ventricular volume. Therefore, a cutpoint of 8% for an increase in EDVI was chosen.

We agree with Dr Armstrong that the results of discriminant analysis should be applied with caution, as outlined in the discussion on page 762. Of particular importance are the baseline characteristics of the study population, which include age as well as other variables (Table 1). Multivariate discriminant analysis in the present study was used to derive variables that allow to predict the development of left ventricular dilatation and dysfunction, which belong to the most powerful determinants of mortality after infarction. The finding of Pfeffer et al. to which Dr Armstrong’s last comment might refer to—that captopril significantly reduced the risk for reinfarction—is an important and extremely exciting finding. However, the respective mechanisms and the characteristics of the patients at risk should be known before angiotensin converting enzyme inhibitors may be recommended in general for the prevention of reinfarction. Nevertheless, the variables identified by multivariate analysis in our study (Table 4) allow identification of patients at high risk for progressive left ventricular dilatation and late deterioration of ventricular performance within 4 weeks after infarction who, at current understanding, may have the greatest benefit from therapy with angiotensin converting enzyme inhibitors.

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References

Progressive Left Ventricular Dysfunction and Remodeling After Myocardial Infarction

The study of Gaudron and coworkers provides new and important information concerning the evolution changes of left ventricular structure and function following acute myocardial infarction. The generalizability of their findings and the usefulness in decision making regarding “unnecessary preventive therapy” for patients with low probability for chronic heart failure after acute myocardial infarction deserve further scrutiny.

It would be particularly useful if the authors could provide information on the frequency of use of thrombolytic therapy, the presence of intercoronary collaterals, and the influence of concomitant nitrate therapy that frequently was used early in the convalescence of their patients.

Were the baseline characteristics of the noncompliers and those who reinfarcted and died distinctive, and how might their inclusion have influenced the results? What information exists concerning coronary disease outside the culprit vessel and its potential impact on left ventricular performance during exercise? Did any patients develop ischemia during exercise?

Since a large cohort of patients at substantial increased risk (ie, those over 70 years of age) were not included in this study and since their response to myocardial infarction may differ, caution should be exercised about extrapolating the results to this group. It is unclear what the basis for the use of the cutpoint of 8% increase in EDVI was for classification into subgroups. Given that preventive therapy with angiotensin converting enzyme inhibitors following infarction may have previously unexpected benefit on acute ischemic events, caution concerning the use of the discriminant analysis for avoiding therapy should be exercised.

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Is Implantable Defibrillator Therapy the Therapy Of Choice for All Patients With Malignant Ventricular Tachyarrhythmias?

In a recent editorial regarding the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial, Greenspan stated that “although it would still be of value academically to know which of the two approaches is more accurate...it may become a moot point, clinically.” To support his statement, he compared sudden death rates of patients treated with implantable defibrillators (ICD) (0.5% to 1.0% per year) with those treated medically guided by electrophysiological testing (3% to 10% per year). From this, he suggested that antiarrhythmic drug therapy for malignant ventricular tachyarrhythmia may be relegated to a second-line approach. Others have made a similar suggestion.

Although the suggestion that ICD therapy may become the first-line approach may be valid, it may have been based on improper comparison of outcomes of patients because sudden death rates were used for the comparison. Sudden death rates are inadequate endpoints because benefits of ICD therapy are overestimated by sudden death rates. To compare ICD therapy with medical therapy, one must consider not only sudden death rates but also other arrhythmia-related deaths such as surgical mortality, deaths due to drug side effects, or nonsudden arrhythmic death. However, such subclassifications of mode of deaths are imprecise and subject to bias. Therefore, total deaths should be used for this purpose. When this is done, the superiority of ICD therapy is less evident. Preliminary results of a randomized study suggest that total mortality rates are not significantly different between ICD and medical patients despite lower sudden death rates in ICD patients. In a study of 194 survivors of sudden death without inducible ventricular tachycardia, results were similar. In another study of the 1-5-year survival rates were 80%, 65%, and 35% in ICD patients and 72%, 49%, and 30% in medical patients, respectively.

With technological advances, surgical mortality rates will decrease. Total cardiac deaths and total deaths of ICD patients will decrease accordingly and may become significantly lower than those of medically treated patients. However, controlled studies are needed to confirm this hypothesis. Fortunately, a randomized study sponsored by the National Institutes of Health has been started recently to address the issue. In the study, total mortality rather than sudden death will be the primary end point of follow-up.

