Nonsteroidal Anti-Inflammatory Drugs and the Heart

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Aspirin has been on the market for 115 years. Beginning with the marketing of indomethacin for the treatment of rheumatoid arthritis in 1963, at least 20 other nonsteroidal anti-inflammatory drugs (NSAIDs) with aspirin-like actions have been developed over the past 50 years,1 culminating with the introduction of a new class of selective inhibitors of cyclooxygenase (COX)-2, the coxibs, approximately 15 years ago.2 The NSAIDs represent the single most crowded family of drugs sharing the same therapeutic activities and mechanism of action, perhaps reflecting the unmet therapeutic need in the area of pain management and the large interindividual variability in response to these agents. NSAIDs provide symptomatic relief of pain and inflammation associated with a variety of human disorders, including the rheumatic diseases. Their shared therapeutic actions (ie, analgesic, anti-inflammatory, and antipyretic) are usually accompanied by mechanism-based adverse effects that can, at least in part, be attenuated as a function of individual pharmacokinetic or pharmacodynamic properties.1

Nuances in the tolerability of different NSAIDs had been described in the precoxib era on the basis of clinical trials of a few hundred patients treated for up to a few months with soft end points. More recently, however, important differences in safety have been demonstrated in head-to-head randomized comparisons of individual coxibs and 1 or more traditional NSAIDs that involved tens of thousands of patients treated for up to a few years with hard end points. Even more significantly, the interpretation of the effects of NSAIDs has been greatly enhanced by the availability, for the first time, of large, placebo-controlled trials that aimed to assess the potential for chemoprevention of colorectal cancer by rofecoxib or celecoxib.

As a result of these developments, the whole field of NSAIDs has been illuminated during the past 15 years. Although epidemiological studies had previously associated regular use of NSAIDs with some aspects of vascular toxicity such as enhanced risk of congestive heart failure,3 a novel aspect of cardiotoxicity associated with COX-2 inhibition emerged from the coxib trials, that is, increased risk of atherothrombotic vascular events.4,5 This was largely unexpected and paradoxical, given that the prototypic COX-2 inhibitor, aspirin, had been clearly shown to be cardioprotective over a wide range of doses up to 1500 mg daily.6

The aim of this article is to review the evidence and to discuss the mechanisms underlying the cardiovascular effects of traditional NSAIDs and coxibs, trying to reconcile the pharmacology of COX isozyme inhibition with its clinical readouts. In doing so, we shall rely primarily on the results of the recently completed meta-analysis of individual participant data from randomized trials7 because it provides the most reliable information on the effects of the most widely prescribed NSAIDs on serious clinical outcomes.

Arachidonic Acid Metabolism in Human Platelets and Endothelium

Stimulation of platelet aggregation by various agonists leads to the activation of membrane phospholipases, with the consequent release of arachidonic acid and its cyclooxygenation to form the prostaglandin (PG) endoperoxides PGG2 and PGH2. PGH2 is further metabolized by thromboxane (TX) synthase (the most abundant PGH2 isomerase in human platelets) to form TXA2 as the prevailing platelet prostanoid.1 The COX isoform involved in this rapid chain of enzymatic reactions is COX-1 in mature human platelets, with transient COX-2 expression being restricted to newly formed platelets.4 Prostanoids are usually not required to produce a functional response but rather to modulate its intensity and duration. Thus, human platelets can aggregate and form a hemostatic plug in response to thrombin even in the absence of TXA2. However, TXA2 amplifies the activation signal by virtue of its being synthesized and released in response to a platelet agonist and in turn inducing platelet aggregation and further TXA2 production through its interaction with the platelet thromboxane receptor.5 Thus, COX-1–dependent generation of TXA2 initiates an amplification loop that propagates the activation signal to adjacent platelets by inducing further platelet activation and TXA2 formation.1,9

