European Heart Journal Advance Access published August 3, 2007

European Heart Journal

Letter to the Editor

doi:10.1093/eurheartj/ehm257

Improved clinical outcome after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial

We read with great interest the recent article by Schächinger *et al.*[1] showing improved 1 year clinical outcomes in patients with acute myocardial infarction receiving intracoronary administration of bone marrow-derived progenitors cells (BMCs) after successful reperfusion therapy. The authors attribute the improved clinical outcomes in the treatment group to the recovery of global left ventricular contractile function within 4 months, as recently reported in the same patient population.[2]

However, we believe that factors other than administration of BMCs may have influenced left ventricular ejection fraction (LVEF) recovery and, hence, clinical outcomes in their study. First, we can suppose that spontaneous LVEF recovery was already occurring in both groups before BMCs or placebo administration. Indeed, baseline LVEF was 46.7 ± 10 and $47.5 \pm 10\%$ in controls and BMC-treated patients, respectively—values higher than that used as a threshold for patient inclusion in the study ($\leq$45%). This spontaneous recovery may be explained by the mean delay between enrolment and baseline LVEF measurement (4.3 ± 1.3 days). Secondly, and more importantly, two major determinants of LVEF recovery—time-to-reperfusion and infarct location—are possible confounders in this study. According to Sheiban *et al.*,[3] LVEF recovery is usually observed after primary angioplasty if coronary flow is restored $\leq$4 h from symptom onset, whereas no significant improvement occurs afterwards. This time "window" may be even narrower in anterior infarctions. Indeed, we have observed no significant recovery in LVEF after primary angioplasty despite an average shorter time-to-reperfusion (2.5 ± 1.4 h) when only anterior myocardial infarctions were considered.[4] In the REPAIR-AMI study, however, the authors analysed anterior and inferior infarctions together, despite the fact that these two infarct locations differ in terms of acute left ventricular impairment severity, LVEF recovery and clinical outcome after reperfusion therapy.[5,6] In BMC-treated patients, anterior infarctions were less represented (64 vs. 76%), which may explain the small difference in LVEF recovery between the placebo and treated groups (3.0 ± 6.5 vs. $5.5 \pm 7.3\%$), and in clinical outcomes.[1,2] Moreover, mean reperfusion time was $\geq$7 h, an interval usually not associated with LVEF improvement, particularly in anterior infarctions.[3,4] The combination of different times to treatment and infarct locations may have a major influence on LVEF recovery and long-term event rate. It is surprising that these two critical factors were not taken into account among the variety of covariates considered by the authors. Thus, we believe that the LVEF changes and clinical outcomes should be re-analysed after adjustment for infarct location and time-to-reperfusion.

References

1. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Werner N, Haase J, Neuzner J, Germing A, Mark B, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J* 2006;**27**:2775–2783.
2. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006;**355**:1210–1221.
3. Sheiban I, Fragasso G, Rosano GMC, Dharmadhikari A, Tzifos V, Pagnotta P, Chierchia SL, Trevi G. Time course and determinants of left ventricular function recovery after primary angioplasty in patients with acute myocardial infarction. *J Am Coll Cardiol* 2001;**38**:464–471.
4. Trabattoni D, Bartorelli AL, Fabbiocchi F, Montorsi P, Ravagnani P, Pepi M, Celeste F, Maltagliati A, Marenzi G, O'Neill WW. Hyperoxemic perfusion of the left anterior descending coronary artery after primary angioplasty in anterior ST-elevation myocardial infarction. *Cathet Cardiovasc Interv* 2006;**67**:859–865.
5. Ottervanger JP, van't Hof AWJ, Reiffers S, Hoorntje JCA, Suryapranata H, de Boer MJ, Zijlstra F. Long-term recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *Eur Heart J* 2001;**22**:785–790.
6. Topol EJ, Ohman EM, Armstrong PW, Wilcox R, Skene AM, Aylward P, Simes J, Dalby A, Betriu A, Bode C, White HD, Hochman JS, Emanuelson H, Vahanian A, Sapp S, Stebbins A, Moliterno DJ, Califf RM, on Behalf of the GUSTO-III Investigators*. Survival outcomes 1 year after reperfusion therapy with either alteplase or reteplase for acute myocardial infarction. Results from the global utilization of streptokinase and t-PA for occluded coronary arteries (GUSTO) III trial. *Circulation* 2000;**102**:1761–1765.

Giancarlo Marenzi
Centro Cardiologico Monzino
I.R.C.C.S
Institute of Cardiology
University of Milan
Via Parea 4
20138 Milan
Italy
Tel: +39 2 58002331
Fax: +39 2 58002398
E-mail address: giancarlo.marenzi@ccfm.it

Antonio L. Bartorelli
Centro Cardiologico Monzino
I.R.C.C.S.
Institute of Cardiology
University of Milan
Milan
Italy