

CLINICAL REVIEWS

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ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

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Preamble

This document has been developed by the American College of Cardiology Foundation (ACCF) Task Force on Clinical Expert Consensus Documents, the American College of Gastroenterology (ACG), and the American Heart Association (AHA). Expert consensus documents (ECDs) are intended to inform practitioners, payers, and other interested parties of the opinion of the ACCF and document cosponsors concerning evolving areas of clinical practice and/or technologies that are widely available or new to the practice community. Topics chosen for coverage by ECDs are so designed because the evidence base, the experience with technology, and/or the clinical practice are not considered sufficiently well developed to be evaluated by the formal American College of Cardiology/American Heart Association (ACC/AHA)

practice guidelines process. Often the topic is the subject of ongoing investigation. Thus, the reader should view ECDs as the best attempt of the ACCF and other cosponsors to inform and guide clinical practice in areas where rigorous evidence may not be available or the evidence to date is not widely accepted. When feasible, ECDs include indications or contraindications. Topics covered by ECDs may be addressed subsequently by the ACC/AHA Practice Guidelines Committee as new evidence evolves and is evaluated.

The Task Force on ECDs makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest to inform the writing effort. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur. The relationships with industry information for writing committee members and peer reviewers are listed in Appendixes 1 and 2, respectively.

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Introduction

The use of antiplatelet therapies continues to increase as a result of accumulation of evidence of benefits in both primary and secondary treatment strategies for cardiovascular disease (1, 2). These antiplatelet agents, however, have recognizable risks—in particular, gastrointestinal (GI) complications such as ulceration and related bleeding. These risks may be further compounded by the ancillary use of other adjunctive medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anticoagulants. Given the high prevalence of antiplatelet therapy in clinical practice, coupled with a greater emphasis on their extended use, especially after implantation of a drug-eluting stent (3, 4), it is imperative that physicians know the potential benefits and the associated risks of antiplatelet therapy for primary or secondary prevention of cardiac ischemic events when combined with NSAID agents. Only with this understanding can physicians appropriately and fully evaluate the risk profile for each patient and either change medications or initiate prophylactic therapy in an attempt to reduce GI complications. This document provides consensus recommendations from the ACCF, the AHA, and the ACG on the combined use of antiplatelets and NSAID agents.

Many NSAIDs, both selective and nonselective, increase the risk of cardiovascular and cerebrovascular events. This issue was addressed in a scientific statement from the AHA (5). In terms of cardiovascular, GI, renal, and hypertension-

inducing risks, there are important differences among the NSAIDs (especially the cyclo-oxygenase-2 [COX-2] inhibitors), which should also be understood and considered in managing patients in need of these agents (6). The AHA statement introduces a stepped-care approach for selection of drugs to manage musculoskeletal discomfort in patients with known cardiovascular disease or risk factors for ischemic heart disease, based on the risk/benefit balance from a cardiovascular perspective. A further discussion of the cardiovascular and cerebrovascular risks of NSAIDs is beyond the scope of this report but may be found in several reviews (5, 7).

Prevalence of Use—NSAIDs/Aspirin (ASA)

The use of NSAIDs, including ASA, is common in the treatment of pain, inflammation, and fever. Additionally, low-dose ASA is used routinely in primary and secondary prophylaxis of cardiovascular and cerebrovascular events. These agents, both through prescription and over-the-counter (OTC) use, are the most widely used class of medications in the United States (8). Not surprisingly, NSAID use increases among the elderly. In a survey of people 65 yr of age and older, 70% used NSAIDs at least once weekly, and 34% used them at least daily. The prevalence of at least weekly ASA usage was 60% (9). More than 111 million NSAID prescriptions were written in 2004 (10).

Recognizably, much of this usage comes from noncardiac indications, such as arthritis and related musculoskeletal complaints, in particular. In 1990, the estimated prevalence of self-reported arthritis in the United States was 37.9 million cases, or 15% of the population. By 2020, it is projected that 59.4 million will be affected—a 57% increase from 1990 (11). As the incidence of arthritis complaints increases, the use of prescription and OTC NSAIDs is also expected to increase.

Mechanisms of GI Injury—NSAIDs

A complete discussion of the pathogenesis of ASA- and NSAID-associated injury is beyond the scope of this article; however, ASA, like all NSAIDs, injures the gut by causing topical injury to the mucosa and systemic effects induced by prostaglandin depletion. Tissue prostaglandins are produced via 2 pathways: a COX-1 and a COX-2 pathway. The COX-1 pathway is the predominant constitutive pathway; prostaglandins derived from this enzyme mediate many effects, most notably facilitating gastroduodenal cytoprotection, renal perfusion, and platelet activity. The COX-2 pathway, in contrast, is inducible by inflammatory stimuli and mediates effects through prostaglandins, which result in inflammation, pain, and fever.

Inhibition of the COX-1 pathway blocks production of prostaglandins that play an important protective role in the stomach by increasing mucosal blood flow and stimulating

the synthesis and secretion of mucus and bicarbonate, as well as promoting epithelial proliferation. Accordingly, the inhibition of these prostaglandins impairs these protective factors, resulting in a gastric environment that is more susceptible to topical attack by endogenous factors, such as acid, pepsin, and bile salts (12). A major consequence of prostaglandin depletion is to create an environment that is conducive to peptic ulcer formation and serious GI complications. Since prostaglandins are essential to both the maintenance of intact GI defenses and normal platelet function, nonselective NSAIDs such as ASA promote ulcer formation as well as bleeding (13).

Because COX-2 is the primary intended target for anti-inflammatory drug therapy, agents that selectively block COX-2, while having little to no effect on COX-1, should result in effective pain relief with reduced GI toxicity. This concept, called the “COX-2 hypothesis,” has been challenged by data from animal studies, which indicated that *both* COX-1 and COX-2 must be inhibited for gastric ulceration to occur. Interestingly, while the selective inhibition of either COX-1 or COX-2 alone failed to cause gastric damage, inhibition of both COX isoforms produced gastric ulceration (14). Thus, the explanation for reduced GI toxicity for COX-2-specific inhibitors may be their lack of dual COX inhibition rather than their COX-1-sparing effects.

