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

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells, **is considered experimental, investigational and/or unproven** as a treatment of damaged myocardium.

Infusion of growth factors (i.e., granulocyte colony stimulating factor) **is considered experimental, investigational and/or unproven** as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium.

Policy Guidelines

There are no specific codes for this procedure, either describing the laboratory component of processing the harvested autologous cells or for the implantation procedure. In some situations, the implantation may be an added component of a scheduled coronary artery

bypass graft; in other situations, the implantation may be performed as a unique indication for a cardiac catheterization procedure.

Description

Progenitor cell therapy describes the use of multipotent cells of various cell lineages (autologous or allogeneic) 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.

Background

Ischemia

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. According to the American Heart Association, coronary heart disease has a prevalence of 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people. (1) For all age strata, the incidence of myocardial infarction is higher in Black males than in Black females, White males, and White females. Heart failure has the highest prevalence among Black males (3.8%) followed by Black females (3.3%), White males (2.9%), Hispanic males (1.8%), Hispanic and White females (both1.6%), Asian males (1.4%), and Asian females (0.5%). Age-adjusted death rates per 100,000 individuals with coronary heart disease and heart failure are higher for Black males and females than their counterparts of other races.

Treatment

Current treatments for ischemic heart disease seek to revascularize occluded arteries, optimize pump function, and prevent future myocardial damage. However, current treatments do not reverse existing heart muscle damage. (2) Treatment with progenitor cells (i.e., 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, adult testis pluripotent stem cells, mesothelial cells, adipose-derived stromal cells, embryonic cells, induced pluripotent stem cells, and bone marrow mesenchymal stem cells, all of which can differentiate into cardiomyocytes and vascular endothelial cells for regenerative medicine advanced therapy (RMAT). (3) The RMAT designation may be given if: 1) the drug is a regenerative medicine therapy (i.e., a cell therapy), therapeutic tissue engineering product, human cell and tissue product, or any combination product; 2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and 3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs.

Regulatory Status

Multiple progenitor cell therapies such as MyoCell® (U.S. Stem Cell, formerly Bioheart), Ixmyelocel-T (Vericel, formerly Aastrom Biosciences), MultiStem® (Athersys), and CardiAMP™ (BioCardia) are being commercially developed, but none has been approved by the U.S. Food and Drug Administration (FDA) so far.

MyoCell 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. In 2017, U.S. Stem Cell reprioritized its efforts away from seeking RMAT designation for MyoCell. The expanded cell product enriched for mesenchymal and macrophage lineages might enhance potency. Vericel has received RMAT designation for Ixmyelocel-T.

MultiStem is an allogeneic bone marrow-derived adherent adult stem cell product that has received RMAT designation.

The CardiAMP Cell Therapy system consists of a proprietary assay to identify patients with a high probability to respond to autologous cell therapy, a proprietary cell processing system to isolate process and concentrate the stem cells from a bone marrow harvest at the point of care, and a proprietary delivery system to percutaneously inject the autologous cells into the myocardium. BioCardia has received an investigational device exemption from the FDA to perform a trial of CardiAMP and is designated as an FDA Breakthrough Device.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these

purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The present medical policy focuses on phase 3 trials with at least 100 patients per arm and systematic reviews of RCTs. The relevant clinical trials and meta-analyses are reviewed for 3 different indications: 1) acute cardiac ischemia (myocardial infarction [MI]), 2) chronic cardiac ischemia, and 3) refractory or intractable angina in patients who are not candidates for revascularization. This evidence review focuses on the impact of progenitor cell therapy on clinical outcomes but also includes data on physiologic outcomes, such as a change in left ventricular ejection fraction (LVEF).

Progenitor Cells to Treat Acute Cardiac Ischemia

Clinical Context and Therapy Purpose

The purpose of progenitor cell therapy in individuals with acute cardiac ischemia is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medication, angioplasty and stenting, bypass surgery, and enhanced external counterpulsation.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with acute cardiac ischemia.

Interventions

The therapy being considered is progenitor cell therapy. Progenitor cell therapy is the use of multipotent cells of various cell lineages (autologous or allogeneic) to repair and/or regenerate tissue, including damaged myocardium caused by cardiac ischemia.

Comparators

Comparators of interest are standard of care measures, such as medication, angioplasty and stenting, bypass surgery, and enhanced external counterpulsation.

Outcomes

The general outcomes of interest are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. For studies, follow-up of at least 6 months to 2 years is preferable; however, cardiac ischemia can be a chronic condition, and individuals are managed by cardiologists for all their lives.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systemic Reviews

Bone Marrow Cells

Several meta-analyses, including a Cochrane review and an individual patient data meta-analysis evaluating the use of progenitor cell therapy for treating acute ischemia (e.g., MI) are described below. Table 1 details the reviews and summarizes the analyses.

Two meta-analyses on bone marrow cell (BMC) infusion for the treatment of acute myocardial infarction (AMI) were published in 2014 and included many of the same studies. Delewi et al. (2014) published a meta-analysis of 16 trials (N=1641). (4) De Jong et al. (2014) included 22 RCTs (N=1513) in their meta-analysis. (5) Thirteen RCTs (n=1300) appeared in both systematic reviews. Both analyses found statistically significant increases in LVEF with BMC infusion compared with placebo. In subgroup analyses, Delewi et al. (2014) showed that the treatment benefit was greater among younger patients (age <55 years) and among patients with more severely depressed LVEF at baseline (<40%). In contrast, the de Jong et al. (2014) subgroup analysis, which included only trials with outcomes derived from magnetic resonance imaging (MRI) (9 trials), showed that the therapy did not have an effect on cardiac function, volumes, or infarct size. With a median follow-up of 6 months, there was no difference between BMC infusion and placebo in all-cause mortality, cardiac mortality, restenosis rate, thrombosis, target vessel revascularization, stroke, recurrent AMI, or implantable cardioverter defibrillator usage. Based on these findings, de Jong et al. concluded that, although safe, intracoronary infusion of BMCs did not improve clinical outcomes.

