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Bone Marrow Mononuclear Cell Therapy for Acute Myocardial Infarction

A Perspective From the Cardiovascular Cell Therapy Research Network

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Abstract—To understand the role of bone marrow mononuclear cells in the treatment of acute myocardial infarction, this overview offers a retrospective examination of strengths and limitations of 3 contemporaneous trials with attention to critical design features and provides an analysis of the combined data set and implications for future directions in cell therapy for acute myocardial infarction. (*Circ Res.* 2014;114:1564-1568.)

Key Words: diagnostic imaging ■ myocardial infarction ■ population

Recent meta-analyses of cell therapy clinical trials have suggested that bone marrow mononuclear cell (BMC) delivery after acute myocardial infarction (AMI) may result in modest improvement in left ventricular (LV) function.¹ Despite this, the uniformly null findings emerging from the most current trials, Transplantation In Myocardial infarction Evaluation (TIME),² LateTIME,³ and Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction (SWISS-AMI),⁴ have prompted careful reconsideration of this approach.

Background

By late 2006, multiple preclinical models of AMI suggested that the delivery of BMC-derived cells improved LV function after AMI.^{5,6} Although the original study by Orlic et al⁵ suggested transdifferentiation as the mechanism of action, this was not confirmed by others.^{7,8} However, the study by Balsam et al⁸ demonstrated functional benefits despite failing to provide data supporting transdifferentiation. It is thought that BMCs might have pleiotropic and diverse effects in this setting, including stimulating angiogenesis and other paracrine effects.⁹ These findings fueled intense interest in assessing the effects of autologous BMC delivery on LV function in clinical trials.¹⁰⁻¹³ Although initial studies showed somewhat mixed results, meta-analyses supported a significant effect of intracoronary delivery of BMCs on LV ejection fraction (LVEF). Three points are important to note. (1) These trials varied

widely in design and subject characteristics. (2) None of these meta-analyses used patient-level data. (3) The trial responsible for driving the perceived benefit was Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI),¹⁰ the largest (n=204) trial reported by 2006, with ≈2-fold difference in LVEF improvement in the active group versus placebo and nonrandomly allocated assignment of time of cell delivery. The Cardiovascular Cell Therapy Research Network (CCTRN) was designed to execute multiple, simultaneous cell therapy protocols in the clinical setting of LV dysfunction.¹⁴ After consideration, the investigators decided to test the effect of timing of administration of BMCs while using standard approaches to other features of trial design common to other studies.

Although a prespecified variable in REPAIR-AMI, the timing of cell delivery was not subject to randomization in it or earlier studies. Thus, the TIME and LateTIME trials were initiated to study the impact of timing of BMC delivery after AMI. During the same time period, Swiss investigators, working independently, also decided to focus on timing of BMC administration after AMI (SWISS-AMI).¹⁵ TIME evaluated cell delivery at day 3 or day 7 after reperfusion (primary percutaneous coronary intervention [PCI] with stenting); LateTIME evaluated cell delivery 2 to 3 weeks postreperfusion; and SWISS-AMI compared the effects of delivery on days 5 to 7 versus 3 to 4 weeks post-PCI (Figure 1).

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Nonstandard Abbreviations and Acronyms	
AMI	acute myocardial infarction
BMC	bone marrow mononuclear cell
CCTRN	Cardiovascular Cell Therapy Research Network
cMR	cardiac magnetic resonance
LV	left ventricular
LVEF	left ventricular ejection fraction
PCI	percutaneous coronary intervention

