

REVIEWS

Factors Affecting Outcomes of Bone Marrow Stem Cell Therapy for Acute Myocardial Infarction

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Myocardial infarction (MI) poses a significant burden to both patients and the health care system. The irreversible loss of functional cardiomyocytes due to ischemia threatens both patients' immediate survival and quality of life over their lifespan. Stem cell therapy has been proposed as a solution to salvage cardiac contractility through the regeneration of cardiomyocytes, and bone marrow–derived stem cells (BMSc) are among the category of stem cells most extensively studied. Despite the promising theoretical potential of BMSc in tissue regeneration, several key aspects remain to be better understood to enable large-scale clinical application, including safety and efficacy. Our current work in synthesizing and evaluating both preclinical and clinical studies using stem cell applications in acute MI has demonstrated that BMSc transplantation is a safe therapy for MI. Although this therapy's efficacy is not consistently proven, we have significantly improved our understanding of factors contributing to its success, such as the stem cell type, patients' baseline left ventricular ejection fraction, individual hemodynamic factors, and differential expressions of specific genes. In future investigations, researchers should focus on the cellular and individual attributes of BMSc treatment to achieve maximal efficacy and outcomes for patients receiving this therapy after acute MI.

INTRODUCTION

Myocardial infarction (MI) remains one of the most common causes of cardiovascular mortality and comorbidity in developed countries, yet its current long-term treatment options remain sparse. In 2020, the prevalence of MI was 3.0% in the United States, affecting approximately 8.4 million people, and it is suggested that 1 US resident experiences an MI almost every 40 seconds.¹ In addition to its deadly short-term effects, MI causes numerous complications that can manifest years later, such as stroke, heart failure, and hypertension, each of which has its own compounding effect on overall mortality.² To treat this disease, several therapies have been proposed. One area of intensive research in the last decade has involved regenerative medicine, specifically involving bone marrow–derived stem cells (BMSc).

BMScs are adult stem cells characterized by their harvest from bone marrow. Although adult stem cells are not totipotent-like embryonic stem cells, their multipotency and the ability to be harvested from postnatal bone marrow, blood, skeletal muscle, fat, and heart tissue support their use as treatment for MI.³ Undifferentiated BMScs, including hematopoietic stem cells and nonhematopoietic mesenchymal precursor cells that bring about mesenchymal stem cells (MSCs), are isolated through the process of density gradient centrifugation and, once isolated, are referred to as bone marrow mononuclear

cells.³ Expressing CD31, CD34, CD45, CD133, and kinase domain–related cell surface antigens, HSCs produce hematopoietic lineages. MSCs, in contrast, differentiate into adipocytes, chondroblasts, and osteoblasts.³

To understand the theoretical reasoning behind the use of BMSCs as a potential therapeutic, it is important to explain their benefits on reversing the deleterious effects of MI at the cellular level. At its core, MI causes cell death due to the blockage of blood flowing from the coronary arteries, thus causing coagulative necrosis. The current mainstay of MI therapy is reperfusion, either through thrombolytic or percutaneous intervention. Regardless of the speed at which reperfusion occurs, cellular injury is inevitable after MI. It manifests in dysfunctioning with the microvascular system, destruction of the cell sarcolemma and mitochondria, and resulting influx of inflammatory cells and mediators.⁴ Eventually, these cellular changes materialize into tangible, physiologic disturbances in heart functioning, such as arrhythmias arising from necrotic tissue; dilated, stiff, and poorly functioning atria and ventricles; and ultimately heart failure and death.⁵

While the evidence related to their ability to fuse with or transform into fully functional cardiomyocytes is still inconclusive,³ there is excitement over the ability of BMSCs to contribute to healing after MI. In a review, Michler³ reported that BMSCs secrete factors to stimulate angiogenesis after vascular disarray from MI. Moreover, BMSCs can activate preexisting cardiac progenitor cells to become new cardiomyocytes along with preventing the harmful remodeling of the heart that occurs post-MI.³ In short, the potential beneficial effects of BMSCs for patients with MI warrant further research. In the context of these cells, this review examines the preclinical evidence, safety of usage, and clinical outcomes after receiving BMSC therapy for MI.

