

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Use of Nonsteroidal Antiinflammatory Drugs: An Update for Clinicians: A Scientific Statement From the American Heart Association

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Circulation 2007;115;1634-1642; originally published online Feb 26, 2007;

DOI: 10.1161/CIRCULATIONAHA.106.181424

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Use of Nonsteroidal Antiinflammatory Drugs

An Update for Clinicians

A Scientific Statement From the American Heart Association

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Clinical trial data have prompted questions about the degree to which patients and their physicians should consider an increased risk of cardiovascular or cerebrovascular events when selecting medications for pain relief. Since the 2005 publication of a Science Advisory on the use of nonsteroidal antiinflammatory drugs (NSAIDs) by the American Heart Association,¹ several important events have occurred that have served as the catalyst for this update for clinicians. (1) Additional data from randomized controlled trials of cyclooxygenase (COX)-2-selective agents have been reported and summarized in meta-analyses, which has reinforced the concern about cardiovascular events with COX-2 inhibitors (coxibs; Figure 1). (2) Several reports have appeared that have identified an increased risk of cardiovascular events even with the nonselective NSAIDs, which has raised concern about the use of those agents as well (Table). (3) Regulatory authorities in several regions of the world have introduced warning statements and advisories to both health-care professionals and the lay public about the use of various NSAIDs (Figures 2 and 3).

In September 2004, Merck announced a voluntary worldwide withdrawal of Vioxx (rofecoxib) because of an increased risk of heart attack and stroke.⁵ In early December 2004, the US Food and Drug Administration (FDA) announced a “black box” warning for valdecoxib (Bextra), stating that its use in patients undergoing coronary artery bypass graft surgery is contraindicated. A week later, the National Institutes of Health (NIH) suspended the use of celecoxib (Celebrex) in the Adenoma Prevention with Celecoxib (APC) clinical trial because of increased cardiovascular events. The drug was not removed from the market, but the FDA advised physicians to consider alternative therapy or to use the smallest effective dose of Celebrex. Three days later,

the NIH announced that the Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT) showed an increase in the risk of cardiovascular events in patients given naproxen but not in those given celecoxib; the trial was halted. At the end of 2004, the FDA issued a public health advisory summarizing the agency’s recent recommendations for the use of the NSAID products Vioxx, Bextra, Celebrex, and naproxen.⁶ To quote from the public health advisory:

- “Physicians prescribing Celebrex (celecoxib) or Bextra (valdecoxib) should consider this emerging information when weighing the benefits against risks for individual patients. Patients who are at a high risk of gastrointestinal (GI) bleeding, have a history of intolerance to nonselective NSAIDs, or are not doing well on nonselective NSAIDs may be appropriate candidates for Cox-2 selective agents.”
- “Individual patient risk for cardiovascular events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation.”
- “Consumers are advised that all over-the-counter (OTC) pain medications, including NSAIDs, should be used in strict accordance with the label directions. If use of an (OTC) NSAID is needed for longer than ten days, a physician should be consulted.”

At a joint meeting, 2 FDA Advisory Committees and 12 ad hoc members discussed the overall benefit-to-risk considerations for selective COX-2 NSAIDs and related agents in mid-February 2005. The 32-person panel was unanimous in its conclusion that celecoxib significantly increases the risk of cardiovascular events in a dose-dependent manner. The committee recommended,⁷ however, that celecoxib be allowed to remain on the US market under several conditions, such as the addition of a “black box” warning to the labeling, restrictions on direct-to-consumer advertising, and the development of a patient medication guide. Assumptions included

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 20, 2006. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0396. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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(*Circulation*. 2007;115:1634-1642.)

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DOI: 10.1161/CIRCULATIONAHA.106.181424

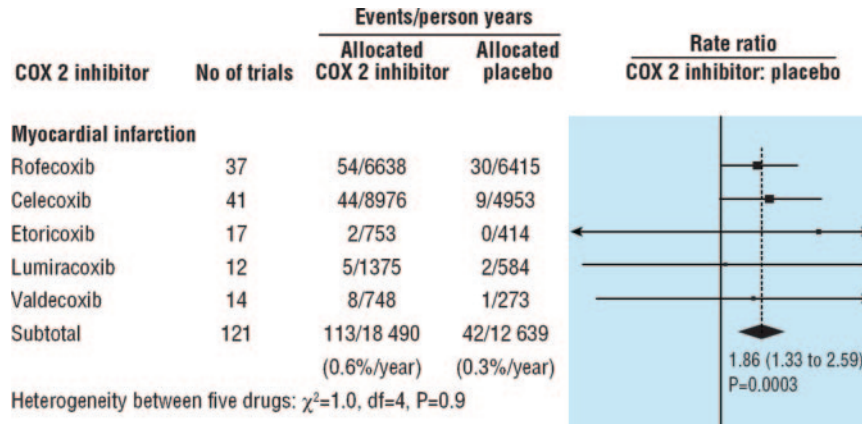


Figure 1. Comparison of effects of different selective COX-2 inhibitors vs placebo on myocardial infarction. Event numbers and person-years of exposure, with corresponding mean annual event rates in parentheses, are presented for patients allocated to selective COX-2 inhibitor or placebo. Event rate ratios for pooled data with 95% CIs are indicated by a diamond; rate ratios for individual selective COX-2 inhibitors, with 99% CIs, are indicated by a square and horizontal line. Diamonds to the right of the solid line indicate hazard with a selective COX-2 inhibitor compared with placebo. As noted, there was a significant increase in the rate ratio for myocardial infarction with COX-2 inhibitors compared with placebo. Similar analyses (data not shown) include rate ratios of 1.42 (1.13 to 1.78; $P=0.003$) for vascular events, 1.02 (0.71 to 1.47; $P=0.9$) for stroke, and 1.49 (0.97 to 2.29; $P=0.07$) for vascular death with COX-2 inhibitors compared with placebo. Modified and reproduced from Kearney et al.² with permission from the BMJ Publishing Group.

