



Medical Coverage Policy

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Autologous Cell Therapy for Cardiac and Peripheral Arterial Disease

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Overview

This Coverage Policy addresses autologous cell therapy using several cell types, proposed as a method to treat heart damage or peripheral arterial disease.

Coverage Policy

Transplantation of cells into the myocardium is considered experimental, investigational or unproven for ANY indication.

Autologous intra-arterial or intra-muscular bone marrow cell transplantation is considered experimental, investigational or unproven for peripheral arterial disease and other occlusive conditions.

General Background

Autologous Cell Therapy for Treatment of Damaged Myocardium

Autologous cell therapy has been proposed for the treatment of damaged myocardium associated with cardiovascular disease, including acute myocardial infarction (MI), cardiomyopathy, and heart failure. The use of several cell types, including skeletal myoblasts, mesenchymal stem cells (also referred to as bone marrow stromal cells), and hematopoietic stem cells, has been explored for myocardial repair. Skeletal myoblasts are tissue-specific stem cells. Immature myoblasts contained in skeletal muscle can fuse with surrounding myoblasts or with damaged muscle fibers to regenerate functional skeletal muscle. Mesenchymal stem cells and hematopoietic stem cells have the capacity to differentiate into any type of cell, depending on their microenvironment. As they mature, they can acquire all the characteristics of the target tissue, such as myocardium and cardiac vessels. Cells may be delivered systemically or locally, and must then proliferate to provide adequate new tissue prior to differentiating into functional cardiomyocytes that couple with the myocardium. Some cells may require significant manipulation prior to implantation. Stem cells may be delivered via infusion into the coronary arteries or injection into the ventricular wall. The mechanism of action of cell therapy for damaged myocardium is not entirely clear and is likely multifactorial. Stem cells may improve cardiac function by increasing vascularity in the area of ischemia, and may also acquire phenotypic properties of the neighboring cardiac myocytes. In the case of acute MI, improved microvascular function may result in improved regional and global left ventricular function.

Although cell therapy for damaged myocardium is a promising treatment option, randomized controlled trials with long-term follow-up are necessary to establish the efficacy of these procedures and address a number of unresolved, technical issues, including optimum cell type, ideal number of cells, factors that promote engraftment, surgical delivery method and patient selection criteria.

U.S. Food and Drug Administration (FDA)

The U.S. Food and Drug Administration (FDA) regulates cells that are processed in commercial laboratories, as well as the surgical devices used to inject the cells into the myocardium. There are several products being commercially developed for the treatment of damaged myocardium. However, the FDA has not yet issued approvals for any technology associated with the transplantation of autologous cells for the treatment of damaged myocardium. MyoCell (US Stem Cell, Inc, Sunrise, FL), consists of expanded autologous skeletal myoblast, is delivered by the MyoCath, a transendocardial injection catheter. The system is being evaluated for feasibility as well as safety and efficacy in the treatment of post-infarct deterioration of cardiac function in subjects with congestive heart failure. MultiStem® (Athersys Inc., Cleveland, OH) is a proprietary stem cell product for the treatment of diseases and conditions in the neurological, inflammatory, immune and cardiovascular disease areas, as well as other indications. Multipotent adult progenitor cells (MAPC) are obtained from healthy adult bone marrow and can be expanded outside the human body using proprietary manufacturing processes. CardiAMP™ (BioCardia® Inc., San Carlos, CA) is a proprietary molecular diagnostic assay that identifies the potency of a patient's own bone marrow cells and determines if they are an optimal candidate for therapy

Literature Review: Autologous Cell Therapy for Treatment of Damaged Myocardium

Randomized Controlled Trials: Sung et al. (2020) conducted a phase II randomized controlled trial (RCT) that assessed whether intracoronary autologous CD34+ cell therapy could further improve left ventricular (LV) systolic function in patients with diffuse coronary artery disease (CAD) with relatively preserved LV ejection fraction (defined as LVEF > 40%) unsuitable for coronary intervention. Patients (n=60) were randomized to receive to either CD34+ cell therapy (group 1) (n=30) or optimal medical therapy with standard pharmacotherapy (group 2) (n = 30). All patients were followed for one year. Patients were included if they were aged 21–79 years with diffuse obstructive CAD (including stable/unstable angina, prior myocardial infarction > 3 months or elective stenting for stable CAD) with coronary angiographic findings of at least one severe diffuse CAD. Eligible patients were not-candidates for PCI or CABG, had Grade II-IV angina, and reversible myocardial ischemia was shown on thallium scan. The primary endpoints measured the safety and improvement in LV function. Secondary endpoints included (1) overall survival rate; (2) incidence of CD34+ cell transfusion-related clinical adverse event; (3) significant symptomatic improvement in the degrees of angina pectoris assessed by the Canadian Cardiovascular Society (CCS) Angina Grade Score and heart failure (HF) assessed by the New York Heart Association Functional Classification (NYHA Fc). Coronary angiography was done before treatment and after nine months and three-dimensional echocardiography done at three, six and 12 months. Three-dimensional echocardiography demonstrated no significant difference in LVEF between groups 1 and 2 (p=0.295) at 12

months. However, compared with baseline, 12-month LVEF was significantly increased in group 1 ($p < 0.001$) but not in group 2 ($p = 0.297$). From baseline, there were gradual increases in LVEF in group 1 compared to those in group 2 at 1-month, 3-months, 6-months and 12 months (all $p < 0.05$). Additionally, one-year angiogenesis, angina and HF scores were significantly improved in group 1 compared to those in group 2 (all $p < 0.001$). Author noted limitations included the small sample size and short term follow-up. Additionally, current anti-HF medications potential for diastolic dysfunction (e.g., ARB, spironolactone and sodium-glucose transport protein 2 inhibitor) were not investigated for their impact on the LVEF improvement.

Yau et al. (2019) conducted a randomized controlled trial that evaluated the efficacy and safety of injecting mesenchymal precursor cells (MPCs) into the myocardium of patients undergoing a left ventricular assist device (LVAD) implant. End-stage heart failure patients were included if they were age ≥ 18 years and hospitalized for a clinically indicated LVAD as a bridge to a heart transplant or to destination therapy. Patients ($n = 159$) were randomly assigned in a 2:1 ratio to an intramyocardial injection of 150 million MPCs ($n = 106$) or an injection of a cryoprotective medium as sham treatment ($n = 53$). All patients were followed for up to 12 months after randomization or until heart transplant, whichever came first, with end points evaluated at two, four, six, nine, and 12 months. The ongoing two year follow-up assessment documents vital status, transplant, and LVAD explant or replacement. The primary efficacy end point was the proportion of successful temporary weans (of three planned assessments) from LVAD support within six months of randomization. The primary safety end point was the incidence of study intervention-related adverse events (infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, and immune sensitization syndrome) during the one year follow-up period. Secondary end points measured readmissions, adverse events at six months and one year survival. Other end points included survival, anti-HLA antibody sensitization and transplant, and serious adverse events. At the six month follow-up, the mean proportion of successful temporary weaning from LVAD support was 61% among patients who received MPCs and 58% among controls, the difference was not statistically significant. The probability that MPCs increased the likelihood of successful temporary weaning was 69%, which did not meet the predefined 80% threshold for success. No patient experienced a primary safety end point (infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, immune sensitization syndrome) over the one year follow-up. The secondary outcomes measured did not attain statistical significance. Author noted limitations included the efficacy end points, used in traditional heart failure trials, may not apply equally to patients receiving mechanical circulatory support and the high rate of suspected pump thrombosis affected the ability to wean patients, thus limiting the ability to interpret the primary end point. Additionally, enrollment included a wide spectrum of patients (heart failure etiology, age range, LVAD indications) receiving one of two LVAD types (axial and centrifugal flow), which in a relatively small trial may have increased variability and reduced the likelihood of detecting a signal of treatment effect. Finally, international normalized ratio values or platelet counts were not systematically collected nor were anticoagulation regimens. The author concluded that intramyocardial injections of mesenchymal precursor cells, compared with injections of a cryoprotective medium as sham treatment, did not improve successful temporary weaning from left ventricular assist device support at six months.

