could demonstrate in TEN-HMS. We had no learning period to identify appropriate triggers and responses to the new information being acquired. The analyses they request are only now being done; the techniques required are complex to apply. We also agree that remote telemonitoring by people who have little knowledge of the patient and who are not in a position to offer practical help if needed is unlikely to be optimal. Telemedicine that integrates care at the local and regional level is most likely to meet with success.

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Pleiotropic Effects of Statins and Early Benefit in the PROVE IT–TIMI-22 Study

Ray et al. (1) discuss the early and late benefits of 80 mg/day of atorvastatin in the acute coronary syndrome patients of the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Trial–Thrombolysis In Myocardial Infarction-22), and they conclude that the early benefit observed in this trial is likely due to the pleiotropic effects of the statin used.

Conversely, the difference in the triple end-point incidence they observe after 30 days, as can be seen in Table 1 of their study, is limited to patients with plasma low density lipoprotein (LDL) cholesterol levels ≥125 mg/dl at randomization (hazard ratio [HR] 0.31; 95% confidence interval [CI] 0.15 to 0.64; $p < 0.002$), whereas it is completely absent in patients with LDL cholesterol <125 mg/dl at randomization (HR 0.92; 95% CI 0.63 to 1.36; $p = 0.7$). It is intriguing that a purported nonlipidic effect of a statin is observed only in patients with elevated LDL cholesterol. Pleiotropic effects should, conceptually, exert their protective properties at any lipid level.

Attribution of the early protective action observed in the PROVE IT–TIMI-22 trial to the pleiotropic effects of the statin used should be, in our opinion, more cautious. In actuality, a clear demonstration of the clinical relevance of these effects is still lacking. A recent meta-regression of published clinical trials testing different hypolipidemic treatments concludes that cholesterol reduction is likely to be the major (or unique) determinant of coronary heart disease and stroke events reduction (2).

Indeed, LDL reduction obtained by a single LDL apheresis markedly reduces C-reactive protein and ameliorates the endothelial function of coronary arteries (3), suggesting that LDL reduction, by itself, can rapidly translate into a variety of biochemical or clinical benefits. Perhaps we should abandon the concept of "pleiotropic effects of statins" in favor of that of "pleiotropic effects of cholesterol reduction."

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REPLY

We thank Drs. Poli and Pujia for their interest in our report (1). They suggest that the more significant reduction in clinical events observed among patients with a high low-density lipoprotein cholesterol (LDL-C) versus those with a low LDL-C at baseline provides evidence that the early benefits observed at 30 days are related more to lipids than any potential pleiotropic effects. Acute coronary syndrome (ACS) patients have a high early recurrence of adverse events after ACS. The significant early benefits of intensive statin therapy observed by day 30 in the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22) trial seem more striking when compared to the benefits of intensive LDL-C reduction by ileal bypass in the POSCH (Program on the Surgical Control of the Hyperlipidemias) study, which took nearly seven years to translate into clinical benefit (2). Similarly, in the early statin trials in stable coronary artery disease (CAD) the benefits of statins were observed after one to two years, suggesting that in stable patients the benefits of modest reductions in LDL-C take place over a period of years rather than days. Whereas we agree that LDL-C reduction itself is associated with reductions in C-reactive protein (CRP) and endothelial function, we have demonstrated that, independent of achieved LDL-C and other correlates,