In this framework, taking both a cardioprotective dose of ASA (primarily a COX-1 inhibitor at low dose [*i.e.*, 325 mg or less]) and a COX-2 inhibitor creates the ulcer risk of a traditional NSAID. A high percentage of individuals requiring cardioprotective doses of ASA have chronic pain and receive a traditional NSAID or a COX-2-selective NSAID (coxib). A survey that queried chronic coxib users found that 50% or more users were also taking ASA (15). Moreover, because coxibs were heralded as having an improved safety profile, related primarily to a lower rate of GI toxicity than traditional NSAIDs, the potential loss of this safety advantage when a COX-2 inhibitor is combined with ASA or an OTC NSAID remains underappreciated by clinicians. Heightened attention to the cardiovascular risks of NSAIDs has likely further increased the rate of addition of ASA to anti-inflammatory therapy (16).

Mechanisms of Gastroduodenal Injury—Clopidogrel

Platelet aggregation plays a critical role in healing through the release of various platelet-derived growth factors that promote angiogenesis. Angiogenesis, in turn, is critical for the repair of GI mucosal disruptions. Experimental animals with thrombocytopenia have been shown to have reduced ulcer angiogenesis and impaired ulcer healing (17). Additionally, adenosine diphosphate-receptor antagonists impair the healing of gastric ulcers by inhibiting platelet release of pro-angiogenic growth factors, such as vascular endothelial growth factor, which promotes endothelial proliferation and accelerates the healing of ulcers. GI bleeding is also a major

toxic effect of chemotherapeutic agents that use monoclonal antibodies directed at circulating vascular endothelial growth factor (18). Although clopidogrel and other agents that impair angiogenesis may not be a primary cause of gastroduodenal ulcers, their anti-angiogenic effects may impair healing of gastric erosions or small ulcerations that develop because of other medications or *Helicobacter pylori* infection. This may then, in the presence of acid, lead to clinically significant ulceration and related complications.

1. GI Complications of ASA and Non-ASA NSAIDs

Recommendation: As the use of any NSAID, including COX-2-selective agents and OTC doses of traditional NSAIDs, in conjunction with cardiac-dose ASA, substantially increases the risk of ulcer complications, a gastroprotective therapy should be prescribed for at-risk patients.

Upper gastrointestinal events (UGIE), symptomatic or complicated ulcers, occur in one of every 20 NSAID users and in one of seven older adults using NSAIDs (19), accounting for 30% of UGIE-related hospitalizations and deaths (20–22). Dyspepsia, defined as upper abdominal pain or discomfort, may occur in individuals taking NSAIDs, including ASA. Dyspepsia is not clearly predictive of the presence of an ulcer, as it is far more prevalent. Some patients may also experience an increase in symptoms of gastroesophageal reflux disease on NSAIDs as well (23). Endoscopic ulcers are used as a surrogate marker in clinical trials for risk of medications and in treatment trials; this document focuses on patients with dyspepsia and an ulcer (symptomatic ulcer) or those with serious (life-threatening) ulcer complications such as bleeding or perforation. The annual incidence of NSAID-related UGIE is 2.0–4.5% (19), and the risk of bleeding, perforation, or obstruction is 0.2–1.9% (19, 24). NSAIDs contribute to 10–20/1,000 hospitalizations per year and are associated with a fourfold increase in mortality (20). In the United States alone, NSAID use has been extrapolated to account for approximately 107,000 hospitalizations and 16,500 deaths per year among patients with arthritis (25). More recent information regarding these estimates related to NSAIDs suggests that these numbers may be too high, but increasing use of antiplatelet medications may contribute to a greater burden of GI bleeding (26–28). According to these reports, GI hospitalization rates markedly declined (from 1.5% to 0.5%) between 1992 and 2000. Four potential explanations were given: use of lower doses of NSAIDs, less use of “more toxic” NSAIDs, greater use of “safer” NSAIDs, and greater use of proton pump inhibitors (PPIs).

Among elderly veterans, NSAID exposure has been shown to increase risk of UGIE-related mortality threefold, even after adjustment for advancing age, comorbidity, and proportion of time spent on a traditional or COX-2-selective NSAID (26). In fact, if deaths resulting from NSAID-associated upper GI complications were tabulated separately, it would

represent the 15th most common cause of death in the United States (29). National data from the Department of Veterans Affairs reveal that 43.0% of the veterans prescribed NSAIDs are considered to be at high risk for UGIE and that patients 65 yr or older constitute the largest high-risk subset (87.1%) (8). Among elderly veterans, the risk of NSAID-related UGIE has been estimated as 2,753 UGIE in 220,662 person-years of follow-up (30).

Those who combine an NSAID with ASA represent another high-risk group. When patients combine an NSAID with ASA, the annual risk of UGIE is 5.6%, with coxibs providing no additional gastroprotection (7.5% UGIE/year). A number of observational studies have noted a two- to fourfold greater risk of UGIE associated with the concomitant prescription of NSAIDs with low-dose ASA. Data from Scandinavia indicated an annual incidence of hospital admission for UGIE of 1.4% related to use of NSAIDs plus low-dose ASA *versus* 0.6% for low-dose ASA. Estimates of the relative risk (RR) of UGIE for NSAID plus ASA range from 3.8 (95% confidence interval [CI] 1.8–7.8) (14) to 5.6 (95% CI 4.4–7.0) when compared with ASA alone (30).

Endoscopic trials suggest that the GI toxicity of a coxib plus ASA is additive, resulting in an overall risk of endoscopic ulcer formation that parallels that seen with a nonselective NSAID (25, 31). Additionally, evidence from observational studies and randomized controlled trials (RCTs) reveals that the risk of an NSAID plus ASA exceeds that of a coxib plus ASA, although both were markedly increased by ASA (9, 27, 29). In this context, whether one chooses a nonselective NSAID or a selective COX-2 inhibitor has a minimal, and perhaps clinically insignificant, impact on the likelihood of serious adverse GI outcomes. Thus, the selection of anti-inflammatory drug therapy in such patients must involve consideration of overall GI and cardiovascular risk of NSAIDs (32). The ongoing PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen; NCT00346216) study, which is randomizing arthritis patients with or at risk of cardiovascular disease to ibuprofen, naproxen, or celecoxib, should provide more data to help clarify these issues.