Fernández-Avilés et al. (2018) conducted a multicenter, double-blind, placebo-controlled randomized controlled trial that evaluated the safety and efficacy of intracoronary infusion of allogeneic human cardiac stem cells (AlloCSC-01) in patients with ST-segment elevation myocardial infarction and left ventricular dysfunction (CAREMI study). Patients were eligible for inclusion if they were aged 18–80 years, presented with STEMI along with a medium-high risk of developing chronic HF. Stent implantation and Thrombolysis in Myocardial Infarction Flow (TIMI) grade three had to be achieved within 12 hours after symptom onset. All critical, non-infarct-related artery lesions should have been treated percutaneously at least 24 hours before magnetic resonance (MR) evaluation. Patients ($n = 49$) were randomly assigned to receive AlloCSC-01 ($n = 33$) or placebo ($n = 16$). The primary outcome measured safety and included all-cause death and major adverse cardiac events at 30 days (all-cause death, reinfarction, hospitalization because of heart failure, sustained ventricular tachycardia, ventricular fibrillation, and stroke). Secondary outcomes measured major adverse cardiac events at six and 12 months, adverse events and immunologic surveillance. Secondary exploratory efficacy end points were changes in infarct size (percentage of left ventricular mass) and indices of ventricular remodeling by magnetic resonance at 12 months. Attended hospital visits were scheduled at one week and at one, three, six, and 12 months following treatment. Telephone visits were scheduled after treatment at two, four, five, and nine months. Two patients allocated to the AlloCSC-01 group were lost to follow-up but were included in the safety analysis. No deaths or major adverse cardiac events were reported at 12 months. AlloCSC-01 elicited low levels of donor-

specific antibodies in two patients. No immune-related adverse events were found, and no differences between groups were observed in magnetic resonance–based efficacy parameters at 12 months. Author noted limitations included the small sample size, short term follow-up and the design of the trial allowed only valid conclusions on safety but no definitive evaluation of efficacy. The authors concluded that the study demonstrated no incremental benefit in infarct size reduction, indices of LV remodeling, laboratory assessments, functional class, or quality of life scores between CSC and placebo-treated patients. Adequately powered studies with larger populations at increased risk for adverse remodeling are needed to demonstrate the potential efficacy of AlloCSC-01 on structural parameters and clinical outcome in STEMI.

Frljak et al. (2018) conducted a sub-study of a parent prospective randomized study (Vrtovec, et al.,2018) comparing the effects of repetitive and single-dose cell therapy in patients with nonischemic dilated cardiomyopathy (DCM). Patients enrolled in the present sub-study included patients enrolled in the repetitive arm of the parent study, who received transendocardial cell therapy at baseline and again six months after enrollment. This design allowed for the analysis of the repetitive electroanatomical mapping, which was performed before cell injections at both time points. Patients were eligible for inclusion if they were aged 18 to 70 years, had a diagnosis of nonischemic DCM, received optimal medical management for ≥ 3 months, had left ventricular ejection fraction (LVEF) $< 40\%$, and New York Heart Association functional class III for ≥ 3 months before referral. Patients (n=60) were randomized to CD34+ cell therapy (Stem Cells Group; n=30), or no cell therapy (Controls; n=30). The Stem Cell (SC) Group received granulocyte-colony stimulating factor, and CD34+ cells were collected by apheresis and injected transendocardially. The primary outcome measured the change in tricuspid annular plane systolic excursion (TAPSE). Secondary outcomes measured were the changes in peak systolic tissue Doppler velocity of tricuspid annulus (St), percent of fractional area change (FAC), left ventricular ejection fraction (LVEF), plasma levels of N-terminal probrain natriuretic peptide (NT-proBNP) and 6-minute walk test distance. In an exploratory analysis, a correlation of RV function and viability of the interventricular septum (IVS) was investigated. At the six month follow-up, there was significant improvements in RV function, peak systolic tissue Doppler velocity of tricuspid annulus and percent of fractional area change ($p=0.001$, $p=0.001$, $p=0.01$, respectively) in the SC Group but not in Controls. On repeat electroanatomical mapping, there was an improvement in interventricular septum (IVS) viability in 19 of 30 patients from the SC Group; this correlated with the improvements in RV function. Author noted limitations included the unblinding nature of the study, small patient population and short-term follow-up. The authors concluded that CD34+ cell therapy appears to be associated with increased IVS viability and improved RV function in patients with DCM. Further studies are warranted to verify the preliminary findings, better define the underlying mechanisms, and investigate whether or not this therapeutic approach could offer benefit in a broader population of patients with chronic heart failure and RV dysfunction.

Nicolau et al (2018) performed a multicenter, double-blind randomized controlled trial (RCT) that evaluated whether autologous bone marrow–derived mononuclear cell (BM-MMC) therapy affects left ventricular (LV) function in patients with ST elevation myocardial infarction (STEMI) who were successfully reperfused with either primary percutaneous coronary intervention (PCI) or a fibrinolytic. This study included patients 30–80 years old with a left ventricular ejection fraction (LVEF) $\leq 50\%$, a successful angioplasty of infarct-related artery and regional dysfunction in the infarct-related area analyzed before cell injection. The patients (n=121) were randomized into two groups. Group one (n=66) received BM-MMC and group two (n=55) received placebo. The primary endpoint was mean improvement in LVEF at six months, analyzed by MRI. Secondary endpoints included other LV remodeling. The primary endpoint, mean LVEF, was not clinically significant between both groups at baseline and at six months ($p=0.21$, $p=0.59$, respectively). Parameters of left ventricular remodeling, such as systolic and diastolic volumes, as well as infarct size, were also similar between groups. Author noted limitations of the study included the lack of a core cell-processing laboratory, the unbalanced enrollment by the centers, and the use of the LVEF improvement may not be the ideal endpoint to investigate cell-infusion efficacy due to its dynamic changes in the acute phase. The study concluded that intracoronary delivery of autologous BM-MC to patients with STEMI did not improve LV function or decrease scar size.

