AJC Editor's Consensus: Selective and Nonselective Nonsteroidal Anti-Inflammatory Drugs and Cardiovascular Risk

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Objectives

Upon completion of the activity, the participant should be able to:

2. Identify the mechanism of action and interaction of NSAIDs with other drugs in specific patient subsets.
3. Select treatment approaches appropriate to specific patient subtypes receiving NSAIDs with regard to cardiovascular risk, including patients taking low-dose aspirin for cardio-protection.
4. Reduce the prevalence of the deleterious cardiovascular effects of NSAIDs through improved treatment approaches.

Target Audience: This article is designed for cardiologists and all other health care specialists caring for patients taking selective and nonselective NSAIDs (ns-NSAIDs).

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Introduction

NSAIDs are commonly used for anti-inflammatory, analgesic, and antipyretic effects. More than 30 million individuals worldwide take ≥ 1 NSAID daily. More than 20 prescription and nonprescription NSAIDs are approved for adult use by the United States Food and Drug Administration (FDA), and several also are approved for the treatment of children with juvenile idiopathic arthritis. The conditions most commonly treated with NSAIDs are acute and chronic musculoskeletal disorders, most often osteoarthritis, which affects 20 million individuals in the United States. More than 20% of individuals aged > 65 years take prescription NSAIDs, and many more take nonprescription NSAIDs. Thus, older individuals, who have the highest risk for cardiovascular (CV) disease, are also the largest segment of the population regularly taking NSAIDs.

The inhibition of cyclooxygenase (COX) by NSAIDs is central to their desired therapeutic effects. However, the inhibition of COX enzymes (COX-1 and COX-2) affects the CV system, including platelet aggregation, lipid oxidation, endothelial function, apoptosis, cardiac fibrosis, acute myocardial infarction (AMI) (such as post-AMI size and remodeling) arrhythmias, blood pressure (BP), interference with antihypertensive therapy, sodium and water retention, and aggravation of congestive heart failure. Thus, the widespread use and potential CV impact of NSAIDs in a population with underlying CV risk places a special responsibility on cardiologists to remain informed about effects of this drug class on the CV system.

Selective COX-2 inhibitor NSAIDs (COX-2 inhibitors) increase CV disease risk, perhaps through the inhibition of the protective mechanisms of the COX-2 isoform. NS-NSAIDs inhibit the COX-1 and COX-2 isoforms and may increase the risk for CV disease through a similar mechanism. Treatment with NSAIDs is further complicated by (1) their adverse effects on the gastrointestinal (GI) mucosa, including ulcer bleeding and perforation, and (2) their interference with the cardioprotective effect of aspirin in primary and secondary CV disease prevention.

The primary purpose of this Editor’s Consensus is to provide appropriate guidelines to optimize the efficacy and safety of NSAIDs for patients with established CV disease and individuals at increased risk for CV disease. The intent is to complement, not to supplant, published guidelines that address this matter, such as documents previously published by the American Heart Association (AHA) and the American College of Rheumatology.

Categories of Nonsteroidal Anti-Inflammatory Drugs

There are ≥ 4 categories of NSAIDs:

1. Salicylates: includes acetylsalicylic acid (ASA) and the nonacetylated derivatives choline magnesium trisalicylate and salicylate. Salicylates were introduced in the tablet form of ASA in 1899, primarily for pain relief, and are now prescribed mainly for the inhibi-
tion of platelet aggregation in select individuals at increased risk for CV disease.\textsuperscript{1} The salicylates are collectively grouped to distinguish them from the newer categories of NSAIDs.

2. Propionic acid derivatives: ns-NSAIDs, including ibuprofen, fenoprofen, and naproxen sodium. Ibuprofen was the first propionic acid derivative approved for general use in the United States, attaining over-the-counter status in 1984. Naproxen was approved in the United States as a prescription drug in 1982 and received over-the-counter approval in 1994.\textsuperscript{1}

3. Para-aminophenol: includes only acetaminophen, which is classified as an NSAID because of its weak anti-inflammatory effects, although it has a different mechanism of action from other NSAIDs.\textsuperscript{10,11} Acetaminophen is an active metabolite of phenacetin, an analgesic and antipyretic drug that is no longer approved for clinical use, because of its association with hemolytic anemia, renal toxicity, and bladder carcinoma.\textsuperscript{12,13}

