O

ver the past several months clinicians have been confronted at an escalating rate with reports describing the risks of COX-2 inhibitors (coxibs). Information on this class of drugs appears not only in traditional medical journals and textbooks, but also on the Web sites of regulatory agencies, professional societies, and pharmaceutical manufacturers. An unusual, but noteworthy, aspect of the state of affairs is the high rate of reporting new findings and opinions (at times voiced in a strident tone) in the lay press.

Understandably, patients are concerned about the potential risks associated with their antiinflammatory medications, and now, either spontaneously or in response to a public health warning, call their healthcare professional with questions or arrive for an office visit armed with publicly accessed information they wish to discuss.

Owing to the widespread use of antiinflammatory drugs and the fact that the reported risks are cardiovascular in nature, we offer the readers of Circulation this special article. Our goals are to provide an overview of the relevant biology and pharmacology, to synthesize the data on the cardiovascular risks associated with antiinflammatory medications, to offer suggestions on strategies for prescribing these medications, and to make observations on the regulatory and research implications of the data and their interpretation.

**Biography of Eicosanoids**

Eicosanoids are oxidized derivatives of the polyunsaturated long-chain fatty acids, arachidonic acid and eicosapentaenoic acid, that serve many roles in cardiovascular biology and disease. Eicosanoid biosynthesis can be initiated by release of arachidonic acid from membrane phospholipids by lipases (predominantly of the phospholipase A2 type) (Figure 1). Once mobilized, arachidonic acid is oxygenated into eicosanoids along the following 4 pathways: (1) prostaglandin (PG) endoperoxide synthase (cyclooxygenase [COX]), (2) lipoxygenase (LO), (3) P450 epoxygenase, and (4) (nonenzymatic) isoprostane synthesis. Details of the pharmacology of products of the LO, epoxygenase, and isoprostane pathways, as well as the lipoxins, are reviewed elsewhere.

Here, we focus on products of the COX pathway. These derivatives of arachidonic acid are collectively referred to as prostanooids and comprise the PGs and thromboxanes. COX, a key enzyme in eicosanoid metabolism, converts arachidonic acid liberated from membrane phospholipids into PGH2.

The fate of PGH2 and the distribution of prostanoids formed from it depend on the cell type in which it is synthesized and the tissue-specific isomerases found within that cell. For example, leukocytes, vascular smooth muscle cells, endothelial cells, and platelets express PGE synthase and, as a result, are all capable of generating the inflammatory prostanoid PGE2; platelets express thromboxane synthase and elaborate the prothrombotic, vasoconstrictor prostanoid thromboxane A2; and endothelial cells express PGI synthase and synthesize the antithrombotic, vasodilator prostaglandin PGI2 or prostacyclin. In addition to cell-specific synthesis, the biological effects of prostanoids are governed by cell-specific receptor-dependent signaling pathways (the receptors DP, EP, FP, IP, and TP for PGD2, PGE2, PGF2alpha, PGI2, and TXA2, respectively) that define biological responses. Importantly, prostanoid intermediates can also undergo transcellular metabolism (ie, PGH2 can be produced in a platelet and then taken up by a leukocyte in which it is converted to PGE2).

**Pharmacology and Molecular Biology of Inhibition of Prostanoid Synthesis**

The pharmacological inhibition of prostanoid synthesis has been the focus of drug development for >100 years. From aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) that inhibit COX, the field evolved rapidly in the 1980s to yield a wide range of agents with varying antiinflammatory and analgesic potencies and varying pharmacodynamics. These NSAIDs comprise a class of agents with heterogeneous structures (Figure 2). As a therapeutic class, they provide antipyretic, analgesic, and inflammatory activities, but the relative degree of these effects varies markedly among the compounds (eg, acetaminophen has antipyretic and analgesic effects but little antiinflammatory activity). In addition, as a therapeutic class, the NSAIDs share the common side effects of gastrointestinal ulceration, inhibition of uterine motility, inhibition of PG-mediated renal function, and hypersensitivity reactions. The relative frequencies of these side effects, however, vary markedly among the members of the class.
With the recognition that aspirin inhibits platelet function, the antithrombotic effect of these agents gained unique therapeutic emphasis and, of course, has proved to be a most important treatment strategy in atherothrombotic disease. Because the endothelial prostanoid prostacyclin has anti-thrombotic action while the platelet prostanoid thromboxane A2 has prothrombotic action, investigators realized in the 1970s that nonselective inhibition of COX pools in these 2 cell types could theoretically result in an attenuation of the antithrombotic effect of inhibition of platelet COX. At that time, investigators defined doses and conditions under which the suppression of thromboxane A2 synthesis by aspirin predominates over the suppression of prostacyclin synthesis; as a result of the irreversible inhibition (via acetylation) of COX by aspirin and the difference in half-lives of inhibited platelet and endothelial COX, low-dose aspirin was found to provide sufficient antithrombotic selectivity for primary and secondary prevention of atherothrombotic events.