In summary, it may be premature to state that ICD therapy is the therapy of choice for all patients with malignant ventricular tachyarrhythmias and that antiarrhythmic drug therapy may become a second-line approach. The role of ICD therapy and other therapies such as amiodarone and drug therapies guided by electrophysiological testing or Holter monitoring should be defined in prospective studies. Total mortality rates should be the primary end point of such studies.

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Coronary Spasm and the Development of Coronary Atherosclerosis

In an important study described in Circulation, Kaski et al. in Maseri’s laboratory noted a lack of progression of sites of coronary spasm to coronary atherosclerosis in 10 patients with chronic variant angina. At first sight, this might be taken to put to rest the recurring notion that episodic increases in coronary arterial tone could contribute to progressive coronary atheroma. Yet Maseri’s group found themselves with a patient with continuing very severe vasospastic angina over an 8-month period in whom just such a situation arose.2 The authors are therefore rightly guarded about what can be concluded from their results. They point to several study limitations, not the least of which was the small number of patients. However, there are others.

First, although these patients had “hot phases” of angina (varying from 4 days to several weeks), in the absence of any knowledge about the number and particularly the duration of attacks during these phases, it is difficult to know what intimal damage might have been done. Gertz et al.3 have shown that with experimental focal vasoconstriction in the rabbit, 1 hour is enough to produce endothelial change, but whether attacks of lesser duration can do the same is unknown.

Second, although the severity of attacks is undoubted (ST segment elevation), it also matters whether this occurred in focal or relatively long segments of the coronary arteries concerned. Clearly from Table 1 of Kaski et al., at least three patients had fairly long stenoses, affecting proximal as well as middle aspects of various arteries. In these cases, resistance being proportional to length, coronary blood flow in the segment may have actually been reduced, particularly during episodes of superimposed vasospasm, in which case increased hemodynamic shear stress would be unlikely. By contrast, if any of the narrowed segments were localized, then even quite marked point constrictions would not likely make much difference to overall coronary blood flow through the segment, in which case blood flow velocity would be expected to go up in proportion to the square of the degree of the diameter reduction, with consequent marked alteration in hemodynamic shear stresses, and probable endothelial damage at the point—at least in more prolonged bouts.3

Third, the study was understandably limited by the fact that patients were all on long-term antianginal medication, which was, of course, stepped up during “hot phases,” perhaps lessening the time and intensity of spasm and therefore the likelihood of finding a relationship between spasm and progressive atherosclerosis.

All this may sound like special pleading, even self-interest, but the experimental studies of Gertz et al.3 and the previous study from Maseri and colleagues themselves2 suggest that recurrent prolonged focal coronary vasospasm does have a real potential to lead to atherosclerosis. In the absence of knowledge about the length of the spastic segments and the duration of the recurrent bouts of angina in the small study of Kaski et al.,1 no firm conclusions about this relationship can be drawn. It would be valuable to have further details from Maseri’s group on these two specific points.

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References


Reply

In the first two paragraphs of his letter, Dr Ravnskov creates an erroneous impression by juxtaposing two different methods of measuring change in coronary lesions. The mean changes of lumen diameter in cholesterol-lowering trials are small, often less than 2%, because most lesions do not change during the 2-year interval of an angiographic study, so that the effect of the lesions that do change is diluted. However, one fourth to one half of patients have at least one lesion that progresses beyond a cutpoint such as 15% for stenosis diameter. Our study7 and the work of Buchwald et al.8 indicate that this progression is a strong predictor of subsequent coronary events.

The contention that changes in blood lipid levels do not correlate with angiographic changes in these studies is not supported by the evidence. Fig 1 plots change in LDL-cholesterol levels against mean change in percent diameter stenosis for the 12 treatment groups from the five angiographic studies5-7 that used quantitative arteriography. A reduction of ≤10% in LDL-cholesterol was associated with a mean change in the direction of progression in 5 of 6 treatment groups; all 6 groups with a greater reduction in LDL-cholesterol had a mean change in the direction of regression. As noted by Dr Ravnskov, total and LDL-cholesterol were not significantly different between nonprogressors and nonprogressors in our study1. However, in a paper that is currently in press, we report that HDL-cholesterol, remnant VLDL cholesterol, and intermediate density lipoprotein levels correlated with both angiographic changes and coronary events in this population.

Lipid-lowering therapy has been convincingly shown to reduce the incidence of myocardial infarction in patients who have already had such an event.9 An effect on total mortality has been more difficult to
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