4. COX-2 inhibitors: includes celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib. COX-2 inhibitors were developed with the intent to minimize GI toxicity in the treatment of patients with inflammatory disorders because COX-2 is abundant in inflamed tissues (i.e., synovial tissue in arthritis) but is present in only small amounts in the GI tract.\textsuperscript{1} Rofecoxib (1998) and celecoxib (1999) were the first 2 COX-2 inhibitors approved by the FDA, but celecoxib is currently the only drug in this class on the market in the United States. Rofecoxib was withdrawn by its sponsor from the world market in October 2004, after it was shown to significantly increase the incidence of AMI, stroke, and, in older individuals, heart failure.\textsuperscript{14–20} Valdecoxib was withdrawn from the market by its sponsor in 2005 after it was shown to increase severe cutaneous reactions and to increase CV events in patients treated in the postoperative period after coronary artery bypass grafting. Neither lumiracoxib nor etoricoxib was ever approved for use in the United States, but etoricoxib is widely used for the treatment of patients with arthritis outside the United States, and parecoxib, the parenteral prodrug of valdecoxib, is widely used outside the United States for perioperative pain.

Nonsteroidal Anti-Inflammatory Drug Pharmacology

NSAIDs (other than acetaminophen) act primarily through the inhibition of COX, the enzyme that converts arachidonic acid to prostaglandins, which sensitize sensory pain nerve fibers. COX consists of ≥2 isoforms, COX-1 and COX-2. In addition to its effect on nerve function, COX-1, which is ubiquitous and generally expressed constitutively in the human body, produces prostaglandins involved in other physiologic processes, including platelet aggregation and the maintenance of GI mucosal integrity.\textsuperscript{21,22} COX-2, which is less prevalent in the body than COX-1, is rapidly induced by cytokines or growth factors to regulate tissue inflammation and pain perception through the blockage of local prostanoid production.\textsuperscript{2,5} Thus, ns-NSAIDs produce therapeutic effects through the inhibition of COX-1 and COX-2, but their main adverse GI effects, erosive gastritis and GI bleeding, arise primarily from COX-1 inhibition. The magnitude of COX inhibition, however, is highly variable among different ns-NSAIDs, based mainly on in vitro testing: naproxen is approximately 20 times more potent than ASA in COX inhibition, and ibuprofen and ASA are about equivalent.\textsuperscript{1} NSAIDs also vary greatly in half-life: ASA has a plasma half-life of 15 minutes, ibuprofen and acetaminophen 2 hours, and naproxen about 14 hours.\textsuperscript{1}

ASA has the unique pharmacologic property of irreversible acetylation of serine 529, a residue proximal to, but not within, the COX catalytic site. ASA blocks access of arachidonic acid into the site, inhibiting the formation of prostaglandin H\textsubscript{2} and its derivative, thromboxane A\textsubscript{2} (TxA\textsubscript{2}) for the lifetime of platelets. This is the basis for the antiplatelet effect of ASA.\textsuperscript{1,23,24} Other NSAIDs, however, bind reversibly to the residue and are generally eliminated quickly, with some variation, eradicating significant inhibition of platelet TxA\textsubscript{2} and thereby permitting unimpeded platelet aggregation.\textsuperscript{1,25}

COX-2 inhibitors vary in their selectivity for the COX-2 versus the COX-1 enzymes in the following order: rofecoxib > valdecoxib > parecoxib > celecoxib, accounting for tissue-specific variation in the effects of COX-2 compared to COX-1 inhibitors.\textsuperscript{10,26} For example, rofecoxib and/or its metabolites are associated with marked degradation of aortic elastin through a condensation reaction that prevents the formation of cross-linkages, proposed as a factor in the increased risk for CV events observed with rofecoxib compared to other COX-2 inhibitors.\textsuperscript{27,28} Another difference among COX-2 inhibitors relates to the expression of tissue factor, the transmembrane protein responsible for the initiation of coagulation, potentially affecting the progression of atherogenesis and secondary acute arterial thrombosis. Thus, there appears to be significant heterogeneity among the COX-2 inhibitors as well as ns-NSAIDs that may be clinically relevant to atherosclerotic CV disease.\textsuperscript{39}

The analgesic mechanism of action of acetaminophen differs from that of other NSAIDs; inhibition of COX-mediated prostaglandin production in the brain is 1 possible mechanism.\textsuperscript{30–32} N-arachidonoyl phenol amine, which is a metabolite of acetaminophen, may inhibit COX-1 and COX-2, thereby activating the cannabinoid system.\textsuperscript{33,34} The inhibition of COX-3, which is a splice variant of COX-1 of unknown clinical significance, has been suggested as another possible mechanism of the analgesic action of acetaminophen.\textsuperscript{30}

Clinical Evidence of Adverse Cardiovascular Effects Due to Nonsteroidal Anti-Inflammatory Drugs

Several clinical trials have found increased risk for adverse CV events in patients taking NSAIDs.

