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Effect of Cyclooxygenase-2 Inhibition With Rofecoxib on Endothelial Dysfunction and Inflammatory Markers in Patients With Coronary Artery Disease

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OBJECTIVES The aim of this study was to determine whether selective cyclooxygenase-2 (COX-2) inhibition with rofecoxib can modulate endothelial dysfunction and levels of circulating inflammatory markers in patients with established coronary artery disease (CAD).

BACKGROUND Expression of COX-2 is upregulated in atherosclerosis. Thus, it has been hypothesized that COX-2 may contribute to atherogenesis by producing eicosanoids, which mediate vascular inflammation and endothelial dysfunction.

METHODS In a randomized, double-blind, placebo-controlled, parallel-design trial, we studied the vascular effects of rofecoxib on brachial artery vasoreactivity and inflammatory markers in 60 patients with angiographically proven CAD who were taking concomitant low-dose aspirin. Patients were randomly assigned to receive either rofecoxib (25 mg/day; n = 30) or placebo (n = 30) for eight weeks. Brachial artery endothelium-dependent flow-mediated dilation (FMD), endothelium-independent nitroglycerin-mediated dilation (NMD), and inflammatory markers (i.e., high-sensitivity C-reactive protein [CRP], soluble intercellular adhesion molecule-1 [sICAM-1], and soluble interleukin-6 receptor [sIL-6r]) were measured at baseline and after eight-week follow-up.

RESULTS Baseline clinical characteristics were similar in the two groups. After eight weeks of treatment, FMD did not significantly change in either the rofecoxib or placebo group (4.0 ± 3.0% to 4.0 ± 3.8% vs. 2.7 ± 2.7% to 3.1 ± 2.7%, respectively; p = 0.6 by two-way analysis of variance). Similarly, NMD remained unchanged in both groups. Levels of CRP, sICAM-1, and sIL-6r were not significantly altered in either the rofecoxib or placebo group.

CONCLUSIONS The addition of selective COX-2 inhibition with rofecoxib did not appear to have any favorable or adverse effects on endothelial dysfunction or vascular inflammation in patients with CAD using concomitant low-dose aspirin. (J Am Coll Cardiol 2003;42:1747–53)

Increasingly, it has been recognized that both vascular inflammation and endothelial dysfunction play a key role in the pathogenesis of atherosclerosis (1,2). Clinically, there is substantial evidence that elevated levels of circulating inflammatory markers, including high-sensitivity C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble interleukin-6, can predict the risk of future cardiovascular events (2). This epidemiologic association may be related to changes in endothelial function, as it has been shown that systemic inflammation can impair endothelial function (3) and endothelial dysfunction may be predictive of a poor prognosis (4). Moreover, there is evidence that CRP may directly induce endothelial dysfunction by reducing the release of endothelium-derived nitric oxide (5). Thus, there may be a rationale for targeting inflammation and endothelial dysfunction with novel anti-inflammatory drugs to reduce cardiovascular events.

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Cyclooxygenases convert arachidonic acid to prostaglandin G/H_2, the precursor for prostacyclin, thromboxane A_2, prostaglandin E_2, and other eicosanoids that are important in vascular pathophysiology. Cyclooxygenase-2 (COX-2), the inducible form of the enzyme, is expressed in atherosclerotic vessels but not in normal arteries (6,7). Thus, it has been hypothesized that COX-2 may contribute to vascular inflammation and atherosclerosis. This may have therapeutic implications given the availability of selective COX-2 inhibitors such as rofecoxib and celecoxib, which could suppress vascular inflammation and atherogenesis (6–11).

Conversely, there is evidence suggesting that the COX-2 enzyme may be protective against atherosclerosis (9,12). Consequently, COX-2 inhibition may have adverse vascular effects by altering the prostacyclin/thromboxane balance in

