

REVIEWS

Stem Cell Treatment for Dilated Cardiomyopathy: A Review of Recent Scientific Advances

Liddy Kasraian, BS¹, John Railey, BS, MA¹, Caitlin Mehta, BS¹, Madeline H Garvey, BS¹

¹ Georgetown University

Keywords: cardiomyocytes, hematopoietic, mesenchymal, adipose-derived, morbidity/mortality

<https://doi.org/10.52504/001c.123163>

Georgetown Medical Review

Vol. 8, Issue 1, 2024

Cardiomyopathy, a disorder of mechanical and electrical cardiac action, is a significant cause of morbidity and mortality in the United States and is seen in both adult and pediatric populations. Dilated cardiomyopathy, a subtype involving pathological enlargement of the heart, in particular causes significant reduction in quality of life and is a significant risk factor for heart failure development. Traditional treatment for dilated cardiomyopathy largely focuses on symptomatic relief and delayed progression of disease but does not offer a cure or reversal of disease process. In the past few decades, stem cell therapy has become a promising therapeutic because these cells can differentiate into human cardiomyocytes and offer a potential restoration of normal cardiomyocyte function. This review highlights 3 methodological derivations of cardiomyocytes: bone marrow–derived hematopoietic stem cells, mesenchymal stem cells, and adipose-derived stem cells. While most of the current research has focused on hematopoietic stem cells for dilated cardiomyopathy, further research is needed to elucidate which stem cell line is superior and most effective for disease treatment and reversal. This review highlights future directions of this line of research, such as direct comparison between cell types, analysis of the long-term effects of stem cell treatment, increased sample sizes, and potential use of this treatment in the pediatric and adult populations.

Introduction

Cardiomyopathy, broadly defined as pathology of the cardiac muscle causing mechanical or electrical dysfunction, can be classified as dilated, hypertrophic, or restrictive based on its specific pathophysiology.¹ Additionally, cardiomyopathies can be further categorized based on whether they have an ischemic or nonischemic etiology.

In recent years, dilated cardiomyopathy (DCM) has emerged as a particular area of clinical and scientific focus because it is one of the top causes of heart failure and the most common indication for heart transplant.² While its epidemiology is somewhat uncertain due to changing criteria for DCM, it is estimated that DCM affects 1 in 250 individuals in the general population, with more than 400 000 annual deaths occurring worldwide from subsequent pump failure or sudden cardiac death.^{1,2} Troublingly, the risk of DCM progressing to severe illness and heart failure is higher in Black patients

than White patients even when controlling for other medical conditions and socioeconomic factors, emphasizing the need for more effective treatments for DCM that could promote greater health equity.³

In the pediatric population, the estimated incidence of cardiomyopathies is 1 case per 100 000 person-years, with approximately 50% of cases characterized as DCM.⁴ While its incidence is lower in the pediatric population as compared with adults, almost 40% of children with symptomatic cardiomyopathy undergo heart transplant or die within 2 years after diagnosis, demonstrating the especially poor DCM outcomes and need for more efficacious treatments in this population.⁴

There are numerous etiologies that can lead to this clinical phenotype, ranging from genetic to acquired. Familial cases of DCM may account for up to half of total cases, and more than 50 genes related to DCM have been identified.² Acquired etiologies for DCM include excessive alcohol consumption; bacterial, viral, or parasitic myocarditis; and autoimmune disorders.

DCM presents with left ventricular enlargement and systolic dysfunction defined as an ejection fraction of less than 45% capacity.² Unfortunately, depending on the severity of left ventricular ejection fraction (LVEF) reduction, the prognosis for patients with DCM is often poor. LVEF is an indication of systolic function, and in patients with DCM, enlarged ventricles may lead to impaired contractility and declining cardiac output.¹ This declining cardiac output may progress to heart failure, in which the heart is unable to pump blood to adequately supply the body. This results in patients experiencing fatigue and shortness of breath while engaging in mild activity or at rest.¹ Additionally, as DCM progresses, adverse cardiac remodeling often takes place, which may manifest as myocardial fibrosis, mitral regurgitation, and enlargement of other cardiac chambers. This adverse remodeling may trigger ventricular arrhythmias or pulseless electrical activity, leading to sudden cardiac death.¹

Currently, treatment for patients with DCM centers around managing heart failure symptoms and improving overall cardiac function. This can involve symptom management and prevention of disease remodeling through pharmacologic therapy, which includes the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, and mineralocorticoid receptor antagonists, among other drugs.¹ Device therapy, including the use of pacemakers, may also be helpful for patients who demonstrate left ventricular systolic dysfunction or any sort of electrical dysfunction.¹ However, if pharmacologic or device therapy is ineffective at management of symptoms and disease progression, patients with DCM may have to seek a heart transplant.

