

Adult stem cells and induced pluripotent stem cells: Innovative options for the treatment of cardiovascular diseases

Katherine Campos-Pineda ¹, Stephanie Ceciliano-Villalobos ¹, Maripaz Rojas-Mora ¹, Mariela Ponce-Torres ¹, Sara Raquel Rojas-Abarca ¹, Karina Morales-Ramírez ¹ and Juan José Mora-Román ^{2,*}

¹ Pharmacy student, Faculty of Pharmacy, Universidad de Costa Rica, San José, Costa Rica.

² Industrial Pharmacy Department, Faculty of Pharmacy, Universidad de Costa Rica, San José, Costa Rica.

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Abstract

Cardiovascular diseases are the leading cause of death worldwide, claiming approximately 17.9 million lives each year. They include acute myocardial infarction, ischemic heart disease, heart failure, and coronary artery disease. The cardiology societies have published recommendations on their management, advocating for lifestyle modifications and secondary preventive treatment. Although current therapies have demonstrated significant benefits, many individuals continue to experience a decline in their quality of life because the available options are palliative. Regarding this scenario, the stem cell characteristics and properties, especially those of adult stem cells and induced pluripotent stem cells, have been studied as alternatives for these pathologies. Even though there are many preclinical and clinical trials associated with this biotechnological approach, significant clinical and technical obstacles remain, including the lack of standardized protocols, variability in clinical outcomes, and difficulty achieving functional, lasting integration of transplanted cells into cardiac tissue. Additionally, factors such as the patient's health status, age, pre-existing conditions, the administered cell type, and the administration method are crucial to the treatment's effectiveness. Consequently, it is essential to continue researching these therapies to ensure that, when applied to humans, they are safe and effective, as patients expect.

Keywords: Cardiovascular Diseases; Regenerative Medicine; Adult Stem Cells; Induced Pluripotent Stem Cells; Preclinical Trials; Clinical Trials.

1. Introduction

Cardiovascular diseases are the leading cause of death worldwide, claiming approximately 17.9 million lives each year. They include various heart and blood disorders, encompassing stroke, coronary heart disease, and rheumatic heart disease [1].

In addition to being deadly, they are highly prevalent. In the United States, they affect more than 83 million individuals aged 20 and older. It is estimated that by 2030, the associated costs in that nation will exceed \$800 billion [2]. In Latin America and the Caribbean, approximately 1.6 million people die from these illnesses each year, half a million of them before the age of 70 [3].

Regarding their treatment, several cardiology societies have published recommendations on their management, advocating for lifestyle modifications and secondary preventive treatment. These therapeutic options include the combined use of β -blockers, antiplatelet agents, statins, and angiotensin-converting enzyme (ACE) inhibitors [4].

* Corresponding author: Juan José Mora-Román.

Although current therapies have demonstrated significant benefits, many individuals continue to experience a decline in their quality of life. This situation has driven the search for new strategies. Currently, advanced biological alternatives, such as stem cell therapies, are being investigated. These cells possess the capacity for self-renewal and differentiation into different cell types [5, 6]. The aim is to replace damaged cardiac cells and/or improve cardiac function.

Their potential to differentiate into cardiomyocytes makes them an up-and-coming tool in regenerative medicine [7]. Given this context, the objective of this review is to determine the therapeutic potential of stem cells in the treatment of cardiovascular pathologies.

2. Stem cell types used in cardiovascular therapies and their regenerative properties

In recent years, the stem cell characteristics and properties have been studied as an alternative treatment for cardiovascular disorders. These cells have the capacity for self-renewal and differentiation into distinct lineages [8]. Furthermore, they constitute the building blocks of all tissues and organs [8, 9, 10]. They can be classified according to their differentiation potential and origin [8].

Regarding their differentiation potential, totipotent stem cells are found in embryonic tissue and have the most significant potential to differentiate. They can generate all embryonic and extraembryonic cells [11, 12].

Pluripotent stem cells, on the other hand, have the capacity to differentiate into all three germ layers and are therefore present in diverse phases of human growth and can give rise to almost all body cell types [12, 13]. However, they have a limited capacity to produce extraembryonic cells and do not contribute to the development of placental cells [12].

Multipotent stem cells can give rise to all cell types within a single embryonic germ layer [14, 15]. Finally, unipotent stem cells can differentiate into only a single cell type, with the lowest differentiation potential [16, 17]. Examples are muscle cells, epidermal cells, and megakaryocytes [17, 18].

Regarding their origin, they are usually classified as embryonic or adult. Embryonic stem cells (ESCs) are derived from preimplantation embryos and originate from the blastocyst-stage embryo's inner cell mass. They have the capacity to proliferate indefinitely and in an undifferentiated manner and can differentiate into practically all cells and tissues, making them attractive for the treatment of pathologies [19].

Despite being a promising option for multiple ailments, its utilization presents some limitations. They have a high potential to form tumors, so if transplanted in an undifferentiated state, they can give rise to teratomas (tumors derived from the three germ layers) [20]. Plus, there are alarms because, since they are acquired at the blastocyst stage, the ethical dilemma arises that obtaining them requires the destruction of human embryos. These problems have limited research. Some nations, such as Italy, prohibit all studies based on them, while the United States has banned any cell line production that implies embryo annihilation [21].

Adult stem cells have the potential to self-renew and differentiate into specialized cells that make up the tissues in which they reside [22, 23, 24]. They include hematopoietic stem cells (HSCs), bone marrow mesenchymal stem cells, adipose stem cells, neural stem cells, muscle satellite cells, and epidermal stem cells [22]. Despite being available in small numbers, they maintain tissue homeostasis and support regeneration following damage [23]. This ability is significant for the treatment of disorders, including cardiovascular diseases, resulting from tissue damage that is difficult to reverse or treat.

