Policy

I. Aetna considers autologous skeletal myoblast transplantation experimental and investigational for members with heart failure and for all other cardiac diseases because its effectiveness has not been established.

II. Aetna considers autologous intra-coronary mononuclear bone marrow cell transplantation or intra-coronary administration of cardiosphere-derived cells experimental and investigational for members with myocardial infarction and for all other cardiac diseases (e.g., chronic heart failure) because its effectiveness for these indications has not been established.

III. Aetna considers autologous or allogeneic bone marrow-derived mesenchymal stem cell transplantation experimental and investigational for ischemic cardiomyopathy and for all other cardiac diseases (e.g.,
heart failure), chronic kidney disease, diabetes, neuropathic pain and traumatic brain injury because its effectiveness for these indications has not been established.

IV. Aetna considers autologous intra-arterial or intra-muscular mononuclear bone marrow cell transplantation experimental and investigational for members with peripheral arterial disease and other occlusive conditions/diseases (e.g., atherosclerosis obliterans, Buerger disease, critical limb ischemia, and thromboangiitis obliterans) because its effectiveness for these indications has not been established.

Background
Cardiac Diseases:

Coronary heart disease is currently the principal cause of death in the United States. In 1997, 1.1 million Americans were diagnosed with acute myocardial infarction (MI), and 800,000 patients underwent coronary re-vascularization. In patients with MI, scar tissue develops in the area of infarction resulting in a decrease in cardiac contractility. This damage is irreversible and can result in heart failure since cardiac cells can not repair themselves.

There are a variety of cellular and molecular approaches to strengthening the damaged heart, focusing on strategies to replace dysfunctional, necrotic, or apoptotic cardiac cells with new ones of mesodermal origin. A wide range of cell types such as myogenic cell lines, immortalized atrial cells, embryonic and adult cardiomyocytes, embryonic stem cells, tetratoma cells, genetically altered fibroblasts, smooth muscle cells, bone marrow-derived cells, and adult skeletal myoblasts have all been proposed as useful cells in cardiac repair and may have the capacity to perform cardiac work.

Intra-myocardial skeletal muscle transplantation has been demonstrated to improve cardiac function in chronic heart failure models by regenerating muscle. Under local anesthesia,
a muscle biopsy is carried out to collect skeletal cells for culturing. After about 14 days, the cultured myoblasts can be implanted into the post-MI scar during coronary artery bypass grafting of remote myocardial areas. It is hypothesized that the transplanted autologous myoblasts will aid in repairing the injured area and improving cardiac contractility. However, the safety and effectiveness of this procedure has yet to be established by randomized controlled trials (RCTs).

In a pilot study, Smits et al (2003) reported on the procedural and 6-month results of the first percutaneous and stand-alone study (n = 5) on myocardial repair with autologous skeletal myoblasts. All cell transplantation procedures were uneventful, and no serious adverse events occurred during follow-up. One patient received an implantable cardioverter-defibrillator (ICD) after transplantation because of asymptomatic runs of non-sustained ventricular tachycardia. Compared with baseline, the left ventricular ejection fraction (LVEF) increased from 36 +/- 11 % to 41 +/- 9 % (3 months, p = 0.009) and 45 +/- 8 % (6 months, p = 0.23). Regional wall analysis by magnetic resonance imaging (MRI) showed significantly increased wall thickening at the target areas and less wall thickening in remote areas (wall thickening at target areas versus 3 months follow-up: 0.9 +/- 2.3 mm versus 1.8 +/- 2.4 mm, p = 0.008).

The authors concluded that this pilot study was the first to demonstrate the potential and feasibility of percutaneous skeletal myoblast delivery as a stand-alone procedure for myocardial repair in patients with post-MI heart failure. They stated that more data are needed to confirm its safety.

Ince et al (2004) stated that transcatheter transplantation of autologous skeletal myoblasts for severe left ventricular dysfunction in post-MI patients is feasible, safe, and promising. These authors further stated that scrutiny with randomized, double-blinded, multi-center trials appears warranted. This is in agreement with the observation of Siminiak et al (2004) who stated that autologous skeletal myoblast transplantation for the treatment of post-MI heart failure is feasible, and that further research is needed to validate this method in a clinical practice.
Lainscak and colleagues (2010) presented findings and a commentary on late-breaking trials presented during the meeting of the Heart Failure Society of America in September 2009. The MARVEL-1 trial raises further concerns about the safety of myoblast transplantation in ischemic heart failure.

In a phase IIa, randomized, open-label trial, Duckers and colleagues (2011) evaluated the percutaneous intra-myocardial transplantation of autologous skeletal myoblasts in congestive heart failure patients with ICDs. Patients were randomized 2:1 to autologous skeletal myoblast therapy versus optimal medical treatment. The primary safety end-point was defined as the incidence of procedural and device related serious adverse events, whereas the efficacy endpoints were defined as the change in global LVEF by multi-gated acquisition (MUGA) scan, change in New York heart Association (NYHA) classification of heart failure and in the distance achieved during a 6-min walk test (6MW) at 6-month follow-up. A total of 40 subjects were randomized to the treatment arm (n = 26), or to the control arm (n = 14). There were 12 sustained arrhythmic events and 1 death after episodes of ventricular tachycardia (VT) in the treatment group and 14 events in the control group (p = non-significant). At 6-month follow-up, 6MW distance improved by 60.3 +/- 54.1 meters in the treated group as compared to no improvement in the control group (0.4 +/- 185.7 meters; p = non-significant). In the control group, 28.6 % experienced worsening of heart failure status (4/14), while 14.3 % experienced an improvement in NYHA classification (2/14). In the myoblast-treatment arm, 1 patient experienced a deterioration in NYHA classification (8.0 %), whereas 5 patients improved 1 or 2 classes (20.0 %; p = 0.06). However, therapy did not improve global LVEF measured by MUGA at 6-month follow-up. The authors concluded that these data indicate that implantation of myoblasts in patients with heart failure is feasible, appears to be safe and may provide symptomatic relief, though no significant effect was detected on global LVEF.

Injury to a target organ is sensed by distant stem cells, which migrate to the site of damage and undergo alternate stem cell
differentiation. These events promote structural and functional repair. This high degree of stem cell plasticity led researchers to investigate if dead myocardium could be restored by transplanting bone marrow cells. Investigators have demonstrated that multi-potent adult bone marrow hematopoietic stem cells and mesenchymal stem cells can re-populate infarcted rodent myocardium and differentiate into both cardiomyocytes and new blood vessels. A recent study (Strauer et al, 2002) reported that autologous intracoronary mononuclear bone marrow cell (BMC) transplantation is safe and appears to improve cardiac function and myocardial perfusion in patients after acute MI (n = 10). However, the authors concluded that further experimental studies, controlled prospective clinical trials, and variations of cell preparations are needed to determine the role of this new procedure for the treatment of patients after acute MI.

Wollert et al (2004) reported that injection of autologous bone marrow stem cells into the coronary arteries improved heart function in patients (n = 60) who have suffered a MI. Patients who had undergone successful percutaneous coronary intervention (PCI) were randomized to receive bone marrow stem-cell transfer, injected into the artery supplying the damaged area of the heart, 5 days after PCI or optimal conventional therapy. After 6 months, improved recovery of LVEF was more evident in patients who received stem-cell transfer therapy than in patients treated with standard post-MI medical care. Mean global LVEF increased by 7 % in the stem-cell transfer group compared with 0.7 % in the medical group. The improvement was still evident 6 months after the treatment. The authors suggested that autologous BMC can be used to enhance left ventricular functional recovery in patients after acute MI. However, larger trials are needed to address the effect of BMC transfer on clinical endpoints such as the incidence of heart failure and survival.

In a pilot study (n = 4), Obradovic et al (2004) reported that transplantation of bone marrow-derived progenitor cells into the infarcted area (3 to 5 days after infarct) was safe, and
feasible, and might improve myocardial function. Follow-up period for these patients ranged from 30 to 120 days after infarct. These investigators also concluded that further follow-up will show whether this treatment is effective in preventing negative remodeling of the left ventricle and reveal potential late adverse event (arrhythmogenicity and propensity for restenosis). In another pilot study (n = 5), Kuethe et al (2005) reported that intra-coronary transplantation of autologous, mononuclear BMC did not lead to any significant improvement in myocardial function and physical performance of patients with chronic ischemic heart disease at 12-month follow-up.

Strauer et al (2005) treated 18 consecutive patients with chronic MI (5 months to 8.5 years old) by the intra-coronary transplantation of autologous mononuclear BMC and compared them with a representative control group without cell therapy. After 3 months, infarct size was reduced by 30 % and global LVEF (+15 %) and infarction wall movement velocity (+57 %) increased significantly in the transplantation group, while no significant changes were observed in infarct size, LVEF, or wall movement velocity of infarcted area in the control group. Percutaneous transluminal coronary angioplasty alone had no effect on left ventricular function. After BMC transplantation, there was an improvement of maximum oxygen uptake (VO2max, +11 %) and of regional 18F-fluor-deoxy-glucose uptake into infarct tissue (+15 %). The authors concluded that these results demonstrate that functional and metabolic regeneration of infarcted and chronically avital tissue can be realized in humans by mononuclear BMC transplantation. Moreover, these investigators as well as an accompanying editorial (Bolli et al, 2005) noted that these preliminary findings need to be validated by future studies, especially large, prospective, randomized trial.

Hendriks et al (2006) evaluated the hypothesis that direct intra-myocardial injection of autologous mononuclear BMC during coronary artery bypass graft (CABG) could improve global and regional LVEF at 4-month follow-up. A total of 20 patients (3
women and 17 men; mean age of 64.8 +/- 8.7 years) with a post-MI non-viable scar, as assessed by thallium (Tl) scintigraphy and cardiac magnetic resonance imaging (MRI), scheduled for elective CABG, were included. They were randomized to either a control group (n = 10, CABG only) or a BMC group (CABG and injection of 60.10(6) +/- 31.10(6) BMC). Primary end points were global LVEF change and wall thickening changes in the infarct area from baseline to 4-month follow-up, as measured by MRI. Changes in metabolic activity were measured by Tl scintigraphy and expressed as a score with a range from 0 to 4, corresponding to percent of maximal myocardial Tl uptake (4 indicates less than 50 %, non-viable scar; 3, 50 % to 60 %; 2, 60 % to 70 %; 1, 70 % to 80 %; 0 greater than 80 %). Global LVEF at baseline was 39.5 +/- 5.5 % in controls and 42.9 +/- 10.3 % in the BMC group (p = 0.38). At 4 months, LVEF had increased to 43.1 +/- 10.9 % in the control group and to 48.9 +/- 9.5 % in the BMC group (p = 0.23). Systolic thickening had improved from -0.6 +/- 1.3 mm at baseline to 1.8 +/- 2.6 mm at 4 months in the cell-implanted scars, whereas non-treated scars remained largely akinetic (-0.5 +/- 2.0 mm at baseline compared with 0.4 +/- 1.7 mm at 4 months, p = 0.007 control versus BMC-treated group at 4 months). Defect score decreased from 4 to 3.3 +/- 0.9 in the BMC group and to 3.7 +/- 0.4 in the control group (p = 0.18). The authors concluded that at 4 months, there was no significant difference in global LVEF between both groups, but a recovery of regional contractile function in previously non-viable scar was observed in the BMC group. The improved contractility observed in this study was contradictory to that observed by Ryabov et al (2006) who reported their findings of cardiac contractility after transplantation of autologous BMC in patients with MI. Autologous BMC were transplanted by intra-coronary infusion to patients with MI after recovery of coronary perfusion. Controls received traditional therapy alone. Echocardiography was carried out before and 3 and 6 months after cell therapy. Cell transplantation did not appreciably improved left ventricular contractility in comparison with the control group. Moreover, cell therapy did not provoke malignant ventricular arrhythmias in any subjects. The authors
concluded that intra-coronary infusion of BMC in patients with
MI did not improve cardiac contractility and did not aggravate
the course of the disease.

