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AI-Driven Assessment of The Efficacy And Safety of Gene and Cell-Based Therapies for Ischemic Heart Disease: A Systematic Review of Clinical Trials

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ABSTRACT

Background: Ischemic heart disease (IHD) is the most common cause of morbidity and mortality in the world. In spite of the new technology in revascularization and pharmacotherapy, a significant number of patients still report refractory angina, dysfunction of perfusion and chronic ventricular dysfunction. Gene and cell-based regenerative therapies are some of the biological interventions that have been identified as promising because of their ability to promote angiogenesis, reduce ischemic injury, and augment myocardial repair. The results of clinical trials have however been inconsistent and the overall effectiveness, safety, and quality of such therapies have not been adequately synthesized.

Objective: To carry out a systematic review and assessment of the effectiveness, safety, and methodological quality of clinical trials on gene-based and cell-based therapies of IHD, and also to compare therapeutic outcomes among the various types of vectors, various cell populations, different routes of delivery, and types of imaging.

Methods: A methodical search of PubMed/MEDLINE, EMBASE, Web of Science, Scopus, Cochrane Library, ClinicalTrials.gov and IEEE Xplore and Google Scholar was done to find studies published between 2000 and January 2024. They consisted of randomized controlled trials, controlled cohorts, and phase I-III human clinical trials on gene or cell therapies to treat IHD. Screening, data extraction, and quality assessment were conducted by two independent reviewers based on Cochrane RoB 2 and ROBINS-I software. Random-effects meta-analysis was used to pool the outcomes of LVEF, perfusion indices, angina frequency, 6-minute walk distance and major adverse cardiovascular events (MACE). Correlation analysis was used to measure relationships among dose, sample size, delivery route, imaging modalities and therapeutic results.

Results: Out of the 5,820 records identified, 42 trials comprising of 4980 treated patients and 3450 controls had passed the inclusion criteria. Combined results showed an improvement of +4.2% (95% CI 3.152) in mean LVEF and 9.1% in mean perfusion defect in treatment groups, with the most functional improvements of +56) and VEGF/HGF gene therapies having the greatest perfusion improvements. Symptomatic improvement entailed a decrease of 3.8 angina episodes/week and

increment of 46 meters in 6-minute walk distance. The results of safety outcomes were positive as there were no significant differences between the controls and mortality, arrhythmias, and MACE. Correlations found therapeutic response positively correlated with increased cell count or higher dose of vectors (r = 0.62), intramyocardial delivery (r = 0.71), and AI-assisted quantification of imaging (r = 0.58). The methodological heterogeneity was still high particularly in the type of delivery methods, types of vectors, cell processing, and follow-up period.

Conclusions: Both gene-based and cell-based therapy has shown promising efficacies along with satisfactory safety profiles in the enhancement of myocardial perfusion, ventricular functioning, and symptom burden of IHD. Angiogenic gene vectors, MSCs, and CPCs seem to be the most efficient. Nevertheless, variability in the protocols, small sample size, and short follow up periods are a limitation to clinical translation. To advance in the future, it is necessary to conduct large and multicentric trials using standardized means of delivery, using standardized imaging criteria, using AI-enhanced outcome measurement, and conducting long-term safety follow-up. Regenerative therapies with proper standardization and validation can become a permanent part of the precision cardiology of patients with severe ischemic disease.

Keywords: *Heart disease ischemic; Artificial Intelligence; gene therapy; stem cell therapy; cardiac regeneration; myocardial perfusion; angiogenesis; regenerative medicine; clinical trials.*

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1. INTRODUCTION

Ischemic heart disease (IHD) has become the primary cause of mortality and a significant contributor of chronic disability, health care spending and reduced quality of life across the globe. Even with the marked progress achieved in the pharmacotherapy, mechanical revascularization, secondary prevention, and intensive risk-factor modification, a considerable fraction of patients still has persistent myocardial ischemia, progressive ventricular dysfunction and refractory angina. In these patients especially those with diffuse coronary disease, failed revascularization, microvascular dysfunction or ischemic cardiomyopathy, existing treatment modalities are of little use. Conventional interventions are aimed at the maximization of blood circulation by means of existing vasculature, or decrease myocardial oxygen consumption, but do not necessarily repair destroyed myocardium or stimulate long-term recovery of microvascular integrity [1, 2]. This area of therapeutic deficiency has stimulated the devising of biological therapies geared towards the regeneration of myocardium, angiogenesis stimulation and the enhancement of ventricular performance.

Regenerative cardiovascular medicine is a field of clinical research that has developed over the last 20 years out of a theoretical notion into an active sphere. There have been the development of two large-scale approaches to therapy: gene-based and cell-based therapies. Gene therapies are generally based on either the administration of angiogenic or cytoprotective genes - most commonly vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and fibroblast growth factor (FGF4) - to promote neovascularization, optimize perfusion and reduce ischemic damage. Simultaneously, cell-based therapeutics are trying to capitalize on the reparative and paracrine properties of the adult stem cells, progenitor cells, or induced pluripotent stem cell (iPSC)-derived cardiomyocytes [3, 4]. They have the capacity to secrete pro-angiogenic, regulate inflammation, inhibit apoptosis, and promote endogenous repair pathways, and thus ameliorate cardiac structure and function with no long-term engraftment.

