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REVIEW ARTICLE

Stem Cell Therapy in Ischemic Heart Disease and Heart Failure: An Integrated Systematic Review of Recent Meta-Analyses and Randomized Clinical Evidence

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Abstract

Background: Heart failure (HF), particularly heart failure with reduced ejection fraction (HFrEF), remains one of the leading causes of cardiovascular morbidity and mortality worldwide despite substantial advances in pharmacological therapy, device implantation, and revascularization strategies [4,5]. Progressive ventricular remodeling, irreversible cardiomyocyte loss, chronic inflammation, impaired angiogenesis, and myocardial fibrosis continue to limit myocardial recovery in many patients. Consequently, regenerative therapies, particularly mesenchymal stem cell (MSC)-based interventions, have emerged as promising strategies to restore myocardial function through immunomodulation, angiogenesis, anti-fibrotic activity, mitochondrial transfer, and paracrine signaling [6,13]. Nevertheless, the clinical efficacy of stem cell therapy remains controversial because published randomized trials have reported inconsistent findings [7–12].

Objective: This systematic review integrates findings from three recent high-quality systematic reviews and meta-analyses to evaluate the current evidence regarding stem cell therapy in ischemic heart disease and ischemic heart failure, focusing on efficacy, safety, cardiac remodeling, and clinical outcomes [1–3].

Methods: Three recent systematic reviews/meta-analyses published in 2025–2026 were analyzed. Collectively, these reviews synthesized evidence from more than one hundred randomized clinical trials evaluating intracoronary, transendocardial, intramyocardial, and other catheter- based stem cell delivery techniques in patients with acute myocardial infarction (AMI), chronic ischemic heart disease (CIHD), and ischemic heart failure (IHF). Primary outcomes included left ventricular ejection fraction (LVEF), while secondary outcomes included ventricular remodeling indices, NYHA functional class, myocardial perfusion, exercise capacity, quality of life, major adverse cardiovascular events (MACE), hospitalization, and mortality [1–3].

Results: The largest meta-analysis included 82 randomized controlled trials comprising 5,781 patients and demonstrated a statistically significant overall improvement in LVEF, with greater benefits observed among patients with chronic ischemic heart disease and ischemic heart failure than in acute myocardial infarction [3]. In contrast, a recent meta-analysis restricted to contemporary HFrEF trials found no statistically significant improvement in LVEF but demonstrated significant enhancement in patients' quality of life without increased major adverse cardiovascular events [1]. A third meta-analysis focusing exclusively on transendocardial delivery revealed significant reductions in LV end-systolic volume, improved myocardial perfusion, and functional status while confirming an acceptable safety profile despite neutral effects on LVEF [2].

Conclusions: Current evidence suggests that stem cell therapy is safe and capable of improving several markers of cardiac remodeling and functional recovery. Nevertheless, improvement in global systolic function, particularly LVEF, remains inconsistent across contemporary studies. Future investigations should prioritize standardized cell manufacturing protocols, optimized delivery techniques, appropriate patient selection, and mechanistic biomarkers to better define the role of regenerative therapy in ischemic heart failure [1–6].

Keywords: Mesenchymal stem cells, ischemic heart failure, HFrEF, myocardial infarction, cardiac regeneration, left ventricular ejection fraction, regenerative medicine.

Introduction

Heart failure (HF) represents the terminal clinical manifestation of numerous cardiovascular disorders and remains one of the leading causes of morbidity, mortality, repeated hospitalization, and healthcare expenditure

worldwide despite remarkable advances in pharmacological treatment and device-based therapy [4,5]. According to the latest European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines, the prevalence of HF continues to increase owing to population aging, improved survival following acute myocardial infarction (AMI), and the growing incidence of hypertension, diabetes mellitus, obesity, and chronic kidney disease [4,5]. Although contemporary guideline-directed medical therapy (GDMT), including angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and implantable cardiac devices, has substantially improved survival, many patients continue to experience progressive ventricular dysfunction and symptomatic deterioration [4,5].

The pathophysiology of ischemic heart failure extends beyond simple loss of contractile myocardium. Acute myocardial ischemia initiates a cascade of inflammatory responses, oxidative stress, endothelial dysfunction, mitochondrial injury, extracellular matrix remodeling, and activation of profibrotic signaling pathways, ultimately resulting in irreversible cardiomyocyte loss and adverse ventricular remodeling [4,5]. Progressive dilation of the left ventricle, increased wall stress, myocardial fibrosis, impaired angiogenesis, and persistent neurohormonal activation contribute to declining systolic function and poor long-term prognosis. Importantly, currently available therapies primarily slow disease progression rather than regenerate damaged myocardium, leaving a substantial unmet therapeutic need [4,5].

Regenerative medicine has therefore emerged as one of the most promising therapeutic approaches in cardiovascular research during the past two decades [6,13]. Unlike conventional pharmacological therapies, regenerative strategies aim to restore myocardial structure and function through activation of endogenous repair mechanisms. Among the various regenerative approaches investigated, mesenchymal stem cells (MSCs) have attracted considerable attention because of their favorable biological properties, relatively low immunogenicity, multilineage differentiation potential, and excellent safety profile observed across numerous clinical studies [6,15].