Internal Consistency of TIME, LateTIME, and SWISS-AMI

TIME, LateTIME, and SWISS-AMI were contemporaneous, prospective, randomized, controlled trials. TIME and LateTIME recruited predominantly ST-segment–elevation myocardial infarction and were both placebo-controlled and double-blind design; SWISS-AMI recruited exclusively ST-segment–elevation myocardial infarctions but did not have placebo controls and was an open design and used LV angiograms post-PCI to qualify subjects. The primary end points focused on global LVEF measured by cardiac magnetic resonance (cMR) imaging, but the timing of this was different (TIME/LateTIME at 6 months and SWISS-AMI at 4 months). Intention-to-treat analyses were conducted in each study. Each was designed to detect moderate to large placebo-adjusted changes in LVEF. Randomizations were 2:1 (active:placebo) in both TIME and LateTIME and 1:1:1 in SWISS-AMI. Cell processing was by manual Ficoll processing at a central center in SWISS-AMI, whereas the 2 CCTRN studies used onsite automated Ficoll processing (SEPAX; Biosafe, SA). Cell dose and delivery were the same in each of these 3 studies using the intracoronary stop-flow technique. Although differences did exist between the 2 studies (in SWISS-AMI, there was an open design, use of LV angiography immediately post-PCI for qualification of subjects, no requirement of primary PCI or stents in eligible patients, and central cell processing requiring >24-hour delayed delivery of BMC), the similarities suggested that a comparison of their results would be productive.

Overall, the primary results for TIME,² LateTIME,³ and SWISS-AMI⁴ were each null with no detectable benefit of cell therapy evident when administered at day 3, day 7, 2 to 3 weeks, or 3 to 4 weeks post-PCI. Thus, despite previous clinical studies and recent meta-analyses¹⁶ supporting an effect of BMC delivery on echocardiogram-derived LV function post-AMI, these 3 studies did not detect a significant treatment effect on LV function. The evaluation of clinical end points revealed no safety concerns, but the intracoronary administration of BMCs did not improve LV function after AMI irrespective of the timing of administration.

Variables Addressed in These Studies

Study Population

Because compelling work from the REPAIR-AMI trial¹⁷ suggested that patients with AMI with the greatest impairment of LVEF seemed to gain the most benefit from BMC therapy, the CCTRN chose to study patients with infarctions resulting in an LVEF of <45% after successful reperfusion by PCI. Given the need to randomize patients in TIME by day 2, local echocardiographic readings were used to screen patients, whereas baseline and end point values were determined by core laboratory assessment of cMR imaging. In TIME and LateTIME, these qualifying echocardiograms, which were obtained closer in time to reperfusion than the following baseline cMRs, revealed lower LVEF compared with baseline cMR (Figure 2A), resulting in the inclusion of a population with less LV dysfunction than proposed. As a result, a significant part of our patient population in both TIME and LateTIME had less LV dysfunction (as measured by cMR) than anticipated. Reducing the threshold for enrollment, to say LVEF ≤ 40%, or obtaining screening core cMR closer to the time of delivery are admissible alternatives for future trials, although each comes with greater logistical challenges, financial cost, and risks to timely recruitment.

In SWISS-AMI that randomized subjects to early treatment (5–7 days), late treatment (3–4 weeks), or control, patients were screened by LV angiogram or echocardiography (<45%) the day of or after AMI. The median baseline LVEF was 37% by cMR. The delivery of BMCs demonstrated no benefit

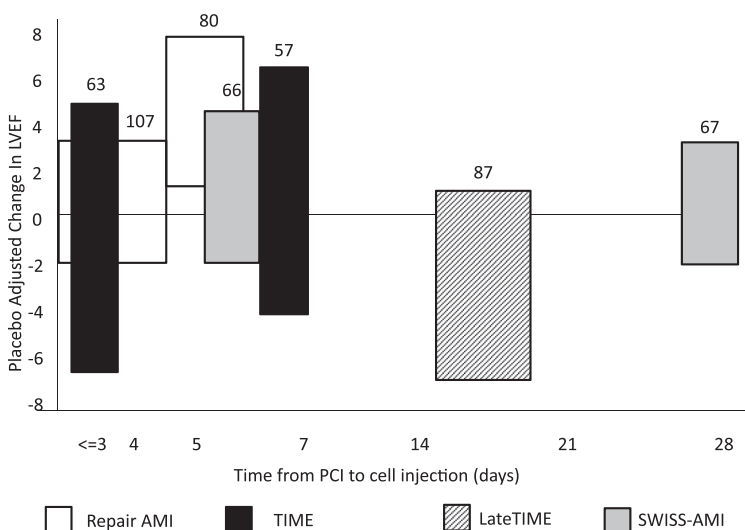


Figure 1. Placebo-adjusted effect size for change in left ventricular ejection fraction (LVEF) over time as a function of time from primary percutaneous coronary intervention (PCI) in 4 clinical trials. The upper and lower bar limits reflect the upper and lower confidence interval of the effect size; the bar width is proportional to the sample size. REPAIR-AMI indicates Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; SWISS-AMI, Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction; and TIME, Transplantation In Myocardial infarction Evaluation.

