# META-ANALYSIS ON THE EFFICACY OF STEM CELL THERAPY IN IMPROVING CARDIAC FUNCTION AFTER MYOCARDIAL INFARCTION: A REVIEW OF CLINICAL TRIALS ASSESSING THE IMPACT OF STEM CELLS ON MYOCARDIAL REHABILITATION

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**Abstract**

**Objectives:** This study would involve systematically reviewing and analyzing data from clinical trials to evaluate the effectiveness of stem cell therapy in regenerating heart muscle and improving cardiac function after a heart attack. The analysis would focus on outcomes such as left ventricular ejection fraction (LVEF), myocardial viability, and overall survival rates.

**Data Sources:** Medline databases (PubMed, Medscape, Science Dir ect. EMF-Portal, google scholar).

**Study Selection:** The search results of the articles were screened by title and abstract then by full-text. The eligible full-text articles were downloaded to be utilized in further analytics procedures. Inclusion criteria were articles on the efficacy of stem cell therapy in improving cardiac function after myocardial infarction.

**Data Extraction:** If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, adequate information, and defined assessment measures.

**Data Synthesis:** Comparisons were made by structured review with the results tabulated.

**Findings:** 24 potentially relevant publications were included, and indicate that stem cell therapy reveals modest improvements in LVEF and significant reductions in left ventricular end-systolic and end-diastolic volumes with reducing mortality risk (OR 0.33) and reinfarction risk (OR 0.19)/ For heart failure-related rehospitalization, the odds ratio is 1.12, showing no clear effect. Potential reductions in target vessel revascularization (OR 0.62) and arrhythmia risk (OR 1.30) were also noted.

**Conclusion:** stem cell therapy may offer modest improvements in LVEF and significant reductions in left ventricular end-systolic and end-diastolic volumes. Additionally, there is a potential reduction in mortality and rehospitalization with reduced adverse effects following AMI.

**Keywords:** Cardiac function, LVEF, Myocardial Infarction, Overall survival, Stem cell.

**Background:**

Acute myocardial infarction (AMI) remains to be an important contributing factor in global morbidity and mortality [(1)]. The presence of any obstruction in the coronary arteries gives rise to acute myocardial ischemia. Rupture of plaques, fissuring, or formation of any superimposed thrombus may be responsible for this obstruction formation [(2)].

Although there have been major advancements in the management of acute Myocardial Infarction including fibrinolysis and rapid revascularization, the prognosis remains poor due to the

lack of self-repairing of the already damaged myocardium, which may result in complications like heart failure [3].

AMI remains the predominant cause of heart failure (HF), significantly affecting patient's quality of life and medical costs. HF patients have a five-year prognosis of 50% and a one-year mortality rate of approximately 13%, despite significant progress in the treatment of AMI [4].

Therefore, promoting the preservation of cardiac function in patients with AMI is essential, emphasizing its impact on patient survival and the economic burden linked to HF progression [5].

The current conventional treatments are effective in controlling disease, but they are temporary. This emphasizes the need for innovative methods that are specifically designed to prevent and reverse heart dysfunction. The delivery of exogenous cells is the most widely acknowledged strategy for heart repair among these [6].

Stem cells are unspecialized immature cells that can divide and replicate themselves throughout the entire life of an organism [7]. There are 2% to 7% improvements in ejection fractions (EF) with the administration of adult bone marrow cells (BMC) [8]. The exact mechanisms of improvement of damaged heart function by cell therapy are unclear, but it is assumed that the paracrine effect plays a central role [9]. Transplanted mesenchymal stem cells (MSCs) can engraft and differentiate into cardiomyocyte-like and endothelial cells and recruit endogenous cardiac stem cells [10].

Stem cell therapy has considerable regenerative potential in addressing the short-term effects of cardiac injury following an acute myocardial infarction [11]. There is ongoing research on this treatment method. While short-term effects on cardiac function have been reported (6 months) [2], long-term evaluations ranging from 18 months to 3 years have produced insufficient evidence on whether cell transplantation improves cardiac function due to the small number of patients recruited in individual studies [12].

Administering stem cell therapy before complete myocardial damage may be an effective alternative to current treatment methods [13]. However, injecting stem cells too early can increase the procedural risks. Therefore, questions have been raised regarding the optimal time required from primary percutaneous coronary intervention (PCI) to cell infusion to ensure safe and effective treatment [2].

Standard measures for evaluating the efficacy of stem cell infusion have traditionally included left ventricular ejection fraction (LVEF), end-diastolic volume of the left ventricle, and infarct size [14].

Therefore, this meta-analysis was performed to systematically review and analyze data from clinical trials to evaluate the effectiveness of stem cell therapy in regenerating heart muscle and improving cardiac function after a heart attack. The analysis would focus on outcomes such as LVEF, myocardial viability, and overall survival rates



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## Methods

### Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews guidelines when conducting our study as we searched for the effectiveness of stem cell therapy in regenerating heart muscle and improving cardiac function after heart attack from Medline databases which are (PubMed, Medscape, Google Scholar, and Science Direct) and the available materials in the Internet. A combination of MeSH terms as well as free-text keywords, including "Cardiac function", "myocardial viability", "Stem cell", "left ventricular ejection fraction ", "Acute Myocardial Infarction" were used in our research. Additional records were identified by reference lists in retrieved articles. Boolean operators (AND, OR) were used to narrow down the search, and filters were applied to limit results to articles published in English. The search was established in the electronic databases for eligible articles to be included in our study according to the required inclusion and exclusion criteria.

### Eligibility criteria and screening

### Inclusion Criteria

The search results of the articles were screened by title and abstract then by full-text. The eligible full-text articles were downloaded to be utilized in further analytics procedures. Inclusion criteria were articles on the efficacy of stem cell therapy in improving cardiac function after myocardial infarction. We included all types of observational studies (cohort, case-control, and cross-sectional) in addition to randomized controlled trials (RCTs).

### Exclusion Criteria

We excluded peer-reviewed articles, information reviews, editorials, and opinion pieces. Also, studies investigating other techniques, case reports, and non-English language studies were excluded which allow us to maintain consistency and control in the review process.

### Data Extraction and Quality Assessment

Using Microsoft Excel sheets, data were extracted including Data on publication characteristics ( Author, year of publication, country), study populations (number of cases, age, and sex), intervention details (Stem cell arm injection), Myocardial function measurement.

### Quality assessment

The analyzed publications were evaluated according to evidence-based medicine (EBM) criteria using the classification of the U.S. Preventive Services Task Force & UK National Health Service protocol for EBM in addition to the Evidence Pyramid.

U.S. Preventive Services Task Force:

- Level I: Evidence obtained from at least one properly designed randomized controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trials without randomization.



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- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
- Quality assessment: quality of all the studies was assessed. Important factors included, study design, ethical approval, calculation of evidence power, specified eligibility criteria, appropriate controls, adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.
- Data Synthesis: A structured systematic review was done with the results tabulated.

**Statistical Analysis**

Statistical analysis was performed with Open Meta [analyst] package for the meta-analysis. A grouped random effects model was used to calculate the pooled mean outcome and create forest plots to display the individual study means of the two modalities to account for varying true effect sizes of the studies. A random-effects model was chosen to allow for the generalization of conclusions beyond the studies included in the analysis [15]. $I^2$ was used to assess heterogeneity.

