# Medical Coverage Policy

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# Cell-Based Therapy for Cardiac and Peripheral Arterial Disease

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## Related Coverage Resources

Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost
Stem Cell Transplantation: Blood Cancers
Stem Cell Transplantation: Solid Tumors

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## Overview

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

## Coverage Policy

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

**Autologous intra-arterial or intra-muscular bone marrow cell transplantation is considered not medically necessary for peripheral arterial disease and other occlusive conditions.**

## Coding Information

**Notes:**

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Experimental/Investigational/Unproven when used to report transplantation of cells into the myocardium:**

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

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

**Considered Not Medically Necessary when used to report autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions:**

| CPT®* Codes | Description |
|---|---|
| 38206 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous |
| 38232 | Bone marrow harvesting for transplantation; autologous |



## General Background

**U.S. Food and Drug Administration (FDA**
The U.S. Food and Drug Administration (FDA) regulates cells that are processed in commercial laboratories, as well as the surgical devices used to inject the cells. There are several products being commercially developed for the treatment of damaged myocardium and/or peripheral arterial disease. However, the FDA has not yet issued approvals for any products for the transplantation of autologous cells for these purposes. See appendix for examples of unapproved products.

**Cell-Based Therapy for Treatment of Damaged Myocardium**
Cardiovascular-oriented research of cell-based therapy has largely focused on myocardial repair, with particular emphasis on replacement and/or restoration of the damaged myocardium after acute myocardial infarction (AMI) or in individuals with heart failure with reduced ejection fraction (HFrEF).

Transplantable cell types being researched include skeletal myoblasts, bone marrow mononuclear cells (BM-MNC), hematopoietic stem cells (HSC), endothelial progenitor cells (EPC), mesenchymal stem cells (MSC), and pluripotent stem cell (PSC)-derived cardiomyocytes (CM) (PSC-CM). In clinical trials, route of delivery has included through vessels (intracoronary or intravenous) as well as direct injection into the heart muscle (intramyocardial or transendocardial).

Skeletal myoblasts are tissue-specific stem cells. Immature myoblasts contained in skeletal muscle can fuse with surrounding myoblasts or with damaged muscle fibers to regenerate functional skeletal muscle. Mesenchymal stem cells and hematopoietic stem cells have the capacity to differentiate into any type of cell, depending on their microenvironment. As they mature, they can acquire all the characteristics of the target tissue, such as myocardium and cardiac vessels. Cells may be delivered systemically or locally and must then proliferate to provide adequate new tissue prior to differentiating into functional cardiomyocytes that couple with the myocardium. Some cells may require significant manipulation prior to implantation. Stem cells may be delivered via infusion into the coronary arteries or injection into the ventricular wall. The mechanism of action of cell therapy for damaged myocardium is not entirely clear and is likely multifactorial.

Cell therapy for damaged myocardium is a promising treatment option. Yan et al. (2024) noted that transplanted stem cells are poorly engrafted in the infarcted myocardium due to multiple factors. It has been shown that improving their retention often leads to improved functional outcomes. Strategies such as biomaterial utilization, cell combinations, and repeated IV injections can be optimized for cell-based therapy for myocardial infarction (MI).

**Literature Review: Cell-Based Therapy for Treatment of Damaged Myocardium**
Studies and professional society opinion are needed to address a number of unresolved technical and clinical issues, including optimum cell type, ideal number of cells, factors that promote engraftment, delivery methods and frequency, surgical delivery method, and patient selection criteria. Current data are insufficient to support routine clinical use and emphasize the need for better-targeted patient selection, standardized cell products, and trials powered for clinically meaningful endpoints before adoption into practice.

