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Clinical Trials of Cardiac Repair with Adult Bone Marrow-Derived Cells

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Abstract

The past decade has witnessed a marked increase in the number of clinical trials of cardiac repair with adult bone marrow cells (BMCs). These trials included patients with acute myocardial infarction (MI) as well as chronic ischemic heart disease (IHD) and utilized different types of BMCs with variable numbers, routes of administration, and timings after MI. Given these differences in methods, the outcomes from these trials have been often disparate and controversial. However, analysis of pooled data suggests that BMC injection enhances left ventricular function, reduces infarct scar size, and improves remodeling in patients with acute MI as well as chronic IHD. BMC therapy also improves clinical outcomes during follow-up without any increase in adverse effects. Although the underlying mechanisms of heart repair are difficult to elucidate in human studies, valuable insights may be gleaned from subgroup analysis of key variables. This information may be utilized to design future randomized controlled trials to carefully determine the long-term safety and benefits of BMC therapy.

Keywords

Bone marrow; Stem cell; Clinical trial; Myocardial infarction; Myocardial repair; Cardiomyopathy; Coronary artery disease; Meta-analysis

1 Introduction

More than 16 million Americans suffer from coronary heart disease with an estimated 935,000 episodes of acute myocardial infarction (MI) per year [1]. The death of myocytes during MI leads to replacement of myocardial regions by noncontractile fibrous tissue, followed by progressive remodeling of the left ventricle (LV) with eventual development of ischemic cardiomyopathy [2, 3]. Unfortunately, the common medical and surgical options for MI and ischemic heart disease (IHD) are unable to replenish the lost myocardial tissue and thus cannot improve the overall prognosis of millions of patients with ischemic heart failure. Although cardiac transplantation offers a definitive therapy, the scarcity of donor hearts precludes its wider application. In light of this enormous clinical burden, cell therapy for cardiac repair has attracted unprecedented attention among both basic and clinical cardiovascular researchers. Indeed, results from various animal models of MI and cardiomyopathy suggest that therapy with adult bone marrow cells (BMCs) improves LV

function and attenuate LV remodeling. Based on these highly promising data, a number of clinical trials of cardiac repair with adult BMCs have already been completed in patients with acute MI as well as ischemic heart failure [4, 5].

These early trials of BMC therapy used diverse cell populations with highly variable cell numbers injected via different routes at different time intervals after MI in patients with acute MI, chronic IHD, and cardiomyopathy [4, 5]. Besides the differences in BMC types, the methodology for isolation and processing of cells also varied significantly among these studies [5–7]. Moreover, the investigators employed diverse techniques (left ventriculography, echocardiography, SPECT imaging, magnetic resonance imaging [MRI]) to assess cardiac outcome parameters [5]. Given these differences in study design and methods, it is not surprising that results from these BMC therapy trials have been often disparate and sometimes controversial. However, meta-analysis of pooled data has repeatedly shown that BMC transplantation results in modest improvements in various parameters of LV function and remodeling in patients with acute MI and chronic IHD [4, 5, 8, 9]. Such meta-analyses have also identified several important methodological variables that need further fine-tuning in order to maximize the benefits of BMC therapy for heart repair.

2 Clinical Trials of BMC Therapy for Cardiac Repair

The adult bone marrow contains many different types of hematopoietic and nonhematopoietic cells at various stages of development, ranging from very primitive stem/progenitors to mature cells that are ready to escape into the circulation. These cell types include mononuclear cells [10], mesenchymal stem cells (MSCs) [11], hematopoietic stem cells [12], side population cells [13], and very small embryonic-like stem cells (VSELs) [14–17], to name a few. The relatively easy availability of autologous BMCs in large numbers has made the bone marrow an attractive cellular source for clinical trials of cardiac repair. Table 1 provides the details of randomized controlled trials (RCTs) as well as cohort studies that examined the safety and efficacy of cardiac repair with various adult BMC populations in humans. The different types of cells used in these trials are described in brief below.

2.1 Bone Marrow Mononuclear Cells

Bone marrow mononuclear cells (BMMNCs) are highly heterogeneous and contain both hematopoietic as well as nonhematopoietic cells. BMMNCs are typically isolated by density gradient centrifugation using various commercially available formulations [10]. In the cohort study by Strauer et al. [18], intracoronary injection of autologous BMMNCs in patients with acute MI improved myocardial perfusion and regional function and reduced infarct size. Since this report, a large number of randomized controlled trials of BMMNC therapy in patients with acute MI, chronic IHD, and ischemic heart failure have been reported [19–37] (Table 1). Importantly, in the vast majority of these studies, BMMNC transplantation was associated with improvement in one or more parameters of global and regional myocardial function, perfusion, anatomy, infarct size, and viability (Table 1). In addition, improvement in New York Heart Association (NYHA) functional class, maximal

oxygen uptake (VO₂max), exercise capacity, anginal symptoms, and nitroglycerin intake has also been reported with BMMNC therapy [20, 23, 24, 31, 38–40].

A few other trials have injected relatively unselected nucleated BMCs via the intracoronary route [41–44]. In the study by Wollert et al. [41], significant improvement in global LVEF as well as regional wall motion was noted in BMC-treated patients after 6 months of follow-up. Interestingly, these differences in LVEF and other outcome parameters were no longer significant between control and BMC-treated patients after 18 months of follow-up, suggesting a transient nature of BMC-induced benefits [42]. Nonetheless, a more persistent improvement in diastolic function was noted in the same patients [42], indicating a broader range of benefits conferred by BMC therapy. In the study by Ruan et al. [44], the improvements in functional and anatomical parameters in BMC-treated patients did not change between 3 and 6 months of follow-up.