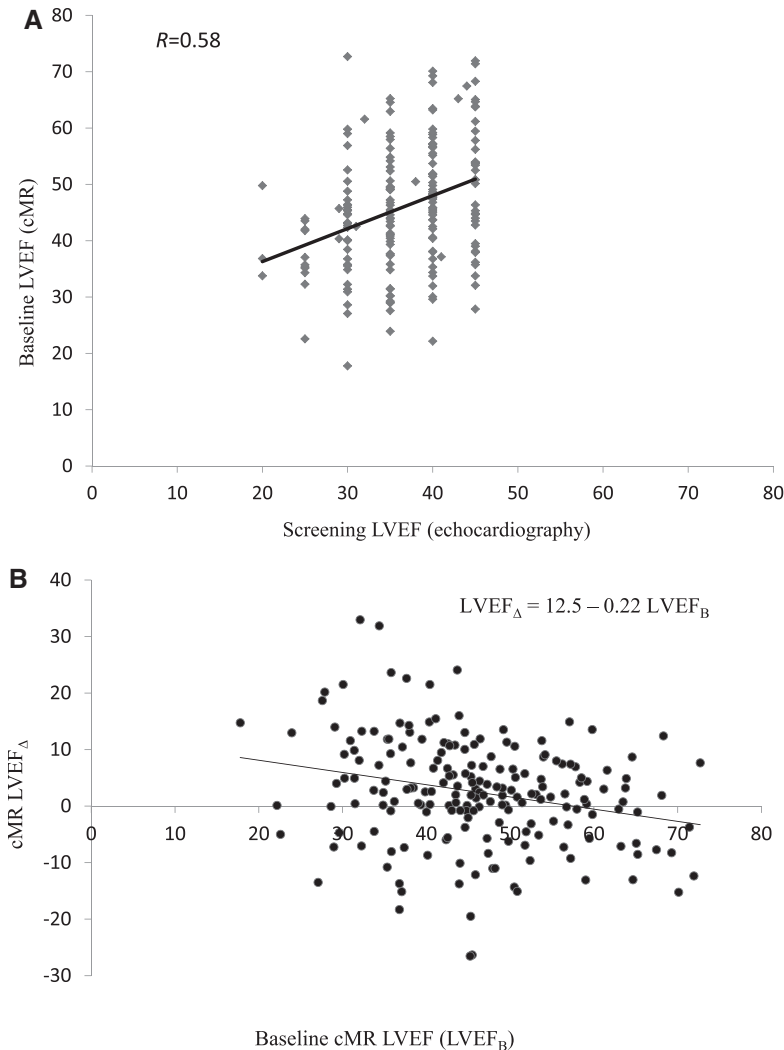


Figure 2. A, Relationship between the baseline left ventricular ejection fraction (LVEF) MRI-based assessment and the screening echocardiographic (echo)-based LVEF. The correlation is substantial, and in general the core laboratory assessment is greater than the echo-based assessment. **B, Relationship between change in LVEF over time and baseline EF in the TIME and LateTIME trials.** On average, the greater the baseline LVEF, the smaller the increase in LVEF from baseline to 6 mo. cMR indicates cardiac magnetic resonance; and TIME, Transplantation In Myocardial infarction Evaluation.

despite the greater baseline degree of dysfunction. Thus, we think that it is unlikely that the degree of baseline LV dysfunction was a major reason for the null results.

In the face of these null findings for LVEF, power becomes a critical factor. SWISS-AMI was powered to detect a 3.5 (absolute LVEF unit) placebo-adjusted change (>4 months) in EF. TIME was powered to detect a 5-unit placebo-adjusted change (>6 months). Although TIME and LateTIME were adequately powered overall, the sample sizes in LVEF ≤ 40 subgroups were too small and underpowered to detect these same effect sizes.