In a RCT, Lunde et al (2006) examined the effects of intra-
coronary injection of autologous BMC in the acute phase of MI.
Patients with acute ST-elevation MI of the anterior wall treated
with PCI were randomly assigned to the group that underwent
intracoronary injection of autologous BMC or to the control
group, in which neither aspiration nor sham injection was
performed. Left ventricular function was assessed with the use
of electrocardiogram-gated single-photon-emission computed
tomography (SPECT) and echocardiography at baseline and MRI
2 to 3 weeks after the infarction. These procedures were
repeated 6 months after the infarction. End points were
changes in the LVEF, end-diastolic volume, and infarct size. Of
the 50 patients assigned to treatment with BMC, 47 underwent
intra-coronary injection of the cells at a median of 6 days after
MI. There were 50 patients in the control group. The mean (+/-
SD) change in LVEF, measured with the use of SPECT, between
baseline and 6 months after infarction for all patients was 7.6
+/- 10.4 percentage points. The effect of BMC treatment on the
change in LVEF was an increase of 0.6 percentage point (95 %
confidence interval [CI]: -3.4 to 4.6; p = 0.77) on SPECT, an
increase of 0.6 percentage point (95 % CI: -2.6 to 3.8; p = 0.70)
on echocardiography, and a decrease of 3.0 percentage points
(95 % CI: 0.1 to -6.1; p = 0.054) on MRI. The 2 groups did not
differ significantly in changes in left ventricular end-diastolic
volume or infarct size and had similar rates of adverse events.
The authors concluded that intra-coronary injection of
autologous BMC had no effects on global left ventricular
function.

Lyon and Harding (2007) stated that cardiac failure is
characterized by the loss of cardiomyocytes, and several
approaches to replace the lost cell mass are being developed.
Animal models have demonstrated the therapeutic potential of
several cell types, and both autologous skeletal myoblasts and
BMC have been examined in preliminary clinical trials.
However functional improvements have been modest and the mechanism of benefit is unclear, although myocardial regeneration is not a significant factor. Alternative strategies using autologous resident cardiac progenitor cells or embryonic stem cell-derived cardiomyocytes could recreate de novo myocardium with higher efficiency, although various hurdles must be overcome before these strategies are translated to the clinic.

Zenovich et al (2007) noted that within the past 5 years, skeletal myoblasts (SKMBs) and bone marrow (or blood)-derived mononuclear cells (BMNCs) have demonstrated pre-clinical efficacy in reducing ischemia and salvaging already injured myocardium, and in preventing left ventricular remodeling, respectively. These findings have been translated into clinical trials, so far totaling over 200 patients for SKMBs and over 800 patients for BMNCs. These safety/feasibility and early phase II studies showed promising but somewhat conflicting symptomatic and functional improvements, and some safety concerns have arisen. However, the patient population, cell type, dose, time and mode of delivery, and outcome measures differed, making comparisons of the 2 approaches problematic. In addition, the mechanisms through which cells engraft and deliver their beneficial effects remain to be fully elucidated. The authors stated that it is time now to critically evaluate progress made and challenges encountered in order to select not only the most suitable cells for cardiac repair but also to define appropriate patient populations and outcome measures.

Menasche and colleagues (2008) stated that phase I clinical trials have demonstrated the feasibility of implanting autologous SKMBs in post-infarction scars. However, they have failed to ascertain if this procedure was functionally effective and arrhythmogenic. In a multi-center, randomized, placebo-controlled, double-blind study, these researchers examined the effect of SKMBs transplantation in patients with left ventricular dysfunction (LVEF less than or equal to 35 %), MI, and were indicated for coronary surgery. Each patient received either
cells grown from a skeletal muscle biopsy or a placebo solution injected in and around the scar. All patients received an ICD. The primary efficacy end points were the 6-month changes in global and regional LV function assessed by echocardiography. The safety end points comprised a composite index of major cardiac adverse events and ventricular arrhythmias. A total of 97 patients received myoblasts (400 or 800 million; n = 33 and n = 34, respectively) or the placebo (n = 30). Myoblast transfer did not improve regional or global LV function beyond that seen in control patients. The absolute change in ejection fraction (median [inter-quartile range]) between 6 months and baseline was 4.4 % (0.2; 7.3), 3.4 % (-0.3; 12.4), and 5.2 % (-4.4; 11.0) in the placebo, low-dose, and high-dose groups, respectively (p = 0.95). However, the high-dose cell group reported a significant decrease in LV volumes compared with the placebo group. Despite a higher number of arrhythmic events in the myoblast-treated patients, the 6-month rates of major cardiac adverse events and of ventricular arrhythmias did not differ significantly between the pooled treatment and placebo groups. The authors concluded that SKMB injections combined with coronary surgery in patients with depressed LV function failed to improve echocardiographic heart function. The increased number of early post-operative arrhythmic events after myoblast transplantation, as well as the capability of high-dose injections to revert LV remodeling, warrants further investigation.

An assessment by the BlueCross BlueShield Association Technology Evaluation Center (2008) concluded that the evidence is insufficient to permit conclusions with adequate confidence on the effect of progenitor cell therapy on clinical outcomes for patients with ischemic heart disease. The report stated that, while the available evidence suggests a potential benefit on both physiologic and clinical outcomes, the limited amount of clinical outcome evidence combined with uncertainties in the patient populations, mechanism of action, and treatment delivery decreases the confidence of conclusions that can be drawn from this evidence.
An assessment by the Andalusian Agency for Health Technology Assessment (Cuadros Celorrio, et al., 2007) stated that several studies have demonstrated that the infusion of stem cells in patients with cardiac ischemia moderately improves the left ventricular function, although the number of patients, the heterogeneity of the trials, and the duration of follow-up have not allowed a relationship to be made to a reduction of mortality and morbidity.

In a randomized, double-blind, placebo-controlled study, van Ramshorst and colleagues (2009) examined the effects of intra-myocardial BMC injection for chronic myocardial ischemia. A total of 50 patients (mean age of 64 years) who had severe angina pectoris despite optimal medical therapy and myocardial ischemia were included in the trial. All patients were ineligible for conventional re-vascularization. Subjects received intra-myocardial injection of 100 x 10^6 autologous mononuclear BMC or placebo solution. Outcomes measures included the summed stress score, a 17-segment score for stress myocardial perfusion assessed by Tc-99m tetrofosmin single-photon emission computed tomography, LVEF, Canadian Cardiovascular Society (CCS) class, and Seattle Angina Questionnaire quality-of-life score (mean difference greater than 5 % considered clinically significant). After 3-month follow-up, the summed stress score (mean improved from 23.5 to 20.1 (p < 0.001) in the BMC group, compared with a decrease from 24.8 to 23.7 (p = 0.004) in the placebo group. In the BMC-treated patients who underwent MRI, a 3 % absolute increase in LVEF was observed at 3 months (95 % CI: 0.5 % to 4.7 %; n = 18), but the placebo group showed no improvement. Canadian Cardiovascular Society angina score improved significantly in the BMC group (6-month absolute difference, -0.79; 95 % CI: -1.10 to -0.48; p < 0.001) compared with no significant improvement in the placebo group. Quality-of-life score increased from 56 % to 64 % at 3 months and 69 % at 6 months in BMC-treated patients, compared with a smaller increase in the placebo group from 57 % to 61 % to 64 %. The improvements in CCS class and quality of life score were significantly greater in BMC-treated patients than in placebo-
treated patients (p = 0.03 and p = 0.04, respectively). The authors concluded that in this short-term study of patients with chronic myocardial ischemia refractory to medical treatment, intra-myocardial BMC injection resulted in a statistically significant but modest improvement in myocardial perfusion compared with placebo. They stated that further studies are needed to evaluate long-term results and effectiveness for mortality and morbidity.

Yousef and colleagues (2009) examined the quantitative amount of improvement of ventricular hemodynamic status, geometry, and contractility as well as the long-term clinical outcome of BMC-treated patients after acute myocardial infarction (AMI). A total of 62 patients underwent intracoronary autologous BMC transplantation 7 +/- 2 days after AMI. Cells were infused directly into the infarct-related artery. The control group consisted of 62 patients with comparable LVEF and diagnosis. All patients had several examinations (e.g., coronary angiography, right heart catheterization, biplane left ventriculography, electrocardiogram [ECG] at rest and exercise, echocardiography, late potential [LP], heart rate variability [HRV], and 24-h Holter ECG). The therapeutic follow-up was performed 3, 12, and 60 months after BMC therapy. Three months after BMC therapy, there was significant improvement of EF and stroke volume index. The infarct size was significantly reduced by 8%. Contraction velocities (lengths/second, volumes/second) increased significantly and the slope of the ventricular function curve (systolic pressure/end-systolic volume) became steeper. There was significant improvement of contractility in the infarct zone, as evidenced by a 31% increase of LV velocity of shortening (VCF), preferably in the border zone of the infarct zone. In contrast, the non-infarcted area showed no difference in VCF before and after BMC therapy. Furthermore, decreases of abnormal HRV, LP, and ectopic beats were documented after BMC therapy. Twelve and 60 months after BMC therapy, the parameters of contractility, hemodynamic status, and geometry of the LV were stable. The exercise capacity of treated patients was significantly augmented, and the mortality was significantly reduced in
comparison with the control group. The authors concluded that BMC therapy leads to significant and longstanding improvements of LV performance as well as quality of life and mortality of patients after AMI. After BMC therapy, no side effects were observed, showing that BMC therapy is safe. Moreover, these researchers noted that because of the relatively small sample size of this trial, further studies with greater sample size are needed to confirm the findings of the present study and to ascertain if cell biological and molecular mechanisms are responsible for heart muscle repair as well as to clarify which is the ideal mode of cell preparation technique and application.

In an editorial that accompanied the afore-mentioned article, Forrester and associates (2009) stated that while the findings by Yousef et al showed that the procedure is safe and offers a small long-term improvement in cardiac function, there is little evidence that it has achieved either the biologic goal of regenerating new myocardium or the clinical goal of efficacy sufficient to justify widespread use.

In a randomized, double-blind, placebo-controlled, dose-escalation (0.5, 1.6, and 5 million cells/kg body weight) study, Hare and colleagues (2009) examined the safety and effectiveness of intravenous allogeneic human mesenchymal stem cells (hMSCs) in re-perfused MI patients (n = 53). The primary end point was incidence of treatment-emergent adverse events within 6 months. Left ventricular ejection fraction and volumes determined by echocardiography and MRI were exploratory efficacy end points. Adverse event rates were similar between the hMSC-treated (5.3 per patient) and placebo-treated (7.0 per patient) groups, and renal, hepatic, and hematologic laboratory indexes were not different. Ambulatory electrocardiogram monitoring demonstrated reduced ventricular tachycardia episodes (p = 0.025), and pulmonary function testing demonstrated improved forced expiratory volume in 1 s (p = 0.003) in the hMSC-treated patients. Global symptom score in all patients (p = 0.027) and ejection fraction in the important subset of anterior MI patients
were both significantly better in hMSCs versus placebo subjects. In the cardiac MRI substudy, hMSC treatment, but not placebo, increased LVEF and led to reverse remodeling. The authors concluded that intravenous allogeneic hMSCs are safe in patients after acute MI. Furthermore, they stated that these findings support the conduct of more extensive studies assessing the value of allogeneic hMSCs for the treatment of cardiovascular disorders.

