Available online on 15.12.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access

Review Article

Stem Cell Therapy Used For Treatment of Heart Disease

Mahale Nikita S., Chothave Sayali J, Muthe Sakshi S, Barokar Pooja G, Kapadi Suvarna S.

Pravara Rural Education Society's College of Pharmacy (for women's), Chincholi, Nashik, Maharashtra, India

A B S T R A C T

Heart disease continues to be the foremost cause of death globally, largely due to the heart's limited capacity for self-repair following injury. Conventional treatments, such as pharmacological therapy, mechanical support, and surgical interventions, primarily manage symptoms and slow disease progression but cannot regenerate damaged myocardium. In recent years, stem cell therapy has emerged as a promising regenerative strategy aimed at restoring cardiac structure and function. Various stem cell types—including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and cardiac progenitor cells (CPCs)—have shown potential to promote myocardial regeneration through differentiation into cardiomyocytes, stimulation of angiogenesis, and paracrine signaling mechanisms. Preclinical studies have demonstrated improved ventricular function and reduced infarct size, while clinical trials have reported modest yet encouraging functional recovery in patients with ischemic heart disease. However, several challenges limit widespread clinical application, including poor cell survival and engraftment, immune rejection, risk of arrhythmogenesis and tumorigenicity, and ethical concerns regarding cell sources. Recent advances in tissue engineering, gene editing, and exosome-based cell-free therapies may help overcome these limitations. This review highlights the current progress, therapeutic potential, and major challenges of stem cell-based therapies in cardiac repair, emphasizing the need for standardized protocols and long-term clinical evaluation to achieve safe and effective translation into clinical practice.

Keywords: Heart disease, stem cell therapy, myocardial regeneration, mesenchymal stem cells, induced pluripotent stem cells, cardiac repair.

A R T I C L E I N F O: Received 16 Sept. 2025; Review Complete 17 Oct. 2025; Accepted 21 Nov. 2025; Available online 15 Dec. 2025

Cite this article as:

Mahale N S, Chothave S J, Muthe S S, Barokar P G, Kapadi S S, Stem Cell Therapy Used For Treatment of Heart Disease, Asian Journal of Pharmaceutical Research and Development. 2025; 13(6):79-86, DOI: http://dx.doi.org/10.22270/ajprd.v13i6.1659

*Address for Correspondence:

Mahale Nikita S, Pravara Rural Education Society's College of Pharmacy (for women's), Chincholi , Nashik,422102,Maharashtra,India

INTRODUCTION

Because the blood vessels giving oxygen and nutrients to the local zone are blocked, ischemia is defined by insufficient blood flow to that area. When an organ, such as the heart, brain, limbs, etc., does not receive enough blood and oxygen, it is said to be ischemic. Worldwide, ischemic illnesses result in mortality and disability in people. Consequently, one of the main goals of treating ischemia illnesses is to restore the blood supply. Angiogenesis is a crucial treatment for ischemic illnesses since it is a process that creates new capillaries from the vascular bed.[1] The primary cause of morbidity and mortality globally is cardiovascular (CV) events, which are frequent aftereffects of ischemic heart disease (IHD) . Acute myocardial infarction (AMI) and chronic ischemic heart failure (HF) are becoming more common despite the tremendous advancements in interventional cardiology, cardiac surgery, and medication .A common characteristic of AMI that underlies HF is the progressive loss of cardiomyocytes due to apoptosis, or programmed cell death. Many patients develop HF and dilated cardiomyopathy (CM) as a result of the current standard invasive and non-invasive cardiac therapies' inability to effectively repair the damaged cardiac tissue following an AMI.

The leading cause of death worldwide, including in the majority of low- and middle-income nations, is ischemic heart disease, which is typified by a decreased blood supply to the heart muscle. [2]Cardiomyocyte death results from myocardial infarction, or heart attack, which is caused by blockage of the coronary arteries. Heart failure results from overloading the remaining myocardium.

A progressive loss of cardiomyocytes is another feature of heart failure caused by chronic high blood pressure, and experimental inhibition of programmed cell death can enhance cardiac function.Heart transplantation is the only conventional treatment for heart failure that tackles the underlying issue of cardiomyocyte loss. Clinical research has exploded as a result of new findings regarding the regenerative potential of stem cells and progenitor cells for the treatment and prevention of heart failure. It is pertinent toexamine the current status of this field because the critical point at which it is determined that laboratory data adequately supports clinical experimentation is especially contentious in the case of stem-cell therapy for heart failure. We go over what is currently known about adult mammalian heart regeneration in this review.We also examine the main obstacles to such therapy and take into account the different types of stem cells and progenitor cells that may be able to regenerate the myocardium. [3]

In cardiovascular medicine, stem cells have become a viable treatment option for a number of conditions, including CHD, due to their capacity for regeneration. This method was first investigated for the treatment of adult patients suffering from heart failure (HF) and myocardial infarction.. Numerous preclinical and clinical investigations have evaluated the viability and effectiveness of stem cell therapy in both ischemic and nonischemic cardiomyopathy in recent years. Numerous stem cell populations, such as bone marrow mononuclear cells, mesenchymal, and cardiac stem cells, have been assessed; their safety and effectiveness appear to be promising. [4]In the US and around the world, cardiovascular disease is the primary cause of death and morbidity.One

Cardiovascular diseases, which are primarily caused by myocardial infarction (MI) and its deadly aftereffects, heart failure, and sudden cardiac death, place a heavy financial and psychological burden on patients, their families, and society as a whole. CV mortality has dramatically decreased as a result of numerous advancements in conventional medicine and surgery over the last 50 years.One The only proven cure for chronic heart disease is heart transplantation; despite significant advancements, medical or surgical treatment only results in a temporary delay in the disease's progression.In the past ten years, the use of stem or precursor cells has become a prominent regenerative strategy for the treatment of heart disease.