First-generation stem cells have been applied in clinical trials. This classification involves adult stem cells derived from bone marrow and adipose tissue [25]. Mesenchymal stem cells (MSCs) are among the most studied. According to the International Society for Cell Therapy, they are defined grounded on a series of criteria: adherence to plastic under certain culture conditions, expression of cell markers CD73 (from cluster of differentiation 73), CD90, and CD105, absence of cell markers CD34, CD45, human leucocyte antigen-DR isotype (HLA-DR), CD14 or CD11b, and CD79A or CD19, and the ability to differentiate into osteoblasts, adipocytes, and chondroblasts *in vitro* [25, 26, 27]. **Table 1** summarizes the associations or functions of these markers.

Table 1 Surface markers in MSCs: positive or negative expression and association or function [27, 28, 29].

Marker	Expression in MSCs	Association/function
CD73	Positive	Ecto-5'-nucleotidase, which converts extracellular adenosine monophosphate (AMP) to adenosine. It is related to cell adhesion mechanisms.
CD90 or Thy-1	Positive	It is a glycosylphosphatidylinositol-linked protein involved in cell-cell and cell-matrix interactions and is considered a marker of early mesenchymal precursors.
CD105 or endoglin	Positive	Type I membrane glycoprotein with accessory receptor function for ligands of the transforming growth factor- β (TGF- β) superfamily.
CD34	Negative	Transmembrane sialomucin with adhesive or anti-adhesive function, depending on the cellular environment. It is selectively expressed in HSCs.
CD45	Negative	Pan-leukocyte marker, standard in leukocytes. It is a constitutive protein of all hematopoietic cells.
HLA-DR	Negative	It is a peptide antigen presenter to the helper T lymphocytes, mediating the immune response.
CD14 or CD11b	Negative	Markers that are expressed in monocytes and macrophages.
CD79A or CD19	Negative	B lymphocyte markers.

Moreover, they can secrete pro-angiogenic paracrine factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), and anti-apoptotic factors such as interleukin 10 (IL-10), HGF, and B-cell lymphoma protein 2 (Bcl-2). Collectively, these molecules induce cardiac repair [25, 30, 31].

Another characteristic is their lack of major histocompatibility complex class II (MHC-II) markers, making them an optimal choice for autografts [25, 26]. Lacking this complex, they are not recognized by immune system components such as alloreactive cytotoxic T lymphocytes (CD4+). Therefore, an immune response against the graft is not triggered due to its low immunogenicity [32]. Regarding their mechanism of action, they produce three main effects on the heart: reducing fibrosis, stimulating angiogenesis, and restoring contractile function. This latter effect is mediated by endogenous cardiac stem cells engraftment, differentiation, and stimulation for proliferation. All these functions together promote the replacement of scarred or dysfunctional myocardial tissue. Thus, several preclinical and clinical studies have demonstrated cardioprotection and scar tissue reduction after MSC transplantation [26].

Another property is their ability to secrete small vesicles called exosomes. These structures have functions related to the transport of bioactive molecules (ribonucleic acid or RNA and proteins) that exert effects on recipient cells. In the heart, they promote cardiomyocyte survival and proliferation, improve angiogenesis, and inhibit inflammatory responses and fibrosis [31].

An additional group that has gained importance and interest as therapeutic options for cardiovascular conditions is induced pluripotent stem cells (iPSCs). They can be obtained by dedifferentiating skin tissue and blood cells (adult somatic cells) in the presence of growth factors known as Yamanaka factors [33, 34], described in **Table 2**.

Table 2 Yamanaka factors and their functional characteristics [35].

Yamanaka factor	Functional characteristics
Oct4	Activates the protein called T-cell leukemia/lymphoma 1 (TCL1), which is involved in the proliferation and differentiation of extracellular reticulocytes. It is a biomarker in colon, lung, breast, and oral cancers.
Sox-2	Maintains self-renewal, and its negative regulation triggers ESC differentiation. Its overexpression is associated with squamous cell carcinoma.
Klf4	It is essential for the maintenance of tumor stem cells and can act as a tumor suppressor gene or oncogene.
c-Myc	Reprograms tumor cells into pluripotent cells in the tumor microenvironment.

These cells develop the ability to differentiate into any of the body's somatic cells [36, 37]. Differentiating into cardiomyocytes offers the advantage of regenerating cardiac tissue from a person's own cells, thereby mitigating the drawbacks of immunological incompatibility [31].

Some preclinical trials have shown substantial improvement in left ventricular ejection fraction and a reduction in left ventricular fibrosis when treated with cardiac cells derived from iPSCs. These comparisons were done against untreated animals [35].

Other studies have reinforced these observations through innovative tools, such as a living patch for injured hearts made with cardiac cells cultured from iPSCs and endothelial cells, which have been placed on damaged areas of rodent hearts, such as guinea pigs [39, 40]. These are scaffolds or loaded therapeutic agents that provide mechanical reinforcement, synchronous electrical conduction, and localized delivery within the infarct zone to promote cardiac restoration. They are designed as cellular sheets and offer advantages such as minimal immune rejection and maximal utilization of cellular therapeutic potential [41]. Their application has been shown to have beneficial effects, comprising augmented myocyte proliferation, vascularization, and electrical coupling with the intact heart [39].

The key advantage of MSCs and iPSCs is that, in some acute cardiac conditions, transplantation is the only available option. Therefore, their consideration is an alternative due to the benefits described above, making them a robust choice for cardiovascular pathologies. It is relevant to note the need for a thorough study of this strategy, as it may have adverse effects or complications that become challenges. These limitations will be described later.

