

Protocol

Mesenchymal Stem Cell Therapy for Acute Myocardial Infarction: Protocol for a Systematic Review and Meta-Analysis

Michael Vincent DiCaro^{*}, MD, MS; Brianna Yee^{*}, MD; KaChon Lei, MD; Kavita Batra, BDS, MPH, PhD; Buddhadeb Dawn, MD

Division of Cardiovascular Medicine, Department of Internal Medicine, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV, United States

^{*}these authors contributed equally

Corresponding Author:

Buddhadeb Dawn, MD

Division of Cardiovascular Medicine

Department of Internal Medicine

Kirk Kerkorian School of Medicine at UNLV

1701 W Charleston Blvd

Suite 230

Las Vegas, NV, 89102

United States

Phone: 1 (702) 671 2345

Email: buddha.dawn@unlv.edu

Abstract

Background: Medical therapy and interventional approaches have improved outcomes in patients with acute myocardial infarction (MI). However, these strategies are inadequate for replacing cells lost during tissue ischemia, thereby leaving behind noncontractile scar tissue. The anti-inflammatory and immune modulating properties of mesenchymal stem cells (MSCs) may prove useful in inducing functional cardiac regeneration following acute MI.

Objective: This is a protocol for systematic review and meta-analysis that will aggregate and synthesize high-level clinical data on the effects of MSC therapy for acute MI. The findings of this study may serve as evidence for clinicians and researchers in guiding the use of MSC therapy as an adjunct to reperfusion and optimal medical therapy in patients with acute MI.

Methods: The proposed systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews). A systematic search of bibliographical databases, including Embase, PubMed, and Cochrane was conducted from inception to June 2023 to identify English-language human studies with adult patients receiving MSC therapy and optimal medical therapy for acute MI in comparison with respective controls. Article screening was performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Data on functional cardiac outcomes and major adverse cardiac events were extracted and analyzed as primary outcomes.

Results: Literature search and article screening commenced in June 2023. Data extraction and analysis will be completed by October 2024. The findings will be synthesized and reported by the end of November 2024.

Conclusions: This systematic review and meta-analysis will summarize the best available updated evidence from published randomized controlled trials on the effects of MSC therapy for the treatment of acute MI. The findings of this systematic review and meta-analysis may shed light on the efficacy of MSC therapy in improving cardiac functional and structural parameters and reducing adverse cardiac events following acute MI.

Trial Registration: PROSPERO CRD42024522398; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=522398

International Registered Report Identifier (IRRID): DERR1-10.2196/60591

(*JMIR Res Protoc* 2025;14:e60591) doi: [10.2196/60591](https://doi.org/10.2196/60591)

KEYWORDS

mesenchymal stem cells; mesenchymal stromal cells; progenitor cells; acute myocardial infarction; outcomes; stem cell; myocardial; protocol; systematic review; meta-analysis; medical therapy; therapy; cardiac; efficacy

Introduction

Background

Acute myocardial infarction (MI) remains a significant cause of morbidity and mortality globally, with nearly 3 million people experiencing an acute MI annually worldwide [1]. During acute MI, blood flow to the myocardium is reduced, resulting in tissue hypoxia, ischemia, and eventual cell death, which in turn, may result in adverse consequences, including left ventricular (LV) dysfunction, heart failure, arrhythmias, cardiogenic shock, and death. Myocardial reperfusion with percutaneous coronary intervention is a standard treatment for acute MI. Time to reperfusion is directly correlated with prognosis; therefore, prompt revascularization should be pursued [2]. After reperfusion, patients receive optimal medical therapy, which has significantly improved outcomes since its advent [3]. However, reperfusion and medications are unable to replenish necrotic cardiac myocytes, and many patients still experience significant morbidity and mortality following acute MI [4]. Following significant tissue infarction, large areas of the myocardium are scarred and rendered nonfunctional, leading to the adoption of regenerative therapies as a possible solution.

