

Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs

SUMAPA CHAIAMNUAY, JEROAN J. ALLISON, AND JEFFREY R. CURTIS

Cyclooxygenase-2 (COX-2)-selective nonsteroidal antiinflammatory drugs (NSAIDs) have often been used in recent years due to their apparent gastrointestinal (GI) safety advantage over traditional or nonselective NSAIDs (hereafter referred to as traditional NSAIDs). In the United States, there were three COX-2-selective NSAIDs available (celecoxib, rofecoxib, valdecoxib). The labeling for celecoxib, rofecoxib, and valdecoxib was approved by the Food and Drug Administration (FDA) in December 1998, May 1999, and November 2001, respectively. Celecoxib is the only agent in this class currently available in the United States. In Europe, three additional agents are available: lumiracoxib, etoricoxib, and parecoxib, the parenteral form of valdecoxib.

Although traditional and COX-2-selective NSAIDs have commonly been used for their antiinflammatory and analgesic effects in many diseases, such as rheumatoid arthritis (RA) and osteoarthritis (OA), concerns regarding the safety of these drugs have been raised, particularly for increased risk of arterial thrombotic events (i.e., myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or

Purpose. A summary of the basic science underlying the current controversies regarding cyclooxygenase-2 (COX-2)-selective nonsteroidal antiinflammatory drugs (NSAIDs), including data on their cardiovascular safety, their gastrointestinal (GI) benefits, cost-effectiveness, physician-prescribing trends, and recommendations for prescribing these agents is presented.

Summary. A number of randomized controlled trials (RCTs) have reported that COX-2-selective NSAIDs increase cardiovascular events, although there appear to be gradations of risks among the COX-2-selective NSAIDs. In addition, traditional NSAIDs may increase the risk for cardiovascular events, complicating the interpretation of RCTs that use traditional NSAIDs as comparators. Selective inhibitors of COX-2-selective NSAIDs are effective antiinflammatory and analgesic drugs with improved upper-GI safety compared to traditional NSAIDs. Data on the cost-effectiveness of COX-2-selective NSAIDs indicate that they should be limited to patients at high risk for upper-GI adverse effects. However, they had been increasingly used in patients with lower

GI risks until recent events reversed that trend. Circumstances under which COX-2-selective NSAIDs may be appropriate are in patients at high GI risk and in patients who did not respond to multiple traditional NSAIDs. The national spotlight in the United States on NSAID-related adverse events and recent lawsuits against health care providers prescribing COX-2-selective NSAIDs further highlights the need for provider-patient communication and risk disclosure. The relative cardiovascular risks of NSAIDs are similar in magnitude to other currently prescribed therapies.

Conclusion. Health care providers must consider the efficacy, GI and cardiovascular risks, concomitant medications, and costs when determining the appropriateness of COX-2-selective NSAID therapy.

Index terms: Antiinflammatory agents; Costs; Drug interactions; Drug use; Laws; Patient information; Pharmacoeconomics; Physicians; Prescribing; Rational therapy; Toxicity

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unexplained death, ischemic stroke, and transient ischemic attacks). In light of the overwhelming and sometimes contradictory information for patients and physicians regarding the apparent safety of NSAIDs, this ar-

ticle will summarize the basic science underlying the current controversies for the cardiovascular safety data, the GI protective benefits of COX-2-selective NSAIDs, cost-effectiveness, trends in physician prescribing of

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NSAIDs in response to recently released cardiovascular safety data, and, finally, contemporary recommendations for prescribing of COX-2-selective NSAIDs.

Mechanisms of action

The COX enzyme is required for the rate-limiting step of converting arachidonic acid into prostaglandins, which are inflammatory mediators. There are two well-recognized isoforms of COX: COX-1 and COX-2. COX-1 is expressed ubiquitously, and COX-2 is expressed less constitutively and is more commonly up-regulated at sites of inflammation.¹ Prostaglandins, derived largely from COX-1, provide hemostatic integrity and participate in cytoprotection of gastric mucosa, renal hemodynamics, and platelet thrombogenesis. In contrast, prostaglandins derived from COX-2 contribute dominantly to inflammation and malignancy; however, they are also expressed constitutively in tissues of the central nervous system, trachea, and kidneys. Theoretically, selective inhibition of COX-2 would provide antiinflammatory effects without disrupting gastric cytoprotection and platelet function.

However, COX-2 also appears to mediate normal function of the vascular endothelium. In animal models, COX-2 is upregulated in vascular segments under conditions of increased shear stress.² Furthermore, prostacyclin I₂, a product of arachidonic acid from COX-2, plays a role in a homeostatic defense mechanism that promotes vasodilation and fibrinolysis and limits platelet activation.³ In contrast, thromboxane A₂, a product of arachidonic acid from COX-1, is thought to promote vasoconstriction and platelet aggregation. Thus, selectively inhibiting COX-2 may create an imbalance between thromboxane A₂ and prostacyclin I₂, leading to vasoconstriction and thrombosis. This hypothesis was demonstrated in knockout mice models in which

injury-induced vascular proliferation and platelet activation are enhanced but are suppressed in mice genetically deficient in the thromboxane A₂ receptor or treated with a thromboxane antagonist.⁴ In another mouse model, deletion of the prostacyclin receptor removed the atheroprotective effect of estrogen.⁵

Whether the balance between prostacyclin I₂ and thromboxane A₂ is the dominant mechanism that might lead to an increased risk of thrombosis in humans remains unclear but is supported by these animal data. It is likely, however, that there are mechanisms other than the relative inhibition of the prostacyclin and thromboxane balance that account for the cardiovascular risks associated with the use of COX-2-selective NSAIDs. These additional mechanisms will be discussed later.

A third isoform of COX, COX-3, was recently discovered; it is produced by the COX-1 gene and is expressed in the cerebral cortex and heart. It is selectively inhibited by analgesic and antipyretic drugs such as acetaminophen, phenacetin, antipyrine, and dipyrrone and is potentially inhibited by some NSAIDs. It is unclear if COX-2-selective NSAIDs also inhibit COX-3 and whether this inhibition could represent a primary central mechanism by which these drugs decrease pain and possibly fever.⁶

Cardiovascular safety of COX-2-selective NSAIDs

Randomized controlled trials in the United States. The first sign that COX-2-selective NSAIDs might increase cardiovascular risk was from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial.⁷ This randomized controlled trial (RCT) included 8076 patients with RA who were randomized to two groups (rofecoxib 50 mg daily or naproxen 500 mg twice a day) to examine if rofecoxib prevented clinically significant upper-GI events (gastroduodenal

perforation or obstruction, bleeding and symptomatic ulcers) as compared with naproxen. Patients using concomitant aspirin were excluded. The relative risk of developing a confirmed adjudicated thrombotic cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, transient ischemic attacks) in the rofecoxib group compared with the naproxen group was 2.38 (95% confidence interval [CI], 1.39–4.00; *p* = 0.002, incidence rate 1.1% in the rofecoxib group and 0.5% in naproxen group).^{8,9} However, having naproxen as the active comparator complicated the interpretation; the relative increase in cardiovascular events associated with rofecoxib in the VIGOR trial could be due to either an increased cardiovascular risk associated with rofecoxib or a cardioprotective effect of naproxen.

