Cardiovascular Risks of Cyclooxygenase-2 Inhibitors: Where We Stand Now

Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), including nonselective nonaspirin NSAIDs and cyclooxygenase-2 selective (COX-2) inhibitors, are widely used for various arthritides and pain syndromes. Cyclooxygenase-2 inhibitors in particular have been an enormous financial success, with more than $5 billion in sales in the United States in 2003 (1). That market took a huge hit recently with the withdrawal of rofecoxib (Vioxx, Merck & Co., Inc., Whitehouse Station, New Jersey) after the release of the worrisome data on the excessive cardiac morbidity attributed to rofecoxib in a trial attempting to prove that it could reduce the occurrence of colonic adenomas. The nearly simultaneous report by Pfizer, Inc., of the adverse cardiac effects of valdecoxib (Bextra, Pfizer, Inc., New York, New York) after cardiac surgery (1) raised the issue of whether other drugs in the class are safe to use. Patients and clinicians are anxious to know whether cardiotoxicity is a class effect, and thereby applicable to any COX-2 inhibitor, or whether cardiotoxicity is limited to certain drugs in the class. In this issue, Kimmel and colleagues (2) shed some light on this question by examining whether the risk for cardiotoxicity differs among the COX-2 inhibitors celecoxib (Celebrex, Pfizer, Inc.) and rofecoxib and nonselective nonaspirin NSAIDs.

Traditional nonselective nonaspirin NSAIDs inhibit both isoforms of the COX enzyme, COX-1 and COX-2. Cyclooxygenase catalyzes the conversion of arachadonic acid to prostaglandins, prostacyclin, and thromboxane. The COX-1 enzyme is expressed constitutively in tissues, such as the gastrointestinal mucosa, where it induces mucoprotective prostaglandins, while the COX-2 enzyme expression is inducible, in particular by inflammation. The inhibition of the COX-1–related production of prostaglandins by nonselective nonaspirin NSAIDs increases the risk for gastrointestinal bleeding. The recognition of 2 isoforms of COX soon led to the hypothesis that selective COX-2 inhibitors would have the beneficial properties of nonselective nonaspirin NSAIDs without gastrointestinal toxicity (3). Large clinical trials (4–6) validated this hypothesis and confirmed that COX-2 inhibitors are associated with less gastrointestinal toxicity than nonselective nonaspirin NSAIDs. However, these trials have also raised concerns about the cardiovascular safety of this class of drugs (7).

The role of COX-2 inhibition in atherogenesis is complex and is not fully understood. While nonselective nonaspirin NSAIDs and aspirin inhibit the formation of platelet-derived thromboxane and endothelial prostacyclin, COX-2 inhibitors preferentially suppress the vasodilator and platelet inhibitory prostaglandins without blocking the vasoconstrictive and platelet-activating prostaglandins, which could result in a prothrombotic effect. Accelerated atherogenesis of COX-2 inhibitors might be further modulated by renovascular hypertension, inhibition of vascular inflammation, improvement of endothelial function, and changes in atherosclerotic plaque stability (8–10). These effects may differ among structurally distinct COX-2 inhibitors with different levels of COX-1 or COX-2 selectivity (10–12), but evidence for a differential cardiovascular effect in this class is limited.

We should not be surprised that toxicity differs among drugs in a class (for example, the biguanides with metformin vs. phenformin and the risk for lactic acidosis). Kimmel and colleagues offer evidence for a differential effect on cardiotoxicity among COX-2 inhibitors (2). They used a case–control design to study patients presenting with a first nonfatal myocardial infarction in several medical centers and hospitals in southeastern Pennsylvania. After discharge, patients and controls were asked about exposure to nonselective nonaspirin NSAIDs, as well as COX-2 inhibitors (including rofecoxib and celecoxib). Kimmel and colleagues found no evidence for a class effect of COX-2 inhibitors for cardiovascular toxicity but demonstrated that rofecoxib use was associated with a statistically significant 2.72 increased odds of myocardial infarction when compared with celecoxib use. While case–control studies are prone to various selection biases, such as recall and nonparticipation bias, these should have applied equally to both rofecoxib and celecoxib, thereby giving credence to the hypothesis that a differential effect on cardiotoxicity is within the COX-2 inhibitor class.