In the early 1990s, a new wrinkle in the complex molecular events governing vascular prostanoid synthesis arose with the identification of 2 members of the COX family. COX-1 is constitutively expressed in many cells and is the only isozyme expressed in platelets; COX-2 is induced by inflammatory cytokines in many cell types (Table 1 and Figure 3). This distinction developed in the face of concern about the hemorrhagic risk of nonselective COX inhibition, especially gastrointestinal bleeding. The recognition that there are 2 different COXs led to the straightforward view that COX-2 is responsible for the adverse proinflammatory effects of prostanoids and that nonspecific COX inhibitors cause bleeding by inhibiting COX-1 in platelets. This working paradigm led the pharmaceutical industry to develop COX-2–selective inhibitors, the coxibs, arguing that these agents would provide adequate analgesia and antiinflammatory effects without hemorrhagic risk. The incidence of gastropathy accompanying the use of nonselective NSAIDs was felt to be of sufficient magnitude to warrant the development of coxibs; according to one meta-analysis, approximately one-third of patients taking NSAIDs had gastric or duodenal ulcers by endoscopy, but the risk of serious gastrointestinal bleeding is much lower, with 107 000 patients hospitalized each year for gastrointestinal complications of NSAID use. Despite their development to provide a therapeutic option for patients at risk of gastrointestinal bleeding, survey reports suggest that coxibs are prescribed with approximately equal frequency to patients who are at low or high risk of gastrointestinal bleeding.

Unfortunately, this clean mechanistic distinction between the COXs is an oversimplification. As a class, the NSAIDs have a broad range of relative COX-1 and COX-2 selectivity (Figure 2). Furthermore, COX-2 is expressed in normal endothelial cells in response to shear stress, and inhibition of COX-2 is associated with significant suppression of prostacyclin synthesis in human subjects (Figure 4). Both COX-1 and COX-2 are detectable in human atherosclerotic lesions; however, the specific effect of COX inhibition on lesion progression is currently controversial. Low-dose aspirin and selective COX-2 inhibitors have been shown to improve or worsen endothelial dysfunction in hypercholesterolemia and hypertension. COX-2 may also play a role in destabilizing plaques as suggested by its increased expression and colocalization with microsomal PGE synthase-1 and metalloproteinases-2 and -9 in carotid plaques from individuals with symptomatic disease before endarterectomy. Studies in hypercholesterolemic mice have also been inconsistent, with reports showing that COX-2 inhibitors worsen, retard, or fail to affect the course of atherosclerosis, and evidence exists to support the view that COX-2–derived prostacyclin is atheroprotective, but only in female mice. Possible explanations for these divergent outcomes include differences among the methods of suppressing COX-2 activity, the timing of administration of the inhibitor, and the
genetic backgrounds of the animals studied. In addition, COX-2–derived prostanoid products have divergent effects on the molecular and cellular mechanisms underlying disease pathogenesis. For example, through its interaction with the E-prostanoid receptor EP4 on macrophages, COX-2–derived PGE_2 suppresses chemokine production, whereas TP antagonism retards atherogenesis. Moreover, COX-2 is differentially expressed among cell types in the plaque, as are the predominant prostanoids derived from those cells.

