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Consensus Development Conference on the Use of Nonsteroidal Anti-Inflammatory Agents, Including Cyclooxygenase-2 Enzyme Inhibitors and Aspirin

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See CME exam on page 1075.

The American Gastroenterological Association (AGA) convened a panel of physicians in gastroenterology, rheumatology, cardiology, and internal medicine who developed this statement based on expert presentations of current scientific knowledge and through subsequent group discussion.

This statement reflects the panel's assessment of medical knowledge available when written. Thus, readers should view this statement in the context of data that invariably will accumulate after its creation.

Consensus Panel Statement

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the world. Well-recognized gastrointestinal (GI) complications and identification of previously unrecognized cardiac risks have amplified concerns about their use. The extent of these risks varies by patient, specific agent, dosage, and concomitant medications. To increase awareness about the benefits and the risks of gastrointestinal toxicity and myocardial infarction associated with these medications and to improve the use of NSAIDs, the American Gastroenterological Association (AGA) convened a Consensus Development Conference on the Use of NSAIDs from September 30 to October 2, 2005. The Consensus Development Panel and the speakers are listed in Appendix 1 (see supplementary material online at www.cghjournal.org). This conference examined what is known about risks of myocardial infarction and gastrointestinal toxicities of these medications, their risks in specific patients, and what interventions, if any, may diminish these risks. This conference did not address specifically the known risks of kidney disease and heart failure associated with NSAID and coxib use. These risks are well described in the medical literature. Clinicians should familiarize themselves with the existing and evolving data about these risks; in addition, more information about these issues is available at www.gastro.org.

During the first day of the conference, experts presented the most recent pharmacologic, clinical, and epidemiologic research about NSAIDs and their use. These presentations, summarized in Appendix 2 (see supplementary material online at www.cghjournal.org) addressed the following key questions:

1. Who is at risk and what is the risk?
2. Who needs these medications and what are their benefits over non-NSAIDs?
3. Can the risk of NSAID-induced GI toxicity be modified?
4. Coxib risks and benefits.
5. Aspirin risks and benefits.

After weighing this scientific evidence, the panel developed a consensus view of the gastrointestinal and cardiovascular risks of NSAIDs, and ways in which such risks may be attenuated. Lastly, the panel identified outstanding questions that warrant further study.

Conclusions

Most health professionals are aware of the increased risk of gastrointestinal toxicity associated with NSAID use. There is less familiarity, however, with the magnitude of this risk, with risks associated with specific medications, and with ways to reduce these risks.

Traditional NSAIDs (or nonselective NSAIDs), coxibs (or selective NSAIDs), and aspirin (ASA) inhibit prostaglandin synthesis to varying degrees and, in turn, have anti-inflammatory, antipyretic, and analgesic effects. Nonselective NSAIDs reversibly inhibit both cyclooxygenase (COX)-1 and COX-2 activity. Coxibs reversibly inhibit COX-2 more than COX-1 because of their higher affinity for COX-2. ASA irreversibly blocks the COX enzymes. All agents discussed in this article are nonsteroidal, inhibit inflammation,

Abbreviations used in this paper: ASA, aspirin; COX, cyclooxygenase; CV, cardiovascular; GI, gastrointestinal; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; nsNSAID, nonselective nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

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and thus technically are NSAIDs. For the purposes of this article, traditional NSAIDs will be denoted as nonselective NSAIDs (nsNSAIDs), and coxibs and ASA will be denoted as such.

Are nonsteroidal anti-inflammatory drugs necessary? NSAIDs, including nsNSAIDs, ASA, and coxibs are among the most widely used medications in the world. It is estimated that as many as 50 billion ASA tablets are consumed annually worldwide.¹ In the United States, approximately 60 million prescriptions for NSAIDs are written each year, predominantly for older patients.² The broad use of these compounds speaks to their benefits and relative safety. These drugs are effective in acute and chronic treatment of painful and inflammatory musculoskeletal conditions, among others. Their anti-inflammatory properties appear to drive much of their benefits. Data from studies of patients with arthritis indicate that, compared with full-dose acetaminophen (1000 mg/day), NSAIDs provide superior pain control, functional outcomes, and are preferred by patients.³⁻⁵ Such data suggest that even patients with low-grade inflammation derive greater benefits with anti-inflammatory and analgesic combinations than analgesics alone. This is not to say that patients cannot benefit from simple analgesics in some cases; however, by the time such patients present to health care providers they often already have failed such approaches. It also is important to note, although beyond the scope of this article, that data suggest that the non-NSAID analgesic, acetaminophen, when used at high doses may behave pharmacologically similar to NSAIDs. Thus, it is possible that high-dose chronic acetaminophen may confer as of yet unidentified NSAID-like risks and benefits.⁶

What are the gastrointestinal consequences of nonsteroidal anti-inflammatory drug use? Gastrointestinal morbidities are the most common adverse effects associated with NSAID use, including complications in both the upper- and lower-GI tracts. Although physicians are aware of upper-GI risks attendant to NSAID use, there is less awareness of lower-GI sequelae.

Gastrointestinal risks of nonselective nonsteroidal anti-inflammatory drugs. Serious GI tract complications occur in 1%–4% of NSAID users annually.^{7,8} Although there is a high risk after initiation, there remains a continued risk over time such that the patient is always at risk while taking NSAIDs. Symptomatic or complicated ulcers (with bleeding, perforation, or obstruction) are the most serious GI side effects. NSAID use has surpassed *Helicobacter pylori* as the most commonly identified risk factor among patients with bleeding ulcers, found in 53% of patients in 1 study.⁹ The average relative risk of developing a serious GI complication is 3- to 5-fold greater among NSAID users than among nonusers.¹⁰ Estimates suggest that NSAID use results in about 100,000 hospitalizations annually in the United States.¹¹ The incidence of serious lower-GI tract complications from NSAID use is not well defined, but may account for 20% of total NSAID-associated GI morbidity.¹²

NSAID use increases the risk for death; however, the magnitude of this increase is uncertain. A yearly mortality rate from NSAID use of 16,500 in the United States was estimated using the Arthritis, Rheumatism, and Aging Medical Information System database, a large long-term surveillance program of patients with rheumatoid arthritis.¹¹ However, this may represent an overestimate because these data were extrapolated to a non-age-adjusted rheumatoid arthritis population, a group with higher all-cause mortality than the population in general. In a recent study using

comprehensive data from the Spanish National Health system, the rate of NSAID-associated deaths was 15.3 per 100,000 users.¹² Still, this lower estimate is substantial given the scope of NSAID use.

