

CARDIAC STEM CELL THERAPY FOLLOWING MYOCARDIAL INFARCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ТЕРАПИЯ СЪС СЪРДЕЧНИ СТВОЛОВИ КЛЕТКИ СЛЕД МИОКАРДЕН ИНФАРКТ – СИСТЕМАТИЧЕН ПРЕГЛЕД И МЕТААНАЛИЗ НА РАНДОМИЗИРАНИ КОНТРОЛИРАНИ ПРОУЧВАНИЯ

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Abstract.

Objectives: Myocardial infarction (MI) remains a major cause of morbidity and mortality worldwide, primarily due to irreversible cardiomyocyte injury and minimal regenerative potential. While mesenchymal and bone-marrow-derived stem cells have been widely studied, evidence for cardiac stem cells (CSCs) remains limited. This systematic review and meta-analysis evaluate the efficacy of cardiac stem cell therapy after MI. **Methods:** We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Eligible studies were identified from electronic searches of PubMed, EBSCO, and ProQuest for randomized controlled trials (RCTs) evaluating the efficacy of cardiac stem cell therapy after MI. The random effect analysis was performed using R v4.4.1. **Results:** Four randomized controlled trials comprising 329 participants were included. At six months, cardiac stem cell therapy was associated with a significant reduction in scar mass (MD: -4.25 g, 95% CI: -7.16 to -1.34, $p = 0.004$) and infarct size (MD: -2.32%, 95% CI: -3.91 to -0.73, $p = 0.004$) compared with placebo. No significant differences were observed in left ventricular ejection fraction (LVEF), left ventricular end-systolic volume index (LVESVi), left ventricular end-diastolic volume index (LVEDVi) at either six or twelve months, or in the 6-minute walk test at 12 months. **Conclusion:** Cardiac stem cell therapy after MI is associated with modest reductions in scar mass and infarct size at six months, without significant improvement in global ventricular function or functional capacity up to twelve months. These findings suggest that while CSCs may confer early structural benefits, their clinical impact remains uncertain and requires confirmation in larger trials with longer follow-up.

Key words:

myocardial infarction, cardiac stem cells, stem cell, infarct size

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Резюме.

Цели: Миокардният инфаркт (МИ) остава основна причина за заболяемост и смъртност в световен мащаб, главно поради необратимо увреждане на кардиомиоцитите и минимален регенеративен потенциал. Въпреки че мезенхимните и костномозъчните стволови клетки са широко проучени, доказателствата за сърдечни стволови клетки (ССК) остават ограничени. Този систематичен преглед и метаанализ оценява ефикасността на терапията със сърдечни стволови клетки след МИ. **Методи:** Метаанализът е проведен в съответствие с насоките PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses). Подходящите проучвания са идентифицирани от електронни търсения в PubMed, EBSCO и ProQuest за рандомизирани контролирани проучвания (РКИ), оценяващи ефикасността на терапията със сърдечни стволови клетки след МИ. Анализът на случайните ефекти е извършен с помощта на програмен продукт R v4.4.1. **Резултати:** Включени са общо четири рандомизирани контролирани

проучвания, с 329 участници. На шестия месец след прекаран инфаркт терапията със сърдечни стволови клетки се свързва със значително редуциране на масата на белега (MD: -4,25 g, 95% CI: -7,16 до -1,34, $p = 0,004$) и на размера на инфаркта (MD: -2,32%, 95% CI: -3,91 до -0,73, $p = 0,004$) в сравнение с плацебо. Не са наблюдавани значими разлики във фракцията на изтласкване на лявата камера (LVEF), индекса на крайния систолен обем на лявата камера (LVESVi), индекса на крайния диастолен обем на лявата камера (LVEDVi) нито на шестия, нито на дванадесетия месец, нито при 6-минутния тест с ходене на 12-ия месец от проследяването. **Заключение:** Терапията със сърдечни стволови клетки след инфаркт на миокарда е свързана с умерено намаляване на масата на белега и размера на инфаркта след шест месеца, без значително подобрене в глобалната камерна функция или функционалния капацитет до 12-ия месец. Тези открития показват, че макар CSC да могат да доведат до ранни структурни ползи, клиничното им въздействие остава несигурно и изисква потвърждение в по-големи проучвания с по-дълго проследяване.

Ключови думи: миокарден инфаркт, сърдечни стволови клетки, стволови клетки, размер на инфаркта

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INTRODUCTION

Myocardial infarction (MI) remains a major global health burden and one of the leading causes of mortality, with an estimated 17.9 million cardiovascular-related deaths annually. In the United States alone, more than 800,000 cases of MI are reported each year [1]. Despite advances in acute management strategies, particularly the widespread use of percutaneous coronary intervention (PCI), a substantial proportion of patients continue to experience adverse long-term outcomes. Approximately 20% to 30% of post-MI patients eventually develop heart failure (HF), which is associated with a significant healthcare burden and reduced quality of life [2]. One of the primary limitations in post-MI recovery is the minimal regenerative capacity of cardiac tissue [3, 4]. Terminally differentiated cardiomyocytes demonstrate negligible proliferative activity, leading to inadequate repair following ischemic injury. Consequently, necrotic myocardial regions are replaced by non-contractile fibrotic tissue, leading to maladaptive left ventricular (LV) remodeling and progressive systolic dysfunction [4].