Accordingly, regenerative therapies that aim to restore functional cardiac tissue continue to be a topic of clinical research interest. Recent evidence suggests that stem cells may be useful as a method of repairing damaged myocardial tissue [5,6]. In animal models, studies have shown the potential of Mesenchymal stem cells (MSCs) to differentiate into cardiac myocytes, to participate in regenerative signaling through immunomodulation, and paracrine actions [7-9]. So far, human clinical trials have yielded mixed results. Several randomized control trials (RCTs) in patients with acute MI have demonstrated improvement in LV ejection fraction (LVEF), remodeling, myocardial viability, and reduction in hospitalization rates following treatment with MSCs [10-13]. Conversely, other RCTs have shown no difference in LVEF between MSC-treated patients and the standard-of-care [14,15]. Concerns for safety has arisen with the novelty of regenerative therapy, and the evaluation of major adverse cardiac events (MACE) has been the hallmark for safety [10-15]. Particularly, mortality rates (periprocedurally and long-term), malignant arrhythmias, recurrent MI, cerebral vascular accident, and revascularization are among the most common evaluated adverse events [10-15]. Although with no significant difference was noted in previous RCTs, our meta-analysis aims to evaluate the safety of MSC therapy through the evaluation of MACE. There may be added benefit to decreasing MACE outcomes through the use of MSC therapy, which will also be evaluated.

While many clinical trials have examined the efficacy of MSCs in acute MI treatment, the data collection methods, timing of MSC administration, route of MSC administration, and evaluated end points have been heterogeneous. Several articles representing long-term follow-up of original studies have recently been published, which collectively provide additional insights. Aggregation and analysis of the updated data are needed to gain a better understanding of the effects of MSC administration in patients with acute MI.

Objectives

Several previous meta-analyses have been published on the outcomes of stem cell therapy for acute MI, however, these were based on studies with a heterogeneous mixture of stem cells, not exclusively MSCs. In addition, the existing meta-analyses included only original RCTs without the follow-up studies, thereby obscuring insights related to longer-term outcomes. The current systematic review aims to provide the most comprehensive and updated evidence regarding MSC transplantation solely for the treatment of acute MI, along with a meta-analysis focused specifically on RCTs, including follow-up RCTs to evaluate long-term outcomes of MSC therapy. The meta-analysis will compare the effects of MSC injection and standard therapy on LVEF, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and MACE as primary end points. Secondary end points will include, but not limited to, myocardial viability, myocardial perfusion defect, and stroke volume.

Methods

Review Question

This study aimed to answer the following question: “What are the short-term and long-term effects of MSC therapy in patients with acute MI?”

Eligibility Criteria

Inclusion and exclusion criteria were initially determined using the PECOS (Population, Exposure, Comparator, Outcome, Study Design) framework. Detailed PECOS criteria for the meta-analysis are denoted in [Multimedia Appendix 1](#).

The initial systematic review included RCTs, single-arm studies, and case series. The meta-analysis included RCTs and secondary reports based on the original studies. English-only original articles published before June 15, 2023, were included; case reports, abstract-only articles, systematic reviews, meta-analyses, animal studies, commentaries, position papers, opinions, and editorials were excluded from the meta-analysis. Studies enrolling adult patients aged 18 years and older with acute MI who received MSC therapy within 1 month of MI were included. Studies using MSCs, mesenchymal stromal cells, and mesenchymal progenitor cells as therapeutic substrates were included. Studies that included patients with recurrent MI in their study were excluded. Studies with other types of stem cells or combinatorial cellular mixtures were excluded. Studies that did not report the outcomes of interest were excluded.

Information Sources and Search Strategy

Bibliographic databases, including PubMed, Cochrane, and Embase were queried from inception to June 2023. The search strategy was guided by 2 librarian experts in medical sciences and was reviewed and devised in accordance with the Peer-Reviewed Electronic Search Strategy guidelines [16].

The original search strategy was formulated for PubMed and used PubMed syntax. Additional searches were modified and optimized for subsequent databases. Given the specificity of the question at hand, the search strategy used key search terms without the use of MeSH (Medical Subject Headings).

The full search strategy, including the development of the final search terms, can be found in Table S1 in the [Multimedia Appendix 2](#). Keywords in the final search strategy included the following: mesenchymal stem cell, progenitor cell, mesenchymal stromal cell, ST-elevation MI, ST-elevation myocardial infarction, and acute MI.