2. GI Effects of ASA

Recommendation: The use of low-dose ASA for cardioprophylaxis is associated with a two- to fourfold increase in UGIE risk. Enteric-coated or buffered preparations do not reduce the risk of bleeding. For patients at risk of adverse events, gastroprotection should be prescribed. The risk of UGIE increases with ASA dose escalation; thus, for the chronic phase of therapy, doses >81 mg should not be routinely prescribed.

The AHA recommends low-dose ASA use among patients with a 10-yr cardiovascular risk that is $\geq 10\%$ (33, 34), and the U.S. Preventive Services Task Force recommends ASA cardioprophylaxis for patients with a 5-yr risk of $\geq 3\%$ (35). It has

been estimated that 50 million Americans use low-dose ASA (*i.e.*, 325 mg/day or less) regularly for cardioprophylaxis (36). The use of low-dose ASA is associated with a two- to fourfold greater risk of UGIE (37, 38), which is not reduced by the use of buffered or enteric-coated preparations (39, 40). Fourteen randomized placebo-controlled trials have presented data on UGIE with cardiac-dose ASA (75–325 mg/day) in adults. When these data are pooled, the absolute greater risk per year of UGIE with ASA is 0.12% when compared with placebo (number needed to harm = 833), with conflicting evidence of risk reduction with lower doses (75–162.5 mg) *versus* higher doses (>162.5–325 mg) (41).

The estimated average excess risk of UGIE related to cardioprophylactic doses of ASA is 5 cases per 1,000 ASA users per year (42). Among elderly patients, the odds ratios (ORs) of bleeding with daily doses of ASA of 75, 150, and 300 mg are 2.3, 3.2, and 3.9, respectively (37). Dose reduction does not appear to reduce antithrombotic benefits; however, dose escalation does seem to increase bleeding complications (43). Additionally, case series implicate OTC use of low-dose ASA in over one-third of the patients admitted for GI hemorrhage (44), suggesting that patients who self-medicate may be unaware of the significant increase in their risk of UGIE.

The complexities of confirming a significant difference across the range of the low doses of ASA used for cardioprotection are discussed below. Meta-analyses have been contradictory in demonstrating a significant difference in the risk of GI bleeding (45, 46). Observational studies are somewhat contradictory, supporting evidence of a trend for an association between higher ASA dose and risk of upper GI complications (37, 47). The ACC and AHA recommend lowering the dose from 325 to 81 mg among those with a high risk of UGIE (2). However, some experts feel it may be prudent to use up to 325 mg a day of ASA for 1 month after a stent procedure, although it is not clear from the data whether this dose is really necessary (2). While this low-dose ASA approach makes sense intuitively because of the lack of demonstrated additional cardiovascular benefits at the higher dose (with certain limited exceptions, such as acute coronary syndrome [ACS]), coupled with a likelihood of greater risk of GI harm at the higher dose, the key point is that the benefit, in terms of GI bleeding risk reduction with the lower dose, remains insufficient to protect high-risk patients and mandates the addition of other GI bleeding risk-reduction approaches. However, it is unknown what the optimal dose of ASA really is. The Antithrombotic Trialists' Collaboration meta-analysis provides indirect evidence that higher doses of ASA are not more effective, at least at a population level (48). There are observational data from the CURE (Clopidogrel in unstable angina to prevent recurrent events) trial that suggest no benefit from higher doses of ASA but a greater risk of bleeding (49). The CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for InterventionS-7; NCT00335452) trial is randomizing ACS patients to higher (300–325 mg) or lower (75–100 mg) ASA doses in the range used for cardiovascular

disease and may help to clarify this issue once the results are known.

The use of enteric-coated or buffered formulations does not appear to reduce the risk of GI bleeding complications (39, 40, 50), a finding that suggests that the upper GI side effects of ASA are a result of a systemic effect, in addition to its potent topical action to induce chemical injury. Anecdotal reports of reduced dyspepsia with these products likely contribute to their uptake in practice (51).

While the risk factors for NSAID-related UGIEs have been well characterized, there are much less data on the risk of antiplatelet therapy. The synergism between ASA and NSAIDs was reviewed in detail in the previous section. A history of peptic ulcer, particularly with associated bleeding, appears to be the most important risk factor. Age is an important risk factor as well, with the relative increase beginning at age 60 yr and rising in a nonlinear fashion with age. Gender is a less important concern, although the risk of men is slightly higher than that of women (42). The risk associated with combination antiplatelet and anticoagulant therapies is substantial as well, and each is discussed below given their importance in cardiology clinical practice.

3. GI Effects of Combined ASA and Anticoagulant Therapy

Recommendation: The combination of ASA and anticoagulant therapy (including unfractionated heparin, low-molecular-weight heparin, and warfarin) is associated with a clinically meaningful and significantly greater risk of major extracranial bleeding events, a large proportion from the upper GI tract. This combination should be used with established vascular, arrhythmic, or valvular indication; patients should receive concomitant PPIs as well. When warfarin is added to ASA plus clopidogrel, an international normalized ratio (INR) of 2.0 to 2.5 is recommended (52).

The use of antiplatelet drugs for the initial management of ACS is common and known to be effective (1, 2). In some clinical settings, such as the initial and long-term management of ACS, the combination of anticoagulant and antiplatelet therapy is superior to antiplatelet therapy alone (53) but is associated with a substantial increase in UGIE, as shown in observational studies (54–56) and multiple RCTs.

A meta-analysis of four RCTs of unfractionated heparin plus ASA *versus* ASA alone for ACS demonstrated a 50% increase in major bleeds (57), representing an excess of three major bleeds per 1,000 patients. Low-molecular-weight heparin given in conjunction with ASA also increases major bleeding, as demonstrated in the FRISC-1 (Fragmin during Instability in Coronary Artery Disease-1) study (58) and CREATE (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation) (59). A comprehensive meta-analysis of over 25,307 patients demonstrated that the benefits of adding warfarin to ASA

in the treatment of ACS must be weighed against a twofold greater risk in major extracranial bleeding (OR 2.4, 95% CI 1.4–4.1), suggesting that as few as 67 additional patients would need to be treated with ASA plus warfarin to result in one additional major extracranial bleeding event (60).

