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Cyclooxygenase-2 Inhibitors and Most Traditional Nonsteroidal Anti-inflammatory Drugs Cause Similar Moderately Increased Risks of Cardiovascular Disease

Charles H. Hennekens, MD, and Steven Borzak, MD

Cyclooxygenase-2 inhibitors relieve pain from inflammatory conditions by decreasing the gastrointestinal side effects from traditional nonsteroidal anti-inflammatory drugs. Basic research provided plausible mechanisms and some observational epidemiological studies, case-control and cohort, indicated that patients prescribed with cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs had increased risks for myocardial infarction and stroke. Because patients prescribed with cyclooxygenase-2 inhibitors were systematically different, uncontrolled and uncontrollable confounding by indication was as large as the observed risks. Thus, epidemiological studies or their meta-analyses could not discern

whether, and if so, how much, the risks were real. A comprehensive meta-analysis of randomized trials indicated that cyclooxygenase-2 inhibitors increased the risk of vascular events by 42%, almost exclusively myocardial infarction, as did high-dose regimens of ibuprofen and diclofenac, but not naproxen. Individual clinical judgments and policy decisions should include cardiovascular disease and noncardiovascular disease risks including gastrointestinal side effects and clinical benefits including improved quality of life from less pain and disability.

Keywords: cyclooxygenase-2 inhibitors; nonsteroidal anti-inflammatory drugs; cardiovascular disease

Cyclooxygenase-2 inhibitors (COXIBS) were developed, approved, and marketed to achieve effective pain relief in patients with inflammatory conditions by decreasing gastrointestinal side effects,¹ a major concern with the use of the traditional nonsteroidal anti-inflammatory drugs (NSAIDS; Table 1). Patients with inflammatory conditions tend to have higher risks of cardiovascular disease (CVD) so they are more likely to require

prophylactic aspirin, which also increases gastrointestinal side effects. Major clinical and public health concerns have been raised leading to controversies about the true magnitude of the deleterious effects of COXIBS, as well as traditional NSAIDS, on the risks of CVD. In this article, we assess the strengths and the limitations of the different types of evidence and conclude that the benefit to risk ratio of COXIBS is larger and of traditional NSAIDS, other than naproxen, is smaller on risks of CVD than has been reported previously.

Types of Evidence

Advances in medical knowledge proceed along several fronts, optimally simultaneously.² Basic research provides plausible biological mechanisms to explain why an agent affects outcomes and has a high degree of precision but the relevance to free-living humans is

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Table 1. Cyclooxygenase-2 Inhibitors

Generic Name	Manufacturer	Trade Name	Regulatory Status
Rofecoxib	Merck	Vioxx	Voluntarily withdrawn by manufacturer, September 30, 2004
Celecoxib	Pfizer	Celebrex	Approved in United States December 1998
Valdecoxib	Pfizer	Bextra	Approved in United States November 2001, voluntarily withdrawn by manufacturer at FDA request, February 2005
Etoricoxib	Merck	Arcoxia	Investigational in United States
Lumiracoxib	Novartis	Prexige	Investigational in United States

Abbreviation: FDA, Food and Drug Administration.