Selection Process

All retrieved articles were reviewed by 2 independent investigators to check for inclusion and exclusion criteria in a stepwise process to include title screening, abstract screening, and full-text screening. Reasons for the exclusion of articles will be addressed in greater detail in the final publication.

Study Records

Data Collection Process and Management

Data extraction from the eligible full-text articles was performed by 2 investigators who independently extracted the data elements of interest to ensure accuracy and completeness. Extracted data and records are maintained in separate Microsoft Excel sheets by the 2 investigators, as well as a combined Microsoft Excel sheet after consensus.

Incongruencies in data extraction were resolved through discussion with a third senior investigator to achieve consensus.

Data Items/Elements

Data extraction elements for both systematic review and meta-analysis are outlined in Table S2, which can be found in [Multimedia Appendix 3](#).

Information that required further clarification and/or required additional data were attempted to be resolved by contacting the

corresponding authors of the respective articles; queries that yielded no response were not included in the data extraction or analysis.

Outcomes

The primary outcomes of the meta-analysis included (1) effects of transplantation on LVEF, (2) LVESV, (3) LVEDV, and (4) MACE.

The secondary outcomes that included (1) myocardial viability, (2) myocardial perfusion defect index, (3) coronary flow reserve, (4) adenosine-induced minimal vascular resistance index, and (5) stroke volume.