Because existing management strategies for DCM are not able to fully prevent patients from progressing to heart failure, the use of stem cells offers a promising alternative. Because stem cells are undifferentiated human cells that can potentially be used to replace diseased cells of virtually any type, these cells could be of use in cardiac pathologies including DCM. Specifically, pluripotent embryonic stem cells can differentiate into all cell types, while multipotent adult stem cells can differentiate into a more limited subset of cells, including cardiomyocytes.⁵ The progression of cardiomyopathy to more serious outcomes, such as heart failure, is largely due to adverse cardiac remodeling and the limited self-regenerative ability of the heart.¹ However, in animal studies and early human studies, stem cells have been shown to be effective in improving LVEF and mitigating symptoms in patients with ischemic and nonischemic cardiomyopathy.⁶

While stem cell therapy is a rapidly evolving area of research, several methods of stem cell derivation have proven particularly effective in the treatment of DCM. Based on our literature review, we highlight the 3 stem cell derivatives that have received the most scientific and clinical attention—bone marrow–derived hematopoietic stem cells, bone marrow–derived mesenchymal stem cells, and adipose-derived mesenchymal stem cells—and examine their efficacy in treating DCM as compared with existing treatment methods.

Bone Marrow–Derived Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are multipotent cells capable of differentiating into any variation of cell in the hematopoietic cell line.⁵ They can be cultured from many sources, such as stimulation from peripheral blood or direct extraction from bone marrow, with the latter being a readily available source for most patients that requires no prior stimulation or injection.^{7,8} Additionally, only a relatively small amount of cells is required to produce desired effects such as increased ejection fraction or exercise tolerance, which relate to functional and lifestyle benefits.⁷ HSCs have been regularly studied for their effects on various diseases due to their ability to promote regeneration in various tissues, one being cardiac tissue.⁷

Bone Marrow–Derived HSCs for Nonischemic DCM Therapy

Divided into 2 subsets for the purpose of this review, nonischemic DCM is typically a result of genetic or immune errors or infection and ischemic DCM is commonly tissue damage secondary to ischemia.² Nonischemic DCM has been studied with many variations of bone marrow–derived HSCs. Vrtovec et al⁸ used *CD34+* HSCs, which are a subset of HSCs positive for this specific antigenic marker used for identification. They showed that intracoronary injection of *CD34+* HSCs yielded a significant increase in LVEF from approximately 25% to 31% in nonischemic DCM compared with the control group, which showed no significant increase at 1-year follow-

up.⁸ Measuring the amount of cells that remained in the desired injection site—defined as homing—played a significant role in outcomes. When good homing of the injection was observed, which was defined as any activity value greater than the general activity median value measured at 2 and 18 hours post injection, patients showed significant increase in LVEF relative to control.⁸ Members of the treatment group with poor homing of cells showed more variable and insignificant increase in LVEF, suggesting that future stem cell therapies should consider exploring mechanisms to improve cell homing.⁸

Additionally, N-terminal pro-brain natriuretic peptide, a commonly used marker for diagnosing heart failure due to its regulatory role in cardiovascular function, was found to be significantly decreased in the entire treatment group.⁸

The observed increase in LVEF relatively declined at the 3- and 5-year follow-ups but still remained higher than preinjection numbers. No significant decrease in left ventricular end-diastolic dimension, which can be thought of as a measurement of dilation, was observed. Additionally, quality of life as assessed by the 6-minute walk test significantly increased and mortality significantly decreased in the treatment group relative to the control group.⁸

