Preamble
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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).

**Recommendations**

**GI Complications of ASA and Non-ASA NSAIDs**

- 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.

**GI Effects of ASA**

- The use of low-dose ASA for cardio-prophylaxis 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.

**GI Effects of Combined ASA and Anticoagulant Therapy**

- 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, arrhythmia, 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).
**GI Effects of Clopidogrel**
- 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.

**GI Effects of Combined Clopidogrel and Anticoagulant Therapy**
- 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).

**Treatment and Prevention of ASA- and NSAID-Related Gastroduodenal Injury**
- PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury.

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**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.
Recommendations continued

Role of *H. pylori*

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

Discontinuation of Antiplatelet Therapy Because of Bleeding

- 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.

Endoscopy in Patients on Mono- or Dual Antiplatelet Therapy

- 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.

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