EDITORIAL COMMENT

Coxibs and the Endothelium*

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In this issue of the Journal, Title et al. (1) present the results of the much-awaited randomized double-blind evaluation of rofecoxib on endothelial function in patients with coronary artery disease (CAD). From a cardiovascular standpoint, cyclooxygenase-2 (COX-2) inhibitors have been the topic of much discussion, debate, andrepidation (2–5). Mechanistically, the concern about the use of these agents stemmed from observations suggesting that under physiologic conditions COX-2 is a major source of endothelium-derived prostacyclin (PGI₂) and that selective blockade of COX-2 may result in a disproportionate and unopposed increase in COX-1–derived thromboxane (TXA₂) (an endothelium-derived contracting factor and prothrombotic molecule) relative to PGI₂. Such an imbalance might favor endothelial dysfunction and uncover a prothrombotic phenotype. Although an attractive hypotheses, in healthy volunteers rofecoxib administration was associated with no effect on endothelium-dependent or -independent vasomotion (6). However, healthy volunteers may be less susceptible to the effects of a potential imbalance between PGI₂ and TXA₂ compared with patients with CAD in whom decreased basal production of nitric oxide may serve to exaggerate this relative imbalance. Surprisingly, the first preliminary evaluation of this concept revealed that coxib treatment in patients with severe CAD was associated with an improvement in endothelial function and an associated decrease in C-reactive protein (CRP) levels (7), a powerful risk marker and mediator of inflammation and atherothrombosis (8–10). Title et al. (1) report the randomized evaluation of coxib therapy on endothelial function and inflammation in patients with angiographically proven CAD, which suggests that rofecoxib neither improves nor adversely affects endothelial function or inflammatory marker production during an eight-week treatment period.

**Endothelial function: a biomarker for vascular risk.**

Dysfunction of endothelial cells is probably the earliest event in the process of lesion formation and hence the concept that assessment of endothelial function may be a useful prognostic tool for CAD (11). Coronary endothelial cell perturbations often are reflected in peripheral vasodilator abnormalities, thereby allowing the assessment of peripheral endothelial function as a measure of coronary vasomotion (12). The interest in endothelial function testing is based on the premise that: 1) the healthy endothelium is nonthrombogenic; 2) endothelial dysfunction occurs in response to vascular risk factors and is an early event in atherosclerosis; 3) endothelial dysfunction precedes structural atherosclerosis; 4) interventions that improve endothelial function also decrease cardiovascular events in patients with stable coronary disease; 5) reproducible, noninvasive assessments of endothelial function exist; and 6) endothelial function testing fulfills the criteria for an acceptable biomarker (11).

Recent studies also suggest that there is a correlation between endothelium-dependent vasodilation and CRP levels (13). C-reactive protein is a powerful independent predictor of myocardial infarction (MI), stroke, and vascular death in a variety of settings (8–10) and appears to be a better prognosticator of cardiovascular events than low-density lipoprotein (LDL) cholesterol (10). Over the past few years, much interest has been generated into unraveling the mechanistic basis of the CRP-atherosclerosis connection. Indeed, recent studies, including work from our laboratory, suggest that CRP not only is a predictor but also a mediator of lesion formation (14–23). C-reactive protein, at concentrations known to predict vascular disease, has a direct effect in stimulating diverse early atherosclerotic processes, including endothelial cell adhesion molecules, chemoattractant chemokines, and macrophage LDL uptake. In addition, CRP directly modulates the production of endothelium-derived vasoactive factors, including down-regulating endothelial nitric oxide synthase–derived nitric oxide while augmenting production of the potent endothelium-derived vasoconstrictor endothelin-1. Additionally, CRP facilitates endothelial cell apoptosis and attenuates angiogenesis, which is an important compensatory mechanism in ischemia. More recently, CRP has also been demonstrated to promote the release of plasminogen activator inhibitor–1 from endothelial cells, upregulate angiotensin-mediated neo-intimal formation, and alter endothelial progenitor cell survival and differentiation (14–23).

Invasive and noninvasive endothelial vasomotion testing appears to have prognostic value in diverse patient populations and in response to a variety of cardiovascular risk factors (11,24–30). Although large-scale validation of this concept is currently underway (31), the balance of published information thus far supports the notion that vasomotion assessment reflects endothelial cell dysfunction or integrity in vivo.