3. Cardiovascular diseases that can be treated with stem cells

Cardiovascular illnesses are among the leading causes of death globally, whether inherited or acquired, despite medical advances in recent decades [42, 43]. They have significant emotional and economic consequences, affecting those who suffer from them, their families, and society [26].

Heart conditions involve acute myocardial infarction, ischemic heart disease, heart failure, and coronary artery disease, all of which have been extensively studied within the regenerative medicine field [42]. Therefore, each of these will be discussed, along with its epidemiology, traditional treatments, and stem cell research.

3.1. Acute myocardial infarction

It occurs when there is a sudden decrease in blood flow to the coronary arteries, leading to abnormal myocardial perfusion [44]. It is the first manifestation of ischemic heart disease in approximately 50 to 70 % of individuals [45].

The disorder represents one of the leading causes of morbidity and mortality worldwide, with a dynamic epidemiology. In high-income countries, hospitalizations have declined since the late 1980s. In the United States, approximately 750,000 new and recurrent cases are reported each year [46]. In England, the incidence is projected to remain stable, but it could rise in men by 2035 [47]. Globally, its frequency is higher in low- and middle-income countries because preventive and therapeutic measures are less frequently implemented [44, 48].

For cases of ischemic heart disease that are not urgent, management options include procedures such as percutaneous transluminal coronary angioplasty (PTCA), a minimally invasive procedure to unblock coronary arteries and allow free blood flow to the heart muscle [49]. Another possibility is stent placement, which is a small tubular device implanted in a heart artery after percutaneous angioplasty [50]. Coronary artery bypass grafting (CABG) is also available for maintaining patency, as is long-term pharmacological management [38].

The pharmacological approach involves a combination of drugs to limit myocardial damage, reduce mortality, and prevent complications. One group includes antiplatelet agents. Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1) in platelets, blocking thromboxane A₂ synthesis and platelet aggregation [51, 52]. Clopidogrel, prasugrel, and ticagrelor block the P₂Y₁₂ receptor on the platelet surface, preventing platelet activation and the binding of more platelets. In selected situations, glycoprotein IIb/IIIa inhibitors such as abciximab, eptifibatide, and tirofiban are considered [51].

Besides, anticoagulants are available. Heparin prevents new clot formation by inhibiting thrombin and factor Xa [53]. Lepirudin and bivalirudin have the same mechanism of action [51]. Other substances comprise β -blockers [54], ACE inhibitors [55, 56], statins [55], and nitrates [57].

3.2. Ischemic heart disease

This condition occurs when coronary blood flow is inadequate to support cardiac performance at a level sufficient to sustain the full range of the body's physiological activity [58]. It is among the top causes of death and disability worldwide [59]. Although age-standardized mortality rates and age-standardized disability-adjusted life years have diminished, the total number of cases continues to rise due to aging and population growth [60, 61].

Areas with low or intermediate sociodemographic levels have the highest incidence rates, disability-adjusted life years, and mortality, most notably in East Asia. In contrast, areas with a high sociodemographic index have achieved significant reductions in these indicators [62]. Men are more affected than women, and cases are increasing slightly among young people in countries with a medium sociodemographic index, which is a composite indicator of development status strongly correlated with health outcomes [63]. Risk factors involve hypertension, high low-density lipoprotein (LDL) cholesterol levels, smoking, poor diet, and environmental pollution, the importance of which varies by region [62, 63]. Therapeutically, in acute situations, revascularization should be performed, preferably via angioplasty, a minimally invasive procedure that opens blocked or narrowed arteries [64]. If this technique is not possible, fibrinolysis, a process that dissolves fibrin-based blood clots, is employed [65].

In the chronic form, medical measures to control cardiovascular risk factors are considered, reserving revascularization for patients with persistent symptoms or high-risk anatomy, including heart failure and decreased left ventricular function [66, 67]. In cases of ischemia without non-obstructive coronary arteries, treatment is guided by the predominant pathophysiological mechanism, such as vasospasm or microvascular dysfunction [66, 68].

The pharmacological approach to this condition aims to prevent major cardiovascular complications and control symptoms, especially angina and ischemic episodes. The medications act on different processes, regulating both the supply and demand of oxygen to the heart muscle, improving vascular function and microcirculation. The main classes are antiplatelet agents, statins [66], ACE inhibitors [69], β -blockers, nitrates [70], calcium channel antagonists [71], ranolazine [72], and nicorandil [73].

3.3. Heart failure

It is a clinical condition in which the heart loses its ability to pump enough blood to meet the body's needs, even when filling pressures are within normal ranges. Its main manifestations include shortness of breath, fatigue with minimal exertion, and fluid retention [74].

Following a myocardial infarction, complex pathophysiological mechanisms are triggered, leading to ventricular remodeling through alterations in ventricular size and shape, and a decline in cardiac function in response to various factors, comprising neurohormonal, mechanical, inflammatory, and ischemia-reperfusion injury mediators, energy metabolism, and genetic predisposition [75]. Consequently, ischemic heart failure can develop, accounting for approximately 50 % of all cases. This condition is associated with increased hospitalizations and a five-year survival rate of less than 50 % [38].

Heart failure affects 1 to 3 % of the population in industrialized territories and more than 56 million people worldwide. It has a high prevalence, especially in older adults. This rate varies by region, being highest in Europe (up to 6.8 %) and lowest in Asia (0.4 to 2 %), and similar in the United States (1.9 to 2.6 %) [76, 77, 78, 79]. There are considerable

differences in incidence, risk factors, care needs, and outcomes among specific patient populations [80]. The death risk is higher in those with associated conditions, such as diabetes or heart pathology and/or a reduced ejection fraction [81, 82]. Therefore, it remains a significant public health problem [83].

