Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic stem cells as a treatment of damaged myocardium to be investigational.*

Based on review of available data, the Company considers infusion of growth factors (ie, granulocyte colony stimulating factor [GCSF]) as a technique to increase the numbers of circulating hematopoietic stem cells as treatment of damaged myocardium to be investigational.*

Background/Overview
Progenitor cell therapy describes the use of multipotent cells of various cell lineages (autologous or allogenic) for tissue repair and/or regeneration. Progenitor cell therapy is being investigated for the treatment of damaged myocardium resulting from acute or chronic cardiac ischemia and for refractory angina.

Ischemia is the most common cause of cardiovascular disease and myocardial damage in the developed world. Despite impressive advances in treatment, ischemic heart disease is still associated with high morbidity and mortality. Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments are unable to reverse existing heart muscle damage. Treatment with progenitor cells (ie, stem cells) offers potential benefits beyond those of standard medical care, including the potential for repair and/or regeneration of damaged myocardium. Potential sources of embryonic and adult donor cells include skeletal myoblasts, bone marrow cells, circulating blood-derived progenitor cells, endometrial mesenchymal stem cells (MSCs), adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow MSCs, all of which are able to differentiate into cardiomyocytes and vascular endothelial cells.

The mechanism of benefit after treatment with progenitor cells is not entirely understood. Differentiation of progenitor cells into mature myocytes and engraftment of progenitor cells into areas of damaged myocardium has been suggested in animal studies using tagged progenitor cells. However, there is controversy concerning whether injected progenitor cells actually engraft and differentiate into mature myocytes in humans to a degree that might result in clinical benefit. It also has been proposed that progenitor cells may improve perfusion to areas of ischemic myocardium. Basic science research also suggests that injected stem cells secrete cytokines with antiapoptotic and proangiogenesis properties.

*Does not apply to treatment of refractory angina.
Clinical benefit may result if these paracrine factors limit cell death from ischemia or stimulate recovery. For example, myocardial protection can occur through modulation of inflammatory and fibrogenic processes. Alternatively, paracrine factors may affect intrinsic repair mechanisms of the heart through neovascularization, cardiac metabolism and contractility, increase in cardiomyocyte proliferation, or activation of resident stem and progenitor cells. The relative importance of these proposed paracrine actions depends on the age of the infarct (eg, cytoprotective effects in acute ischemia and cell proliferation in chronic ischemia). Investigation of the specific factors induced by administration of progenitor cells is ongoing.

There also are a variety of potential delivery mechanisms for donor cells, encompassing a wide range of invasiveness. Donor cells can be delivered via thoracotomy and direct injection into areas of damaged myocardium. Injection of progenitor cells into the coronary circulation also is done using percutaneous, catheter-based techniques. Finally, progenitor cells may be delivered intravenously via a peripheral vein. With this approach, the cells must be able to target damaged myocardium and concentrate at the site of myocardial damage.

Adverse effects of progenitor cell treatment include risks of the delivery procedure (eg, thoracotomy, percutaneous catheter-based) and risks of the donor cells themselves. Donor progenitor cells can differentiate into fibroblasts rather than myocytes. This may create a substrate for malignant ventricular arrhythmias. There also is a theoretical risk that tumors, such as teratomas, can arise from progenitor cells, but the actual risk in humans is currently unknown.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

U.S. Food and Drug Administration marketing clearance is not required when autologous cells are processed on site with existing laboratory procedures and injected with existing catheter devices. However, there are several products that require FDA approval. MyoCell® (Bioheart Inc., Sunrise, FL) comprises patient autologous skeletal myoblasts that are expanded ex vivo and supplied as a cell suspension in a buffered salt solution for injection into the area of damaged myocardium. MyoCell SDF-1 (Bioheart) is similar to MyoCell, but before injection, myoblast cells are genetically modified to release excess stromal-derived factor-1 (SDF-1). Increased SDF-1 levels at the site of myocardial damage may accelerate recruitment of native stem cells to increase tissue repair and neovascularization. For both products, myoblast isolation and expansion occur at a single reference laboratory (Bioheart); both products are therefore subject to FDA approval. Currently, neither product is FDA-cleared. Implantation may require use of a unique catheter delivery system, MyoCath (Bioheart) that is FDA-cleared.

An allogeneic human mesenchymal stem cell (hMSC) product (Prochymal®) is being developed by Osiris Therapeutics (Baltimore, MD) for treatment of acute myocardial infarction (AMI). Prochymal (also referred to as Provace®) is a highly purified preparation of ex vivo cultured adult hMSCs isolated from the bone marrow of healthy young adult donors. Prochymal has been granted “fast track” status by the FDA for Crohn disease and graft-versus-host disease (GVHD), and has orphan drug status for GVHD from FDA and the European Medicines Agency. Prochymal is being studied in phase 2 trials for the treatment of AMI, pulmonary disease, and type 1 diabetes.
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MultiStem® (Athersys) is an allogeneic bone marrow–derived adherent adult stem cell product. MultiStem has received orphan drug status from FDA for GVHD and has received authorization from FDA for a phase 2 trial for treatment of AMI with an adventitial delivery system.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
The evidence review for this policy is derived in part from a 2008 Technology Evaluation Center (TEC) Assessment, with the literature updated periodically since the 2008 TEC Assessment using the MEDLINE database. The Assessment was a systematic review that included randomized controlled trials (RCTs) of progenitor cell therapy versus standard medical care for treatment of either acute or chronic myocardial ischemia. The TEC Assessment focused on the impact of progenitor cell therapy on clinical outcomes but also included data on physiologic outcomes, such as change in left ventricular ejection fraction (LVEF). The most recent literature review since the 2008 TEC Assessment was performed through May 18, 2015.

