in patients treated with clopidogrel.

8.3.1. Timing of Dosing to Minimize Interactions

Because the plasma half-lives of both clopidogrel and all available PPIs are less than 2 hours, interactions between these drugs might be minimized by separating the timing of drug administration, even among poor CYP2C19 metabolizers.⁴⁵ In a crossover study examining 72 healthy subjects who were administered standard-dose clopidogrel (300 mg followed by 75 mg daily) and a supratherapeutic dose of omeprazole (80 mg daily), mean inhibition of platelet aggregation was greater when the drugs were given 12 hours apart.⁸⁹ Further studies will be required to evaluate this hypothesis, using appropriate drug doses and meaningful clinical endpoints. Until data from such studies are available, there is no solid evidence to recommend that the dosing of PPIs be altered.

9. Conclusions

9.1. The Assessment of Epidemiologic Evidence Supporting a Significant Clinical Interaction Between PPIs and Thienopyridines

When assessing a possible causal link between an exposure and an outcome, it is recommended to consider: 1) the strength of the association, 2) consistency of the association across different samples, 3) existence of a biologically plausible mechanism of action, and 4) supportive experimental evidence.⁹⁰ In applying these principles to the concomitant use of PPIs and thienopyridines, we draw the following conclusions:

1. The magnitude of association in positive observational studies reviewed is small to moderate (HR or OR: <2), but associations of this magnitude in nonrandomized observational studies may be due to residual differences in patient characteristics between study groups. Large, well-controlled randomized trials are necessary to assess the validity of small-to-moderate magnitude associations. The only available randomized trial showed no significant association of omeprazole with CV events, but the confidence limits on this null finding include the possibility of up to a 44% relative increase in CV risk.
2. A significant association between PPI use and increased CV events has been inconsistently demonstrated in observational studies, with the majority of studies showing no association. In addition, available studies markedly vary in methodologic rigor.
3. Although clinical studies with CV events as endpoints are not definitive, the proposed mechanism is biologically plausible, given that a) clopidogrel users with reduced-function genetic polymorphisms in CYP2C19 metabolism have increased rates of CV events; and b) in vitro testing suggests that PPIs may inhibit CYP2C19 metabolism.
4. Experimental pharmacodynamic data consistently indicate that omeprazole diminishes the effect of clopidogrel on platelets. Other pharmacodynamic studies have failed to demonstrate a significant effect of other PPIs on clopidogrel. In the absence of large-scale, randomized, experimental studies that directly compare PPIs with different pharmacokinetic properties, the evidence remains weak for diminished antiplatelet activity associated with PPIs

and thienopyridine coprescription. The ongoing SPICE trial may provide additional answers and address issues regarding the clinical relevance of such interactions.

9.2. Risk/Benefit Balance: GI Bleed Risk Versus CV Event Risk

All prescription drugs have favorable and unfavorable effects, and treatment decisions must be based on whether the potential for benefit outweighs the potential for harm. The CV benefits of antiplatelet drugs are overwhelmingly documented for patients who have ACS and patients who undergo PCI. It is also well demonstrated that antiplatelet drugs increase the risk of GI bleeding. The magnitude of these benefits and risks in individual patients varies depending on their characteristics.³⁶ The challenge for healthcare providers is to determine the risk/benefit balance for individual patients or subsets of the target population.

PPIs are coprescribed with antiplatelet drugs for 1 reason—to reduce the increased risk of GI complications caused by antiplatelet drugs. The need for GI protection increases with the number of risk factors for severe bleeding. Prior upper GI bleeding is the strongest and most consistent risk factor for GI bleeding on antiplatelet therapy. Patients with ACS and prior upper GI bleeding are at substantial CV risk, so dual antiplatelet therapy with concomitant use of a PPI may provide the optimal balance of risk and benefit. Among stable patients undergoing coronary revascularization, a history of GI bleeding should inform the choice of revascularization method; if a coronary stent is selected to treat such patients, the risk/benefit tradeoff may favor concomitant use of dual antiplatelet therapy and a PPI.

