Evidence-based Guidelines for the use of Stem Cell Therapy

Cardiac Conditions



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DISCLAIMER

The Evidence-based Guidelines for the use of Stem Cell Therapy published by the MoHFW/DHR-DGHS provides recommendations made after careful consideration of the available evidence. This evidence has been synthesized by collation of systematic reviews (SR) and meta-analysis (MA) of the existing randomized controlled trials (RCTs) on well-defined review questions on the subject matter. The guideline reflects the best available data as per the criteria laid down for the study inclusion set by the guideline development group. Considerable care has been taken to ensure that the information contained in these guidelines is accurate, evidence-based and up-to-date at the time of publication. However, there is a possibility that new studies may have been published too late during the guideline development process or after publication and are not incorporated into the guideline.

ICMR-DHR, DGHS and its scientists, members of the Steering Group, GDG and systematic review teams disclaim all liability for the accuracy or completeness of the guideline. The team further disclaims all liability for any damages whatsoever (direct or indirect) arising out of the use or inability to use the information and procedures mentioned in this guideline. New studies in the future may lead to a revision in the existing recommendations. All MoHFW guidelines are subject to regular review and may be updated or withdrawn.

MESSAGE





In this evolving and promising landscape of modern medicine, stem cell therapy stands as one of the most dynamic areas of scientific enquiry. Its potential to revolutionize the treatment of a wide array of conditions, from degenerative diseases to traumatic injuries, has generated immense excitement and hope. Keeping the highest quality of evidence as the foundational base for formulating recommendations is of utmost importance.

The Evidence-based guidelines for the use of stem cell therapy represent a comprehensive synthesis of the best available evidence providing a framework for clinicians, researchers, and policymakers alike. Devised to support the responsible integration of stem cell treatment into clinical practice, these guidelines offer clear and transparent evidence-based recommendations that are based upon latest scientific knowledge backed by a rigorous methodology.

As we navigate the complexities of stem cell therapy, it is imperative that we balance innovation with caution. The guidelines aim to address this balance by emphasizing the importance of rigorous clinical trials, ethical considerations, and patient safety. In closing, we commend the contributors for their dedication in creating these evidence-based guidelines for the use of stem cell therapy and look forward to more such guidelines in the future.

Kajn Bill

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ACKNOWLEDGEMENTS

These Evidence-based Guidelines have come into existence due to the vision of MoHFW to develop one comprehensive guideline for the entire country based on the best available evidence. The current Evidence-based Guidelines on the use of Stem Cell Therapy were taken up by the DHR and DGHS to resolve the uncertainty associated with the effectiveness of stem cell therapy and help the practitioners in making informed decisions about the use of this intervention. The secretariat thanks the members of the Steering Group for spearheading the process of guideline development. We wish to extend our heartfelt gratitude to the members of the Guideline Development Group for being the driving force behind the recommendations formulated in these guidelines. The secretariat would also like to thank the systematic review teams for being the most vital pillar of this guideline by synthesizing evidence which formed the basis of the recommendations. The secretariat is also indebted to the guideline methodologists Dr. Kameshwar Prasad, Dr. Rakesh Lodha and Dr. M. Jeeva Sankar for their untiring inputs and efforts throughout the guideline development process.

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ABBREVIATIONS

BM	:	Bone Marrow
BMMCs	:	Bone Marrow Mononuclear Cells
BMSCs	:	Bone Marrow Stem Cells
CI	:	Confidence Interval
DCMP	:	Dilated Cardiomyopathy
DoIs	:	Declaration of Interests
EtD	:	Evidence to Decision
EoI	:	Expression of Interest
G-CSF	:	Granulocyte Colony Stimulating Factor
GDG	:	Guideline Development Group
GDT	:	Guideline Development Tool
GRADE	:	Grading of Recommendations Assessment, Development
		and Evaluation
LVEF	:	Left Ventricular Ejection Fraction
MACEs	:	Major Adverse Cardiovascular Events
MA	:	Meta-analysis
MCID	:	Minimal Clinically Important Difference
MD	:	Mean Difference
MI	:	Myocardial Infarction
6MWT	:	6 Minute Walk Test
NICE	:	National Institute for Health and Care Excellence
NYHA	:	New York Heart Association
OIS	:	Optimal Information Size
PBMCs	:	Peripheral Blood Mononuclear Cells
PICO	:	Population Intervention Comparison Outcome
RCTs	:	Randomized Controlled Trials
Re-MI	:	Recurrent-Myocardial Infarction
RoB2	:	Risk of Bias2
RR	:	Risk Ratio
SAEs	:	Serious Adverse Events
SMD	:	Standard Mean Difference
SRs	:	Systematic Reviews
WHO	:	World Health Organization

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EXECUTIVE SUMMARY

1. Background & Rationale:

Cardiovascular diseases are a major cause of morbidity and mortality worldwide. Most of the risk factors such as unhealthy diet, physical inactivity and tobacco use are modifiable and preventable. Lifestyle modifications, medications and cardiac revascularization procedures comprise the mainstay of treatment. Cardiac dysfunction is permanent in majority of the cases, necessitating the lifelong medication dependence. Stem cell therapy is an upcoming novel therapeutic approach that utilizes the unique properties of self-renewal and differentiation of stem cells, to regenerate or replace damaged cells and tissues in the human body. Stem cell therapy is lately being offered as a potential solution for some cardiovascular diseases like dilated cardiomyopathy and myocardial infarction. It is quintessential to take an evidence-based approach during the development of such regenerative therapies, with the best quality evidence being sought to determine the true effectiveness and efficacy of such approaches. The overall goal of these guidelines is to provide guidance and evidence-based recommendations for the use of stem cell therapy in two cardiological conditions: dilated cardiomyopathy (DCMP) and myocardial infarction (MI).

2. Target audience:

The recommendations in this guideline are intended to inform the policymakers, patients, health care professionals, especially cardiologists practicing in secondary and tertiary care centers as well as researchers and scientists regarding the efficacy and safety of stem cell therapy in the aforementioned disease conditions.

3. Guideline Development Methods:

The guideline was developed using standard methodology as described by international agencies like the WHO and NICE. This involved the creation of a steering group, a guideline development group (GDG) and systematic review teams. Briefly, the process involved: (i) Identifying priority review questions (PICOs), (ii) Evidence synthesis by systematic review & meta-analysis, (iii) Review of evidence profiles and grading the certainty of evidence (iv) Formulation of recommendations using the Evidence to Decision (EtD) framework (v) Drafting the guideline (vi) External review and (vii) Dissemination of guidelines. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to assess the certainty of evidence for each review question. The evidence generated was analyzed by the GDG to make judgments and formulate recommendations based on the EtD Framework provided in the GRADEpro GDT software. This included assessment of the effects (benefits to harms ratio) of the intervention, values and preferences of the patients, resources required, cost effectiveness, acceptability and feasibility of the intervention and equity considerations. In brief, the GDG members examined the evidence, made judgments in the EtD framework for each disease condition, and formulated the wording of the final recommendations. This was followed by external peer review before the final release of guidelines.

4. SUMMARY OF RECOMMENDATIONS:

S. No.	Key Question	Recommendation	Rationale/Justification					
1.	In patients with dilated cardiomyopathy (DCMP), what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is not recommended in routine clinical practice for the treatment of ischemic as well as non-ischemic dilated cardiomyopathy. Strength: Conditional# Certainty of Evidence: Very Low <i>#It may be used only in the context</i> of rigorously conducted randomized controlled trials.	There is very low certainty limited evidence of a trivial to small improvement in function and mortality. There is little or no difference in undesirable effects between stem cell therapy and usual care.					
2.	In patients with myocardial infarction (MI), what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is not recommended in routine clinical practice for the treatment of myocardial infarction. Strength: Conditional# Certainty of Evidence: Very Low <i>#It may be used only in the context</i> <i>of rigorously conducted</i> <i>randomized controlled trials.</i>	There is very low certainty evidence of trivial improvement in function and mortality. There is little or no difference in undesirable effects between stem cell therapy and usual care.					

I. GUIDELINE DEVELOPMENT PROCESS

1. Introduction:

A new process has been established in the MoHFW where in one comprehensive evidence-based guidelines have been jointly developed by DoHFW, DGHS and DHR using a rigorous and robust scientific process to bring clarity among stakeholders i.e. patients, clinicians, and the society in general. The generation of such evidence included collation of evidence from systematic review (SR) and meta-analysis (MA) of existing literature on well-defined review questions (PICOs). Finally, the evidence obtained from SR & MA was graded for its certainty using the GRADE approach. This grading was done to assess the certainty of evidence and formulate recommendations using the EtD framework. Such rigorously developed evidence-based guidelines have the potential to address the research to policy gap by translating the best available evidence of any healthcare intervention into practice (Figure 1).



Figure 1: Guideline Development Process – adapted from WHO¹

2. Rationale/ Scope:

The rapid advances in stem cell research have created high expectations in the field of cell-based therapies. Because of its regenerative potential, stem cell therapy has garnered significant interest among patients and practitioners. As a result, there has been rampant use of this experimental therapy despite limited knowledge of its safety and efficacy. Realizing that therapeutic applications

need to be based on rational and ethical premises, these guidelines aim to summarize the evidence available on the efficacy and safety of stem cell therapy to guide informed decisions.

The disease conditions included for review in the present guidelines are dilated cardiomyopathy (DCMP) and myocardial infarction (MI). DCMP and MI run a chronic disease course necessitating the few forms of lifelong pharmacologic therapy for all patients. These were selected based on the directives from the MoHFW and a review of literature on the therapeutic use of stem cell therapy in cardiological conditions. The guidelines aim to provide guidance for the responsible, safe, and effective use of stem cell therapy and highlight the research gaps at which future endeavors need to be targeted.

3. Target audience:

The recommendations in this guideline are intended to inform the policymakers, patients, health care professionals especially cardiologists practicing in secondary and tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the efficacy and safety of stem cell therapy in the aforementioned cardiological conditions.

4. Contributors:

The guideline was developed using standard methodology as described by international agencies like the WHO and NICE.^{1,2} This involved the creation of a steering group, a guideline development group and systematic review teams (List Annexure 1):

Steering Group: This group was jointly chaired by the Secretary, DHR & DG, ICMR and DGHS in overseeing the entire process of guideline development. The steering group identified priority disease conditions, helped in the formulation of GDG, reviewed the declaration of interest of members, reviewed the draft guidelines and managed the guideline publication and dissemination.

Guideline Development Group: This group was constituted to formulate review questions relevant for the guidelines for conducting systematic reviews for addressing the question, decide on the critical outcomes and formulate the recommendations based upon evidence generated by the systematic review teams. It is a multi-disciplinary group composed of methodologists, stem cell experts, subject experts, ethics expert, public health expert, pharmacologist, social scientist as well as patient group representatives. Potential members of the GDG were identified by the Steering Group based on the requisite technical skills and diverse perspectives needed for the formulation of the guidelines. These members were free from any conflict of interest in order to formulate unbiased recommendations. The subject experts, stem cell experts and methodologists provided critical inputs on the formulation of review questions in the PICO format. After completion of the systematic reviews, the evidence profiles were reviewed by the DHR secretariat and guideline methodologists with the help of subject experts. Finally, the GDG examined and interpreted the whole body of evidence and made judgments in the meetings using the GRADEpro EtD framework. **Systematic Review Teams:** These teams were commissioned to review and evaluate all available evidence in the form of randomized controlled trials (RCTs). The certainty of this evidence was assessed by the established GRADE criteria on the basis of risk of bias, imprecision, inconsistency, indirectness and publication bias.

External Reviewers: Relevant subject experts were identified to review the final guideline document and comment upon the clarity of the recommendations, validity of the justification provided for each recommendation and the completeness of evidence.

ICMR-DHR Secretariat: The secretariat was responsible for providing technical and administrative support in the entire process of guideline development.

5. Management of Conflict of Interests (CoIs):

All the GDG members need to be free from any conflict of interests in order to formulate the unbiased recommendations. A CoI is a set of circumstances that creates a risk that professional judgment given regarding a primary interest will be unduly influenced by a secondary interest. The primary interest in developing guidelines is improving quality of clinical care while secondary interests include all other interests that could be affected or potentially affected by a recommendation in the guideline and may be either financial or non-financial. Any kind of CoI is an important source of bias in the development of guidelines.