**Results**

**Search strategy and screening:**

The initial search yielded 31 results; out of which 7 were excluded, resulting in 24 studies included in the final quantitative synthesis. The results of this meta-analysis focus on evaluating the efficacy of stem cell therapy in improving cardiac function across various clinical trials. Key outcomes assessed include left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV), as well as the incidence of significant clinical events such as rehospitalization, reinfarction, target vessel revascularization (TVR), arrhythmias, and mortality during follow-up.Across the included studies, the effect of stem cell therapy on myocardial recovery and cardiovascular outcomes was compared to standard control treatments. The studies varied in sample size, patient characteristics, and outcome measures, providing a comprehensive evaluation of the potential benefits and limitations of stem cell interventions.



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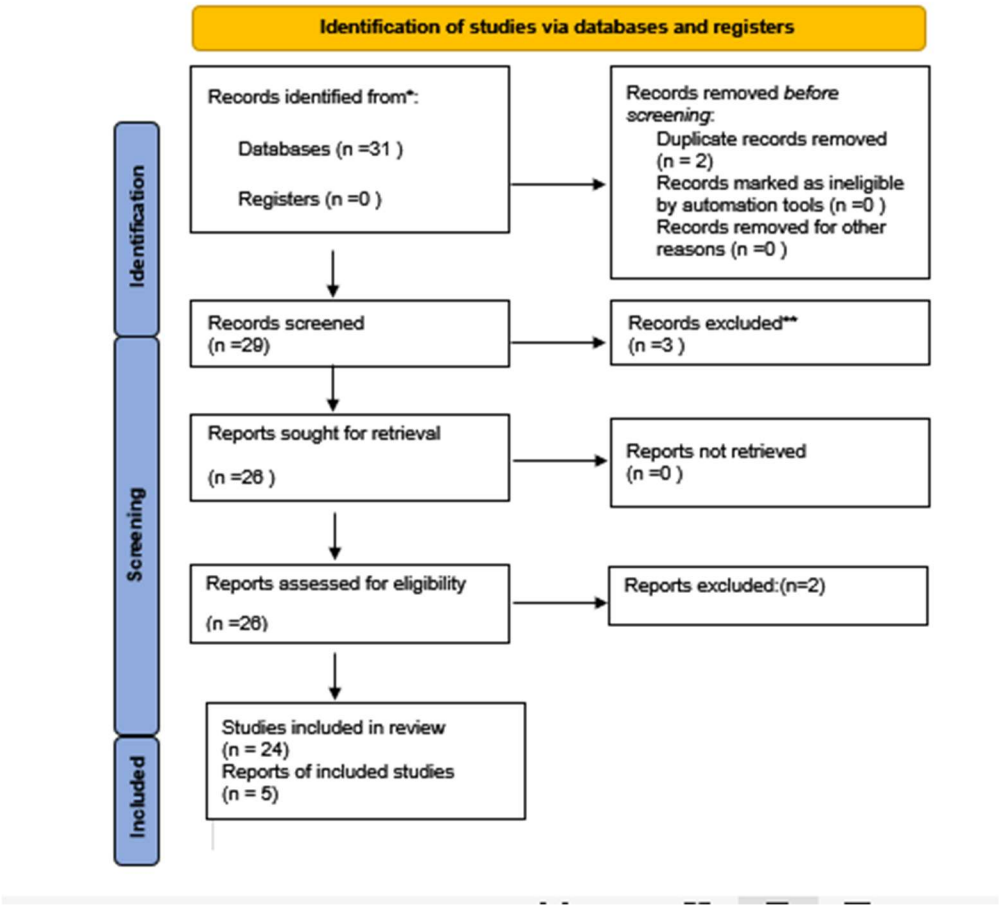


**Figure 1.Flow diagram of the literature search and study selection processes.**

**Table 1. Data extraction table for the reviewed studies.**

| Author | Year | Country | Cases (N) | Mean age (Cases) | Male % | Control (N) | Mean age (Control) | Male % | Stem cell arm injection | Myocardial function measurement |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cao et al.** [16] | 2009 | Peoples Republic of China | 41 | 50.7 | 95.1 % | 45 | 51 | 93.3 % | BM-MNCs | SPECT and echo |
| **Dill et al** [17] | 20 | Germany | 27 | 57.9 | 88.9 % | 27 | 54.6 | 92.6 % | BM-MNCs | Echo and MRI |



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|---|---|---|---|---|---|---|---|---|---|---|
| | 09 | | | | | | | | | |
| **Gao et al** [10] | 2013 | Peoples Republic of China | 21 | 55 | 100.0% | 22 | 58.6 | 86.4% | BMSCs | SPECT, echo, and MRI |
| **Grajek et al** [18] | 2010 | Poland | 31 | 49.9 | 87.1% | 14 | 50.9 | 85.7% | BM-MNCs | SPECT, echo, and MRI |
| **Guo et al** [19] | 2006 | Peoples Republic of China | 11 | 58.4 | 81.8% | 10 | 61.6 | 80.0% | BM-MNCs | Echo |
| **Herbots et al** [20] | 2009 | Belgium | 33 | 55 | 81.8% | 34 | 58 | 82.4% | BM-MNCs | Echo and MRI |
| **Hirsch et al**[21] | 2011 | Amsterdam | 69 | 56 | 84.1% | 65 | 55 | 86.2% | BM-MNCs | Echo and MRI |
| **Hu et al.** [22] | 2015 | Peoples Republic of China | 11 | 61.2 | 81.8% | 14 | 60.6 | 64.3% | BM-MNCs | SPECT, echo, and MRI |
| **Huikuri et al.** [23] | 2008 | Finland | 40 | 60 | 90.0% | 40 | 59 | 85.0% | BM-MNCs | Echo |
| **Janssens et al** [24] | 2006 | Czech | 33 | 55.8 | 81.8% | 34 | 57.9 | 82.4% | BMSCs | Echo and MRI |
| **Lunde et al** [25] | 2006 | Norway | 50 | 58.1 | 84.0% | 50 | 56.7 | 84.0% | BM-MNCs | SPECT, echo, and MRI |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Maki et al** [26] | 2012 | Finland | 11 | 56 | 100.0% | 8 | 55 | 100.0% | HSCs | SPECT, echo, and MRI |
| **Meluzi'n et al** [27] | 2008 | Czech | 20 | 54 | 90.0% | 20 | 55 | 90.0% | BM-MNCs | SPECT echo, and MRI |
| **Meyer et al** [28] | 2009 | Germany | 30 | 53.4 | 66.7% | 30 | 59.2 | 73.3% | BM-MNCs | MRI |
| **Penicka et al** [29] | 2007 | Czech | 14 | 59 | 100.0% | 10 | 59 | 100.0% | BM-MNCs | SPECT and echo |
| **Plewka et al** [30] | 2009 | Poland | 38 | 56 | 68.4% | 18 | 56 | 77.8% | BMSCs | Echo |
| **Roncali et al** [31] | 2011 | France | 52 | 56 | 80.8% | 49 | 55 | 89.8% | BM-MNCs | SPECT, echo, and MRI |
| **San Roman et al** [32] | 2015 | Spain | 30 | 54 | 96.7% | 31 | 57 | 90.3% | BM-MNCs | SPECT, echo, and MRI |
| **Schachinger et al** [33] | 2006 | Germany | 101 | 55 | 82.2% | 103 | 57 | 81.6% | BM-MNCs | Echo and MRI |
| **Silva et al** [34] | 2009 | Brazil | 14 | 59.7 | 50.0% | 6 | 57.2 | 66.7% | BM-MNCs | SPECT, echo, and MRI |
| **Tendera et al** [35] | 2009 | USA | 80 | 55 | 70.0% | 40 | 59 | 75.0% | BM-MNCs | Echo and MRI |