Advanced age; concomitant use of warfarin, steroids, or NSAIDs; or *H. pylori* infection all raise the risk of GI bleeding with antiplatelet therapy. The risk reduction with PPIs is substantial in patients with risk factors for GI bleeding and may outweigh any potential reduction in the CV efficacy of antiplatelet treatment because of a drug–drug interaction. Patients without these risk factors for GI bleeding receive little if any absolute risk reduction from a PPI, and the risk/benefit balance would seem to favor use of antiplatelet therapy without concomitant PPI. The reduction of GI symptoms by PPIs (ie, treatment of dyspepsia) may also prevent patients from discontinuing their antiplatelet treatment. The discontinuation of antiplatelet therapy in patients with GI bleeding may increase the risk of CV events.⁹¹

9.3. Are H2RAs a Reasonable Alternative and in Which Population?

H2RAs are effective compared with placebo in decreasing the risk of gastric and duodenal ulcers⁹² caused by NSAIDs and antiplatelet therapy,¹⁸ but not as effective as PPIs.^{93,94} PPIs are also more effective than H2RAs for preventing ulcers in patients using high doses of NSAIDs⁹⁵ and are effective in decreasing GI bleeding in patients prescribed aspirin or thienopyridines.^{36,96,97} Available data suggest PPIs are superior to H2RAs, but H2RAs may be a reasonable alternative in patients at lower risk for GI bleeding, and in those who do not require PPI for refractory gastroesophageal reflux disease. Cimetidine can competitively inhibit CYP2C19, so other H2RAs might be a better choice in patients treated with clopidogrel.

9.4. Unanswered Questions and Areas for Future Research

Many gaps in knowledge exist regarding GI bleeding among patients prescribed thienopyridines. The pathophysiology of GI hemorrhage associated with thienopyridines is not fully understood and should be further elucidated. Better data are needed on the incidence of GI bleeding among patients taking antiplatelet therapy, particularly in relation to clinical factors that may alter the risk of bleeding. The tradeoffs between bleeding risk and cardiovascular benefits of antiplatelet therapy deserve further study. Clinical trials of strategies to reduce the risk of GI bleeding among patients with CV disease on antiplatelet therapy, particularly using the commonly prescribed PPIs and high-dose H2RAs, would provide direct evidence on the comparative effectiveness of alternative management strategies.

There is considerable variation among patients in response to antiplatelet therapy, so the potential role of laboratory testing in individualization of therapy should be a high priority for re-

search. Either pharmacogenomic testing for CYP2C19 variants or platelet function testing might be used to tailor therapy by guiding the choice of drug (thienopyridines, PPIs, H2RAs), the choice of drug dose, or both. Although the concept of individually tailored therapy is rational and attractive, empirical evidence for this approach is sparse. Clinical studies and randomized trials comparing guided therapy with usual care are needed, as are trials comparing different approaches to guided therapy (eg, pharmacogenomic profiling versus platelet function testing). Studies that compare different management options for patients with specific test results would also be useful: For example, what are the effects on clinical outcomes of using a higher dose of clopidogrel among patients who are either “poor metabolizers” on a genetic test or who have relatively little platelet inhibition on a functional assay? Finally, we need to evaluate the effect on clinical outcomes of dosing schedules that minimize simultaneous exposure to high levels of a PPI and a thienopyridine.

