

COX-2 Inhibitors and NSAIDs Have Cardiotoxic Effects CME

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September 13, 2006 — **Further information on the cardiotoxicity of cyclooxygenase-2 (COX-2) inhibitors and regular nonsteroidal anti-inflammatory drugs (NSAIDs) has come from 2 systematic reviews published in the September 12 Early Release issue of *JAMA*.**

In an editorial accompanying the 2 *JAMA* articles, David J. Graham, MD, from the Food and Drug Administration (FDA) in Silver Spring, Maryland, welcomes the 2 reviews, which he says "provide clarity on a topic that has been dominated more by disinformation than reason."

Another article by Solomon and colleagues focusing specifically on the cardiotoxicity of celecoxib, published in the September 5 issue of *Circulation*, suggests that cardiac adverse effects are also an issue with celecoxib and follow a dose-response relationship.

And, coinciding with these publications, the FDA has issued an alert notifying consumers and healthcare professionals that taking **ibuprofen for pain relief may interfere with the benefits of aspirin taken for heart disease** and advising that these 2 drugs should be taken at different times to avoid such an interaction.

Effects of Diclofenac, Indomethacin, and Meloxicam

The *JAMA* article by Patricia McGettigan, MD, and David Henry, MD, from the University of Newcastle in New South Wales, Australia, consists of a systematic review of observational studies focusing on the cardiovascular risk of COX-2 selective and nonselective NSAIDs. Results showed that cardiovascular risk was increased with **diclofenac, indomethacin, and meloxicam as well as with rofecoxib. Naproxen was not cardioprotective**, as has been previously suggested, but appeared to have a neutral risk, and results with ibuprofen were inconclusive.

The authors conclude, "This review confirms the findings from randomized trials regarding the risk of cardiovascular events with rofecoxib and suggests that celecoxib in commonly used doses may not increase the risk, contradicts claims of a protective effect of naproxen, and raises serious questions about the safety of diclofenac, an older drug."

Renal and Proarrhythmic Effects With Rofecoxib

The second article, published in the current issue of *JAMA*, by Jingjing Zhang, MD, from Harvard School of Public Health in Boston, Massachusetts, and colleagues, focuses on renal and proarrhythmic effects of COX-2 inhibitors. The authors analyzed data from 114 clinical trials involving 116,094 patients, which showed that rofecoxib was associated with increased risk for peripheral edema, hypertension, and renal dysfunction at low and high doses. Risk for cardiac arrhythmias was also increased with rofecoxib, but neither renal effects nor arrhythmias were seen with the other COX-2 inhibitors — celecoxib, valdecoxib, or etoricoxib.

Dr. Zhang and colleagues point out that their results also suggest that "a time-cumulative meta-analytic approach for examining available trial safety data would have helped clarify apparently adverse effects several years earlier than the current report" and that "future drug safety monitoring of emerging clinical treatments may benefit from continuous cumulative meta-analytic aggregation of safety data for all drug-approval applications and experimental agents."

Systematic Review of Observational Studies

McGettigan and Henry included 17 case-control and 6 cohort studies in their review — 13 studies focusing on COX-2 inhibitors, 23 on NSAIDs, and 13 on both groups of drugs. The investigators found a dose-related risk for cardiovascular events (predominantly myocardial infarction) with rofecoxib, which was evident during the first month of treatment. But, they did not show an increased risk for celecoxib at doses of around 200 mg/day, although they add that the data did not exclude an increased risk with higher doses, noting that the randomized data only showed an increased risk with daily celecoxib doses of 400 mg and above.

Among older nonselective drugs, diclofenac, had the highest risk, appearing harmful at commonly used doses, which the authors say provides grounds for reviewing its regulatory status. Meloxicam did show an elevated relative risk, but this was largely due to the results of a single study and does not allow any definite conclusions to be drawn, the authors add. They point out that meloxicam has replaced rofecoxib and celecoxib in some markets, but these results could suggest that it may not be different in terms of cardiotoxicity from other relatively COX-2-selective drugs. The authors also point out that they found an elevated risk for cardiovascular events with indomethacin, which they say is not easily explained as it is not a selective COX-2 inhibitor. "The data reviewed here were sparse and indomethacin is seldom recommended because of gastrointestinal and central nervous system toxicity. This review provides an additional reason not to use indomethacin," Drs. McGettigan and Henry state.