An increased cardiovascular risk associated with rofecoxib was confirmed by the Adenomatous Polyp Prevention on Vioxx (APPROVE) study, a placebo-controlled RCT of rofecoxib 25 mg daily in 2586 patients with a prior adenomatous polyp.¹⁰ The risk of cardiovascular events was 1.92 times higher in patients taking rofecoxib after 18 months of treatment (1.50 events per 100 patient-years in the rofecoxib group and 0.78 event per 100 patient-years in the placebo group). These data led to withdrawal of rofecoxib from the world market in September 2004.

In contrast, the data from the Celecoxib Long-term Arthritis Safety Study (CLASS), the Prevention of Spontaneous Adenomatous Polyps (PreSAP) study, and the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) did not show an increased risk for cardiovascular events in patients taking celecoxib. CLASS included 8059 patients with OA or RA. Patients were randomized to three groups: celecoxib 800 mg dai-

ly, diclofenac 75 mg twice daily, and ibuprofen 800 mg three times daily.¹¹ The incidences of serious cardiovascular events (myocardial infarction, stroke, cardiovascular deaths, peripheral events) were not significantly different between celecoxib and NSAID comparators (combined or individually), regardless of concomitant aspirin use. The relative risks for celecoxib versus NSAIDs for serious cardiovascular events were 1.1 for all patients and 1.1 for the subgroup of patients not taking aspirin (95% CI, 0.7–1.6 and 0.6–1.9, respectively). In addition, the incidences of other cardiovascular-related adverse events such as hypertension, edema, and congestive heart failure were similar to, or significantly lower than, NSAID comparators regardless of concomitant use of aspirin.¹²

The PreSAP trial was a placebo-controlled RCT of celecoxib 400 mg daily in 1561 patients with prior adenomatous polyps; there was no significant cardiovascular risk difference between celecoxib and placebo after 33 months of follow-up.¹³ The ADAPT, a placebo-controlled RCT, was conducted to evaluate the potential for naproxen sodium 220 mg orally twice a day versus celecoxib 200 mg orally twice a day to delay or prevent the onset of Alzheimer's disease and age-related cognitive decline. Aspirin use was permitted. The ADAPT was stopped after an average follow-up of three years because of an apparent increase in cardiovascular and cerebrovascular events in the naproxen group compared to placebo, but no increase in cardiovascular and cerebrovascular events was observed in the celecoxib group. This trial was the first placebo-controlled trial to indicate that naproxen might be associated with an increased risk of cardiovascular events, even at dosages available in nonprescription products in the United States.¹⁴

In contrast, the Adenoma Prevention with Celecoxib (APC) trial showed an increase in cardiovascular

events in patients taking celecoxib. The APC trial was a placebo-controlled trial of celecoxib 200 mg twice a day and celecoxib 400 mg twice a day versus placebo in 2035 patients with prior adenomatous polyps cosponsored by the National Cancer Institute and Pfizer. The primary endpoint was the reduction of the occurrence of adenomatous polyps. The data from the safety monitoring board revealed a dose-dependent increase in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, and congestive heart failure in both groups of patients taking celecoxib 200 mg twice a day and 400 mg twice a day (incidence rates for the placebo, lower-dose celecoxib, and higher-dose celecoxib groups were 1.0%, 2.3%, and 3.4%, respectively; the hazard ratio for lower-dose celecoxib was 2.3 [95% CI, 0.9–5.5]; for higher-dose celecoxib, the hazard ratio was 3.4 [95% CI, 1.4–7.8]).¹⁵ These preliminary results led to early termination of this trial by the data and safety monitoring board. In the post hoc subgroup analyses, there was no difference in the risk of a composite cardiovascular event when patients were stratified by age, sex, baseline cardiovascular risk factors, diabetes, aspirin use, or lipid-lowering agent use. These results from the APC trial were supported by the recent meta-analysis of four RCTs comparing celecoxib with other traditional NSAIDs that celecoxib increased the risk of myocardial infarction compared with placebo and traditional NSAIDs (odds ratios [ORs] were 2.26 and 1.88, respectively; 95% CI 1.0–5.1 and 1.15–3.08, respectively).¹⁶

The discordance between the APC trial and the PreSAP trial could be partly due to the higher dosage of celecoxib (400 mg twice a day) used in the APC trial. This explanation is also supported by the evidence from the CLASS and the observational data that indicated that the increased risk of cardiovascular events with

COX-2-selective NSAIDs was dose dependent.^{10,17-24} However, an increased risk for cardiovascular events was not observed in patients receiving celecoxib 800 mg once a day in the CLASS trial. Another potential explanation proposed is that differences between the frequency of celecoxib dosing (i.e., once daily versus twice daily) might differentially affect platelet activity, particularly in patients using concomitant aspirin. Finally, the choice of comparator drug may account for apparent differences in cardiovascular risk, particularly if traditional NSAIDs also confer increased cardiovascular risk. In the CLASS trial, which showed no increased cardiovascular risk for celecoxib, the active comparators were ibuprofen and diclofenac, while in the APC trial, celecoxib was compared with placebo.

There were not enough patients in early RCTs of valdecoxib for the treatment of arthritis to examine its cardiovascular safety.²⁵⁻³⁰ However, a meta-analysis of 8000 patients from 10 randomized OA and RA trials did not reveal any significant increase in the incidence of cardiovascular events (cardiac, cerebrovascular and peripheral vascular, arterial thrombotic) in patients taking valdecoxib (10–80 mg daily) as compared with patients taking a traditional NSAID (diclofenac sodium 75 mg twice daily, ibuprofen 800 mg three times daily, or naproxen 500 mg twice daily).³¹ Furthermore, the risk of serious thrombotic events was also similar for each valdecoxib dosage.³¹ Concern about the cardiovascular safety of valdecoxib was raised when data from two trials, coronary artery bypass graft (CABG) I and II trials, examining whether valdecoxib and parecoxib (the prodrug of valdecoxib, given intravenously) might be useful for management of postoperative pain, were analyzed. These short-term studies were conducted among high-risk patients, and much higher dosages were used than those

for the treatment of arthritis in the earlier RCTs.