Quality Analysis

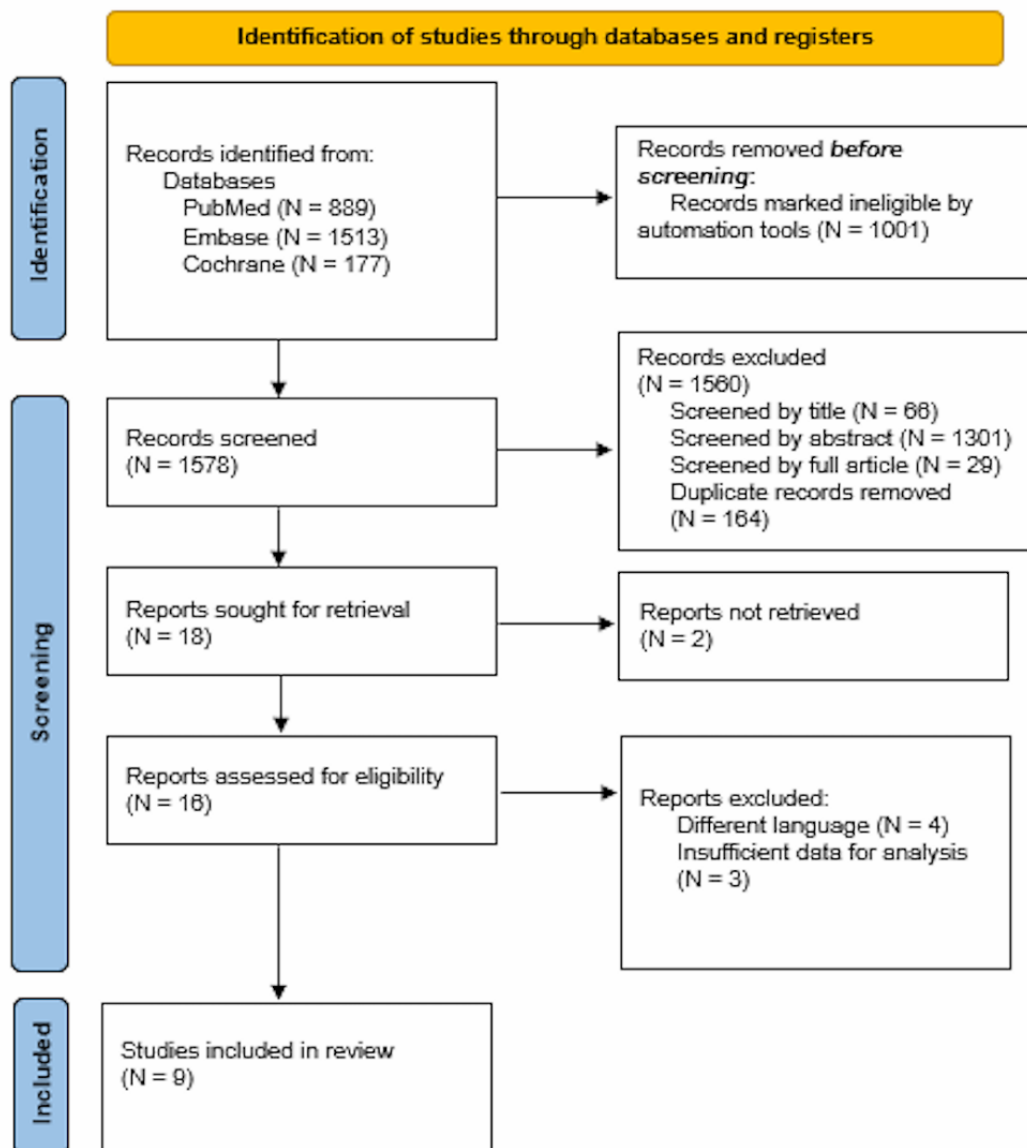
Overview

Quality assessments for strength of the body of evidence of all included studies will be performed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool. A total of 2 investigators will independently screen full texts for quality. Scoring will be performed independently. All essential components of original research studies will be evaluated using the NHLBI scoring checklist ([Multimedia Appendix 4](#)). Study quality will model the scoring protocol performed by Elks et al [17].

Risk of Bias Assessment

Within the quality assessment, articles selected for analysis underwent assessment for risk of bias. Bias was assessed by examining randomization and adequacy of randomization, blinding, and attrition. Specific questions are outlined in [Figure 1](#) below. Meta-biases will be assessed as appropriate.

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram modified for the current study selection process.



Data Synthesis

First results of all finally included studies will be described succinctly in the form of a summary table. A random-effects model will be used to calculate pooled estimates as this is a more robust estimate regardless of heterogeneity [18]. Cochran Q and I^2 statistics will be used as indicators of heterogeneity. The pooled estimates of the primary end points (eg, LVEF, LVESV, and LVEDV) will be calculated as the weighted mean differences with 95% CIs using the Comprehensive Meta-analysis Package (CMA version 3.0). For dichotomous outcomes, Peto odds ratios will be used as this allows the inclusion of the continuity correction of 0.5 to all 0 cells outcomes and accounts for the expected rarity of events. Sensitivity analysis will be conducted to identify studies that may severely affect the pooled estimates. The Exploratory subgroup analyses by different moderator variables (eg, MSC source, MSC route of administration, location of MI, and duration of follow-up, etc) will also be conducted to examine

sources of heterogeneity. A funnel plot and Egger linear regression test will be used to assess publication bias [19]. The significant level will be set as 2-sided and $P < .05$. Forest plots will be used to present the data.

Data Analysis and Presentation

Data will be presented in a tabular form and as a conclusive summary of our analysis. A data extraction form will be developed and agreed upon by all investigators before article analysis occurs. Selected articles will be present in the rows of the table, and variables will be present in the columns of the table. Quantitative analysis of all extracted variables will be performed.

Ethical Considerations

IRB or institutional review was not needed in this systematic review and meta-analysis since this design relies only on the findings from the previously published data and did not involve direct interaction with human participants. However, to adhere to a strict methodology, the protocol of this systematic review

and meta-analysis was registered with PROSPERO (International Prospective Register of Systematic Reviews) registration number CRD42024522398. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number

to the protocol that prevents duplication, thereby reducing reporting bias. In addition, PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist was completed during the process to ensure comprehensive and quality results (Figure 2).

Figure 2. PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist completed for the current study.