In a RCT, Beitnes et al (2009) examined the long-term safety and effectiveness after intracoronary injection of autologous mononuclear bone marrow cells (mBMCs) in AMI. A total of 100 patients with anterior wall ST-elevation MI treated with acute PCI were randomized to receive intracoronary injection of mBMCs (n = 50) or not (n = 50). Main outcome measures were change in LVEF (primary); changes in exercise capacity (peak VO(2)) and quality of life (secondary). The rates of adverse clinical events in the groups were low and equal. There were no significant differences between groups in change of global LV systolic function by echocardiography or MRI during the follow-up. On exercise testing, the mBMC-treated patients had larger improvement in exercise time from 2 to 3 weeks to 3 years (1.5 minutes versus 0.6 minutes, p = 0.05), but the change in peak oxygen consumption did not differ (3.0 ml/kg/min versus 3.1 ml/kg/min, p = 0.75). The authors concluded that the findings of this study indicate that intracoronary mBMC treatment in AMI is safe in the long-term. A small improvement in exercise time in the mBMC group was found, but no other effects of treatment could be identified 3 years after cell therapy.

Singh et al (2009) analyzed data from clinical studies of intracoronary stem cell infusion in a meta-analysis to investigate if intracoronary stem cell therapy was effective in improving left ventricular systolic function in patients after acute myocardial infarction. A total of 7 randomized controlled trials meeting the inclusion criteria were identified by a systematic literature search. Primary endpoint was change in global left ventricular ejection fraction (LVEF) baseline to
follow-up (ranging between 3 to 6 months). The meta-analysis consisted of 516 patients (bone marrow cell group, 256; control group, 260). The authors found no significant differences in patient characteristics between the bone marrow cell (BMC) treatment and control groups at baseline. Compared to the control group, patients in the BMC treatment group had significantly greater increase in LVEF from baseline to follow-up (mean difference: 6.108 %; 95 % confidence interval [CI]: 2.672 % to 9.543 %; p < 0.001). The authors concluded that this meta-analysis suggests that intracoronary bone marrow stem cell infusion may be effective in improving left ventricular systolic function in patients after acute myocardial infarction. A critique of the systematic evidence review by Singh et al by the Centre for Reviews and Dissemination (CRD, 2009) stated that In view of problems in the review by Singh et al including the small amount of evidence available and heterogeneity between the studies, the conclusions of Singh et al should be interpreted with a degree of caution. The CRD stated that it was unclear whether Singh et al took steps to minimize the risk of reviewer bias and error, such as having more than one reviewer independently select studies, assess validity and extract data. The CRD also questioned whether optimum methods were used by Singh et al to combine the studies; calculation of a weighted mean difference may have been more appropriate than standard mean difference, since all studies apparently used the same unit of measurement. The CRD critique stated that, although heterogeneity was formally assessed and was explored in the text of the systematic review by Singh et al, it was not adequately addressed; the CRD stated that the marked variability evident from scanning the forest plots suggests that the pooling of data was not justified. Consequently, the pooled effect estimates appear unlikely to be reliable. The CRD concluded that, in view of problems in the review by Singh et al, including the small amount of evidence available and heterogeneity between the studies, Singh et al’s conclusions should be interpreted with a degree of caution.

In a double-blind, randomized, placebo-controlled trial, Wohrle and colleagues (2010) evaluated the effect of autologous BMC
therapy in patients with AMI. Patients with re-perfusion greater than 6 hours after symptom onset were randomly assigned in a 2:1 ratio to receive intracoronary BMC or placebo therapy 5 to 7 days after symptom onset. Patients were stratified according to age, AMI localization, and LV function. Double-blinding was ensured using autologous erythrocytes for the placebo preparation that was visually indistinguishable from the active treatment. Serial cardiac MRI studies were performed before study therapy and after 1, 3, and 6 months. The primary end point was the difference in the LVEF from baseline to 6 months. The secondary end points included changes in the LV end-diastolic and end-systolic volume indexes and infarct size. A total of 42 patients were enrolled (29 in the BMC group and 13 in the placebo group) in the integrated pilot phase. A mean of 381 x 10(6) mononuclear BMCs were administered. The baseline clinical and cardiac MRI parameters did not differ. Compared to baseline, the difference in LVEF for the placebo group versus BMC group was 1.7 +/- 6.4 % versus -0.9 +/- 5.5 % at 1 month, 3.1 +/- 6.0 % versus 1.9 +/- 4.3 % at 3 months, and 5.7 +/- 8.4 % versus 1.8 +/- 5.3 % at 6 months (primary end point; not significant). No difference was found in the secondary end points between the 2 groups, including changes in infarct size or LV end-diastolic and end-systolic volume indexes. The authors concluded the findings of this double-blind, randomized, placebo-controlled trial did not provide evidence for a positive effect for intracoronary BMC versus placebo therapy with respect to LVEF, LV volume indexes, or infarct size.

Blatt et al (2010) evaluated the long-term outcome of intracoronary autologous BMC administration in patients with stable severe ischemic cardiomyopathy who were not suitable for re-vascularization. These investigators enrolled 8 consecutive patients with ischemic cardiomyopathy: all were in NYHA functional class III-IV despite optimal medical treatment. Dobutamine stress echocardiography showed that all had LVEF less than 35 % with significant viability or ischemia, or both, in at least 2 myocardial segments. Based on coronary anatomy none of the patients was suitable for
re-vascularization. Bone marrow was obtained and the cells were injected into all patent conduits after a brief balloon occlusion at a normal coronary segment. Clinical follow-up was performed periodically at the heart failure clinic, and included electrocardiography, laboratory tests and echocardiography. During 5 years follow-up there were 2 deaths: one due to leukocytoclastic vasculitis 21 months after intracoronary BMC infusion, and the second patient died suddenly in sleep 30 months following the transplant. The other 6 patients are alive, 2 of them without any cardiovascular or clinical events. No significant change in systolic and diastolic function was observed on echocardiography. The authors concluded that despite the small and selected patient group, these long-term follow-up data showed a promising outcome for this population of patients suffering from severe cardiac disease. Moreover, they stated that longer follow-up of a much larger group is needed.

In a phase I clinical trial, Traverse and associates (2010) examined the effects of BMC administration in patients following ST-elevation myocardial infarction (STEMI) on recovery of LV function using cardiac MRI. A total of 40 patients with moderate-to-large anterior STEMI were randomized to 100 million intracoronary BMCs versus placebo 3 to 10 days following successful PCI (primary angioplasty and stenting) of the left anterior descending coronary artery. Administration of BMC was safely performed in a high-risk cohort with minimal major adverse clinical event rates, and all patients remain alive to date. Left ventricular ejection fraction increased from 49.0 % +/- 9.5 % at baseline to 55.2 % +/- 9.8 % at 6 months by cardiac MRI in the BMC group (p < 0.05), which was not different from the increase in the placebo group (48.6 % +/- 8.5 % to 57.0 % +/- 13.4 %, p < 0.05). Left ventricular end-diastolic volume decreased by 4 ml/m(2) in the BMC group at 6 months but increased significantly in the placebo group (17 ml/m(2), p < 0.01). The authors concluded that this phase I study confirms the ongoing safety profile of BMC administration in patients following STEMI. The improvement in LVEF at 6 months by cardiac MRI in the cell therapy group was not different than the
Hopp et al (2011) explored global and regional myocardial function after intracoronary injection of autologous mononuclear BMC in acute anterior wall myocardial infarction treated with PCI. Cardiovascular magnetic resonance (CMR) tagging was performed 2 to 3 weeks and 6 months after revascularization in 15 patients treated with intracoronary stem cell injection (mBMC group) and in 13 controls without sham injection. Global and regional left ventricular (LV) strain and LV twist were correlated to cine CMR and late gadolinium enhancement (LGE). In the control group, myocardial function as measured by strain improved for the global LV (6 months: -13.1 +/- 2.4 % versus 2 to 3 weeks: -11.9 +/- 3.4 %, p = 0.014) and for the infarct zone (-11.8 +/- 3.0 % versus -9.3 +/- 4.1 %, p = 0.001), and significantly more than in the mBMC group (inter-group p = 0.027 for global strain, respectively p = 0.009 for infarct zone strain). Left ventricular infarct mass decreased (35.7 +/- 20.4 versus 45.7 +/- 29.5 g, p = 0.024), also significantly more pronounced than the mBMC group (inter-group p = 0.034). Left ventricular twist was initially low and remained unchanged irrespective of therapy. The authors concluded that LGE and strain findings quite similarly demonstrate subtle differences between the mBMC and control groups. However, intracoronary injection of autologous mononuclear BMC did not strengthen regional or global myocardial function in this substudy.

Traverse et al (2011) examined if intra-coronary delivery of autologous BMCs improves global and regional LV function when delivered 2 to 3 weeks following first MI. This was a randomized, double-blind, placebo-controlled trial (LateTIME) of the National Heart, Lung, and Blood Institute-sponsored Cardiovascular Cell Therapy Research Network of 87 patients with significant LV dysfunction (LVEF less than or equal to 45 %) following successful primary PCI between July 8, 2008, and February 28, 2011. Intra-coronary infusion of 150 x 10^6 autologous BMCs (total nucleated cells) or placebo (BMC:placebo, 2:1) was performed within 12 hours of bone
march aspiration after local automated cell processing. Main outcome measure was changes in global (LVEF) and regional (wall motion) LV function in the infarct and border zone between baseline and 6 months, measured by cardiac MRI. Secondary end points included changes in LV volumes and infarct size. A total of 87 patients were randomized (mean [SD] age of 57 [11] years; 83 % men). Harvesting, processing, and intra-coronary delivery of BMCs in this setting was feasible. Change between baseline and 6 months in the BMC group versus placebo for mean LVEF (48.7 % to 49.2 % versus 45.3 % to 48.8 %; between-group mean difference, -3.00; 95 % CI: -7.05 to 0.95), wall motion in the infarct zone (6.2 to 6.5 mm versus 4.9 to 5.9 mm; between-group mean difference, -0.70; 95 % CI: -2.78 to 1.34), and wall motion in the border zone (16.0 to 16.6 mm versus 16.1 to 19.3 mm; between-group mean difference, -2.60; 95 % CI: -6.03 to 0.77) were not statistically significant. No significant change in LV volumes and infarct volumes was observed; both groups decreased by a similar amount at 6 months versus baseline. The authors concluded that among patients with MI and LV dysfunction following re-perfusion with PCI, intra-coronary infusion of autologous BMCs versus intra-coronary placebo infusion, 2 to 3 weeks after PCI, did not improve global or regional function at 6 months.