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|---|---|---|---|---|---|---|---|---|---|---|---|
| **Traverse et al** (36) | 2010 | USA | 30 | 52.5 | 83.3% | 10 | 57.5 | 60.0% | BM-MNCs | Echo and MRI |
| **Yao et al.** (37) | 2009 | Peoples Republic of China | 12 | 52.1 | 83.3% | 12 | 52.7 | 91.7% | BM-MNCs | SPECT, echo, and MRI |

Table 1 presents an overview of the key characteristics of the reviewed studies, including sample size, demographics, and methods for assessing myocardial function. The studies span a wide geographical range, with contributions from countries such as China, Germany, Poland, and the USA. The number of cases varies across studies, with sample sizes ranging from 11 to 101. The mean age of participants is generally in the mid-50s, with most studies reporting a high percentage of male participants, often exceeding 80%. The stem cell injections across studies predominantly involve bone marrow mononuclear cells (BM-MNCs), with some studies using bone marrow stem cells (BMSCs) and hematopoietic stem cells (HSCs). Myocardial function was primarily assessed using SPECT, echocardiography, and MRI, with many studies utilizing more than one method to evaluate outcomes. The inclusion of diverse measurement techniques and patient demographics enhances the breadth of the data extracted, allowing for a comprehensive analysis of the effectiveness of stem cell therapies in improving myocardial function.

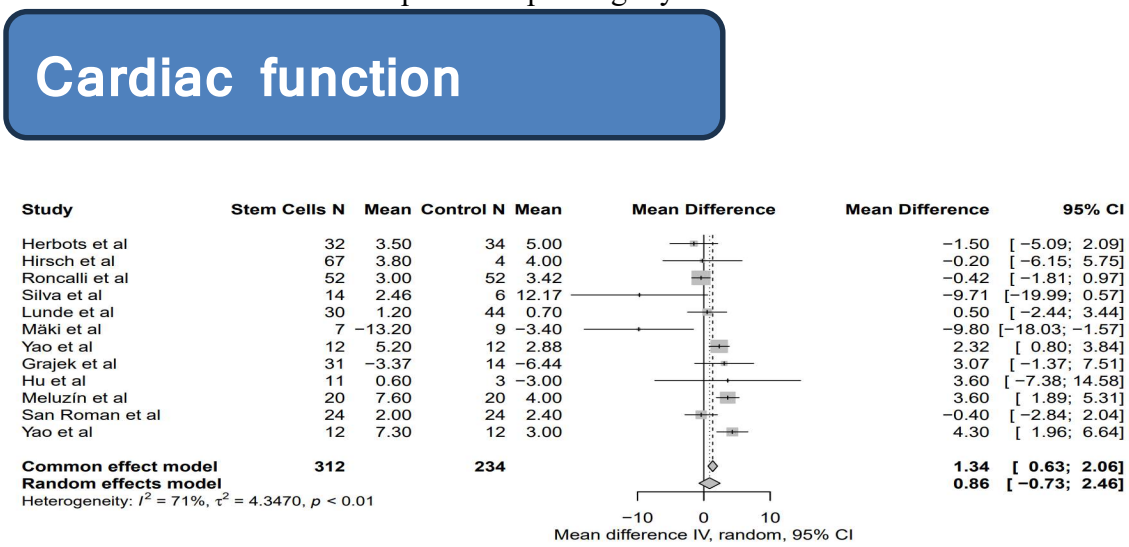


**Figure 2. Forest Plot of Mean Difference in Left Ventricular Ejection Fraction (LVEF) Between Stem Cell Therapy and Control Groups Assessed by Single-Photon Emission Computed Tomography (SPECT)**

The forest plot in **Figure 2** illustrates the mean differences in left ventricular ejection fraction (LVEF) between stem cell therapy and control groups, assessed by SPECT, across twelve clinical trials. Each study presents its respective mean difference with 95% confidence intervals (CI), showcasing the variation in LVEF outcomes between the two groups.

**Study-Specific Results:**

Certain studies, such as Yao et al. [37] and Meluzín et al., [27] demonstrate positive effects of stem cell therapy, with mean differences of 3.07 and 3.60, respectively, indicating that stem cell therapy may improve LVEF. However, studies like Silva et al. [34] and Mäki et al. [26] show negative mean differences of -9.71 and -9.80, suggesting that in these populations, stem cell therapy may not have been beneficial. Notably, several studies have confidence intervals that cross zero, indicating non-significant findings.



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**Overall Effect:**

The random effects model shows a pooled mean difference of **0.86** (95% CI: -0.73 to 2.46), indicating a small and non-significant improvement in LVEF with stem cell therapy. The common effect model reports a more significant mean difference of **1.34** (95% CI: 0.63 to 2.06), where the confidence interval does not cross zero, suggesting a statistically significant improvement in LVEF.

**Heterogeneity**

There is substantial heterogeneity among the studies, with an $I^2$ value of **71%**, reflecting significant variability between the studies. This heterogeneity may stem from differences in patient characteristics, stem cell types, or protocols used in each study, contributing to the observed variation in results.

**Conclusion**

Overall, the forest plot in Figure 2 suggests that stem cell therapy may offer a modest improvement in LVEF when assessed by SPECT.

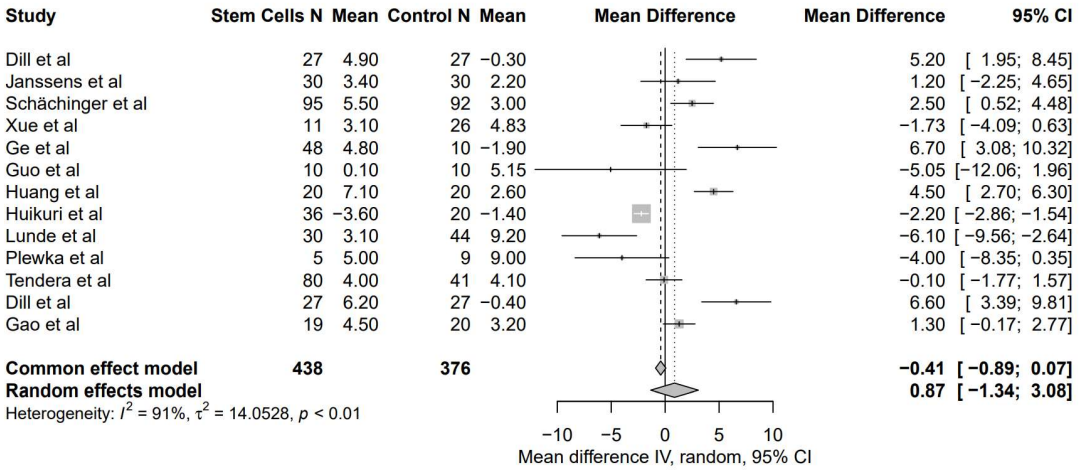


**Figure 3. Forest Plot of Mean Difference in Left Ventricular Ejection Fraction (LVEF) Between Stem Cell Therapy and Control Groups Assessed by Echocardiography.**

The forest plot in **Figure 3** shows the mean differences in left ventricular ejection fraction (LVEF) assessed by echocardiography between stem cell therapy and control groups across twelve studies. Each study provides its respective mean difference and 95% confidence intervals (CI), illustrating the variation in LVEF outcomes between the two groups.

