When cyclooxygenase (COX)-2–selective inhibitors (coxibs) first entered the market about 5 years ago, the major concern with regard to cardiovascular side effects related to their potential to increase blood pressure and cause salt and water retention, in a manner similar to conventional (nonselective) nonsteroidal anti-inflammatory drugs (NSAIDs). In the short time since, wariness about these side effects has grown into widespread alarm about putative prothrombotic actions and generation of excess major cardiovascular events with these agents.

In September 2004, safety findings of the Adenomatous Polyposis Prevention on Vioxx (APPROVe) study indicated an increase in risk for myocardial infarction and stroke among subjects randomized to rofecoxib compared with those randomized to placebo. This study had been designed to examine recurrent colonic polyps rather than cardiovascular disease end points and therefore could only be considered hypothesis generating. Subsequent data from a number of observational studies further implicated the drug’s association with arterial thromboembolic disease. As with APPROVe, no single study generated sufficiently robust attestations by itself, but they provided concordant signals, and the accumulating evidence eventually reached a critical mass.

As the data on rofecoxib emerged, concerns about other COX-2–selective agents on the market also grew. This was based on the assumption of a “class effect” for an increase in risk of cardiovascular disease related to preferential inhibition of prostacyclin over thromboxane and thus a tendency toward prothrombosis.

The results presented by McAdam and colleagues in this issue of Circulation1 challenge our view with regard to this prostanooid hypothesis and raise new questions about the mechanisms underlying the potential cardiovascular side effects of coxibs and traditional NSAIDs. The authors hypothesized that the enhanced systemic biosynthesis of prostacyclin in smokers was dependent on COX-2 activity. They also sought to determine the functional importance of COX-2–derived prostacyclin (PGL2) in limiting platelet activation in smokers in vivo. Contrary to the conventional wisdom of an expected increase in the biosynthesis of TXA2 (related to increased platelet activation via COX-1), the authors demonstrated the opposite finding—ie, that COX-2 contributed to, and a COX-2 inhibitor reduced, TXA2 biosynthesis in smokers.

COX-2, Smoking, and Atherosclerosis

Cigarette smoking is one of the most important risk factors for the development and progression of atherosclerosis. Although the mechanisms underlying how smoking promotes atherogenesis are still not fully understood, activation of platelets and the coagulation cascade, reduced nitric oxide (NO) bioavailability, increased oxidative stress, and inflammation are all considered to play major roles. The article by McAdam and colleagues adds to the growing evidence that COX-derived prostanooids at least in part mediate the pathogenic effects of cigarette smoking on vascular health. The net balance of effect of the prostanooids PGI2 and thromboxane A2 (TXA2), in particular, is crucial in the discussion of the cardiovascular safety of selective COX-2 inhibitors, like rofecoxib and celecoxib, as well as of traditional nonaspirin NSAIDs, which nonselectively block both COX isoenzymes to various degrees. Indeed, the increase in cardiovascular events with rofecoxib in the Vioxx Gastrointestinal Outcomes Research trial (VIGOR) and APPROVe trial as well as with celecoxib in the Adenoma Prevention with Celecoxib (APC) trial2 points toward a potential class effect for coxibs. The hypothesis proposed by some to explain the excess of cardiovascular events with COX-2–selective inhibitors in these studies is that all of these agents invariably cause a (clinically significant) imbalance between PGI2 and thromboxane. However, the present study adds to the increasing body of evidence that this view is not only highly simplistic but is also lacking in support from available clinical data.

The authors of the present study clearly demonstrate that urinary excretion of PGI2 and TXA2 metabolites (PGI-M and TX-M) is increased in cigarette smokers as compared with non-smokers. Interestingly, COX-2 inhibition with rofecoxib reduced urinary excretion of PGI-M and TX-M, but not TXB2 plasma levels, in smokers. Similarly, a recent study further questions whether a decrease in PGI2, either alone or in combination with increased TXA2, provides the only explanation for the increased cardiovascular risk of selective and non-selective COX-inhibitors.3 Indeed, aldosterone induced COX-2 expression and release of PGI2 metabolites but impaired endothelial function in Wystar Kyoto and spontaneously hypertensive rats. Inhibition of PGI2 synthesis improved endothelial function, whereas inhibition of TX syn-
thesis showed no effect. Importantly, clinical data to support the clinical relevance of the thromboxane/prostacyclin hypothesis are still lacking. Specifically, none of the cardiovascular mechanistic studies of COX-2 selective inhibitors undertaken in humans thus far (including for rofecoxib) have demonstrated detrimental effects of these agents on endothelial function, as should be expected if the prostacyclin/thromboxane hypothesis holds. In contrast, there are recent data which suggest that celecoxib (but not rofecoxib) actually improves endothelial function when administered to subjects with known cardiovascular disease. As endothelial function represents the net effect of vascular active hormones, any potential impact of celecoxib on prostanoids may be relatively outweighed by beneficial effects on vessel wall function, particularly improvement of nitric oxide bioavailability with its vasodilatory, antiaggregatory, antiproliferative, and antimigratory effects. It is of note that improvement of endothelial function when administered to subjects with known cardiovascular disease. As endothelial function represents the net effect of vascular active hormones, any potential impact of celecoxib on prostanoids may be relatively outweighed by beneficial effects on vessel wall function, particularly improvement of nitric oxide bioavailability with its vasodilatory, antiaggregatory, antiproliferative, and antimigratory effects. It is of note that improvement of endothelial function when administered to subjects with known cardiovascular disease.