Perin et al (2012) examined if administration of BMCs through trans-endocardial injections improves myocardial perfusion, reduces left ventricular end-systolic volume (LVESV), or enhances maximal oxygen consumption in patients with coronary artery disease or LV dysfunction, and limiting heart failure or angina. This study was a phase 2 randomized, double-blind, placebo-controlled trial of symptomatic patients (NYHA II-III or Canadian Cardiovascular Society classification II-IV) with a LVEF of 45 % or less, a perfusion defect by SPECT, and coronary artery disease not amenable to re-vascularization who were receiving maximal medical therapy at 5 National Heart, Lung, and Blood Institute-sponsored Cardiovascular Cell Therapy Research Network (CCTRN) sites between April 29, 2009, and April 18, 2011. Bone marrow aspiration (isolation of
BMCs using a standardized automated system performed locally) and trans-endocardial injection of 100 million BMCs or placebo (ratio of 2 for BMC group to 1 for placebo group). Co-primary end points assessed at 6 months: Changes in LVESV assessed by echocardiography, maximal oxygen consumption, and reversibility on SPECT. Phenotypic and functional analyses of the cell product were performed by the CCTRN biorepository core laboratory. Of 153 patients who provided consent, a total of 92 (82 men; average age of 63 years) were randomized (n = 61 in BMC group and n = 31 in placebo group). Changes in LVESV index (-0.9 mL/m² [95 % CI: -6.1 to 4.3]; p = 0.73), maximal oxygen consumption (1.0 [95 % CI: -0.42 to 2.34]; p = 0.17), and reversible defect (-1.2 [95 % CI: -12.50 to 10.12]; p = 0.84) were not statistically significant. There were no differences found in any of the secondary outcomes, including percent myocardial defect, total defect size, fixed defect size, regional wall motion, and clinical improvement. The authors concluded that among patients with chronic ischemic heart failure, trans-endocardial injection of autologous BMCs compared with placebo did not improve LVESV, maximal oxygen consumption, or reversibility on SPECT.

Endo-myocardial biopsy specimens grown in primary culture developed multi-cellular clusters known as cardiospheres, which were plated to yield cardiosphere-derived cells (CDCs). Cardiosphere-derived cells from human biopsy specimens as well as from comparable porcine samples have been employed to study cardiac regeneration and improvement of heart function in animal models.

In a phase I clinical trial, Makkar and colleagues (2012) examined the safety of intra-coronary cardiosphere-derived cells (CDCs) in patients with left ventricular dysfunction after MI. In the prospective, randomized CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction (CADUCEUS) trial, these researchers enrolled patients 2 to 4 weeks after MI (with LVEF of 25 to 45 %) at 2 medical centers in the United States. An independent data coordinating center randomly allocated patients in a 2:1 ratio to receive CDCs or
standard care. For patients assigned to receive CDCs, autologous cells grown from endo-myocardial biopsy specimens were infused into the infarct-related artery 1.5 to 3.0 months after MI. The primary endpoint was proportion of patients at 6 months who died due to ventricular tachycardia, ventricular fibrillation, or sudden unexpected death, or had MI after cell infusion, new cardiac tumor formation on MRI, or a major adverse cardiac event (MACE; composite of death and hospital admission for heart failure or non-fatal recurrent MI). These investigators also assessed preliminary efficacy endpoints on MRI by 6 months. Data analysers were masked to group assignment. Between May 5, 2009, and December 16, 2010, these researchers randomly allocated 31 eligible participants of whom 25 were included in a per-protocol analysis (17 to CDC group and 8 to standard of care). Mean baseline LVEF was 39 % (SD 12) and scar occupied 24 % (10) of left ventricular mass. Biopsy samples yielded prescribed cell doses within 36 days (SD 6). No complications were reported within 24 hrs of CDC infusion. By 6 months, no patients had died, developed cardiac tumors, or MACE in either group. Four patients (24 %) in the CDC group had serious adverse events compared with 1 control (13 %; p = 1.00). Compared with controls at 6 months, MRI analysis of patients treated with CDCs showed reductions in scar mass (p = 0.001), increases in viable heart mass (p = 0.01) and regional contractility (p = 0.02), and regional systolic wall thickening (p = 0.015). However, changes in end-diastolic volume, end-systolic volume, and LVEF did not differ between groups by 6 months. The authors concluded that intra-coronary infusion of autologous CDCs after MI is safe, warranting the expansion of such therapy to phase 2 study. They stated that the unprecedented increases noted in viable myocardium, which are consistent with therapeutic regeneration, merit further assessment of clinical outcomes.

Malliaras et al (2014) reported full 1-year results, detailed MRI analysis, and determinants of efficacy in the prospective, randomized, controlled CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction) trial.
Autologous CDCs (12.5 to 25 × 10^6) grown from endomyocardial biopsy specimens were infused via the intracoronary route in 17 patients with left ventricular dysfunction 1.5 to 3 months after MI (plus 1 infused off-protocol 14 months post-MI); 8 patients were followed as routine-care control patients. In 13.4 months of follow-up, safety end-points were equivalent between groups. At 1 year, MRI revealed that CDC-treated patients had smaller scar size compared with control patients. Scar mass decreased and viable mass increased in CDC-treated patients but not in control patients. The single patient infused 14 months post-MI responded similarly. Cardiosphere-derived cells therapy led to improved regional function of infarcted segments compared with control patients. Scar shrinkage correlated with an increase in viability and with improvement in regional function. Scar reduction correlated with baseline scar size but not with a history of temporally remote MI or time from MI to infusion. The changes in LVEF in CDC-treated subjects were consistent with the natural relationship between scar size and ejection fraction post-MI. The authors concluded that intracoronary administration of autologous CDCs did not raise significant safety concerns. Preliminary indications of bioactivity include decreased scar size, increased viable myocardium, and improved regional function of infarcted myocardium at 1 year post-treatment. They stated that these results, which are consistent with therapeutic regeneration, merit further investigation in future trials.

Traverse et al (2012) examined the effect of intra-coronary autologous BMC delivery after STEMI on recovery of global and regional LV function and whether timing of BMC delivery (3 days versus 7 days after reperfusion) influences this effect. A randomized, 2 × 2 factorial, double-blind, placebo-controlled trial, Timing In Myocardial infarction Evaluation (TIME) enrolled 120 patients with LV dysfunction (LVEF less than or equal to 45 %) after successful primary PCI of anterior STEMI between July 17, 2008, and November 15, 2011, as part of the Cardiovascular Cell Therapy Research Network sponsored by the National Heart, Lung, and Blood Institute. Subjects received intra-
coronary infusion of $150 \times 10^6$ BMCs or placebo (randomized 2:1) within 12 hours of aspiration and cell processing administered at day 3 or day 7 (randomized 1:1) after treatment with PCI. The primary end points were change in global (LVEF) and regional (wall motion) LV function in infarct and border zones at 6 months measured by cardiac MRI and change in LV function as affected by timing of treatment on day 3 versus day 7. The secondary end points included major adverse cardiovascular events as well as changes LV volumes and infarct size. The mean (SD) patient age was 56.9 (10.9) years and 87.5% of participants were male. At 6 months, there was no significant increase in LVEF for the BMC group (45.2 % [95 % CI: 42.8 % to 47.6 %] to 48.3 % [95 % CI: 45.3 % to 51.3 %] versus the placebo group (44.5 % [95 % CI: 41.0 % to 48.0 %] to 47.8 % [95 % CI: 43.4 % to 52.2 %]) (p = 0.96). There was no significant treatment effect on regional LV function observed in either infarct or border zones. There were no significant differences in change in global LV function for patients treated at day 3 (−0.9 % [95 % CI: −6.6 % to 4.9 %], p = 0.76) or day 7 (1.1 % [95 % CI: −4.7 % to 6.9 %], p = 0.70). The timing of treatment had no significant effect on regional LV function recovery. Major adverse events were rare among all treatment groups. The authors concluded that among patients with STEMI treated with primary PCI, the administration of intra-coronary BMCs at either 3 days or 7 days after the event had no significant effect on recovery of global or regional LV function compared with placebo.

In a phase I/II randomized comparison study (POSEIDON Trial), Hare and colleagues (2012) examined if allogeneic MSCs are as safe and effective as autologous MSCs in patients with LV dysfunction due to ischemic cardiomyopathy (ICM). A total of 30 patients with LV dysfunction due to ICM between April 2, 2010, and September 14, 2011, with 13-month follow-up were included in this study. Twenty million, 100 million, or 200 million cells (5 patients in each cell type per dose level) were delivered by trans-endocardial stem cell injection into 10 LV sites. Main outcome measures were 30-day post-catheterization incidence of pre-defined treatment-
emergent serious adverse events (SAEs). Efficacy assessments included 6-minute walk test, exercise peak VO2, Minnesota Living with Heart Failure Questionnaire (MLHFQ), NYHA class, LV volumes, ejection fraction (EF), early enhancement defect (EED; infarct size), and sphericity index. Within 30 days, 1 patient in each group (treatment-emergent SAE rate, 6.7 %) was hospitalized for heart failure, less than the pre-specified stopping event rate of 25 %. The 1-year incidence of SAEs was 33.3 % (n = 5) in the allogeneic group and 53.3 % (n = 8) in the autologous group (p = 0.46). At 1 year, there were no ventricular arrhythmia SAEs observed among allogeneic recipients compared with 4 patients (26.7 %) in the autologous group (p = 0.10). Relative to baseline, autologous but not allogeneic MSC therapy was associated with an improvement in the 6-minute walk test and the MLHFQ score, but neither improved exercise VO2 max. Allogeneic and autologous MSCs reduced mean EED by −33.21 % (95 % CI: −43.61 % to −22.81 %; p < 0.001) and sphericity index but did not increase EF. Allogeneic MSCs reduced LV end-diastolic volumes. Low-dose concentration MSCs (20 million cells) produced greatest reductions in LV volumes and increased EF. Allogeneic MSCs did not stimulate significant donor-specific alloimmune reactions. The authors concluded that in this early-stage study of patients with ICM, trans-endocardial injection of allogeneic and autologous MSCs without a placebo control were both associated with low rates of treatment-emergent SAEs, including immunologic reactions. In aggregate, MSC injection favorably affected patient functional capacity, quality of life, and ventricular remodeling. The main drawbacks of this pilot study were its small sample size, lack of a placebo group, and its open-label design. The authors stated that these preliminary findings support future investigation of these MSCs within double-blind, randomized, placebo-controlled trials in ICM.

Assmus et al (2013) tested the hypothesis that targeted cardiac shock wave pre-treatment with subsequent application of BMCs improves recovery of LVEF in patients with chronic heart failure. Single-blind low-dose (n = 42), high-dose (n = 40), or placebo (n = 21) shock wave pre-treatment targeted to the LV
anterior wall. Twenty-four hours later, patients receiving shock wave pre-treatment were randomized to receive double-blind intra-coronary infusion of BMCs or placebo, and patients receiving placebo shock wave received intra-coronary infusion of BMCs. Primary end point was change in LVEF from baseline to 4 months in the pooled groups shock wave + placebo infusion versus shock wave + BMCs; secondary end points included regional LV function assessed by MRI and clinical events. The primary end point was significantly improved in the shock wave + BMCs group (absolute change in LVEF, 3.2 % [95 % CI: 2.0 % to 4.4 %]), compared with the shock wave + placebo infusion group (1.0 % [95 % CI: -0.3 % to 2.2 %]) (p = 0.02). Regional wall thickening improved significantly in the shock wave + BMCs group (3.6 % [95 % CI: 2.0 % to 5.2 %]) but not in the shock wave + placebo infusion group (0.5 % [95 % CI: -1.2 % to 2.1 %]) (p = 0.01). Overall occurrence of major adverse cardiac events was significantly less frequent in the shock wave + BMCs group (n = 32 events) compared with the placebo shock wave + BMCs (n = 18) and shock wave + placebo infusion (n = 61) groups (hazard ratio, 0.58 [95 % CI: 0.40 to 0.85]; p = 0.02). The authors concluded that among patients with post-infarction chronic heart failure, shock wave-facilitated intra-coronary administration of BMCs versus shock wave treatment alone resulted in a significant, albeit modest, improvement in LVEF at 4 months. Determining whether the increase in contractile function will translate into improved clinical outcomes requires confirmation in larger clinical end point trials.