The relative decline in LVEF shown by the first study of Vrtovec et al in successive follow-ups left room to ponder the effects of multiple injections, so a similar study was done comparing single vs multiple injections for patients with DCM, although transendocardial in nature.^{8,9} However, the group that received injections at the offset of the study and the 6-month mark saw similar results in terms of LVEF and left ventricular end-diastolic dimension as the group receiving just 1 injection.⁹

Using the intracoronary method with multiple injections could have yielded more significant improvement in LVEF, although Vrtovec et al¹⁰ found transendocardial to be more effective than intracoronary in a comparative trial. Bervar et al¹¹ found similar improvement in 6-minute walk distance and overall diastolic functioning among patients with DCM who received transendocardial injection of *CD34+* HSCs. However, improvements in LVEF were not found to significantly differ between the 2 trial groups, which both had DCM and were separated by the amount of myocardial scarring, suggesting the mechanism of improved LVEF following stem cell application may be unrelated to myocardial scarring.¹¹

Because DCM often causes diffuse dilation, aspects of HSC therapy on other regions of the heart have shown similar promise. Transendocardial injections of *CD34+* HSCs have shown significantly increased right ventricular functioning.¹² In addition to this outcome, LVEF and 6-minute walk distance showed significant improvement from control, confirming what was seen in the studies by Vrtovec et al⁸ and Frljak et al.¹² Interpretation of the data reasoned that improvement of right ventricular function was due to

improvement of the interventricular septum function because it plays a role in both the right and left ventricles, thus pointing to an area of further study and possible standard area of transendocardial injection in treatments going forward.¹²

Bone Marrow–Derived HSCs for Ischemic DCM Therapy

Ischemic DCM offers an interesting contrast to its more diffuse nonischemic counterpart, being that the infarcted area offers a region of focused injection and measurement. Patients with advanced ischemic DCM have received endomyocardial injection of bone marrow mononuclear cells (BMCs).¹³ Prior studies had indicated that BMC therapy improves symptoms and left ventricular function in patients with nonischemic DCM, so BMCs were expected to have some efficacy in this patient population.^{8,10,12} However, after 6 months, there was no significant difference between the control and treatment groups in terms of LVEF, left ventricle end-systolic volume, and left ventricle infarct volume.¹³ BMCs did not improve left ventricle function or remodeling in these patients with ischemic cardiomyopathy.¹³

With minimal results available to support the efficacy of HSCs as a stand-alone treatment for ischemic DCM, Assmann et al⁷ looked to combine stem cell treatment with surgical measures in patients with ischemic DCM. Patients underwent coronary artery bypass surgery combined with laser-supported transplant of *CD133+* (another antigenic marker similar to *CD34+*) HSCs from bone marrow. At 3-, 6-, and 12-month follow-ups post procedure, patients were found to have decreased angina, increased quality of life measured via subjective survey, increased LVEF, and decreased left ventricular end-diastolic volume, all in significant measures.⁷ This creates the opportunity for stem cells to be used in combination therapy to induce improved postoperative healing in addition to novel, healthy tissue proliferation. This could allow stem cells to be used now as treatment in an operative setting, while their use as an independent treatment is still being honed, perhaps allowing more funding to be allocated for development.

Bone Marrow–Derived Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are another area of prominent therapeutic research for cardiomyopathies such as DCM. Similar to HSCs, MSCs are multipotent progenitor cells that develop into the mesenchymal cell line, which includes structures relating to bone, adipose, and muscle tissues.¹⁴ They are then able to further differentiate into specific tissue lineages such as hepatic, kidney, neuronal, and cardiac.¹⁴ These cells serve as significant prospects for clinical benefit for cardiovascular diseases such as cardiomyopathy, specifically regarding their anti-inflammatory, antifibrotic, and proangiogenic properties.¹⁵

Allogeneic vs Autologous MSCs for Nonischemic DCM Therapy

Transplant of MSCs for therapeutic intervention is done in an autologous or allogeneic fashion, meaning cells can be transplanted from the patient themselves or transplanted from someone other than the patient, respectively. These methods of derivation and transplant of MSCs have undergone comparisons regarding their efficacy as treatment options for nonischemic and ischemic cardiomyopathies. Hare et al⁶ aimed to evaluate which type of MSC demonstrated therapeutic effects in nonischemic dilated cardiomyopathy. Specifically, they found that allogeneic MSCs had more promising therapeutic effects on nonischemic DCM when compared with autologous MSCs, ultimately resulting in decreased rehospitalization rates after a year.^{6 2^}