Indeed, McAdam and colleagues clearly demonstrate that rofecoxib reduced TX-M as well as PGI-M, suggesting that platelets might not be the only important source of TXA₂. Although aspirin was recently shown to decrease TXA₂ and PGI levels, evidence for a nonplatelet source of biosynthesis of TXA₂ during aspirin treatment has been provided by Cipollone et al., who demonstrated in patients with unstable angina that the nonselective COX inhibitor, indobufen, lowered TX-M levels to a greater extent than aspirin.

**Differential Effects of Coxibs**

Although the authors chose to use rofecoxib because of its relatively high selectivity for the COX-2 enzyme, it remains to be determined whether effects seen with rofecoxib can be extrapolated to the entire class of coxibs. Indeed, differences in chemical structure (rofecoxib is a sulfone, whereas celecoxib is a sulfonamide), pharmacokinetic properties, and subsequent metabolism (cytosol reductase versus cytochrome P450) may account for differential effects of coxibs in experimental studies as well as in large-scale meta-analysis, case-control analysis, and population-based cohort studies comprising several million patients.

If the PGI₂ and TXA₂ imbalance theory holds, then adding aspirin should eliminate risk. However, in the coronary artery bypass grafting (CABG) study, in which patients undergoing CABG surgery received either placebo or 40 mg parecoxib (the intravenously administered prodrug of valdecoxib), followed by oral valdecoxib 40 mg BID for 14 days, and also received low-dose aspirin (75 to 325 mg daily), a cluster of cardiovascular events was observed. This is in line with results from other randomized clinical trials indicate that adding a COX-1 inhibitor does not prevent the cardiovascular adverse effects observed with coxibs and NSAIDs. Moreover, if the prostacyclin/thromboxane hypothesis represented the only mechanistic explanation for these events, one would have expected the use of NSAIDs (which have considerable COX-1 effect) to be associated with fewer cardiovascular side effects. The recent observation of a trend toward increased cardiovascular events with naproxen when compared with placebo and celecoxib in the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) highlights the need to scrutinize these agents as rigorously as COX-2–selective inhibitors.

Several recent meta-analyses, case-control analyses, and population-based cohort studies in several million patients support the above notion. Notwithstanding interpretation of observational studies being limited because of their retrospective design and selection bias, rofecoxib, but not celecoxib, was associated with an increased risk for myocardial infarction, development of chronic heart failure, and new onset of hypertension. Graham et al. analyzed data from >1.4 million patients in the Kaiser Permanente in California and found no increased risk for acute myocardial infarction and sudden cardiac death for celecoxib, but this risk was present for rofecoxib and several NSAIDs. Studies by Johnsen and Singh found increased cardiovascular risk not only for rofecoxib but also for NSAIDs like naproxen, meloxicam, and sulindac. In view of these findings, the US Food and Drug Administration has mandated new warnings about cardiovascular side effects to be part of labeling for not only all coxibs but also the entire class of traditional NSAIDs.

Not even aspirin appears to be exempt from this potential for increased cardiovascular events. A dose-dependent risk, similar to that observed with celecoxib in the Adenoma Prevention with Celecoxib (APC) trial, was demonstrated for aspirin in a study of prevention of colorectal adenoma. In addition, results of a randomized clinical trial in patients after endarterectomy suggested that low-dose aspirin protects against but high-dose aspirin may enhance cardiovascular risk in long-term studies. These data indicate that higher doses of aspirin exert COX-1–independent NSAID-like effects. Interestingly, although previous studies in smokers used aspirin as a pharmacological probe for platelet COX-1, recent studies suggest that aspirin indeed inhibits COX-2–derived thromboxane in vitro.