Treatment with Progenitor Cells
The overall body of evidence is characterized by many RCTs and a number of meta-analyses of these RCTs. Randomized controlled trials are mostly small in size and highly variable in terms of patient population, type of progenitor cells used, and delivery method. For the purpose of this literature review, relevant clinical trials and meta-analyses are reviewed for 3 different indications: (1) acute ischemia (myocardial infarction [MI]); (2) chronic ischemia; and (3) refractory/intractable angina in patients who are not candidates for revascularization.

Acute Ischemia
Systematic Reviews
The 2008 TEC Assessment reviewed a total of 10 publications from 6 unique trials enrolling 556 patients with acute ischemia. These trials had similar inclusion criteria, enrolling patients with acute ST-segment elevation MI (STEMI) treated successfully with percutaneous coronary intervention (PCI) and stenting, with evidence of residual myocardial dysfunction in the region of the acute infarct. Progenitor cell therapy was delivered via an additional PCI procedure within 1 week of the acute event. The REPAIR-AMI trial (described next) is the largest trial included in the TEC Assessment and had the largest number of clinical outcomes reported. The other 5 trials included in the TEC Assessment had very few clinical events, precluding meaningful analysis of clinical outcomes. Primary evidence from these other trials comprised physiologic outcome measures, such as change in LVEF and change in infarct size. The primary end point in all 6 trials was change in LVEF. In each trial, there was a greater increase in LVEF for the progenitor cell group compared with the control group. In 4 of the 6 trials, this difference reached statistical significance; in 2 trials, there was a nonsignificant increase in favor of the treatment group. Magnitude of the incremental improvement in LVEF was not large in most cases, with 5 of 6 studies reporting an incremental change of 1% to 6% and the sixth study reporting a larger incremental change of 18%.
In 2007, Lipinski et al published a meta-analysis of studies that estimated the magnitude of benefit of progenitor cell treatment on left ventricular (LV) function and infarct size. This analysis included 10 controlled trials with a total of 698 patients. Results for the primary end point, change in LVEF, showed a statistically significant greater improvement of 3% (95% confidence interval [CI], 1.9 to 4.1; p<0.001) for the progenitor cell group. There also was a statistically greater reduction in infarct size for the progenitor cell group, with an incremental change of -5.6% over the control group (95% CI, -8.7 to -2.5; p<0.001). At least 4 meta-analyses of bone marrow progenitor cell treatment for acute MI (AMI) have been published since the 2008 TEC Assessment, each examining between 6 and 13 RCTs. All 4 meta-analyses concluded that there was a modest improvement in LVEF for patients treated with progenitor cells. The mean estimated improvement in ejection fraction over control ranged from 2.9% to 6.1%. Studies concluded that myocardial perfusion and/or infarct size also were improved in the progenitor cell treatment group, although different outcome parameters were used. All 4 meta-analyses concluded that there were no demonstrable differences in clinical outcomes for patients treated with progenitor cells.

A 2012 Cochrane review included 33 RCTs (39 comparisons with 1765 participants) of bone marrow–derived stem cell therapy for AMI. Twenty-five trials compared stem/progenitor cell therapy with no intervention, and 14 trials compared the active intervention with placebo. There was a high degree of statistical and clinical heterogeneity in the included trials, including variability in cell dose, delivery, and composition. Overall, stem cell therapy was found to improve LVEF in both the short (<12 months; weighted mean difference [WMD], 2.9 percentage points; 95% CI, 2.0 to 3.7; I²=73%), and long term (12-61 months; WMD, 3.8 percentage points; 95% CI, 2.6 to 4.9; I²=72%). Stem cell treatment reduced LV end-systolic and end-diastolic volumes at certain times and reduced infarct size in long-term follow-up. There were positive correlations between mononuclear cell dose infused and effect on LVEF and between the timing of stem cell treatment and effect on LVEF. Although the quality of evidence on LVEF was rated as high, clinical significance of the change in LVEF is unclear. Quality of evidence on health outcomes was rated as moderate. Stem/progenitor cell treatment was not associated with statistically significant changes in the incidence of mortality or morbidity (reinfarction, arrhythmias, hospital readmission, restenosis, target vessel revascularization), although studies may have been underpowered to detect differences in clinical outcomes. Due to variability in outcomes measured, it was not possible to combine data on health-related quality of life or performance status.