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ANOVA	= analysis of variance
CAD	= coronary artery disease
COX-2	= cyclooxygenase-2
CRP	= C-reactive protein
FMD	= flow-mediated dilation
NMD	= nitroglycerin-mediated dilation
NSAID	= nonsteroidal anti-inflammatory drug
sICAM-1	= soluble intercellular adhesion molecule-1
sIL-6r	= soluble interleukin-6 receptor
VIGOR	= VIoxx Gastrointestinal Outcomes Research

favor of thromboxane (9,13). Clinically, the safety of the COX-2 inhibitors has been recently questioned in the VIoxx Gastrointestinal Outcomes Research (VIGOR) study, which showed that rofecoxib was associated with significantly more cardiovascular events (14). However, this remains controversial, as other studies, including those permitting concomitant low-dose aspirin, showed no increased risk (15,16). Moreover, rofecoxib, despite blocking prostacyclin production, does not appear to impair endothelial function in healthy volunteers (17). Conversely, a recent study has suggested that celecoxib may improve endothelial dysfunction and reduce CRP levels in patients with CAD on background aspirin therapy (18). Accordingly, the aim of this study was to determine whether the COX-2 inhibitor rofecoxib could modulate endothelial dysfunction and markers of inflammation in patients with established coronary artery disease (CAD) who were using concomitant low-dose aspirin.

METHODS

Study design and study population. The study was a randomized, double-blind, placebo-controlled, parallel-design trial conducted between March 2001 and February 2002. The protocol was approved by the Queen Elizabeth II Health Sciences Centre Research Ethics Committee.

Patients undergoing cardiac catheterization at the Queen Elizabeth II Health Sciences Centre were screened for entry into the trial. Patients between 18 and 75 years of age were eligible if they had angiographically proven CAD, defined as stenosis of 50% or more of the luminal diameter in a major epicardial coronary vessel and stable angina pectoris (Canadian Cardiovascular Society class I/II) within three months of randomization. To minimize any confounding effects on endothelium-dependent flow-mediated dilation (FMD) and inflammatory markers, patients were excluded if they had unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery within three months of screening; an anticipated need for bypass surgery or percutaneous coronary intervention in the subsequent two months; uncontrolled hypertension; diabetes mellitus; ongoing congestive heart failure or left ventricular ejection fraction <40%; or fasting total cholesterol >6.0 mmol/l (232 mg/dl) with or without lipid-lowering medications. Patients taking high-dose aspirin (>650 mg/day), nonsteroidal anti-inflammatory drugs (NSAIDs), or COX-2 inhibitors within three months of screening and those with known intolerance or sensitivity to aspirin or COX-2 inhibitors, active peptic ulcer disease, gastritis, esophagitis, or previous upper gastrointestinal bleeding were also excluded. All patients received low-dose aspirin (325 mg/day), which was maintained throughout the study. Patients on lipid-lowering therapy and angiotensin-converting enzyme (ACE) inhibitors were included, as long as they were on a stable dose for two months before enrollment. All patients gave written, informed consent. Of the 135 consecutive patients screened, 60 were enrolled.

Study protocol. After enrollment, patients underwent baseline clinical assessment and noninvasive assessment of endothelial function. A fasting blood sample was obtained on the morning of the endothelial function test for serum lipids and inflammatory markers. Then, patients were randomly assigned to one of two groups: placebo (n = 30) or rofecoxib (25 mg/day, Vioxx, Merck; n = 30). This dose of rofecoxib was chosen because it is associated with significant inhibition of COX-2 (19). Moreover, it has been shown that concomitant use of rofecoxib at this dose does not antagonize the cardioprotective, antiplatelet effects of low-dose aspirin (20). Randomization was performed according to a sealed envelope assignment. Treatment assignments were blinded, with matching placebo capsules. The assigned treatment was continued for eight weeks. Patients and their referring physicians were instructed to avoid additional "open-label" COX-2 inhibitor or NSAID use during the eight-week study. All patients were maintained on their usual anti-anginal regimen throughout the study. Lipid-lowering drugs and ACE inhibitors were maintained at constant dosages throughout the study. None of the smokers quit during the study. After eight weeks of treatment, noninvasive endothelial function, serum lipids, and inflammatory markers were re-evaluated. Baseline and follow-up endothelial function testing was carried out after a 12-h overnight fast. Long-acting vasoactive medications were withheld for 24 h before endothelial function testing, and smokers refrained from smoking on the morning of the test. Compliance at the end of eight weeks was assessed by a pill count and was defined as taking >80% of the study capsules.

Noninvasive assessment of endothelial function. Endothelium-dependent and endothelium-independent dilation of the brachial artery was assessed noninvasively using a high-resolution ultrasound system (Philips HDI 5000, Philips Medical Systems, Andover, Massachusetts) with a 7- to 12-MHz linear-array vascular transducer, as previously described (4,21). The brachial artery was imaged longitudinally, 2 to 15 cm above the antecubital crease, ensuring optimal visualization of the anterior and posterior wall-lumen interfaces. This position was maintained throughout

the test, and a similar position was used in the follow-up study. A pneumatic tourniquet placed proximally on the forearm was inflated to 250 mm Hg for 5 min and rapidly deflated, resulting in reactive hyperemia. Brachial artery images were obtained continuously for 30 s before cuff inflation (first baseline), at 50 to 110 s after cuff deflation (post-reactive hyperemia), for another 30 s after 10-min rest (second baseline), and for a further 60 s beginning 3 min after sublingual nitroglycerin (0.3 mg). All images were digitally recorded on magneto-optical disks for subsequent off-line quantitative analysis.