All the potential GDG members were asked to fill up the Declaration of Interests (DoIs) form that was adapted from the WHO.¹ These declarations were then reviewed by the steering group and managed appropriately. A summary of the DoIs and how they were managed is provided in Annexure 2.

6. Defining the Scope and Key Questions:

The steering group held a meeting on 11thApril 2023 with the potential GDG members to identify the priority disease conditions on which the efficacy and safety of stem cell therapy need to be reviewed. A list of 10 broad disease groups was finalized with a total of 28 conditions. For group of cardiology disease conditions myocardial infarction and dilated cardiomyopathy were included for review. Thereafter, the GDG held a meeting to decide on the key review questions relevant for the selected diseases in the PICO format i.e. Population Intervention, Comparator and Outcome. The outcomes that matter most to the concerned population were carefully selected and specified as critical outcomes for the guideline development. *These questions were formulated without keeping the literature in mind in order to obviate bias. Considering the scarcity of evidence for this experimental intervention, it was decided to keep the PICO question as broad as possible and do a subsequent subgroup analysis for the relevant subgroups as needed. These PICO questions are available in the respective disease section.*

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7. Systematic Reviews:

Commissioning of Systematic Reviews: Once the review questions were identified, the ICMR-DHR secretariat floated an EoI inviting the experts in the respective fields from all over the country to conduct systematic reviews and meta-analysis. Out of a total of 130 applications received, 28 teams were selected to conduct SRs and MA. The criteria for evaluation included methodological expertise, subject expertise, quality of systematic reviews published, database access, strength of team and CoIs, if any. The systematic reviews were thus commissioned, and all the teams were provided with the review questions in PICO format as finalized by the GDG. The ICMR-DHR secretariat and the methodologists provided oversight, including assessment and feedback on each SR protocol. The data extraction was checked to ensure uniformity and transparency in the entire process of guideline development.

Literature search strategy: To maintain a uniform methodology, all the SR teams were instructed to design the literature searches on the following databases: PubMed, Embase, Web of Science, and Cochrane CENTRAL. **Only randomized controlled trials were included in the systematic review.** No grey literature was included. However, hand-searching of references of relevant review articles was done. Non-English articles were excluded only if translation was not possible. Regarding 'Population,' for any disease condition, all the grades of severity were included, and subgroup analyses (if mentioned apriori in the protocol) was done wherever needed. All interventions that include well characterized stem cells or stem cell-derived products were included.

In addition, few conditions precluded the trial from being included in the final body of evidence in the evidence to decision framework. They were as follows:

- Flawed process of random sequence generation and/or concealment of allocation
- More than 30% of enrolled patients deviated from allocated intervention postrandomization
- Absence of stem cell characterization (flow cytometry or immunophenotyping or culture)

Therefore, the systematic review teams were asked to do a meta-analysis excluding such trials and the evidence produced thereafter was presented to the GDG.

Data extraction methods: Data extraction was conducted by the systematic review teams and reviewed by the ICMR-DHR secretariat and the methodologists. The teams were advised to use plot digitizer wherever feasible, if values were not available in text. Imputations and assumptions were avoided. All the methodological queries were resolved with the help of guideline methodologists and the teams were also advised to refer to the *Cochrane Handbook for Systematic Reviews of Interventions* to resolve any methodological queries.³While doing meta-analysis, the use of standardized mean difference (SMD) has to be minimized, as it is easier to interpret the mean difference (MD) regarding the minimal clinically important difference (MCID).

Risk of Bias Assessment: Risk of bias for each study outcome was assessed using the Revised Cochrane Risk of Bias-2 tool. For assessment, the following terms of reference were agreed upon by the GDG and provided to all the systematic review teams:

- Use only the RoB-2 Tool for assessment of the risk of bias of RCTs and mention the reasons for the risk of bias judgments for all the domains of the RoB-2 Tool.
- The downgrading of evidence due to the risk of bias judgment should be decided by the following criteria:
 - i. If >2/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as not serious in the GRADE Table.
 - ii. If 2/3rd-1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as serious in the GRADE Table.
 - iii. If <1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as very serious in the GRADE Table.
- The teams were asked to review the RCTs with extreme results in the pooled analysis cautiously, to search for any major methodological discrepancy.

The progress of the systematic review teams was monitored monthly, and queries were resolved by the secretariat after discussion with the methodologists.

8. Determination of Minimal Clinically Important Difference (MCID):

The minimal clinically important difference (MCID) is defined as the smallest change in any outcome that is considered as clinically meaningful or important by the patient and the health care providers. It is that difference at which a large set of clinicians will be willing to change their practice for this benefit and the certainty of evidence is rated in relation to this threshold. A thorough literature search was done to identify the MCIDs for each critical outcome. If multiple references were available for one outcome, the GDG deliberated and finalized one threshold for each outcome. In cases, where the MCID was not found in the literature, the thresholds were defined by the GDG. The criteria used for deciding the MCID were as follows: severity of the condition, maximum potential of improvement in the condition, how meaningful are the consequences of the improvement, risks associated with the treatment, and costs as well as feasibility of the treatment.

9. Grading of the certainty of the evidence:

The GRADE approach was used to access the certainty of evidence using the GRADEpro GDT software (https://www.gradepro.org/). At baseline, RCTs start with high certainty of evidence and this certainty can be downgraded based on pre-defined criteria like the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Publication bias was evaluated only if the number of studies for a particular meta-analysis were more than 10. In cases where the number of studies were less than 10, it was considered unvaluable. The SR teams completed their reviews and shared the evidence profiles with the guideline secretariat. The secretariat then reviewed the evidence profiles

with the help of guideline methodologists and any discrepancies in the review were resolved through discussion with the systematic review teams. The table below highlights the significance of the certainty of evidence as per GRADE.⁴

Certainty level	Significance
High	We are very confident that the true effect lies close to that of the
	estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is
	likely to be close to the estimate of the effect, but there is a possibility
	that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be
	substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is
	likely to be substantially different from the estimate of effect

10. Drafting of Recommendations using Evidence to Decision frameworks:

The Guideline secretariat prepared the draft EtD frameworks. The EtD Framework available on the GRADEpro GDT software was used to draft recommendations. It consists of a set of criteria that determine the strength and direction of a recommendation. These bring transparency in the formulation of recommendations and include the certainty of evidence, the balance between benefits and harms, the acceptability and feasibility of the intervention, patient values and preferences, equity considerations, resource use and cost effectiveness. Prior to drafting recommendations, all the GDG members were apprised of this framework and every criterion was explained in detail. The secretariat presented these frameworks along with a review of evidence profile and forest plots provided by the systematic review teams to the GDG.

11. Formulation of Recommendations:

The GDG members were asked to make judgments on each of the domain of the EtD framework based on the evidence presented to them. The judgments on the desirable and undesirable effects were based on the findings of the systematic reviews and meta-analysis. The review of literature/research evidence as well as the experience of the GDG members was used to inform the discussions pertaining to patient values and preferences, resource use and cost effectiveness, acceptability, feasibility of the intervention along with equity considerations. In cases where research evidence was unavailable, the opinion of the GDG was recorded in additional considerations. The entire body of evidence was put into the GRADE EtD framework for drafting the final recommendation for each review question. The voting for each domain was done through WhatsApp poll. Thorough discussions and deliberation were held on each of the domain with an aim to reach consensus on each judgment. Based on the voting for judgments for each domain, final voting was done to determine the strength and direction of the recommendation. The final recommendation for each disease condition was made by

consensus, defined as the agreement by 75% or more of the GDG members. Consensus was reached for all recommendations in this guideline and there were no strong disagreements. The GDG also identified caveats in the existing evidence and highlighted the areas for future research.

12. Strength of Recommendations:

The strength of a recommendation is the extent to which the GDG is confident in the balance between the desirable and undesirable effects of the intervention, across the range of patients for whom the recommendations are intended. When a GDG was very certain about this balance (for example the desirable effects clearly outweigh the undesirable effects), a strong recommendation in favor of an intervention or against the intervention was issued and vice versa. However, when the GDG was uncertain about this balance, a conditional recommendation was issued. *Owing to the experimental nature of the stem cell therapy, a separate column of "may be used only in the context of rigorously conducted randomized controlled trials" was added by the GDG in the Evidence to Decision framework of these guidelines.*⁵

13. Document preparation and peer review:

After the completion of the EtD meetings, the ICMR-DHR secretariat prepared a draft of the guideline document to accurately reflect the deliberations and decisions taken by the GDG. This draft was reviewed by the guideline methodologists followed by the external review group. The external reviewers were requested to comment upon the clarity of the recommendations so that there is no ambiguity about the decision among the end-users, validity of the justification provided for each recommendation, accuracy and completeness of the evidence (randomized controlled trials only). The steering group carefully evaluated the input of the GDG members and the comments by the external reviewers. The revisions to the draft document were done as needed, to correct for any factual errors and the document was finalized, thereafter.

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II. RECOMMENDATIONS

1. DILATED CARDIOMYOPATHY (DCMP):

A. BACKGROUND:

Dilated cardiomyopathy is a chronic disorder that leads to the enlargement of ventricles with impairment in contractility of cardiac muscles. It is one of the major causes of chronic heart failure and recurrent hospitalizations. It is multifactorial in etiology, major causes being genetic mutations, inflammation, autoimmune disorders and infections. Over the past decade the prevalence and mortality associated with DCMP has increased globally.¹

B. RECOMMENDATIONS:

Stem cell therapy is **<u>not recommended</u>** in routine clinical practice for the treatment of ischemic as well as non-ischemic dilated cardiomyopathy.

Strength: Conditional[#] Certainty of Evidence: Very Low

**It may be used only in the context of rigorously conducted randomized controlled trials.*

Rationale/Justification:

This recommendation has been made as there is very low certainty limited evidence of a trivial to small improvement in function and mortality. There is little or no difference in undesirable effects between stem cell therapy and usual care. Additionally, the follow up period is too small to comment on the side effect profile and long-term safety is also not known. Results should be interpreted with caution in view of few studies with low sample size and/or events.

C. SUMMARY OF EVIDENCE:

Key question: In patients with dilated cardiomyopathy, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included studies: A total of 4285 studies were identified in the initial search from various databases. Out of these, 962 were found to be duplicates, leaving 3323 articles for title and abstract screening. Among these, only 201 articles were eligible for full-text screening. These selected articles were retrieved for full-text review, and after full-text screening, 9 met the criteria for final inclusion in this study. Additionally, 2 articles were also found through a citation search. In total, 11 articles were finally included in the review.²⁻¹² The study by Pincott et al. 2017 has been excluded from the meta-analysis due to inclusion of only pediatric population.¹²

The studies predominantly comprised randomized trials with varying designs, including RCTs, double-blind, placebo-controlled, single-center phase II trials, and open-label, multicenter trials. These trials primarily focused on patients suffering from non-ischemic DCM, characterized by significantly LVEF and classified mostly according to the NYHA functional classification. Only one study included patients with both non-ischemic and ischemic DCM⁴, providing insights into the varied responses of these two groups under SCT. However, two studies reported were on ischemic DCM.^{4,11} A wide variety of autologous stem cell types were employed across the studies, including CD34⁺ stem cells, bone marrow mononuclear cells (BMNCs), and granulocyte colony-stimulating factor (G-CSF) stimulated autologous CD34⁺ peripheral blood mononuclear cells (PBMCs). The administration routes were also varied, encompassing trans endocardial injections, intracoronary injections, and intramyocardial catheter injections, tailored to optimize delivery and the effectiveness of the therapy.

