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Effect of Intracoronary Delivery of Autolologous Bone Marrow Mononuclear Cells Two to Three Weeks Following Acute Myocardial Infarction on Left-Ventricular Function: The LateTIME Randomized Trial

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Abstract

Context—Clinical trial results suggest that intracoronary delivery of autologous bone marrow mononuclear cells (BMCs) may improve left ventricular (LV) function when administered within the first week following myocardial infarction (MI). However, since a substantial number of patients may not present for early cell delivery, we investigated the efficacy of autologous BMC delivery 2–3 weeks post-MI.

Objective—To determine if intracoronary delivery of autologous BMCs improves global and regional LV function when delivered 2–3 weeks following first MI.

Design, Setting, and Patients—LateTIME is a randomized, double-blind, placebo-controlled trial of the National Heart, Lung, and Blood Institute - sponsored Cardiovascular Cell Therapy Research Network (CCTRN) of 87 patients with significant LV dysfunction (LVEF ≤ 45%) following successful primary percutaneous coronary intervention (PCI).

Interventions—Intracoronary infusion of 150×10^6 autologous BMCs (total nucleated cells) or placebo (2:1 BMC:placebo) was performed within 12 hours of bone marrow aspiration after local automated cell processing.

Main Outcome Measures—The primary endpoints were changes in global (LVEF) and regional (wall motion) LV function in the infarct and border zone from baseline to 6 months as measured by cardiac MRI at a core lab blinded to treatment assignment Secondary endpoints included changes in LV volumes and infarct size.

Results—87 patients were randomized between July 2008 and February 2011: mean age = 57 ± 11 yrs, 83% male. Harvesting, processing, and intracoronary delivery of BMCs in this setting was feasible and safe. The change from baseline to six months in the BMC group, when compared to the placebo group, for LVEF (48.7 to 49.2% vs. 45.3 to 48.8%; Difference = −3.0, 95% CI −7.0 to 0.9), wall motion in the infarct zone (6.2 to 6.5 vs. 4.9 to 5.9 mm; Difference = −0.7, 95% CI −2.8 to 1.3), and wall motion in the border zone (16.0 to 16.6 mm vs. 16.1 to 19.3 mm; Difference = −2.6; 95% CI −6.0 to 0.8) were not statistically significant. There was no significant change in LV volumes and infarct volumes decreased by a similar amount in both groups at 6 months compared to baseline.

Conclusions—Among patients with MI and LV dysfunction following reperfusion with PCI, intracoronary infusion of autologous BMCs compared to intracoronary placebo infusion, 2–3 weeks after PCI did not improve global or regional function at 6 months.

Keywords

Acute myocardial infarction; bone marrow mononuclear cells; LVEF; cardiac MRI

INTRODUCTION

Several randomized trials have demonstrated that administration of autologous bone marrow mononuclear cells (BMCs) following acute myocardial infarction may result in improvement in left-ventricular ejection fraction (LVEF)[1–3] or regional LV function[4] and may be associated with decreased clinical adverse events[5]. However, the majority of trials[1–4,6–11] have administered BMCs within the first week following primary percutaneous coronary intervention (PCI). As the optimal time to administer BMCs has not been determined, the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Cardiovascular Cell Therapy Research Network (CCTRN) developed two prospective clinical trials, TIME[12] and LateTIME[13]. TIME was designed to compare the effects of BMC delivery in patients with predominantly STEMIs at 3 versus 7 days post-MI, while LateTIME was designed to explore whether delayed BMC delivery 2–3 weeks following MI could improve global and regional LV function.

The time frame of 2–3 weeks post-MI may be particularly important for those patients who present to centers that lack expertise in cell therapy or those patients initially too sick as a result of cardiogenic shock or other medical issues. These patients may particularly benefit from cell therapy given that several trials have demonstrated that those patients with the most depressed LV function appear to derive the most improvement[1,6,14] from BMC delivery.

LateTIME is a novel, randomized, double-blind, placebo-controlled trial designed to investigate the utility and therapeutic efficacy of intracoronary autologous BMC delivery 2–3 weeks following MI using rigorous methods of cell isolation in conjunction with local cell processing[15]. It is the first BMC trial to deliver a standardized dose of cells following stenting of the infarct vessel during primary PCI.