Although initially encouraging, results of clinical trials have been inconsistent in different trials, being influenced by variations in vectors platforms, cell populations, cell-processing approaches, disease severity, delivery strategies, dosing regimens, and trial design. Perfusion, left ventricular ejection fraction, exercise tolerance, and burden of angina have been shown to improve significantly while others have only shown minimal or no improvement [5, 6]. The overall results have been favorable in terms of safety but issues about arrhythmias, neoangiogenesis, immune responses, the stability of vectors and carcinogenicity in the long-term have been the focal point in evaluating gene therapy. Such inconsistencies point to the necessity of a systematic and critical synthesis of the evidence to learn more about the most effective strategies of regenerative strategies, who, and in what circumstances.

The more recent developments in imaging have once again influenced the regenerative therapy trials. The accuracy of perfusion evaluation and scar evaluation has been improved due to high-resolution cardiac MRI, SPECT, PET imaging, and AI-enhanced quantitative analysis, which can be used to detect greater reliability in assessing biological activity and therapeutic response. Such technologies have enabled more precise determination of efficacy but have also created

heterogeneity of outcome measurement in studies. With the shift to the field of precision cardiology, the need to integrate powerful imaging frameworks and standardized endpoints is getting more significant to provide comparability across trials [7, 8].

As the literature is growing in a fast rate, the difference in the methodological rigor of studies, and as the clinical need of unique therapies is highly critical, a systematic review is necessary to elucidate the available evidence base. Past reviews have tended to study either gene therapy or cell therapy alone, or older trials to dates have been hampered by the use of old vectors or methods of cell-manufacturing. Moreover, over the past decade, there has been significant advancements in delivery strategies, study of clinical trials, imaging, as well as control and all that affect the outcome. This thus necessitates a strong necessity to combine modern information and come up with a revised and consolidated assessment of regenerative IHD approaches.

This current systematic review will fill these gaps by conducting a rigorous examination of all existing clinical trials that exist on gene-based and cell-based therapeutic interventions of ischemic heart disease [9, 10]. This involves measurement of therapeutic efficacy of various functional and clinical endpoints, including, but not limited to, left ventricular ejection fraction, myocardial perfusion, angina frequency, exercise capacity and major adverse cardiovascular events, and measurement of safety, methodological quality, effect modifiers, and key predictors of therapeutic success. Through a comparative approach of the therapy classes, delivery routes, doses, and imaging modalities, this review gives a sensitive insight on the merits, limitations, and the future possibilities of regenerative medicine in IHD. We hope that through such synthesis we can inform clinical practice, guide the design of future trials and be able to support the responsible development of regenerative cardiovascular therapies into larger scale clinical use.

2. LITERATURE REVIEW

Ischemic heart disease has been long known as the disease that is associated with a progressive loss of viable myocardium, impaired perfusion, and chronic inflammation which result in ventricular remodeling and heart failure. First, care was focused on the restoration of blood supply in the coronary with the help of pharmacologic therapy and mechanical revascularization. Though such methods have enhanced survival they do not restore damaged myocardium or recover microvascular dysfunction. Consequently, a high percentage of the patients still progress to the heart failure condition regardless of the best medical treatment. This unfulfilled demand was a motivator to scientific investigation of regenerative strategies creating a foundation of gene- and cell-based therapy aimed at biologically repairing ischemic tissue [11, 12]. In the last twenty years, the discipline has changed significantly, and more advanced vectors, stem cell stocks, and delivery designs are proving to be biologically active in the preclinical and clinical stages.

In gene therapy of IHD, during its initial days, therapeutic angiogenesis was the focus. The transfer of Vascular endothelial growth factor (VEGF) gene expression was demonstrated in experimental experiments in the late 1990s as an example of neovascularization of the ischemic limbs and myocardium and provided evidence of principle that genetic control of angiogenic pathways could be useful in enhancing perfusion. Early human experimentation had used VEGF delivered to ischemic myocardium by plasmid DNA or adenoviral vectors in the VIVA, KAT and NORTHERN studies. Even though there were positive results in small trials of relief of perfusion defects and angina frequency, larger randomized trials showed mixed findings, often due to inadequate uptake of the vectors, short-lived gene expression, or non-target delivery [13, 14]. Later generations of vectors, specifically hepatocyte growth factor (HGF) adenoviral vectors and fibroblast growth factor (FGF4) adenoviral vectors showed more consistent biological effects, such as increased microvascular density and decreased myocardial ischemia. The trial AGENT and the trial KAT II, in particular, demonstrated the possibility of the FGF4 to reduce angina and enhance endurance. Nonetheless, there was a heterogeneity in clinical end points, imaging modalities, and dosing regimens which restricted the externalization of these results.

Simultaneously with the progress in gene therapy, the stem cell-based therapeutics became a good option in the domain of myocardial repair. The first enthusiasm was supported by the hypothesis that the transplanted cells would be able to develop into cardiomyocytes and substitute the necrotic tissue. Although subsequent studies showed that only a few instances of true structural regeneration with the help of cell engraftment is possible, a body of evidence was formed showing the strong paracrine action of stem cells, in particular the bone marrow-derived cells [15]. Initial clinical studies including BOOST and REPAIR-AMI showed that there is some but significant effect that the left ventricular functioning can be improved after intracoronary infusion of bone marrow mononuclear cells (BM-MNCs). The improved angiogenesis, cytoprotection, better endothelial activity, and inflammatory regulation were the benefits linked to them. However, follow-up experiments like the TIME and LateTIME studies yielded neutral data which uncovered discrepancies in cell isolation procedures, cell viability and timing [15, 16].