Initially, stem cell therapy was expected to improve cardiac function through direct differentiation of transplanted cells into functional cardiomyocytes. However, accumulating experimental and clinical evidence has fundamentally changed this concept. It is now widely accepted that only a very small proportion of transplanted cells permanently engraft within injured myocardium, whereas the majority exert their therapeutic effects through indirect paracrine mechanisms [6,13]. Mesenchymal stem cells secrete a broad spectrum of cytokines, chemokines, growth factors, extracellular vesicles, and exosomes capable of promoting angiogenesis, suppressing inflammation, reducing apoptosis, inhibiting fibrosis, modulating immune responses, and stimulating endogenous cardiac repair [6,13,15].

Among the most important biological mediators released by MSCs are vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), stromal cell-derived factor-1 (SDF-1), transforming growth factor-β modulators, and numerous microRNA-containing extracellular vesicles [6,13].

Collectively, these mediators enhance neovascularization, improve endothelial function, reduce scar formation, preserve viable myocardium, and facilitate reverse ventricular remodeling. More recently, mitochondrial transfer from MSCs to injured cardiomyocytes has been recognized as an additional mechanism capable of restoring cellular bioenergetics and reducing oxidative stress, further expanding the biological rationale for regenerative cell therapy [6].

Several cellular products have been investigated in clinical cardiovascular regenerative medicine. These include bone marrow mononuclear cells (BMMNCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), umbilical cord- derived MSCs, mesenchymal precursor cells (MPCs), cardiopoietic stem cells, cardiac progenitor cells (CPCs), cardiosphere-derived cells (CDCs), and skeletal myoblasts [7–13].

Although these cell populations differ considerably regarding phenotype, proliferative capacity, secretory profile, and immunomodulatory potential, most contemporary clinical research has focused on MSC-based therapies because of their reproducible manufacturing, relatively favorable safety profile, and potent paracrine activity [6,15].

The route of stem cell delivery represents another critical determinant of therapeutic efficacy. Intracoronary infusion has historically been the most widely utilized technique because of its simplicity and compatibility with routine interventional cardiology procedures. Nevertheless, concerns regarding limited myocardial retention have stimulated increasing interest in transendocardial and intramyocardial delivery techniques, which allow direct injection of stem cells into viable peri-infarct myocardium using electromechanical mapping systems such as NOGA® [2,7–12]. Surgical epicardial implantation and tissue-engineered cardiac patches have also been investigated in selected patient populations, although their clinical application remains limited [13].

During the past twenty years, numerous randomized clinical trials have evaluated stem cell therapy in ischemic heart disease and heart failure. Landmark investigations including POSEIDON, TAC-HFT, MSC-HF, DREAM-HF, CHART-1, and

CONCERT-HF have collectively demonstrated encouraging but frequently heterogeneous clinical outcomes [7–13]. While several studies reported improvements in left ventricular ejection fraction (LVEF), ventricular remodeling, myocardial perfusion, exercise tolerance, and New York Heart Association (NYHA) functional class, others failed to demonstrate statistically significant benefits beyond those achieved with optimal medical therapy. These conflicting findings have generated ongoing debate regarding the true clinical efficacy of regenerative therapy and underscore the need for careful interpretation of the available evidence [7–13].

Recently published systematic reviews and meta-analyses have substantially strengthened the evidence base by integrating results from large numbers of randomized controlled trials. Puppo et al. analyzed 82 randomized trials involving 5,781 patients undergoing intracoronary stem cell transplantation and reported significant improvements in LVEF, particularly among patients with chronic ischemic heart disease and ischemic heart failure [3]. In contrast, Muslem et al. demonstrated that although stem cell therapy significantly improved quality of life, no statistically significant increase in LVEF could be demonstrated in contemporary HFrEF trials [1]. Similarly, Al-Sawalha et al. reported significant improvements in ventricular remodeling, myocardial perfusion, and NYHA functional class following transendocardial stem cell therapy while confirming an excellent procedural safety profile despite neutral effects on LVEF [2].

These apparently contradictory findings likely reflect important differences in patient selection, stem cell source, manufacturing protocols, dosage, delivery techniques, imaging modalities, endpoint definitions, and follow-up duration rather than an absence of biological efficacy.

Consequently, interpretation of individual meta-analyses in isolation may not fully capture the current state of evidence.

The objective of the present review is therefore to integrate the findings of these three contemporary systematic reviews and meta-analyses in order to provide a comprehensive and critically appraised overview of the efficacy, safety, ventricular remodeling, functional recovery, and future perspectives of stem cell therapy in ischemic heart disease and heart failure. By synthesizing the highest level of currently available evidence, this review aims to clarify areas of consensus, identify remaining controversies, and highlight priorities for future clinical investigation.

Methods

Study Design

The present study was designed as an integrated systematic review aimed at synthesizing the highest level of currently available evidence regarding stem cell therapy for ischemic heart disease and heart failure. Rather than performing a de novo meta-analysis of individual randomized clinical trials, this review critically integrated data from three recently published systematic reviews and meta-analyses, each evaluating distinct aspects of regenerative cardiovascular therapy [1–3]. The review was conducted according to the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement wherever applicable to evidence synthesis of published systematic reviews.

Literature Sources

Three contemporary systematic reviews and meta-analyses published between 2025 and 2026 were selected because they collectively represent the most comprehensive and up-to-date evidence regarding stem cell therapy in ischemic cardiovascular disease [1–3].

Muslem et al. performed a systematic review and meta-analysis focusing on cardiac repair and clinical outcomes in patients with heart failure treated with stem cell therapy, emphasizing ventricular function, quality of life, and safety outcomes [1].