Naseri et al. (2018) reported the results of a phase II/III, double blind, randomized controlled trial (COMPARE CPM-RMI) which assessed the safety and efficacy of autologous bone marrow-derived cell therapy (CD133+ and mononuclear cells [MNCs]) compared to placebo in patients with recent myocardial infarction (RMI) status post coronary artery bypass graft. Patients were included if they were age 18 to 75 years, 10 days to three months following first ST elevation myocardial infarction (STEMI), left ventricular ejection fraction (LVEF) of 20–45%,

target lesion located in the left anterior descending (LAD) section, candidate for coronary artery bypass graft (CABG) and at least four akinetic segments. Patients (n=77) were randomly assigned to receive CD133+ (n=21), MNC (n=30) or placebo (n=26). The primary outcome was the improvement of myocardial perfusion and left ventricular (LV) function in STEMI patients after injections of bone marrow derived cells into the infarcted myocardium compared to the placebo group. In addition, different effects of CD133+ and MNC cells at determined endpoints were evaluated. The primary outcome was assessed by changes in global left ventricular ejection fraction (LVEF) at rest by gated single photon emission computed tomography (SPECT). Secondary outcomes were: adverse cardiac events that included death, reinfarction, implantable cardioverter defibrillator (ICD) placement, infection, and arrhythmia. Changes in wall motion score (WMS), decreased systolic wall thickening of the myocardium, non-viable (NV) segments, and perfusion defect score (PDS) were assessed by gated SPECT, and NYHA classification. Nine patients were lost to follow-up. There were no related serious adverse events reported. The intramyocardial transplantation of both cell types indicated a clinically significant increase in left ventricular ejection fraction by 9% (p=0.01) and improved decreased systolic wall thickening by -3.7 (p=0.03). The CD133+ group showed a clinically significant decrease in non-viable segments by 75% (p=0.001) compared to the placebo and 60% (p=0.01) compared to the MNC group. We observed this improvement at both the six and 18 month time points. Author noted limitations included the small patient size and due to limited access, the patients did not undergo MRI imaging which is the gold standard for cardiac function. The study concluded that intramyocardial injections of CD133+ cells or MNCs appeared to be safe and efficient with superiority of CD133+ cells for patients with RMI. Larger studies are needed to validate the outcomes of this study.

Bartunek et al. (2017) conducted a double-blind, sham-randomized controlled trial (CHART-1) which evaluated the therapeutic efficacy and safety of cardiopoietic cells delivered endomyocardially in patients with symptomatic ischemic heart failure on guideline-directed therapy. The study included patients between 18 and 79 years old, left ventricular ejection fraction (LVEF) \geq 35%, ischemic heart failure without the need for revascularization, heart failure hospitalization, or outpatient vasoactive heart failure therapy (e.g. vasodilators, positive inotropic agents, vasopressors or diuretics) within 12 months. Patients were in New York Heart Association (NYHA) class II or greater at screening, and within 12 months were NYHA class III or IV or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class four. Required inclusion criteria was guideline-directed medical therapy, a six minute walk distance $>$ 100 to \leq 400 meters and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score $>$ 30. Patients (n=271) were randomly assigned to receive a cardiopoietic cell injection (n=120) or a sham control procedure (n=151). The outcome efficacy was assessed at 39 weeks measuring all-cause mortality, worsening heart failure events, MLHFQ score, 6-min walk distance, left ventricular end-systolic volume (LVESV) and LVEF. The safety assessment through week 39 included all-cause mortality, rehospitalization, cardiac transplantation, myocardial infarction, stroke, aborted sudden death (resuscitated sudden death or appropriate implantable cardioverter defibrillator [ICD] shocks), along with serious and non-serious adverse events. The primary endpoint across the total study cohort was neutral (p=0.27). There was no significant between-group differences noted for individual components of the primary outcome, but there was a clinically significant improvement in the six minute walk distance (p=0.07) in the cardiopoietic cell injection group compared to the sham control group. Fourteen patients experienced catheter-procedure related serious adverse events which included the following: ventricular tachyarrhythmia, left bundle branch block, dissection of the ascending aorta requiring surgery, transient ischemic attack, femoral artery stenosis, and pericardial effusion. No difference was observed in serious adverse events between groups. Limitations noted by the authors included the short-term follow-up and the study population was Caucasian and predominantly male. The authors concluded that further evaluation of cardiopoietic cell therapy in patients with elevated end-diastolic volume is warranted.

Xiao et al. (2017) performed an RCT (n=52) to compare efficacy of intracoronary administration of bone marrow mononuclear cells (BMMC) or mesenchymal stem cells (BMSC) in patients with dilated cardiomyopathy (DCM). Patients were randomized to receive intracoronary infusion of BMMC (n=16), BMSC (n=17) or equal volume normal saline (n=20/control group). Inclusion criteria were age 18–75 years with normal coronary arteries, LVEF $<$ 40%, New York Heart Association (NYHA) functional class II-IV, and a proportion of fixed defects $<$ 40%. Patients were excluded who had coronary artery disease based on coronary angiography prior to cell delivery, ventricular arrhythmias, and any comorbidity with an impact on survival. All patients received optimal medical therapy as recommended by current guidelines. The primary endpoints of the study were changes in NYHA class, LVEF, left ventricular end-diastolic diameter (LVEDd), and the proportion of fixed defects. Major adverse

cardiovascular events (MACE) included procedural complications, any new-onset arrhythmia, hemodynamic instability, death by any cause. At three months of follow-up, LVEF, NYHA class, and myocardial perfusion had improved significantly in the BMSC group ($p=0.004$, 0.020 , and 0.019 , respectively) and there were significant changes in LVEF and NYHA class in the BMMC group compared with control patients ($p=0.042$ and 0.047 , respectively). LVEDd was unchanged. At the 12-month follow-up, compared to the control group, LVEF, NYHA class, and myocardial perfusion improved significantly in the BMSC group ($p=0.005$, 0.050 and 0.038 , respectively), but not in the BMMC group ($p>0.05$). There were no differences in MACE among the three groups ($p=0.817$). Study limitations include the small sample size and short-term follow-up period. It was concluded that intracoronary administration of autologous BMC in patients with DCM is safe and effective and that BMMC transplantation only accelerates cardiac function recovery while the improvement in BMSC therapy is sustained. However, additional large randomized placebo-controlled clinical trials are needed to confirm these findings.