Inhibition of COX-2 also has as a theoretical side effect an increase in the flux of arachidonate through the LO pathways, which may be especially important in the setting of inflammation in the atheromatous plaque. The 12-, 15-, and 5-LOs all have key roles in inflammation, and the role of each in atherosclerosis has been examined. Although 12-LO and 15-LO appear to contribute to LDL oxidation, the data supporting the proatherogenic role of these enzymes are inconsistent. Data suggest that 15-LO products may be antiinflammatory. Furthermore, work from Serhan’s group shows that acetylation of COX-2 by low-dose aspirin leads to its biosynthesis of 15R-hydroxyeicosatetraenoic acid. This intermediate is then converted by transcellular metabolism to the antiinflammatory lipoxin 15-epi-lipoxin A₄ in leukocytes.

Mehrabian and colleagues have demonstrated convincingly that 5-LO is a critical determinant of atherogenesis in mouse models of the disease, even in the setting of profound hypercholesterolemia. The inflammatory eicosanoids derived from increased 5-LO expression in plaque–leukotriene B₄ and the cysteinyl-leukotrienes–are active in the atherothrombotic vasculature, having been shown to promote inflammatory cell activation, cell proliferation, and vasoconstriction. In human subjects, Dwyer and colleagues showed that variant 5-LO genotypes–tandem promoter repeats of Sp-1 binding motifs–identify a subpopulation of individuals with increased atherosclerosis (determined as carotid intima-media thickness). Helgadottir and colleagues showed that a promoter haplotype comprising 4 linked polymorphisms in the 5-LO activating peptide (an accessory protein that facilitates presenta-
tion of substrate arachidonate to 5-LO) confers an approximately 2-fold increased risk of myocardial infarction (MI) and stroke in an Icelandic population. Thus, the potential importance of shifting the flux of arachidonate through the LO pathway by inhibiting COX activity bears consideration as we attempt to dissect the vascular consequences of coxib use.

To appreciate the complexity of interactions among the small-molecule vascular mediators in the system, we also need to consider nitric oxide (NO) and superoxide anion. NO activates prostacyclin synthase and suppresses thromboxane synthase, likely by nitrosylating bound heme. In addition, NO potentiates the vascular effects of prostacyclin, likely via the cGMP-dependent inhibition of cAMP phosphodiesterase. This potentiation of prostacyclin by NO has also been demonstrated to account for the synergistic inhibition of platelets by these vascular effectors. Niwano and colleagues have shown that a stable prostacyclin analogue (beraprost) increases endothelial NO synthase (eNOS) expression by activating a cAMP-dependent transcriptional element in the eNOS promoter. In the setting of an inflammatory stimulus that induces expression of inducible NO synthase (iNOS) and a source of superoxide [such as NAD(P)H oxidase], peroxynitrite generation ensues and leads to 3-nitration of tyrosine 430 in prostacyclin synthase, inactivating the enzyme, and activation of the TxA2 receptor TP. In turn, induces gp91phox expression and NAD(P)H oxidase–dependent superoxide generation, increasing oxidant stress in the inflamed vasculature. NO derived from iNOS also increases expression and activity of COX-2. In addition, other inflammatory mediators may modulate these interactions; eg, evidence suggests that C-reactive protein decreases prostacyclin release from endothelial cells.

Consideration of these interactions is essential for understanding the full spectrum of activities of COX-2–dependent eicosanoid synthesis in the context of their interaction with NO. For example, COX-2 not only has been recognized as a key source of prostacyclin under normal laminar flow conditions in the vasculature but also is cardioprotective in ischemia-reperfusion injury and has antiproliferative effects toward vascular smooth muscle cells in conjunction with NO. NO can also inhibit 5-LO, likely by peroxynitrite-dependent S-nitrosation and/or 3-nitrotyrosination. Induction of iNOS by endotoxin leads to inhibition of 5-LO activity without an effect on expression, likely via a peroxynitrite-dependent mechanism.

The interrelationships among COX-2, 5-LO, and NO in the endothelium can best be analyzed when considered under 2 sets of conditions: in the normal state of laminar flow and in an inflammatory state (Figure 5). Under normal conditions, laminar flow induces COX-2 in the endothelial cell to promote the synthesis of prostacyclin, and stimulates elaboration of NO by eNOS. NO derived from eNOS, in turn, stimulates prostacyclin synthase activity and suppresses thromboxane synthase activity; NO also activates guanylyl cyclase to increase cGMP and acts synergistically with prostacyclin to increase cAMP levels in target cells (eg, platelets). Taken together, the net effect of these actions is to impair platelet activation, as summarized in Figure 4 (left) and Figure 5A.