Al-Sawalha et al. evaluated randomized controlled trials investigating transendocardial stem cell administration in patients with chronic ischemic heart failure with reduced ejection fraction (HFrEF), focusing primarily on ventricular remodeling, myocardial perfusion, functional capacity, and adverse cardiovascular events [2].

Puppo et al. published the largest contemporary meta-analysis, incorporating 82 randomized controlled trials involving 5,781 patients treated with intracoronary stem cell transplantation for acute myocardial infarction, chronic ischemic heart disease, and ischemic heart failure [3].

Together, these reviews summarize evidence from more than one hundred randomized clinical trials and therefore constitute one of the largest contemporary datasets in regenerative cardiology.

Eligibility Criteria

The original meta-analyses included randomized controlled clinical trials enrolling adult patients diagnosed with ischemic heart disease, ischemic cardiomyopathy, or heart failure with reduced ejection fraction [1–3].

Eligible studies compared stem cell therapy with placebo, sham intervention, or guideline- directed medical therapy and reported clinically relevant efficacy or safety outcomes.

Non-randomized studies, observational cohorts, case reports, editorials, narrative reviews, conference abstracts, animal experiments, and studies lacking sufficient clinical outcome data were excluded from the original meta-analyses [1–3].

Patient Population

The integrated evidence included patients with diverse manifestations of ischemic cardiovascular disease.

These populations comprised:

- Acute ST-segment elevation myocardial infarction;
- Chronic ischemic heart disease;
- Ischemic cardiomyopathy;
- Chronic heart failure with reduced ejection fraction;
- Symptomatic patients receiving optimal guideline-directed medical therapy [1–5].

Baseline left ventricular ejection fraction generally ranged between 20% and 45%, while most patients presented with New York Heart Association (NYHA) functional class II–IV symptoms despite contemporary pharmacological management [1–3].

Stem Cell Products

A wide variety of regenerative cellular products were investigated across the included randomized trials.

The principal stem cell populations included:

- Bone marrow-derived mesenchymal stem cells (BM-MSCs);
- Adipose-derived mesenchymal stem cells (AD-MSCs);
- Bone marrow mononuclear cells (BMMNCs);
- Mesenchymal precursor cells (MPCs);
- Cardiopoietic stem cells;
- Cardiac progenitor cells (CPCs);
- Cardiosphere-derived cells (CDCs);
- Skeletal myoblasts [1–3].

Both autologous and allogeneic cellular products were represented. However, mesenchymal stem cells constituted the predominant therapeutic platform across contemporary randomized trials because of their favorable immunological characteristics, potent paracrine activity, and reproducible manufacturing protocols [6,15].

Delivery Strategies

Several delivery techniques were evaluated throughout the included studies. The principal administration routes included:

- Intracoronary infusion;
- Transendocardial injection;
- Intramyocardial injection;
- Catheter-guided endomyocardial delivery;
- Surgical epicardial implantation [2,3].

Intracoronary infusion represented the largest body of clinical evidence, whereas transendocardial injection was specifically evaluated in chronic ischemic HFrEF because of its potential to enhance myocardial cell retention through direct injection into viable peri-infarct tissue [2].

Outcome Measures

The primary endpoint across the included meta-analyses was change in left ventricular ejection fraction (LVEF) [1–3].

Secondary efficacy endpoints included:

- Left ventricular end-systolic volume (LVESV);
- Left ventricular end-diastolic volume (LVEDV);
- Ventricular remodeling;
- Myocardial perfusion assessed by stress SPECT imaging;
- Six-minute walk distance (6MWD);
- Peak oxygen consumption (VO_2peak);
- New York Heart Association (NYHA) functional class;
- Quality of life assessments [1–3].

Safety outcomes included:

- Major adverse cardiovascular events (MACE);
- Cardiovascular mortality;
- All-cause mortality;
- Recurrent myocardial infarction;
- Stroke;
- Ventricular arrhythmias;
- Heart failure hospitalization;
- Procedure-related complications [1–3].

Data Synthesis

Rather than pooling individual patient data, the present review integrated the principal findings reported within each meta-analysis.

Comparative evaluation focused on:

- Ventricular systolic function;
- Ventricular remodeling;
- Myocardial perfusion;
- Symptomatic improvement;
- Quality of life;
- Exercise capacity;
- Mortality;
- Procedural safety.

Areas of agreement and disagreement among the three meta-analyses were critically examined to identify potential explanations for conflicting clinical outcomes.

Assessment of Methodological Quality

All three included reviews performed formal methodological quality assessment of the original randomized clinical trials.

Muslem et al. and Al-Sawalha et al. utilized the Cochrane Risk of Bias tool, evaluating randomization, allocation concealment, blinding, incomplete outcome reporting, and selective reporting [1,2].

Table 1: PICO Framework

Component	*Description*
Population	Adults with AMI, chronic ischemic heart disease, ischemic cardiomyopathy, and HFrEF
Intervention	Stem cell therapy (MSCs, BMMNCs, MPCs, CPCs, CDCs, ADSCs, skeletal myoblasts)
Comparison	Placebo, sham procedure, or guideline-directed medical therapy
Primary Outcome	Left ventricular ejection fraction (LVEF)
Secondary Outcomes	LV remodeling, LVESV, LVEDV, NYHA, QoL, myocardial perfusion, 6MWD, MACE, mortality, safety

Table 2: Characteristics of Included Meta-Analyses

Study	*Population*	*Delivery Route*	*Number of Studies*	*Main Findings*
Muslem et al. [1]	HFrEF	Multiple	12	Improved QoL; neutral LVEF
Al-Sawalha et al. [2]	Chronic ischemic HFrEF	Transendocardial	20	Improved LV remodeling and NYHA
Puppo et al. [3]	AMI, CIHD, IHF	Intracoronary	82	Improved LVEF and ventricular remodeling

Similarly, Puppo et al. assessed methodological quality according to internationally accepted standards for systematic reviews and meta-analyses while performing subgroup and sensitivity analyses to explore clinical heterogeneity [3].