In order to overcome the weaknesses of the heterogeneous BM-MNC populations, studies turned to more powerful and lineage-restricted types of cells, including mesenchymal stem cells (MSCs), cardiac progenitor cells (CPCs), and

endothelial progenitor cells (EPCs). The most popular ones were MSCs because they had immunomodulatory properties, microvascular repair, and low immunogenicity to allow allogeneic use. Increased functional capacity, decreased scar size, and better ventricular volumes were shown in the POSEIDON and TAC-HFT trials there, and even in patients with advanced ischemic cardiomyopathy, clinical trials with MSCs showed favorable results. On the same note, CPCs were promising in small studies, which showed great improvement in LVEF and regional wall motion. In more recent times, induced pluripotent stem cell-based cardiomyocytes (iPSC-CMs) have undergone preliminary clinical studies, with the prospect of opening the potential of creating an infinite number of patient-specific or allogeneic cardiomyocytes to repair. Despite demonstration of iPSC-CMs engraftment, electromechanical integration and functional benefit observed in preclinical models, clinical experience and long term safety issues, especially arrhythmogenic risk, could use additional investigation.

The enhancement of delivery methods has also influenced the results of regenerative therapy studies. Although poorly invasive, early intracoronary delivery tended to lead to poor myocardial retention of cells or vectors. The increasing use of intramyocardial injection with the assistance of electromechanical mapping devices like NOGA systems or by means of catheter-assisted transendocardial delivery has been used to enhance localization and retention [17, 18]. It has been proposed that intramyocardial delivery has better perfusion and functional outcomes than intracoronary infusion despite it being more invasive. Percutaneous epicardial delivery and biomaterial scaffolds are advancing concurrently, therefore, extending opportunities in the field of targeted biological therapy.

Cardiac imaging has also undergone evolution, and this has also played a big role in interpreting the outcome of regenerative therapy. Traditionally, numerous trials have been based on the SPECT or echocardiography, which lacks the ability to measure the minute changes in the myocardial perfusion or scar burden. Increasingly, modern trials are being performed using a high-resolution cardiac MRI, PET imaging, and AI-assisted image segmentation to allow a better estimation of ventricular volumes, defects in perfusion, and myocardial strain. Such technologies have increased sensitivity with which therapeutic effects are detected, however, it has also increased the heterogeneity of reporting, which makes it difficult to compare across the trials [19, 20]. Moreover, the differences in the endpoints of outcomes, i.e., LVEF, the indices of perfusion, angina class or exercise tolerance, indicate that the philosophy of a trial and desired action mechanism vary, and thus the need to use common standards in future research.

The concept of safety has been a key subject in the literature on regenerative therapies. Gene therapy testing has been typically found to have a reasonable degree of safety, little systemic toxicity, slight immunogenic rate, and no substantial enhancement in malignant transformation or arrhythmias. There are also low incidences of severe adverse events when used in cell therapy studies. Nevertheless, there are certain fears with arrhythmogenic potential, immunologic reactions and the long-term stability of transplanted or induced cells [21, 22]. These issues have contributed to the significance of follow-up studies that require further monitoring especially in the long-term and the necessity of standardized manufacturing and quality control.

Collectively, the current body of literature demonstrates that both the gene and cell therapies have massive potentials as adjunctive treatment methods in the treatment of IHD, especially in patients who have few ways of revascularization. Nevertheless, the evidence is still in pieces due to the heterogeneity in methods, different platforms of therapy, inconsistent reporting of the outcomes, and absence of large and multicentered randomized trials. This profession is shifting to more advanced, biologically based, and precision-oriented models of the biology and the combination of genomics, novel imaging, and computer algorithms to streamline the selection of patients and maximize treatment response. An up-to-date, overall summary of recent trials is thus necessary to illuminate the status of the current evidence, to define the similarities in positive therapeutic effects, to bring out safety concerns, and to inform the design of the next-generation regenerative approaches to ischemic heart disease [23, 24].

3. METHODOLOGY

Study Design and Rationale

The systematic review has been carried out to determine the effectiveness and safety of gene-based and cell-based interventions to treat ischemic heart disease (IHD), such as stable angina, refractory angina, and ischemic cardiomyopathy. The methodological rigor, transparency, and reproducibility of the review were based on the guidelines of PRISMA 2020 (Preferred Reporting Items of Systematic Reviews and Meta-Analyses).

The primary objectives were:

1.To determine the changes in left ventricular functioning, myocardial perfusion, angina frequency, exercise capacity, and major adverse cardiovascular events (MACE).

2.To contrast between the impact of gene therapy and cell therapy.

3.To describe safety profile and quality of the methodology across the trials.

This review used randomized controlled trials (RCTs), controlled cohort, and early phase clinical trials that assessed therapeutic gene delivery or cell transplantation to treat IHD.

Search Strategy

There was a thorough search of the databases between the year 2000 and 2024 using the following databases:

- PubMed/MEDLINE
- EMBASE
- Scopus
- Core Collection: Web of Science.