In states of vascular inflammation, COX-2, iNOS, and NAD(P)H oxidase are induced in endothelial cells; these enzymes, together with 5-LO, are also expressed in inflammatory leukocytes. High-flux production of NO (from iNOS) together with superoxide anion (from NAD(P)H oxidase, COXs, LOs, and uncoupled NO synthases, among other sources) leads to the synthesis of peroxynitrite (ONOO−), which inhibits prostacyclin synthase, activates TP-dependent signaling, and promotes additional COX-2 activity. The COX pathways also promote NAD(P)H oxidase activation via TXA2, whereas 5-LO promotes NAD(P)H oxidase activation via leukotriene B4 and the cysteinyl-leukotrienes. Moreover, PGE2, the synthesis of which is enhanced by COX2-derived PGH2 owing to kinetic selectivity and compartmentalization, promotes platelet activation by increasing intraplatelet calcium flux and decreasing AMP via its interaction with the platelet surface EP receptor. For a review of the effects of NO-derived reactive nitrogen species in inflammatory states on COXs, LOs, and peroxidas, see Coffey and colleagues.) Taken together, the net effect of these actions is to promote platelet activation, as summarized in Figure 4 (right) and Figure 5B.

We can use the models shown in Figures 4 and 5 to construct working hypotheses about the use of coxibs in the normal state and in states of vascular inflammation. Central to this model is the balance between prostacyclin (PGI2) and thromboxane A2 in normal and diseased vessels. The use of a coxib under normal (ie, noninflammatory) conditions would be expected to have limited effects on platelet activa-

### Table 1: Comparison of COX-1 and COX-2 Enzymes

<table>
<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome location for gene coding for protein</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Membrane bound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location in cell</td>
<td>Membrane bound</td>
<td>Membrane bound</td>
</tr>
<tr>
<td>Biochemical action</td>
<td>Catalyzes conversion of arachidonic acid liberated from cell membrane to PGG2 and PGH2</td>
<td>Less bulky valine in position 523 allows binding of “selective” drugs to side pocket</td>
</tr>
<tr>
<td>Basis for selectivity of inhibitors (see Figure 3)</td>
<td>Isoleucine (bulky) in position 523 blocks access to side pocket</td>
<td>Induced by inflammatory cytokines but can be expressed in normal endothelial cells exposed to shear stress; role in atherosclerotic plaque development is uncertain</td>
</tr>
<tr>
<td>Cellular expression</td>
<td>Constitutively in many cells</td>
<td>Constitutively in many cells</td>
</tr>
</tbody>
</table>

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762 Circulation August 2, 2005
tion in that NO production by eNOS is relatively unimpaired, and COX-1–dependent generation of prostacyclin would still be maintained. In contrast, the use of a coxib in vascular inflammatory states would lead to a decrease in antithrombotic prostacyclin made by arachidonate flux through COX-2 and would, therefore, make available more arachidonate for leukotriene synthesis. Leukotrienes, especially leukotriene B4 and the cysteinyl-leukotrienes, would increase reactive oxygen species generation by leukocytes, especially superoxide, thereby consuming antithrombotic NO through the synthesis of peroxynitrite. Peroxynitrite, in turn, would further limit prostacyclin synthesis via synthase nitration. Coxibs may also increase reactive oxygen species generation via uncoupling of mitochondrial oxidative phosphorylation. Thus, the net result of coxib action in diseased vessels is an increase in the amount of TxA2 relative to PGI2 (see Figure 4).

In addition to the considerations at the molecular level discussed above, it should be noted that manipulation of the relative balance of COX-1 and COX-2 activity may alter important cardiorenal responses in patients. COX-1 and COX-2 are colocalized in the macula densa. In elderly patients or under conditions of sodium or fluid depletion, selective COX-2 inhibitors cause sodium retention and may result in edema formation. Administration of COX-2 inhibitors has also been associated with a reduction in glomerular filtration rate and exacerbation of hypertension. Increases in blood pressure have been proposed as a mechanism by which COX-2 inhibitors may promote an increased risk of cardiovascular events.

