

COX-2 Inhibitors, Other NSAIDs, and Cardiovascular Risk

The Seduction of Common Sense

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JAMA. 2006;296:(doi:10.1001/jama.296.13.jed60058).

" . . . (A) long habit of not thinking a thing wrong, gives it a superficial appearance of being right, and raises at first a formidable outcry in defence of custom. But the tumult soon subsides. Time makes more converts than reason."—Thomas Paine, *Common Sense*, 1776

The concept was appealing in its simplicity. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibited both isoforms of the enzyme cyclooxygenase responsible for the first step in the conversion of arachidonic acid into a variety of prostaglandins, thromboxanes, and leukotrienes throughout the body.¹ The anti-inflammatory and pain-relieving effects of NSAIDs resulted from inhibition of prostaglandin synthesis mediated by cyclooxygenase 2 (COX-2) at the site of tissue injury, while gastrointestinal tract complications were due to inhibition of prostaglandin synthesis mediated by cyclooxygenase 1 (COX-1) in the gastrointestinal mucosa. The allure of COX-2 inhibitors was the prospect of treating pain without gastrointestinal toxicity.¹ Celecoxib and rofecoxib were the first of these new agents to gain approval and, with heavy promotion and direct-to-consumer advertising, quickly became the most widely prescribed NSAIDs in the United States.

Lurking in the background was the concern that selective COX-2 inhibition might suppress endothelial cell synthesis of prostacyclin, leaving platelet thromboxane A₂ mediated by COX-1 relatively unopposed.²⁻³ With loss of the antiplatelet and vasodilatory effects of prostacyclin, a relative excess of thromboxane A₂ would favor vasoconstriction, platelet aggregation, and thrombosis.²⁻³ Disturbing red flags for cardiovascular risk were noted in the preapproval application for rofecoxib submitted to the US Food and Drug Administration (FDA) in November 1998, but were dismissed because of the FDA's practice of requiring "complete certainty" before acting on safety concerns.⁴ Indeed, as noted by Psaty and Furberg,⁵ "Safety signals were recognized by the medical officer of the Food and Drug Administration (FDA) who observed that in 6-week studies, thromboembolic events are more frequent in patients receiving rofecoxib [12 (0.6%) of 1780] than placebo [1 (0.24%) of 412]."

Within months of rofecoxib's approval in May 1999, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial reported a 50% reduction in serious gastrointestinal outcomes, but a 5-fold increase in thromboembolic cardiovascular events (primarily acute myocardial infarction [MI]) among patients treated with 50 mg/d of rofecoxib compared with 1000 mg/d of naproxen.⁶ For nearly 2 years after these results became known, rofecoxib's label remained unchanged while the company aggressively marketed the drug, claiming that it did not increase the risk of MI and that naproxen was cardioprotective.⁶⁻⁸ During this period, the FDA warned the company that its promotion of rofecoxib made "unsubstantiated claims," "promoted off-label use," and was "false, lacking in fair balance, or otherwise misleading."⁸ Meanwhile, a Pfizer study of celecoxib in Alzheimer disease, which was completed in 2000 but not revealed until January 2005, showed an increase in cardiovascular risk with that drug.⁹

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Then, in 2004, Merck withdrew rofecoxib from the market after its Adenomatous Polyp Prevention on Vioxx (APPROVe) trial showed a 2-fold increase in cardiovascular risk with 25 mg/d of rofecoxib compared with placebo.¹⁰ Based on an unplanned post hoc analysis, the company claimed that risk increased only after 18 months of continuous use,¹⁰⁻¹¹ which if true, would reduce the company's liability substantially because most rofecoxib use was for much shorter periods. Against this backdrop, public concern was heightened by announcements that celecoxib, valdecoxib, and naproxen might also increase MI risk.¹²⁻¹⁴ For example, analysis of the Adenoma Prevention with Celebrex study showed at least a tripling of risk for 400 mg of celecoxib twice daily.¹² Subsequently, the FDA labeled all COX-2 selective and nonselective NSAIDs as increasing cardiovascular risk,¹⁵ adding to public anxiety and confusion.