Notably, both NSAID-associated GI complications and deaths have been decreasing in recent years, after peaking in 1992.¹³ This decrease has been attributed to many factors including the use of lower-dose (particularly over-the-counter) NSAIDs, the decreasing prevalence of *H pylori*, the increasing use of proton-pump inhibitors (PPIs), and the introduction of NSAIDs with greater GI safety, such as the coxibs.¹⁴

Some NSAID users are at greater risk for the development of GI complications. Risk factors include history of previous peptic ulcer; history of NSAID-related GI complications; advanced age; concomitant use of corticosteroids, anticoagulants, and the use of high-dose NSAIDs; or combinations of NSAIDs including ASA, coxibs, and over-the-counter products.^{7,8,12,15-17} Of these, the most significant is history of previous ulcer or complication, which increases the likelihood of a GI event substantially; studies cite an odds ratio as high as 13.5.^{7,8,12,15-17} Advancing age increases risk by about 4% per year.¹¹ This relationship likely stems from the presence of other risk factors that are more prevalent with advancing age, such as comorbidities and concomitant use of ASA, NSAIDs, or anticoagulants, and age-related physiologic changes such as decreasing GI prostaglandin concentrations.

Among nsNSAIDs, data indicate that GI safety may be superior with ibuprofen, etodolac, and nabumetone.¹⁸⁻²⁰ In contrast, NSAIDs with prominent enterohepatic circulation and significantly prolonged half-lives such as sulindac, indomethacin, piroxicam, and ketorolac have been linked to greater GI toxicity related to prolonged gastric and duodenal mucosal exposure.²¹ As a class, coxibs are associated with less GI risk.

All NSAID classes—nsNSAIDs, coxibs, and ASA—have a dose-response relationship to adverse GI events, and this relationship appears linear.^{11,15} Concurrent NSAID use, a common clinical scenario as more patients take prophylactic ASA and/or over-the-counter NSAIDs, increases risk.^{7,12,22-24} When ASA is combined with NSAIDs, the relative risk of GI bleeding increases to more than 10 times that seen among those using either nsNSAIDs or ASA.¹² Among NSAID users, glucocorticoid use increases risk; although alone, they confer no additional risk.²⁵ The use of alcohol and comorbidities appear to increase GI risk among NSAID users, although the strength and magnitude of such associations are less clear.^{15,25-27}

Gastrointestinal risks of aspirin. Low-dose ASA (<325 mg/day) increases the risk for GI bleeding and hospitalization. An increasing amount of literature suggests that even cardiovascular doses of ASA increase GI risk 2–4 times.²⁸ Among osteoarthritis patients taking enteric-coated ASA (81 mg/day), a study revealed endoscopic ulcers and erosions in 7.3% at 12 weeks.²⁴ In a different study of patients taking ASA for more than 3 months (at either 100 or 325 mg/day), 48% of asymptomatic patients developed endoscopic ulcers and erosions.²⁹ Although the relationship of endoscopic lesions to clinically relevant GI complications is controversial, clearly even lower doses of ASA result in GI toxicity. Thus, it appears that no risk-free dose of ASA exists. Further, attempts to coat or buffer ASA to mitigate GI effects have not attenuated complications.³⁰

Gastrointestinal risks of coxibs. Coxibs were developed to decrease the GI toxicity associated with NSAIDs. These efforts stemmed from increasing understanding of specific physiologic

roles that COX isoenzymes play. COX-1-mediated prostaglandin synthesis promotes the generation of the gastric mucosal protective barrier, decreases gastric acid secretion, increases production of superoxide scavenging glutathione, and promotes adequate mucosal blood flow.³¹⁻³⁴ Thus, medications that inhibit these actions could lead to GI toxicity. COX-2, in contrast, increases local inflammation and modulates pain, and hence became a more attractive therapeutic target. Coxibs, designed to spare COX-1 and primarily inhibit COX-2 function, decrease but do not eliminate NSAID-associated GI toxicity. They are as efficacious as nsNSAIDs in relieving pain in patients with rheumatoid arthritis and osteoarthritis.^{7,35-37}

Data from large GI outcomes studies have characterized the GI effects of coxibs. The Celecoxib Long-term Arthritis Safety Study compared 3 groups of arthritis patients treated with high-dose celecoxib (400 mg twice daily), diclofenac (75 mg twice daily), and ibuprofen (800 mg, 3 times daily).⁷ The primary outcome measure, gastroduodenal ulcer complications, was lower, although not statistically significantly, among those using celecoxib. Symptomatic ulcers were significantly less common among celecoxib users. Of note, 21% of patients in this study also were taking concomitant ASA. In post hoc analyses, there was no difference in ulcer complications between those taking ASA plus celecoxib compared with those taking ASA plus nsNSAIDs. Complications were significantly lower, however, between the coxib and nsNSAIDs groups among those not using ASA.