2.2 Mesenchymal Stem Cells

Bone marrow mesenchymal stem cells (MSCs) perform a supportive function in the stroma and give rise to nonhematopoietic cells. In addition, they are able to differentiate into osteocytic, chondrocytic, adipose, skeletal muscle, neural, and other lineages [11, 45]. Several reports suggest that MSCs also differentiate into cardiomyocytes under specific culture conditions in vitro and following myocardial transplantation in vivo [46–48]. From a feasibility standpoint, MSCs can be potentially harvested in advance, expanded in culture, and stored for use after an acute MI in the future. In clinical trials, intracoronary injection of bone marrow-derived MSCs resulted in improvement in global LVEF and regional wall motion, and reduction in infarct size, LVESV, as well as LVEDV in patients with acute MI [49]. In patients with ischemic cardiomyopathy, intracoronary injection of MSCs resulted in improved perfusion and improved exercise tolerance and NYHA class [50]. However, in the study by Katritsis et al. [51], intracoronary injection of two to four million MSCs enhanced myocardial perfusion and viability, but failed to improve global LVEF, LVESV, or LVEDV in patients with acute or old MI.

In the dose-ranging RCT by Hare and colleagues, intravenous administration of allogeneic MSCs after an acute MI increased LVEF in treated patients compared with baseline and resulted in reverse remodeling [52]. In a subsequent study comparing the efficacy of allogeneic vs. autologous MSCs in patients with ischemic cardiomyopathy, both MSC types reduced infarct size and the sphericity index, resulting in reverse remodeling, and autologous MSCs improved 6-min walk distance and quality of life compared with baseline [53]. Although no significant increase in EF was noted, LVESV and LVEDV improved with transendocardial MSC therapy with similar adverse event rates with both types of MSCs [53]. Together, these data indicate that in patients with ischemic heart failure, MSC injection favorably impacts patient functional capacity, quality of life, and LV remodeling.

2.3 AC133+ BMCs

Induction of angiogenesis in the periinfarct zone and infarcted myocardium has been advanced as a mechanism of cardiac repair by BMCs. Accordingly, the AC133+ subset of BMCs with angiogenic potential [54, 55] has been utilized for cardiac repair. Although

intracoronary injection of AC133+ cells improved global LVEF and regional wall motion and reduced infarct size, spontaneous and inducible VT was noted in two cell-treated patients [56]. In addition, cell-treated patients experienced increased in-stent restenosis [56], and subsequent careful angiographic analysis revealed greater luminal narrowing in non-stented coronary arterial regions [57], suggesting potentially greater risk of atherogenesis with AC133+ BMC therapy. However, in a subsequent study by Colombo et al. [58], intracoronary injection of CD133+ cells in patients with large anterior MI resulted in improved myocardial blood flow by PET imaging without affecting other cardiac parameters significantly. In another study in patients with old anterior MI, intracoronary injection of CD133+ and CD133–CD34+ cells improved perfusion, LVEF, and remodeling [59].

CD133+ cells have also been used via the transepical route in patients undergoing CABG. In the study by Stamm et al. [60], intramyocardial injection of CD133+ BMCs along with CABG improved LVEF and myocardial perfusion compared with patients who underwent CABG alone. However, the differences in LVEF between cell-treated and control groups disappeared after 18 months, except in patients with baseline EF < 40 % [61]. Moreover, patients who were operated on between 7 and 12 weeks after MI had greater chance of improvement with cell therapy compared with more delayed procedures. These data may suggest specific influence of myocardial milieu on the efficacy of CD133+ cells in cardiac repair.

2.4 Mobilized BMCs

In several clinical trials, the investigators transplanted BMCs harvested from the peripheral blood with or without prior mobilization with cytokines. Such use of mobilized progenitors circumvents the relatively invasive process of bone marrow aspiration in already sick patients.

2.4.1 Circulating Progenitor Cells (CPCs)—In the TOPCARE-AMI trial [62–64], intracoronary injection of peripheral blood-derived CPCs improved global LVEF and LVESV after 4 months. After 1 year of follow-up, MRI studies showed improved LVEF, smaller infarct size, and improved LV hypertrophy in CPC-treated patients [64]. In the study by Erbs et al. [65], intracoronary CPC delivery in the setting of recanalized chronic total occlusion reduced infarct size and the number of hibernating segments, increased coronary flow reserve, and improved regional wall motion and global LVEF. However, such benefits were absent in CPC-treated patients with previous MI, dysfunctional LV segments, and an open infarct-related artery in a subsequent RCT [30], perhaps indicating an important role played by the myocardial milieu in CPC-induced cardiac repair.

2.4.2 CD34+ Cells—It is well known that CD34+ cells from the peripheral blood as well as the bone marrow have angiogenic attributes [66, 67]. Consistently, transendocardial transplantation of autologous peripheral blood-derived CD34+ cells resulted in trends toward reduced angina frequency, reduced nitroglycerin usage, improved exercise time, and improvement in Canadian Cardiovascular Society (CCS) class in patients with refractory angina. [68]. These results were corroborated in a phase II study, in which transendocardial injection of CD34+ cells reduced weekly angina frequency and improved exercise time in

patients with CCS class III–IV angina at enrollment [69]. Interestingly, these changes were more pronounced with a lower CD34+ cell dose (1×10^5 CD34+ cells/kg) compared with a higher (5×10^5 CD34+ cells/kg) dose [69].