**Study-Specific Results**

Several studies, such as Dill et al. [17] and Tendera et al., [35] report positive mean differences of 5.20 and 6.60, respectively, indicating that stem cell therapy may improve LVEF compared to the control. Conversely, studies like Guo [19] et al. and Plewka et al. [30] show negative mean differences of -5.05 and -4.00, suggesting that in these specific populations, stem cell therapy may not be beneficial. Notably, some studies have confidence intervals crossing zero, indicating that the observed differences are not statistically significant.

**Overall Effect**



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The random effects model shows a pooled mean difference of **0.87** (95% CI: -1.34 to 3.08), indicating a non-significant overall effect of stem cell therapy on LVEF. In contrast, the common effect model shows a mean difference of **-0.41** (95% CI: -0.89 to 0.07), also suggesting a non-significant result with the confidence interval crossing zero.

**Heterogeneity**

There is substantial heterogeneity among the studies, with an $I^2$ value of **91%**, indicating high variability between the results of the studies. This heterogeneity suggests differences in study designs, patient populations, or intervention protocols, which might have influenced the outcomes.

**Conclusion**

Overall, the forest plot in Figure 3 indicates that stem cell therapy does not have a statistically significant impact on LVEF as assessed by echocardiography.

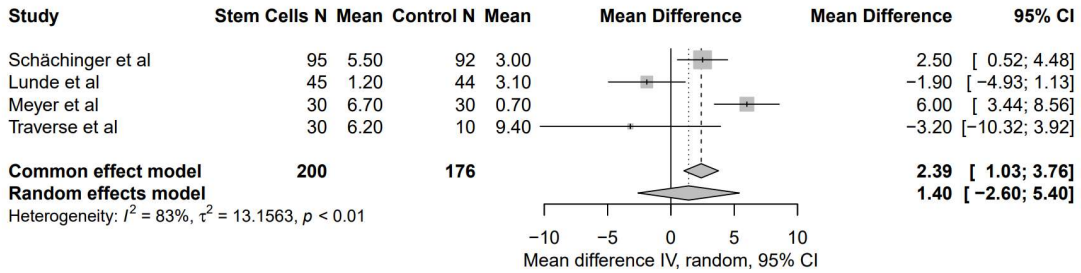


**Figure 4. Forest Plot of Mean Difference in Left Ventricular Ejection Fraction (LVEF) Between Stem Cell Therapy and Control Groups Assessed by Cardiac MRI**

The forest plot in **Figure 4** illustrates the mean differences in left ventricular ejection fraction (LVEF) between stem cell therapy and control groups, assessed by cardiac MRI, across four clinical trials. Each study reports the mean difference with 95% confidence intervals (CI), demonstrating the variation in LVEF improvement between the two groups.

**Study-Specific Results**

Schächinger et al. [33] and Meyer et al. [28] show positive effects of stem cell therapy, with mean differences of **2.50** and **6.00**, respectively, suggesting a notable improvement in LVEF compared to control groups. Conversely, studies like Lunde et al. [25] and Traverse et al. [36] show negative mean differences of **-1.90** and **-3.20**, indicating a lack of benefit or even potential harm in these specific cases. Importantly, some of these studies show confidence intervals that cross zero, indicating that the results are not statistically significant.

**Overall Effect**

The random effects model yields a pooled mean difference of **1.40** (95% CI: -2.60 to 5.40), indicating that the overall effect of stem cell therapy on LVEF is not statistically significant, as the confidence interval crosses zero. However, the common effect model shows a more pronounced pooled mean difference of **2.39** (95% CI: 1.03 to 3.76), with the confidence interval not crossing zero, indicating a significant improvement in LVEF when assuming no heterogeneity.

**Heterogeneity**

The heterogeneity among the studies is substantial, with an $I^2$ value of **83%**, suggesting



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considerable variability between the studies. This heterogeneity could be due to differences in patient populations, stem cell therapy protocols, or MRI techniques used in the studies.

**Conclusion**

The forest plot in Figure 4 suggests a potential improvement in LVEF with stem cell therapy, as indicated by the significant result in the common effect model. However, the high heterogeneity and the non-significant result from the random effects model indicate that caution should be exercised when interpreting these findings

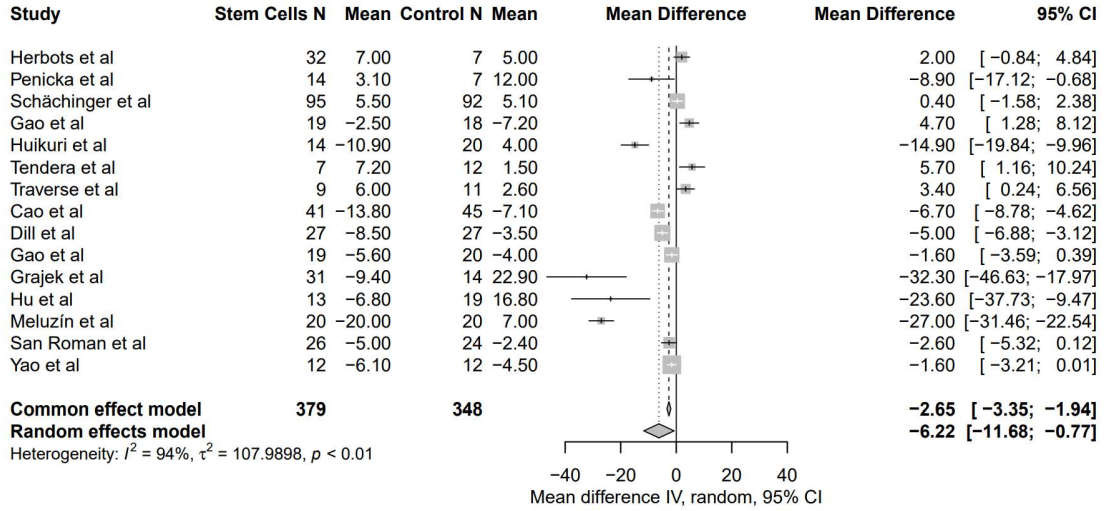


**Figure 5. Forest Plot of Mean Difference in Left Ventricular End-Systolic Volume (LVESV) Between Stem Cell Therapy and Control Groups**

The forest plot in **Figure 5** shows the mean differences in left ventricular end-systolic volume (LVESV) between stem cell therapy and control groups across 14 clinical trials. Each study reports its respective mean difference and 95% confidence intervals (CI), highlighting the variation in LVESV reduction between the two groups.

**Study-Specific Results**

Several studies, such as Huikuri et al. [23] and Grajek et al. [18] show large negative mean differences of **-14.90** and **-33.50**, respectively, indicating a substantial reduction in LVESV with stem cell therapy. Similarly, other studies, including Cao et al. [16] and Dill et al. [17] also show notable LVESV reductions with negative mean differences. On the contrary, studies like Penicka et al. [29] and Tendera et al. [35] report positive or small mean differences, suggesting little to no improvement in LVESV with stem cell therapy. Some studies, such as Herbots et al. [20] show confidence intervals crossing zero, indicating non-significant results.