Fisher et al. (2015) published a Cochrane review on stem cell treatment for AMI that included 41 trials (N=2732). (6) Many were small trials conducted outside of the U.S.; others were reported only as conference proceedings. Studies varied by cell dose, cell type, and timing of administration. Overall, cell treatment was not associated with any changes in the risk of all-cause mortality, cardiovascular mortality, or a composite measure of mortality, reinfarction, and rehospitalization for heart failure at long-term follow-up. Reviewers concluded that there was insufficient evidence to support a beneficial effect of cell therapy for patients experiencing an AMI and that adequately powered trials are needed.

Gyöngyösi et al. (2015) conducted an individual patient data meta-analysis of 12 RCTs (N=1252) with data from a collaborative, multinational database, Meta-analysis of Cell-Based Cardiac Study (ACCRUE; NCT01098591). (7) The meta-analysis included the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial (reviewed below). Eight trials had a low risk of bias, and 4 single-blind (assessor) trials had a medium to low risk of bias. Adjusted (for cardiovascular risk factors) random-effects meta-analyses showed no effect of cell therapy on the primary outcomes of major adverse cardiac and cerebrovascular events (a composite of all-cause death, AMI recurrence, coronary target vessel revascularization, and stroke). The meta-analysis was limited by variations in the time

from AMI to cell delivery (median, 6.5 days) and in imaging modalities used to assess cardiac function (MRI, single-photon emission computed tomography, angiography, echocardiography).

Fisher et al. (2016) reported on the results of a trial sequential analysis using cumulative data obtained from 2 previous Cochrane reviews with updated results to March 2015. (8) The intent of the analysis was to obtain estimates of sample sizes required for a meta-analysis to detect a significant treatment effect while controlling for random errors due to repeat testing. Thirty-seven AMI trials that assessed BMCs and reported on mortality as an outcome were included. Of the 37 trials, 14 reported no deaths. Of 23 trials that observed incidences of mortality in either trial arm, there were 43 deaths in 1073 patients (4.0%) who received cell therapy compared with 38 deaths in 754 patients (5.0%) who did not. Results showed that there was insufficient evidence to detect a significant treatment effect of bone marrow-derived cells on mortality and rehospitalization in AMI (relative risk [RR], 0.92; 95% confidence interval [CI], 0.62 to 1.36). Results of the sequential analysis showed that at least 4055 participants would be required to detect a relative reduction in the risk of mortality of 35% in AMI patients. Most of the meta-analyses reported so far have not reached this sample size.

Lalu et al. (2018) reported results of a systematic review and meta-analyses including both randomized and nonrandomized studies. (9) The review did not include any RCTs in acute cardiac ischemia published after the preceding Fisher et al. (2015) review and will not be discussed further.

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 than that for the use of stem cells. A few RCTs on the treatment of acute ischemia have reported physiologic outcomes. Additionally, meta-analyses of the available trials have been published. Moazzami et al. (2013) published a Cochrane review evaluating G-CSF for AMI. (10) Literature was searched in November 2010, and 7 small, placebo-controlled, randomized trials (N=354) were included. The 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=.55; I^2=0%). Similarly, change in LVEF, left ventricular end-systolic volume, and left ventricular end-diastolic volume did not differ between groups. Evidence was insufficient to draw conclusions about the safety of the procedure. Similarly, reviewers concluded there was a lack of evidence for the benefit of G-CSF therapy in patients with AMI.

Table 1a. Summary of Systematic Reviews Assessing Use of Progenitor Cell Therapy to Treat Acute Ischemia

Study	Dates	Trials	Patients	Design	Mean Time Between Acute Event and Cell Infusion	Median Trial Duration (Range), mo
Delewi et al. (2014) (4)	1980 to Feb 2013	16	1641	RCT	≤1 mo	6 (3 to 6)

de Jong et al. (2014) (5)	Jan 2002 to Sep 2013	22	1513	RCT	≤1 mo	6 (3 to 60)
Fisher et al. (2015) (6)	Through Mar 2015	41	2732	RCT	≤14 d	<12
						≥12
Gyöngyösi et al. (2015) (7)	NR	12	1252	RCT or cohort	≤14 d	6 (3 to 12)

d: day(s); mo: month(s); NR: not reported; RCT: randomized controlled trial.

Table 1b. Summary of Systematic Reviews Assessing Use of Progenitor Cell Therapy to Treat Acute Ischemia

	Outcomes (95% CI)		
Study	**Mean Change or % Change in LVEF**	**Risk of All-Cause Mortality**	**Risk of CV Mortality**
Delewi et al. (2014) (4)	2.55% (1.83% to 3.26%) I^2=84%	NR	NR
De Jong et al. (2014) (5)	2.10% (0.68% to 3.52%) I^2=80%	0.68[a] (0.36 to 1.31)	0.73[a] (0.32 to 1.65)
Fisher et al. (2015) (6)	1.05[b] (-0.56 to 2.67)	0.80[c] (0.43 to 1.49)	0.72[c] (0.28 to 1.82)
	1.27[b] (-1.14 to 3.68)	0.93[c] (0.58 to 1.50)	1.04[c] (0.54 to 1.99)
Gyöngyösi et al. (2015) (7)	0.96 (-0.2 to 2.1)	0.70 (p=.499)	NR

CI: confidence interval; CV: cardiovascular; LVEF: left ventricular ejection fraction; NR: not reported.
[a] Mantel-Haenszel odds ratio (95% CI).
[b] As measured by magnetic resonance imaging.
[c] Relative risk (95% CI).

Randomized Controlled Trials

Key studies, including phase 3 RCTs with more than 100 patients per arm, are described next. Summaries of trial characteristics and results are in Tables 2 and 3.

