Stem Cell-Based Repair and Regeneration of Cardiovascular Tissues: A Narrative Review

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ABSTRACT

BACKGROUND

Cardiovascular diseases remain the leading cause of global morbidity and mortality, with the limited intrinsic regenerative capacity of the adult heart contributing to poor outcomes. Stem cell therapy represents a promising strategy to restore myocardial function; however, the evidence base is fragmented, with limited comprehensive synthesis on the applications of stem cells in human cardiovascular regeneration. This review aimed to assess current evidence on stem cell applications for cardiovascular repair and regeneration.

METHODS

A search of PubMed, Web of Science, and the Cochrane Library was performed, supplemented by Google Scholar, to identify clinical studies published between January 1, 2020 and December 31, 2025. Data extraction focused on study design, patient demographics, interventions, delivery methods, and outcomes. Findings were synthesized narratively.

RESULTS

A total of 27 clinical studies, reporting findings on diverse stem cell populations, were included. Stem cells used in cardiac regenerative therapy include mesenchymal stromal cells, bone marrow-derived mesenchymal stromal cells, mesenchymal precursor cells, adipose-derived stem cells, stem/progenitor cells, umbilical cord blood-derived mononuclear cells, cardiosphere-derived cells, cardiopoietic stem cells, human-induced pluripotent stem cell-derived cardiomyocytes, and multilineage-differentiating stress-enduring cells. Findings demonstrate that stem cell therapies are safe and feasible, with improvements observed in surrogate endpoints. However, long-term follow-up often reveals attenuation of early benefits. Advancements in therapy include delivery methods, with hydrogel encapsulation, engineered grafts, and patch-based implantation showing promise in enhancing cell survival and retention. Paracrine-focused approaches, including extracellular vesicle-enhanced therapy and secretome administration, show promising advancements, and novel cell types such as Muse cells, mesenchymal progenitor cells, and cardiosphere-derived cells represent frontiers in regenerative cardiology.

CONCLUSION

Current evidence supports the promise of stem cells for cardiovascular repair and regeneration, though robust long-term clinical outcomes remain to be established.

HIGHLIGHTS

- Stem cell therapies are safe and feasible for the repair and regeneration of cardiomyocytes
- Long-term efficacy of stem cell therapy remains inconsistent
- Hydrogel, grafts, and patches can improve survival and retention
- Paracrine and secretome therapies offer cell-free alternatives
- Muse cells, mesenchymal progenitor cells, and cardiosphere-derived cells represent novel cell types for regenerative cardiology

Keywords: Cardiomyocytes; Cardiovascular diseases; Mesenchymal stromal cells; Regenerative cardiology; Stem cell therapy

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, accounting for an estimated 17.9 million deaths annually.[1] This broad category encompasses a spectrum of disorders affecting the heart and vasculature, including coronary artery disease, ischemic heart disease, stroke, atherosclerosis, hypertension, cardiomyopathy, and arrhythmias such as atrial fibrillation and flutter.[2] Beyond their impact on individual health, CVDs impose substantial economic and social burdens on families and healthcare systems globally.

A major challenge in the management of CVDs is the irreversible loss of cardiac tissue following injury. It has been estimated that approximately one billion or nearly 25% cardiomyocytes are lost during a single myocardial infarction.[3] Given that the adult heart possesses limited intrinsic regenerative capacity, fibrotic scar tissue forms at the site of injury to preserve structural integrity. While this compensatory mechanism prevents rupture, it compromises contractile function, as surviving cardiomyocytes are unable to proliferate sufficiently to replace lost tissue.[4] This maladaptive remodeling leads to reduced cardiac output, progressive ventricular dysfunction, and ultimately heart failure or death.

Conventional therapeutic strategies, including pharmacological agents such as β-blockers and angiotensin-converting enzyme inhibitors, lifestyle interventions such as diet and exercise, and surgical procedures such as coronary artery bypass grafting (CABG), primarily aim to alleviate symptoms, restore perfusion, and delay disease progression.[5] However, these approaches do not reverse the fundamental loss of functional cardiomyocytes. Heart transplantation remains the definitive treatment for end-stage heart failure, but its application is limited by donor scarcity, immunological rejection, and long-term complications.[6] These limitations underscore the urgent need for innovative regenerative therapies capable of restoring myocardial function.

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Stem cell therapy has emerged as a promising frontier in regenerative medicine, offering potential solutions for conditions that cannot be cured by conventional treatments. Stem cells are the foundational units of all tissues and organs, with the capacity for self-renewal, differentiation, immunomodulation, and tissue repair.[7] They can transdifferentiate into diverse cell types, regenerate damaged tissue, and modulate pathological processes, making them attractive candidates for cardiovascular regeneration.[8] Based on their differentiation potential, stem cells are classified as totipotent, pluripotent, multipotent, oligopotent, and unipotent (Figure 1). Among these, induced pluripotent stem cells (iPSCs) have garnered particular attention due to their ability to be reprogrammed from somatic cells and differentiated into virtually any cell type of interest.[9]

In cardiovascular medicine, several stem cell populations have been identified and investigated for their regenerative potential.[1] As of 2020, more than 1200 clinical trials exploring mesenchymal stromal cells (MSCs) for a wide range of diseases had been registered, reflecting the intense global interest in this therapeutic approach.[10] Preclinical studies in animal models have demonstrated enhanced myocardial repair and functional recovery, yet clinical translation remains limited. While some stem cell therapies have progressed from bench to bedside, the evidence base is fragmented, and no comprehensive synthesis has fully evaluated their applications in human cardiovascular regeneration. This narrative review, therefore, aimed to critically assess current evidence on the use of stem cells for cardiovascular repair and regeneration, identify prevailing scientific and clinical challenges, and highlight future directions for the field.

Methods

Search Strategy

A narrative study design was adopted for this review. To comprehensively assess the current evidence on stem cell therapy for the repair and regeneration of cardiovascular tissues, a structured literature search was performed across three major electronic databases:

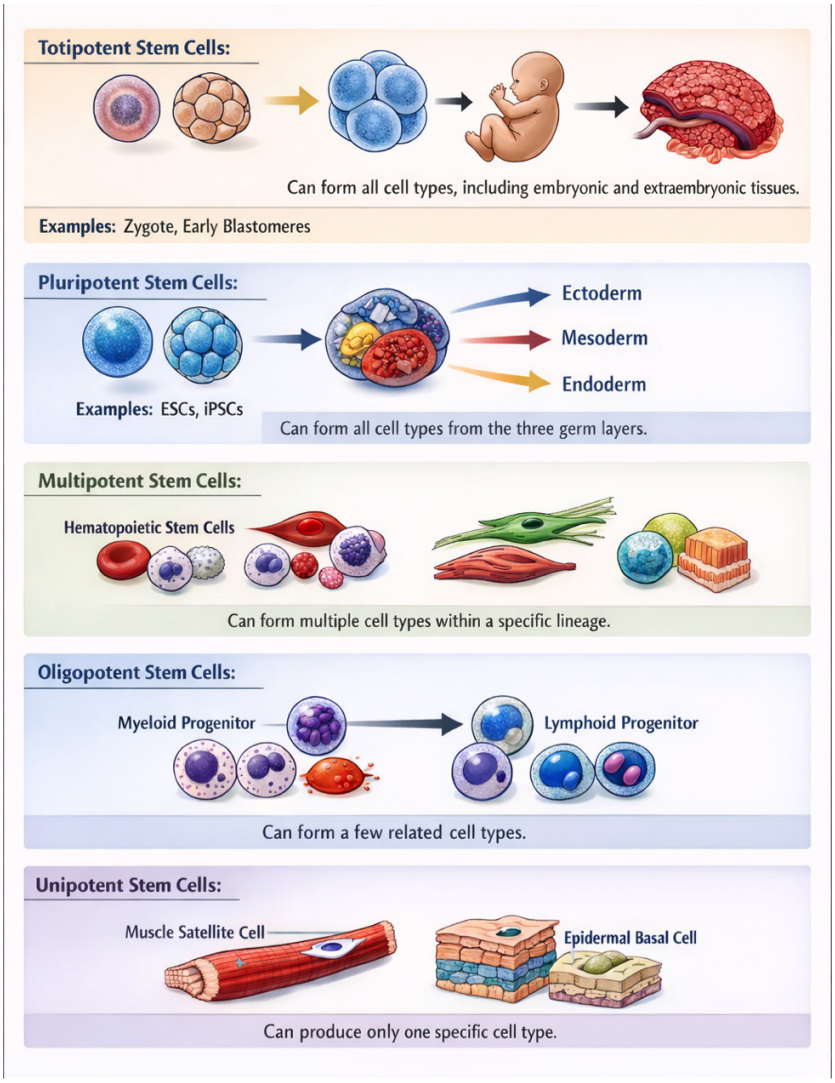

Fig 1 | Classification of stem cells based on potency. ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells

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PubMed, Web of Science, and the Cochrane Library. The search strategy combined keywords, subject headings (MeSH terms), and Boolean operators to maximize sensitivity and specificity. Key terms included "cardiovascular," "regeneration," "repair of cardiovascular tissues," and "stem cells." Boolean operators such as "AND," "OR," and "NOT" were applied to refine the search and strategically combine terms to retrieve publications explicitly addressing stem cell interventions in cardiovascular disease. To ensure comprehensiveness, additional sources were explored, including Google Scholar. The PICO framework (Population, Intervention, Comparator, Outcome)[11] was employed to guide the search and ensure alignment with the review objectives. The search was limited to the human population with stem cell therapy and corresponding outcomes. Other limiters, such as publication date (restricted to January 1, 2020–December 31, 2025) and language (English only), were applied to optimize search outcomes and ensure reproducibility.

The PubMed search strategy included terms such as:

("stem cells" OR "mesenchymal stromal cells" OR "cardiac stem cells" OR "induced pluripotent stem cells" OR "cardiosphere-derived cells") AND ("cardiovascular disease" OR "myocardial infarction" OR "heart failure" OR "cardiac regeneration" OR "cardiac repair").

Equivalent keyword combinations adapted to database indexing systems were used for Web of Science and the Cochrane Library. The final searches were executed on December 31, 2025. Reference lists of included articles were also manually screened to identify additional eligible studies. The full, databasespecific search strings (with filters/limits), exact run dates per database, and deduplication steps are provided in the SDC, Methods.

Study Selection

Study selection was conducted in two stages. First, two reviewers screened the titles and abstracts of retrieved studies to identify potentially eligible articles based on predefined inclusion and exclusion criteria. In the second stage, the full texts of potentially relevant studies were independently assessed by the same reviewers to determine final eligibility. Any disagreements between reviewers during the screening process were resolved through discussion and consensus. When consensus could not be reached, a third reviewer was consulted to make the final decision. Inclusion criteria were clinical or randomized controlled trials (RCTs) investigating stem cell therapy for cardiovascular conditions in human patients. Studies from any country were eligible, provided they were published in English between January 1, 2020 and December 31, 2025. Exclusion criteria included experimental, animal, or *in vitro* studies, research protocols, reviews, conference abstracts, letters to the editor, and articles not directly addressing cardiovascular disease treatment in patients.

Data Extraction

Data extraction was performed independently by two reviewers. Extracted information included study characteristics (design, sample size, setting), type of stem cell intervention, delivery method, and reported outcomes. The primary outcome was improvement (or lack thereof) in cardiovascular function or clinical endpoints. Secondary outcomes included safety, feasibility, and quality of life measures. All extracted data were documented for organization and subsequent synthesis. A meta-analysis was not conducted due to substantial heterogeneity across studies in terms of cell types, delivery methods, dosing, and outcome measures. Instead, a narrative synthesis was adopted to explore relationships within the data and assess the strength of the evidence.

Quality Assessment

Given the narrative design of this review, a formal quality appraisal or risk-of-bias assessment of individual studies was not conducted. Narrative reviews aim to provide a broad and interpretative synthesis of existing literature rather than a systematic evaluation of methodological quality. Consequently, the findings were synthesized descriptively to highlight emerging themes, advances, and research gaps in stem cell-based cardiovascular regeneration.

Data Synthesis

Given the heterogeneity of study designs, interventions, and outcome measures, a narrative synthesis was adopted. This approach allowed exploration of patterns and relationships across the data, identification of consistencies and discrepancies, and assessment of the overall strength of the evidence. The synthesis emphasized safety, efficacy, delivery methods, mechanisms, and long-term outcomes, providing a comprehensive overview of the current state of stem cell therapy for CVDs.

Use of Artificial Intelligence

Figures 1, 2, and 3 were generated using OpenAI's GPT-5-mini based on the authors' descriptions. The figures were created de novo and do not incorporate any third-party copyrighted materials. The authors take full responsibility for the content and have verified its scientific accuracy prior to inclusion in the manuscript.

Results

The initial search results yielded a total of 1080 articles. After the removal of duplicates and the exclusion of ineligible studies, 27 results were identified for the review. SDC, Figure 1 shows the screening workflow diagram of the included studies.

Study Characteristics

Overall, 27 studies[12–38] were included in this narrative review, comprising 16 RCTs, six clinical trials, three case studies, one observational cohort study, and one pilot study. The study characteristics are included in Table 1. The studies reported differing stem cells, interventions, and outcomes and were therefore categorized according to the stem cell types.