S. No.	Outcome reviewed	What does it measure?	MCID (if decided
			by the GDG)
1.	Mortality	Number of deaths in a given period of time.	-
2.	Left ventricular ejection fraction (LVEF)	LVEF% as measured by echocardiography/central measure of left ventricular systolic function. It is the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end-diastolic volume).	An absolute change in LVEF by 5%.
3.	6-minute walk test (6 MWT)	The distance a person is capable of walking on a flat surface in 6 minutes. It assesses the functional capacity of the individual.	An absolute change in distance walked by 150 metres.
4.	MACE	Major adverse cardiovascular events	

Critical outcomes reviewed and their MCID:

Risk of Bias Assessment:

				Risk of bia	<u>is domains</u>					
		D1	D2	D3	D4	D5	Overall			
	Frljak et al. 2018	+	+	-	+	+	-			
	Hamshere et al. 2015	+	+	+	-	+	+			
	Henry et al. 2014	+	+	X	-	+	-			
	Martino et al. 2015	+	+	+	+	-	+			
	Sant' et al. 2014	+	X	X	X	-	X			
Study	Seth et al. 2010	-	-	X	X	X	X			
	Vrtovec et al. 2011	-	-	+	+	+	X			
	Vrtovec et al. 2013	-	-	+	X	+	X			
	Xiao et al. 2012	-	-	X	+	-	X			
	Xiao et al. 2017	-	-	X	+	-	X			
	Pincott et al. 2017	+	+	+	+	+	+			
Domains: D1: Bias arising from the randomization process. D2: Piace due to deviations from internation										

D3: Bias due to deviations from interded inD3: Bias due to missing outcome data.D4: Bias in measurement of the outcome.D5: Bias in selection of the reported result.

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Some concerns

Low

ISCHEMIC DILATED CARDIOMYOPATHY:

Desirable Effects:

- **1. All-cause mortality:** Two RCTs reported mortality with stem cell therapy in ischemic DCMP with 28 patients in the stem cell treatment group and 25 in the usual care group. For mortality at 6 months from one study, the calculated RR was 1.00 (95% CI: 0.112 to 8.947), and for mortality at 3 months from another study, the calculated RR was 0.394 (95% CI: 0.017 to 9.036). The pooled risk ratio (RR) for mortality was 0.736 (95% CI: 0.003 to 191.206). The values were statistically non-significant.
- 1.1 Forest plot showing mortality stem cell therapy as compared to usual care

Study or Subgroup	Stem Events	cells Total	C Events	ontrol Total	Weight	RR [95%	CI]	Mortality				
Time.point = 6 Henry TD 2014	months 2	12	1	6	67.1%	1.000 [0.112;	8.947]			-		
Time.point = 3 Xiao 2012	months 0	16	1	19	32.9%	0.394 [0.017;	9.036]	_	-			
Pooled RR Heterogeneity: T Test for subgrou	2 au ² = 0; C o differenc	28 hi ² = 0 ces: Ch	2 .23, df = n ² = 0.23	25 1 (P = 0 , df = 1	100.0% 0.63); I ² = (P = 0.63	0.736 [0.003; 1 0%)	191.206]	0.01 Favor	0.1	1	10 Favours	100

- **2.** Left Ventricular Ejection Fraction (LVEF): One RCT with 27 participants reported the change in LVEF% from baseline at the end of 12 months and showed a MD of 2.601 (95% CI: -6.546 to11.747) between the stem cell arm and the usual care arm. The change was statistically non-significant.
- 2.1 Forest plot showing change in LVEF: the effect of stem cell therapy as compared to usual care

Stem cells					Contol		Mean Difference	Mean Difference				
Study	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI		V, Rand	om, 9	95% C	
Henry TD 2014	-0.59	6.6233	19	-3.19	12.4799	8	2.601 [-6.546; 11.747]			-		
								-10 Favou	-5 rs contro	0 I Fa	5 ivours	10 stem cells

3. 6-minute walk test (6-MWT): Only one RCT with 27 participants reported the effect of stem cell therapy on the 6-minute walk test distance at the end of 12 months. The MD between the stem cell arm and the usual care arm was 151.98 meters (95% CI: 0.68 to 303.28). The difference was found to be statistically significant and clinically important (MCID 150 meters).

3.1 Forest plot showing the effect of stem cell therapy on change in 6 MWT as compared to usual care



Undesirable effects:

4. Major Adverse Cardiovascular Events (MACEs): One RCT with a total of 12 participants reported the incidence of MACE at two time points. The risk ratio of MACE between the stem cell arm and the usual care arm was 0.167 (95% CI: 0.022 to 1.248) at 12 months, which was statistically non-significant.

4.1 Forest plot showing the effect of stem cell therapy on incidence of MACE as compared to usual care

Study	Sterr Events	i cells Total	C Events	Contol Total	Risk Ratio MH, Random, 95% CI	Risk Ratio MH, Random, 95% Cl					
Henry TD 2014	1	9	2	3	0.167 [0.022; 1.248]						
					Fav	0.1 0.5 vours stem cells	1 2 10 Favours Control				

NON-ISCHEMIC DILATED CARDIOMYOPATHY:

Desirable Effects:

1. All-cause mortality: Seven RCTs with a total of 382 participants (207 received stem cells and 175 were in the control group) reported all-cause mortality at one year. The pooled analysis yielded a risk ratio of 0.692 (95% CI: 0.32 to 1.48), which was statistically non-significant.

1.1 Forest plot showing mortality - stem cell therapy as compared to usual care: 12 months



2. LVEF: Seven RCTs with a total of 394 participants (218 received stem cells and 176 were in the control group) reported change in ejection fraction from baseline in non-ischemic DCM. The mean difference observed was 3.827(95% CI: 1.042 to 6.612) between the stem cell arm and the usual care arm. The difference was statistically significant but clinically unimportant (less than the MCID of 5%).

2.1 Forest plot showing change in LVEF -the effect of stem cell therapy as compared to usual care: 12 months

Study	St Mean	tem cells SD	Total	Mean	Contol SD	Total	Weight	Mean Difference IV, Random, 95% C	Mean Difference I IV, Random, 95% CI
Hamshere 2015	7.04	7.7700	13	-1.92	9.1300	13	13.3%	8.963 [2.446; 15.480	
Henry TD 2014	-0.56	12.8931	18	-2.14	15.8939	11	5.6%	1.578 [-9.544; 12.700	
Martino 2015	-5.40	20.7000	61	-2.90	18.9600	54	11.3%	-2.500 [-9.750; 4.750	
Sant' Anna 2014	30.70	7.2500	15	30.23	7.3900	9	14.7%	0.470 [-5.594; 6.534	
Vrtovec 2011	4.55	10.2975	26	-1.92	10.6239	19	14.2%	6.476 [0.273; 12.680	
Vrtovec 2013	31.52	39.7657	55	27.39	30.6289	55	4.0%	4.131 [-9.134; 17.396	51
Xiao 2017 (BMMC)	36.70	6.7000	14	34.30	5.3000	8	18.5%	2.400 [-2.680; 7.480	ni +++
Xiao 2017 (BMSC)	41.00	6.7000	16	34.30	5.3000	7	18.4%	6.700 [1.582; 11.818	3]
Total (95% CI)		0. 01 ² - 0	218	- 7 /0	- 0.001 12	176	100.0%	3.827 [1.042; 6.612	
Heterogeneity: Tau*	= 4.166	$2; Chi^* = 8$	5.86, df	= 7 (P	= 0.26); l*	= 21%			
									-15 -10 -5 0 5 10 15 Favours control Favours stem cell

3. 6-MWT: Four studies with a total of 294 participants (157 received stem cells and 137 were in the control group) reported a change in 6MWT at the end of 12 months. The mean difference observed was 46.698 (95% CI: -28.589 to 121.985; I² = 30%) between the stem cell arm and the usual care arm. The pooled estimate was statistically non-significant.

3.1 Forest plot showing the effect of stem cell therapy on change in 6-MWT as compared to usual care

	Stem cells		Contol				Mean Difference	Mean Difference	
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Martino 2015	-47.50	282.8800	61	-18.00	260.0400	54	32.5%	-29.500 [-128.746; 69.746]	
Sant' Anna 2014	370.41	91.5600	15	330.00	123.4200	9	34.9%	40.410 [-52.588; 133.408]	
Vrtovec 2011	125.61	251.4836	26	-5.39	197.3849	19	22.8%	131.001 [-0.229; 262.231]	
Vrtovec 2013	467.24	639.3505	55	341.38	562.5928	55	9.7%	125.860 [-99.211; 350.931	
Total (95% CI) Heterogeneity: Tak	u ² = 1974	4.8903; Chi ⁱ	157 ² = 4.29	9. df = 3 ((P = 0.23); I	137 ² = 30%	100.0%	46.698 [-28.589; 121.985]	
									-300 -100 0 100 200 300 Favours control Favours stem cells

Undesirable effects:

4. Major Adverse Cardiovascular Events (MACEs): Three studies with a total of 83 participants (50 received stem cells and 33 were in the control group) reported MACE at the end of 12 months. The risk ratio of MACE between the stem cell arm and the usual care arm was 0.879 (95% CI: 0.573, 1.348) at 12 months. The ratio was statistically non-significant.

4.1 Forest plot showing the effect of stem cell therapy on incidence of MACE as compared to usual care

Study	Sterr Events	n cells Total	C Events	ontrol Total	Weight	RR [95%	CI]		MAC	E	
Hamshere 2015	2	13	1	13	6.9%	2.000 [0.206;	19.437]	-			
Henry TD 2014	3	6	2	3	27.8%	0.750 0.242;	2.325]		— <u> </u>		
Xiao 2017 (BMSC)	6	16	4	9	38.2%	0.844 [0.321;	2.217				
Xiao 2017 (BMMC)	5	15	3	8	27.1%	0.889 [0.283;	2.795]				
RR	16	50	10	33	100.0%	0.879 [0.573;	1.348]				
Heterogeneity: I au ⁻	= 0; Chi⁻	= 0.58,	df = 3 (P	= 0.90); I [_] = 0%			, ,		, ,	10
								0.1	0.5 1	2	10
							Fav	ours ste	m cells F	avours	s Contro

ng: Hospital/Tertiary care vention: Stem cells therap varison: Usual care	у					
	Anticipated a	tbsolute effects* 3% CI)		θυσΝ	Contrainty of the	
Outcomes	Risk with usual care	Risk with Stem cells therapy	Relative effect (95% CI)	participants (studies)	certainty of the evidence (GRADE)	Comments
Mortality assessed with: RR ow-up: mean 3 months	53 per 1,000	21 per 1,000 (1 to 476)	RR 0.394 (0.017 to 9.036)	35 (1 RCT)	⊕⊖⊖⊖ Very low ^{a,b,c}	
Mortality assessed with: RR ow-up: mean 6 months	167 per 1,000	167 per 1,000 (19 to 1,000)	RR 1.000 (0.112 to 8.947)	18 (1 RCT)	⊕⊖⊖⊖ Very low ^{abc}	
MACE assessed with: RR wv-up: mean 12 months	667 per 1,000	111 per 1,000 (15 to 832)	RR 0.167 (0.022 to 1.248)	12 (1 RCT)	⊕⊕⊖⊖ Lowbc	
LVEF assessed with: MD wv-up: mean 12 months	ı	MD2.6 higher (6.5 lower to 11.7 higher)	ŗ	27 (1 RCT)	⊕⊖⊖⊖ Very low ^{a,b,c}	
nute walk test (6-MWT) assessed with: MD wv-up: mean 12 months		MD 151.98 meters higher (0.681 higher to 303.27 higher)		27 (1 RCT)	⊕⊖⊖⊖ Very low ^{abd}	

Evidence-based Guidelines for the use of Stem Cell Therapy: Cardiac Conditions

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

a. Downgraded by two levels, as > 2/3rd studies by weight are at high risk of bias.

b. Single study was downgraded one level for inconsistency as it was unevaluable.

c. Confidence levels are wide and overlapping with null effect; OIS not met.

d. Very wide CI; OIS not met.