Adenoma Prevention With Celecoxib (APC) trial\textsuperscript{35,36}: Patients taking celecoxib in doses of 400 to 800 mg/day had 2 to 3 times increased relative incidence of CV events compared to placebo after a mean treatment duration of 33
months. A dose-response relation was present, with hazard ratios for a composite end point of death due to coronary artery disease and stroke of 2.5 for patients taking celecoxib 200 mg twice daily and, although of questioned statistical significance, 3.4 for patients taking celecoxib 400 mg twice daily.

Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)\textsuperscript{37}: ADAPT evaluated naproxen and celecoxib for the primary prevention of Alzheimer dementia and was stopped early because interim data analysis suggested increased CV disease and stroke risk in the low-dose naproxen group compared to placebo, while celecoxib risk was about the same as placebo.

Vioxx Gastrointestinal Outcomes Research Study (VIGOR)\textsuperscript{17,38}: VIGOR showed a small but significantly increased risk for CV events in patients with rheumatoid arthritis taking rofecoxib, compared to naproxen, <2 months after beginning treatment.

Adenomatous Polyp Prevention on Vioxx (APPROVe)\textsuperscript{39}: APPROve found a relatively greater incidence of CV disease in patients taking rofecoxib compared to placebo after 18 months of treatment. The results of this study led to the withdrawal of rofecoxib from the market.

Celecoxib Long-Term Arthritis Safety Study (CLASS)\textsuperscript{28}: CLASS showed comparable CV risk for celecoxib compared to ibuprofen and diclofenac. Although the incidence of de novo hypertension and stroke was highest in the ibuprofen group, there was no difference in serious CV disease among the drugs. The 2 major differences between the CLASS and VIGOR trials are that (1) CLASS used different non-ASA NSAIDs as comparators, and (2) VIGOR enrolled only patients with rheumatoid arthritis, a disease that may independently increase the risk for CV events.\textsuperscript{40,41} In addition, VIGOR did not include patients taking cardioprotective doses of ASA, whereas 21% of patients took ASA in CLASS.

Study by Hippsley-Cox and Coupland\textsuperscript{42}: This study found an overall increased risk for AMI associated with the current use of rofecoxib, diclofenac, and ibuprofen, even when patient subpopulations were adjusted for possible confounders such as smoking, co-morbid conditions, and the commonly prescribed drugs ASA, lipid-modifying agents, and antidepressants. These results fail to support the hypothesis that the VIGOR results were due to a cardioprotective effect of naproxen.

Multinational Etoricoxib and Diclofenac Arthritis Long-Term Medal (MEDAL) program\textsuperscript{43}: MEDAL was a combined analysis of 3 randomized controlled trials in 34,000 subjects, comparing etoricoxib and diclofenac taken for 18 months by arthritis patients. Etoricoxib was associated with a significantly lower risk for adverse upper GI disease such as symptomatic peptic ulcer disease, but the overall risk for CV events was not significantly different.

Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)\textsuperscript{144}: TARGET compared lumiracoxib 400 mg/day with naproxen and ibuprofen in patients with osteoarthritis and showed no significant difference in the incidence of CV events among these drugs. TARGET's results, however, are of limited value because the study included separate substudies comparing the combined lumiracoxib group with the combined naproxen and ibuprofen group. The rates for serious CV disease (defined as nonfatal and silent AMI, stroke, or CV death) in the lumiracoxib groups in the 2 substudies differed greatly: 1.1 events/100 patient-years for lumiracoxib in the naproxen group and 0.58 events/100 patient-years for lumiracoxib in the ibuprofen group. Although patients in the naproxen substudy had greater risk for CV events entering the trial, the outcome event rates were similar in the 2 substudies: 0.76 for naproxen and 0.74 for ibuprofen. Despite the large sample size of TARGET, the CV event rate was unexpectedly low, precluding meaningful information regarding the CV safety of the study drugs.

Tennessee Medicaid Study on Stroke Risk\textsuperscript{45}: This retrospective cohort study among Tennessee Medicaid enrollees examined the 7 most commonly taken NSAIDs (celecoxib, rofecoxib, valdecoxib, ibuprofen, naproxen, diclofenac, and indomethacin) and found an increased risk for stroke associated only with rofecoxib and valdecoxib. (Current exposure to NSAIDs has not been found to be a risk factor for intracerebral hemorrhage or subarachnoid hemorrhage.\textsuperscript{46})

Possible Mechanisms of Increased Cardiovascular Disease Risk Due to Nonsteroidal Anti-Inflammatory Drugs

Preexisting clinical or subclinical CV disease increases NSAID-induced CV disease risk, and the relative importance of possible mechanisms of increased risk is unresolved. The 3 most likely mechanisms are as follows.