METHODS

Organizational Structure and Oversight

The CCTRN was established by the NHLBI to develop, coordinate, and simultaneously conduct multiple collaborative trials testing the effects of cell therapy on cardiovascular disease. The CCTRN consists of five clinical research centers (Cleveland Clinic Foundation, University of Florida, Minneapolis Heart Institute Foundation, Texas Heart Institute, and Vanderbilt University) and their satellite sites, a data coordinating center (DCC) (The University of Texas School of Public Health) which provides trial management and data analysis, a cell processing quality control center, and six core laboratories[16]. All clinical centers (CC) participate in the selection and design of Network protocols which are also reviewed by an independent Protocol Review Committee (PRC) and a Gene Therapy/Cell Therapy Data Safety and Monitoring Board (DSMB) under the aegis of the NHLBI. Each CC and the DCC have independent Institutional Review Board (IRB) approvals and oversight.

Study Design

LateTIME is a Phase-II, randomized, double-blinded, placebo-controlled trial developed to determine if delayed (2–3 weeks) intracoronary administration of 150×10^6total nucleated cells (TNCs) to patients with predominantly anterior MIs, can safely produce a measurable improvement in global and regional LV function as determined by cardiac MRI (cMRI) at 6-months compared to baseline. Patients with an LVEF ≤ 45% by echocardiography post-PCI were randomized in a 2:1 ratio of BMC to placebo following successful stenting of the infarct-related coronary artery. All patients will be followed for two years to assess clinical events.

Study Protocol

All patients provided written informed consent following broad discussions of the risks, benefits of the trial and alternatives explained by the investigative team. Race and ethnicity were documented as self-described by subjects. Demographic and clinical variables were determined by interview and the patient's medical record. Patients were randomized in a 2:1 ratio to cell therapy or placebo. All patients underwent bone marrow aspiration and intracoronary infusion of BMCs or cell-free solution (placebo). All caregivers and patients were blinded to treatment. Approximately 80–90 mls of bone marrow were aspirated from the iliac crest using standard techniques. The aspirate was processed at all sites with a closed, automated cell processing system (*Sepax*, Biosafe SA, Geneva, Switzerland)[15] to ensure a uniform cellular product. After BMC enrichment, cells were washed three times and suspended in 5% human serum albumin / saline. The composition of $CD34^+$ and $CD133^+$ cells was determined by fluorescent activated cell sorting. After the cells passed stipulated lot release criteria, including viability (>70%) and sterility, randomization was carried out according to the DCC. Treatment assignment was masked to all but one designated cell processing team member who was not involved in patient care. The target dose for the treatment group was 150×10^6 TNCs. Patients randomized to placebo received 5% HSA/saline to which 100 microliters of autologous blood was added to ensure that the color and consistency of the solution matched that of the BMC product.

Within 12 hours of aspiration, the BMCs or cell-free product was delivered to the infarct-related artery via a percutaneous transluminal coronary angioplasty (PTCA) catheter (*Maverick*, Boston Scientific Corporation, Natick, Massachusetts) using the Stop-Flow technique in six aliquots of five ml each, given over two minutes with balloon inflation at low pressures within the previously placed stent. Each infusion cycle was separated by balloon deflation and two minutes of reperfusion. All patients were treated with aspirin and 75 mg of clopidogrel in addition to guideline recommended post-MI medications.

Study End-Points

Wall Motion Imaging—All imaging was performed using 1.5T MRI scanners with imaging protocols developed by the MRI core laboratory (University of Florida) certified before the study began. The MRI core lab was blind to study group assignment. Both global and segmental LV function measurements were obtained using a steady-state free-precession (SSFP) or fast gradient echo technique. Long axis cine images in the 2-chamber and 4-chamber projections were acquired. In addition, a set of contiguous short axis slices (8–10 mm thick) were obtained from the mitral valve annulus through the apex of the LV throughout the cardiac cycle. Data were analyzed using the Cardiovascular Angiography Analysis System/Magnetic Resonance Ventricular analysis software (PIE Medical Imaging BV, Maastricht, The Netherlands). Global LV parameters assessed included: end-diastolic volume, end-systolic volume, stroke volume, ejection fraction, and left ventricular mass. Volumetric measurements were performed by direct planimetry on the contiguous short axis images at both end-systole and end-diastole. Regional measurements include wall thickening

and wall motion, and were calculated using 100 chords spaced every 3.6° originating from the centroid of the left ventricle, for each short axis image. Regional data were reported using the American Heart Association (AHA) 17-segment model. The minimum spatial and temporal resolution requirements of the SSFP sequence are 2.5 × 2.5 mm voxels and 40 milliseconds, respectively.