Section and topic	Item No	Checklist item	Completed? (Y or N)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Y
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Y
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	Y
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Y
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y

Results

The development of the search strategy for this systematic review and meta-analysis began in June 2023. The search strategy underwent peer-reviewed electronic search strategy review with 2 academic librarians in June 2023. The final search strategy was agreed upon by all investigators in July 2023. Databases were queried and articles were screened between September 2023 and October 2023. Data extraction took place between November 2023 and February 2024. Data analysis is currently taking place as of March 2024 with the final analysis anticipated to be completed in October 2024. It is anticipated

that findings will be synthesized and reported by the end of November 2024. Findings will be organized, summarized, and submitted for publication in a peer-reviewed journal. The goal of this work is to provide a comprehensive analysis and enhance the understanding of the safety and effectiveness of MSC therapy in acute MI. A timeline is provided in Table 1.

Preliminary searches performed in PubMed, Embase, and Cochrane databases yielded 1578 articles after appropriate filters were applied. A total of 889 articles were returned from PubMed, of which 521 were human studies. A total of 1,513 articles were returned from Embase, of which 880 were human studies. A total of 177 articles were returned from the Cochrane

database, which were all reviews of human studies (Figure 1). A detailed step-by-step outline of our search strategy, including

search terms, limit criteria, and results is provided in Table S1 of the Multimedia Appendix 2 (adapted from Page et al [20]).

Table 1. Timeline of project task completion.

Task	Jun 2023	Jul 2023	Aug 2023	Sep 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024	Mar 2024	Apr 2024	May 2024	Jun 2024	Jul 2024	Aug 2024	Sep 2024	Oct 2024	Nov 2024	
Design search strategy	✓	✓																	
Title screening			✓																
Abstract screening				✓															
Full-text screening			✓		✓														
Data extraction						✓	✓	✓	✓										
Synthesis and risk of bias assessment										✓	✓								
Data analysis										✓	✓	✓	✓	✓	✓	✓	✓	✓	
Abstract and manuscript drafting												✓	✓	✓	✓	✓	✓	✓	✓
Data dissemination																			✓

Discussion

Overview

This systematic review and meta-analysis will be a comprehensive review and analysis of the existing relevant literature pertaining to the efficacy of MSC therapy in patients enduring from acute MI. We anticipate that the current findings will be congruent with the previous observations regarding the outcomes and safety of MSC therapy. We also aim to glean insights with regard to changes in LVEF, LVESV, and LVEDV as a result of MSC therapy. In addition, we will examine the pooled event ratio estimates of MACE, including death, recurrent MI, need for revascularization, and stroke, compared with control, to draw conclusions on the safety of MSC therapy.

In an attempt to ensure the comprehensiveness of the assessment of relevant data, a narrative synthesis of studies that lie at relatively lower levels of hierarchical evidence as compared with the gold standard (RCTs) was also performed. These additional qualitative findings allow us to gain a complete understanding of several factors, including timing and route of administration, source of cells, and other variables that may impact the outcomes of MSC therapy.

Significance

We anticipate that our results, by virtue of including data from recently published RCTs, will significantly advance the existing evidence regarding the safety and efficacy of MSC therapy. Previous meta-analyses examining the effects of MSC therapy

in ischemic heart diseases often combined with chronic and acute ischemic heart diseases [21,22], whereas we plan to focus on acute MI therapy alone. In addition, previous meta-analyses reviewed a variety of regenerative cells [6] for the treatment of acute MI, whereas our focus specifically on mesenchymal stem and progenitor cells will allow us to comment on the efficacy of a specific cell type in the management of acute MI. Finally, while our meta-analysis examines primary RCTs, we have also included secondary/follow-up RCTs of original studies in our analysis, which will provide additional information regarding the longer-term and additional end points for subgroup analysis.

Limitations

This meta-analysis will have several limitations. First, there will be inherent heterogeneity among included studies due to the variability of research methodologies undertaken by each unique study. We anticipate heterogeneity in several variables, including the timing and route of MSC administration, the tissue source of MSCs, the methods used to measure primary and secondary end points (for example, echocardiogram vs angiography vs cardiac magnetic resonance imaging), and the follow-up period after MSC transplantation. Second, there is a risk that relevant literature will be missed because studies with insignificant findings or low sample size are seldom published, thus leading to publication bias. Finally, there will be inherent reviewer bias when selecting articles during the screening process, which will be mitigated by using an individualized screening process with 2 independent reviewers, along with a

third senior reviewer to resolve disagreements on article selection.

