Bone Marrow Cell Therapy for Ischemic Heart Disease
The Never Ending Story

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In the past 15 years, bone marrow (BM) cell (BMC) therapy has emerged as a potential novel strategy for the treatment of ischemic heart disease (IHD). The fervor for this novel promising therapy arose from the first studies on BMC differentiation into cardiomycocyte-like cells.\(^1\) After this discovery, research proceeded rapidly from preclinical models to clinical studies to test BMC’s potential to recover cardiac function and facilitate scar healing in ischemic cardiomyopathy.\(^2-6\) To mention just a few pioneering in vivo studies, Tomita et al\(^7\) reported that in adult rats, BMC injection into a left ventricular (LV) cryoinjury-induced myocardial infarction (MI) promotes the generation of cardiomycocyte-like cells and neoangiogenesis. Concomitantly, Kocker et al\(^8\) showed that BMC therapy prevents cardiomycocyte apoptosis and stimulates neovascularization of the ischemic heart, leading to an improvement of LV ejection fraction (LVEF) and survival.

Notably, after >15 years, the mechanisms through which BMCs exert cardioprotection in acute IHD and chronic IHD (CIHD) have not been completely unraveled yet. Different therapeutic properties have been ascribed to BMCs, including the ability to form new contractile cardiac tissue by differentiating into cardiomycocytes,\(^9,10\) as well as the capacity to limit ischemic damage through direct cell-mediated and indirect paracrine-mediated mechanisms, promoting the induction of angiogenesis, inhibition of cell death, and formation of scar tissue.\(^11,12\) Over the years, this latter concept has gained a broader consensus.

Notwithstanding the uncertainties about mode of action, the large body of positive preclinical studies spurred enthusiasm for immediate clinical translation, taking advantage of the relatively easy accessibility of BM as a cell source. Hamano et al\(^13\) were the first, in 2001, to report a pilot clinical trial on BMCs, although more recently allogeneic mesenchymal cells have been proposed as an off-the-shelf treatment option for IHD.\(^14\) To date, the outcome of such studies has been inconclusive; RCTs yielded mixed results, and the debate on BMC efficacy in IHD still continues.

To disentangle such a complex subject, a series of meta-analyses (MAs) were conducted during the past 8 years: 12 were focused on patients with acute MI (AMI),\(^15-26\) 7 evaluated cell therapy in the context of CIHD,\(^27-33\) and 4 took into account both conditions.\(^34-37\) Although, overall, 81% and 92% of MAs on AMI and CIHD, respectively, yielded positive outcomes (Figure 1), it has been recently suggested that published MAs on BMC therapy for IHD far outnumber well-conducted RCTs.\(^38\)

Abdel-Latif et al\(^39\) were the first, in 2007, to provide a comprehensive synthesis of data obtained from patients receiving BMCs for IHD: the results of that review suggested that BMC therapy for cardiac repair exhibited a good safety profile and yielded modest improvements in LV function. Subsequently, several positive MAs were published. Among these, the study by Jeevanantham et al\(^40\) comprised pooled data from 50 clinical trials (36 RCTs and 14 cohort) providing strong indications that BMC therapy in patients with IHD reduces the incidence of major cardiac events and induces long-term improvement in cardiac parameters. On the other hand, more recently, negative MAs\(^15,19,34\) challenged cardiac BMC therapy. De Jong et al\(^41\) analyzed 22 RCTs using magnetic resonance to evaluate LV recovery after AMI and failed to show any beneficial effect on cardiac performance. Gyongyosi et al\(^42\) analyzed individual patient data from 12 randomized trials of intracoronary BMC therapy after AMI, showing no benefit in the occurrence of adverse clinical events or improvement of LV function. Moreover, concerns regarding the high rate of discrepancies and contradictions in the literature on cardiac cell therapy have been recently raised.\(^34,39\)

Admittedly, MAs have suffered from the variability in RCT design: differences in cell types, cell preparation standards, delivery techniques, imaging methods, and patient profile have weakened inferences and made the results difficult to interpret. It is also noteworthy that all published

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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DOI: 10.1161/CIRCRESAHA.115.307184.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.115.307184
MAs failed to take advantage of individual patient data, with the exception of the MA of Cell-based CaRdiac stUdeEs (ACCRUE).15

In this issue of Circulation Research, Afzal et al17 reported the largest study-level MA published to date on cardiac BMC therapy to comprehensively integrate and analyze data from 48 RCTs cumulatively enrolling 2602 patients. In an admirably detailed work, the authors took into account a considerable number of variables potentially influencing BMC therapy outcome, as well as the interpretation of results.

The salient findings of this MA confirm that autologous BMC cardiac cell therapy is safe and induces significant albeit modest positive effects on LVEF recovery, infarct size reduction, and LV adverse remodeling attenuation. Remarkably, the results remained positive when data were analyzed after excluding studies reporting on discrepancies in outcomes39 and when studies only on magnetic resonance were included. Of note, consistent with previous MAs,15,19,21,25 scar size reduction was the only surrogate end point that did not achieve statistical significance when assessed by magnetic resonance. However, was the only surrogate end point that did not achieve statistical significance when assessed by magnetic resonance. However, WEXOR, need to be considered with caution because other MAs15,19,21,25 did not find any significant difference in major adverse cardiac event rates. In addition, the vast majority of RCTs using BMCs lack the statistical power to test hard clinical end points.