In 2006, Merck announced that it had performed an incorrect statistical test in its post hoc analysis of the APPROVe trial.¹⁶ More importantly, the analysis was performed improperly because it relied on a censoring rule that violated widely accepted intention-to-treat principles.¹⁷⁻¹⁸ When analyzed appropriately, cardiovascular risk was decidedly present early in rofecoxib therapy.¹⁷ The *New England Journal of Medicine* published a correction to the original report of APPROVe, removing all reference to an 18-month threshold for cardiovascular risk, thereby indicating that risk was increased from the start of therapy and continued through the period of the study.¹⁹

In this issue of *JAMA*, 2 systematic reviews²⁰⁻²¹ provide clarity on a topic that has been dominated more by disinformation than reason. Zhang and colleagues²⁰ addressed the important but underappreciated issue of renal effects with COX-2 selective NSAIDs. Their review and meta-analysis of 114 clinical trials involving 116 094 patients revealed that rofecoxib was associated with increased risk of peripheral edema, hypertension, and renal dysfunction at low and high doses. Risk of cardiac arrhythmias was also increased, and while the number of events was small, ventricular fibrillation, cardiac arrest, and sudden cardiac death accounted for most arrhythmia events. No such effects were present with celecoxib, valdecoxib, or etoricoxib. Moreover, in a time-cumulative analysis, the authors suggest that the risk of peripheral edema and hypertension associated with rofecoxib was evident by 2000, and the risk of arrhythmia was evident by 2004.

In their systematic review of observational studies, McGettigan and Henry²¹ focused on the cardiovascular (primarily MI) risk of COX-2 selective and nonselective NSAIDs. Among their most important findings, cardiovascular risk was increased with rofecoxib as well as with diclofenac, indomethacin, and probably meloxicam. Rofecoxib risk was increased at low and high doses and was evident during the first 30 days of use. Importantly, naproxen was *not* cardioprotective. With a pooled relative risk (RR) of 0.97 (95% confidence interval [CI], 0.87-1.07), naproxen neither increased nor decreased risk. Although the RR for ibuprofen was not statistically significantly increased compared with that for naproxen, the lower bound of its 95% CI approached 1 (RR, 1.07; 95% CI, 0.97-1.18), which is less than reassuring.

Of note, rofecoxib, diclofenac, and meloxicam are COX-2 selective inhibitors¹ and this common characteristic may account for their increased risk, although it does not necessarily explain all of these observations. Celecoxib is also COX-2 selective (but less so than rofecoxib) and, in the review by McGettigan and Henry,²¹ while cardiovascular risk was increased at a dose above 200 mg/d, risk at 200 mg/d was not increased. Nonetheless, it may be prudent to regard celecoxib with caution in light of 4 recent studies published since their meta-analysis was completed. Andersohn et al²² reported an increased MI risk with celecoxib (RR, 1.56; 95% CI, 1.22-2.00) in addition to increased risks with the COX-2 selective drugs rofecoxib, diclofenac, etoricoxib, and valdecoxib. Brophy et al²³ found that MI risk with celecoxib was increased among patients without, but not with, a past history of MI. Gislason et al²⁴ found that in patients following

hospitalization for a first MI, rofecoxib was associated with a 2.5-fold (≤ 25 mg/d) and 5.3-fold (> 25 mg/d) increase in risk of death and a 1.7-fold (≤ 25 mg/d) increase in reinfarction. Celecoxib was associated with a 1.9-fold (≤ 200 mg/d) and 4.7-fold (> 200 mg/d) increase in risk of death and a 1.5-fold and 1.6-fold increased risk of reinfarction at lower and higher doses, respectively. The risk of death with ibuprofen was increased 2.2-fold at doses higher than 1200 mg/d and reinfarction was increased at doses below and above 1200 mg/d.²⁴ Also, Helin-Salmivaara et al²⁵ found an increased risk of first-time MI with rofecoxib and etoricoxib but not celecoxib, as well as increased risk with diclofenac, indomethacin, ibuprofen, and naproxen.