The Vioxx Gastrointestinal Safety Of Rofecoxib trial evaluated the GI safety of rofecoxib among patients with rheumatoid arthritis. In this large trial, rofecoxib users had 50% fewer GI events compared with naproxen users.⁸ Subsequent comparisons of lumericoxib with naproxen and ibuprofen showed a 75% decrease in symptomatic ulcers and their complications.²² Furthermore, aggregate epidemiologic data suggest that the introduction and broader use of coxibs has led to a significant decrease in deaths owing to GI effects of NSAIDs among chronic users.¹⁴ Because these apparent GI benefits have become clearer, it has become increasingly apparent that at least some coxibs increase the risk for cardiovascular events.³⁸

What are the cardiovascular effects of nonsteroidal anti-inflammatory use? Cardiovascular risks of coxibs. With the increasing use of coxibs, growing data have implicated their use, particularly rofecoxib, in increasing the risk for cardiothrombotic events. In the Vioxx Gastrointestinal Safety Of Rofecoxib trial, those participants were excluded from taking low-dose ASA, statistically more thromboembolic events occurred in those receiving rofecoxib (50 mg/day) than in those taking naproxen (500 mg twice daily) (.5% vs .1%, respectively).⁸ In contrast, the Celecoxib Long-term Arthritis Safety Study data revealed a small, statistically insignificant difference between ibuprofen or diclofenac and celecoxib in cardiovascular or cerebrovascular events, regardless of ASA exposure.^{7,39} Similarly, studies of lumericoxib have yielded no statistically increased risk of cardiovascular (CV) events.⁴⁰

Such conflicting data led to the re-evaluation of existing coxib databases and further epidemiologic study. The Adenomatous Polyp Prevention on Vioxx trial, designed to test the chemopreventive properties of coxibs for colorectal adenoma prevention, was stopped after 36 months when it revealed a 2 times greater risk of stroke, myocardial infarction (MI), and sudden cardiac death among those taking rofecoxib 25 mg/day.³⁸ A second trial examining the effect of coxibs on polyp prevention, the Adenoma

Prevention with Celecoxib trial, showed a dose-response relationship between celecoxib use and risk of stroke, MI, sudden cardiac death, and congestive heart failure, but this relationship was significant only at higher doses (400 mg twice daily).⁴¹ Other studies have yielded conflicting coxib results.⁴²⁻⁴⁷ Cohort studies have indicated that rofecoxib, particularly when used at doses of more than 25 mg/day, is associated with greater cardiovascular risk. This risk, however, did not extend to users of celecoxib or nsNSAIDs, and appeared greatest among new users.^{46,47} Data from Medicare, Medicaid, and Kaiser Permanente indicate that celecoxib may be associated with a decreased risk of MI, compared with other agents.⁴⁶⁻⁴⁸ Further complicating the picture is the fact that the data from Kaiser Permanente showed an increased risk of thromboembolic events among users of indomethacin (relative risk, 1.33) and naproxen (relative risk, 1.18).⁴⁸

These data suggest a spectrum of cardiovascular risks of coxibs and potentially of nsNSAIDs as well. Rofecoxib has been withdrawn from the market. The relative cardiovascular safety of celecoxib, particularly at higher doses, remains uncertain.

The potential mechanism(s) of CV toxicity among coxibs suggest a need to understand which patients are at higher risk and ways to potentially modify these risks. On a physiologic level, it appears that COX-2-derived prostaglandins (eg, prostacyclin) mediate vascular function, thrombosis, and blood pressure.^{49,50} An increase in blood pressure may represent one important mechanism through which coxibs increase the risk of MI. Sustained hypertension increases rates of ischemic heart disease and stroke. Typically, both nsNSAIDs and coxibs increase blood pressure. One meta-analysis suggested that such medicines lead to a mean increase in supine blood pressure of 5 mm Hg.⁵¹ In this study, piroxicam resulted in the greatest increases whereas sulindac and ASA led to the smallest changes. No studies specifically have linked NSAID-associated increases in blood pressure to specific outcomes. Other studies have shown, however, that small persistent diastolic blood pressure increases over many years can increase cardiovascular and cerebrovascular risks substantially.⁵²

Therapeutic doses of celecoxib and rofecoxib are associated with an approximately 2% rate of hypertension and edema, similar to those associated with nsNSAIDs.^{7,53} A dose-response effect exists, particularly with rofecoxib at doses of 50 mg/day.⁵⁴ A recent randomized controlled trial using continuous ambulatory monitoring confirmed that both rofecoxib and celecoxib increase blood pressure, although the effect was greater with rofecoxib.⁵⁵ Studies of valdecoxib have shown blood pressure effects.⁵⁶

Other mechanisms of increased CV risk have been proposed for coxibs, although most are not well explored in human beings. Coxibs do not significantly affect platelet function because they do not inhibit thromboxane. In murine models, it appears that selective inhibition of some prostacyclins may result in an imbalance of their procoagulant and anticoagulant effects, leading to a thrombotic diathesis.⁵⁷ Likewise, depression of COX-2-derived PGI-2 (prostacyclin) accelerates the initiation and development of atherosclerosis in mice, and suggests a possible mechanism by which, over time, coxib use could alter an individual's risk for CV events.^{58,59} Based on these mechanistic considerations, and the aggregate clinical data, it appears that all coxibs may confer some degree of increased CV risk. Further, such associations suggest that relative effects on various COX isozymes can explain the apparent drug-specific effects seen with the coxib group, and may account for the apparent CV risks that some nsNSAIDs may confer.

Cardiovascular benefits of aspirin. Many people take ASA to reduce the risks of MI and stroke. The United States Food and Drug Administration has approved the use of ASA for secondary prevention, to decrease the risk of vascular mortality in patients with suspected MI, and to decrease the risk of death and nonfatal MI in patients with known coronary disease. A meta-analysis of large randomized trials showed that for every 1000 patients treated with ASA, there would be a decrease of 10 to 20 vascular events and 1 to 2 additional cases of major GI bleeding.⁶⁰ Among high-risk patients, antiplatelet therapy decreases the risk of nonfatal MI by approximately one third, nonfatal stroke by one fourth, and vascular death by one sixth. This has led to recommendations that patients with vascular disease take ASA or other antiplatelet therapy in the absence of contraindications.