The planned similarities between TIME and LateTIME permit the opportunity to conduct additional evaluation of the combined data sets. An analysis was completed using a data set containing 81 of 87 patients from LateTIME, and 112 of 120 patients from TIME, all of whom had paired cMR LV images at baseline and 6 months. We observed no overall effect of BMC therapy on the change in LVEF over time (placebo-adjusted change in LVEF, -1.4 ± 9.5 ; $P=0.967$; 95% confidence interval, -4.2 to 1.5) in this combined data set. Furthermore, the placebo-corrected changes from baseline to 6 months in the 2 studies were not statistically different from each other.

Examination of this combined data set for the effects of age, baseline LVEF, and time from PCI to infusion identified

only baseline LVEF as significantly associated with change in LVEF regardless of treatment ($b=-0.22$; $P=0.001$; 95% confidence interval, -0.34 to -0.10 ; Figure 2B). This effect remained after adjusting for age and time from PCI to infusion. Neither age nor time from PCI to cell infusion (days) had a significant relationship with change in LVEF from baseline to 6 months in either study or the combined data set as was the case in SWISS-AMI.⁴ These analyses suggest but do not prove that the greatest change in LVEF during the study period occurs in the cohort with the most severe baseline LV dysfunction.

Size of the Study Population

In view of the results, questions have been raised about the size and power of these studies. These 3 trials were powered to detect placebo-adjusted LVEF increases from 3.5% to 5%. Great variability and heterogeneity across clinical centers all but preclude identifying small effect sizes. However, we did not anticipate the small effect sizes that we observed. These miniscule effects were not presaged by the literature, which instead reported (eg, REPAIR-AMI) much larger effects of cell therapy. Presuming that these moderate to large effects would be discoverable in our trials, we focused on whether the timing of administration of cells would influence these

effects. In addition, these effect sizes were beyond the ability of clinical centers to measure with requisite precision.

Additionally, smaller study sizes may result in incomplete randomization of baseline variables as was the case in these studies. Additionally, and perhaps unexpectedly, the randomization to different delivery times affected the study populations. The intended delay between enrollment and delivery resulted in greater numbers of patients withdrawing from the studies from groups that received delivery at later time points. Thus, considerations balancing the costs of larger trials and the inherent uncertainty of smaller trials are critical to the field of cell therapy. Furthermore, in trials of AMI in which subjects need to return to the hospital after discharge, designs need to account for the possibility of withdrawal of subjects once discharged.

Randomization Models

In CCTRN studies, a 2:1 ratio of BMC-treated subjects to placebo was used to balance the rigor of the study with the need to recruit subjects to a trial that required BM harvest and invasive delivery of cells. However, in addition to reducing statistical power, it also generated a placebo group 50% smaller than that of an equal randomization model, creating inequalities in the baseline characteristics and increased variability because of small sample sizes in the placebo group. The CCTRN favors designs that include a placebo group as robust as possible for comparisons; in general, the Network endorses equal randomization as was done in SWISS-AMI.

Standardization of Cell Processing

To limit the potential sources of variability related to cell product, the CCTRN adopted distributed and automated cell processing (Sepax; Biosafe) at each of the 5 regional centers as opposed to centralized processing. This decision was based on several lines of reasoning. First, the use of open Ficoll systems for BMC isolation was becoming less standard in the United States with the advent of cell mobilization and isolation for clinical hematopoietic stem cell transplantation. Second, the use of a closed-automated system enabled local preparation and standardization. Despite the striking similarity to the negative results of SWISS-AMI, which used manual Ficoll processing, concerns have been raised about the functionality of the BMC product used in TIME and LateTIME. These included the potential effects of erythrocytes and heparin³¹ in the study product.¹⁸ We have presented data to suggest that these concerns are not warranted.^{19,20} Notably, in the First Mononuclear Cells injected in the United States conducted by the CCTRN (FOCUS-CCTRN) trial, with Sepax-processed cells, there was an observed increase in LVEF in the BMC group versus placebo at 6 months in patients with chronic LV dysfunction.²¹

Additional studies performed by the Network compared the effects of human BM separated by Sepax or by manual Ficoll preparation in 2 distinct immunodeficient murine models, hindlimb ischemia, and myocardial infarction. Results of these studies indicate that Sepax and manual Ficoll-isolated cells resulted in similar effects in these complementary models (Online Figure). Although several differences exist that distinguish SWISS-AMI from TIME and LateTIME taken together, the data suggest that the negative results of TIME, LateTIME, and SWISS-AMI are more likely to be because of

the inherent nature of BMCs than the means by which they are isolated or stored.