In CABG I, 462 patients who underwent coronary artery bypass surgery were randomized to two groups; the active treatment group received 40 mg of i.v. parecoxib every 12 hours for 3 days, followed by 40 mg of oral valdecoxib every 12 hours for 14 days; the control group received standard care (patient-controlled analgesia with morphine, oral opioids, or acetaminophen as required). Parecoxib and valdecoxib appeared to be effective in controlling postoperative pain; however, the cerebrovascular complications and myocardial infarction rates were higher in the active treatment group, although they did not reach statistical significance (valdecoxib versus placebo: myocardial infarction 1.6% versus 0.7%, $p = 0.669$; cerebrovascular events 2.9% versus 0.7%, $p = 0.177$).³²

In a larger trial, CABG II, an RCT of 1671 patients who underwent coronary artery bypass surgery were randomized to one of three treatment groups that included 40 mg i.v. parecoxib for the first dose, then 20 mg i.v. every 12 hours for 3 days followed by valdecoxib 20 mg orally every 12 hours, for a total of 10 days or placebo for 10 days. Cardiovascular events (including myocardial infarction, cardiac arrest, stroke, and pulmonary embolism) were more frequent among the patients receiving parecoxib for 3 days followed by oral valdecoxib versus placebo (2.0% versus 0.5%; risk ratio, 3.7; 95% CI, 1.0–13.5).³³ A meta-analysis of CABG I and II confirmed a three-fold increased risk of cardiovascular events in patients who received parecoxib followed by valdecoxib compared with patients who received placebo.³⁴ These data are summarized in Table 1.

RCTs conducted in Europe. Although etoricoxib and lumiracoxib are not approved by FDA or available in the United States, data regarding their efficacy and safety have been

obtained from Phase III RCTs. In the Etoricoxib Diclofenac Gastrointestinal Evaluation, 7111 patients with OA were randomized to etoricoxib 90 mg daily or diclofenac sodium 75 mg twice daily, and there was no significant difference between them in the incidence of cardiovascular events.³⁵⁻³⁷ For lumiracoxib, the one-year Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) involved 18,325 patients with OA who were randomized to receive lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily in two substudies of identical design. Irrespective of aspirin use, there were no significant differences in vascular event rates (myocardial infarction, stroke, cardiovascular death); crude event rates were slightly higher in the lumiracoxib group than in the combined naproxen and ibuprofen groups (0.65% versus 0.55%).³⁸ In the subanalysis of patients with high cardiovascular risks (prior cardiovascular events, high Framingham risk score, diabetes plus one other cardiovascular risk factor) using aspirin, cardiovascular events were higher in the ibuprofen group as compared with lumiracoxib group (2.14% versus 0.25%; hazard ratio, 9.08; 95% CI, 1.13–72.8). Among patients who did not use aspirin, cardiovascular events were lower in the naproxen group as compared with the lumiracoxib group (0% versus 1.57%, $p = 0.027$).³⁹

There are several difficulties in using RCT data to study the increased risk of cardiovascular events in patients taking COX-2-selective NSAIDs. None of these RCTs, which were primarily conducted to examine efficacy for pain relief and GI safety, were designed to examine cardiovascular safety as a primary endpoint. Adjudication of cardiovascular endpoints was therefore inconsistent. Because most RCTs had relatively short follow-up, they were underpowered to detect increased cardiovascular event rates. Moreover, generaliz-

ability may be limited because many of them excluded patients at high cardiovascular risk. Thus, negative results from these studies cannot exclude the possibility of increased cardiovascular risk of these two newer agents. These data are summarized in Table 1.

Observational studies

The epidemiologic analyses of postmarketing data are helpful to provide further information regarding adverse events associated with COX-2-selective NSAIDs. These observational studies allow us to examine the use of these agents in much larger populations and in subgroups of interest that were not included in the RCTs, including those at extreme age, with various comorbidities of interest, and with concomitant medications with potentially important interactions. In summary, these data indicate that rofecoxib is associated with an increased risk of cardiovascular events in a dose-dependent fashion as compared with traditional NSAIDs and celecoxib in most studies,^{15,17-22,24,40} except in studies conducted by Mamdani et al.,⁴¹ Kimmel et al.,⁴² and Shaya et al.⁴³ In these latter three studies, data from all rofecoxib dosages were combined. In contrast to the APPROVe data, which showed significantly increased cardiovascular risk after only 18 months, data from observational studies suggest that rofecoxib increases risk early in the course of usage.¹⁹ The population-based cohort study by Levesque et al.^{20,44} showed that aspirin mitigates the cardiovascular risk in patients taking low-dosage rofecoxib but not in those taking high dosages.

Celecoxib has not been found to be associated with an increased risk of cardiovascular events. However, at the FDA Arthritis Advisory Committee meeting on February 17, 2005, an unpublished, nested, case-controlled study conducted by Singh et al. was presented. The study used data from the California Medicaid

database that revealed an increased risk of acute myocardial infarction with celecoxib dosages exceeding 200 mg/day.²³ The Drug Safety Research Unit in England conducted two separate studies: one study compared the incidence of cardiovascular and cerebrovascular events in celecoxib users with meloxicam users, and the other study compared rofecoxib users with meloxicam users.^{45,46} The results of these two studies revealed that compared to meloxicam, both celecoxib and rofecoxib increased cerebrovascular events but not cardiovascular events. There were non-users as a comparator group in these studies. Observational safety data for valdecoxib are limited, although one epidemiologic study published only in abstract form suggests that valdecoxib was not associated with increased cardiovascular events.⁴⁷

Traditional NSAIDs may also exhibit different gradients of cardiovascular risk. The nested case-control study by Hippisley-Cox and Coupland²² revealed an increased risk of myocardial infarction in patients taking ibuprofen, diclofenac, or naproxen. Another nested case-control study by Graham et al.¹⁷ using data from the Kaiser Permanente database in California revealed an increased risk of serious cardiac events (acute myocardial infarction and sudden cardiac death) in patients who were currently using high-dosage rofecoxib (>25 mg/day), indomethacin, or naproxen as compared with remote users of these agents (more than 60 days since use). A study by Johnsen et al.⁴⁰ showed that increased rates of hospitalization for myocardial infarction occurred in patients receiving celecoxib, rofecoxib, or traditional NSAIDs and found similar relative risks for patients with or without strong cardiovascular risk factors (low-risk patients included those with no previous hospitalizations for cardiovascular disease, hypertension, diabetes mellitus, or coronary revascularization or one or

Table 1.
Relative Risk of Cardiovascular Events Observed in Randomized Controlled Trials

Ref.	No. Patients	Follow-up Time (mo)	Patient Population	Aspirin Users (%)	Medication and Daily Dose	Comparator and Daily Dose	Relative Risk (95% Confidence Interval)
67	8,076	9	Rheumatoid arthritis	0	Rofecoxib 50 mg	Naproxen 1,000 mg	2.4 (1.4–4.0)
9	2,586	30	Adenomatous polyp	16	Rofecoxib 25 mg	Placebo	1.9 (1.2–3.1)
10	8,059	9	Osteoarthritis and rheumatoid arthritis	22	Celecoxib 800 mg	Ibuprofen 2,400 mg Diclofenac sodium 150 mg	0.83 ^a 1.07 ^a
14	2,035	≥33	Adenomatous polyp	30	Celecoxib 400 mg Celecoxib 800 mg	Placebo	2.3 (0.9–5.5) 3.4 (1.4–7.8)
12	1,561	≥33	Adenomatous polyp	16	Celecoxib 800 mg	Placebo	1.1 (0.6–2.3)
71	13,274	3	Osteoarthritis	7	Celecoxib 200 and 400 mg	Naproxen 1,000 mg and diclofenac sodium 100 mg	0.2 (0.0–1.6)
30	462	1.5	Postoperative CABG ^b	100	Parecoxib–valdecoxib 20 mg twice daily	Placebo	2.9 ^a
31	1,671	1.5	Postoperative CABG	100	Parecoxib–valdecoxib 20 mg twice daily	Placebo	3.7 (1.0–13.5)
33	7,111	12	Osteoarthritis	30	Etoricoxib 90 mg	Diclofenac sodium 150 mg	1.1 ^a
36	18,325	12	Osteoarthritis	22 25	Lumiracoxib 400 mg	Naproxen 1,000 mg Ibuprofen 2,400 mg	0.8 (0.4–1.4) 1.5 (0.9–2.4)

^aWhen not available, the relative risks were calculated as the crude event rate in users of COX-2-selective nonsteroidal antiinflammatory drugs divided by the crude event rate in the comparator group.
^bCABG = Coronary artery bypass graft.