The use of ASA for primary prevention is less clear-cut. Meta-analyses indicate that for patients without vascular disease but with an annual coronary risk of at least 1.5%, ASA is beneficial.⁶¹ For those whose annual risk of a CV event is 1%, ASA's benefits are limited. For those whose risks are lower, harm may outweigh benefits. The Women's Health Study found that ASA in doses of 100 mg every other day decreased first strokes 17% and ischemic strokes 24%.⁶² A nonsignificant increase in the rate of hemorrhagic stroke occurred; no change in the risk of fatal or nonfatal MI emerged. GI bleeding was more common among ASA users, although fatal GI bleeds were not significantly different.

Other potential benefits of aspirin therapy. Aspirin has been proposed as a potential cancer chemopreventive agent. Many observational studies show a decreased GI cancer risk among patients with regular ASA use. Meta-analyses have shown a dose-dependent protective effect of ASA against esophageal, gastric, and colorectal cancer with regular use.⁶³⁻⁶⁵ Furthermore, a recently conducted study among patients with stage III colorectal cancer indicated that regular ASA use reduced the risk of recurrence and death.⁶⁶ Aspirin's anticancer effects, however, are not uniform. Studies in breast, ovarian, and prostate cancer have shown minimal to no benefits.⁶⁷⁻⁶⁹

Concomitant therapy: aspirin and nonselective nonsteroidal anti-inflammatory drugs vs aspirin and coxibs. As news of the real and potential benefits of ASA spreads, more patients have adopted its use both with and without their physician's guidance. This has increased interest in the relative risks of ASA plus nsNSAIDs vs ASA plus coxibs.

The comparative GI risks associated with nsNSAID plus ASA vs coxibs plus ASA have not been assessed in a randomized fashion. In the Celecoxib Long-term Arthritis Safety Study, celecoxib did not reduce the risk of GI endpoints in patients taking concomitant aspirin. In a retrospective cohort study of elderly patients identified through the Quebec health insurance database, nsNSAID plus ASA use increased the relative risk of GI hospitalization (hazard ratio, 1.61).⁷⁰ In 2 meta-analyses of arthritis patients, those taking celecoxib plus ASA had 50% fewer endoscopic ulcers than those taking nsNSAIDs and ASA.^{71,72} Subgroup analyses suggested that the protective advantage of coxib use was somewhat smaller when ASA also was used.⁷¹ Overall, the combination of ASA and an nsNSAID increased the rate of clinical GI events 2- to 5-fold, an increase similar to that with an ASA plus a coxib. Thus, the use of ASA in combination with a coxib may attenuate or eliminate the GI advantage of a coxib over an nsNSAID.

Because the GI benefits of coxibs may be decreased or eliminated by concomitant ASA use, conversely, new data suggest that concomitant nsNSAID use may attenuate the benefits of ASA

therapy. Specifically, recent studies of ibuprofen, often chosen for its relatively better GI safety profile, indicate that it may inhibit ASA's CV benefits and may even increase the risk of CV events.^{73,74} Further study also is warranted to evaluate interactions of other nsNSAIDs with aspirin.

Can the gastrointestinal risks of nonsteroidal anti-inflammatory drug therapy be reduced? Attempts to reduce the risks of NSAID-associated GI toxicity should begin with assessment of the need for and relative risks and benefits of NSAID treatment—whether for chronic pain or cardiovascular prophylaxis. As previously noted, for many people the risks may outweigh the benefits. Furthermore, although studies have not evaluated the contribution of NSAIDs, particularly coxibs, in relation to other CV risk factors, it seems reasonable for physicians to attend closely to other modifiable CV risks among NSAID users. Data clearly support the benefits of tobacco cessation and careful management of blood pressure, cholesterol, and, for diabetic patients, glucose control in general. As of yet, no data show that such interventions modify the effects of NSAIDs on CV risk.

GI risks may be decreased through similar attention to risk factors and use of cotherapy. Risk can be reduced through the use of the lowest effective dose for the shortest duration of time. Among NSAIDs, consideration should be given to using those with relatively lower GI risk, such as coxibs, and certain nsNSAIDs, such as ibuprofen. The use of a coxib requires careful consideration of the relative GI benefit vs potential CV risk. Combinations of NSAIDs including low-dose ASA, other antiplatelet drugs, and anticoagulants should be avoided if possible.

Among potentially modifiable risk factors, *H pylori* eradication warrants consideration. *H pylori* is a known risk factor for GI bleeding, however, its relative impact in the presence of NSAIDs is unclear. Short-term endoscopy studies show that eradication of *H pylori* decreases the incidence of peptic ulcers in patients who begin taking NSAID therapy.⁷⁵⁻⁷⁸ These protective effects do not seem to extend to patients with previous ulcer history.^{78,79}

Cotherapy with gastroprotective agents is another means to reduce NSAID-associated toxicity. The exogenous administration of prostaglandin was an early approach. Misoprostol, a synthetic PGE-1 (prostaglandin E1), is the only gastroprotective agent studied in large outcome trials of ulcer prevention. After 6 months, its use as cotherapy reduced NSAID-associated GI complications by 40%.¹⁵ Misoprostol also significantly reduces gastroduodenal ulcers. A meta-analysis showed that its use as cotherapy decreased the rate of endoscopic gastric ulcers by 74% and duodenal ulcers by 53% compared with placebo.⁸⁰ Adverse effects limit its widespread adoption. To be effective, doses of at least 600 mg/day are needed. These doses cause abdominal pain, diarrhea, and nausea rates of approximately 20%, resulting in its frequent discontinuation.