Safety and Efficacy of Bone Marrow–Derived Stem Cell Therapy

The safety of using BMSCs as treatment following acute MI was assessed and confirmed across multiple clinical trials at multiple points following BMSC transplantation.³ The TOPCARE-AMI study, one of the first clinical trials in the arena of BMSC therapy for MI, measured patient safety through documentation of procedural complications such as ventricular arrhythmias and thrombus formation, measurements of C-reactive protein and troponin T, and telemetry of ventricular arrhythmias among other clinical events during hospitalization.⁶ Schächinger et al⁶ also assessed safety at clinical follow-ups at 4 months with coronary angiography and 12 months with 24-hour Holter monitoring. The TOPCARE-AMI clinical trial concluded that BMSC transplantation was generally well-tolerated and the process of BMSC transplantation itself did not cause any complications; the incidence of reinfarction and/or death following BMSC therapy was comparable with that associated with standard percutaneous coronary intervention (PCI); and there was no evidence of malignant ventricular arrhythmias throughout the 12 months following BMSC transplantation.⁶ The more recent PreSERVE-AMI clinical trial, which

focused on the incidence of adverse events, severe adverse events, and major adverse cardiovascular end points (MACE), corroborated the safety of BMSc therapy.⁷ Quyyumi et al⁷ demonstrated not only similar incidences of adverse events, serious adverse events, and MACEs in CD34+ BMSc therapy and control groups, but also decreasing incidence of MACEs and increasing number of days alive and not hospitalized as CD34+ BMSc dose increased.⁷

It has been hypothesized that the use of BMScs as treatment for MI fosters regeneration of cardiomyocytes and revascularization, ultimately translating to enhanced contractility and cardiac function.³ Clinical trials have measured cardiac function following BMSc transplantation with several parameters: left ventricular ejection fraction (LVEF), infarct size, mean resting total severity score, wall thickening, and wall motion, among others.⁶⁻⁹ LVEF, the quotient of stroke volume divided by end-diastolic volume, has been deemed the most representative of cardiac function across multiple clinical trials.³ While the TOPCARE-AMI and REPAIR-AMI clinical trials measured LVEF with left ventricular angiography, the BOOST and PreSERVE-AMI clinical trials, among other more recent clinical trials, relied on cardiac magnetic resonance imaging.^{3,6-9} In general, clinical trials have reported modest increases in LVEF, a key indicator of efficacy, at multiple points following BMSc transplantation.³ Differences in cellular characteristics and patient conditions affect the efficacy of BMSc therapy, making it more or less favorable as a treatment for MI in certain circumstances.

Cellular Characteristics Affecting Therapeutic Outcomes

Type of Cells Used for Transplantation

With the stem cell population harvested from human bone marrow, an increasing number of stem cell subtypes have been evaluated for efficacy in recovering myocardial tissue after myocardial infarction.¹⁰⁻¹³ Some researchers elected to harvest and culture a mixture of BMScs without selection or purification, while others chose to select for cells expressing specific markers.^{10, 13} There are also studies in which several cell subpopulations are selected and injected.^{14,15} Among the great diversity of stem cell types used, we will review 3 major categories of stem cell subpopulations that have been extensively studied: CD34+, CD133+, and MSCs.

CD34+ SUBPOPULATION

A subpopulation of BMScs expressing CD34 on their cell surface was shown to differentiate into endothelial cells and enhance revascularization of infarcted myocardial tissue in rodent models.¹⁶⁻¹⁸ Gunetti et al¹⁸ further confirmed that mice with CD34+ BMScs transplanted via intracoronary approach exhibited a more than 50% increase in LVEF 4 weeks after surgery. However, clinical trials using purified CD34+ BMScs either did not find any statistically significant increase in perfusion of infarcted areas or failed to establish a statistically significant advantage of CD34+ BMScs over standard of care.^{19,20} A more

recent randomized clinical trial attempted to better understand CD34+ BMSc behaviors by experimenting with different intracoronary cell delivery methods.²¹ That study demonstrated that regardless of delivery route, CD34+ BMScs generally exhibited low capability of cardiac regeneration because they could only be incorporated into the margins of the infarcted area.²¹ Although the researchers did not examine the long-term changes in LVEF, their conclusion revealed one possible explanation for the lack of clinical significance of CD34+ BMSc therapy in treating patients with MI.