In this regard, mesenchymal stem cells (MSCs) are promising options for cellular therapy for a number of fibrotic diseases in addition to heart disease. [5]One of the most promising areas of contemporary science and medicine is cell-based therapy, a type of regenerative medicine. Such cutting-edge technology presents countless opportunities for revolutionary and possibly curative therapies for some of the most serious illnesses facing humanity.

Regenerative medicine is rapidly becoming the next big thing in health care with the particular aim of repairing and possibly replacing diseased cells, tissues or organs and eventually retrieving normal function. Thankfully, the idea of using regenerative medicine instead of traditional drug-based treatments is becoming more and more real every day because of the research communities' strong dedication to examining the potential uses for a variety of illnesses, including diabetes and neurodegenerative diseases, among many others. [6]

TYPES OF STEM CELLS USED FOR HEART DISEASE

Mesenchymal Stem Cells (MSCs)

Adipose tissues, muscles, bone marrow, and umbilical cord blood are among the tissues that contain mesenchymal stem cells, which are stem cells derived from mesoderm. Cell therapy studies have increasingly examined both BM- and non-BM-derived (such as adipose tissue) MSCs, as well as "pre-conditioned" cardiopoietic MSCs, even though it is still unknown how biologically similar MSCs from different tissue sources are. [7]The precursors of non-hematopoietic tissues, such as muscle, bone, tendons, ligaments, adipose tissue, and fibroblasts, are mesenchymal stem cells (MSCs), also known as bone marrow stromal cells. MSCs can be used for cardiac regeneration under specific circumstances when they differentiate into cells that resemble cardiac myocytes . [8]

MSCs were initially identified from a population of nonhematopoietic cells found in bone marrow . Since then, MSCs have been effectively isolated from nearly every tissue found in mammals, including dental pulp, skeletal muscle, adipose tissue, heart, placenta, UCB, menstrual blood, circulating blood, and pancreatic tissue . [9]

Multipotent cells with low immunogenic potential, known as MSCs, can be extracted from a variety of adult tissues, such as bone marrow, adipose tissue, and the umbilical cord. Since microenvironmental changes can have a significant impact on MSC properties, the niche of origin is a crucial consideration when assessing biological differences between cell types.Bone marrow-derived MSC (BM-MSC) has been used in the majority of experimental and clinical studies; however, these cells have drawbacks for clinical use, such as an invasive harvesting process and a reduced capacity for proliferation and differentiation due to donor age and comorbidity.

On the other hand, umbilical cord-derived MSCs (UC-MSC) are readily available, can be grown in vitro, exhibit less cellular aging, and pose no ethical issues.According to preclinical research, UC-MSC can express molecules specific to the heart (troponin-I, connexin-43), differentiate in vitro into endothelial and cardiomyocyte-like cells, and have paracrine effects that improve cardiomyocyte protection and vascular regeneration.

These processes could be the cause of the enhancement of cardiac function seen in animal models of dilated cardiomyopathy and chronic ischemic cardiomyopathy in response to UC-MSCs.Assessing the safety and effectiveness of an established intravenous source of UC-MSCs in patients with chronic HFrEF was the goal of this prospective, randomized, double blinded, placebo-controlled study [10].

MSCs can be made to differentiate into adipocytes, osteoblasts, chondrocytes, tenocytes, myocytes, and hematopoietic-supporting stroma with the right stimulation. Furthermore, demonstrating a high degree of plasticity, MSCs may also give rise to other lineages like endothelial, kidney, and neural. MSCs with a high ex vivo expansion capacity can be isolated from a variety of human sources, such as bone marrow and peripheral and umbilical cord blood.

This characteristic has been used to evaluate MSCs' biologic qualities carry out viral vector transfection , and start research on using MSCs in clinical approaches.MSCs' potential for long-term survival and engraft in specific target tissues is what gives them their promising therapeutic effect or effects.

It has been shown using animal models that donor cells engraft into the recipient animal's various mesenchymal tissues following syngeneic and/or xenogeneic transplantation of MSCs [11].

MSC Isolation and Growth

From a 10 mL BM aspirate, 50–400 million or even more cells can be obtained (after expansion). The ability of MSCs to adhere to plastic, the ability of monocytes to be separated from MSCs by trypsinization, and the use of density gradient centrifugation (i.e., Ficoll or Percoll) to separate non-nucleated red blood cells from nucleated cells or cell mobilization and isolation are the three essential steps that enable MSCs to be isolated from other BM cells. Samples are fractionated by density gradient for mononuclear cell isolation, resuspended in suitable culture medium containing specific batches of fetal bovine serum, and allowed to adhere to plastic dishes for two days.