that if celecoxib were to be used, it should be in patients who have not achieved pain control with nonselective NSAIDs, it should be used in the lowest possible dose for the shortest time necessary, and high-risk cardiac patients should be fully informed about the excess cardiovascular risks. Unanimous votes also supported the conclusions that the other 2 FDA-approved selective COX-2 inhibitors, valdecoxib and rofecoxib, increase the risk of cardiovascular events, which signaled a class effect of the selective COX-2 inhibitors. At

the hearing, in a split vote, it was recommended that valdecoxib remain on the market; rofecoxib had already been withdrawn from the US market by the manufacturer. Finally, the panel voted unanimously that the labeling for the nonselective NSAIDs include information on the absence of long-term clinical trial data to assess the potential cardiovascular effects of these drugs. It also recommended that future active-control trials include naproxen as the primary comparator. Caution was advised to prevent warnings on over-the-

TABLE. Nonselective NSAIDs and CV Risk

Type of Study	Outcome	RR	95% CI
Versus placebo or no treatment			
Naproxen			
Meta-analysis of RCTs ²	Vascular events	0.92	0.67–1.26
Meta-analysis of OSs ³	CV events, mostly MI	0.97	0.87–1.07
Ibuprofen			
Meta-analysis of RCTs ²	Vascular events	1.51	0.96–2.37
Meta-analysis of OSs ³	CV events, mostly MI	1.07	0.97–1.18
Registry ⁴	Recurrent MI	1.25	1.07–1.46
Registry ⁴	Mortality	1.50	1.36–1.67
Diclofenac			
Meta-analysis of RCTs ²	Vascular events	1.63	1.12–2.37
Meta-analysis of OSs ³	CV events, mostly MI	1.40	1.16–1.70
Registry ⁴	Recurrent MI	1.54	1.23–1.93
Registry ⁴	Mortality	2.40	2.09–2.80
Versus selective COX-2 inhibitor			
Naproxen			
Meta-analysis of RCTs ²	Vascular events	0.64	0.49–0.83
Any non-naproxen NSAID (primarily diclofenac or ibuprofen)			
Meta-analysis of RCTs ²	Vascular events	1.14	0.89–1.45

RCTs indicates randomized, controlled trials; OSs, observational studies; CV, cardiovascular; and MI, myocardial infarction.

Diclofenac sodium enteric-coated tablets

Tablets of 25 mg, 50 mg, and 75 mg

Rx only

Prescribing information

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)
- Voltaren® (diclofenac sodium enteric-coated tablets) is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

Figure 2. Black box warning for NSAIDs. This black box warning statement now appears in the package insert for agents in the “traditional” NSAID group, emphasizing the increased risk of cardiovascular events with their use. This example is from the package insert (January 2006) of diclofenac, a commonly prescribed NSAID. Similar black box warnings appear in the package inserts for other NSAIDs (see Figure 4).

counter products about the risks of long-term use from causing undue concern in the lay public.

FDA decisions⁸ only partially followed the recommendations by the advisory panel. The black box warning states that celecoxib may cause increased risk (Figure 3). There is no comment on the magnitude of the increase in risk, relative or absolute, and no mention of the recommendation for low doses and short durations of treatment. The box contains the general statement that “[a]ll NSAIDs may have a similar risk” but includes no recognition of known differences among the nonselective NSAIDs (Figure 2).

The European Medicine Agency⁹ issued the recommendations that selective COX-2 inhibitors be considered contraindicated in patients with ischemic heart disease and/or stroke, that they be avoided in patients with risk factors for coronary heart disease, and that all patients take the lowest effective dose for the shortest time necessary to control symptoms. It is

Celecoxib capsules

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS).
- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

unclear whether the findings for selective COX-2 inhibitors are also relevant for nonselective NSAIDs.¹⁰

Background Scientific Information on COX Inhibitors

The primary property of this class of drugs is the inhibition of COX.^{11–13} There are 2 major COX isoenzymes: COX-1 is expressed constitutively (constantly) in most tissues, whereas COX-2 is induced in inflammation. Both COX-1 and COX-2 use arachidonic acid to generate the same product, prostaglandin H₂. A number of enzymes further modify this product to generate bioactive lipids (prostanoids) such as prostacyclin, thromboxane A₂, and prostaglandins D₂, E₂, and F₂. These prostanoids influence immune, cardiovascular, gastrointestinal (GI), renovascular, pulmonary, central nervous system, and reproductive function.¹² Of note, it is now recognized that COX-2 is expressed in normal endothelial cells in response to shear stress and that inhibition of COX-2 is associated with suppression of prostacyclin synthesis.¹⁴ On the basis of experiments in animals and observations from clinical trials and registries, it has been proposed that major cardiovascular consequences of COX-2 inhibition include a shift in the prothrombotic/antithrombotic balance on endothelial surfaces toward thrombosis; an increase in sodium and water retention, leading to edema, as well as exacerbations of heart failure and hypertension; and loss of the protective effects of COX-2 upregulation in the setting of myocardial ischemia and infarction, which leads to a larger infarct size, greater thinning of the left ventricular wall in the infarct zone, and an increased tendency to myocardial rupture.^{12,13,15,16}