■ CLINICAL REVIEWS Antiinflammatory drugs

more prescriptions for a cardiovascular drug; high-risk patients were those with at least one of the above risk factors). Results from these observational studies are summarized in Table 2.

Results from these studies should be interpreted with caution. First, the ability to control for confounders is variable in each study. Potential confounders of particular interest include nonprescription NSAID use and cardiovascular risk factors (e.g., age, smoking, quantitative

lipid levels, and blood pressure). For example, the studies by Solomon et al.¹⁶ and Mamdani et al.⁴⁸ included only senior patients (>65 years old) who likely had higher cardiovascular risk based on their age, and in the study by Shaya et al.,⁴³ patients in the COX-2-selective NSAID group had a high baseline cardiovascular risk. Moreover, the potential for channeling patients at higher cardiovascular risk to newer NSAIDs based on their expected GI safety may affect study results. Second, the cardiovascular

outcome definition and reference group were different in each study, which might affect study results and interpretations. For example, the outcome in the Graham et al.¹⁷ study was hospitalized acute myocardial infarction; in the Hudson et al.²¹ study, the outcome was congestive heart failure or death; and in Shaya et al.,⁴³ the outcome was acute myocardial infarction, stroke, or death. Third, potential drug interactions with NSAIDs, particularly aspirin, make the interpretation of some

Table 2.
Relative Risk of Cardiovascular Events in Observational Studies^a

Ref.	Data Source	Mean Age	Data on Aspirin Use	Case or Outcome Definition
22	Medicaid (Tennessee)	62	No	Acute MI or death from coronary heart disease
39	Ontario	76	Yes	Acute MI
17	Medicare (Pennsylvania and New Jersey)	79	No	Acute MI
15	Kaiser Permanente (California)	68	Yes	Acute MI or sudden cardiac death
20	United Kingdom (England, Scotland, Wales)	87	Yes	Acute MI
19	Hospital discharge summaries and prescription database (Quebec)	76–79	Yes	Recurrent congestive heart failure and death
38	Hospital discharge registries and the Danish Civil Registration System (Denmark)	NA	Only by prescription (325 mg/day)	Acute MI
40	Philadelphia	55	Yes	First nonfatal MI
18	Quebec's health database	75	Yes	Acute MI
41	Medicaid (Maryland)	NA	No	Death from cardiovascular, hemorrhagic, and unknown causes, nonfatal MIs, nonfatal strokes
21	Medicaid (California)	71	Yes	Acute MI

^aCOX-2 = cyclooxygenase-2, NSAID = nonsteroidal antiinflammatory drug, MI = myocardial infarction, NA = not available.

^bSome studies included multiple comparator groups. To simplify comparisons across studies, the number of comparators has been limited.

^cAdjusted odds ratio.

observational studies extremely challenging. Despite the clear cardioprotective benefits of once-daily aspirin, aspirin users generally are at higher cardiovascular risk than nonusers.⁴⁹ Furthermore, the drug interaction between aspirin and NSAIDs has been described. The administration of ibuprofen with or before the administration of aspirin appears to abrogate the antiplatelet effect of aspirin.^{50,51} Patients taking both ibuprofen and low-dose aspirin (<325 mg/day) have been shown to

have increased cardiovascular (adjusted hazard ratio, 1.73; 95% CI, 1.05–2.84) and all-cause mortality (adjusted hazard ratio, 1.93, 95% CI; 1.30–2.87) compared with patients who take aspirin alone.⁵²

Ibuprofen binds to a serine residue in the channel required for aspirin to access the platelet COX-1 enzyme. This interference also applies to indomethacin but not acetaminophen, diclofenac, celecoxib, and rofecoxib.^{50,53,54} Naproxen has been shown to reversibly and competitive-

ly inhibit COX-1 and prevent aspirin from inhibiting COX-1.⁵⁵ However, administration of naproxen and aspirin simultaneously, irrespective of whether naproxen was taken before or after aspirin, provided similar and complete inhibition of serum thromboxane and arachidonic acid-induced platelet aggregation. The fact that chronic, concomitant naproxen and aspirin therapy did not negatively influence platelet COX activity may seem contrary to the previous results with ibuprofen and suggest a

COX-2-Selective NSAID			Comparator ^b			Adjusted Relative Risk (95% Confidence Interval)
Agent and Daily Dose	n	No. Events	Agent and Daily Dose	n	No. Events	
Rofecoxib 50 mg	20,245	55	Nonuse	202,916	3,085	1.70 (0.98–2.95)
Rofecoxib 25 mg	3,887	13				1.01 (0.77–1.33)
Celecoxib any dose	22,337	74				0.96 (0.76–1.21)
Rofecoxib any dose	12,156	58	Nonuse	100,000	418	1.00 (0.80–1.40)
Celecoxib any dose	15,271	75				0.90 (0.70–1.20)
Rofecoxib ≤25 mg	876	202	Nonuse	49,044	9,793	1.21 (1.01–1.44)
Rofecoxib >25 mg	65	23				1.70 (1.07–2.71)
Celecoxib ≤200 mg	1,767	341				0.92 (0.83–1.03)
Celecoxib >400 mg	373	74				0.94 (0.74–1.19)
Rofecoxib 50 mg	246	58	Remote use	23,378	4,658	3.00 (1.09–8.31)
Rofecoxib 25 mg	18	10				1.23 (0.89–1.71)
Celecoxib any dose	617	126				0.84 (0.67–1.04)
Rofecoxib any dose	1,021	151	Nonrofecoxib use	83,991	8,848	1.32 (1.09–1.61)
Celecoxib any dose	727	93	Noncelecoxib use	84,762	8,988	1.21 (0.96–1.54)
Rofecoxib any dose	NA	NA	Celecoxib	NA	NA	1.27 (1.09–1.49)
Celecoxib any dose	NA	NA	Other NSAIDs	NA	NA	1.26 (1.00–1.57), NSAIDs versus celecoxib
Rofecoxib any dose	730	119	Nonuse	51,300	4,178	1.80 (1.47–2.21)
Celecoxib any dose	592	71				1.25 (0.97–1.62)
Other COX-2-selective NSAIDs	453	57				1.45 (1.09–1.93)
Rofecoxib any dose	105	27	Nonuse	5,845	1,354	1.16 (0.70–1.93)
Celecoxib any dose	105	18				0.43 (0.23–0.79)
Rofecoxib 50 mg	244	21	Nonuse	17,473	793	1.73 (1.09–2.76)
Rofecoxib 25 mg	3,703	218				1.21 (1.02–1.43)
Celecoxib any dose	5,585	287				0.99 (0.86–1.15)
Rofecoxib any dose	497	NA	Other NSAIDs	5,245	NA	0.99 (0.76–1.30)
Celecoxib any dose	507	NA				1.19 (0.93–1.51)
Rofecoxib any dose	3,501	1,117	Remote use	35,507	8,447	1.32 (1.22–1.42) ^c
Celecoxib any dose	7,044	1,862				1.09 (1.02–1.15) ^c