Timing of Cell Harvest and Delivery

The timing of harvest and delivery in SWISS-AMI affected the content of the BM product. CD34 cell content was marginally higher at 3 to 4 weeks than at 5 to 7 days after myocardial infarction (%CD34: 1.31% late, 1.02% early; $P=0.01$), but this was not seen when comparing cells from TIME and LateTIME. These studies do not support a major impact of timing of cell harvest on BMC product.

End Point Selection

Each study used cMR as the most rigorous method to assess LVEF, whereas TIME and LateTIME used a coprimary end point of regional LV function. CCTRN followed the concept used in Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST), using wall motion in the infarct zone and border zone.¹² Precision for the assessment of regional LV function was substantially better than for global LV function, suggesting that the sample size for a 2-armed clinical trial is substantially smaller when designed around regional function rather than global LV function.

Future Directions for Cell Therapy After AMI

In 2007, cell therapy clinical trials of BMCs in AMI were considered highly innovative with a growing safety profile and hopes for effects. Despite early positive studies including BOOST, which used cMR as the primary end point, a meta-analysis of studies using LVEF by cMR as the primary end point did not show a statistically significant effect of unfractionated BMCs on LVEF.¹⁶ Why, in aggregate, the studies using echo end points demonstrate differences in LV function assessment whereas those using cMR do not remains an unsettled question.

Early preclinical and clinical trial findings suggested that BMC delivery could improve LV function. This coupled with the strong public demand for new interventional strategies propelled this collection of clinical investigations. Although the impact of BMCs on survival after AMI remains to be determined, there may be a future for incorporation of some aspects of BM-derived cells with selected or enriched populations. However, the promise of a major impact of BMCs on LV function seems unfounded. A potential effect on mortality will be examined in the prospective Bone Acute Myocardial Infarction (BAMI) trial, a phase III trial in Europe aimed to test the hypothesis that BMCs improve 2-year survival after AMI.²² The CCTRN eagerly awaits the results of BAMI as they will effectively make all of the ongoing discussion surrounding the effects of BMC after AMI on LVEF moot, because the study is purely designed to test the effects on mortality.

Meanwhile, concepts of off-the-shelf cell delivery after AMI with an allogeneic cell (eg, allogeneic mesenchymal stem cells)²³ delivered at multiple doses and timing (even as early as reperfusion) are promising. Another alternative is one in which cells are delivered in the postacute period after the initial phases of recovery and remodeling, which would permit their intramyocardial effect to develop in the presence of stable LV function. This research pathway is lit by a collection of post-myocardial infarction LV dysfunction trials, including FOCUS-CCTRN, POSEIDON (The Percutaneous

Stem Cell Injection Delivery Effects on Neomyogenesis Pilot Study), TAC-HFT (The Transendocardial Autologous Cells [hMSC or hBMC] in Ischemic Heart Failure Trial), SCPIO (Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy), CADUCEUS (Cardiosphere-Derived Autologous Stem Cells to Reverse ventricular dysfunction), and C-CURE.^{21,24–28} Although BMC use in patients with AMI has dimmed (at least temporarily), the future of cell therapy for LV dysfunction resulting from AMI remains bright.

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Disclosures

None.