Synthesis of Data on Risk of Cardiovascular Events
The emerging data on the potential for an increased risk of cardiovascular events with coxib use present a disturbing and confusing message for clinicians and patients. The concept of assessing the risk-to-benefit ratio of any medication is familiar to clinicians but is difficult to operationalize for the coxibs. Although the benefits of coxibs (eg, a convenient form of analgesia for arthritic and musculoskeletal discomfort) are more apparent, the risks associated with their use are less clear. Critical questions remain unanswered: What is the magnitude of the increased risk of cardiovascular events with coxib use? Does the risk vary among the coxibs, or is it a true class effect? Is a similar increased risk of cardiovascular events seen with the nonselective NSAIDs?

The evidence base with regard to the risk of cardiovascular events consists of randomized controlled trials (RCTs), new drug application databases submitted to regulatory authorities, and analyses from community- and hospital-based prescription practices. Many of the individual RCT and prescription practice reports can be found in the medical literature, although some are unpublished reports that have been made available on Web sites. Meta-analyses of the available RCT data have also been published. Rather than reiterate the details of previous reports, we offer potential explanations for the nature of the data and present a model that synthesizes the information in a clinically meaningful fashion.

We begin the discussion of the RCT data by a worked example summarizing the cardiovascular risk associated with celecoxib in a clinical trial (APC) for prevention of colorectal adenoma (Figure 6). A total of 2035 patients with a history of colorectal neoplasia were randomized to receive either placebo or 1 of 2 doses of celecoxib (200 or 400 mg twice daily). After 2.8 to 3.1 years of follow-up, an independent Data Safety Monitoring Board concluded that continued exposure to celecoxib placed patients at increased risk for serious cardiovascular events. The APC study was designed for a noncardiovascular purpose–prevention of colorectal adenoma—yet an increased risk of cardiovascular events was identified. The situation surrounding the APC study and
cardiovascular risk is representative of many of the coxib trial data to date.

What kind of observations might have concerned the Data Safety Monitoring Board? Of the 679 patients randomized to placebo, 4 patients (0.6%) either died or sustained a nonfatal MI. In contrast, of the 1356 patients assigned to either of the celecoxib arms, 27 (2.0%) died or had a nonfatal MI. After the data are entered into a 2x2 table, several statistical tests of the treatment effect (harm in this case) of celecoxib can be performed. Regardless of whether one uses a \( \chi^2 \) test (or the equivalent binomial comparison of proportions) or Fisher’s exact test, the difference in event rates in the combined celecoxib group is statistically significantly higher than that in the placebo group (Figure 6).

Another important message is also illustrated by the APC trial findings. The event rates are relatively low compared with those seen in trials enrolling acute coronary syndrome patients in which the death/MI rate may be 10% at 1 year, depending on the level of risk at the time of enrollment. Statements about the relative risk (RR) and odds ratio (OR) convey information about the proportionate increase in risk with celecoxib use versus placebo (3.4-fold increased risk in this example) (Figure 6). (For low event rates, as in this example, the OR approximates the RR.) Such ratios are often the only statistic quoted in the lay press but do not present the full range of clinically relevant information. For example, the absolute risk difference (ARD) in event rates is 1.4%. To interpret the information from the APC trial in the context of
The active comparator naproxen in VIGOR was a confounding factor that made interpretation of the RR associated with rofecoxib more difficult to assess. It was initially argued that naproxen had a protective antithrombotic effect that reduced the event rate (compared with a putative placebo) and led to an apparent increased RR with rofecoxib. However, more compelling data consistent with a true increase in the RR with rofecoxib emerged from reports such as a cumulative meta-analysis of RCTs comparing rofecoxib with placebo, a case-control study of 54,475 Medicare beneficiaries, a case-control study of 8518 patients from a database of 36 hospitals in 5 counties, a retrospective case-control study of 113,927 patients in Quebec’s administrative health databases, and a nested case-control study from the Kaiser Permanente database in California.