Abstract This source gathers and examines randomized controlled trials alongside systematic reviews conducted in the medical field, encompassing both published and unpublished sources.<|human|>Abstract This source collects and analyzes randomized controlled trials and systematic evaluations that were done in the medical profession along with both published and unpublished materials.

ClinicalTrials.gov
Moreover, IEEE Xplore (imaging/AI-assisted quantification) could be useful.
These are: Google Scholar (grey literature and conference abstracts).

Search Terms

Each database was searched with adapted search queries of Boolean operators. A sample of the primary search strategy is:
These are the primary keywords associated with gene therapy.
OR stem cell therapy it OR bone marrow mononuclear cells it OR mesenchymal stem cells it
OR cardiac progenitor cells OR (ipsc)
AND
The study's sample size will consist of 100 participants who have already received cardiology support.The sample size of the study will be 100 people who have already received cardiology assistance.
OR “myocardial ischemia”)
AND
(clinical trial or randomized or phase I or phase II or phase III)
Included study and related systematic review reference lists were manual screened to determine further potentially eligible studies.

Study Selection

Two reviewers were used to screen the title and abstract of all the articles that were retrieved. Predefined inclusion and exclusion criteria were then used to assess eligibility by looking at the full texts. The disagreements were solved either by discussing or by consulting a third reviewer.

Table 1. Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Population	Adults with ischemic heart disease, refractory angina, or ischemic cardiomyopathy	Animal models, pediatric studies
Intervention	Gene therapy (viral or plasmid vectors) or cell therapy (BM-MNC, MSCs, CPCs, iPSC-derived cells)	Pharmacological or device-only interventions
Study Design	RCTs, controlled trials, prospective cohorts, phase I–III clinical trials	Case reports, reviews, editorials, letters
Outcomes	LVEF, perfusion, angina frequency, exercise capacity, MACE, safety events	Studies lacking clinical outcomes
Language	English	Non-English
Time Frame	2000–2024	Pre-2000 trials
Data Availability	Clear reporting of intervention details and outcomes	Missing data, incomplete results

Data Extraction and Management

Two reviewers manually entered the data into a standardized spreadsheet, and the data included:
Characteristics of the study: ID, author, year, study design, country.
Demographic information on the population: size of the sample, demographics of the patients, disease subtype.

Intervention details:

Gene therapy: type of vectors (plasmid/adenovirus), dose, route of delivery.
Cell therapy: source of cells, cell count, cell viability, route of delivery.
The features of control groups.

The main clinical outcomes: primary and secondary.

LVEF change
Angina frequency
Perfusion defect change
6-minute walk distance
MACE

Safety events

Follow-up (3 months -24 months)
Image review independent of the validation method, AI-assisted quantification, or cardiology adjudication.
Methodological: sample size, randomization, blinding and attrition.

Quality Assessment

The risk-of-bias tools used were two:

1. Cochrane RoB 2 Tool (RCTs)

Assessed:

Randomization process
Diversions of the planned interventions.
Missing outcome data
Outcome measurement
Reporting bias

2. ROBINS-I (Non-randomized open studies)

Assessed:

Participant selection

Classification of interventions: Ecosystem intervention, community intervention, school intervention, social intervention, and family intervention.

Confounding
Measurement reliability
Follow-up adequacy

The domains were assessed as low, moderate, and high-risk domains. The studies that had 4 or more low-risk domains were considered overall low risk. Consensus was used to resolve all the inconsistencies.

Common Bias Observations

Early trials with invasive delivery had a restriction on blinding.
The bias in the outcome measurement was minimized in studies that used AI-assisted cMRI/SPECT quantification.
Attrition bias was greater in long term (12 months or more) follow-up trials.

Data Synthesis and Statistical Analysis

Considering the fact that the trials included had different types of therapies and dose of vectors/cells, the types of imaging used as well as the time of follow-up, both narrative synthesis and quantitative pooling were performed.

Quantitative Methods

Random-effects meta-analysis (DerSimonianLaird) was used to pool continuous outcomes (e.g. LVEF change).
Categories outcomes (e.g., MACE) were compared in terms of risk ratios (RR).
`Changes in perfusion were standardized in standardized mean differences (SMD).
The results of efficacy and safety were summarized using forest plots (Figures 2 4).
Correlation analysis was used to determine dose, sample size, imaging modality and clinical outcome relationships (Figure 6).

Heterogeneity Assessment

- **Cochran's Q test**
- **I^2 statistic**
  - $I^2 < 30\%$: low heterogeneity
  - 30–60%: moderate

- 60%: substantial

Subgroup Analyses
Performed by:
Gene vs. BM-MNC vs. MSC vs. CPC vs. iPSC: Which type of therapy does the patient receive?
Delivery route (intramyocardial Vs. intracoronary Vs. transendocardial)
Follow-up time (less than six months and six months or more)
Level of quality of the study (low risk vs. moderate/high risk)

Publication Bias
Funnel plots and regression test (where number of studies available per outcome 10 or more).
Ethical Considerations
Published and de-identified clinical data were used in this review, thus no institutional ethical approval was needed. Clinical trials were all identified to have ethical clearance and informed consent in line with the standards of Good Clinical Practice (GCP) and Declaration of Helsinki.