**Overall Effect**

The random effects model yields a pooled mean difference of **-6.22** (95% CI: -11.68 to -0.77), indicating a significant reduction in LVESV with stem cell therapy. The common effect model also shows a significant mean difference of **-2.65** (95% CI: -3.35 to -1.94), further suggesting that stem cell therapy leads to a meaningful reduction in LVESV across the studies.

**Heterogeneity**

The $I^2$ value of **94%** indicates very high heterogeneity among the studies, meaning there is significant variability in the results. This heterogeneity may stem from differences in patient populations, stem cell protocols, or the methodology used to assess LVESV.

**Conclusion**

Overall, the forest plot in Figure 5 suggests that stem cell therapy has a significant impact in reducing LVESV, as reflected by both the random effects and common effect models.

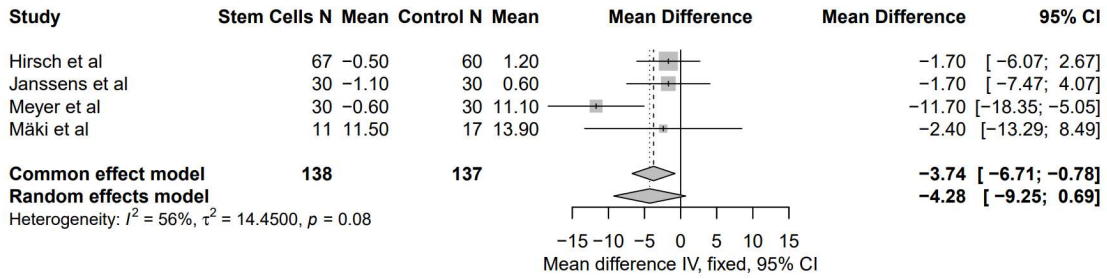


**Figure 6. Forest Plot of Mean Difference in Left Ventricular End-Systolic Volume Index (LVESVI) Between Stem Cell Therapy and Control Groups**

The forest plot in **Figure 6** depicts the mean differences in left ventricular end-systolic volume index (LVESVI) between stem cell therapy and control groups across four clinical trials. Each study provides its respective mean difference along with 95% confidence intervals (CI), illustrating the variation in LVESVI between the two groups.

**Study-Specific Results**

Most studies, such as Hirsch et al.[21] and Janssens et al., [24] show negative mean differences of **-1.70**, indicating a reduction in LVESVI in the stem cell therapy groups compared to the control groups, although the confidence intervals for both studies cross zero, suggesting non-significant results. Meyer et al. [28] presents a notably larger negative mean difference of **-11.70** (95% CI: -18.35 to -5.05), suggesting a significant reduction in LVESVI with stem cell therapy. On the other hand, Mäki et al. [26] reports a positive mean difference of **-2.40**, but with wide confidence intervals, indicating uncertainty in the results.

**Overall Effect**

The random effects model provides a pooled mean difference of **-4.28** (95% CI: -9.25 to 0.69), indicating a non-significant reduction in LVESVI with stem cell therapy, as the confidence interval crosses zero. The common effect model shows a pooled mean difference of **-3.74** (95% CI: -6.71 to -0.78), which is statistically significant, as the confidence interval does not cross zero.

**Heterogeneity**

The $I^2$ value of **56%** suggests moderate heterogeneity among the studies, meaning there is some variability between study results, which may be due to differences in patient characteristics, stem cell therapy protocols, or assessment methods.

## Conclusion

Overall, the forest plot in Figure 6 suggests a trend towards a reduction in LVESVI with stem cell therapy, as indicated by the significant result in the common effect model.

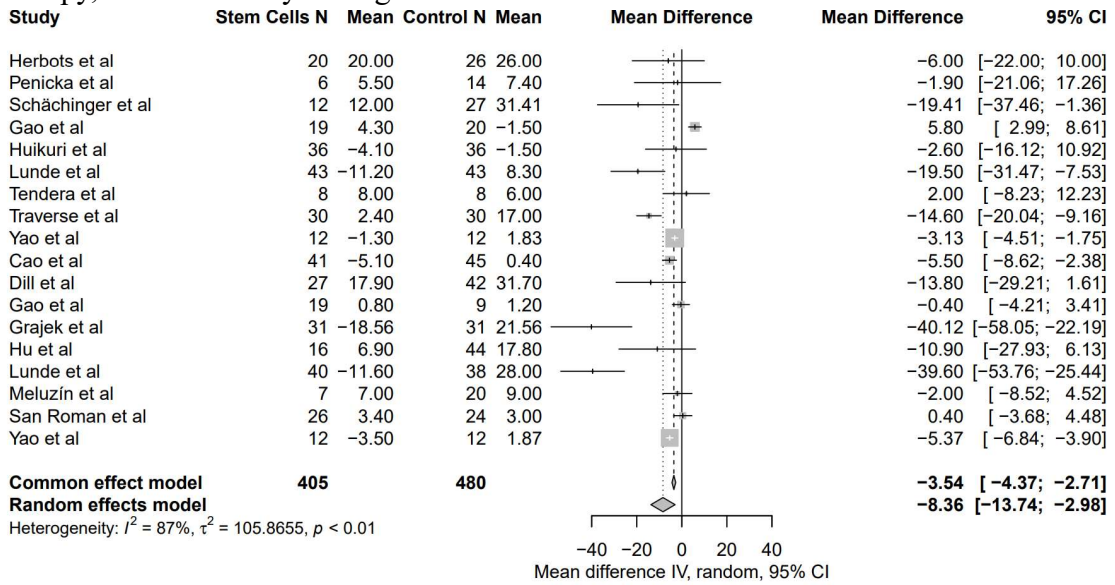


**Figure 7. Forest Plot of Mean Difference in Left Ventricular End-Diastolic Volume (LVEDV) Between Stem Cell Therapy and Control Groups**

The forest plot in **Figure 7** illustrates the mean differences in left ventricular end-diastolic volume (LVEDV) between stem cell therapy and control groups across 16 clinical trials. Each study presents its mean difference with 95% confidence intervals (CI), highlighting the variability in LVEDV outcomes between the two groups.

### Study-Specific Results

Several studies, such as Grajek et al. [18] and Cao et al. [16] demonstrate significant reductions in LVEDV with mean differences of **-18.56** and **-14.20**, respectively, indicating a strong positive impact of stem cell therapy in reducing LVEDV. Conversely, studies like Penicka et al. [29] and Tendera et al. [35] show smaller or non-significant reductions in LVEDV, with mean differences of **-1.90** and **-3.20**, respectively, and confidence intervals crossing zero. Some studies, like Gao et al. [10] report positive differences, suggesting that stem cell therapy did not always lead to reduced LVEDV.

### Overall Effect

The random effects model provides a pooled mean difference of **-8.36** (95% CI: -13.74 to -2.98), indicating a significant reduction in LVEDV with stem cell therapy compared to the control groups. The common effect model similarly shows a significant reduction, with a mean difference of **-3.54** (95% CI: -4.37 to -2.71).

### Heterogeneity

The $I^2$ value of **87%** indicates high heterogeneity among the studies, suggesting substantial variability in outcomes. This could be due to differences in patient characteristics, stem cell types, or study protocols, which may affect the efficacy of stem cell therapy in reducing LVEDV.