**COX-2, endothelial function, and cardiovascular risk.**

There is considerable debate as to whether COX-2 is proatherogenic or antiatherogenic in nature. In support of a prothrombotic role of COX-2 are concerns that COX-2 blockade causes a relative imbalance of PGI₂ and TXA₂,
which theoretically could uncover a prothrombotic and proatherosclerotic phenotype (32). Indeed deletion of PGI\textsubscript{2} in mice exaggerates vascular injury, supporting the role of PGI\textsubscript{2} in vascular homeostasis (33). However, it is important to note that COX-2 blockade does not mimic a PGI\textsubscript{2} deletion in vivo because COX-2 blockade still allows COX-1-mediated PGI\textsubscript{2} production to occur. The cardiovascular safety of COX-2 inhibitors have been questioned by other experimental studies demonstrating that COX-2 is important for the late phase of ischemic preconditioning (34) and that celecoxib increases the risk of thrombosis in canine models of vascular injury (35). More recently, COX-2 blockade was demonstrated to increase atherosclerosis in apoE-deficient mice, casting further doubt on the cardiovascular effects of coxibs (36). From a clinical standpoint, much controversy surrounds the observations of atherothrombotic risk of coxibs in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (37), and the retrospective analysis reported by Mukherjee et al. (5). It is important to note that meta-analysis of all rofecoxib studies have not uncovered any prothrombotic effect of this COX-2 blocker (38). More recently, in a large population-based retrospective analysis from Ontario, Canada, no increase in short-term risk of MI was found with the use of selective COX-2 blockers in the elderly population (39). In healthy patients, short-term rofecoxib treatment was demonstrated to have no adverse effect on endothelial function (6) and actually improved endothelial function in patients with severe atherosclerosis (7). In yet another recent study, healthy men were randomized to receive a seven-day treatment with rofecoxib (50 mg/day), naproxen (1,000 mg/day), aspirin (75 mg/day), or diclofenac (150 mg/day) and formation of thromboxane, prostacyclin, and thrombin in the bleeding-time blood at the site of standardized microvascular injury was assessed before and after treatment. Rofecoxib had no effect on any variables measured (40). At the other end of the spectrum are intriguing data that COX-2 inhibitors might actually be antiatherogenic. Preliminary evidence suggests that celecoxib lowers CRP levels, which are a powerful marker of future cardiovascular events, and reduces oxidative stress in patients with CAD (7). Furthermore, meloxicam, a preferential COX-2 blocker, was associated with significant reductions in adverse outcomes in acute coronary syndrome patients (41). The enzyme COX-2 is markedly upregulated in atherosclerotic plaques (42,43) and, indeed, in LDL receptor-deficient mice, rofecoxib treatment is associated with reduction in atherosclerosis despite an imbalance between PGI\textsubscript{2} and TXA\textsubscript{2} (44). The COX-2 blockers, including rofecoxib, have been demonstrated to be beneficial after acute experimental MI (45,46). Clearly, as the debate between the experimental and clinical evidence continues, it is important to realize that until a large-scale randomized controlled trial with hard end points (MI, stroke, and cardiovascular death) is conducted we will not have a definitive answer as to whether coxibs are neutral, promote atherothrombosis, or are actually antiatherogenic.

The study by Title et al. (1) demonstrates in a double-blind, placebo-controlled, parallel design fashion, that eight-week treatment with rofecoxib in patients with established CAD neither adversely affects endothelium-dependent or -independent vascular function nor alters inflammatory biomarker profiles (CRP, soluble intercellular adhesion molecule, and soluble interleukin-6 receptor). Although these data suggest that in patients with known atherosclerosis there may be no detrimental effect of rofecoxib therapy on endothelial function and inflammatory profile, a number of important points need to be considered in evaluating these data. First, the study contrasts that recently published by Chenevard et al. (7) demonstrating a beneficial effect of celecoxib on endothelial function and CRP in patients with atherosclerosis. As acknowledged by the authors, these differences may be related to sample size or may actually reflect a difference between celecoxib and rofecoxib. Second, there appears to be an imbalance in baseline angiotensin-converting enzyme inhibitor (ACE) use between the two groups (p = 0.07). Given the powerful effects of ACE inhibitors on vascular function, this remains an important limitation. Third, the lack of effect of rofecoxib on inflammatory biomarkers and endothelial function may reflect the high background use of statin and ACE inhibitors in the two groups, in addition to low-dose aspirin. Although these agents can directly modulate endothelial function, these are proven contemporary treatments for patients with established CAD, and the study in this regard mimics the real-life scenario. Fourth, the authors failed to uncover a relationship between inflammatory markers and flow-mediated dilation over time, a relationship that has been demonstrated by other studies (13). Fifth, the study was powered primarily to detect a difference in flow-mediated dilation and not biomarker production. Given the variability in the results presented for the biomarkers, a considerably larger sample size may have been required to determine changes in CRP in response to coxib therapy. Lastly, it is important to note that these results apply to patients who were taking low-dose aspirin concomitantly, and the presence of low-dose aspirin may prevent the potential imbalance between PGI\textsubscript{2} and TXA\textsubscript{2}. Again, one of the limitations of the study is the lack of data on PGI\textsubscript{2} and TXA\textsubscript{2}, a critical point in the debate of COX-2 inhibitors and vascular function. Notwithstanding these criticisms, the study by Title et al. (1) is a very important addition to the clinical data on coxibs and cardiovascular risk, which suggests that rofecoxib does not adversely affect endothelial function or CRP in patients with known coronary atherosclerosis and on background aspirin therapy.
REFERENCES