Several systematic reviews and meta-analysis have analyzed available randomized control trials focused on the effect of cell-based treatment of acute MI or ischemic cardiomyopathy. Many of these systematic reviews have overlap of included trials (e.g., REPAIR-AMI, BOOST, HEBE, and TOPCARE-AMI). Across the data, stem cell therapy for acute myocardial infarction or ischemic cardiomyopathy does not appear to improve survival, reduce major adverse cardiovascular events, or provide durable clinical benefit, despite some modest improvements in surrogate measures such as left ventricular ejection fraction (LVEF) or left ventricular (LV) volume. Reviews with broader or more exploratory scope acknowledge early positive signals in small trials but confirm that benefits have not been consistently reproduced in larger or higher-quality studies (Ali et al., 2025; Mahnoor, et al., 2025). Little benefit is demonstrated in size of infarct (Yang et al., 2020; Lee et al., 2024; Moeswire, et al., 2025). High-certainty evidence from a Cochrane review demonstrated no mortality or major outcome benefit for autologous bone marrow–derived cell therapy (Zwetsloot, et al., 2025). Aggarwal 2025 and Lee 2024 similarly reported no clinically meaningful benefit for mortality or hospitalization outcomes. Moeswire et al., 2025 noted there was no significant difference in mortality between groups, but that overall safety remains favorable. Abouzid et al., (2023) evaluated human umbilical cord-derived mesenchymal stromal cells (HUC-MSCs) in three small RCTs (n=201). Although an improvement in ejection fraction (EF) was observed at 12 months, no reduction in readmission or mortality rates was demonstrated. Attar et al., (2022) reported a lower risk of reinfarction and heart failure-related hospitalization with BM-MNC therapy in pooled analyses; however, cardiac-related mortality was not reduced, and the authors noted substantial heterogeneity, non-uniform outcome definitions, and that many included trials were not designed to assess clinical endpoints. Yang et al., (2020) found no significant differences in major adverse cardiac events (MACE) despite modest improvements in surrogate LVEF and LV volumes. Small improvements in LVEF, generally 1-3 percentage points, are seen in other trials (Ali, et al., 2025; Moeswir, et al., 2025; Aggarwal, et al., 2025; Mahnoor, et al., 2025; Zwetsloot, et al., 2025; Lee, et al., 2024). Abouzid et al., 2023 found EF improvement with HUC-MSCs at 12 months but not at 6 months, reinforcing that longer follow-up may influence surrogate responses without establishing clinical benefit. Attar et al., 2022 noted that many trials emphasized LVEF as a primary endpoint and were not powered to detect clinical events, limiting interpretability. Heterogeneity remains a common challenge in the generalizability of results across literature. Regarding safety, stem cell therapy demonstrated a favorable trend towards a short-term procedural safety profile with low rates of procedure-related serious adverse events (Ali, et al., 2025; Moeswir, et al., 2025; Aggarwal, et al., 2025; Mahnoor, et al., 2025; Zwetsloot, et al., 2025; Lee et al., 2024).

Additional evidence from individual trials mirrors the findings of previous studies. In a study of 28 individuals with previous chronic total occlusion status post percutaneous coronary intervention, infusion of bone marrow mononuclear cells (BMMC) appeared to be safe and resulted in slight change in LVEF, but the improvement was without statistical significance (Maestre-Luque, et al., 2026). The EXCELLENT trial investigated the safety and feasibility of CD34+ cells in 77 individuals with a large recent MI at risk of subsequent heart failure. Approximately 30% of intervention participants experienced MACE, including cardiac tamponade, pericarditis, and ischemic stroke. The trial was not powered to assess efficacy, but the authors noted that changes in LV remodeling and viability in the active group suggest possible benefit (Roncalli, et al., 2025). An observational

cohort of 47 individuals by Saltzman et al., 2025 found no difference in event-free survival between cell therapy and placebo in individuals with ischemic cardiomyopathy.

Similar to the research of cell-based therapy in MI, several systematic reviews and meta-analysis are available which review the findings of clinical trials on the effect of cell-based treatment of heart failure (HF) or heart failure with reduced ejection fraction (HFrEF). Again, there is some overlap of trials across the literature (e.g., MSC-HF (Mathiasen), CONCERT-HF, DREAM-HF, SCIENCE, and Danish phase II). Across reviews, small to modest improvements in LVEF were frequently reported following stem cell therapy, particularly in individuals with reduced baseline EF. Alizadehasl et al., (2025) found that a majority of included BMMNC trials reported numerical improvements in LVEF and ventricular remodeling indices, though effect sizes varied and were not uniform across studies. Wu et al., (2025) observed no statistically significant pooled improvement in LVEF in BMMNC trials from 2015–2025, despite some individual studies reporting short-term gains. Ahmed et al., (2024) demonstrated that MSC therapy was associated with LVEF improvement primarily in low-dose regimens (< 100 million cells), while higher doses did not confer benefit and in some analyses showed neutral or negative effects. Muslem et al., (2025) reported a small, non-significant pooled effect on LVEF, with low between-study heterogeneity, suggesting consistency of limited benefit across contemporary MSC trials. Hosseinpour et al., 2024 concluded that both MSC and BMMNC therapies significantly improved LVEF compared with controls noting that future studies should focus on clinical outcomes to further refine findings of the study. Another consistent finding in the literature is the absence of a statistically significant reduction in MACE with stem cell therapy in heart failure. Wu et al., 2025, Alizadehasl et al., 2025, Ahmed et al., 2024, Hosseinpour et. al., 2024, Kavousi et al., 2024, and Muslem et al., 2025 all reported no significant difference in MACE between stem cell–treated patients and controls. Regarding functional outcomes, Kavousi et al., reported a non-significant trend toward reduced rehospitalization, with meta-regression indicating higher rehospitalization risk with increasing cell dose and more favorable outcomes with < 100 million cells and autologous sources. Several reviews noted improvements in surrogate functional measures (e.g., 6-minute walk test, NYHA class, quality-of-life scores), though these improvements were inconsistent and not always sustained (Alizadehasl, et al., 2025; Ahmed, et al., 2024; Muslem, et al., 2025). Only one source reported statistically significant mortality reduction, albeit noting these results should be interpreted with caution as the included studies used various routes of transplantation, number of cells, and duration of follow-up (Kavousi, et al., 2024).