During the baseline and second baseline phases, a total of four end-diastolic frames (coincident with the peak of the electrocardiographic R wave) were selected, acquiring one frame every 5 s from the recorded digital sequences. End-diastolic frames from three consecutive cardiac cycles were selected at 60, 70, 80, and 90 s after cuff release to assess the peak FMD response after reactive hyperemia. End-diastolic frames from four consecutive cardiac cycles were selected at 3 min after sublingual nitroglycerin administration. Average end-diastolic brachial artery diameters were measured using commercially available, computer-assisted, brachial artery quantitative software (Dynamic Endothelial Assessment, Vasometrix, Montreal, Canada) by one observer blinded to the patients' treatment assignment. Unless the intima-lumen border was clearly defined, the media-lumen border for the anterior and posterior walls was determined by automated edge-detection software over a 10- to 20-mm arterial segment, and the average diameter over this segment was determined (intra-assay coefficient of variation for diameter −0.3%). The same region of interest was used for measurements of the baseline, post-reactive hyperemia, second baseline, and post-nitroglycerin images. Measurements of the four sequential first baseline, second baseline, and post-nitroglycerin frames were averaged at each phase. Measurements of the three sequential post-reactive hyperemia frames at 60, 70, 80, and 90 s were averaged to determine the maximal FMD diameter between 60 and 90 s. Endothelium-dependent FMD was defined as the *maximal* percent change in brachial artery diameter (between 60 and 90 s) after reactive hyperemia compared with baseline (intra-assay coefficient of variation for FMD −1.9%). Endothelium-independent nitroglycerin-mediated dilation (NMD) was calculated as the percent change in brachial artery diameter at 3 min after nitroglycerin compared with the second baseline. Brachial artery flow was calculated as the product of the Doppler velocity-time integral, heart rate, and brachial artery cross-sectional area ($\pi D^2/4$), where D = average arterial diameter at that phase. Reactive hyperemia was calculated as the percent change in arterial flow after tourniquet deflation compared with baseline.

Biochemical analyses. Venous blood was collected for the measurement of serum lipids and the inflammatory markers of high-sensitivity CRP, sICAM-1, and soluble interleukin-6 receptor (sIL-6r). Serum was separated immediately and frozen at −70°C for subsequent analysis. Serum lipids were measured with a Beckman Synchron CX7 system (Beckman Coulter, Inc., Brea, California). Inflammatory markers were measured at McMaster University. High-sensitivity CRP levels were measured by nephelometric assay (Dade-Behring, Inc., Deerfield, Illinois). Levels of sICAM-1 and sIL-6r were measured with commercially available ELISA assays (R&D Systems; Minneapolis, Minnesota).

Statistical analysis. Baseline characteristics of the two groups were compared using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. The primary end point, the effect of treatment on endothelium-dependent FMD and endothelium-independent NMD over time, was assessed by two-way repeated measures ANOVA on an intention-to-treat basis. Secondary end points, the effects of treatment on serum lipids and inflammatory markers, were also assessed by two-way repeated measures ANOVA. As CRP, sICAM-1, and sIL-6r levels values were skewed, a logarithmic transformation was performed, and the results are expressed as geometric mean values. Linear regression was used to assess the relationship between the change in FMD and the change in inflammatory markers. Our sample size was determined in order to demonstrate an absolute 2% change in FMD (assuming a standard deviation of 2.5%) in the rofecoxib group, compared with placebo (alpha = 0.05 and beta = 0.20; two-tailed test). Given the variability of repeat FMD measurements, the minimal statistically significant change in FMD with intervention that can be detected is 1.5% to 2.0% in parallel-design studies of 40 to 60 subjects (4). As previous studies with ACE inhibitors and statins (both pharmacologic agents with proven clinical cardioprotective effects) have shown an absolute 1.8% to 2.7% change in FMD (22,23), we believe an absolute 2% change in FMD is clinically significant. Two-sided p values <0.05 were considered to indicate statistical significance. Continuous data are expressed as the mean value ± SD, unless stated otherwise.