REPAIR-AMI was a double-blind trial that infused bone marrow-derived progenitor cells or a placebo control infusion of the patient's serum. The trial enrolled 204 patients from 17 centers in Germany and Switzerland who had acute ST-segment elevation MI and met strict inclusion criteria. (11, 12) 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<.03) and revascularization (22 vs. 37; p<.03), as well as for the composite outcome of death, MI, and revascularization (24 vs. 42; p<.009). Two-year clinical outcomes from the REPAIR-AMI trial, performed according to a study protocol amendment filed in 2006, were reported in 2010. (12, 13) Eleven 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, 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 determine definitively whether administration of progenitor cells reduces mortality and morbidity after AMI.

Hirsch et al. (2011) reported on a multicenter, phase 3 RCT that compared bone marrow or peripheral blood mononuclear cell infusion with standard therapy in 200 patients with AMI treated with primary percutaneous coronary intervention. (14) In the Clinical Study to Examine the Effects of Erythropoietin on Left Ventricular Function After Acute Myocardial Infarction (HEBE) trial, mononuclear cells were delivered 3 to 8 days after AMI. Blinded assessment of the primary outcome (the percentage of dysfunctional left ventricular segments that had improved segmental wall thickening at 4 months) found no significant difference between the treatment groups (38.5% for bone marrow vs. 36.8% for peripheral blood) and controls (42.4%). There were no significant differences between groups in LVEF; change in left ventricular volumes, mass, or infarct size; or rates of clinical events. At 4 months, a similar percentage of patients had New York Heart Association (NYHA) class II or higher heart failure (19% for bone marrow, 20% for peripheral blood, 18% for controls).

Table 2. Randomized Controlled Trial Characteristics of Progenitor Cell Therapy for Acute Ischemia

					Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Cell Therapies**	**Comparator**
Schächinger et al. (2006) (11, 12); REPAIR-AMI	Germany; Switzerland	17	2004-2005	Acute ST-elevation MI; successfully re-perfused; LVEF ≤45%	Intracoronary infusion of BMCs (n=101)	Sham infusion (n=103)
Hirsch et al. (2011) (14); HEBE	Netherlands	8	2005-2008	ST-segment elevation MI; treated with primary PCI and stent implantation	• Intracoronary infusion of autologous mononuclear BMCs (n=69) • Intracoronary infusion of mononuclear peripheral blood cells (n=66)	Standard of care without sham infusion (n=65)

BMC: bone marrow cell; HEBE: Clinical Study to Examine the Effects of Erythropoietin on Left Ventricular Function After Acute Myocardial Infarction; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; REPAIR-AMI: Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction.

Table 3. Randomized Controlled Trial Results of Progenitor Cell Therapy for Acute Ischemia

Study	**Mortality, n**	**Major Adverse Events, n**	**Rehospitalization for Heart Failure, n**	**LVEF**
	By 1 Year	*Death, MI, Revascularization by 1 Year*	*By 1 Year*	*Mean Change from BL to 4 Months (SD)*
Schachinger et al. (2006) (11, 12)				
N	204	204	204	187
Cell Therapy	6	23	0	5.5 (7.3)
Sham	2	40	3	3.0(6.5)
TE (95% CI); p-value	NR; p=0.28	NR; p=0.01	NR; p=0.25	NR; p=0.01
	By 4 Months	*Death, MI, Revascularization by 4 months*	*By 4 Months*	*Mean Change from BL to 4 Months (SD)*
Hirsch et al. (2011) (14)				
N	200	200	200	189
BMC therapy	0	4	0	3.8 (7.4)
PBC therapy	1	9	1	4.2 (6.2)
SOC	0	6	1	4.0 (5.8)
TE (95% CI); p-value	NR	NR	NR	BMC vs. SOC: 0.1 (-2.2 to 2.4); p=.94 PBC vs. SOC: 0.1 (-2.0 to 2.2); p=.9

BL: baseline; BMC: bone marrow cell; CI: confidence interval; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NR: not reported; PBC: peripheral blood cell; SD: standard deviation; SOC: standard of care; TE: treatment effect.

Section Summary: Progenitor Cells to Treat Acute Cardiac Ischemia

The evidence on progenitor cell therapy for patients with MI includes 2 phase 3 RCTs including more than 100 patients, numerous small, early-phase RCTs, and meta-analyses of these RCTs. Studies varied by types of cells used and methods and timing of delivery. Most studies reported outcomes for LVEF and/or myocardial perfusion at 3 to 6 months. These studies generally reported small to modest improvements in these intermediate outcomes. Limited evidence on clinical outcomes has suggested that there may be benefits in improving LVEF, reducing recurrent MI, decreasing the need for further revascularization, and perhaps decreasing

mortality although a recent, large, individual patient data meta-analysis reported no improvement in these outcomes. No single adequately powered trial has reported benefits in clinical outcomes, such as mortality, adverse cardiac outcomes, exercise capacity, or quality of life. Overall, this evidence has suggested 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.

Progenitor Cells to Treat Chronic Cardiac Ischemia

Clinical Context and Therapy Purpose

The purpose of progenitor cell therapy in individuals with chronic cardiac ischemia is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medication, angioplasty and stenting, bypass surgery, and enhanced external counterpulsation.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with chronic cardiac ischemia.

Interventions

The therapy being considered is progenitor cell therapy. Progenitor cell therapy is the use of multipotent cells of various cell lineages (autologous or allogeneic) to repair and/or regenerate tissue, including damaged myocardium caused by cardiac ischemia.

Comparators

Comparators of interest are standard of care measures, such as medication, angioplasty and stenting, bypass surgery, and enhanced external counterpulsation.

Outcomes

The general outcomes of interest are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. Available literature reports follow-up of up to 5 years; however, cardiac ischemia is a chronic condition, and patients are managed by cardiologists for all their lives.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The evidence for stem cell therapy for chronic ischemic heart disease includes systematic reviews, many small, early-phase RCTs, 1 phase 3 RCT with more than 100 participants, and nonrandomized studies.

