Cyclooxygenase-2 Inhibition and Cardiovascular Events

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The Promise
Introduction of selective cyclooxygenase (COX)-2 inhibitors held a promise of improved treatment of arthritis without the gastrointestinal effects associated with aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), which effect both COX-1 and COX-2 activity. Celecoxib, etodolac, meloxicam, and rofecoxib are classified as selective COX-2 inhibitors. Initial placebo and large scale comparative trials with NSAIDs have shown the effectiveness of selective COX-2 inhibition with a lower incidence of gastrointestinal side effects in patients with arthritis. These data, along with extensive marketing programs such as direct-to-consumer advertising, led to wide scale use.

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The Controversy
Caution to this enthusiasm was raised by suggestions that prostacyclin (PGI-2) inhibition with relatively unopposed platelet thromboxane (TX)A2 generation may lead to thrombotic risk. Then, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial comparing rofecoxib to the NSAID naproxen in patients with rheumatoid arthritis showed a 5-fold increase in atherothrombotic cardiovascular events associated with rofecoxib. In contrast, the Celecoxib Long-Term Arthritis Safety Study (CLASS) showed no increase in cardiovascular events with celecoxib compared with an NSAID in patients with osteoarthritis. One possible explanation for the differences between these studies may relate to findings from a direct, double-blind, randomized comparison of rocoxib significantly raised blood pressure and edema frequency reported by Whelton.

VIGOR trial, whereas ibuprofen, the comparator in CLASS, did not reduce cardiovascular events, thereby making celecoxib seem relatively safer than rofecoxib. They also indicated that the apparent neutral effect of celecoxib on cardiovascular events may have been related to the fact that some patients in CLASS used low-dose aspirin. This would tend to reduce events, whereas in the VIGOR study of rofecoxib, aspirin was not given to a subgroup of patients with definite indications for its use in prophylaxis of cardiovascular events. It has also been noted that although it reduces the potential for cardiovascular events, concomitant aspirin would increase the potential for gastrointestinal side effects, thereby negating the potential advantage of selective COX-2 inhibition in comparison to other NSAIDs.

Are the Selective COX-2 Inhibitors all the Same?
It should be noted that although both drugs selectively inhibit COX-2, they are chemically different compounds. Celecoxib is a sulfonamide, which is extensively distributed into tissues (volume of distribution is 400L for the 200mg dose) and is metabolized by the cytochrome P450 2C9, 3A4 system. Indeed, interaction with other P450 inhibitors has been observed. Its half-life is 11 hours, and it was dosed b.i.d. in CLASS. Rofecoxib, on the other hand, is a sulfone, which is not as well distributed into tissues (volume of distribution is 86L for the 25mg dose) and is metabolized principally by cytosolic reduction. Cytochrome P450 plays only a minor role; thus, no important interaction with other P450 inhibitors has been observed. Its half-life is 17 hours, and it was dosed every day in the VIGOR study. These differences may result in variations in the degree of COX-2 versus COX-1 inhibition or in additional effects unrelated to COX-2 inhibition at the tissue level. This might also explain the differences in blood pressure elevation and edema frequency reported by Whelton et al.

Are the Findings Suggestive of Increased Cardiovascular Events of Concern?
The overview by Mukherjee et al. case reports suggesting an increase in thrombotic risk for COX-2 inhibitors in patients with connective tissue disease, and studies showing that COX-2 inhibition with celecoxib increases the chance of coronary thrombosis in experimental canine models with vascular injury are of concern. The fact that COX-2 seems to be important for the late phase of ischemic pre-conditioning further suggests that COX-2 inhibition might be associated with an increased cardiovascular risk. This issue is of great public health importance because the large number of patients with arthritis, most of whom are elderly, have a relatively high incidence of co-morbidity, including hypertension, dia-

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betes, and atherosclerosis, thereby placing them at an increased risk for ischemic events.

Although Mukherjee et al\(^4\) noted potential risks of cardiovascular events for both rofecoxib and celecoxib, subsequent clinical reports have been less clear about these risks. For example, Mukherjee et al\(^4\) suggested that naproxen, the comparator NSAID in the VIGOR trial, decreased ischemic events. A subsequent epidemiological analysis,\(^9\) however, failed to support this finding, as naproxen was not found to have any detectable effect on ischemic events. Three recently published case-control studies did, however, suggest that naproxen use was associated with a modest reduction in acute myocardial infarction, ranging from an odds ratio of 0.61 to 0.84.\(^{10-12}\)

The situation was further complicated by a recent analysis of cardiac events in almost 4000 patients randomized to celecoxib versus either ibuprofen or diclofenac.\(^{13}\) In this analysis, no evidence for an increase in cardiovascular risk was detected, irrespective of whether patients were treated with concomitant aspirin. These findings refute the suggestion that COX-2 inhibitors, as a class, increase cardiovascular events. The situation is complicated further still by a subsequent analysis by Konstam et al\(^{14}\) of all randomized trials in rofecoxib which failed to show an increased cardiovascular risk in comparison to other NSAIDs. These reports resulted in the following FDA actions. Language was added to the label of rofecoxib about myocardial infarction risks, and celecoxib was permitted to remove the warning about adverse cardiovascular effects from its label.