CD133+ SUBPOPULATION

The BMSc subpopulation expressing CD133 antigen has also been shown to promote revascularization, specifically through promoting proangiogenic factor release and localizing to the site of angiogenesis.²² In vivo studies in post-MI mice models revealed that CD133+ BMSc injections could improve ejection fraction 3 weeks after transplantation compared with animals who had their infarctions untreated.²³ In a recent randomized clinical trial, patients with autologous CD133+ progenitor cells transplanted after MI benefited from improved LVEF throughout the 18-month follow-up period.²⁴ The same study also demonstrated that CD133+ cells showed superior efficacy compared with mononuclear BMSc transplantation, specifically in reducing “non-viable segment” in infarcted tissue.²⁴ Another earlier clinical study highlighted that CD133+ cell transplantation had significantly improved LVEF vs the control group with standard of care over the 4-month follow-up period.²⁵ The same study also reported an improvement in myocardial perfusion measured by a reduction in MIBI perfusion defect, which is a valid and commonly used marker for myocardial function.^{25,26}

MESENCHYMAL CELL SUBPOPULATION

MSCs harvested from bone marrow are another subpopulation of stem cells receiving attention from researchers.^{23,27} Multiple research teams demonstrated MSC transplantation’s ability to improve LVEF after MI events.^{28,29} Zhang et al²⁸ also showed that purified MSCs were superior to mononuclear stem cells and unpurified counterparts in generating vascular cells and cardiomyocytes.²⁸ In the PROMETHEUS clinical trial, patients who underwent autologous MSC injection without revascularization improved LVEF 18 months after transplantation compared with the control group, who underwent revascularization alone.¹⁰ In other clinical trials in which revascularization was performed prior to stem cell or placebo injection, bone marrow MSC transplantation was found to be advantageous over standard of care in improving LVEF after MI.^{30,31}

In summary, among the 3 bone marrow–derived stem cell subpopulations we reviewed, transplanting CD133+ hematopoietic populations and MSC subpopulations were reported to provide clinically significant improvement in patient outcome after acute MI. On the other hand, CD34+ subpopulation failed to deliver such benefits in clinical studies. However, this does not

necessarily mean that CD34+ is inferior to the other 2 subpopulations because the findings could have been complicated by factors such as the time when the studies were done. For example, most of the studies using CD34+ for acute MI were conducted more than a decade ago, when the transplantation techniques or research design may still have been immature compared with more recent counterparts.

Quantity of Cells Injected

Many clinical studies highlighted injection of insufficient amounts of cells as a primary concern.³² Part of such concern stems from the observation that the number of living stem cells within the heart after transplantation is positively correlated with preservation of LVEF clinically.^{32,33} While this finding aids in the understanding of the long-term implications of stem cell therapy for MI, the number of remaining viable cells and the number of cells injected are 2 distinct concepts. In fact, most clinical studies have rejected any correlation between the quantity of cells injected and therapeutic outcome. For example, Karantalis et al¹⁰ reported that an increased injection dosage was only positively associated with better anatomical scar reduction in myocardial tissue but not improved LVEF.¹⁰ Moreover, Schächinger et al found no association between quantity of injected cells and LVEF improvement or scar tissue reduction. A more recent study by Wollert et al³⁴ injected different amounts of BMSCs into infarcted myocardial tissue as one of their study's independent variables. They found no correlation between the quantity of cells injected and LVEF 6 months after the initial MI event.³⁴ Choudhury et al³⁵ complicated this viewpoint, adding that such correlation was observed only when cells were delivered directly to the myocardium but not via intracoronary approach.

To better understand the range of time after MI when stem cell injections are performed, we summarized reported data from several clinical studies ([Table 1](#)). Because multiple stem cell subpopulation options exist, as illustrated in the previous section, we standardized our comparison by only selecting studies that used bone marrow stem cells without further selection or purification. Additionally, we only selected studies that delivered cells through intracoronary injection. In general, the number of cells injected ranged from $\times 10^8$ to $\times 10^{10}$ cells ([Table 1](#)). Trials that showed a larger improvement in LVEF in the BMSC treatment group did not necessarily have a higher number of cells injected than their counterparts. The study that injected the most amount of cells did show a significant LVEF response compared with the placebo group, but more studies are needed to establish any trend.³⁶

In summary, both the type and quantity of BMSCs injected are important for treatment efficacy in patients with MI and serve as the foundation for the use of BMSCs in clinical trials. Based on the evidence currently available, injections of CD133+ or MSC subpopulations show the most promising results in improving patients' LVEF months after treatment. On the other hand, there is no clinical evidence suggesting any associations between the number of cells

Table 1. A summary of the number of unpurified bone marrow derived stem cells (BMSc) used for injected for each patient and the reported comparison of LVEF between experiment and control group at the end of follow-up.