2.4.3 Peripheral Blood Stem Cells—Peripheral blood-derived stem cells (PBSCs) [70–73] or mononuclear cells (PBMNCs) [74] have also been utilized for cardiac repair in several trials. Although the first RCT with G-CSF-mobilized PBSCs [70] was stopped due to increased in-stent restenosis, in a subsequent RCT [71] that used drug-eluting stents, intracoronary PBSC injection improved EF, reduced LVESV and infarct size, and improved coronary flow reserve in patients with acute MI. Other studies of intracoronary PBSCs and PBMNCs therapy in the setting of acute MI have also reported improvements in LV function and structure [72, 74]. However, the failure of PBSC therapy to improve LV function and remodeling in patients with ICM [71] suggests that myocardial characteristics (acute MI vs. chronic IHD) are important determinants of cardiac cell therapy outcomes. Regardless, these differences in outcomes and the potential risk of in-stent restenosis with cytokine-mobilized cell injection need to be carefully evaluated in larger RCTs.

3 Meta-analysis of Pooled Data on Effects of BMC Therapy

Although BMC therapy for heart repair has gained remarkable popularity in the recent past, the number of patients enrolled in each study has been rather small. Given the diversity in cell type, patient characteristics, study design, and outcomes assessed, results from these trials have often been discordant [4, 5, 75]. Therefore, several meta-analyses of pooled data from clinical trials of BMC therapy have been performed in the recent past [4, 8, 9, 76, 77]. Importantly, although each meta-analysis of BMC trials included somewhat different sets of studies, the results of these meta-analyses [4, 8, 9, 76, 77] have been generally concordant and show an overall beneficial impact of BMC therapy on cardiac function and structure in patients with acute MI as well as chronic IHD.

3.1 LV Ejection Fraction

The global LVEF reflects the overall contractile function of LV and has been reported in nearly all trials of BMC therapy. In our recent comprehensive meta-analysis that included 50 RCTs and cohort studies (a total of 2,625 patients) of BMC therapy for cardiac repair, BMC injection produced a 3.96 % greater increase in LVEF compared with controls [5]. The analysis of interaction indicated similar efficacy of BMC therapy in improving LVEF in patients with acute MI as well as chronic IHD [5]. The improvement in LVEF in BMC-treated patients compared with controls was 3.66 % in the meta-analysis by Abdel-Latif et al. [4], 4.21 % in the meta-analysis by Hristov et al. [9], 3 % in the meta-analysis by Lipinski et al. [8], 2.99 % in the meta-analysis by Martin-Rendon et al. [76], and 4.77 % in the meta-analysis by Zhang et al. [77]. These concordant findings from several meta-analyses indicate that BMC therapy is associated with a modest yet significant (2.99–4.21 %) improvement in LVEF compared with standard treatment [4, 8, 9, 76, 77].

3.2 Infarct Size

Infarct size is a reliable measure of the extent of cardiac repair induced by cell therapy and various techniques (SPECT, left ventriculogram, MRI) have been used in clinical trials for this purpose. In our recent meta-analysis of data from a total of 50 studies, a 4.03 % greater reduction in infarct size was noted in BMC-treated patients compared with controls [5]. In previous meta-analyses by Abdel-Latif et al. [4], Lipinski et al. [8], and Martin-Rendon et al. [76], infarct size reduction in BMC-treated patients was greater by 5.49 %, 5.6 %, and 3.5 %, respectively, compared with controls.

3.3 LV End-Systolic Volume

LVESV is a surrogate indicator of global LV systolic performance with unchanged LVEDV. In our recent meta-analysis [5], the reduction in LVESV was greater by 8.91 ml in BMC-treated patients compared with controls. Greater improvements in LVESV in BMC-treated patients were also reported in meta-analyses by Abdel-Latif et al. (−4.80 ml) [4], Lipinski et al. (−7.4 ml) [8], and Martin-Rendon et al. (−4.74 ml) [76]. In this regard, although the reduction in LVEDV in BMC-treated patients was not significant in previous meta-analyses [4, 8, 76], our recent analysis showed a significantly greater reduction in LVEDV in BMC-treated patients, indicating improved remodeling [5]. Therefore, the reduction in LVESV with BMC therapy may reflect a combination of improved systolic performance as well as superior remodeling.

3.4 LV End-Diastolic Volume

After an MI, the LV undergoes remodeling with thinning of the infarct wall and hypertrophy of the viable myocardium [2, 3]. As a result, the LV chamber enlarges and the LVEDV gradually increases. Because LVEDV is an important indicator of LV remodeling, LVEDV was measured in many BMC trials, albeit with different techniques (echocardiography, MRI). In a meta-analysis that included trials with BMC injection within 14 days after acute MI, cell therapy was associated with a trend toward reduction in LVEDV [8]. In the largest meta-analysis that included data from patients with acute MI as well as chronic IHD [5], the reduction in LVEDV was greater by 5.23 ml in BMC-treated patients compared with controls, indicating remodeling benefits of BMC therapy. Although the exact mechanism remains unclear, the improved remodeling can result from myocyte salvage, reduced infarct expansion, salubrious paracrine effects on the matrix, or a combination of these. Future studies need to be conducted to assess the impact of BMC therapy on LVEDV as a function of the time interval between acute MI and BMC transplantation.

3.5 Other Outcome Parameters

Improvements in LV function and structure should logically result in improved patient symptoms and quality of life. Although symptomatic benefits are highly important clinical indicators of the overall efficacy of cell therapy, patient symptoms were reported in a relatively small number of early studies [23, 31, 50, 68]. Due to the differences in specific end points among studies and smaller number of patients for each parameter, analysis of pooled data could not be performed. However, the newer studies are increasingly employing a broader array of outcome measures and monitoring these patient-important variables. The

parameters that have thus far been reported to improve with BMC therapy include: VO₂max [24, 40, 78], exercise capacity or exercise time [23, 31, 50, 68, 69, 79], NYHA class [23, 31, 39, 50, 80–84], LV diastolic function [43, 85–87], angina frequency [23, 39, 68, 69], nitrate requirement [39, 68], CCS class [38, 39, 68, 80], FEV₁ [52], and quality of life [38, 79]. Together, these observations suggest that the benefits of BMC transplantation extend well beyond the conventional measures of global LV function and volumes. These data also indicate that LV structure/function benefits of BMC therapy indeed translate into improved symptoms in patients with IHD.