questionable. Epidemiology explains whether an agent affects outcomes and has a high degree of imprecision but the relevance to free-living humans is clear. Epidemiology is crude and inexact, as observations on free-living humans can never take place under the controlled conditions of basic research. The strategies of epidemiology include descriptive studies, useful to formulate hypotheses or analytical studies, useful to test hypotheses. Analytical epidemiology can be observational, either case-control or cohort studies, or experimental, namely randomized trials. For large effects (ie, a doubling or more of risk or benefit), observational studies in the context of basic research can provide a sufficient totality of evidence for rational clinical decision making and public policy. When the effect sizes are small to moderate (ie, less than a doubling of the benefit or risk), however, the amount of uncontrolled and uncontrollable confounding inherent in all observational designs can be about as big as the effect sizes. For example, COXIBS are preferentially prescribed over nonselective NSAIDS to older patients and to those with a higher baseline risk of myocardial infarction (MI) leading to confounding by indication.^{3,4} Although observational epidemiological studies have attempted to control confounding in their analyses by indication due to differential prescribing of COXIBS and NSAIDS, many studies have derived claims from databases so the information available is limited. In addition, many studies lack detailed information regarding other potential confounders, such as use of over-the-counter medications (eg, aspirin or other NSAIDS), cigarette smoking, alcohol consumption, body mass index, physical activity, and diet. Furthermore, data on comorbid conditions, such as diabetes, hypertension, and renal disease, even when available, tend to lack information on severity or extent of disease. Because most of the observational studies of COXIBS rely on data collected primarily for administrative purposes, misclassification is likely due to an inability to verify information by clinical chart review.⁴ However, it is important to note that in all observational

study designs the availability of the most precise and complete information still could not allow for adequate control of confounding as some variables are unknown. Further, meta-analyses of the observational studies will decrease the role of chance as a plausible alternative explanation but, as the individual studies are not randomized, may even increase the amount of uncontrolled and uncontrollable confounding as each individual observational study has its own unique set of confounders. Thus, a meta-analysis of observational studies cannot be used to confirm or refute findings from randomized trials.^{5,6} For all these reasons, to assess small to moderate effects, randomized trials of sufficient size, dose, and duration represent the most reliable design strategy.² The statistical power of a trial is the ability to reject null hypothesis when it is false. Statistical power is proportional to the number of end points, not merely the sample size. The statistical power is low when the end point of interest is vascular events, which have been studied in randomized trials designed to evaluate pain relief, gastrointestinal bleeding, or prevention of other diseases, such as colon cancer or dementia. In such circumstances, an overview or meta-analysis of individual trials, which gives proportionately more weight to those of larger sample size may provide a totality of evidence upon which more rational clinical decision making for individual patients or policy decisions for the health of the general public can safely be based.²

Further, randomized trials are optimally informative when conducted for their scheduled duration. Statistical stopping guidelines are usually asymmetric for benefit and risk but should always be viewed as 1 component of the totality of evidence upon which early termination is based.⁷

Subgroup analyses can be particularly misleading even in randomized trials as the sample size is decreased and the comparisons are no longer randomized. Thus, the play of chance, as well as uncontrolled and uncontrollable confounding, is always plausible alternative explanations. In general, subgroup analyses should be

viewed as hypothesis-formulating, not hypothesis-testing.²

Basic Research

Detailed reviews of basic research and mechanisms of action of COXIBS and NSAIDS concerning risks of CVD have been published previously.⁸⁻¹⁴ In brief, traditional NSAIDS inhibit cyclooxygenase (COX), required for the production of prostaglandins and thromboxanes, that serve various functions in many tissues throughout the body. Two isoforms of COX (COX-1 and COX-2) are inhibited differentially by various NSAIDS resulting in different physiologic effects. Aspirin almost exclusively blocks COX-1, whereas COXIBS preferentially block COX-2. Traditional NSAIDS inhibit both isoforms.

In the platelet, aspirin permanently blocks thromboxane production by irreversibly binding to COX-1, reducing platelet aggregation. Traditional NSAIDS also inhibit platelet COX-1 but only when their metabolites are in the bloodstream raising the possibility that longer acting NSAIDS might have clinically important antithrombotic effects. The COXIBS appear to have little or no effect on thromboxane production in the platelet.