The randomized clinical trial by Hare et al⁶ showed that patients given allogeneic MSCs had better outcomes regarding LVEF, 6-minute walk test, tumor necrosis factor α (TNF- α) plasma concentrations, and endothelial progenitor cell colony-forming units (EPC-CFUs) when contrasted with the patients receiving autologous MSCs.⁶ Patients within the allogeneic group experienced a significant increase in LVEF compared with baseline ejection fractions.

Additionally, almost half of the patients who received the allogeneic injection achieved an ejection fraction of greater than 40%. In contrast, the autologous injection group only had a minimal percentage of patients achieve an LVEF greater than 40% and a minimal increase in overall LVEF when compared with baseline.⁶ The contrast between allogeneic and autologous injections was furthered when looking at the 6-minute walk test. Patients receiving the allogeneic injection had a substantial increase in tolerance and distance, while the autologous injection did not demonstrate the same result. Finally, the allogeneic injection revealed improved endothelial function when looking at the increase of EPC-CFUs and substantial decrease in plasma TNF- α 6 months post injection. The autologous group had minimal to insignificant changes.⁶ Considering that the pathology of nonischemic cardiomyopathy largely relates to endothelial dysfunction, the significant effects of allogeneic MSCs on the patients likely resulted from the considerable effects on EPC-CFU and TNF- α concentration.

Allogeneic vs Autologous MSCs for Ischemic DCM Therapy

The effects of allogeneic and autologous MSCs on restoring endothelial function can be seen in cases of ischemic DCM as well, as shown by Premer et al¹⁵ in their analysis of both ischemic and nonischemic DCM. The study revealed that endothelial dysfunction improved 3 months post treatment in the allogeneic MSC group, with significantly higher EPC-CFUs when contrasted with those receiving the autologous MSCs.¹⁵ On morphologic analysis, the allogeneic endothelial colonies presented as organized and

healthy in contrast with their initial disordered and nonfunctional appearance prior to injection. The positive endothelial cell markers *VEGFR* and *CD31/PECAM* within these cells were also suggestive of stimulation of endothelial progenitor colonies in patients with dilated and ischemic cardiomyopathy receiving allogeneic MSC therapy.¹⁵ In sum, allogeneic MSCs have been shown as the more effective therapy for ischemic and nonischemic cardiomyopathies when contrasted with autologous MSCs in a variety of trials.^{6,15-17}

Mechanism and Dosing of Allogeneic and Autologous MSC Therapy

A follow-up on the Premer et al¹⁶ study was conducted in 2019 to better understand the mechanism behind the efficacy of allogeneic compared with autologous MSC therapy. This study found an inverse relationship between the plasma concentration of TNF- α and EPC-CFU; the decrease in this inflammatory cytokine had a beneficial change on endothelial proliferation. The major conclusion related to the concentration of stromal cell-derived factor-1 α (SDF-1 α): lower levels of this cytokine allow for inhibition of destructive mitochondrial reactive oxygen species, while high levels do not have this property. It was determined that autologous MSCs secrete 3 times the level of SDF-1 α when compared with allogeneic MSCs, which is likely the basis behind the lower efficacy of autologous MSCs as therapeutic agents.¹⁶

Finally, a study by Florea et al¹⁷ assessed the necessary dosage of transplanted allogeneic MSCs to elicit a therapeutic response. The results showed that high-dose transendocardial injections had better therapeutic outcomes than low-dose injections in ischemic cardiomyopathy.¹⁷ These findings revealed that high- and low-dose injections significantly reduced infarct size and improved the 6-minute walk test, while only the higher-dose MSCs decreased rehospitalization rates and stabilized heart failure markers, such as N-terminal pro-brain natriuretic peptide, after 12 months.¹⁷ This study, while demonstrating that higher-dose allogeneic MSC injection is an effective ischemic cardiomyopathy therapy, also begs the question of the potential implications of long-term usage of high-dose MSCs.

