neutropenia or neutropenia from other causes among patients taking clopidogrel in CAPRIE from the neutropenia seen in >1% of patients treated with ticlopidine for greater than 1 month in whom profound life-threatening neutropenia develops requiring cessation of the drug and often requiring therapeutic interventions. This sort of severe neutropenia did not occur in any of the more than 9,000 patients in CAPRIE treated with clopidogrel and has been reported very rarely in the greater than 4 million people treated with clopidogrel since the drug was approved for use in the United States based on post-market surveillance (Dr. Melvin Blumenthal, MD, Bristol-Myers Squibb, personal communication).

In conclusion, the frequency of neutropenia among patients taking clopidogrel appears to be similar to the background occurrence of neutropenia in patients taking aspirin, and the evidence from CAPRIE and all other randomized trials suggests clopidogrel does not cause neutropenia, as we stated in the article.

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Improvement of Myocardial Blood Flow to Ischemic Regions by Angiotensin-Converting Enzyme Inhibition

Schneider et al. (1) analyzed the effects of acute angiotensin-converting enzyme (ACE) inhibition on myocardial blood flow (MBF) in ischemic and nonischemic regions of 10 symptomatic patients with coronary artery disease (CAD). They used [15O] water positron emission tomography at rest and during maximal dobutamine stress before and after angiotensin converting enzyme (ACE) inhibition and demonstrated that quinaprilat 10 mg intravenously was able to improve MBF to ischemic regions in patients with CAD.

There is some experimental and clinical evidence that ACE inhibitors can increase regional oxygen supply to ischemic areas of myocardium through a redistribution of regional blood flow in humans and animals (2–7). However, there is not evidence that ACE-inhibitors are able to improve the main clinical outcomes in evaluation of anti-ischemic efficacy of cardiovascular drugs as angina, ST segment depression and echocardiographic wall motion abnormalities during exercise or pharmacological stress test. In this regard we demonstrated, using exercise and dipyridamole echocardiographic stress tests, that neither captopril nor enalapril (sulfhydryl and not sulphydryl ACE-inhibitors, respectively) had a significant antiischemic effect in patients with stable angina pectoris (8).

In our point of view, the main questions are: Has the improvement of MBF induced by acute administration of quinaprilat a clinical significance? Is it useful to evaluate the effects of a cardiovascular drug by an advanced technique as [15O] water positron emission tomography without the evidence of clinical, mechanical or electrocardiographic markers of myocardial ischemia in all patients during stress test?

Analyzing the methods used by authors (1), we found that most patients did not have clinical, electrocardiographic or mechanical criteria of ischemia during dobutamine stress test. Therefore, there is not evidence in the results section that the quinaprilat is able to reduce myocardial ischemia. This restricts the relevance of the conclusions for the average clinical reader. We think that the quinaprilat-induced changes in MBF are not enough to establish whether ACE-inhibitors are the anti-ischemic drugs or not.

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REPLY

We appreciate the interest of Dr. Langobardi and his colleagues concerning our analysis of the antiischemic effect of 10 mg quinaprilat (intravenous) assessed by [15O] water positron emission tomography (PET) (1) and questioning the clinical value of our observation. The clear advantage of the PET technique we have used is the noninvasive, quantitative analysis of changes in regional myocardial blood flow, which is currently only possible with positron tracers. Using this technique we demonstrated a significant improvement in myocardial blood flow after quinaprilat intravenous could be demonstrated. We agree with Dr. Langobardi that the incidence of clinical signs of ischemia was low in our patient population as it was
observed by others in patients with coronary artery disease undergoing dobutamine-stress (2). However, the PET technique enabled us to detect very early changes in myocardial blood flow before these clinical signs of ischemia eventually developed. Since we know that the presence of clinical signs of ischemia are inconsistent, subjective and variable in the same patient, we decided to focus on quantifiable, regional measures of myocardial blood flow.

In contrast to Dr. Langobardi’s statement, there are data about the anti-ischemic effect of quinapril on clinical variables of myocardial ischemia in patients with coronary artery disease. Bussmann et al. (3) have previously reported the results of a randomized, double-blind, cross-over study of 16 men with coronary artery disease receiving oral quinapril or placebo. They were able to show that quinapril (10 mg) lead acutely, and after two weeks of treatment, to a significant reduction in the extent of ST depression during exercise electrocardiogram.

Taken together these data indicate that quinapril has an anti-ischemic potential. However, we agree with Dr. Langobardi and have this clearly stated in our paper, that we do not treat myocardial blood flow values but patients with coronary artery disease. Therefore, the unique, anti-ischemic potential of quinapril in the treatment of patients with coronary artery disease must be substantiated in large clinical trials. From our data quinapril seems to be a promising choice for such studies.

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Pressure Relaxation of the Left Ventricle and Filling Pressures

We read with great interest the article by Senzaki et al. (1). In a careful study, the authors contrasted various methods for assessing the time constant tau of left ventricular (LV) pressure decay. They observed that pressure relaxation consistently deviated from a monoexponential (ME) decay in dilated cardiomyopathy and concluded that this deviation induced inaccuracies in the interpretation of the time constant tau. They proposed that the use of the hybrid-logistic (HL) method (2) resulted in more consistent data fits in various heart diseases.

The manuscript by Senzaki et al. yields important novel information on the analysis of LV pressure decay by focusing on the goodness of fit. Pressure decay is the best reflection of myocardial relaxation so far (3). Impaired myocardial relaxation will interfere with LV filling and result in elevated end-diastolic pressure (4). Senzaki et al. did not discuss the information that LV pressure decay might provide on incomplete myocardial relaxation and, as a consequence, on increased end-diastolic pressure. From a clinical and physiological point of view, it appears to us that this issue is at least as important as the goodness of fit.

We compared the ME method with the HL method. Single beat aortic clamping was performed in healthy hearts from dogs and rabbits (4). Leg elevation and phenylephrine administration were performed in coronary surgery patients (5). The goodness of fit was improved by the use of the HL-method in accordance to the paper under scrutiny. In these experimental and clinical studies, load dependence of LV pressure decay was less pronounced with the HL-method, but still was present and even highly significant. Changes in end-diastolic LV pressure induced by increasing cardiac load were closely correlated with relaxation rate, assessed both by the ME and HL methods (4,5). Of note, the ME method provided a better prediction of changes in end-diastolic pressure than did the HL method. The predictive value of the ME method was confirmed in more than 120 coronary surgery patients subjected to leg elevation (6).

Senzaki et al. suggested that increased load dependence of pressure decay in congestive heart failure, as was observed in dogs by Ishizaka (7) and in patients by Eichhorn (8), would not have been observed if these authors would have used the HL method. However, it should be noted that Ishizaka (7) not only reported increased load dependency of pressure decay (ME method) in cardiomyopathic hearts but also an upward shift of the diastolic pressure-volume loops. Eichhorn showed in a subsequent study (9) that load dependency of relaxation could predict the chronic response to a beta-adrenergic blocking agent and decreased in parallel with decreases in LV filling pressures.

Independently from its mathematical limitations and drawbacks, the ME time constant of LV pressure decay remains a good predictor of load-dependent changes of diastolic LV pressures. For this reason the previous reports on increased load dependence of pressure decay in cardiac overload and in diseased hearts keep for us their scientific and clinical value.

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