Conditions such as venous thromboembolism or mechanical heart valves may necessitate long-term anticoagulation. With certain mechanical heart valves, an INR target of 2.0–2.5 may not be appropriate, and a higher INR may be required. Depending on the patient's specific bleeding and thrombotic risks, consideration may be given to stopping the antiplatelet agent, as warfarin also has cardioprotective effects (61).

4. GI Effects of Clopidogrel

Recommendation: Substitution of clopidogrel for ASA is not a recommended strategy to reduce the risk of recurrent ulcer bleeding in high-risk patients and is inferior to the combination of ASA plus PPI.

Because of their alternative molecular targets and inhibition of platelet activation, thienopyridines (*i.e.*, clopidogrel, ticlopidine) taken on their own, or in combination with ASA, have been compared with ASA. The ACC/AHA practice guidelines recommend the use of clopidogrel for hospitalized patients with ACS who are unable to take ASA because of major GI intolerance (Class I, Level of Evidence: A recommendation) (2). This recommendation was largely based on the safety data of the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) study (62). This study compared clopidogrel 75 mg daily with a relatively high cardioprotective dose of ASA (325 mg daily) for the prevention of ischemic events, including myocardial infarction, stroke, and peripheral arterial disease. After a median follow-up of 1.91 yr, the incidence rate of major GI bleeding was lower in the clopidogrel group (0.52%) when compared with the ASA group (0.72%, $P < 0.05$). The rate of hospitalization for GI bleeding was 0.7% with clopidogrel *versus* 1.1% with ASA ($P = 0.012$) (63). Although the risk of GI bleeding with clopidogrel was lower than that with ASA, the difference was small (0.2%). Clopidogrel with ASA for at least 1 month is also recommended for patients with a recent non-ST-segment elevation-ACS, with a preference of 12 months if the bleeding risk is not high (2, 64). In patients who have received drug-eluting stents, at least 12 months of uninterrupted dual antiplatelet therapy is recommended (65). Data from the CURE (66), MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients) (67), and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) studies (68) provide confirmatory evidence that combined ASA and clopidogrel therapy is associated with significantly greater risk of UGIE complications when compared with either agent alone (69). In patients at high risk of bleeding who require a stent, a bare-metal stent, with its

shorter requisite duration of dual antiplatelet therapy, may be preferable (4, 70).

Concomitant use of clopidogrel and an NSAID (including low-dose ASA) has been associated with impaired healing of asymptomatic ulcers (17) and disruption of platelet aggregation (71), with a consequent increase in serious UGIE (OR 7.4, 95% CI 3.5–15) (28). Few human studies document clopidogrel's potential for independent injury to the GI mucosa. A single endoscopic study with limited follow-up failed to demonstrate mucosal injury in humans (72). In a hospital-based, case-control study of 2,777 consecutive patients with major upper GI bleeding and 5,532 controls, it was found that non-ASA antiplatelet drugs (clopidogrel, ticlopidine) had a similar risk of upper GI bleeding (adjusted RR 2.8, 95% CI 1.9–4.2) to ASA, at a dose of 100 mg/day (adjusted RR 2.7, 95% CI 2.0–3.6), or anticoagulants (adjusted RR 2.8, 95% CI 2.1–3.7) (73).

A prospective, double-blind RCT comparing ASA plus esomeprazole against clopidogrel among *H. pylori*-negative patients with recent UGIE secondary to low-dose ASA demonstrated a significantly higher proportion of recurrent UGIE in the clopidogrel arm *versus* the ASA plus esomeprazole (20 mg twice daily) arm during the 12 months of study (8.6% *vs* 0.7%, 95% CI on the difference 3.4–12.4%) (74). A subsequent randomized trial with very similar design has shown virtually identical results (13.6% UGIE in the clopidogrel group *vs* 0% in the ASA plus esomeprazole group [20 mg daily]; 95% CI on the difference 6.3–20.9%) (75). These data suggest that use of clopidogrel alone to reduce GI bleeding as an alternative to ASA is not a safe strategy and support ASA cotherapy with once-daily PPI. It remains unclear whether clopidogrel exerts an independent injurious effect on the GI mucosa, or whether it merely induces bleeding in already damaged mucosa via its antiplatelet effects. Observational studies have suggested that PPI cotherapy is beneficial to reduce the risk of clopidogrel monotherapy as well (76).

5. GI Effects of Combined Clopidogrel and Anticoagulant Therapy

Recommendation: The combination of clopidogrel and warfarin therapy is associated with a greater incidence of major bleeding when compared with monotherapy alone. Use of combination antiplatelet and anticoagulant therapy should be considered only in cases in which the benefits are likely to outweigh the risks. When warfarin is added to ASA plus clopidogrel, an INR of 2.0–2.5 is recommended (52).

A paucity of evidence informs the clinical risk of combination therapy with clopidogrel or ticlopidine. Anticoagulant agents are not by themselves ulcerogenic; however, they are associated with a greater risk of UGIE because of an exacerbation of pre-existing lesions in the GI tract associated with NSAIDs, ASA, or *H. pylori* infection (76). Clinically, this combination of ASA plus clopidogrel or ticlopidine together

with anticoagulation, while not routinely recommended, is sometimes utilized among patients with atrial fibrillation, peripheral arterial disease, and coronary artery disease with percutaneous coronary intervention. With certain mechanical heart valves, an INR target of 2.0–2.5 may be too low (61), and a patient's individual thrombotic and bleeding risks need to be assessed.