It is of note that the activity of platelet COX-1 has to be almost completely (>95%) and continuously inhibited to translate into a detectable cardiovascular protection. Aspirin irreversibly inactivates platelet COX-1 activity through a selective acetylation of human COX-1 lasting for up to 10 days. In contrast, traditional nonaspirin NSAIDs are reversible inhibitors of platelet COX-1 resulting in an incomplete inhibition of platelet TXA₂, which may be inadequate to prevent cardiovascular events. Intriguingly, ibuprofen and naproxen have recently been shown to interfere with the inhibitory effect of aspirin on platelet COX-1 activity and function and thus diminish aspirin’s cardioprotective effects.

Furthermore, it remains to be determined how the cardiovascular (and gastroenterological) effects of coxibs are influenced by other concomitant medications as used in cardiovascular patients—clopidogrel and statins in particular.

Further evidence for differential effects of coxibs comes from experimental studies. A head-to-head study in salt-sensitive hypertensive Dahl-rats showed that endothelial dysfunction was improved with celecoxib but not with rofecoxib or diclofenac. In addition, renal function and morphology as well as cellular inflammation and C-reactive protein (CRP)—
mRNA in the kidney of salt-sensitive hypertensive rats was attenuated after treatment with celecoxib but not rofecoxib or diclofenac. Similarly, differential effects of celecoxib and rofecoxib were demonstrated in vascular endothelial and cancer cell lines. Indeed, although celecoxib inhibited the proliferation of human umbilical vein endothelial cells (HUVECs) and modulated cell cycle proteins, rofecoxib had no effect on cell proliferation, apoptosis, or cell cycle distribution, indicating that celecoxib and rofecoxib do not affect the same signal transduction pathways in endothelial cells. Because both drugs selectively inhibited COX-2 activity and the applied concentrations lay beyond the IC50 for inhibition of prostacyclin production, the observed effects on vascular cells appear to be COX independent.

Likewise, Yang et al have investigated the impact of COX inhibitors on smooth muscle cell proliferation in a mouse carotid artery balloon injury model. Celecoxib reduced injury-induced phosphorylation of Akt and GSK, resulting in antiproliferative effects, whereas aspirin did not inhibit neointimal formation after carotid artery injury. Furthermore, coxibs exert differential effects independent of COX-2 inhibition, predominantly mediated by the Akt pathway, in cancer cell lines. A correlation between inflammation markers like CRP and smoking has been known for some time. CRP, high-sensitive CRP in particular, has been shown to be an excellent marker for endothelial dysfunction as an early surrogate for atherosclerosis, and antiinflammatory strategies can reduce CRP levels as well as improve endothelial function. Interestingly, rofecoxib does not improve endothelial function despite a reduction of inflammatory parameters like CRP and IL-6.

In the study by McAdam et al, there was only a trend for increased CRP levels in smokers, and antiinflammatory treatment with rofecoxib did not reduce CRP levels in either smokers or nonsmokers. This is somewhat at variance with recent studies demonstrating that increased CRP levels were reduced by 300 mg/d of aspirin in smokers with coronary artery disease as well as in healthy smokers. Urinary excretion of TX-M was increased in smokers and reduced by aspirin, but absolute TX levels were about 10-fold increased in the study of Ikonomidis et al compared with that of healthy smokers in the McAdam study. The increase in COX-2–derived TXA2 biosynthesis in smokers, therefore, raises the question of whether the vascular inflammation in smokers that engenders a high risk of coronary events may also lead to an elevation in TXA2 biosynthesis via COX-2 in plaques. COX-2–dependent biosynthesis by plaque macrophages would be of considerable interest in light of the fact that TXA2 stimulates basic fibroblast growth factor protein synthesis in vascular smooth muscle cells.

**Role of Smoking-Induced Oxidative Stress and Effect of Antiinflammatory Treatment**

Smoking reduces NO bioavailability by direct delivery of oxygen-derived free radicals, induction of generation of free radicals within the cell, and reduction of antioxidative capacity. Dietary supplementation of antioxidants reduces oxidative stress but has no beneficial effects in cardiovascular disease, as recently demonstrated by Ridker et al. Interestingly, antiinflammatory treatment with celecoxib reduces oxidative stress in patients with coronary artery disease, as well as in experimental models of hypertension and endotoxic shock, an effect that was not observed for rofecoxib. Platelet aggregation is mainly induced by increased oxidative stress and a reduced bioavailability of NO and can be reversed by endogenous NO. In addition, smoking induces oxidative stress and increases platelet activation. Cessation of smoking improves platelet aggregability and intraplatelet redox imbalance, even in long-term smokers. Activation of platelets by smoke has been known for almost 2 decades and has been attributed to interaction with prosta-glandins. However, in the study by McAdam et al, no increase in platelet markers was observed in smokers despite the relatively high dose of rofecoxib given (50 mg/d). This raises further questions about the importance of PGI2/TXA2 imbalance for cardiovascular risk in coxibs.