Its treatment requires a multidisciplinary, personalized approach that combines pharmacological and non-pharmacological therapies. The goals are to alleviate symptoms, reduce hospitalizations and mortality, and improve individuals' quality of life. The strategy is based on categorizing the illness according to ejection fraction. Heart failure with reduced ejection fraction has the most substantial scientific evidence supporting therapeutic interventions [84].

In heart failure with preserved and slightly reduced ejection fraction, the data are more limited [85]. Management focuses primarily on attending to comorbidities such as hypertension, atrial fibrillation, diabetes, and obesity, as well as relieving symptoms with diuretics. Recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to decrease hospitalizations [86].

In acute heart failure, diuretics are used to relieve congestion. Additionally, vasodilators and non-invasive ventilatory support are available [87].

The dosage and sequence of medications should be tailored to each person, contemplating their associated conditions, treatment tolerance, and risk of side effects, always promoting the patient's active participation in clinical decisions [88, 89]. Regarding heart failure with reduced ejection fraction, pharmacological management is based on four key drugs that should be initiated early and in combination, starting with low doses that are gradually increased according to the patient's tolerance. These are ACE inhibitors, β -blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors [85, 86, 90, 91]. The latter drugs, such as dapagliflozin, empagliflozin, and canagliflozin, block the SGLT2 transporter in the kidney proximal tubule, reducing glucose reabsorption and favoring its excretion in the urine [92, 93, 94]. Other pharmacological substances to consider are loop diuretics [95, 96, 97, 98], hydralazine, nitrates, ivabradine, and veriquat [90].

3.4. Coronary artery disease

It is a condition in which the coronary arteries are obstructed or narrowed [99]. Its etiology is complex and involves genetic and environmental factors. This disorder progresses dynamically, due to the accumulation of atherosclerotic plaques and changes in coronary blood flow, and can remain in a relatively stable state for a prolonged period before becoming unstable, generally because of erosion or rupture of atherothrombotic plaques [38].

Regarding its clinical presentation, it can be classified as acute or chronic. The acute form is characterized by a sudden onset, resulting from the rupture of an unstable plaque associated with a thrombotic process, provoking a sudden decrease in blood flow to the heart and subsequent myocardial ischemia. In contrast, the chronic form has a slower course, with stable plaques that partially obstruct coronary flow, stable symptoms, and a lower probability of acute events [55, 100, 101]. Although acute coronary syndrome encompasses a broad spectrum, its severity ranges from unstable angina to myocardial infarction [55]. In nations with a high sociodemographic index, rates are lower, but in low- and middle-index regions, they remain the same or increase [102].

Current therapeutic approaches for acute and chronic coronary syndromes include coronary revascularization to restore adequate blood flow to blocked or narrowed coronary arteries [103]. This restoration can be performed using two main approaches: percutaneous coronary intervention (PCI) and CABG. PCI is a procedure that involves opening blocked or narrowed arteries employing a catheter equipped with a small balloon, which is inflated to widen the blood vessel [104]. As a complement, CABG allows blood to flow through the coronary artery that is blocked or narrowed [105].

Medical treatment options consider antiplatelet agents, statins, β -blockers [66], and ACE inhibitors [55]. In addition, Lifestyle modifications, like maintaining a balanced diet, engaging in regular physical activity, maintaining a healthy weight, and avoiding tobacco use, are necessary [106].

3.5. Pathologies causing alterations in heart rhythm

Heart rhythm disturbances, primarily atrial fibrillation and ventricular arrhythmias, are growing globally, impacting cardiovascular health. Atrial fibrillation is the most common arrhythmia, with 50 million cases in 2020 and a rising prevalence due to aging and risk factors [107, 108, 109]. Its mortality rate has also increased, especially in women, and varies by region and socioeconomic status [108, 110]. Ventricular arrhythmias are the leading source of sudden cardiac death, accounting for half of all cardiovascular deaths, with low survival rates after cardiac arrest [111, 112].

Electronic pacemakers are implanted devices that emit electrical signals to correct slow heart rhythms or disturbances in the electrical impulse conduction in the heart [113]. Although commonly utilized to treat these pathologies, their employment has limitations such as limited battery life, the risk of infectious complications, and the inability to provide a truly autonomous response [42].

Their frequency arises with age. An example is sinus node dysfunction, which occurs in approximately 0.03 % of the population, while atrioventricular conduction disorders occur in approximately 0.04 %, with a higher incidence in older adults and men. Likewise, aging is associated with a progressive cardiomyocyte loss, contributing to heart dysfunction, especially in acute events such as myocardial infarction, where up to 25 % of cardiac tissue can be lost [42].

The regeneration of endogenous cardiomyocytes is limited. A natural strategy for loss compensation is the formation of fibrotic scar tissue, which alters heart function [114]. According to research, its renewal rate reaches 1 % at age 20 and declines to 0.4 % at age 70 [42]. These numbers highlight the urgent need to explore more effective treatments.

4. Preclinical and clinical trials regarding stem cells for the treatment of cardiovascular diseases

Due to the growing global impact of cardiovascular illnesses and the limited efficacy of available treatments, it is essential to develop new strategies that leverage the regenerative capacity of cardiac tissue. In this context, stem cell therapies are emerging as a promising opportunity, aiming to repair myocardial damage and restore cardiac function. This alternative goes beyond a palliative approach [25, 115]. Hope has been heightened by preclinical research demonstrating a positive impact on ischemia and infarction, modulating cellular processes and biological pathways [8, 31].

