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Stem cell therapy in treatment of heart failure – a literature review

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ABSTRACT

Introduction

Heart failure is a condition defined as insufficient supply of oxygen to tissues, caused by a reduced cardiac output. It is usually associated with myocardial infarction or valve malfunction, but can also be a result of chronic diseases, such as hypertension or alcohol abuse. Despite the good state of knowledge about this disease and modern forms of treatment, heart failure remains a major therapeutic problem and a common cause of death around the world. The evolution of heart failure treatment over the years has revolved around managing

the symptoms, yet failed to develop a causal treatment. Stem cell therapy has risen interest among researchers, as promising studies had emerged. The regenerative potential of stem cells and their paracrine properties are believed to improve cardiac function in patients with heart failure.

Aim of study

The aim of this study is to review randomized clinical trials published in the last 5 years and evaluate the safety and potential role of stem cell therapy in managing patients suffering from heart failure.

State of knowledge

Stem cells are capable of self-renewal and differentiating into other types of cells. They hold great promise in the field of regenerative medicine as a factor inducing tissue repair, reducing apoptosis and promoting angiogenesis. Animal studies have shown their positive effect on cardiac contractility and also reducing the amount of scar tissue, but subsequent studies in humans have not yielded consistent results.

Conclusion

Heart failure therapy using stem cells is a safe method. Promising results of clinical studies have been reported related to the improvement of contractile function of the heart, as well as reduction of scar mass and improvement of quality of life. However, there is still a lack of consistent data and guidelines regarding the selection of the type of cells and the method of their administration in specific clinical situations. This topic requires broader studies, on larger groups of patients.

Keywords: Ischaemic heart failure; heart failure; Myocardial infarction; Stem cell therapy, Adipose stem cell;

INTRODUCTION

About heart failure

Heart failure is defined as the inability to provide adequate oxygen supply to tissues, caused by reduced cardiac output. The pathophysiology of this disease entity is complex and involves many mechanisms. One of the most common causes of heart failure, however is ischemic damage to the heart muscle. The damaged heart tissue forms scar tissue that disrupts

haemodynamics and the ability of the heart to proper contraction, leading to deterioration of the organ's function. Despite extensive research, treatment and prevention programs, heart failure continues to be a growing clinical problem and a common cause of death worldwide. It is estimated that about 6.7 million Americans over the age of 20 suffer from heart failure, and it is expected that the incidence will increase to about 8.5 million by 2030. ([18],[20]) Despite great efforts and good guidelines for the treatment of HF, there is still a lack of causal treatment options[19]. Heart transplantation is associated with significant perioperative risks and an insufficient number of organs for transplantation. In recent years, stem cell therapy has emerged as a promising solution, with clinical trials showing the potential to regenerate myocardium, reduce scar tissue mass, and improve left ventricular systolic function([16,17]). The aim of this paper is to review the current state of knowledge on the use of stem cells in heart failure, the safety of this therapy, and the difficulties associated with it.

About stem cells

Stem cells are capable of self-renewal and differentiation into other cell types, which makes them a very promising tool for regenerating damaged heart muscle. We distinguish different types of stem cells based on their origin, regenerative potential and mechanisms of action. The most important of them, in the context of treating heart failure, are hematopoietic stem cells (HSC), mesenchymal stem cells (MSC) and induced pluripotent stem cells (iPSC)

Hematopoietic stem cells (HSC) are mainly responsible for the production of blood cells in the body, but they raise some hopes for stimulating heart regeneration. Their source is primarily bone marrow, but also peripheral and umbilical cord blood. Although they do not have the ability to differentiate into cardiomyocytes, it is believed that they can have a positive effect on the function of damaged heart muscle, most likely by modulating inflammatory processes and stimulating angiogenesis through the secretion of VEGF([2],[3],[8],[11]).

Mesenchymal stem cells (MSC) can be found in bone marrow, adipose tissue and umbilical cord. Their main function is to respond to damage and regenerate tissue. They have the ability to differentiate into various tissues, including nervous, adipose, bone and muscle. They also have a strong immunomodulatory effect, which has a beneficial effect on the survival of transplanted cells. It is believed that MSC can stimulate myocardial regeneration by secreting growth factors, stimulating angiogenesis, reducing inflammation and, to some extent, by differentiating into cardiomyocytes. MSCs are the most promising cell type for the treatment of heart failure([24][25]).