Prostacyclin is an eicosanoid, which is produced in endothelial cells from prostaglandin H₂ by the action of the enzyme prostacyclin synthase, also appears in many other tissues, including the lung, brain, and kidney, and has an important role as a platelet antiaggregant and vasodilator. The COX-1 isoform is also expressed in platelets and mediates production of thromboxane A₂, a potent platelet activator and aggregator, and so plays an important role in thrombotic processes. The NSAIDS may affect prostacyclin in the endothelium, which could increase the risk of thrombosis.^{8,9} In 1 study, COXIBS produced a significant decrease in a urinary metabolite of prostacyclin, raising the possibility that COXIBS could increase thrombosis if the prostacyclin reduction were from the endothelium. According to this hypothesis, traditional NSAIDS would have a similar effect on endothelial prostacyclin levels but would also reduce thromboxane production in the platelet. If so, traditional NSAIDS would not and COXIBS would be prothrombotic.¹⁰

However, it remains unclear whether COX-1 or COX-2 is responsible for prostacyclin production in the endothelium. Some studies in animals and apparently healthy human volunteers have associated

prostacyclin production in the endothelium with COX-1, and not with COX-2.¹¹⁻¹³ Aspirin, which has about 170 times more affinity for COX-1 than COX-2, inhibits arterial prostacyclin by 100%.^{14,15} Traditional NSAIDS can reduce urinary metabolites of prostacyclin at least as much or more than COXIBS.⁸

Some basic research is also compatible with the possibility that COXIBS might even be cardioprotective due to anti-inflammatory effects. Inflammation is a precursor and C-reactive protein (CRP), an inflammatory marker, predicts the future risks of CVD.¹⁶ In mice, inhibition of COX-2 from white blood cells reduced CRP, as well as the development of early atherosclerotic lesions.¹⁷

With respect to the issue of whether COXIBS affect CRP, 34 patients recovering from acute coronary syndrome had lower levels of CRP and interleukin-6 (IL-6) at 1 month and lower CRP levels at 3 months when treated with rofecoxib plus aspirin, suggesting that suppression of inflammatory processes may lead to retardation of coronary atherosclerosis and coronary events.¹⁸ Similarly, 35 patients with a history of recurrent acute coronary events had decreased IL-6 and CRP when prescribed with rofecoxib for 6 months, continuing for a further 3 months after discontinuation.¹⁹ It is important to note, however, that levels of CRP and IL-6 were not affected by prescription of rofecoxib versus placebo in patients with stable coronary artery disease in another randomized placebo-controlled study after 8 weeks, suggesting that these effects occur predominantly with prolonged COX-2 inhibition.²⁰

Observational Studies

A retrospective cohort study using the Tennessee Medicaid database assessed whether patients who self-selected for COXIBS or other nonselective NSAIDS had higher risks of coronary heart disease (CHD), defined as acute MI or CHD death.²¹ Among 251 046 users and 202 916 nonusers who developed 5316 end points there was no association. However, in subgroup analysis, based on 12 exposed cases, patients prescribed with rofecoxib at doses greater than 25 mg daily had a 93% increased risk (relative risk (RR) = 1.93; 95% confidence interval (CI), 1.09-3.43) of CHD.

A population-based retrospective cohort study using administrative databases in Ontario, Canada was conducted among 66 964 elderly patients taking selective COX-2 inhibitors, naproxen or nonaspirin NSAIDS, and 100 000 controls not using these drugs.²² On the

basis of 701 events, there were no significant differences in the rates of acute MI.

A prescription-event monitoring cohort study compared the incidence rates of selected thromboembolic (cardiovascular, cerebrovascular, and peripheral venous thrombotic) events reported for patients prescribed with rofecoxib and meloxicam in general practice.²³ After adjustment for age and sex, the RRs for rofecoxib compared with meloxicam were 1.68 (95% CI, 1.15-2.46) for cerebrovascular events, 0.29 (95% CI, 0.11-0.78) for peripheral venous thrombotic events, and 1.38 (95% CI, 0.71-2.67) for cardiovascular thromboembolic events.

In a retrospective case-control study among 54 475 elderly recipients of Medicare in New Jersey and Pennsylvania,²⁴ there were no statistically significant differences in MI between users of rofecoxib and nonusers of traditional NSAIDs, nor between users of rofecoxib and users of traditional NSAIDs. In subgroup analysis, there was a possible increased risk associated with rofecoxib when compared with celecoxib, which was no longer present after the first 90 days of use.