Viability Imaging—Fifteen to twenty minutes following administration of a gadolinium-chelate contrast agent (0.05 mmol/kg, IV), delayed-enhancement (DE) imaging was performed with a T1-weighted inversion-recovery prepared gradient-echo sequence (DE-MRI). The inversion delay time was iteratively adjusted for optimal nulling of normal myocardium. Contrast-enhanced viability imaging was performed using the standard 2D technique in the short-axis projections, which acquires a single slice each breath hold using the same plane prescription as the functional short axis cine series. Regions of irreversible myocardial damage are manifested by “hyperenhancement” (bright white areas) on the images, while normal and/or viable tissue is “nulled” (black) on the acquired images. The presence, location, and extent of irreversibly damaged tissue was assessed and reported using the AHA 17-segment model, in order to permit direct correlation with regional functional measurements. Pre- and post-therapy imaging, both cine wall motion and DE-MRI, were carefully matched using internal landmarks including the insertion sites of the right ventricular free-wall and the papillary muscle insertions.

Safety Monitoring

All participants were closely monitored for adverse events and this information was transmitted to the Food and Drug Administration (FDA), the NHLBI Gene and Cell Therapy DSMB, and IRBs of each center. A set of stopping rules was developed in consultation with the FDA. The DCC was responsible for coordination of collection, standardization, integration, and analysis of study data from the various study components (enrolling sites and core facilities) and the preparation and distribution of the required reports to each of the safety oversight entities.

Statistical Analyses

The statistical methods utilized in LateTIME have been reported previously[13]. The primary endpoints were 1) change in global LV function over time and 2) change in regional function over time as assessed by change in wall motion in the infarct and border zones. The pre-specified analyses for the primary endpoint compared the change over six months in the endpoint for the BMC group to the same change over time in the placebo group.

Sample Size Consideration

The sample size was calculated using a two-sample *t*-test statistic. During the design phase of LateTIME, the literature[1,3] suggested that the placebo adjusted change in the global LVEF (change in global LVEF in the BMC group minus change in global LVEF in the placebo group) was 4% and common group standard deviation of the difference of LVEF over time was expected to be σ_{Δ}=6. Anticipating that 5% of patients would be lost to follow-up, and a 2:1 (BMC:placebo) ratio, a trial size of 86 was required. For the regional function wall motion evaluation, we assumed a placebo adjusted change of 6.7 with σ_{Δ} = 9.5 from the Boost trial[3]; again assuming 5% loss to follow-up and 2:1 randomization, the study sample size was 77 patients. In order to have adequate power for both endpoints, a final sample size of 87 patients was selected (58 patients in the BMC group, 29 patients in the placebo group), providing 83% power for the global and 87% power for the regional measures of LV function.

The regional LV function endpoint was defined as change in wall motion over time in the infarct and border zone of the infarct. The infarct zone was defined as the segments with the largest two signal intensity enhancement (SIE) measures with gadolinium (using a 17 segment model). The border zone was defined as those regions adjacent to the infarct zone in which the SIE were in the 10% to 75% range.

Exact testing for categorical variables and Student's t-testing for continuous variables assessed the comparability of baseline variables between treatment groups. All hypotheses testing, and all effect sizes with their 95% confidence intervals, were evaluated using the general mixed linear model (adjusted forheart rate) and unadjusted comparisons of treatment effects. The primary and secondary evaluations compared the randomized study groups using an intention-to-treat analysis. No adjustments for multiple comparisons were made, and a *p*-value threshold of 0.05 was used to assess statistical significance. An imputation analysis of the primary endpoints was also performed by including all patients with incomplete follow-up data by Last Observation Carried Forward (LOCF) method.

RESULTS

Screening and Enrollment

Between July 2008 and February 2011, a total of 2201 patients were screened, with the majority excluded for LVEF > 45% (Figure 1). There were no statistically significant differences in baseline characteristics between the BMC and placebo groups except for heart rate on presentation, which was higher in the placebo group (Table 1). The median time from chest pain onset to PCI was 3.4 hours in the BMC group and 3.3 hours in the placebo group. The LVEF on the qualifying echocardiogram performed following PCI during the initial hospitalization was 36.4 ± 6.5% in the BMC group and 35.0 ±7.6% in the placebo group. As expected, this was significantly less than the baseline LVEF obtained by cMRI several weeks later, in part due to resolution of myocardial stunning.

Cell Processing

Bone marrow aspiration and intracoronary infusion were performed a median of 17.4 days (interquartile range 15.5–20.0) in the BMC group and 16.8 days (interquartile range 15.8–17.8) in the placebo group following primary PCI (Table 1). There were no complications associated with the bone marrow aspiration. All patient products underwent automated cell processing with Ficoll using the *Sepax* device[15].