Table 1 | Characteristics of included studies

S/N	Author, year	Patient population	Design	Cell type/source	Dose	Delivery route/ timing	Follow-up	Primary/secondary outcome	Adverse events
1	Qayyum et al., 2023a[12]	81 symptomatic HFrEF patients (mean age 67.0 ± 9.0 CSCC_ASCs vs. 66.6 ± 8.1 placebo)	RCT	CSCC_ASCs	12–15 injections of 0.3 mL CSCC_ASC (total cell dose 100 × 10^6 cells)	Injection into the viable myocardium in the border zone of infarcted tissue	3 years	No significant changes in LVESV, LVEDV, or LVEF at 6 months between groups	Not significant
2	Qayyum et al., 2023b[13]	133 symptomatic HFrEF patients	Multicenter RCT	CSCC_ASCs	15 injections of 0.3 mL CSCC_ASC CryoStor solution (total cell dose 100 × 10^6)	Injection into viable myocardium	3 years	No significant differences in LVESV or secondary endpoints during follow-up	Not significant
3	Bolli et al., 2021[14]	125 patients with ischemic HF and reduced LVEF	Multicenter randomized double-blind placebo-controlled Phase II trial	MSCs + CPCs, MSCs alone, CPCs alone, or placebo	150 × 10^6 MSCs and 5 × 10^6 CPCs	Transendocardial injection	12 months	Compared to placebo, significantly reduced HF-MACE risk for both CPCs [HR 0.20 (95% CI 0.04–0.93), $P = 0.041$] and MSCs + CPCs [HR 0.26 (95% CI 0.07–0.93), $P = 0.043$]	Not significant
4	Mathiasen et al., 2020[15]	60 patients (age 30–80) with ischemic HF, NYHA II–III, LVEF < 45%	Randomized double-blind, placebo-controlled trial	Autologous BM-MSC	10–15 injections of 0.2 mL MSC	Intramyocardial injections	4 years	At 12 months: MSC showed significant improvement vs. placebo, with a reduction in LVESV (−17.0 ± 16.2 mL; 95% CI 8.3–25.7; $P = 0.0002$), alongside increases in LVEF (+6.2%; $P < 0.0001$), stroke volume (+16.1 mL; $P < 0.0001$), and myocardial mass ($P = 0.009$)	Ventricular tachycardia, double-vision, and dizziness
5	Chan et al., 2020[16]	14 patients with ischemic heart disease and depressed LVEF	Clinical trial: Phase 1, non-randomized, open-label treatment trial	Autologous BMSCs	Thirty 100 µL injections	Direct intramyocardial injection	1 year	Regional contractility in cell-treated areas improved at 12 months, with strain reductions of −4.6% ± 2.1% for TMR+BMSCs ($P = 0.02$) and −4.2% ± 6.0% for CABG+MSCs ($P = 0.30$) vs. baseline; Quality of life also improved, reflected by reduced angina scores at 1 year (TMR+BMSCs: 1.3 ± 1.2; CABG+MSCs: 1.0 ± 1.4).	None
6	Zhang et al., 2021[17]	43 STEMI patients post-PCI (BM-MSC group $n = 21$, control $n = 22$)	Multicenter randomized single-blind controlled trial	Autologous BM-MSCs	6–8 injections of 2 mL BM-MSC suspension	Intracoronary injection	1 year	No improvement in LV function or myocardial viability after AMI	Not significant
7	Mathur et al., 2022[18]	85 patients post-AMI (BMC $n = 46$, placebo $n = 39$)	Multicenter, double-blind, randomized, placebo-controlled trial	Autologous BMCs	10 ml of the cell suspension infused in three portions (each 3.3 mL)	Intracoronary injection	5 years	At 5 years, no improvement in clinical outcomes; early surrogate benefits not sustained	Not reported
8	Soetisna et al., 2020[19]	30 CHD patients with EF < 35%	Single-blind RCT	CABG alone vs. CABG + CD133+ stem cell	40 injections of 0.5 mL of CD133+ cells	Transepicardial and transseptal implantation	6 months	At 6 months, CD133+ therapy improved EF by 8.7% ± 9.5% ($P = 0.04$) and showed benefits in wall motion score index ($P = 0.003$) and scar size ($P = 0.047$) vs. controls	None
9	Bolli et al., 2020[20]	37 cancer survivors with chronic anthracycline-induced cardiomyopathy (AIC)	Phase 1, randomized, double-blind, placebo-controlled trial	Allo-MSCs	1 × 10^8 allo-MSCs (20 injections of 0.4 mL each)	Transendocardial injection	1 year	Safe and feasible; no significant differences in clinical outcomes	None related to therapy

S/N	Author, year	Patient population	Design	Cell type/source	Dose	Delivery route/ timing	Follow-up	Primary/secondary outcome	Adverse events
10	Bayes-Genis et al., 2024[21]	12 patients with non-acute MI eligible for revascularization	Randomized, controlled, double-blind, phase I trial	PeriCord graft (decellularized pericardial matrix + UC Wharton's jelly MSCs)	1 or 2 PeriCords Average: 1.01×10^7 viable WJ, MSC	Myocardial implantation	1 year	Safe; demonstrated immunomodulatory properties	None related to therapy
11	He et al., 2020[22]	50 patients with chronic ischemic heart disease (LVEF ≤ 45%) undergoing CABG	Randomized double-blind clinical trial	hUC-MSC-laden collagen hydrogel injection vs. hUC-MSCs alone vs. CABG only	Collagen/cell group: hUC-MSCs 1×10^8/1.5 mL phosphate-buffered saline) plus collagen scaffold (1 mL) and CABG Cell group: hUC-MSCs (1×10^8/2.5 mL phosphate-buffered saline)	Intramyocardial injection	1 year	No significant differences in SAEs, myocardial damage markers, and renal or liver function; adverse events observed in cell groups (HF hospitalization); the control group had no SAEs	Not significant
12	Saltzman et al., 2025[23]	155 patients (134 men, 21 women) with ICM or NIDCM	Single-center, observational, ambispective, long-term follow-up study	MSC injection	20–200 million auto-MSCs/ allo-MSCs	Transendocardial injection	13 years	At 5 years, ICM improvers' LVEDV decreased from 225.7 ± 95.9 mL to 209.0 ± 100.6 mL ($P = 0.046$), and NIDCM improvers' LVEF increased from 27.2% ± 8.9% to 36.1% ± 11.6% ($P = 0.018$)	Not significant
13	Florea et al., 2020[24]	34 patients (male $n = 24$, female $n = 10$) with NIDCM	Clinical trial	MSC	100 million Allo-MSCs vs. 100 million Auto-MSCs	Transendocardial injections	12 months	EF increased by 6.2 units in males ($P = 0.04$) and 8.6 units in females ($P = 0.04$; males vs. females $P = 0.57$)	Not reported
14	Sato et al., 2021[25]	5 patients with LVEF ≤ 45%	Pilot study	MSCs	1.0×10^8 MSCs	Intravenous injection	2 years	No significant vital sign changes; one transient fever; labs normal; no malignancy	None
15	Hüzmeli et al., 2025[26]	1 patient with recent AMI post-failed PCI	Case report	MSCs	33×10^6 allogeneic hUC-MSCs and 5×10^9 particles of hUC-MSC-derived extracellular vesicles	Direct injection into the myocardium	6 months	EF improved from 28% to 43% at 6 months; reduced EDV and ESV; benefits persisted despite graft occlusion	Pulmonary embolism
16	Perin et al., 2023[27]	65 HFrEF patients on guideline-directed therapy	Randomized, double-blind, multicenter study	Single transendocardial MPC administration	150 million MPCs in 15 to 20 injection sites (in 0.2 mL volume containing 810 million MPCs)	Transendocardial injection	30 months	MPCs increased LVEF at 12 months, reduced MI/stroke risk by 58%, and lowered 3-point MACE	Not significant
17	Traxler et al., 2023[28]	15 patients	Multicenter, randomized, double-blinded, placebo-controlled study	ADSC	-	Percutaneous intramyocardial application	12 months	At 12 months, miR-126 decreased in the ADSC group; cardiac miRNAs correlated with plasma biomarkers; no significant regulation of EV miRNAs	Not significant
18	Kawamura et al., 2024[29]	6 patients with ischemic cardiomyopathy scheduled for CABG (LVEF ≤ 40%)	Single-center randomized double-blind study	ADSC spray therapy ($n = 3$) vs. placebo ($n = 3$) combined with CABG	3×10^8 ADSCs	CABG and cell spray transplantation	24 weeks	One pleural effusion resolved; ADSC spray therapy was safe and enhanced cardiac function via capillary network reconstruction	Pleural effusion, transient perioperative paroxysmal atrial fibrillation, and a wound infection
19	Peregud-Pogorzelska et al., 2020[30]	34 Patients with STEMI with one-vessel CAD treated with PCI	Clinical trial: prospective, open-label, non-RCT	Intracoronary infusion of autologous BM-derived lineage-negative SPCs	-	Infusion into the infarct-related coronary artery	12 months	Feasible and safe; improved LVEF (>10% at 12 months) without adverse remodeling	None
20	Gallego-Navarro et al., 2025[31]	95 children with HLHS variants undergoing stage II palliation (<13 months)	Clinical trial: Phase IIb multicenter open-label nonrandomized study	Autologous UCB-MNCs into the RV myocardium	1–3 million total nucleated cells per kg of body weight of the autologous UCB-MNC product	Intramyocardial injection	12 months	Unfavorable change in longitudinal strain vs. controls ($P = 0.032$); no differences in other endpoints; higher SAE incidence (20%)	None related to the product