Antisecretory treatments, including both H₂-receptor antagonists and PPIs, have been studied widely for gastroprotection among NSAID users. H₂-receptor antagonists decrease the risk of NSAID-associated duodenal ulcers but not gastric ulcers.⁸¹ Epidemiologic and endoscopic studies and evaluations comparing PPIs with misoprostol, however, suggest that PPIs may be a reasonable choice for cotherapy, although no outcome study of PPIs exists.⁸²⁻⁸⁶ In 1 small study among patients with high risk for GI bleeding, omeprazole decreased the risk of recurrent bleeding ulcer among NSAID users more than *H pylori* eradication alone; recurrent bleeding rates were 4.4% vs 18.8%, respectively.⁷⁹ Another study showed that patients taking diclofenac in combination with

omeprazole had a GI bleeding risk similar to those taking celecoxib alone.⁸⁷

Despite the lack of any adequately powered outcome trial, the use of NSAIDs combined with PPIs has been adopted widely in clinical practice. It is estimated that the use of PPIs could reduce the rate of endoscopic NSAID-related ulcers by 90%.⁸⁸

Little data have explored adequately whether coxibs plus PPIs will add more benefit, but such a strategy has been suggested for high-risk patients. The ability of concomitant PPI therapy to decrease GI risks of ASA therapy in high-risk patients should be considered.

The addition of PPIs to therapy may carry risks, such as increased rates of pneumonia.⁸⁹ Also, as a strategy to reduce NSAID-related complications, PPIs work only when taken. Thus, considerations of compliance and costs merit further attention.

The mechanisms of and risks for lower GI tract lesions are not understood; therefore, gastroprotective and risk-modifying approaches to modify lower-GI tract toxicity currently are limited.

Recommendations. The current recommendations for all patients receiving NSAIDs are as follows.

1. Review treatment indications and risk factors. Physicians should assess carefully the indications for NSAID treatment and thoroughly review risk factors for both GI and CV complications. CV risk factor modification, such as tobacco cessation and blood pressure, cholesterol, and, for diabetic patients, glucose control, is warranted in general, although unproven to specifically reduce NSAID- and coxib-associated CV risks.
2. Prescribe lower-risk agents. The decision to use COX-2 inhibitors requires a risk-benefit analysis that weighs the GI vs the CV risk in an individual patient. (a) For patients in whom the estimated risk of life-threatening GI bleeding outweighs the risk of CV events, consideration should be given to the use of NSAIDs with lower GI risk, including nsNSAIDs such as ibuprofen, etodolac, and diclofenac, and coxibs. Data do not support the use of buffered or coated ASA as effective ways to significantly decrease GI risk. (b) For patients in whom the risk of CV events is greater than the risk of GI bleeding, COX-2 inhibitors should be avoided. (c) In patients with known CV disease or at high CV risk, low-dose ASA should be prescribed, although the benefits of COX-2 selectivity in the presence of aspirin is unclear and it similarly is unclear whether aspirin reduces the risk of COX-2 selectivity. In addition, ibuprofen, and perhaps other nsNSAIDs, may interfere with the CV benefit of aspirin.
3. Limit duration and dosage.
4. Ask about and avoid combination NSAID therapy. Polyparmacy is common; many patients combine therapy, particularly ASA, without specific direction or discussion with their physicians. In addition, given the increased CV risks associated with coxib use, concomitant ASA therapy may be important in patients taking coxibs. The addition of ASA, however, may negate the GI-sparing effects of coxibs and remains an unproven means to decrease the risk of coxib-associated CV events.
5. Treat known *H pylori*. Routine *H pylori* testing should not be pursued in average-risk patients starting NSAID therapy. Patients with known *H pylori* infection, however, should undergo eradication.

6. Monitor patients taking both nsNSAIDs and coxibs for cardiovascular side effects.

For patients receiving NSAIDs with higher risk for GI complications, the physician should pursue the measures outlined previously. In addition, it is recommended that physicians should follow these additional recommendations.

1. Assess for and treat *H pylori* if present. The benefits of pursuing *H pylori* testing and subsequent treatment is not proven, but may be worthwhile, particularly among those with a history of a previous ulcer or ulcer complication. Importantly, *H pylori* eradication alone is not sufficient in these patients, and cotherapy with gastroprotective treatment should be considered strongly.
2. Institute gastroprotection. Gastroprotection with misoprostol (≥ 600 mg/day), if tolerated, or PPIs should be considered strongly in high-risk patients. Nonselective NSAIDs plus PPIs are significantly safer than nsNSAIDs alone. H2-receptor antagonist therapy is inadequate. Coxib therapy alone similarly is beneficial in reducing GI risks, but with the possible trade-off of increasing CV risk. It should be emphasized, however, that the addition of gastroprotection, although significantly beneficial, does not eliminate risk, particularly among patients at high risk for GI complications.

Areas for Future Research

Ongoing research is needed to clarify the relative risks and benefits of nsNSAIDs and coxibs for individual patients. The absolute relationships between decreased GI events and increased CV events with specific coxibs and NSAIDs for specific patients must be defined. Future trials must consider long-term risks of both GI and CV complications through prospective studies that stratify patients according to baseline risks and ASA use, and that enroll patients reflective of those likely to use NSAIDs in clinical practice. The net total benefit or detriment of such therapy is not clear, especially in elderly individuals whose background risk of both GI and CV events is markedly greater.

Of particular interest will be a better understanding of the CV risks of nsNSAIDs, and the general interactions of NSAIDs with ASA and other anticoagulants such as ticlopidine. Specific data regarding the interactions between individual NSAIDs and ASA, and ways to reduce any deleterious effects, also will be needed to guide clinicians. Regarding coxibs, further clarification of their CV effects in relation to known CV risk factors, such as diabetes, hypertension, and tobacco use, also will be of great import. The relative benefits of PPIs used with nsNSAIDs and coxibs will be important to clarify, particularly when ASA is added to these combinations.

Other important risks for GI bleeding may emerge. For example, emerging observational data suggest that selective serotonin reuptake inhibitors increase the risk for GI bleeding, and that this effect is potentiated by concomitant ASA use. The true nature of this association, and, if real, what factors may reduce such risks, are unknown. Given the large numbers of patients using both types of medicines, further investigation will be of particular interest.

The association of NSAID use with lower-GI tract complications is important diagnostically and therapeutically. A better understanding of risk factors for and mechanisms of lower-GI

tract bleeding in NSAID users will be required to address risk reduction.

