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Abbreviation List
ACCS = acute coronary syndromes; ADP = adenosine diphosphate; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HR = hazard ratio; H2RA = histamine H2 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 health care-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—
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.

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.

Conclusions

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.

**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 (i.e., 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).
Are H2RAs a Reasonable Alternative and in Which Population?

H2RAs are effective compared with placebo in decreasing the risk of gastric and duodenal ulcers (92) 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 NSAIDs (95) 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.

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 research. 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 (e.g., 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.