Table 1 | Continued

S/N	Author, year	Patient population	Design	Cell type/source	Dose	Delivery route/ timing	Follow-up	Primary/secondary outcome	Adverse events
21	Ostovaneh et al., 2021[32]	124 post-MI patients with LVEF < 45% and ≥15% LV scar	RCT	Allogeneic CDCs	25 million human allogeneic CDCs	Intracoronary infusion	12 months	Improved segmental myocardial strain (Ecc) in the CDC group	-
22	Makkar et al., 2020[33]	134 post-MI patients (LVEF ≤ 45%, scar ≥15% LV mass)	Multicenter, randomized, double-blind, placebo-controlled trial	Allogeneic CDCs	25 million allogeneic CDCs	Intracoronary infusion	6 months	No scar size reduction at 6 months; CDCs reduced LVEDV, LVESV, and NT-proBNP	Acute MI and femoral artery pseudoaneurym
23	Menasché et al., 2024[34]	1 patient with drug-refractory LV dysfunction (non-ischemic DCM)	Case report	EV-enriched secretome	20×10^9 particles/kg administered three times at 3 weeks interval	Intravenous infusion	6 months	Well tolerated; improved NYHA class, echo parameters, reduced diuretic need, no alloimmunization	None
24	Drabik et al., 2022[35]	Patients with iCHF, LVEF < 35%, recent HF hospitalization	RCT	Transmyocardial CSC transplantation via perforated needle vs. sham	At least 24 million autologous CSCs	Transendocardial injection	30 days	Decreased regional contractility in 30.6% (day 1) and 18.9% (day 30); increased WMSI and reduced LVEF	None
25	Domae et al., 2021[36]	24 NIDCM patients with LVEF < 35% on optimal therapy	Clinical trial	Autologous skeletal cell-patch implantation via minithoracotomy	5 to 6 cell patches containing 6.0×10^7 cells	Cell patch implantation in the anterior and lateral left ventricular walls	Average: 47.5 ± 4.3 months	13 responders improved symptoms, exercise capacity, and cardiac performance; 11 nonresponders showed no improvement	-
26	Horvath et al., 2020[37]	1 patient	Case report	Electrophysiological assessment of hiPSC-CMs	-	-	-	hiPSC-CMs expressed non-cardiac ion channels, causing oscillating afterdepolarizations	-
27	Noda et al., 2020[38]	STEMI patients with LVEF ≤ 45% post-PCI	Clinical trial	IV infusion of 1.5×10^7 Muse cells (CL2020)	1.5×10^7 cells/15 mL	Intravenous infusion	12 weeks	Safe; markedly improved LV function	None

Abbreviations: ADSCs, adipose-derived stem cells; AIC, anthracycline-induced cardiomyopathy; AMI, acute myocardial infarction; AP, action potential; BMCs, bone marrow-derived cells; BM-MSCs, bone marrow-derived mesenchymal stromal cells; BMSCs, bone marrow stromal cells; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CDC, cardiosphere-derived cells; CHD, coronary heart disease; CI, confidence interval; CPCs, cardiac progenitor cells; CSC, cardiopoietic stem cell; CSCC_ASC, cardiology stem cell centre adipose tissue derived mesenchymal stromal cell product (specific product used in Qayyum trials); DCM, dilated cardiomyopathy; Ecc, circumferential strain (a measure of myocardial deformation); EF, ejection fraction; EV, extracellular vesicles; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HLHS, hypoplastic left heart syndrome; hiPSC-CMs, human-induced pluripotent stem cell-derived cardiomyocytes; HR, hazard ratio; hUC-MSCs, human umbilical cord-derived mesenchymal stromal cells; ICM, ischemic cardiomyopathy; LIN-SPCs, lineage-negative stem/progenitor cells; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiovascular events; MPCs, mesenchymal precursor cells; MSC, mesenchymal stromal cells; MI, myocardial infarction; NIDCM, non-ischemic cardiomyopathy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QoL, quality of life; RCT, randomized controlled trial; RV, right ventricle; SAE, serious adverse events; SPCs, stem/progenitor cells; STEMI, ST-elevated myocardial infarction; TMR, transmyocardial revascularization; UCB-MNCs, umbilical cord blood-derived mononuclear cells; UC-MSCs, umbilical cord mesenchymal stromal cells; WMSI, wall motion score index.

Table 2 | Summary of stem cell types, delivery routes, clinical indications, and endpoint classes in studies of stem cell therapy for cardiovascular disease

S/N	Cell type	Delivery route	Indication	Endpoint class
1	Adipose-derived stem cells	Intramyocardial injection (border-zone myocardium); Epicardial spray during CABG	Symptomatic HFrEF; Ischemic cardiomyopathy	Structural/functional cardiac endpoints
2	Cardiac progenitor cells	Transendocardial injection	Ischemic heart failure; STEMI with coronary artery disease	Structural/functional endpoints; clinical outcomes; quality-of-life
3	Bone-marrow mesenchymal stromal cells	Intramyocardial injection	Ischemic heart failure; STEMI after PCI	Structural/functional endpoints; quality-of-life
4	CD133+ stem cells	Transepicardial/transseptal implantation during CABG	Coronary heart disease with reduced EF	Structural/functional endpoints
5	Mesenchymal stromal cells	Transendocardial injection	Anthracycline-induced cardiomyopathy; Non-acute myocardial infarction requiring revascularization; Chronic ischemic heart disease	Safety/feasibility; clinical outcomes; Structural/functional endpoints; survival
6	Mesenchymal precursor cells	Transendocardial injection	HFrEF on guideline-directed therapy	Structural/functional endpoints; clinical outcomes (MACE)
7	Umbilical cord blood mononuclear cells	Intramyocardial injection	Hypoplastic left heart syndrome (pediatric)	Structural/functional endpoints; safety
8	Cardiosphere-derived cells	Intracoronary infusion	Post-MI with LV scar	Structural/functional endpoints
9	Cardiac stem cells	Transendocardial injection	Ischemic chronic heart failure	Structural/functional endpoints
10	Extracellular-vesicle enriched secretome	Intravenous infusion	Non-ischemic dilated cardiomyopathy	Clinical outcomes; functional status
11	Skeletal myoblast cell patches	Surgical epicardial implantation	Non-ischemic dilated cardiomyopathy	Clinical outcomes; functional capacity
12	Induced pluripotent stem cell-derived cardiomyocytes	Electrophysiological assessment (experimental)	Cardiac arrhythmia modeling	Mechanistic endpoints
13	Multilineage-differentiating stress-enduring (Muse) cells	Intravenous infusion	STEMI after PCI	Structural/functional endpoints

Abbreviations: CABG, coronary artery bypass grafting; EF, ejection fraction; EVs, extracellular vesicles; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Stem Cell Therapy Approach