RESULTS

Patient characteristics. The baseline clinical and angiographic characteristics for the two groups of patients are shown in Table 1. There were no significant differences between the two groups, although there was a trend toward less ACE inhibitor use in the placebo group (p = 0.07). However, three-way ANOVA demonstrated no significant interaction between ACE inhibitor use and the treatment effect on FMD or inflammatory markers over time. Utilization and dosages of ACE inhibitor and lipid-lowering therapy did not change at follow-up.

Effects on FMD and NMD. End-diastolic brachial artery diameters, brachial artery flow, and reactive hyperemia were similar in the two groups at baseline and follow-up (Table 2). Heart rate and blood pressure were

Table 1. Clinical and Angiographic Characteristics of the Study Patients

Characteristic	Placebo (n = 30)	Rofecoxib (n = 30)
Mean age (yrs)	58.3 ± 7.1	57.5 ± 8.0
Female gender (%)	7	10
Current smoker/ex-smoker (%)	13/63	0/63
History of dyslipidemia (%)	87	90
History of hypertension (%)	37	59
Previous MI (%)	47	47
Previous PCI (%)	57	50
Previous CABG (%)	47	37
Aspirin use (%)	100	100
Lipid-lowering therapy (%)	76	80
ACE inhibitors (%)	33	57
No. of vessels diseased (%)		
1	33	35
2	27	17
3	40	48
CCS anginal class (%)		
I	90	90
II	10	10

There were no significant differences for the characteristics listed.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; MI = myocardial infarction; PCI = percutaneous coronary intervention.

similar in the two groups at baseline and remained unchanged at follow-up (data not shown).

Overall, the baseline FMD was 3.3 ± 2.9%, which is similar to that in previous reports on CAD patients using lower arm occlusion (21,24). The FMD and NMD responses at baseline and follow-up for the two groups are shown in Table 2. Although baseline FMD tended to be higher in the rofecoxib group, this was not statistically significant (4.0 ± 3.0% vs. 2.6 ± 2.7%; p = 0.08). After eight weeks of treatment, FMD did not significantly change in either the placebo or rofecoxib group (p = 0.6 by two-way ANOVA) (Table 2).

Table 2. Brachial Artery End-Diastolic Diameters and Flow, Flow-Mediated Dilation, and Nitroglycerin-Mediated Dilation

Characteristic	Placebo (n = 30)	Rofecoxib (n = 30)	p Value*
Brachial artery measurements			
Basal end-diastolic diameter (mm)			
At baseline	4.61 ± 0.74	4.32 ± 0.69	
At follow-up	4.54 ± 0.74	4.34 ± 0.70	0.4
Basal brachial artery flow (ml/min)			
At baseline	195 ± 120	183 ± 105	
At follow-up	181 ± 70	211 ± 113	0.1
Reactive hyperemia (%)			
At baseline	359 ± 278	342 ± 338	
At follow-up	372 ± 183	256 ± 192	0.2
Flow-mediated dilation (%)			
At baseline	2.7 ± 2.7	4.0 ± 3.0	
At follow-up	3.1 ± 2.7	4.0 ± 3.8	0.6
Nitroglycerin-mediated dilation (%)			
At baseline	13.2 ± 4.5	14.6 ± 5.8	
At follow-up	13.1 ± 5.1	13.8 ± 5.5	0.6

*The change in flow-mediated (and nitroglycerin-mediated) dilation from baseline to follow-up was compared between the placebo and rofecoxib groups by two-way analysis of variance for repeated measures. Data are presented as the mean value ± SD.

Overall, endothelium-independent NMD was 14 ± 5%. At baseline, NMD was similar between the two groups and remained unchanged at follow-up (p = 0.6 by two-way ANOVA) (Table 2).

Effects on serum lipids, CRP, sICAM-1, and sIL-6r. Serum lipids, high-sensitivity CRP, sICAM-1, and sIL-6r levels are shown in Table 3. The baseline lipids and inflammatory markers were similar in both groups. Serum lipids and circulating levels of the inflammatory markers were not significantly altered in either the rofecoxib or placebo group.

There were no significant correlations between the change in maximal FMD at follow-up and the change in any of the inflammatory markers at follow-up.