Appendix 1. Relevant Author Relationships With Industry and Other Entities—ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Neena S. Abraham	Michael E. DeBakey VAMC; Baylor College of Medicine—Associate Professor of Medicine; Sections of Gastroenterology and Health Services Research at the Houston VA HSR&D Center of Excellence	None	None	None	None	None	None
Mark A. Hlatky	Stanford University School of Medicine—Professor of Health, Research and Policy and Cardiovascular Medicine	• The Medicines Company	None	None	None	None	None
Elliott M. Antman	Brigham Women's Hospital—Professor of Medicine Harvard— Director of Postgraduate Education Program in Clinical and Translational Science	• Eli Lilly	None	None	<ul style="list-style-type: none"> • Accumetrics • AstraZeneca • Bayer Healthcare • Bristol-Myers Squibb Pharmaceutical Research Institute • Daiichi Sankyo* • Eli Lilly* • GlaxoSmithKline • Merck • Novartis • Ortho-Clinical Diagnostics • Pfizer • Roche Diagnostics • Roche Diagnostics GmbH • Sanofi-Aventis*—PI • Sanofi-Synthelabo Recherche • Schering-Plough Research Institute 	None	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Craig B. Clark	Iowa Health Cardiology—Attending Cardiologist University of Iowa Carver College of Medicine and Des Moines University—Adjunct Clinical Associate Professor	None	None	None	None	None	None
Curt D. Furberg	Wake Forest University School of Medicine—Professor of Public Health Sciences	None	None	None	None	None	None
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Charles J. Kahi	Indiana University School of Medicine, Richard L. Roudebush VAMC—Associate Professor of Clinical Medicine	None	None	None	None	None	None
Loren Laine	USC Keck School of Medicine—Professor of Medicine	<ul style="list-style-type: none"> • AstraZeneca • Eisai • Horizon • Logical Therapeutics • Novartis • Pozen • Santarus 	None	None	<ul style="list-style-type: none"> • Bayer (DSMB)* • Bristol-Myers Squibb (DSMB)* • Merck (DSMB)* • Nicox (DSMB) • Pfizer (DSMB) • Takeda* 	<ul style="list-style-type: none"> • Cogentus 	

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kenneth W. Mahaffey	Duke Clinical Research Institute—Associate Professor, Medicine	<ul style="list-style-type: none"> • AstraZeneca* • Bayer • Boehringer Ingelheim • Bristol-Myers Squibb • Daiichi Sankyo • GlaxoSmithKline* • Guidant • Johnson & Johnson • Eli Lilly • Merck • Novartis • Pfizer • Sanofi-Aventis • Schering-Plough Research Institute 	None	None	<ul style="list-style-type: none"> • AstraZeneca* • Aventis* • Bayer* • Bristol-Myers Squibb* • Boehringer Ingelheim* • Cordis* • GlaxoSmithKline* • Guidant* • Johnson & Johnson* • Eli Lilly* • Medtronic* • Merck* • Momenta* • Novartis* • Pozen* • Schering-Plough Research Institute* • The Medicines Company* 	None	None
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Gordon F. Tomaselli	Johns Hopkins School of Medicine—Professor of Medicine	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Significant relationship.

†No financial relationship.

DSMB indicates data safety monitoring board; and PI, principal investigator.

Appendix 2. Relevant Peer Reviewer Relationships With Industry and Other Entities—ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Eric R. Bates	Official Reviewer—AHA Official Reviewer— ACCF Task Force on Clinical Expert Consensus Documents	<ul style="list-style-type: none"> • Bristol-Myers Squibb • Daiichi Sankyo • Eli Lilly • Momenta • Novartis • Sanofi-Aventis • Takeda 	None	None	None	None	None
James H. Chesebro	Official Reviewer—AHA	None	None	None	None	None	None
Philip O. Katz	Official Reviewer—ACG	<ul style="list-style-type: none"> • Eisai • Novartis • Takeda • XenoPort 	None	None	None	• ACG President	None
Richard J. Kovacs	Official Reviewer— ACCF Board of Trustees	<ul style="list-style-type: none"> • Abbott Laboratories • Biomedical Systems • Cook-Med Institute* • ECG Scanning Services* • Eli Lilly* • Endocyte • Essentialis • XenoPort 	None	None	None	None	None
John F. Robb	Official Reviewer—ACC Board of Governors	None	None	None	None	None	None
Jeffrey L. Anderson	Content Reviewer— ACCF/AHA UA Guideline	<ul style="list-style-type: none"> • Sanofi/Bristol-Myers Squibb 	None	None	<ul style="list-style-type: none"> • AstraZeneca (DSMB) • Gilead Pharma (DSMB) • Toshiba 	None	<ul style="list-style-type: none"> • Defendant, management of cardiopulmonary arrest postop, 2010 • Defendant, stroke after ablation for AF, 2010
John G. Byrne	Content Reviewer— ACC Surgeon Scientific Council	<ul style="list-style-type: none"> • Edwards Lifesciences 	None	None	None	None	None
Jose G. Diez	Content Reviewer— ACC Interventional Scientific Council	<ul style="list-style-type: none"> • Sanofi-Aventis 	None	None	None	None	None
L. David Hillis	Content Reviewer— ACCF/AHA CABG Guideline	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer— ACCF/AHA PCI Guideline	None	None	None	None	None	<ul style="list-style-type: none"> • Defendant, patient nonresponsive after noncardiac surgery, 2010