A variety of NSAIDs can block the enzymatic activity of COX; they vary in their chemical structure and relative ability to block the COX-1 versus the COX-2 isoenzymes (Figure 4). The COX-2 inhibitors also vary in their selectivity for the COX-2 versus the COX-1 enzyme (for medications currently or formerly on the market in the United States, rofecoxib > valdecoxib > parecoxib > celecoxib). Other COX-2 inhibitors are under development and may be introduced into the US market in the future. The differences in the biological effects of COX inhibitors are a consequence of the degree of selectivity for COX-2 versus COX-1 and tissue-specific variations in the distribution of COX and related

Figure 3. Black box warning for COX-2–selective drugs. This black box warning statement now appears in the package insert (July 2005) for celecoxib, the only COX-2 inhibitor currently on the market in the United States, emphasizing the increased risk of cardiovascular events with its use.

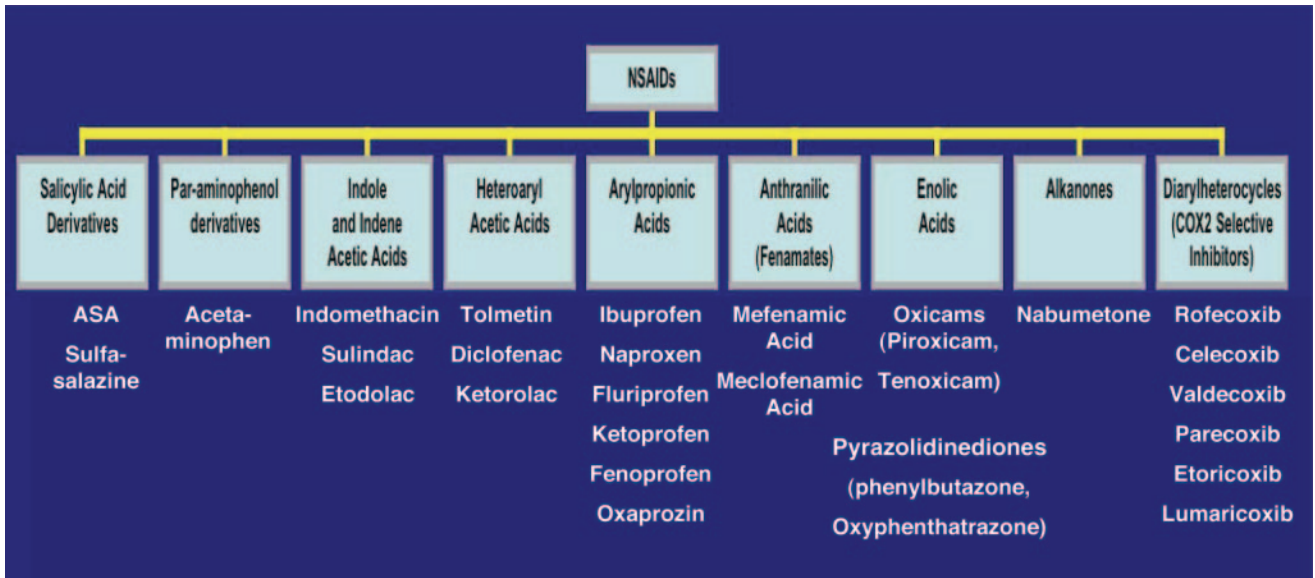


Figure 4. NSAIDs. The 9 chemical groupings of NSAIDs are shown, along with key compounds in each class. Common therapeutic effects (with varying degrees of activity) for NSAIDs are antipyretic, analgesic, and antiinflammatory. Common side effects (with varying relative frequencies) are GI ulceration, inhibition of platelet aggregation, inhibition of uterine motility, inhibition of prostaglandin-mediated renal function, and hypersensitivity reactions. Proprietary names for the drugs shown in this Figure and other NSAID agents can be found in the medication guides for patients that have been prepared for the various agents marketed in the United States (<http://www.fda.gov/cder/drug/infopage/COX2/NSAIDmedguide.htm>). ASA indicates acetylsalicylic acid (aspirin). Modified and reproduced from Antman et al¹¹ with permission from the American Heart Association. Copyright 2005.

enzymes that convert prostaglandin H_2 into specific prostanoids.

For example, several prostanoids, including prostaglandin E_2 and prostacyclin, are both hyperalgesic (elicit an increased sense of pain) and gastroprotective. Thus, nonselective COX inhibition with agents such as aspirin, ibuprofen, indomethacin, and naproxen, which inhibit both COX-1 and COX-2 enzymes, provides effective pain relief for inflammatory conditions but carries with it a risk for erosive gastritis and GI bleeding. Selective COX-2 inhibitors (valdecoxib, rofecoxib, celecoxib, and others yet in development) were developed to minimize GI toxicity because of the relative paucity of COX-2 expression in the GI tract and the relative abundance of COX-2 expression in inflamed and painful tissues.