Cardiac stem cells (CSCs) are a population of tissue-resident progenitor cells within the myocardium. These cells exhibit self-renewal, clonogenicity, and multipotency, with demonstrated capacity to differentiate into cardiomyocytes and vascular cell types both *in vitro* and *in vivo* [5, 6]. Several randomized controlled trials have evaluated the therapeutic potential of intracoronary CSC administration following acute MI. Among the early clinical trials, the CADUCEUS trial conducted by Malliaras et al. demonstrated a significant reduction in myocardial scar size at six months after intracoronary infusion of autologous cardiosphere-derived cells (CDCs) in patients with acute MI, supporting a potential role for CSCs in promoting myocardial tissue regeneration and reverse remodeling [7]. This systematic review

and meta-analysis aims to comprehensively evaluate the efficacy of CSC therapy in improving cardiac function and structural outcomes in post-MI patients.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement guideline [8]. This study was registered on PROSPERO with the registration number CRD42024586771.

Search Strategy

In this systematic review, a comprehensive literature search was conducted across three databases: PubMed, EBSCO, and ProQuest, up to July 16, 2025. Keywords used within each database were “Myocardial infarction”, “Stem cells”, “Cardiac stem cells”, “Cardiac progenitor cells”, “Infarct size”, “Scar mass”, “Ventricular ejection fraction,” “Ventricular end-systolic volume”, and “Ventricular end-diastolic volume.” Filters were applied to exclude animal studies and to include only randomized controlled trials (RCTs). Additionally, the search was limited to articles published in English.

Eligibility criteria

The intervention group consisted of patients with a history of acute myocardial infarction (AMI) who received standard therapy, including PCI with guideline-directed medical therapy, plus cardiac stem cell therapy. The control group consisted of AMI patients who received either standard therapy alone or standard therapy with placebo administration. Eligible studies were required to meet the following criteria: (1) randomized controlled trials (RCTs); (2) Inclusion of patients with a history of acute myocardial infarction (post-MI), confirmed by clinical presentation, biomarker evidence of myocardial injury, and/or imaging or angio-

graphic findings, according to the definitions applied in each original trial; (3) administration of either autologous or allogeneic stem cells; and (4) reporting at least one clinically relevant outcome, such as infarct size, scar mass, left ventricular ejection fraction (LVEF), left ventricular end-systolic volume index (LVESVi), and left ventricular end-diastolic volume index (LVEDVi). Studies were excluded if they met any of the following conditions: (1) conducted on non-human subjects or classified as pre-clinical research; (2) non-original articles (systematic reviews, editorials, letter to the editor, commentaries, or clinical guidelines); (3) non-RCT designs; (4) studies not published in English; (5) lack of access to full text.

Study selection and quality assessment

Results from the database searches were imported into EndNote X9, and duplicates were removed. The titles and abstracts of all retrieved studies were independently screened by two reviewers according to the prespecified inclusion criteria. Discrepancies were resolved through discussion, and a third reviewer was involved to resolve the conflict. The Cochrane Collaboration's

Risk of Bias 2 (RoB 2) tool was used to assess the quality of randomized studies, categorizing each RCT as having low, high, or unclear risk of bias across five domains: selection, performance, detection, attrition, and reporting biases. Two reviewers (LF, FAT) independently evaluated each study, and any disagreements were resolved through discussion with the full review team.

Data extraction

Two independent reviewers (LF and DAT) systematically extracted data using pre-standardized data collection forms. These data encompassed publication characteristics (study title, author information, country of origin, and year of publication), study design characteristics (study type, methodology, total sample size, and follow-up duration), and baseline characteristics of the study population (inclusion criteria, age, and sex). Details of the intervention were also recorded, such as cardiac stem cell type, cell dose, route of administration, and timing of cell injection relative to MI onset. Clinical outcome measures related to efficacy, such as infarct size, scar mass, LVEF, LVESVi, LVEDVi, and the 6-minute walk test, were also extracted.

Statistical analysis

We analyzed infarct size, scar mass, LVEF, LVESVi, and LVEDVi using mean differences (MD) with 95% confidence intervals (CIs). The statistical analysis for between-group comparisons was performed using the inverse variance method. Due to variations in how the

primary outcomes were reported or calculated across studies, we used a random-effects model for the meta-analyses. Heterogeneity among trials was evaluated using the I^2 statistic. An I^2 value below 25% indicated low heterogeneity, values between 26% and 50% suggested moderate heterogeneity, values from 51% to 75% indicated substantial heterogeneity, and values above 75% reflected high heterogeneity. A p-value of less than 0.05 was considered statistically significant. Differences across studies were assessed based on sample size. All analyses were conducted using RevMan software version 5.4.