Overall, the included evidence demonstrated predominantly low-to-moderate risk of bias. Nevertheless, important heterogeneity persisted because of differences in stem cell source, manufacturing procedures, dosage, delivery techniques, imaging modalities, patient selection, endpoint definitions, and duration of follow-up [1–3].

Results

Characteristics of the Included Evidence

The present integrated review synthesized findings from three recently published systematic reviews and meta-analyses evaluating stem cell therapy in ischemic heart disease and heart failure [1–3]. Collectively, these reviews summarized evidence from more than one hundred randomized controlled trials involving over 6,000 patients, representing one of the largest contemporary evidence bases in cardiovascular regenerative medicine.

The studies included heterogeneous patient populations, including acute myocardial infarction (AMI), chronic ischemic heart disease (CIHD), ischemic cardiomyopathy, and heart failure with reduced ejection fraction (HFrEF). Although all studies investigated regenerative cell therapy, considerable variation existed regarding stem cell source, manufacturing protocols, delivery routes, follow-up duration, and imaging modalities used to evaluate cardiac function [1–3].

Among the analyzed reviews, Puppo et al. incorporated the largest number of randomized trials (82 studies, 5,781 patients) and primarily evaluated intracoronary stem cell transplantation [3]. Muslem et al. focused on modern heart failure trials using various stem cell products and emphasized functional outcomes and quality of life [1]. Al-Sawalha et al. concentrated specifically on transendocardial stem cell therapy in chronic ischemic HFrEF, providing one of the most detailed analyses of ventricular remodeling and procedural safety [2].

Despite these methodological differences, all three reviews consistently demonstrated that stem cell therapy was well tolerated and associated with a favorable safety profile [1–3].

Left Ventricular Ejection Fraction

Improvement in left ventricular ejection fraction (LVEF) has traditionally been regarded as the principal indicator of successful myocardial regeneration. However, considerable heterogeneity was observed among the three meta-analyses regarding this outcome.

Puppo et al. reported a statistically significant overall improvement in LVEF following stem cell therapy. The pooled analysis demonstrated an average increase of approximately 3.3%, with subgroup analyses showing greater benefit among patients with chronic ischemic heart disease (approximately 8.2%) and ischemic heart failure (approximately 5.3%) than among patients treated following acute myocardial infarction (approximately 2.7%) [3].

In contrast, Muslem et al. found that although stem cell therapy improved several clinically relevant outcomes, pooled analysis failed to demonstrate a statistically significant improvement in LVEF. The authors suggested that improvements in myocardial biology may not necessarily translate into measurable changes in global systolic function, particularly during relatively short follow-up periods [1].

Similarly, Al-Sawalha et al. demonstrated no statistically significant improvement in LVEF after transendocardial stem cell administration despite favorable changes in ventricular remodeling and myocardial perfusion [2].

Taken together, these findings indicate that while stem cell therapy may improve myocardial recovery, LVEF alone may inadequately reflect its biological effects. Contemporary regenerative medicine increasingly recognizes that ventricular remodeling, myocardial viability, and patient- centered clinical outcomes may provide more sensitive indicators of therapeutic efficacy than conventional ejection fraction measurements [1–3].

Ventricular Remodeling

Compared with LVEF, ventricular remodeling demonstrated substantially more consistent improvement across the included evidence.

Al-Sawalha et al. reported a statistically significant reduction in left ventricular end-systolic volume (LVESV), indicating attenuation of adverse ventricular remodeling following transendocardial stem cell delivery [2]. Sensitivity analyses additionally demonstrated improvement in left ventricular end-diastolic volume after exclusion of heterogeneous studies, suggesting that methodological

differences among randomized trials contributed to variability in pooled estimates [2].

Similarly, Puppo et al. reported improvements in ventricular remodeling among patients with chronic ischemic heart disease receiving intracoronary stem cell transplantation [3]. Reverse remodeling appeared particularly pronounced among patients with longstanding ischemic myocardial dysfunction, supporting the hypothesis that regenerative therapy may exert greater benefit in chronically remodeled myocardium than during the acute inflammatory phase following myocardial infarction.

Muslem et al. likewise concluded that structural myocardial recovery may represent one of the principal mechanisms underlying clinical improvement despite neutral effects on LVEF [1].

Collectively, these findings suggest that reverse ventricular remodeling constitutes one of the most reproducible therapeutic effects of stem cell therapy.

Functional Capacity

Functional improvement represented one of the most consistent clinical findings across all three meta-analyses.

Al-Sawalha et al. demonstrated significantly greater odds of improvement in New York Heart Association (NYHA) functional class among patients receiving transendocardial stem cell therapy compared with placebo-treated individuals [2].

Similarly, Puppo et al. reported improvements in clinical status among patients with chronic ischemic heart disease, particularly those with advanced ventricular dysfunction [3].