In a high risk Medicaid population-based, case-control study, patients who self-selected for COXIBS compared to nonnaproxen NSAIDs had no significantly increased risk of a combined end point of nonfatal MI, nonfatal stroke and fatal CVD (RR = 1.09; 95% CI, 0.90-1.33).²⁵ In another case-control study, there was no increased and a possible but not significant decreased risk of MI among those who self selected for COXIBS compared with nonusers of NSAIDs (RR = 0.73; 95% CI, 0.49-1.07).²⁶ In subgroup analyses, rofecoxib users had no statistically significant increase in risk (RR = 1.16; 95% CI, 0.70-1.93), but celecoxib users had a significantly lower risk (RR = 0.43; 95% CI, 0.23-0.79) compared with nonusers. Thus, when rofecoxib was compared with celecoxib there appeared to be an increased risk.

In an analysis of prescription data in New Zealand, there was no increase in risk among patients prescribed with celecoxib compared with rofecoxib (RR = 0.94; 95% CI, 0.51-1.70).²⁷ A case-control study from the Kaiser Permanente health care database compared the risk of acute MI and sudden cardiac death among users of celecoxib, ibuprofen, naproxen, rofecoxib, and other NSAIDs.²⁸ Although the overall effect of rofecoxib was lower than that for diclofenac, based on a subgroup analysis for rofecoxib >25 mg compared with use of any NSAID, based on 10 exposed cases there was a statistically

significant increased risk (RR = 3.00; 95% CI, 1.09-8.31). In a retrospective cohort study of 113 000 patients using Quebec's administrative health database,²⁹ self-selection for any NSAIDs was not associated with MI (RR = 0.91; 95% CI, 0.77-1.09). In addition, use of rofecoxib (RR = 0.97; 95% CI, 0.85-1.10) or celecoxib (RR = 1.00; 95% CI, 0.88-1.13) was not associated with any increased risk of MI. In subgroup analyses based on 21 MIs, current users of rofecoxib (RR = 1.24; 95% CI, 1.05-1.46) but not celecoxib (RR = 0.99; 95% CI, 0.85-1.16) had an increased risk.

In a population-based case-control study in Denmark,³⁰ current and new users of several selective and traditional NSAIDs had increased risks of hospitalization for MI. In data from 367 general practices in the patients from United Kingdom prescribed rofecoxib (RR = 1.32; 95% CI, 1.09-1.61), diclofenac (RR = 1.55; 95% CI, 1.39-1.72), and ibuprofen (RR = 1.24; 95% CI, 1.11-1.39) had increased risks of MI.³¹ In a nested case-control study of oral cancer among a cohort of heavy smokers in Norway,³² long-term users of traditional NSAIDs had a statistically significant increased risk (RR = 2.05; 95% CI, 1.33-3.16) of death from CVD and a decreased risk of oral cancer (RR = 0.47; 95% CI, 0.37-0.60).

Not surprisingly, the findings from the observational epidemiological studies are inconsistent. Some conclude harm, others no effect, whereas still others conclude it has beneficial. The results comparing patients who self-select for COXIB use to those who self-select for traditional NSAID use are also inconsistent. In subgroup analyses for dose and duration the findings are also inconsistent. For example, in 1 study,²⁹ users of rofecoxib had a significantly increased risk of acute MI compared with users of celecoxib. This finding, however, was apparent only during the first 90 days of use. It is interesting to note that in this same study, users of statins had no decreased risk of CVD despite proof beyond a reasonable doubt of clinical benefits on MI, stroke, and CVD death from randomized trials and their meta-analyses.

