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EXPERT CONSENSUS DOCUMENT

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 Clinical Expert Consensus Documents

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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 consensus 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 an increased 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

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 years 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 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

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 1 of every 20 NSAID users and in 1 of 7 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% to 4.5% (19), and the risk of bleeding, perforation, or obstruction is 0.2% to 1.9% (19,24). NSAIDs contribute to 10–20/1000 hospitalizations per year and are associated with a 4-fold 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 an increased 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, increased use of "safer" NSAIDs, and increased use of proton pump inhibitors (PPIs).

Among elderly veterans, NSAID exposure has been shown to increase risk of UGIE-related mortality 3-fold, even after adjustment for advancing age, comorbidity, and proportion of time spent on a traditional or COX-2–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 years or older constitute the largest high-risk subset (87.1%) (8). Among elderly veterans, the risk of NSAID-related UGIE has been estimated as 2753 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 2- to 4-fold increased 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 to 7.8) (14) to 5.6 (95% CI: 4.4 to 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 2- to 4-fold 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 greater than 81 mg should not be routinely prescribed.

The AHA recommends low-dose ASA use among patients with a 10-year cardiovascular risk that is greater than

tients with a 5-year risk of greater than or equal to 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 2- to 4-fold increased 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 to 325 mg per day) in adults. When these data are pooled, the absolute increased 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 to 162.5 mg) versus higher doses (greater than 162.5 to 325 mg) (41).

The estimated average excess risk of UGIE related to cardioprophylactic doses of ASA is 5 cases per 1000 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 increased 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 Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS-7; NCT00335452) trial is randomizing ACS patients to higher (300 to 325 mg) or lower (75 to 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 years 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 increased 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 4 RCTs of unfractionated heparin plus ASA versus ASA alone for ACS demonstrated a 50% increase in major bleeds (57), representing an excess of 3 major bleeds per 1000 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

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