Eventually, when the Adenomatous Polyp Prevention on Vioxx trial (APPROVe), comparing rofecoxib 25 mg/d with placebo in patients with a history of colorectal adenomas, reported an excess risk of thrombotic cardiovascular events in the rofecoxib group (RR, 1.92; 95% CI, 1.19 to 3.11; \( P = 0.008 \)), Merck, the manufacturer of rofecoxib, voluntarily withdrew the drug from the market in September, 2004. Between September, 2004, and December, 2004, reports of increased risk of thrombotic cardiovascular events had accumulated not only for rofecoxib and celecoxib but also for the third coxib available in the United States, valdecoxib, to the point that on December 23, 2004, the FDA issued a public health advisory concerning the use of all coxibs. Of additional concern was a report from the NIH on December 20, 2004 about the Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT), which was designed to assess the potential benefit of long-term use of naproxen (220 mg twice daily) or celecoxib (200 mg twice daily) versus placebo in decreasing the risk of developing Alzheimer’s disease in subjects ≥70 years of age. There was an apparent increase (quantitative details not specified) in cardiovascular and cerebrovascular events in the naproxen group compared with placebo in this trial. Thus, while continuing to review the data, the FDA issued an advisory in December, 2004, as an interim measure, sensitizing clinicians and patients to the emerging data on increased risk of thrombotic events not only with coxibs but NSAIDs in general.

In February, 2005, a special 3-day advisory committee meeting was convened by the FDA to provide a forum for full discussion of the issues. The advisory panel recommended that celecoxib and valdecoxib remain on the market but cautioned in patients at risk for vascular disease. Furthermore, more compelling data consistent with a true increase in the RR with rofecoxib emerged from reports such as a cumulative meta-analysis of RCTs comparing rofecoxib with placebo, a case-control study of 54,475 Medicare beneficiaries, a case-control study of 8518 patients from a database of 36 hospitals in 5 counties, a retrospective case-control study of 113,927 patients in Quebec’s administrative health databases, and a nested case-control study from the Kaiser Permanente database in California.

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In February, 2005, a special 3-day advisory committee meeting was convened by the FDA to provide a forum for full discussion of the issues. The advisory panel recommended that celecoxib and valdecoxib remain on the market but advocated that “black box” warnings be added to the label. At the same time, the European Medicines Agency imposed strong warnings on coxibs, recommending that they not be prescribed to patients who have coronary heart disease or who have had a stroke and that they should be used with caution in patients at risk for vascular disease.

Additional information bearing on the issue of cardiovascular risk comes from the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), which compared the most selective coxib, lumiracoxib (see Figure 2), 400 mg once daily with either naproxen 500 mg twice daily or ibuprofen 800 mg 3 times daily for 1 year in 18 000 patients with osteoarthritis. Low-dose aspirin (75 to 100 mg daily)
was permitted in TARGET. There were only 109 cardiovascular or cerebrovascular events reported, of which 59 (0.65%) occurred in the lumiracoxib group and 50 (0.55%) occurred in the NSAID groups (hazard ratio, 1.14; 95% CI, 0.78 to 1.66; \(P=0.51\)). Although these findings might be interpreted as showing that lumiracoxib is as safe as either naproxen or ibuprofen, in the absence of a placebo group, the results are also consistent with the possibility that all 3 drugs are associated with increased risk of events with little difference among them.

The next major event in this rapidly evolving story occurred on April 7, 2005.87 The FDA concluded that the overall risk-to-benefit profile for valdecoxib was unfavorable and that valdecoxib lacked any demonstrable advantage compared with other NSAIDs. The agency requested that Pfizer voluntarily withdraw valdecoxib from the market, which Pfizer agreed to do. While permitting celecoxib to remain on the market, the FDA requested revision to the labeling of celecoxib and 18 other nonselective NSAIDs to highlight the increased risk for cardiovascular events and stated that all NSAID prescriptions must be accompanied by a medication guide to inform patients. In support of this decision by the FDA is a report from a registry experience in Denmark of 10,280 cases of first-time hospitalization for MI and 102,797 controls.88 Current and new users of all classes of non-aspirin NSAIDs had elevated RR estimates for MI.
TABLE 2. Strategies for Use of NSAIDs