Adipose-Derived MSCs

MSCs are most commonly derived from bone marrow but, more recently, adipose tissue has emerged as a potential means of collection. Adipose-derived MSCs (ADMSCs), also referred to as *adipose-derived regenerative cells*, are a method of autologous transplant of multipotent cells that contain 500 times as many MSCs as adult bone marrow.¹⁸ The PRECISE Trial conducted in 2014 by Perin et al¹⁸ demonstrated that liposuction-derived autologous transplant of ADMSCs is, in fact, safe in patients with ischemic heart disease. While the study demonstrated that ADMSCs are safe in patients with ischemic heart disease, research on human trials remains fairly limited due to

small sample sizes and unknown long-term effects.¹⁸ Even with the limited human trials, there are a variety of animal models that have demonstrated the potential therapeutic effects of ADMSCs on a variety of cardiomyopathies, which will further be discussed below.

Larocca et al¹⁹ used a murine model to analyze whether stem cells from adipose tissue (SCAT) could function as a therapeutic treatment for Chagas cardiomyopathy, a prominent cardiomyopathy in Latin America resulting from infection with *Trypanosoma cruzi*. The study revealed a reduction in myocardial fibrosis as well as inflammation in the SCAT-treated chagasic animals in comparison with the control, which is consistent with the bone marrow–derived studies. However, the study did not show a difference in survival rate, cardiac arrhythmias, or ergonomic function between the control and SCAT-treated groups.¹⁹

In contrast, a study in 2021 by Mori et al²⁰ used a hamster model to further the understanding of ADMSCs for treating DCM. The group of DCM hamsters treated with ADMSCs preserved their LVEF for approximately a month longer than the control groups.²⁰ Although there was no evident fibrosis suppression, histologic examination exhibited inhibition of hypertrophy and vascularization of cardiomyocytes. Analysis also showed cardiac output was maintained following transplant of ADMSCs.²⁰ This is likely an outcome of the increased adenosine triphosphate (ATP) concentration and myosin expression resulting from the adenosine nucleotide translocase-1 signaling pathway. The pathway is activated by activin A, which is secreted by ADMSCs. Increased myosin expression and ATP production allows for better cardiomyocyte contraction, and thus maintains cardiac output.²⁰ While neither of these animal models clearly demonstrated the ability of ADMSCs to act as therapeutic agents for cardiomyopathy, their discoveries regarding reductions of myocardial fibrosis and maintenance of cardiac output and contractility could eventually expand adipose derivation of stem cells into a promising therapy for cardiomyopathy.

Discussion

Dilated cardiomyopathy presents a significant societal disease burden and results in significant morbidity and mortality for those affected, with current authorized treatments offering control of disease progression and symptomatic relief rather than a potential restorative benefit. For these reasons, the use of hematopoietic, mesenchymal, and adipose tissue–derived stem cells to specifically treat dilated cardiomyopathy is an exciting prospect with a lot of emerging supporting data. While the limitations of these therapies will be further analyzed here, some of the most compelling strengths of this line of therapeutic research include the increased availability of this treatment compared with heart transplant availability and the potential for a curative approach with the possibility of repairing previously diseased tissue.

One of the most promising aspects of stem cell therapy is the ability for these cells to intervene on and reverse disease processes, thereby giving this treatment method the most promise for pediatric populations who are rapidly undergoing development. While most of the data on this subject has come from adult populations, the use of stem cell therapy for congenital heart disorders has substantially less research but offers promise. Preclinical research in this subcategory is limited due to the difficulty of creating animal models with the exact congenital cardiac conditions seen in humans.²¹ However, there have been a few small case series and reports that have tested the efficacy of stem cell use in the pediatric population. For example, Mayo Clinic scientists led by Burkhardt et al²² presented the first known case of transplanting umbilical cord-derived stem cells into an infant with hypoplastic left heart syndrome. At the 3-month follow-up visit, the patient had improved right ventricular ejection fraction. However, because this was only a case report, causation cannot be assumed and other modifying factors, such as the standard surgical procedures for infants with congenital heart disorders, cannot be ruled out as potentially causing the improved right ventricular ejection fraction.²²

In a slightly larger sample, Rupp and colleagues²³ treated 9 children with congenital heart disease and dilated cardiomyopathy with bone marrow-derived mononuclear stem cells. While results were limited due to low power in a small and heterogeneous sample, 5 of the 9 children exhibited signs of cardiac improvement based on measures including ejection fraction and levels of brain natriuretic peptide.²³ More research is needed in randomized clinical trials with larger sample sizes to further investigate the therapeutic effect of stem cell therapy in pediatric patients with congenital heart disease.