Nonadherent cells are then removed, and the remaining cells are allowed to grow for two to three weeks in order to isolate MSC from a BM aspirate, cord blood, or peripheral blood. After multiple culture passages, cells appear uniformly spindle-shaped, although initially generating a heterogeneous adherent cell layer that includes small round cells and fibroblast-like cells. Confluent cells retain their multipotentiality after being trypsinized and permitted to divide for up to 40 generations. Phenotypic characterization is done using a panel of monoclonal antibodies that are directed against epitopes that are expressed on their surface [12].

In addition to immunomodulation, MSC therapy for cardiovascular disorders shows promise because it can regenerate and repair cardiac tissues. In addition to targeting myocardial damage sites, MSCs are immune-privileged, meaning allogeneic MSCs are well tolerated because they lack major MHCII and T-cell co-stimulatory signals. In addition to differentiating into cardiomyocytes and vascular lineages, they also secrete a variety of angiogenic, mitogenic, anti-apoptotic, and growth factor cocktail factors and have paracrine effects that aid in cardiac regeneration. Using MSCs has shown improvement in cardiac repair in both clinical trials and preclinical models of heart disease. Currently, there are nearly 90 registered trials examining the impact of MSC therapy on cardiac conditions [13].

Induced Pluripotent Stem Cells (IPSCS) and Derived Cells:

In the field of regenerative medicine, iPSCs—which are reprogrammed from somatic cells with specific factors—become more appealing. Initially, four factors—Oct3/4, Sox2, c-Myc, and Klf4—were introduced into mouse embryonic or adult fibroblasts to induce iPSCs

The transcription factors that produce iPSCs—c-Myc, Oct4, and Kruppel-like factor 4—are known oncogenes that can result in teratomas, despite the fact that they have enormous potential for cardiac regeneration. Although this issue may be avoided by more recent techniques that use temporary expression of the reprogramming factors, the pluripotent nature of these cells may still encourage the development of tumors.

The low iPSC generation efficiency and cell line variability are additional issues. Although iPSCs are currently not prepared for clinical application, it is possible that these technological obstacles will soon be removed and that iPSC-based approaches will prove beneficial for the therapy of HF given the quickly developing technology in this field [14].

The creation of pluripotent stem cells (SCs) from mouse fibroblasts through the retroviral introduction of four distinct transcription factors (c-Myc, octamer-binding transcription factor (Oct)3/4, Sox2, and Kruppel-like factor (Klf)4) was first reported by Takahashi and Yamanaka in 2006 These so-called iPSCs shared characteristics with murine ESCs, such as their ability to differentiate, their morphology, and the expression of SC markers . A year later, human fibroblasts were treated with the same technology to create human iPSCs . These days, a number of cardiac differentiation protocols have been created for humans and mice [15].

According to a prior study, exosomes derived from embryonic stem cells improve cardiac function and encourage endogenous repair following MI.26 iPSC culture medium reduces lung fibrosis in vivo and improves alveolar epithelial wound repair properties in a lung epithelial wound-healing model, despite the fact that the contents of the secretome of iPSCs are not entirely understood. The ischemic myocardium appeared to benefit from the protective effects of isolated exosomes and extracellular vesicles released from the iPSC culture medium. By preventing caspase3/7 activation, iPSC-derived exosomes shield H9C2 cells from oxidative stress brought on by H2 O2 [16].

CARDIAC STEM CELLS (CSCS) / ENDOGENOUS PROGENITORS (FOR CARDIAC ISCHEMIA):

Myocytes were thought to be incapable of regeneration until recently, but there is evidence that they can undergo mitotic division after MI. The same author investigated a subset of heart cells and demonstrated that they possess characteristics of cardiac stem cells, including the capacity to differentiate into myocytes, smooth muscle, and endothelial cells.

These cells were shown to express early markers of cardiogenesis (platelet derived growth factor receptor-α), mesenchymal stem cells (CD90, CD105), and embryonic stem cells (Rex1, Nanog, Sox2).

Cardiosphere-derived cells, cardiac mesoangioblasts, ckit+ cells, Isl 1+ cells, and epicardial progenitors are among the various types of cardiac stem cells (CSCs), and they all express surface markers that are marginally different but overlap [17].

The ability of resident cardiac stem cells (RCSCs) to regenerate in human endomyocardial regions is restricted (Ballard and Edelberg, 2008). They probably help with turnover-mediated cell replacement and minor repairs.According to Rota et al. (2008) and Yamahara and Nagaya (2008), transplanting RCSC into a heart infarction can encourage the formation of cardiomyocytes and enhance systolic activity. However, because RCSCs are scarce, their isolation and growth are labor-intensive and inefficient.

Clinical evaluations of their potential as an autologous stem cell therapy have revealed that the main positive effects are most likely caused by arteriogenesis and neovascularization rather than by the replacement of cardiomyocytes (van Vliet et al., 2008) [18].