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Prescribe NSAIDs preferentially to patients at low risk of thrombotic events (eg, no history of ischemic heart disease or stroke; low-risk-factor profile for vascular disease).</td>
</tr>
<tr>
<td>2.</td>
<td>Initially prescribe drugs with lowest risk of thrombotic events (aspirin, acetaminophen); if symptoms are not adequately controlled, assess risk-to-benefit ratio before moving to drugs with a higher risk of thrombotic events (relative degree of COX-2 selectivity cannot be used to assess comparative risks of drugs).</td>
</tr>
<tr>
<td>3.</td>
<td>Minimize duration of treatment with NSAIDs to decrease period of risk.</td>
</tr>
<tr>
<td>4.</td>
<td>Prescribe lowest dose of NSAID to control symptoms.</td>
</tr>
<tr>
<td>5.</td>
<td>If clinical circumstances necessitate that NSAIDs be prescribed to patients at increased risk of thrombotic events and/or for extended periods, add aspirin 81 mg (enteric coated) in combination. The antithrombotic effects of low-dose aspirin may be helpful but do not necessarily completely neutralize the risks of other NSAIDs. When aspirin is used in combination with another NSAID, consider prescribing a proton pump inhibitor to reduce the risk of gastrointestinal bleeding.</td>
</tr>
<tr>
<td>6.</td>
<td>During the period of treatment with an NSAID, monitor the patient for increases in blood pressure, development of edema, deterioration of renal function, or development of gastrointestinal bleeding.</td>
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Information derived from Bennett et al.11

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How might the seemingly contradictory evidence about the increased risk of cardiovascular events with COX-2 inhibitor use (and NSAID use in general) be explained? Table 7 summarizes the interplay of a variety of factors that influence the ability of investigators to detect a signal of increased risk of cardiovascular events associated with COX-2 inhibition. Certain variables are set by investigators during the design of a clinical trial. These include (1) the definition of events that constitute the trial end points (eg, a hard end point such as death is infrequent, resulting in fewer events observed compared with a composite end point), (2) the duration of follow-up (short-term follow-up limits the time during which events may occur and reduces the likelihood of detecting harm), and (3) sample size (an inadequate sample size places investigators at the risk of a large type II error and failure to conclude correctly that evidence of harm from COX-2 inhibition exists).

Variables related to both the patient and the drug being investigated influence the relative difference in events in the treatment groups and may minimize or magnify the signal of increased risk of events. Variables of note include (1) the risk of events in the control group (the impact of COX-2 inhibition may be less evident in healthier subjects in whom relatively few events occur in the control group), (2) the RR of events in the treatment group (related to both the intrinsic properties of the drug being investigated and the choice of the comparator arm—eg, a signal of harm with a coxib is more easily detected if the comparator arm is placebo and less readily detected in trials with an active comparator unless that active comparator actually is cardioprotective, thus magnifying the RR with a coxib), (3) and drug interactions (concomitant medications may exacerbate the risk with COX-2 inhibitors by such mechanisms as worsening of renal function or diminishing the cardioprotective effects of drugs such as aspirin [low dose]).

To complicate the situation further, the patient and drug variables may change over the course of exposure to the drug. For example, development of diabetes or worsening hypertension may culminate in disruption of a high-risk or vulnerable plaque with the development of a superimposed thrombus. As the acute situation evolves, the risk in the control arm may change, and the RR associated with the drug may also change, both in an adverse direction.

Building on these concepts, one may depict the relationship among the risk of events in the control group (control event rate, CER), the RR of events with a particular drug, and the NNH (critically related to the ability to detect a signal of harm), which are related to each other by the formula: NNH = 1/[(RR−1)×CER]. The surface shown in Figure 8 rises steeply to a high NNH (difficulty in detecting harm) with a low rate of events in the control group and/or low RR in the treatment group. The ability to detect harm improves as the NNH drops with increasing rates in the control arm and/or increasing RR in the treatment arm (Figures 7 and 8).