EVIDENCE PROFILE: Stem cells therapy as compared to usual care for Ischemic Dilated Cardiomyopathy

		Cer	rtainty assessme	ent					Summary o	f findings	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Study e	vent rates %)	Relative effect	Anticipate	ed absolute effects
dn- wollou						of evidence	Usual care	With Stem cells therapy	(ID %c8)	Risk with usual care	Risk difference with Stem cells therapy
Mortality (follov	v -up: me	an 3 months; as:	sessed with: RF	(2							
35 (1 RCT)	Very serious ^a	Inevaluable	Not serious	Serious	None	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ^{a,b,c}	1/19 (5.3%)	0/12 (0.0%)	RR 0.394 (0.017 to 9.036)	1/19 (5.3%)	32 fewer per 1,000 (from 52 fewer to 423 more)
Mortality (foll	ow-up: me	an 6 months; as	sessed with: RF	()							
18 (1 RCT)	Very serious ^a	Inevaluable	Not serious	Serious	None	⊕⊖⊖⊖ Very lowa,b,c	1/6 (16.7 %)	2/12 (16.7%)	RR 1.000 (0.112 to 8.940)	1/6 (16.7%)	0 fewer per 1,000 (from 148 fewer to 1,000 more)
MACE (follow-	up: mean	12 months; asse	ssed with: RR)								
12 (1 RCT)	Serious	Not serious	Not serious	Serious	None	⊕⊕⊖⊖ Low ^{b,c}	2/3 (66.7 %)	1/9 (11.1%)	RR 0.167 (0.022 to 1.248)	2/3 (66.7%)	555 fewer per 1,000 (from 652 fewer to 165 more)

Evidence-based Guidelines for the use of Stem Cell Therapy: Cardiac Conditions

Evidence-based Guidelines for the use of Stem Cell Therapy: Cardiac Conditions

Stem cells therapy compare	d to usual care fo	r Non-Ischemic Dilated	cardiomyopathy			
Patient or population: Non-I. Setting: Hospital setting Intervention: Stem cells ther Comparison: Usual care	schemic Dilated ca apy	ırdiomyopathy				
	Anticipated abs	olute effects*(95% CI)				
Outcomes	Risk with No intervention or standard intervention	Risk with Stem cells therapy	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Mortality (Mortality) assessed with: RR follow-up: mean 12 months	189 per 1,000	130 per 1,000 (61 to 280)	RR 0.692 (0.322 to 1.484)	382 (6 RCTs)	⊕⊖⊖⊖ Very low ^{ab}	
MACE (MACE) assessed with: RR follow-up: mean 12 months	303 per 1,000	266 per 1,000 (174 to 408)	RR 0.879 (0.573 to 1.348)	83 (3 RCTs)	⊕⊖⊖⊖ Very low ^{a,b}	
Left ventricular ejection fraction (LVEF) assessed with: % follow-up: mean 12 months		MD 3.82 % higher (1.04 higher to 6.61 higher)		394 (7 RCTs)	⊕⊖⊖⊖ Very lowac	
6 MWT assessed with: MD follow-up: mean 12 months		MD 46.69 Meters higher (28.59 lower to 121.98 higher)		294 (4 RCTs)	⊕⊖⊖⊖ Very low ^{ab,d}	

NON-ISCHEMIC DILATED CARDIOMYOPATHY

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% Cl). Cl: confidence interval; MD: mean difference; RR: risk ratio

Evidence-based Guidelines for the use of Stem Cell Therapy: Cardiac Conditions

GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:

- a. >2/3rd studies by weight are at high risk of bias.
 b. Wide CI, crossing the line of null effect; OIS not met.
 c. OIS not met.
 d. Results inconsistent; I²-46%.

EVIDENCE PROFILE: Stem cells therapy compared to usual care for Non-Ischemic Dilated cardiomyopathy

	ects	Risk diff with Stem cells therapy		58 fewer per 1,000 (from 128 fewer to 91 more)		37 fewer per 1,000 (from 129 fewer to 105 more)
ıdings	Anticipate eff	Risk with Usual care		33/175 (18.9%)		10/33 (30.3%)
mmary of fir		Relative effect (95% CI)		RR 0.692 (0.322 to 1.484)		RR 0.879 (0.573 to 1.348)
Su	vent rates %)	With Stem cells therapy		27/207 (13.0%)		16/50 (32.0%)
	Study ev (With usual care		33/175 (18.9%)		10/33 (30.3%)
		Overall certainty of evidence		⊕⊖⊖⊖ Very low ^{a,b}		⊕⊖⊖⊖ Very low ^{a,b}
	Publication			None		None
ent	Imprecision			Serious ^b		Serious ^b
rtainty assessm		Indirectness		Not serious	sed with: RR)	Not serious
Ce	Inconsistency		san 12 months; a	Not serious	12 months; asses	Not serious
		Risk of bias	low-up: me	Very serious ^a	-up: mean	Very serious ^a
		Participants (studies) Follow-up	Mortality (fol	382 (6 RCTs)	MACE (follow	83 (3 RCTs)

Evidence-based Guidelines for the use of Stem Cell Therapy: Cardiac Conditions

Summary of findings EVIDENCE PROFILE: Stem cells therapy compared to usual care for Non-Ischemic Dilated cardiomyopathy **Certainty assessment**

Left ventricular ejection fraction (follow-up: mean 12 months; assessed with: %)

394	Very	Not serious	Not serious	Serious ^c	None	0000	ı	,	ı	MD 3.82
(7 RCTs)	serious ^a					Very low ^{a,c}				% higher
										(1.04)
										higher to
										6.61
										higher)
6-MWT (follo	w-up: mea	n 12 months; asse	essed with: MD)							

יdn-wטווטו) ו אוא

- MD 46.69	Meters	higher	(28.59	lower to	121.98	higher)
I						
ı						
,						
000⊕	Very low ^{a,b,d}					
None						
serious ^b						
Not serious						
Not serious						
Very	serious ^a					
294	(4 RCTs)					

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations a. >2/3rd studies by weight are at high risk of bias. b. Wide CI, crossing the line of null effect; OIS not met.

c. OIS not met. d. Results inconsistent; 1²-46%.

Evidence-based Guidelines for the use of Stem Cell Therapy: Cardiac Conditions

D. SUMMARY OF JUDGEMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

ISCHEMIC DILATED CARDIOMYOPATHY

Desirable Effects	Small*
Undesirable Effects	Trivial**
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required	Moderate
resources	
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is	s <u>not recommended</u> in routine clinical practice for the

treatment of ischemic dilated cardiomyopathy.

*This judgment was made as there is very low certainty limited evidence of a trivial to small improvement in function and mortality.

** This judgment was made as there is little or no difference in undesirable effects between stem cell therapy and usual care.

*** The committee opined that stem cell treatment is associated with large costs.

NON-ISCHEMIC DILATED CARDIOMYOPATHY:

Desirable Effects	Small*
Undesirable Effects	Trivial**
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required	Moderate
resources	
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes

Recommendation: Stem cell therapy is **not recommended** in routine clinical practice for the treatment of ischemic as well as non-ischemic dilated cardiomyopathy.

*This judgment was made as there is very low certainty limited evidence of a trivial to small improvement in function and mortality.

** This judgment was made as there is little or no difference in undesirable effects between stem cell therapy and usual care.

*** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

- Lack of sufficient number of blinded RCTs with low risk of bias
- Heterogeneity in cohorts of patient populations with DCM
- Limited sample size with short follow-up periods
- Lack of cost effectiveness data

____**

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2. MYOCARDIAL INFARCTION (MI)

A. BACKGROUND:

Myocardial infarction is a major cause of cardiovascular mortality and morbidity, wherein the blood flowing one or more of the coronary arteries supplying the cardiac muscle is blocked. The cardiovascular disease (CVD) epidemic in Indians is characterized by a higher relative risk burden, an earlier age of onset, higher case fatality and higher premature deaths.¹ Myocardial injury during the episode is not fully reversible by the available treatment options and there is an unmet need for developing novel methods or interventions for reversing the ischemic damage.

B. RECOMMENDATIONS:

Stem cell therapy is **<u>not recommended</u>** in routine clinical practice for the treatment of myocardial infarction.

Strength: Conditional[#] Certainty of Evidence: Very Low

#It may be used only in the context of rigorously conducted randomized controlled trials.

Rationale/Justification:

This recommendation has been made as there is very low certainty evidence of improvement in function and mortality. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is too small to comment fully on the side effect profile and long-term safety is not known. Results should be interpreted with caution in view of studies with high risk of bias and/or fewer events.

C.SUMMARY OF EVIDENCE:

Key Question: In patients with myocardial infarction, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: A total of 9506 studies were identified based on electronic search of PubMed, Web of Science, EMBASE and CENTRAL. A total of 48 studies were finally included for qualitative and quantitative evaluation.²⁻⁴⁹ Patients having acute STEMI with LVEF <45% had been selected in most of the trials. The mean age of the patients in the trials were ranged from 50 to 62 years. The median duration of follow-up for the studies was 12 months, ranging from 3 to 100 months. The type of stem cells used were bone marrow mononuclear cells and mesenchymal stem cells. The route of administration of stem cell therapy was intracoronary in most trials with only a few trials using the intravenous route.

Critical outcomes reviewed and their MCID:

S. No	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	Mortality	Number of deaths in a defined period of time	-
2.	LVEF	Left ventricular ejection fraction as measured by echocardiography/ Central measure of left ventricular systolic function. It is the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end- diastolic volume).	A change of 5% in LVEF% was considered as MCID
3.	SAEs	Serious adverse events	-
4.	Hospitalization	Incidence of hospitalization due to heart failure	-
5.	Stroke,Recurrent-myocardialinfarction,cancer incidence	Incidence of stroke, recurrent-myocardial infarction, cancer in stem cell therapy group as compared to usual care.	-

Risk of Bias assessment:

		D1	D2	Risk of bia	as domains	D5	Overall
	Angeli 2012	-				-	
	Assmus 2014				$\mathbf{+}$	-	+
	Attar 2023				$\mathbf{+}$	$\overline{+}$	
	Cao 2009				$\mathbf{+}$	$\overline{+}$	
	Chen 2004		$\overline{\mathbf{+}}$		$\mathbf{+}$	$\overline{+}$	
	Choudry 2016	$\overline{\mathbf{+}}$	$\overline{+}$		$\mathbf{+}$	$\overline{+}$	
	Chullikana 2015	$\overline{}$	$\overline{+}$	$\overline{+}$	$\overline{+}$	$\overline{+}$	+
	Colombo 2011		$\overline{+}$	$\overline{+}$	$\overline{+}$	$\overline{+}$	$\overline{+}$
	Delewi 2011	$\overline{+}$			$\overline{+}$	$\overline{+}$	
	Dill 2009	-	-		$\overline{+}$	$\overline{+}$	
	F. Aviles 2018	$\overline{+}$	-	$\overline{+}$	$\overline{+}$	$\overline{+}$	+
	Gao 2013	-	-	$\overline{+}$	+	$\overline{+}$	
	Gao 2015	-	$\overline{+}$	$\overline{+}$	$\overline{+}$	$\overline{+}$	+
	Ge 2006	+	-	+	+	+	
	Grajek 2010				+	+	
	Haddad 2020	+	+	+	+	+	+
	Hare 2009	$\overline{+}$	$\overline{+}$	-	$\overline{+}$	$\overline{+}$	-
	Huikuri 2008	+			$\overline{+}$	+	
	Janssens 2006	+	×		$\overline{+}$	+	
	Kaminek 2008	-	-	+	+	+	
	Kim 2018	-	—	$\overline{+}$	$\overline{+}$	+	<u> </u>
	Laguna 2018	+	+	$\overline{+}$	+	+	+
	Lezo J S D 2007	-			+	+	
	Lee 2014		+	+	+	+	
	Lunde 2007	-	-		+	+	
À.	Lunde 2007 sub	-	-			+	
ŝ	Mathur 2020 BAMI	$\mathbf{\times}$	+	-	+	+	
	Meyer 2009	+	+	+	+	-	-
-	Meyer 2009 sub	+	+	+	+	-	-
	Naseri 2018	+	+	+	+	+	+
	Ostovaneh 2021	+	+	+	+	+	+
	Penicka 2007	-	-		+	+	\mathbf{X}
	Piepoli 2010	-	\sim	+	+	+	\mathbf{X}
	Plewka 2009	-	+	+	+	+	-
	Quyyumi 2011	×	+	+	+	+	\mathbf{x}
	Quyyumi 2017	+	+	+	+	+	+
	Roman 2015		+	+	+	+	\mathbf{x}
	Roncalli 2011	-	+	+	+	+	-
	Srimahachota 2011	-	+	+	+	+	-
	Srimahachota 2011 sub	-	+	+	$\mathbf{\times}$	+	$\mathbf{\times}$
	Surder 2016	$\overline{\mathbf{x}}$	+	$\overline{}$	+	+	\mathbf{x}
	Tendra 2009	-	+	+	+	+	-
	Traverse 2010	-	+	-	+	+	<u> </u>
	Traverse 2011	-	-	-	(+)	+	—
	Traverse 2018	<u> </u>	-	—	—	+	<u> </u>
	Wang 2014	-	-	\sim	+	+	
	WEN X 2012	• •		—	—	—	+
	Wohrle 2010						-
	Wollert 2017			—	+	—	+
	Yao 2009						\mathbf{x}
	Zhang 2021		-	—		—	-
	Zhang 2021 sub		-	+		—	
		D1: Bias ari D2: Bias du	sing from the e to deviation	randomizations from intend	on process. ded interventio	Judge on. 🗙 I	ligh
		D3: Bias du D4: Bias in D5: Bias in	e to missing o measuremen selection of th	outcome data t of the outco ne reported r	a. ome. esult.	- •	Some concerns _ow

Desirable Effects:

1. Mortality: All-cause mortality was reported by 30 RCTs with 2879 participants (1633 participants in the stem cell group and 1246 participants in the control group) at the end of follow up (< than 6 months to > 12 months). Pooled analysis revealed a risk ratio of 0.73 (95% CI: 0.50 to 1.05) which was statistically non-significant. The subgroup analysis based on cell type, route of administration and source (autogenic vs allogenic) were all statistically non-significant.