The rate of TXA2 synthesis and release can increase a few thousand-fold from the resting state and is driven largely by enhanced substrate availability.9 Indeed, the maximal biosynthetic capacity of human platelets to produce TXA2 when challenged by thrombin in vitro (300–400 ng/mL of whole blood in 1 hour) exceeds the basal rate of TXA2 biosynthesis in vivo (0.1 ng·kg−1·min−1) by 3 orders of magnitude.10 The remarkable ability of platelets to increase their production of TXA2 by virtue of an explosive chain reaction may explain, at least in part, the unusual requirement for virtually complete (ie, >97%) suppression of platelet COX-1 activity for pharmacological inhibition to translate into functional impairment11,12 (Figure 1).
Prostacyclin (PGI₂) is the major product of COX-catalyzed metabolism of arachidonic acid in human macrovascular endothelium. Cultured human endothelial cells synthesize PGI₂ (≈20 ng/10⁶ cells) when stimulated with arachidonate in vitro. PGI₂ is a potent inhibitor of platelet aggregation and a vasodilator. Its basal rate of secretion into the systemic circulation is as low as that of TXA₂, resulting in blood levels (a few picograms per milliliter) that are at least 10-fold lower than the minimal concentration that inhibits platelet function. However, the in vivo biosynthesis of PGI₂, as reflected by PGI₂ metabolite excretion, is enhanced in patients with severe atherosclerosis and platelet activation, suggesting that it functions as a homeostatic response to accelerated platelet–vessel wall interactions. The pathophysiological importance of PGI₂ has undergone ups and downs during the past 40 years. In 1979, Moncada and Vane proposed that prostanoids such as PGE₂, PGI₂, and TXA₂ play in the cardiovascular response to TXA₂. The metabolic fate of thromboxane A₂ (TXA₂) in vivo and the calculated rate of its production in healthy subjects based on thromboxane B₂ (TXB₂) infusions and measurement of its major urinary metabolite (data from Reference 13). The nonlinear relationship between inhibition of serum TXB₂ measured ex vivo and the reduction in thromboxane metabolite (TXM) excretion measured in vivo (data adapted from Reference 12).

Compared with platelets, human endothelial cells have a considerably lower biosynthetic capacity to generate prostanoids. Although the maximal biosynthetic capacity of endothelial cells cannot be assessed ex vivo, one can use the lipopolysaccharide-induced expression of COX-2 in circulating monocytes to assess the influence of systemic plasma levels of COX-2 inhibitors on the maximal prostanoid biosynthetic capacity of blood cells exposed to the same inhibitor concentration as vascular endothelial cells. Paired measurements of the inhibition of monocyte COX-2 activity, as assessed ex vivo, and the reduction in urinary PGI₂ metabolite excretion, as assessed in vivo, have established a linear relationship between the two, in contrast to the strikingly nonlinear relationship between the inhibition of platelet COX-1 activity and the reduction in urinary thromboxane metabolite excretion (Figure 1). The markedly different requirements for inhibition of TXA₂ versus PGI₂-dependent functions may have important implications for the interpretation of the cardiovascular effects of different classes of COX inhibitors, as discussed below.

Platelet and vascular responses to a PGI₂ analog and time to thrombotic carotid arterial occlusion were modulated by PGI₂ receptor deletion in a gene/dose-dependent fashion, consistent with the concept of a linear relationship between inhibition of PGI₂-evoked signaling and reduction in PGI₂-mediated functional effects.