Systematic Reviews

Fisher et al. (2016) published a systematic review that updated a 2014 Cochrane review. (15, 16) In 2016, literature was searched through December 2015, and 38 RCTs (N=1907) were included. The overall quality of the evidence was considered low because selected studies were small (only 3 included >100 participants) and the number of events was low, leading to a risk of small-study bias and spuriously inflated effect sizes. The analysis found significantly lower long-term (≥12 months) mortality (risk ratio, 0.42; 95% CI, 0.21 to 0.87), non-fatal MI (risk ratio, 0.38; 95% CI, 0.15 to 0.97), and arrhythmias (risk ratio, 0.42; 95% CI, 0.18 to 0.99) with cell therapy versus placebo. Cell therapy did not improve heart failure hospitalization or change in LVEF. Although reviewers were unable to detect evidence of publication bias using funnel plots, they noted that of 28 identified ongoing trials, 11 trials with 787 participants were recorded as having been completed or were due to have been completed in advance of the search date but had no publications. Therefore, publication bias cannot be ruled out. Xu et al. (2014) and Xiao et al. (2014) reported similar results in 2014 in their meta-analyses. (17, 18)

Lalu et al. (2018) reported results of a systematic review and meta-analyses including both randomized and nonrandomized studies. (9) The review did not include any RCTs on chronic cardiac ischemia published after the preceding Fisher et al. (2016) review or otherwise discussed in the section below and will not be discussed further.

Randomized Controlled Trials

Qayyum et al. (2023) published results of a phase 2, international, multicenter, placebo-controlled, double-blind RCT (SCIENCE). (19) The SCIENCE trial objective was to see if a single treatment with direct intramyocardial injections of allogeneic adipose tissue-derived mesenchymal stromal cells (ASCs) would be safe and effective at improving cardiac function in individuals with chronic ischemic heart failure with reduced ejection fraction (HFrEF) compared to placebo. A total of 133 patients with symptomatic HFrEF (defined as LVEF <45%) on guideline-directed medical therapy were included. At baseline, mean age was 64 to 66 years, mean LVEF was 32%, and most patients were NYHA class II and male. Race and ethnicity of included patients were not disclosed. The primary outcome was change in left ventricular end-systolic volume at 6-month follow-up, as measured by echocardiography. Quality of life endpoints and change in LVEF and NYHA class were secondary outcomes. Patients were randomized 2:1 to receive either intramyocardial injections of ASC or placebo. After 6 months, there were no differences in changes in left ventricular end-systolic volume from baseline between the 2 groups (-3.5 ± 2.8 mL in ASC vs. -3.9 ± 4.1 mL in placebo; difference, 0.3 ± 5 mL; p=.945). There were also no significant differences at 6 months in changes associated with LVEF, 6-minute walk test, NYHA functional class, or other quality of life or biomarker secondary outcomes between the groups. Over 12 months, there were no significant differences in occurrence of adverse events between the 2 groups. There were 3 deaths due to progression of

HFrEF in the ASC group and 2 in the placebo group. The study was not powered to detect quality of life outcomes or changes in NYHA functional class or LVEF, limiting interpretation.

Bolli et al. (2021) conducted a phase 2, double-blind, placebo-controlled RCT (CONCERT-HF) on behalf of the Cardiovascular Cell Therapy Research Network with funding from the National Heart, Lung, and Blood Institute. (20) This multicenter trial included 125 patients with ischemic heart failure and ejection fraction ≤40% and on guideline-directed therapy. Most patients were NYHA class II. At baseline, the mean age was about 62 years, mean LVEF was 28.6%, about 90% of patients were White, about 8% of patients were Black, and about 16% of patients were Hispanic. Patients were randomized to 1 of 4 treatment groups: autologous bone marrow-derived mesenchymal stromal cells, c-kit positive cardiac cells, a combination of both cell types, or placebo, all given by transendocardial injection. After 12 months, heart failure-related major adverse cardiac events (MACE) occurred in 24.1%, 6.5%, 9.1%, and 28.1% of patients who received mesenchymal stem cells, cardiac cells, combination cell therapy, and placebo, respectively (p=.049). Other clinical event outcomes, including heart failure hospitalization, heart failure exacerbation, death, stroke, MI, and coronary artery revascularization, did not differ between groups. Quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire was improved at 12 months with combination cell therapy versus placebo (p=.02); other secondary outcomes did not differ between groups at 12 months. The clinical applicability of this trial is limited by a small sample size and limited power to detect differences in clinical outcomes.

Bartunek et al. (2017) reported on a multinational, sham-controlled RCT on cardiopoietic cell therapy for advanced ischemic heart failure. (21) Researchers for the Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) trial initially screened 484 patients with symptomatic ischemic heart failure who were on standard therapy. All patients (100%) were White. Of those, 348 underwent bone marrow harvest and mesenchymal stem cell expansion. The 315 who achieved >24 million mesenchymal cells were randomized to either cardiopoietic stem cell therapy (n=157) or sham treatment (n=158). Before treatments began, 37 patients in the stem cell group and 7 patients in the control group withdrew from the study; therefore, the 39-week follow-up analysis included 120 patients who had received stem cells and 151 who had undergone sham treatment. Also, 19 patients whose cell product did not meet release criteria were excluded from analysis in the cardiopoietic cell group. The probability that the treatment group had a better outcome on the composite primary outcome was 0.54 (a value >0.5 favors active treatment; 95% CI, 0.47 to 0.61; p=.27). Exploratory subgroup analysis reported treatment benefit in patients, with baseline left ventricular end-diastolic volumes of 200 to 370 mL (60% of patients) (0.61; 95% CI, 0.52 to 0.70; p=.015). There was no statistical difference in serious adverse events between treatment arms. One (0.9%) cardiopoietic cell patient and 9 (5.4%) sham patients experienced aborted or sudden cardiac death. A long- term follow-up study showed similar results at week 52 with regard to the primary composite outcome for all patients (0.52; 95% CI, 0.45 to 0.59; p=.51) and for patients with left ventricular end-diastolic volume of 200 to 370 mL (0.6; 95% CI, 0.51 to 0.69; p=.024). (22) After a median follow-up of 104.9 weeks, death was not statistically significant between cell-treated and sham-treated patients (21.7% vs. 25.9%, respectively; hazard ratio, 0.84; 95% CI, 0.51 to 1.38; p=.49).