At a low basal level, pools of cardiac progenitor cells (CPCs) may contribute to the ongoing replacement of apoptotic cardiomyocytes throughout the myocardium. CPCs are tiny cells with the ability to self-renew and multiply, in contrast to terminally differentiated cardiac cells that do not express cardiac markers.

In vitro, it is possible to induce the activation of cardiomyocyte-specific genes in a number of seemingly distinct but overlapping populations of progenitor cells (such as Sca-1- (ref. 2), c-Kit- (ref. 3), and Abcg2- (ref. 4) expressing side populations); however, mesenchymal stem cells, which do not fully differentiate into functional heart cells5, have also been shown to exhibit this effect.

The limited quantity of endogenous CPCs also limits the potential of Sca1- or c-Kit-expressing cells, which may differentiate into cardiomyocytes in vivo and aid in the repair of the damaged heart following an acute myocardial infarction [19].

Mechanisms of Action of Stem Cell Therapy in the Treatment of Heart Disease

become a viable method for cardiac regeneration and repair. Numerous mechanistic pathways, such as differentiation, paracrine signaling, immunomodulation, angiogenesis, and the activation of endogenous repair processes, mediate the positive effects of stem cells. After myocardial infarction (MI) and other cardiovascular disorders, stem cell therapy has

1. Development into Cardiomyocytes

Some stem cell types, including induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), have the ability to develop into viable cardiomyocytes and repair damaged myocardium. Contractile function is partially restored as a result of this process. The long-term survival and engraftment efficiency of differentiated cells are still restricted, though [20] [21].

2. Signaling by Paracrine

The paracrine effect is one of the main processes behind stem cell-mediated cardiac repair. Growth factors, cytokines, and extracellular vesicles (EVs) like exosomes are among the bioactive substances released by transplanted stem cells. These elements influence fibrosis in the infarcted area, increase angiogenesis, decrease apoptosis, and support cell survival [22] [23].

3. Neovascularization and Angiogenesis

Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and other angiogenic mediators are secreted by stem cells, which promote the development of new blood vessels in the ischemic myocardium. Better cardiac function is a result of increased oxygen and nutrient delivery to the infarcted area due to improved vascularization [24] [25].

4. Anti-inflammatory and immunomodulatory effects

By inhibiting the activation of pro-inflammatory T-cells, macrophages, and dendritic cells, stem cells, especially mesenchymal stem cells (MSCs), have strong immunomodulatory effects. This lessens the inflammatory reaction that leads to scarring and remodeling of the heart [26] [27].

5. Endogenous Cardiac Repair Activation

By stimulating resident cardiac stem/progenitor cells (CPCs), stem cell therapy may encourage natural healing processes. These endogenous cells migrate, proliferate, and differentiate more readily when paracrine factors like hepatocyte growth factor (HGF) and stromal cell-derived factor-1 (SDF-1) are released [28] [29].

6. Anti-fibrotic and Anti-apoptotic Properties

By secreting anti-apoptotic factors (such as IGF-1 and HGF) and matrix-remodeling enzymes, stem cells reduce cardiomyocyte apoptosis and fibrosis, improving myocardial compliance and reducing scarring [30].

7. Effects Mediated by Exosomes and MicroRNA

Recent research emphasizes the function of exosomes derived from stem cells that carry microRNAs (miRNAs), which control the expression of genes linked to angiogenesis, cardiac protection, and anti-apoptotic signaling pathways [31] [32].