Summary

NSAIDs provide a broad range of benefits for patients who require their use. Their risks, however, include GI, renal, and cardiovascular complications, including heart failure and myocardial infarction, only some of which have been reviewed in this article. Clinicians should prescribe the lowest effective dose for the shortest duration. GI risk can be modified, but not eliminated, through careful use of coxibs and gastroprotective therapies. CV risks associated with coxibs, especially at higher doses, and nsNSAIDs, have been identified. In addition, it appears that the use of ibuprofen, indomethacin, and naproxen may decrease the cardiovascular benefits of ASA therapy. ASA may decrease or eliminate the GI benefits of coxib therapy. Close attention to accumulating data will clarify these effects further.

Supplementary Data

Note: to access the supplementary material accompanying this article, including Presentation Summaries, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org.

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A list of the Consensus Development Panel and Speakers may be viewed online at www.cghjournal.org.

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Appendix 2

1. Presentation Summaries

1. Byron Cryer, MD: Who is at risk and what is the risk? NSAID-related GI complications may account for 100,000 hospitalizations annually in the U.S.⁵ The average relative risk (RR) of developing a serious GI complication in patients exposed to NSAIDs, as a group, is 5–6-fold that of those not taking NSAIDs.^{6,7} NSAIDs are the leading cause of bleeding peptic ulcers; when sensitive biochemical assays are used, NSAIDs, including low-dose ASA, may have been used in over 90% of patients with bleeding ulcers.⁹ Deaths related to NSAID-induced GI complications have been estimated to be as high as 16,500 deaths per year in the U.S.⁵ Recent observational data from the Spanish National Health System indicate a much lower frequency of 15.3 deaths per 100,000 NSAID users.⁴

Risk factors for the development of NSAID-related GI complication include prior peptic ulcer disease, prior NSAID GI complication, advanced age, concomitant use of corticosteroids or anticoagulants, high doses of NSAIDs, multiple doses or combinations of NSAIDs. Among these, the most significant is history of prior peptic ulcer disease or a prior ulcer complication, which confers a 2–4-fold increased risk.^{2–4,12–15} Advancing age is associated with risk that increases linearly at rate of approximately 4% per year of advancing age.⁵

Recent controlled prospective studies of arthritis patients chronically taking NSAIDs suggest that the risk of serious NSAID-induced GI complications is cumulative and linear.^{2,13,15,16} A linear, dose-response relationship also exists, and is seen across all classes of NSAIDs.^{5,13} Low daily doses of ASA, usually 325 mg per day or less, increase risks of GI bleeding and increased the likelihood of hospitalization for ulcers in a dose-dependent fashion. The combined use of ASA with an NSAID increases the risk of ulcer and ulcer complications^{2,4,16,17,25} with the RR of combined NSAID plus ASA over 10-fold greater than the risk among those not using NSAIDs.⁴ Concurrent use of more than one NSAID, such as the combined use of prescribed NSAIDs with concurrent low-dose ASA^{2,4,16,17} or with concurrent OTC NSAIDs,¹⁸ and concomitant use of corticosteroids or anticoagulants also increase the risk of GI complications.

Though NSAID-associated adverse events have been identified in the renal, coagulation and cardiovascular system, GI complications are the most common. These adverse effects occur in the upper and lower GI tracts, and include: ulcers and their complications in the upper GI tract, and, in the small intestine and colon, ulcers and their complications, as well as strictures, diaphragms,

enteropathy, diverticular bleeding and various forms of colitis. The magnitude of NSAID-related lower GI effects is uncertain; however, a recent study indicated that about 16% of the clinically significant NSAID-related GI events occur in the lower GI tract.⁴

In summary, strong evidence characterizes the GI risk associated NSAID use and identifies specific risk factors for development of NSAID-related complications. NSAIDs, including low-dose ASA and coxibs, affect both the upper and lower GI tract.

2. Lee S. Simon, MD: Risks and Benefits of Non Selective and Selective NSAIDs and Coxibs. Each year health care providers write approximately 60 million prescriptions for various forms of NSAIDs,² many of which are for the treatment of osteoarthritis in the elderly.¹¹ It appears that NSAIDs (and their attendant anti-inflammatory effects) are superior to simple analgesics for pain relief in these patients, demonstrating better performance on a range of outcomes.^{14,15}

The benefits of such anti-inflammatory effects must be weighed against known upper and lower GI toxicity and even death.^{5–8,54–63} Multiple studies have demonstrated that coxibs are equally effective as nsNSAIDs.^{38,39–42,44–47} Thus, coxibs, with their relative COX-1 sparing effects and decreased mucosal damage have gained broader use.

The GI benefits of coxibs have been shown in a number of studies.^{41,70,46,71} Aggregate data suggest that the availability of coxibs has significantly decreased deaths due to GI-related NSAID complications. Evidence of coxib-associated cardiovascular risk, however, has tempered enthusiasm about coxibs.

In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial⁴⁶ statistically more thromboembolic cardiovascular events occurred in those receiving rofecoxib than among those taking naproxen (0.5% vs 0.1%).⁴⁶ This contrasted with findings from the CLASS study,^{41,70} which found no differences in cardiovascular or cerebrovascular event rates between the celecoxib and diclofenac or ibuprofen. In the APPROVe trial, an evaluation of rofecoxib versus placebo for polyp prevention, showed a rofecoxib-associated greater than 2-fold increased relative risk for either stroke, myocardial infarction (MI) or sudden cardiac death vs placebo.³⁸ Three epidemiologic studies found similar results for rofecoxib doses greater than 25 mg daily.^{83,84,85} In one of these studies, rofecoxib was associated with more than a 3-fold increased incidence of acute MI and sudden cardiac death compared to nsNSAIDs or to *other* coxibs.⁸⁵ Notably, studies by Rahme et al⁴⁴ and Solomon et al⁴⁵ failed to show such differences in cardiovascular risk with rofecoxib.⁸²

Conflicting data likewise exist for celecoxib. In the APC trial⁴¹ a dose-response relationship of celecoxib to statistically significant risk for stroke, MI, sudden cardiac death and congestive heart failure emerged, but only at doses of 400 mg twice daily, a dose not typically used for treatment of pain or arthritis. Of interest, in the large database studies, acute MI incidence with celecoxib use was *lower* than with other agents.^{83,84,85} Analysis indicated that naproxen and indomethacin were associated with statistically *greater* risks of cardiovascular events.⁸⁵ Thus, the risks associated with specific coxibs, and with nsNSAIDs in general, remain poorly characterized.