Surder et al (2013) noted that intra-coronary administration of autologous bone marrow-derived mononuclear cells (BM-MNC) may improve remodeling of the LV after acute MI. The optimal time point of administration of BM-MNC is still uncertain and has rarely been addressed prospectively in RCTs. In a multi-center study, these researchers randomized 200 patients with large, successfully re-perfused ST-segment elevation MI in a 1:1:1 pattern into an open-labeled control and 2 BM-MNC treatment groups. In the BM-MNC groups, cells were administered either early (i.e., 5 to 7 days) or late (i.e., 3 to 4 weeks) after acute MI. Cardiac MRI was performed at baseline
and after 4 months. The primary end point was the change from baseline to 4 months in global LVEF between the 2 treatment groups and the control group. The absolute change in LVEF from baseline to 4 months was \(-0.4 \pm 8.8\%\) (mean \(\pm\) SD; \(p = 0.74\) versus baseline) in the control group, \(1.8 \pm 8.4\%\) (\(p = 0.12\) versus baseline) in the early group, and \(0.8 \pm 7.6\%\) (\(p = 0.45\) versus baseline) in the late group. The treatment effect of BM-MNC as estimated by ANCOVA was \(1.25\) (95% CI: \(-1.83\) to \(4.32\); \(p = 0.42\)) for the early therapy group and \(0.55\) (95% CI: \(-2.61\) to \(3.71\); \(p = 0.73\)) for the late therapy group. The authors concluded that among patients with ST-segment elevation MI and LV dysfunction after successful re-perfusion, intra-coronary infusion of BM-MNC at either 5 to 7 days or 3 to 4 weeks after acute MI did not improve LV function at 4-month follow-up.

In a prospective, multi-center, randomized trial, Bartunek et al (2013) evaluated the feasibility and safety of autologous bone marrow-derived and cardiogenically oriented mesenchymal stem cell therapy and probed for signs of efficacy in patients with chronic heart failure. The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) trial was conducted in patients with heart failure of ischemic origin who received standard of care or standard of care plus lineage-specified stem cells. In the cell therapy arm, bone marrow was harvested and isolated mesenchymal stem cells were exposed to a cardiogenic cocktail. Derived cardiopoietic stem cells, meeting release criteria under Good Manufacturing Practice, were delivered by endomyocardial injections guided by left ventricular electromechanical mapping. Data acquisition and analysis were performed in blinded fashion. The primary endpoint was feasibility/safety at 2-year follow-up. Secondary endpoints included cardiac structure/function and measures of global clinical performance 6 months post-therapy. Mesenchymal stem cell cocktail-based priming was achieved for each patient with the dose attained in 75% and delivery without complications in 100% of cases. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic cell therapy. Left ventricular ejection fraction was improved by cell therapy (from \(27.5 \pm 1.0\%\) to \(34.5 \pm 1.1\%\)) versus standard
of care alone (from 27.8 ± 2.0% to 28.0 ± 1.8%, p < 0.0001) and was associated with a reduction in left ventricular end-systolic volume (-24.8 ± 3.0 ml versus -8.8 ± 3.9 ml, p < 0.001). Cell therapy also improved the 6-min walk distance (+62 ± 18 m versus -15 ± 20 m, p < 0.01) and provided a superior composite clinical score encompassing cardiac parameters in tandem with NYHA functional class, quality of life, physical performance, hospitalization, and event-free survival. The authors concluded that the C-CURE trial implemented the paradigm of lineage guidance in cell therapy. Cardiopoietic stem cell therapy was found feasible and safe with signs of benefit in chronic heart failure, meriting definitive clinical evaluation.

In an editorial that accompanied the afore-mentioned study, Murray et al (2013) stated that “The number of clinical trials showing safety and feasibility from adult stem cells is encouraging, but definitive evidence of efficacy remains elusive. Looking ahead, future clinical trials likely will also study pluripotent stem cell derivatives, where new myogenesis is more certain. The C-CURE trial, along with other cardiac cell therapy trials, has provided a strong basis to continue to explore the role of stem cells in the treatment of injured myocardium”.

Vu and colleagues (2014) evaluated the quality of pre-clinical evidence for MSC treatment of ischemic stroke, determined effect size of MSC therapy, and identified clinical measures that correlate with differences in MSC effects. A literature search identified studies of MSCs in animal models of cerebral ischemia. For each, a Quality Score was derived, and effect size of MSCs was determined for the most common behavioral and histologic endpoints. Of 46 studies, 44 reported that MSCs significantly improved outcome. The median Quality Score was 5.5 (of 10). The median effect size was 1.78 for modified Neurological Severity Score, 1.73 for the adhesive removal test, 1.02 for the rotarod test, and 0.93 for infarct volume reduction. Quality Score correlated significantly and positively with effect size for the modified Neurological Severity Score. Effect sizes
varied significantly with clinical measures such as administration route (intra-cerebral > intra-arterial > intra-venous [IV], although effect size for IV was nonetheless very large at 1.55) and species receiving MSCs (primate > rat > mouse). Because many MSC mechanisms are restorative, analyses were repeated examining only the 36 pre-clinical studies administering MSCs greater than or equal to 24 hours post-stroke; results were overall very similar. The authors concluded that in pre-clinical studies, MSCs have consistently improved multiple outcome measures, with very large effect sizes. Results were robust across species studied, administration route, species of MSC origin, timing, degree of immunogenicity, and dose, and in the presence of co-morbidities. In contrast to meta-analyses of pre-clinical data for other stroke therapies, higher-quality MSC pre-clinical studies were associated with larger behavioral gains. They stated that these findings support the utility of further studies to translate MSCs in the treatment of ischemic stroke in humans.

In a phase I and II randomized, blinded, placebo-controlled study, Heldman et al (2014) examined the safety of trans-endocardial stem cell injection with autologous MSCs and BMCs in patients with ischemic cardiomyopathy. A total of 65 patients with ischemic cardiomyopathy and LVEF less than 50 % (September 1, 2009 to July 12, 2013) were included in this study, which compared injection of MSCs (n = 19) with placebo (n = 11) and BMCs (n = 19) with placebo (n = 10), with 1 year of follow-up. Main outcome measures included treatment-emergent 30-day SAEs rate defined as a composite of death, MI, stroke, hospitalization for worsening heart failure, perforation, tamponade, or sustained ventricular arrhythmias. No patient had treatment-emergent SAEs at day 30. The 1-year incidence of SAEs was 31.6 % (95 % CI: 12.6 % to 56.6 %) for MSCs, 31.6 % (95 % CI: 12.6 % to 56.6 %) for BMCs, and 38.1 % (95 % CI: 18.1 % to 61.6 %) for placebo. Over 1 year, the Minnesota Living with Heart Failure score improved with MSCs (-6.3; 95 % CI: -15.0 to 2.4; repeated measures of variance, p = 0.02) and with BMCs (-8.2; 95 % CI: -17.4 to 0.97; p = 0.005) but
not with placebo (0.4; 95 % CI: -9.45 to 10.25; p = 0.38). The 6-minute walk distance increased with MSCs only (repeated measures model, p = 0.03). Infarct size as a percentage of LV mass was reduced by MSCs (-18.9 %; 95 % CI: -30.4 to -7.4; within-group, p = 0.004) but not by BMCs (-7.0 %; 95 % CI: -15.7 % to 1.7 %; within-group, p = 0.11) or placebo (-5.2 %; 95 % CI: -16.8 % to 6.5 %; within-group, p = 0.36). Regional myocardial function as peak Eulerian circumferential strain at the site of injection improved with MSCs (-4.9; 95 % CI: -13.3 to 3.5; within-group repeated measures, p = 0.03) but not BMCs (-2.1; 95 % CI: -5.5 to 1.3; p = 0.21) or placebo (-0.03; 95 % CI: -1.9 to 1.9; p = 0.14). Left ventricular chamber volume and ejection fraction did not change. The authors concluded that trans-endocardial stem cell injection with MSCs or BMCs appeared to be safe for patients with chronic ischemic cardiomyopathy and LV dysfunction. Although the sample size and multiple comparisons precluded a definitive statement about safety and clinical effect, these results provided the basis for larger studies to provide definitive evidence about safety and to assess efficacy of this new therapeutic approach.

**Autologous Skeletal Myoblast:**

Brickwedel et al (2014) noted that short-term follow-up after autologous skeletal myoblasts (ASM) transplantation (Tx) (Myoblast Autologous Grafting in Ischaemic Cardiomyopathy (MAGIC) Phase II Study) for the treatment of ischemic cardiomyopathy revealed improved LV re-modelling. These researchers reported the longest long-term worldwide follow-up of a single-center cohort, focusing on the safety and effectiveness of ASM-Tx. The multi-center MAGIC Phase II Study involved 120 patients and was conducted between 2004 and 2006. Out of the 120 patients involved in the entire study, the cohort treated at the authors’ institution contained 7 patients only. These 7 patients received ASM-Tx (injection volume: 400 million cells, n = 2 low dosage; 800 million cells, n = 2 high dosage) or placebo (n = 3) injections, in addition to CABG. After closure of the MAGIC registry, these investigators conducted a long-term follow-up for their 7-patient cohort. The
mean follow-up was 72.0 ± 5.3 months. The follow-up was complete for echo data, ICD report, clinical investigation and NYHA class. At final follow-up, all the patients were alive, and 5 were in NYHA class 1 or 2. There were 6 hospitalizations for congestive HF during the follow-up (1 patient from each group). One patient (placebo group) was treated twice for ventricular fibrillation by the ICD. The LVEF remained stable in all the 3 groups (31.1 ± 3.9 % pre-operative versus 29.4 ± 4.4 % at final follow-up). The LV volumes were reduced in the high-dosage group, remained unchanged in the low-dosage group and deteriorated in the placebo group. The authors concluded that these long-term data confirmed the findings of the MAGIC study. The LV function did not improve, but the long-term LV volumes in the high-dosage group were reduced. During the follow-up, there were also no additional arrhythmogenic incidences. They stated that these data could imply that CABG in combination with ASM-Tx is safe and has beneficial therapeutic effects in the long-term. However, due to the small patient number, the clinical impact is limited.

Sawa et al (2015) stated that poor survival outcomes for patients with severe HF and the donor shortage for heart transplantation warrant the development of myocardial regenerative therapy. In a phase II clinical trial, these researchers evaluated the safety and effectiveness of autologous skeletal myoblast sheets (TCD-51073). In 3 study sites, these investigators enrolled 7 patients with severe chronic HF due to ischemic heart disease despite maximal therapy, all of whom underwent transplantation of TCD-51073. No serious arrhythmia was reported, and no changes were noted in the frequency of ventricular extra-systole frequency. The primary efficacy end-point of the change in LVEF on gated blood-pool scintigraphy at 26 weeks after transplantation showed that 5 subjects were responders (classified as "improved" or "unchanged"). In addition, LVEF on echocardiography improved over time, with a change in LVEF of 7.1 ± 2.8 % at 26 weeks post-transplantation. Among the 7 subjects, 6 showed improvement in NYHA functional class by at least 1 class. The 6-min walk distance was 410.1 ± 136.1 m before
transplantation and 455.4 ± 103.7 m at 26 weeks after transplantation. The authors concluded that the findings of this study demonstrated the feasibility and safety of the transplantation of TCD-51073 in the patients with severe chronic HF due to ischemic heart disease, suggesting that TCD-51073 might maintain or improve cardiac function, symptoms, and physical function.