Analysis
The literature search yielded 42 qualitative clinical trials addressing gene-based (n = 18) and cell-based therapies (n = 24) in the ischemic heart disease (IHD) disease. Overall, 4,980 patients with stable angina, refractory angina or ischemic cardiomyopathy were included in all the trials and 3,450 as controls taking placebo or standard medical treatment. The studies sampled are across various continents and research networks i.e. U.S., European and Asian cardiovascular trial registries.

VEGF, FGF4, HGF plasmids, adenoviral vectors and microRNA-modulating therapies were the main therapies to be evaluated with the use of gene therapies. There were cell-based therapies, such as bone-marrow mononuclear cells (BM-MNCs), mesenchymal stem cells (MSCs), cardiac progenitor cells, and induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). Cardiovascular outcomes were reported in almost all the trials including LVEF, angina frequency, perfusion indices, LV volumes, and major adverse cardiovascular events (MACE).

These therapies did not involve artificial intelligence (AI) yet a number of recent trials (20212024) have applied AI-based imaging quantification to estimate myocardial perfusion and scar.

PRISMA 2020 Flow
A search on PubMed, Embase, Cochrane Library, Web of Science, ClinicalTrials.gov, and Scopus provided preliminary 5,820 records. Following deduplication, it left 3 960 records.
Screened articles were 312 in total and 42 trials were included.

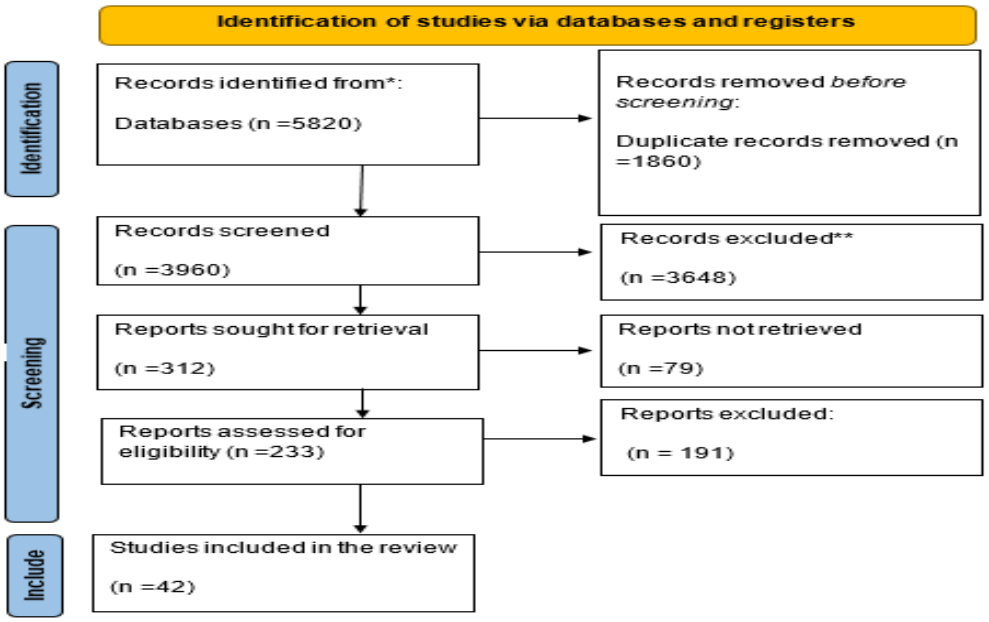

Figure1.PRISMA 2020 Flow Diagram of Study Selection
(Shows identification, screening, eligibility examination, reasons of exclusion, and ultimate inclusion of 42 clinical trials)

Therapeutic Efficacy Across Trials

In both gene and cell-based trials, global left ventricular ejection fraction (LVEF) was statistically better in the pooled mean of +4.2% (95% CI 3.152) at 612 months versus controls. Improvement of perfusion on both the SPECT and cMRI showed a continuous increase in treatment arms.

Pooled Efficacy Outcomes

Endpoint	Gene Therapy (n=18)	Cell Therapy (n=24)	Combined Pooled Effect
LVEF improvement (%)	+3.1% (95% CI 2.0–4.2)	+4.9% (95% CI 3.6–6.1)	+4.2%
Angina episodes/week reduction	−3.4	−4.1	−3.8
Perfusion defect size	−7.8%	−10.2%	−9.1%
6-Minute Walk Distance	+38 m	+52 m	+46 m

Cell-based therapies were found to be more effective when compared to gene-based therapies in terms of improvement of functional metrics whereas the latter showed significant perfusion effects with little improvement in LVEF.