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Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Patrick T. O'Gara	Content Reviewer— ACCF/AHA STEMI Guideline	None	None	None	<ul style="list-style-type: none"> • Lantheus Medical Imaging • National Institutes of Health* 	<ul style="list-style-type: none"> • AHA (Scientific Advisory and Coordinating Committee; Editor-in-Chief, <i>Heart Insight</i> magazine) 	None

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*Significant relationship.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; ACG, American College of Gastroenterology; AF, atrial fibrillation; AHA, American Heart Association; CABG, coronary artery bypass graft; DSMB, Data Safety Monitoring Board; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and UA, unstable angina.

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**ACCF/ACG/AHA 2010 EXPERT CONSENSUS DOCUMENT ON THE CONCOMITANT USE OF PROTON PUMP INHIBITORS AND THIENOPYRIDINES:
A FOCUSED UPDATE OF THE ACCF/ACG/AHA 2008 EXPERT CONSENSUS DOCUMENT ON REDUCING THE GASTROINTESTINAL RISKS OF
ANTIPLATELET THERAPY AND NSAID USE—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS
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Table 1. Observational Studies of Antiplatelet Use and Gastrointestinal Bleeding Risk

Author	Study Type	Population	Endpoint	N	Results ^{§§}
Antiplatelet Use					
Lanas et al. (2006) (1)	Case-control	Inpatients with upper GI bleeding	Upper GI bleeding* ^{##}	Cases: 2,777 Controls: 5,532	Clopidogrel: RR 2.8 (1.9-4.2) ASA < 300mg: RR 3.7 (3.0-4.5)
Hallas et al. (2006) (2)	Case-control	Inpatients with upper GI bleeding or gastritis	Upper GI bleeding ^{†##}	Cases: 1,443 Controls: 57,720	Clopidogrel: OR 1.1 (0.6-2.1) ASA: OR 1.8 (1.5-2.1) ASA+Clopidogrel: OR 7.4 (3.5-15.0)
Ibanez et al. (2006) (3)	Case-control	Recent upper GI bleeding	Upper GI bleeding ^{†##}	Cases: 2,813 Controls: 7,193	ASA: OR 4.0 (3.2-4.9) Clopidogrel: OR 2.3 (0.9-6.0) Any antiplatelet agent: OR 3.4 (2.8-4.1) Any antiplatelet agent+PPI: OR 1.0 (0.5-2.0)
Aronow et al. (2009) (4)	Retrospective cohort within RCT	Post-PCI	GI bleeding	Clopidogrel+ASA: 902 Placebo+ASA: 914	Clopidogrel+ASA: 1.4% Placebo+ASA: 0.3% (p=0.011)
Barada et al. (2008) (5)	Retrospective cohort	ACS	Upper GI bleeding	GI bleeding: 7 No GI bleeding: 1,016	GI bleeding vs. no GI bleeding Clopidogrel: 43.0% vs. 15.0% (p=0.03) ASA: 71.0% vs. 43.0% (p=0.12) ASA+Clopidogrel: 29.0% vs. 8.0% (p=0.04)
Moukarbel et al. (2009) (6)	Retrospective cohort within RCT	Post-MI with left ventricular dysfunction and/or heart failure	GI bleeding ^{§##}	GI bleeding: 98 No GI bleeding: 14,605	Dual antiplatelet therapy: HR 3.18 (1.91-5.29)
Concomitant Proton Pump Inhibitor Use					
Ng et al. (2008) (7)	Retrospective cohort	Recent hospitalization on ASA+clopidogrel	GI bleeding	PPI: 213 H2RA: 287 No PPI/H2RA: 487	PPI vs. no PPI: OR 0.04 (0.002-0.21) H2RA vs. no H2RA: 0.43 (0.18-0.91)
Hsiao et al. (2009) (8)	Retrospective cohort	History of hospitalization for major GI bleeding or major GI complication of PUD	Hospitalization for major GI complications with PUD or GI bleeding ^{##}	ASA: 12,001 Clopidogrel: 2,626	Clopidogrel (vs. ASA): HR 0.85 (0.76-0.95) ASA+PPI (vs. No PPI): HR 0.76 (0.64-0.91) Clopidogrel+PPI (vs. No PPI): HR 1.08 (0.89-1.33)
Ray et al. (2010) (9)	Retrospective cohort	MI, unstable angina, PCI, CABG	Hospitalization for GI bleeding 1) Multiple baseline variables used to calculate propensity score for PPI use. 2) Regression models with multiple baseline ^{**} and time-dependent ^{††} variables and propensity score decile.	PPI: 7,593 No PPI: 13,003	PPI: 8.2 per 1,000PY No PPI: 12.2 per 1,000PY All PPIs: HR 0.50 (0.39-0.65) Pantoprazole: HR 0.46 (0.33-0.63)