Muslem et al. also observed symptomatic improvement despite neutral effects on LVEF, suggesting that patients may experience clinically meaningful benefit even in the absence of measurable changes in global systolic performance [1].

Exercise capacity assessed by the six-minute walk distance (6MWD) showed variable improvement across studies. Although some randomized trials reported significant gains in walking distance, pooled analyses generally demonstrated only modest overall improvement, likely reflecting differences in rehabilitation protocols, baseline functional impairment, and follow-up duration [1-3].

Quality of Life

Quality of life emerged as one of the strongest clinical endpoints supporting stem cell therapy.

Muslem et al. demonstrated statistically significant improvement in patient-reported quality-of- life measures despite the absence of significant improvement in LVEF [1]. This observation suggests that regenerative therapy may improve symptoms, exercise tolerance, and daily functioning independently of conventional echocardiographic measurements.

These findings are consistent with improvements in NYHA functional class reported by Al- Sawalha et al. [2] and with the symptomatic improvements summarized by Puppo et al. [3].

Consequently, future regenerative cardiology trials should consider quality of life as a major efficacy endpoint alongside structural and functional imaging parameters.

Myocardial Perfusion

Improvement in myocardial perfusion represents another important biological consequence of stem cell therapy.

Al-Sawalha et al. demonstrated significant improvement in myocardial perfusion assessed by stress single-photon emission computed tomography (SPECT), suggesting enhanced microvascular function following transendocardial MSC administration [2].

Likewise, Puppo et al. summarized multiple randomized trials demonstrating improved myocardial perfusion after intracoronary stem cell transplantation, particularly in patients with chronic ischemic myocardium [3].

These observations support the hypothesis that MSC-mediated angiogenesis and endothelial repair contribute substantially to reverse ventricular remodeling and symptomatic improvement.

Table 3: Integrated Comparison of Clinical Outcomes

Clinical Outcome	*Muslem et al. [1]*	*Al-Sawalha et al. [2]*	*Puppo et al. [3]*
Left ventricular ejection fraction	No significant improvement	Neutral	Significant improvement
Ventricular remodeling	Mild improvement	Significant improvement	Significant improvement
LVESV	Neutral	Significant reduction	Significant reduction
NYHA functional class	Improved	Improved	Improved
Quality of life	Significant improvement	Improved	Improved
Myocardial perfusion	Not evaluated	Significant improvement	Significant improvement
Major adverse cardiovascular events	No increase	No increase	No increase
Mortality	Neutral	Neutral	Neutral
Overall safety	Excellent	Excellent	Excellent

Safety Outcomes

Safety findings were remarkably consistent across all three meta-analyses.

Muslem et al. reported no increase in major adverse cardiovascular events (MACE) associated with stem cell therapy compared with placebo or standard treatment [1].

Similarly, Al-Sawalha et al. found no statistically significant differences regarding all-cause mortality, cardiovascular mortality, recurrent myocardial infarction, stroke, ventricular arrhythmias, rehospitalization, or procedure-related complications [2].

Puppo et al. reached similar conclusions after analyzing more than eighty randomized clinical trials, confirming that stem cell therapy possesses an excellent procedural and clinical safety profile regardless of delivery technique or stem cell source [3].

Collectively, these findings provide strong evidence supporting the safety of regenerative cell therapy in patients with ischemic heart disease and heart failure.

Discussion

The present integrated systematic review synthesized the findings of three contemporary meta- analyses evaluating stem cell therapy in ischemic heart disease and heart failure, providing one of the most comprehensive overviews of current regenerative cardiovascular medicine [1–3]. Although the included reviews differed with respect to patient populations, stem cell products, delivery techniques, and clinical endpoints, several consistent observations emerged. First, stem cell therapy demonstrated an excellent safety profile across all randomized trials. Second, improvements in ventricular remodeling, functional status, and quality of life were more reproducible than improvements in global systolic function. Third, substantial methodological heterogeneity continues to limit definitive conclusions regarding the magnitude of therapeutic efficacy.

One of the most important findings of the present review is the apparent discrepancy between structural myocardial recovery and changes in left ventricular ejection fraction. Historically, LVEF has been considered the principal endpoint for evaluating novel therapies in heart failure. However, contemporary evidence increasingly suggests that LVEF alone incompletely reflects myocardial repair and may underestimate the biological effects of regenerative therapies [1–3].

Mesenchymal stem cells are now recognized to function primarily through indirect biological mechanisms rather than direct cardiomyocyte replacement [6,13]. Experimental studies have demonstrated that only a small proportion of transplanted MSCs permanently engraft within injured myocardium. Instead, their therapeutic activity is mediated predominantly through secretion of extracellular vesicles, cytokines, chemokines, and growth factors that promote angiogenesis, suppress inflammation, inhibit apoptosis, reduce fibrosis, and stimulate endogenous cardiac repair [6,13,15]. Consequently, improvements in myocardial biology may occur long before measurable increases in global systolic function become apparent.

This concept provides a plausible explanation for the divergent findings observed among the included meta-analyses. Puppo et al. demonstrated significant improvement in LVEF following intracoronary stem cell transplantation, particularly among patients with chronic ischemic heart disease and ischemic heart failure [3]. In contrast, both Muslem et al. and Al-Sawalha et al. reported neutral effects on LVEF despite demonstrating improvements in ventricular remodeling, NYHA functional class, myocardial perfusion, and quality of life [1,2]. Rather than representing conflicting evidence, these findings likely indicate that different outcome measures capture different aspects of myocardial recovery.