different effect of naproxen.^{54,55} These data highlight potential biological mechanisms that may account for increased or decreased cardiovascular risk of some traditional NSAIDs and may complicate the interpretation of studies of COX-2-selective NSAIDs that use traditional NSAIDs (rather than placebo) as the comparator group.

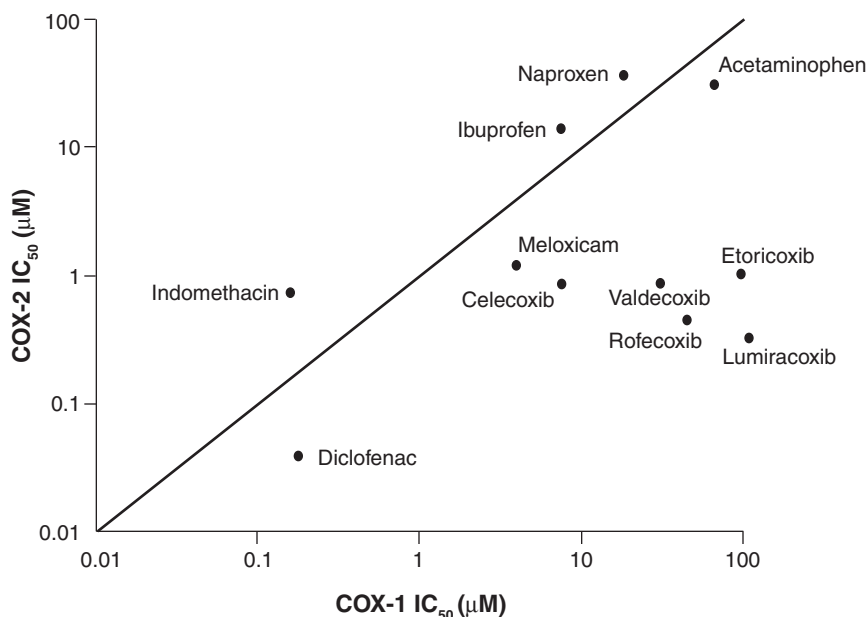
Effects of COX-2-selective NSAIDs on vascular endothelium: Class or individual effect?

To date, the mechanism of increased cardiovascular risk associated with COX-2-selective NSAIDs remains incompletely understood. Although it could be a class effect, there are several differences between these agents that might lead to distinct cardiovascular risk profiles.

First, the ratio of COX-2 to COX-1 inhibition, using human whole-blood assay, is 30, 272, and 61 for celecoxib, rofecoxib, and valdecoxib, respectively.⁵⁶ Traditional NSAIDs also inhibit COX-1 and COX-2 in different ratios; for example, meloxicam and diclofenac inhibit COX-2 more selectively than COX-1, whereas ibuprofen and naproxen are more COX-1 selective (Figure 1). Although these differences in selectivity were done by in vitro assay and might not fully explain clinical importance in vivo, these differences in selectivity could lead to variable degrees of imbalance of thromboxane A₂ and prostacyclin I₂, which might increase platelet aggregation and vasoconstriction. Therefore, all NSAIDs might carry some cardiovascular risks but with different gradients.

Second, the COX-2-selective NSAIDs also differ structurally, and this might contribute to differences in cardiovascular risk profiles. Celecoxib and valdecoxib are sulfonamide derivatives, whereas rofecoxib and etoricoxib are methylsulfons. Rofecoxib and etoricoxib exhibit dose-dependent prooxidant activity as shown by increasing low-density

Figure 1. Concentrations of selected nonsteroidal antiinflammatory drugs required to inhibit 50% of the cyclooxygenase-1 (COX-1) and COX-2 enzymatic reactions in assays of whole human blood (50% inhibition concentrations [IC₅₀]). Reproduced with permission from *Arthritis & Rheumatism*, 2005; 52:1968-78.



lipoprotein oxidation, decreasing oxygen radical antioxidant capacity in human plasma, and increasing nonenzymatic generation of isoprostanes.⁵⁷ These prooxidant activities are not observed with other COX-2-selective or traditional NSAIDs, and these prooxidant activities may be related to their sulfone structure. In contrast, celecoxib has been shown to decrease oxidative stress.⁵⁸ Further x-ray diffraction analysis has shown that sulfone COX-2-selective NSAIDs interact differently with membrane phospholipids than sulfonamide COX-2-selective NSAIDs, suggesting that the prooxidant activities are most likely due to structural differences rather than enzyme inhibition.⁵⁷

Third, despite challenges in comparing between dissimilar studies, flow-mediated dilatation appears to be improved in patients taking celecoxib but not in patients treated with rofecoxib. The flow-mediated dilatation reflects nitric oxide release from the endothelium, and reduced flow-

mediated dilatation is associated with a higher risk of cardiovascular events.⁵⁸⁻⁶²

Other COX independent signaling pathways (e.g., c-jun NH2-terminal kinase) also appear to be differentially affected by various COX-2-selective NSAIDs.⁶³ These agents may also affect systemic inflammation and thereby affect cardiovascular risk. Celecoxib has been shown to reduce C-reactive protein (CRP) in patients with coronary artery disease.⁵⁸ However, data about rofecoxib and CRP reduction are controversial. Rofecoxib was found to reduce levels of CRP in a six-month follow-up study of patients with established coronary artery heart disease⁶² and in a three-month follow-up study of patients with acute coronary artery syndrome⁶⁴ but not in two shorter follow-up studies.^{61,65} There are no head-to-head studies that compare this effect between celecoxib and rofecoxib.