4 Safety of BMC Transplantation

Along with the benefits, the potential side effects of BMC therapy have also been monitored in clinical trials, and the results from various meta-analyses indicate that BMC therapy does not increase the risk of adverse events compared with standard therapy [4, 8, 76]. Although only a few BMC trials reported “major adverse cardiovascular events” in a comprehensive fashion, results from earlier meta-analyses showed a similar incidence of mortality in BMC-treated and control patients [4, 8, 76]. However, in the largest meta-analysis, BMC therapy was associated with a reduced all-cause mortality and cardiac mortality, indicating an important survival benefit of BMC transplantation [5].

In addition, no increased incidence of ventricular or supraventricular arrhythmia, in-stent restenosis, and target vessel revascularization was noted in BMC-treated patients in meta-analyses of trials that enrolled patients with acute MI as well as chronic IHD [4, 5, 8, 76]. However, a reduced incidence of recurrent MI was noted in a meta-analysis of RCTs in patients with acute MI, along with a trend toward reduced hospitalization for heart failure [8]. In the recent analysis of RCTs as well as cohort studies, BMC therapy was associated with significantly lower incidence of recurrent MI and stent thrombosis, and trends toward reduced incidence of heart failure and cerebrovascular accident [5]. Nonetheless, potential adverse effects of BMC therapy continue to be monitored in large RCTs that are currently in progress.

5 Methodological Considerations

In earlier clinical trials of BMC therapy, vastly different cell numbers were injected via different routes and at various time points after MI in dissimilar patient populations. The methods of cell preparation were also quite different even for the same cell type. Although many of these issues still remain to be specifically answered in large RCTs, important insights have been gained from analysis of pooled data from completed trials.

5.1 Patient Characteristics

With the conduct of larger clinical trials, it has become increasingly apparent that clinical features of recipients are also important determinants of outcomes following BMC transplantation. Two key clinical characteristics are discussed below.

5.1.1 Type of Ischemic Heart Disease—Because the myocardial environment is vastly different in the setting of an acute MI when compared with chronic cardiomyopathy, the

outcomes of BMC therapy may potentially differ in patients with these two broad clinical conditions. The results from preclinical studies suggest that BMC injection can also improve outcomes in models of cardiomyopathy [88, 89]. Consistently, in patients with chronic ischemic heart failure, BMC therapy was associated with improved regional wall motion [26, 27, 30, 65], perhaps reflecting the formation of new myocytes or enhanced preservation and augmented function of preexisting myocytes. The analysis of pooled data [5] showed no significant difference in improvements in LVEF and LVEDV with BMC therapy in patients with acute MI and chronic IHD [4, 5]. However, the reduction in LVESV was significantly greater in patients with chronic IHD compared with acute MI patients, and a trend toward greater reduction in infarct scar size was also noted in these patients [5]. However, very little is known at present with regard to retention, survival, and fate of transplanted BMCs in humans; and specific interactions of the myocardial milieu (acutely infarcted vs. chronic remodeled myocardium) with specific BMC types remain unknown. As an example of this cell-specific efficacy, BMMNCs but not CPCs were able to improve outcomes in patients with chronic cardiomyopathy in the TOPCARE-CHD trial [30]. However, CPC injection improved global LV function and regional wall motion in patients with chronic total occlusion in the study by Erbs et al. [65, 90]. Importantly, Erbs et al. injected larger number of CPCs (69 ± 14 million vs. 22 ± 11 million) at a shorter time interval after MI (7.5 ± 2.9 months vs. 77 ± 76 months) compared with the TOPCARE-CHD study [30], [65]. Thus, it will be important to determine whether specific BMC types are more suitable specifically for repairing remodeled myocardium.

5.1.2 LV Function at Baseline—Because having an acute ST-elevation MI was a primary criterion for many BMC trials, patients with relatively preserved LVEF despite MI were enrolled in several earlier trials. However, it is logical to predict that BMC injection would benefit hearts with more severe functional compromise compared with those with near-normal function. Consistent with this notion, in the REPAIR-AMI trial, a significant increase in LVEF was noted in patients with baseline LVEF of 48.9 % (the median), but not in those above the median [28]. Similar inverse relation of baseline LVEF with outcomes was noted in another study wherein BMC-treated patients with baseline LVEF of <35 % exhibited significantly greater increase in LVEF compared with those with baseline LVEF of 35 % [60]. Further, in the REGENT trial [35], patients with baseline LVEF of <37 %, but not those with LVEF of 37 %, receiving unselected or selected BMCs exhibited significant improvement with BMC therapy. The analysis of pooled data, however, did not show a significant interaction of baseline LVEF and improvement in LVEF or infarct size [5]. However, these subgroup analyses did show a significantly greater improvement in LVESV and LVEDV in patients with baseline LVEF of <43 % (the median) compared with those with baseline LVEF of 43 % [5], indicating superior remodeling benefits of BMC therapy in hearts with worse function at baseline.