Two 2014 systematic reviews with meta-analysis evaluated bone marrow stem cell infusion for the treatment of AMI. Delewi et al searched the literature in February 2013 and included 16 RCTs (total N=1641). De Jong et al searched the literature through August 2013 and included 22 RCTs (total N=1513). Thirteen RCTs (1300 patients) appeared in both studies. In meta-analysis of placebo-controlled RCTs that reported LVEF, both studies reported statistically significant increases in LVEF with bone marrow stem cell infusion compared with placebo: Delewi et al reported a mean difference of 2.6 percentage points (95% CI, 1.8 to 3.3; p<0.001; I²=84%) with up to 6 months of follow-up, and de Jong et al reported a mean difference of 2.1 percentage points (95% CI, 0.7 to 3.5; p=0.004; I²=80%) with up to 18 months of follow-up. Both studies reported statistically significant reductions in LV end systolic volumes, but only Delewi et al reported statistically significant reductions in LV end diastolic volumes. Statistical heterogeneity was substantial for all meta-analyses (I²≥55%). Based on these findings, Delewi et al concluded that intracoronary bone marrow cell infusion “is associated with improvement of LV function and remodeling in patients after...
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STEMI." In contrast, de Jong et al undertook additional analysis of major adverse cardiac and cerebrovascular events. With median follow-up of 6 months, there was no difference between bone marrow cell infusion and placebo in all-cause mortality, cardiac mortality, restenosis rate, thrombosis, target vessel revascularization, stroke, recurrent AMI, or implantable cardioverter defibrillator implantations. Infusion with bone marrow progenitor cells, but not bone marrow mononuclear cells, led to a statistically significant reduction in rehospitalizations for heart failure (odds ratio vs placebo, 0.14; 95% CI, 0.04 to 0.52; p=0.003). Based on these findings, de Jong et al concluded that, although safe, intracoronary infusion of bone marrow stem cells does not improve clinical outcome, and clinical efficacy “needs to be defined in clinical trials.”

Gyöngyösi et al (2015) conducted an individual patient data meta-analysis of 12 RCTs (N=1252) on autologous intracorony cell therapy after AMI, including the REPAIR-AMI and ASTAMI trials reviewed next, using a collaborative, multinational database, ACCRUE (meta-Analysis of Cell-based CaRdiac study; NCT01098591). All patients had STEMI treated with PCI. Mean (SD) baseline LVEF was approximately 46% (12%). Most studies used bone marrow mononuclear cells and administered cell therapies within 2 weeks after AMI. Median follow-up duration was 6 months. Eight trials had low risk of bias, and 4 single-blind (assessor) trials had medium-low risk of bias. Adjusted (for cardiovascular risk factors) random effects meta-analyses showed no effect of cell therapy on the primary end point, MACCE (major adverse cardiac and cerebrovascular events, a composite of all-cause death, AMI recurrence, coronary target vessel revascularization, and stroke) (186 events; 14.0% cell therapy vs 16.3% control; hazard ratio, 0.86; 95% CI, 0.63 to 1.18; I²=0%); death (21 events; 1.4% cell therapy vs 2.1% control); or a composite of clinical hard end points (death, AMI recurrence, and stroke; 45 events; 2.9% cell therapy vs 4.7% control). Compared with controls, changes in LVEF (mean difference, 0.96%; 95% CI, −0.2 to 2.1), end-diastolic volume (mean difference, 1.2 mL; 95% CI, -3.4 to 5.8), or end-systolic volume (mean difference, 3.6 mL; 95% CI, -3.4 to 4.1) were not observed. The study was limited by variation in the time from AMI to cell delivery (median, 6.5 days) and in imaging modality for assessing cardiac function (magnetic resonance imaging [MRI], single-proton emission computed tomography [SPECT], angiography, echocardiography).

Key studies, including more recent RCTs not included in this meta-analysis are described next.

REPAIR-AMI Trial
This was a double-blinded trial that infused bone marrow–derived progenitor cells or a placebo control infusion of the patient’s own serum and enrolled 204 patients from 17 centers in Germany and Switzerland who had acute STEMI and met strict inclusion criteria. At 12-month follow-up, there were statistically significant decreases in the progenitor cell group compared with the control group for MI (0 vs 6, p<0.03) and revascularization (22 vs 37, p<0.03, both respectively), as well as for the composite outcome of death, MI, and revascularization (24 vs 42, p<0.009, respectively). Two-year clinical outcomes from the REPAIR-AMI trial, performed according to a study protocol amendment filed in 2006, were reported in 2010. Three of the 204 patients were lost to follow-up (2 patients in the placebo group, 1 in the progenitor cell group). A total of 11 deaths occurred during the 2-year follow-up, 8 in the placebo group and 3 in the progenitor cell group. There was a significant reduction in MI (0% vs 7%), and a trend toward a reduction in rehospitalizations for heart failure (1% vs 5%) and revascularization (25% vs 37%) in the active treatment group. Analysis of combined events (all combined events included infarction), showed significant improvement with progenitor cell therapy after AMI. There was no increase in ventricular arrhythmia or...
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Syncope, stroke, or cancer. It was noted that investigators and patients were unblinded at 12-month follow-up. Also, the REPAIR-AMI trial was not powered to definitively answer the question of whether administration of progenitor cells can improve mortality and morbidity after AMI; the relatively small sample size might limit the detection of infrequent safety events. Thus, this analysis should be viewed as hypothesis-generating, providing the rationale to design a larger trial that addresses clinical end points.

