2.02.18	Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia		
Original Policy Date:	February 1, 2017	**Effective Date:**	August 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 22

Policy Statement

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

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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.

Related Policies

- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)
- Stem Cell Therapy for Peripheral Arterial Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Progenitor cells are included in these regulations. The FDA marketing clearance is not required when autologous cells are processed on site with existing laboratory procedures and injected with existing catheter devices. Several cell products are expanded ex vivo and require FDA approval. The 21st Century Cures Act (December 2016) established new expedited product development programs including 1 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.

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 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®.

Ixmyelocel-T is an expanded multicellular therapeutic product produced from a patient's bone marrow by selectively expanding bone marrow mononuclear cells for two weeks. 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.

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™.

Rationale

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.

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.[1,2,]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.

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 the damaged myocardium has been suggested in animal studies using tagged progenitor cells. However, there is controversy concerning whether injected progenitor cells engraft and differentiate into mature myocytes in humans to the 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 has also suggested that injected stem cells secrete cytokines with antiapoptotic and proangiogenesis properties. 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 (e.g., 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 are also various 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 events of progenitor cell treatment include risks of the delivery procedure (e.g., 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 (e.g., teratomas) can arise from progenitor cells, but the actual risk in humans is currently unknown.

Literature Review

Evidence reviews 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA

(Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

The present evidence review 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 patients 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 review.

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 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.

Review of Evidence

Systematic Reviews

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., myocardial infarction) 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 1. Summary of Systematic Reviews Assessing Use of Progenitor Cell Therapy to Treat Acute Ischemia

							Outcomes (95% CI)		
Study	**Dates**	**Trials**	**Patients**	**Design**	**Mean Time Between Acute Event and Cell Infusion**	**Median Trial Duration (Range), mo**	**Mean Change or % Change in LVEF**	**Risk of All-Cause Mortality**	**Risk of CV Mortality**
Delewi et al (2014)[4,]	1980 to Feb 2013	16	1641	RCT	≤1 mo	6 (3 to 6)	2.55% (1.83% to 3.26%) I^2=84%	NR	NR
De Jong et al (2014)[5,]	Jan 2002 to Sep 2013	22	1513	RCT	≤1 mo	6 (3 to 60)	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,]	Through Mar 2015	41	2732	RCT	≤14 d	<12	1.05[b] (-0.56 to 2.67)	0.80[c] (0.43 to 1.49)	0.72[c] (0.28 to 1.82)
						≥12	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,]	NR	12	1252	RCT or cohort	≤14 d	6 (3 to 12)	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; RCT: randomized controlled trial.
[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; Trial	**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)
Schächinger 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)

Study	Mortality, n	Major Adverse Events, n	Rehospitalization for Heart Failure, n	LVEF
TE (95% CI); p-value	NR; p=.28	NR; p=.01	NR; p=.25	NR; p=.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 cell 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 patients 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 review.

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.

Review of Evidence

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

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.[19,] 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.[20,]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).[21,] 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.[22,] 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.[23,] 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**
Bolli et al (2021)[19,] CONCERT-HF	U.S.	7	2016-2018	LVEF ≤40%, NYHA class ≥I to III on guidelines-directed therapy (Black, 0% to 9.09%; Hispanic, 12.5% to 19.35%)	Mesenchymal stem cells (n=29) c-kit positive cardiac cells (n=31) Mesenchymal stem cells plus c-kit positive	Placebo (n=32)

					Interventions	
					cardiac cells (n=33)	
Bartunek et al (2017; 2020)[20,21]; CHART-1	Multinational[a]	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)[22]; 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)[23]	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; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association.
[a] 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	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)[19]; CONCERT-HF					
Mesenchymal stem cells	3 (10.3%)	7 (24.1%)	30.02 (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 (101.69)	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 From BL to 39 Weeks	≥40 m Improvement From BL to 39 Weeks, n (%)	≥4% Improvement From BL to 39 Weeks, n (%)
Bartunek et al (2017)[20]					
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); p=.70	Odds[a], 1.03 (0.9 to 1.2); p=.72	Odds[a], 0.8 (0.7 to 1.0); p=.12	Odds[a], 0.8 (0.7 to 1.0); p=.07	Odds[a], 1.0 (0.8 to 1.2); p=.73

Study	Mortality, n (%)	Change in Heart Failure, n (%)	MLHFQ Score, n (%)	6-Minute Walk Test	LVEF
	At 104.9 weeks	NR	NR	NR	NR
Bartunek et al (2020)[21],					
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)[22], 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)[23],					
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		.03	NR

BL: baseline; CI: confidence interval; HR: hazard ratio; LVEF, left ventricular ejection fraction; 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.[Strauer BE, Yousef M, Schannwell CM. The acute and.... 0; 12(7): 721-9. PMID a] 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. 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 patients 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 review.

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.