Patel et al. (2016) conducted a multicenter, double-blind RCT (ixCELL-DCM) of ixmyelocel-T in patients with ischemic heart failure. (23) Ixmyelocel-T is an autologous mixed cell therapy that contains CD90+ mesenchymal stem cells and activated macrophages. The ixCELL-DCM trial was a double-blind, phase 2b RCT in patients with NYHA class III or IV ischemic heart failure, LVEF ≤35%, and had an automatic implantable cardioverter defibrillator who received transendocardial ixmyelocel-T (n=66) or placebo (n=60). At baseline, the mean age was 65 years, the majority of patients were White (ixmyelocel-T, 91%; placebo, 88%), and baseline LVEF was about 25%. After 12 months, the primary outcome (composite of all-cause death, cardiovascular hospital admission, or unplanned clinic visits for acute decompensated heart failure) occurred in 38% of the ixmyelocel-T group and 49% of the placebo group (risk ratio, 0.63; 95% CI, 0.42 to 0.97; p=.0344). Serious adverse events were more common with placebo than ixmyelocel-T (p=.0197).

Pokushalov et al. (2010) reported on the results of an RCT of intramyocardial injections of autologous bone marrow mononuclear cells (n=55) compared with optimal medical management (n=54) in patients who had chronic, ischemic heart failure. (24) The trial appears to have been conducted in Russia; dates of study conduct were not reported. Power calculations were not reported, and it is not clear if the trial was registered. Comparative treatment effects were not calculated for many outcomes. The RCT reported statistically significant improvements in mortality rates at 12 months for cell therapy (11%) versus medical therapy (39%) favoring cell therapy (<.001). Tables 4 and 5 summarize the characteristics and results of the RCTs.

Table 4. Randomized Controlled Trial Characteristics of Progenitor Cell Therapy for Chronic Ischemic Heart Disease

					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Cell Therapy**	**Comparator**
Qayyum et al. (2023) (19) SCIENCE	Multinational[a]	6	2017-2018	Chronic ischemic HFrEF, LVEF <45%, NYHA class II to III on guideline-directed therapy	Adipose tissue-derived mesenchymal stromal cells (n=90)	Placebo (n=43)
Bolli et al. (2021) (20) CONCERT-HF	U.S.	7	2016-2018	LVEF ≤40%, NYHA class ≥I to III on guidelines-directed therapy (Black, 0% to 9.09%;	Mesenchymal stem cells (n=29) c-kit positive cardiac cells (n=31)	Placebo (n=32)

				Hispanic, 12.5% to 19.35%)	Mesenchymal stem cells plus c-kit positive cardiac cells (n=33)	
Bartunek et al. (2017, 2020) (21, 22) CHART-1	Multinational[b]	39	2012-2015	LVEF ≤35%, NYHA class ≥II on guidelines-directed therapy (White, 100%)	Cardiopoietic cells (n=157)	Sham (n=158)
Patel et al. (2017) (23) ixCELL-DCM	U.S., Canada	31	2013-2016	LVEF ≤35%, NYHA class III or IV, with an AICD, not eligible for revascularization (Black, 2% to 10%; American Indian or Alaska native, 2% in both groups)	Ixmyelocel-T (n=66)	Placebo (n=60)
Pokushalov et al. (2010) (24)	Russia	NR	NR	LVEF <35%, end-stage, chronic heart failure, on optimal medical therapy, not eligible for revascularization	Bone marrow cells (n=55)	Medical management, no sham (n=54)

AICD: automatic implantable cardioverter defibrillator; CHART-1: Congestive Heart Failure Cardiopoietic Regenerative Therapy; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association.

[a] Denmark, Germany, The Netherlands, Austria, Slovenia, and Poland.

[b] Belgium, Bulgaria, Hungary, Ireland, Israel, Italy, Poland, Serbia, Spain, Sweden, Switzerland, and United Kingdom.

Table 5. Randomized Controlled Trial Results of Progenitor Cell Therapy for Chronic Ischemic Heart Disease

Study	Mortality, n (%)	Change in Heart Failure, n (%)	MLHFQ Score, n (%)	6-Minute Walk Test	LVEF
	at 12 months	*LVESV at 6 months*	*mean overall KCCQ (SD) at baseline and at 12 months*	*mean (SD) distance walked at 6 months; at 12 months*	*at 6 months*
Qayyum et al. (2023) (19) SCIENCE					
Adipose tissue-derived mesenchymal stromal cells	3 (3.3%)	-3.5 ± 2.8 mL	72.5 (2.3); 79.4 (2.5)	422 (13); 432 (13)	1.2 ± 0.6% (p=.044 compared to baseline)
Placebo	2 (4.7%)	-3.9 ± 4.1 mL	75.7 (3.2); 85.1 (3.8)	450 (20); 451 (19)	2.8 ± 0.9% (p=.003 compared to baseline)
difference between groups ± SD		0.3 ± 5 mL			-1.6 ± 1.0%
p-value	1.0	.945	NS	between-group differences baseline to FU, .089; .097	.119
	at 12 months	*Heart failure-related MACE at 12 months*	*mean (SD) at 12 months*	*mean (SD) distance walked at 12 months, m*	*mean (SD) at 12 months, %*
Bolli et al. (2021) (20) CONCERT-HF					
Mesenchymal stem cells	3 (10.3%)	7 (24.1%)	30.2 (19.67)	400.38 (98.55)	31.12 (7.06)
c-kit positive cardiac cells	2 (6.5%)	2 (6.5%)	25.68 (19.02)	391.65 (102.56)	26.96 (5.12)
Combination cell therapy	2 (6.1%)	3 (9.1%)	25.35 (15.77)	397.07 (87.66)	29.91 (6.74)
Placebo	4 (12.5%)	9 (28.1%)	36.55 (21.13)	384.88 (101.069)	29.35 (5.88)
p-value	.767	.049	.02 for combination cell therapy vs. placebo	NS	NS
	At 39 Weeks	*Worsening; ≥ 1 Event Through 39 Weeks*	*≥ 10-point Improvement*	*≥ 40 m Improvement*	*≥ 4% Improvement*