Increased BP: NSAIDs cause salt and water retention by reducing renal blood flow and by inhibiting renal excretory function. Healthy individuals compensate for increased sodium intake by a homeostatic-induced hyper-nephron drive to expel sodium, thereby avoiding excess water retention and secondary effects such as peripheral edema, hypertension, and heart failure. Patients taking renin-angiotensin--blocking drugs are more sensitive to volume excess, and for patients taking angiotensin-converting enzyme (ACE) inhibitors, the removal of prostaglandin I\textsubscript{2} may be associated with less vasodilatory benefit. BP elevation has been induced by rofecoxib and, to a lesser extent, by celecoxib in patients treated with ACE inhibitors and \( \beta \) blockers, but not with calcium channel antagonists or diuretic monotherapy. In 1 study, however, systolic BP destabilization did not occur in patients with hypertension treated with renin-angiotensin blockade who received an NSAID containing nitric oxide--donating properties, perhaps because of the role of vascular prostacyclin and/or nitric oxide as part of the mechanism of action with renin-angiotensin system blockade.\textsuperscript{56}

Many individuals taking NSAIDs have osteoarthritis, are older, have major CV disease risk factors such as hypertension or diabetes mellitus, and often have had previous episodes of overt CV disease.\textsuperscript{47,57} Thus, the use of NSAIDs in this higher risk population, who also often have renal impairment, increases the propensity to develop salt and water...
retention and subsequent hypertension, increasing the risk for a future CV event.54,58-60

Endothelial cell dysfunction or altered arterial vaso-
motor function: The selective inhibition of COX-2 may produce a relative reduction in endothelial production of prostacyclin. Prostacyclin has ≥2 significant circulatory effects: (1) arterial vasodilation through arteriolar smooth muscle cell relaxation and (2) the inhibition of platelet aggregation with preservation of platelet production of the active form of TxA2. Thus, selective COX-2 inhibition may cause a prostanooid imbalance that increases the propensity for intravascular thrombosis, along with increased myocardial tissue edema and secondary increase in infarct size in patients with AMI.10,61,62

Dysrhythmias: Patients receiving rofecoxib may have an increased frequency of ventricular and supraventricular arrhythmias,63 but proarrhythmic effects have not been reported with other NSAIDs.

Coadministration of Acetylsalicylic Acid and other Nonsteroidal Anti-Inflammatory Drugs

Low-dose ASA is protective against AMI, stroke, and overall death from CV disease through the inhibition of platelet activation11,23,24,64,65 and is recommended for the prevention of CV disease by the United States Preventive Services Task Force.56,67 ASA is the only NSAID that conveys primary and secondary CV disease prevention, lowering total CV risk by up to 25%. ASA acts by inhibiting platelet COX-1 and platelet TxA2 through the acetylation of serine 529, located in proximity to the COX-1 catalytic site.64,68,69 Exposure to ASA renders platelets permanently dysfunctional because they cannot regenerate COX-1.

The sequence of drug ingestion when ASA is taken in combination with some other NSAIDs is important for maintaining the antiplatelet effect of ASA. Platelet aggre-
gation is unaffected when ASA is taken 2 hours before the ns-NSAID ibuprofen. When the sequence is reversed (ibu-
profen followed 2 hours later by ASA), however, ASA has no effect on platelet aggregation, thereby decreasing or elimin-
ating its CV protective effect.25,70 This may occur because ibuprofen may impair access of ASA to its serine target in COX-1. The coadministration of other prescription and non-

prescription ns-NSAIDs, including naproxen, has not been studied as extensively as with ibuprofen but also may interfere with the cardioprotective effect of ASA.69,71-74 The ns-NSAID diclofenac has a unique docking at the top of the active-site channel, and this inverted binding also might impede the ASA-platelet effect.75 When COX-2 inhibitors are taken before ASA, the antiplatelet effect of ASA is unaffected.25,70

Food and Drug Administration Warnings About Nonsteroidal Anti-Inflammatory Drugs

The effect of ns-NSAIDs on ASA antiplatelet action has resulted in specific FDA labeling (Appendix) when these drugs are coadministered. Since 2004, the FDA has required the inclusion of other warnings about CV risk on the labels of all prescription and nonprescription NSAIDs. These warnings are based on the FDA’s assumption that there is a “class effect” for risk for increased CV disease for all nonaspirin NSAIDs (i.e., ns-NSAIDs and COX-2 inhibitors) on the basis of evidence that (1) all NSAIDs are associated with increased CV risk; (2) increased CV risk varies with the agent, dose, and duration of NSAID use; and (3) increased CV risk encompasses a wide range of events, including acute Q and non-Q AMI, sudden and unexplained cardiac death, and acute cerebrovascular disease.76