Randomized Trials

Randomized trials of sufficient size, dose, and duration provide the most reliable design strategy to test the most plausible small to moderate benefits (or harm) of interventions. For COXIBS, the randomized trials were not specifically designed to evaluate

Table 2. Large, Long-term Randomized Trials of Cyclooxygenase-2 Inhibitors

Study Name	COX-2 Drug Dose	Population	Sample Size	Duration	Comparator	Cardiovascular RR for COX-2
APPROVe	Rofecoxib 25 mg daily	Polyps	2586	3 y	Placebo	1.92 (1.19-3.11)
APC	Celecoxib 200 mg bid, 400 mg bid	Colorectal adenomatous polyps	2035	33 mo	Placebo	low dose 2.5 (0.9-5.5), high dose 3.4 (1.4-7.8)
PreSAP	Celecoxib 400 mg daily	Polyps	1561	3 y	Placebo	1.3 (0.65-2.62)
ADAPT	Celecoxib 200 mg bid	Alzheimer's	2528	20 mo	Placebo, Naproxen 220 mg bid	About 1
Post CABG	(Parecoxib) valdecoxib	Immediately Post CABG	1671	10 d	Placebo	2
VIGOR	Rofecoxib 50 mg daily	RA	8076	<12 mo	Naproxen 500 mg bid	5
CLASS	Celecoxib 400 mg bid	OA, RA	7968	6 mo	Diclofenac 75 mg bid, Ibuprofen 800 mg tid	1.1 (0.7-1.16)
TARGET	Lumiracoxib 400 mg daily	OA	18 325	1 y	Naproxen 500 mg bid, Ibuprofen 800 mg tid	Naproxen 1.44, Ibuprofen 0.79
MEDAL program	Etoricoxib 60 or 90 mg daily	OA	34 701	18 mo	Diclofenac 150 mg daily	0.95 (0.81-1.11)

Abbreviations: COX-2, cyclooxygenase-2; RR, relative risk; APPROVe, Adenomatous Polyp Prevention on Vioxx; APC, Adenoma Prevention With Celecoxib; PreSAP, Prevention of Colorectal Sporadic Adenomatous Polyps Trial; ADAPT, Alzheimer's disease Anti-Inflammatory Prevention Trial; CABG, coronary artery bypass graft; VIGOR, Vioxx Gastrointestinal Outcomes Research; CLASS, Celecoxib Long-term Arthritis Safety Study; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event Trial; MEDAL, Multinational Etoricoxib and Diclofenac Arthritis Long-term Study; RA, rheumatoid arthritis; OA, osteoarthritis; bid, twice a day; tid, thrice a day.

CVD, which increases the need for a comprehensive meta-analysis (Table 2).

The Vioxx Gastrointestinal Outcomes Research (VIGOR) Study was a large-scale, randomized trial, which included 8000 patients with rheumatoid conditions designed to compare 50 mg of rofecoxib twice daily with naproxen on gastrointestinal perforations, ulcers, and bleeds.³³ In VIGOR, patients assigned at random to rofecoxib experienced significantly fewer serious gastrointestinal symptoms, perforations, ulcers, and bleeds than those assigned to naproxen. However, the data also showed that patients assigned to naproxen experienced significantly fewer serious thrombotic cardiovascular events than those assigned at random to rofecoxib. Specifically, there were 19 events among naproxen users and 45 among rofecoxib users, a statistically significant difference due largely to MI, where the numbers of events were 4 and 20, respectively (0.1% vs 0.4%; RR = 0.2; 95% CI, 0.1-0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the 2 groups.³⁴ At that time, it was unclear whether these results reflected a beneficial effect of naproxen, and/or a harmful effect of rofecoxib.

In basic research, naproxen significantly reduced arachidonic acid-induced platelet aggregation and prevented an increase in thromboxane levels during myocardial ischemia.³⁵ In a randomized research, placebo-controlled ex vivo blood assay study of a number of nonselective NSAIDs and selective COX-2 inhibitors, naproxen sodium at 550 mg twice daily caused 95% platelet inhibition during the entire dosing interval, a level comparable to that of aspirin.³⁶ The possibility that the results of the VIGOR trial may reflect, at least in part, an antiplatelet effect of naproxen, is supported by an earlier open-label crossover study of low-dose aspirin and naproxen given at 500 mg twice daily.³⁷ In this study, platelet inhibition from naproxen up to 12 hours after dosing was at approximately the same level as platelet inhibition induced by aspirin.