RESULTS

Search Strategy

Figure 1 illustrates the flowchart of the study selection process. The initial research identified 275 potentially relevant records after duplicates were removed. Following title and abstract screening, six full-text articles were retrieved for detailed assessment. Of these, two studies were excluded: one due to insufficient outcome data, and another because it represented a secondary analysis of an already included trial. As a result, four studies met the inclusion criteria and were included in the systematic review and meta-analysis [7, 9, 10, 11].

Quality Assessment

The risk of bias of the included RCTs was evaluated using the Cochrane Risk of Bias Tool 2.0 (RoB 2) for randomized controlled trials. Two reviewers (FAT, LA) independently assessed the risk of bias, and any disagreements were resolved through discussion with a third reviewer (LF). Inter-rater agreement was high, with a Cohen's kappa of 0.85, reflecting a substantial agreement. The risk of bias assessment using the Cochrane RoB 2 tool identified concerns in several of the included studies, primarily in Domain 3 (missing outcome data). The trials by Ostovaneh et al., Bolli et al., and Avilés et al. were rated as having some concerns because a proportion of patients without complete follow-up cardiac MRI, either due to loss to follow-up or inadequate image quality, ranged from approximately 10% to 20% of participants. (Figure 2).

Characteristics of Included Studies

All four randomized controlled trials that met the inclusion criteria were included in this review. The studies were published between 2009 and 2018 and were conducted in the United States ($n = 3$) and Spain ($n = 1$). Follow-up periods ranged from 6 to 12 months. Across the studies, the total number of participants was 178, with sample sizes varying from 25 to 124 individuals. The proportion of male participants was consis-

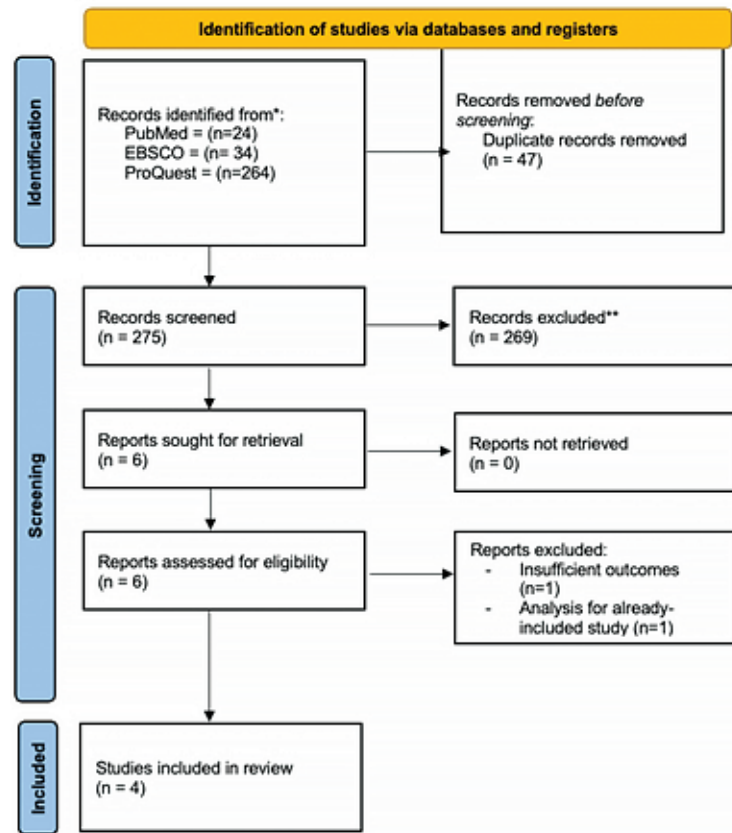


Fig. 1. PRISMA 2020 Flow Diagram of Included Studies

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Malliaras 2014	+	+	-	+	+	-
	Avilés 2018	+	+	+	+	+	+
	Bolli 2021	+	+	-	+	+	-
	Ostovaneh 2021	+	+	-	+	+	-

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 - Some concerns
 + Low

Fig. 2. RoB 2 Tool Risk of Bias Assessment

tently higher than that of female participants across all included studies [7, 9, 10, 11]. A detailed summary of the included randomized controlled trials, including study design, follow-up duration, type of cardiac stem cells utilized, inclusion criteria, participant characteristics, and study protocols for both intervention and control groups, is detailed in Table 1. Three studies utilized intracoronary delivery methods, while one study employed transendocardial injection. The types of stem cells varied: two studies used CDCs, one used allogeneic cardiac stem cells (CSCs), and one used c-kit-positive cardiac progenitor cells (CPCs). Inclusion criteria generally focused on patients with a history of myocardial infarction, left ventricular ejection fraction (LVEF) below 45%, and evidence of myocardial scar-

ring as detected by cardiac MRI. The timing of cell administration differed slightly among studies. In two trials (CADUCEUS trial and ALLSTAR trial), cell therapy was administered between 2 to 12 weeks post-MI [7, 11]. In the study by Avilés et al (CAREMI trial), the intervention was performed 5 to 7 days after reperfusion [9]. In the CONCERT-HF trial, CPCs were delivered by transendocardial injection in patients with chronic ischemic heart failure, without a specified interval from the index MI [10]. In ALLSTAR and CAREMI trials, the control groups received placebo infusions with delivery matched to intervention arms [9, 11]. In contrast, CADUCEUS and CONCERT-HF trials used standard care (guideline-directed medical therapy) without placebo administration [7, 10].

