depression. However, our experience, supported by several studies that were not quoted by Yamaji et al. (1) is that the predominant ECG manifestation of left main stenosis is diffuse ST depression in both the inferior and precordial leads (2–4).

It was shown in both the experimental laboratory and in clinical studies that a sudden obstruction of a left main coronary artery induces an increase of the end diastolic pressure without increasing the end diastolic volume, thus shifting the pressure/volume curve upright (5,6). The sudden increase of the end diastolic pressure reduces the subendocardial coronary flow, resulting in a circumferential subendocardial ischemia (6). The electrical vector is shifted from the epicardium toward the subendocardium, causing diffuse ST depression with inverted T waves in the precordial leads on the surface ECG (2,3,7). Lead aVR faces the cavity of the left ventricle from a right superior axis and thus records a mirror image of the apical leads V5 and V6. Hence, if there is ST depression in leads V5 and V6, lead aVR will usually show ST elevation. This phenomenon is seen on the ECG in various clinical situations associated with an increase of the left ventricular end diastolic pressure, such as tachycardia-induced ischemia and in chronic infarction with restrictive remodeling (8).

In their study, Yamaji et al. (1) reported on the incidence of ST elevation in each lead, but not on the incidence of ST depression. In two of the three cases reported by Frierson et al. (4) there was ST elevation in lead aVR in addition to marked ST depression in leads V3 through V6. In the third case with acute ischemia due to left main stenosis, only mild ST depression was seen in leads V3 through V6 and no ST elevation in lead aVR, supporting the concept of lead aVR representing the mirror image of leads V5 and V6. Figure 1a of Yamaji et al. (1) shows ST elevation in leads aVR, aVL and V2, with marked ST depression in the inferior leads. We have previously reported this pattern to represent mid-anterior myocardial infarction (MI) caused by first diagonal branch occlusion (9). In the classic presentation, there is ST elevation in leads I, aVL and V2, reciprocal ST depression with negative T waves in the inferior leads, and ST depression with tall positive T waves in leads V4 and V5 (representing anterior subendocardial ischemia). Four of the eight patients reported in that study had ST elevation in lead aVR in the acute phase and six had ST elevation in lead aVR in the predischarge ECG. All these patients had an occlusion of the first diagonal branch without stenosis of the left main coronary artery. Thus, it might be that the ECG in Figure 1a presented by Yamaji and colleagues (1) represents ischemia induced by embolization of a thrombus from the left main coronary artery to the first diagonal branch.

It might be that there are cases in which the “reciprocal” ST elevation in lead aVR is more prominent than the ST depression in the leads facing the apex. Previously we reported that “reciprocal” ST depression in lead aVL is seen more often than ST elevation in leads II, III and aVF in the early stages of inferior acute MI (10).

In conclusion, ST elevation in lead aVR is probably a “reciprocal” change to ST depression in leads oriented toward the cardiac apex. Although ST elevation in lead aVR may occur with left main coronary artery occlusion, it may also be detected in other situations with ST depression, such as infarction caused by a first diagonal branch occlusion.

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REPLY
Our series presented all the characteristics of acute myocardial infarction (AMI), including elevated creatine kinase (CK), hemodynamic deterioration, associated with acute left main coronary artery (LMCA) obstruction, not LMCA stenosis (1). Patients in the reports published by Sclarovsky et al. (2,3) showed manifestations of unstable angina. Therefore, we do not believe that 12-lead electrocardiogram (ECG) findings in our patients (LMCA AMI patients) can be compared with findings in their patients (LMCA unstable angina patients). For this reason, our study did not refer to the reports by Sclarovsky et al. (2,3). In our patients, ST-segment depression was found in leads V5 and V6 in 38% (6/16) and 44% (7/16) of patients, respectively, whereas lead aVR ST-segment elevation was found in 88% (14/16) of patients. Moreover, lead aVR ST-segment shift was not correlated with
ST-segment depression in lead V₅ or lead V₆. Stepwise multivariate discriminant analysis did not select V₅ or V₆ as leads in which ST-segment shift distinguished patients with acute LMCA obstruction from patients with acute obstruction of the left anterior descending coronary artery (LAD). Therefore, we do not consider ST-segment depression in leads V₅ and V₆ to be a characteristic finding in "LMCA AMI patients." The findings of our patients indicated that lead aVR ST-segment elevation is not a mirror image of ST-segment depression in leads V₅ and V₆.

Engelen et al. (4) reported that lead aVR ST-segment elevation was observed in acute obstruction of the LAD proximal to the major septal branch but not in acute LAD obstruction distal to the major septal branch. They concluded that lead aVR ST-segment elevation associated with proximal LAD obstruction was caused by transmural ischemia of the basal part of the septum. Our findings were completely in agreement with the findings by Engelen et al. (4).

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