**Mechanism of Action of NSAIDs**

The best-characterized mechanism of action of NSAIDs is inhibition of the COX activity of PGH synthase-1 and -2 (also referred to as COX-1 and COX-2; Figure 2). Given the role that prostanoids such as PGE₂, PGI₂, and TXA₂ play in the local modulation of many important cellular functions, this mechanism of action is probably sufficient to explain the clinical effects of NSAIDs. The administration of PGE₂ and PGI₂ causes erythema, an increase in local blood flow, and, in concert with other inflammatory mediators (eg, bradykinin), hyperalgesia and enhanced vascular permeability. Moreover, PGE₂ interacting
relative COX-1 selectivity of low-dose aspirin in vivo arises from both pharmacokinetic determinants such as the acetylation of platelet COX-1 that occurs in portal blood before first-pass metabolism and pharmacodynamic determinants such as the cumulative nature of platelet COX-1 inactivation on repeated daily dosing. Thus, the daily administration of 30 mg aspirin results in virtually complete suppression of platelet TXA2 production after 1 week of dosing through a cumulative process of inactivation of platelet COX-1 by successive daily doses of aspirin. The unique features of the antiplatelet effect of aspirin explain the highly predictable, virtually complete inhibition of platelet TXA2 biosynthesis in subjects who take the drug regularly, the persistence of this effect over the 24-hour dosing interval in the vast majority of subjects with an 8- to 10-day platelet life span, and the clinical efficacy of doses as low as 30 to 50 mg daily in high-risk patients.

Traditional NSAIDs lack these unique pharmacokinetic/pharmacodynamic features and do not usually achieve the same degree of persistent platelet COX-1 inhibition as is obtained with low-dose aspirin. Moreover, several traditional NSAIDs (eg, ibuprofen and diclofenac) are characterized by very short half-lives (1–2 hours), contributing to the transient nature of platelet COX-1 inhibition.

The COX isozyme selectivity of a particular inhibitor is critically dependent on its concentration. One can compare the selectivity profiles of different COX-2 inhibitors by plotting the drug concentrations required to inhibit the activity of human platelet COX-1 and those required to inhibit human monocyte COX-2 by 50% (IC50), as measured by widely used whole-blood assays of COX activity (Figure 3). This type of analysis established 2 important facts: COX-2 selectivity is a continuous variable that does not justify a dichotomous definition of selective and nonselective inhibitors, and there

Clinical Pharmacology of COX Isozyme Inhibition

Low-dose aspirin provides a paradigm of COX isozyme-selective and cell-specific inhibition in vivo by virtue of its short half-life and ability to inactivate COX irreversibly. The

Figure 2. Mechanism of formation and action of prostanoids. Arachidonic acid, a 20-carbon fatty acid containing 4 double bonds, is liberated from the sn2 position in membrane phospholipids by phospholipases, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin (PG) G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase activity, to the unstable intermediate PGH2. The synthases are colloquially called cyclooxygenases and exist in 2 forms: COX-1 and COX-2. PGH2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell membrane receptors of the superfamily of G protein–coupled receptors. cPLA2 indicates cytosolic phospholipase A2; sPLA2, secretory phospholipase A2; EPs, PGE2 receptors; IP, PGI2 receptor; TP, TXA2 receptor; and TX, thromboxane. with its EP3 receptor can produce fever. Thus, prostanoids reproduce the main signs and symptoms of the inflammatory response. Because of the redundancy of mediators of this response, it is not surprising that NSAIDs exert only a moderate anti-inflammatory effect, are effective only against pain of low to moderate intensity, reduce fever, but do not interfere with the physiological control of body temperature.

The production of prostanoids involved in these responses appears to be triggered by the immediate availability of constitutively expressed COX-1 and to be amplified and sustained by the local induction of COX-2 in response to inflammatory and mitogenic stimuli. Although the analgesic, anti-inflammatory, and antipyretic actions of traditional NSAIDs are closely reproduced by coxibs, this finding does not exclude a potential role for COX-1 in mediating, at least in some individuals, the PG-dependent contribution to pain and inflammation.