			From BL to 39 Weeks	*From BL to 39 Weeks, n (%)*	*From BL to 39 Weeks, n (%)*
Bartunek et al. (2017) (21)					
N	271	271	244	239	226
Cell therapy	11 (9%)	20 (17%)	64 (59%)	50 (46%)	69 (68%)
Sham	12 (8%)	23 (15%)	66 (49%)	40 (31%)	82 (66%)
TE (95% CI); p-value	HR=1.2 (0.5 to 2.7); 0.70	Odds[a] = 1.03 (0.9 to 1.2 (0.5 to 2.7); 0.72	Odds[a] = 0.8 (0.7 to 1.0); .12	Odds[a] = 0.8 (0.7 to 1.0); .07	Odds[a] = 1.0 (0.8 to 1.2); .73
	At 104.9 weeks	NR	NR	NR	NR
Bartunek et al. (2020) (22)					
N	271				
Cell therapy	26 (21.7%)				
Sham	39 (25.9%)				
TE (95% CI); p-value	HR, 0.84 (0.51 to 1.38); p=.49				
	At 12 months	*Composite clinical cardiac events at 12 months*		*at 12 months*	*at 12 months*
Patel et al. (2017) (23) ixCELL-DCM					
N	109	109		82	85
Ixmyelocel-T	2 (3%)	22 (38%)		NR	NR
Placebo	7 (14%)	25 (49%)		NR	NR
TE (95% CI); p-value	NR	RR, 0.63 (0.42 to 0.97); p=.0344		.9303	NR
	At 12 Months	*Improvement in NYHA Class by 1 Class at 3 Months*		*Mean Distance Walked at 12 Months (SD), m*	*LVEF (SD)*
Pokushalov et al. (2010) (24)					
N	109	107		NR	107
Cell Therapy	6 (11%)	25 (46%)		359 (69)	28 (6)
Sham	21 (39%)	4 (8%)		196 (42)	27 (6)
TE; p-value	<.001	NR		0.03	NR

BL: baseline; CI: confidence interval; FU: follow-up; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MACE: major adverse cardiovascular events; MLHFQ: Minnesota Living with Heart Failure Questionnaire;

NR: not reported; NS: not significant; NYHA: New York Heart Association; RR: relative risk; SD: standard deviation; TE: treatment effect.
[a] Mann-Whitney odds for worse outcome in cell therapy versus sham for ordered categories; note, not all categories are shown in this table. Values <1.0 favor cell therapy treatment.

Nonrandomized Controlled Trials

The acute and long-term effects of intracoronary Stem Cell Transplantation in 191 Patients With Chronic Heart Failure (STAR-heart) trial evaluated stem cell therapy for chronic heart failure due to ischemic cardiomyopathy. Strauer et al. (2010) reported on this nonrandomized open-label study, which evaluated 391 patients with chronic heart failure. (25) In this trial, 191 patients received intracoronary BMC therapy, and 200 patients who did not accept the treatment agreed to undergo follow-up testing, serving as controls. The mean time between percutaneous coronary intervention 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. At up to 5 years after intracoronary BMC therapy, there was a significant improvement in hemodynamics (LVEF, cardiac index), exercise capacity (NYHA classification), oxygen uptake, and left ventricular 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<.01). However, the trial was limited by the potential for selection bias (patient self-selection into treatment groups). For example, there was a 7% difference in baseline ejection fraction rates between 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.

Section Summary: Progenitor Cells to Treat Chronic Cardiac Ischemia

The evidence on progenitor cell therapy for chronic ischemia includes RCTs, systematic reviews of RCTs, and a nonrandomized comparative trial. The studies included in the meta-analyses were generally early-phase, small (<100 participants) trials; they only reported on a small number of clinical outcome events. Two phase 2 RCTs (CONCERT-HF and ixCELL-DCM) found significant benefit on heart failure-related death and other cardiac events with cell therapy compared to placebo. One well-conducted, phase 3 trial failed to demonstrate superiority for cell therapy for the primary outcomes, including death, worsening heart failure, and other events. Another RCT found that cell therapy was safe but did not impact left ventricular end-systolic volume or secondary quality of life and cardiac outcomes compared to placebo. The nonrandomized STAR-Heart trial showed a mortality benefit as well as a favorable hemodynamic effect, but the lack of randomization limits interpretation due to concerns about selection bias and differences in known and unknown prognostic variables at baseline between arms. 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.

Progenitor Cell Therapy to Treat Refractory Angina

Clinical Context and Therapy Purpose

The purpose of progenitor cell therapy in individuals with refractory angina is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medication, angioplasty and stenting, bypass surgery, and enhanced external counterpulsation.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with refractory angina.

Interventions
The therapy being considered is progenitor cell therapy. Progenitor cell therapy is the use of multipotent cells of various cell lineages (autologous or allogeneic) to repair and/or regenerate tissue, including damaged myocardium.

Comparators
Comparators of interest are standard of care measures, such as medication, angioplasty and stenting, and bypass surgery.