Coxibs and nsNSAIDs appear equally efficacious, but have differing GI and cardiovascular risk profiles. Further, it appears that within groups, specific coxibs and nsNSAIDs differ. In certain patients, particularly those at high risk for GI complications, coxibs provide a better safety profile than do nsNSAIDs. Whether concurrent nsNSAID and proton pump inhibitors use will suffice in place of coxibs is unclear. Also, the cardiovascular risk conferred by specific coxibs, and by nsNSAIDs remains unclear. Additional large outcome trials will be required to definitively answer these questions, and allow better weighing of cardiovascular and GI risks in patients for whom anti-inflammatory analgesia is required.

3. Angel Lanas, MD, PhD: Can the Risk of NSAID-induced Gastrointestinal Toxicity be modified? NSAID use increases the risk of gastrointestinal (GI) toxicity; however, the magnitude of increased risk varies according to NSAID type and dose, and by other factors.¹ Modification of risk factors and co-therapy, aimed at alleviating specific NSAID effects, may help reduce the burden of toxicity.

The choice of NSAID associated with the lowest risk, and the use of the lowest effective NSAIDs dose can decrease risk.¹ Similarly, combined therapy with more than one NSAID (including low-dose ASA), other non-ASA anti-platelet drugs, anticoagulants or steroids should be avoided, if possible.^{5,6,7}

Peptic ulcer and/or ulcer complication history carry the highest relative risk for NSAID-associated upper GI complications.^{3,8} Such ulcers may be linked to *H pylori* infection, NSAID use or both, which are modifiable risk factors. *H pylori* eradication is a therapeutic option that will reduce NSAID-associated GI toxicity in, at least, a subset of patients. Many trials show that *H pylori* eradication reduces the incidence of peptic ulcers in patients who start NSAID therapy.^{10,11,12} For patients with previous ulcer history who need NSAIDs or ASA, *H pylori* eradication is not sufficient to prevent damage from the

upper GI tract and additional therapies must be considered.^{13,14}

Co-therapy with drugs that modify NSAID-induced pathogenic mechanisms may also help. Misoprostol, a synthetic PGE₁, has been shown in numerous short-term endoscopy trials to significantly reduce the incidence of gastroduodenal ulcers. When taken in doses of 200 µg t.i.d. or q.i.d. A meta-analysis indicated that misoprostol reduced the gastric ulcer risk 74% and duodenal ulcer risk 53%, compared to placebo.¹⁵ Misoprostol's use, however, is limited in many patients due to adverse effects, including diarrhea, nausea and abdominal pain.¹⁶

Antisecretory therapy with H₂-RA and PPI has been studied. Data indicate that H₂-RA reduce the incidence of endoscopic duodenal, but *not* gastric ulcers in patients taking NSAIDs. Standard doses of PPIs significantly reduce gastric *and* duodenal ulcers associated with NSAID use in numerous clinical trials using endoscopic endpoints.^{18,19,20,21} No large GI outcome studies have evaluated the effect of PPI agents on upper GI complications. In one small study, among patients with a recent complicated peptic ulcer using naproxen, omeprazole was much more effective than *H pylori* eradication in the prevention of ulcer bleeding recurrence after 6 months.¹⁴ In a similar study of high-risk patients, those taking daily omeprazole and diclofenac had similar rates of recurrent ulcer bleeding as those taking celecoxib 200 mg b.i.d.²² Some epidemiological studies demonstrate that antisecretory drugs, especially PPIs, significantly reduce the relative risk of upper gastrointestinal bleeding.^{7,23}

The protection afforded by prescription of gastroprotective agents will have some limits. Poor compliance may render them less useful, and over one third of patients prescribed gastroprotective therapy are partially- or non-adherent. A recent study shows that poor compliance increases the relative risk of NSAID-induced upper GI adverse events 4–6 times.²⁶ Long-term use of PPIs are associated with a very low rate of side effect, but recent data suggest that they may be associated with increased risks of some adverse events, such as pneumonia and hip fracture,^{24,25} but this need to be confirmed.

Co-therapy with anti-ulcer agents does not clearly address NSAID-associated adverse lower gastrointestinal events. While less common, NSAIDs may induce significant lower GI tract problems, but the risk factors for these are not well defined. Post-hoc analysis of the VIGOR study indicates that rofecoxib was associated with less serious adverse events from the lower GI tract than naproxen.²⁸

4. Tilo Grosser, MD, PhD - Coxibs: Risk and Benefit. Traditional nonsteroidal anti-inflammatory drugs (or non-selective NSAIDs, nsNSAIDs) and selective inhibitors of cyclooxygenase (COX)-2, the coxibs, exert their anti-inflammatory, analgesic and antipyretic activity by inhibiting prostaglandin biosynthesis. While increasing selection for inhibition of COX-2 reduces serious gastrointestinal adverse events,^{1,2} three structurally distinct compounds, rofecoxib/Vioxx, valdecoxib/Bextra (Pfizer), and celecoxib/Celebrex, have increased the incidence of cardiovascular complications in placebo controlled trials,^{1,3-5} consistent with a biologically plausible,⁶ small, but absolute cardiovascular risk. Thus, drug selectivity for COX-2 provides a mechanism which would be expected to augment the likelihood of thrombosis, hypertension, myocardial infarction and stroke by inhibition of prostaglandins⁷⁻⁹ with homeostatic roles in platelet function, blood pressure regulation and vascular integrity.¹⁰⁻¹³ Observational studies of variable quality have been published since the withdrawal of rofecoxib. However, the best evidence, which is biologically plausible through the same mechanism, suggests heterogeneity amongst nsNSAIDs with respect to cardiovascular risk.¹⁴ In the absence of information from randomized trials on nsNSAIDs, the U.S. Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMA) have differed. FDA attached a similar “black box” warning of cardiovascular events to nsNSAIDs as is the case with celecoxib. EMA felt that the absence of evidence did not support altering advice to patients about the use of nsNSAIDs.

