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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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doi:10.1016/j.jacc.2009.08.056

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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

into an ischemic area results in modulation of the local tissue immune system and altered cytokine production (4). Indeed, BMC transplantation results in local inflammatory changes that activate myofibroblasts, thus reducing infarct size (5). Thus, modulation of pro- and anti-inflammatory intramyocardial cytokine levels by transplanted cells and their crosstalk with the local tissue environment likely affect survival and differentiation of progenitor cells, as well as overall cardiac outcome.

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doi:10.1016/j.jacc.2009.07.064

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Reply

The letter by Drs. Thum and Anker touches various aspects of cardiac stem cell therapy (e.g., mortality, paracrine effects, and inflammation), all of which may be briefly addressed as follows.

Intracoronary stem cell therapy seems to represent a safe and effective regimen for treatment of heart failure after acute myocardial infarction (1,2), in an old myocardial infarction (≥8 years) with ischemic cardiomyopathy (3), and in advanced dilated cardiomyopathy (4). Our study (5) did not aim to speculate (Drs. Thum and Anker) on stem cell-induced inflammation (which has not yet been documented in the overwhelming majority of studies) and on possible paracrine effects by stem cells, but fortunately was able to analyze the different parameters of ventricular performance and potential effects on cardiac mortality in large patient groups, treated and untreated, in long-term follow-up after myocardial infarction.

When carefully reading our paper (5), the BALANCE (Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction) study showed that mortality, as a consequence of stem cell therapy, is significantly reduced; in a median follow-up time of 4.6 ± 2.1 years in the bone marrow cell group 1 patient died, and in 4.8 ± 2.2 years, 7 patients in the control group died ($p = 0.03$).

Mortality is dependent on both the degree of ventricular impairment and the amount of arrhythmogenicity. Dependent on the multifactorial mode of action of stem cells, systolic function (e.g., ejection fraction, stroke volume, contractility) and diastolic performance are improved; infarct size, end-systolic volume, and systolic wall stress decrease; and the arrhythmogenicity of the heart is presumably reduced. Thus, several of the main myocardial determinants of cardiac mortality are influenced in favor of reduced mortality by stem cell treatment in chronically ill cardiac patients.

Undoubtedly, further large studies are needed to analyze the action of stem cells on ventricular performance and cardiac mortality in different stages of chronic cardiac failure, especially with regard to the distinct origin of this chronic disease.

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Grade of Ischemia to Assess No Reflow After Reperfusion

We read with great interest the excellent review by Niccoli et al. (1) about the no-reflow phenomenon in humans. In their paper, the authors describe various techniques for the prediction of no-reflow. As far as electrocardiography is concerned, the authors only mention the QRS score as a predictor of ischemia-related injury.

The extent of terminal QRS distortion on the admission electrocardiogram, known as the grade of ischemia, is a strong predictor of failure of ST-segment resolution as well as of