be truly representative of freshly isolated lipoproteins. However, the stock time and the dialysis conditions were not different among the groups. Recently, we reported that vitamin E was also deficient in plasma from patients with variant angina (2). The vitamin E level was found to be significantly correlated between isolated LDL fraction that had been dialyzed and plasma (2). Fatty acid composition may also affect LDL oxidizability and remains to be determined, as suggested by Napoli. We agree that the propagation phase of lipid peroxidation is a more adequate estimation of LDL susceptibility to peroxidation, as suggested by Napoli, although the production of thiobarbituric acid–reactive substances after 24-h incubation with 0.5 μmol/liter Cu^{2+} was used as a convenient index for the resistance or oxidizability in a previous study (3) and in the present study as well.

Our study demonstrated an association between vitamin E deficiency and coronary spasm. However, the exact causal relation between them is unknown. The low levels of vitamin E may be the result of exhaustion of this antioxidant by increased lipid oxidation stress, such as free radical production induced by frequently repeated alteration between severe transient regional myocardial ischemia and reperfusion. In contrast, it is also possible that the oxidizability of LDL could be directly related to the pathogenesis of coronary spasm. Oxygen-derived free radicals within the vasculature may initiate a vicious cycle by oxidizing LDL, which in turn may inhibit endothelium-dependent vasodilation and may also potentiate agonist-induced vasoconstriction, leading to transient regional myocardial ischemia. Vitamin E deficiency may be involved in this vicious cycle in the pathogenesis of coronary artery spasm.

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Non-Q Wave Infarction After Thrombolytic Therapy

I am concerned by the potential for misinterpretation of data presented by Langer et al. (1) with respect to non-Q wave infarction after thrombolytic therapy in the Late Assessment of Thrombolytic Efficacy (LATE) study. They interpret their results to show that "patients with a non-Q wave infarction who have received thrombolytic therapy may have a better prognosis than those given placebo." Although the study is provocative in many regards, as presented it raises substantial concern for misinterpretation and bias.

Non-Q wave myocardial infarction was determined at hospital discharge. Hence, it was not a baseline variable (present at the time of randomization), but rather an "outcome variable." As such, it was subject to bias, for example, a treatment effect that most likely led to noncomparable groups (i.e., the comparability expected at randomization was lost). A greater percentage of patients with ST segment elevation myocardial infarction (MI) treated at baseline may have developed non-Q wave infarction, yielding an overall group with a better prognosis. A second and somewhat related problem is definitional. On the presenting electrocardiogram, ST elevation versus non-ST elevation can be determined, but only at discharge can a clear interpretation of non-Q wave versus Q wave MI be made. The two contrasts are not equivalent. ST elevation MI may evolve to non-Q wave MI, and, less commonly, patients initially presenting without ST elevation may evolve through additional changes, resulting in Q wave MI. Finally, as the authors point out, their results are post hoc analyses. They propose two new treatment-related hypotheses: First, patients with ST elevation presenting "late" benefit from thrombolytic therapy only if treated within 3 h of symptom onset, whereas those presenting late but treated late show an adverse trend. This hypothesis suggests that two fundamentally different groups of patients were recruited into the LATE study and that these two groups need to be better defined. One group of patients with prolonged pain (>6 h) and marked ST depression (>2 mm) may benefit from thrombolysis, although previous studies have shown that these patients, presenting early, will not benefit. In view of the much larger data base including studies showing an absence of benefit with ST depression using primary hypothesis testing (Thrombolysis in Myocardial Infarction-III), the contradictory findings of Langer et al. clearly will require prospective verification.

Given the potential for bias and for confusion of these data and the unusual heterogeneity of patient groups recruited, a cautionary note should be raised. It certainly would be unwise to change our current thrombolytic therapy algorithm for acute MI on the basis of the results presented by Langer et al.