Additional evidence from randomized control trials provides similar results. Chaaban et al., 2025, evaluated the findings from the SCIENCE II and Danish ASC trials encompassing a total of 214 individuals with HFrEF. No statistically significant cardiac improvements (LVESV, LVEF) were demonstrated after analysis of the data from the two trials (Chaaban, et al., 2025).

A Cochrane systematic review of 13 randomized controlled trials (RCTs) (n=762 [n=452 cell therapy and n=310 controls]) by Diaz-Navarro et al., (2021) assessed the effectiveness and safety of stem cell transplant in adults with non-ischemic dilated cardiomyopathy (DCM). The RCTs included compared the infusion of bone marrow derived stem cells into the heart muscle with the usual care (control) treatment in people diagnosed with DCM. Studies were classified and analyzed into three categories according to the comparison intervention, which consisted of no intervention/placebo, cell mobilization with cytokines, or a different mode of stem cell therapy (SCT). The studies included an average of 60 people aged 45 to 58.5 years and 50%–89% men in each trial. Following therapy, the participants were assessed from six months to five years, with most studies at one year. The outcomes measured all-cause mortality, safety, health-related quality of life (HRQoL), performance status and major adverse cardiovascular events. The evidence reviewed was considered low to very low quality due to the small number of events, the results were not similar across studies, risk of bias and issues with study design. The study reported that there is uncertainty regarding mortality, procedural complications, health-related

quality of life and exercise capacity when comparing SCT to the control. Low-quality evidence suggested that SCT may slightly improve deterioration of heart function and may not increase the risk of abnormal heartbeats in people with DCM. There were not any studies that reported other relevant outcomes such as major adverse cardiac events. When comparing SCT plus cytokine to control there is uncertainty regarding mortality. SCT plus cytokine may not improve health-related quality of life but may improve exercise capacity as well as some physiological measures related to cardiac function (it is unclear the extent and clinical benefits for patients). No studies reported major cardiac adverse events or abnormal heartbeats. The authors concluded based on low-quality evidence that more research is needed to establish the role of SCT in the treatment of DCM and the most effective therapies. No health disparities were identified by the investigators, however there were more males enrolled than females.

**Professional Societies/Organizations: Cell-Based Therapy for Treatment of Damaged Myocardium**
American College of Cardiology (ACC)/American Heart Association (AHA): The 2023 AHA/ACC Guideline for the Management of Patients with Chronic Coronary Disease noted the following under section 8.2. Evidence Gaps and Areas of Future Research Needs:

- In patients with CCD and refractory angina, research is needed to assess the utility of neuromodulation andthoracic spinal cord stimulation, therapeutic angiogenesis with cell/gene therapies, coronary sinus occlusion, and shockwave therapy.

**Cell-Based Therapy for Peripheral Arterial Disease**
An advanced form of peripheral arterial disease (PAD) known as chronic limb-threatening ischemia (CLTI) is associated with gangrene formation, ulceration, and amputation of the limb. Nearly 10% of individuals with PAD suffer from CLTI but > 50% eventually become candidates to amputation and/or succumb to death due to cardiovascular causes. Surgical and endovascular interventions to restore vascularization to the ischemic limb are effective but not suitable for all individuals with PAD, leaving those individuals with limited treatment options.