Recommendations

I. ASA for the primary prevention of CV disease:
RECOMMENDATION A. The use of ASA for primary CV disease prevention should be governed by definite increases in 10-year risk for CV disease in individual patients. (ASA is not labeled for “primary” CV disease prevention in the United States).
According to recommendations of the AHA and the Preventive Services Task Force, a patient’s 10-year risk should be either ≥6% (AHA) or ≥10% (Preventive Services Task Force) for a CV event before the patient is prescribed ASA for primary prevention.77 The Framingham risk calculator can be used to calculate the 10-year risk on the basis of total serum cholesterol, smoking, and age. However, because ASA increases the risk for hemorrhagic stroke and GI hemorrhage, it should be prescribed only for individuals in whom there is good reason to believe that the progression of atherosclerosis and its complications may be favorably altered by the use of low-dose ASA. In low-risk populations, CV risk reduction should rely mainly on optimal lifestyle habits, including weight maintenance, dietary restriction of fat intake, exercise, and other lifestyle measures.

RECOMMENDATION B. When taking an ns-NSAID, ASA should be taken ≥2 hours before the ns-NSAID, to avoid interference by the ns-NSAID on the cardioprotective effect of low-dose ASA on platelet aggregation.

The ns-NSAID naproxen, because of its long half-life, may have a neutral or less negative effect on ASA antiplate-
let activity than other ns-NSAIDs, although this is unproved. The COX-2–selective NSAID celecoxib, however, can be taken before or concurrently with ASA.78

II. NSAID use in patients with recent CV events: lifestyle measures. RECOMMENDATION. NSAIDs (ns-
NSAIDs and COX-2 inhibitors) should not be taken within 3 to 6 months after an acute cardiac event, including AMI with or without coronary artery intervention (i.e., percutaneous coronary angioplasty with intracoronal stent implantation or coronary artery bypass grafting).

COX-2 inhibitors in all dosages and ns-NSAIDs in high dosages increase morbidity for patients with previous AMIs.78 Parecoxib, the parenteral produg of valdecoxib, is widely used outside the United States for perioperative pain. In a study of coronary artery bypass grafting patients receiving intravenous parecoxib sodium followed by oral parecoxib, patients had a postoperative CV disease composite event rate of 2%, compared to 0.5% in patients receiving placebo.79,80
III. BP management in patients taking NSAIDs: RECOMMENDATION A. Patients with preexisting hypertension should have careful BP monitoring when taking nonaspirin NSAIDs, including COX-2 inhibitors, especially within the first 3 months of the start of treatment with NSAIDs.

Meta-analyses have shown that NSAIDs elevate supine mean arterial BP by an average of 5 mm Hg in patients with hypertension.\textsuperscript{81-84} In theValsartan Antihypertensive Long-Term Evaluation (VALUE) trial, systolic BP increases of 4 mm Hg increased the risk for CV events by >40% in older populations of hypertensive patients.\textsuperscript{80} Thus, hypertensive patients, especially those with histories of myocardial diastolic dysfunction or left ventricular myocardial hypertrophy, should be reevaluated <1 to 3 weeks after NSAID treatment is begun.\textsuperscript{84} Particular caution should be taken when ns-NSAIDs and COX-2 inhibitors are given to patients with hypertension who also have diabetes mellitus or any level of renal impairment due to other causes and are taking ACE inhibitors, angiotensin receptor blockers, or \( \beta \) blockers, because these patients also are at increased risk for the destabilization of BP and the development of heart failure.\textsuperscript{20,84} Selective COX-2 inhibition may improve endothelium-dependent vasodilation and reduces low-grade chronic inflammation and oxidative stress in patients with preexisting atherosclerotic CV disease,\textsuperscript{85} but the clinical significance, if any, of these effects of COX-2 inhibitors is unproved.

RECOMMENDATION B. Normotensive individuals with multiple CV risk factors or histories of CV events should have close BP monitoring for \( \geq 2 \) to 4 weeks after starting COX-2 inhibitors ns-NSAIDs and, even if there is no increase in BP, at least every 3 months thereafter. Self-monitoring of BP should be encouraged in patients with CV disease who are taking NSAIDs.

RECOMMENDATION C. Patients with CV disease who develop hypertension after starting NSAIDs, as the first step in BP control, should discontinue the NSAIDs or decrease the NSAID doses, if possible.

NSAIDs are associated with a modest risk for first-time AMI that may be due in part to increased BP.\textsuperscript{86} A dose-response relation, however, has not been established between NSAID use and BP elevation, so dose reduction may not decrease the BP.

RECOMMENDATION D. Patients developing hypertension on NSAIDs should receive antihypertensive pharmacologic treatment when NSAID discontinuation is not possible or dose reduction is ineffective or is not feasible.