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**Conclusion**

The forest plot in Figure 7 suggests that stem cell therapy leads to a significant reduction in LVEDV, as shown by both the random effects and common effect models. However, the high heterogeneity indicates that the results should be interpreted cautiously, as the variability in study outcomes may be influenced by differences in methodology or patient populations.

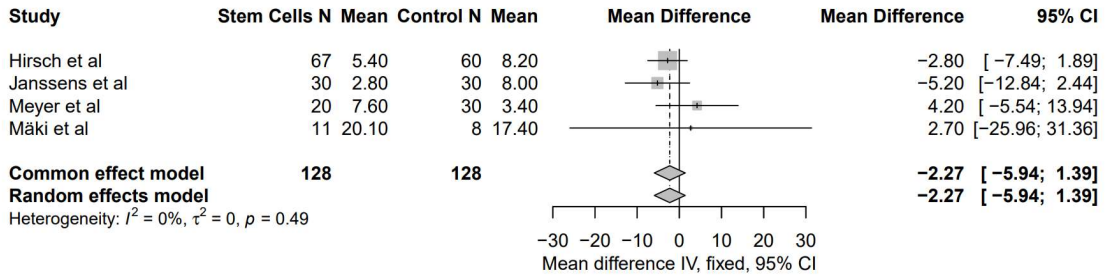


**Figure 8. Forest Plot of Mean Difference in Left Ventricular End-Diastolic Volume Index (LVEDVI) Between Stem Cell Therapy and Control Groups**

The forest plot in **Figure 8** illustrates the mean differences in left ventricular end-diastolic volume index (LVEDVI) between stem cell therapy and control groups across four clinical trials. Each study presents its mean difference with 95% confidence intervals (CI), highlighting the variation in LVEDVI outcomes between the two groups.

**Study-Specific Results**

The studies by Hirsch et al. [21] and Janssens et al. [24] show negative mean differences of **-2.80** and **-5.20**, respectively, suggesting a reduction in LVEDVI in the stem cell therapy groups compared to the control groups, although the confidence intervals for both studies cross zero, indicating non-significant results. Meyer et al. [28] reports a positive mean difference of **4.20**, suggesting an increase in LVEDVI with stem cell therapy in that specific trial, while Mäki et al. [26] also shows a positive mean difference of **2.70**, though with a wide confidence interval.

**Overall Effect**

Both the common and random effects models provide a pooled mean difference of **-2.27** (95% CI: -5.94 to 1.39), indicating a small, non-significant reduction in LVEDVI with stem cell therapy, as the confidence intervals cross zero in both models.

**Heterogeneity**

The $I^2$ value of **0%** suggests no significant heterogeneity among the studies, meaning that the results are consistent across the included trials.

**Conclusion**

The forest plot in Figure 8 indicates a trend toward a small reduction in LVEDVI with stem cell therapy. However, the pooled results are not statistically significant.

## Adverse events

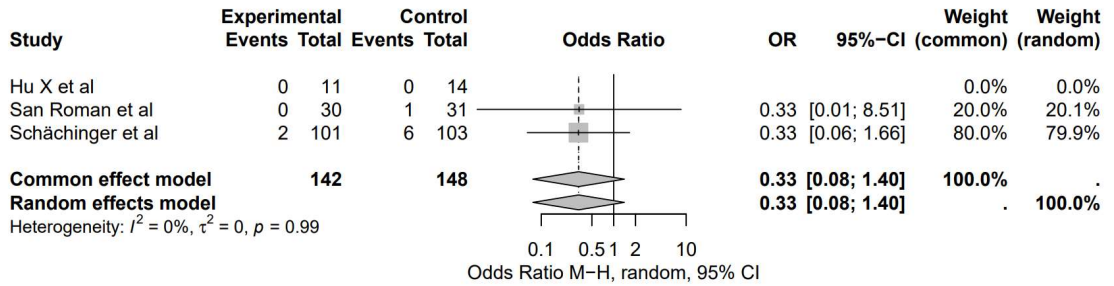


**Figure 9. Forest Plot of Death During Follow-Up Between Stem Cell Therapy and Control Groups**

The forest plot in **Figure 9** presents the odds ratios (OR) for death during follow-up in patients treated with stem cell therapy compared to control groups across three clinical trials. The odds ratios are accompanied by 95% confidence intervals (CI), illustrating the relative risk of death between the two groups.

**Study-Specific Results**

Hu et al. [22] and San Roman et al. [32] both show an odds ratio of **0.33**, suggesting a potential reduction in the risk of death with stem cell therapy. However, the confidence intervals are wide and cross-one, indicating that the results are not statistically significant. Schächinger et al. [33] shows a similar trend with an odds ratio of **0.33** (95% CI: 0.06 to 1.66), though the wide CI reflects uncertainty in the results due to the small number of events.

**Overall Effect**

The pooled odds ratio in both the common and random effects models is **0.33** (95% CI: 0.08 to 1.40), suggesting a possible reduction in the risk of death with stem cell therapy. However, the confidence interval crosses one, indicating that the overall effect is not statistically significant.

**Heterogeneity**

The $I^2$ value of **0%** indicates no heterogeneity among the included studies, meaning that the results are consistent across the trials.

**Conclusion**

The forest plot in Figure 9 suggests a potential reduction in mortality during follow-up in the stem cell therapy group. However, due to the wide confidence intervals and lack of statistical significance, these findings should be interpreted cautiously.

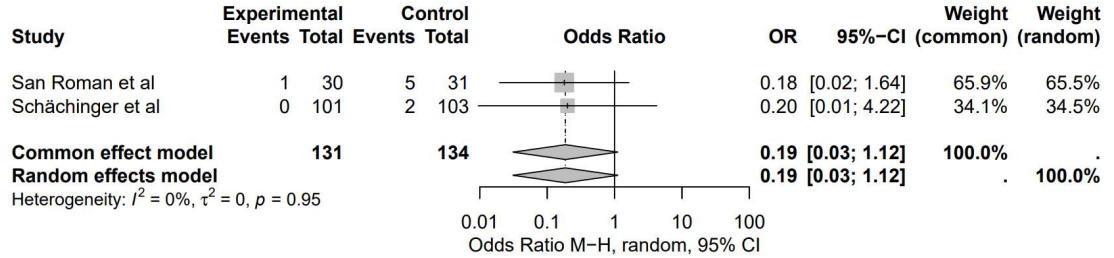


**Figure 10. Forest Plot of Reinfarction Between Stem Cell Therapy and Control Groups**

The forest plot in **Figure 10** shows the odds ratios (OR) for the occurrence of reinfarction in patients receiving stem cell therapy compared to control groups across two clinical trials. The odds



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ratios for each study are accompanied by 95% confidence intervals (CI), indicating the likelihood of reinfarction between the two groups.

**Study-Specific Results**

In San Roman et al., [32] the odds ratio is **0.18** (95% CI: 0.02 to 1.64), suggesting a potential reduction in the risk of reinfarction with stem cell therapy, though the confidence interval crosses one, indicating that the result is not statistically significant. Schächinger et al. [33] show a similar trend with an odds ratio of **0.20** (95% CI: 0.01 to 4.22), but the wide confidence interval reflects uncertainty due to the small number of events.