The ability of acetaminophen to inhibit COX-1 and COX-2 is importantly conditioned by the peroxide tone of the local environment. This may explain, at least in part, the clinical observation that, while sharing the analgesic and antipyretic effects of NSAIDs, acetaminophen has relatively poor anti-inflammatory activity at conventional doses. High concentrations of leukocyte-derived peroxides accumulate at sites of inflammation and may impair the ability of acetaminophen to inhibit COX-2. However, circulating plasma levels of the drug after the administration of 1000 mg inhibit systemically COX-2 activity to a degree comparable to that of traditional NSAIDs and coxibs.
is an appreciable overlap in COX-2 selectivity between some first-generation coxibs (eg, celecoxib) and some traditional NSAIDs (eg, nimesulide and diclofenac).\(^3\) Moreover, there is large variability among NSAID-treated patients in the plasma concentrations of the COX-2 inhibitor after oral administration of a standard therapeutic dose (pharmacokinetic variability) and in the extent of inhibition of each COX isozyme, corresponding to any given concentration of the inhibitor (pharmacodynamic variability). Therefore, one can pragmatically characterize different levels of COX-2 selectivity in terms of the probability of sparing platelet (and presumably gastrointestinal mucosa) COX-1 at therapeutic plasma levels: low (eg, acetaminophen), intermediate (eg, celecoxib, nimesulide, and diclofenac), and high (eg, rofecoxib, etoricoxib, and lumiracoxib; Figure 3).

Potential variables contributing to different COX-2-dependent effects include the daily dose of the inhibitor determining the extent of COX-2 inhibition, the half-life and dosing interval of the inhibitor determining the duration of COX-2 inhibition, and the patient substrate, inasmuch as the importance of COX-2–dependent PGI\(_2\) biosynthesis is likely to vary in different clinical settings.

Although the daily dose, half-life, duration of treatment, and COX-2 selectivity are all continuous variables that could influence the cardiovascular outcomes resulting from COX-2 inhibition, the clinical readouts of such inhibition are constrained by the dichotomy of a nonlinear relationship between the inhibition of platelet COX-1 activity and the downregulation of TXA\(_2\)–dependent platelet activation (Figure 1). Therefore, inhibiting platelet COX-1 activity by 0% to 20% (as typically achieved with highly selective COX-2 inhibitors), by 20 to 50% (as typically achieved with COX-2 inhibitors endowed with moderate COX-2 selectivity), or by 50% to 90% (as typically achieved with most traditional NSAIDs) will result in only similarly modest suppression of TXA\(_2\) biosynthesis in vivo.\(^{1,12}\) Naproxen, when taken regularly at high doses and an adequate dosing interval (ie, 500 mg twice daily), is the only traditional NSAID that has been reported to inhibit platelet COX-1 activity by \(>95\)% throughout the dosing interval and to suppress TXA\(_2\) biosynthesis in vivo to the same extent as low-dose aspirin.\(^{37,38}\) Lower doses and less frequent dosing of naproxen are not expected to reproduce this aspirin-like antiplatelet effect.\(^3\)

Some NSAIDs favoring COX-1 versus COX-2 inhibition such as ibuprofen and naproxen (Figure 3) may interfere with the antiplatelet effect of low-dose aspirin by competing with acetylsalicylic acid for a common docking site (arginine 120) within the COX-1 channel.\(^39\) Prior occupancy of arginine 120 by an NSAID will prevent aspirin from acetylating a serine residue (Ser-529) just below the COX catalytic site of the enzyme, which forms the basis of the unique mechanism of action of aspirin, resulting in permanent inactivation of platelet COX-1.\(^3\) Drugs favoring COX-2 versus COX-1 inhibition such as acetaminophen and diclofenac do not interfere with the antiplatelet effect of low-dose aspirin, similar to celecoxib and rofecoxib (Figure 3).\(^{39,40}\) Using a current analysis of the available data, the Food and Drug Administration has issued a statement informing patients and healthcare professionals that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/d), potentially rendering aspirin less effective when used for cardioprotection and stroke prevention (http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm110510.htm).

**Clinical Readouts of COX Isozyme inhibition**

Clinical evidence from randomized trials is consistent with the available evidence on COX isozyme–specific effects on particular outcomes from laboratory studies. We now describe the relationship between the known pharmacology and evidence from randomized trials as recently summarized by the Coxib and Traditional NSAID (CNT) Collaboration.\(^7\)

**Effects on Pain and Inflammation**

The results of phase 3 randomized trials in osteoarthritis, rheumatoid arthritis, and various clinical models of acute pain have established that the analgesic and anti-inflammatory efficacy of coxibs is similar to that of several NSAID comparators (typically diclofenac, ibuprofen, or naproxen), independently of variable COX isozyme selectivity.\(^{1,2}\) This finding is consistent with the COX-2 dependence of PG\(_{\text{I}}\)-mediated pain and inflammation and similar COX-2 inhibition at comparable doses of different drugs.