MSCs have been explored as a therapeutic alternative for diseases, including cardiac surgery, because of their ability to differentiate into cardiomyocytes. Their primary source is bone marrow. Also, they are found in mobilized peripheral blood and umbilical cord blood. The limitations associated with their administration include the lack of a standardized technique for obtaining them and a specific molecule that enables their selective isolation [116].

On the other hand, adipose tissue has gained greater relevance in recent decades due to its abundance of MSCs. These cells are notable for their *ex vivo* expansion capacity, versatility in differentiating into distinct cell lineages, immunomodulatory properties, and ability to release angiogenic factors, making them a promising alternative in regenerative medicine. Their employment has been the subject of research in ischemic heart disease, with experimental studies supporting their safety and efficacy, especially after a myocardial infarction. However, cardiovascular risk factors such as hypertension, diabetes, or obesity can affect their functionality, generating uncertainty about their viability in the clinical setting [117].

Furthermore, iPSCs can differentiate into some cardiac cell types, like contractile cardiomyocytes. This capacity has enabled *in vitro* modeling of cardiac development and physiopathology, as well as the improvement of novel therapies. Nevertheless, a challenge has been the difficulty in purifying and expanding intermediate cardiovascular progenitor cells. Overcoming this challenge would enable improved control of lineage differentiation and facilitate the identification of genes responsible for cardiac potential in these cell populations [118].

Despite efforts to isolate and expand progenitors derived from iPSCs, their proliferation has been limited, and most studies have focused on their differentiation potential (cardiomyocytes, smooth muscle cells, and endothelial cells). They may be in a transient state that favors differentiation over expansion, thereby representing an obstacle to their direct application in cardiovascular regenerative medicine [118].

Given these possibilities, some clinical studies with MSCs and iPSCs as potential therapeutic options are shown.

4.1. Acute myocardial infarction

In cell therapy for acute myocardial infarction, a wide range of cell sources, including ESCs, adult stem cells, and iPSCs, have been used. Of adult stem cells, MSCs have been extensively studied. Despite numerous preclinical and clinical trials conducted with diverse subpopulations, the ideal cell with definitive therapeutic capacity has not yet been identified. This scenario represents a challenge for cardiac regenerative medicine, whose ultimate goal is to regenerate damaged tissue by forming new blood vessels and functional cardiomyocytes that help restore the oxygen and nutrient supply to the affected areas [119].

A multicenter phase II randomized, double-blind, placebo-controlled study investigated whether intracoronary delivery of autologous bone marrow-derived cells could improve left ventricular function one to seven days post-acute myocardial infarction in the anterior region of the heart. To this end, 100 patients were selected and randomized 1:1 to receive either cell therapy or a placebo, 24 hours after percutaneous coronary intervention to restore blood flow. The objective was to compare the change in left ventricular ejection fraction, a key measure of cardiac function [120].

The results showed that, even though both groups improved cardiac function after one year, the difference between those who received stem cells and those who received a placebo was slight. Nonetheless, the former group showed a higher rate of cardiac tissue salvaged after the infarction, suggesting a possible benefit for the recovery of damaged heart muscle, even if short-term pumping function did not improve significantly. This research was the first of its kind to explore the impact of stem cell administration so early after a myocardial infarction, aiming to harness its regenerative potential and reduce damage from this cardiovascular event [120].

In another randomized, multicenter, placebo-controlled, double-blinded phase III trial, the safety and efficacy of intramyocardial application of autologous CD133+ bone marrow-derived stem cells were evaluated in combination with coronary artery bypass graft revascularization for post-infarction myocardial ischemia and reduced left ventricular ejection fraction. Of the 119 individuals enrolled, 82 were randomly assigned in a 1:1 ratio to receive 500,000 to 5,000,000 purified autologous CD133+ bone marrow stem cells or a placebo [121]. Both groups showed a meaningful improvement in ejection fraction at 180 days, but the difference between them was not statistically significant. Conversely, post hoc analysis showed that approximately 60 % of patients responded positively, with no significant difference between the groups. Those who did not respond had fewer CD133+ endothelial progenitor cells and platelets, as well as higher SH2B3 expression, which is associated with inhibition of the HSC response in these progenitor cells and megakaryocytes. Therefore, the treatment was safe and had limited overall efficacy. Additionally, a review of biomarkers for predicting the cell therapy response was established [121].

4.2. Ischemic heart disease

Adipose-derived stem cells have been the subject of extensive research in animal models owing to their potential usefulness in regenerating cardiac tissue damaged by ischemia. Preclinical studies have shown that, when administered, they can lodge in the myocardium, express cardiomyocyte markers, improve myocardial function, and promote the formation of new blood vessels in affected areas. However, doubts remain about their actual capacity for cell differentiation, as some studies have not replicated these findings. These discrepancies could be explained by differences in extraction procedures, culture methods, or animal models utilized [117].

Beyond their differentiation potential, the paracrine factors secreted by these cells exhibit proangiogenic and cytoprotective properties. These factors promote vessel formation and reduce cell death. As a complement, they increase the production of factors such as VEGF and stromal cell-derived factor 1 (SDF-1). Still, their low persistence rate in injured tissue has prompted complementary strategies, such as genetic modifications and the construction of scaffold biomaterials [117].

Phase I and II clinical trials have confirmed that their administration in patients with chronic ischemic heart disease is safe and feasible, with evidence of preserved cardiac function, improved perfusion, and reduced necrotic area. Even so, further information is needed to confirm their long-term efficacy [117].

In its treatment, adipose-derived MSCs have shown therapeutic potential, as they are abundant, easy to obtain, and capable of transforming into cells with cardiac characteristics, contributing to new blood vessel formation and improved perfusion in injured areas. Although various types and subtypes exist, it has not been clearly defined which is the most effective for this condition. To enhance their therapeutic effect, *ex vivo* cell modification techniques are currently being explored to improve their regenerative properties and their ability to survive in the environment where they must exert their action [122].