References

- Delewi R, Hirsch A, Tijssen JG, et al. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. *Eur Heart J*. 2014;35:989–998.
- Traverse JH, Henry TD, Pepine CJ, et al; Cardiovascular Cell Therapy Research Network (CCTRN). Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA*. 2012;308:2380–2389.
- Traverse JH, Henry TD, Ellis SG, et al; Cardiovascular Cell Therapy Research Network. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA*. 2011;306:2110–2119.
- Sürder D, Manka R, Lo Cicero V, et al. Intracoronary injection of bone marrow-derived mononuclear cells early or late after acute myocardial infarction: effects on global left ventricular function. *Circulation*. 2013;127:1968–1979.
- Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium. *Nature*. 2001;410:701–705.
- Yoon YS, Wecker A, Heyd L, Park JS, Tkebuchava T, Kusano K, Hanley A, Scadova H, Qin G, Cha DH, Johnson KL, Aikawa R, Asahara T, Losordo DW. Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction. *J Clin Invest*. 2005;115:326–338.
- Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, Pasumarthi KB, Virag JI, Bartelmez SH, Poppa V, Bradford G, Dowell JD, Williams DA, Field LJ. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature*. 2004;428:664–668.
- Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature*. 2004;428:668–673.
- Dimmeler S, Burchfield J, Zeiher AM. Cell-based therapy of myocardial infarction. *Arterioscler Thromb Vasc Biol*. 2008;28:208–216.
- Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Hölschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM; REPAIR-AMI Investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. 2006;355:1210–1221.
- Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet*. 2006;367:113–121.
- Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet*. 2004;364:141–148.
- Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med*. 2006;355:1199–1209.
- Simari RD, Moyé LA, Skarlatos SI, Ellis SG, Zhao DX, Willerson JT, Henry TD, Pepine CJ. Development of a network to test strategies in cardiovascular cell delivery: the NHLBI-sponsored Cardiovascular Cell Therapy Research Network (CCTRN). *J Cardiovasc Transl Res*. 2010;3:30–36.
- Sürder D, Schwitter J, Moccetti T, et al. Cell-based therapy for myocardial repair in patients with acute myocardial infarction: rationale and study design of the SWISS multicenter Intracoronary Stem cells Study in Acute Myocardial Infarction (SWISS-AMI). *Am Heart J*. 2010;160:58–64.
- Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation*. 2012;126:551–568.
- Schächinger V, Erbs S, Elsässer A, et al; REPAIR-AMI Investigators. 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.
- Assmus B, Tonn T, Seeger FH, Yoon CH, Leistner D, Klotsche J, Schächinger V, Seifried E, Zeiher AM, Dimmeler S. Red blood cell contamination of the final cell product impairs the efficacy of autologous bone marrow mononuclear cell therapy. *J Am Coll Cardiol*. 2010;55:1385–1394.
- Gee AP, Richman S, Durett A, et al. Multicenter cell processing for cardiovascular regenerative medicine applications: the Cardiovascular Cell Therapy Research Network (CCTRN) experience. *Cytotherapy*. 2010;12:684–691.
- Moyé LA, Simari RD, Skarlatos SI; Cardiovascular Cell Therapy Research Network (CCTRN). Bone marrow-derived cell therapy after myocardial infarction. *JAMA*. 2013;309:1459.
- Perin EC, Willerson JT, Pepine CJ, et al; Cardiovascular Cell Therapy Research Network (CCTRN). Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. *JAMA*. 2012;307:1717–1726.
- Barts and The London NHS Trust. BAMI. the effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all cause mortality in acute myocardial infarction. ClinicalTrials.gov Identifier: NCT01569178. <http://clinicaltrials.gov/ct2/show/NCT01569178>. Accessed March 28, 2014.
- John MES, Xie J, Heidman AW, Stewart GC, Cattaneo SM, Caparelli DJ, Baumgartner WA, Martin BJ, Hare JM. Catheter-based percutaneous cellular cardiomyoplasty using allogeneic bone marrow derived mesenchymal stem cells. *J Am Coll Cardiol*. 2003;41:67–67.
- Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCPIO): initial results of a randomised phase 1 trial. *Lancet*. 2011;378:1847–1857.
- Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, Czer LS, Marbán L, Mendizabal A, Johnston PV, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marbán E. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet*. 2012;379:895–904.
- Bartunek J, Behfar A, Dolatabadi D, et al. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failure) multicenter randomized trial with lineage-specified biologicals. *J Am Coll Cardiol*. 2013;61:2329–2338.
- Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. *JAMA*. 2012;308:2369–2379.
- Heldman AW, DiFede DL, Fishman JE, et al. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. *JAMA*. 2014;311:62–73.