1.1. Effect of stem cell on all-cause mortality in acute myocardial infarction:

	Interver	ntion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Assmus 2014	7	101	15	103	23.3%	0.48 [0.20, 1.12]	
Cao 2009	0	41	1	45	2.2%	0.37 [0.02, 8.72]	
Chodry F 2016	1	54	0	44	0.9%	2.45 [0.10, 58.80]	
Chullikana 2015	0	10	1	10	2.4%	0.33 [0.02, 7.32]	
Delewi 2015	1	69	2	65	3.2%	0.47 [0.04, 5.07]	
Gao 2013	1	21	0	21	0.8%	3.00 [0.13, 69.70]	
Gao 2015	0	58	1	57	2.4%	0.33 [0.01, 7.88]	
Grajek 2010	1	31	0	14	1.1%	1.41 [0.06, 32.53]	
Haddad 2020	0	17	1	20	2.2%	0.39 [0.02, 8.97]	
Huikuri 2008	0	40	1	40	2.4%	0.33 [0.01, 7.95]	
Janssens 2006	1	33	0	34	0.8%	3.09 [0.13, 73.20]	
Laguna 2018	0	10	1	10	2.4%	0.33 [0.02, 7.32]	
Mathur A 2020	6	185	7	190	10.9%	0.88 [0.30, 2.57]	
Meyer GP 2009	2	30	2	30	3.1%	1.00 [0.15, 6.64]	
Naseri 2018	1	51	0	26	1.0%	1.56 [0.07, 36.96]	
Penicka 2007	3	17	0	10	1.0%	4.28 [0.24, 75.20]	
Piepoli MF 2010	2	19	4	19	6.3%	0.50 [0.10, 2.41]	
Plewka 2009	2	40	2	20	4.2%	0.50 [0.08, 3.29]	
Quyyumi 2011	1	16	0	15	0.8%	2.82 [0.12, 64.39]	
Quyyumi 2017	1	100	6	95	9.7%	0.16 [0.02, 1.29]	
Roman 2015	0	59	1	61	2.3%	0.34 [0.01, 8.29]	
Roncalli 2011	1	52	0	49	0.8%	2.83 [0.12, 67.87]	
Surder 2016	4	133	0	67	1.0%	4.57 [0.25, 83.60]	
Tendera 2009	2	160	1	40	2.5%	0.50 [0.05, 5.38]	
Traverse 2011	0	58	1	29	3.1%	0.17 [0.01, 4.04]	←
Traverse 2018	3	79	0	41	1.0%	3.67 [0.19, 69.48]	
Wang 2014	1	28	2	30	3.0%	0.54 [0.05, 5.59]	
Whorle J 2010	1	29	1	13	2.2%	0.45 [0.03, 6.63]	
Wollert 2017	1	71	1	26	2.3%	0.37 [0.02, 5.64]	
Zhang 2021	1	21	0	22	0.8%	3.14 [0.13, 72.96]	
Total (95% CI)		1633		1246	100.0%	0.73 [0.50, 1.05]	•
Total events	44		51				
Heterogeneity: Chi ² =	15.51, df:	= 29 (P	= 0.98); P	²=0%			
Test for overall effect:	Z=1.70 (P = 0.0	9)				Favours (experimental) Favours (control)

1.2. Effect of stem cell on all-cause mortality in acute myocardial infarction based on time of assessment:



1.3. Effect of stem cell on all-cause mortality in acute myocardial infarction based on the type of stem cells:

Study or Subgroup	Intervent	tion Total	Contr	ol Total	Weight	Risk Ratio	Risk Ratio
1 15 1 Mononuclear	Events	Tutai	LVCIIIS	Total	weight	M-n, nxeu, 55% ci	m-n, rixed, 55% ci
Acomus 2014	7	1.01	15	100	<u> </u>	0 40 00 20 4 4 21	
ASSINUS 2014 Coo 2000	, 0	101	10	103	23.370	0.40 [0.20, 1.12]	-
Cau 2009 Chodry E 2016	1	41 54	, 0	40	2.2.70	0.37 [0.02, 0.72]	
Choury F 2016 Dolouri 2015	1	04	U 2	44	0.970	2.40 [0.10, 00.00]	
Delewi Zuro Oroiok 2010	1	09	2	00	3.270		
Grajek ZUTU Maddad 2020		31	0	14	1.1%	1.41 [0.06, 32.53]	
Haddad 2020	0	17	1	20	2.2%	0.39 [0.02, 8.97]	
Hulkuri 2008	0	40	1	40	2.4%		
Laguna 2018 Mathum 6, 2020	U	10	1	10	2.4%	0.33 [0.02, 7.32]	
Mathur A 2020	0	185		190	10.9%	0.88 [0.30, 2.57]	
Meyer GP 2009	2	30	2	30	3.1%	1.00 [0.15, 6.64]	
Naseri 2018	1	51	U	26	1.0%	1.56 [0.07, 36.96]	
Penicka 2007	3	17	U	10	1.0%	4.28 [0.24, 75.20]	
Piepoli MF 2010	2	19	4	19	6.3%	0.50 [0.10, 2.41]	
Plewka 2009	2	40	2	20	4.2%	0.50 [0.08, 3.29]	
Quyyumi 2011	1	16	0	15	0.8%	2.82 [0.12, 64.39]	
Quyyumi 2017	1	100	6	95	9.7%	0.16 [0.02, 1.29]	
Roman 2015	0	59	1	61	2.3%	0.34 [0.01, 8.29]	
Roncalli 2011	1	52	0	49	0.8%	2.83 [0.12, 67.87]	
Surder 2016	4	133	0	67	1.0%	4.57 [0.25, 83.60]	
Tendera 2009	2	160	1	40	2.5%	0.50 [0.05, 5.38]	
Traverse 2011	0	58	1	29	3.1%	0.17 [0.01, 4.04]	·
Traverse 2018	3	79	0	41	1.0%	3.67 [0.19, 69.48]	
Whorle J 2010	1	29	1	13	2.2%	0.45 [0.03, 6.63]	
Wollert 2017	1	71	1	26	2.3%	0.37 [0.02, 5.64]	
Subtotal (95% CI)		1462		1072	89.9%	0.69 [0.47, 1.03]	\bullet
Total events	40		47				
Heterogeneity: Chi ² = 1	12.38, df=	23 (P	= 0.96); P	²= 0%			
Test for overall effect: 2	Z = 1.83 (F	P = 0.07	7)				
1.15.2 Mesenchymal							
Chullikana 2015	0	10	1	10	2.4%	0.33 [0.02, 7.32]	
Gao 2013	1	21	0	21	0.8%	3.00 [0.13, 69.70]	
Gao 2015	0	58	1	57	2.4%	0.33 [0.01, 7.88]	
Wang 2014	1	28	2	30	3.0%	0.54 [0.05, 5.59]	
Zhang 2021	1	21	0	22	0.8%	3.14 [0.13, 72.96]	
Subtotal (95% CI)		138		140	9.3%	0.85 [0.27, 2.73]	
Total events 3 4							
Heterogeneity: Chi ^z = 2.13, df = 4 (P = 0.71); I ^z = 0%							
Test for overall effect: Z = 0.27 (P = 0.79)							
1.15.3 Both							
Janssens 2006	1	33	0	34	0.8%	3.09 [0.13, 73.20]	
Subtotal (95% CI)		33		34	0.8%	3.09 [0.13, 73.20]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.70 (F	e = 0.49	3)				
Total (95% CI)		1633		1246	100.0%	0.73 [0.50, 1.05]	◆
Total events	44		51				
Heterogeneity: Chi ² = 1	15.51, df=	29 (P	= 0.98); P	2 = 0%			
Test for overall effect: 2	Z = 1.70 (F	e = 0.09	3)				Eavours [experimental] Eavours [control]
Test for subgroup diffe	erences: C	hi²=0	.93, df = 1	2 (P = 0	l.63), ² = I	0%	ravous (experimental) in avours (control)

1.4. Effect of stem cell on all-cause mortality in acute myocardial infarction based on the route of administration:

	Interver	ntion	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
1.16.1 Intracoronary								
Assmus 2014	7	101	15	103	23.3%	0.48 [0.20, 1.12]		
Cao 2009	Ó	41	1	45	2.2%	0.37 [0.02, 8,72]		
Chodry F 2016	1	54	n	44	0.9%	2.45 [0.10, 58.80]		
Delewi 2015	1	69	2	65	3.2%			
Gan 2013	1	21	- 0	21	0.8%	3 00 10 13 69 701		
Gan 2015	N	58	1	57	24%	0.33/0.01/7.881		
Graiek 2010	1	31	'n	14	1 1 96			
Haddad 2020	'n	17	1	20	2.2%	0.39 [0.02, 8.97]		
Huikuri 2008	ň	40	1	40	2.4%	0.33 [0.01 7.95]		
Janssens 2006	1	33	'n	34	0.8%	3 09 0 13 73 201		
Mathur A 2020	6	185	7	190	10.9%	0.88 [0.30, 2.57]		
Mever GP 2009	2	30	2	30	31%	1 00 [0.00, 2.01]		
Penicka 2007	2	17	ñ	10	1.0%	4 28 [0 24 75 20]		
Pienoli ME 2001	2	19	4	10	63%	0.50 [0.10, 2.41]		
Plewka 2009	2	40	2	20	4 7%	0.50 [0.10, 2.41]		
Ouwumi 2000	1	16		15	0.8%	2 82 [0.00, 0.20]		
Quyyumi 2017 Quyyumi 2017	1	100	0 8	96	0.07%	0.1610.02.1.201		
Domon 2015	0	60	1	3J 61	3.770	0.10[0.02, 1.23]		
Roman 2015 Doncolli 2011	1	53		10	2.3%	202101201,023		
Rundar 2016	4	102	0	43	1 0.0%	4.67 [0.12, 07.07]		
Tondoro 2000	- 4	100	1	40	1.0%	4.07 [0.20, 60.00]		
Tenuera 2009	2	100	1	40	2.070	0.00 [0.00, 0.00]	•	
Traverse 2011	U 2	00 70		29	3.170	0.17 [0.01, 4.04]	,	
Wong 2014	J 1	79	0 2	41	1.0%	0.54 (0.19, 09.40)		
Wang 2014 Wheele 10040	1	20	2	30	3.0%	0.04 [0.00, 0.09]		
Whone J ZUTU	1	29	1	13	2.2%	0.45 [0.03, 6.63]		
Wollen 2017 Zhang 2024	1	24		20	2.3%	0.37 [0.02, 5.64]		
Subtotal (95% CI)	I	1562	U	1200	0.8% 94.3%	0.74 [0.13, 72.96] 0.74 [0.50, 1.08]	•	
Total events	43		49					
Heterogeneity: Chi ² = 14.83, df = 26 (P = 0.96); l ² = 0%								
Test for overall effect: Z = 1.58 (P = 0.11)								
1.16.3 direct intramy	ocardia							
Laguna 2018	0	10	1	10	2.4%	0.33 [0.02, 7,32]		
Naseri 2018	1	51	Ó	26	1.0%	1.56 (0.07, 36,96)		
Subtotal (95% CI)		61	_	36	3.4%	0.71 [0.09, 5.53]		
Total events	1		1					
Heterogeneity: Chi ² = 0.47, df = 1 (P = 0.49); I ² = 0%								
Test for overall effect: Z = 0.33 (P = 0.74)								
1.16.4 anticubital veir	1 of forea	rm						
Chullikana 2015	0	10	1	10	2.4%	0.33 [0.02, 7.32]		
Subtotal (95% CI)		10		10	2.4%	0.33 [0.02, 7.32]		
Total events	0		1					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.70 (P = 0.4	9)					
Total (95% CI)		1633		1246	100.0%	0.73 [0.50, 1.05]	•	
Total events	4.4		51				•	
Heterogeneity: Chi ² =	15 51 df:	= 29 (P	= 0.98) [,] P	²= 0%				
Test for overall effect:	7 = 1.70 (- 20 () P = 0 0)	= 0.00), i 9)	-070			0.01 0.1 1 10 100	
Test for subaroun diff	erences:(. = 0.0. Chi²= 0	-/ 125 df=1	7 (P = 1	.88) I ^z =	0%	Favours (experimental) Favours (control)	