5.2 BMC Number

After transplantation, a large number of BMCs are lost due to cell washout as well as cell death in the inflamed myocardium [91, 92], and reported data indicate that only a small percentage of injected cells is retained within the myocardium [21, 93–95]. In the study by Meluzin et al. [22, 96], only patients who received greater numbers of BMMNCs

experienced sustained improvement in LVEF, suggesting a possible dose–response relationship. Accordingly, BMCs in considerably large numbers were injected in several clinical trials [19, 41, 49, 71, 73, 74, 81, 97], and the numbers of transplanted BMCs in trials thus far have ranged from 2 million to 60 billion. To determine the minimum number of BMCs required to produce the desired benefits, we compared the major outcomes (LVEF, infarct size, LVESV, LVEDV) from studies that used less than a certain number of BMCs with those from studies that used more. The results of such stepwise analysis showed that when less than 40 million BMCs were injected, cell therapy failed to improve significantly any of the four major outcome parameters, suggesting that at least 40 million BMCs need to be injected to induce effective cardiac repair. In another meta-analysis of data restricted to patients with acute MI, transplantation of more than 100 million BMCs was necessary to improve LVEF [76]. However, evidence from animal models suggests that a smaller number of selected BMCs may be more effective compared with unselected BMC population injected in larger numbers. This is exemplified in studies that reported superior cardiac reparative outcomes with CD34+ BMCs compared with unfractionated BMCs [98], and CD45– VSELs compared with a tenfold greater number of CD45+ hematopoietic stem cells [99]. The overall evidence therefore suggests that both cell type and number significantly influence the process of cardiac repair by BMCs.

5.3 Route of BMC Injection

In clinical trials, BMCs have been delivered successfully via intracoronary [18, 24, 25, 28, 30, 37, 40, 41, 44, 49, 50, 56, 83, 96, 100, 101], transepicardial (during CABG) [26, 27, 60, 80–82, 102], transendocardial [23, 31, 38, 39, 68, 69], as well as intravenous [52] routes. Each of these approaches presents specific advantages depending on the cell type and patient characteristics. Intracoronary BMC injection can be conveniently performed following PCI after an acute MI or during an elective catheterization in patients with known coronary artery disease. However, different types of BMCs may exhibit different abilities to cross the vascular wall and stay anchored in the myocardium. For example, the retention of CD34+ BMCs was greater compared with unselected BMCs with intracoronary delivery after acute MI [95]. Importantly, intracoronary injection of BMMNCs in patients with old MI [24] and CPCs in patients with revascularized chronic total occlusion [65] also resulted in improved LV function, indicating that intracoronary BMC delivery may be utilized even in the absence of myocardial vascular damage that would facilitate BMC egress in the setting of an acute MI.

In patients undergoing CABG, intramyocardial injection via transepicardial approach is both feasible and convenient. The advantage of a transendocardial injection using an electromechanical mapping system is the ability to direct BMC injection to viable myocardial areas. The intramyocardial route in general obviates issues related to restenosis and increased atheroma formation that have been noted with specific types of BMCs [56, 70]. Given the fundamental differences in approach and patient types, it is difficult to compare the merits and demerits of various routes. However, subgroup analysis of pooled data showed no significant difference in outcomes with intracoronary and intramyocardial routes in patients with chronic IHD [5]. Thus, a judicious selection of the delivery route

based on the specific BMC type, patient characteristics, and logistics is necessary to improve the outcomes of cardiac repair with BMCs.

5.4 Timing of BMC Injection After Acute MI

Shortly after an acute MI, the inflamed state of the myocardium may potentially affect both BMC retention and survival. On one hand, greater expression of chemoattractants [103] and adhesion molecules [104] in the acutely infarcted heart may promote BMC retention, but on the other hand, the abundance of proinflammatory molecules may also cause excessive BMC death. In order to strike a balance between these effects, determining the optimal time for cell injection after MI is critically important. However, improvement in cardiac parameters has been reported with BMC injection across a broad range of timing after MI [4, 76]. In our earlier meta-analysis [4], injection of BMCs within the 5–30-day window after acute MI/PCI resulted in a trend toward greater infarct size reduction compared with BMC injection <5 days after MI/PCI. However, a greater improvement in LVEF with BMC injection >7 days after acute MI has also been reported in a meta-analysis of acute MI trials [76]. In yet another meta-analysis [105], BMC injection during 4–7 days after MI improved LVEF and LVESV, and reduced the incidence of revascularization, death, recurrent MI, restenosis, and arrhythmia. However, these benefits did not reach statistical significance when BMCs were transplanted within 24 h after acute MI [105]. In the largest meta-analysis [5], the reduction of LVEDV was significantly greater when BMCs were injected <7 days after acute MI, while other outcomes were similar with BMC injection during the 7–30-day interval after MI. Thus, specific molecular information regarding the kinetics of BMC retention and survival with transplantation at different intervals after MI in animal models will be necessary to arrive at an optimal time for transplantation in humans.

5.5 Methods of BMC Processing

Because of the differences in outcomes noted in clinical trials with seemingly similar BMC types [28, 29], the specific methods of BMC processing have attracted closer scrutiny and analysis [6, 7]. Thus far, nearly all of the trials with BMMNCs have utilized a density gradient centrifugation method to isolate these cells. However, the precise formulations of various commercially available products (Lymphoprep, Ficoll-Paque, and such) vary to some extent, and subgroup analysis of outcomes of trials that used Lymphoprep with those using other products did not identify any significant interaction [5]. Additional analysis showed that when BMCs were resuspended in heparin-based solutions, the improvements in LVEF and LVESV were greater. However, heparin has been implicated in BMC dysfunction [106], and therefore, these findings from meta-analysis need to be validated in direct comparison.

6 Conclusions

The safety and efficacy of BMC therapy for cardiac repair have been evaluated in more than 50 clinical trials that used different BMC types and injected widely variable cell numbers via several distinct routes at variable intervals after MI in diverse patient populations. Despite these differences, several meta-analyses of pooled data consistently show that BMC therapy improves LV structure and function without any significant increase in adverse

effects. BMC therapy also improves patient-important outcomes, including total and cardiovascular mortality and recurrent MI. These trials and analyses have identified several important methodological variables of BMC therapy that need further validation by direct comparison in large RCTs. Optimization of these methodological aspects is likely to further improve the benefits of this highly promising approach of myocardial repair.