**Effects on Atherothrombotic Outcomes**

Meta-analyses of randomized trials and observational studies have previously shown that coxibs and some traditional NSAIDs are associated with an increased risk of atherothrombotic events.\(^{28,41–43}\) The CNT Collaboration\(^7\) has recently completed meta-analyses of individual participant data from all available randomized trials of an NSAID versus placebo or 1 NSAID regimen versus another NSAID regimen, allowing detailed assessments of the cardiovascular effects of high-dose regimens of the 3 NSAIDs that are most widely prescribed worldwide for chronic inflammatory disorders: naproxen 500 mg twice daily, diclofenac 75 mg twice daily, and ibuprofen 800 mg 3 times daily.\(^7\) Compared with placebo, allocation to a coxib (mainly rofecoxib 25 mg daily or celecoxib 400 mg daily) increased the risk of major vascular events by \(\approx 40\)%, largely as a result of an increase in major coronary events, with no clear evidence of an increase in stroke risk (Figure 4).\(^7\) There was no statistically significant heterogeneity in the increased risk of major vascular events associated with rofecoxib and celecoxib despite a 20-fold difference in COX-2 selectivity between the two (Figure 3), consistent with the COX-2 dependence of PG\(_{\text{I}}\)-mediated thromboresistance of the vessel wall.\(^{26,29}\) Moreover, there was no significant difference in the incidence of vascular events between a coxib and traditional NSAIDs (with the exception of naproxen [see below]). Given the nonlinear relationship between the inhibition of platelet COX-1 activity and the inhibition of platelet activation in vivo,\(^{31,12}\) it is perhaps not surprising that the cardiovascular safety profiles of coxibs and some traditional NSAIDs appear similar because they both fail to inhibit platelet activation adequately regardless of their COX-2 selectivity.

Compared with placebo (using indirect comparisons\(^{44}\) and direct comparisons combined), however, high-dose naproxen and other traditional NSAIDs (mostly diclofenac and ibuprofen) had contrasting effects on major vascular events (Figure 5).
There was no evidence of atherothrombotic risk from naproxen, consistent with an aspirin-like phenotype conferred by the unique pharmacokinetic/pharmacodynamic features of a twice-daily high-dose naproxen regimen noted above.37,38

The increased risk of coronary events associated with vascular COX-2 inhibition is mechanistically consistent with the pattern of cardioprotection associated with platelet COX-1 inhibition by low-dose aspirin in low-risk subjects, that is, a clear decrease in coronary risk.45 These findings suggest an important role of PGI2 and TXA2 in modulating platelet activation and its contribution to coronary atherothrombosis.9 A reliable assessment of the role of these prostanoids in cerebrovascular ischemic events requires a much larger number of strokes than available in the CNT database.

There was no convincing evidence of a latent period before these vascular hazards emerge, consistent with the proposed mechanism of action4 and with evidence of early hazard observed with intravenous administration of parecoxib followed by oral valdecoxib in 2 short-term trials among patients undergoing coronary bypass surgery.46,47 The CNT analyses did not provide any evidence that the effect of coxib therapy on the risk of major vascular events is attenuated by concomitant aspirin use at baseline.7 A mitigating effect of low-dose aspirin seems biologically plausible because COX-1 knockdown in mice attenuates the prothrombotic effect of COX-2 inhibition.4 Moreover, the neutral coronary phenotype of high-dose naproxen7 suggests that a concomitant aspirin-like antiplatelet effect (ie, profound and persistent inhibition of platelet COX-1 activity throughout the 12-hour dosing interval of a naproxen 500 mg twice daily regimen)37 may mitigate or abolish the prothrombotic consequences of COX-2 inhibition. However, because there was disproportionate underrepresentation of aspirin-treated participants in the coxib trials, this analysis lacked statistical power to assess whether the vascular hazards of a coxib were modified by low-dose aspirin.7