HEBE Trial
In 2011, Hirsch et al reported a multicenter RCT of bone marrow or peripheral blood mononuclear cell infusion compared with standard therapy in 200 patients with AMI treated with primary PCI. Mononuclear cells were delivered 3 to 8 days after MI. Blinded assessment of the primary end point, the percentage of dysfunctional LV segments that had improved segmental wall thickening at 4 months, found no significant difference between either of the treatment groups (38.5% for bone marrow, 36.8% for peripheral blood) and control (42.4%). There was no significant difference between the groups in LVEF; change in LV volumes, mass, or infarct size; or rates of clinical events. At 4 months, there was a similar percentage of patients with New York Heart Association (NYHA) class II or higher heart failure (19% for bone marrow, 20% for peripheral blood, 18% for control).

TIME Trial
Investigators from the Cardiovascular Cell Therapy Research Network reported 2012/2013 results from the randomized double-blind controlled, Timing in Myocardial Infarction Evaluation (TIME) trial. One hundred twenty patients with LV dysfunction were randomized to placebo or to bone marrow mononuclear cell administration in the infarct-related artery at either 3 or 7 days after PCI. At 6 months, there was no significant difference in LVEF or LV function (assessed by MRI) for the cell-infusion group compared with the placebo group. Rates of major adverse events were low in all treatment groups (11 patients underwent repeat vascularization, 6 received implantable cardioverter defibrillators). In a 2014 letter to the editor, these investigators reported prespecified 1-year outcomes. Analyzable MRI data were available for 95 (79%) of 120 randomized patients. There were no statistically significant between-group differences at 6 months or 1 year in change from baseline LVEF, regional LV function in infarct and border zones, LV volumes, infarct size, or LV mass. At 1 year, similar proportions of patients in each group experienced adverse clinical outcomes (eg, placement of implantable cardioverter-defibrillator, reinfarction, or repeat revascularization), 23% of the cell-infusion group and 22% of the placebo group.

ASTAMI Trial
Beitnes et al (2009) reported the unblinded 3-year reassessment of 97 patients (of 100) from the randomized ASTAMI trial. The group treated with bone marrow progenitor cells had a larger improvement in exercise time between baseline and 3-year follow-up compared with patients who received usual care (1.5 minutes vs 0.6 minutes, respectively), but there was no difference between groups in change in peak oxygen consumption (3.0 mL/kg/min vs 3.1 mL/kg/min, respectively), and there was no difference between groups in change of global LVEF or quality of life. Rates of adverse clinical events in both groups were low (3 infarctions, 2 deaths). These 3-year findings are similar to the 12-month results from this trial.
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SWISS-AMI Trial
In 2013, Surder et al reported 4-month results of the open-label SWISS-AMI trial. Two hundred patients with successfully reperfused (PCI in ≥95%) STEMI were randomized to placebo or 1 of 2 groups treated with autologous bone marrow mononuclear cells, infused 5 to 7 days or 3 to 4 weeks after the initial event. Mononuclear cells were infused directly into the infarct-related coronary artery. Mean (SD) absolute change in LVEF from baseline to 4 months (primary efficacy end point) was -0.4 (8.8) percentage points in the control group, 1.8 (8.4) percentage points in the early infusion group, and 0.8 (7.6) percentage points in the late infusion group. Differences in LVEF compared with placebo control were 1.3 percentage points (95% CI, -1.8 to 4.3; analysis of covariance [ANCOVA], p=0.42) for the early treatment group and 0.6 percentage points (95% CI, -2.6 to 3.7; ANCOVA, p=0.73) for the late treatment group. Adverse outcomes (eg, death, MI, rehospitalization for heart failure, revascularization, or cerebral infarction) occurred with approximately equal frequency in both groups.

Section Summary
Evidence for this question comprises numerous small RCTs and several meta-analyses that evaluated the impact of bone marrow progenitor cells on outcomes for patients with MI. Most studies included patients with AMI and reported outcomes of LVEF and/or myocardial perfusion at 3 to 6 months. These studies generally reported small to modest improvements in these intermediate outcomes, although 2 RCTs (HEBE, TIME) found no benefit of stem cell treatment for AMI. No trial published after the 2008 TEC Assessment has reported benefits in clinical outcomes, such as mortality, adverse cardiac outcomes, exercise capacity, or quality of life. Overall, this evidence suggests that progenitor cell treatment may be a promising intervention, but robust data on clinical outcomes are lacking. High-quality RCTs powered to detect differences in clinical outcomes are needed to answer this question.

Chronic Ischemia
Systematic Reviews
The 2008 TEC Assessment included a total of 6 RCTs in 231 patients with chronic ischemic heart disease. Three trials randomly assigned 125 patients to progenitor cell therapy versus standard medical care. The other 3 trials randomly assigned 106 patients undergoing coronary artery bypass grafting (CABG) to CABG plus progenitor cell treatment versus CABG alone. Four trials employed bone marrow–derived progenitor cells as the donor cell source, 1 trial used circulating progenitor cells (CPCs), and the final trial included both a CPC treatment group and a bone marrow–derived treatment group. The primary physiologic measurement reported in these trials was change in LVEF. In all 6 trials there was greater improvement in LVEF for the treatment group compared with the control group, and in 4 of 6 trials, this difference reached statistical significance. For trials of progenitor cell treatment versus standard medical care, the range of incremental improvement in LVEF was 2.7% to 6.0%. For trials of progenitor cell treatment plus CABG versus CABG alone, the range of improvement in LVEF was 2.5% to 10.1%. Only 1 trial reported comparative analysis of data on the change in size of ischemic myocardium, finding no difference. Only 2 of 6 trials reported any clinical outcomes, and both trials reported on change in NYHA class between groups, as discussed next.

