Coxibs and Cardiovascular Disease

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The coxibs are a subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) designed to inhibit selectively cyclooxygenase-2 (COX-2). Their development was based on the hypothesis that COX-2 was the source of prostaglandins E₂ and I₂, which mediate inflammation, and that cyclooxygenase-1 (COX-1) was the source of the same prostaglandins in gastric epithelium, where they afford cytoprotection. Three coxibs — celecoxib, rofecoxib, and valdecoxib — have been approved for use by the Food and Drug Administration (FDA); a fourth, etoricoxib, has been approved by the European regulatory authority, and it and a fifth, lumiracoxib, are currently under consideration for FDA approval.

Coxibs have been aggressively marketed directly to consumers in the United States and have rapidly dominated the prescription-drug market for NSAIDs, accounting for worldwide sales of roughly $10 billion. Rofecoxib has now been withdrawn from the market by Merck, following the premature cessation, by the data and safety monitoring board, of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which was designed to determine the drug’s effect on benign sporadic colorectal adenomas. This action was taken because of a significant increase by a factor of 3.9 in the incidence of serious thromboembolic adverse events in the group receiving 25 mg of rofecoxib per day as compared with the placebo group. Blood pressure was elevated in patients in the rofecoxib group early in the course of the study, but the incidence of myocardial infarction and thrombotic stroke in the two groups began to diverge progressively after a year or more of treatment.

Coincident with the approval of rofecoxib and celecoxib in 1999, my colleagues and I reported that both drugs suppressed the formation of prostaglandin I₂ in healthy volunteers. Prostaglandin I₂ had previously been shown to be the predominant cyclooxygenase product in endothelium, inhibiting platelet aggregation, causing vasodilatation, and preventing the proliferation of vascular smooth-muscle cells in vitro. However, it was assumed that prostaglandin I₂ was derived mainly from COX-1, the only cyclooxygenase species expressed constitutively in endothelial cells. This assumption later proved incorrect, since studies in mice and humans showed that COX-2 was the dominant source. The individual cardiovascular effects of prostaglandin I₂ in vitro contrast with those of thromboxane A₂, the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction, and vascular proliferation.

Whereas aspirin and traditional NSAIDs inhibit both thromboxane A₂ and prostaglandin I₂, the coxibs leave thromboxane A₂ generation unaffected, reflecting the absence of COX-2 in platelets. Increasing laminar shear stress in vitro increases the expression of the gene for COX-2, leading our group to suggest that COX-2 might be hemodynamically induced in endothelial cells in vivo. If so, suppression of the COX-2–dependent formation of prostaglandin I₂ by the coxibs might predispose patients to myocardial infarction or thrombotic stroke.

Thus, a single mechanism, depression of prostaglandin I₂ formation, might be expected to elevate blood pressure, accelerate atherogenesis, and predispose patients receiving coxibs to an exaggerated thrombotic response to the rupture of an atherosclerotic plaque. The higher a patient’s intrin-
The final gastrointestinal-outcome study — the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) — was reported recently.3,4 TARGET compared lumiracoxib with naproxen or ibuprofen. The primary end point was the incidence of serious gastrointestinal events, which was reduced significantly among patients receiving lumiracoxib. However, this difference was only observed in patients who were not taking aspirin. Although the trial, much like the CLASS trial, was not powered to detect a difference in the rates of cardiovascular events in nonaspirin users, more such events occurred in the lumiracoxib group than in the other group (0.26 vs. 0.18 per 100 patient-years; hazard ratio, 1.47), although the difference was not significant.

No study of the gastrointestinal effects of valdecoxib treatment has been reported. However, in a study in patients undergoing coronary-artery bypass grafting,2 treatment with the valdecoxib prodrug, parecoxib, was associated with a cluster of cardiovascular events, and the drug was rejected by the FDA. Although parecoxib is effective as an analgesic only when it is converted to valdecoxib in vivo, and approval of the latter drug was based on studies in patients with low cardiovascular risk, the labeling of valdecoxib does not reflect the experience with parecoxib.

Finally, a series of epidemiologic analyses have also raised questions about the cardiovascular safety of the coxibs. Although the epidemiologic approach has commonly relied on databases of prescriptions and is particularly subject to bias due to the over-the-counter consumption of NSAIDs and aspirin, these studies broadened the context of the available evidence by relating risk to the dose of rofecoxib used.5

Before the results of the APPROVe study were released, the scientific evidence of gastrointestinal benefit from coxibs in the VIGOR and TARGET trials appeared to outweigh the evidence of cardiovascular risk. The FDA pursued a cautious policy, labeling celecoxib and rofecoxib in ways that reflected the outcomes of the CLASS and VIGOR trials. However, the APPROVe study has shifted the burden of proof. We now have clear evidence of an increase in cardiovascular risk that revealed itself in a manner consistent with a mechanistic explanation that extends to all the coxibs. It seems to be time for the FDA urgently to adjust its guidance to patients and doctors to reflect this new reality. Only the FDA can provide unbiased and informed guidance; it has a role to play beyond watchful waiting. In the absence of such guidance, what should physicians and their patients do? Selective inhibitors of COX-2 remain a rational choice for patients at a low cardiovascular risk who have had serious gastrointestinal events, especially while taking traditional NSAIDs. It would also seem prudent to avoid coxibs in patients who have cardiovascular disease or who are at risk for it.
The rofecoxib story also reflects poorly on the process that leads to drug approval. The rational basis for addressing the cardiovascular effects of these drugs has been clear for the past five years, yet even the most fundamental questions have not been addressed directly. Much information could have been derived from careful mechanistic studies in small numbers of patients and volunteers. However, drug companies are driven by the current requirements for drug approval to design studies such as TARGET. This most expensive and largest of the outcome studies involved exposing more than 18,000 patients to lumiracoxib for a year. It laid the foundation for the approval of another coxib, but it failed to address important questions about cardiovascular risk raised by the VIGOR trial and by mechanistic and epidemiologic studies.

Patients in the APPROVe study should continue to be followed. This will allow some estimate of how quickly the developed risk may dissipate. Given the relatively short half-lives of these compounds, such a dissipation may occur rapidly. On the other hand, if treatment has accelerated atherosclerosis, the offset of risk may be more gradual. Finally, it is essential to determine whether the cardiovascular risk is or is not a class effect. 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.

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