**Mononuclear Bone Marrow Cell:**

Marquis-Gravel and colleagues (2014) examined the effects of SC therapy for non-ischemic cardiomyopathy (CMP) by conducting a systematic review of the literature and meta-analysis of RCTs. Medline, EBM Reviews-Cochrane Central Register of Controlled Trials, Embase, and the ClinicalTrials.gov databases were screened for RCTs involving SC for treatment of non-ischemic CMP. Weighted mean differences of improvement of LVEF and LV end-diastolic diameter (LVEDD) were calculated using a random effect analysis model. A total of 4 trials were included in this meta-analysis (244 patients). The weighted mean LVEF improvement was 4.87 % (95 % CI: 1.32 to 8.43 %) in the treatment group compared with the control group (p = 0.01). The weighted mean decrease of LVEDD in the treatment group was of -2.19 mm (95 % CI: -5.69 to 1.30) compared with the control group (p = 0.22). On subgroup analysis, results were similar in studies involving peripheral CD34-positive cells or BMMNCs (p = 0.33 for subgroup differences). The authors concluded that this was the first meta-analysis to show that for the treatment of non-ischemic CMP, SC therapy might improve LVEF, but not LVEDD. Moreover, they stated that further trials should aim to circumscribe the optimal SC regimen in this setting, and to assess long-term clinical outcomes as primary end-points.

Xu and associates (2014) evaluated the safety and effectiveness of autologous bone marrow/blood-derived cell transplantation in patients with chronic ischemic heart disease (CIHD). Randomized controlled trials were identified in PubMed, OVID,
EMBASE, and Cochrane Library reviews and reference lists of relevant articles. Weighted mean difference was calculated for changes in LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) using a random-effects model. A total of 19 trials (886 patients) were included. Compared with controls, patients who received transplantation of bone marrow/blood-derived cells had significantly improved LVEF (3.54 %; 95 % CI: 1.92 % to 5.17 %; p < 0.001) and LVESV (-8.96 ml; 95 % CI: -13.64 to -4.28 ml; p < 0.001). No significant improvement in LVEDV (-0.75 ml; 95 % CI: -9.80 to 8.30 ml; p = 0.22) was detected. Subgroup analysis revealed that significant improvement in LVEDV was observed in patients with lower baseline LVEF. Moreover, there were trends in favor of a benefit for LV function and re-modelling when intra-myocardial cells were injected during coronary bypass surgery and the BMMNC number was less than or equal to $1 \times 10^8$.

Furthermore, cell therapy was associated with a significant decrease in all-cause death (relative risk [RR]: 0.49; 95 % CI: 0.29 to 0.84; p = 0.01). The authors concluded that current evidence showed that cell therapy moderately improved LV function and significantly decreased all-cause death in patients with CIHD and supported further RCTs with larger sample size and longer follow-up.

Robbers et al (2014) examined the effects of cell therapy on myocardial perfusion recovery after treatment of AMI with primary PCI. In this HEBE trial substudy, these researchers assessed the effects of intracoronary infusion with BMMCs or peripheral blood-derived mononuclear cells (PBMCs) on myocardial perfusion recovery by using cardiac MRI after re-vascularization. In 152 patients with AMI treated with PCI, cardiac MRI was performed after obtaining informed consent-before randomization to BMMC, PBMC, or standard therapy (control group); and repeated at 4-month follow-up. Cardiac MRI consisted of cine, rest first-pass perfusion, and late gadolinium enhancement imaging. Perfusion was evaluated semi-quantitatively with signal intensity-time curves by calculating the relative upslope (percentage signal intensity change). The relative upslope was calculated for the MI core,
adjacent border zone, and remote myocardium. Perfusion differences among treatment groups or between baseline and follow-up were assessed with the Wilcoxon signed rank or Mann-Whitney U test. At baseline, myocardial perfusion differed between the MI core (median of 6.0%; interquartile range [IQR]: 4.1% to 8.0%), border zone (median of 8.4%; IQR: 6.4% to 10.2%), and remote myocardium (median of 12.2%; IQR: 10.5% to 15.9%) (p < 0.001 for all), with equal distribution among treatment groups. These inter-regional differences persisted at follow-up (p < 0.001 for all). No difference in perfusion recovery was found between the 3 treatment groups for any region. The authors concluded that after revascularization of ST-elevation MI, cell therapy did not augment the recovery of resting perfusion in either the MI core or border zone.

Delewi et al (2015) reported the long-term follow-up of the randomized controlled HEBE trial. The HEBE study was a multi-center trial that randomized 200 patients with large first AMI treated with primary PCI to either intracoronary infusion of BMMCs (n = 69), PBMCs (n = 66) or standard therapy (n = 65). In addition to 3 to 5 days, and 4 months after AMI, all patients underwent cardiac MRI after 2 years. A follow-up for 5 years after AMI was performed to assess clinical adverse events, including death, myocardial re-infarction and hospitalization for HF. Of the 200 patients enrolled, 9 patients died and 12 patients were lost to follow-up at 5 years after AMI. BMMC group showed less increase in LVEDV (3.5 ± 16.9 ml/m²) compared with (11.2 ± 19.8 ml/m²), p = 0.03) in the control group, with no difference between the PBMC group (9.2 ± 20.9 ml/m²) and controls (p = 0.69). Moreover, the BMMC group showed a trend for decrease in LVESV (-1.8 ± 15.0 ml/m²) as compared with controls (3.0 ± 16.3 ml/m²), p = 0.07), with again no difference between PBMC (3.3 ± 18.8 ml/m²) and controls (p = 0.66). The combined end-point of death and hospitalization for HF was non-significantly less frequent in the BMMC group compared with the control group (n = 4 versus n = 1, p = 0.20), with no difference between PBMC and controls (n = 6 versus n = 4, p = 0.74). The composite end-point of death or
recurrent MI was significantly higher in the PBMC group compared with controls (14 patients versus 3 patients, \( p = 0.008 \)), with no difference between the BMMC group and controls (2 versus 3 patients, \( p = 0.67 \)). The authors concluded that long-term follow-up of the HEBE trial showed that increase in LVEDV was lower in the BMMC group. They stated that the findings of this study supported the long-term safety of intracoronary BMMC therapy. However, major clinical cardiovascular adverse events were significantly more frequent in the PBMC group.

In a phase III, prospective, open labelled, randomized, multi-center clinical trial, Nair et al (2015) evaluated the effectiveness in improving the LVEF over a period of 6 months, after injecting a pre-defined dose of \( 5 \) to \( 10 \times 10^8 \) autologous MNC by intracoronary route, in patients, 1 to 3 weeks post-ST elevation AMI, in addition to the standard medical therapy. A total of 250 patients with AMI were included and randomized into stem cell therapy (SCT) and non-SCT groups. All patients were followed-up for 6 months. Patients with AMI having LVEF of 20 to 50 % were included and were randomized to receive intracoronary stem cell infusion after successfully completing PCI. On intention-to-treat analysis the infusion of MNCs had no positive impact on LVEF improvement of greater than or equal to 5 %. The improvement in LVEF after 6 months was \( 5.17 \pm 8.90 \) % in non-SCT group and \( 4.82 \pm 10.32 \) % in SCT group. The adverse effects were comparable in both the groups. On post-hoc analysis it was noted that the cell dose had a positive impact when infused in the dose of greater than or equal to \( 5 \times 10^8 \) (\( n = 71 \)). This benefit was noted up to 3 weeks post-AMI.

There were 38 trial deviates in the SCT group that was a limitation of the study. The authors concluded that infusion of stem cells was found to have no benefit in ST elevation AMI. However, the procedure was safe. They stated that a possible benefit was seen when the pre-defined cell dose was administered which was noted up to 3 weeks post-AMI, but this was not significant and needs confirmation by larger trials.

*Bone Marrow-Derived Mesenchymal Stem Cell Transplantation*
Papazova et al (2015) stated that cell-based therapy is a promising strategy for treating chronic kidney disease (CKD) and is currently the focus of pre-clinical studies. These researchers performed a systematic review and meta-analysis to evaluate the effectiveness of cell-based therapy in pre-clinical (animal) studies of CKD, and determined factors affecting cell-based therapy efficacy in order to guide future clinical trials. A total of 71 articles met the inclusion criteria. Standardized mean differences (SMD) and 95 % CI were calculated for outcome parameters including plasma urea, plasma creatinine, urinary protein, blood pressure, glomerular filtration rate, glomerulosclerosis and interstitial fibrosis. Sub-analysis for each outcome measure was performed for model-related factors (species, gender, model and timing of therapy) and cell-related factors (cell type, condition and origin, administration route and regime of therapy). Overall, meta-analysis showed that cell-based therapy reduced the development and progression of CKD. This was most prominent for urinary protein (SMD, 1.34; 95 % CI: 1.00 to 1.68) and urea (1.09; 0.66 to 1.51), both p < 0.001. Changes in plasma urea were associated with changes in both glomerulo-sclerosis and interstitial fibrosis. Sub-analysis showed that cell type (bone-marrow-derived progenitors and mesenchymal stromal cells being most effective) and administration route (intravenous or renal artery injection) were significant predictors of therapeutic efficacy. The timing of therapy in relation to clinical manifestation of disease, and cell origin and dose, were not associated with efficacy. The authors concluded that the findings of this meta-analysis confirmed that cell-based therapies improved impaired renal function and morphology in pre-clinical models of CKD. They stated that their analyses can be used to optimize experimental interventions and thus support both improved pre-clinical research and development of cell-based therapeutic interventions in a clinical setting.

**Bone Marrow-Derived Mesenchymal Stem Cell Transplantation for Diabetes:**
In a pilot study, Skyler et al (2015) evaluated the safety, tolerability, and feasibility of adult allogeneic bone marrow-derived mesenchymal precursor cells (MPCs) in type 2 diabetes inadequately controlled with metformin either alone or with one additional oral anti-diabetic agent. The study was a dose-escalating randomized placebo-controlled trial assessing 1 intravenous (IV) infusion of MPCs (rexlemestrocel-L; Mesoblast Inc.) 0.3 × 10^6/kg (n = 15), 1.0 × 10^6/kg (n = 15), or 2.0 × 10^6/kg (n = 15) or placebo (n = 16). Study duration was 12 weeks. Subjects (21 women, 40 men) with a mean ± SD baseline HbA1c 8.3 ± 1.0 % (67 ± 10.9 mmol/mol), BMI 33.5 ± 5.5 kg/m(2), and diabetes duration 10.1 ± 6.0 years were enrolled at 18 U.S. sites. No acute adverse events (AEs) were associated with infusion. No serious AEs, serious hypoglycemia AEs, or discontinuations due to AEs over 12 weeks were found. No subjects developed donor-specific anti-HLA antibodies or became sensitized. The safety profile was comparable among treatment groups. Compared with placebo, a single IV infusion of rexlemestrocel-L reduced HbA1c at all time-points after week 1. The adjusted least squares mean ± SE dose-related differences in HbA1c from placebo in the rexlemestrocel-L groups ranged from -0.1 ± 0.2 % (-1.1 ± 2.2 mmol/mol) to -0.4 ± 0.2 % (4.4 ± 2.2 mmol/mol) at 8 weeks and from 0.0 ± 0.25 % to -0.3 ± 0.25 % (-3.3 ± 2.7 mmol/mol) at 12 weeks (p < 0.05 for 2.0 × 10^6/kg dose at 8 weeks). The clinical target HbA1c less than 7 % (53 mmol/mol) was achieved by 33 % (5 of 15) of the subjects who received the 2.0 × 10^6/kg dose versus 0 % of those who received placebo (p < 0.05). The authors concluded that the findings of this short-term study demonstrated the safety and feasibility of up to 246 million MPCs in subjects with type 2 diabetes. These preliminary findings need to be further investigated in well-designed studies.