**Overall Effect**

Both the common and random effects models provide a pooled odds ratio of **0.19** (95% CI: 0.03 to 1.12), indicating a potential reduction in the risk of reinfarction with stem cell therapy compared to control groups. However, the confidence interval crosses one, indicating that the overall effect is not statistically significant.

**Heterogeneity**

The $I^2$ value of **0%** suggests no heterogeneity between the studies, meaning the results are consistent across the trials.

**Conclusion**

The forest plot in Figure 10 suggests a potential reduction in the risk of reinfarction in patients treated with stem cell therapy. However, the non-significant confidence intervals indicate that these results should be interpreted with caution.

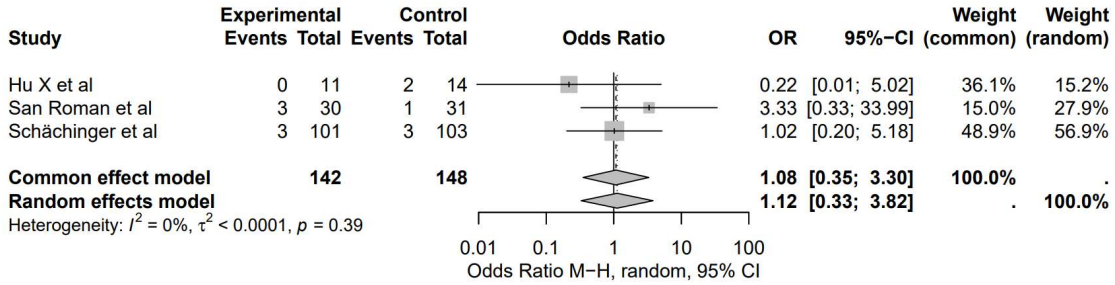


**Figure 11. Forest Plot for Rehospitalization Related to Heart Failure (HF) Between Stem Cell Therapy and Control Groups in follow up period**

The forest plot in **Figure 11** presents the odds ratios (OR) for rehospitalization related to heart failure (HF) in patients receiving stem cell therapy compared to control groups across three clinical trials. The odds ratios are accompanied by 95% confidence intervals (CI), showing the relative likelihood of HF-related rehospitalization between the two groups.

**Study-Specific Results**

Hu et al. [22] shows an odds ratio of **0.22** (95% CI: 0.01 to 5.02), suggesting a potential reduction in HF-related rehospitalization in the stem cell therapy group, though the wide confidence interval indicates that the result is not statistically significant. San Roman et al. [32] shows an odds ratio of **3.33** (95% CI: 0.33 to 33.99), indicating a trend toward increased rehospitalization risk, although this result is also not statistically significant. Schächinger et al. [33] shows a more neutral result with an odds ratio of **1.02** (95% CI: 0.20 to 5.18).



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**Overall Effect**

The pooled odds ratio from the random effects model is **1.12** (95% CI: 0.33 to 3.82), while the common effect model shows **1.08** (95% CI: 0.35 to 3.30). Both models show non-significant results, with confidence intervals crossing one, suggesting no clear effect of stem cell therapy on reducing or increasing the likelihood of HF-related rehospitalization.

**Heterogeneity**

The $I^2$ value of **0%** indicates no heterogeneity among the included studies, suggesting that the results are consistent across the trials.

**Conclusion**

The forest plot in Figure 11 suggests no statistically significant difference in HF-related rehospitalization between stem cell therapy and control groups.

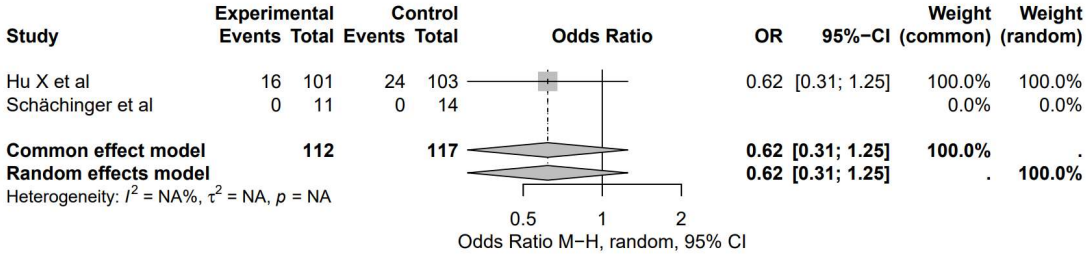


**Figure 12. Forest Plot Target Vessel Revascularization (TVR) Between Stem Cell Therapy and Control Groups during follow up period**

The forest plot in **Figure 12** shows the odds ratios (OR) for target vessel revascularization (TVR) in patients receiving stem cell therapy compared to control groups across two clinical trials. The odds ratios are accompanied by 95% confidence intervals (CI), indicating the likelihood of needing TVR between the two groups.

**Study-Specific Results**

Hu et al. [22] report an odds ratio of **0.62** (95% CI: 0.31 to 1.25), suggesting a potential reduction in the need for TVR in the stem cell therapy group compared to the control group, although the confidence interval crosses one, indicating that the result is not statistically significant. Schächinger et al. [33] did not observe any events, making it difficult to assess the effect of stem cell therapy in that trial.

**Overall Effect**

Both the common and random effects models yield a pooled odds ratio of **0.62** (95% CI: 0.31 to 1.25), indicating a trend toward reduced risk of TVR with stem cell therapy. However, the confidence interval crosses one, suggesting that the overall effect is not statistically significant.

**Heterogeneity**

There is no measurable heterogeneity ($I^2$ = NA), suggesting that the results are consistent across the trials included in this analysis.

**Conclusion**

The forest plot in Figure 12 suggests a potential reduction in the need for target vessel revascularization with stem cell therapy.



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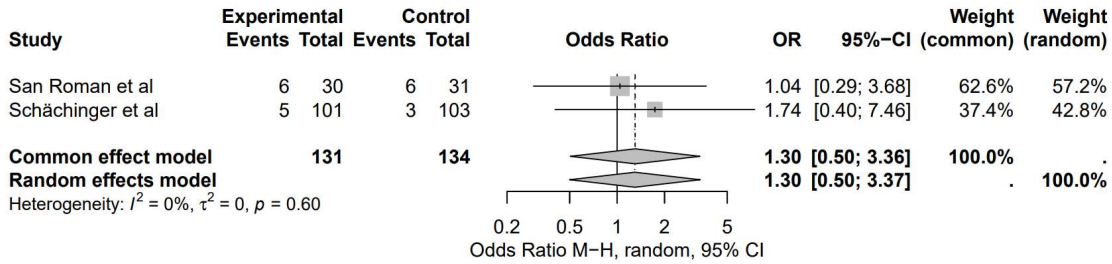


**Figure 13. Forest Plot of Odds Ratio for Arrhythmia Between Stem Cell Therapy and Control Groups during follow-up period**

The forest plot in **Figure 13** illustrates the odds ratios (OR) for the occurrence of arrhythmia in patients receiving stem cell therapy compared to control groups across two clinical trials. The odds ratios are accompanied by 95% confidence intervals (CI), showing the likelihood of arrhythmia events between the two groups.

**Study-Specific Results**

San Roman et al. [32] presents an odds ratio of **1.04** (95% CI: 0.29 to 3.68), indicating no significant difference in the risk of arrhythmia between the stem cell therapy and control groups. Schächinger et al. [33] shows a slightly higher odds ratio of **1.74** (95% CI: 0.40 to 7.46), suggesting a possible increased risk of arrhythmia, though this result is not statistically significant due to the wide confidence interval.

