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The Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) A Science Advisory From the American Heart Association

Joel S. Bennett, MD; Alan Daugherty, PhD; David Herrington, MD, MHS; Philip Greenland, MD;
Harold Roberts, MD; Kathryn A. Taubert, PhD

Recent clinical trial data have raised 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. In September 2004, Merck announced a voluntary worldwide withdrawal of Vioxx (rofecoxib) because of an increased risk of heart attack and stroke. In early December 2004, the US Food and Drug Administration (FDA) announced a “black box” warning for Bextra (valdecoxib), stating that its use in patients undergoing coronary artery bypass grafting is contraindicated. A week later, the National Institutes of Health suspended the use of Celebrex (celecoxib) in the APC (Adenoma Prevention with Celecoxib) clinical trial because of increased cardiovascular events. The drug was not removed from the market, but the FDA advised physicians to consider alternate therapy or to use the smallest effective dose of Celebrex. Three days later, the National Institutes of Health announced that the ADAPT (Alzheimer’s Disease Anti-inflammatory Prevention Trial) 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 concerning the use of the nonsteroidal anti-inflammatory drug products (NSAIDs) Vioxx, Bextra, Celebrex, and naproxen.¹ Quoting 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 non-selective NSAIDs, or are not doing well on non-selective 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.”

We support these recommendations and here provide a brief scientific background for them. We also expand on the relevance of these recommendations to patients with or at risk for cardiovascular disease.

The primary property of this class of drugs is the inhibition of cyclooxygenase (COX). COX enzymes have 2 major classes. COX-1 is broadly considered to be expressed constitutively (constantly) in most tissues, whereas COX-2 is induced in inflammation. Both COX-1 and -2 enzymes use arachidonic acid to generate the same product, prostaglandin H₂ (PGH₂). A number of enzymes further modify this product to generate bioactive lipids (prostanoids), including prostacyclin, thromboxane A₂, and prostaglandins D₂, E₂, and F₂, which influence immune, cardiovascular, GI, renovascular, pulmonary, central nervous system, and reproductive function. The COX-2 inhibitors vary in their selectivity for the COX-2 versus the COX-1 enzyme (for medications currently or formerly on the market in the US, rofecoxib > valdecoxib > parecoxib > celecoxib). Other COX-2 inhibitors are under development and may be introduced onto 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 enzymes that convert prostaglandin H₂ into specific prostanoids. For example, several prostanoids, including prostaglandin E₂ and prostacyclin, are both hyperalgesic (ie, 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,

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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.^{2,3} In addition to producing local smooth muscle cell relaxation and vasodilation, prostacyclin can also interact with platelet IP receptors, thereby antagonizing aggregation. Platelets contain only COX-1, which converts arachidonic acid to the potent proaggregatory, vasoconstrictive eicosanoid thromboxane A₂ (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, but leave the platelet production of TXA₂ intact. It has been speculated that this imbalance of hemostatic prostanoids may increase the risk for cardiovascular events.^{4,5} COX-2 inhibitors, like NSAIDs, also raise blood pressure slightly, and in one study the incidence of heart failure was significantly increased compared with placebo.⁶ Prostacyclin may also retard the pathogenesis of atherosclerosis,⁴ and inhibition of prostacyclin with a COX-2 inhibitor has been predicted to promote lesion formation⁴; however, results in different mouse models of atherosclerosis have been contradictory.^{7–13}

In mid-February 2005, the FDA conducted an extensive review of all of the data concerning the cardiovascular risks of selective and nonselective COX inhibitors. It is anticipated that more information and guidance are forthcoming as a result of this meeting. In the meantime, practical guidance is needed by patients (and their physicians) who are making decisions about the use of these drugs for pain relief, especially if the patients are also at high risk for cardiovascular events. The importance of these issues for patients with or at risk for cardiovascular or cerebrovascular disease cannot be overstated because it is in these patients that the absolute risks are likely the greatest.

From the patient's—and the physician's—perspective, the decision turns on balancing the risks and benefits of medications for pain relief. Of course, risks and benefits are not unique to these medications, but their use highlights the issues to be considered. The following lists several issues that should be considered when treatment decisions are made concerning pain medications in patients with or at high risk for cardiovascular disease.