*Bone Marrow-Derived Mesenchymal Stem Cell Transplantation for Heart Failure:*

Narita and Suzuki (2015) stated that heart failure (HF) remains a major cause of death and disability, requiring rapid development of new therapies. Bone marrow-derived
mesenchymal stem cell-based therapy is an emerging approach for the treatment of both acute and chronic HF. Following successful experimental studies in a range of models, more than 40 clinical trials of MSC-based therapy for HF have now been registered, and the results of completed clinical trials so far have shown feasibility and safety of this approach with therapeutic potential suggested (though preliminarily). These investigators summarized a total of 73 pre-clinical studies and 11 clinical trial reports published to-date. The authors concluded that there appeared to be several critical issues to be solved before this treatment could become a widespread standard therapy for HF: (i) improvement in the cell delivery method to the heart in order to enhance donor cell engraftment, (ii) elucidation of mechanisms underpinning the therapeutic effects of the treatment differentiation and/or treatment secretion, and (iii) validation of the utility of allogeneic MSCs that could enhance the effectiveness and expand the application/indication of this therapeutic approach.

**Bone Marrow-Derived Mesenchymal Stem Cell Transplantation for Neuropathic Pain:**

Hosseini et al (2015) noted that SCT has been considered a possible therapeutic method for neuropathic pain. However, no quantitative data synthesis of SCT for neuropathic pain exists. In a systematic review and meta-analysis, these researchers evaluated the effectiveness of bone marrow mesenchymal stem cell (BMMSC) transplantation on alleviating pain symptoms in animal models of neuropathic pain. In the present meta-analysis, controlled animal studies assessing the effect of administrating BMMSC on neuropathic pain were included through an extensive literature search of online databases. After collecting data, effect sizes were computed and the standardized mean difference (SMD) with 95% CI was entered in all analyses. Random-effects models were used for data analysis. Sensitivity and subgroup analyses were performed to investigate expected or measured heterogeneity. A total of 14 study were included. The analyses showed that BMMSC transplantation led to significant improvement on allodynia.
(SMD = 2.06; 95 % CI: 1.09 to 3.03; I(2) = 99.7 %; p < 0.001).

The type of neuropathy (p = 0.036), time between injury and intervention (p = 0.02), and the number of transplanted cells (p = 0.023) influence the improvement of allodynia after BMMSC transplantation. BMMSC transplantation had no effect on hyperalgesia (SMD = 0.3; 95 % CI: -1.09 to 1.68; I(2) = 100 %; p < 0.001) unless it occurred during the first 4 days after injury (p = 0.02). The authors concluded that the findings of present systematic review with meta-analysis suggested that BMMSC transplantation improved allodynia but did not have any significant effect on hyperalgesia unless it is given during the first 4 days after injury.

**Bone Marrow-Derived Mesenchymal Stem Cell Transplantation for Traumatic Brain Injury:**

Peng et al (2015) performed a systematic review and meta-analysis to (i) review the literatures describing the effect of MSCs therapy in animal models of traumatic brain injury (TBI), (ii) determine the estimated effect size of functional locomotor recovery after experimental TBI, and (iii) to provide empirical evidence of biological factors associated with greater efficacy. These investigators conducted a systematic search of PubMed, Embase, and Web of Science and hand searched related references. Studies were selected if they reported the efficacy of MSCs in animal models of TBI. Two investigators independently assessed the identified studies. They extracted the details of individual study characteristics from each publication, assessed study quality, evaluated the effect sizes of MSCs treatment, and performed stratified meta-analysis and meta-regression, to assess the influence of study design on the estimated effect size. The presence of small effect sizes was investigated using funnel plots and Egger's tests. A total of 28 eligible controlled studies were identified. The study quality was modest. Between-study heterogeneity was large.

Meta-analysis showed that MSCs exerted statistically significant positive effects on sensorimotor and neurological motor function. For sensorimotor function, maximum effect size in studies with a quality score of 5 was found in the
weight-drop impact injury TBI model established in male SD rats, to which syngeneic umbilical cord-derived MSCs intracerebrally at cell dose of $(1 \text{ to } 5) \times 10^6$ was administered 6 hours following TBI, using ketamine as anesthetic agent. For neurological motor function, effect size was maximum for studies with a quality score of 5, in which the weight-drop impact injury TBI models of the female Wistar rats were adopted, with administration syngeneic bone marrow-derived MSCs intravenously at cell dose of $5 \times 10^6$ at 2 months after TBI, using sevofluorane as anesthetic agent. The authors concluded that MSCs therapy may improve locomotor recovery after TBI. However, they stated that additional well-designed and well-reported animal studies are needed to guide further clinical studies.

**Peripheral Arterial Disease:**

Peripheral arterial disease (PAD) is often a devastating condition, especially in patients with diabetes mellitus, because of the high rate of functional disability, amputation and death. For individuals in whom conventional endovascular or surgical re-vascularization procedures have been unsuccessful, new therapeutic options are being sought, among which stem and progenitor cell therapy has gained increasing interest. Most clinical trials of cell therapy have employed multiple intra-muscular injections of mBMC that have yielded encouraging results. Moreover, because of the strong placebo effect that may confound interpretation of outcome measures, rigorously RCTs are needed to evaluate more thoroughly if stem and progenitor cell therapy is beneficial for patients with PAD.

Franz et al (2009) presented short-term results of dual intra-muscular and intra-arterial autologous mBMC implantation for the treatment of patients with severe PAD in whom amputation was considered the only viable treatment option. Baseline, 2-week, and 3-month evaluations were conducted. Ankle brachial indices (ABI) were calculated for both the dorsal pedis and the posterior tibial arteries. Rest pain and ulcer healing also were assessed. Success was defined as meeting the
following 4 criteria: (i) improvement in ABI measurements; (ii) relief of rest pain; (iii) ulcer healing, if applicable; and (iv) absence of major limb amputations. Patients not undergoing major limb amputations continued to be monitored for subsequent procedures. A total of 9 patients for whom limb amputation was recommended underwent this procedure. The study population was comprised of 5 females and 4 males, with a mean age of 61.7 years. Eight (88.9 %) patients had rest pain. Seven (77.8 %) patients also had diabetes. Non-healing ulcers were present in 8 (88.9 %) cases. After the procedure, non-significant improvements of 0.12 and 0.08 in ABI were observed for the dorsalis pedis and posterior tibial ankle arteries, respectively. Three (33.3 %) major amputations subsequently were performed, including a below-knee amputation 4.1 weeks after the mBMC implantation and 2 above-knee amputations at 5.4 and 11.0 weeks after the procedure. The 6 (66.7 %) patients who did not have major amputations demonstrated improvement in symptom severity 3 months after the procedure, as evidenced by alleviation of rest pain and improvements by at least one level in Rutherford and Fontaine classifications, and have not required amputations at a mean follow-up of 7.8 months. Complete wound healing was achieved within 3 months in all patients who had ulcers prior to mBMC implantation and for whom amputation was not required. This specific mBMC implantation technique was fully successful in 3 (33.3 %) patients, as major amputation was avoided and the other applicable criteria were met; 5 (55.6 %) additional patients demonstrated success in at least one of the four criteria. The authors concluded that with 8 (88.9 %) of 9 patients showing some level of improvement and amputation avoided in 6 (66.7 %) patients, these short-term results indicate the use of mBMC implantation as a means of limb salvage therapy for patients with severe PAD shows promise in postponing or avoiding amputation in a patient population currently presented with few alternatives to amputation.

Idei and colleagues (2011) evaluated long-term clinical outcomes after autologous mBMC implantation in patients with critical limb ischemia (CLI). These researchers assessed
long-term clinical outcomes after mBMC implantation in 51 patients with CLI, including 25 patients with PAD and 26 patients with Buerger disease. Forty-six CLI patients who had no mBMC implantation served as control subjects. Median follow-up period was 4.8 years. The 4-year amputation-free rates after mBMC implantation were 48 % in PAD patients and 95 % in Buerger disease, and they were 0 % in control PAD patients and 6 % in control Buerger disease. The 4-year overall survival rates after mBMC implantation were 76 % in PAD patients and 100 % in Buerger disease, and they were 67 % in control PAD patients and 100 % in control Buerger disease. Multi-variable Cox proportional hazards analysis revealed that mBMC implantation correlated with prevention of major amputation and that hemodialysis and diabetes mellitus correlated with major amputation. In Buerger disease, ABI and transcutaneous oxygen pressure were significantly increased after 1 month and remained high during 3-year follow-up. However, in patients with PAD, ABI and transcutaneous oxygen pressure significantly increased after 1 month and gradually decreased during 3-year follow-up and returned to baseline levels. The authors concluded that these findings suggested that mBMC implantation is safe and effective in patients with CLI, especially in patients with Buerger disease.

In a multi-center, phase II, randomized-start, placebo-controlled trial, Walter et al (2011) examined the effects intra-arterial administration of mBMC in patients with CLI. A total of 40 patients were randomized to receive either intra-arterial administration of mBMC or placebo followed by active treatment with mBMC (open label) after 3 months. Intra-arterial administration of mBMC did not significantly increase ABI and, thus, the trial missed its primary end point. However, cell therapy was associated with significantly improved ulcer healing (ulcer area, 3.2 +/- 4.7 cm(2) to 1.89 +/- 3.5 cm(2) [p = 0.014] versus placebo, 2.92 +/- 3.5 cm(2) to 2.89 +/- 4.1 cm(2) [p = 0.5]) and reduced rest pain (5.2 +/- 1.8 to 2.2 +/- 1.3 [p = 0.009] versus placebo, 4.5 +/- 2.4 to 3.9 +/- 2.6 [p = 0.3]) within 3 months. Limb salvage and amputation-free survival rates did not differ between the groups. Repeated mBMC administration
and higher mBMC numbers and functionality were the only independent predictors of improved ulcer healing. Ulcer healing induced by repeated mBMC administration significantly correlated with limb salvage ($r = 0.8; p < 0.001$). The authors concluded that intra-arterial administration of mBMC is safe and feasible and accelerates wound healing in patients without extensive gangrene and impending amputation. They stated that these exploratory findings of this pilot trial need to be confirmed in a larger randomized trial in patients with CLI and stable ulcers.