In 2014, Fisher et al published a Cochrane review of autologous stem cell therapy for chronic ischemic heart disease and congestive heart failure. Literature was searched through March 2013, and 23 RCTs...
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(total N=1255) were included. Overall quality of the evidence was considered low because there were few events of interest (deaths and hospital readmissions). In long-term (≥12 months), but not short-term (<12 months), follow-up, there were statistically significant reductions in all-cause mortality (relative risk [RR], 0.3; 95% CI, 0.1 to 0.5; p<0.001; I²=0%) and rehospitalizations due to heart failure (RR=0.3; 95% CI, 0.1 to 0.9; p=0.039; I²=0%) in patients who received stem cell infusion compared with controls (no stem cell infusion). Statistically significant improvements in LVEF and in NYHA classification in stem cell groups were observed at both 6 months and 1 year or later. Evidence was considered of moderate quality for these outcomes, but statistical heterogeneity was moderate to substantial. Similar results were achieved in meta-analyses conducted by Xu et al and by Xiao et al in 2014. Additional research in larger studies is required to confirm these results.

Representative individual RCTs are discussed next.

The largest trial on chronic ischemia that was included in the 2008 TEC Assessment was Assmus et al (REPAIR-AMI Investigators). This was a single-center, open-label trial that enrolled 75 patients into 3 groups: treatment with bone marrow‒derived progenitor cells, treatment with CPCs, or usual medical care. Improvements in mean NYHA class (0-4 scale) were 0.25 for the bone marrow treatment group and 0.2 for the CPC group compared with a worsening of 0.18 for the standard medical therapy group (p<0.01). This publication also reported on adverse cardiac events, but there were extremely small numbers of any of these clinical outcomes and no differences between groups.

CELLWAVE Trial
Assmus et al (2013) reported a phase 1/2 double-blind randomized trial in patients with chronic heart failure. This trial tested the hypothesis that shock wave‒facilitated intracoronary cell therapy improves LVEF to a greater degree than does non-shock-wave‒facilitated cell therapy, due to an effect of shock wave treatment on facilitating the homing ability of progenitor cells to their target. Patients were randomized to low-dose (n=42), high-dose (n=40), or sham (n=21) shock wave pretreatments of the left ventricle. Twenty-four hours later, patients assigned to receive shock wave treatment were randomized to an intracoronary infusion of either placebo or bone marrow‒derived mononuclear cells, and patients assigned to the sham shock wave treatment were given an infusion of bone marrow‒derived mononuclear cells. Improvement in LVEF at 4 months was significantly greater in groups that received shock wave plus mononuclear cells (3.2 percentage points; 95% CI, 2.0 to 4.4), compared with the placebo infusion group (1.0 percentage point; 95% CI, -0.3% to 2.2%; p=0.02). LVEF improved in 93% of patients receiving shock wave plus mononuclear cells compared with 64% of patients who received shock wave plus placebo infusion, and 64% of patients who received sham shockwave plus mononuclear cells. Regional wall thickening improved significantly in the shock wave‒treated mononuclear cell group (3.6%), but not in the placebo infusion group (0.6%). Symptomatic heart failure status assessed by NYHA class showed a modest improvement with low-dose shock wave plus mononuclear cells (-0.3) and with high-dose shock wave plus mononuclear cells (-0.4).
STAR-Heart Trial

Results from the intracoronary stem cell transplantation in patients with chronic heart failure (STAR-Heart) trial were reported by Strauer et al in 2010. In this nonrandomized open-label trial, 391 patients with chronic heart failure due to ischemic cardiomyopathy were enrolled; 191 patients received intracoronary bone marrow cell (BMC) therapy, and 200 patients who did not accept the treatment but agreed to undergo follow-up testing served as controls. Mean time between PCI for infarction and admission to the tertiary clinic was 8.5 years. For BMC therapy, mononuclear cells were isolated and identified (included CD34-positive cells, AC133-positive cells, CD45/CD14-negative cells). Cells were infused directly into the infarct-related artery. Follow-up on all patients was performed at 3, 12, and 60 months and included coronary angiography, biplane left ventriculography, electrocardiogram (ECG) at rest, spiroergometry, right heart catheterization, and measurement of late potentials, short-term heart rate variability, and 24-hour Holter ECG. At up to 5 years after intracoronary BMC therapy, there was significant improvement in hemodynamics (LVEF, cardiac index), exercise capacity (NYHA classification), oxygen uptake, and LV contractility compared with controls. There also was a significant decrease in long-term mortality in the BMC-treated patients (0.75% per year) compared with the control group (3.68% per year, p<0.01). These results are encouraging, especially the mortality outcomes, because this is the first controlled trial that reported a significant mortality benefit for progenitor cell treatment. However, the study is limited by the potential for selection bias due to patient self-selection into treatment groups. For example, there was a 7% difference in baseline ejection fraction between the 2 groups, suggesting that the groups were not comparable on important clinical characteristics at baseline. Additionally, lack of blinding raises the possibility of bias in patient-reported outcomes such as NYHA class. RCTs are needed to confirm these health outcome benefits for chronic ischemia.