Outcomes
The general outcomes of interest are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. Available literature reports follow-up of up to 2 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The evidence for stem cell therapy for patients with intractable angina who are not candidates for revascularization includes a systematic review, (26) 4 trials from 2007 through 2014 with fewer than 100 patients, (27-30) 2 phase 1/2 trials with more than 100 patients, (31, 32) and 1 phase 3 trial with more than 100 participants, (33) which is discussed more in the section on RCTs.

Systematic Reviews
Khan et al. (2016) reported on the results of a systematic review of RCTs evaluating cell therapy in patients with refractory angina who were ineligible for coronary revascularization. (26) The risk of bias in the included studies was rated as low. All selected randomized trials were placebo-controlled; 5 RCTs were blinded and in 1 blinding was not reported. The systematic

review characteristics and results are shown in Tables 6 and 7. The trials varied in durations of follow-up but appear to have been pooled regardless of the timing of the outcome in the analysis. Although there was a beneficial effect of cell therapy on frequency of angina in the pooled analysis, there was significant heterogeneity for the angina outcome, which was attributed to 1 RCT. With removal of this RCT, there was an attenuation of the effect (mean difference, -3.38; 95% CI, -6.56 to 0.19).

Table 6. Systematic Review Characteristics of Progenitor Cell Therapy for Refractory Angina

Study	Dates	Trials	Participants	N (Range)	Design	Length of FU
Khan et al. (2016) (26)	Up to Sep 2015	6	Refractory angina who were ineligible for coronary revascularization	353 (24 to 112)	RCT	6 months to 2 years

FU: follow-up; RCT: randomized controlled trial.

Table 7. Systematic Review Results of Progenitor Cell Therapy for Refractory Angina

Study	Frequency of Angina	CCS Angina Class	MACE
Khan et al. (2016) (26)			
Total N	271	210	NR
PE (95% CI); p-value	MD = -7.8 (-15.2 to -0.41); 0.04	MD = -0.58 (-1.00 to -0.16); .007	OR = 0.49 (0.25 to .98); .04
I^2 (p-value)	90% (<.001)	0% (.67)	0% (NR)

CCS: Canadian Cardiovascular Society; CI: confidence interval; MACE: major adverse cardiac events; MD: mean difference; OR: odds ratio; PE: pooled effect; NR: not reported.

Randomized Controlled Trials

One phase 3 trial of cell therapy in patients with refractory angina who were ineligible for coronary revascularization including more than 100 participants has been reported. Characteristics and results are shown in Tables 8 and 9.

Povsic et al. (2016) reported on the industry-sponsored Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells (RENEW) trial. (33) This 3-arm multicenter trial compared outcomes from the intramyocardial administration of autologous CD34-positive cells using exercise capacity at 3, 6, or 12 months. Patients underwent cell mobilization with G-CSF for 4 days followed by apheresis. The peripheral cell product was shipped to a central processing facility (Progenitor Cell Therapy) for selection of CD34-positive cells. The trial was terminated after enrollment of 112 of a planned 444 patients before data analysis due to strategic considerations. The progenitor cell group had greater exercise capacity than the standard therapy group but was no better than the double-blind placebo group, consistent with a placebo effect. Additionally, with only 122 participants, the trial was not adequately powered to detect a between-group difference.

Table 8. Randomized Controlled Trial Characteristics of Progenitor Cell Therapy for Refractory Angina

					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Cell Therapy**	**Comparator**
Povsic et al. (2016) (33); RENEW	U.S.	41	2012-2013	CCS class III/IV angina, LVEF ≥25%, on maximally tolerated drug therapy, not eligible for revascularization (White, 90.2%)	Autologous CD34- positive (G-CSF stem cell mobilization, apheresis, and IM CD34-positive injection) (n=54)	• Standard of care: no additional intervention, not blinded (n=28) • Active control: G-CSF stem-cell mobilization, apheresis, and IM placebo injection (n=27)

CCS: Canadian Cardiovascular Society; G-CSF: granulocyte colony stimulating factor; IM: intramyocardial; LVEF: left ventricular ejection fraction; RENEW: Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells.

Table 9. Randomized Controlled Trial Results of Progenitor Cell Therapy for Refractory Angina

Study	**Angina Frequency**	**Exercise Time, s**	**MACE, n (%)**	**Death, n (%)**
	Mean Episodes/ Week at 12 Months (SD)	**Mean Change from BL to 12 Months (SD)**	**At 24 Months**	**At 24 Months**
Povsic et al. (2016) (33)				
N	84	84	106	106
CT	3.8 (6.2)	109 (194)	23 (46%)	2 (4%)
SOC	NR	NR	19 (68%)	2 (7%)
AC	2.7 (4.6)	90 (185)	12 (43%)	3 (11%)
TE for CT vs. AC (95% CI); p-value	RR=1.02 (NR); .95	20.4 (-68.9 to 109.6); .65	NR	NR
TE for CT vs. SOC (95% CI); p-value	NR	NR	NR	NR

AC: active control; BL: baseline; CT: cell therapy; MACE: major adverse cardiac events; NR: not reported; RR: relative risk; SD: standard deviation; SOC: standard of care; TE: treatment effect.

Section Summary: Progenitor Cell Therapy to Treat Refractory Angina

Evidence on stem cell therapy for refractory angina includes early-phase trials, as well as a phase 3 pivotal trial that was terminated early and insufficiently powered to evaluate clinical

outcomes. Additional larger trials are needed to determine whether progenitor cell therapy improves health outcomes in patients with refractory angina.