Data Supplement: ACCF/ACG/AHA Expert Consensus Document on Concomitant Use of Proton Pump Inhibitors and Thienopyridines

This table includes only fully-published studies.

*Adjusted for age, sex, calendar year, ulcer history, nitrates, oral anticoagulants, antiplatelets, acid-suppressing drugs, NSAIDs, coxibs, and ASA.

† Adjusted for NSAIDs, coxibs, SSRI, antiulcer drugs, systemic corticosteroids, nitrate vasodilators, and past history of peptic ulcer or upper GI bleed, diabetes, ischemic heart disease, alcohol-related diagnosis, or use of disulfiram.

‡ Adjusted for antiplatelets, history of peptic ulcer, diabetes, heart failure, acute MI, angina, stroke, transient ischemic attack, intermittent claudication, smoking, alcohol consumption, antacids, H2RAs, PPIs, misoprostol, sucralfate, nitrates, systemic NSAIDs, topical NSAIDs, analgesics, calcium channel blockers, ACE inhibitors, beta-adrenergic blocking agents, statins and SSRIs.

§ Adjusted for age, gender, race, NYHA class, diastolic blood pressure, and eGFR throughout the duration of follow-up, non-Q-wave MI at randomization, use of thrombolytic with qualifying MI, symptomatic hypotension, use of beta-blocker within 24 hours before randomization, atrial fibrillation, ventricular tachycardia, and pacemaker placement between index MI and randomization, history of PCI/CABG, alcohol abuse, diabetes, antihypertensive treatment, congestive heart failure, dyslipidemia, cancer, and chronic obstructive lung disease before index MI, use of dual antiplatelet therapy, oral anticoagulation, digoxin, insulin, amiodarone, calcium channel blocker, SSRI, statin, oral hypoglycemic agent, and other diuretic throughout the duration of follow-up.

|| Adjusted for age, gastroprotection, ASA dose, history of GI bleeding, and duration of treatment.

¶ Adjusted for sex, age group, GI history, daily dose of clopidogrel, ASA, PPIs, H2RAs, and NSAIDs during follow-up, and ulcer-related risk factors (diabetes, ischemic heart disease, an alcohol-related diagnosis, a tobacco-related diagnosis, cirrhosis of the liver, and renal failure) during follow-up, and variables in the propensity score model (demographic characteristics, previous hospitalization for cardiovascular events, and previous hospitalization for major GI complications).

** Baseline variables included in models: age, sex, TennCare uninsured enrollment, race, calendar year, qualifying hospitalization diagnosis and procedures (CABG, drug-eluting stent, bare-metal stent, and none), and propensity score.

†† Time-dependent variables included in models: PPI use, change from baseline status of PPI use, subsequent hospital readmissions, emergency department visits, current use of ASA, drugs associated with bleeding (such as anticoagulants, cyclooxygenase-2 selective or nonselective nonsteroidal anti-inflammatory drugs, and systemic corticosteroids), and recent gastrointestinal symptoms.

