Cyclooxygenase-2 Inhibitors Are They Really Atherothrombotic, and If Not, Why Not?

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Background and Summary—Selective cyclooxygenase (COX)-2 inhibitors are increasingly being used in place of “conventional” nonsteroidal anti-inflammatory drugs (NSAIDs). This is because they are just as effective as NSAIDs in relieving arthritic pain and yet less gastrotoxic. However, the cardiovascular safety of selective COX-2 inhibitors has been questioned because they selectively reduce prostacyclin production, thus disrupting the normal homeostatic balance and promoting a prothrombotic state. These theoretical concerns appear to be supported by the results of clinical trials demonstrating an increased risk of myocardial infarction with COX-2 inhibitors compared with a conventional NSAID, and indirect comparisons of the rates of myocardial infarction among patients treated with a selective COX-2 inhibitor compared with aspirin in different trials. However, emerging data from animal, experimental and clinical studies suggest that COX-2 is atherogenic and thrombogenic, and that selective COX-2 inhibitors may be cardioprotective. Meta-analyses of randomized trials of selective COX-2 inhibitors compared with placebo have demonstrated no excess of cardiovascular events among patients allocated COX-2 inhibitors, and preliminary data from a randomized controlled trial of the selective COX-2 inhibitor meloxicam, in patients with acute coronary syndrome who were treated with aspirin, demonstrated a reduction in cardiovascular events among patients allocated the COX-2 inhibitor.

Conclusions—Continuing uncertainty regarding the direction and magnitude of any cardiovascular effects of selective COX-2 inhibitors, coupled with their widespread and increasing use, mandates prospective randomized evaluation of their efficacy and safety in patients at increased risk of future cardiovascular events. (Stroke. 2003;34:2736-2740.)

Key Words: arteriosclerosis ■ cyclooxygenase inhibitors ■ thrombosis

Since 1999, the introduction of the selective cyclooxygenase (COX)-2 inhibitors (celecoxib, etoricoxib, and rofecoxib) has been hailed as a major therapeutic advance. COX-2 inhibitors are as effective as aspirin and other “conventional” nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2 activity, in relieving arthritic pain, yet they cause only half the number of adverse upper gastrointestinal events.1,2 Central to their effectiveness is selective inhibition of the conversion of arachidonic acid to prostaglandin H2 by COX-2, which is upregulated in inflamed tissues, without also inhibiting the cytoprotective effects of COX-1 in the gastric mucosa (which causes upper gastrointestinal events in 2% to 4% of patients per year).2

However, the “honeymoon” has been threatened by theoretical arguments that selective COX-2 inhibitors increase the risk of arterial thrombosis, which are supported by secondary analyses of phase III clinical trials.3 The theory is that selective COX-2 inhibitors may promote atherothrombosis by inhibiting the formation, via COX-2 isoenzymes in macrovascular endothelial cells, of prostacyclin (PGI2), which is a potent vasodilator, and inhibitor of smooth muscle cell proliferation and platelet aggregation.4–6 In addition, selective COX-2 inhibitors fail to inhibit the formation, via COX-1 isoenzymes in platelets, of thromboxane A2 (TXA2), which facilitates vasoconstriction, platelet activation, and smooth muscle cell proliferation.4–6

The theory is supported by the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, which reported a 2.38-fold (95% CI, 1.4 to 4.0) increase in the relative risk (RR) of atherothrombotic cardiovascular events among all 8076 patients with rheumatoid arthritis (RA) who were randomly allocated to rofecoxib treatment compared with those allocated to naproxen treatment.2 Aspirin use was not permitted in this study, but the increase in vascular events was even greater (RR, 4.9; 95% CI, 1.4 to 16.9) among the subgroup of patients with a clear indication for aspirin because of previous symptomatic atherothrombosis.2 Although there was no significant difference in cardiovascular event rates between 8059 patients allocated to celecoxib and NSAID treatment in the Celecoxib Long-term Arthritis Safety Study (CLASS), a summary of major comparative trials of selective COX-2