Delewi et al. (2015) reported long-term follow-up results of the randomized controlled HEBE trial ($n=200$). In the HEBE study patients who had a large first acute myocardial infarction (AMI) treated with primary percutaneous coronary intervention were randomized to intracoronary infusion of bone marrow mononuclear cells (BMMCs) ($n=69$), peripheral blood mononuclear cells (PBMCs) ($n=66$) or standard therapy ($n=65$). Outcome measures of LV end-diastolic volume (LVEDV) and clinical adverse events, including death, myocardial re-infarction and hospitalization for heart failure were assessed at five years of follow-up after AMI. Of the 200 patients enrolled, nine patients died and 12 patients were lost to follow-up at five years after AMI. At five-year follow-up, the BMMC group showed less of an increase in LVEDV compared to the control group ($p=0.03$). No difference was found between the PBMC group and controls ($p=0.69$). The combined endpoint of death and hospitalization for heart failure was not significantly different between the BMMC ($n=4$) and control ($n=1$) groups ($p=0.20$). There was also no difference for this combined endpoint between PBMC ($n=6$) and controls ($n=4$) ($p=0.74$). The composite endpoint of death or recurrent myocardial infarction was significantly higher in the PBMC group compared with controls ($p=0.008$), with no difference between the BMMC group and controls ($p=0.67$). Although these study results suggest that BMMC therapy may decrease the progression of LVEDV, additional well-designed, large-scale trials are needed to confirm findings.

Traverse et al., for the Cardiovascular Cell Therapy Research Network (CCTRN) (2012) conducted a randomized, double-blind placebo controlled trial to determine the effect of intracoronary autologous bone marrow mononuclear cell (BMC) delivery after ST elevated myocardial infarction (STEMI). The primary end points were change in global (left ventricular ejection fraction [LVEF]) and regional (wall motion) LV function in infarct and border zones at six months, and change in LV function as affected by timing of treatment on day three vs. day seven. At six months, there was no significant increase in LVEF for the BMC group vs. the placebo group ($p=0.96$). There was no significant treatment effect on regional LV function observed in either infarct or border zones, and there were no significant differences in change in global LV function for patients treated at day three or day seven ($p=0.70$). Treatment timing had no significant effect on regional LV function recovery. In 2018 Traverse et al. reported the final two year results for the TIME study. Pre-specified patients were followed for two years with additional serial cardiac magnetic resonance imaging (cMRI) at one and two years. 85 patients completed baseline, six month, one year and two year cardiac magnetic resonance imaging (cMRI). At two years, LVEF was similar in the BMC (48.7%) and placebo groups (51.6%) with no difference in regional LV function. Infarct size and LV mass decreased $\geq 30\%$ in each group at six months and declined gradually to two years. LV volumes increased approximately 10% at six months and remained stable to two years. The authors concluded that in patients with large anterior STEMIs, BMC administration did not improve recovery of LV function over 2-years. Importantly, no concerns associated with the safety of using BMCs were observed in this high-risk cohort who demonstrate ongoing stability of LV function and volumes out to two years.

Duckers et al. (2011) reported on a Phase II, randomized trial that evaluated the percutaneous intramyocardial transplantation of autologous skeletal myoblasts in congestive heart failure patients (SEISMIC trial). The patients were randomized 2:1 to autologous skeletal myoblast therapy vs. optimal medical treatment. The primary safety end-point was identified as the incidence of procedural and device related serious adverse events, whereas the efficacy endpoints were defined as the change in global left ventricular ejection fraction (LVEF) by multigated acquisition (MUGA) scan, change in New York Heart Association (NYHA) classification of heart failure and in the distance achieved during a six minute walk test (6MW) at six month follow-up. Forty subjects were randomized to the treatment arm ($n=26$), or to the control arm ($n=14$). There were 12 sustained arrhythmic events and one death after episodes of ventricular tachycardia (VT) in the treatment group and 14

events in the control group ($p=ns$). At six 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; $p=ns$). 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, one patient experienced a deterioration in NYHA classification (8.0%), whereas five patients improved one or two classes (20.0%; $p=0.06$). However, therapy did not improve the global LVEF as measured by MUGA at the six month follow-up. This study is preliminary and further evaluation of efficacy and safety needs to be validated in future phase II/III studies.

Traverse et al. (2011) reported on results of 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 (LV ejection fraction [LVEF] $\leq 45\%$) following successful primary percutaneous coronary intervention (PCI). The study examined if intracoronary delivery of autologous BMCs improves global and regional LV function when delivered two to three weeks following first MI. The authors noted that clinical trials suggest that intracoronary delivery of autologous bone marrow mononuclear cells (BMCs) may improve left ventricular (LV) function when administered within the first week following myocardial infarction (MI). Since a substantial number of patients may not present for early cell delivery, the efficacy of autologous BMC delivery two to three weeks post-MI warrants investigation. Intracoronary infusion of autologous BMCs (total nucleated cells) or placebo (BMC: placebo, 2:1) was performed. The main outcomes were changes in global (LVEF) and regional (wall motion) LV function in the infarct and border zone between baseline and six months, measured by cardiac magnetic resonance imaging. Secondary end points included changes in LV volumes and infarct size. Change between baseline and six months in the BMC group vs. placebo for mean LVEF (48.7% to 49.2% vs. 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 vs. 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 vs. 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 six months vs. baseline. The authors concluded that among patients with MI and LV dysfunction following reperfusion with PCI, intracoronary infusion of autologous BMCs vs. intracoronary placebo infusion, two to three weeks after PCI, did not improve global or regional function at six months.

Menasche et al. (2008) reported on results of a Phase II study of skeletal myoblast transplantation referred to as the myoblast autologous grafting in ischemic cardiomyopathy or MAGIC trial (Menasche, et al., 2004; Menasche, et al., 2008). The randomized, placebo-controlled, double-blind trial involved 97 patients in 30 clinical centers in several European countries and Canada. Patients received either cells grown from a skeletal muscle biopsy or a placebo solution injected in and around the scar. An implantable cardioverter-defibrillator was placed in all patients. The primary outcomes were the six-month changes in global and regional LV function as assessed by echocardiography. The safety end-points included a composite index of major cardiac adverse events and ventricular arrhythmias. Patients were randomized to receive myoblasts (400 [$n=33$] or 800 [$n=34$] million) or the placebo ($n=30$). The myoblast transfer did not improve regional or global LV function beyond that seen in the control group. The absolute change in ejection fraction (median [interquartile range]) between six 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 ($p=0.95$). There were a higher number of arrhythmic events in the myoblast-treated patients, but six-month rates of major cardiac adverse events and of ventricular arrhythmias did not differ significantly between the groups.

The REPAIR-AMI trial (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction), a double-blind, placebo–controlled, multicenter trial, included 204 patients and examined whether intracoronary infusion of enriched BMC is associated with improved global LV function in patients with MI treated with state-of-the-art methods (Schachinger, et al., 2006). At four months, it was noted that the absolute improvement in the global LVEF was significantly greater in the BMC group than in the placebo group. Patients with baseline LVEF at or below the median value of 48.9% appeared to derive the most benefit. At one year, intracoronary infusion of BMC was associated with a reduction in the prespecified combined clinical end point of death, recurrence of MI, and any revascularization procedure. Assmus, et al. (2010) reported on two-year outcomes from the REPAIR-AMI trial. At two years, the cumulative end point of death, myocardial infarction, or necessity for revascularization was noted to be reduced in the BMC group compared with placebo group (hazard ratio, 0.58; 95% CI, 0.36–0.94; $p=0.025$). In addition, the combined end point death and recurrence of myocardial

infarction and rehospitalization for heart failure, reflecting progression toward heart failure, was reduced in the BMC group (hazard ratio, 0.26; 95% CI, 0.085–0.77; $p=0.015$). The authors note that larger studies focusing on clinical event rates are warranted to confirm the effects of BMC administration on mortality and progression of heart failure in patients with AMIs.