A randomized placebo-controlled trial showed that flurbiprofen, a long-acting NSAID like naproxen, significantly reduced the rate of rethrombosis after coronary angioplasty.³⁸ In another randomized trial of secondary prevention, indobufen, another nonselective NSAID, significantly reduced the risk of serious cardiovascular events in patients with CHD.³⁹

The Celecoxib Long-term Arthritis Safety Study (CLASS) was a large-scale randomized trial designed to test whether celecoxib compared with nonselective NSAIDs (diclofenac and ibuprofen) reduced gastrointestinal side effects.²⁴ In CLASS, celecoxib had better gastrointestinal safety and no excess risk of thrombotic cardiovascular events (RR = 1.1; 95% CI, 0.7-1.16). Among the subgroup of patients not taking aspirin the results were similar (RR = 1.1; 95% CI, 0.6-1.9). Plausible explanations for these findings include equal risks of the COXIB to that of diclofenac and ibuprofen or no risk of any agent.

Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), a randomized trial of lumiracoxib,⁴⁰ consisted of 2 subtrials: 1 subtrial compared lumiracoxib to ibuprofen and the other subtrial compared lumiracoxib to naproxen. In the comparison between lumiracoxib and ibuprofen, there were 5 MIs in the lumiracoxib arm compared with 7 MIs in the ibuprofen arm. In the comparison between lumiracoxib and naproxen, there were 18 MIs in the lumiracoxib arm compared with 10 in the naproxen arm. For the composite cardiovascular end point, there were 19 events in the lumiracoxib arm compared with 23 in the ibuprofen arm and 40 in the lumiracoxib arm compared with 27 in the naproxen arm. None of these results achieved statistical significance. In subgroup analyses, naproxen users who self-selected for aspirin appeared to have a diminished benefit compared with naproxen users who did not take aspirin.

To test the potential benefits of COXIBS in cancer prevention several long-term randomized trials were carried out. The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial was designed to test whether 25 mg of rofecoxib daily compared with placebo decreased the recurrence of cancerous colon polyps.⁴¹ In a subgroup analysis, during the first 18 months, there was no apparent difference in the rate of confirmed thrombotic events, but after 18 months, the RR was 1.92 (95% CI, 1.19-3.11).

The Adenoma Prevention With Celecoxib (APC) trial was designed to test whether celecoxib reduced the risks of colon cancer.⁴² Patients assigned to celecoxib had a RR of 2.3 (95% CI, 0.9-5.5) for 200 mg twice daily and a RR of 3.4 (95% CI, 1.4-7.8) for 400 mg twice daily for cardiovascular events beginning after approximately 12 months of treatment. The Prevention of Colorectal Sporadic Adenomatous Polyps Trial (PreSap) indicated that those assigned to celecoxib compared with placebo had increased risks.⁴³ Unlike earlier trials, such as the VIGOR and CLASS trials,

which were designed to study gastrointestinal events, the APC and the PreSAP trials specifically incorporated cardiovascular outcomes as secondary end points.

No long-term randomized trials have been conducted with valdecoxib. The 2 short-term placebo-controlled trials using parecoxib (a pro-drug for valdecoxib, given intravenously) followed by oral valdecoxib in patients following coronary artery bypass graft surgery found a significantly increased risk of serious cardiovascular events.^{29,44}

The Multinational Etoricoxib and Diclofenac Arthritis Long-term Study (MEDAL) program was prospectively designed to pool data from 3 randomized, double-blind clinical trials; the MEDAL, the Etoricoxib Versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial (EDGE), and the EDGE II study. Among 34 701 patients treated and followed for 18 months, the hazard ratio for thrombotic cardiovascular events was 0.95 (95% CI, 0.81-1.11) for etoricoxib versus diclofenac. Rates of upper gastrointestinal clinical events were lower with etoricoxib, but complicated events were similar for both drugs.⁴⁵