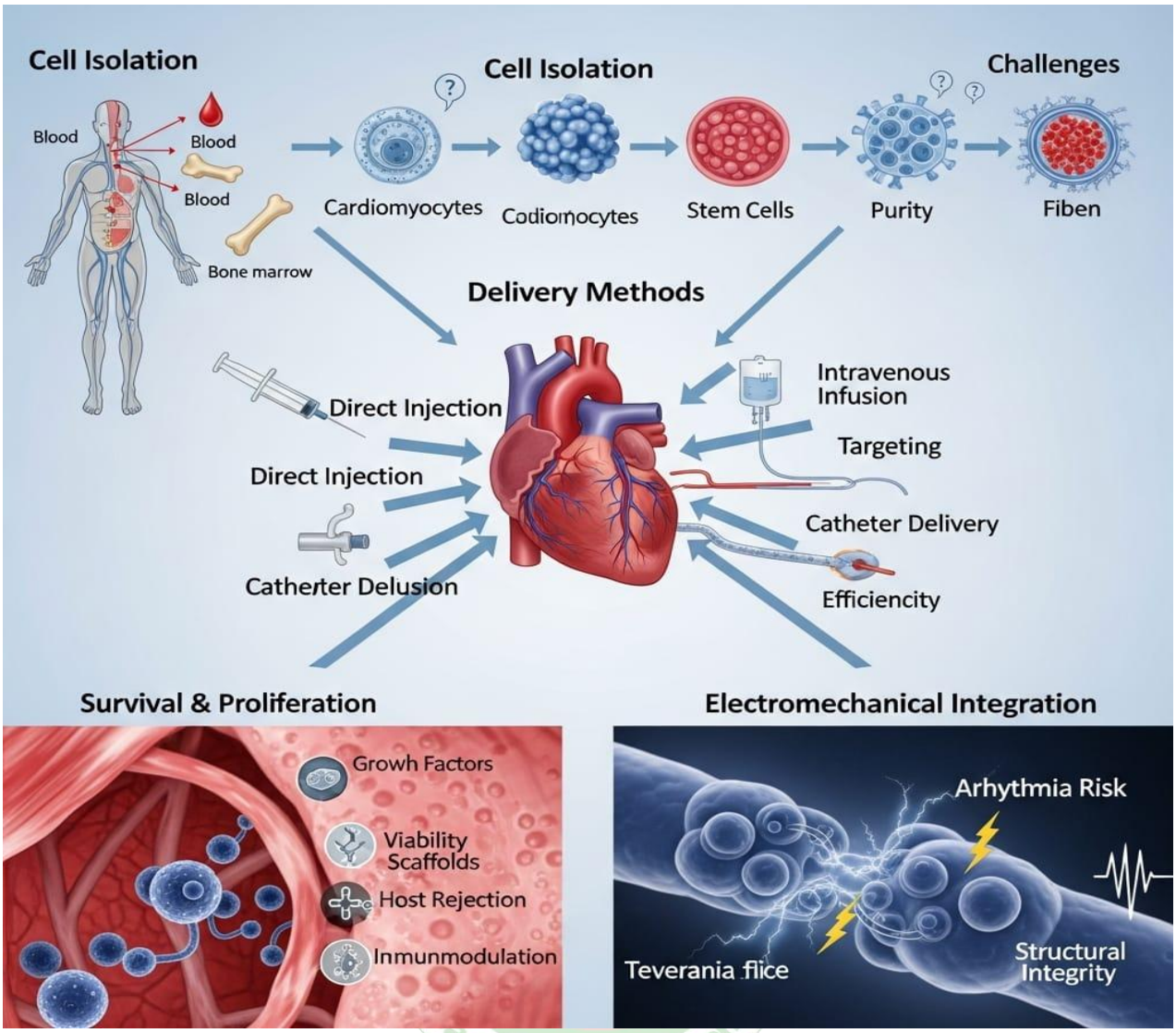

Figure 1: Chellenges to stem cell therapy for cardiac disease

PRELINICAL STUDIES

Globally, cardiovascular disease is the primary cause of death. Nevertheless, 1 in 3 men and 1 in 4 women pass away within a year of having their first myocardial infarction (MI), even with advancements in pharmaceutical and interventional therapies.One

Due to the prevalence of MI and heart failure (HF), new therapeutic approaches are needed; however, before being used in humans, they must first be tested in animal models to ensure safety and therapeutic efficacy. An outline of the numerous difficulties involved in preclinical and clinical research on stem cell therapy for heart failure can be found in the most recent scientific statement released by the TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes). and is offering a number of recommendations and guidelines to advance this field.The administration of stem cells encourages the restoration of lost functionality, in contrast to pharmaceutical treatments, which mainly manage the disease. However, we must keep looking for better strategies to guarantee the success of human trials due to unfavorable trial results and the current discussion regarding the effectiveness of human clinical cell-based therapy in patients with acute MI (AMI) [33].

CLINICAL STUDIED AND MECHANISMS OF ACTION

Intramyocardial delivery and intracoronary injection are the two primary methods of cell administration that the researchers have employed in the clinical trials. An antegrade intracoronary artery injection or a retrograde sinus injection can be used for coronary stem cell injection, whereas direct cardiac muscle injections can be carried out surgically or with percutaneous endocardial injection catheters. Because it is the least invasive, antegrade intracoronary artery injection is more appealing; however, when the injected cells are too big for the capillary bed, microvascular plugging may result from the stem cell injection, which could cause microinfections. This method has been shown to be less successful than intramyocardial delivery because the stem cells must also pass through the capillary wall.

The data that is currently available is inconclusive, and more early phase studies will be required before moving forward with pivotal clinical trials, even though the cell type, dosage, concentration, and delivery modalities are

crucial factors for regenerative cell therapy clinical trials [34].Since hematopoietic stem cells, MSCs, and bone marrow aspirates from patients do not typically contribute to the desired cardiac lineage types, their use in heart muscle tissue repair can be perplexing. Though sustained patient recovery has not been clearly demonstrated, there is some preclinical evidence supporting the use of umbilical cord blood for improved cardiac function in cases of myocardial infarction . These blood and stromal cells have been demonstrated to express certain genes expected of these cell types, such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and contractile proteins like myosin heavy chain, myosin light chain, and alpha actin, and to form sarcomeric structures typical of cardioimyocytes in vitro [35].Chronic Ischemia with Intractable Angina: Stem cell therapy may also help patients with intractable angina brought on by ischemia that is not otherwise responsive to revascularization. The first Phase I/IIa trial assessing the safety and effectiveness of autologous CD34+ stem cell transplantation into the heart in 24 patients with intractable angina was published by Losordo et al. The treatment group showed improvements in angina and exercise time without any safety concerns, but the results were not statistically significant because of the small sample size. Crucially, in a follow-up study with a bigger patient sample (n=167).The cell therapy group reported better exercise tolerance and fewer episodes of angina.However, following cell mobilization with G-CSF, cardiac enzyme elevation was noted in both the treatment and control groups. Wang et al. more recently reported comparable efficacy outcomes when EPCs were administered intracoronarily [36].The following sections of this study will elaborate on the clinical applications of stem cell-based therapies for heart diseases, which have recently been thoroughly discussed in reviews. These discussions will center on hPSCs and MSCs. A substantial amount of preclinical and clinical research generally supports the safety profiles of stem cell-based therapies, particularly adult stem cell therapy (such as MSC-based products)Clinical trials, however, have not yet produced evidence of the treatment's effectiveness because, even in phase III trials, multiple studies have produced contradictory findings and no statistically significant variations in infarct size, cardiac function, or clinical outcomes. A meta-analysis's findings demonstrated that stem cells from various sources hadno therapeutic effects on improving cardiovascular remodeling, myocardial contractility, or clinical outcomes [37].