What Is the Risk/Benefit Ratio?

When a choice is being made about medication, both safety and efficacy should be considered. In general, the least risky medication should be tried first, with escalation considered only if this medication is ineffective. In practice, this usually means starting with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term needs. The poten-

tial for abuse notwithstanding, a role remains for narcotic medications for short-term pain relief as well. 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.

For 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 amounts of alcohol. When acetaminophen, aspirin, and perhaps even narcotic medications (for acute pain) are not effective, tolerated, or appropriate, it may then be reasonable to consider more selective COX-2 inhibition; 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. Recently published results of three randomized, placebo-controlled clinical trials, although not primarily designed to evaluate the effects of COX-2 inhibitors on cardiovascular outcomes, provide some estimates of absolute risk associated with COX-2 inhibitor use in various populations. The APC trial included patients with a history of colorectal neoplasia who were given two different doses of celecoxib or placebo. There was a 1% composite cardiovascular end point of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or nonfatal heart failure in the placebo group, compared with a 2.3% composite cardiovascular end point in patients receiving a total dose of 400 mg per day celecoxib and a 3.4% composite cardiovascular end point in those taking 800 mg celecoxib per day.¹⁴ The APPROVe trial included patients with a history of colorectal adenomas who received long-term rofecoxib or placebo. An increased risk of thrombotic events was observed in the treatment group after 18 months of treatment (0.78 events/100 patient-years versus 1.5 events/100 patient-years in the rofecoxib group).⁶ Finally, a study in post-CABG patients compared valdecoxib/parecoxib with placebo and found that cardiovascular events were more frequent in the treatment group (2.0% versus 0.5% for the placebo group).¹⁵

What Patient Characteristics Should Be Considered?

Patients with a history or risk of GI bleeding, especially in relationship to aspirin or other nonspecific NSAID use, may be given acetaminophen initially. Alternatively, proton-pump inhibitors may diminish the risk of recurrent GI bleeding in subjects who require low-dose aspirin.^{16,17} If these alternatives are not possible, then it may be reasonable to consider a COX-2 inhibitor, if the potential benefits of treatment are felt to outweigh the potential cardiovascular risks. Patients who can tolerate nonspecific NSAIDs but find them insufficient also could 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, may have greater increases in absolute risk for adverse cardiovascular effects

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Joel S. Bennett	University of Pennsylvania	None	None	None	None	None	None
Alan Daugherty	University of Kentucky	None	None	None	None	None	None
David Herrington	Wake Forest University	None	None	None	None	Merck*	None
Philip Greenland	Northwestern University	None	None	None	None	None	None
Harold Roberts	University of North Carolina	None	None	None	None	None	None
Kathryn A. Taubert	American Heart Association	None	None	None	None	None	None

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. A relationship is considered to be "significant" if (1) the person receives \geq \$10 000 during any 12-mo period or \geq 5% of the person's annual gross income, or (2) the person owns \geq 5% of the voting stock or share of the entity or owns \geq \$10 000 of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

when given a COX inhibitor. In these patients, prudence dictates extra caution in the use of COX-2 inhibitors, which should include recommended doses only. 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. The extent to which these effects may contribute to adverse cardiovascular effects of COX-2 is unclear. However, renal function and blood pressure should be monitored in subjects taking COX-2 inhibitors and extra caution should be taken when giving these drugs to subjects with preexisting hypertension, renal disease, and heart failure.

Does Selectivity Matter to Patients Who Use a COX-2 Inhibitor?

In theory, the relative degree of COX-1 versus COX-2 inhibition may alter the adverse cardiovascular effect profile of the COX inhibitors, with valdecoxib being the most COX-2 selective of the available agents; however, the available data have implicated several COX-2 inhibitors with varying degrees of COX-2 selectivity. Thus, until more data are available, it is not entirely clear how much weight should be placed on COX-2 selectivity.