Follow-up, side effects, and compliance. During follow-up, there were no cardiovascular events. In general, the study medication was well tolerated, and side effects were more commonly noted in the placebo group (27% vs. 20% in rofecoxib group). Side effects included dyspepsia, heartburn, epigastric discomfort, diarrhea, constipation, and rash. There were no adverse effects on blood pressure or peripheral edema with rofecoxib. Based on pill counts, four patients in the placebo group (13%) were thought to be noncompliant with their study medications.

DISCUSSION

Our study shows that eight weeks of treatment with the COX-2 inhibitor rofecoxib (25 mg/day) did not significantly alter endothelium-dependent FMD or inflammatory markers in patients with established CAD who were taking concomitant low-dose aspirin.

To date, there are limited data on the direct vascular effects of selective and nonselective COX inhibition. The cardioprotective effects of aspirin, a nonselective COX inhibitor, have largely been attributed to its antiplatelet effects via thromboxane inhibition. Yet, aspirin may also act through improving endothelial dysfunction (25,26) and reducing inflammation (27,28). Husain et al. (25) demonstrated that short-term administration of intravenous aspirin improved acetylcholine-mediated vasodilation in patients with established atherosclerosis. Similarly, Kharbanda et al. (26) demonstrated that pretreatment with high-dose oral aspirin could prevent inflammation-induced endothelial dysfunction. However, whether low-dose aspirin can reduce circulating levels of CRP and other inflammatory markers remains controversial (28,29). Verma et al. (17) studied the effects of selective COX-2 versus nonselective COX inhibition (with rofecoxib and naproxen, respectively) on endothelium-dependent vasodilation in healthy volunteers. They found that selective COX-2 inhibition with rofecoxib did not significantly alter acetylcholine-induced

Table 3. Effects of Rofecoxib on Serum Lipids and Inflammatory Marker Levels

Variable	Placebo (n = 30)	Rofecoxib (n = 30)	p Value*
Total cholesterol (mmol/l)†			
Arithmetic mean ± SD			
At baseline	4.7 ± 0.9	4.5 ± 0.9	
At follow-up	4.7 ± 0.8	4.4 ± 0.9	0.7
LDL cholesterol (mmol/l)†			
Arithmetic mean ± SD			
At baseline	2.9 ± 0.7	2.7 ± 0.7	
At follow-up	2.8 ± 0.7	2.7 ± 0.7	0.7
HDL cholesterol (mmol/l)†			
Arithmetic mean ± SD			
At baseline	1.0 ± 0.3	0.9 ± 0.2	
At follow-up	1.0 ± 0.3	1.0 ± 0.2	0.2
Triglycerides (mmol/l)‡			
Arithmetic mean ± SD			
At baseline	1.7 ± 0.9	1.9 ± 0.9	
At follow-up	1.7 ± 0.8	1.8 ± 0.8	0.3
High-sensitivity CRP (mg/l)§			
Geometric mean value (95% CI)			
At baseline	1.6 (1.1–2.3)	1.5 (1.0–2.1)	
At follow-up	1.8 (1.2–2.8)	1.6 (1.0–2.5)	0.8
sICAM-1 (ng/ml)§			
Geometric mean value (95% CI)			
At baseline	263 (242–286)	272 (250–295)	
At follow-up	259 (239–280)	268 (246–292)	0.9
sIL-6r (ng/ml)§			
Geometric mean value (95% CI)			
At baseline	33 (30–37)	34 (32–37)	
At follow-up	33 (29–36)	33 (30–35)	0.9

*The changes in lipids, CRP, sICAM-1, and sIL-6r from baseline to follow-up were compared between the placebo and rofecoxib groups by two-way analysis of variance for repeated measures. †To convert values for total cholesterol, LDL cholesterol, and HDL cholesterol to mg/dl, divide by 0.02586. ‡To convert values for triglycerides to mg/dl, divide by 0.01129. §Normal reference values for CRP: 0.5–2.5 mg/l; sICAM-1: 115–306 ng/ml; and sIL-6r: 14–46 ng/ml.

CI = confidence interval; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; sICAM-1 = soluble intercellular adhesion molecule-1; sIL-6r = soluble interleukin-6 receptor.

vasodilation in these healthy subjects. Potentially, patients with atherosclerosis may be more sensitive to the effects of COX inhibition, as COX-dependent vasodilator prostaglandins are important in controlling vascular function in subjects with atherosclerosis (30). Our findings are in agreement with the results of Verma et al. (17) and extend their findings to patients with established coronary atherosclerosis and endothelial dysfunction who are using concomitant low-dose aspirin. Conversely, Chenevard et al. (18) recently studied the effect of the COX-2 inhibitor celecoxib (200 mg twice daily for 2 weeks) on FMD and CRP in a randomized, cross-over study in 14 patients with CAD using concomitant aspirin and statins. In contrast to our study, they found that celecoxib significantly improved FMD (+1.3% absolute increase) and reduced CRP levels. These conflicting results may relate to differences in their study design and small sample size or may reflect differences between the cardiovascular effects of rofecoxib and celecoxib. Currently, it remains unknown whether such differences exist among the various selective COX-2 inhibitors (10).