CHALLENGES IN CATEGORIZING STEM CELLS AS DRUGS

Research on strategies to increase stem cell survival and long-term engraftment following administration should be the main focus of efforts to develop stem cell theraeutic agents to treat cardiovascular diseases. Since only a very tiny percentage of transplanted stem cells divide, large doses of stem cells are required to demonstrate normal function apfter transplantation.

Finding stem cells with the capacity to repair a damaged heart is another factor to take into account. Despite the potential for cardiac regeneration, several stem cell types have not been shown to directly impact heart regeneration or functional enhancement, according to some researchers [38].

1. Poor engraftment, retention, and survival of cells

- Because the infarcted heart tissue is a harsh environment with poor blood flow and oxygenation, inflammation, and fibrosis, many transplanted stem cells (also known as progenitor/cardiac lineage cells) die shortly after delivery [39].
- Even when cells do survive, they frequently do not engraft, or integrate into the myocardium in sufficient numbers, and instead stay at the site of injury [40].
- Many trials have shown a modest therapeutic benefit, which may be due to insufficient cell dose, delivery, or engraftment [41].

2. Unpredictable differentiation and cell population heterogeneity

- Results are unpredictable because stem/progenitor cell preparations are frequently heterogeneous (having different phenotypes, potencies, and viability) [42].
- Certain cell types may fail to develop into mature, functional cardiomyocytes or may differentiate along undesirable lineages, such as non-cardiac cells. In ventricular tissue, for instance, mesenchymal stem cells (MSCs) that had been implanted occasionally differentiated into osteoblast-type cells, according to one review [43].

Future Directions

1. Switch from cell therapy to cell-free methods (EVs/exosomes)

Justification: Secreted extracellular vesicles (EVs) or exosomes, as opposed to long-term engraftment, mediate many of the therapeutic effects of transplanted stem cells. Lower immunogenicity, decreased tumorigenicity, easier storage and standardization, and targeted delivery of miRNAs and repair-mediating proteins are all promised by exosome-based therapies. Scalable isolation, payload engineering, and delivery vehicles (hydrogels, targeted nanoparticles) are the main areas of ongoing research [44].

2. Use biomaterials and engineered tissues to enhance cell survival, retention, and electrical integration.

Justification: Two significant benefit limitations are low cell retention and inadequate electromechanical coupling. Cells can be combined with injectable hydrogels, biomaterial scaffolds, or engineered heart tissues (EHTs) to (a) improve vascularization, (b) provide mechanical support, and (c) encourage synchronized electrical coupling to lower the risk of arrhythmia. Two promising methods for creating transplantable cardiac patches are 3D bioprinting and decellularized matrices [45].

3. Use gene editing in conjunction with iPSC technology to create patient-matched, improved cell products.

Justification: autologous (or HLA-matched) sources and the capacity to use CRISPR/Cas to fix disease mutations are provided by iPSC-derived cardiomyocytes. Future research must concentrate on guaranteeing scalable, GMP-grade manufacturing, fully controlled differentiation (to lower tumor risk), and genomic stability. Additionally, pro-survival, pro-angiogenic, or immunomodulatory factors could be expressed by edited iPSC lines [45].

4. Convert clinical trials to more transparent reporting, larger randomized studies, and standardization.

Justification: Underreporting and trial heterogeneity (cell type, dose, delivery method, and endpoints) impede meta-analyses and regulatory advancements. To prove true efficacy and safety, future trials should use longer follow-up, preregistration with full reporting of negative results, and standardized endpoints (e.g., consistent imaging metrics, hard clinical outcomes) [46].

5. Improve regenerative and precision medicine by selecting patients with AI and multi-omics

Justification: Not every patient experiences the same level of benefit. It is possible to determine responders versus non-responders, optimize timing (acute vs. chronic MI), and customize cell/product selection by combining genomics, transcriptomics, imaging biomarkers, and machine learning. Additionally, graft-host interactions and arrhythmia risk can be predicted by computational models.

6. Create more effective delivery systems (minimally invasive techniques, controlled release, targeting).

Justification: There are trades-offs between intramyocardial injection, epicardial patches, and intracoronary infusion. Targeted homing peptides, catheter-compatible patches, and controlled-release biomaterials that increase therapeutic factor exposure while lowering procedural risk should be the main topics of future research [44].