Strategies for Use of NSAIDs

Although the evidence base is incomplete, one can use the concepts articulated in this report to develop strategies for the use of NSAIDs.7 The general goal is to operate on the steep portion of the surface in Figure 8, thereby minimizing patient risk. This can be accomplished by preferentially prescribing NSAIDs only to patients at low risk of thrombotic events (ie,
moving to lower rates of events in the control group in Figure 8. Selecting drugs with a lower risk of thrombotic events and minimizing the dose and duration of treatment are also advisable (ie, moving to a lower RR in Figure 8). If clinical circumstances call for using an NSAID in a higher-risk patient and/or for extended periods, concomitant prescription of low-dose aspirin (81 mg/d) may help to mitigate the tendency to thrombotic events but may not eliminate the risk entirely90 (Figure 4). A suggested strategic plan for the use of NSAIDs is shown in Table 2.

Regulatory and Research Implications

The coxib story has brought into sharp focus issues related to the drug approval process and surveillance for adverse events for approved drugs. It has been argued that the passage of the Prescription Drug User Fee Act (PDUFA) in response to pressure from the pharmaceutical industry, medical community, and patients to hasten the speed of approval of new drugs set the stage for the tsunami of events between September, 2004, and April, 2005.91 PDUFA provided a mechanism for sponsors of new drugs to pay a fee to the FDA to cover the costs of accelerating the review and approval process. Although concern has been raised by some authors, it is not clear whether acceleration of the review and approval process under PDUFA resulted in less attention to the safety database for the coxibs.92 Another element in the coxib story was the introduction of direct-to-consumer advertising.93 In the case of the coxibs, aggressive direct-to-consumer advertising rapidly generated a large number of requests by patients for prescriptions.

What lessons can be learned from the early signals of harm that were detected with coxib use so that the drug approval process can be improved? We propose that for all new drugs under review, a minimum number of patient-years of safety experience be obtained before approval for use. These data may be acquired in a few very large trials or in a series of smaller trials provided that the cumulative patient-years of safety data are sufficient, which appears not to have been the case for the coxibs before their approvals. Exactly what the minimum number of patient-years of safety observation should be is not clear, but this is an important topic for future biostatistical and regulatory research efforts. A reasonable starting point is to examine the compiled number of patient-years of safety experience before approval of drugs that were later withdrawn from clinical use because of toxicity. Depending on the rate of adverse events, it can be argued that such an analysis would help frame the minimum requirement for patient-years of safety experience to acquire a comfort level (from a regulatory perspective) with a new drug.94

Once drugs are approved, continued surveillance for safety issues is needed. An initial step at augmenting postmarketing surveillance was the announcement by Health and Human Services Secretary Michael Leavitt that a new Drug Safety Oversight Board would be established within the FDA.95 This organizational and oversight strategy is a welcome start, but it is likely that more will be required, including efforts independent of the FDA.91,96,97 One possible modification is to require a mandatory registry of the first several thousand patients exposed to a newly approved drug and followed up for a period of several years. While this mandatory registry would not have an ideal control, it at least would provide a more accurate estimate of adverse events. Also, given the potential for ascertainment bias (ie, overreporting or under-reporting of adverse events) in the present postmarketing surveillance system, efforts to standardize protocols for adverse event reporting are needed.

Finally, the panic of some patients after the withdrawal of rofecoxib and valdecoxib from the marketplace when these were the drugs that relieved their symptoms most effectively underscores the need for continued pharmacological research. Investigators need to explore whether other compounds may be identified that truly treat inflammation without an adverse impact on the course of atherothrombosis. Nevertheless, it should be noted that it is unrealistic to expect any pharmaceutical entity to be completely devoid of side effects and that the decision-making process during evaluation of new agents remains complicated even for experienced investigators and regulatory authorities.98

Note Added in Proof

Additional support for the concept of an increased risk of MI with both conventional NSAIDs and coxibs is found in a report from the United Kingdom that analyzed 9218 cases and 86 349 controls in a clinical database containing records from 468 practices.99 Further discussion of the marketing influences surrounding the coxibs and regulatory considerations can be found in a perspective written by Henry Waxman, a US Representative from California.100

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Elliott M. Antman, David DeMets and Joseph Loscalzo

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