Intracoronary Infusion

The median time from bone marrow aspiration to intracoronary infusion was 8.5 hours in the BMC group (Table 1). All patients received 150×10^6 TNCs (average 60–70% BMCs; 2.6% CD34+ cells and 1.2% CD133+ cells) except three patients received a lower than target TNC dose due to the low cell numbers in the initial bone marrow. The mean viability of the cell product was 98.5%. One patient did not receive the BMC infusion due to the presence of a severe left main coronary stenosis which was identified prior to infusion and was referred for coronary artery bypass surgery. Two patients underwent additional stenting at the time of the intracoronary infusion; one for the discovery of a distal stent edge dissection related to the primary PCI procedure and another for a possible dissection related to the stop-flow procedure. One patient who had a post-partum spontaneous coronary dissection was found to have diffuse thrombus throughout the stented region of the left anterior descending artery. The patient successfully underwent aspiration thrombectomy with ultrasound guided stent expansion followed by infusion of study product. No patients experienced a post-procedural elevation in cardiac enzymes and they were routinely discharged the following day.

Safety

Despite a high-risk cohort of patients with moderate to severe LV dysfunction following predominantly large, anterior MIs, there were very few clinical events (Table 2). In the placebo group, there was one death due to recurrent pancreatitis three months following randomization. Three patients underwent repeat revascularization and two patients received implantable cardiac defibrillators (ICDs). The BMC group had fewer events than the placebo group. They included one re-infarction, one repeat revascularization and one hospitalization for heart failure.

Analysis of Global and Regional LV Function

A total of 55 patients in the BMC group and 26 patients in the placebo group had paired cMRI data at baseline and 6-months available for analysis of global and regional LV function. Six patients were excluded from the global analysis (LVEF) due to the following reasons: death [1], withdrawal from study due to presence of severe left main stenosis prior to cell infusion [1], placement of ICDs [2], and lost to follow-up [2]. One additional patient was excluded from the infarct zone regional analysis due to incomplete SIE data and 4 additional patients did not undergo regional measurements in the border zone because of lack of an a SIE signal in the border zone.

Baseline and follow-up endpoint measures for the primary endpoints are provided (Table 3, Figure 2). The difference in the change from baseline to six months in the BMC group when compared to the placebo group for LVEF was not different (48.7 to 49.2% vs. 45.3 to 48.8% between group difference = −3.0, 95% CI −7.0 to 0.9; $p = 0.135$). The difference in the change in wall motion in the infarct zone for the BMC group versus the placebo group was also not different (6.2 to 6.5 mm vs. 4.9 to 5.9 mm; Between group difference = −0.7, 95% CI −2.8 to 1.3; $p = 0.493$). Similarly, the difference in the change in wall motion in the border zones between the BMC and placebo group (16.0 to 16.6 mm vs. 16.1 to 19.3 mm; between group difference = −2.6; 95% CI −6.0 to 0.8; $p = 0.129$) was not different. An analysis using a mixed linear model adjusted for heart rate did not change these findings. Inclusion of patients lacking paired cMRI data by LOCF imputation had no effect on the primary results. LVEF measured by echocardiography was consistent with the cMRI findings in showing no treatment effect (BMC= 44.3±8.4% to 47.6 ±11.0%, placebo= 42.4 ± 6.5% to 46.5 ± 8.0%, p=0.636).

Secondary endpoints of LV volumes demonstrated a small, but non-significant increase in LV end diastolic volume index (EDVI) and end systolic volume index (ESVI) in the BMC group at 6 months (Table 3). Infarct volume uniformly decreased in both groups without significant difference (BMC = −3.5 ±19 ml, Placebo = −2.0 ± 14.4 ml; difference = −1.5 ml, CI = −9.89 to 6.88).

Several predetermined subgroup analyses were performed in the treatment group. In contrast to previous studies[1,6,14], there was no observed improvement in recovery of LV function in the group of patients with the most depressed LVEF at baseline. No difference was observed in global or regional function in patients stratified by ischemic time. Patients with age > 65 demonstrated a small, but non-significant decrease in LVEF at 6 months following cell therapy (p=0.106).