For patients without previous hypertension, calcium channel-blocking drugs are preferred because other antihypertensive drugs, including \( \beta \) blockers, diuretics, ACEs, and angiotensin receptor blockers, generally require higher doses for control of NSAID-induced hypertension. According to current guidelines, patients with histories of CV disease, renal disease, or diabetes mellitus should maintain BP <130/80 mm Hg.\textsuperscript{87-89}

IV. ASA for secondary CV disease prevention: RECOMMENDATION. When prescribed for the secondary prevention of CV disease, the recommended dose of ASA is 81 mg/day.

ASA at low doses has been shown to be cardioprotective in most types of patients who are at increased risk for CV events, including patients with AMIs, ischemic stroke or cerebral ischemia, unstable or stable angina pectoris, peripheral arterial disease, or atrial fibrillation.\textsuperscript{89} ASA >81 mg/day, however, causes GI toxicity, and ASA >325 mg/day causes more GI toxicity than other NSAIDs. Low-dose ASA is associated with increased risk for upper GI bleeding, and this risk further increases when ASA is combined with NSAIDs. Enteric-coated ASA has not been proved to reduce the risk for GI bleeding.\textsuperscript{90}

V. Use of NSAIDs by patients taking ASA for elevated CV risk who also have high risk for GI bleeding: RECOMMENDATION A. Patients taking ASA for increased CV risk who also are at high risk for GI bleeding (e.g., those with histories of GI bleeding or ulcer disease) should take proton pump inhibitors (PPIs) when taking ns-NSAIDs or COX-2 inhibitors.

In patients with very high risk for GI bleeding, however, PPIs may not provide complete protection against the adverse GI effects of NSAIDs. GI ulcer scars rely on induced COX-2 to maintain integrity; thus, ns-NSAIDs and COX-2 inhibitors increase the risk for GI bleeding.\textsuperscript{26,51,92} Histamine antagonists are not recommended for reducing GI bleeding risk when taking NSAIDs, because they cost about the same, are less effective than generic PPIs, and exhibit tachyphylaxis with long-term use.

RECOMMENDATION B. Pain control with opioids should be considered for patients in whom CV risk and GI risk are sufficiently elevated that any class of NSAID, even with a PPI, cannot be used safely.

Opioids may be considered in CV high-risk patients with moderate to severe pain, pain-induced functional limitations, or for other adverse consequences of pain-related inflammation. Clinicians should closely monitor patients for potential adverse effects such as dysphoria, sedation, obstruction, respiratory depression, and other adverse effects commonly observed with this class of drugs. Compliance strategies such as urine testing and opioid agreements should be implemented, and patients should be continually assessed for the attainment of therapeutic goals as well as safe and responsible opioid use. Tramadol is effective in pain control for osteoarthritis and neuropathic pain. It should be taken with some caution because of risks associated with decreasing and other events, and it can induce seizures when combined with antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants), which are often prescribed for major depression in patients with CV disease.

VI. Patients with impaired renal function: RECOMMENDATION. Patients with impaired renal function receiving COX-2 inhibitors or ns-NSAIDs should have close monitoring of BP and renal function, including measurement of blood urea nitrogen, serum potassium, and serum creatinine <2 weeks after beginning the NSAID.

COX-2 inhibitors and ns-NSAIDs adversely affect renal function, producing increased BP, peripheral edema, sodium retention, and hyperkalemia in some patients with renal impairment. Less than 1 month after starting an NSAID, there is a two- to fourfold increase in the risk for
acute renal failure when taking $\geq 1$ NSAIDs. Healthy men and women aged $>30$ years have a decrease in glomerular filtration rate of about 10 ml/min/1.73 m$^2$ per life decade. Thus, older patients, who often have significantly decreased renal perfusion, must be closely monitored when taking NSAIDs.

Acetaminophen in moderate doses (<3 g/day total) may be considered an alternative for pain control in patients with established renal disease.

VII. Communication with patients about NSAIDs: RECOMMENDATION. Because nonprescription NSAIDs carry the same CV risks as prescription NSAIDs, physicians should proactively inquire of all patients, especially patients with increased CV risk or histories of CV disease, whether they are taking NSAIDs and, if so, take appropriate measures, including specific risk assessments, according to the aforementioned recommendations.

Future Recommendations

Part of the uncertainty about NSAID use, including treatment with COX-2 inhibitors, is due to the exclusion of patients with CV disease from randomized controlled trials, making it difficult to determine the true risks of NSAIDs for CV disease. Another difficulty involves the choice of comparator ns-NSAIDs in trials of COX-2 inhibitors. Diclofenac, for example, was used for comparison in clinical trials assessing the efficacy of celecoxib and etoricoxib. However, diclofenac has been associated with higher CV risk than other ns-NSAIDs.