Other RCTs

Smaller RCTs have been published subsequently. Pätilä et al (2014) randomized 39 patients with ischemic heart failure (NYHA II-III) who were scheduled for elective CABG to double-blind, intraoperative myocardial injections of bone marrow mononuclear cells (BMMC) or placebo. Patients had been optimized on medical therapy for 1 to 3 months before randomization. At 1-year follow-up, there was no statistical difference in LVEF or wall thickening (assessed by MRI) or viability by positron emission tomography and SPECT scan. Statistically significant reductions in scar volume and transmural scar were observed in patients who received BMMC compared with controls. Perin et al (2014) investigated transendocardial injections of adipose-derived regenerative cells (ADRC) in 27 patients with ischemic cardiomyopathy (NYHA II-III and LVEF ≤45%) who were ineligible for revascularization. Patients were randomized 3:1 to receive autologous ADRC or placebo control in double-blind fashion. Patients were followed for up to 18 months for efficacy outcomes. There was no statistical difference in LVEF or LV volumes (assessed by echocardiography). Although some measures of exercise capacity improved more in ADRC-treated patients compared with controls (eg, maximal oxygen consumption), there were no statistical changes from baseline SPECT stress and rest total severity scores in either group.

Section Summary

For chronic ischemic heart disease, there is limited evidence on clinical outcomes. The studies reviewed reported only a handful of clinical outcome events, too few for meaningful analysis. Other clinical outcomes, such as change in NYHA class, are confined to very small numbers of patients and not reported with
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sufficient methodologic rigor to permit conclusions. Therefore, the evidence is insufficient to permit conclusions on the impact of progenitor cell therapy on clinical outcomes for patients with chronic ischemic heart disease.

Refractory Angina
Stem cell therapy also is being investigated in patients with intractable angina who are not candidates for revascularization.

ACT34-CMI Trial
In 2011, Losordo et al reported an industry-funded multicenter, randomized double-blind phase 2 trial that included 167 patients with refractory angina and no suitable revascularization options. Patients were randomized to 1 of 2 doses of mobilized autologous CD34+ cells from peripheral blood (1×10^5 or 5×10^5) or to placebo injections. The cell dose was delivered via intramyocardial injection into 10 sites identified as viable, ischemic areas of the myocardium by electromechanical endocardial mapping. One patient died during the procedure. Angina frequency was documented by daily phone calls to an interactive voice responsive system. The primary outcome was weekly angina frequency at 6 months. Weekly angina frequency was significantly lower in the low-dose group than in placebo-treated patients at both 6 months (6.8 vs 10.9) and 12 months (6.3 vs 11.0). Weekly angina frequency in the high-dose group tended to be lower at 6 (8.3) and 12 (7.2) months, but this did not attain statistical significance. Secondary end points included exercise tolerance testing, use of antianginal medications, Canadian Cardiovascular Society (CCS) functional class, and health-related quality of life. Improvement in exercise tolerance was significantly greater in low-dose patients than in placebo-treated patients at 6 (139 seconds vs 69 seconds) and 12 months (140 seconds vs 58 seconds). Exercise tolerance in the high-dose group tended to be higher at 6 (110 seconds) and 12 months (103 seconds), but this did not reach statistical significance. Time to onset of angina during treadmill exercise was not significantly different between either transplanted group and the placebo group. The percentage of patients who improved on the Seattle Angina Questionnaire was greater in the low-dose group (69.2%) and high-dose group (67.3%) compared with controls (40.8%), and some measures of changes in CCS class were significantly better in both the low- and high-dose groups. Most parameters from SPECT were not significantly different between either transplanted group and the placebo group. Mortality at 12 months was 5.4% in the placebo-treated group with no deaths among cell-treated patients (p=0.107). Interpretation of these results is limited by the trend (p=0.091) for a greater percentage of patients in the control group (41.1%) to have had prior heart failure than the low- (21.8%) or high-dose (28.6%) groups. Additional study in a larger number of patients is needed to confirm these results.

Van Ramshorst et al (2009)
In 2009, Van Ramshorst et al reported a randomized, double-blind trial of autologous bone marrow–derived mononuclear cell or placebo infusion. Fifty patients who had intractable angina despite optimal medical therapy and were not candidates for revascularization therapy were enrolled. The main outcomes were measures of myocardial perfusion derived from SPECT scanning at rest and after exercise stress at 3 months posttreatment. Secondary outcomes included LVEF, CCS angina class, and Seattle Angina Questionnaire measured at 6 months posttreatment. There were modest improvements for most of the outcomes in favor of the experimental group compared with placebo. For the primary outcome, a significantly greater improvement was found in stress perfusion score for the progenitor cell group (mean
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difference, -2.44; 95% CI, -3.58 to -1.30; p<0.001) but no significant difference in at-rest perfusion score (mean difference, -0.32; 95% CI, -0.87 to 0.23; p=0.25). There also was a significant decrease in the mean number of ischemic segments for the progenitor cell group (mean decrease, 2.4 vs 0.8; p<0.001). LVEF improved slightly in the progenitor cell group and decreased slightly in the placebo group (mean [SD] change, 3% [5] vs -1% [3], respectively, p=0.03). At 6 months, CCS class decreased more for the progenitor cell group (mean difference, -0.79; 95% CI, -1.10 to -0.48; p<0.001), and the Seattle Angina Quality-of-Life score increased more for the progenitor cell group (mean increase, 12% vs 6.3%, respectively; p=0.04).