7. Put safety first, taking into account immunology, arrhythmia, tumorigenicity, and regulatory frameworks.

Justification: Translation requires long-term security. This includes arrhythmia surveillance in preclinical large-animal models, immunogenicity testing for allogeneic products (or immune-evasive engineering), standardized assays for oncogenic risk, and early interaction with regulators to establish acceptable endpoints for approval [46].

8. Examine hybrid strategies that combine gene, drug, or mechanical therapies with cell therapy.

Justification: Compared to monotherapies, synergistic approaches (such as cells plus angiogenic gene therapy or cells seeded into mechanically active patches) may produce more durable repair. Combinatorial approaches also enable each component's dose to be decreased, which could increase safety [46].

CONCLUSION

Stem cell therapy represents one of the most promising frontiers in regenerative medicine for the treatment of heart disease. Over the past two decades, significant progress has been made in understanding the regenerative potential of various stem cell types, including mesenchymal stem cells, cardiac progenitor cells, and induced pluripotent stem cells. Preclinical and early clinical studies have demonstrated encouraging results in terms of myocardial repair, improved cardiac function, and reduced infarct size. However, translation to consistent clinical success remains limited due to challenges such as poor cell survival, low engraftment rates, immune rejection, arrhythmogenic risks, and ethical concerns regarding cell sources.Recent advances in bioengineering, gene editing, and exosome-based or cell-free therapies have opened new avenues to enhance the efficacy and safety of stem cell-based cardiac regeneration. Combining stem cells with supportive biomaterials, optimized delivery systems, and paracrine-factor-focused strategies holds promise for achieving more stable and functional myocardial repair.To realize the full therapeutic potential of stem cell therapy in heart disease, future research should focus on standardized protocols for cell preparation and delivery, large-scale randomized clinical trials, long-term follow-up for safety and efficacy, and deeper mechanistic understanding of stem cell-mediated cardiac repair. With continued interdisciplinary collaboration between clinicians, biologists, and bioengineers, stem cell therapy may eventually evolve from an experimental approach to an established clinical treatment capable of reversing heart failure and restoring cardiac function.

REFERENCE

1. Babaei M, Rezaie J. Application of stem cell-derived exosomes in ischemic diseases: opportunity and limitations. J Transl Med. 2021;19(1):196.
2. Katarzyna R. Adult stem cell therapy for cardiac repair in patients after acute myocardial infarction leading to ischemic heart failure: an overview of evidence from the recent clinical trials. CurrCardiol Rev. 2017; 13(3):223–31.
3. Segers VF, Lee RT. Stem-cell therapy for cardiac disease. Nature. 2008;451(7181):937–42.
4. Tsilimigras DI, Oikonomou EK, Moris D, Schizas D, Economopoulos KP, Mylonas KS. Stem cell therapy for congenital heart disease: a systematic review. Circulation. 2017;136(24):2373–85.
5. Karantalis V, Hare JM. Use of mesenchymal stem cells for therapy of cardiac disease.Circ Res. 2015;116(8):1413–30.
6. Aly RM. Current state of stem cell-based therapies: an overview. Stem Cell Investig. 2020;7:8.
7. Nguyen PK, Rhee JW, Wu JC. Adult stem cell therapy and heart failure, 2000 to 2016: a systematic review. JAMA Cardiol. 2016;1(7):831–41.
8. Hao L, Zou Z, Tian H, Zhang Y, Zhou H, Liu L. Stem cell-based therapies for ischemic stroke. Biomed Res Int. 2014;2014:468748.
9. Bartolucci J, Verdugo FJ, González PL, Larrea RE, Abarzua E, Goset C, et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: a phase 1/2 randomized controlled trial (RIMECARD). Circ Res. 2017; 121(10):1192–204.