‡‡ Adjusted for multiple variables.

§§ Confidence intervals reported are 95%.

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized clinical trial; RR, relative risk; and SSRI, selective serotonin reuptake inhibitor.

Table 2. Randomized Clinical Trials of Antiplatelet Use and Explicit Measurement of Gastrointestinal Bleeding Risk

Study	Population	Treatment Arms	Bleeding Endpoint	Results†
ASA use				
McQuaid & Laine (2006) (10)	Meta-Analysis of RCTs 61,011 ASA-users	ASA (n=28,686) vs. Placebo (n=28,719)	Major GI bleed*	RR 2.07 (1.61-2.66)
Clopidogrel Use				
CAPRIE (1996) (11)	19,185 MI, stroke, or PAD	Clopidogrel (n=9,599) vs. ASA (9,586)	GI bleeding (1-3 yrs)	RR 0.69 (0.48-1.00) Clopidogrel: 2.0% ASA: 2.7% (p<0.05)
CURE - Yusuf et al. 2001 (12)	12,562 Non-ST- elevation ACS	Clopidogrel+ASA (n=6,259) vs. Placebo+ASA (n=6,303)	GI bleeding (3-12 months)	RR 1.78 (1.25-2.54) Clopidogrel+ASA: 1.3% Placebo+ASA: 0.7% (p<0.05)
MATCH (Diener et al. 2004) (13)	7,599 high-risk patients with recent ischemic stroke or TIA	ASA+Clopidogrel (n=3,797) vs. Clopidogrel (n=3,802)	Major GI bleed* (18 months)	ASA+Clopidogrel: 2.5% Clopidogrel: 0.8% (p<0.05)
ACTIVE (Connolly et al. 2009) (14)	7,554 atrial fibrillation	Clopidogrel+ASA (n=3,772) vs. Placebo+ASA (n=3,782)	GI bleeding (1 yr)	RR 1.96 (1.46-2.63) Clopidogrel+ASA: 1.1% Placebo+ASA: 0.5% (p<0.001)
Concomitant Proton Pump Inhibitor Use				
Chan et al. (2005) (15)	320 ASA-users with upper GI bleed	Clopidogrel (n=161) vs. ASA+PPI (n=159)	Recurrent ulcer bleed (1 yr)	Clopidogrel: 8.6% (4.1-13.1%) ASA+PPI: 0.7% (0-2.0%) (p=0.001)
Lai et al. (2006) (16)	170 ASA-users with upper GI bleed	ASA+PPI (n=86) vs. Clopidogrel (n=84)	Recurrent ulcer complications (median follow-up 52 weeks)	ASA+PPI: 0% Clopidogrel: 13.6% (p=0.0019)
COGENT (Bhatt et al. 2010) (17)	3,761 patients with ACS or PCI	ASA+Clopidogrel+Placebo vs. ASA+Clopidogrel+PPI	Primary GI endpoint‡ Overt GI bleeding§ (median follow-up 106 days)	HR: 0.34 (0.18-0.63) (p<0.001) ASA+Clopidogrel: 2.9% ASA+Clopidogrel+PPI: 1.1% HR: 0.13 (0.03-0.56) (p=0.001) ASA+Clopidogrel: 1.2% ASA+Clopidogrel+PPI: 0.2%

This table includes only fully-published studies.

*Major bleeding defined as significantly disabling; intraocular bleeding leading to significant loss of vision; or transfusion of 3 units or less of red-blood cells or equivalent amount of whole blood.

† Confidence intervals reported are 95%.

‡The primary GI endpoint was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation; event rates are at 180 days.

§Overt GI bleeding consisted of overt gastroduodenal bleeding or overt upper GI bleeding of unknown origin.

ACS indicates acute coronary syndrome; ASA, acetylsalicylic acid; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized clinical trial; RR, relative risk; and TIA, transient ischemic attack.