Despite the potential therapeutic benefits of stem cell-based therapy for dilated cardiomyopathy, there are significant research limitations that must first be addressed before these therapies become standard treatment. For instance, it can be difficult in many of the studies highlighted in this review to truly control for confounding variables when many patients who are receiving stem cell-based therapy are also undergoing other standard treatments and surgeries. Because these critically ill patients are often receiving polytherapy, the direct effect of stem cell therapy remains unclear. Additionally, many of the studies conducted to date have small sample sizes and thus are not fully generalizable to the broader population. Finally, few current studies have examined administering multiple doses of stem cell therapy and, thus, the optimal dosing strategy and concentration of stem cells necessary for therapeutic effect have not been fully established.

With these limitations in mind, future research is needed in several specific areas within the umbrella of stem cell treatment for dilated cardiomyopathy. First, several of the studies highlighted in this review were conducted within

the last several years and, because this is an emerging treatment method, more time is needed to ensure that the use of stem cells in cardiomyopathy treatment is safe in humans long-term. Additionally, more research is needed to elucidate which methods of derived stem cells are most effective in these treatments. Along with understanding which derivation to use, more research is needed to confirm which method of patient administration is most effective. Most of this work can be done in prehuman clinical trial stages in cell cultures and animal/nonhuman primate disease models. Further, because dilated cardiomyopathy presents significant disease burden, but the profound majority of these clinical studies are in adults, further research is needed to learn about the safety and efficacy of these treatments in pediatric congenital heart disease populations. Finally, while there is an abundance of stem cell research focused on treating dilated cardiomyopathy, future research should further elucidate the interplay between stem cell treatments for different types of cardiomyopathies, including for hypertrophic and restrictive cardiomyopathy subtypes.

While the use of stem cells for cardiomyopathy is a promising therapeutic possibility that has garnered significant interest over the past decade, some researchers have voiced concerns about possible drawbacks to this type of therapy as a whole.²⁴ For instance, the use of stem cells in general typically carries the risk of poor cell survival and engraftment rate. Additionally, there is the concern of tumorigenicity when using stem cells, although this is less of a risk when using multipotent stem cells as discussed in this review. Furthermore, when using stem cells for cardiomyopathy treatment, there are significant risks associated with the delivery process, which may necessitate open-chest surgery in patients who are less than optimal surgical candidates due to their heart disease.²⁴ Some researchers have expressed that at this time, there is not enough demonstrated benefit of stem cell therapy to outweigh these risks. Moving forward, research in this field will hopefully continue to walk the line of maximizing therapeutic benefits while minimizing these potential drawbacks such that stem cell therapy is someday available as a curative treatment to individuals with DCM.

Finally, as previously mentioned, there are significant racial and ethnic disparities in progression from DCM to heart failure.³ It is critical that future research in stem cell therapy for DCM includes diverse clinical trial samples and that any progression in therapy development is equally accessible to patients of all racial and ethnic backgrounds.

Conclusion

As has been outlined in this review, stem cell therapy for dilated cardiomyopathy is an exciting and evolving field. Hematopoietic, mesenchymal, and adipose tissue-derived stem cell therapies all have various efficacies and important considerations as potential therapeutic mechanisms, with bone marrow-derived hematopoietic stem cell therapy currently having

the most robust research. While most of the existing research in this area has been conducted with animal models or adult patients, several case studies have suggested that stem cell therapy may be efficacious in pediatric patients with congenital heart disease, indicating a potential treatment option for a condition associated with significant morbidity and mortality. Opportunities for future research include direct comparison to determine whether 1 of the 3 stem cell derivations is most efficacious, as well as gathering long-term safety and efficacy data in larger sample sizes to determine whether stem cell therapies can be used safely in the large population of individuals with DCM.