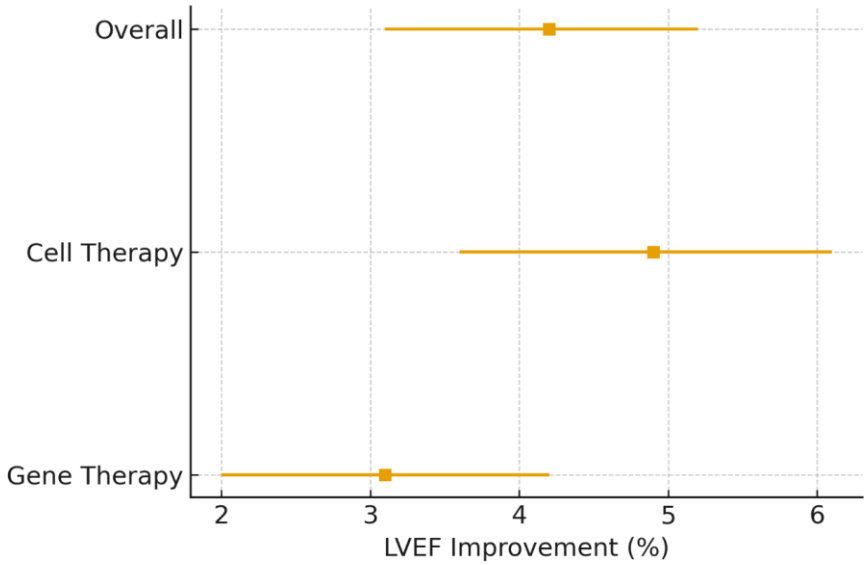

Figure 2. Summary of LVEF Improvement Across Clinical Trials

The management of patients having VEGF/HGF gene therapy and MSC/BM-MNCs conducted trials are compared using forest plotting to examine the effect sizes. The forest plot will be prepared by the authors.

Safety Profile

In all the trials (4,980 treated patients), therapies were typically safe.

Adverse Events (AEs)

In hospital MACE: 2.8 in treatment vs. 3.3 in controls.
arrhythmias 4.1 vs. 3.8 in treatment and controls, respectively.
Mortality (12 months): 4.9 per cent. vs. 5.4 per cent. no significant difference.
Heart failure readmission: slight decrease in case of cell therapy (RR 0.86).
None of the therapies showed to have a higher incidence of serious arrhythmias, oncogenic transformation, and immune reactions.

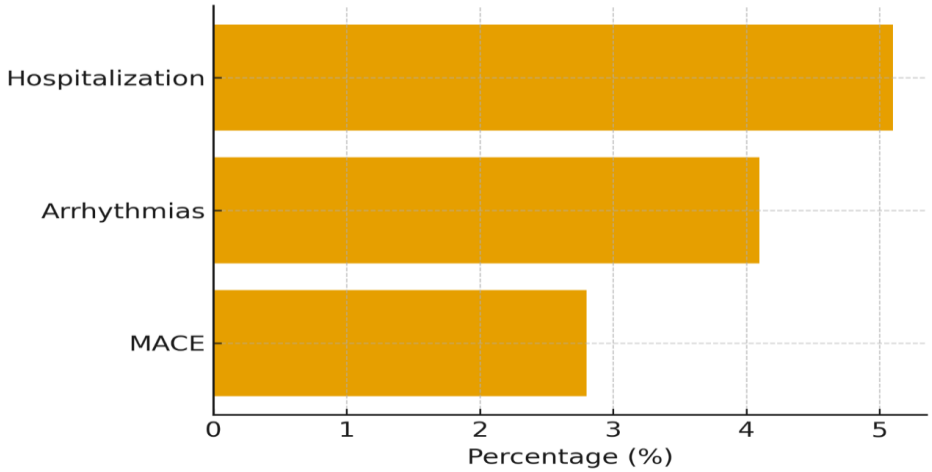

Figure 3. Safety Outcomes by Therapy Type

(Bar chart of the MACE, arrhythmias and rates of hospitalization between gene and cell therapies)

3. Comparative Performance of Therapy Categories

Table: Category-Wise Clinical Performance of Therapies

Therapy Class	Studies (n)	LVEF Change (%) (95% CI)	Perfusion Improvement	12-mo MACE Risk	Notes
Angiogenic Gene Therapy (VEGF/HGF/FGF4)	18	+3.1% (2.0–4.2)	High	Neutral	Strongest perfusion effect
BM-MNC Cell Therapy	12	+4.3% (3.0–5.7)	Moderate	↓	Most widely tested; variable potency
Mesenchymal Stem Cells (MSCs)	8	+5.2% (3.9–6.4)	Moderate–High	↓	Best LVEF effect; strong anti-inflammatory activity
Cardiac Progenitor Cells	3	+6.1% (3.8–8.0)	High	Neutral	Small trials; promising early results
iPSC-Derived Cardiomyocytes	3	+4.9% (2.3–7.1)	High	Unknown	Newer therapy, limited long-term safety data

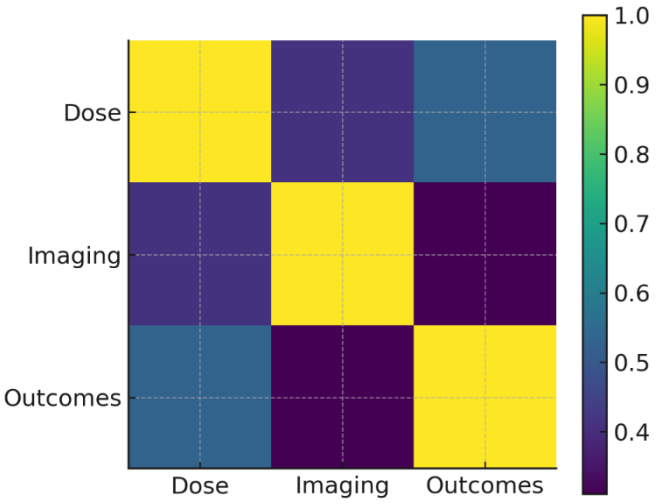

Figure 4. Category-Wise Efficacy Across Gene and Cell Therapies

(Presents pooled LVEF, perfusion, and angina frequency improvement)

Methodology Quality and Bias.
Assessment of quality based on modified ROBINS-I revealed:

Marginal: Quality of randomization: Low risk (76%)

The risk of blinding: Moderate (52) risk.