Systematic Reviews: Yang et al. (2020) conducted a systematic review and meta-analysis of the evidence ($n=43$ RCTs) evaluating the short and long-term efficacy of mononuclear cell transplantation (MNC) in patients with myocardial infarction. The primary outcomes measured the changes in left ventricular ejection fraction (LVEF) and infarct size from baseline to follow-up. Secondary outcomes measured changes in the left ventricular end-systolic volume, left ventricular end-diastolic volume, brain natriuretic peptide/N-terminal pro-B-type natriuretic peptide, 6-minute walk test, New York Heart Association class, and major adverse cardiac events (MACE). Randomized controlled trials (RCTs) were eligible for inclusion if the transplanted cells were limited to unsorted MNC cell types without using pretreated or engineered MNCs; the patients had ST-segment elevation myocardial infarction (STEMI) and ischemic cardiomyopathy (ICM) with previous MI; and more than one month of follow-up was recorded. The follow-up ranged from 3–96 months. In the short-term follow-up, patients treated with MNCs demonstrated a significant increase in absolute LVEF of 2.21% ($p<0.001$) and 6.01% ($p<0.001$) in acute myocardial infarction (AMI) and ischemic cardiomyopathy studies, respectively. This effect was sustained in long-term follow-up. MNC therapy significantly reduced left ventricular end-systolic volume; however, infarct size, 6-minute walk test, New York Heart Association class, and MACE rates were comparable. Author noted limitations included the clinical heterogeneity across trials, particularly with regard to cell dosage, the timing of infusion, and imaging modalities. Another limitation was the small number of patients that were available for analysis of performance status and functional biomarkers. The authors concluded that MNC therapy may convey a modest but sustained increase in LVEF in ischemic cardiomyopathy patients. Well-designed, adequately powered RCTs using optimized delivery and doses are needed to support the outcome of this study.

Lalu et al. (2018) conducted a systematic review of randomized controlled trials, nonrandomized controlled trials and observational studies that evaluated the safety and efficacy of mesenchymal stem cells (MSCs) for acute myocardial infarction (AMI) and ischemic heart failure (IHF). A total of 23 studies (1167 patients) met the inclusion criteria. Of these, 11 studies evaluated AMI ($n=528$) and 12 studies evaluated IHF (639 patients). There was no association between MSCs and acute adverse events. The primary outcome was safety, which was assessed by adverse events. The secondary outcome was efficacy, which was assessed by mortality and left ventricular ejection fraction (LVEF). No significant difference in mortality was noted. There was a significant improvement in overall LVEF in patients who received MSCs. In a post hoc analysis using weighted mean difference, patients treated with MSCs had a 4% increase in ejection fraction compared to control. Results of the study indicated that MSC therapy for ischemic heart disease appears to be safe. The authors concluded that there is a need for well-designed randomized control trials with rigorous adverse event reporting and comprehensive assessment of cardiac function to further establish a clear risk-benefit profile and efficacy of MSCs.

Clifford et al. (2012) conducted a Cochrane systematic review to evaluate the effectiveness of adult bone marrow-derived stem cells to treat acute myocardial infarction (AMI). The trial included 33 randomized controlled trials (1765 participants) that compared autologous stem/progenitor cells with no autologous stem/progenitor cells in patients with AMI. Stem/progenitor cells were not associated with statistically significant changes in the incidence of mortality or morbidity. In short term follow-up, stem cell treatment was observed to improve LVEF significantly (weighted mean difference [WMD] 2.87, 95% CI 2.00 to 3.73). The improvement in LVEF was maintained over long-term follow-up of 12 -61 months (WMD 3.75, 95% CI 2.57-4.93). The authors concluded that the results of systematic review suggest that moderate improvement in global heart function is significant and sustained long-term. However, because mortality rates after successful revascularization of the culprit arteries are very low, larger number of participants would be required to assess the full clinical effect of this treatment. Standardization of methodology, cell dosing and cell product formulation, timing of cell transplantation and patient selection may also be required to reduce the substantial heterogeneity observed among the included studies.

Abdel-Latif et al. (2007) conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies of bone marrow derived cells (BMCs) transplantation to treat ischemic heart disease. Eighteen studies (12 randomized controlled studies and six cohort studies) with 999 patients were included in the review.

The main outcomes for the review were change from baseline in mean LV ejection fraction, infarct scar size, LV end-systolic volume and LV end-diastolic volume. The adult BMCs used in the studies included BM mononuclear cells, BM mesenchymal stem cells, and BM-derived circulating progenitor cells. When BMC transplantation was compared to controls, the results included: improved left ventricular ejection fraction (pooled difference, 3.66%; 95% confidence interval [CI], 1.93%–5.40%; $p < 0.001$); reduced infarct scar size (–5.49%; 95% CI, –9.10% to –1.88%; $p = 0.003$); and reduced left ventricular end-systolic volume (–4.80 ml; 95% CI, –8.20 to –1.41 ml; $p = 0.006$). The authors note that the available evidence suggests that BMC transplantation is associated with modest improvements in physiologic and anatomic parameters in patients with both acute MI and chronic ischemic heart disease. The results support the conduction of large randomized trials to evaluate the long-term impact of BMC therapy as compared with standard of care on patient-important outcomes.

Lipinski et al. (2007) performed a meta-analysis of clinical trials on intracoronary cell therapy after acute MI to determine the impact of intracoronary cell therapy on post-infarction LV function. Ten controlled studies with 698 patients were included in the review, with a median follow-up of six months (range of three to 18 months). The primary end point in the studies was change in LVEF, with secondary end points including changes in infarct size, cardiac dimensions, and dichotomous clinical outcomes. Review of the studies indicated that subjects that received intracoronary cell therapy had a significant improvement in LVEF (3.0% increase; 95% CI 1.9 to 4.1; $p < 0.001$), as well as a reduction in infarct size (–5.6%; 95% CI –8.7 to –2.5; $p < 0.001$) and end-systolic volume (–7.4 ml; 95% CI –12.2 to –2.7; $p = 0.002$), and a trend toward reduced end-diastolic volume (–4.6 ml; 95% CI –10.4 to 1.1; $p = 0.11$). It was also noted that intracoronary cell therapy was associated with a minimally significant reduction in recurrent acute MI ($p = 0.04$) and with trends toward reduced death, rehospitalization for heart failure and repeat revascularization. Meta-regression suggested the possibility of an existence of a dose-response association between injected cell volume and LVEF change ($p = 0.066$). The authors concluded that the data confirms the beneficial impact of this therapy, and further multicenter randomized trials are supported.