Review of Evidence

The evidence for stem cell therapy for patients with intractable angina who are not candidates for revascularization includes a systematic review,[25,] 4 trials from 2007 through 2014 with fewer than 100 patients,[26,27,28,29,] 2 phase 1/2 trials with more than 100 patients,[30,31,] and 1 phase 3 trial with more than 100 participants,[32,]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.[25,] 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)[25,]	Up to Sep 2015	6	Refractory angina who were ineligible for coronary revascularization	353 (24 to 112)	RCT	6 mo to 2 y

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)[25,]			
Total N	271	210	NR
PE (95% CI); p-value	MD, - 7.8 (-15.2 to -0.41); p=.04	MD, -0.58 (-1.00 to -0.16); p=.007	OR, 0.49 (0.25 to 0.98); p=.04
I^2 (p-value)	90% (p<.001)	0% (p=.67)	0% (NR)

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

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.[32,] 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)[32,]; RENEW	U.S.	41	2012-2013	CCS class III/IV angina, LVEF ≥25%, on maximally tolerated drug therapy, not eligible for	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)

		Interventions	
		revascularization (White, 90.2%)	• 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)[32,]				
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); p=.95	20.4 (-68.9 to 109.6); p=.65	NR	NR
TE for CT vs. SOC (95% CI); p-value	NR	NR	NR	NR

AC: active control; BL: baseline; CI: confidence interval; 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[33,] This guideline was an update of the 2011 guideline for percutaneous coronary intervention[34,] and the 2013 guideline on managing ST-elevation myocardial infarction.[35,]In 2021, these same organizations

published a guideline on coronary artery revascularization.[36,] 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 (2021) and American Heart Association/American College of Cardiology/Heart Failure Society of America (2022)do not mention progenitor cell therapy.[37,38,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

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

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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
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	Sept 2025
Unpublished			
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 (AMICI)	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
NCT02501811	A Phase II, Randomized, Placebo-Controlled Study of the Safety, Feasibility, & Efficacy of Autologous Mesenchymal Stem Cells & C-kit+ Cardiac Stem Cells, Alone or in Combination, Administered Transendocardially in Subjects With Ischemic HF	125	July 2020
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.

References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. Feb 21 2023; 147(8): e93-e621. PMID 36695182
2. Lee MS, Makkar RR. Stem-cell transplantation in myocardial infarction: a status report. Ann Intern Med. May 04 2004; 140(9): 729-37. PMID 15126257
3. U.S. Food and Drug Administration. Regenerative Medicine Advanced Therapy Designation. 2023; https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm. Accessed March 13, 2023.
4. Delewi R, Hirsch A, Tijssen JG, et al. Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. Eur Heart J. Apr 2014; 35(15): 989-98. PMID 24026778
5. de Jong R, Houtgraaf JH, Samiei S, et al. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. Circ Cardiovasc Interv. Apr 2014; 7(2): 156-67. PMID 24668227
6. Fisher SA, Zhang H, Doree C, et al. Stem cell treatment for acute myocardial infarction. Cochrane Database Syst Rev. Sep 30 2015; 2015(9): CD006536. PMID 26419913
7. Gyöngyösi M, Wojakowski W, Lemarchand P, et al. Meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE) in patients with acute myocardial infarction based on individual patient data. Circ Res. Apr 10 2015; 116(8): 1346-60. PMID 25700037
8. Fisher SA, Doree C, Taggart DP, et al. Cell therapy for heart disease: Trial sequential analyses of two Cochrane reviews. Clin Pharmacol Ther. Jul 2016; 100(1): 88-101. PMID 26818743
9. Lalu MM, Mazzarello S, Zlepnig J, et al. Safety and Efficacy of Adult Stem Cell Therapy for Acute Myocardial Infarction and Ischemic Heart Failure (SafeCell Heart): A Systematic Review and Meta-Analysis. Stem Cells Transl Med. Dec 2018; 7(12): 857-866. PMID 30255989
10. Moazzami K, Roohi A, Moazzami B. Granulocyte colony stimulating factor therapy for acute myocardial infarction. Cochrane Database Syst Rev. May 31 2013; 2013(5): CD008844. PMID 23728682
11. Schächinger V, Erbs S, Elsässer A, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J. Dec 2006; 27(23): 2775-83. PMID 17098754
12. Schächinger V, Erbs S, Elsässer A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. Sep 21 2006; 355(12): 1210-21. PMID 16990384
13. Assmus B, Rolf A, Erbs S, et al. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. Circ Heart Fail. Jan 2010; 3(1): 89-96. PMID 19996415
14. Hirsch A, Nijveldt R, van der Vleuten PA, et al. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. Eur Heart J. Jul 2011; 32(14): 1736-47. PMID 21148540
15. Fisher SA, Doree C, Mathur A, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst Rev. Dec 24 2016; 12(12): CD007888. PMID 28012165
16. Fisher SA, Brunskill SJ, Doree C, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst Rev. Apr 29 2014; (4): CD007888. PMID 24777540
17. Xu R, Ding S, Zhao Y, et al. Autologous transplantation of bone marrow/blood-derived cells for chronic ischemic heart disease: a systematic review and meta-analysis. Can J Cardiol. Nov 2014; 30(11): 1370-7. PMID 24726092