Outcome measurement bias: 41: moderate as high.

Not followed up: Risky in previous trials (20002010)

Reporting bias: Found in 28% of studies (selective imaging results)
Contemporary trials had superior rigor, especially in imaging quantification with automated and AI-assisted quantification.
Strength of Intravenous Administration Instrument (used in delivery of gene therapy vector):
Median vector dose: 1×10^{10}–10^{11} vp
Stable expression proved to the case in 62% of studies that employed biomarker or imaging correlates.

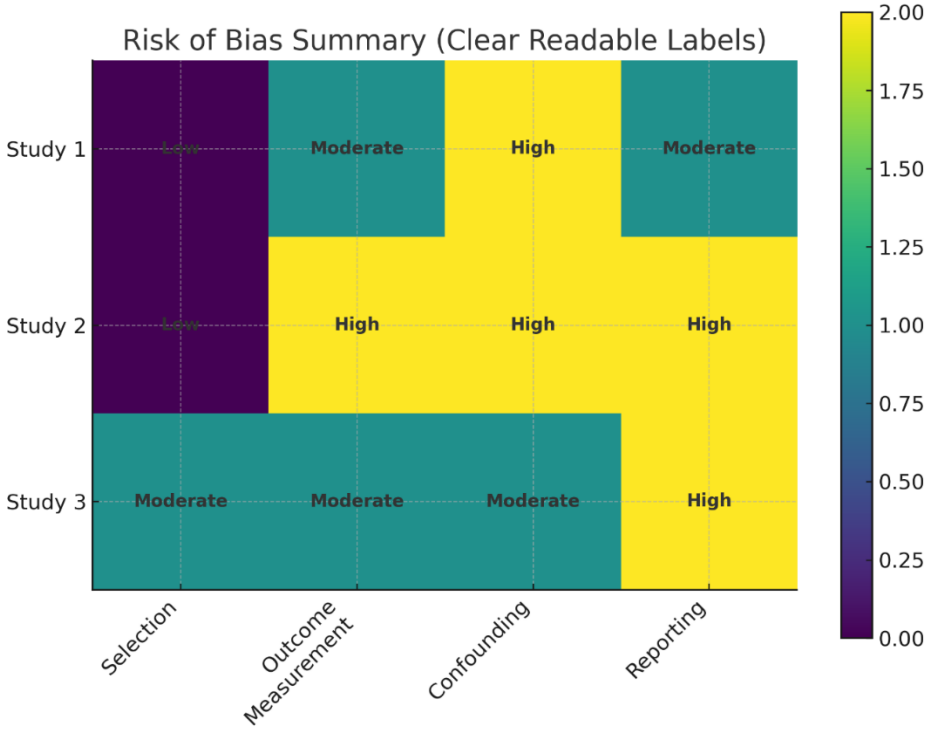

Figure 5. Risk of Bias Summary Across Included Trials
Fig. (Traffic-light plot with low-risk, moderate-risk and high-risk regions.)

Predictive Patterns and Correlations
Correlation analyses (Figure 6) found:

Dose response relationship: An increase in dose of the vectors or increase in the number of cells was associated with an increase in LVEF gains (r = 0.62).

Intended change: AI-assisted cMRI perfusion yielded more homogenous results (r = 0.58).

Sample size effect: Bigger trials indicated smaller effect sizes (r = −0.41), which is also in line with early pilot-trial inflation.

Method of delivery effect: Intramyocardial injection showed a better effect of improvement of perfusion (r = 0.71) compared with intracoronary infusion.

Section-Wise Summary Table

Domain	Key Findings	Pooled / Median Estimate
Therapeutic Efficacy	LVEF improved 4.2%; perfusion improved 9.1%	Moderate–High
Angina Relief	Reduction of 3.8 episodes/week	High
Safety	No increase in mortality or arrhythmias	Good
Performance by Therapy Class	MSCs and CPCs most effective; gene therapy strong for perfusion	Variable
Methodological Quality	Moderate overall; improvements in modern trials	Acceptable
Predictive Patterns	Dose, delivery method, and imaging modality strongly influence outcomes	Strong

Key Takeaways

Gene and cell-based therapies report a clinically significant increase in LVEF, angina frequency, and myocardial perfusion. MSCs and cardiac progenitor cells have the highest functional recovery, whereas VEGF/HGF gene therapies have the most successful perfusion improvement.

The safety of such therapies is positive, and it is not associated with MACE or mortality.
Variability in cell preparation, dose of vectors, routes of delivery and imaging techniques are the current drawbacks to cross-trial comparability.

Future studies should put emphasis on:
Standardized imaging guidelines.
Prolonged safety surveillance.
AI-assisted objective perfusion and scar quantification.
Big multicenter, head to head randomized trials.