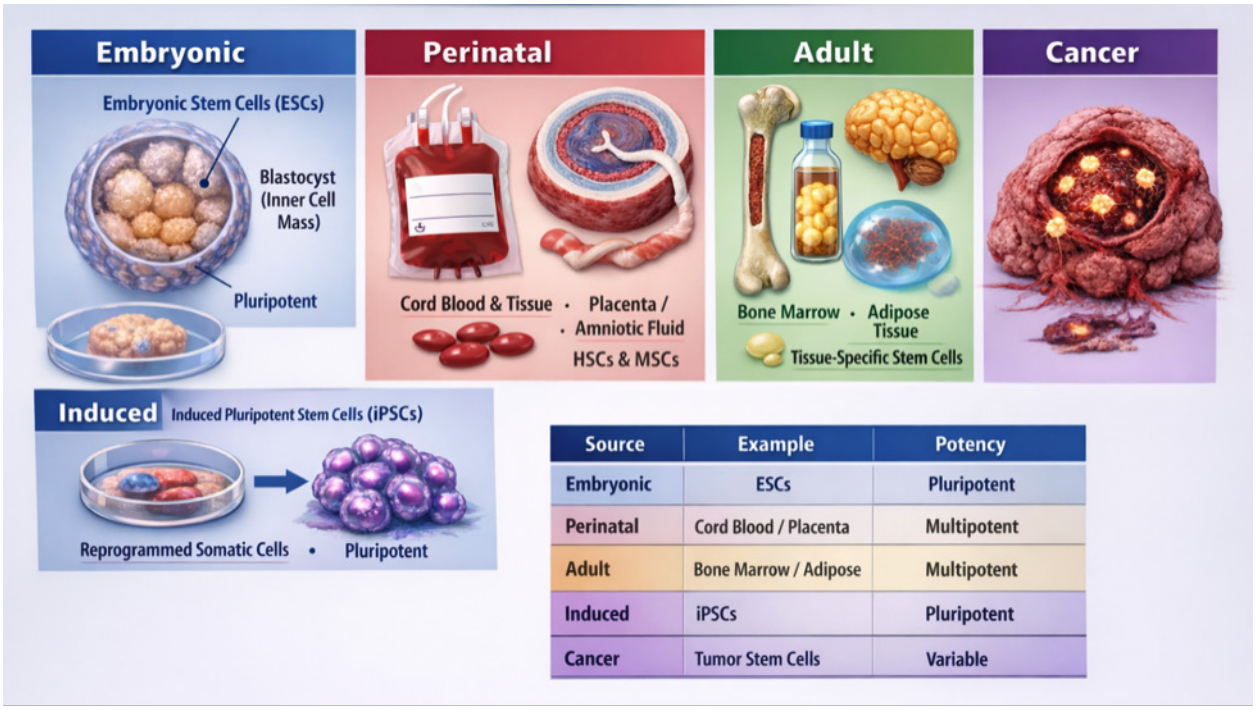
A summary of the stem cell types, delivery routes, clinical indications, and endpoint classes reported across the included studies is presented in Table 2.

MSCs

MSCs have attracted considerable interest in cardiovascular regeneration due to their stem cell-like properties, including paracrine signaling, immunomodulation, and potential for tissue repair. They have been investigated as therapeutic agents in both ischemic and non-ischemic heart failure, with sources ranging from bone marrow to adipose tissue. MSCs may be administered either autologously or allogeneically, offering flexibility in clinical application. Figure 2 highlights the classification of stem cells based on sources. A summary of stem cell delivery approaches is provided in Figure 3.

Adipose tissue-derived MSCs have been tested in clinical trials with mixed results. In a Danish Phase II trial, Qayyum et al. reported that intramyocardial CSCC_ASC (Cardiology Stem Cell Center Adipose tissue derived mesenchymal Stromal Cell) injections in patients with chronic ischemic heart failure with reduced ejection fraction (HFrEF) were safe but failed to improve myocardial function, structure, or clinical symptoms.[12] Moreover, adverse events were more frequent than with the placebo, with no significant differences at 1-year follow-up. Similar findings were observed in the European multicentre SCIENCE trial involving 133 patients, where predefined endpoints and restoration of cardiac function or clinical symptoms were not achieved.[13]

In contrast, bone marrow-derived MSCs (BM-MSCs) have demonstrated more promising outcomes. Bolli et al. showed that MSCs combined with c-kit-positive cardiac cells were safe, feasible, and beneficial in patients with ischemic cardiomyopathy, leading to reduced scar tissue and major adverse cardiovascular events (MACE), and enhanced quality of life, although left ventricular function remained unchanged.[14] Autologous MSCs administered via intramyocardial injections in patients with ischemic heart failure resulted in reduced left ventricular end-systolic volume (LVESV) and significant improvements in ejection fraction, stroke volume, and myocardial mass.[15] Chan et al. assessed the safety and feasibility of direct intramyocardial injection of autologous BMSCs in patients with ischemic heart disease and depressed ejection fraction undergoing transmyocardial revascularization or CABG.[16] The procedure was technically feasible and safe, with preliminary results at 1 year showing improved cardiac function and quality of life. However, long-term outcomes have been less encouraging. With BMSCs,



Source	Example	Potency
Embryonic	ESCs	Pluripotent
Perinatal	Cord Blood / Placenta	Multipotent
Adult	Bone Marrow / Adipose	Multipotent
Induced	iPSCs	Pluripotent
Cancer	Tumor Stem Cells	Variable

Fig 2 | Classification of stem cells based on sources. HSCs, hematopoietic stem cells; MSCs, mesenchymal stromal cells

a dose-response effect has been observed, and after 4 years, patients experienced significantly fewer hospitalizations for angina. However, Mathur et al. reported that after 5 years, the incidence of major adverse cardiac events was similar between BMSC-treated patients and placebo, with an increase in non-cardiac deaths in the BMSC group.[17] While surrogate outcomes such as ejection fraction and myocardial salvage index improved at 1 year, these benefits did not translate into sustained clinical outcomes. Safety analyses revealed one death and one coronary microvascular embolism in the bone marrow MSC group, but otherwise no