Another notable observation concerns the influence of disease stage on therapeutic response. The largest meta-analysis demonstrated greater improvement among patients with chronic ischemic heart disease than among those treated immediately following acute myocardial infarction [3].

Several biological mechanisms may account for this phenomenon. Chronic ischemic myocardium is characterized by persistent inflammation, microvascular dysfunction, extracellular matrix remodeling, and progressive fibrosis, all of which represent important therapeutic targets for MSC-derived paracrine mediators [6,13]. Conversely, the acute inflammatory environment following myocardial infarction may reduce cell survival and myocardial retention, thereby limiting regenerative efficacy.

The route of stem cell delivery represents another important determinant of therapeutic success. Intracoronary administration has historically been the most widely used technique because of its technical simplicity and compatibility with standard percutaneous coronary intervention.

Nevertheless, only a limited proportion of infused cells remain within the target myocardium, as many are rapidly washed into the systemic circulation [3]. Transendocardial injection, particularly when guided by electromechanical mapping systems such as NOGA®, permits direct delivery of stem cells into viable peri-infarct myocardium and may therefore improve local cellular retention [2]. This hypothesis is supported by the findings of Al-Sawalha et al., who demonstrated significant improvements in ventricular remodeling despite neutral effects on LVEF following transendocardial administration [2].

Cell source also represents a major contributor to heterogeneity among published clinical trials. Earlier investigations predominantly utilized bone marrow

mononuclear cells, whereas contemporary studies increasingly employ culture-expanded mesenchymal stem cells, adipose-

derived stromal cells, mesenchymal precursor cells, cardiopoietic stem cells, and cardiac progenitor cells [7–13]. These products differ substantially with respect to proliferative capacity, secretory profile, immunomodulatory properties, and regenerative potential. Consequently, pooling all stem cell products within a single meta-analysis may obscure the efficacy of individual cell populations.

Among currently available regenerative products, mesenchymal stem cells remain the most promising therapeutic platform. Their relatively low immunogenicity permits both autologous and allogeneic administration, while their potent anti-inflammatory, angiogenic, immunomodulatory, and anti-fibrotic effects have been consistently demonstrated in experimental and clinical investigations [6,15]. Moreover, MSCs possess an excellent safety profile, a finding strongly supported by all three contemporary meta-analyses included in the present review [1–3].

Perhaps the most robust finding emerging from this review is the remarkable consistency of safety outcomes. None of the included meta-analyses demonstrated increased rates of major adverse cardiovascular events, recurrent myocardial infarction, stroke, ventricular arrhythmias, cardiovascular mortality, all-cause mortality, or heart failure hospitalization following stem cell therapy [1–3]. These observations are particularly important because safety remains a fundamental prerequisite for future large-scale phase III clinical trials and eventual clinical implementation.

Despite encouraging biological rationale and favorable safety outcomes, several important limitations continue to hinder widespread clinical adoption. Considerable heterogeneity persists regarding patient selection, stem cell manufacturing, culture conditions, cryopreservation techniques, dosage, timing of administration, delivery route, imaging modalities, and endpoint definitions [1–3]. Such variability inevitably complicates interpretation of pooled analyses and limits direct comparison among randomized trials.

Future investigations should therefore prioritize standardization of stem cell production according to Good Manufacturing Practice (GMP) principles, harmonization of clinical endpoints, optimization of delivery techniques, and identification of biomarkers capable of predicting therapeutic responsiveness. Advanced cardiac magnetic resonance imaging, myocardial strain analysis, scar quantification, extracellular volume assessment, and circulating molecular biomarkers may provide more sensitive indicators of myocardial regeneration than conventional ejection fraction alone [4–6].

Taken together, the evidence synthesized in this review indicates that stem cell therapy should not currently be viewed as a replacement for guideline-directed medical therapy. Rather, regenerative therapy appears to represent a promising adjunctive strategy capable of improving myocardial biology, ventricular remodeling, functional capacity, and patient-reported outcomes while maintaining an excellent safety profile. The principal challenge for future cardiovascular regenerative medicine is therefore not to establish whether stem cell therapy is biologically active, but to determine which patients, which cell products, which delivery techniques, and which treatment protocols are most likely to achieve clinically meaningful benefit.

Clinical Implications

The findings of the present review have several important implications for contemporary clinical practice. Although stem cell therapy has not yet become part of routine guideline-directed management of ischemic heart failure, the accumulated evidence indicates that regenerative therapy has progressed beyond the experimental proof-of-concept stage and is emerging as a potentially valuable adjunctive treatment in carefully selected patients [1–5].

Current pharmacological therapy effectively attenuates neurohormonal activation and delays disease progression but is unable to regenerate damaged myocardium or reverse established myocardial fibrosis. Stem cell therapy offers a fundamentally different therapeutic approach by targeting the biological mechanisms responsible for myocardial repair, including angiogenesis, immunomodulation, extracellular matrix remodeling, and endogenous tissue regeneration [6,13]. Consequently, regenerative therapy should be regarded as complementary rather than competitive with existing heart failure therapies.

Patient selection is likely to be one of the most important determinants of future clinical success. The evidence synthesized in this review suggests that patients with chronic ischemic heart disease and established ischemic cardiomyopathy derive greater benefit than those treated during the acute phase following myocardial infarction [3]. This observation may reflect the prolonged inflammatory and fibrotic processes characteristic of chronic ischemic myocardium, which provide a more favorable biological substrate for the paracrine actions of mesenchymal stem cells [6,13].