Dissemination Plan

The findings of this systematic review and meta-analysis will be submitted as a manuscript to a peer-reviewed journal by the end of 2024. Derivations of this work will be submitted as abstracts to academic conferences.

Conclusions

This systematic review and meta-analysis will provide a comprehensive review of the safety and efficacy of MSC therapy

in patients with acute MI. It will include an analysis of data on clinically relevant primary end points pertaining to functional cardiac parameters, such as LVEF, LVESV, and LVEDV. It will also examine specific safety outcomes by performing a subgroup analysis on MACE. This review will also provide qualitative synthesis of evidence related to MSC therapy, which will generate additional insights toward its potential future clinical applications in a broader spectrum of cardiovascular pathologies.

Acknowledgments

The authors would like to acknowledge the Ana Coral and Aidybert Weeks at the University of Nevada, Las Vegas Library for their assistance with developing the search strategy and for conducting the PRESS (Peer-Reviewed Electronic Search Strategy) review. The authors did not use AI for any portion of manuscript generation.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization was undertaken by MD, BY, and BD. Methodology and project administration was performed by MD, BY, KB, and BD. Formal analysis was handled by KB. Investigation, resources, and data curation was conducted by MD and BY. Writing-original draft preparation was performed by MD, BY, and KB. Writing-review and editing and visualization was conducted by MD, BY, KB, and BD. Supervision was handled by KB and BD.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The PECOS (P-Population; E/I-Exposure/Intervention; C-Comparator; O-Outcome; S-Study design) framework for the eligibility criteria.

[\[PNG File , 208 KB-Multimedia Appendix 1\]](#)

Multimedia Appendix 2

Full search strategy for utilized databases.

[\[DOCX File , 19 KB-Multimedia Appendix 2\]](#)

Multimedia Appendix 3

Elements included in data extraction for meta-analysis purposes.

[\[DOCX File , 18 KB-Multimedia Appendix 3\]](#)

Multimedia Appendix 4

National Heart, Lung, and Blood Institute scoring checklist.

[\[DOCX File , 16 KB-Multimedia Appendix 4\]](#)

References

1. Martin SS, Aday AW, Almarzooq ZI, Anderson C, Arora P, Avery C, et al. 2024 Heart disease and stroke statistics: a report of US and global data from the American heart association. *Circulation*. 2024;149(8):-567. [[FREE Full text](#)] [doi: [10.1161/cir.0000000000001209](https://doi.org/10.1161/cir.0000000000001209)]
2. Guerchicoff A, Brener SJ, Maehara A, Witzenbichler B, Fahy M, Xu K, et al. Impact of delay to reperfusion on reperfusion success, infarct size, and clinical outcomes in patients with ST-segment elevation myocardial infarction: the INFUSE-AMI Trial (INFUSE-Anterior myocardial infarction). *JACC Cardiovasc Interv*. 2014;7(7):733-740. [[FREE Full text](#)] [doi: [10.1016/j.jcin.2014.01.166](https://doi.org/10.1016/j.jcin.2014.01.166)] [Medline: [25060015](https://pubmed.ncbi.nlm.nih.gov/25060015/)]