COMMENT

The CCTRN was created by the NHLBI to accelerate development of cell-based therapies in the United States, utilizing a network approach to facilitate patient recruitment, standardization of cell processing, and development of core labs for outcome measures analysis. LateTIME is the first trial to be completed from the CCTRN[13], and it was

developed to test the hypothesis that delayed delivery of autologous BMCs following MI would improve global and regional LV function when measured 6 months later by cMRI. However, we observed that BMC delivery 2–3 weeks following MI resulted in no detectable improvement in LV function over that observed in the placebo group. The findings were consistent in demonstrating a lack of benefit in both global and regional wall motion in the infarct and border zone and stand in contrast to several studies[1–3] that demonstrated benefit in LV function when BMCs were administered within the first week following MI. Additionally, measurement of infarct size, which may be a more sensitive marker of cell therapy efficacy, decreased by a similar amount in both groups.

Patients recruited to LateTIME constituted a high-risk cohort with depressed LV function that persisted several weeks following successful revascularization with stenting. Although retrospective analyses suggest that these patients may derive the most benefit from cell therapy in this setting[1,6,14], no improvement in LV function was noted, even in the subgroup with the most depressed LVEF. LateTIME is the first BMC trial in MI to deliver a uniform number of cells to its cohort in a dose thought sufficient to modify LV function[17]. However, our results suggest that intracoronary BMC delivery at this later time period is not effective.

Timing of Cell Delivery Following Acute Myocardial Infarction

The vast majority of randomized cell therapy trials using BMCs in the setting of MI have delivered cells within the first seven days following STEMI[1–4,6–10]. The REPAIR-AMI trial[1] observed, in a subgroup analysis, that the most favorable effects on LV function were observed with BMC delivery on day 5–7 post-MI. However, no trial has been specifically designed to identify the optimum time of cell delivery. LateTIME was designed to determine if delayed delivery of BMCs to patients following MI would be safe and effective in improving LV function.

It is likely that the timing of cell delivery post-MI may have a major influence on treatment effect and ultimately, may have contributed to our negative findings. Following MI, significant temporal changes occur in the myocardium and bone marrow that may affect engraftment and retention of delivered cells[18–24]. As a result, the myocardial environment during later treatment as in LateTIME is likely to be considerably different than that present during the first week post-MI when BMCs were delivered in other trials. In the first few days following MI, there is an extensive inflammatory response triggered by infiltration of neutrophils and other cells that may lead to an increase in cytokines, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), and reactive oxygen species that may adversely influence delivered cells[18,19,21]. Microvascular obstruction in the infarct zone may impair inflow of oxygen and nutrients to support stem cell survival. This is countered by an increased expression of stromal-derived factor-1 (SDF-1)[25] in the first few days following MI that may increase stem cell trafficking and engraftment. Over the next 1–2 weeks, there is a transition from an inflammatory phase to a proliferative phase where extracellular matrix is formed and neovascularization is increased[18]. The net impact of these changes may have negatively impacted the potential beneficial effects of BMC delivery[26].

Changes in Circulating Progenitor Cells Derived from Bone Marrow Following Acute Myocardial Infarction

Within hours of MI, there is a well-documented increase in circulating progenitor cells released from bone marrow that may contribute to myocardial repair[22–24,27]. These include release of hematopoietic stem cells, endothelial progenitor cells, mesenchymal stem cells (MSCs), and very small embryonic-like cells, a novel progenitor cell with pluripotent properties that express early markers of cardiomyocyte differentiation[22]. Many of these cells contain a variety of cell surface markers, including CD34, c-kit, c-met, vascular endothelial

growth factor (VEGF) - 2R, and CXCR4 that actively participate in ischemic tissue repair, in part through homing in response to gradients of VEGF, hepatocyte growth factor-1 (HGF-1) and SDF-1. The peak release of these bone marrow-derived cells has been measured in hours to days[22–24,27], but would appear to be outside the window of when cells were delivered in the current study. Thus, a possible synergistic effect between intracoronary delivered and circulating progenitor cells may not have been possible in the current study.

With the rapid egress of stem cells shortly after MI, it is possible that the bone marrow was relatively depleted of progenitor cells when the bone marrow aspiration was performed in our study. As a result, the reparative quality of the BMC product may be different from those delivered in the first week post-MI. However, a recent pre-clinical study in mice observed that BMCs are significantly more potent at 21 days compared to those obtained at 3–5 days following MI due to IL-1 -mediated inflammatory changes in the bone marrow[16]. These effects will be studied by the CCTRN Biorepository Core lab[28] in the future through analysis of peripheral blood and bone marrow of patients enrolled in the current study and the ongoing TIME trial[12], that performed bone marrow aspirations and intracoronary infusions in patients randomized to day 3 or 7 post acute MI.

Are BMCs the Proper Cell Type to be Utilized in the Setting of Acute Myocardial Infarction?