Section Summary
Evidence on stem cell therapy for refractory angina includes at least 2 RCTs, including a phase 2 RCT that examined 2 doses of mononuclear cells compared with placebo. Functional outcomes such as angina frequency and exercise tolerance showed modest improvements with the lower dose of mononuclear cells. Limitations of the literature include the small size of available trials, along with differences between groups at baseline that increase uncertainty of the findings. Additional, larger studies are needed to determine with greater certainty whether progenitor cell therapy improves health outcomes in patients with refractory angina.

Treatment with Granulocyte Colony Stimulating Factor
The body of evidence on the use of granulocyte colony stimulating factor (G-CSF) as a treatment for coronary heart disease is smaller compared with that for the use of stem cells. A few RCTs on treatment of acute ischemia report physiologic outcomes. Additionally, meta-analyses of the available trials have been published.

Moazzami et al (2013) published a Cochrane review of G-CSF for AMI. Literature was searched in November 2010, and 7 small, placebo-controlled RCTs (total N=354) were included. Overall risk of bias was considered low. All-cause mortality did not differ between groups (RR=0.6; 95% CI, 0.2 to 2.8; p=0.55; I²=0%). Similarly, change in LVEF, LV end systolic volume, and LV end diastolic volume did not differ between groups. Evidence was insufficient to draw conclusions about the safety of the procedure. The study indicated a lack of evidence for benefit of G-CSF therapy in patients with AMI.

Subsequent to the Cochrane review, Achilli et al published 6-month and 3-year results of their multicenter, placebo-controlled RCT, STEM-AMI. Sixty consecutive patients with first anterior STEMI, who underwent primary PCI within 12 hours after symptom onset and had LVEF of 45% or less were enrolled. Patients were randomized 1:1 to G-CSF 5 mg/kg body weight administered subcutaneously starting within 12 hours after PCI and continuing twice daily for 5 days, or placebo. Standard STEMI care was provided to all patients. Among cardiac MRI outcomes (LVEF, LV end systolic volume, LV end diastolic volume) at 6 months and 3 years, only LV end diastolic volume at 3 years was statistically significantly improved in the G-CSF group compared with placebo. At 3 years, there was no statistical difference in clinical outcomes, including death, reinfarction, target vessel restenosis or revascularization, heart failure, and stroke. The study was likely underpowered to detect statistically significant differences in most of these parameters.
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Section Summary
The small number of trials that use G-CSF as a treatment for acute ischemia (MI) generally do not report an improvement in physiologic or clinical outcomes, and a Cochrane review of 7 placebo-controlled trials reported a lack of evidence for benefit. This evidence is not supportive of the use of G-CSF in the treatment of acute ischemia.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
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<tr>
<td>NCT01569178</td>
<td>The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction</td>
<td>3000</td>
<td>May 2018</td>
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<tr>
<td>NCT02032004a</td>
<td>A Double-blind, Randomized, Sham-procedure-controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (CEP-41750) in Patients With Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology</td>
<td>1730</td>
<td>Aug 2018</td>
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<tr>
<td>NCT01969890</td>
<td>Phase III Study on Stem Cells Mobilization in Acute Myocardial Infarction</td>
<td>1530</td>
<td>Oct 2018</td>
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<tr>
<td>NCT01693042</td>
<td>Randomized Controlled Trial to Compare the Effects of Single Versus Repeated Intracoronary Application of Autologous Bone Marrow-derived Mononuclear Cells on Total and SHFM-predicted Mortality in Patients With Chronic Post-infarction Heart Failure</td>
<td>676</td>
<td>Jan 2022</td>
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<tr>
<td>NCT01458405</td>
<td>Randomized, Double-Blind, Placebo-Controlled Phase II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients With an Anterior Myocardial Infarction and Ischemic Left Ventricular Dysfunction</td>
<td>274</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT01781390a</td>
<td>A Prospective, Double Blind, Randomized, Placebo-controlled Clinical Trial of Intracoronary Infusion of Immunoselected, Bone Marrow-derived Stro3 Mesenchymal Precursor Cells (MPC) in the Treatment of Patients With ST-elevation Myocardial Infarction</td>
<td>225</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>NCT00877903a</td>
<td>A Phase II, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of PROCHYMAL (Ex Vivo Cultured Adult Human Mesenchymal Stem Cells) Intravenous Infusion Following Acute Myocardial Infarction</td>
<td>220</td>
<td>Feb 2016</td>
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<tr>
<td>NCT02323620</td>
<td>The Impact of Repeated Intracoronary Injection of Autologous Bone-marrow Derived Mononuclear Cells for Left Ventricle Contractility and Remodeling in Patients With STEMI. Prospective Randomized Study</td>
<td>200</td>
<td>Dec 2018</td>
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<tr>
<td>NCT00526253a</td>
<td>A Multicenter Study to Assess the Safety and Cardiovascular</td>
<td>170</td>
<td>Feb 2017</td>
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Effects of MyoCell Implantation by a Catheter Delivery System in Congestive Heart Failure Patients Post Myocardial Infarction(s)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Description</th>
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<tr>
<td>NCT02368587</td>
<td>Randomised, Double-blind, Placebo-controlled, Intracoronary or Intravenous Infusion Human Wharton' Jelly-derived Mesenchymal Stem Cells in Patients With Ischemic Cardiomyopathy</td>
<td>160</td>
<td>Oct 2015</td>
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<tr>
<td>NCT00950274a</td>
<td>Intramyocardial Transplantation of Bone Marrow Stem Cells for Improvement of Post-infarct Myocardial Regeneration in Addition to CABG Surgery; a Controlled, Prospective, Randomised, Double Blinded Multicenter Trial (PERFECT)</td>
<td>142</td>
<td>Dec 2014</td>
</tr>
<tr>
<td>NCT01905475a</td>
<td>CXCR4 Antagonism for Cell Mobilisation and Healing in Acute Myocardial Infarction (CATCH-AMI). A Phase Ila, Double-Blind, Placebo-Controlled, Randomised, Multi-centre Study of POL6326, a CXCR4 Antagonist, in Patients With Large Reperfused ST Elevation Myocardial Infarction</td>
<td>140</td>
<td>Dec 2015</td>
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<tr>
<td>NCT01436487a</td>
<td>Double-Blind, Randomized, Placebo-Controlled Phase 2 Safety and Efficacy Trial of MultiStem in Adults With Ischemic Stroke</td>
<td>140</td>
<td>Dec 2015</td>
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<tr>
<td>NCT01652209a</td>
<td>A Multi-center, Open-label, Comparison and a Parallel Group Study (3 Groups) Phase 3 Clinical Trial for a Comparative Evaluation With the Existing Treatments, in Order to Verify the Long-term Efficacy and Safety of the First Cell Treatment Using Hearticeligram-AMI(Autologous Human Bone Marrow Derived Mesenchymal Stem Cells) in AMI Patients, and to Observe the Efficacy of the Second Cell Treatment</td>
<td>135</td>
<td>Dec 2018</td>
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<tr>
<td>NCT00936819</td>
<td>A Phase Iib, Randomized, Double-blind, Placebo Controlled Study Using Transplantation of Autologous Early Endothelial Progenitor Cells(EPCs) for Patients Who Have Suffered Acute Myocardial Infarction</td>
<td>100</td>
<td>Dec 2016</td>
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<tr>
<td>NCT00765453</td>
<td>Randomised Controlled Clinical Trial of the Use of Autologous Bone Marrow Derived Progenitor Cells to Salvage Myocardium in Patients With Acute Anterior Myocardial Infarction</td>
<td>100</td>
<td>Jun 2014</td>
</tr>
<tr>
<td>NCT02059512</td>
<td>Influence of the Administration of Autologous Bone Marrow Mononuclear Cells for the Duration of Functioning Aorto-coronary Bypass Grafts in the Surgical Treatment of Coronary Heart Disease</td>
<td>100</td>
<td>Feb 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

