Our previous study (5) clearly demonstrated that isolated diagonal branch occlusion caused ECG abnormalities in leads I and aVL, while less frequently causing changes in the precordial leads compared with those caused by acute LAD obstruction, indicating that leads I and aVL represent myocardium perfused by the diagonal branch. Acute LMCA obstruction causes ischemia in myocardium perfused by the diagonal branch. Our finding that ST-segment elevation in lead aVL was observed in high incidence in LMCA AMI patients was completely in agreement with our previous study (5). The ST-segment elevation in leads aVL and I in LMCA AMI patients was caused by ischemia in myocardium perfused by the diagonal branch associated with acute LMCA obstruction.

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Cyclooxygenase–2 Inhibitors and Cardiovascular Thromboembolic Events

In the recent perspective published by Bing and Lomnicka in the Journal (1), several hypotheses were given for why cyclooxygenase–2 (COX–2) inhibitors may cause cardiovascular events. The investigators even stated in their abstract that their report "confirms evidence that selective nonsteroidal anti-inflammatory drugs [NSAID] such as celecoxib can lead to thrombotic cardiovascular events." In fact, there are no data provided by Bing and Lomnicka (1) nor from the clinical literature that clinical cardiovascular events, defined as acute myocardial infarction, stroke and cardiovascular death, are increased owing to the COX-2 inhibitor, celecoxib. Thus, I believe that their study is potentially misleading to the readership of the Journal.

Using well-known basic pharmacology literature as a resource, Bing and Lomnicka (1) stated that selective COX-2 inhibitors attenuate the production of prostacyclin, but do not alter thromboxane A2 levels and therefore may theoretically tip the balance in favor of thrombosis. Thus, certain types of high-risk patients treated with COX-2 inhibitors could be predisposed to increases in cardiovascular events. To further support their hypothesis, however, they use the highly controversial post hoc analysis of data from Mukherjee et al. (2), which suggested that the COX-2 inhibitors celecoxib and rofecoxib had a higher myocardial infarction event rate compared to an entirely unrelated, separate cohort of generally healthy individuals in the placebo arm of four primary prevention trials using aspirin (2). The sources of the pooled analyses for the COX-2 inhibitors from the analysis of Mukherjee et al. (2) derived from the Celecoxib Long-term Arthritis Safety Study (CLASS) (3) and Vioxx Gastrointestinal Outcomes Research (VIGOR) (4) trials using celecoxib and rofecoxib, respectively, and two clinical trials that compared rofecoxib with a nonselective NSAID, nabumetone. The CLASS and VIGOR trials were conducted in approximately 8,000 arthritis patients each and compared the gastrointestinal safety of the COX-2 inhibitors versus the widely used NSAIDs, ibuprofen and diclofenac (in CLASS) and naproxen (in VIGOR) for a median period of about nine months in each trial.

A number of errors made by Mukherjee et al. (2) have now been documented by numerous letters to the editor of JAMA in December 2001. For example, patients in the CLASS trial who were treated with low-dose aspirin (owing to prior cardiac or cerebrovascular disorders) were compared to placebo patients who had no known prior history of myocardial infarction (MI) from four primary prevention trials evaluating the beneficial effects of aspirin. The annual MI rates reported for celecoxib in CLASS and rofecoxib in VIGOR by Mukherjee et al. for the entire group were 0.7% to 0.8% compared to a rate of 0.52% of MI observed in the placebo group from the primary prevention trials. When the patients who were nonusers of aspirin in the CLASS trial (about 3,100 patients) on celecoxib were assessed, the incidence of MI was just 0.3%.

We recently reported on an extensive analysis of these thromboembolic events in the CLASS trial (5) that study showed no evidence that high doses of celecoxib (400 mg twice daily) increased the risk of acute MI, stroke, or venous thromboembolic events compared to the conventional NSAIDs, ibuprofen and diclofenac. This was true for the entire study population, both in patients not taking aspirin and in patients taking aspirin. Similarly, there have been no data from the premarketing clinical trials that
show an increase in cardiovascular events on celecoxib versus placebo nor celecoxib versus other nonselective NSAIDs (6). One would have to conclude, then, that there are no clinical outcome data that support the hypothesis and statement of Bing and Lomnicka (1) that the COX-2 inhibitor celecoxib causes cardiovascular events.

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REPLY
White, in his response to our study “Cyclooxygenase (COX-2) Inhibitors and Cardiovascular Thromboembolic Events,” stated “there are no clinical outcome data that support the hypothesis and statement of Bing and Lomnicka that the COX-2 inhibitor celecoxib causes cardiovascular events.” We have indeed no clinical material of our own that demonstrates the effect of this selective nonsteroidal anti-inflammatory compound (NSAID) on cardiac events. But it was not our purpose to cite clinical material of our own in support of the effects of celecoxib. Rather, we attempted to demonstrate an experimental basis for the clinical trials by Mukherjee et al. (1). We primarily wanted to stress the importance of changes in prostanoids in heart muscle, specifically of thromboxane and prostacyclin. Prostacyclin is a vasodilator that prevents cardiac arrhythmias and platelet aggregation; thromboxane, in contrast, acts as a vasoconstrictor initiating ventricular arrhythmias (2). Therefore, in the heart a decline in prostacyclin results in coronary vasoconstriction, as does an increase in thromboxane. In the kidney, a disproportionate decline in prostacyclin has even more dire consequences (3), because both nonselective and selective NSAIDs cause acute renal failure (4–6). Changes in prostanoids in heart and kidney are related to the activity of cyclooxygenases (COX), which catalyze the conversion of arachidonic acid.

It was not our intention to present clinical evidence about the effect of celecoxib. Rather, we wanted to stress reasons for the possible relationship of NSAIDs to cardiac events. The decline in prostacyclin following administration of NSAIDs and the resulting deterioration in function confirm the predominant role of prostanoids in organ function.

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