Our decision to utilize unselected BMCs for this late post-MI therapy was based on extensive pre-clinical data indicating that no specific cell type clearly exceeded another in regards to enhanced potency for altering ventricular remodeling and function[29–31]. Use of a closed and standardized commercial device, with central quality control for cell processing, facilitated provision of a uniform cell product. Extensive pre-clinical testing demonstrated a product with similar composition but less variability to that obtained by traditional manual separation methods with Ficoll[15]. Accordingly, autologous bone marrow-derived stem and progenitor cells could be produced at most hospitals and would be more convenient for transplantation by intracoronary infusion, if this strategy were successful. The CCTRN developed several satellite centers of cell delivery, including one located over 100 miles from the center where cell processing occurred. The quality control, processing metrics, and out of body times were equivalent, even at this distance supporting the feasibility of this approach.

In addition to timing, an ongoing concern is the ultimate effectiveness of BMCs to improve LV function following MI. LateTIME was developed at a time when several studies demonstrated significant improvement in LV function with BMC therapy[1,3] and meta-analyses confirmed a small, but significant improvement in LVEF and attenuation of LV remodeling[19,32,33]. Since these initial publications, several studies that have failed to demonstrate that BMCs improve LV function in this setting[6–11]. Indeed a recent analysis found that the improvement in LVEF following BMCs was < 1% when cMRI was utilized for measurement of LVEF in nearly 700 patients[34]. Although concerns of cell processing were initially thought to contribute to some of the negative findings[35], these concerns have largely been allayed[36]. Furthermore, it is well understood that the reparative properties of autologous stem and progenitor cells derived from bone marrow are negatively influenced by a variety of factors, including advanced age, diabetes, and other cardiovascular risk conditions, all common to patients enrolled in clinical trials. Whether newer cell types under investigation including MSCs[37], mesenchymal precursor cells[38], multipotent adult progenitor cells (NCT00677222), adipose-derived cells (NCT00442806), or encompassing allogeneic products obtained from young healthy donors, can improve LV function to a greater degree than BMCs following MI remains to be determined.

Limitations

LateTIME is the first cell therapy trial in MI to use a standardized, automated, closed system of cell processing. Rigorous pre-clinical testing determined that this system produced a similar cell product compared to manual Ficoll separation in regards to cell recovery, viability and CFU formation[17]. However, because the cell product was not tested *in-vivo*, we cannot rule out that unknown modifications occurred in the cell product that could have contributed to our negative findings. In addition, while there are several different approaches to measure myocardial strain (myocardial tagging, DENSE, etc.), these were not employed in this study due to the need for specialized expertise that may not have been available at all of the clinical sites that collected the MRI data.

Conclusion

Among patients with MI and LV dysfunction following reperfusion with PCI, intracoronary infusion of autologous BMCs compared to intracoronary placebo infusion 2–3 weeks after PCI did not improve global or regional LV function at 6 months.

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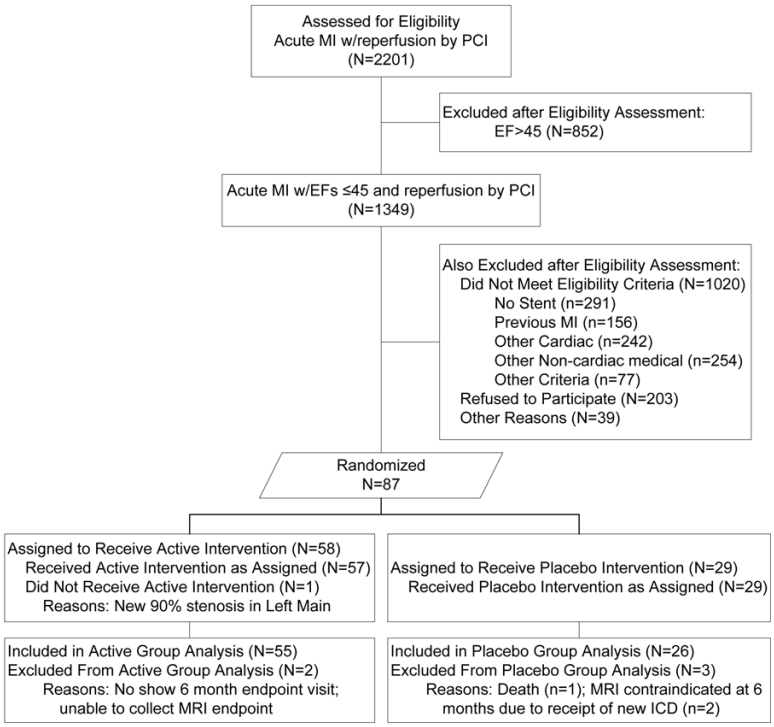