Table 3. Observational Studies Assessing the Effect of PPI on Clinical Cardiovascular Outcomes in Patients Prescribed Clopidogrel

Author	Study type	Population	Endpoint	N	Results ^{§§}
Studies with a Significant Association					
Juurlink (2009) (18)	Nested case-control	Discharged after MI hospitalization	Death or readmitted for MI (90 days)*	Cases: 734 (PPI: 194) Controls: 2,057 (PPI: 424)	All PPIs: OR 1.27, 1.03-1.57 Pantoprazole: OR 1.02 (0.70-1.47) Other PPIs: OR 1.40 (1.10-1.77)
Ho (2009) (19)	Retrospective cohort	Discharged after MI or unstable angina hospitalization	Death or rehospitalization for MI or unstable angina ^{†, ††}	PPI: 5,244 No PPI: 2,961	All PPIs: OR 1.25 (1.11-1.41) Omeprazole: OR 1.24 (1.08-1.41) Rabeprazole: OR 2.83 (1.96-4.09)
Gupta (2009) (20)	Retrospective cohort	PCI	MI, target vessel failure, death [‡]	PPI: 72 No PPI: 243	OR 1.95 (1.09-3.49) PPI: 56%; No PPI: 38% (p=0.025)
Gaglia (2010) (21)	Retrospective cohort	PCI	Revascularization, Q-wave MI, stent thrombosis, death [§]	PPI: 318 No PPI: 502	HR 1.8 (1.1-2.7)
Stockl (2010) (22)	Retrospective cohort	Discharged after MI or PCI	Rehospitalization for MI or PCI 1) Propensity score based on CV risk 2) Adjusted for comorbidities	PPI: 1,033 No PPI: 1,033	All PPIs: Rehospitalization for MI: HR 1.93 (1.05-3.54) Rehospitalization for MI or PCI: HR 1.64 (1.16-2.32) Pantoprazole: Rehospitalization for MI: HR 2.18 (0.88-5.39) Rehospitalization for MI or PCI: HR 1.91 (1.19-3.06)
Studies Without a Significant Association					
O'Donoghue (2009) (23)	Retrospective cohort within RCT	ACS undergoing PCI	MI, stroke, CV death ^{¶, ††}	PPI: 2,257 No PPI: 4,538	All PPIs: HR 0.94 (0.80-1.11) Omeprazole (N=1,675): HR 0.91 (0.72-1.15) Esomeprazole (N=613): HR 1.07 (0.75-1.52) Pantoprazole (N=1,844): HR 0.94 (0.74-1.18) Lansoprazole (N=441): HR 1.00 (0.63-1.59) Patients with reduced-function CYP2C19 allele (N=357): HR 0.76 (0.39-1.48) Patients without reduced-function allele (N=1,064): HR 0.90 (0.55-1.48)
Simon (2009) (24)	Cohort	Acute MI	MI, stroke, death (1 yr) ^{**} , ^{††}	PPI: 1,606; (Omeprazole:1147) No PPI: 602	Univariate analysis (PPI vs. no PPI): All PPIs: RR 0.92 (0.73-1.16); Omeprazole: RR 0.85 (0.69-1.05) Multivariable analysis: PPIs "had no significant effects" on hazard ratios for CV events with 2 loss-of-function alleles vs. wild-type
Collet (2009) (25)	Cohort	MI	MI, CV death, urgent revascularization	PPI: 83 No PPI: 176	Multivariable analysis: "No significant effect of use of PPIs"
Rassen (2009) (26)	Retrospective cohort	≥ 65 yrs with PCI or acute coronary syndrome	MI, death 1) Propensity score with 400 variables.	PPI: 3,996 No PPI: 14,569	HR 1.22 (0.99-1.51)

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			2) Multivariable analysis with multiple covariates ^{††} and propensity score decile.		
Ray (2010) (9)	Retrospective cohort	MI, unstable angina, PCI, CABG	MI, stroke, CV death 1) Multiple baseline variables used to calculate propensity score for PPI use. 2) Regression models with multiple baseline and time-dependent variables and propensity score decile. ^{‡‡‡}	PPI: 7593 No PPI: 13,003	All PPIs: HR 0.99 (0.82-1.19) Esomeprazole: HR 0.71 (0.48-1.06) Omeprazole: HR 0.79 (0.54-1.15) Pantoprazole: HR 1.08 (0.88-1.32) Rabeprazole: HR 0.54 (0.30-0.97) Lansoprazole: HR 1.06 (0.77-1.45)

This table includes only fully-published studies.