1.5. Effect of stem cell on all-cause mortality in acute myocardial infarction based on Autologous vs Allogeneic:

Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 1.17.1 Autologous 7 101 15 103 23.3% 0.48 [0.20, 1.12]							
1.17.1 Autologous Assmus 2014 7 101 15 103 23.3% 0.48 [0.20, 1.12] Cao 2009 0 41 1 45 2.2% 0.37 [0.02, 8.72] Chodry F 2016 1 54 0 44 0.9% 2.45 [0.10, 58.80] Delewi 2015 1 69 2 65 3.2% 0.47 [0.04, 5.07] Gao 2013 1 21 0 21 0.8% 3.00 [0.13, 69.70] Grajek 2010 1 31 0 14 1.1% 1.41 [10.6, 32.53] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Huikur 2008 0 40 1 40 2.4% 0.33 [0.01, 7.95] Janssens 2006 1 33 0 34 0.8% [0.30, 2.57]							
Assmus 2014 7 101 15 103 23.3% 0.48 [0.20, 1.12] Cao 2009 0 41 1 1 45 2.2% 0.37 [0.02, 8.72] Chody F 2016 1 54 0 44 0.9% 2.45 [0.10, 58.80] Delewi 2015 1 69 2 65 3.2% 0.47 [0.04, 50.7] Gao 2013 1 21 0 21 0.8% 3.00 [0.13, 69.70] Gao 2013 1 21 0 21 0.8% 3.00 [0.13, 69.70] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Huikuri 2008 0 40 1 40 2.4% 0.33 [0.01, 7.95] Laguna 2018 0 10 1 10 2.4% 0.33 [0.02, 7.32] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.02, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.02, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.02, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 8 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 9 2 40 2 20 4.2% 0.50 [0.08, 3.29] Quyyuni 2011 1 16 0 15 0.8% 2.82 [0.12, 64.39] Roman 2015 0 59 1 61 2.3% 0.34 [0.01, 8.29] Roman 2015 0 59 1 61 2.3% 0.34 [0.01, 8.29] Roman 2015 0 59 1 61 2.3% 0.34 [0.01, 8.29] Roman 2015 0 59 1 61 2.3% 0.34 [0.01, 8.29] Roman 2015 0 59 1 61 2.3% 0.34 [0.01, 8.29] Roman 2015 0 59 1 61 2.3% 0.34 [0.01, 8.29] Roman 2016 4 133 0 67 1.0% 4.57 [0.25, 63.80] Traverse 2011 0 58 1 29 3.1% 0.17 [0.01, 4.04] Wang 2014 1 28 2 30 3.0% 0.54 [0.05, 5.59] Whorle 2010 1 29 1 13 2.2% 0.45 [0.03, 6.63] Wang 2014 1 28 2 30 3.0% 0.54 [0.05, 5.59] Whorle 2017 1 71 1 22 0.22 0.8% 3.14 [0.13, 72.96] Subtrati (95% CI) 1565 1179 95.3% 0.75 [0.51, 1.08] Mathur Chi ² = 15.08, df = 27 (P = 0.97); P = 0%							
Cao 2009 0 41 1 45 2.2% 0.37 [0.02, 8.72] Chodry F 2016 1 54 0 44 0.9% 2.45 [0.10, 68.80] Delewi 2015 1 69 2 65 3.2% 0.47 [0.04, 5.07] Gao 2013 1 21 0 21 0.8% 3.00 [0.13, 69.70] Grajek 2010 1 31 0 14 1.1% 1.41 [0.06, 32.53] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Huikuri 2008 0 40 1 40 2.4% 0.33 [0.01, 7.95] Janssens 2006 1 33 0 34 0.8% 3.09 [0.13, 73.20] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Meyer OP 2009 2 30 3.1% 1.00 [0.15, 6.64]							
Chodry F 2016 1 54 0 44 0.9% 2.45 [0.10, 58.80] Delewi 2015 1 69 2 65 3.2% 0.47 [0.04, 5.07] Grajek 2010 1 31 0 14 1.1% 3.00 [0.13, 69.70] Grajek 2010 1 31 0 14 1.1% 1.41 [0.06, 32.53] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Janssens 2006 1 33 0 34 0.8% 3.09 [0.13, 73.20] Laguna 2018 0 10 1 10 2.4% 0.33 [0.02, 7.32] Meyer GP 2009 2 30 2 30 3.1% 1.00 [0.15, 6.64] Naseri 2018 1 51 0 2.6 1.0% 4.28 [0.24, 75.20] Pienicka 2007 3 17 0 10 8.0% [0.10, 2.41] — Plexibit 2010 2 19 4.2% [0.24, 75.20] — — Quyumi 2017 1 100 6 59 9.7% [0.16] [0.02, 1.29] —							
Delewi 2015 1 69 2 65 3.2% 0.47 [0.04, 5.07] Gao 2013 1 21 0 21 0.8% 3.00 [0.13, 69.70] Grajek 2010 1 31 0 14 1.1% 1.41 [0.6, 32.53] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Huikuri 2008 0 40 1 40 2.4% 0.33 [0.01, 7.95] Janssens 2006 1 33 0 34 0.8% 3.09 [0.13, 73.20] Laguna 2018 0 10 1 10 2.4% 0.33 [0.02, 7.32] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Maseri 2018 1 51 0 26 1.0% 1.56 [0.07, 36.86] Penicka 2007 3 17 0 10.9% 0.50 [0.10, 2.41]							
Gao 2013 1 21 0 21 0.8% 3.00 [0.13, 69.70] Grajek 2010 1 31 0 14 1.1% 1.41 [0.06, 32.53] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Janssens 2006 1 33 0 34 0.8% 3.09 [0.13, 73.20] Laguna 2018 0 10 1 10 2.4% 0.33 [0.02, 7.32] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 6 185 7 190 1.0% 0.88 [0.30, 2.57] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2.57] Mathur A 2020 1 10 2.6 1.0% 1.86 [0.01, 2.41]							
Grajek 2010 1 31 0 14 1.1% 1.41 [0.06, 32.53] Haddad 2020 0 17 1 20 2.2% 0.39 [0.02, 8.97] Huikuri 2008 0 40 1 40 2.4% 0.33 [0.01, 7.95] Janssens 2006 1 33 0 34 0.8% 3.09 [0.13, 73.20] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2, 732] Mathur A 2020 6 185 7 190 10.9% 0.88 [0.30, 2, 732] Mathur A 2020 6 185 7 100 10.9% 0.88 [0.30, 2, 73] Meyer GP 2009 2 30 3.1% 1.00 [0.15, 6.64]							
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Heterogeneity: Chi ² = 15.08, df = 27 (P = 0.97); i ² = 0%							
Test for overall effect: Z = 1.53 (P = 0.13)							
1.17.2 Allogeneic							
Chullikana 2015 0 10 1 10 2.4% 0.33 [0.02, 7.32]							
Subtotal (95% CI) 10 10 2.4% 0.33 [0.02, 7.32]							
Total events 0 1							
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.70 (P = 0.49)							
1.17.3 Not mentioned							
Gao 2015 0 58 1 57 2 4% 0 33 /0 01 7 881							
Subtotal (95% Cl) 58 57 2.4% 0.33 [0.01,7,88]							
Hotomonoity: Not anninghia							
Testfor overall effect $7 = 0.69$ ($P = 0.49$)							
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Test for system energy Chile 0.50 // Favours [experimental] Favours [control]							

2. Serious adverse events:

Twelve RCTs with 1161 participants (571 participants in the stem cell group and 590 participants in the control group) reported SAEs at the end of follow up (<6 months to > 12 months). Pooled analysis revealed a risk ratio of 0.93 (95% CI: 0.76 to1.14), which was statistically non-significant.

2.1. Comparison of serious adverse events reported in stem cell therapy group in comparison with control based on time of assessment:

	Interven	tion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.26.1 time of assess	ment upt	o 6 mo	nths				
Huikuri 2008	6	40	9	40	6.6%	0.67 [0.26, 1.70]	- _
Janssens 2006	2	33	2	34	1.5%	1.03 [0.15, 6.89]	
Roncalli 2011	26	52	19	49	14.4%	1.29 [0.83, 2.01]	- + •
Subtotal (95% CI)		125		123	22.5%	1.09 [0.73, 1.62]	•
Total events	34		30				
Heterogeneity: Chi ² =	1.62, df=	2 (P = 0	0.45); I ^z =	0%			
Test for overall effect: .	Z = 0.42 (P = 0.67	7)				
1.26.2 time of assess	ment upt	o 12 m	onths				
Grajek 2010	1	31	1	14	1.0%	0.45 [0.03, 6.71]	
Hare 2009	8	39	6	21	5.8%	0.72 [0.29, 1.79]	
Laguna 2018	0	10	1	10	1.1%	0.33 [0.02, 7.32]	
Piepoli MF 2010	5	19	5	19	3.7%	1.00 [0.35, 2.90]	
Quyyumi 2011	3	16	2	15	1.5%	1.41 [0.27, 7.28]	
Roman 2015	4	59	6	61	4.4%	0.69 [0.20, 2.32]	
Subtotal (95% CI)		174		140	17.4%	0.79 [0.46, 1.36]	-
Total events	21		21				
Heterogeneity: Chi ² = 1.22, df = 5 (P = 0.94); l ² = 0%							
Test for overall effect: Z = 0.85 (P = 0.40)							
1.26.3 time of assess	ment mo	re than	12 mont	ths			
Assmus 2014	9	101	11	103	8.0%	0.83 [0.36, 1.93]	
Chullikana 2015	0	10	3	10	2.6%	0.14 [0.01, 2.45]	· · · · · · · · · · · · · · · · · · ·
Mathur A 2020	57	161	78	214	49.4%	0.97 [0.74, 1.28]	
Subtotal (95% CI)		272		327	60.0%	0.92 [0.71, 1.19]	•
Total events	66		92				
Heterogeneity: Chi ² =	1.86, df=	2 (P = 0	0.39); I ² =	0%			
Test for overall effect: .	Z = 0.65 (I	P = 0.52	2)				
Total (95% CI)		571		590	100.0%	0.93 [0.76, 1.14]	•
Total events	121		143				
Heterogeneity: Chi ² =	5.87, df=	11 (P =	0.88); l²:	= 0%			
Test for overall effect: .	Z = 0.66 (P = 0.51	1)				Favours [experimental] Favours [control]
Test for subgroup diffe	erences: (Chi²= O	.96, df = 3	2 (P = 0	l.62), I ² =	0%	r arears (experimental) in arears (certably

3. Recurrent-myocardial infarction:

Eighteen RCTs with 1981 participants (1158 in the stem cell group and 823 in the control group) reported the incidence of recurrent-myocardial infarction at the end of follow up (<6 months to > 12 months). Pooled analysis revealed a risk ratio of 0.67 (95% CI: 0.43 to 1.05), which was statistically non-significant.