Study	BMSc injected (amount)	Does BMSc application yield a greater LVEF improvement than control?
Leistner et al., (2011) ³⁷	2.38×10^8	Yes
Wollert et al., (2017) ^{a 34}	7.0×10^8	No
Wollert et al., (2017) ^{b 34}	2.06×10^9	No
Nicolau et al., (2018) ³⁸	$1,0 \times 10^8$	No
Chen et al., (2004) ³⁶	$4.8 \sim 6 \times 10^{10}$	Yes
Choudhury et al., (2017) ³⁵	1.15×10^8	Yes
Traverse et al., (2019) ³⁹	1.5×10^8	No

^a low-dose injection group ^b high-dose injection group

injected and patient outcome. However, both prior research and our review highlight that these characteristics are often confounded by multiple other variables, such as time of injection after infarction and cell delivery approach.³⁵⁻³⁷ Future clinical studies with these characteristics incorporated as independent variables in the study design and with other factors controlled will provide more insight into this topic.

Patient Characteristics Impacting Therapeutic Outcomes

There are a number of patient factors that have been correlated with better outcomes in BMSc therapy. A few of these various patient factors are discussed here.

Role of Hemodynamics

The levels of N-terminal probrain natriuretic peptides (NT-proBNP) in patients receiving BMSc therapy after acute MI followed by PCI are relevant for patient outcomes. Natriuretic peptides, especially NT-proBNP, are associated with an increased risk of mortality following MI treated with primary PCI.⁴⁰ In patients with elevated preoperative NT-proBNP and N-terminal proatrial natriuretic peptide (NT-proANP) levels, Miettinen et al⁴⁰ demonstrated that BMSc therapy will have a greater LVEF recovery compared with those with lower NT-proBNP and NT-proANP at 6 months. This may indicate that there is an improved benefit for those with more marked hemodynamic deterioration.⁴⁰

As mentioned in the introduction, microvascular dysfunction after MI is an important complication for patients and has a differential impact on those receiving BMSc transplantation. In contrast to its benefits to patients with greater hemodynamic deterioration related to natriuretic peptides levels, BMSc therapy produces more favorable outcomes for patients with less microvascular obstruction as seen in a subgroup analysis of 153 patients with large STEMI.³³ Evidently, a patient's hemodynamic status before BMSc injection has relevant implications for the patient and how they respond to the treatment.

Low Baseline LVEF

There is a wide breadth of studies that investigate how patients with decreased LV function, specifically measured by decreased LVEF, may experience more benefits from BMSc treatment than their higher LVEF counterparts.

Miettinen et al. also investigated various determinants of improvement in LVEF—including inflammatory peptides (TnI and CRP) and baseline LVEF in addition to natriuretic peptides (NT-proBNP and NT-proANP)—in its cohort.⁴⁰ From this, baseline LVEF was found to be the most important predictor of improvement in LVEF for those receiving BMSc treatment. Patients with a preoperative LVEF below the median of 62.5% had a significant improvement in LVEF following BMSc therapy, while those with LVEF above an EF of 62.5% did not.⁴⁰ In another study, 200 randomized patients received BM-derived unselected mononuclear cells or BM-derived selected CD34 CXCR4+ cells.¹⁴ After 6 months, both groups saw a significant improvement in LVEF, regardless of whether they received selected or unselected BM cells, while the control group remained unchanged. However, LVEF was only seen in patients with LVEF below the median of 37%. This study demonstrated that baseline LVEF, once again, was the only patient-related variable that predicted LVEF improvement in patients treated with BMScs. Moreover, Schächinger et al.⁸ had the same finding: patients with a preoperative LVEF below the median (48.9% in this cohort) saw a significant absolute improvement in LVEF that was 5% greater than that of patients whose baseline LVEF was above the median.

When considered together, these studies demonstrate how low baseline LVEF predicts LVEF improvement even between cohorts with different medians.

Preoperative Characteristics of Responders vs Nonresponders

Of particular concern for BMSc therapies are mutations that may impact the well-organized system of hematopoiesis and thus the proliferative and differentiative capabilities of BM-derived stem cells.