Table 1. Characteristic of the included studies

Study ID	Country and Study Period (Follow-up Duration)	Type of Cardiac Stem Cells	Inclusion Criteria	Participants			Study protocol	
				Groups n (%)	Age (mean)	M:F (male: female)	Intervention group	Control group
Makkar, et al	USA, 2009-2010 (6 months, 12 months)	Cardiosphere d-derived cells (CDCs)	<ul style="list-style-type: none"> Patients 2 weeks to 4 weeks after MI Had undergone successful PCI with resultant TIMI flow of 2 in the infarct-related artery Post infarction LVEF 25-45% 	I = 17 (68%) C = 8 (32%)	I = 54 C = 50.9	I = 17 : 0 C = 8 : 0	Intracoronary infusion of CDCs through the over-the-wire angioplasty catheter, with the balloon inflated at the (stented) site of the previous blockage in the infarct-related artery	Intracoronary infusion of placebo through the over-the-wire angioplasty catheter, with the balloon inflated at the (stented) site of the previous blockage in the infarct-related artery
Ostovaneh, et al	USA, 2014-2016 (6 months)	Cardiosphere d-derived cells (CDCs)	<ul style="list-style-type: none"> Patients 4 weeks to 12 weeks after MI Had undergone successful PCI with resultant TIMI flow grade 3 in the infarct-related artery Post infarction LVEF \leq 45% LV scar size 15% of LV mass by MRI 	I = 83 (67%) C = 41 (33%)	I = 54.7 C = 53.5	I = 72 : 11 C = 36 : 5	Intracoronary infusion of CAP-1002 (25 million human allogeneic CDCs) on day 0, at least 4 weeks after the index MI	Intracoronary infusion of placebo on day 0, at least 4 weeks after the index MI
Avilés, et al	Spain, 2014-2016 (6 months, 12 months)	Allogeneic Cardiac Stem Cells (CSCs)	<ul style="list-style-type: none"> Patients 18-80 years old, presented with STEMI and had a medium-high risk of developing chronic HF (LVEF \leq 45%, LV scar size 25% of LV mass) Had undergone successful PCI with TIMI flow grade 3 	I = 33 (67%) C = 16 (33%)	I = 56 C = 55	I = 8 : 4 C = 16 : 0	Intracoronary infusion of AlloCSC-01 in the culprit vessel performed 5 to 7 days after reperfusion using an over-the-wire coronary perfusion catheter	Intracoronary infusion of placebo in the culprit vessel performed 5 to 7 days after reperfusion using an over-the-wire coronary perfusion catheter

I = intervention group; C = control group. Abbreviations: MRI = Magnetic resonance imaging, MI = Myocardial infarction, PCI = Percutaneous coronary intervention, TIMI = Thrombolysis in myocardial infarction, LVEF = Left ventricular ejection fraction, HF = Heart failure, NYHA = New York Heart Association

META-ANALYSIS RESULT

Infarct size

Pooled analysis of the four RCTs showed a mean reduction in infarct size of -2.32% (95% CI: -3.91 to -0.73 ; $p = 0.004$) at 6 months in the cardiac stem cell group compared with placebo. Heterogeneity was low ($I^2 = 0\%$, $p = 0.43$) across the four included studies. Three studies reported smaller infarct sizes in the treatment group, with the largest contributions to the pooled estimate derived from the studies by Ostovaneh et al. and Bolli et al., both of which showed significant reductions. At 12 months, the pooled effect continued to favor cardiac stem cell therapy, but the difference was not statistically significant (mean difference -10.18% , 95% CI -21.48 to 1.12 ; $p = 0.08$), with high heterogeneity across studies ($I^2 = 93\%$).

Scar Mass

Pooled analysis of three trials reporting outcomes at 6 months demonstrated a significant reduction in scar mass of -4.25 g (95% CI -7.16 to -1.34 ; $p = 0.004$) in the cardiac stem cell group compared with placebo, with low heterogeneity ($I^2 = 0$) across studies. While some individual trials reported scar mass outcomes at 12 months, Ostovaneh et al. provided only 6-month data, resulting in an insufficient number of studies for a pooled 12-month analysis. Consequently, the available evidence for scar mass remains limited to the 6-month follow-up period.