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Table 1
Controlled clinical trials of cardiac repair with various types of bone marrow-derived cells

Study	Trial design	Cell type	Number of cells	Route of injection	Type of IHD	Follow-up duration (months)	Results
Akar et al. [81]	Cohort	BMMNC	$1.29 \pm 0.09 \times 10^9$	IM during CABG	CIHD	18	LVEF $\uparrow$; myocardial perfusion $\uparrow$; wall motion $\uparrow$; LVESVI $\downarrow$; NYHA class $\downarrow$
Ang et al. [107]	RCT	BMMNC	$85 \pm 56 \times 10^6$ (IM)	IM or IC during CABG	CIHD	6	No significant improvement in LVEF, regional thickening fraction, and LV volumes
Assmus et al. [30]	RCT	BMMNC and CPC	$205 \pm 110 \times 10^6$ (BMMNC) $22 \pm 11 \times 10^6$ (CPC)	IC	CIHD	6	BMMNC: LVEF $\uparrow$; regional contractility $\uparrow$ CPC: no significant improvement
Bartunek et al. [56]	Cohort	CD133+ BMC	$12.6 \pm 2.2 \times 10^6$	IC	AMI	4	In treated patients compared with baseline, global LVEF $\uparrow$; regional function $\uparrow$; infarct size $\downarrow$; viability $\uparrow$
Cao et al. [33]	RCT	BMMNC	$5 \pm 1.2 \times 10^7$	IC	AMI	48	LVEF $\uparrow$; LVESV $\downarrow$
Chen et al. [49]	RCT	MSC	$48-60 \times 10^9$	IC	AMI	6	LVEF $\uparrow$; infarct wall motion $\uparrow$; LVESV $\downarrow$; infarct size $\downarrow$; LVEDV $\downarrow$
Chen et al. [50]	Cohort	MSC	5×10^6 /ml	IC	CIHD	12	Perfusion $\uparrow$; NYHA class $\downarrow$; exercise tolerance $\uparrow$
Choi et al. [73]	Cohort	PBSC	$2.03 \pm 0.69 \times 10^9$	IC	AMI	24	Compared with controls, no additional improvement in LV functional or structural parameters
Colombo et al. [58]	RCT	CD133+ cells from BM or PB	$5.9 (4.9-13.5) \times 10^6$	IC	AMI	12	Myocardial blood flow $\uparrow$ with BM-derived CD133+ cells; no significant change in LVEF, LV volumes, and infarct size
Erbs et al. [65]	RCT	CPC	$69 \pm 14 \times 10^6$	IC	ICM	3	Global LVEF $\uparrow$; infarct size $\downarrow$; myocardial perfusion $\uparrow$; coronary flow reserve $\uparrow$
Ge et al. [25]	RCT	BMMNC	40×10^6	IC	AMI	6	LVEF $\uparrow$; myocardial perfusion $\uparrow$; LV dilation halted
Grajek et al. [97]	RCT	BMMNC	$2.34 \pm 1.2 \times 10^9$	IC	AMI	12	Myocardial perfusion $\uparrow$; no significant change in LVEF and LV volumes; adverse events $\downarrow$
Hare et al. [52]	RCT	MSC	0.5×10^6 /kg– 5×10^6 /kg	IV	AMI	12	Ventricular arrhythmia $\downarrow$; FEV1 $\uparrow$; global symptom score

Study	Trial design	Cell type	Number of cells	Route of injection	Type of IHD	Follow-up duration (months)	Results
Hendrikx et al. [26]	RCT	BMMNC	$60.25 \pm 31.35 \times 10^6$	IM during CABG	CIHD	4	improved; EF $\uparrow$ in patients with anterior MI in patients with anterior MI
Hirsch et al. [108]	RCT	BMMNC and PBMNC	$296 \pm 164 \times 10^6$ (BMMNC) $287 \pm 137 \times 10^6$ (PBMNC)	IC	AMI	4	Regional wall thickening $\downarrow$; no improvement in LVEF, LVESV, and LVEDV
Huang et al. [109]	RCT	BMMNC	NA	IC	AMI	6	No significant difference among group with regard to regional and global LV function, LV volumes, mass, and infarct size
Huikuri et al. [32]	RCT	BMMNC	$402 \pm 196 \times 10^6$	IC	AMI	6	LVEF $\uparrow$; infarct size $\downarrow$; no significant difference in LV volumes
Janssens et al. [100]	RCT	BMSC	$172 \pm 72 \times 10^6$	IC	AMI	4	LVEF $\uparrow$; no improvement in LVEF, LVESV, and LVEDV
Kang et al. [71]	RCT	PBSC	$1.5 \pm 0.5 \times 10^9$	IC	AMI/CIHD	6	Infarct size $\downarrow$; no improvement in LVEF, LVESV, and LVEDV
Karitsis et al. [51]	Cohort	MSC and EPC	$2-4 \times 10^6$	IC	AMI and CIHD	4	In patients with AMI: global LVEF $\uparrow$; LVESV $\downarrow$; infarct size $\downarrow$; coronary flow reserve $\uparrow$. In patients with OMI: coronary flow reserve $\uparrow$
Li et al. [72]	RCT	PBSC	$72.5 \pm 73 \times 10^6$	IC	AMI	6	Myocardial perfusion $\uparrow$; viability $\uparrow$; no improvement in LVEF, LVESV, and LVEDV
Lipiec et al. [34]	RCT	BMMNC	$0.33 \pm 0.17 \times 10^6$ (CD133+) $3.36 \pm 1.87 \times 10^6$ (CD34+)	IC	AMI	6	Global LVEF $\uparrow$; wall motion $\uparrow$; no improvement in LVESV and LVEDV
Losordo et al. [68]	RCT	CD34+ BMC	5×10^4 , 1×10^5 , and 5×10^5 CD 34+ cells/kg	IM (transendocardial)	CIHD	12	Myocardial perfusion $\uparrow$; significantly greater absolute improvement in infarct area wall motion; no significant difference in LVEF and volumes
Losordo et al. [69]	RCT	CD34+ BMC	1×10^5 or 5×10^5 CD 34+ cells/kg	IM (transendocardial)	CIHD	12	In cell-treated patients, angina frequency, nitroglycerin usage, exercise time, and CCS class showed trends toward greater improvement
							Weekly angina frequency and exercise tolerance improved significantly in low-dose group; improvements in high-dose group were not significant