Similarly, patients with persistent symptoms despite optimal guideline-directed medical therapy may represent the population most likely to benefit from regenerative interventions.

Improvements in New York Heart Association functional class, ventricular remodeling, and quality of life observed across contemporary randomized trials suggest that stem cell therapy may provide clinically meaningful symptomatic improvement even when conventional echocardiographic indices remain unchanged [1–3].

The choice of delivery technique also warrants careful consideration. Intracoronary administration remains the most practical and widely available approach because it can be performed during routine coronary catheterization procedures [3]. However, evidence from transendocardial studies indicates that direct intramyocardial delivery may enhance cellular retention and produce greater improvements in ventricular remodeling [2]. Future comparative trials are therefore needed to determine whether improved myocardial retention translates into superior long-term clinical outcomes.

Equally important is the selection of the stem cell product itself. Earlier clinical trials utilized heterogeneous cellular populations, including bone marrow mononuclear cells, skeletal myoblasts, and cardiac progenitor cells [7–13]. Contemporary evidence increasingly favors mesenchymal stem cells because of their reproducible manufacturing, low immunogenicity, favorable safety profile, and potent paracrine activity [6,15]. Nevertheless, further studies comparing different MSC sources—including bone marrow, adipose tissue, and umbilical cord- derived cells—remain necessary before definitive recommendations can be established.

An additional implication concerns endpoint selection in future regenerative trials. Left ventricular ejection fraction has traditionally served as the primary endpoint for evaluating novel therapies; however, the present review demonstrates that improvements in LVEF are inconsistent despite reproducible improvements in ventricular remodeling, functional status, myocardial perfusion, and quality of life [1–3]. Accordingly, future clinical trials should adopt a multidimensional assessment strategy incorporating cardiac magnetic resonance imaging, myocardial strain analysis, scar quantification, biomarker evaluation, exercise capacity, and validated patient-reported outcome measures alongside conventional echocardiographic indices [4–6].

Finally, the consistently favorable safety profile demonstrated across all three contemporary meta-analyses provides reassurance regarding continued clinical investigation of stem cell therapy. No significant increases in mortality, recurrent myocardial infarction, stroke, malignant ventricular arrhythmias, or major adverse cardiovascular events were identified [1–3]. These findings strongly support the continuation of large-scale multicenter randomized clinical trials designed to establish definitive evidence of efficacy.

Strengths and Limitations

The present review possesses several notable strengths. First, it integrates evidence from the three most recent and comprehensive systematic reviews and meta-analyses evaluating stem cell therapy in ischemic heart disease and heart failure [1–3]. Collectively, these studies summarize findings from more than one hundred randomized controlled trials and represent one of the largest contemporary evidence bases in cardiovascular regenerative medicine.

Second, unlike previous reviews that focused exclusively on a single delivery route or specific stem cell population, the present review integrates evidence across multiple therapeutic strategies, including intracoronary infusion, transendocardial injection, and various mesenchymal stem cell products. This broader perspective provides a more comprehensive understanding of the current state of regenerative cardiovascular therapy.

Third, the present review evaluates not only conventional echocardiographic outcomes but also ventricular remodeling, myocardial perfusion, functional capacity, quality of life, and procedural safety, thereby providing a clinically meaningful assessment of therapeutic efficacy.

Several limitations should nevertheless be Acknowledged

The principal limitation arises from the substantial heterogeneity among the original randomized clinical trials. Significant differences exist regarding patient selection, ischemic burden, stem cell source, cell manufacturing protocols, cryopreservation methods, administered cell dose, delivery technique, follow-up duration, imaging modalities, and endpoint definitions [1–3]. These methodological differences inevitably contribute to variability among pooled estimates.

Another limitation concerns sample size. Although the cumulative evidence includes thousands of patients, many original randomized trials were relatively small phase I or phase II investigations primarily designed to evaluate procedural safety rather than clinical efficacy.

Consequently, statistical power for mortality and hospitalization endpoints remains limited [1– 3].

Furthermore, left ventricular ejection fraction continues to dominate outcome assessment despite its recognized limitations as a surrogate marker of myocardial regeneration. Structural remodeling, myocardial strain, scar burden, tissue perfusion, and patient-reported functional outcomes may provide more sensitive indicators of regenerative efficacy than ejection fraction alone [4–6].

Finally, publication bias cannot be completely excluded. Positive randomized studies may be more likely to undergo publication than neutral investigations, potentially influencing pooled estimates despite rigorous meta-analytic methodology [1–3].

Future Perspectives

The field of cardiovascular regenerative medicine is rapidly evolving from first-generation cell transplantation toward advanced biologically engineered therapies. Although contemporary clinical evidence supports the safety of stem cell therapy and suggests beneficial effects on ventricular remodeling and functional recovery, several scientific and

technical challenges must be addressed before regenerative therapy can be incorporated into routine clinical practice [1–6].

One of the highest priorities for future research is the standardization of stem cell manufacturing. Considerable variability currently exists regarding donor selection, tissue source, cell isolation techniques, culture conditions, passage number, cryopreservation methods, viability assessment, and administered cell dose [6,15]. Such differences inevitably influence the biological characteristics of transplanted cells and contribute to heterogeneity among clinical trials.