The dilution of relative risk associated with many COX-2 inhibitors over successive studies combined with the significantly lower rates of their prescription for recurrent heart failure suggests that prescribers have heeded messages that NSAIDs may precipitate heart failure and other heart conditions in vulnerable individuals and have applied the same strategy in the use of COX-2 inhibitors.

Future research should include the development of new medications for pain control. New classes of anti-inflammatory and analgesic agents are in development, such as COX-inhibiting nitric oxide donors and selective E prostanoid receptor antagonists. These agents may induce less destabilization of BP control in treated patients with hypertension, including patients taking renin-angiotensin system–blocking drugs. Finally, of special importance to cardiologists, the possibility of significant adverse interactions between NSAIDs and angiographic contrast agents should be studied.

Appendix

Adapted from Food and Drug Administration Science Paper 9/8/2006

Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin

Healthcare professionals should be aware of an interaction between low dose aspirin (81 mg per day) and ibuprofen which might render aspirin less effective when used for its anti-platelet cardioprotective effect. Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of ibuprofen and aspirin.

Summary

- Existing data using platelet function tests suggest there is a pharmacodynamic interaction between 400mg ibuprofen and low dose aspirin when they are dosed concomitantly. The FDA is unaware of data addressing whether taking less than 400 mg of ibuprofen interferes with the antiplatelet effect of low dose aspirin.
- The clinical implication of this interaction may be important because the cardioprotective effect of aspirin, when used for secondary prevention of myocardial infarction, could be attenuated.
- For single doses of ibuprofen, the pharmacodynamic interaction can be minimized if ibuprofen is given at least 8 hours before or at least 30 minutes after immediate release aspirin (81mg; not enteric coated).
- The clinical implication of the interaction has not been evaluated in clinical endpoint studies.
- There is no clear data regarding the potential effect of chronic ibuprofen dosing of greater than 400mg on the antiplatelet effect of aspirin.
- The timing of dosing of ibuprofen and low-dose aspirin is important for preserving the cardioprotective effect of aspirin.

Recommendations for Concomitant Use

- Health care providers should counsel patients about the appropriate timing of ibuprofen dosing if the patients are also taking aspirin for cardioprotective effects.
- With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low dose aspirin.
- Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion to avoid any potential interaction.
- Other nonselective OTC NSAIDs should be viewed as having potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.
- Analgesics that do not interfere with the antiplatelet effect of low dose aspirin should be considered for populations at high risk for cardiovascular events.

Recommendations about concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based upon available data. One study showed that the antiplatelet effect of enteric-coated low dose aspirin is attenuated when ibuprofen 400mg is dosed 2, 7, and 12 hours after aspirin.

Discussion

Background: Ibuprofen has been marketed in the United States as an anti-inflammatory, analgesic, and antipyretic
drug for decades. It is widely available in a variety of strengths and formulations for children and adults as single-ingredient over-the-counter (OTC) and prescription products, and can also be found in combination OTC and prescription products.

Chemically, ibuprofen is a propionic acid derivative and a member of the class of non-steroidal anti-inflammatory drugs (NSAIDs). The NSAIDs include aspirin, and several other classes of organic acids, including the propionic acid derivatives naproxen and ketoprofen, acetic acid derivatives diclofenac and indomethacin, and the enolic acid piroxicam, and newer agents such as celecoxib.

How does ibuprofen work and why does it interact with aspirin?: All NSAIDs work by inhibiting the enzyme cyclooxygenase (COX). Aspirin inhibits COX irreversibly, while all non-aspirin NSAIDs are reversible inhibitors of COX. There are two forms of cyclooxygenase: namely, COX-1 found in blood vessels, stomach and kidney, and COX-2, which is induced in settings of inflammation by cytokines and inflammatory mediators. A putative COX-3 has been suggested but not proven in humans. 30 All currently available OTC NSAIDs are nonselective COX inhibitors, and inhibit both COX-1 and COX-2 to varying degrees. The antipyretic, analgesic, and antiinflammatory actions of NSAIDs are related to their ability to inhibit COX-2. Side effects such as gastrointestinal (GI) bleeding and renal toxicity are a result of the inhibition of COX-1 and are well known complications of NSAID therapy. 106-108 By inhibiting COX-1, the NSAIDs prevent the formation of thromboxane from arachidonic acid, and thereby prevent thromboxane-induced platelet aggregation. Aspirin has an irreversible anti-platelet effect, while other NSAIDs, including ibuprofen, have a reversible anti-platelet effect. 109 Low dose aspirin is effective in the secondary prevention of cardiovascular events because of its antiplatelet effect. Because they bind at similar sites on COX, concurrent use of aspirin and ibuprofen may change the pharmacodynamic effect of either drug depending on the timing of dosing of each drug.