The WAVE (Warfarin and Vascular Evaluation) study randomized 2,161 patients with peripheral arterial disease to receive warfarin plus antiplatelet therapy (ASA or thienopyridine) or warfarin monotherapy. No substantial difference was noted in the composite cardiovascular outcome of myocardial infarction, stroke, or death; however, more bleeding events requiring significant transfusion or surgical intervention were noted among patients receiving combination therapy (RR 3.4, 95% CI 1.8–6.4) (53), despite the fact that few participants had an INR in excess of 3.0 (77). Unfortunately, the number of patients prescribed ticlopidine or clopidogrel in combination with an anticoagulant in the WAVE trial was very small (6%); thus, the magnitude of risk of combined anticoagulant-thienopyridine therapy remains unclear. However, despite *a priori* exclusion of patients on NSAIDs and with prior history of UGIE, nearly 30% of patients terminated anticoagulation therapy because of bleeding episodes; no comment was made on the number of major bleeding events that originated from the GI tract. In a recent article describing bleeding risk in patients receiving triple therapy with ASA, clopidogrel, and anticoagulation, the incidence of both major and minor bleeding was substantially increased (78). Such combination therapy should be maintained only in patients in whom the benefit in cardiovascular protection outweighs these significant risks and a combination therapy with chronic PPI use seems prudent.

6. Treatment and Prevention of ASA- and NSAID-Related Gastroduodenal Injury

Recommendation: PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury.

The selection of patients for therapy to reduce the risk of antiplatelet therapy should consider the risk factors discussed in the preceding section, as well as concurrent medical illness. A suggested approach is outlined in Figure 1. Given the relative safety of cotherapy to reduce risk, consideration of risk factors mainly relates to the provision of cost-effective care.

Prostaglandin depletion is the central mechanism for NSAID-ulcer development, and replacement therapy with the synthetic prostaglandin, misoprostol, reduces NSAID toxicity. Little data specifically address the impact of misoprostol on ASA-related injury, although one would expect, given the reduced ulcerogenic effects of low-dose ASA compared with those of full-dose NSAIDs, that it would be effective for that purpose as well. In an endoscopic study,

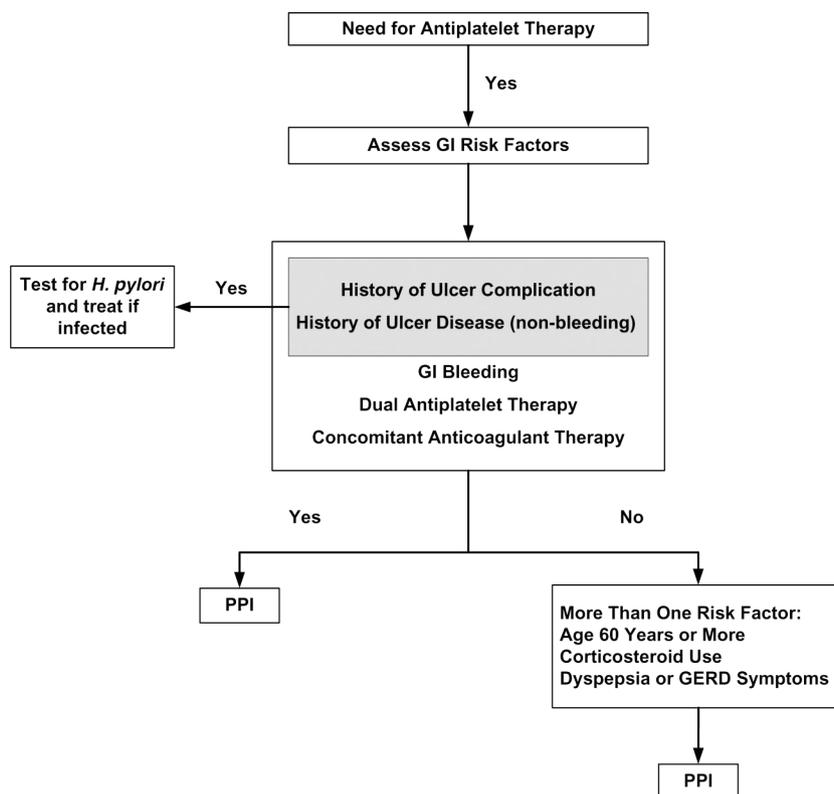


Figure 1. Steps for minimizing gastrointestinal bleeding. PPI therapy is believed to reduce the risk in all patients; the more risk factors present, the more cost-effective the additional therapy likely becomes. See text for additional considerations. GI = gastrointestinal; GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.

misoprostol 100 mcg/day significantly reduced the development of erosions in healthy volunteers taking ASA 300 mg/day (79). In addition, misoprostol has been shown to be superior to placebo for preventing recurrence of gastric ulcers among patients with a history of gastric ulcer who were receiving low-dose ASA and another NSAID (80). However, misoprostol is associated with side effects, particularly diarrhea, that often lead to treatment discontinuation. For example, in a study of more than 8,000 rheumatoid arthritis patients, 20% of patients receiving misoprostol withdrew within the first month of treatment because of diarrhea (81). Although it is the only U.S. Food and Drug Administration-approved regimen for the prevention of NSAID ulcers and complications, it is rarely used because of the prevalence of the side effects of diarrhea and abdominal cramping.

Sucralfate, a basic aluminum salt of sucrose octasulfate, forms an ulcer-adherent complex at duodenal ulcer sites, protecting the ulcer and promoting healing; sucralfate may also inhibit pepsin activity in gastric fluid. Sucralfate has been shown to be effective in the treatment of NSAID-associated duodenal ulcers, particularly when the NSAID is stopped, but is not effective in the treatment or prevention of NSAID-related gastric ulcers. Its use is not recommended because of the availability of far superior alternatives.

The level of acid suppression provided by traditional doses of H₂-receptor antagonists (H₂RAs) does not prevent most NSAID-related gastric ulcers. There are little data on their

use in conjunction with ASA. The H₂RA ranitidine, at a dose of 150 mg/day, significantly increased intragastric pH and reduced the amount of gastric bleeding in subjects taking ASA 300 mg/day (82). Similar results were seen in two further trials in volunteers (83). Despite a single endoscopic study demonstrating that H₂RAs at double the usual dose may be effective compared with placebo, studies comparing high doses of H₂ blockers to misoprostol or PPIs for the prevention of NSAID ulcers are not available. Given compliance concerns with twice daily dosing, PPI therapy is the rational alternative to H₂RAs in this clinical setting. PPIs have been proven superior to both ranitidine and misoprostol in preventing NSAID ulcer recurrence and overall symptom control, largely related to their ability to reduce ulcers and improve NSAID-associated dyspepsia, thereby affecting overall quality of life. No randomized controlled data are available from studies evaluating the impact of H₂ blockers on low-dose ASA-related injury.