Figure 1.
CONSORT Diagram

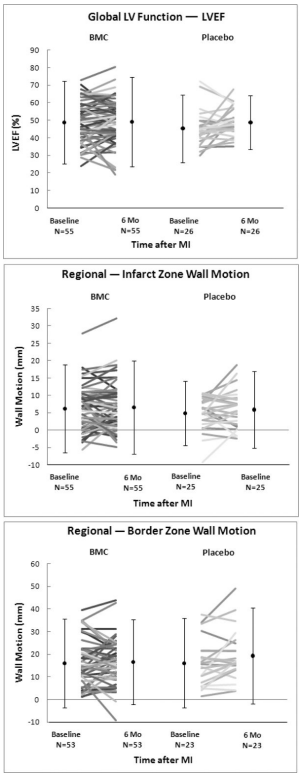

Figure 2.
Primary Endpoint Analysis
Solid circles represent the means and I-bars represent the confidence intervals.

Table 1

Baseline and Cell Characteristics

N (%) unless otherwise specified	BMC N=58	Placebo* N=29
Age in years, mean (SD)	57.6 (11)	54.6 (11)
Female	12 (21)	3 (10)
Race:		
White	51 (88)	24 (83)
Non-white	7 (12)	5 (17)
History of:		
Diabetes	11 (19)	7 (24)
High Blood Pressure	32 (55)	14 (48)
Hyperlipidemia	43 (74)	20 (69)
Angina	15 (26)	4 (14)
Smoking	36 (62)	15 (52)
Pre-infarction Angina (N=57 BMC)	14 (24)	9 (31)
Height in inches, mean (SD)	68(4)	70(3)
Weight in pounds, mean (SD)	183 (37)	194 (33)
BMI, mean (SD)	27.7 (5.5)	28.0 (4.3)
BP in mmHg, mean (SD):		
Systolic, initial discharge	111.1 (13.9)	110.1 (11.7)
Diastolic, initial discharge	68.0 (10.1)	68.4 (9.0)
Heart Rate		
Initial at ER, mean (SD) (N=54 BMC; N=28 placebo) **median (range)**	77.5 (18)	90.3 (26)†
	74 (50, 124)	85 (54–170)†
Initial discharge, mean (SD) (N=55 BMC; N=27 placebo) **median (range)**	73.2 (12)	77.2 (9)
	73 (52–100)	77 (57–99)
Qualifying LVEF (echo), mean (SD)‡	36.4 (6.5)	35.0 (7.6)
Hemoglobin in gm/dL, mean (SD)	13.5 (0.2)	13.1 (1.8)
hsCRP in mg/L, mean (SD) (N=51 BMC; N=25 placebo)	20.1 (6)	14.2 (4)
BNP, mean (SD) (N=52 BMC; N=24 placebo)	273.9 (210)	528.8 (1291)
Peak CKMB, mean (SD) (N=38 BMC; N=23 placebo)	234.0 (212)	318.2 (203)
Peak Troponin, mean(SD)		
T (N=23 BMC; N=10 placebo)	6.8 (6.3)	10.3 (5.9)
I (N=15 BMC; N=14 placebo)	163.3 (197.6)	144.2 (129.5)
Time from chest pain to ER, in hours, median (interquartile range) (N=53 BMC; N=28 placebo)	1.95 (1.0–10.7)	2.01 (0.8–5.3)
Time from chest pain to PCI in hours, median (interquartile range)	3.4 (2.3–14.3)	3.3 (2.2–7.5)
Door-to-balloon time in hours, median (interquartile range) (N=28 placebo)	1.73 (0.9–3.4)	1.52 (0.8–2.3)
Transferred from outside hosp. after PCI (N=57 BMC)	10 (17)	6 (21)
Time from bone marrow aspiration to infusion in hours, median (interquartile range) (N=57 BMC)	8.5 (7.95–9.25)	8.6 (7.8–9.8)
Time from PCI to infusion in days, median (interquartile range) (N=57 BMC)	17.4 (15.5–20.0)	16.8 (15.8–17.8)
Drug-eluting stent	45 (78)	20 (69)