Left ventricular ejection fraction, left ventricular end-systolic volume index, and left ventricular end-diastolic volume index

In contrast, pooled analysis of left ventricular ejection fraction (LVEF), left ventricular end-systolic volume index (LVESVi), and left ventricular end-diastolic volume index (LVEDVi) at 6 months showed no significant differences between the cardiac stem cell and placebo groups. The mean differences (MDs) were -0.77 (95% CI: -3.08 to 1.54 , $p = 0.51$) for LVEF, -2.00 (95% CI: -8.65 to 4.66 , $p = 0.56$) for LVESVi, and -3.11 (95% CI: -10.05 to 3.82 , $p = 0.38$) for LVEDVi. These findings indicate that cardiac stem cell therapy did not improve ventricular function after myocardial infarction. Heterogeneity was low ($I^2 = 25\%$ for LVEF; $I^2 = 0\%$ for LVESVi and LVEDVi). Similar results were observed at 12-month follow-up, with no significant improvement in any ventricular function parameters.

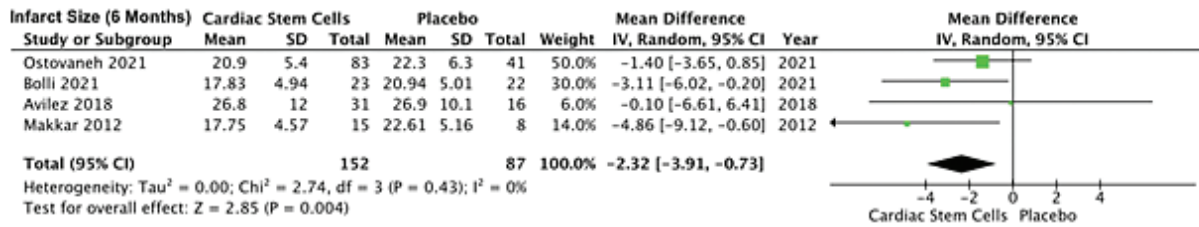


Fig. 3. Forest Plot of infarct size (%) after 6-month follow-up

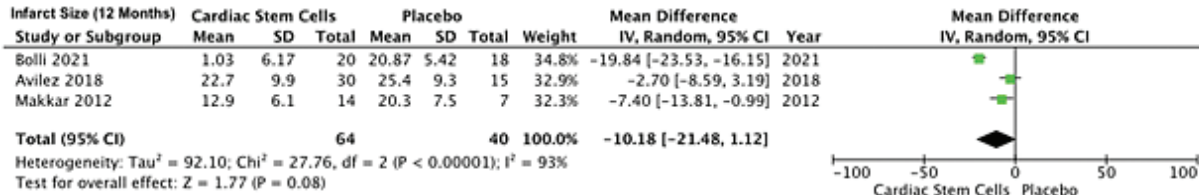


Fig. 4. Forest Plot of infarct size (%) after 12-month follow-up

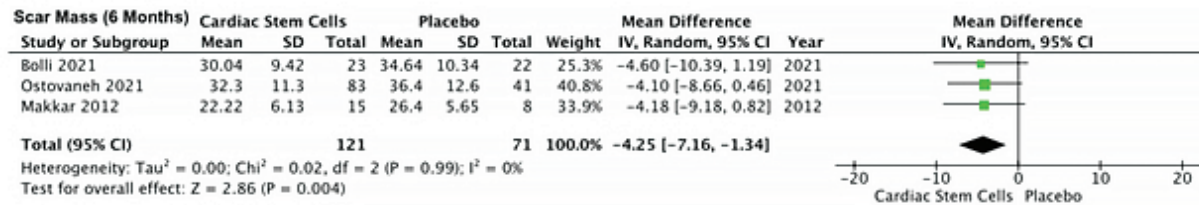