PPIs inhibit the parietal cell proton pump, thus exerting a suppressive effect on gastric acid. In endoscopic studies involving healthy volunteers, both lansoprazole and omeprazole significantly reduced the risk of gastroduodenal lesions in patients taking ASA 300 mg/day (51). These results were confirmed by epidemiological studies in which concomitant antisecretory therapy, especially PPI therapy, was associated with a significant RR reduction of upper GI bleeding among patients receiving low-dose ASA (76, 84). These data in the

literature do not demonstrate evidence that supports the need for greater than the standard once daily dosing for PPI therapy as indicated in labeling for ulcer disease indications, despite the greater levels of acid suppression afforded by more frequent or higher daily dosing. Maximal acid inhibitory effects of most PPIs are achieved if food is consumed within 30 min of dosing; this is most relevant for gastroesophageal reflux disease symptom control, but it is not known if this concern is relevant for ulcer prevention therapy.

Lansoprazole 30 mg/day was compared with placebo for recurrence of ulcer complications in patients taking ASA 100 mg/day for 12 months after eradication of *H. pylori* and healing of ulcers. Patients in the lansoprazole group were significantly less likely to have a recurrence of ulcer complications, suggesting that PPI therapy plus *H. pylori* eradication is superior to *H. pylori* eradication alone (85). Although four of nine patients in the placebo group who rebled had either failed eradication or had *H. pylori* reinfection, this study indicates that antibiotic treatment alone provides insufficient protection for low-dose ASA users at high risk. Chan *et al.* (86) reported that among patients with *H. pylori* infection and a history of upper GI bleeding, omeprazole therapy was equivalent to eradication of *H. pylori* in preventing recurrence of bleeding. However, the follow-up time in this study was relatively short (6 months). In an observational study, Lanas *et al.* (87) reported a low incidence of upper GI complications among high-risk patients receiving low-dose ASA plus omeprazole.

As discussed elsewhere, the predominant antiplatelet effect of ASA promotes bleeding from established lesions (including *H. pylori*-induced ulcers) and creates new ulcers. Based upon data on full-dose NSAID therapy, PPI therapy is believed to tip the balance so that small lesions do not progress to larger lesions that can become symptomatic (88). This is important, as observational studies with the occurrence of GI hemorrhage as their end point may document changes in the rate of ulcer bleeding but fail to assess the prevalence of ASA-related ulcers. This is very relevant to the interpretation of case-controlled studies from areas of high *H. pylori* prevalence, which, indeed, provide much of the data on this issue and which also suggest a possible role for H2RA therapy. The administration of an H2RA, by reducing the burden of *H. pylori*-related ulcers, lessens the likelihood of GI bleeding events related to the antiplatelet effect of ASA therapy (76, 84).

Combining a PPI with clopidogrel appears to result in less GI bleeding (76, 89). To date, despite some *in vitro* data to suggest an interaction due to metabolism by the cytochrome P450 pathway, there has been relatively little evidence of any clinically significant interaction between clopidogrel and PPIs (90). The ongoing COGENT-1 (Clopidogrel and the Optimization of Gastrointestinal Events; NCT00557921) study is randomizing patients with coronary artery disease to ASA plus clopidogrel in combination with omeprazole 20 mg or placebo and should provide further evidence to help address these issues.

7. Role of *H. pylori*

Recommendation: Testing for and eradicating *H. pylori* in patients with a history of ulcer disease is recommended before starting chronic antiplatelet therapy.

Unlike results of studies among non-ASA NSAID users, case-control studies have consistently shown that *H. pylori* is an important risk factor for ulcer and ulcer bleeding in users of low-dose ASA (38, 91, 92). In a case-control study of 695 consecutive users of low-dose ASA with upper GI bleeding, *H. pylori* infection was identified as an independent risk factor of upper GI bleeding (OR 4.7, 95% CI 2.0–10.9). Other risk factors identified were a previous ulcer history (OR 15.2, 95% CI 3.8–60.1), alcohol use (OR 4.2, 95% CI 1.7–10.4), and use of calcium-channel blockers (OR 2.54, 95% CI 1.25–5.14) (91).

Whether eradication of *H. pylori* infection in patients with a history of ulcer prior to starting ASA will reduce subsequent ulcer risk has been controversial. In a 6-month randomized trial of *H. pylori* eradication versus maintenance therapy with omeprazole in ASA users with *H. pylori* infection and a recent history of ulcer bleeding (N = 250), rates of recurrent ulcer bleeding were comparable between the two treatment groups (1.9% in the eradication therapy group and 0.9% in the omeprazole group, 95% CI for the difference –1.9% to 3.9%) (86). In another randomized trial, all ASA users with *H. pylori* infection and a history of ulcer bleeding received a course of eradication therapy. They were then randomly assigned to receive lansoprazole (N = 62) or placebo (N = 61) for up to 12 months. It was found that 1.6% (95% CI 0–9%) of patients in the lansoprazole group compared with 14.8% (95% CI 7–26%) in the placebo group had recurrent ulcer bleeding (85). In the latter study, however, two-thirds of the patients with recurrent ulcer bleeding in the placebo group either had failure of *H. pylori* eradication or used concomitant NSAIDs. Thus, whether eradication of *H. pylori* alone would adequately reduce the risk of ulcer bleeding in ASA users with high GI risk is uncertain. Nevertheless, prophylaxis with a PPI effectively prevents recurrent upper GI bleeding with low-dose ASA, despite failure of *H. pylori* eradication and concomitant use of non-ASA NSAIDs.