Although the current strategy of companies with withdrawn (rofecoxib, valdecoxib), disapproved (parecoxib/Dynastat), and currently unapproved (etoricoxib/Arcoxia; lumiracoxib/Prexige; GW-406381, GSK) compounds is to complete, utilize or initiate comparative randomized trials to obtain “black box” approval, the emphasis might be more usefully directed towards an individualized approach to efficacy and risk. Thus, marked interindividual variability to coxibs has been demonstrated.⁹ Do patients differ in their analgesic and anti-inflammatory efficacy as often claimed, and if so, why? Similarly, data from two randomized trials^{3,4} are consistent with a biologically plausible,^{11-13,15,16} time dependent transformation of cardiovascular risk. Do these drugs accelerate atherogenesis and if so, do biochemical, physiological and/or genetic biomarkers detect individuals at rapidly evolving risk and can such biomarkers detect dissipation of risk on cessation of dosing?

Neglect of the underlying science led us to the present debacle. It would be tragic to neglect a scientific ap-

proach to defining the individual balance of benefit and risk while pursuing the shortest route to drug approval, relying once again on differential marketing to drive drug selection amongst similarly “black boxed” selective and traditional NSAIDs.

5. Richard H. Hunt, MD - Aspirin: Risk and benefit. Aspirin is the oldest and most widely used NSAID. Its known benefits, however, are tempered by well documented risks. Studies indicate that the odds ratio (OR) for bleeding ranges from about 1.6 with low dose ASA (<100 mg) to an OR of 2.6 with doses of ~300 mg and this risk increases with higher doses (~600 mg and above) and when ASA is combined with a non selective NSAID (OR 5.6).^{98,99}

At ASA doses >100 mg, the rate of bleeding was 2.4%, comparable to that of higher ASA doses (>325 mg) and with adenosine diphosphate-receptor blockers.⁹⁷

The combined use of nsNSAIDs and ASA increases risk. While no randomized, trials have specifically addressed their relative GI safety, a coxib plus ASA appears safer than a nsNSAID plus ASA. Retrospective data found that ASA plus a coxib caused significantly fewer GI hospitalizations than ASA plus a nsNSAID.⁷⁰ Other studies indicate fewer endoscopic ulcers with celecoxib plus ASA than nsNSAIDs plus ASA.³⁰

The secondary prevention benefits of ASA are well established. A meta-analysis of low-dose ASA (≤ 325 mg/d) confirmed that ASA reduced all-cause mortality by 18%, strokes by 20%, myocardial infarctions (MI) by 30%, and other “vascular events” by 30%.¹⁰⁰ However, ASA was associated with a 2.5-fold increase in GI tract bleeding compared with placebo. Another meta-analysis provided an aggregate summary: for every 1000 patients treated yearly with ASA, 10–20 vascular events would be prevented, but treatment would result in 1–2 serious GI bleeds.⁶⁰ In a wide range of high-risk patients, anti-platelet therapy reduces the risk (combined outcome) of any serious vascular event by around 25%, with reductions of about 1/3 in non-fatal MI, 1/4 in non-fatal stroke, and 1/6 in vascular death.^{60,94}

Important differences in platelet inhibition are seen between individual nsNSAIDs and of course with coxibs which spare platelet function. This confers differential cardiovascular risks, and interpretation is further confounded when these drugs are used with ASA. Observational studies have shown conflicting results regarding the effect of combinations of NSAID and ASA therapy on mortality risk and incidence of myocardial infarction.⁹³ For example, ibuprofen when combined with ASA may reduce the protective effects of ASA). In vitro enzyme and human studies indicate

that coadministration of ibuprofen and ASA results in ibuprofen blocking access of ASA to its serine binding site within the COX pocket and this limits the cardioprotective effects of ASA,⁶ and results in an increase in cardiovascular mortality.⁹⁵ It has been suggested that ASA together with a coxib might provide *greater* anti-thrombotic effects than ASA alone;¹⁰¹ this concept requires further study, especially as recent data indicate concerns about the CV safety of all drugs that inhibit cyclo-oxygenase.

Another benefit of ASA treatment is protection against a number of cancer. Meta-analyses demonstrate that regular use of ASA reduces the risk of esophageal,⁶³ gastric,⁶⁵ and colorectal⁶⁴ cancers in a dose-dependent manner. Recent data suggest that ASA use may reduce the risk of recurrence and death among patients with stage III colon cancer study.⁶⁶ Other data, however, do not indicate a uniform anti-cancer benefit.^{68,69,91,96} Data from the Womens

Health Study indicated that ASA in a dose of 100 mg every other day, for an average 10.1 years, did not lower risk of total, breast, colorectal, or other site-specific cancers. A trend existed for reduction in lung cancer. There was also no reduction in overall or site-specific cancer mortality except for lung cancer mortality. A protective effect of ASA against lung cancer or benefit of higher doses of ASA against other cancers cannot be ruled out.⁹²

In summary, the net value of daily ASA treatment taken prophylactically should be considered with the potential benefit and risk in individual patients. In patients with established cardiovascular disease, ASA, or another antiplatelet drugs should be used except when contraindicated.⁶⁰ The benefits of ASA, however, are less clear when underlying vascular risk is not present.⁶¹ The use of ASA for primary prevention of cardiovascular thrombotic disease in unselected individuals may cause more harm than benefit.^{90,94}