we need better reporting of sex-specific results, enrollment of women commensurate with the prevalence of disease, and evidence of net benefit before approval of therapy. The Thoratec HeartMate II (Thoratec Corporation, Pleasanton, California) is a perfect example of this dilemma. There was an under-representation of women in the trial and a trend toward more adverse events. However, the paucity of women prevented a final conclusion. Unfortunately, there was also no alternative life-saving therapy for small women when medical therapy failed and such patients needed long-term mechanical support to bridge them to transplantation. Even pulsatile mechanical devices have a higher incidence of neurologic events and bleeding in women compared with men, which further emphasizes the lack of alternative therapy and the need to better understand sex differences (2). The National Institutes of Health-sponsored Interagency Registry for Mechanically Assisted Circulation database will enable us to follow sex differences prospectively. Because the Thoratec HeartMate II is being used more extensively, the data will continue to accumulate, and sex-specific results will become available.

This dilemma is not unique to heart failure and must change to reduce the cardiovascular disease mortality rate in women. In a study by Blauwet et al. (3) that included 628 cardiovascular trials, only 24% provided sex-specific results. The highest percentage of reporting was in National Institutes of Health-sponsored studies (51% vs. 22%) and those published in general medicine journals when compared with cardiovascular journals (37% vs. 23%). Kim et al. (4) subsequently published a study concentrating on National Heart, Lung, and Blood Institute-funded cardiovascular phase 3 and 4 trials. The mean enrollment of women was lower than the percentage of women with that disease, and 6 of 19 trials did not even publish sex-specific results. This is a disappointment given the federal mandate that requires women and minorities to be included in phase 3 and 4 clinical trials in sufficient numbers to determine the effectiveness of a medical intervention (5).

The effectiveness of any therapy for women can be assessed only if sufficient numbers of women are included in clinical trials. We concur that it would be best to show benefit before approval of any new therapy and that following a post-approval registry is a suboptimal alternative. To make it easier to enroll more women, national organizations should launch educational campaigns to the public regarding the lack of evidence-based sex- and minority-specific therapy. Given the success of the Red Dress Campaign to increase awareness that women are more likely to die of cardiovascular disease than of breast cancer, a similar campaign requesting them to volunteer rather than wait to be approached may be beneficial.

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Noninferiority of Pitavastatin in Intravascular Ultrasound Findings

We read with interest the paper by Hiro et al. (1) comparing the regressive effect of pitavastatin on coronary plaque volume in acute coronary syndrome patients with that of atorvastatin using intravascular ultrasound (IVUS). The authors demonstrated that the upper limit of the 95% confidence interval of the difference in the mean percentage of change in plaque volume between the 2 groups (mean 1.11%, 95% confidence interval: −2.27% to 4.48%) did not exceed the pre-defined noninferiority margin of 5% and concluded that the noninferiority of pitavastatin compared with atorvastatin.

However, although an IVUS study comparing pravastatin with atorvastatin demonstrated a similar result (the difference in the mean percentage of change in atheroma volume was 1.3%, 5.4% in the pravastatin group and 4.1% in the atorvastatin group) (2), a clinical end point study (n = 4,162) using the same drugs demonstrated a significant difference in death or major cardiovascular event rates (26.3% in the pravastatin group and 22.4% in the atorvastatin group) (3). Therefore, it remains uncertain whether the noninferiority of pitavastatin in IVUS findings would translate to clinical noninferiority (4). Even such a small difference in IVUS findings may lead to a significant difference in clinical event rates in a large clinical trial.

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Reply

First, we express our deep appreciation for the sincere criticism by Dr. Kaneda and colleagues of our paper (1). However, we have a few concerns regarding their arguments.

1. The REVERSAL (REVERSing Atherosclerosis with Aggressive Lipid Lowering) study (2) examined patients with stable coronary artery disease who could undergo an elective cardiac catheterization, whereas the PROVE-IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) (3) and our JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study examined patients with acute coronary syndrome. Several reports have been published that nonculprit plaque differs in tissue characteristics between acute coronary syndrome and stable coronary artery disease. Therefore, extrapolations of the data between the REVERSAL and the PROVE-IT–TIMI 22 studies have major limitations.
2. Their criticism was not based on any kind of rational statistical meta-analysis. The value of the difference in the mean percentage of change in plaque volume of 1.3% in the REVERSAL study cannot necessarily be considered similar to the 1.1% in our study. The value of 1.3% of the REVERSAL study came from the difference between 5.4% and 4.1%, whereas the value of 1.1% in our study resulted from the difference between −16.9% and −18.1%. Therefore, 1.3% of the REVERSAL study might be considerably more remarkable than 1.1% in our study.
3. The intravenous ultrasound measurement of plaque volume differed between the REVERSAL study and our study. The REVERSAL study measured the longer segment with a total of 30 mm or more integrated with 1-mm interval cross-sectional area tracings, whereas our study measured a specific plaque segment of a total length of approximately 7 mm with 0.1-mm interval tracings. Therefore, even a similar difference in the mean percentage of change in plaque volume in the REVERSAL study might have a more significant clinical impact on future cardiac events than that in our study.

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The BALANCE Study

Too Early to Speculate on Mortality Effects

We read with great interest the paper by Yousef et al. (1) and the accompanying editorial (2) demonstrating and discussing long-term data on cardiac function and mortality in patients treated with autologous bone marrow cell (BMC) transplantation after myocardial infarction.

We do not agree with the editorial's statement that, based on the new data, BMC infusion "can now be considered safe and modestly efficacious" (2), despite the finding that fatal events were more frequent in the control group. The patient cohort studied and the event rate observed were far too small to draw such conclusions. The total number of fatal events was only 8. Also, if the authors had included hospitalizations in the analyses, as is often done in outcome studies, such a combined end point would not have provided conclusive results. Of note, taking the results from Table 1 of their paper (1), there were 9 unplanned hospitalizations in the BMC group and 8 in the intervention group.

In addition, a recent 4-year follow-up study with 86 patients, despite slight improvements in cardiac function, could not identify significant differences in myocardial viability or mortality (3). The BALANCE (Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction) trial thus may be viewed as a successful proof-of-principle study, but there still is a need for large-scale, placebo-controlled, double-blind clinical end point studies to justify any conclusion with regard to safety or even mortality. Fortunately, such large trials are currently underway at several places worldwide and will clarify those important outstanding issues.

Furthermore, the authors addressed paracrine effects of transplanted autologous cells as the major mechanism explaining the beneficial effects of BMC transplantation. In our view, additional mechanisms should be taken into account. BMC transplantation