Cell Therapy for Peripheral Arterial Disease

Peripheral arterial (PAD) generally refers to a disorder that obstructs the blood supply to the lower or upper extremities. It is generally caused by atherosclerosis, but may result from thrombosis, embolism, vasculitis, fibromuscular dysplasia, or entrapment. PAD correlates strongly with risk of major cardiovascular events, and is frequently associated with coronary and cerebral atherosclerosis (Creager, et al., 2011). The main symptom of PAD is intermittent claudication. More severe symptoms include pain at rest, ulceration and gangrene. Worsening of the condition may lead to critical limb ischemia. The goal for treatment of PAD is reduction in cardiovascular morbidity and mortality, and improvement in quality of life by decreasing symptoms of claudication, eliminating rest pain, and preserving limb viability. Treatment may include risk factor modification by lifestyle measures and pharmacologic therapy to reduce the risk of adverse cardiovascular events, such as MI, stroke, and death. The symptoms of claudication may be treated with pharmacotherapy or exercise rehabilitation. Management of critical limb ischemia often includes endovascular interventions or surgical reconstruction to improve blood supply and to maintain limb viability. Revascularization may be performed in some patients with disabling symptoms of claudication that persist despite exercise therapy and pharmacotherapy (Creager, et al., 2011).

To treat the symptoms of severe forms of PAD where revascularization procedures are not possible, research has been focusing on the use of bone marrow (BM)-derived stem and progenitor cells, which have been utilized in a potential new therapeutic option to induce therapeutic angiogenesis. The goal with this treatment is to improve the vascularization of the ischemic leg so that perfusion increases sufficiently for wound healing to occur, and to resolve pain at rest. Intramuscular and intra-arterial injection or a combination of both has been investigated in treatment of PAD. The underlying principle of intramuscular injection is the creation of a cell depot with paracrine activity in the ischemic area, although the mechanisms by which transplanted cells improve the patients' clinical status are unclear (Lawall, et al., 2011). Intramuscular injection is generally administered into the gastrocnemius muscle along a symmetric grid with a fixed number of injections (between 20 and 60) in most trials. There is no apparent direct comparison between different intramuscular injection sites and numbers of injections. Issues to be resolved include selection of optimal cell type, isolation method, cell number, and the role of colony stimulating factors, route of administration, and paracrine stimulation mechanisms (Lawall, et al., 2011).

Autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions is an emerging technology. Studies evaluating this treatment approach are limited. Additional well designed randomized controlled trials are needed to evaluate the safety, efficacy, and long-term outcomes of this procedure.

Literature Review: Stem-Cell Transplantation for Peripheral Arterial Disease

Randomized Controlled Trials: Sharma et al. (2021) conducted a double-blind, placebo, randomized controlled trial that evaluated safety and efficacy of angiogenesis induced by intra-arterial autologous bone marrow-derived stem cell (BMSC) injection in patients with severe peripheral arterial disease (PAD). Eighty-one patients with severe PAD, including 56 with critical limb ischemia (CLI) and 25 with severe claudication, were randomized to receive sham injection (group A; n=40) or intra-arterial BMSC injection at the site of occlusion (group B; n=41). Patients were included in the study based on clinical criteria (in cases of claudication, walking distance of < 200 m; in cases of CLI, Fontaine class IIC–IV and Rutherford class III/VI), hemodynamic criteria (ankle systolic pressure < 50 mm Hg and/or resting ankle-brachial index [ABI] < 0.5 in the affected limb on 2 consecutive examinations \geq 2 d apart), and imaging criteria (occluded femoral, popliteal, or infrapopliteal arteries, with no distal below-ankle flow). Primary endpoints measured the improvement in ankle-brachial index (ABI) of > 0.1 and transcutaneous pressure of oxygen (TcPO₂) of > 15% at the mid and lower foot at six months. Secondary endpoints included relief from rest pain, > 30% reduction in ulcer size and reduction in major amputation in patients with CLI and > 50% improvement in pain-free walking distance in patients with severe claudication. Technical success was achieved in all patients, without complications. At six months, group B showed significant improvements in ABI of > 0.1, TcPO₂ of > 15% at the midfoot and lower foot ($p < 0.0001$, $p = 0.0001$ and $p < 0.0001$, respectively). No patients with CLI underwent major amputation in group B, compared with four in group A ($p = 0.0390$). No significant difference was observed in relief from rest pain or > 30% reduction in ulcer size among patients with CLI or in > 50% improvement in pain-free walking distance among patients with severe claudication.

Lindeman et al. (2018) reported the results of a phase-III randomized controlled trial that evaluated the potential benefit of intramuscular injections with high dose Bone Marrow-derived Mononuclear Cells (BM-MNC) for patients with no-option end-stage peripheral artery disease. Inclusion criteria included stable or progressive disabling peripheral artery disease (PAD), no imminent need for amputation and no options for revascularization. Patients (n=54) were randomized to receive BM-MNCs (n=28) or placebo (n=26). Primary clinical endpoints measured limb salvage or the pain-free walking distance in case of intermittent claudication. Secondary follow-up parameters measured Ankle-brachial pressure index (ABI), the 36-Item Short-Form Health Survey SF-36, 11 and the Brief Pain Inventory score (BPI-SF). Patients were evaluated at one, six, and 12 months after implantation. No significant differences were observed for the primary (number of amputations, (pain free) walking distance) and secondary outcome parameters (ankle brachial index, pain scores, quality of life [SF-36]). Author noted limitations included a protracted period of inclusion due to the lower than anticipated number of eligible patients and functional outcomes (walking distances) could not be performed for all patients (amputation, severe foot ulcer). The authors concluded that there was no clinical benefit of intramuscular delivery of BM-MNC in patients with disabling PAD or chronic limb ischemia.

Perin et al. (2017) published results of a randomized, double-blind, placebo-controlled clinical trial (n=82) to evaluate the effect of administration of autologous bone marrow-derived aldehyde dehydrogenase bright (ALDHbr) cells (n=41 subjects) versus cell-free placebo (n=41 subjects) in individuals with PAD and intermittent claudication. Patients aged 40 years and older with a diagnosis of atherosclerotic lower extremity PAD and symptom-limiting intermittent claudication were recruited for the Patients with Intermittent Claudication Injected with ALDH Bright Cells (PACE) trial. Subjects had to exhibit greater claudication symptoms in one leg (the index leg), with documentation of no aorto-iliac (inflow) stenosis and with a significant (\geq 50%) stenosis or occlusion of at least one infra-inguinal arterial segment (e.g., the superficial femoral artery, popliteal artery, and/or infra-popliteal arteries). Patients with prior index leg bypass grafts were included only when the bypass graft was occluded. The primary endpoints included change from baseline to six months in peak walking time (PWT), capillary perfusion measured by magnetic resonance imaging (MRI), and safety. The treated study cohort included 38 participants in the ALDHbr group and 40 participants in the placebo group. At six-month follow-up, no statistically significant changes were found for any of the four primary efficacy endpoints in response to the administration of ALDHbr cells. Between onset of study procedures and the six month follow-up visit, one serious

adverse event (limb ischemia requiring revascularization) occurred in the ALDHbr group. There were five serious adverse events in five participants in the placebo group, including a diagnosis of bladder cancer, limb ischemia requiring revascularization, a coronary artery bypass graft (CABG) procedure, one percutaneous intervention (PCI), and one hospitalization for anemia. In terms of safety, all reported events were determined to be unrelated to therapy, however ALDHbr cell administration was not found to be effective in changing the stated outcome measures.