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inhibitors (VIGOR, CLASS, and 2 smaller clinical trials that compared rofecoxib with a nonselective NSAID, nabumetone) concluded that both rofecoxib and celecoxib may be associated with an increase in cardiovascular events. The conclusion was based on the significantly higher annual rates of myocardial infarction (MI) among RA patients in the VIGOR trial who were allocated to rofecoxib treatment (0.74%) and other patients in the CLASS trial allocated to celecoxib treatment (0.80%) compared with the 0.52% annual rate of MI observed among 23 407 individuals allocated to placebo in a meta-analysis of the 4 trials of aspirin versus placebo for the primary prevention of vascular events: the US Physicians’ Health Study, the UK Doctors Study, the Thrombosis Prevention Trial, and the Hypertension Optimal Treatment trials ($P=0.04$ and $P=0.02$ for the rofecoxib and celecoxib versus placebo comparisons, respectively). Because rofecoxib and celecoxib are chemically different compounds (rofecoxib is a sulfone that is not well distributed into tissues and is metabolized principally by cytosolic reduction, whereas celecoxib is a sulfonamide that is well distributed into tissues and is metabolized by the cytochrome P450 2C9, 3A4 system), it was also hypothesized that an increased risk of cardiovascular events among patients randomized to celecoxib and rofecoxib and an increased risk of cardiovascular disease has gained additional support from a report of 4 cases of thrombosis in patients with connective tissue diseases who were treated with COX-2 inhibitors and the results of several laboratory studies, which showed that PGI$_2$ modulates the cardiovascular actions of TXA$_2$. COX-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning (the ability of myocytes to survive repeated ischemia) in rabbits, and COX-2 inhibition by celecoxib increases thrombosis in canine coronary arteries.

Indeed, the hypothesis that COX-2 inhibitors increase the risk of cardiovascular disease has gained additional support from a report of 4 cases of thrombosis in patients with connective tissue diseases who were treated with COX-2 inhibitors and the results of several laboratory studies, which showed that PGI$_2$ modulates the cardiovascular actions of TXA$_2$. COX-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning (the ability of myocytes to survive repeated ischemia) in rabbits, and COX-2 inhibition by celecoxib increases thrombosis in canine coronary arteries.

However, before the apparent association between the use of celecoxib and rofecoxib and an increased risk of cardiovascular events becomes entrenched in clinical practice, there are alternative explanations to consider. The most compelling is that the differences in the raw MI rates among the “cases” (patients treated with a selective COX-2 inhibitor [rofecoxib in the VIGOR trial and celecoxib in the CLASS trial]) and the literature “controls” (entirely unrelated, separate cohorts of generally healthy individuals in the placebo arms of the 4 primary prevention trials of aspirin) are nonrandomized, indirect comparisons. There was not even any statistical adjustment for the prevalence and level of known, let alone unknown, important prognostic factors in the cases and controls. The comparisons are therefore potentially flawed because any differences in raw MI event rates could simply be accounted for by differences in case mix among the cases and controls. For example, there is some evidence that patients with RA (ie, the type of patients enrolled in the VIGOR trial) have higher vascular event rates than individuals of the same age and sex who do not have RA, such as the cases enrolled in CLASS and the controls in primary prevention trials of aspirin.

Another limitation of the summary of trials is that the analysis was restricted to MI and not all vascular outcome events (eg, stroke and death from other vascular causes). Finally, the 95% CIs of the reported annual MI rates for patients allocated to rofecoxib (0.74%) and celecoxib (0.80%) treatment were wide and overlapped with those of the events rates for the trials used to construct the placebo group in the meta-analysis (annual event rates 0.36% to 1.33%) and the 95% CIs of the summary point estimate.

An alternative interpretation of the VIGOR trial is that rofecoxib causes no excess risk of vascular events, and any excess RR of vascular events associated with rofecoxib, compared with naproxen, could be attributable to the effectiveness of naproxen in decreasing cardiovascular risk. An antiplatelet effect of naproxen is supported by a systematic review of all rofecoxib trials conducted by the manufacturer (fewer vascular events in the naproxen group) and 3 recent case-control studies that found that naproxen was associated with a modest (16% to 39%) reduction in odds of serious coronary heart disease. However, not all observational studies have shown a cardioprotective effect of naproxen.

The results of CLASS, which showed an equal rate of vascular events among patients randomized to celecoxib and to ibuprofen, may also reflect that ibuprofen is a NSAID that does not reduce vascular events any more than celecoxib.

In the midst of the present ongoing controversy and uncertainty over whether selective COX-2 inhibitors increase cardiovascular events (by blocking PG1$_2$ and leaving TXA$_2$ unopposed) and whether there are differences in cardiovascular risk between different COX-2 inhibitors, we hypothesize that selective COX-2 inhibitors may actually reduce, rather than cause, atherothrombotic vascular events. The rationale for our hypothesis is that COX-2 could be both atherogenic and thrombogenic (Figure).