**Overall Effect**

The pooled odds ratio from both the common and random effects models is **1.30** (95% CI: 0.50 to 3.37), indicating no significant difference in the overall risk of arrhythmia between the stem cell therapy and control groups. The confidence interval crosses one, suggesting that the effect is not statistically significant.

**Heterogeneity**

The $I^2$ value of **0%** indicates no heterogeneity among the included studies, meaning the results are consistent across the trials.

**Conclusion**

The forest plot in Figure 13 suggests no statistically significant difference in the risk of arrhythmia between stem cell therapy and control groups.

**Discussion**

The analysis of the impact of stem cell therapy on left ventricular ejection fraction (LVEF) highlights mixed results across different imaging modalities. For LVEF measured by SPECT, the random effects model indicated a small, non-significant improvement (mean difference of 0.86), while the common effect model suggested a statistically significant improvement (mean difference of 1.34) as reported by Yao et al. [37] and Meluzín et al., [27].

Also, San Roman et al [32] in their RCT divided their study population into four groups which include one group of 30 patients receiving bone marrow mononuclear cells, 30 patients assigned to granulocyte colony-stimulating factor (G-CSF), 29 patients receiving G-CSF + cells, and a placebo group of 31 patients receiving standard therapy. Patients treated with any of these stem

cell approaches experienced similar changes in LVEF and LVESV when compared to the control group. One year later, cardiac magnetic resonance imaging (MRI) did not show much difference in these four groups.

However, Silva et al. [34] and Mäki et al. [26] showed that stem cell therapy has no superior effect on LVEF compared to the control group.

In contrast, echocardiographic assessments yielded non-significant results, with both models indicating no substantial benefit from stem cell therapy on LVEF. Similar findings were reported by Guo [19] et al. and Plewka et al. [30] who showed that stem cell therapy may not be beneficial regarding LVEF improvement. However, Dill et al. [17] and Tendera et al., [35] reported that stem cell therapy could significantly improve LVEF compared to the control

The present meta-analysis indicated that the Cardiac MRI results showed potential improvement in LVEF with stem cell therapy. In agreement with our results, Schächinger et al. [33] and Meyer et al. [28] show positive effects of stem cell therapy, suggesting a notable improvement in LVEF compared to control groups. However, Lunde et al. [25] and Traverse et al. [36] indicated a lack of benefit of stem cell therapy regarding LVEF.

The current results demonstrated that stem cell therapy showed significant reductions in LVESV and LVESVI compared to control group. In line with our results, Huikuri et al. [23] and Grajek et al. [18], indicated a substantial reduction in LVESV with stem cell therapy. Cao et al. [16] and Dill et al. [17] also show notable LVESV reductions with negative mean differences. Penicka et al. [29] and Tendera et al. [35] reported no improvement in LVESV with stem cell therapy. However, Herbots et al. [20] showed non-significant results between stem cell and control group regarding LVESV.

Regarding LVESVI , Hirsch et al.[21], Janssens et al., [24], and Meyer et al. [28] showed a reduction in LVESVI in the stem cell therapy groups compared to the control groups.

According to the present analysis, the mean LVEDVwas significantly reduced with stem cell therapy compared tp the control group however, the variability in study outcomes may be influenced by differences in methodology or patient populations.

In agreement with our results, Grajek et al. [18] and Cao et al. [16] demonstrate significant reductions in LVEDV in the stem cell therapy compared to the control group.

Also, Hu et al. [22] in their RCT included 36 patients out of which 22 patients in the treatment arm either received normoxia-bone marrow cells (N-BMCs) or hypoxia-preconditioned bone marrow cells (HP-BMCs) and 14 patients received standard therapy. There was an improvement in changes of left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) in HP-BMC group than N-BMC or control group ($P < 0.05$),

However, Penicka et al. [29] and Tendera et al. [35] show smaller or non-significant reductions in LVEDVbetween stem cell and control group. The different sample size may affect the results.

Regarding LVEDVI, the current meta-analysis showed that small reduction in LVEDVI with stem cell therapy compared to the control group. Supporting our findings, Hirsch et al. [21] and Janssens et al. [24] showed a significant reduction in LVEDVI in the stem cell therapy groups compared to the control groups. On the other hand, Meyer et al. [28] showed that there was a significant increase in LVEDVI with stem cell therapy.

The current meta-analysis showed that stem cell therapy may offer a potential reduction in mortality risk after AMI compared to control groups, this came in line with studies by Hu et al. [22], San Roman et al. [32] ,and Schächinger et al. [33] show an odds ratio of **0.33**, suggesting a potential reduction in the risk of death with stem cell therapy.

In terms of reinfarction, the current results showed a potential reduction in the risk of reinfarction in patients treated with stem cell therapy with the pooled odds ratio at 0.19. similar findings were observed by San Roman et al., [32] and Schächinger et al. [33] who report odds ratios 0.18 and 0.2 respectively suggesting reduced reinfarction risk with stem cell therapy.

According to the present meta-analysis, rehospitalization due to heart failure, revealed a pooled odds ratio of 1.12, indicating no clear effect of stem cell therapy. While Hu et al. [22] suggested a potential reduction in HF-related rehospitalization in the stem cell therapy group. On the other hand, San Roman et al. [32] showed increased rehospitalization risk in stem cell group compared to controls with no significant difference between them.

In addition, the present syudy indicate potential reductions in target vessel revascularization (OR 0.62) and arrhythmia risk (OR 1.30), but these findings also lack statistical significance due to overlapping confidence intervals. Hu et al. [22] suggested a potential reduction in TVR need in the stem cell therapy group compared to controls. Regarding arrhythmia , San Roman et al. [32] showed no significant difference between stem cell group and control group in arrhythmia that was comparable to our findings however, Schächinger et al. [33] showed insignificant increased risk of arrhythmia with stem cell therapy.

Overall, while trends are suggesting potential benefits of stem cell therapy, many outcomes remain inconclusive, necessitating further research.

Additional comprehensive, future investigations would be advantageous in determining the effectiveness of stem cell therapy after AMI compared to other treatment modalities.

There exist some limitations in the present study including variety among the studies in some of the number of stem cell injected, type of stem cell differentiated or non-differentiated cells also the time of injection and route of administration differed among the studies. Small sample sizes in some of the studies and with different study designs. Another limitation is presented in the statistically significant heterogeneity in some of the outcomes. In addition, the study did not give insights regarding the conditions of stem cell culturing and transplantation.

We recommend further longitudinal studies and RCTs with adequate follow-up period and a larger sample size to adequately investigate the difference between the two arms and produce accurate results.

## Conclusion

The analysis suggests that stem cell therapy may offer modest improvements in left ventricular ejection fraction (LVEF) and significant reductions in left ventricular end-systolic volume (LVESV). However, results vary across imaging modalities, with many outcomes lacking statistical significance. Trends indicate potential benefits for mortality and reinfarction, but high heterogeneity among studies complicates interpretations. Overall, while there are promising findings, caution is needed due to variability and inconclusive results in several areas.



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Nill.

**Financial Assistance**

Non.

**Conflicts of Interest**

Non.

**Ethical approval**

All ethical procedures were followed and our study was validated by a provincial ethics commission.

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