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

There is evidence that ibuprofen, but not the COX-2 inhibitor rofecoxib, acetaminophen, or diclofenac,¹⁸ interferes with the ability of aspirin to irreversibly acetylate the platelet COX-1 enzyme, and it would be expected, although it has not been proven, that this would reduce the protective effect of aspirin on risk for atherothrombotic events.

Summary

Current evidence indicates that selective COX-2 inhibitors have important adverse cardiovascular effects including increased risk for myocardial infarction, stroke, heart failure,

and hypertension. The risk for these adverse effects are 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 concerning 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.

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KEY WORDS: AHA Science Advisory ■ anti-inflammatory agents, nonsteroidal ■ cyclooxygenase inhibitors ■ risk factors ■ aspirin

Corrections

In the article by Leon et al, “Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease: An American Heart Association Scientific Statement From the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in Collaboration With the American Association of Cardiovascular and Pulmonary Rehabilitation,” which appeared in the January 25, 2005, issue of the journal (*Circulation*. 2005;111:369–376), an error appears on page 372. In the paragraph that begins, “Furthermore, in the presence of advanced CAD. . .,” the last sentence of the paragraph should read, “Aerobic exercise training also may decrease the risk of sudden cardiac death due to ventricular tachyarrhythmias by reducing sympathetic and enhancing parasympathetic (vagal) activity, as evidenced by increased heart rate variability and increased baroreceptor sensitivity.^{69–71}”

The corrected version of this article is available online at <http://circ.ahajournals.org/cgi/content/full/111/3/369>. (The previous version, if needed, can be accessed by selecting the “Previous Version of This Article” link.)

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In the article by Lu et al, “Water Ingestion as Prophylaxis Against Syncope,” which appeared in the November 25, 2003, issue of the journal (*Circulation*. 2003;108:2660–2665), Figure 4 was not the correct figure; a duplicate of Figure 5 was inadvertently placed above the Figure 4 legend. The correct Figure 4 appears below. Its legend was correct as originally printed. We regret this error.

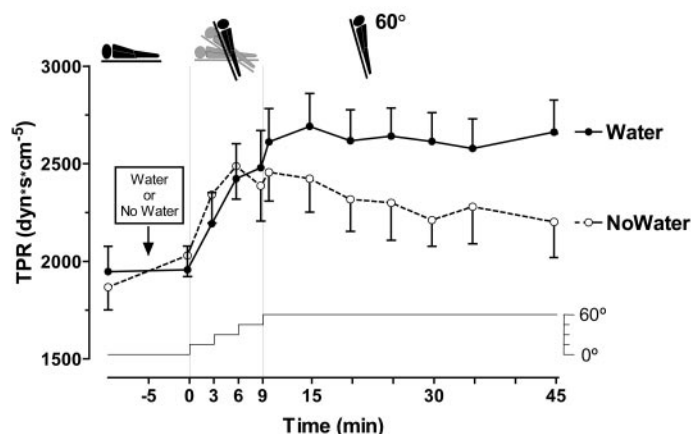


Figure 4. Total peripheral resistance (TPR) during head-up tilt. Water ingestion accentuated the increasing TPR during tilt-table testing. $P < 0.001$.

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In the March 21, 2005, online posting of the article by Bennett et al, “The Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): A Science Advisory From the American Heart Association” (*Circulation*. 2005;111:1713–1716; DOI: 10.1161/01.CIR.0000160005.90598.41), the discussion of the Adenoma Prevention with Celecoxib (APC) trial contained some unclear text about the results of the trial. The printed version as it appears in this issue has been changed to improve clarity, as has the online version.

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In the article by Urbich et al, "Relevance of Monocytic Features for Neovascularization Capacity of Circulating Endothelial Progenitor Cells," which appeared in the November 18, 2003, issue of the journal (*Circulation*. 2003;108:2511–2516), the authors have identified incorrect representative laser Doppler images in Figure 4. The representative images were inadvertently mixed up during electronic compilation of the original laser Doppler recordings for composition of the representative figure. The quantitative data shown in the analysis are not affected because quantitative analysis was performed using the original recordings. The corrected images for Figure 4A and 4B appear below. The authors regret this error.