A more recent study, and the largest to date, has gone some way toward clarifying this issue. In this prospective cohort study, the incidence rates of ulcer bleeding were compared among three different cohorts of low-dose ASA users, namely, patients without prior ulcer history who just started using ASA (N = 548), ASA users with prior ulcer bleeding and *H. pylori* infection who had successful eradication of *H. pylori* (N = 250), and *H. pylori*-negative ASA users who had prior ulcer bleeding (N = 118). All patients received low-dose ASA (<160 mg daily) without a gastroprotective agent. After a median follow-up of 48 months, the annualized incidence rate of ulcer bleeding in the three groups was 0.5%, 1.1%, and 4.6%, respectively (93). Thus, current evidence suggests that confirmed eradication of *H. pylori* in ASA

users with prior ulcer bleeding significantly and substantially reduces the risk of recurrent bleeding. Whether this strategy would be beneficial in emergent situations such as ACS is unknown.

A. Diagnosis of *H. pylori*

A recently published ACG guideline provides a comprehensive source of information on *H. pylori* (94). Noninvasive *H. pylori* testing is currently recommended for patients who do not need endoscopy. Two general categories of noninvasive tests are now available: tests that identify active infection and tests that detect antibodies (exposure). This distinction is important because antibodies (*i.e.*, positive immune response) indicate only the presence of *H. pylori* at some time. Antibody tests do not differentiate between previously eradicated and currently active *H. pylori*. Compared with tests for active infection, tests for antibodies are simpler to administer, provide a faster result, and are less expensive. However, the probability that a positive antibody test reflects active infection decreases as the proportion of patients with previously eradicated *H. pylori* increases. Successfully treated patients include both patients given antibiotics specifically for *H. pylori* and patients with undiagnosed *H. pylori* who had their *H. pylori* eradicated by antibiotics given for another infection; less common is spontaneous eradication of *H. pylori* infection.

H. pylori serologic tests that detect antibodies to *H. pylori* have a sensitivity and specificity of approximately 90%. In populations with low disease prevalence, the positive predictive value of the test falls dramatically, leading to unnecessary treatment. Office-based serologic tests are less accurate than laboratory-based enzyme-linked immunosorbent assay tests but have the advantage of providing a result within 30 min. Serology tests should be used only for initial diagnosis, because antibody levels often remain elevated after *H. pylori* is eliminated. Serology tests should not be used to confirm a cure after a patient has been treated for *H. pylori*.

B. Tests for Active *H. pylori*

Tests for active *H. pylori* include fecal *H. pylori* antigen testing and urea breath testing (UBT). For the UBT, the patient drinks an oral preparation containing ¹³C or ¹⁴C-labeled urea. *H. pylori* bacteria in the stomach metabolize this urea; the blood stream absorbs the carbon and it travels to the lungs, which exhale it as carbon dioxide. The carbon dioxide isotope is measured to determine the presence or absence of *H. pylori*. This test has a sensitivity and specificity of more than 90% for active infection. A number of drugs can adversely affect the accuracy of UBT. Prior to any form of active testing, antibiotics and bismuth should be withheld for at least 4 wk, PPIs should be withheld for at least 7 days, and patients should fast for at least 6 h.

The stool antigen test has been reported to have a sensitivity and specificity of more than 90% in untreated patients with suspected *H. pylori* infection. It requires collection of a stool sample the size of an acorn by either the clinician or the

patient. This test must be performed in a laboratory by trained personnel. Based upon available data, it is reasonable to conclude that the fecal antigen test can be used interchangeably with the UBT to identify *H. pylori* before antibiotic therapy.

C. Treatment of *H. pylori*

The choice of therapy should consider effectiveness and cost of various regimens versus side effects. PPIs have *in vitro* activity against *H. pylori*. A PPI plus clarithromycin (500 mg) plus either amoxicillin (1 g) or metronidazole (500 mg) given twice daily has demonstrated eradication rates near 90% when used for 10–14 days. Amoxicillin is preferred for patients who have been treated with metronidazole previously. Metronidazole is preferred for patients allergic to penicillin. “Bismuth-based triple therapy” is a less costly alternative: (bismuth subsalicylate) 2 tablets daily, metronidazole 250 mg four times daily, and tetracycline 500 mg four times daily for 2 wk is the best studied, highly effective anti-*H. pylori* therapy ($\geq 85\%$ eradication). The duration and multidrug nature of this regimen have been associated with decreased compliance, leading to potential failure to eradicate. The complexity of testing and treatment of *H. pylori*, despite its apparent value as a sole therapy to reduce risk, supports the superiority of PPI therapy alone in its simplicity and efficacy, even for *H. pylori*-infected patients, as demonstrated by the study by Lai *et al.* (85).

8. Discontinuation of Antiplatelet Therapy Because of Bleeding

Recommendation: Decision for discontinuation of ASA in the setting of acute ulcer bleeding must be made on an individual basis, based upon cardiac risk and GI risk assessments to discern potential thrombotic and hemorrhagic complications.

Patients receiving low-dose ASA who develop upper GI bleeding are often advised to discontinue ASA until ulcers have healed. A particular dilemma arises in patients requiring continuous antiplatelet therapy (*e.g.*, with ACS, acute cerebrovascular insufficiency, or recent percutaneous revascularization) who develop actively bleeding ulcers. Can ASA be reintroduced immediately after endoscopic hemostasis has been achieved, given that prolonged discontinuation of ASA increases thrombotic risk in patients with unstable cardiovascular diseases?

Hemodynamic instability and hemostatic changes induced by acute bleeding may further increase the risk of thrombosis in the absence of antiplatelet therapy. On the other hand, continuation of ASA in the setting of acute ulcer bleeding may provoke recurrent bleeding. There is no evidence that non-ASA antiplatelet drugs such as clopidogrel will reduce this bleeding risk in the presence of active ulcers (73). A meta-analysis of randomized trials showed that the IV administration of a PPI after endoscopic therapy for bleeding ulcers reduced the risk of recurrent bleeding (OR 0.39, 95%

CI 0.18–0.87) and the need for surgery (OR 0.61, 95% CI 0.40–0.93) (95). However, no previous trials permitted continuation of antiplatelet therapy during the study period. An *in vitro* study suggested that hemostasis depends on pH and the stability of the platelet plug (96). Antiplatelet drugs may negate the hemostatic effect of a PPI by impairing platelet-plug formation.