In the cardiovascular system, the products of COX regulate complex interactions between platelets and the vessel wall. Prostacyclin is the dominant prostanoid produced by endothelial cells.^{17,18} In addition to producing local smooth muscle cell relaxation and vasodilation, prostacyclin can interact with platelet IP receptors, thereby antagonizing aggregation. Platelets contain only COX-1, which converts arachidonic acid to the potent proaggregatory, vasoconstrictive eicosanoid thromboxane A_2 (TXA₂), the major COX product formed by platelets. Nonselective COX inhibition with aspirin is effective for arterial thrombosis because of its ability to reduce COX-1-dependent production of platelet TXA₂; however, selective inhibition of COX-2 could produce a relative reduction in endothelial production of prostacyclin, while leaving the platelet production of TXA₂ intact. It has been speculated that this imbalance of hemostatic prostanoids might increase the risk for thrombotic cardiovascular events^{19,20} (Figure 5). COX-2 inhibitors, like NSAIDs, also raise blood pressure and increase the incidence of

heart failure significantly compared with placebo.^{21,22} By elevating blood pressure, NSAIDs, particularly coxibs, attenuate the benefit of previously prescribed antihypertensive therapy and may also move certain patients not previously diagnosed as hypertensive over the threshold for initiation of treatment for hypertension.^{23,24}

It has been postulated that the differences in relative selectivity for COX inhibition affect the likelihood of a patient experiencing adverse cardiovascular or GI complications as a consequence of using NSAIDs (Figure 6). An example of the importance of understanding the relative selectivity for COX inhibition is found in the interpretation of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program.^{25,26} This program (consisting of the Etoricoxib versus Diclofenac sodium Gastrointestinal tolerability and Effectiveness [EDGE], EDGE II, and MEDAL trials) evaluated the highly COX-2-selective agent etoricoxib (not marketed in the United States) versus diclofenac, a commonly prescribed NSAID that is relatively more selective for COX-2 inhibition than for COX-1 inhibition and has a black box warning in the package insert (Figure 2).^{27,28} The MEDAL program randomized 34 701 patients with either rheumatoid arthritis or osteoarthritis to either etoricoxib or diclofenac and reported noninferiority of etoricoxib compared with diclofenac with regard to cardiovascular thrombotic (arterial and venous) events (hazard ratio 0.95, 95% confidence interval [CI] 0.81 to 1.11) in a prespecified per-protocol analysis.²⁹ According to an intention-to-treat analysis through the end of follow-up, the hazard ratio for the primary composite end point of vascular death, myocardial infarction, or stroke through the end of follow-up was 1.02 (95% CI 0.87 to 1.18). Although the results of the MEDAL

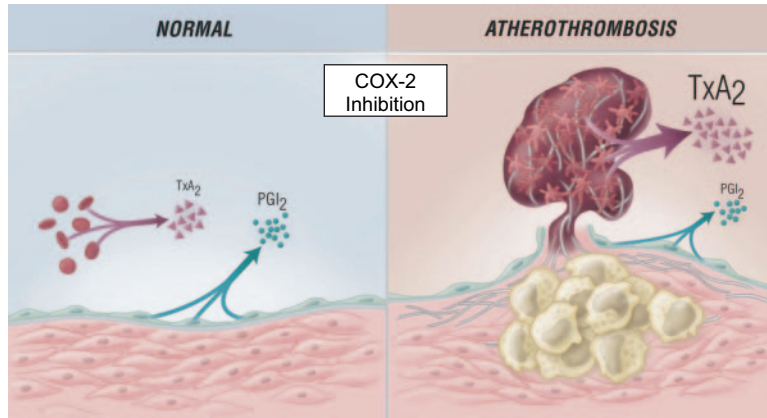


Figure 5. Consequences of COX inhibition for prostacyclin and TXA₂ production in normal and atherosclerotic arteries. Endothelial cells are shown as a source of prostacyclin (PGI₂) and platelets as a source of TXA₂. COX-2 inhibition suppresses COX-2–dependent PGI₂ production in endothelial cells, which has only a marginal effect on the net antithrombotic balance owing to the importance of COX-1 as a source of PGI₂ in the normal state. In the setting of atherosclerosis, however, COX-2 plays a greater role as a source of PGI₂, and more TXA₂ is produced; thus, inhibiting COX-2 has a more profound effect on prostanoid balance, favoring TXA₂ production and promoting platelet-dependent thrombosis. Modified and reproduced from Antman et al¹¹ with permission from the American Heart Association. Copyright 2005.

program satisfied the prespecified definition of noninferiority (upper bound of the 95% CI of the hazard ratio <1.3), clinicians are cautioned against concluding that etoricoxib is as safe as “traditional” NSAIDs.^{25,30} As illustrated in Figure 6, because etoricoxib and diclofenac lie on the more COX-2–selective end of the spectrum of COX inhibition, it is not unexpected that they would have similar profiles for risk of thrombotic events.³¹ Because diclofenac has been associated with an increased risk of thrombotic events^{3,30} (Table) and the risk with etoricoxib is at least similar, it does not appear that either of these medications would be among the first choices for pain relief with regard to safety, especially in individuals with or at risk for cardiovascular disease. Of note, the

MEDAL program also reported higher rates of discontinuation for edema and hypertension with etoricoxib, two complications that may represent important limitations to its use.^{23,29,32}

Prostacyclin may also retard the pathogenesis of atherosclerosis,¹⁹ and inhibition of prostacyclin with a COX-2 inhibitor has been predicted to promote lesion formation¹⁹; however, results in different mouse models of atherosclerosis have been contradictory.^{33–39}

Recommendations for Management

From both the patient’s and the physician’s perspectives, the problem lies in balancing the risks and benefits of medica-