A promising approach to induce revascularization is therapeutic angiogenesis, which aims to induce the formation of new blood vessels from preexisting ones. Numerous strategies to augment therapeutic angiogenesis have been tested in clinical studies, including cell, protein, and gene therapies, although the results have only shown minimal-to-moderate therapeutic benefit. Some of the limitations of the cell-based strategies include poor transplant cell survival, short-lived gene/protein delivery, harsh inflammatory host response, and suboptimal therapeutic dosing or frequency. Therapeutic cells that have been tested in clinical trials of PAD include bone marrow–derived mononuclear cells, mesenchymal stromal cells (MSCs), and subpopulations within these cell types based on surface antigen expression. Considering the variable approaches used by different groups, the wide range of cell types used, and the absence of standardized protocols for characterization of the cells and for evaluation of clinical outcome, there is substantial uncertainty regarding the effectiveness of various cell types in individuals with PAD (Huang, et al., 2024; Desai, et al., 2024; Frangogiannis, et al., 2019).

**Literature Review: Cell-Based Therapy for Treatment of Peripheral Arterial Disease**
Despite extensive research, robust clinical evidence supporting the use of cell therapy in individuals with critical limb ischemia is lacking. Randomized controlled clinical trial results are mixed. Considering the variable approaches used by different groups, the wide range of cell types used, and the absence of standardized protocols for characterization of the cells and for evaluation of clinical outcome, there is substantial uncertainty regarding the effectiveness of various cell types in PAD. There is a need for high-quality clinical studies to test the effectiveness of cell therapy in PAD. Moreover, studies are needed to identify the optimal candidate selection criteria

for treatment, optimal cell types, method of administration, and to develop strategies that may enhance homing, survival, and effectiveness of the injected cells.

Trials evaluating cell-based therapy for PAD and CLTI have produced mixed results. A systematic review by Sojáková et al., (2024) summarized five randomized trials (PROVASA, JUVENTAS, RESTORE-CLI, Sharma, et al. 2021, and PACE), highlighting important methodological limitations that complicate interpretation. Several trials included in the review enrolled individuals with relatively preserved ankle-brachial index (ABI), toe pressures, or transcutaneous oxygen pressure ($TcPO_2$), or included individuals with intermittent claudication without ischemic ulcers, populations that do not meet contemporary definitions of CLTI. In addition, some studies relied on surrogate endpoints such as ABI as primary outcomes, which may be unreliable in individuals with diabetes due to medial arterial calcification. Variability in cell dose, route of administration, and choice of control (including autologous serum or blood, which may not be biologically inert) further limited comparability across trials. Cochrane systematic reviews have consistently characterized the certainty of randomized evidence as low or very low. The updated Cochrane review by Moazzami et al., (2022), which evaluated intramuscular transplantation of autologous bone marrow mononuclear cells in CLI, found no clear evidence of benefit for mortality and uncertainty regarding reductions in amputation rates. Pain outcomes could not be pooled due to heterogeneity in measurement instruments, and perfusion outcomes such as ABI were reported inconsistently. Similarly, an earlier Cochrane review by Abdul Wahid et al., (2018) comparing different cell sources, doses, and delivery routes found no clear differences between regimens for outcomes such as amputation, mortality, ulcer healing, or rest pain, and concluded that long-term efficacy and safety could not be determined due to the low quality of evidence.

Some systematic reviews and meta-analyses incorporating randomized and nonrandomized studies have reported favorable effects of cell-based therapy on intermediate and clinical outcomes, including ulcer healing rates, perfusion parameters (ABI and $TcPO_2$), pain scores, and overall amputation rates. For example, meta-analyses by Gao et al., (2019), Xie et al., (2018), Pu et al., (2022), and Rigato et al., (2017) suggested improvements in ulcer healing and reductions in overall amputation risk. However, these analyses consistently noted substantial heterogeneity, small sample sizes, variable follow-up, and high or unclear risk of bias across included studies. Importantly, Rigato et al., demonstrated that when analyses were restricted to placebo-controlled trials or to RCTs assessed as having lower risk of bias, observed benefits for major amputation, amputation-free survival, and wound healing were attenuated or no longer statistically significant. These findings suggest that positive pooled estimates may be driven in part by lower-quality evidence.