Summary of Evidence

For individuals who have acute cardiac ischemia who receive progenitor cell therapy, the evidence includes 2 phase 3 randomized controlled trials (RCTs), numerous small, early-phase RCTs, and meta-analyses of these RCTs. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. Limited evidence on clinical outcomes has suggested there may be benefits from improving left ventricular ejection fraction (LVEF), reducing recurrent myocardial infarction (MI), decreasing the need for further revascularization, and perhaps decreasing mortality, although, a recent, large, individual patient data meta-analysis reported no improvement in these outcomes. No adequately powered trial has reported benefits in clinical outcomes (e.g., mortality, adverse cardiac outcomes, exercise capacity, quality of life). Overall, this evidence has suggested 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic cardiac ischemia who receive progenitor cell therapy, the evidence includes 1 phase 3 RCT with more than 100 participants, 3 phase 2 RCTs with more than 100 participants, systematic reviews of smaller, early-phase RCTs, and a nonrandomized comparative trial. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The studies included in the meta-analyses have reported only on a small number of clinical outcome events. Two phase 2 RCTs (CONCERT-HF and ixCELL-DCM) found significant benefit on heart failure-related death and other cardiac events with cell therapy compared to placebo. Another phase 2 RCT found that cell therapy was safe but did not impact left ventricular end-systolic volume or secondary quality of life and cardiac outcomes compared to placebo. A well-conducted phase 3 trial failed to demonstrate superiority of cell therapy for its primary composite outcome that included death, worsening heart failure events, and other multiple events. The nonrandomized STAR-Heart trial showed a mortality benefit as well as favorable hemodynamic effect, but a lack of randomization limits interpretation due to the concern about selection bias and differences in known and unknown prognostic variables at baseline between both arms. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have refractory angina who receive progenitor cell therapy, the evidence includes a systematic review of RCTs, phase 2 trials, and a phase 3 pivotal trial. Relevant outcomes are disease-specific survival, morbid events, functional outcomes, quality of life, and hospitalizations. The only phase 3 trial identified was terminated early and insufficiently powered to evaluate clinical outcomes. Additional larger trials are needed to determine whether progenitor cell therapy improves health outcomes in patients with refractory angina. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions

In 2015, the American College of Cardiology Foundation, American Heart Association, and the Society for Cardiovascular Angiography and Interventions issued a Focused Update on Primary Percutaneous Coronary Interventions for Patients With ST-Elevation Myocardial Infarction. (34) This guideline was an update of the 2011 guideline for percutaneous coronary intervention (35) and the 2013 guideline on managing ST-elevation myocardial infarction. (36) In 2021, these same organizations published a guideline on coronary artery revascularization. (37) Progenitor cell therapy was not mentioned in any of these guidelines.

The most recent guidelines on treatment of heart failure with reduced ejection fraction from the American College of Cardiology (2023) and American Heart Association/American College of Cardiology/Heart Failure Society of America (2022) do not mention progenitor cell therapy. (38, 39)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 10.

Table 10. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01693042	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 (REPEAT)	81	Jan 2025
NCT03455725[a]	Prospective, multi-center, 2:1 randomized (Treatment vs. Sham Control), blinded trial comparing 2 parallel groups of patients with CMI treated with CardiAMP cell therapy system vs. sham treatment (CardiAMP CMI)	343	Dec 2026
NCT05711849	A Phase II Randomised Sham-controlled Trial Assessing the Safety and Efficacy of Intracoronary Administration of Autologous Bone Marrow Cells in Patients With Refractory Angina	110	Feb 2026
Unpublished			

NCT02323620	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 (RACE-STEMI)	200	Dec 2022
NCT03129568	A Prospective Phase 1 Trial of Cardiac Progenitor Cell Therapy in Children With Dilated Cardiomyopathy	5	Dec 2020
NCT01781390[a]	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	106	Apr 2021
NCT03418233[a]	Regeneration of Ischemic Damages in Cardiovascular System Using Wharton's Jelly as an Unlimited Source of Mesenchymal Stem Cells for Regenerative Medicine. Project of the National Centre for Research and Development (Poland) 'STRATEGMED II'. Randomized Clinical Trial to Evaluate the Regenerative Capacity of CardioCell in Patients With Chronic Ischaemic Heart Failure (CIHF)	115	Mar 2021
NCT02032004[a]	Efficacy and Safety of Allogeneic Mesenchymal Precursor Cells (Rexlemestrocel-L) for the Treatment of Heart Failure (DREAM HF-1)	566	May 2020

NCT: National Clinical Trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	38205, 38206, 38230, 38232, 38240, 38241
HCPCS Codes	C9782

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2024	Document updated with literature review. Coverage unchanged. Added references 19 and 39.
01/01/2024	Document updated with literature review. Coverage unchanged. Reference 38 added; others updated.
01/15/2023	Document updated with literature review. Simplified “stem- or progenitor-cell therapy” to “progenitor cell therapy” throughout document, without change to policy intent. Added the following references: 1, 19, 21, 22, 36 and 37. Title changed from “Stem-Cell Therapy for the Treatment of Damaged Myocardium Due to Ischemia”.
08/01/2021	Reviewed. No changes.
07/15/2020	Document updated with literature review. Coverage unchanged. References 9, 30, 31 were added and some references removed.
08/01/2019	Reviewed. No changes.
10/01/2018	Document updated with literature review. Coverage unchanged. References 3, 7, 9, 15, 19-20, 24-29 added, and some references removed.
06/01/2017	Reviewed. No changes.
10/01/2016	Document updated with literature review. Coverage unchanged.
11/01/2015	Reviewed. No changes.
12/01/2014	Document updated with literature review. Coverage unchanged. Rationale and References significantly reorganized and revised. “Due to Ischemia” was added to the policy title.
01/01/2012	Document updated with literature review. Policy titled changed from Autologous Cell Therapy for the Treatment of Damaged Myocardium to Stem-Cell Therapy for the Treatment of Damaged Myocardium. Coverage unchanged.
09/15/2009	Routine scheduled review; Revised/updated entire document; no changes to coverage statement.
09/15/2007	Revised/updated entire document
03/01/2005	New medical document