10. Minguell JJ, Erices A. Mesenchymal stem cells and the treatment of cardiac disease. Exp Biol Med. 2006;231(1):39–49.
11. Karantalis V, Hare JM. Use of mesenchymal stem cells for therapy of cardiac disease. Circ Res. 2015;116(8):1413–30.
12. Saeedi P, Halabian R, Fooladi AAI. A revealing review of mesenchymal stem cells therapy, clinical perspectives and modification strategies. Stem Cell Investig. 2019;6:34.
13. Hao L, Zou Z, Tian H, Zhang Y, Zhou H, Liu L. Stem cell-based therapies for ischemic stroke. Biomed Res Int. 2014;2014:468748.
14. Sanganalmath SK, Bolli R. Cell therapy for heart failure: a comprehensive overview of experimental and clinical studies, current challenges, and future directions. Circ Res. 2013;113(6):810–34.
15. Müller P, Lemcke H, David R. Stem cell therapy in heart diseases–cell types, mechanisms and improvement strategies. Cell PhysiolBiochem. 2018;48(6):2607–55.
16. Jung JH, Fu X, Yang PC. Exosomes generated from iPSC-derivatives: new direction for stem cell therapy in human heart diseases. Circ Res. 2017;120(2):407–17.
17. Faiella W, Atoui R. Therapeutic use of stem cells for cardiovascular disease. Clin Transl Med. 2016;5(1):34.
18. Li SC, Wang L, Jiang H, Acevedo J, Chang AC, Loudon WG. Stem cell engineering for treatment of heart diseases: potentials and challenges. Cell Biol Int. 2009;33(3):255–67.
19. Srivastava D, Ivey KN. Potential of stem-cell-based therapies for heart disease. Nature. 2006;441(7097):1097–9.
20. Laflamme MA, Murry CE. Heart regeneration. Nature. 2011;473(7347):326–35.
21. Chong JJ, Yang X, Don CW, Minami E, Liu YW, Weyers JJ, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. Nature. 2014;510(7504):273–7.
22. Gnecchi M, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. Circ Res. 2008;103(11):1204–19.
23. Narmi MT, Darbandi NB, Gharavi AT, Babaeizad A, Sheykhhasan M. Exosomes from stem cells as therapeutic agents for cardiovascular regeneration. Stem Cell Ther. 2025;:227–308.
24. Kinnaird T, Stabile E, Burnett MS, Lee CW, Barr S, Fuchs S, et al. Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote arteriogenesis through paracrine mechanisms. Circ Res. 2004; 94(5):678–85.
25. Liu C, Xue J, Xu B, Zhang A, Qin L, Liu J, et al. Exosomes derived from miR-146a-5p-enriched mesenchymal stem cells protect cardiomyocytes and myocardial tissues through regulating MYBL1. Stem Cells Int. 2021;2021:1530445.
26. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007; 110(10):3499–506.
27. Squillaro T, Peluso G, Galderisi U. Clinical trials with mesenchymal stem cells: an update. Cell Transplant. 2016;25(5):829–48.
28. Ellison GM, Vicinanza C, Smith AJ, Aquila I, Leone A, Waring CD, et al. Adult c-kitpos cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. Cell. 2013;154(4):827–42.
29. Srivastava SD. Metformin impairs homing ability and efficacy of mesenchymal stem cells for cardiac repair in streptozotocin-induced diabetic cardiomyopathy in rats. Unpublished data.
30. Phinney DG, Di Giuseppe M, Njah J, Sala E, Shiva S, St Croix CM, et al. Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. Nat Commun. 2015;6:8472.
31. Luther KM, Haar L, McGuinness M, Wang Y, Lynch TL IV, Phan A, et al. Exosomal miR-21a-5p mediates cardioprotection by mesenchymal stem cells. J Mol Cell Cardiol. 2018;119:125–37.
32. Barile L, Vassalli G. Exosomes: therapy delivery tools and biomarkers of diseases. PharmacolTher. 2017;174:63–78.
33. Tompkins BA, Balkan W, Winkler J, Gyöngyösi M, Goliasch G, Fernández-Avilés F, et al. Preclinical studies of stem cell therapy for heart disease. Circ Res. 2018;122(7):1006–20.
34. Terashvili M, Bosnjak ZJ. Stem cell therapies in cardiovascular disease. J CardiothoracVascAnesth. 2019;33(1):209–22.
35. Trounson A, Thakar RG, Lomax G, Gibbons D. Clinical trials for stem cell therapies. BMC Med. 2011;9(1):52.
36. Nguyen PK, Rhee JW, Wu JC. Adult stem cell therapy and heart failure, 2000 to 2016: a systematic review. JAMA Cardiol. 2016;1(7):831–41.
37. Hoang DM, Pham PT, Bach TQ, Ngo AT, Nguyen QT, Phan TT, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Ther. 2022;7(1):272.
38. Choi SH, Jung SY, Kwon SM, Baek SH. Perspectives on stem cell therapy for cardiac regeneration–advances and challenges–. Circ J. 2012;76(6):1307–12.
39. Liew LC, Ho BX, Soh BS. Mending a broken heart: current strategies and limitations of cell-based therapy. Stem Cell Res Ther. 2020;11(1):138.
40. Joggerst SJ, Hatzopoulos AK. Stem cell therapy for cardiac repair: benefits and barriers. Expert Rev Mol Med. 2009;11:e20.
41. Nguyen PK, Rhee JW, Wu JC. Adult stem cell therapy and heart failure, 2000 to 2016: a systematic review. JAMA Cardiol. 2016;1(7):831–41.
42. Joggerst SJ, Hatzopoulos AK. Stem cell therapy for cardiac repair: benefits and barriers. Expert Rev Mol Med. 2009;11:e20.
43. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal Transduct Target Ther. 2024;9(1):17.
44. He X, Good A, Kalou W, Ahmad W, Dutta S, Chen S, et al. Current advances and future directions of pluripotent stem cells-derived engineered heart tissue for treatment of cardiovascular diseases. Cells. 2024;13(24):2098.
45. Wulfse M, Vervoorn MT, Amelink JJ, Ballan EM, de Jager SC, Sluijter JP, et al. Past trends and future directions of cardiac regenerative medicine–a systematic analysis of clinical trial registries. J Cardiovasc Transl Res. 2025; 18(1):209–20.
46. Hussen BM, Taheri M, Yashooa RK, Abdullah GH, Abdullah SR, Kheder RK, et al. Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. Int J Surg. 2024;110(12):8002–24