Teraa et al. (2015) conducted the double-blind, randomized, placebo-controlled Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial (n=160) to examine the effectiveness of repetitive intra-arterial infusion of bone marrow mononuclear cells (BMMNCs) (n=81) versus placebo (n=79) for the prevention of major amputation in patients with severe, non-revascularizable limb ischemia. Inclusion criteria were severe infra-popliteal PAD, or evident non-revascularizable severe atherosclerotic lesions confirmed by imaging studies. Patients were excluded if there was a history of neoplasm or malignancy in the past 10 years or concomitant disease with life expectancy of less than one year. A total of 15 patients, six in the BM-MNC and nine in the placebo group, did not complete the scheduled three infusions due to the occurrence of a major amputation or mortality. The primary outcome was major amputation at six months, with secondary outcomes of all-cause mortality, occurrence of malignancy, or hospitalization due to infection. No significant differences were observed for any outcome measures. Therefore it was concluded that 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.

A Phase II double-blind placebo-controlled study was conducted by Poole et al. (2013) to investigate whether therapy with granulocyte-macrophage colony-stimulating factor (GM-CSF improves exercise capacity in patients with intermittent claudication (n=159). Patients were randomized to receive four weeks of subcutaneous injections of GM-CSF, 5000 ug/day three times per week (n=79), or placebo (n=80). There was no significant difference between groups in the primary outcome measure, peak treadmill walking time (PWT), at three months (mean difference in change in PWT, 53 seconds [95% CI, -6 to 112], p=0.08).

Walter et al. (2011) reported on a Phase II, double-blind, randomized-start trial (PROVASA). Forty patients with critical limb ischemia received either intra-arterial administration of BMMNC or placebo followed by active treatment with BMMNC (open label) after three months. Intra-arterial administration of BMMNC did not significantly increase ankle-brachial index and, therefore, the trial missed its primary end point. It was found that cell therapy was associated with significantly improved ulcer healing (ulcer area: $3.2 \pm 4.7 \text{ cm}^2$ to $1.89 \pm 3.5 \text{ cm}^2$ [p=0.014]) versus placebo, $2.92 \pm 3.5 \text{ cm}^2$ to $2.89 \pm 4.1 \text{ cm}^2$ [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 three months. Limb salvage and amputation-free survival rates did not change between the groups. Repeated BMMNC administration and higher BMMNC numbers and functionality were found to be the only independent predictors of improved ulcer healing. Ulcer healing induced by repeated BMMNC administration significantly correlated with limb salvage (r=0.8; p<0.001). The authors concluded that intra-arterial administration of BMMNC is safe and feasible and accelerates wound healing in patients without extensive gangrene and impending amputation. They state that exploratory findings of this pilot trial need to be confirmed in a larger randomized trial in patients with critical limb ischemia and stable ulcers.

Procházka et al. (2010) conducted a randomized study of 96 with critical limb ischemia (CLI). A total of 96 patients with CLI and foot ulcer (FU) were randomized into two groups. Patients in group I (n=42) underwent local treatment with autologous bone marrow stem cells (ABMSC) concentrate while those in group II (n=54) received standard medical care. The bone marrow concentrate was administered by 40 injections, into the ischemic limb along the posterior and anterior tibial artery. The frequency of major limb amputation in groups I and II was 21% and 44% within the 120 days of follow up, respectively (p<0.05). In the salvaged limbs of group I both toe pressure and toe brachial index increased (from 22.66 ± 5.32 to $25.63 \pm 4.75 \text{ mmHg}$ and from 0.14 ± 0.03 to 0.17 ± 0.03 , respectively). The CD34+ cell counts in bone marrow concentrate (BMC) decreased (correlation: p=0.024) with age, even though no correlation was found between age and healing. An unexpected finding in the study was made of relative, bone marrow lymphopenia in the initial bone marrow concentrates in patients who failed ABMSC therapy (21% of major limb amputation), with the difference noted to be statistically significant (p<0.040). The authors concluded ABMSC therapy results in 79% limb salvage in patients suffering from CLI and FU. Lymphopenia and thrombocytopenia were identified as potential causative factors in the remaining 21% that

suggest that at least a partial correction with platelet supplementation may be of use. Further studies are needed to validate these findings.

Systematic Reviews: Gao et al. (2019) conducted a systematic review and meta-analysis that evaluated the efficacy and safety of autologous implantation of stem cells for peripheral artery disease. The primary outcomes measured amputation rate, major amputation rate, ulcer healing rate, and side effects. The second outcomes measured were ankle-brachial index (ABI), transcutaneous oxygen tension (TcO₂), rest pain score, and pain-free walking distance (PFWD). The review consisted of 27 RCTs (n=1186 patients) with 1280 limbs. Meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy on the healing rate of ulcers. There was also significant improvement in ABI, TcO₂, and PFWD while significant reduction was shown in amputation rate and rest pain scores. But the result presented no significant improvement in major limb salvage. Eight trials reported the side effects of autologous stem cell therapy, and no serious side effects related to stem cells were reported. Author noted limitations included low quality studies with unclear or high risk of bias. Secondly, several studies had a small patient population with limited information for outcomes, such as adverse events. Thirdly, the included patients, types of stem cells, methods of transplantation, control group, and follow-up time were different among RCTs, which could cause heterogeneity. The author concluded that autologous stem cell therapy may have a positive effect on “no-option” patients with PAD, but presented no significant improvement in major limb salvage. The evidence is insufficient to due to high risk of bias and low-quality evidence of outcomes. Larger, randomized, double-blind, placebo-controlled, and multicenter trials are needed.

Abdul Wahid et al. (2018) conducted a Cochrane systematic review to compare the efficacy and safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' critical lower limb ischemia (CLI) patients. The trial included 7 randomized controlled trials (359 participants) that compared bone marrow-mononuclear cells (BM-MNCs) versus mobilized peripheral blood stem cells (mPBSCs), BM-MNCs versus bone marrow-mesenchymal stem cells (BM-MSCs), high cell dose versus low cell dose, and intramuscular (IM) versus intra-arterial (IA) routes of cell implantation. The authors concluded that based on low- and very low-quality evidence there are no clear differences between different stem cell sources and different treatment regimens of autologous cell implantation for outcomes such as all-cause mortality, amputation rate, ulcer healing, and rest pain for 'no option' CLI patients. Do to the lack of high-quality evidence the efficacy and long-term safety of autologous cells derived from different sources, prepared using different protocols, administered at different doses, and delivered via different routes for the treatment of 'no-option' CLI patients, cannot be determined. RCTs with larger numbers of participants and longer follow-up are needed to determine the efficacy and safety of cell-based therapy for CLI patients.