3. Lee K, Han S, Lee M, Kim D, Kwon J, Park G, et al. Evidence - based optimal medical therapy and mortality in patients with acute myocardial infarction after percutaneous coronary intervention. *JAHA*. 2023;12(10):e024370. [doi: [10.1161/jaha.121.024370](https://doi.org/10.1161/jaha.121.024370)]
4. Kloner R, Dai W, Hale S, Shi J. Approaches to improving cardiac structure and function during and after an acute myocardial infarction: acute and chronic phases. *J Cardiovasc Pharmacol Ther*. 2016;21(4):363-367. [FREE Full text] [doi: [10.1177/1074248415616187](https://doi.org/10.1177/1074248415616187)] [Medline: [26612091](https://pubmed.ncbi.nlm.nih.gov/26612091/)]
5. Gill JK, Rehsia SK, Verma E, Sareen N, Dhingra S. Stem cell therapy for cardiac regeneration: past, present, and future. *Can J Physiol Pharmacol*. 2024;102(3):161-179. [FREE Full text] [doi: [10.1139/cjpp-2023-0202](https://doi.org/10.1139/cjpp-2023-0202)] [Medline: [38226807](https://pubmed.ncbi.nlm.nih.gov/38226807/)]
6. Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, et al. Adult bone marrow cell therapy for ischemic heart disease. *Circulation Research*. 2015;117(6):558-575. [doi: [10.1161/circresaha.114.304792](https://doi.org/10.1161/circresaha.114.304792)]
7. Ward MR, Abadeh A, Connelly KA. Concise review: rational use of mesenchymal stem cells in the treatment of ischemic heart disease. *Stem Cells Transl Med*. 2018;7(7):543-550. [FREE Full text] [doi: [10.1002/sctm.17-0210](https://doi.org/10.1002/sctm.17-0210)] [Medline: [29665255](https://pubmed.ncbi.nlm.nih.gov/29665255/)]
8. Gallina C, Turinetto V, Giachino C. A new paradigm in cardiac regeneration: the mesenchymal stem cell Secretome. *Stem Cells Int*. 2015;2015:765846. [FREE Full text] [doi: [10.1155/2015/765846](https://doi.org/10.1155/2015/765846)] [Medline: [26074978](https://pubmed.ncbi.nlm.nih.gov/26074978/)]
9. Gnechchi M, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. *Circulation Research*. 2008;103(11):1204-1219. [FREE Full text] [doi: [10.1161/circresaha.108.176826](https://doi.org/10.1161/circresaha.108.176826)]
10. Chen S, Fang W, Ye F, Liu Y, Qian J, Shan S, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol*. 2004;94(1):92-95. [doi: [10.1016/j.amjcard.2004.03.034](https://doi.org/10.1016/j.amjcard.2004.03.034)] [Medline: [15219514](https://pubmed.ncbi.nlm.nih.gov/15219514/)]
11. Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. *J Am Coll Cardiol*. 2009;54(24):2277-2286. [FREE Full text] [doi: [10.1016/j.jacc.2009.06.055](https://doi.org/10.1016/j.jacc.2009.06.055)] [Medline: [19958962](https://pubmed.ncbi.nlm.nih.gov/19958962/)]
12. Wang X, Xi WC, Wang F. The beneficial effects of intracoronary autologous bone marrow stem cell transfer as an adjunct to percutaneous coronary intervention in patients with acute myocardial infarction. *Biotechnol Lett*. 2014;36(11):2163-2168. [FREE Full text] [doi: [10.1007/s10529-014-1589-z](https://doi.org/10.1007/s10529-014-1589-z)] [Medline: [24975729](https://pubmed.ncbi.nlm.nih.gov/24975729/)]
13. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Kofoed KF, Haack-Sørensen M, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial. *Eur J Heart Fail*. 2020;22(5):884-892. [FREE Full text] [doi: [10.1002/ejhf.1700](https://doi.org/10.1002/ejhf.1700)] [Medline: [31863561](https://pubmed.ncbi.nlm.nih.gov/31863561/)]
14. Gao LR, Pei XT, Ding QA, Chen Y, Zhang NK, Chen HY, et al. A critical challenge: dosage-related efficacy and acute complication intracoronary injection of autologous bone marrow mesenchymal stem cells in acute myocardial infarction. *Int J Cardiol*. 2013;168(4):3191-3199. [doi: [10.1016/j.ijcard.2013.04.112](https://doi.org/10.1016/j.ijcard.2013.04.112)] [Medline: [23651816](https://pubmed.ncbi.nlm.nih.gov/23651816/)]
15. Chullikana A, Majumdar AS, Gottipamula S, Krishnamurthy S, Kumar AS, Prakash V, et al. Randomized, double-blind, phase I/II study of intravenous allogeneic mesenchymal stromal cells in acute myocardial infarction. *Cytotherapy*. 2015;17(3):250-261. [doi: [10.1016/j.jcyt.2014.10.009](https://doi.org/10.1016/j.jcyt.2014.10.009)] [Medline: [25484310](https://pubmed.ncbi.nlm.nih.gov/25484310/)]
16. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46. [FREE Full text] [doi: [10.1016/j.jclinepi.2016.01.021](https://doi.org/10.1016/j.jclinepi.2016.01.021)] [Medline: [27005575](https://pubmed.ncbi.nlm.nih.gov/27005575/)]
17. Elks W, Rooks A, Schulte S, Batra K, Burke J, Jain V. Resistance training in patients after metabolic and bariatric surgery: protocol for a systematic review. *JMIR Res Protoc*. 2023;12:e49513. [FREE Full text] [doi: [10.2196/49513](https://doi.org/10.2196/49513)] [Medline: [37995123](https://pubmed.ncbi.nlm.nih.gov/37995123/)]
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. [FREE Full text] [doi: [10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2)] [Medline: [3802833](https://pubmed.ncbi.nlm.nih.gov/3802833/)]
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. [FREE Full text] [doi: [10.1136/bmj.315.7109.629](https://doi.org/10.1136/bmj.315.7109.629)] [Medline: [9310563](https://pubmed.ncbi.nlm.nih.gov/9310563/)]
20. Page M, Moher D, Bossuyt P, Boutron I, Hoffmann T, Mulrow C, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. [FREE Full text] [doi: [10.1136/bmj.n160](https://doi.org/10.1136/bmj.n160)] [Medline: [33781993](https://pubmed.ncbi.nlm.nih.gov/33781993/)]
21. Lalu MM, Mazzarello S, Zlepzig J, Dong YY, Montroy J, McIntyre L, et al. Safety and efficacy of adult stem cell therapy for acute myocardial infarction and ischemic heart failure (SafeCell Heart): a systematic review and meta-analysis. *Stem Cells Transl Med*. 2018;7(12):857-866. [FREE Full text] [doi: [10.1002/sctm.18-0120](https://doi.org/10.1002/sctm.18-0120)] [Medline: [30255989](https://pubmed.ncbi.nlm.nih.gov/30255989/)]
22. Jeong H, Yim HW, Park H, Cho Y, Hong H, Kim NJ, et al. Mesenchymal stem cell therapy for ischemic heart disease: systematic review and meta-analysis. *Int J Stem Cells*. 2018;11(1):1-12. [FREE Full text] [doi: [10.15283/ijsc17061](https://doi.org/10.15283/ijsc17061)] [Medline: [29482311](https://pubmed.ncbi.nlm.nih.gov/29482311/)]