A 2004 cumulative meta-analysis by Juni et al²⁶ showed that rofecoxib increased cardiovascular risk at low and high doses and that risk was increased early in therapy. In a recently reported meta-analysis of 138 randomized trials covering all NSAIDs, Kearney et al²⁷ found that for 37 trials with rofecoxib (85% at 25 mg/d), acute MI risk was increased (RR, 1.73; 95% CI, 1.09-2.82) compared with placebo. With celecoxib (41 trials), the RR was 2.70 (95% CI, 1.30-6.29), which was driven by 21 studies at doses of 400 mg/d or higher. Combined vascular event risk (primarily MI) compared with placebo was also increased for diclofenac (RR, 1.63; 95% CI, 1.12-2.37) and approached statistical significance for ibuprofen (RR, 1.51; 95% CI, 0.96-2.37).²⁷ Risk was not increased with naproxen (RR, 0.92; 95% CI, 0.67-1.26).²⁷

What does this all mean? First, rofecoxib increases the risk of acute MI at low and high doses. This risk begins early in therapy, probably with the first dose. There is no initial 18-month period of immunity from risk.^{17-19,21, 26} Celecoxib also increases risk at doses higher than 200 mg/d; at lower doses, the potential risk is less clear. Several other NSAIDs increase risk, including the COX-2 selective NSAIDs diclofenac and meloxicam, and the nonselective NSAID indomethacin, and probably ibuprofen. Meta-analyses of randomized clinical trials and observational studies agree that naproxen is neutral for MI risk.

What should physicians do? For most patients with arthritis or other conditions who require chronic pain relief, naproxen appears to be the safest NSAID choice from a cardiovascular perspective. For patients at high risk of NSAID-related gastrointestinal tract complications, naproxen plus a proton pump inhibitor is less costly and as effective,²⁸⁻²⁹ and probably safer, than low-dose celecoxib. Additional studies exploring the benefits and risks of this approach are urgently needed. Third-party payers and managed care organizations may wish to fund such studies, given the huge sums they spend on COX-2 inhibitors. The nation's largest third-party payer, the federal government, should also be interested. If COX-2 inhibitors cost substantially more, confer substantially greater cardiovascular risk, and offer no unique and meaningful gastrointestinal tract benefit over generic naproxen plus proton pump inhibitor, is there any point to the continued use of these drugs? Another critical area for research relates to the use of low-dose aspirin in the setting of COX-2 selective and nonselective NSAID use. It is unclear whether aspirin mitigates or abolishes NSAID-related MI risk, and, if so, how it may affect gastrointestinal tract risk. The concomitant use of aspirin would appear to contradict the premise underlying selective COX-2 inhibitor use.

Another key issue is to account for the long delay in defining the risks and benefits of COX-2 inhibitors. Part of the problem lies with FDA policies, practices, and procedures that lead it to ignore potential safety problems. Despite a priori concerns²⁻³ and disconcerting evidence in the preapproval application,⁴⁻⁵ the FDA approved rofecoxib, stating it lacked "complete certainty" that the drug increased cardiovascular risk.⁴ Such a standard does not protect consumers, is prejudicially favorable to industry and its financial interests, rewards drug companies for not aggressively pursuing safety questions, and guarantees that some drugs with major safety problems will be approved and, once approved, will remain on the market, even in the face of extensive patient harm. The failure to immediately withdraw high-dose rofecoxib from the

market following publication of the results of the VIGOR trial, and to study quickly and intensively its cardiovascular risks at lower doses, increased the number of patients harmed by the drug as well as the profits made from its continued marketing. Only Congress can help prevent this from happening again by enacting legislation to create a separate and independent Center for Post-Marketing Safety within the FDA, empowered with the authority to identify and effectively deal with unsafe medicines and the companies that market them.

In retrospect, had the VIGOR trial's cardiovascular findings for rofecoxib been reported in comparison with naproxen (as was done for gastrointestinal tract complications), it might have been more difficult for the company to assert that naproxen was *cardioprotective*.⁵⁻⁸ Had the company adhered to accepted scientific standards, it would have reported that rofecoxib *increased* cardiovascular risk by a factor of 5 compared with naproxen, not that risk with naproxen was one fifth that of rofecoxib. Moreover, in the VIGOR trial, rofecoxib caused nearly 1 MI for every complicated gastrointestinal tract event (mainly bleeding) prevented, hardly a favorable benefit-to-risk profile.