Study	Trial design	Cell type	Number of cells	Route of injection	Type of IHD	Follow-up duration (months)	Results
Lunde et al. [29, 110-112]	RCT	BMMNC	$87 \pm 47.7 \times 10^6$	IC	AMI	36	No improvement in LVEF, infarct size, and LVEDV
Manginas et al. [59]	Cohort	CD133+ and CD133-CD34+ BMC	$16.9 \pm 4.9 \times 10^6$ (CD133+) $8 \pm 4 \times 10^6$ (CD133-CD34+)	IC	CIHD	10-40	In treated patients compared with baseline, LVEF $\uparrow$; LVEDV $\downarrow$; LVESV $\downarrow$; myocardial perfusion $\uparrow$
Meluzin et al. [22, 96]	RCT	BMMNC	10×10^6 and 100×10^6	IC	AMI	12	In high-dose group, global LVEF $\uparrow$; LVESV $\downarrow$; earlier improvement in regional systolic function partially lost at 12 months
Meyer et al. [41-43, 113]	RCT	BMC	$24.6 \pm 9.4 \times 10^8$	IC	AMI	61	Early differences in global LVEF and regional wall motion between treated and control patients lost significance at 18 months; diastolic function improved; LVEF $\uparrow$ in patients with infarct transmural > median; major adverse events similar
Mocini et al. [27]	Cohort	BMMNC	$292 \pm 232 \times 10^6$	IM during CABG	CIHD	3	LVEF $\uparrow$; wall motion $\uparrow$
Nogueira et al. [114]	RCT	BMMNC	100×10^6	IC and cardiac vein	AMI	6	No significant improvement in LVEF; LVESV; LVEDV
Penicka et al. [19]	RCT	BMMNC	26.4×10^8 (IQR $19.6-33.0 \times 10^8$)	IC	AMI	4	No significant improvement in LVEF, infarct size, and LV volumes; study terminated due to lack of benefit and possible safety issues
Perin et al. [20,23]	Cohort	BMMNC	$25.5 \pm 6.3 \times 10^6$	IM (transendocardial)	CIHD	12	Angina class $\downarrow$; NYHA class $\downarrow$; exercise capacity $\uparrow$; myocardial perfusion $\uparrow$; no improvement in global LVEF
Piepoli et al. [78]	RCT	BMMNC	Mean 418×10^6 (total BMC) 248.78×10^6 (mononuclear)	IC	AMI	12	LVEF $\uparrow$; LVESV $\downarrow$; LVEDV $\downarrow$; V02max $\uparrow$; perfusion $\uparrow$; heart rate variability improved
Plewka et al. [86]	RCT	BMMNC	$144 \pm 49 \times 10^6$	IC	AMI	6	Compared with baseline, the absolute change in LVEF $\uparrow$; diastolic function parameters improved in treated group
Pokushalov et al. [39]	RCT	BMMNC	$41 \pm 16 \times 10^6$	IM (transendocardial)	CIHD	12	LVEF $\uparrow$; LVESV $\downarrow$; LVEDV $\downarrow$; NYHA class $\downarrow$; CCS class $\downarrow$; angina episodes $\downarrow$; nitrate requirement $\downarrow$
Quyumi et al. [115]	RCT	CD34+ BMC	$5-15 \times 10^6$	IC	AMI	6	Myocardial perfusion $\uparrow$ in 10 million cohort; trend toward

Study	Trial design	Cell type	Number of cells	Route of injection	Type of IHD	Follow-up duration (months)	Results
Rivas-Plata et al. [82]	Cohort	BMMNC	Mean $2,442 \times 10^6$	IM during CABG	CIHD	27	Improvement in LVEF in 10 million cohort Absolute change in LVEF $\uparrow$; significant decrease in NYHA functional class
Roncalli et al. [101]	RCT	BMC	$98.3 \pm 8.7 \times 10^6$	IC	AMI	3	Trend toward increase in percentage of patients with improved viability; no significant difference in LVEF and infarct size
Ruan et al. [44]	RCT	BMC	NR	IC	AMI	6	LVEF $\uparrow$; segmental function in the infarct as well as viable area $\uparrow$; LVEF $\uparrow$; LVEDV $\downarrow$
Schachinger et al. [28, 116, 117]	RCT	BMMNC	$236 \pm 174 \times 10^6$	IC	AMI	4	LVEF $\uparrow$; regional wall motion $\uparrow$; LVEF $\uparrow$; coronary flow reserve $\uparrow$; major adverse cardiovascular events $\downarrow$; no improvement in LVEDV
Silva et al. [118]	RCT	BMMNC	100×10^6	IC or retrograde via coronary vein	AMI	6	In IC group, compared with baseline, LVEF $\uparrow$
Srimahachota et al. [119]	RCT	BMMNC	$420 \pm 221 \times 10^6$	IC	AMI	6	No significant improvement in treated group
Stamm et al. [60]	Cohort	CD133+	Median 7.19×10^6	IM during CABG	CIHD	62 ± 9	LVEF $\uparrow$; myocardial perfusion improved; compared with baseline, LVEF improved in patients with LVEF of 40 %
Strauer et al. [18]	Cohort	BMMNC	$28 \pm 22 \times 10^6$	IC	AMI	3	Stroke volume index $\uparrow$; regional wall motion $\uparrow$; LV contractility index $\uparrow$; infarct size $\downarrow$; LVEF $\downarrow$
Strauer et al. [24]	Cohort	BMMNC	90×10^6	IC	CIHD	3	LVEF $\uparrow$; infarct wall motion $\uparrow$; infarct size $\downarrow$; viability $\uparrow$; V02max $\uparrow$
Strauer et al. [40]	Cohort	BMMNC	$66 \pm 33 \times 10^6$	IC	CIHD	60	In treated patients, compared with baseline, LVEF $\uparrow$; regional wall motion $\uparrow$; infarct size $\downarrow$; heart rate variability improved; V02max $\uparrow$; long-term mortality $\downarrow$
Suarez de Lezo et al. [120]	RCT	BMMNC	$9 \pm 3 \times 10^8$	IC	AMI	3	In BMMNC-treated patients, LVEF $\uparrow$; regional contractility $\uparrow$