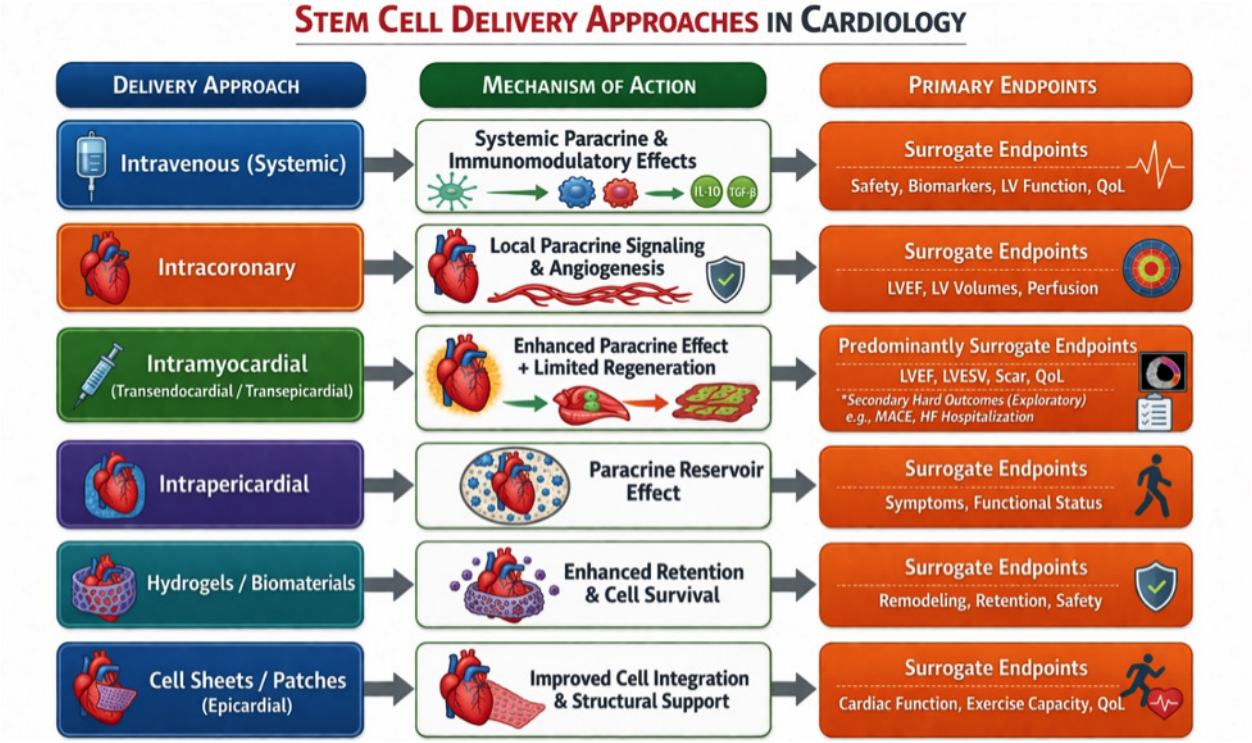


Fig 3 | Stem cell delivery approaches in cardiology. HF, heart failure; IL-10, Interleukin 10; LV, left ventricle; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiovascular events; QoL, quality of life; TGF-β, transforming growth factor beta

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major adverse events. Interestingly, alanine transaminase and C-reactive protein levels were significantly lower in this group compared to controls, suggesting potential systemic effects.

In contrast, intracoronary transfer of autologous BM-MSCs did not promote recovery of left ventricular function or myocardial viability after acute myocardial infarction.[18] Further studies have explored alternative delivery approaches. Zhang et al. found that intracoronary transfer of autologous BM-MSCs did not promote recovery of left ventricular function or myocardial viability after acute myocardial infarction.[17] In contrast, Soetisna et al. demonstrated that combined transepicardial and transseptal autologous CD133+ bone marrow cell implantation during CABG improved cardiac function in patients with low ejection fraction coronary artery disease, highlighting the importance of delivery technique in determining therapeutic efficacy.[19]

Allogeneic MSCs have generally been safe but less effective. Bolli et al. reported no significant differences in clinical outcomes following administration of allogeneic MSCs.[20] However, Bayes-Genis et al. demonstrated that double allogeneic grafts show promise.[21] In their investigation of *PeriCord*, an engineered tissue graft composed of a decellularized pericardial matrix and Wharton's jelly MSCs, a safe profile with notable immunomodulatory properties was observed. The intervention promoted monocyte differentiation toward inflammation-resolving macrophages and altered prognostic markers such as Meteorin-like, although secondary outcomes, including quality of life and cardiac function, remained unchanged.

Despite these advances, poor cell retention and survival after transplantation remain critical challenges; however, novel interventions such as cell-laden hydrogel therapy have been explored to address these limitations. He et al. demonstrated that hydrogel-based delivery was safe and feasible in patients with chronic ischemic heart disease, though caution is warranted due to observed adverse events, including hospitalization for heart failure.[22] Prognostic parameters have also been investigated. Saltzman et al. showed that improvements in ejection fraction and reductions in left ventricular end-diastolic volume (LVEDV) were associated with survival benefits in both ischemic and non-ischemic cardiomyopathy, with effects sustained for up to 5 years.[23] However, Florea et al. highlighted sex-based differences, noting that male patients had lower baseline ejection fraction and higher ventricular volumes compared to females, although functional measures such as the Minnesota Living with Heart Failure Questionnaire and 6-min walk test were similar between groups.[24]

Sato et al. reported that intravenous administration of 1.0 × 108 MSCs in patients with left ventricular ejection fraction (LVEF) ≤ 45% was well tolerated, with no significant changes in vital signs or laboratory parameters during 1 month of follow-up and no evidence of malignancy.[25] Further evidence of therapeutic potential was provided by Hüzmeli et al., describing the use of MSCs and extracellular vesicles derived from these cells during coronary artery bypass grafting (CABG) in a patient with recent acute myocardial infarction.[26] Improvements in cardiac function were observed, including enhanced ejection fraction and reductions in LVEDV and LVESV. Remarkably, these benefits persisted despite graft occlusion, suggesting that extracellular vesicle-enhanced MSC therapy may represent a viable adjunct to surgical revascularization for restoring myocardium in severe ischemic injury.

Furthermore, mesenchymal precursor cells, which are allogeneic, immunoselected cells characterized by potent anti-inflammatory properties, have been explored in patients with HFrEF, particularly in those with heightened inflammatory activity.[27] Transendocardial administration of the precursor cells resulted in significant improvements in LVEF at 12 months, accompanied by a 58% reduction in the risk of myocardial infarction or stroke and a decreased incidence of three-point major adverse cardiovascular events compared with controls. These findings highlight the potential of precursor cells to provide clinically meaningful benefits in the management of HFrEF.

Allogeneic Adipose-Derived Stem Cells

Adipose-derived stem cells (ADSCs) have emerged as an attractive cell source due to their immune-evasive properties and capacity to promote angiogenesis. Clinical studies have demonstrated mixed results. Traxler et al. reported that intramyocardial injection or spray administration of ADSCs in patients with ischemic heart disease did not significantly alter small extracellular vesicle concentrations, although correlations between cardiac microRNAs and plasma biomarkers were observed.[28] In contrast, Kawamura et al. demonstrated that ADSCs used in combination with CABG were safe and effective, enhancing cardiac function and augmenting the benefits of surgical revascularization, likely through capillary network reconstruction.[29]

Stem/Progenitor Cells

Stem/progenitor cells (SPCs) have also been investigated in the context of acute myocardial infarction. Peregud-Pogorzelska et al. evaluated the intracoronary infusion of autologous lineage-negative bone marrow-derived SPCs in patients with ST-elevated myocardial infarction.[30] At 12 months, nine patients demonstrated improvements in LVEF exceeding 10%, with no evidence of adverse remodeling, suggesting that SPC therapy offers potential benefits in post-infarction recovery.

Autologous Umbilical Cord Blood-Derived Mononuclear Cells

The therapeutic potential of autologous umbilical cord blood-derived mononuclear cells (UCB-MNCs) has been explored in both pediatric and adult populations. Gallego-Navarro et al. investigated their efficacy in children with hypoplastic left heart syndrome and its variants, following stage I palliation surgery and prior to stage II palliation at less than 13 months of age.[31] The study revealed an unfavorable change in longitudinal

cardiac strain in the treatment group compared with improvements in the control group in the short term. No differences were observed between groups in other coprimary efficacy endpoints in either the short or long term. Furthermore, the treatment group experienced a higher incidence of serious adverse events compared with controls at 3 months.

Allogeneic Cardiosphere-Derived Cells

Cardiosphere-derived cells (CDCs) represent another promising avenue in regenerative cardiology. Ostovaneh et al. demonstrated that CDC administration in patients with post-myocardial infarction left ventricular dysfunction improved regional myocardial function and contractility.[32] This finding is critical given that most cell therapy trials have failed to show improvements in global left ventricular function after myocardial infarction. Makkar et al. further assessed the safety and efficacy of intracoronary administration of allogeneic CDCs.[33] At 6 months, no difference was observed in the percentage change from baseline in scar size. However, CDC-treated patients demonstrated significant reductions in LVEDV, LVESV, and N-terminal pro B-type natriuretic peptide (NT-proBNP) compared with placebo. These findings indicate that while CDCs did not reduce scar size, they exerted disease-modifying bioactivity by improving ventricular remodeling and reducing biomarkers of cardiac stress, with a favorable safety profile.