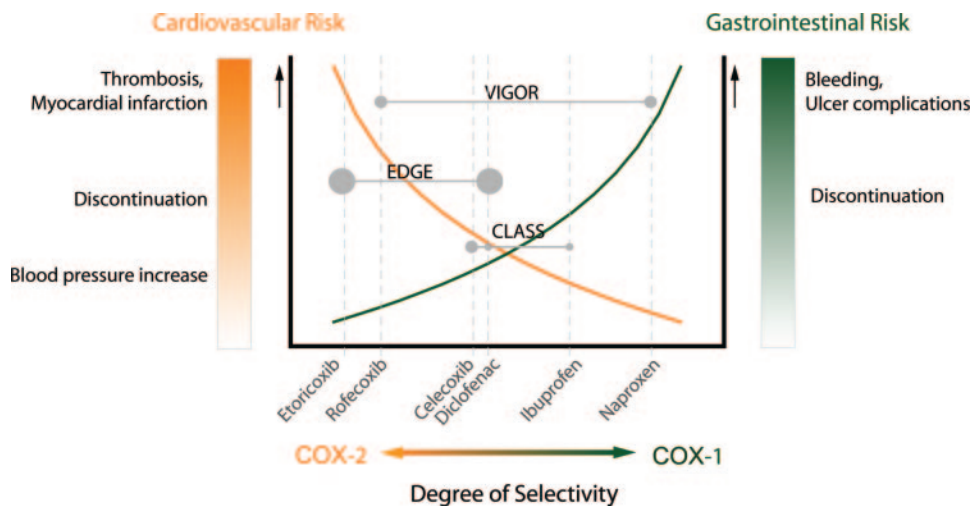


Figure 6. Implication of the relative degrees of selectivity. Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk, whereas increasing degrees of selectivity for COX-1 are associated with augmented GI risk. This has important implications for interpretation of clinical trials. For example, a trial such as VIGOR (Vioxx Gastrointestinal Outcomes Research) is more likely to yield a signal of harm from a COX-2–selective agent given the comparison with naproxen. In contrast, a comparison of etoricoxib with diclofenac, as in EDGE (part of the larger MEDAL program), is likely to yield similar risk profiles of the 2 agents but is unable to provide insight into other clinically important issues such as the relative risk of either etoricoxib or diclofenac against placebo or less COX-2–selective NSAIDs. CLASS indicates Celecoxib Long-Term Arthritis Safety Study. Modified and reproduced from Grosser et al¹² with permission from the American Society for Clinical Investigation. Copyright 2006.

Stepped Care Approach to Pharmacologic Therapy for Musculoskeletal Symptoms With Known Cardiovascular Disease or Risk Factors for Ischemic Heart Disease

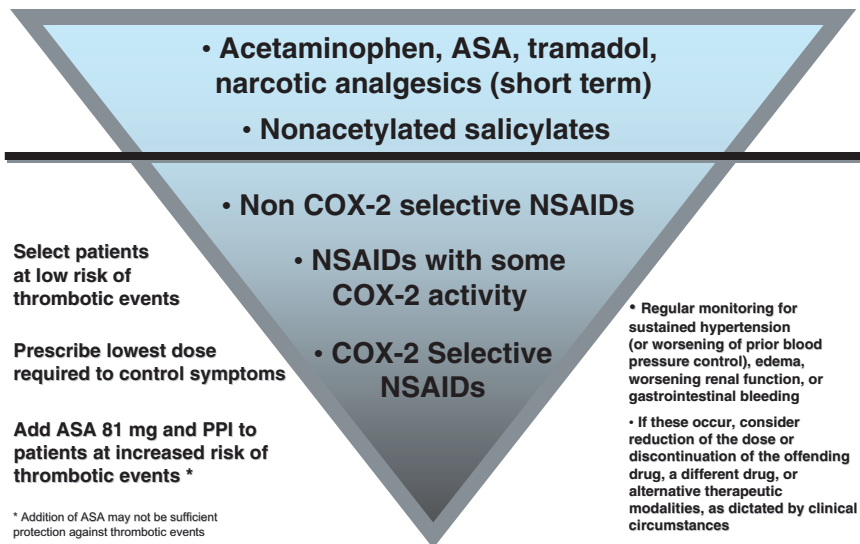


Figure 7. Stepped care approach to management of musculoskeletal symptoms. In patients with known cardiovascular disease or who are at risk for ischemic heart disease, clinicians should use a stepped care approach to pharmacological therapy that focuses on agents with the lowest reported risk of cardiovascular events and then progress toward other agents with consideration of the risk/benefit balance at each step. Once the decision is made to prescribe an NSAID (below the horizontal line), additional considerations assume importance, as illustrated by the recommendations at the bottom left and right of the diagram. See text for further discussion. ASA indicates acetylsalicylic acid (aspirin); PPI, proton-pump inhibitor.

tions for pain relief.³² Of course, this is not unique to these medications, but their use highlights the issues to be considered. Below are several questions that should be considered when one makes treatment decisions about pain medications in patients with or at high risk for cardiovascular disease. A suggested stepped-care approach to management of patients with musculoskeletal symptoms is shown in Figure 7 and discussed in detail below.

First, What Are the Treatment Considerations?

Musculoskeletal symptoms should be categorized as those that result from tendonitis/bursitis, those that result from degenerative joint problems (eg, osteoarthritis), or those that result from inflammatory joint problems (eg, rheumatoid arthritis).⁴⁰ Initial treatment should focus on nonpharmacological approaches (eg, physical therapy, heat/cold, orthotics).⁴¹

For patients whose symptoms are not controlled by nonpharmacological approaches, pharmacological treatments should then be considered. When choosing any medication, both safety and efficacy should be considered. In general, the least risky medication should be tried first, with escalation only if the first medication is ineffective. In practice, this usually means starting with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term needs. Despite the potential for abuse, a role remains for narcotic medications for short-term pain relief. It should be recognized that with the exception of aspirin, the “low-risk” medications mentioned above have not been subjected to randomized clinical trials to conclusively demonstrate their superior safety.