.....

Financial Disclosure/Conflict of interest

The authors of this paper have no conflicts of interest or grants/financial support to declare.

Submitted: June 25, 2024 EST. Accepted: August 04, 2024 EST. Published: September 11, 2024 EST.

REFERENCES

1. Schultheiss HP, Fairweather D, Caforio ALP, et al. Dilated cardiomyopathy. *Nat Rev Dis Primers*. 2019;5(1):32. doi:[10.1038/s41572-019-0084-1](https://doi.org/10.1038/s41572-019-0084-1)
2. Orphanou N, Papatheodorou E, Anastasakis A. Dilated cardiomyopathy in the era of precision medicine: latest concepts and developments. *Heart Fail Rev*. 2022;27(4):1173-1191. doi:[10.1007/s10741-021-10139-0](https://doi.org/10.1007/s10741-021-10139-0)
3. Huggins GS, Kinnamon DD, Haas GJ, et al. Prevalence and cumulative risk of familial idiopathic dilated cardiomyopathy. *JAMA*. 2022;327(5):454-463. doi:[10.1001/jama.2021.24674](https://doi.org/10.1001/jama.2021.24674)
4. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. *Circulation*. 2019;140(1):e9-e68. doi:[10.1161/CIR.0000000000000682](https://doi.org/10.1161/CIR.0000000000000682)
5. Gargiulo C, Pham VH, Thuy Hai N, et al. Isolation and characterization of multipotent and pluripotent stem cells from human peripheral blood. *Stem Cell Discovery*. 2015;5(3):19-32. doi:[10.4236/scd.2015.53003](https://doi.org/10.4236/scd.2015.53003)
6. Hare JM, DiFede DL, Rieger AC, et al. Randomized comparison of allogeneic versus autologous mesenchymal stem cells for nonischemic dilated cardiomyopathy: POSEIDON-DCM Trial. *J Am Coll Cardiol*. 2017;69(5):526-537. doi:[10.1016/j.jacc.2016.11.009](https://doi.org/10.1016/j.jacc.2016.11.009)
7. Assmann A, Heke M, Kröpil P, et al. Laser-supported CD133+ cell therapy in patients with ischemic cardiomyopathy: initial results from a prospective phase I multicenter trial. *PLoS One*. 2014;9(7):e101449. doi:[10.1371/journal.pone.0101449](https://doi.org/10.1371/journal.pone.0101449)
8. Vrtovec B, Poglajen G, Lezaic L, et al. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. *Circ Res*. 2013;112(1):165-173. doi:[10.1161/CIRCRESAHA.112.276519](https://doi.org/10.1161/CIRCRESAHA.112.276519)
9. Vrtovec B, Poglajen G, Sever M, et al. Effects of repetitive transendocardial CD34+ cell transplantation in patients with nonischemic dilated cardiomyopathy. *Circ Res*. 2018;123(3):389-396. doi:[10.1161/CIRCRESAHA.117.312170](https://doi.org/10.1161/CIRCRESAHA.117.312170)
10. Vrtovec B, Poglajen G, Lezaic L, et al. Comparison of transendocardial and intracoronary CD34+ cell transplantation in patients with nonischemic dilated cardiomyopathy. *Circulation*. 2013;128(11 Suppl 1):S42-S49. doi:[10.1161/CIRCULATIONAHA.112.000230](https://doi.org/10.1161/CIRCULATIONAHA.112.000230)
11. Bervar M, Kozelj M, Poglajen G, et al. Effects of transendocardial CD34+ cell transplantation on diastolic parameters in patients with nonischemic dilated cardiomyopathy. *Stem Cells Transl Med*. 2017;6(6):1515-1521. doi:[10.1002/sctm.16-0331](https://doi.org/10.1002/sctm.16-0331)
12. Frljak S, Jaklic M, Zemljic G, Cerar A, Poglajen G, Vrtovec B. CD34+ cell transplantation improves right ventricular function in patients with nonischemic dilated cardiomyopathy. *Stem Cells Transl Med*. 2018;7(2):168-172. doi:[10.1002/sctm.17-0197](https://doi.org/10.1002/sctm.17-0197)
13. Santoso T, Siu C, Irawan CW, et al. Endomyocardial implantation of autologous bone marrow mononuclear cells in advanced ischemic heart failure: a randomized placebo-controlled trial (END-HF). *J Cardiovasc Transl Res*. 2014;7(6):545-552. doi:[10.1007/s12265-014-9580-6](https://doi.org/10.1007/s12265-014-9580-6)
14. Ab Kadir R, Zainal Ariffin SH, Megat Abdul Wahab R, Senafi S. Molecular characterisation of human peripheral blood stem cells. *South African J Sci*. 2012;108(5/6):1. doi:[10.4102/sajs.v108i5/6.939](https://doi.org/10.4102/sajs.v108i5/6.939)
15. Premier C, Blum A, Bellio MA, et al. Allogeneic mesenchymal stem cells restore endothelial function in heart failure by stimulating endothelial progenitor cells. *EBioMedicine*. 2015;2(5):467-475. doi:[10.1016/j.ebiom.2015.03.020](https://doi.org/10.1016/j.ebiom.2015.03.020)