Fig. 5. Forest Plot of scar mass (g) after 6-month follow-up

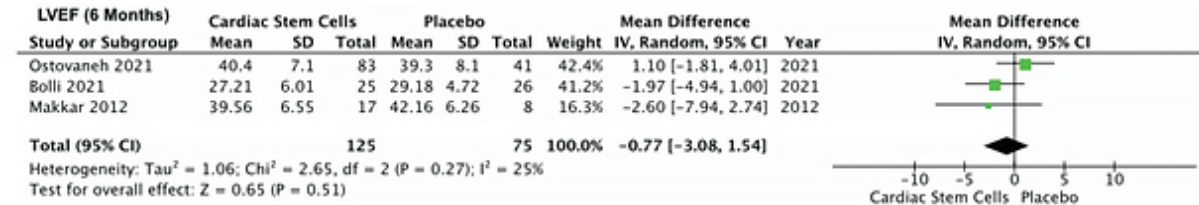


Fig. 6. Forest Plot of LVEF (%) after 6-month follow-up

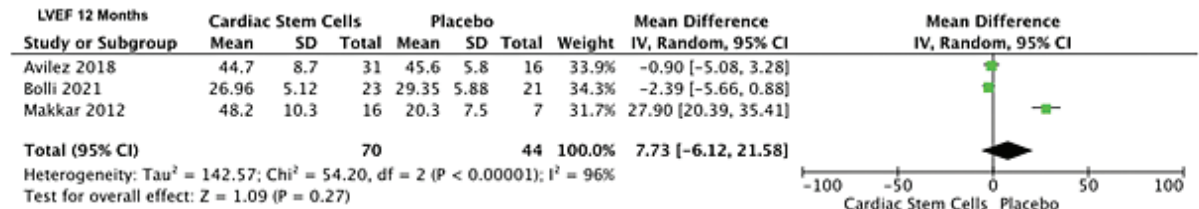


Fig. 7. Forest Plot of LVEF (%) after 12-month follow-up

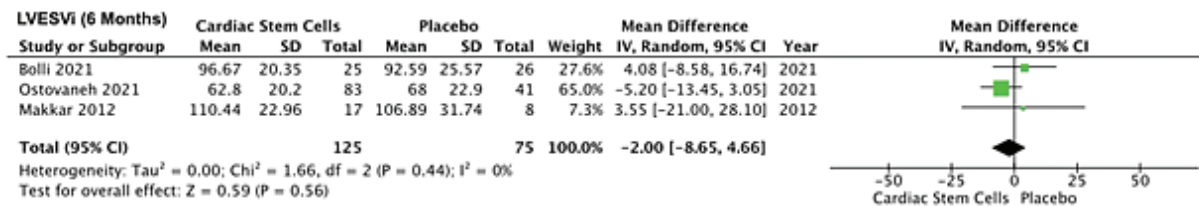


Fig. 8. Forest Plot of LVESVi (mL) after 6-Month Follow-Up

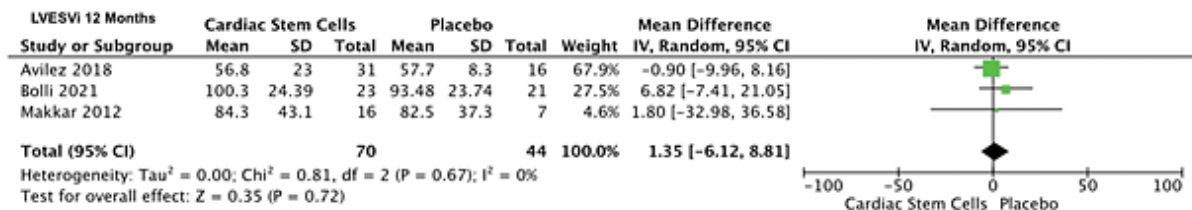


Fig. 9. Forest Plot of LVESVi (mL) after 12-month follow-up

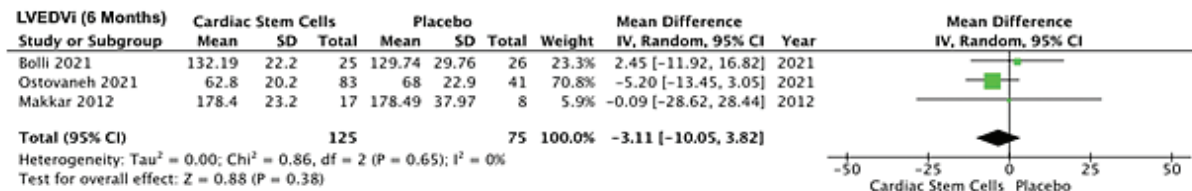


Fig. 10. Forest Plot of LVEDVi (mL) after 6-month follow-up

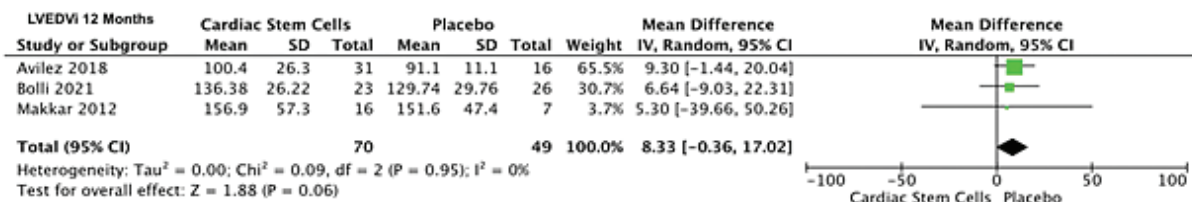


Fig. 11. Forest Plot of LVEDVi (mL) after 12-month follow-up

6-minute walk test

For the 6-minute walk test, the available data at 6 months were insufficient for pooled analysis, as Ostovaneh et al. did not report this outcome, and Avilés et al. did not evaluate it at that time point. At 12 months, the pooled analysis showed no significant difference in walking distance between the cardiac stem cell group and the placebo group (mean difference of 20.22 m, 95% CI: -20.28 to 60.73; $p = 0.33$), with low heterogeneity across studies ($I^2 = 0\%$).