In patients who do not tolerate these simple interventions or who require long-term or high-dose therapy, the issues become more complex. Long-term or high-dose therapy with aspirin and other NSAIDs is associated with increased risk for GI bleeding. Occasionally, high-dose acetaminophen can result in hepatic toxicity, especially in patients who consume excess alcohol. When acetaminophen, aspirin, and perhaps even narcotic medications (for acute pain) are not effective,

tolerated, or appropriate, it may be reasonable to consider an NSAID as the next step; however, this should be coupled with the realization that effective pain relief may come at the cost of a small but real increase in risk for cardiovascular or cerebrovascular complications (moving below the horizontal line in Figure 7).

The scientific evidence to date (Table) indicates that important differences exist between these agents in terms of risk of major thrombotic events. Clinicians are cautioned against relying on meta-analyses that involve an incomplete set of trials, contain small numbers of events, and focus only on short-term follow-up when assessing the relative risks of various agents.⁴² Naproxen appears to be the preferred choice. Although the ADAPT study, which investigated prevention of development of Alzheimer’s disease with either naproxen or celecoxib compared with placebo, raised concerns about the safety of naproxen, the trial had major limitations.^{43,44} These include a very high rate of patients lost to follow-up (almost 10%), a large number of enrollees who did not receive their study medication, a lack of specified criteria for the cardiovascular events, and no central adjudication of the reported nonfatal events. The small number of reported cardiovascular deaths, myocardial infarctions, and strokes in the naproxen and placebo groups in ADAPT do not materially alter the relative risk and 95% CI for naproxen shown in the Table. As noted in Figure 7, if symptoms are not adequately controlled by a nonselective NSAID, subsequent steps involve prescription of drugs with increasing degrees of COX-2-inhibitory activity, ultimately concluding with the COX-2-selective NSAIDs.

Second, What Patient Characteristics Should Be Considered?

Patients with a history of or risk for GI bleeding, especially in relation to aspirin or other nonspecific NSAID use, might be given acetaminophen initially. Alternatively, proton-pump inhibitors may diminish the risk of recurrent GI bleeding in subjects who require low-dose aspirin.^{45,46} If these alterna-

tives are not possible, it may be reasonable to consider a COX-2 inhibitor if the potential benefits of treatment are believed to outweigh the potential cardiovascular risks. Patients who are tolerant of nonspecific NSAIDs but find them insufficient could also consider a COX-2 inhibitor.

Patients with or at risk for active atherosclerotic processes, including those with recent bypass surgery, unstable angina or myocardial infarction, or ischemic cerebrovascular events, have greater increases in absolute risk for adverse cardiovascular effects when given a COX inhibitor. (It is difficult to provide precise estimates of the absolute increase in risk because the excess number of events is related to such factors as the underlying risk of the patient, the relative risk of the drug, and the duration of follow-up.¹¹) The authors of one large report estimated that in patients with a prior myocardial infarction, the excess risk of mortality is ≈ 6 deaths per 100 person-years of treatment with a COX-2 inhibitor compared with no NSAID treatment.⁴ In these patients, prudence dictates extra caution in the use of COX-2 inhibitors, which should include the use of only the recommended doses and for the shortest period of time required to control symptoms. Every effort should be made to assess and treat modifiable risk factors before and during NSAID treatment. COX inhibitors can lead to impaired renal perfusion, sodium retention, and increases in blood pressure, which may contribute to their adverse cardiovascular effects.²² Renal function and blood pressure should be monitored in subjects taking COX-2 inhibitors. This is especially true when these drugs are given to subjects with preexisting hypertension, renal disease, and heart failure (Figure 7).⁴⁷

Third, if You Use a COX-2 Inhibitor, Does Selectivity Matter?

The available data have implicated several COX-2 inhibitors with varying degrees of selectivity. As suggested by the data summarized in the Table, Figure 1, and Figure 6, even a relative lack of COX-2 selectivity does not completely eliminate the risk of cardiovascular events, and in that regard, all drugs in the NSAID spectrum should only be prescribed after thorough consideration of the risk/benefit balance. Additional data bearing on this issue will be provided in the ongoing PRECISION trial (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen; <http://www.clinicaltrials.gov>, No. NCT00346216), which is randomizing patients with rheumatoid arthritis or osteoarthritis to celecoxib, ibuprofen, or naproxen, the latter being 2 NSAIDs that are further toward the non-COX-2 end of the spectrum (Figure 6).

Fourth, Can Patients Using Aspirin for Cardioprotection Also Use NSAIDs or Selective COX-2 Inhibitors for Pain Relief?

Evidence indicates that ibuprofen, but not rofecoxib (a COX-2 inhibitor), acetaminophen, or diclofenac,⁴⁸ interferes

with aspirin's ability to irreversibly acetylate the platelet COX-1 enzyme, and it would be expected, although it has not been proved, that this would reduce the protective effect of aspirin on risk for atherothrombotic events. Per an FDA advisory⁴⁹:

Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400 mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion to avoid any potential interaction. . . . Recommendations about concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based on available data. One study showed that the antiplatelet effect of enteric-coated low dose aspirin is attenuated when ibuprofen 400 mg is dosed 2, 7, and 12 hours after aspirin.