3.1. Effect of stem cell therapy on re-myocardial infarction in subjects with acute myocardial infarction based on time of assessment:

	Interven	tion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.38.1 time of assess	sment upt	o 6 moi	nths				
Huikuri 2008	0	40	2	40	5.9%	0.20 [0.01, 4.04]	• • • • • • • • • • • • • • • • • • • •
Tendera 2009	3	160	2	40	7.5%	0.38 [0.06, 2.17]	
Traverse 2011	1	58	0	29	1.6%	1.53 [0.06, 36.33]	
Subtotal (95% CI)		258		109	15.0%	0.43 [0.11, 1.59]	
Total events	4		4				
Heterogeneity: Chi* =	0.89, df = 1	2 (P = C	J.64); I*=	0%			
Test for overall effect:	Z = 1.27 (F	P = 0.20	J)				
1.38.2 time of assess	sment upt	o 12 m	onths				
Chodry F 2016	3	55	2	45	5.2%	1.23 [0.21, 7.03]	
Grajek 2010	1	31	1	14	3.2%	0.45 [0.03, 6.71]	
Roman 2015	3	59	0	61	1.2%	7.23 [0.38, 137.08]	
Surder 2016	1	133	2	67	6.3%	0.25 [0.02, 2.73]	
Traverse 2018	2	79	3	41	9.3%	0.35 [0.06, 1.99]	=
Yao 2009 a	0	27	1	12	4.8%	0.15 [0.01, 3.55]	<
Subtotal (95% CI)		384		240	30.0 %	0.73 [0.33, 1.59]	
Total events	10		9				
Heterogeneity: Chi ² =	5.19, df = :	5 (P = 0	0.39); I ^z =	4%			
Test for overall effect:	Z = 0.80 (F	P = 0.42	2)				
1.38.3 time of assess	sment mo	re than	12 mont	hs			
Assmus 2014	5	101	7	103	16.3%	0.73 [0.24, 2.22]	
Delewi 2015	1	69	1	65	2.4%	0.94 [0.06, 14.75]	
Gao 2013	1	19	0	20	1.1%	3.15 [0.14, 72.88]	
Haddad 2020	1	17	1	20	2.2%	1.18 [0.08, 17.42]	· · · · · · · · · · · · · · · · · · ·
Mathur A 2020	5	185	7	190	16.3%	0.73 [0.24, 2.27]	
Meyer GP 2009	1	30	1	30	2.4%	1.00 [0.07, 15.26]	
Naseri 2018	0	51	2	26	7.8%	0.10 [0.01, 2.09]	•
Penicka 2007	1	14	0	10	1.4%	2.20 [0.10, 49.06]	
Traverse 2010	0	30	1	10	5.2%	0.12 [0.01, 2.69]	
Subtotal (95% CI)		516		474	55.0%	0.71 [0.39, 1.30]	-
Total events	15		20				
Heterogeneity: Chi ² =	4.45, df=	8 (P = 0).81); I ² =	0%			
Test for overall effect:	Z = 1.12 (F	P = 0.26	6)				
Total (95% CI)		1158		823	100.0%	0.67 [0.43, 1.05]	•
Total events	29		33				
Heterogeneity: Chi ² =	10.91, df=	= 17 (P	= 0.86); P	²= 0%			
Test for overall effect:	Z = 1.74 (F	P = 0.08	3)				Favours (experimental) Favours (control)
Test for subaroun diff	erences: (Chi≝ = 0	53 $df = 3$	7 (P = 1))77) I₹=	0%	areas [experimental] - areas [control]

4. Hospitalization due to heart failure:

Nineteen RCTs with 1641 participants (928 in the stem cell group vs 713 in the control group) reported the incidence of hospitalization due to heart failure at the end of follow up (< than 6 months to > 12 months). Pooled analysis comparing hospitalization due to heart failure between the stem cells and the control group yielded a risk ratio of 0.79 (95% CI: 0.52 to 1.20), which was statistically non-significant.

4.1. Effect of stem cell therapy on hospitalization due to heart failure in comparison with control based on time of assessment

	Intervent	tion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.32.1 time of assess	ment upto	o 6 moi	nths				
Assmus 2014	5	101	9	103	19.4%	0.57 [0.20, 1.63]	
Roncalli 2011	4	52	2	49	4.5%	1.88 [0.36, 9.83]	
Traverse 2011	1	58	0	29	1.4%	1.53 [0.06, 36.33]	
Wollert 2017	1	71	1	26	3.2%	0.37 [0.02, 5.64]	
Subtotal (95% CI)		282		207	28.6%	0.80 [0.36, 1.76]	
Total events	11		12				
Heterogeneity: Chi ² =	1.91, df = 0	3 (P = 0).59); l² =	0%			
Test for overall effect:	Z = 0.56 (F	P = 0.58	3)				
1.32.2 time of assess	ment upto	o 12 m	onths				
Colombo 2011	0	5	1	5	3.3%	0.33 [0.02, 6.65]	
Piepoli MF 2010	1	19	2	19	4.4%	0.50 [0.05, 5.06]	
Quyyumi 2011	1	16	0	15	1.1%	2.82 [0.12, 64.39]	
Roman 2015	3	59	7	61	15.0%	0.44 [0.12, 1.63]	
Surder 2016	4	133	3	67	8.7%	0.67 [0.15, 2.92]	
Traverse 2018	5	79	2	41	5.7%	1.30 [0.26, 6.40]	
Zhang 2021	3	21	4	22	8.5%	0.79 [0.20, 3.10]	
Subtotal (95% CI)		332		230	46.8%	0.71 [0.38, 1.33]	-
Total events	17		19				
Heterogeneity: Chi ² =	2.16, df = 6	6 (P = 0).90); I² =	0%			
Test for overall effect:	Z=1.07 (F	P = 0.28	3)				
1.32.3 time of assess	ment mor	re than	12 mont	hs			
Can 2009	1	41	0	45	1.0%	3 29 (0 14 78 47)	
Delewi 2015	'n	69	3	65	7.9%	0.13 [0.01 2.56]	·
Gan 2013	ñ	19	1	20	3.2%	0.35 [0.07, 2.00]	_
Gao 2015	1	58	, U	57	1 1 96	2 95 0 12 70 92	
Haddad 2020	1	17	1	20	2.0%		
Mever GP 2009	2	30	3	30	6.5%	0.67 [0.12, 3.71]	.
Naseri 2018	2	51	ñ	26	14%	2 60 0 13 52 17	
Whorle J 2010	2	29	ñ	13	1.5%	2 33 [0 12 45 45]	
Subtotal (95% CI)	-	314	Ū	276	24.7%	0.92 [0.40, 2.13]	-
Total events	9		8			- / -	
Heterogeneity: Chi ² =	4.14. df = 3	7 (P = 0).76): I ² =	0%			
Test for overall effect:	Z = 0.19 (F	P = 0.85	5)				
Total (95% CI)		928		713	100.0%	0.79 [0.52, 1.20]	•
Total events	37		20				-
Heterogeneity: Chi ² =	97 851 df=1	18 (P -	0.07\·I≊-	= 0%			
Test for overall effect:	7 = 1 11 /F	· • · • = • = 0.25	7) 7)	0.0			0.01 0.1 1 10 100
Test for subgroup diffe	erences: (:hi² = 0	25 df=0	7 (P = 1)88) I₹=	0%	Favours [experimental] Favours [control]

5. Stroke incidence:

Eight RCTs with 1121 participants (610 in stem cell group and 511 in the control group) reported the incidence of stroke at the end of follow up (< than 6 months to > 12 months). Pooled analysis revealed a risk ratio of 0.81 (95% CI: 0.41 to 1.60), which was statistically non-significant.

5.1. Stroke incidence reported in stem cell group in comparison with control based on time of assessment



6. Cancer incidence:

Six RCTs with 807 participants (411 in stem cell group and396 in control group) reported the incidence of cancer at the end of follow up (< than 6 months to > 12 months). Pooled analysis revealed a risk ratio of 0.82 (95% CI: 0.43 to 1.55), which was statistically non-significant.

6.1. Cancer incidences reported in stem cell group vs control group based on time of assessment:



7. Left ventricular ejection fraction (LVEF):

Nineteen RCTs with 20 comparisons (909 participants, 480 in the stem cell group, and 429 in the control group) reported the LVEF (%) measured by echocardiography at the end of follow up (< than 6 months to >12 months). The mean difference in LVEF was 2.53% (95% CI: 0.95 to 4.10), which was statistically significant but clinically unimportant as it was less than the MCID of 5%.

7.1. Efficacy of stem cell therapy on LVEF (%) (End of the study) in comparison with control LVEF measured by Echocardiography based on the time of assessment:

	Inte	rventio	n		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 time of assessme	ent upto	6 month	IS						
Attar 2023 a	50	10.21	20	44.27	8.65	12	3.5%	5.73 [-0.90, 12.36]	
Attar 2023 b	53	12.11	20	44.27	8.65	13	3.2%	8.73 [1.64, 15.82]	
Ge 2006	58.6	9.9	10	56.3	3.5	10	3.6%	2.30 [-4.21, 8.81]	
Huikuri 2008	60	8	39	56	10	38	5.8%	4.00 [-0.05, 8.05]	
Lee 2014	50	8.4	30	50.4	9.4	28	5.2%	-0.40 [-5.00, 4.20]	
Roncalli 2011	39.1	10.2	48	41.5	8.8	44	6.0%	-2.40 [-6.28, 1.48]	
Srimahachota S 2011	38	9.4	11	42	8.7	12	3.1%	-4.00 [-11.42, 3.42]	• • • • •
Wen X 2012	44	2.6	17	38.6	3.7	21	8.2%	5.40 [3.39, 7.41]	
Subtotal (95% CI)			195			178	38.7%	2.44 [-0.45, 5.33]	
Heterogeneity: Tau ² = 1	0.55; Chi	i ² = 21.6	5, df =	7 (P = 0	.003); l² =	: 68%			
Test for overall effect: Z	= 1.65 (F	P = 0.10)							
122 time of assessme	ent unto	12 mont	he						
Angoli 2012	41.0	0.6	11	42.1	10.6	4.4	2.5%	1 20 60 65 7 251	
Colombo 2011	41.9	5.0	6	40.1	67		2.3%	-1.20 [-9.00, 7.20] 6 00 [-2 10 12 00]	
Grojek 2018	40.2	7.0	27	40.5	11 74	12	2.770	5.90 [-2.19, 13.99]	
Upro 2000	49.90	10.21	24	44.4 56.1	5.0	10	5.170	0.00[2.64,6.14]	
Kaminak M 2010	20.9	10.31	24	30.1	10	26	5.5%	0.00 [-3.34, 5.14]	
Kaminek W 2010	40	40	37	43	2.2	10	7.6%	3.00[-1.37,7.37]	
Thene 2021	40	9.2	10	44.0 60.6	2.3	10	7.0%	0.50 [-2.00, 3.00]	
Subtotal (95% CI)	02	0.0	146	09.0	5.0	113	32.7%	1.65 [0.00, 3.30]	
Heterogeneity: Tau ² = 0.00: Chi ² = 4.06. df = 6 (P = 0.67): I ² = 0%									
Test for overall effect: Z = 1.96 (P = 0.05)									
1.2.3 time of assessme	ent more	than 12	? mont	hs					
Cao 2009	50.5	5	41	46.4	5.2	45	8.0%	4.10 [1.94, 6.26]	
Chullikana 2015	46.98	7.56	8	45	10.21	8	2.4%	1.98 [-6.82, 10.78]	
Gao 2013	55.1	7.846	19	54.9	7.1554	20	5.1%	0.20 [-4.52, 4.92]	
Gao 2015	60	0.5	57	54	0.8	55	9.4%	6.00 [5.75, 6.25]	•
Penicka 2007	45	9	14	47	7	10	3.7%	-2.00 [-8.41, 4.41]	
Subtotal (95% CI)			139			138	28.6%	3.27 [0.64, 5.91]	
Heterogeneity: Tau ² = 5	.05; Chi²	= 15.38	df = 4	(P = 0.1)	004); I ² =	74%			
Test for overall effect: Z	= 2.43 (F	P = 0.01)							
Total (95% CI)			480			429	100.0%	2.53 [0.95, 4.10]	
Heterogeneity: Tau ² = 6	87: Chi ^z	= 78.57	df = 1	9 (P < 0	000011	2 = 76	%		
Test for overall effect: Z	= 3.14 (F	P = 0.002	2)						-10 -5 0 5 10 Favours (experimental) Favours (control)