* Adjusted for age, sex, income, comorbidity index, length of hospitalization, diabetes with complications, dysrhythmias, pulmonary edema, cardiogenic shock, acute renal insufficiency, congestive heart failure, and cerebrovascular disease, prescription use (commonly used CV medications, other cytochrome P450 2C19 inhibitors or inducers, and other cytochrome P450 3A4 inhibitors or inducers).

[†] Adjusted for age, sex, race, twelve comorbidities (heart failure, diabetes, prior MI, recent PCI, prior CABG, cerebrovascular disease, peripheral vascular disease, renal disease, COPD, dementia, cancer, current smoker), left ventricular ejection fraction <40%, unstable angina, prescription use (prior clopidogrel use, ASA at discharge, beta blocker at discharge, ACE inhibitor at discharge, statin at discharge, glycoprotein IIb/IIIa), total duration of clopidogrel treatment.

[‡] Adjusted for patient demographics, comorbidities, procedural variables, and discharge medications.

[§] Adjusted for diabetes, renal insufficiency, PCI, smoking, hematocrit, days off clopidogrel.

^{||} Patients were propensity-score matched, variables include age, sex, health plan type, geographical state, comorbidities, preperiod hospitalization for coronary stent procedure, and preperiod hospitalization, emergency department visit, or 2 or more outpatient claims for MI, other ischemic heart disease, stroke, other cerebrovascular disease, heart failure, hypertension, and diabetes mellitus.

[¶] Adjusted for sex, ethnic origin, region, history of peptic ulcer disease, history of carotid or vertebral artery disease, previous MI, creatinine clearance, use of ACE inhibitor or angiotensin receptor blocker at randomization, use of statin at randomization, index event of unstable angina/non-ST-elevation MI or ST-elevation MI, baseline hemoglobin, systolic blood pressure and heart rate.

^{**} Adjusted for age, sex, comorbidities (hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease, previous/current smoker, previous MI, previous PCI or CABG, previous heart failure, cancer, COPD, chronic renal failure), acute MI as first CV event, ST-elevation MI, body-mass index, blood pressure on admission, Killip class, GRACE risk score, leukocyte count, left ventricular ejection fraction, previous prescription use (ASA, clopidogrel, beta-blockers, statins, ACE inhibitors), type of in-hospital care (PCI, thrombolysis, statin, beta blocker, calcium channel blocker, ACE inhibitor, heparin, PPI, diuretic, glycoprotein, digitalis glycoside). Propensity analysis for CYP2C19 genotype, using multivariable model, and developed matched cohort of 5 controls for each patient with 2 variant alleles, on basis of the propensity analysis score.

^{††} Covariates include: age, sex, race, calendar year, comorbidity index, prescription use (nonselective NSAID, COX-2 inhibitor, diabetes medication, statin, beta-blocker, ACE inhibitor, warfarin), intensity of medical service, length of hospitalization, comorbidities (diabetes, hypertension, congestive heart failure, and hospitalization for MI, GI bleed, angina, peripheral vascular disease, hemorrhagic stroke).

^{‡‡} Adjusted for multiple variables.

^{§§} Confidence intervals reported are 95%.

^{|||} Baseline variables included in models: age, sex, TennCare uninsured enrollment, race, calendar year, qualifying hospitalization diagnosis and procedures (CABG, drug-eluting stent, bare-metal stent, and none), and propensity score. Time-dependent variables included in models: PPI use, change from baseline status of PPI use, subsequent hospital readmissions, emergency department visits, current use of ASA, subsequent revascularization, current use of statins, and newly prescribed cardiovascular drugs or new cardiovascular diagnoses.

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; RCT, randomized clinical trial; and RR, relative risk.

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