Of note, the combination of aspirin (necessary for protection against cardiovascular events) and a coxib may ameliorate the gastric mucosal protective effect of COX-2 inhibition. The combination of the two may also prolong the time for recovery from gastric mucosal injury.

Summary

Current evidence indicates that selective COX-2 inhibitors have important adverse cardiovascular effects that include increased risk for myocardial infarction, stroke, heart failure, and hypertension. The risk for these adverse effects is likely greatest in patients with a prior history of or at high risk for cardiovascular disease. In these patients, use of COX-2 inhibitors for pain relief should be limited to patients for whom there are no appropriate alternatives, and then, only in the lowest dose and for the shortest duration necessary. More long-term data are needed to fully evaluate the extent to which these important adverse cardiovascular effects may be offset by other beneficial effects of these medications. More data are also needed on the cardiovascular safety of conventional NSAIDs. Until such data are available, the use of any COX inhibitor, including over-the-counter NSAIDs, for long periods of time should only be considered in consultation with a physician.

The debate about the increased risk of cardiovascular events attributed to the selective COX-2 inhibitors and the nonselective NSAIDs is part of a broader national debate about drug safety.⁵⁰⁻⁵⁴ Optimal safety evaluation of drugs requires timely and complete submission of scientific data from the manufacturers, as well as increased funding and authority granted to the FDA by Congress.

Acknowledgments

The authors thank Matthew Liang, MD, Department of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, Mass, for his helpful comments on this paper.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

References

- Bennett JS, Daugherty A, Herrington D, Greenland P, Roberts H, Taubert KA. The use of nonsteroidal anti-inflammatory drugs (NSAIDs): a science advisory from the American Heart Association [published correction appears in *Circulation*. 2005;111:1717]. *Circulation*. 2005;111:1713–1716.
- Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332:1302–1308.
- McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296:1633–1644.
- Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, Schramm TK, Abildstrom SZ, Kober L, Madsen M, Torp-Pedersen C. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation*. 2006;113:2906–2913.
- Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from Vioxx? *BMJ*. 2007;334:120–123.
- US Food and Drug Administration Web site. Public health advisory: non-steroidal anti-inflammatory drug products (NSAIDs). December 23, 2004. Available at: <http://www.fda.gov/cder/drug/advisory/nsaids.htm>. Accessed February 4, 2005.
- US Food and Drug Administration Web site. Summary minutes for the joint meeting of the arthritis advisory committee and the drug safety risk management advisory committee. Available at: <http://www.fda.gov/ohrms/dockets/ac/cder05.html#ArthritisDrugs>. Accessed January 29, 2007.
- US Food and Drug Administration Web site. Analysis and recommendations for agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk. April 6, 2005. Available at: <http://www.fda.gov/cder/drug/infopage/cox2/NSAIDdecisionMemo.pdf>. Accessed January 29, 2007.
- European Medicines Agency concludes action on COX-2 inhibitors [press release]. London, UK: European Medicines Agency; June 27, 2005.
- European Medicines Agency press release on the cardiovascular safety of non-selective NSAIDs [press release]. London, UK: European Medicines Agency; August 2, 2005.
- Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation*. 2005;112:759–770.
- Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest*. 2006;116:4–15.
- Mukherjee D. Does a coxib-associated thrombotic risk limit the clinical use of the compounds as analgesic anti-inflammatory drugs? Arguments in favor. *Thromb Haemost*. 2006;96:407–412.
- Topper JN, Cai J, Falb D, Gimbrone MA Jr. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. *Proc Natl Acad Sci U S A*. 1996;93:10417–10422.
- Timmers L, Sluijter JPG, Verlaan CWJ, Steendijk P, Cramer MJ, Emons M, Strijder C, Grundeman PF, Sze SK, Hua L, Piek JJ, Borst C, Pasterkamp G, de Kleijn DP. Cyclooxygenase (COX)-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig. *Circulation*. 2007;115:326–332.
- Jugdutt BI. Cyclooxygenase inhibition and adverse remodeling during healing after myocardial infarction. *Circulation*. 2007;115:288–291.
- Bunting S, Gryglewski R, Moncada S, Vane JR. Arterial walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and coeliac arteries and inhibits platelet aggregation. *Prostaglandins*. 1976;12:897–913.
- FitzGerald GA, Smith B, Pedersen AK, Brash AR. Increased prostacyclin biosynthesis in patients with severe atherosclerosis and platelet activation. *N Engl J Med*. 1984;310:1065–1068.
- Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med*. 2004;351:1709–1711.
- Topol EJ. Failing the public health: rofecoxib, Merck, and the FDA. *N Engl J Med*. 2004;351:1707–1709.
- Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanasa A, Konstam MA, Baron JA; Adenomatous Polyp Prevention on Vioxx (APPROVE) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial [published correction appears in *N Engl J Med*. 2006;355:221]. *N Engl J Med*. 2005;352:1092–1102.
- Solomon SD, Pfeffer MA, McMurray JJ, Fowler R, Finn P, Levin B, Eagle C, Hawk E, Lechuga M, Zauber AG, Bertagnoli MM, Arber N, Wittes J; APC and PreSAP Investigators. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation*. 2006;114:1028–1035.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies [published correction appears in *Lancet*. 2003;361:1060]. *Lancet*. 2002;360:1903–1913.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
- Furberg CD. The COX-2 inhibitors: an update. *Am Heart J*. 2006;152:197–199.
- Garcia Rodriguez LA, Patrignani P. The ever growing story of cyclooxygenase inhibition. *Lancet*. 2006;368:1745–1747.
- Cannon CP, Curtis SP, Bolognese JA, Laine L; MEDAL Steering Committee. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study program:

- cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. *Am Heart J*. 2006;152:237–245.
28. Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB J*. 2004;18:790–804.
 29. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L; MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet*. 2006;368:1771–1781.
 30. Graham DJ. COX-2 inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense. *JAMA*. 2006;296:1653–1656.
 31. Psaty BM, Weiss NS. NSAID trials and the choice of comparators: questions of public health importance. *N Engl J Med*. 2007;356:328–330.
 32. Zarraga IG, Schwarz ER. Coxibs and heart disease: what we have learned and what else we need to know. *J Am Coll Cardiol*. 2007;49:1–14.
 33. Burleigh ME, Babaev VR, Oates JA, Harris RC, Gautam S, Riendeau D, Marnett LJ, Morrow JD, Fazio S, Linton MF. Cyclooxygenase-2 promotes early atherosclerotic lesion formation in LDL receptor-deficient mice. *Circulation*. 2002;105:1816–1823.
 34. Rott D, Zhu J, Burnett MS, Zhou YF, Zalles-Ganley A, Ogunmakina W, Epstein SE. Effects of MF-tricyclic, a selective cyclooxygenase-2 inhibitor, on atherosclerosis progression and susceptibility to cytomegalovirus replication in apolipoprotein-E knockout mice. *J Am Coll Cardiol*. 2003;41:1812–1819.
 35. Pratico D, Tillmann C, Zhang ZB, Li H, FitzGerald GA. Acceleration of atherogenesis by COX-1–dependent prostanoid formation in low density lipoprotein receptor knockout mice. *Proc Natl Acad Sci U S A*. 2001;98:3358–3363.
 36. Belton OA, Duffy A, Toomey S, Fitzgerald DJ. Cyclooxygenase isoforms and platelet vessel wall interactions in the apolipoprotein E knockout mouse model of atherosclerosis. *Circulation*. 2003;108:3017–3023.
 37. Olesen M, Kwong E, Meztili A, Kontny F, Seljeflot I, Arnesen H, Lyngdorf L, Falk E. No effect of cyclooxygenase inhibition on plaque size in atherosclerosis-prone mice. *Scand Cardiovasc J*. 2002;36:362–367.
 38. Bea F, Blessing E, Bennett BJ, Kuo CC, Campbell LA, Kreuzer J, Rosenfeld ME. Chronic inhibition of cyclooxygenase-2 does not alter plaque composition in a mouse model of advanced unstable atherosclerosis. *Cardiovasc Res*. 2003;60:198–204.
 39. Egan KM, Wang M, Fries S, Lucitt MB, Zukas AM, Pure E, Lawson JA, FitzGerald GA. Cyclooxygenases, thromboxane, and atherosclerosis: plaque destabilization by cyclooxygenase-2 inhibition combined with thromboxane receptor antagonism [published correction appears in *Circulation*. 2005;111:2412]. *Circulation*. 2005;111:334–342.
 40. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis Rheum*. 1996;39:1–8.
 41. Griffin MR, Brandt KD, Liang MH, Pincus T, Ray WA. Practical management of osteoarthritis: integration of pharmacologic and nonpharmacologic measures. *Arch Fam Med*. 1995;4:1049–1055.
 42. White WB, West CR, Borer JS, Gorelick PB, Lavange L, Pan SX, Weiner E, Verburg KM. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol*. 2007;99:91–98.
 43. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS Clin Trials*. 2006;1:e33.
 44. Nissen SE. ADAPT: the wrong way to stop a clinical trial. *PLoS Clin Trials*. 2006;1:e35.
 45. Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, Lau JY, Hui Y, Lai MS, Chan HL, Sung JJ. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med*. 2001;344:967–973.
 46. Lai KC, Lam SK, Chu KM, Wong BC, Hui WM, Hu WH, Lau GK, Wong WM, Yuen MF, Chan AO, Lai CL, Wong J. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med*. 2002;346:2033–2038.
 47. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA*. 2006;296:1619–1632.
 48. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345:1809–1817.
 49. US Food and Drug Administration Web site. Food and Drug Administration Science Paper. *Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin*. Available at: http://www.fda.gov/cder/drug/infopage/ibuprofen/science_paper.htm. Accessed January 29, 2007.
 50. *Drug Safety: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*. Washington, DC: Government Accountability Office; 2006. Report No. GAO-06-402.
 51. Committee on the Assessment of the US Drug Safety System; Baciu A, Stratton K, Burke SP, eds. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Washington, DC: National Academies Press; 2006. Available at: <http://www.iom.edu/CMS/3793/26341/37329.aspx>. Accessed October 30, 2006.
 52. Furberg CD, Levin AA, Gross PA, Shapiro RS, Strom BL. The FDA and drug safety: a proposal for sweeping changes. *Arch Intern Med*. 2006;166:1938–1942.
 53. Psaty BM, Burke SP. Protecting the health of the public: Institute of Medicine recommendations on drug safety. *N Engl J Med*. 2006;355:1753–1755.
 54. US Food and Drug Administration. The future of drug safety: promoting and protecting the health of the public: FDA's response to the Institute of Medicine's 2006 report. Available at: <http://www.fda.gov/oc/reports/iom013007.pdf>. Accessed February 1, 2007.

KEY WORDS: AHA Scientific Statements ■ aspirin ■ inhibitors ■ drugs ■ antiinflammatory agents, nonsteroidal ■ coxibs ■ cyclooxygenase 2 inhibitors