Clinical studies suggesting an increased cardiovascular events risk in patients receiving a selective COX-2 inhibitor have been supported by preclinical mechanistic studies. These show that selective COX-2 inhibition blocks PGI-2 formation without inhibiting platelet derived TXA\(_2\).\(^{15,16}\) thereby increasing platelet activation, adhesion, and aggregation with a resultant possibility for thrombosis and ischemic events. The importance of this mechanism has recently been emphasized in studies by Cheng et al\(^{17}\) in mice deficient in the PGI-2 receptor (IP) or TXA\(_2\) receptor (TP). IP-deficient animals have enhanced injury-induced vascular proliferation and platelet activation in comparison to TP-deficient animals or those treated with a TP antagonist. The augmented response to vascular injury seen in IP-deficient mice is abolished in mice deficient for both IP and TP. These studies emphasize the importance of PGI-2 in mediating platelet-vascular interactions and may provide a mechanistic basis to explain the increase in cardiovascular events observed in the VIGOR study with rofecoxib.\(^1\) Meanwhile, the controversy continues as to whether selective COX-2 inhibitors increase cardiovascular events by blocking PGI-2 and leaving TXA\(_2\) unopposed and whether there are true differences in cardiovascular risk between different COX-2 inhibitors.

**Can Selective COX-2 Inhibition Reduce Cardiovascular Events?**

There is emerging evidence that selective COX-2 inhibition may have a beneficial effect on cardiovascular events in atherosclerosis. COX-2 expression is upregulated in atherosclerotic plaques,\(^{18,19}\) and depending upon the stage of atherosclerosis, COX-2 inhibition may decrease vascular inflammation. A decrease in vascular inflammation would be expected to reduce mononuclear cell infiltration, improve nitric oxide availability, reduce progression of atherosclerosis, and enhance plaque stability, possibly resulting in a net decrease in atherothrombotic events. Support for this hypothesis comes from studies in low-density lipoprotein receptor-deficient mice fed a Western diet in which rofecoxib or indomethacin given for 6 weeks resulted in a significant reduction in atherosclerosis.\(^{20}\) This beneficial effect occurred despite the fact that rofecoxib inhibited PGI-2 but not platelet TXA\(_2\) production.

Selective COX-2 inhibition has also been suggested to improve cardiac function when given after the period of acute infarction in some experimental rodent models.\(^{21}\) When rofecoxib was given before and during the period of acute infarction in one such model,\(^{22}\) a reduction in macrophage infiltration and fibroblast proliferation was observed without significant effect on infarct size. COX-2 expression in isolated cardiac fibroblasts was dependent on angiotensin II and P38 mitogen-activated protein kinase.\(^{22}\)

Further support for a possible beneficial role of selective COX-2 inhibition on cardiovascular events comes from the Nonsteroidal Anti-Inflammatory Drugs in Unstable Angina Treatment-2 (NUT-2) pilot study by Altman et al\(^{23}\) in this issue of *Circulation*. In this study, the COX-2 inhibitor meloxicam was administered intravenously and continued orally for 30 days. The design was an open label, prospective, randomized, single-blind pilot study of 120 patients with a non-ST-segment elevation acute coronary syndrome treated with aspirin and heparin. The patients receiving meloxicam were compared with 60 patients who received aspirin and heparin alone. Patients assigned meloxicam had a significant reduction in the primary composite outcome consisting of recurrent angina, myocardial infarction, or death (15% vs. 38%, *P* = 0.007) and a secondary composite outcome consisting of coronary revascularization procedures, myocardial infarction, and death (10% vs. 26.7%, *P* = 0.034) at 30 days. Although these results are encouraging and support the study in low-density lipoprotein receptor-deficient mice\(^{20}\) which suggested that COX-2 inhibition may have a beneficial effect in atherosclerosis, this study has important limitations, including a relatively small sample size and a single-blind design. A major component of the primary outcome in the NUT-2 study was recurrent angina and in the secondary outcome the need for coronary revascularization, which is usually driven by recurrent symptoms. These were the only components of the outcome clusters that were significantly reduced. Both the incidence of recurrent angina and need for coronary revascularization are subjective and are relatively “soft” endpoints. Because COX-2 inhibitors are effective in reducing pain, one may question whether the reduction in cardiovascular events in this pilot study is related to improvement in coronary vascular function and/or plaque stability or merely a non-specific effect on pain threshold and perception.

At best, the NUT-2 pilot study should be considered hypothesis generating. More rigorous trials using a double-blind design and more objective outcomes, such as death, nonfatal myocardial infarction, or recurrent hospitalizations with acute coronary syndromes in a larger number of patients...
are clearly needed. Mechanistic studies, which do providing important insight, certainly will not answer the question as to whether selective COX-2 inhibitors increase or decrease cardiovascular risk, nor will epidemiological studies or underpowered comparative studies with other NSAIDs. It is possible that under certain conditions, selective COX-2 inhibition may have a deleterious effect on the risk of thrombosis, whereas in other situations, they might attenuate atherosclerosis progression and decrease ischemic events. Only well designed large scale clinical trials can provide the answer as to the net effect of selective COX-2 inhibition on cardiovascular events. Such studies remain to be performed.

References

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