Atherosclerosis is an inflammatory disease. Proinflammatory mediators of atherosclerosis induce upregulation of COX-2 in circulating blood monocytes and endothelial cells, smooth muscle cells, and macrophages within atherosclerotic plaque. Upregulation of COX-2 in atherosclerotic tissue enhances the production of a range of inflammatory eicosanoids, including prostaglandin E$_2$, prostaglandin E$_3$, and prostaglandin E$_4$. Prostaglandin E$_2$ promotes the release and activation of matrix metalloproteinases, which promote macrophage migration and rupture of atherosclerotic plaque. COX-2 also promotes the release of active matrix metalloproteinases and has been implicated in the development of early atherosclerotic lesions.

Evidence from a recent randomized trial suggests that simvastatin decreases inflammation and suppresses the expression of cyclooxygenase-2 and prostaglandin E synthase in plaque macrophages, and this effect in turn may contribute to...
plaque stabilization by inhibition of metalloproteinase-induced plaque rupture.\textsuperscript{32}

Upregulation of COX-2 in atherosclerotic plaque also enhances the production of prostaglandin H\textsubscript{2} in monocytes and macrophages, which, because of their large content of thromboxane synthase, involves increased production of TXA\textsubscript{2}, which predisposes to thrombosis\textsuperscript{24–26} and atherogenesis\textsuperscript{33} and is associated with an increased risk of atherothrombosis and death.\textsuperscript{34} The prostaglandin H\textsubscript{2} produced by monocytes/macrophages (and endothelial cells) can also be used by platelet thromboxane synthase to form TXA\textsubscript{2} through a process of “transcellular metabolism,” thereby bypassing the platelet COX-1 blocked by aspirin.\textsuperscript{35–37} COX-2 has recently been demonstrated to be present in platelets and may represent an additional mechanism of thromboxane biosynthesis and thus thrombogenesis.\textsuperscript{38}

Evidence supporting our hypothesis for COX-2 being atherogenic and thrombogenic comes from laboratory and...
clinical studies. The administration of rofecoxib or indomethacin for 6 weeks to mice that are deficient in the LDL receptor and fed a Western diet led to a significant reduction of atherosclerosis.\(^{39}\) Compared with placebo, celecoxib (200 mg BID) significantly improves endothelium-dependent vasodilation and reduces low-grade chronic inflammation and oxidative stress in men with severe coronary artery disease.\(^{39}\) Additionally, the Nonsteroidal Anti-Inflammatory Drugs in Unstable Angina Treatment-2 (NUT-2) pilot study, which compared meloxicam (15 mg daily until 30 days after discharge) with control in 120 patients who had a non-ST-segment elevation acute coronary syndrome, showed that patients allocated to meloxicam treatment had a significant reduction in the primary composite outcome of recurrent angina, myocardial infarction, or death during the coronary care unit stay (15.0% versus 38.3%; relative risk reduction, 61%; 95% CI, 23% to 80%; absolute risk reduction, 23.3%; \(P = 0.007\)).\(^{40}\) Although the sample size was small, treatment allocation was open, and much of the primary outcome was unaware of treatment allocation. While these data may simply reflect the play of chance of a nonspecific effect of COX-2 inhibition on pain generation or perception, they support the hypothesis that COX-2 inhibition may retard atherogenesis (by improving vascular endothelial function and plaque stability) and minimize atherosclerosis (by inhibiting TXA\(_2\) generated from monocytes, endothelial cells, and platelets through the action of COX-2).

The body of laboratory and phase II/III clinical trial evidence is now compelling enough to consider it ethically sound to conduct large, randomized, double-blind, placebo-controlled trials of selective COX-2 inhibitors on the occurrence of “hard” clinical outcome events such as nonfatal stroke, nonfatal myocardial infarction, and death due to vascular causes in patients at high vascular risk who are also being treated with aspirin.\(^{12,24}\) It is, however, essential that such trials adopt broad inclusion criteria and be adequately powered with sufficient duration of follow-up to reliably detect any excess noncardiovascular adverse effects of adding a COX-2 selective inhibitor to aspirin on renal function and gastrointestinal bleeding risk, which could potentially negate any cardiovascular benefits of this combination if ultimately used in everyday clinical practice.

References


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