Finally, the effects of COX-2-selective NSAIDs on blood pressure

might lead to differences in the risk for cardiovascular events. COX-2 is constitutively expressed in the kidneys and is highly regulated in response to alterations in intravascular volume; COX-2 inhibition may transiently decrease urine sodium excretion and induce mild to moderate elevation of blood pressure in some patients. Furthermore, in conditions of relative intravascular volume depletion, COX-2 inhibition can have deleterious effects on maintenance of renal blood flow and the glomerular filtration rate. However, COX-2-selective and traditional NSAIDs have similar effects on renal function as measured by the glomerular filtration rate, creatinine clearance, and urinary and serum sodium and potassium values.^{66,67} A meta-analysis pooled 19 trials (45,451 patients; 29,824 with OA and 15,627 with RA) and showed that the risk of developing clinical hypertension (not directly defined and only assessed as part of the safety data obtained during trial observations) was increased in patients receiving rofecoxib but not celecoxib (relative risk, 2.63 and 0.81; 95% CIs, 1.42–4.85 and 0.13–5.21, respectively) as compared with placebo.⁶⁸ The data from the APPROVe trial, which were not included in this meta-analysis, also reveal an increased risk of hypertension in patients taking rofecoxib as compared with placebo (hazard ratio, 2.02; 95% CI, 1.71–2.38).¹⁰ In contrast, a recent RCT compared celecoxib 200 mg/day, rofecoxib 12.5 and 25 mg/day, and acetaminophen 4000 mg/day in 1578 patients with OA and revealed a similar incidence of hypertension in each group.⁶⁹ The discordance between this study and the others is probably due to a relatively short period of follow-up time (six weeks) and the use of acetaminophen as the active comparator. Whether acetaminophen could increase the incidence of hypertension is not well established.

The GI protection of COX-2-selective NSAIDs

Rofecoxib. After nine months of treatment, the VIGOR study showed that upper-GI events (bleeding, perforation, obstruction, symptomatic ulcers) were significantly lower in patients in the rofecoxib group than in the naproxen group (2.1% versus 4.5% per 100 patient-years; relative risk, 0.5; 95% CI, 0.3–0.6).⁷ The greatest decrease in GI events was observed in patients at highest risk (i.e., those patients with a prior history of upper-GI events, those 75 years of age or more, or those with severe RA).⁷⁰

Celecoxib. In the CLASS, upper-GI complications (bleeding, perforation, obstruction) and symptomatic ulcers were significantly lower in the celecoxib group compared with the combined diclofenac and ibuprofen group (2.08% versus 3.54% annual incidence rate; $p = 0.02$) after six months of treatment. For patients who were not taking aspirin, the annual incidence rate of the combined endpoint of upper-GI complications and symptomatic ulcers was reduced in the celecoxib group compared with the combined nonselective NSAID group (1.4% versus 2.9% annual incidence rate; $p = 0.02$). The protective GI benefit of celecoxib was not found in patients who were concomitantly taking aspirin.¹¹ Furthermore, unlike the 6-month results, the longer-term CLASS data (12 months for the celecoxib versus diclofenac group and 15 months for the celecoxib versus ibuprofen group) failed to show a significant reduction in upper-GI complications in the celecoxib group as compared with the combined diclofenac and ibuprofen group; however, the high dropout rate of the study at 12 months might have reduced detection of the GI protective effect of celecoxib.^{71,72} Unlike the long-term CLASS, SUCCESS-1 (SUccessive Celecoxib Efficacy and Safety Study-1) was a 12-week randomized, placebo-controlled trial

examining the efficacy and upper-GI safety of celecoxib at doses of 100 or 200 mg twice daily, compared with other NSAIDs (diclofenac 50 mg twice daily or naproxen 500 mg twice daily) among 13,274 patients with OA.⁷³ More upper-GI complications (bleeding, perforation, obstruction) occurred in the traditional NSAID groups compared with the celecoxib group (odds ratio, 7.02; 95% CI, 1.46–33.80). In the subgroup of patients taking concomitant aspirin, this difference did not reach statistical significance; however, this subgroup only had a few patients.

A meta-analysis of nine RCTs (CLASS was also included), evaluating celecoxib against other traditional NSAIDs (e.g., naproxen, diclofenac, and ibuprofen) or placebo, found that patients treated with celecoxib had a 46% lower rate of withdrawal due to adverse GI events (abdominal pain, dyspepsia) compared with traditional NSAIDs. At six months, the incidence of ulcers detected by endoscopy was 75% lower and the incidence of symptomatic ulcers, perforations, bleeding, and obstruction was 39% lower compared with traditional NSAIDs. Furthermore, the gastroprotective benefit of celecoxib was reduced in patients taking concomitant aspirin, although the benefit was not statistically significant (a 73% reduction in the incidence of ulcers detected by endoscopy in patients who did not receive aspirin versus a 51% reduction in those receiving aspirin, $p = 0.18$).⁷⁴

Etoricoxib and lumiracoxib. In a meta-analysis comparing etoricoxib with naproxen, diclofenac, and ibuprofen, etoricoxib was associated with less clinical GI toxicity (perforation, symptomatic ulcers, bleeding) than traditional NSAIDs.⁷⁵

From TARGET, patients in the lumiracoxib group who did not take concomitant aspirin had less GI toxicity (perforation, symptomatic ulcers, bleeding) than patients in

the naproxen and ibuprofen group (risk reduction ratio, 0.34; 95% CI, 0.22–0.52).⁷⁶

Risk of GI bleeding in patients receiving warfarin and concomitant COX-2-selective NSAIDs versus traditional NSAIDs. A nested case–control analysis from multiple linked health care databases in Canada was performed in older patients (ages greater than 66 years) taking warfarin. There were 98,821 patients; 361 were admitted for upper-GI bleeding and defined as case patients. Their prescription records before hospitalization were matched 1:4 to those of age-matched and sex-matched controls who were also receiving warfarin. After adjustment for potential confounders, case patients were more likely to have taken traditional NSAIDs (OR, 1.9; 95% CI, 1.4–3.7), celecoxib (OR, 1.7; 95% CI, 1.2–3.6), or rofecoxib (OR, 2.4; 95% CI, 1.7–3.6) before hospitalization relative to controls. The risk of hospitalization for upper-GI bleeding in patients taking warfarin was similar among patients receiving celecoxib, rofecoxib, or nonselective NSAIDs concomitantly.⁷⁷

Risk of GI bleeding in patients receiving COX-2-selective NSAIDs versus traditional NSAIDs and proton pump inhibitors. A study was conducted in 287 patients with a recent history of NSAID-induced GI bleeding who were randomized to celecoxib 200 mg twice a day ($n = 144$) or diclofenac sodium 75 mg twice a day plus omeprazole 20 mg daily ($n = 143$) after their ulcers had healed as documented by endoscopy. At six months, there was no significant difference in the rate of recurrent ulcer bleeding between the two groups (4.9% versus 6.4%, respectively).⁷⁸ A total of 259 patients did not have recurrent gastrointestinal complications at six months; of those, 222 patients agreed to follow-up endoscopy. There were no significant differences in the probability of recurrent endoscopically detected ulcers (18.7%

in the celecoxib group versus 25.6% in the diclofenac plus omeprazole group) or the combined endpoint of clinically apparent GI bleeding or endoscopic ulcers (24.1% versus 32.3%, respectively).^{78,79} However, the high absolute rates of recurrent ulcer bleeding in both groups were high, suggesting that celecoxib and diclofenac plus omeprazole do not prevent recurrent ulcers in patients with history of an NSAID-related ulcer. A recent RCT comparing celecoxib 200 mg daily versus naproxen 750 mg plus lansoprazole 30 mg daily in patients with healed NSAID-induced ulcer complications also supports the previous finding and discovered no significant difference in the rates of recurrent ulcer complications between these two treatment regimens.⁸⁰