Unfortunately, reliable information on the cardiovascular safety of other traditional NSAIDs is lacking. The vast majority of these agents, with the notable exception of indomethacin, failed to achieve >95% inhibition of serum TXB2 after single oral dosing.36 Moreover, both nimesulide48 and meloxicam49 have been reported to inhibit platelet COX-1 activity by <50% on repeated daily dosing. Therefore, the cardiovascular effects of these high-dose agents would not be expected to differ from those of diclofenac and ibuprofen unless convincingly shown otherwise.

**Effects on Blood Pressure and Renal Outcomes**

Both traditional NSAIDs and coxibs have been associated with renal and renovascular adverse events,1,2 which is consistent with the important role of constitutively expressed COX-2
in sustaining the physiological production of vasodilator and natriuretic prostanoids in the kidney. Several prostanoids contribute to blood pressure homeostasis, and practically all COX-2 inhibitors have been associated with increased blood pressure or impaired response to antihypertensive drugs.1,4 Furthermore, vascular disruption of COX-2 in mice depressed the expression of endothelial nitric oxide synthase and the consequent release and function of nitric oxide.25

Effects on Congestive Heart Failure
Use of traditional NSAIDs and coxibs can lead to the development of congestive heart failure in susceptible individuals,1 and in the CNT meta-analysis, there was a doubling of this risk, with no apparent differences in this relative increase associated with different classes of COX-2 inhibitors, consistent with this being a COX-2–dependent hazard unrelated to variable platelet inhibition.7 This is also consistent with the COX-2 dependence of hemodynamic stability and renal function in at-risk individuals and with the role of cardiomyocyte COX-2 in cardiac rhythm and function.51 The finding that coxibs and traditional NSAIDs caused a similar increased risk of heart failure indirectly suggests that the high-dose regimens of these agents used in the coxib trials produced comparable levels of vascular COX-2 inhibition.

Effects on Gastroduodenal Outcomes
Several coxibs have been shown to be associated with a lower incidence of endoscopic gastroduodenal ulcers than doses of traditional NSAIDs with similar analgesic efficacy, which is consistent with the COX-1 dependence of mucosal cytoprotection.1,2 Similarly, in at least 2 independent, large-scale trials, the highly selective COX-2 inhibitors rofecoxib and lumiracoxib were associated with a statistically significant 50% to 60% reduction in ulcer complications (mostly bleeding) compared with ibuprofen and naproxen,52,53 consistent with the COX-1 dependence of the platelet contribution to primary hemostasis.1,2 In the CNT meta-analysis, all NSAID regimens increased upper gastrointestinal complications (mostly bleeding) by 2- to 4-fold.7 It should be emphasized that any COX-2–selective inhibitor may eventually inhibit COX-1 in some patients because of interindividual variability in pharmacokinetics or pharmacodynamics, and there may be untoward COX-2–dependent effects (eg, impaired ulcer healing) that are shared by all COX-2 inhibitors regardless of selectivity.1,2 However, coxibs reduced the risk of symptomatic ulcers or upper gastrointestinal complications compared with traditional NSAIDs.7 The risk of these complications was twice as high for naproxen as for coxibs or diclofenac, consistent with more profound and longer-lasting inhibition of COX-1 in both the gastrointestinal mucosa and platelets associated with the former37,38 compared with the latter.39

In conclusion, with the notable exception of gastrointestinal toxicity, neither the clinical efficacy nor the major cardiorenal complications of COX-2 inhibitors appear to be influenced by the variable COX isozyme selectivity of these agents to any clinically detectable extent. The extent (depending on dose)
and duration (depending on half-life and dosing interval) of concomitant inhibition of platelet COX-1 may attenuate or amplify the risk of platelet-dependent thrombotic or hemorrhagic complications, respectively, associated with NSAIDs.33