The 3 randomized trials terminated early were the Vioxx in Prostate Cancer Prevention Study (ViP), the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime Study (VICTOR), and the Alzheimer's disease Anti-Inflammatory Prevention Trial (ADAPT). The ViP study and VICTOR trial were stopped at the time Merck voluntarily withdrew rofecoxib from the market and the results have not been published. The data and safety monitoring board of ADAPT met just before the trial was terminated early and reported no cogent evidence to recommend alteration or termination. Several days later, a press release stated that the trial was stopped because of harm of both celecoxib and naproxen. The manuscript was published 2 years later,⁴⁶ but there were too few cardiovascular events in the ADAPT trial to permit definitive conclusions regarding the safety of naproxen or celecoxib.

Pooled Analyses

The first attempt at a pooled analysis compared the rate of cardiovascular events in VIGOR and CLASS to those from the placebo groups of the 4 previously published primary prevention trials of aspirin,⁴⁷ but this type of analysis was unreliable because these trials involved different populations studied at different periods of time. The 10-year risks of a first CHD event in the placebo groups from the different

aspirin trials are low and vary from about 3.8% to 14.2%. The patients in VIGOR had rheumatoid arthritis and thus had a higher risk of CVD than the apparently healthy individual in the primary prevention trials of aspirin.

An early pooled analysis included data from 23 randomized trials of rofecoxib involving 28 000 patients.⁴⁸ There were no significant differences in the rates of CVD in patients assigned to rofecoxib compared with those assigned placebo. A pooled analysis of 15 randomized trials of celecoxib⁴⁹ including over 31 000 patients, showed no significant difference in cardiovascular events between patients given celecoxib and those assigned to either placebo or other NSAIDs.

Meta-Analyses

Even the most reliable quantitation of the magnitude of the effects of COXIBS and nonselective NSAIDs on the risk of vascular events is based on relatively small numbers. The findings were derived from a comprehensive worldwide meta-analysis of all available randomized trials.⁵⁰ This analysis used particularly careful ascertainment methods and included all available data from all completed trials, whether published or not. Summary data were available from 138 trials involving a comparison of a COXIB versus placebo or versus a traditional NSAID (or both) in which there were 145 373 participants. The primary prespecified end point was a composite of serious vascular events defined as nonfatal MI, nonfatal stroke, or CVD death. In placebo comparisons, allocation to a COXIB was associated with a 42% relative increase in serious vascular events (1.2% per year vs 0.9% per year, RR = 1.42; 95% CI, 1.13-1.78, $P = .003$), with no statistically significant heterogeneity among the different COXIBS although most of the data were derived from celecoxib and rofecoxib. The increase in this composite end point was chiefly attributable to an increased risk of MI (0.6% per year vs 0.3% per year, RR = 1.86; 95% CI, 1.33-2.59, $P = .0003$), with little apparent difference in nonfatal stroke or fatal CVD. Among trials of at least 1 year's duration (mean = 2.7 years), the relative risk for vascular events was 1.45 (95% CI, 1.12-1.89, $P = .005$). However, statistically significant heterogeneity ($P = .001$) was found between trials of a COXIB versus naproxen (RR = 1.57; 95% CI, 1.21-2.03) and of a COXIB versus non-naproxen NSAIDs (RR = 0.88;

95% CI, 0.67-1.12). The summary RR for vascular events compared with placebo was 0.92 (95% CI, 0.67-1.26) for naproxen, RR = 1.51 (95% CI, 0.96-2.37) for ibuprofen, and RR = 1.63 (95% CI, 1.12 to 2.37) for diclofenac.