Cardiovascular Cell-Derived Secretome

Beyond direct cell transplantation, recent research has highlighted the therapeutic potential of the stem cell secretome. Instead of relying on stem cells to engraft and differentiate, it is reported that the therapeutic effect emanates from these paracrine signals that modulate tissue repair. Menasché et al. provided evidence that the beneficial effects of stem cells can be replicated through administration of their secretome, potentially streamlining clinical translation.[34] In investigated patients, repeated delivery of the secretome was well tolerated, with no adverse events during or after infusion. Six months post-procedure, the patient was classified as NYHA Class II, with improved echocardiographic parameters, reduced daily diuretic requirements (from 240 mg to 160 mg), absence of defibrillator discharges, and no alloimmunization against the product. These findings support the safety, immunologic compatibility, and therapeutic efficacy of secretome-based interventions, underscoring their potential as a cell-free alternative in regenerative cardiology.

Cardiopoietic Stem Cells

Evidence from the CHART-1 study has raised important concerns regarding the therapeutic efficacy of transendocardial cardiopoietic stem cell (CSC) transplantation in patients with chronic ischemic heart failure.[35] The analysis suggested that the beneficial effects of CSC therapy may diminish with an increasing number of injections. Patients demonstrated a decrease in regional contractility, accompanied by an increase in wall motion score index and a reduction in LVEF. Notably, transendocardial injections were associated with myocardial injury, an adverse effect that persisted, albeit to a lesser degree, at 30 days. These findings imply that mechanical trauma caused by the "needle technique" used in transendocardial delivery may offset, at least in part, any potential cell-related benefits.

In contrast, autologous skeletal stem cell–patch implantation, as reported by Domae et al.[36] may represent a potentially safer and more effective alternative to needle-based delivery, although its clinical effectiveness remains incompletely defined. In this study, feasibility, safety, and therapeutic efficacy were evaluated in patients with nonischemic dilated cardiomyopathy who underwent implantation of autologous cell patches over the surface of the left ventricle via left minithoracotomy. The procedure was performed without complications or lethal arrhythmias. Favorable responses were observed in a subset of patients, with improvements in symptoms, exercise capacity, and cardiac performance.

Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes

Unlike the multipotent cells from other included studies, human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) represent an unlimited source of cardiomyocytes. However, concerns remain regarding their electrophysiological fidelity. Horvath et al. reported that hiPSC-CMs may express non-cardiac ion channels, raising questions about their suitability for translational use.[37] The outcomes of this study report large and irregular outward potassium currents, resulting in oscillating afterdepolarizations in the action potential, which may not normally be found in the human heart. Consequently, rigorous screening for non-cardiac ion channel expression is essential before hiPSC-CMs can be reliably applied.

Multilineage-Differentiating Stress-Enduring Cells

Multilineage-differentiating stress-enduring (Muse) cells are pluripotent stem cells with unique regenerative properties. Noda et al. conducted the first in-human trial assessing the safety and efficacy of intravenous Muse cell administration in patients with ST-elevated myocardial infarction.[38] The therapy was safe and demonstrated marked improvements in left ventricular function among responders. These patients also exhibited enhanced symptoms, exercise capacity, and cardiac performance postoperatively. However, such benefits were not observed in nonresponders, underscoring variability in therapeutic outcomes. The trial highlights Muse cells as a promising regenerative therapy, with the potential to achieve functional recovery and favorable clinical outcomes in selected patient populations.

Discussion

Findings from this review highlight the diverse range of stem cell populations employed in cardiac regenerative therapy, including MSCs, BMSCs, mesenchymal

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precursor cells, ADSCs, SPCs, UCB-MNCs, CDCs, CSCs, hiPSC-CMs, and Muse cells. Overall, stem cell therapy has demonstrated safety and feasibility in human cardiac applications, with evidence of efficacy across multiple clinical endpoints, including improvements in LVEF, ventricular remodeling, exercise capacity, quality of life, and reductions in MACE. Importantly, therapeutic outcomes vary across cell type, delivery method, and disease context. The study revealed that while BM-MSCs and precursor cells show promising improvements in ischemic cardiomyopathy, ADSCs and UCB-MNCs yield mixed or limited results. Similarly, advanced approaches such as cell patches, extracellular vesicle-enhanced therapy, and secretome-based interventions suggest that optimizing delivery and harnessing paracrine mechanisms may be critical for sustained benefit.

The majority of the included studies in this review report safety and feasibility as the primary endpoints, indicating that cell-based interventions are technically feasible and safe, with a low incidence of procedure-related complications. Tolerability varied across cell types. UCB-MNCs, particularly in pediatric cohorts with hypoplastic left heart syndrome, were associated with higher rates of serious adverse events, contrasting with the generally favorable safety profiles of MSCs, CDCs, and Muse cells.[31] This variability highlights the importance of patient-specific selection and careful consideration of cell type and delivery strategy. This is also important as sex-based differences and disease etiology can also influence therapeutic response. Florea et al. demonstrated baseline differences in cardiac function between men and women, which may affect prognostic interpretation.[24] Similarly, Saltzman et al. highlighted that those improvements in LVEF and LVEDV were associated with survival benefits in both ischemic and non-ischemic cardiomyopathy, but the durability of these effects varied.[23] Such findings emphasize the importance of patient stratification in future trials.

Furthermore, while the collective evidence highlights that stem cell therapies for CVDs are commonly safe and feasible, especially within the first year of therapy, long-term data reveal that these early benefits do not always translate into sustained clinical outcomes. For example, autologous BMSCs demonstrated improved cardiac function and quality of life at 1 year,[16] yet 5-year follow-up showed no difference in major adverse cardiac events compared with placebo, and even an increase in non-cardiac deaths in the treatment group.[18] Similarly, while MSC therapy has been associated with reductions in LVESV and improved ejection fraction at 1 year,[15] subsequent analyses revealed that these benefits were not consistently sustained across longer follow-up periods. These findings underscore the importance of incorporating extended evaluation in human trials beyond just surrogate endpoints such as ejection fractions and ventricular volumes, but also on outcomes such as overall survival, hospitalization, and MACE.

To optimize the clinical efficacy and long-term outcomes of stem cell-based therapies in CVDs, recent strategies have increasingly focused on mitigating adverse effects and improving delivery methods. One of the most significant advances has been the recognition that traditional delivery approaches critically influence therapeutic efficacy. The variability in outcomes between intracoronary, intramyocardial, and surgical delivery underscores the need for optimization of delivery strategies. Notably, the CHART-1 study revealed that needle-based transendocardial delivery of CSCs was associated with myocardial injury, raising concerns about the safety of this technique and suggesting that mechanical trauma may offset potential cell-related benefits.[35] In response, alternative delivery platforms such as cell patches and engineered tissue grafts have been explored to reduce trauma and improve cell retention. BayesGenis et al. provided important insights into PeriCord grafts, composed of a decellularized pericardial matrix seeded with Wharton's jelly MSCs.[21] These grafts demonstrated immunomodulatory activity, promoting monocyte differentiation toward inflammation-resolving macrophages and altering prognostic markers such as Meteorin-like. Although secondary outcomes such as quality of life and cardiac function remained unchanged, these findings underscore the potential of engineered constructs to enhance the biological impact of cell therapy while maintaining a favorable safety profile. This aligns with evidence supporting hydrogel-based delivery systems, which have shown feasibility in enhancing cell survival through implantation into the myocardium rather than repeated injection.[22] Encapsulation of stem cells within a hydrogel matrix addresses the critical challenge of poor cell survival and retention after transplantation, as the hydrogel protects cells from mechanical stress during delivery and reduces washout by blood flow.