It is still questionable whether the antiplatelet actions of PGI2 can completely explain its antithrombotic effects in vivo. Data about possible effects on plasmatic coagulation are beginning to emerge. Smoke activates platelets, induces tissue factor and thrombin expression, and inhibits tissue factor pathway inhibitor (TFPI) expression and therefore increases the risk of thrombus formation. Again, different effects of coxibs have been observed in this context. Tissue factor (TF), a 263-residue membrane-bound glycoprotein, is a key enzyme for initiation and propagation of thrombus formation and plays an important role in atherogenesis; its expression is upregulated by inflammatory mediators such as tumor necrosis factor-α. Furthermore, elevated levels of TF antigen and activity have been detected in plasma and atherectomy specimens of patients with unstable angina. The generation and activity of tissue factor in human aortic endothelial cells after thrombin stimulation was inhibited by celecoxib, but not rofecoxib or NS-398. This effect was mediated by inhibition of JNK phosphorylation. The interplay of coxibs with the coagulation system, however, appears to be more complex. Indeed, Rabausch et al have proposed platelet-independent antithrombotic effects of prostaglandins, as they showed that COX-2–derived vasodilatory prostaglandins induce thrombomodulin (TM) expression in human smooth muscle cells, whereas diclofenac and etoricoxib attenuated this increase. TM activates protein C and thereby effectively inhibits the plasmatic coagulation cascade. Thus, at least certain COX-2 inhibitors may exhibit prothrombotic effects not only by reduction of the platelet-inhibitory PGI2 (and a resulting increase in TXA2) but also by inhibition of the stimulation of the anticoagulatory TM/activated protein C pathway.

In summary, the McAdam et al study provides new insights into the role of prostanooids in mediating the cardiovascular effects of smoking and further challenges the hypothesis that prostanooid imbalance alone accounts for all the cardiovascular effects of coxibs and traditional NSAIDs. It therefore remains unclear to what extent the COX-2 selectivity of an individual drug predicts the drug’s potential for an increased risk of adverse cardiovascular events compared with drugs that are less COX-2 selective.
The present study indicates there is clearly a potential for harm as well as benefit associated with coxibs. To address the net effect of individual agents, adequately powered, prospective, randomized clinical trials are required to address cardiovascular risk. None of the reported randomized trials undertaken with celecoxib (or any other COX-2–selective agent) have thus far been specifically designed to examine cardiovascular outcomes. As such, no formal cardiovascular hypotheses have yet been tested. In this regard, there are many examples of inappropriate conclusions being drawn from post hoc and nonprespecified analyses. Even in trials that do not demonstrate any increased cardiovascular risk, if the trials had not been purposely designed and adequately powered to capture cardiovascular outcomes, the results are inconclusive. Thus, the current situation is one of classic “equipoise”: uncertainty, with the potential for both cardiovascular harm and benefit.

As required by the Food and Drug Administration, a multicenter, prospective cardiovascular safety trial in >20 000 patients with osteoarthritis is currently planned to be undertaken and led by our institution. Importantly, in this head-to-head, 3-arm trial, patients will be randomized to treatment with celecoxib, naproxen, or a second additional NSAID, because many patients are now being switched from COX-2–selective inhibitors to nonselective agents on the presumption of greater cardiovascular safety. Importantly, the size of the study and the calculated number of events will permit, for the first time, subgroup analysis in patients with cardiovascular risk factors, smokers, and patients on relevant concomitant medications. No such analyses have been previously possible from trials conducted thus far, as these have been underpowered and not purposely designed to address cardiovascular issues. Only a large-scale safety trial will provide further insight into what impact the observations of the McAdam et al article and the interplay of prostanoids, smoking, and coxibs may have on clinical practice.

Until definite cardiovascular safety trials are completed, careful risk-benefit analysis needs to be undertaken of any putative increase in cardiovascular risk versus known gastrointestinal benefit within the context of overall absolute risk of the therapy to the individual patient.

Disclosure

Drs Krum and Ruschitzka have served as consultants to Merck, Novartis, and Pfizer.

References


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