A phase I and II randomized, blinded, placebo-controlled study conducted between 2009 and 2013 evaluated the safety of transendocardial stem cell injection with autologous MSCs and whole bone marrow mononuclear cells in 65 patients with chronic ischemic cardiomyopathy. It reduced left ventricular function (less than 50 %). The results showed that no serious adverse events (hospitalization for worsening heart failure, stroke, myocardial infarction, death, among others) related to the treatment occurred at 30 days. Besides, after one year, the incidence of these events was similar between the two groups, and patients treated with MSCs showed a significant improvement in quality of life and walking ability, with a notably reduced infarct size and improved regional myocardial function. Although there were no changes in left ventricular volume or ejection fraction, transendocardial stem cell injection was safe and potentially beneficial [123].

Another phase I/II randomized trial evaluated the safety and efficacy of allogeneic MSCs compared with autologous ones in 30 patients with left ventricular dysfunction occasioned by ischemic cardiomyopathy. Thirty patients were treated with transendocardial injections of varying doses (20, 100, or 200 million cells; five patients per dose and cell type) and followed for up to 13 months. Serious treatment-related adverse events were low in both groups, and no relevant immunological reactions were observed with the allogeneic cells. Autologous MSCs improved six-minute walk distance and quality of life. Both variants significantly reduced infarct size and favorably remodeled the left ventricle. Lower doses exhibited greater benefit for ventricular volume and ejection fraction, suggesting that 20 million cells are better than higher doses or that the concentrations are noteworthy. Finally, MSCs, both autologous and allogeneic, were safe and potentially beneficial for cardiac function in this population [124].

4.3. Heart failure

Regarding this pathology, a randomized, controlled investigation evaluated the effect of intramyocardial administration of bone-marrow-derived, lineage-directed, autologous cardiopoietic mesenchymal stem cells (C3BS-CQR-1) on left ventricular reverse remodeling in persons with advanced ischemic heart failure. In this post hoc analysis, individuals with a left ventricular ejection fraction of less than 35 % were randomly assigned 1:1 to receive either an injection of up to 600×10^6 C3BS-CQR-1 (120 patients) or a sham procedure (151 patients). Over 52 weeks, treated ones showed a progressive decrease in both end-diastolic and end-systolic volumes, with significant reductions compared to the control group. These results were maintained after adjusting for baseline clinical variables. The most important benefit was detected in those who received fewer than 30 injections. Therefore, stem cells promoted reverse remodeling of the left ventricle, highlighting the need for further trials to define the dose-response relationship [125].

Another prospective, multicenter, unblinded, phase I clinical research established the safety and preliminary efficacy of transcatheter delivery of a mean of 6.57×10^6 autologous bone marrow-derived advanced therapy medicinal product CD133+ cells (ATMP-CD133) in 10 patients with refractory angina and left ventricular dysfunction (ejection fraction equal to or less than 45 %). Patients were evaluated at 6 and 12 months. The results showed that the treatment was safe and produced significant improvements in myocardial perfusion and in Canadian Cardiovascular Society and Heart Association classes. Furthermore, a positive correlation was determined between improvements in perfusion and proangiogenic cytokine release, and an inverse relationship with proinflammatory cytokines, suggesting a possible mechanism of action mediated by the stem cell's secretory profile. Thus, the treatment appeared to be safe and effective in people with these conditions [126].

Meanwhile, a pivotal clinical trial sought to determine whether the intramyocardial delivery of a high dose of autologous bone marrow mononuclear cells in patients with chronic postmyocardial infarction heart failure and pre-specified, evidence-based bone marrow cell potency criteria improves exercise capacity, clinical status, and contractile function. Before initiating, an open-label, roll-in cohort study was conducted to assess the feasibility of the protocol's procedures. Patients with chronic post-myocardial infarction heart failure (New York Heart Association class II-III) with a left ventricular ejection fraction between 20 and 40 %, under stable medical treatment according to clinical guidelines for at least three months before enrollment, were included. They received a single transendocardial injection of 200 million of these cells [127].

The procedure was safe and well-tolerated, with no serious adverse events related to bone marrow aspiration or cell application. At six months, patients showed a significant improvement in distance covered during the six-minute walk test, and a sustained improvement trend was found at 12 months. Likewise, positive trends were observed in heart failure functional class, quality of life, and left ventricular ejection fraction. Preliminary results suggest functional and clinical benefits [127].

4.4. Coronary artery disease

In the context of vascular atherosclerosis, MSCs exhibit protective effects by preventing apoptosis and reducing inflammation. Plus, they possess immunomodulatory capabilities, regulating the activity of immune system cells, such as macrophages, whose function is key to the development of the condition. Their reparative effects may embrace stimulation of angiogenesis, improvement of the microenvironment to promote cardiac tissue recovery, regulation of the immune response, mitigation of inflammation, and reduction of scar tissue formation [8].

In a phase I, non-randomized, open-label study, the safety and feasibility of direct injection of bone marrow-derived stromal mesenchymal stem cells were evaluated in individuals with ischemic heart disease undergoing surgical revascularization via coronary artery bypass graft surgery (4 patients) or transmyocardial revascularization (10 patients). The cells were isolated from bone marrow aspirate, cultured, and expanded for three weeks prior to surgery. Subsequently, they were administered directly into the ischemic myocardium of the left ventricle at the end of the

surgical procedure. No significant complications related to the cell injection were reported. At 12 months of follow-up, regional contractility improved in the treated areas, along with substantial angina reduction and improved quality of life. These preliminary results suggest that intramyocardial injection of bone marrow-derived stromal mesenchymal stem cells is a safe and feasible strategy that provides functional benefit in persons with coronary artery disease undergoing revascularization surgery [128].