- a Denotes industry-sponsored or cosponsored trial.
- b This study is currently recruiting participants.
- c This study is ongoing, but not recruiting participants.

Summary of Evidence

Progenitor cell therapy has been tested in patients with acute ischemia, chronic ischemia, and refractory angina. For all these conditions, there is a similar pattern of outcomes, with modest improvements demonstrated on physiologic outcomes, but limited impacts on clinical outcomes. For acute ischemic heart disease, limited evidence on clinical outcomes suggests that there may be benefits in improving LEVF, reducing recurrent MI, decreasing the need for further revascularization, and perhaps even decreasing...
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mortality, although a recent, large, individual patient data meta-analysis reported no improvement in these outcomes. For chronic ischemic heart disease, only a handful of clinical outcome events have been reported across the included studies, too few for meaningful analysis. For refractory angina, evidence from a phase 2 RCT that examined 2 doses of mononuclear cells compared with placebo reported that functional outcomes such as angina frequency and exercise tolerance showed modest improvements with the lower dose of mononuclear cells.

Progenitor cell therapy for the treatment of damaged and ischemic myocardium is a rapidly evolving field, with several areas of uncertainty, including patient selection, cell type, and procedural details (eg, timing and mode of delivery). Accumulating evidence on this therapy suggests that progenitor cell therapy may be a promising intervention but that ultimate effects on health outcomes are still uncertain. Clinical significance of improvements in physiologic parameters has yet to be demonstrated, and there is very little evidence demonstrating benefit in clinical outcome. Moreover, evidence remains primarily limited to short-term effects; although 1 meta-analysis reported durable (≥1 year) improvements in congestive heart failure classification, this result requires replication, and other durable improvements in clinical outcomes (death, hospitalizations for heart failure) were based on low-quality evidence. Therefore, progenitor (stem) cell therapy for the treatment of damaged or ischemic myocardium is considered investigational.

References
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Progenitor cell therapy for treatment of myocardial damage due to ischemia. TEC Assessments. 2008;Volume 23, Tab 4. PMID
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Policy History

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| Current Effective Date: | 12/21/2016 |
| 12/03/2015 | Medical Policy Committee review |
| 12/16/2015 | Medical Policy Implementation Committee approval. New policy. |
| 12/01/2016 | Medical Policy Committee review |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |

Next Scheduled Review Date: 12/2017

Coding

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<table>
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<td>HCPCS</td>
<td>No codes</td>
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<td>ICD-10 Diagnosis</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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