The incidence of small-bowel injury was examined by video capsule endoscopy in healthy subjects treated with celecoxib 200 mg twice a day or naproxen 500 mg twice a day plus omeprazole 20 mg daily versus placebo for two weeks. Celecoxib was associated with significantly fewer small-bowel mucosal breaks than naproxen plus omeprazole. (The mean \pm S.D. number of small-bowel mucosal breaks per subject and the percentage of subjects with these mucosal breaks were 2.99 ± 0.51 , 55% for naproxen plus omeprazole; 0.32 ± 0.10 , 16% for celecoxib; and 0.11 ± 0.04 , 7% for placebo; $p < 0.001$ for both comparisons.)⁸¹

Risk of GI bleeding in patients receiving COX-2-selective NSAIDs versus COX-2-selective NSAIDs plus proton pump inhibitors. Intuitively, the combination of a COX-2-selective NSAID plus a proton pump inhibitor (PPI) should provide effective analgesia and further decrease the risk of upper-GI events compared to a COX-2-selective NSAID alone, albeit at higher cost. Although one study has shown that omeprazole significantly improved upper-GI symptoms (i.e., pain, discomfort, or burning) in patients treated with

COX-2-selective NSAIDs,⁸² there are no studies comparing these agents plus PPIs versus COX-2-selective NSAIDs alone for the more clinically important outcomes of bleeding, perforation, obstruction, and symptomatic ulcers.

Cost

A cost-effectiveness analysis based on the VIGOR and CLASS trials and excluding information about COX-2-selective NSAID-associated cardiovascular risks was conducted. It concluded that rofecoxib and celecoxib are not cost-effective in patients at average risk of upper-GI events or in a population with a typical mix of average and high risk for upper-GI events. When examined among patients at average GI risk, the cost for each quality adjusted life year (QALY) gained with the use of COX-2-selective NSAIDs was high, estimated at Can\$271,188 for rofecoxib versus naproxen and more than Can\$100,000 for celecoxib versus ibuprofen. This study demonstrated that COX-2-selective NSAIDs are cost-effective only in patients with prior history of upper-GI events. In a sensitivity analysis, and using a willingness to pay of Can\$50,000 per QALY gained, rofecoxib and celecoxib were found to be cost-effective only in older patients.⁸³ However, postmarketing data show that COX-2-selective NSAIDs were commonly prescribed to patients at low to average risk of GI events and that physician preferences, not patient risk factors for GI bleeding, are the dominant factors driving practice-pattern variations observed in prescribing COX-2-selective NSAIDs.^{84–86}

More recent cost-effective analyses have examined cardiovascular risk and GI benefit, together, adding the assumption that aspirin mitigates the gastroprotective effects of COX-2-selective NSAIDs. For patients with average GI risk (the base-case scenario), the use of COX-2-selective NSAIDs instead of traditional NSAIDs

cost an incremental \$275,809 to gain one additional QALY. After accounting for the potential disparity in cardiovascular events with COX-2-selective NSAIDs, the incremental cost increased to \$395,324 per QALY gained. However, if patients had a history of ulcer hemorrhage, the incremental cost per QALY gained decreased to \$55,803 when a COX-2-selective NSAID was used instead of a traditional NSAID.⁸⁷

Clinicians' response to cardiovascular safety concerns of COX-2-selective NSAIDs

Data from the National Ambulatory Medical Care Survey (1999–2002), the medical and prescription claims data from a large preferred provider organization in the Midwest (2000), and the Slone survey (2003) revealed that prescriptions for COX-2-selective NSAIDs had been increasing since their introduction, especially among patients at lower risk of GI bleeding (i.e., no history of upper-GI bleeding or ulcers, NSAID-

induced GI symptoms, and age of <65 years).^{84–86}

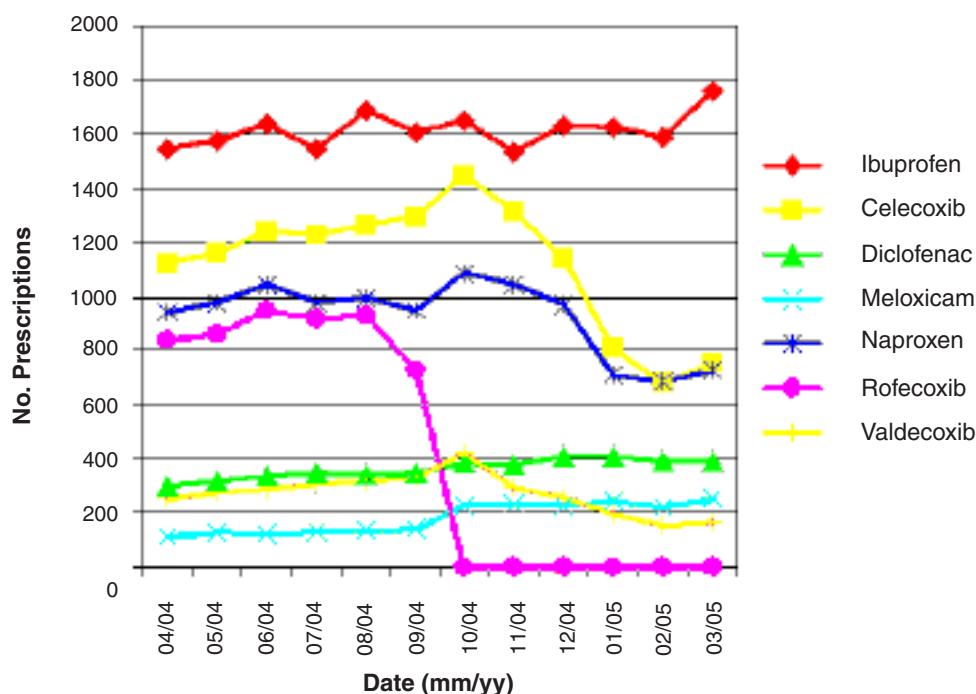
Physician prescribing preferences had more influence on use of COX-2-selective NSAIDs than a patient's GI risk factors.^{88,89} Moreover, data from the Tennessee Medicaid program (2002–03) showed that these agents were commonly prescribed at higher than recommended dosages (33% of OA patients received celecoxib dosages of ≥ 400 mg/day, rofecoxib ≥ 50 mg/day, or valdecoxib ≥ 20 mg/day).⁹⁰ These higher dosages were frequently prescribed in patients with cardiovascular risks (17% of patients with a high-dose COX-2-selective NSAID had pre-existing cardiovascular disease, and 58% had hypertension).⁹⁰ This trend occurred despite FDA warnings and rofecoxib labeling changes (as a result of the cardiovascular findings in the VIGOR trial, February 2001). The relative failure of risk communication to affect prescribing behavior has been observed with a number of other drugs.⁹¹

Subsequent to September 2004, when rofecoxib was withdrawn from the world market, the cardiovascular safety of NSAIDs received national public attention in the lay press; as a result, NSAID prescriptions dramatically decreased both in patients with high cardiovascular risk and in patients with history of peptic ulcer disease.⁹² Using data from a national retail pharmacy, trends in NSAID prescribing through March 2005 are shown in Figure 2. Following September 2004, celecoxib, valdecoxib (before its withdrawal), and naproxen prescriptions transiently increased and subsequently decreased. In contrast, the volume of other traditional NSAID prescriptions stayed the same or increased (12–25%), especially meloxicam (85%).⁹³

What should health care providers do at this time?