Table 1. Risk for Cardiovascular Events With Various COX-2 Inhibitors and NSAIDs*

Drug	Summary Relative Risk for Cardiovascular Event (95% CI)
Rofecoxib, ≤ 25 mg	1.33 (1.00 - 1.79)
Rofecoxib, > 25 mg	2.19 (1.64 - 2.91)
Celecoxib	1.06 (0.91 - 1.23)

Diclofenac	1.40 (1.16 - 1.70)
Naproxen	0.97 (0.87 - 1.07)
Piroxicam	1.06 (0.70 - 1.59)
Ibuprofen	1.07 (0.97 - 1.18)
Meloxicam	1.25 (1.00 - 1.55)
Indomethacin	1.30 (1.07 - 1.60)
*CI indicates confidence interval.	
Source: <i>JAMA</i> . Published online September 12, 2006 (McGettigan and Henry).	

Safety of Celecoxib at Low Doses

Drs. McGettigan and Henry note that the differences between rofecoxib and celecoxib appear important from both a clinical and regulatory standpoint. "The data do not point to a safe dose level with rofecoxib, which justifies the decision taken to withdraw the drug from sale. At doses of 200 mg or less, there is no convincing evidence of an increased risk of cardiovascular events with celecoxib, which remains on international markets. However, based on the randomized data, celecoxib appears unsafe in doses of 400 mg or more. These results seem to point to different dose-effect gradients in the vascular compartment across the ranges of doses of celecoxib and rofecoxib that were used in clinical practice," the authors write. But, they state that "This review does not allow a judgment about whether any claimed advantages of celecoxib outweigh the elevated cardiovascular risk seen with high doses."

In his editorial, Dr. Graham says celecoxib should still be regarded with caution, in light of 4 recent studies published since this meta-analysis was completed, suggesting an increase in myocardial infarction rates with the drug.

More Data on Celecoxib From Colorectal Adenoma Studies

Further data on the cardiovascular safety of celecoxib were previously published. The Adenoma Prevention with Celecoxib (APC) and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials, published in the August 31 issue of the *New England Journal of Medicine*, investigated celecoxib as a treatment of colorectal adenomas. But, the cardiovascular safety of the drug in these 2 placebo controlled trials was also examined in an article published in the September 5 issue of *Circulation*.

Lead author of the article in *Circulation*, Scott Solomon, MD, from the Brigham & Women's Hospital in Boston, Massachusetts, explained to **heartwire** that *The New England Journal of Medicine* articles only had the "bottom line" numbers from the cardiovascular safety analysis, whereas his article provides much more clarity and also includes a detailed assessment of effects on blood pressure. "Also, we performed a combined analysis, and show that there may be a dose-response, with a stepwise increase in risk/events between the 400 once daily, 200 twice daily and 400 twice daily doses that were concordant with the blood pressure data," Dr. Solomon added. "The trend for a dose-related increase in cardiovascular events and blood pressure raises the

possibility that lower doses or other dose intervals may be associated with less cardiovascular risk," the researchers conclude in the article.

Table 2. Cardiovascular Safety of Celecoxib From Combined Analysis of APC and PreSAP Trials*

Dose of Celecoxib	HR (95% CI) vs Placebo for CV Death/MI/Stroke/CHF	Blood Pressure Change at 3 Years
400 mg once daily (PreSAP)	1.3 (0.6 – 2.6)	No change
200 mg twice daily (APC)	2.6 (1.1 – 6.1)	+2.6 mmHg
400 mg twice daily (APC)	3.4 (1.5 – 7.9)	+3.4 mmHg

HR indicates hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; CHF, congestive heart failure; PreSAP, Prevention of Colorectal Sporadic Adenomatous Polyps; and ACP, Adenoma Prevention with Celecoxib.

Source: *N Engl J Med.* 2006;355:873-884, 885-895.

Examining the Results

Dr. Graham stated in the accompanying *JAMA* editorial that although the relative risk for ibuprofen in the review of observational studies was not significantly increased statistically compared with that for naproxen, the lower bound of its 95% confidence interval approached 1 "which is less than reassuring."

Dr. Graham makes the following points about COX-2 inhibitors and NSAIDs:

- Rofecoxib increases the risk for acute myocardial infarction 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.
- Celecoxib also increases risk at doses higher than 200 mg/day; 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 myocardial infarction risk.

Patient Treatment Advice

Dr. Graham advises that 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 for NSAID-related gastrointestinal tract complications, naproxen plus a proton pump inhibitor is less costly and as effective,

and probably safer, than low-dose celecoxib. But, he stresses that additional studies exploring the benefits and risks for this approach are urgently needed. "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?" Dr. Graham asks.