Abbreviations

- LV:** left ventricle
- LVEDV:** left ventricular end-diastolic volume
- LVEF:** left ventricular ejection fraction

LVESV: left ventricular end-systolic volume

MACE: major adverse cardiac events

MeSH: Medical Subject Headings

MI: myocardial infarction

MSC: mesenchymal stem cells

NHLBI: National Heart, Lung, and Blood Institute

PECOS: Population, Exposure, Comparator, Outcome, Study Design

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

PROSPERO: International Prospective Register of Systematic Reviews

RCT: randomized control trial

Edited by A Schwartz; submitted 15.05.24; peer-reviewed by YY Kristian; comments to author 18.09.24; revised version received 10.10.24; accepted 08.11.24; published 06.02.25

Please cite as:

DiCaro MV, Yee B, Lei K, Batra K, Dawn B

Mesenchymal Stem Cell Therapy for Acute Myocardial Infarction: Protocol for a Systematic Review and Meta-Analysis

JMIR Res Protoc 2025;14:e60591

URL: <https://www.researchprotocols.org/2025/1/e60591>

doi: [10.2196/60591](https://doi.org/10.2196/60591)

PMID:

©Michael Vincent DiCaro, Brianna Yee, KaChon Lei, Kavita Batra, Buddhadeb Dawn. Originally published in JMIR Research Protocols (<https://www.researchprotocols.org>), 06.02.2025. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on <https://www.researchprotocols.org>, as well as this copyright and license information must be included.