The use of COX-2 inhibitors in cardiovascular disease is controversial. On one hand, there is evidence to suggest that the COX-2 enzyme may have an important role in atherogenesis, as COX-2 enzyme expression is upregulated within atherosclerotic lesions (6,7). This increased COX-2 expression is localized to macrophages, endothelial cells, and vascular smooth muscle cells within atherosclerotic plaque, all of which are key players in the development and progression of atherosclerosis. Thus, it has been speculated that selective COX-2 inhibition may reduce vascular inflammation and atherosclerotic progression (6–11). In that regard, a recent study has demonstrated that selective COX-2 inhibition with rofecoxib significantly reduced atherosclerosis formation in a low-density lipoprotein receptor-deficient mouse model (11). Also, a recent open-label, pilot study suggested there was benefit in adding the COX-2 inhibitor meloxicam to aspirin and heparin for preventing recurrent cardiac events in patients with acute coronary syndrome (31). Conversely, there is evidence suggesting that the presence of COX-2 within atherosclerotic plaque has a protective role in atherogenesis (9,12). Enhanced COX-2 expression by endothelial cells increases the production of prostacyclin over thromboxane A_2, favoring an antithrombotic state (13). Consequently, selective COX-2 inhibition may lead to prothrombotic effects by inhibiting prostacyclin synthesis (8,9,12,13). Clinically, the recently reported VIGOR study highlighted this potential concern

of COX-2 blockade, as rofecoxib (50 mg/day) was associated with a significant increase in thrombotic cardiovascular events, compared with the nonselective NSAID naproxen (1,000 mg/day) when studied in over 8,000 patients with rheumatoid arthritis (14). However, this report remains controversial as the VIGOR findings were based on relatively few events, and it is possible that the antiplatelet effects of naproxen may have provided some cardioprotective effects (10,15). Moreover, further studies with rofecoxib have shown no increase in cardiovascular risk, especially when concomitant low-dose aspirin use was permitted (15,16). Importantly, our mechanistic study cannot be compared with the VIGOR trial, as we studied a lower dose of rofecoxib (25 mg/day) and our study was not designed to look at clinical events.

Study limitations. There are certain limitations to our study. First, it is possible that rofecoxib may have effects on endothelial function and vascular inflammation at the cellular level, which are not detectable by measuring FMD and nonspecific serum inflammatory markers. Second, the failure to demonstrate a significant effect on the serum inflammatory markers may be related to our low-risk, highly selected, and small study population. It is possible that the concomitant low-dose aspirin, statins, and ACE inhibitors used in our study may have already suppressed the levels of these markers within the normal range. Our study does not allow us to determine the effects of rofecoxib independent of this background treatment. Moreover, as acute coronary syndromes may elevate levels of such markers, the effects of rofecoxib may have been different in a less stable group of patients (31). Also, the study was only powered according to the expected effect on FMD and may have been too small to detect a significant change in the serum markers of inflammation. Third, we cannot be sure that our treatment period was sufficiently long enough to alter endothelial function or inflammatory markers. However, studies using other pharmacologic interventions have demonstrated significant treatment effects with treatment periods of eight weeks or less in patients with CAD (18,22,23,28). Lastly, we did not directly measure COX-2 inhibition with rofecoxib, although previous studies have shown inhibition of COX-2 with a similar dose (19).

Conclusions. The addition of selective COX-2 inhibition with rofecoxib did not appear to have any favorable or adverse effects on endothelial dysfunction or vascular inflammation in stable CAD patients using concomitant low-dose aspirin, along with frequent use of statins and ACE inhibitors. As these findings differ with the recent findings with celecoxib in CAD, additional mechanistic studies may be required to compare the cardiovascular effects of the various COX-2 inhibitors. Given the ongoing controversy surrounding the use of COX-2 inhibitors, further clinical studies with various COX-2 inhibitors are clearly required to establish their safety and therapeutic benefit in a wider spectrum of patients with CAD.

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