Caution About Etoricoxib

Despite being an FDA employee, Dr. Graham has been vocal in his criticism of the agency's inertia over the COX-2 inhibitors, and he continues discussing this in his editorial.

Dr. Graham notes that a cautionary flag was raised about an increased risk for cardiovascular events with COX-2 inhibitors in 2001, but many patients with underlying cardiovascular risk continued to be treated with COX-2 inhibitors. "For tens of thousands of patients who experienced MI [myocardial infarction] while taking rofecoxib, 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," he writes.

The editorialist also points out that with the recent announcement by Merck that it will pursue US approval of its latest COX-2 inhibitor, etoricoxib, "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." Dr. Graham is referring to an analysis of 3 randomized trials, collectively referred to as the Multinational Etoricoxib and Diclofenac Arthritis Long-Term Program (MEDAL), which reported a similar risk for cardiovascular events with etoricoxib and diclofenac. Dr. Graham notes that the implication of these results is that etoricoxib is safe from a cardiovascular perspective, but he argues against such a notion, pointing out that diclofenac has been shown to substantially increase the risk for acute myocardial infarction and so by inference, therefore, etoricoxib also must increase cardiovascular risk.

Dr. Graham writes, "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 [Vioxx Gastrointestinal Outcomes Research] and APPROVe [Adenomatous Polyp Prevention on Vioxx], where the true results were opposite to those claimed and promoted." He says that naproxen should have been the reference drug in MEDAL and 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."

Dr. Graham concludes: "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."

JAMA. Published online September 12, 2006.

Circulation. 2006;114:1028-1035.

The complete contents of [Heartwire](http://www.theheart.org), a professional news service of WebMD, can be found at www.theheart.org, a Web site for cardiovascular healthcare professionals.

Clinical Context

NSAIDs may be associated with multiple complications when used on a chronic basis. A review by McGettigan and Henry in the current issue of *JAMA* found that the risk for cardiovascular events was increased with rofecoxib at both low and high doses. This risk was apparent early in treatment. In addition, the authors found that celecoxib, naproxen, piroxicam, and ibuprofen did not significantly elevate the risk for cardiovascular events, but diclofenac did increase cardiovascular risk.

Based on previous studies as well as the accompanying article in *JAMA* by Zhang and colleagues examining the renal and arrhythmia risks associated with COX-2 inhibitors (summarized in the "Study Highlights" section), an editorial by Graham recommends the use of naproxen for adults who require chronic NSAID therapy. Naproxen may be combined with a proton pump inhibitor in adults with a higher risk for gastrointestinal bleeding.

Study Highlights

- Zhang and colleagues performed a literature review focusing on celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, and lumiracoxib. They specifically sought research with renal endpoints, such as peripheral edema, hypertension, and renal dysfunction as well as studies which followed rates of arrhythmia. Studies that lacked a control group or were not double blinded were not included in the analysis.
- Hypertension events were defined as incident hypertension or worsening of existing hypertension related to COX-2 inhibitor therapy. *Renal disease* was defined by worsening levels of serum creatinine or clinically diagnosed renal disease.
- The authors found 114 studies for analysis, totaling 116,094 patients for the meta-analysis. 40 studies focused on rofecoxib, while 37 and 29 studies examined celecoxib and valdecoxib/parecoxib, respectively. The median age of subjects was in the mid-50s, and most subjects were female. Osteoarthritis was the most common indication for treatment with COX-2 inhibitors.
- There were a total of 6394 renal events, including 3489 reports of hypertension, 2670 reports of peripheral edema, and 235 reports of renal dysfunction. There were also 286 arrhythmia events.
- There was significant heterogeneity regarding renal events among different agents, indicating no class effect of COX-2 inhibitors on this outcome.
- Rofecoxib significantly increased the risk for renal adverse events (relative risk, 1.53), including significantly elevated risks for all 3 individual components of this composite outcome. Higher dosage and longer exposure increased the renal risk associated with rofecoxib. The relationship between rofecoxib and the risk for renal adverse events was evident by the year 2000.
- While there was a trend toward a higher rate of renal adverse events with valdecoxib/parecoxib, no other COX-2 inhibitor significantly increased the risk for

- renal events. Celecoxib was associated with reduced rates of renal dysfunction and hypertension (relative risks, 0.61 and 0.83, respectively).
- Only rofecoxib significantly increased the risk for arrhythmia events (relative risk, 2.90). This effect was evident by late 2004, and the most common arrhythmia events were ventricular fibrillation, cardiac arrest, and sudden cardiac death.