Of note, some novel elements introduced by Afzal et al with respect to current knowledge should be discussed. Surprisingly, BMC therapy was found to improve LVEF regardless of baseline, albeit LV end-systolic volume changes seemed positively influenced by a low ejection fraction. As for ejection fraction, the majority of previous MAs17,20,21,25,28,35 reported that cell therapy is more effective on LV function recovery in the presence of LV dysfunction at baseline (ejection fraction <40%). However, because LV end-systolic volume is the major determinant of prognosis, Afzal et al have highlighted a possible key determinant of positive clinical outcome. This issue clearly needs to be carefully considered when designing future clinical trials.

The method of cell delivery is another crucial point raised by the Afzal et al: no significant differences in LV function recovery were found between intracoronary and intramyocardial routes of cell delivery; however, intramyocardial injection was associated with a greater reduction in LV end-systolic volume. These data are consistent with a previous Cochrane MA39 reporting that the intramyocardial route is the best approach to improve heart function in CIHD. To shed light on this issue, the ongoing AlsterMACS trial (Intracoronary Versus Intramyocardial Application of Enriched CD133pos Autologous Bone Marrow Derived Stem Cells; NCT01337011) has been designed to examine whether there is a difference between intracoronary versus intramyocardial injection of CD133+ autologous BMCs in CIHD.

Furthermore, different methods of cell preparation have been considered a factor that may affect BMC cardiac cell therapy outcome. Afzal et al detected no difference in safety and efficacy of BM mononuclear cells when selected with Ficoll versus Lymphoprep. Further, the authors found that heparin usage in the final cell suspension was associated with a greater improvement in LVEF and infarct size. Although this finding is in agreement with prior MAs,19,35 it is in contradiction with the biological evidence that heparin inhibits BMC homing and functional activity, thereby affecting their therapeutic potential.40,41 In light of these uncertainties, strict guidelines for the preparation of BMCs, based on robust preclinical data, are urgently needed.
As for dose-finding information, Azfal et al\textsuperscript{10} identified 50 to 100 million BMCs as the optimal cell number to induce significant improvements in LVEF and LV end-systolic volume followed by a cell dosage >250 million; no benefit was reported in response to the injection of 100 to 250 million cells. This finding is not easy to interpret in light of previous conflicting reports; for instance, Clifford et al\textsuperscript{11} showed a positive correlation between a cell number >100 million and improvements in infarct size and LVEF in AMI patients, whereas other investigators failed to correlate the cell’s dose-dependent effect with cardiac outcomes.\textsuperscript{15,17,19}

Another crucial issue is timing of cell delivery. Azfal et al reported that injecting BMCs 3 to 10 days after AMI led to the most significant improvement in cardiac functions. However, a reduction in infarct size was only seen when BMCs were transplanted within the first 48 hours after AMI. This is an interesting unprecedented observation; it may suggest that the mode of action of BMCs in AMI setting may vary according to the healing phase and inflammation status of the myocardium after the ischemic event.

In conclusion, Azfal et al should be acknowledged for the effort of evaluating several crucial aspects that may affect the efficacy of cardiac BMC therapy. However, some study limitations have to be mentioned. First, pooling together acute and chronic patients may dilute important specific information. Second, this MA has the same reported bias of other study-level MAs,\textsuperscript{22} including deficiencies in the analysis of patient-specific covariates. From this standpoint, it would have been important to examine treatment effects in relation to patient-specific variables, such as age and presence of risk factors, which are well known to modulate BMC functional properties and eventually cell potency.\textsuperscript{43} Third, as in many previous MAs, RCTs with BMC-mobilizing agents were intentionally excluded, although this represents a form of BMC therapy that, over the course of several days, leads to the transit of a many-fold higher number of BMCs into the culprit artery than intracoronary infusion.\textsuperscript{44,45}

Our final remark concerns the usefulness of MAs in the context of the current debate about the future of cardiac BMC therapy. Because MAs are hypothesis-generating, they do not provide conclusive answers; at best, MAs may provide helpful signposts to guide clinical scientists along the optimal path to design new RCTs. It is apparent that only well-designed and adequately powered RCTs will establish whether BMC therapy offers a new hope to patients with IHD. In this perspective, the BMC therapy field is waiting for the results of the multinational, multicenter phase III BAMI RCT (The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells [BM-MNC] on All Cause Mortality in Acute Myocardial Infarction; NCT01569178), in which the effect of intracoronary reinfusion of BM mononuclear cell on all-cause mortality in AMI will be tested. As for the chronic setting, 2 randomized controlled studies in patients with heart failure secondary to IHD are currently actively enrolling: the CEP-41750 (Efficacy and Safety of a Allogeneic Mesenchymal Precursor Cells for the Treatment of Chronic Heart Failure; NCT02032004), a multicenter RCT, will test in 1730 patients the effect of the intramyocardial injection of allogenic mesenchymal precursor cells on clinical outcomes, and the CHART-2 trial (Congestive Heart Failure Cardiopoietic Regenerative Therapy Trial; NCT02317458) will evaluate the effect of endoventricular injection of BM-derived mesenchymal cardiopoietic cells to improve patient’s functional capacity. In conclusion, these phase III clinical trials will be critical in establishing whether BMC therapy represents a new strategy for the treatment of IHD.

**Sources of Funding**

This work was supported by Ministry of Health funds (RC-2011–2014 to IDI-IRCCS) and the Marie Curie Integration grant (FP7-PEOPLE-2011-CIG-294016 to P. Nigro) and Ministry of Health grant (RF-GR-2010-2321151 to P. Nigro).

**Disclosures**

None.

**References**


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Circ Res. 2015;117:490-493
doi: 10.1161/CIRCRESAHA.115.307184

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