The most reliable evidence of cardiovascular toxicity of the COX-2 inhibitors comes from large randomized, double-blind trials. Results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (4) revealed an increased risk for myocardial infarction for patients treated with 50 mg of rofecoxib, whereas similar large trials with celecoxib (5) or lumiracoxib (6) demonstrated no statistically significant differences in cardiovascular end points compared with nonselective nonaspirin NSAIDs. However, these trials were not primarily designed or powered to prove cardiovascular safety as a primary end point; mean follow-up time was rather short (6 to 12 months), and the selected patient samples had a relatively low rate of cardiovascular events. Therefore, the trials of celecoxib or lumiracoxib do not exclude the possibility of increased cardiovascular toxicity with these drugs. Several large observational studies found an increased rate of coronary heart disease with high-dose rofecoxib but not with celecoxib (13, 14). Solomon and colleagues (15) reported increased risk for acute myocardial infarction with any dosages of rofecoxib but not celecoxib. Mammadani and colleagues found an increased risk for congestive heart failure with rofecoxib and not with
cecloxicib (16) but no difference in the risk for myocardial infarction (17), but they did not address dosage and excluded short-term users. Overall, these studies suggest that not all COX-2 inhibitors share the same cardiovascular risk as rofecoxib, but the evidence is currently too limited to exclude the possibility of a COX-2 inhibitor class effect. Furthermore, nonselective nonaspirin NSAIDs might also increase cardiovascular risk (18). The major unanswered question is whether the unopposed COX-2 inhibition or other drug specific mechanisms cause increased cardiovascular risk.

What should physicians do at this time if they decide to prescribe a nonaspirin NSAID? Studies with rofecoxib indicate that nonaspirin NSAID–related cardiac toxicity occurs primarily in male patients older than 65 years of age with a history of cardiovascular events or at least 1 cardiovascular risk factor (19). We believe that because 2 separate drugs in the class of COX-2 inhibitors have now been associated with increased cardiovascular morbidity (rofecoxib and valdecoxib), physicians should avoid COX-2 inhibitors as a first-line agent in patients with cardiovascular risk factors and average risk for gastrointestinal toxicity. Although much recent attention has been given to the cardiovascular toxicity of COX-2 inhibitors, serious and occasionally life-threatening gastrointestinal toxicity does occur with both nonselective nonaspirin NSAIDs and COX-2 inhibitors, although less so with the COX-2 class. In light of the current uncertainty about whether cardiotoxicity is a class effect of COX-2 inhibitors, we suggest using either a nonselective nonaspirin NSAID with a concomitant gastroprotective agent or cecloxicib (Celebrex) for patients at high risk for gastrointestinal toxicity. Further study is urgently needed to document the safety of COX-2 inhibitors and nonselective nonaspirin NSAIDs.

**ADDENDUM**

Since the original release of this editorial on the Annals Web site, the National Institutes of Health announced that it has suspended a colorectal cancer prevention trial of cecloxicib. On the advice of the data safety monitoring board, they stopped the Adenoma Prevention with Cexoloxicib (APC) trial because of an increased risk for fatal and nonfatal cardiovascular events with cecloxicib (20). According to the data released so far, patients using cecloxicib over the long term (average duration ~ 3 years) at high dosages (>400 mg/d) had 2.5 to 3.4 times increased risk for cardiovascular events compared with those receiving placebo. While the full data are not yet available, the resemblance to the rofecoxib cancer prevention trial is striking and hints at a class effect related to long-term unopposed COX-2 inhibition. Of note, the difference in cardiovascular safety between placebo and the 2 principal COX-2 inhibitors became apparent only after several years of continuous treatment; this emphasizes the importance of long-term studies to assess drug safety.

To underscore the uncertainty that we should have about NSAIDs (selective and nonselective), consider the results of another large long-term trial with cecloxicib at 400 mg/d. In this study, designed to investigate the role of NSAIDs in preventing Alzheimer disease (ADAPT, Alzheimer’s Disease Anti-inflammatory Prevention Trial), the COX-2 inhibitor did not increase cardiovascular risk (21). Surprisingly, in this trial, 440 mg/d of the nonselective nonaspirin NSAID naproxen, which is available over the counter in the United States, was associated with increased cardiovascular risk (21).

The cardiovascular data from the APC trial with cecloxicib and from ADAPT with naproxen are disturbing because they are inconsistent with most observational studies and other randomized, controlled trials with these drugs, which have not shown increased cardiovascular risk (22, 23). The reasons for these discrepancies must be analyzed and understood before any definitive recommendations can be made for the use of cecloxicib and other drugs in this class. Until then, we believe that COX-2 inhibitors, in particular at higher dosages and for longer-term use, should not be a first-line therapy for patients who can tolerate alternative therapies. We reiterate our earlier conclusion that we urgently need further research to document the safety of long-term use of COX-2 inhibitors and nonselective nonaspirin NSAIDs.

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**References**

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