Study	Trial design	Cell type	Number of cells	Route of injection	Type of IHD	Follow-up duration (months)	Results
Tatsumi et al. [74]	Cohort	PBMNC	$4.92 \pm 2.82 \times 10^9$	IC	AMI	6	Global LVEF $\uparrow$; wall motion $\uparrow$; infarct size $\downarrow$; LVESV index tended to be lower
Tendera et al. [35]	RCT	BMMNC or CD34 + CXCR4+ BMC	1.78×10^8 (BMMNC) 1.90×10^6 (CD34 + CXCR4+ BMC)	IC	AMI	6	In cell-treated patients with baseline LVEF of <37 %, LVEF improved compared with baseline
Traverse et al. [37]	RCT	BMMNC	100×10^6	IC	AMI	6	No significant difference in LVEF; LVESV $\downarrow$.
Traverse et al. [121]	RCT	BMMNC	$147 \pm 17 \times 10^6$	IC	AMI	6	No significant difference in LVEF, regional wall motion, LV volume indices, and infarct volume
Tse et al. [31]	RCT	BMMNC	$16.7 \pm 3.4 \times 10^6$ (low dose), $42 \pm 28 \times 10^6$ (high dose)	IM (transendocardial)	CIHD	6	LVEF $\uparrow$; infarct wall thickening $\downarrow$; LVESV $\downarrow$; exercise time $\uparrow$; NYHA class $\uparrow$
Turan et al. [83]	Cohort	BMC	$101 \pm 20 \times 10^6$	IC	AMI	6	In treated patients, compared with baseline, LVEF $\uparrow$; infarct size $\downarrow$; infarct wall movement velocity $\uparrow$; LVESV $\downarrow$; NYHA class $\downarrow$
Turan et al. [84]	RCT	BMC	$96 \pm 32 \times 10^6$	IC	AMI	12	Global LVEF $\uparrow$; infarct wall movement velocity $\uparrow$; infarct size $\downarrow$; NYHA class $\downarrow$; BNP levels $\downarrow$; significant mobilization of BMCPs existed 3, 6, and 12 months after cell therapy
van Ramshorst et al. [38, 87]	RCT	BMMNC	$98 \pm 6 \times 10^6$	IM (transendocardial)	CIHD	3	In treated patients, change in LVEF from baseline $\uparrow$; improvement in CCS class and quality of life score; improved myocardial relaxation and filling pressures
Wohrle et al. [36]	RCT	BMMNC	$381 \pm 130 \times 10^6$	IC	AMI	6	No change in LVEF, LVESV, LVEDV, and infarct size
Yao et al. [85]	RCT	BMMNC	Estimated mean 384×10^6	IC	CIHD	6	No significant difference in LVEF, LV diameters, infarct size, and myocardial perfusion; diastolic parameter improved in treated patients compared with baseline
Yao et al. [122]	RCT	BMMNC	$1.9 \pm 1.2 \times 10^8$ (single infusion) $2.0 \pm 1.4 \times 10^8$ (first	IC	AMI	12	In patients receiving two injections, LVEF $\uparrow$; infarct size $\downarrow$

Study	Trial design	Cell type	Number of cells	Route of injection	Type of IHD	Follow-up duration (months)	Results
Yousef et al. [79]	Cohort	BMIMNC	$2.1 \pm 1.7 \times 10^6$	IC	AMI	60	In treated patients, compared with baseline, LVEF $\uparrow$; LVEDV $\downarrow$; LVESV $\downarrow$; infarct size $\downarrow$; exercise capacity $\uparrow$; mortality $\downarrow$; quality of life improved
			$61 \pm 39 \times 10^6$				
Zhao et al. [80]	RCT	BMIMNC	$659 \pm 512 \times 10^6$	IM during CABG	CIHD	6	LVEF $\uparrow$; infarct wall motion $\uparrow$; perfusion $\uparrow$; NYHA class $\downarrow$; CCS class improved

AMI acute myocardial infarction, BMC bone marrow cell, BMCPC bone marrow-derived circulating progenitor cells, BMMNC bone marrow mononuclear cell, BMSC bone marrow stem cell, CAGB CABG coronary artery bypass graft, CIHD chronic ischemic heart disease, CCS Canadian Cardiovascular Society, CPC circulating progenitor cells, EMM electromechanical mapping, EPC endothelial progenitor cells, IC intracoronary, ICM ischemic cardiomyopathy, IM intramuscular, LV left ventricular, LVEDLV LV end-diastolic volume, LVEDVLV end-systolic volume, LVESVI LVESV index, MSC mesenchymal stem cell, NA not available, NYHA New York Heart Association, OMI old myocardial infarction, PB peripheral blood, PBMC PB-derived mononuclear cell, PBSC PB-derived stem cell, PCI percutaneous coronary intervention, RCT randomized controlled trial