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Reply

We appreciate the opportunity to amplify further some issues arising from our recent report and raised by Anderson's thoughtful letter. Because non-Q wave myocardial infarction is a diagnosis made retrospectively and not on hospital admission, Anderson raises concerns that it is subject to bias. Importantly, however, patients in the Late Assessment of Myocardial Efficacy (LATE) study (1) presenting with ST segment elevation developed non-Q wave myocardial infarction with equal frequency in both tissue-type plasminogen– and placebo-treated groups, and the study remained randomized and placebo controlled. Hence, bias is unlikely.

To be sure, there was heterogeny among patients enrolled in the LATE study, as has been the case with other large thrombolytic trials with a wide temporal window (International Study of Infarct Survival [ISIS] II). Patients in the LATE study with benefit from thrombolytic therapy who had ST segment elevation were those treated within 3 h of presentation to hospital not within 3 h of symptom onset; this point was identified as an important outcome variable in the initial LATE

publication. The apparently contradictory findings between our study and that of others are potentially reconcilable when one appreciates that patients with ST segment depression in the LATE study had at least 2 mm of ST depression. This group was not specifically addressed within the Thrombolysis in Myocardial Infarction III study (2) (temporal window 0 to 12 h vs. 6 to 24 h in the LATE study). Moreover, the natural history studies of Lee et al. (3) have demonstrated that more prominent ST segment depression (i.e., ≥2 mm) is highly specific for the subsequent diagnosis of acute myocardial infarction and is also an indicator of increased risk. It is important to clarify that this group of patients did not have unusually prolonged pain but a prolonged time from the onset of pain to clinical presentation (i.e., >6 h).

We were careful to address obvious limitations of our study in the original manuscript and, in particular, did not advocate a change in the current thrombolytic therapy algorithm for acute myocardial infarction. We remain convinced, however, that some patients with significant ST segment depression may benefit from thrombolytic therapy and are pleased that Anderson shares our interest in the need for prospective validation.

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Basal Nitric Oxide Production by Diseased Coronary Arteries

Egashira et al. (1) in their interesting study examined the effects of intracoronary N^G-monomethyl-L-arginine (LNMMA, an inhibitor of nitric oxide synthesis) on basal coronary artery tone in patients with variant angina and normal coronary arteries and in control subjects. They reported that the constrictor response to LNMMA was significantly greater at spastic sites than at nonspastic sites. The magnitude of constriction in the control subjects did not differ significantly from that at the nonspastic sites. Their results indicate that the basal release of nitric oxide is increased rather than decreased at the spastic site in patients with variant angina. The authors did not examine the effect of atheroma on basal nitric oxide production, but they acknowledge this limitation. This limitation is particularly relevant because many patients with spasm have underlying atheroma.

We recently examined (2,3) the effects of an intracoronary infusion of LNMMA in patients with chronic stable angina and coronary artery disease and in patients with normal coronary arteriograms. The diameter of angiographically normal proximal and distal segments and coronary stenoses was measured by quantitative angiography. In response to an LNMMA infusion of 16 μmol/min for 4 min, there was a significant reduction ($p < 0.01$) in lumen diameter of the distal segments of diseased arteries and at the site of stenosis but no change ($p = NS$) in lumen diameter of the proximal segments (3). In patients with normal coronary arteriograms, there was a significant reduction ($p < 0.01$) in lumen diameter of both proximal and distal segments (2).

These results indicate that basal nitric oxide production is preserved at the site of stenotic atheromatous plaques. Because it appears to be absent in the proximal segments of diseased arteries in which the stenoses were mostly located, it is possible that regeneration of basal nitric oxide production has occurred. There is some laboratory evidence to support this hypothesis because the inducible isoform of nitric oxide synthase has been found in human atherosclerotic lesions ex vivo, where it is localized with macrophages, foam cells and vascular smooth muscle cells (4). Furthermore, the amount of nitric oxide synthase present is related to the severity of the lesion. We therefore propose that atherosclerotic coronary arteries can regenerate basal nitric oxide production from an abnormal source.

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Reply

Our study was designed to test the hypothesis that basal production/release of nitric oxide (NO) is altered at site of spasm in patients with