Across meta-analyses, mortality outcomes have generally not shown consistent improvement with cell-based therapies, and functional outcomes such as walking distance or quality of life have been infrequently and inconsistently reported. While adverse events related directly to cell implantation have been uncommon, most trials and pooled analyses were not powered to detect rare or long-term safety concerns. More recent observational studies have focused on peripheral blood mononuclear cell (PBMNC) based therapies, particularly in diabetic patients with advanced CLTI. A 2024 systematic review and meta-analysis by Rehak et al., evaluated six observational studies involving 256 diabetic patients with no-option CLTI treated with intramuscular PBMNC. Across these studies, the pooled yearly major amputation rate was approximately 15.7%, with a mean ulcer healing rate of 62% and improvements in $TcPO_2$ and pain scores. No serious peri-procedural adverse events were reported. The authors emphasized that these findings are derived from uncontrolled or nonrandomized designs and should be considered hypothesis-generating rather than confirmatory. In parallel, the ROTARI registry reported one-year real-world outcomes of PBMNC therapy used as an adjunct to below-the-knee endovascular revascularization in diabetic patients with revascularizable CLTI (Rutherford class 5). Among individuals completing one-year follow-up, limb salvage exceeded 90%, major amputation occurred in fewer than 6% of

individuals, and complete wound healing was observed in approximately two-thirds of non-amputated individuals. Improvements in pain and $TcPO_2$ were also reported. However, the registry lacked a control group, and outcomes could not be directly compared with revascularization alone or with standard wound care (Furgiuele et al., 2024). In sum, the certainty of evidence for patient-important outcomes remains low, and the incremental benefit of cell-based therapy beyond contemporary revascularization and wound-care strategies is not well established.

**Professional Societies/Organizations: Cell-Based Therapy for Treatment of Peripheral Arterial Disease**

**American College of Cardiology (ACC)/American Heart Association (AHA):** The 2024 ACC/AHA Guideline for the Management of Lower Extremity Peripheral Artery Disease does not address bone marrow cell transplantation for PAD. It stated, "experimental therapies, such as angiogenic gene therapy and growth factors, are unavailable in clinical practice and are beyond the scope of this document" (Gornik, et al., 2024).

## Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Obtaining a diverse sampling population is a noted challenge in the investigation of cell-based therapies for cardiac and peripheral arterial diseases. Male sex is overrepresented in the clinical literature, leading to an inability to generalize findings to female sex. There is also a paucity of literature specifically focused on ethnic minorities despite historically worse outcomes in these populations. One post hoc analysis of the MOBILE trial investigated the impact of cell-based therapy on ethnic minorities with critical limb ischemia. Wang et al., 2018 reported that the studied cell-based therapy was noninferior in minorities compared to the white population. Future studies should seek to enroll a diverse, representative population.

## Appendix

**Stem Cell Products (Not FDA Approved):**

| Product | Cell Type | Proposed Indication | Manufacturer |
|---|---|---|---|
| MultiStem® (invimestrocel) | Multipotent adult progenitor cells from bone marrow | Neurological, inflammatory, immune, cardiovascular, and traumatic conditions | Athersys Inc., Cleveland, OH |
| Ixmyelocel-T | Autologus bone marrow mononuclear cells | Chronic advanced heart failure due to ischemic dilated cardiomyopathy; peripheral arterial disease | Vericel Corporation, Cambridge, MA |

| Product | Cell Type | Proposed Indication | Manufacturer |
|---|---|---|---|
| CardiAMP™ Cell Therapy | Autologous bone marrow cells | Heart failure | BioCardia® Inc., Sunnyvale, CA |
| CardiALLO Cell Therapy System | Bone marrow-derived mesenchymal stem cells | HFrEF | BioCardia® Inc., Sunnyvale, CA |
| Pluristem cell therapy product, PLX-PAD | Allogeneic placental derived, mesenchymal like cells | Critical limb ischemia | Pluri Biotech Ltd. [Israel] previously Pluristem Therapeutics, Inc. |
| MarrowStim PAD Kit™ | Concentrated bone marrow aspirate | Critical limb ischemia | Zimmer Biomet, Warsaw, Ind |

Note: Coverage decisions are not based solely on FDA approval. Device or product names are provided for example purposes only. Their inclusion does not indicate endorsement or preference for any specific brand or model. This list is not intended to reflect all available products or technologies.

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## Revision Details

| Type of Revision | Summary of Changes | Date |
|---|---|---|
| Annual Review | • No clinical policy statement changes. | 5/15/2026 |
| Annual Review | • No clinical policy statement changes. | 5/15/2025 |
| Annual Review | • No clinical policy statement changes. | 5/15/2024 |