Test for subgroup differences: Chi² = 1.09, df = 2 (P = 0.58), I² = 0%

SUMMARY OF FINDIN	IGS:					
Stem cell therapy compar	ed to usual care for l	Myocardial Infarction				
Patient or population: My Setting: Hospital Intervention: Stem cell the Comparison: Usual care	ocardial Infarction rapy					
	Anticipated ab	solute effects*(95% CI)		No. of	Certainty of the	
Outcomes	Risk with No Cell	Risk with Cell	Relative effect (95% CI)	participants (studies)	evidence (GRADE)	Comments
Mortality	41 per 1,000	30 per 1,000 (20 to 43)	RR 0.73 (0.50 to 1.05)	2879 (30 RCTs)	$\oplus \oplus \bigcirc \bigcirc$ Low ^{a,b}	
SAE frequency	242 per 1,000	225 per 1,000 (184 to 276)	RR 0.93 (0.76 to 1.14)	1161 (12 RCTs)	$\oplus \bigcirc \bigcirc$ Very low ^{b,c}	
Re MI frequency	40 per 1,000	27 per 1,000 (17 to 42)	RR 0.67 (0.43 to 1.05)	1981 (18 RCTs)	⊕⊖⊖⊖ Very low ^{b,d}	
Heart Failure Frequency	55 per 1,000	43 per 1,000 (27 to 66)	RR 0.79 (0.50 to 1.20)	1641 (19 RCTs)	$\oplus \oplus \bigcirc \bigcirc$ Low ^{b,e}	
Stroke frequency	27 per 1,000	22 per 1,000 (11 to 44)	RR 0.81 (0.41 to 1.60)	1121 (8 RCTs)	$\oplus \oplus \bigcirc \bigcirc$ Low ^{a,b}	
Cancer incidence	45 per 1,000	37 per 1,000 (20 to 70)	RR 0.82 (0.43 to 1.55)	807 (6 RCTs)	⊕⊕⊕⊖ Moderate ^b	
LVEF (2D ECHO) End of the study	1	MD 2.53 higher (0.95 higher to 4.1 higher)		909 (19RCTs)	⊕⊕⊖⊖ Low ^f	
*The risk in the intervention CI: confidence interval; MD: me	group (and its 95% con ean difference; RR: risk r	fidence interval) is based on the a atio	ssumed risk in the comp	trison group and the re l	lative effect of the interventio	n (and its 95% CI).
GRADE Working Group gradt High certainty: We are very cc Moderate certainty: We are n different. Low certainty: Our confidence Very low certainty: We have v	s of evidence mfident that the true eff anderately confident in t in the effect estimate is 'ery little confidence in t	ect lies close to that of the estimat he effect estimate: the true effect limited: the true effect may be sul he effect estimate: the true effect i	e of the effect. is likely to be close to the sstantially different from is likely to be substantiall	estimate of the effect, b the estimate of the effe	ut with a possibility that it is s. .t. mate of effect.	ubstantially
Explanations a. Only 33.3% of trials have low b. Confidence interval crosses th c. Only 25% of trials have low ri d. Only 22% of trials have low ri f. Only 27% of trials have low ris	risk of bias le point if no difference sk of bias sk of bias sk of bias sk of bias					

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EVIDENCE PROFILE:

			certainty assess	ment				Sum	mary of findi	ugs	
Participants	Dich				Dukli coti cu	Overall	Study even	t rates (%)	Relative	Anticipat eff	ects
(studies) Follow-up	bias	Inconsistency	Indirectness	Imprecision	Fublication bias	certainty of evidence	Usual care	Stem cell therapy	effect (95% CI)	Risk with No Cell	Risk difference with Cell
Mortality											
2879 (30 RCTs)	Serious ^a	Not serious	Not serious	Serious ^b	None	⊕⊕⊖⊖ Low ^{a,b}	51/1246 (4.1%)	44/1633 (2.7%)	RR 0.73 (0.50 to 1.05)	51/1246 (4.1%)	11 fewer per 1,000 (from 20 fewer to 2 more)
SAE frequenc	y										
1161 (12 RCTs)	Very serious ^c	Not serious	Not serious	Serious ^b	None	Φ ΟΟΟ Very low ^{b,c}	143/590 (24.2%)	121/571 (21.2%)	RR 0.93 (0.76 to 1.14)	143/590 (24.2%)	17 fewer per 1,000 (from 58 fewer to 34 more)
Recurrent MI	l frequend	ŷ									
1981 (18 RCTs)	Very serious ^d	Not serious	Not serious	Serious ^b	None	⊕⊖⊖⊖ Very lowbd	33/823 (4.0%)	29/1158 (2.5%)	RR 0.67 (0.43 to 1.05)	33/823 (4.0%)	13 fewer per 1,000 (from 23 fewer to 2 more)
Heart Failur	e Frequer	ıcy									
1641 (19 RCTs)	Serious ^e	Not serious	Not serious	Serious ^b	None	⊕⊕⊖⊖ Lowbe	39/713 (5.5%)	37/928 (4.0%)	RR 0.79 (0.52 to 1.20)	39/713 (5.5%)	12 fewer per 1,000 (from 27 fewer to 11 more)

Stroke frequency

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EVIDENCE PROFILE:

	5 fewer per 1,000 (from 16 fewer to 16 more)		3 fewer per 1,000 (from 26 fewer to 25 more)	
sgr	14/511 (2.7%)		18/396 (4.5%)	
imary of findi	RR 0.81 (0.41 to 1.60)		RR 0.82 (0.43 to 1.55)	
Sum	13/610 (2.1%)		15/411 (3.6%)	
	14/511 (2.7%)		18/396 (4.5%)	
	⊕⊕⊖⊖ Low ^{ab}		⊕⊕⊕⊖ Moderate ^b	
	None		None	
Certainty assessment	Serious ^b		Serious ^b	
	Not serious		Not serious	
	Not serious		Not serious	f the study
	Serious ^a	ence	Not serious	HO) End of
	1121 (8 RCTs)	Cancer incid	807 (6 RCTs)	LVEF (2D EC

	MD 2.53	higher	(0.95 higher	to 4.1	higher)
	-				
	-				
	-				
	ı				
	$\bigcirc\bigcirc\oplus\oplus$	Low^{f}			
	None				
	Not serious				
	Not serious				
•	Not serious				
•	Very	serious ^f			
,	606	(19 RCTs)			

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Only 33.3% of trials have low risk of bias
 b. Confidence interval crosses the point if no difference
 c. Only 25% of trials have low risk of bias
 d. Only 22% of trials have low risk of bias
 e. Only 42% of trials have low risk of bias
 f. Only 27% of trials have low risk of bias

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D. SUMMARY OF JUDGMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Trivial*
Undesirable Effects	Trivial**
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the
	comparison
Resources required	Large costs***
Certainty of evidence of required	Moderate
resources	
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes

Recommendation: Stem cell therapy is **not recommended** in routine clinical practice for the treatment of myocardial infarction.

*This judgment was made as there is very low certainty evidence of trivial improvement in function and mortality. ** This judgment was made as there is little or no difference in undesirable effects between stem cell therapy and usual care.

*** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

- Lack of sufficient number of RCTs with low risk of bias.
- Small number of events in the included trials.
- Heterogeneity across trials in patient population, type of stem cell therapy, cell dosage, route of administration and time of administration.
- Lack of long-term follow up of patients thus providing insufficient evidence on the safety of this experimental therapy.
- Lack of cost effectiveness data.

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III. PRIORITY AREAS FOR FUTURE RESEARCH

Stem cell therapy is a rapidly growing field with significant potential, but continued research is needed to optimize stem cell types, delivery methods, and clinical outcomes. It is essential to adopt an evidence-based approach in the development of these regenerative therapies, ensuring that the best available evidence is used to evaluate their true effectiveness and safety. Currently, most available evidence is of very low certainty.

Based on the assessment of evidence (clinically important difference, statistical significance and certainty of evidence) for the safety and efficacy of stem cell therapy in the included cardiology conditions, priority areas for future research were identified and are as follows:

- Dilated Cardiomyopathy
- Myocardial Infarction

Further studies are required to demonstrate and establish the mechanism of action of stem cell therapy and optimize selection of stem cell type & route of administration through well designed preclinical studies and large multicenter RCTs with adequate long-term follow up. In addition, primary research to understand the values and preferences of Indian patients as well as studies on cost effectiveness of stem cell therapy is also encouraged.

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IV. ANNEXURES

Annexure 1: CONTRIBUTORS

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Annexure 2: DECLARATION OF INTEREST (DoI)

Name	Declaration Interest (s)	Management of conflict(s) of
		interest
Dr. Sushama Nagarkar, Patient representative from Yash Charitable Trust	Declared that the outcome of the meeting or work may affect the interests of people with whom she has substantial personal/professional interests.	The steering group observed this as a potential conflict of interest and therefore decided against her inclusion in the GDG.
Dr. Kameshwar Prasad, Fortis Flt Lt Rajan Dhall Hospital, Vasant Kunj, New Delhi	None declared	Not applicable
Dr. M Jeeva Sankar Mari, AIIMS (AIIMS), New Delhi	None declared	Not applicable
Dr. Rakesh Lodha, AIIMS, New Delhi	None declared	Not applicable
Dr. Anil Gurtoo, Lady Hardinge Medical College (LHMC), New Delhi	None declared	Not applicable
Dr. Ranjan Das, All India Institute of Hygiene & Public Health, Kolkata	None declared	Not applicable
Dr. Shankar Prinja, Post Graduate Institute of Medical Education & Research, Chandigarh	None declared	Not applicable
Dr. Roli Mathur, Indian Council of Medical Research (ICMR) Headquarters, New Delhi	None declared	Not applicable
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Dr. Priya Parmar, India Cancer Society, New Delhi	None declared	Not applicable
Ms. Manisha Bhattacharya, Mental Health Foundation, Kolkata	None declared	Not applicable
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Dr. Alok Srivastava, Christian Medical College, Vellore	None declared	Not applicable
Dr. Sujata Mohanty, AIIMS, New Delhi	She declared that she is a member of the Subject Expert Committees of CDSCO & NMC.	The Steering Group did not see it as a potential CoI.
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CENTRE FOR EVIDENCE-BASED GUIDELINES

The Centre for Evidence based Guidelines was established in February 2023 at the Department of Health Research in collaboration with DGHS, NHSRC, various program divisions of DoHFW, and other stakeholders under the umbrella of Ministry of Health & amp; Family Welfare (MoHFW). The main mandate is to develop evidence-based guidelines by systematically reviewing available evidence and applying the GRADE methodology to assess the certainty of evidence. In addition, the centre conducts capacity-building activities, including workshops on systematic reviews and the GRADE approach, as well as training sessions to enhance the competency of Guideline Development Group (GDG) and other stakeholders in guideline development methodologies. Through these initiatives, it ensures that healthcare decisions are informed by the best available evidence, ultimately improving patient care and health outcomes. In September 2024, the Centre established Technical Resource Centers (TRCs) across the country to assist in evidence synthesis by conducting systematic reviews and meta-analyses, thereby enabling consistent, high-quality guideline development.

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