Conclusions

Basic research provided plausible mechanisms to explain why COXIBS increase risks of CVD. Descriptive studies led to the formulation of the hypothesis that COXIBS, as well as nonselective NSAIDs, increase risks of CVD. Some, but not all, observational analytical studies, both case-control and cohort studies indicated that patients prescribed COXIBS and NSAIDs had increased risks of nonfatal and fatal CVD, both MI and stroke. It was clear that patients prescribed COXIBS were different from those prescribed other drugs for pain relief. Because of uncontrolled and uncontrollable confounding by indication inherent in all observational studies, it was not possible to discern whether, and if so, how much, of the observed increased risks were real.

The early randomized trials tended to be small in size and many were terminated early based on data-dependent emphasis on the aforementioned results, which created considerable confusion for health care providers and patients. Even the most comprehensive worldwide meta-analyses of the 138 randomized trials using placebo is based on relatively small numbers. This meta-analysis showed that COXIBS increased risk of CVD by 42%, principally MI but not stroke or CVD death. Indirect comparisons showed similar increases and confidence limits for rofecoxib and celecoxib, the most widely studied of the COXIBS. Further meta-analyses of the randomized trials using active comparators showed qualitative differences for naproxen and non-naproxen NSAIDs. Specifically, naproxen appeared to be neutral or slightly protective on risk of CVD. This observation is compatible with basic research concerning the reversible inhibition of platelets by NSAIDs which could, at least in theory, result in aspirin-like benefits for naproxen, a long-acting drug. With respect to non-naproxen NSAIDs, ibuprofen and diclofenac appeared to have an effect similar to COXIBS. All the drugs used in these randomized trials were prescription, not over the counter doses. Nonetheless, the comprehensive meta-analysis of the randomized trials, while based on relatively small numbers, provides the most reliable data and indicate that COXIBS are associated with a small to

moderate increased risk of vascular events, as are high-dose regimens of ibuprofen and diclofenac, but high-dose naproxen is not associated with such an excess. Although the totality of evidence is, as yet, incomplete with respect to dose and duration, clinicians may wish to use over the counter doses for short durations of non-naproxen NSAIDs and consider either high-dose naproxen or prescribed doses of a COXIB for long-term use.

Most if not all traditional NSAIDs, as well as COX-IBS, increase salt and fluid retention, leading to edema. Dose-dependent effects of COXIBS and NSAIDs may increase blood pressure and exacerbate heart failure in susceptible patients. Another meta-analysis suggested that rofecoxib increased risks of arrhythmias. Although the number of randomized subjects in the analysis was 116 094, the number of subjects in the rofecoxib group was 13 (vs 2 in control).⁵¹ All such potentially deleterious effects, including clinical heart failure,⁵² need to be distinguished from prothrombotic effects.

Even the overall data from the meta-analyses of the randomized trials, however, are based on individual trials designed to test hypotheses other than CVD. They are further limited by data-dependent early termination. Thus, from a research perspective, to achieve a sufficient totality of evidence would require large-scale randomized trials of COXIBS and NSAIDs among patients with pain from inflammatory conditions designed to directly compare the most plausible small to moderate effects on CVD, and continued for a sufficient duration. Such trials would have to be very large and simple. It would seem desirable to include use of short-acting and long-acting traditional NSAIDs, including aspirin in therapeutic doses, both with and without proton-pump inhibition, as well as acetaminophen, to allow direct comparisons of benefits on pain relief with risks on the liver and the kidney. None of these issues has been adequately studied in large-scale randomized trials of sufficient size, dose, and duration. Further, meta-analysis of trials with individual patient data could shed further light on the issues of whether or not the apparent deleterious effects of COXIBS occur only after longer durations of treatment.

In the meanwhile, from a clinical and policy perspective, the available data suggest that for relief of pain of inflammatory arthritis, naproxen may have the best benefit to risk ratio on CVD. In contrast to naproxen, other traditional NSAIDs and COXIBS confer similar moderately increased risks of CVD. At present, individual clinical judgments about COXIBS and

nonselective NSAIDs should not be limited to risks of CVD.⁵³ They should also include concerns about non-CVD risks, such as gastrointestinal bleeding and other benefits, including improved quality of life resulting from decreases in impairment from musculoskeletal pain syndromes.

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