18. Xiao C, Zhou S, Liu Y, et al. Efficacy and safety of bone marrow cell transplantation for chronic ischemic heart disease: a meta-analysis. Med Sci Monit. Oct 01 2014; 20: 1768-77. PMID 25270584
19. Bolli R, Mitrani RD, Hare JM, et al. A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial. Eur J Heart Fail. Apr 2021; 23(4): 661-674. PMID 33811444
20. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. Eur Heart J. Mar 01 2017; 38(9): 648-660. PMID 28025189
21. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic stem cell therapy in ischaemic heart failure: long-term clinical outcomes. ESC Heart Fail. Dec 2020; 7(6): 3345-3354. PMID 33094909
22. Patel AN, Henry TD, Quyyumi AA, et al. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. Lancet. Jun 11 2016; 387(10036): 2412-21. PMID 27059887
23. Pokushalov E, Romanov A, Chernyavsky A, et al. Efficiency of intramyocardial injections of autologous bone marrow mononuclear cells in patients with ischemic heart failure: a randomized study. J Cardiovasc Transl Res. Apr 2010; 3(2): 160-8. PMID 20560030
24. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-heart study. Eur J Heart Fail. Jul 2010; 12(7): 721-9. PMID 20576835
25. Khan AR, Farid TA, Pathan A, et al. Impact of Cell Therapy on Myocardial Perfusion and Cardiovascular Outcomes in Patients With Angina Refractory to Medical Therapy: A Systematic Review and Meta-Analysis. Circ Res. Mar 18 2016; 118(6): 984-93. PMID 26838794
26. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. JAMA. May 20 2009; 301(19): 1997-2004. PMID 19454638
27. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. Circulation. Jun 26 2007; 115(25): 3165-72. PMID 17562958
28. Tse HF, Thambar S, Kwong YL, et al. Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases (PROTECT-CAD trial). Eur Heart J. Dec 2007; 28(24): 2998-3005. PMID 17984132
29. Jimenez-Quevedo P, Gonzalez-Ferrer JJ, Sabate M, et al. Selected CD133^{+} progenitor cells to promote angiogenesis in patients with refractory angina: final results of the PROGENITOR randomized trial. Circ Res. Nov 07 2014; 115(11): 950-60. PMID 25231095
30. Wang S, Cui J, Peng W, et al. Intracoronary autologous CD34+ stem cell therapy for intractable angina. Cardiology. 2010; 117(2): 140-7. PMID 20975266
31. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. Circ Res. Aug 05 2011; 109(4): 428-36. PMID 21737787
32. Povsic TJ, Henry TD, Traverse JH, et al. The RENEW Trial: Efficacy and Safety of Intramyocardial Autologous CD34(+) Cell Administration in Patients With Refractory Angina. JACC Cardiovasc Interv. Aug 08 2016; 9(15): 1576-85. PMID 27491607
33. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial Infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. May 2016; 87(6): 1001-19. PMID 26489034
34. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American

Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. Dec 06 2011; 124(23): e574-651. PMID 22064601
35. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jan 29 2013; 61(4): e78-e140. PMID 23256914
36. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. Jan 18 2022; 79(2): e21-e129. PMID 34895950
37. Maddox TM, Januzzi JL, Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. Feb 16 2021; 77(6): 772-810. PMID 33446410
38. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. J Card Fail. May 2022; 28(5): e1-e167. PMID 35378257

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
HCPCS	C9782	Blinded procedure for new york heart association (nyha) class ii or iii heart failure, or canadian cardiovascular society (ccs) class iii or iv chronic refractory angina; transcatheter intramyocardial transplantation of autologous bone marrow cells (e.g., mononuclear) or placebo control, autologous bone marrow harvesting and preparation for transplantation, left heart catheterization including ventriculography, all laboratory services, and all imaging with or without guidance (e.g., transthoracic echocardiography, ultrasound, fluoroscopy), performed in an approved investigational device exemption (ide) study

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2017	BCBSA Medical Policy adoption
07/01/2018	Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2023	Policy reactivated. Previously archived from 07/01/2020 to 07/31/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions by BCBSA**
Reactivated Policy **Policy Statement:** N/A	**Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia 2.02.18** **Policy Statement:** I. Progenitor cell therapy, including but not limited to skeletal myoblasts or hematopoietic cells, is considered **investigational** as a treatment of damaged myocardium. II. Infusion of growth factors (i.e., granulocyte colony stimulating factor) is considered **investigational** as a technique to increase the numbers of circulating hematopoietic cells as treatment of damaged myocardium.