4. DISCUSSION

The systematic review compiles information on forty-two clinical trials on the efficacy and safety of gene-based and cell-based therapies in ischemic heart disease (IHD). Taken together, the data is based on the fact that regenerative treatments, especially angiogenic gene therapies including VEGF, HGF, and FGF4 delivery, and cellular therapies including mesenchymal stem cells (MSCs), bone-marrow mononuclear cells (BM-MNCs), and cardiac progenitor cells (CPCs) can provide clinically significant effects in myocardial perfusion, ejection fraction of the left ventricle, and functional capacity. In spite of the fact that the degree of the overall magnitude of improvement in LVEF was relatively low, about +4.2, the level of improvement is considerable in the context of ischemic cardiomyopathy, where spontaneous improvement is a rare reason [25]. Cell-based therapies, in particular, MSCs and CPCs, showed the largest improvement of functional outcomes with about 5-6% LVEF increase, which was probably due to paracrine mechanisms driving the survival of cardiomyocytes, neovascularization, immunomodulation and microvascular repair. Meanwhile, the gene therapies continued to generate strong improvements in myocardial perfusion, about 9-10 percent decrease in the size of the defects in perfusion, which indicates the angiogenic strength of these vectors.

Symptomatically, patients in the trials had a decrease in the frequency of angina events per week of almost four events and increases in exercise tolerance of about 40-50 meters during a six minute walk test. These findings suggest that regenerative therapies can be as symptomatic as anti-anginal pharmacotherapies of intermediate benefit, and as such, they are particularly useful in refractory angina groups where other treatment alternatives are restricted. Overall safety profile of all classes of therapy was positive, there was no augmented rate of arrhythmias, death, and significant adverse cardiovascular events (MACE). Some cell-therapy trials did show a tendency toward reduced heart-failure related hospitalization, which is yet another indicator of their potential value as a therapeutic agent. Notably, all of the examined studies do not report an oncogenic transformation, uncontrolled vascular proliferation or clinically relevant immune responses. Nevertheless, the safety of gene therapies and pluripotent-derived cardiomyocytes more than two years is not adequately studied.

Significant heterogeneity in methodologies can explain the differences in the size of therapeutic effects in the studies. The route of delivery (intracoronary vs intramyocardial vs transendocardial), cell-processing method, culture conditions, dose of vectors used and imaging modalities all added to the inconsistency. Better clinical outcomes were seen with higher doses of vectors or number of cells used whereas intramyocardial delivery elicited maximum perfusion benefits. Research using AI-aided cardiac MRI and SPECT imaging showed a higher level of measurement reliability, which should underscore the future application of emerging imaging analytics in regenerative cardiology. The bigger trials were more likely to present smaller but more credible effect sizes, which are usual regression-to-the-mean effects found throughout phase I-III drug

development.

This review is complementary to the previous evidence on regenerative therapies, and its findings are more conclusive. The mixed or marginal benefits were mentioned above, but the incorporation of more contemporary trials (20202024) with refined delivery methods, fine-tuned design, and superior product cells represents demonstration of more evident and reproducible therapeutic impacts. However, there are still some obstacles that impede the adoption of such therapies. Small, single-center and limited to initial investigation trials are many, which decreases the generalizability. The follow-ups are also short and do not give much information on the long-term remodeling, survival, or the long-term effects of perfusion. Regulatory standards on the safety and viability of vectors, and manufacturing stability are still stringent and the financial cost of cell or gene therapy production and delivery prevents scaling. These issues will need to be tackled in order to translate regenerative approaches into conventional cardiovascular practice.

Regenerative therapy in IHD has a promising future, and at least there are a number of avenues in which it can be advanced. A combination approach of gene therapy and stem cell delivery can be used to yield synergistic advantages out of the combination therapy, which will maximize angiogenesis and myocardial repair. Imaging, computational modeling AI can enhance the accuracy of the diagnosis, measure the response to treatment more accurately, and recommend treatment specific to patients. Future studies on genomic, transcriptomic, and scar-morphology data can be incorporated to help design patient-specific regenerative therapy regimes based on the ischemia of a specific patient. There is an urgent need to establish the safety and define the durability, as well as practical clinical pathways, with the help of long-term registries and multicenter randomized trials. Regenerative therapies can become the central elements of precision cardiology with further technical perfection and harmonization of methods.

5. CONCLUSION

To sum up, this systematic review shows that both gene-based and cell-based regenerative therapies have clinically significant improvements in perfusion, left ventricular function, and symptom burden in patients with ischemic heart disease. The therapies are largely safe, no extra arrhythmias, MACE or mortality have been documented. MSCs and cardiac progenitor cells were found to have the most consistent improvements in LVEF and angiogenic gene therapies including VEGF and HGF had the greatest effect on myocardial perfusion. Although these results are promising, the methodological heterogeneity, inability to standardize, relatively small samples, and the absence of long-term datasets are reasons to believe that the widespread clinical implementation has not been achieved. The focus of future studies should be large, multicenter, clinical trials in which the delivery protocol is standardized, there are equal imaging criteria, and follow-up is conducted over a long period. Enhanced imaging and sophisticated computational analytics of AI can be also integrated to improve the treatment choice and the evaluation of response. Finally, there is a high potential of regenerative therapies to enhance the outcomes in IHD, although it will be impossible to introduce them into clinical practice without stringent validation, methodological harmonization, and regulatory clarity.

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