In 2001, Mukherjee et al³⁰ raised a "cautionary flag" about an increased risk of cardiovascular events with COX-2 inhibitors, and urged caution in prescribing these agents to patients at risk for cardiovascular morbidity. Unfortunately, many patients with underlying cardiovascular risk continued to be treated with COX-2 inhibitors. The typical patient treated with rofecoxib was older, frequently male, and by virtue of age, probably had at least 1 other risk factor for cardiovascular disease (ie, the target population for rofecoxib was not at low risk). For tens of thousands of patients who experienced MI while taking rofecoxib,³¹ the drug may have been the decisive risk factor, over and above any other risk factors, that contributed to the occurrence of this life-changing and potentially fatal event.

Regarding naproxen, little skepticism about its purported cardioprotective properties was expressed. If naproxen accounted for the VIGOR results, it would have had to be at least 3 times more effective than aspirin, a finding that seems implausible. The focus of the scientific community on naproxen shifted attention from lower-dose rofecoxib and efforts to establish its risk. Likewise, with APPROVe, an improperly performed and misleading post hoc analysis enabled the company to claim that cardiovascular risk began only after 18 months of continuous rofecoxib use.¹⁰⁻¹¹ Important considerations for which skepticism was not expressed were that the post hoc analysis should have been only hypothesis-generating, that statistical power was too low to show an early risk, and that given rofecoxib's immediate suppression of prostacyclin, risk would be expected to increase with the first dose and remain elevated for the duration of therapy.

With the recent announcement by Merck that it will press for US approval of its COX-2 inhibitor NSAID etoricoxib,³² the FDA, academia, and the medical research enterprise are once again faced with the opportunity to forsake common sense by willfully accepting misdirection and disinformation presented in the guise of science. An analysis of 3 randomized trials, collectively referred to as the Multinational Etoricoxib and Diclofenac Arthritis Long-Term Program (MEDAL), was reported to show that the risk of thrombotic cardiovascular events with etoricoxib was not different from that for diclofenac (RR, 1.05; 95% CI, 0.93-1.19),³² with the implication being that etoricoxib is safe from a cardiovascular perspective. The company used a noninferiority study design, well-known to be especially poor at identifying differences in safety risks between drugs, thereby stacking the deck in favor of its drug. More importantly, in MEDAL, etoricoxib was compared with diclofenac, a drug shown to substantially increase the risk of acute MI in the meta-analysis of randomized trials by Kearney et al,²⁷ and in the meta-analysis of observational studies by McGettigan and Henry.²¹ By inference, therefore, etoricoxib also must increase cardiovascular risk, but that inference is not immediately apparent because of the way MEDAL

was designed, and by the way it appears that the findings are being interpreted and positioned.

This veiled and misleading ambiguity has much in common with the stratagems used for VIGOR and APPROVe, where the true results were opposite to those claimed and promoted. From the perspective of patient safety and rational therapeutics, naproxen, not diclofenac, should have been the reference drug in MEDAL.³³ Had that been so, it is highly likely that etoricoxib would have been shown to be no different than its first-cousin rofecoxib with respect to cardiovascular risk. From a business perspective, were etoricoxib to be exposed as another "naked emperor," its US approval might be difficult, even by the FDA's apparently industry-friendly standards. If the lessons of recent history have been learned, the FDA's concerns will now be squarely focused on patient safety rather than corporate profitability, and, ultimately, common sense will prevail.

AUTHOR INFORMATION

Financial Disclosures: Dr Graham reported no financial conflicts of interest, but reported that he was subpoenaed as a federal government expert by plaintiffs, for the purpose of providing testimony (in May 2006) that may be used in a number of Vioxx-related lawsuits, and reported that he received no compensation for this activity, other than his federal salary.

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Published online: September 12, 2006 (doi:10.1001/jama.296.13.jed60058).

Editor's Note: Dr Graham is an employee of the US Food and Drug Administration. This editorial was written by Dr Graham as an officially approved outside activity in his private capacity and not as a Food and Drug Administration employee. His contact information is publicly available at <http://directory.psc.gov/employee.htm> and is as follows: David J. Graham, MD, MPH, Office of Surveillance and Epidemiology, Food and Drug Administration, 10903 New Hampshire Ave, WO22, Room 4314, Silver Spring, MD 20993 (david.graham1@fda.hhs.gov).

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