Another non-randomized, prospective phase I/II clinical investigation evaluated the long-term safety and efficacy of intramyocardial injection of autologous bone marrow-derived mesenchymal stromal cells in patients with severe coronary artery disease and refractory angina. This cell therapy was administered to 31 individuals with reversible myocardial ischemia and no revascularization options. The cells were isolated, cultured, and stimulated with VEGF to promote endothelial differentiation. After a three-year follow-up, significant improvements were observed in exercise time, angina class, frequency of angina attacks, and nitroglycerin use, along with an increase in quality of life. Hospitalizations were significantly reduced, and no adverse effects were reported. These data suggest that this therapeutic option is safe, with sustained clinical benefits and the potential to slow illness progression [129].

4.5. Pathologies causing alterations in heart rhythm

For this type of alteration, a preclinical study examined the effects of adipose tissue-derived MSCs on the development of induced ventricular arrhythmias in an animal model of myocardial infarction. Three groups were established: a control group with sham surgery and saline injection, a group whose subjects suffered an infarction and were treated with saline solution, and a group whose subjects suffered an infarction and received MSCs directly into the myocardium. The injections were administered two days after the infarction, and arrhythmia susceptibility was evaluated on the third day [130].

Only 35 % of the animals treated with cell therapy developed arrhythmias, compared to 65 % of the group that suffered this cardiovascular event without treatment. Although the frequency of distinct arrhythmia types was similar between the groups, those treated with MSCs had a shorter episode of non-sustained ventricular tachycardia. Besides, a rise in connexin 43 expression (which facilitates communication between adjacent cells) was detected in non-infarcted areas, even surpassing that of the control group, along with a reduction in the inflammatory cytokine IL-1 β . Additionally, the group receiving biological therapy showed decreased levels of 4-hydroxynonenal, a marker of oxidative damage, in the infarcted region. These findings suggest that stem cells could reduce the risk of arrhythmias through anti-inflammatory and antioxidant mechanisms, as well as promote communication between cardiac cells. Nonetheless, their effect appears limited in animals that have already developed arrhythmias [130].

Another research examined the electrical and molecular characteristics of human cardiomyocytes obtained from donor hearts and from laboratory-cultured stem cells. The cell types were one primary atrial and one primary ventricular cardiomyocyte, and three commercial stem cell lines (iCell cardiomyocytes and two models differentiated toward atrial or ventricular cells). Through electrical measurements in single cells and gene expression analysis, it was found that the cultured stem cells did not accurately represent the specific cell types present in an adult human heart. Single iCell cardiomyocytes showed a mixture of characteristics from several cardiomyocyte types (atrial, ventricular, and nodal), making them difficult to employ as specific models. In contrast, the lines engineered to be atrial or ventricular revealed a tendency toward these specializations, with notable differences from mature human cells. Despite these limitations, all the cells studied expressed genes responsible for fundamental cardiac electrical currents, allowing their consideration in studies of cardiac toxicity and pharmacological effects, though with caution given their heterogeneity and differences from adult human cardiomyocytes [131].

5. Challenges and limitations of stem cell therapy for the treatment of cardiovascular diseases

Over the past two decades, the number of studies and clinical trials using stem cells to treat cardiovascular disorders has augmented, reflecting the growing number of people worldwide diagnosed with cardiovascular disorders [26, 42]. While some progress has been made, many challenges and limitations remain.

One of the most frequently observed is the reduced information on MSC differentiation capacity. Some studies suggest they can differentiate into cardiomyocytes [116, 132], whereas others indicate that, although it can occur, it is rare, complicating heart muscle regeneration [25, 133].

Another drawback is the purification and reproduction process of cardiovascular progenitor stem cells [118], which are primarily responsible for regenerating this tissue. They are inactive under normal physiological conditions and, upon injury, are activated to participate in cardiomyocyte regeneration, mediating increased blood flow, angiogenesis,

cardiomyocyte proliferation, inhibition of apoptosis, and reduced inflammation. Moreover, they can differentiate into cardiomyocytes, vascular smooth muscle cells, and endothelial cells, as required to repair cardiac tissue [134].

Progress has been done in isolating and purifying MSCs [123] and HSCs [25], but additional research is needed to purify them and to more efficiently reproduce the assays, given the variable results across studies. Some research has shown that older patients respond similarly to MSC treatment as younger patients do, while others have found the opposite [135]. Still, some studies show that results vary with patient characteristics, such as age [25].

For its part, iPSCs exhibit limitations in genetic stability. Because they are reprogrammed to behave like embryonic cells, demonstrating their reproducibility and safety has been challenging, and can induce tumorigenicity and immunogenicity [136]. In addition, their metabolism requires intervention from numerous molecules to promote maturation [137]. Measurement methods must be refined, and essential adjustments to the processes must be made to ensure batch-to-batch reproducibility [25].

The above should be studied further to improve formulations and adapt them to patients for satisfactory results. One of the causes of such variations between studies is the standardized techniques to obtain the cells [116, 136]. Under this same analysis, the variability in results also depends on the routes or administration procedures, as some are considered more costly than beneficial for the individual [116]. Even the pre-treatment process influences the chosen route. Cardiovascular systems require *in vitro* expansion, so they cannot be administered on the same day they are collected, limiting their applicability [25]. This problem has been further complicated by the difficulty in characterizing the cells [118].

This situation can be improved by standardizing studies to homogenize them and advance their development as a therapy. Therefore, cell collection systems, administration routes, dosages [25], and the identification of genes with cardiac potential [118] must be defined. Likewise, rigorous controls must be required in studies, such as blinding, participant selection based on specific characteristics, representative sample sizes, and statistical significance [25].