To date, only 1 small-scale, double-blind, randomized trial evaluated the effect of early reintroduction of ASA in patients with cardiovascular diseases who presented with acute bleeding ulcers (97). By the time that an interim analysis was performed, 113 patients receiving ASA for cerebrovascular or cardiovascular diseases who developed bleeding gastroduodenal ulcers confirmed by endoscopy had been enrolled. After endoscopic control of active bleeding, they were randomly assigned to receive ASA 80 mg once daily or placebo. All patients received a continuous infusion of a PPI for 72 h and then a standard dose of an oral PPI for up to 8 wk. The end points included recurrent ulcer bleeding within 30 days and all-cause mortality. The two groups were comparable in terms of age (mean age 74 yr vs 73 yr), gender (men: 62% vs 69%), prior ulcer history (6.9% vs 3.7%), concomitant use of NSAIDs (12% vs 11%), location (gastroduodenal ulcers: 28 vs 32), and diameter of ulcers (1.13 cm vs 1.20 cm). Recurrent ulcer bleeding within 30 days occurred in 18.9% of patients receiving ASA and 10.9% receiving placebo ($P = 0.25$). In the ASA group, 1 patient (1.7%) died of a recurrent cardiovascular event. In the placebo group, 8 patients (14.5%) died (5 recurrent cardiovascular events, 2 recurrent bleeding, and 1 pneumonia; $P = 0.01$ vs ASA group). These results suggested that the discontinuation of ASA was associated with a significant increase in all-cause mortality, with most of the deaths being due to recurrent cardiovascular events. There was a numerical trend toward a higher rate of recurrent ulcer bleeding in the ASA group (18.9%), which suggested that adjuvant PPI after endoscopic therapy could not effectively prevent early rebleeding induced by ASA.

9. Endoscopy in Patients on Mono- or Dual Antiplatelet Therapy

Recommendation: Endoscopic therapy may be performed in high-risk cardiovascular patients on dual antiplatelet therapy, and collaboration between the cardiologist and endoscopist should balance the risks of bleeding with thrombosis with regard to the timing of cessation of antiplatelet therapy.

The American Society of Gastrointestinal Endoscopy practice guideline (98) on the use of antiplatelet and anticoagulant medications in the setting of GI endoscopy considers the risks and benefits of antiplatelet therapy with the need for, and risks of, GI endoscopy with intervention. With regard to the performance of GI endoscopy in the setting of multiple antiplatelet agents, it is quite clear that cardiovascular concerns should remain paramount in the GI endoscopist's

practice; thus, cardiovascular risk weighs heavily in clinical decision making. While many endoscopists would prefer to withhold dual antiplatelet agents in the setting of an elective colonoscopy and polypectomy, the actual evidence that this practice reduces the risk of post-polypectomy bleeding is marginal, at best (98). Therefore, we encourage endoscopists to consider cardiovascular risks and to defer elective procedures in patients in whom a high risk is present (*e.g.*, those with recent placement of cardiovascular stents), for example, for a year after drug-eluting stent placement. It is important to emphasize that the guideline does not mandate discontinuation of ASA or NSAIDs for most endoscopic procedures because of a lack of clear evidence that bleeding rates following an endoscopic procedure, such as a polypectomy, are adversely influenced.

The most likely setting where the issue of possibly discontinuing antiplatelet agents in a high-risk patient will arise will be that of endoscopic therapy for GI bleeding. This should be a rare occurrence, and again, individualized risk stratification should be paramount. Based on the expert consensus of the writing committee, for those with chronic blood loss and high cardiovascular risk, such as a recently placed stent, dual antiplatelet therapy should be continued as mandated by cardiovascular risk, given the lack of a clearly defined contraindication to endoscopic intervention.

In the acute setting following successful endoscopic and medical treatment of major GI hemorrhage, it seems prudent, following discussion among the specialties, to briefly discontinue antiplatelet therapy until lack of rebleeding is observed in the intensive care unit setting. The optimal duration for cessation of antiplatelet therapy leading to a balance of GI and cardiovascular outcomes has not been established by clinical trials. The current efficacy of endoscopic therapy for ulcer bleeding combined with IV continuous-infusion PPI therapy suggests that reintroduction of antiplatelet therapy in such high-cardiovascular-risk patients is reasonable in those who remain free of rebleeding after 3–7 days (97). In the far less common setting of endoscopic therapy for lower GI bleeding, even less available data guide decision making. Since there is no adjunctive medical therapy such as for ulcer bleeding with PPI, endoscopists may favor the use of nonthermal treatment approaches such as clipping and favor a delay of antiplatelet therapy for 7–10 days, based upon lesion size and individualized assessment of adequacy of endoscopic therapy.

Summary

In appropriate patients oral antiplatelet therapy decreases ischemic risks, but this therapy may increase bleeding complications. Of the major bleeding that occurs, the largest proportion is due to GI hemorrhage. Concomitant use of NSAIDs further raises the risk of GI bleeding. Gastroprotection strategies consist of use of PPIs in patients at high risk of GI bleeding and eradication of *H. pylori* in patients with a history of ulcers. Communication between cardiologists, gastroenterologists, and primary care physicians is critical to weigh

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—ACCF/ACG/AHA 2008 EXPERT CONSENSUS DOCUMENT ON REDUCING THE GASTROINTESTINAL RISKS OF ANTIPLATELET THERAPY AND NSAID USE

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ACCF/ACG/AHA = American College of Cardiology Foundation/American Heart Association; NSAID = nonsteroidal anti-inflammatory drugs; PI = principal investigator.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—ACCF/ACG/AHA 2008 EXPERT CONSENSUS DOCUMENT ON REDUCING THE GASTROINTESTINAL RISKS OF ANTIPLATELET THERAPY AND NSAID USE

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ACC = American College of Cardiology; ACCF = American College of Cardiology Foundation; ACG = American College of Gastroenterology; AHA = American Heart Association; NHLBI = National Heart, Lung, and Blood Institute; NSAID = nonsteroidal anti-inflammatory drugs; NSTEMI = non-ST-segment elevation myocardial infarction.

the ischemic and bleeding risks in an individual patient who needs antiplatelet therapy but who is at risk for or develops significant GI bleeding.

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