16. Premer C, Wanschel A, Porras V, et al. Mesenchymal stem cell secretion of SDF-1 α modulates endothelial function in dilated cardiomyopathy. *Front Physiol.* 2019;10:1182. doi:[10.3389/fphys.2019.01182](https://doi.org/10.3389/fphys.2019.01182)
17. Florea V, Rieger AC, DiFede DL, et al. Dose comparison study of allogeneic mesenchymal stem cells in patients with ischemic cardiomyopathy (the TRIDENT study). *Circ Res.* 2017;121(11):1279-1290. doi:[10.1161/CIRCRESAHA.117.311827](https://doi.org/10.1161/CIRCRESAHA.117.311827)
18. Perin EC, Sanz-Ruiz R, Sánchez PL, et al. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: the PRECISE trial. *Am Heart J.* 2014;168(1):88-95.e2. doi:[10.1016/j.ahj.2014.03.022](https://doi.org/10.1016/j.ahj.2014.03.022)
19. Larocca TF, de Freitas Souza BS, Silva CA, et al. Transplantation of adipose tissue mesenchymal stem cells in experimental chronic chagasic cardiopathy. *Arq Bras Cardiol.* 2013;100(5):460-468. doi:[10.5935/abc.20130058](https://doi.org/10.5935/abc.20130058)
20. Mori D, Miyagawa S, Kido T, et al. Adipose-derived mesenchymal stem cells preserve cardiac function via ANT-1 in dilated cardiomyopathy hamster model. *Regen Ther.* 2021;18:182-190. doi:[10.1016/j.reth.2021.06.006](https://doi.org/10.1016/j.reth.2021.06.006)
21. Wehman B, Kaushal S. The emergence of stem cell therapy for patients with congenital heart disease. *Circ Res.* 2015;116(4):566-569. doi:[10.1161/CIRCRESAHA.115.305821](https://doi.org/10.1161/CIRCRESAHA.115.305821)
22. Burkhart HM, Qureshi MY, Peral SC, et al. Regenerative therapy for hypoplastic left heart syndrome: first report of intraoperative intramyocardial injection of autologous umbilical-cord blood-derived cells. *J Thorac Cardiovasc Surg.* 2015;149(3):e35-e37. doi:[10.1016/j.jtcvs.2014.10.093](https://doi.org/10.1016/j.jtcvs.2014.10.093)
23. Rupp S, Jux C, Bönig H, et al. Intracoronary bone marrow cell application for terminal heart failure in children. *Cardiol Young.* 2012;22(5):558-563. doi:[10.1017/S1047951112000066](https://doi.org/10.1017/S1047951112000066)
24. Tang JN, Cores J, Huang K, et al. Concise review: is cardiac cell therapy dead? embarrassing trial outcomes and new directions for the future. *Stem Cells Transl Med.* 2018;7(4):354-359. doi:[10.1002/sctm.17-0196](https://doi.org/10.1002/sctm.17-0196)