With the phase 3 PERFECT trial, Wolfien et al.¹³ used machine learning clustering analysis to compare gene expression in patients with significantly improved LVEF, which they termed *responders*, and those without improvement, or *nonresponders*. For example, *SH2B3/LNK* plays a role in cardiovascular regeneration, although the mechanism, downstream targets, and regulatory role have yet to be fully elucidated.¹³ Not only did their research data suggest distinct profiles between responders and nonresponders for preoperative *SH2B3* gene expression, but also the researchers managed to predict whether a patient would respond positively to BMSc injection with more than 90% accuracy.¹³ The same study also found that other pathways that differentiate responders from nonresponders included proliferation control,

inflammation, and platelet-activating factor synthesis. More research in this area can help better determine the role, if any, that preoperative gene expression signatures may have on outcomes in BMSc therapy.

In an earlier phase of the same clinical trial, Steinhoff et al⁴¹ investigated laboratory parameters and biomarkers that allowed the prediction of responders and nonresponders to BMSc treatment. Predicted responders were characterized by increased endothelial progenitor cells, while nonresponders were characterized by higher levels of erythropoietin and vascular endothelial growth factor. This research may be able to offer potential screening and play an important role in decision-making for clinicians and patients alike when pursuing BMSc therapy after MI.

Crucial to determining the efficacy of BMSc treatment, these patient factors contribute to the understanding that personalized medicine is based on targeted therapeutic treatments that focus on patient-specific characteristics to provide the highest quality of therapy while reducing the risk of adverse effects and the costs of ineffective interventions.

DISCUSSION

Myocardial infarction remains one of the deadliest diseases affecting people worldwide, and accordingly, both the pathophysiology and therapy of MI are subjects of intensive investigation.¹ Since their discovery, BMScs have generated a great deal of excitement over their promise for MI.²¹ Numerous studies, including in-vitro, in-vivo, and large-scale clinical trials, have and are continuing to be conducted to test the limits of this novel treatment.^{8,42,43} At this important cross-section in the field, a few trends and possible future directions can be consistently observed. What is most clear is that the use of BMScs has safely translated from the bench to live, human patients because numerous clinical trials have illustrated and confirmed this notion.^{6,7} Despite the evident safety of BMSc therapy, it has demonstrated only modest efficacy in general, especially in attempts to differentiate these cells into new cardiomyocytes of sufficient caliber.³

Specific characteristics of cells injected seem to impact the therapeutic outcomes. Among the most extensively researched cell subpopulations, CD133+ BMScs and MSCs are 2 types that have shown promising results clinically.^{24,25,30,31} Regarding the quantity of cells injected, neither analysis from current literature nor qualitative summary from our review showed any correlation between the number of stem cells injected and long-term improvement in LVEF³⁴ (Table).

In regard to patient-related factors, baseline LVEF is the most heavily studied and consistent predictor of outcomes, specifically LVEF recovery, following BMSc therapy in patients with MI. However, these studies did not include its impact on mortality.^{8,14,40} Although not as thoroughly investigated, other researchers have explored the role that hemodynamics and preoperative

characteristics play in this field. Regarding hemodynamics, patients with high preoperative natriuretic peptide levels were positively correlated with experiencing better LVEF improvement,⁴⁰ while the presence of microvascular obstruction after reperfusion was negatively associated with LVEF improvement.³⁴ Other studies have used various biomarkers, gene expression levels, and laboratory parameters to characterize patients who do and do not respond well to BMSc injection following MI.^{13,41}

Moving forward, the focus of new research should keep these shortcomings in mind and better understand the roles that cellular and patient characteristics may have on the recovery of cardiovascular function on an individual basis to determine whether BMScs are a suitable alternative to the many other therapeutic options available for patients with MI.

CONCLUSION

As the safety of BMSc therapy for MI has been established, future research should address the mechanisms behind differential response of animal models and patients to such therapy. Growing our understanding of cellular characteristics, such as cell types, injection techniques, and injection quantity, as well as patient characteristics including hemodynamic factors and genetic variations, would be particularly beneficial. Such knowledge, when combined with clinical evidence, could help accomplish better therapeutic precision of BMSc applications in MI.

Conflict of Interest

The authors have no relevant disclosures or conflicts of interests related to this work.

Author Contributions

All authors contributed equally to this work.

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