There are no simple answers about how to select the most appropriate NSAID therapy for an individual patient (i.e., a traditional NSAID versus

Figure 2. Nonsteroidal antiinflammatory drugs (NSAIDs) prescription data from a national retail pharmacy from April 2004 to March 2005 showing changes in NSAID prescribing following release of recent safety data. Reproduced with permission from *Arthritis & Rheumatism*, 2005; 52(9, suppl):S258–9.



a COX-2-selective agent). Rofecoxib clearly was associated with increased cardiovascular risk and has already been withdrawn from the world market. In April 2005, an FDA advisory committee concluded that valdecoxib was associated with an increased rate of serious and potentially life-threatening skin reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other COX-2-selective NSAIDs, and the committee recommended withdrawing valdecoxib. At least in some trials, all three approved COX-2-selective NSAIDs were associated with an increased risk of serious cardiovascular events compared with placebo; however, whether particular agents (e.g., celecoxib) confer a greater risk of serious cardiovascular events than traditional NSAIDs remains uncertain. All NSAIDs likely increase the risk to some degree, and there may be a gradient of risk associated with particular NSAIDs. Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious cardiovascular events for both COX-2-selective and nonselective NSAIDs. Thus, the FDA committee recommended that all labeling for prescription NSAIDs should include a boxed warning highlighting the potential increased risk of serious cardiovascular events.⁹⁴ The ongoing PRECISION trial (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen), a RCT in patients with OA, is designed to compare the risks of cardiovascular events among celecoxib, naproxen, and ibuprofen and will start enrolling patients in 2006. Results from this trial should provide better answers regarding the cardiovascular risks associated with the use of these NSAIDs.

Since NSAIDs are most commonly used for symptom relief rather than for disease modification,

it is worthwhile to comprehensively assess the approach to symptomatic pain control for any patient considering NSAID therapy. Nonpharmacologic approaches to symptom control should be maximized (e.g., exercise for overweight patients with OA). Non-NSAID systemic analgesics (e.g., acetaminophen and tramadol) may be effective, and topical analgesics (e.g., the lidocaine patch and capsaicin) may also help at sites of localized pain (e.g., knee OA).⁹⁵ However, we recognize that these measures will be inadequate for pain control for some patients, and NSAID therapy may still be appropriate. However, before prescribing NSAIDs, health care providers should assess patients' individualized risk factors for NSAID-induced ulcers and cardiovascular diseases and should optimize modifiable cardiovascular risk factors (e.g., hypertension, lipid levels, tobacco use, and obesity). Using the lowest NSAID dose for the shortest duration necessary is advisable. Physicians should be aware of maximum dosages for different indications; for example, celecoxib is approved at a dosage of 200 mg/day for OA, 400 mg/day for RA, and 200 mg/day for ankylosing spondylitis for the first six weeks; if response is suboptimal in patients receiving 200 mg daily, the dosage may be increased up to 400 mg/day.⁹⁶ For patients at high risk for adverse GI effects, a coprescription of a PPI with traditional NSAIDs is appropriate, and if the patients are at low cardiovascular risk, a COX-2-selective NSAID may also be considered.⁹⁷ Although it would be preferable to start patients on safer NSAIDs since some data suggest that certain NSAIDs (e.g., naproxen) may be somewhat less risky than others (e.g., indomethacin), conclusions regarding the comparative safety of different traditional NSAIDs remain tentative. The choice of NSAIDs should incorporate patient preferences into consideration in terms of individualized efficacy, frequency

of administration, cost, and adverse effects. Physicians should periodically monitor for adverse effects. The American College of Rheumatology has recommended monitoring complete blood count (CBC), liver function tests, and renal function at baseline. A CBC should be performed yearly and serum creatinine monitored periodically.⁹⁸ Absolute contraindications for NSAIDs are known hypersensitivity reactions to NSAIDs, a history of NSAID-induced asthma, rhinitis or nasal polyps, and recent postoperative coronary artery bypass surgery.^{96,99} NSAIDs should be avoided in patients with renal insufficiency, recent history of peptic ulcer disease, and GI bleeding, and in pregnancy.⁹⁹ In addition, celecoxib is contraindicated in patients allergic to sulfonamides.

Given the relatively high cost of COX-2-selective NSAIDs, attenuated GI-protective benefits in patients concomitantly using aspirin, and the lack of demonstrated superior efficacy compared to traditional NSAIDs for pain control, is there still a rationale for their use? In the United States, only celecoxib is currently available, although lumiracoxib and etoricoxib are available internationally. Circumstances under which use of these agents may be appropriate are in patients at high GI risk (ages greater than 65 years, history of peptic ulcer disease, concomitant use of glucocorticoids or anticoagulation, recent history of *Helicobacter pylori*-associated ulcer, inflammatory bowel disease)^{70,100} and in patients who did not respond to multiple traditional NSAIDs. However, among patients with risk factors for GI bleeding, the use of a traditional NSAID plus concomitant PPI therapy may be an alternative with comparable efficacy to COX-2-selective NSAIDs.^{7,11,78-80}

The national spotlight on NSAID-related adverse events and recent lawsuits against health care providers prescribing COX-2-selective NSAIDs

further highlights the need for provider–patient communication and risk disclosure. The relative cardiovascular risks of NSAIDs are similar in magnitude to other currently prescribed therapies (e.g., estrogens), and frank discussions between health care providers and patients regarding the individualized risk–benefit profile of NSAID therapy should result in a common understanding regarding the expected benefit and potential risks. Framing discussions in terms of absolute risk should also help patients put relative risk estimates in perspective. For example, a twofold increased *relative* risk of an NSAID-related cardiovascular event in a person with no cardiovascular risk factors still yields a very small *absolute* risk for a cardiovascular event. Unfortunately, our ability to identify patients who may be at greatest risk for NSAID-related toxicity is limited. Until we better understand the underlying mechanisms regarding the cardiovascular effects of NSAIDs, health care providers should continue to reevaluate patients' needs for ongoing NSAID therapy.

Conclusion

Health care providers must consider the efficacy, GI and cardiovascular risks, concomitant medications, and costs when determining the appropriateness of COX-2-selective NSAID therapy.

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