6. Perspectives on stem cell therapy for the treatment of cardiovascular diseases

In recent years, this treatment has gained significant relevance in regenerative medicine, where the cardiovascular system has been one of the most explored areas due to the urgent need for new therapeutic options to address myocardial damage [138, 139]. Several studies indicate that one of the priorities is to optimize MSCs utilization to improve their functionality after transplantation. To this end, the implantation environment must be refined, new delivery techniques that potentiate their efficacy must be developed, and bioengineered materials that prolong their therapeutic effect must be settled. Besides, combinations with growth factors or other compounds that enhance their regenerative action are being investigated [140].

On the other hand, these therapies are expected to be incorporated more regularly into conventional treatments, especially for those who do not respond well to traditional alternatives [138]. At the same time, progress is being made toward more personalized medicine, in which therapy can be tailored to an individual's specific characteristics. This approach focuses treatment on the patient's particular needs, allowing for the identification of those who might benefit most from therapies defined to their clinical features or specific biomarkers. It is contemplated in the management of cardiovascular pathologies, as the treatment response can vary significantly among individuals [141].

Along the same lines, other studies have explored the utility of MSCs for acute myocardial infarction, with encouraging results in preclinical models [139]. An improvement in left ventricular function and a decrease in myocardial fibrosis have been observed following cell transplantation [140]. Furthermore, *in vitro* studies have demonstrated that they can differentiate into phenotypes with characteristics similar to those of cardiac muscle cells [142].

In addition, an emerging strategy is the secretome derived from MSCs, which comprises a fraction rich in soluble bioactive factors and contains extracellular vesicles, such as exosomes and microvesicles. These particles replicate many of the beneficial effects appreciated with whole cells, while avoiding some of the challenges associated with live-cell administration, such as immune responses and low post-transplant viability. Moreover, exosomes offer notable advantages, such as storage without cryoprotectants, high stability, low immunogenicity, and the ability to cross biological barriers, such as the blood-brain barrier [143].

The source of MSCs is another element to consider for their functionality. Cells obtained from the umbilical cord exhibit greater proliferative capacity than those extracted from bone marrow in adult patients. This element is highly relevant because, in persons with advanced cardiovascular disease, chronic inflammatory conditions could negatively affect the

quality of their own stem cells. Therefore, interest in allogeneic therapies using cells from healthy donors has increased. Nevertheless, it requires even stricter control over immunological compatibility and the risks associated with rejection or an unwanted immune response [33, 138, 139].

It is important to note that standardizing cell culture protocols remains a significant challenge for clinical use. One study indicates that they have traditionally employed fetal bovine serum (FBS), which provides essential nutrients for cell growth and proliferation. Despite this, it carries risks associated with the transmission of xenogeneic components, immune response, and alterations in cellular gene expression. Therefore, to reduce these risks, human plasma and platelet lysate have been proposed, as they promote better cell proliferation without compromising functionality. Still, substances such as fibrinogen have been found to activate cell receptors associated with inflammation, so their employment requires further research and some adjustments before they are adopted as a standard in cell therapy production [33].

Regarding the clinical purpose of iPSCs, multiple questions remain that must be overcome to ensure safe and effective therapy. One is the variability in differentiation capacity, making it difficult to obtain homogeneous and functional cell populations [144, 145]. As a complement, a challenge has been identified regarding the potential immune response to iPSC-derived cells, even when autologous, which casts doubt on their complete immunotolerance. Another element concerns reprogramming and culture processes, as epigenetic and genomic alterations can arise during these stages, potentially compromising their safety [144]. In response to this situation, one promising approach to improve their quality and safety is to optimize reprogramming protocols and to apply genetic screening (to detect potential deoxyribonucleic acid or DNA mutations) [146] and epigenetic screening (chemical changes that affect their expression without altering their sequence) [147]. The aim is to select only the most stable and functional cell lines [144].

Regarding this theme, the therapy has revealed variable results. Though it has been established as a safe option, the clinical benefits found have been small in some studies. While animal models have shown increases of up to 11 % in left ventricular ejection fraction, in humans, increases typically range from 2 to 4 % [142]. This situation has led to strategies to improve therapeutic efficacy, such as genetic modification to enhance expression of proangiogenic factors or the utilization of biomaterials that promote cell retention in cardiac tissue [139, 142, 148].

Therefore, stem cell therapy represents a constantly evolving field of research that has demonstrated great potential in cardiac regeneration. Although challenges exist, new approaches are being developed to overcome them. Thus, the future of regenerative medicine in cardiology demands the integration of rigorously evaluated elements approved by the health authorities [149].

7. Conclusions

Research on stem cells, such as MCSs and iPSCs, for the treatment of diverse cardiovascular illnesses is relevant to the health field, offering an alternative to acute conditions where the only options are heart transplantation or palliative drug therapies. These cells have exhibited regenerative properties in various tissues, proliferative properties at the cellular level, and differentiation capabilities.

While these therapies have shown great potential, significant clinical and technical obstacles remain. One of the main drawbacks is the lack of standardized protocols, the variability in clinical outcomes, and the difficulty in achieving functional, lasting integration of transplanted cells into heart tissue. Additionally, factors such as the patient's health status, age, pre-existing conditions, the administered cell type, and the administration method are crucial to the treatment's effectiveness. Similarly, there are risks, such as tumor formation and immunocompatibility.

The evidence of these limitations has led to the fact that, to date, no treatments have been approved by reference health authorities. Therefore, it is essential to continue researching these therapies to ensure that, when applied to humans, they are safe and effective, as patients expect.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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