DISCUSSION

The observed reduction in infarct size and scar mass at 6 months following intracoronary cardiac stem cell (CSC) therapy is supported by underlying biologi-

cal mechanisms. Rather than relying on long-term engraftment, CSCs, particularly CDC-like products, exert their effects mainly through a paracrine “secretome” rich in exosomes, microRNAs (such as miRNA-146a and miRNA-181b), and growth factors. These factors help preserve the regenerative properties of stem cells and create a more favourable environment within the infarcted tissue. They also exert anti-apoptotic effects on cardiomyocytes, stimulate fibroblasts to release vascular endothelial growth factor (VEGF) and stromal cell-derived factor 1 (SDF-1) for angiogenesis, and drive macrophages toward a reparative M2-like phenotype with increased IL-10 expression [5, 12]. These processes limit infarct expansion, enhance microvascular perfusion, and accelerate scar compaction mechanisms reflected by smaller infarct size and reduced scar mass on LGE-MRI [5, 12]. By 12 months, the ben-

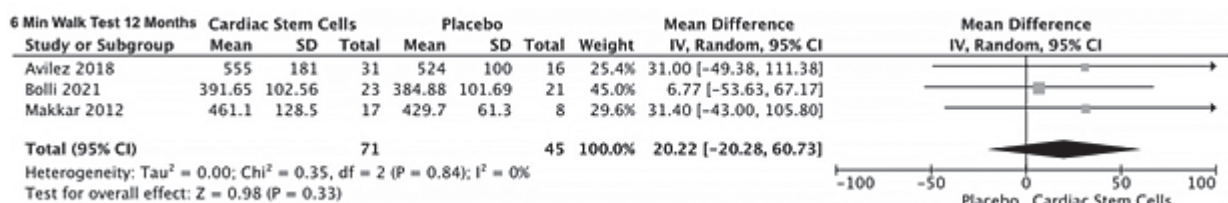


Fig. 12. Forest Plot of 6-minute walk test after 6-month follow-up

efit was no longer significant, which could be related to the limited retention of cells in the myocardium and the short duration of paracrine activity [5]. Additionally, natural infarct resorption and the impact of guideline-directed medical therapy in control groups likely diminish between-group differences over time [13]. Methodological heterogeneity, particularly in terms of cardiac stem cell type, dosing regimen, delivery route, timing of administration, and imaging protocols, further contributes to variability at longer follow-up [7, 9, 10, 11].

Despite these reductions in infarct size and scar mass, there were no significant changes in global cardiac function post-MI, such as LVEF, LVESVi, and LVEDVi. This is in accordance with the 1-year results report from the CADUCEUS trial, which reported that within 1-year follow-up, there was a decrease in scar mass; however, there was still no significant change in left ventricular function in the control group [7]. The mechanism of CDCs in reducing infarct size/scar mass is thought to originate from a paracrine effect that releases endogenous factors to be accepted by surrounding cells, which function as anti-fibrotic, anti-inflammatory, and pro-angiogenic, thereby reducing the size of fibrotic tissue [7]. However, left ventricular contractility did not appear to improve significantly, possibly because the paracrine effect of CDCs is mainly localized to the peri-infarct region, whereas most MI patients present with heterogeneous infarction across multiple segments [12, 14]. Consequently, global parameters such as LVEF, LVESVi, and LVEDVi are difficult to change [14]. In a preclinical study, Reich et al. reported that repeated administration of CDCs was associated with further reductions in infarct size/scar mass, preservation of LVEF, increased myocardial mass, and enhanced vessel density in a rat model of acute myocardial infarction. These findings suggest that the absence of significant functional improvement at later follow-up in clinical settings might be related to the lack of repeated dosing [15].

The adverse effects, or primary safety endpoints, of these four studies were reported as major adverse cardiac events (MACE). Overall, only a limited number of clinically significant events were observed. In the study by Avilés et al., three patients in the intervention group developed fever after intracoronary engraftment, and one experienced allergic dermatitis, while in the control group, one patient had a transient rash [9]. Malliaras et al. reported four severe adverse events in the CDC group: one case of acute myocardial infarction, two cases of chest pain, and one case of atrial fibrillation [7]. In the trial conducted by Bolli et al., 3.6% of patients who received CPCs required hospitalization for HF [10]. Importantly, none of the studies reported hemodynamic instability, myocarditis, ventricular tachycardia, ventricular fibrillation, or death [7, 9, 10, 11].

Most prior meta-analyses and RCTs of post-MI stem cell therapy have focused on mesenchymal or bone marrow-derived cells, whereas evidence for cardiac stem cells (CSCs) remains limited. This meta-analysis focuses exclusively on RCTs evaluating CSC therapy, a myocardium-derived cell type with mechanisms distinct from MSCs, thus potentially offering a greater impact on post-infarct remodeling. Several limitations should be acknowledged. Only four trials met the inclusion criteria, limiting statistical power and the precision of the effect estimates. Follow-up was relatively short, with most outcomes assessed at six months and only three studies extending to 12 months, leaving the long-term durability of benefits uncertain. Methodological variability was also notable, including CSC type (CDCs vs c-kit+ CPCs), dosing strategies, delivery routes, and timing of administration, which may have contributed to heterogeneity in the observed treatment effects [7, 9, 10, 11]. Furthermore, all included trials relied on a single-dose protocol. This may underestimate the therapeutic potential, as a preclinical study by Reich et al. suggests that repeat dosing can enhance infarct reduction, myocardial viability, and functional recovery compared with a single dose [15]. Most of the trials were single center with modest sample sizes, and outcomes were primarily based on surrogate imaging markers rather than hard clinical endpoints such as mortality, heart failure hospitalization, or MACE. The absence of standardized cell manufacturing and delivery protocols, together with limited data on repeated dosing, poses further challenges for reproducibility and clinical translation.