Beyond delivery optimization, recent studies highlight that therapeutic benefit may be mediated less by direct engraftment and more by paracrine signaling, angiogenesis, and immunomodulation. This paradigm shift has important implications, as it suggests that limitations associated with injections and engraftment can be mitigated by harnessing paracrine mechanisms. For instance, secretome-based therapies emphasize the role of immunomodulation and cell-derived factors in cell-free approaches. Menasché et al. showed that repeated administration of the stem cell secretome replicated many of the beneficial effects of cell therapy without the need for transplantation, highlighting the potential of cell-free alternatives in regenerative cardiology.[34] This novel understanding is particularly important given the limitations observed with certain cell types. For example, hiPSC-CMs have raised concerns regarding electrophysiological fidelity, as some batches expressed non-cardiac ion channels leading to abnormal action potentials.[37] Secretome therapy, by focusing on paracrine factors rather than engraftment, may mitigate such risks while still delivering therapeutic benefit.

Another important advance in the field of cardiac regenerative therapy has been the recognition that stem cell interventions may achieve greater efficacy when

combined with other therapeutic modalities. Early studies suggested that stem cells alone often provide transient improvements in surrogate endpoints,[39] but durable clinical benefit has been more consistently observed when cells are delivered in conjunction with complementary strategies. In the study by Bolli et al., MSCs combined with c-kit-positive cardiac progenitors were safe and feasible, and this dualcell approach led to reductions in scar tissue, improvements in major adverse cardiovascular events, and enhanced quality of life, even though global left ventricular function remained unchanged.[14] These findings highlight the potential for synergistic interactions between distinct cell populations, where paracrine signaling and regenerative cues may be amplified. Similarly, Hüzmeli et al. reported that MSCs administered together with extracellular vesicles during CABG improved ejection fraction and reduced ventricular volumes, with benefits persisting despite graft occlusion.[26] This suggests that augmenting cell therapy with paracrine mediators can sustain therapeutic effects beyond what is achievable with cells alone. The integration of cell therapy into surgical revascularization has also proven valuable. Soetisna et al. showed that transepicardial and transseptal implantation of CD133+ bone marrow cells during CABG improved cardiac function in patients with low ejection fraction coronary artery disease, underscoring the importance of delivery context.[19] In parallel, Kawamura et al. demonstrated that ADSCs administered in combination with CABG were safe and effective, enhancing cardiac function and augmenting the benefits of surgical revascularization, likely through reconstruction of the capillary network.[29] These findings suggest that combined therapies, including cell-cell or cellsurgery methods, integrating cells with surgical revascularization, or embedding them in engineered scaffolds, are more likely to yield sustained benefit than singlecell approaches alone.

Finally, the emergence of novel cell types, including Muse cells, mesenchymal progenitor cells (MPCs), and CDCs, represents a frontier in regenerative cardiology. Muse cells, tested in the first human trial by Noda et al., were safe and improved left ventricular function among responders, though variability in outcomes highlights patient heterogeneity.[38] Similarly, MPCs demonstrated potent antiinflammatory activity, reducing the risk of myocardial infarction or stroke by 58% and improving LVEF at 12 months, while CDCs improved regional myocardial function and reduced LV volumes and NTproBNP despite no scar size reduction, indicating diseasemodifying bioactivity.[32,33] Further studies may be needed to validate their functionality and reproducibility before widespread clinical adoption.

Study Limitations

This study has limitations. First, the majority of included studies were small, single-center, or exploratory in nature, which may restrict the generalizability of the findings. Although the studies encompassed varying patient populations, this heterogeneity complicates the interpretation of outcomes and limits the ability to draw definitive conclusions across disease subtypes. Second, while surrogate endpoints such as ejection fraction, ventricular volumes, or scar size were frequently employed, these measures do not always translate into improved survival or reductions in major adverse cardiovascular events. Long-term follow-up often reveals attenuation of early benefits, raising important questions about the durability of regenerative interventions. Yet, these long-term considerations remain underexplored in many trials. Third, the variability in cell preparation, dosing, and delivery methods further complicates comparisons across studies, thus underscoring the need for standardized approaches to ensure reproducibility and facilitate analysis. Fourth, given the narrative study design, no formal risk-of-bias assessment was conducted for the included studies. Hence, the potential impact of methodological biases—such as inadequate randomization, lack of blinding, incomplete follow-up, or confounding in non-randomized studies—cannot be fully evaluated. This limitation may affect the reliability and interpretation of efficacy and safety outcomes reported in the studies. Future reviews incorporating standardized risk-of-bias tools would provide a more rigorous appraisal of study quality and strengthen the overall conclusions.

Future Research

Despite substantial progress in stem cell-based therapies for cardiovascular repair, several critical gaps remain that warrant further investigation. Large-scale, multicenter randomized controlled trials with extended follow-up periods are required to establish the long-term safety, durability, and clinical efficacy of stem cell therapies in cardiovascular disease. Additionally, future research should focus on optimizing cell sources and identifying the most therapeutically effective stem cell populations. Comparative studies evaluating different stem cell types may help determine the most suitable candidates for myocardial regeneration. Enrichment strategies for stem cells represent a promising avenue to enhance the efficacy of cardiac cell therapy. Future studies should focus on identifying and selecting subpopulations of cells with superior therapeutic potential, such as MPCs with high anti-inflammatory or pro-angiogenic phenotypes.

Furthermore, improving cell survival, engraftment, and retention within the hostile post-ischemic myocardial microenvironment remains a major challenge. Advanced biomaterials, tissue engineering approaches, and scaffold-based delivery systems—including hydrogels, bioengineered patches, and three-dimensional cardiac constructs—should be further explored to enhance therapeutic efficacy. Cell-free therapies, including secretomes and extracellular vesicles, offer a novel strategy to overcome the limitations of live cell administration. Moreover, greater attention should be given to translational challenges, including standardized manufacturing protocols, regulatory considerations, cost-effectiveness, and scalable production of clinical-grade stem cell products. Addressing these

challenges will be essential for facilitating the safe integration of regenerative therapies into routine cardiovascular clinical practice.

Finally, core outcome sets are urgently needed to standardize the evaluation of cardiac regenerative therapies. Current trials often report heterogeneous endpoints, limiting comparability and meta-analytic synthesis. Future research should adopt harmonized clinical, functional, and quality-of-life measures.

Conclusion

Cell-based therapies for cardiovascular regeneration show promise for critically addressing unmet clinical needs and have consistently demonstrated safety and feasibility. However, clinical efficacy remains heterogeneous. While short-term improvements in surrogate endpoints, long-term follow-up often reveals attenuation of these benefits, underscoring the necessity for robust clinical endpoints. Recent advances in stem cell research highlight that therapeutic benefit is mediated less by direct engraftment and more by paracrine signaling, angiogenesis, and immunomodulation, shifting the paradigm toward enhancing these mechanisms or developing cell-free alternatives such as secretome therapy. Innovations in delivery, including hydrogel encapsulation, engineered grafts, and patch-based implantation, address persistent challenges of poor cell survival and retention, while combination strategies with surgical revascularization or dualcell approaches demonstrate synergistic potential. The emergence of novel cell types, including Muse cells, MPCs, and CDCs, represents a frontier in regenerative cardiology, and the future of regenerative cardiology may lie in refining delivery methods, enhancing paracrine mechanisms, and embracing innovative cell types or cell-free approaches to achieve durable and clinically meaningful benefits. The need for patient-specific selection, disease context, and the choice of appropriate stem cell type in tailoring regenerative strategies should also be emphasized.

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