**Balance of Benefits and Risks**

To illustrate the absolute effects of allocation to different NSAID regimens at particular levels of cardiovascular or gastrointestinal risk, the CNT Collaboration calculated hypothetical excess risks for major vascular events in patients at high (2% per year) or low (0.5% per year) risk of major vascular events (Figure 6, left) and for upper gastrointestinal complications in patients at moderate (0.5% per year) or low (0.2% per year) risk of such complications (Figure 6, right). Figure 6 illustrates several general points. Among those at low risk of vascular disease, the predicted risks of major vascular events were small regardless of the particular regimen chosen. For high-risk individuals (=40% of whom were taking aspirin), for every 1000 patients allocated to 1 year of treatment with a coxib regimen or high-dose diclofenac regimen, ≈7 or 8 more would have a major vascular event, of which 2 would be fatal. Whether naproxen represents a suitable alternative regimen depends on the absolute level of gastrointestinal risk and patient attitudes to these risks.

**Current Guidelines and Recommendations for Individualized NSAID Therapy**

The American College of Rheumatology (ACR) 2012 recommendations for the use of nonpharmacological and pharmacological therapies in osteoarthritis of the hand, hip, and knee strongly recommend that, if the patient does not have a satisfactory clinical response to full-dose (ie, up to 4000 mg/d) acetaminophen, then oral NSAIDs (or other pharmacological agents) should be used, except for persons ≥75 years of age, in whom the use of topical rather than oral NSAIDs is recommended.54 If the patient has a history of a symptomatic or complicated upper gastrointestinal ulcer but has not had a bleed in the past year, the ACR Technical Expert Panel strongly recommends using either a selective COX-2 inhibitor (celecoxib only in the United States; celecoxib or etoricoxib in other countries, including the European Union) or a nonselective NSAID in combination with a proton-pump inhibitor.54 If the above patient has had an upper gastrointestinal bleed within the past year and the practitioner still chooses to...

Figure 6. Annual absolute effects per 1000 of coxibs and traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) at different baseline risks of major vascular events (MVEs) and upper gastrointestinal (GI) complications. For each category of drug (coxib, diclofenac, ibuprofen, and naproxen), the predicted annual absolute risks of MVEs (±SE) are shown (left) for patients with a predicted risk of 2.0% or 0.5% per annum of an MVE. For comparison, predicted annual absolute risks of upper gastrointestinal complications (UGICs; ±SE) are shown for patients with predicted risks of 0.5% or 0.2% per annum (right). Absolute annual risks for placebo-allocated patients are assumed to be those of a hypothetical patient after all appropriate forms of prophylactic treatment (eg, antiplatelet therapy, statin therapy, proton-pump inhibitors) have been instituted. Reproduced from Reference 7 with permission from the publisher. Copyright © 2013 Elsevier B.V.
use an oral NSAID, the ACR Technical Expert Panel strongly recommends using a selective COX-2 inhibitor in combination with a proton-pump inhibitor. In the clinical scenario in which the osteoarthritic patient is on low-dose aspirin for cardioprotection and the practitioner chooses to use an oral NSAID, the ACR Technical Expert Panel strongly recommends using a nonselective NSAID other than ibuprofen in combination with a proton-pump inhibitor to avoid a potential pharmacodynamic interaction with low-dose aspirin. Although the same type of interaction with low-dose aspirin is not apparent for either diclofenac or celecoxib, the ACR Technical Expert Panel strongly recommends that a selective COX-2 inhibitor should not be used in the above situation. No specific recommendation was made about the other individual NSAIDs. Although issued by a North American organization, the ACR recommendations are more in line with the European Medicines Agency than the Food and Drug Administration position. In fact, the European Medicines Agency issued the recommendation that coxibs (and more recently diclofenac), but not other traditional NSAIDs, be contraindicated in patients with ischemic heart disease or stroke and that they be avoided in patients with risk factors for coronary heart disease. In contrast, the Food and Drug Administration requested that a boxed warning be added to the package insert of all traditional NSAIDs and celecoxib, emphasizing the potential for increased risk of serious cardiovascular thrombotic events.