N (%) unless otherwise specified	BMC N=58	Placebo* N=29
Stent Region:		
LAD	53 (91)	27 (93)
LAD only	49	24
LAD + LCX	1	2
LAD + RCA	3	1
LCX (only)	1 (2)	1 (3)
RCA (only)	4 (7)	1 (3)
Cell Characteristics:		
Total Nucleated Cells/Product (x10^6), mean (SD) % Viability/Product	147 (17)	-
By Trypan Blue Exclusion		
Mean (SD)	98.5 (1.3)	98.6 (1.2)
Median (Range)	99.0 (94.0–100.0)	99.0 (96.0–100.0)
By 7-AAD Staining		
Mean (SD)	95.2 (5.4)	95.7 (5.1)
Median (Range)	97.4 (77.5–99.8)	97.0 (72.1–99.3)
%CD34+ Cells/Product, mean (SD) §	2.6 (1.0)	2.7 (1.4)
%CD133+ Cells/Product, mean(SD) §	1.2 (0.5)	1.2 (0.6)
Colony-Forming Units-Hill/Product, mean (SD)§ (N=45 BMC; N=23 placebo)	139 (251)	194 (277)
Endothelial Colony-Forming Cells/Product, mean (SD)§ (N=38 BMC; N=21 placebo)	184 (250)	163 (218)

*BMC versus Placebo comparisons are not statistically significant unless otherwise noted

†Mean HR at initial presentation, P=0.011; Median HR at initial presentation, P=0.024 (Wilcoxon rank-sum)

‡'Qualifying' defined as LVEF≤45 from MI through consent (at any point over this 2–3 week period)

§Seven patients either declined participation or had insufficient product for the Biorepository

Table 2

Clinical/Safety Outcomes at 6-month Endpoint Window

	BMC (n=58)	Placebo (n=29)
Death	0	1
Reinfarction	1	0
Repeat Revascularization	1	3
Target Vessel	1	2
Non-Target Vessel	0	1
Heart Failure Hospitalization	1	0
ICD Placement	0	2
Total Events	**3**	**6**
Patients	**3 (5%)**	**5 (17%)**

Table 3

Endpoint Analyses

	BMC			Placebo			Analysis			
Global LV Function										
LVEF (%)								95% Confidence Interval		
	N	Mean	SD	N	Mean	SD	Between-group difference in 6-mo change	P-value	LB	UB
Baseline	55	48.7	12.0	26	45.3	9.9				
Followup	55	49.2	13.0	26	48.8	7.8				
Within-group Change	55	0.5	8.2	26	3.6	9.3	-3.0	0.135	-7.05	0.95
Regional LV Function										
Infarct Zone										
Wall Motion (mm)								95% Confidence Interval		
	N	Mean	SD	N	Mean	SD	Between-group difference in 6-mo change	P-value	LB	UB
Baseline	55	6.2	6.5	25	4.9	4.8				
Followup	55	6.5	6.8	25	5.9	5.7				
Within-group Change	55	0.3	4.3	25	1.0	4.5	-0.7	0.493	-2.78	1.34
Regional LV Function										
Border Zone										
Wall Motion (mm)								95% Confidence Interval		
	N	Mean	SD	N	Mean	SD	Between-group difference in 6-mo change	P-value	LB	UB
Baseline	53	16.0	9.9	23	16.1	10.0				
Followup	53	16.6	9.6	23	19.3	10.9				
Within-group Change	53	0.5	7.2	23	3.2	6.3	-2.6	0.129	-6.03	0.77
Global LV Function										
EDVI (ml/m^2)								95% Confidence Interval		
	N	Mean	SD	N	Mean	SD	Between-group difference in 6-mo change	P-value	LB	UB
Baseline	55	89.1	23.9	26	82.8	26.4				
Followup	55	92.5	32.7	26	85.5	22.7				
Within-group Change	55	3.4	23.4	26	2.7	18.1	0.7	0.890	-9.47	10.91
ESVI (ml/m^2)								95% Confidence Interval		
	N	Mean	SD	N	Mean	SD	Between-group difference in 6-mo change	P-value	LB	UB
Baseline	55	47.8	21.4	26	46.3	20.4				
Followup	55	48.0	25.1	26	44.0	14.8				
Within-group Change	55	0.2	14.0	26	-2.3	14.7	2.5	0.456	-4.11	9.15
Infarct Volume (ml)										
	N	Mean	SD	N	Mean	SD	Between-group difference in 6-mo change	95% Confidence Interval		
								P-value	LB	UB
Baseline	55	34.2	23.7	25	33.3	15.6				
Followup	55	30.7	15.8	25	31.4	15.1				
Within-group Change	55	-3.5	19.0	25	-2.0	14.4	-1.5	0.725	-9.89	6.88