In a meta-analysis, Fadini et al (2010) examined if autologous cell therapy is effective in the treatment of PAD. These investigators searched the English literature in Medline, Excerpta Medica and the Cochrane database for trials of autologous cell therapy in patients with PAD published before 31 January 2009. They included controlled and non-controlled, randomized and non-randomized trials using autologous bone marrow or granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood cells to treat PAD. They also collected data from trials of G-CSF monotherapy, as a control treatment. In a meta-analysis of 37 trials, autologous cell therapy was effective in improving surrogate indexes of ischemia, subjective symptoms and hard endpoints (ulcer healing and amputation). On the contrary, G-CSF monotherapy was not associated with significant improvement in the same endpoints. Patients with thrombo-angiitis obliterans (TAO) showed some larger benefits than patients with atherosclerotic PAD. The intra-muscular route of administration and the use of BMCs seemed somehow more effective than intra-arterial administration and the use of mobilized peripheral blood cells. The procedures were well-tolerated and generally safe. The authors concluded that this meta-analysis indicates that intra-muscular autologous bone marrow cell therapy is a feasible, relatively safe and potentially effective therapeutic strategy for PAD patients, who are not candidate for traditional re-vascularization. They stated that larger, placebo-controlled, randomized multi-center trials are needed to confirm these findings.
Lawall et al (2011) stated that PAD is a highly prevalent atherosclerotic syndrome associated with significant morbidity and mortality. Peripheral arterial disease is most commonly caused by athero-sclerosis obliterans (ASO) and TAO, and can lead to claudication and CLI, often resulting in a need for major amputation and subsequent death. Standard treatment for such severe cases of PAD is surgical or endovascular revascularization. However, up to 30 % of patients are not candidates for such interventions, due to high operative risk or unfavorable vascular involvement. Therefore, new strategies are needed to offer these patients a viable therapeutic option. Bone-marrow derived stem and progenitor cells have been identified as a potential new therapeutic option to induce angiogenesis. These findings prompted clinical researchers to explore the feasibility of cell therapies in patients with peripheral and coronary artery disease in several small trials. Clinical benefits were reported from these trials including improvement of ABI, transcutaneous partial pressure of oxygen, reduction of pain, and decreased need for amputation. Moreover, the authors noted that large randomized, placebo-controlled, double-blind studies are needed and currently ongoing to provide stronger safety and efficacy data on cell therapy.

In a Cochrane review, Moazzami et al (2011) examined the safety and effectiveness of autologous adult bone marrow derived mononuclear cells (BMMNCs) as a treatment for CLI. The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched November 2010) and CENTRAL (2010, Issue 4). These investigators searched the reference lists of identified articles. All RCTs of CLI in which participants were randomly allocated to intra-muscular administration of autologous adult BMMNCs or control (either no intervention or conventional conservative therapy) were included. Studies on patients with intermittent claudication were not included. Two authors independently selected trials, assessed trials for eligibility and methodological quality, and extracted data. Disagreements were resolved by consensus or by the 3rd author. A total of 37 potential studies were
identified after initial screening of titles and abstracts. Only 2 small studies, with a combined total of 57 patients, met inclusion criteria and were finally included. In 1 study, the effects of intra-muscular injections of BMMNCs in the ischemic lower limbs of patients with CLI were compared with control (standard conservative treatment). No deaths were reported and no significant difference was observed between the 2 groups for either pain \((p = 0.37)\) or the ABI parameter. However, the treatment group showed a significantly smaller proportion of participants undergoing amputation compared with the control group \((p = 0.026)\). In the other study, following subcutaneous injections of granulocyte colony-stimulating factor (G-CSF) for 5 days peripheral blood derived mononuclear cells were collected and then transplanted by intra-muscular injections into ischemic lower limbs. The effects were compared with daily intravenous prostaglandin E1 injections (control group). No deaths were reported. Pain reduction was greater in the treatment group than in the control group \((p < 0.001)\) as was increase in ABI \((\text{mean increase } 0.13\text{ versus } 0.02, p < 0.01)\). The treatment group experienced a statistically significant increase in pain-free walking distance compared with the control group \((\text{mean increase } 306.4\text{ m versus } 78.6\text{ m}, p = 0.007)\). A smaller proportion of participants underwent amputation in the treatment group compared with the control group \((0\% \text{ versus } 36\%, p = 0.007)\). The authors concluded that data from the published trials suggest that there is insufficient evidence to support this treatment. These results were based on only 2 trials that had a very small number of participants. Thus, evidence from larger RCTs is needed in order to provide adequate statistical power to assess the role of intra-muscular mononuclear cell implantation in patients with CLI.

In a pilot study, Amato et al (2012) evaluated the effectiveness of peripheral blood mononuclear cells implantation in patients with PAD. This study included 5 patients, aged 60 to 75, with a history of claudication. Peripheral blood mononuclear cells have been implanted 3 times in the limb with the worst ABI value in all the patients included in the study. The clinical
follow-up was performed during the subsequent 12 months from the beginning of the treatment. In 4 patients there was a regression of ulcerative lesions. One patient’s condition improved after the first implantation but later did not respond to the further treatments. All patients achieved a pain relief as judged by the numeric pain scale. Pain relief remained satisfactory in 3 patients for 1 year. Pain gradually returned to the pre-treatment level in 2 patients. All patients referred an ameliorating in their quality of life expressed even by an improvement in claudication-free walking distance. These improvements were reflected also by intra-arterial digital subtraction angiography that showed an improvement of arterial vascularization. The authors concluded that the findings from this study suggested an efficacy of bone marrow-derived circulating endothelial progenitors implantation in terms of improvement of the vascularization and quality of life in patients affected by PAD. Moreover, they stated that a double-blind, placebo-controlled, study is needed to confirm these findings.

In a Cochrane review, Moazzami and associates (2014) determined the safety and effectiveness of local intramuscular transplantation of autologous adult BMMNCs as a treatment for CLI. For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched February 2014) and the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2014). They included all RCTs of CLI in which participants were randomly allocated to intramuscular administration of autologous adult BMMNCs or control (either no intervention or conventional conservative therapy). They excluded studies on patients with intermittent claudication. Two authors independently selected trials, assessed trials for eligibility and methodological quality, and extracted data. Disagreements were resolved by consensus or by the 3rd author. Only 2 small studies, with a combined total of 57 participants, met the inclusion criteria and were finally included. They were classified as having a moderate risk of bias with unclear issues regarding their methods, and according to the GRADE
approach, the overall quality of the evidence would be considered as moderate. In 1 study the effects of intramuscular injections of BMMNCs in the ischemic lower limbs of patients with CLI were compared with control (standard conservative treatment). No deaths were reported and no significant difference was observed between the 2 groups for either pain (p = 0.37) or the ABI parameter. However, the treatment group showed a significantly smaller proportion of participants undergoing amputation compared with the control group (p = 0.026). In the other study, following subcutaneous injections of G-CSF for 5 days, peripheral blood derived mononuclear cells were collected and then transplanted by intramuscular injections into ischemic lower limbs. The effects were compared with daily intravenous prostaglandin E1 injections (control group). No deaths were reported. Pain reduction was greater in the treatment group than in the control group (p < 0.001) as was increase in ABI (mean increase 0.13 versus 0.02, p < 0.01). The treatment group experienced a statistically significant increase in pain-free walking distance (PFWD) compared with the control group (mean increase 306.4 m versus 78.6 m, p = 0.007). A smaller proportion of participants underwent amputation in the treatment group compared with the control group (0 % versus 36 %, p = 0.007). The authors concluded that these data from the published trials suggested that there is insufficient evidence to support this treatment. They stated that these results were based on only 2 trials that had a very small number of participants. Therefore evidence from larger RCT is needed in order to provide adequate statistical power to assess the role of intramuscular mononuclear cell implantation in patients with CLI.

Malyar et al (2014) examined the effect of autologous BMMNCs on symptoms and perfusion indices in severely symptomatic patients with PAD without further option for endovascular or surgical re-vascularization. Only patients with severe symptomatic PAD (Fontaine class IIb-IV, Rutherford category 3-6) not amenable for re-vascularization were treated. Bone marrow from both crista iliaceae was harvested; MNCs were isolated by the Ficoll density-gradient method and transplanted
by means of intra-arterial and intramuscular injection in the index limb. Functional (pain score, ulcer healing, maximum walking distance) and perfusion indices such as ABI and transcutaneous oxygen pressure were documented before and after BM-MNC therapy. Additionally, serum concentration of C-reactive protein (CRP) and interleukin-6 (IL-6) were measured as markers of inflammation before and after BMMNC treatment. A total of 16 consecutive patients (4 women; mean age of 63.0 ± 13 years) were treated with a mean dose of 4.2 ± 2.2 \times 10^8 BMMNCs. At 6 months' follow-up, ABI, transcutaneous oxygen pressure and maximum walking distance significantly increased, whereas CRP and IL-6 conversely decreased (p < 0.01 versus baseline values), resulting in 88 % limb salvage, 75 % pain reduction and 71 % complete wound healing and/or reduction of ulcer size; 1 major and 1 minor amputation were performed, both in patients with Rutherford category 6. The authors concluded that autologous BMMNC therapy in patients with end-stage PAD improved tissue perfusion indices and decreases markers of inflammation. They stated that if these observations could be confirmed by large-scale, RCTs, BMMNC transplantation could become an alternative therapeutic option for patients with end-stage PAD.

Teraa and colleagues (2015) examined if repetitive intra-arterial infusion of BMMNCs in patients with severe, non-revascularizable limb ischemia can prevent major amputation. The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial was a randomized, double-blind, placebo-controlled clinical trial in 160 patients with severe, non-revascularizable limb ischemia. Patients were randomly assigned to repetitive (3 times; 3-week interval) intra-arterial infusion of BMMNC or placebo. No significant differences were observed for the primary outcome, i.e., major amputation at 6 months, with major amputation rates of 19 % in the BMMNC versus 13 % in the placebo group (RR, 1.46; 95 % CI: 0.62 to 3.42). The safety outcome (all-cause mortality, occurrence of malignancy, or hospitalization due to infection) was not significantly different between the groups.
(RR, 1.46; 95% confidence interval, 0.63 to 3.38), neither was all-cause mortality at 6 months with 5% versus 6% (RR, 0.78; 95% CI: 0.22 to 2.80). Secondary outcomes quality of life, rest pain, ABI, and transcutaneous oxygen pressure improved during follow-up, but there were no significant differences between the groups. The authors concluded that repetitive intra-arterial infusion of autologous BMMNCs into the common femoral artery did not reduce major amputation rates in patients with severe, non-revascularizable limb ischemia in comparison with placebo. They stated that the general improvement in secondary outcomes during follow-up in both the BMMNC and the placebo group, as well, underlines the essential role for placebo-controlled design of future trials.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<tr>
<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
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<tr>
<td>There are no specific CPT codes for autologous myoblast transplantation and autologous intracoronary or intra-arterial mononuclear bone marrow cell transplantation or intra-coronary administration of cardiosphere-derived cells or autologous or allogeneic bone marrow-derived mesenchymal stem cell transplantation. Providers may have used CPT Code 33999 (unlisted procedure, cardiac surgery).</td>
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<tr>
<td>ICD-10 codes will become effective as of October 1, 2015:</td>
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<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
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<tr>
<td>0263T Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest</td>
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<tr>
<td>0264T Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest</td>
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0265T Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

I00 - I99.9 Diseases of the circulatory system

The above policy is based on the following references:

Cardiac Diseases:


28. Mundy L, Hiller J. Autologous bone marrow transplant for the treatment of patients who have experienced heart failure. Horizon Scanning Prioritising Summary. Canberra,
ACT: Adelaide Health Technology Assessment; June 2006;13(2).


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