Future research should address these gaps through adequately powered, multicenter randomized trials with standardized cell processing and delivery methods, longer follow-up durations, and clinically relevant endpoints. Strategies to enhance efficacy, such as repeated dosing or improved myocardial cell retention, should also be systematically investigated. Incorporating advanced imaging for precise scar characterization and conducting patient-level meta-analyses may help identify subgroups most likely to benefit, thereby enabling a more personalized approach to CSC therapy.

CONCLUSION

Cardiac stem cell therapy is associated with a modest but consistent reduction in infarct size and scar mass at six months after MI, but without significant improvement in global ventricular function, and these benefits appear to attenuate by 12 months. In the current era of optimized PCI and guideline-directed medical therapy, CSC-based interventions may serve more as an adjunct than as a standalone treatment for preventing adverse remodeling. Future research should

prioritize large, multicenter trials with longer follow-up, standardized protocols, and hard clinical endpoints, while also exploring strategies such as repeated dosing and patient phenotyping to better identify those most likely to benefit.

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References

1. Martin SS, Aday AW, Almarzooq ZI et al. 2024 heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2024;149(8):e347-913. doi:10.1161/CIR.0000000000001190
2. Bahit MC, Kochar A, Granger CB. Post-myocardial infarction heart failure. *JACC Heart Fail*. 2018;6(3):179-86. doi:10.1016/j.jchf.2017.09.015
3. Broughton KM, Wang BJ, Firouzi F et al. Mechanisms of cardiac repair and regeneration. *Circ Res*. 2018;122(8):1151-63. doi:10.1161/CIRCRESAHA.117.312586
4. Leri A, Rota M, Pasqualini FS et al. Origin of cardiomyocytes in the adult heart. *Circ Res*. 2015;116(1):150-66. doi:10.1161/CIRCRESAHA.116.303567
5. Mehanna RA, Essawy MM, Barkat MA et al. Cardiac stem cells: current knowledge and future prospects. *World J Stem Cells*. 2022;14(1):1-21. doi:10.4252/wjsc.v14.i1.1
6. Kasai-Brunswick TH, Carvalho AB, de Carvalho AC. Stem cell therapies in cardiac diseases: current status and future possibilities. *World J Stem Cells*. 2021;13(9):1231-1248. doi:10.4252/wjsc.v13.i9.1231
7. Malliaras K, Makkar RR, Smith RR et al. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial. *J Am Coll Cardiol*. 2014;63(2):110-122. doi:10.1016/j.jacc.2013.08.724
8. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J* 2021 Mar 29;372. <https://doi.org/10.1136/bmj.n71>.
9. Fernández-Avilés F, Sanz-Ruiz R, Bogaert J et al. Safety and efficacy of intracoronary infusion of allogeneic human cardiac stem cells in patients with ST-segment elevation myocardial infarction and left ventricular dysfunction: a multicenter randomized, double-blind, and placebo-controlled clinical trial. *Circulation Research*. 2018 Aug 17;123(5):579-89.
10. Bolli R, Mitrani RD, Hare JM et al. A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial. *European journal of heart failure*. 2021 Apr;23(4):661-74.
11. Ostovaneh MR, Makkar RR, Ambale-Venkatesh B et al. Effect of cardiosphere-derived cells on segmental myocardial function after myocardial infarction: ALLSTAR randomised clinical trial. *Open Heart*. 2021 Jul 1;8(2):e001614.
12. Rafatian G, Davis DR. Concise review: heart-derived cell therapy 2.0: paracrine strategies to increase therapeutic repair of injured myocardium. *Stem Cells*. 2018 Dec 1;36(12):1794-803.
13. Pokorney SD, Rodriguez JF, Ortiz JT et al. Infarct healing is a dynamic process following acute myocardial infarction. *Journal of Cardiovascular Magnetic Resonance*. 2012 Jan 6;14(1):62.
14. Maltais S, Tremblay JP, Perrault LP, Ly HQ. The paracrine effect: pivotal mechanism in cell-based cardiac repair. *Journal of cardiovascular translational research*. 2010 Dec;3(6):652-62.
15. Reich H, Tseliou E, de Couto Get al. Repeated transplantation of allogeneic cardiosphere-derived cells boosts therapeutic benefits without immune sensitization in a rat model of myocardial infarction. *J Heart Lung Transplant*. 2016;35(11):1348-57.