What types of aspirin are currently available Over-the-Counter?: Aspirin is available over-the-counter as a tablet, buffered tablet, effervescent tablet, or caplet in immediate-release formulations and as a tablet in enteric-coated formulations in strengths ranging from 81 mg to 500 mg.

What is the interaction between aspirin and ibuprofen in single dose studies?: It has been demonstrated in published and unpublished human ex vivo studies, that ibuprofen interferes with the antiplatelet activity of low dose aspirin (81 mg; not enteric coated) when they are ingested concurrently. 25 The mechanism by which this occurs may be through competitive inhibition of the acetylation site of cyclooxygenase in the platelet. Both ibuprofen (reversible inhibition) and aspirin (irreversible inhibition) occupy nearby sites on cyclooxygenase, such that the presence of ibuprofen interferes with aspirin binding. Once the ibuprofen releases from the binding site, COX will not be inhibited because some aspirin available to bind will have been excreted due to aspirin’s short half-life. This ibuprofen interference attenuates the expected aspirin-mediated irreversible inhibition of thromboxane B2 (TXB2) production and attenuates the expected inhibition in platelet aggregation.

There are no clinical endpoints studies conducted specifically to evaluate the interaction. Attenuation of 90% or more of the antiplatelet effect of aspirin has been defined as clinically significant 10 by some investigators. Unpublished single dose trials with ibuprofen 400 mg indicate that interference with aspirin’s antiplatelet activity, as measured by TXB2 levels and platelet activation studies, occurs when ibuprofen is taken within 30 minutes after immediate release aspirin dosing. The interaction also occurs when a single dose of ibuprofen 400 mg is taken within 8 hours prior to aspirin dosing. At least 8 hours should elapse after ibuprofen dosing, before giving aspirin, in order to avoid significant interference.

What is the interaction between aspirin and ibuprofen in a multiple dose study?: One published study demonstrated that if immediate-release aspirin 81 mg is given daily for an 8 day run-in, followed by ibuprofen 400 mg dosed at 1, 7, and 13 hours after the daily aspirin dose for the next 10 days, then no interference is found with the aspirin-induced inhibition of thromboxane, when measured as TXB2 production ex vivo. 110

How can the data regarding the interaction between aspirin and ibuprofen from the single and multiple dose studies be interpreted?: It thus appears that taking low-dose immediate release aspirin at least 30 minutes before ibuprofen will preserve the anti-platelet effect of aspirin.

Does the same interaction occur with enteric-coated aspirin?: A published study showed that with no aspirin run-in period, enteric-coated aspirin 81 mg given daily with ibuprofen 400 mg dosed 2, 7, and 12 hours after aspirin, leads to interference with aspirin-induced inhibition of thromboxane, when measured as TXB2 production ex vivo. 25 This seems to contradict the observations of other studies using non-enteric-coated aspirin but may be explained by the absorption of enteric-coated aspirin being delayed compared to non-enteric-coated aspirin. More data are needed to reach a conclusion about the interaction between a single daily enteric-coated low dose aspirin and multiple daily doses of ibuprofen.

What is the relationship between these observations and clinical outcomes?: There has not been a prospective, randomized clinical trial with pre-identified cardiovascular endpoints that could provide data to clarify the clinical consequence of such concomitant dosing with ibuprofen and low dose aspirin. Epidemiological data on the cardiovascular event clinical outcome of concomitant dosing has been equivocal. 111-117

Do other nonprescription pain relievers show a similar interaction with aspirin?: Acetaminophen appears to not interfere with the antiplatelet effect of low dose aspirin. 25 FDA is unaware of studies that have looked at the same type of interference by ketoprofen with low dose aspirin. One study of naproxen and low-dose aspirin has suggested
naproxen may interfere with aspirin’s anti-platelet activity when they are coadministered. However, naproxen 500 mg administered two hours before or after the administration of aspirin 100 mg did not interfere with aspirin’s anti-platelet effect. There is no data looking at doses of naproxen less than 500 mg. Naproxen is available OTC only as 220 mg. Prescription strengths of naproxen are 250, 375, and 500mg.

**Conclusions**

- There may be a pharmacodynamic interaction between ibuprofen and aspirin when they are dosed concomitantly. This interaction may interfere with the anti-platelet activity of the aspirin, as measured by TXB2 levels and platelet activation.
- The clinical implication of this interaction is unclear, but may be important since the cardioprotective effect of aspirin, when used for secondary prevention of myocardial infarction, could be minimized or negated.
- A negative clinical impact on aspirin’s cardioprotection is unlikely from an occasional dose of ibuprofen because the effect of aspirin taken daily is long-lasting.
- Ibuprofen given at least 30 minutes after immediate-release aspirin or at least 8 hours before taking immediate-release aspirin does not appear to interfere with aspirin’s anti-platelet effect.

**References**