Xie et al. (2018) conducted a systematic review and meta-analysis of 23 randomized controlled trials (n=962 patients) to review evidence for the safety and efficacy of autologous stem cell therapy in critical limb ischemia (CLI). The included patients were ineligible for surgical or percutaneous revascularization. The studies included the following types of stem cells: bone marrow mononuclear cells, bone marrow mesenchymal stem cells, bone marrow stem cells, peripheral blood mononuclear cells, peripheral blood stem cells, CD34+, or CD133+ stem cells. The transplantation method of stem cell was intramuscular or intra-arterial. The mean follow-ups of the studies were three months, six months and 12 months. Meta-analysis showed that cell therapy significantly increased the probability of ulcer healing, angiogenesis and reduced the amputation rates (p<0.00001, p<0.0001, and p<0.0001, respectively) compared to the control group. Ankle-brachial index (ABI) and pain-free walking distance were significantly better in the cell therapy group than in the control group (p<0.01). The authors concluded that autologous stem cell therapy is safe and effective in CLI. However, higher quality and larger RCTs are required for further investigation to support clinical application of stem cell transplantation.

Rigato et al. (2017) performed a systematic review and meta-analysis to evaluate the safety and effectiveness of autologous cell therapy for intractable peripheral arterial disease (PAD)/critical limb ischemia (CLI). RCTs (19 studies/837 patients), non-randomized trials (n=7 studies/338 patients), and non-controlled studies (n=41 studies/1177 patients) were included in the analysis. Patients selected in studies were ineligible for surgical or percutaneous revascularization. The cell products used in studies included BMMNCs, BMMSCs, or PBMNCs. The primary outcome was the rate of major amputation (defined as the removal of the limb of a part of it above the ankle) in the cell therapy versus control group. Secondary outcomes included amputation free survival and complete wound healing. Follow-up timeframes ranged from six to ten months. A primary meta-analysis was

performed on all RCTs (n=19 studies). For the primary outcome, cell therapy was associated with a statistically significant reduction in amputation rate (p=0.0004) and increased probability of amputation-free survival (p=0.01). Mortality was not significantly improved (p=0.39). Cell therapy increased the probability of complete wound healing by 59%. In a sub-analysis of only randomized placebo-controlled trials (n=11 studies), cell therapy was associated with non-significant improvements in amputation rate (p=0.12), amputation-free survival (p=0.36), and wound healing (p=0.07). When the analysis was further limited to RCTs with a low risk of bias (n≤3 studies depending on the outcome), cell therapy appeared to confer no benefit for all endpoints. In general cell therapy was found to be associated with mild and primarily transient adverse events. The secondary analysis (i.e., all controlled trials; n=1175 patients) showed that approximately one amputation per year could potentially be avoided for every two patients successfully treated with cell therapy. Although the overall results of this analysis suggest that cell therapy may be safe and effective in treating this subset of patients with PAD/CLI, the validity is challenged by limitations of low-moderate quality and high heterogeneity of studies. Additional well designed RCTs with long-term follow-up are needed to confirm these findings.

Moazzami et al. (2011) reported on a Cochrane review of local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischemia. Two small, randomized studies, with a combined total of 57 patients, met the inclusion criteria. In one study the effects of intramuscular injections of bone marrow derived mononuclear cells (BMMNCs) in the ischemic lower limbs of patients with critical limb ischemia (CLI) were compared with control (standard conservative treatment). No significant difference was observed between the two groups for either pain (p=0.37) or the ankle brachial pressure index (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 five 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). Pain reduction was greater in the treatment group than in the control group (p<0.001) as was an increase in ABI (mean increase 0.13 vs. 0.02; p<0.01). The treatment group experienced a statistically significant increase in pain-free walking distance compared with the control group (mean increase 306.4m vs. 78.6m, p=0.007). A smaller proportion of participants underwent amputation in the treatment group as compared with the control group (0% versus 36%, p=0.007). The author concluded that the data from the published trials suggest that there is insufficient evidence to support this treatment. These results were based on only two trials which had a very small number of participants. Therefore evidence from larger, randomized, controlled trials is needed in order to provide adequate statistical power to assess the role of intramuscular mononuclear cell implantation in patients with critical limb ischemia.

Fadini et al. (2010) conducted a meta-analysis and systematic review of the literature regarding autologous stem cell therapy for PAD. Most were pilot studies that assessed the safety and feasibility of cell therapy. There were six controlled trials (four randomized and two non-randomized), plus four trials in which the non-treated limbs served as internal controls. The route of cell administration was intramuscular in 33 studies, intra-arterial in four trials and combined intra-arterial plus intramuscular in one trial. The median follow-up was six months. A meta-analysis of 37 trials indicated that autologous cell therapy was effective in improving surrogate indexes of ischemia, subjective symptoms and hard endpoints (i.e., ulcer healing and amputation). However, G-CSF monotherapy was not associated with significant improvement in the same endpoints. Patients with thromboangiitis obliterans demonstrated some larger benefits than those with atherosclerotic PAD. The intra-muscular route of administration and the use of bone marrow cells appeared to be more effective than the intra-arterial administration and the use of mobilized peripheral blood cells. The procedures appeared to be well-tolerated and generally safe. The authors concluded that the meta-analysis indicates that intramuscular autologous bone marrow cell therapy is a feasible, relatively safe and potentially effective therapeutic strategy for PAD patients, who are not candidates for traditional revascularization. Larger, placebo-controlled, randomized multicenter trials need to be planned and conducted to confirm these findings.

Professional Societies/Organizations

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): The use of cell therapy is not mentioned in the 2017 ACC/AHA/HFSA focused update of the 2013 American College of Cardiology Foundation (ACCF)/AHA guidelines for the management of heart failure (Yancy, et al., 2017) or in the 2016 AHA/ACC guidelines on the management of patients with lower peripheral artery disease (Gerhard-Herman, et al., 2017)

Use Outside the U.S.

The 2019 European Society for Vascular Surgery (ESVS), Society for Vascular Surgery (SVS), and World Federation of Vascular Societies (WFVS) global vascular guidelines on chronic limb-threatening ischemia (CLTI) management stated that there have been promising early safety and efficacy trial data for cellular therapies in patients with CLTI. However, until further evidence is available, these therapies should be considered investigational (Conte, et al., 2019).

A consensus statement issued by the European Society of Cardiology (ESC) provided recommendations regarding the clinical investigation of the use of autologous adult stem cells for the treatment of acute myocardial infarction (AMI) and heart failure (HF). According to the ESC, several systematic reviews/meta-analyses have suggested that cell therapy is beneficial, however these methods are controversial and large-scale, blinded clinical trials are necessary to determine efficacy of cell therapy (Mathur, et al., 2017).

The ESC in collaboration with the European Society for Vascular Surgery (ESVS) published guidelines on the diagnosis and treatment of peripheral arterial diseases. The guidelines stated that stem cell therapy is still being investigated with insufficient evidence in favor of this treatment (Aboyans, et al., 2017).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Cellular Therapy (30.8)	NA

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

- Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
33999	Unlisted procedure, cardiac surgery
37799	Unlisted procedure, vascular surgery
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
93799	Unlisted cardiovascular service or procedure
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
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
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

HCPCS Codes	Description
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition

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