Establishment of universally accepted Good Manufacturing Practice (GMP) protocols is therefore essential to ensure reproducibility and facilitate comparison between future studies.

Advances in cell engineering are expected to further improve therapeutic efficacy. Genetically modified mesenchymal stem cells capable of overexpressing angiogenic, anti-apoptotic, or immunomodulatory molecules may demonstrate greater regenerative potential than conventional MSC preparations [6,13]. Similarly, preconditioning of stem cells through hypoxia, pharmacological stimulation, or biomaterial scaffolds has shown promising experimental results by enhancing cellular survival, migration, and paracrine activity following transplantation.

Extracellular vesicles and exosome-based therapies have recently emerged as particularly promising alternatives to whole-cell transplantation [6,13]. Since many beneficial effects of MSC therapy are mediated through secreted extracellular vesicles rather than direct cellular engraftment, administration of purified exosomes may reproduce therapeutic benefits while avoiding several limitations associated with living cell transplantation, including poor myocardial retention, limited survival, immune compatibility, and manufacturing complexity. Furthermore, exosome-based therapies offer improved storage stability, simplified quality control, and lower theoretical risks of ectopic tissue formation.

Another rapidly developing area involves induced pluripotent stem cell (iPSC)-derived cardiomyocytes and cardiac progenitor cells. Unlike adult mesenchymal stem cells, iPSC- derived cardiac cells possess the potential to directly replace damaged myocardium and restore contractile tissue [13]. However, significant challenges remain regarding cellular maturation, electrical integration, arrhythmogenic potential, immunogenicity, and long-term safety.

Continued advances in gene editing and tissue engineering may help overcome these limitations and facilitate future clinical application.

Artificial intelligence and precision medicine are also expected to play increasingly important roles in regenerative cardiology. Integration of advanced imaging, genomic profiling, circulating biomarkers, and machine learning algorithms may enable identification of patient subgroups most likely to respond to specific regenerative therapies. Such personalized approaches could substantially improve treatment efficacy while reducing unnecessary procedures in patients unlikely to derive significant benefit. Future randomized clinical trials should therefore focus on several key priorities:

- Standardized GMP-compliant stem cell manufacturing;
- Uniform definitions of clinical endpoints;
- Optimization of stem cell dose and delivery route;
- Longer follow-up periods extending beyond two years;
- Incorporation of advanced cardiac magnetic resonance imaging;
- Comprehensive biomarker analysis;
- Evaluation of patient-reported quality-of-life outcomes;

Direct comparison of different stem cell populations and delivery strategies [1–6].

Ultimately, the future of regenerative cardiology is likely to involve multimodal therapeutic approaches integrating advanced cell therapy, extracellular vesicles, gene editing, tissue engineering, biomaterial scaffolds, and precision medicine. Such strategies may substantially enhance myocardial regeneration beyond the capabilities of first-generation stem cell transplantation.

Conclusion

Stem cell therapy represents one of the most extensively investigated regenerative strategies for the treatment of ischemic heart disease and heart failure. The integrated analysis of three contemporary systematic reviews and meta-analyses demonstrates that regenerative cell therapy has consistently exhibited an excellent safety profile while providing meaningful improvements in several clinically relevant outcomes, particularly ventricular remodeling, myocardial perfusion, functional status, and quality of life [1-3].

Despite these encouraging findings, improvements in left ventricular ejection fraction remain inconsistent across contemporary randomized clinical trials. This apparent discrepancy should not be interpreted as evidence of therapeutic failure but rather as an indication that conventional measures of global systolic function incompletely reflect the complex biological mechanisms underlying myocardial regeneration. Increasing evidence suggests that the principal therapeutic effects of mesenchymal stem cells are mediated through paracrine signaling, immunomodulation, angiogenesis, extracellular vesicle secretion, mitochondrial transfer, and attenuation of myocardial fibrosis rather than direct differentiation into functional cardiomyocytes [6,13].

The present review also highlights several important factors contributing to heterogeneity among published studies, including differences in patient selection, stem cell source, manufacturing protocols, dosage, delivery techniques, imaging modalities, endpoint definitions, and duration of follow-up. These methodological variations remain major obstacles to direct comparison among clinical trials and underscore the necessity for internationally standardized protocols.

Among currently available regenerative products, mesenchymal stem cells continue to represent the most promising therapeutic platform because of their favorable biological characteristics, reproducible manufacturing, low immunogenicity, and consistently demonstrated procedural safety [6,15]. Contemporary evidence further suggests that patients with chronic ischemic heart disease and established ischemic cardiomyopathy may derive greater benefit than those treated during the acute phase following myocardial infarction, emphasizing the importance of careful patient selection [3].

Although stem cell therapy cannot yet be recommended as a replacement for guideline-directed medical therapy, accumulating evidence strongly supports its role as a promising adjunctive treatment capable of enhancing myocardial repair and improving clinically meaningful outcomes. Future large-scale multicenter randomized clinical trials employing standardized manufacturing protocols, optimized delivery strategies, advanced imaging biomarkers, and longer follow-up periods will be essential to define the precise role of regenerative therapy in modern cardiovascular medicine.

Overall, the current body of evidence indicates that regenerative cell therapy has progressed beyond proof-of-concept and is entering a stage of clinical refinement. Continued advances in cell engineering, extracellular vesicle biology, tissue engineering, and precision medicine are expected to further improve therapeutic efficacy and may ultimately establish stem cell-based interventions as an integral component of future heart failure management.

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