

COX-2 Inhibitor Use After Vioxx: Careful Balance or End of the Rope?

"Being on a tightrope is living; everything else is waiting."

—Karl Wallenda

This issue of *The American Journal of Managed Care* examines interventions aimed at improving drug safety.¹⁻⁴ The need for a rigorous research agenda in pharmaceutical safety is highlighted by Merck's decision to voluntarily withdraw rofecoxib (Vioxx) on September 30, 2004. The cyclo-oxygenase-2 (COX-2) selective inhibitor was pulled from the market after it was revealed that subjects receiving rofecoxib had roughly twice the rate of myocardial infarction and stroke when compared to the rate in placebo controls.⁵

This widely publicized recall prompted tremendous media attention, much of which focused on financial markets and decision making by the US Food and Drug Administration (FDA). Although tens of millions of Americans were using rofecoxib and the other 2 FDA-approved COX-2 selective inhibitors (celecoxib [Celebrex] and valdecoxib [Bextra]) when the withdrawal was announced, media reports provided little information to assist patients and their clinicians regarding therapeutic options. Largely lost in the firestorm over the cardiovascular safety of COX-2 selective agents was the fact that *these innovative drugs were never intended to provide pain relief superior to that of traditional non-steroidal anti-inflammatory drugs (NSAIDs). Rather, the COX-2 selective inhibitors were meant to reduce the risk of gastrointestinal adverse events, common with NSAIDs, while affording patients symptomatic relief comparable to that of the NSAIDs.* Thus, the use of the available treatment alternatives in the "post-Vioxx" era must balance competing risks and benefits.

"Perspective" articles in the October 21, 2004, issue of *The New England Journal of Medicine* called for extensive reexamination of the safety of the COX-2 selective agents, but also of how the entire class of drugs has been approved and marketed.^{6,7} The following day, the European Medicines Agency announced that it would reexamine all aspects of the cardiovascular safety of the COX-2 inhibitors to assess whether changes need to be made to existing labeling and whether additional studies are needed. In the meantime, millions of patients looked for counsel as to whether they should continue taking their COX-2 inhibitors.

Given the undesirable cardiovascular findings for rofecoxib, the lack of long-term, placebo-controlled cardiovascular safety studies for either celecoxib or valde-

coxib raises concern regarding continued use of these other COX-2 selective agents. Fitzgerald emphasized this point, stating "the burden of proof now rests with those who claim that this is a problem for rofecoxib alone and does not extend to other coxibs. We must remember that the absence of evidence is not the evidence of absence."⁷

COX-2 selective agents were developed and prescribed with the best intentions, to relieve patients' pain and disability. Nevertheless, clinicians must always be aware that treatment decision making has always been, and likely always will be, about balancing potential benefits against potential risks. With the alarming revelation that many COX-2 users may be at increased risk for myocardial infarction or stroke, this tightrope balancing act is in the spotlight.

Knowing what we now know, clinicians should begin by assessing each patient's risk factors for cardiovascular events and consider initiating aspirin prophylaxis before prescribing pain relief. User-friendly tools are easily accessed from the Internet to assess cardiovascular risk and indications for aspirin.⁸ For patients with an increased risk of myocardial infarction and stroke, none of the COX-2 selective agents may be the ideal pain treatment for 2 important reasons. First, long-term cardiovascular safety data for the available COX-2 selective agents in at-risk patients are currently lacking.^{6,7} Second, the gastrointestinal risk-reducing effect of COX-2 agents is diminished, if not eliminated, with concomitant aspirin use, an underappreciated fact.⁹⁻¹¹ One national survey reported that more than 50% of chronic COX-2 users over the age of 55 took regular aspirin therapy,¹² potentially negating the safety advantage of this class of drugs in a majority of users.

For patients who do not have cardiovascular risk factors that require aspirin prophylaxis and who are at low or no risk for gastrointestinal complications (Table, upper left quadrant), monotherapy with one of the traditional nonselective NSAIDs offers a sound approach to anti-inflammatory therapy. For patients who do not require aspirin prophylaxis and are at risk for NSAID-induced gastrointestinal complications (upper right quadrant), a suitable initial approach would be to prescribe either a COX-2 selective inhibitor or a traditional NSAID and a proton pump inhibitor (PPI). In a

Table. A Clinician's Guide to NSAID Therapy After Vioxx Recall

	No/Low NSAID GI Risk	NSAID GI Risk
No CV risk (no aspirin)	Traditional NSAID	Coxib or Traditional NSAID + PPI Consider non-NSAID therapy
CV risk (consider aspirin)	Traditional NSAID* plus PPI if GI risk warrants gastroprotection Consider non-NSAID therapy	A gastroprotective agent must be added if a traditional NSAID* is prescribed Consider non-NSAID therapy

*Ibuprofen should be used cautiously in individuals taking aspirin.

NSAID indicates non-steroidal anti-inflammatory drug; GI, gastrointestinal; CV, cardiovascular, PPI, proton pump inhibitor.

randomized, controlled study of patients at high risk for gastrointestinal complications, recurrent gastrointestinal bleeding rates were not different for those taking a traditional NSAID and a PPI compared to a COX-2 agent alone.¹³ While no statistical differences were seen between the 2 treatment arms, the high rates of events in both groups (approximately 5% at 6 months) draws attention to the important clinical point that a "safer" treatment option does not mean completely safe.

For NSAID users with cardiovascular risk who require aspirin prophylaxis, COX-2 selective agents should be avoided for the reasons noted above. Since it is well established that multiple NSAID use (ie, aspirin and any NSAID) raises the likelihood of gastrointestinal complications,¹⁴ prophylaxis against the development of gastrointestinal adverse events may be warranted. Recommending that COX-2 users at risk for cardiovascular events simply switch to traditional NSAIDs ignores the profound clinical and economic effects of NSAID-related gastrointestinal adverse events, the reason the COX-2 agents were developed. For individuals with no gastrointestinal risk factors (lower left quadrant), a traditional nonselective NSAID should be prescribed with a PPI if the absolute risk of a gastrointestinal complication warrants gastroprotection. For the large number of individuals at risk for cardiovascular and gastrointestinal adverse events (lower right quadrant), if a traditional NSAID must be used (in lieu of non-NSAID therapy), the additional measure of prescribing a gastroprotective agent is strongly recommended.

In light of the Vioxx withdrawal and the subsequent reassessments of COX-2 agents underway to definitively establish cardiovascular safety, clinicians should balance the benefits and risks of available agents in terms of pain relief and cardiovascular and gastrointestinal safety. Until the burden of safety is met, we should con-

sider taking our patients "back to the future" and use older, well-studied agents to safely provide symptomatic relief.

—A. Mark Fendrick, MD
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