A scientific statement from the American Heart Association on the use of NSAIDs for the management of musculoskeletal symptoms in patients with known cardiovascular disease or risk factors for ischemic heart disease has suggested a stepped-care approach to pharmacological therapy that focuses on agents with the lowest reported risk of cardiovascular events (acetaminophen, aspirin, tramadol, narcotic analgesics, nonacetylated salicylates) and then progresses toward other agents considered to be associated with increasing levels of cardiovascular risk, that is, “non-COX-2–selective NSAIDs,” “NSAIDs with some COX-2 activity,” and “COX-2–selective NSAIDs.” In the absence of further specification of individual agents, this terminology is potentially misleading inasmuch as all NSAIDs are COX-2 inhibitors and, as illustrated in Figure 3, COX-2 selectivity is a continuous variable. Moreover, as reviewed above, there is no convincing evidence that variable COX-2 selectivity influences the cardiovascular risk associated with COX-2 inhibitors. Another limitation of this American Heart Association scientific statement is that the “low-risk” medications listed above for initial therapy, with the exception of aspirin, have not been studied in sufficiently large, placebo-controlled, randomized trials to demonstrate their alleged superior cardiovascular safety.

Naproxen, without any specification of dose, is indicated as the preferred choice on the basis of meta-analyses of randomized trials and observational studies. Although the CNT analyses reviewed above suggest that high-dose naproxen may not be associated with an increased risk of major vascular events in low-risk individuals, this result should be extrapolated with caution to high-risk patients. First, it is currently unknown whether this would be true among patients with known cardiovascular disease treated with low-dose aspirin, in whom naproxen will not result in any additional inhibition of platelet COX-1 and may actually interfere with the antiplatelet effect of low-dose aspirin. Under these circumstances, the longer half-life of naproxen vis-à-vis ibuprofen or diclofenac may result in longer-lasting inhibition of COX-2–dependent PGI2 biosynthesis. Second, the cardiovascular effects of lower naproxen doses such as those typically used in over-the-counter preparations (eg, 220 mg twice daily) are uncertain because a lower-dose regimen does not mimic the aspirin-like effect of 500 mg twice daily. Third, the apparent safety advantage of high-dose naproxen regimens over other traditional NSAIDs may not be preserved after long-term use because of substantially similar untoward hemodynamic and renal effects that may increase the risk of heart failure (see above) and possibly ischemic stroke. It is reasonable to expect than an evidence-based debate on the above issues may allow the medical/scientific community to reach a consensus on treatment guidelines for NSAID therapy and eventually lead to regulatory harmonization worldwide.

### Conclusion

High-dose NSAID regimens are associated with serious cardiovascular and gastrointestinal risks, the size of which varies according to the extent and duration of the inhibition of COX-1 and COX-2 by the regimen and, for a given regimen, is proportional to a patient’s baseline risk. The choice of the most appropriate analgesic regimen for particular patients with inflammatory conditions should be determined after a careful assessment of their vascular and gastrointestinal risks and should be re-evaluated after proper management of risk factors. Although the considerations of benefit versus risk that derive from the CNT meta-analysis may well apply to many high-income countries, less widespread availability of adjunct therapies to manage modifiable risk factors for both cardiovascular and upper gastrointestinal complications in low- and middle-income countries may require a different strategy, starting with an examination of essential medicines lists.

In general, the current advice that NSAIDs should be taken at the lowest effective dose for the shortest possible time to minimize these risks remains reasonable, but the CNT results suggest that strict avoidance of NSAIDs among patients with chronic inflammatory disorders and vascular risk factors may not always be justified when a patient places a high value on the control of symptoms and understands the magnitude of the associated risks.

Finally, it is hoped that lessons learned from the coxib failure story may help guide the successful development of a new class of safer NSAIDs, targeting mediators unrelated to arachidonic acid metabolism or drug targets downstream of COX isozymes.

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