Induced pluripotent stem cells (iPSCs) are mature somatic cells that have been dedifferentiated to a pluripotent state. They have the ability to differentiate into any cell type, similar to the embryonic stem cells ([21],[22]). It is believed that they can lead to the regeneration of heart tissue by differentiating into cardiomyocytes, and they also stimulate angiogenesis and regulate inflammation[23].

Ways of cell administration

The type of cells used for therapy is of fundamental importance, and the method of administration is no different. There are several methods of applying stem cells, differing in both the level of invasiveness and effectiveness of action.

The least invasive method of administering stem cells is their intravenous injection. The undoubted advantage of this method is its simplicity and safety. On the other hand, this method shows lower effectiveness due to the low number of cells reaching the heart tissue([26],[27]).

Stem cells can also be administered directly into the coronary arteries using catheterization. This method guarantees greater precision of administration than intravenous injection, has a beneficial effect on angiogenesis and myocardial perfusion. Unfortunately, this method carries the risk of embolism and is also characterized by low cell retention in the myocardium[28].

Another method of administering stem cells is to inject them directly into the myocardium using a catheter or directly. This procedure allows for very precise cell deposition and ensures high retention of the administered cells. The disadvantage of this method is its invasiveness, associated with open-chest surgery, as well as a significant risk of arrhythmia[28].

A promising method of administering stem cells is to implant them into the heart on a scaffold made of biomaterials. Such a procedure allows for improved cell survival and increases the effectiveness of the therapy, but it is also associated with complicated surgical procedures[9].

Adverse effects

Despite great enthusiasm and numerous clinical studies on the use of stem cells in heart failure, this method still poses many challenges for researchers. One of them is the side effects of the therapy. The main problem is episodes of arrhythmia in patients treated with STEM cells. Cells administered directly to the heart muscle can change the electrical conductivity of the heart, creating arrhythmogenic foci. Studies have observed episodes of atrial fibrillation and ventricular arrhythmias in patients after stem cell implantation([1],[2],[3],[5],[6],[7]). In addition, there is a risk of carcinogenesis, especially when using induced pluripotent stem cells, as well as an inflammatory response of the recipient's organism[13].

METHODOLOGY

This article describes the current state of knowledge on stem cell therapy for heart failure, with a focus on randomized clinical trials published between 2020 and 2025. The analysis was performed using the PubMed platform. The search terms were “Stem cell in heart failure”; “Stem cell therapy”; “Ischaemic heart failure”.

REVIEW OF LITERATURE

Allogeneic adipose tissue-derived mesenchymal stromal cells

The effectiveness and potential use of adipose tissue-derived mesenchymal stromal cells in the treatment of heart failure have been demonstrated in animal models[14], but the results of subsequent clinical trials have been inconsistent, probably due to the variety of routes of drug administration and the lack of systematic protocols([16],[17]). In the last 5 years, four clinical trials have been published in this field, three of them in ischemic heart failure and one in non-ischemic heart failure. In the SCIENCIE trial, a group of 133 patients with ischemic heart failure with reduced ejection fraction were treated with allogeneic adipose tissue-derived mesenchymal stromal cells administered intramyocardially or placebo. After 6 months of follow-up,,no statistically significant change in left ventricular systolic function, improvement in quality of life, nor change in NYHA class was observed[1]. Kawamura et al. (2024) compared the efficacy of adipose tissue-derived mesenchymal stromal cells administered by spray transplantation during CABG surgery versus CABG alone in a group of 26 patients with ischemic HF. After 6 months of follow-up, significant improvement in left ventricular systolic function and increased ejection fraction was noted in the ADMSC group[5]. Qayum et al. (2023) studied the efficacy of adipose tissue-derived mesenchymal stromal cells administered intramyocardially compared to placebo in a group of 81 patients with ischemic HF. There were no significant differences in left ventricular function, NYHA class or 6-minute walk test between the groups at 6 months of follow-up. There were also no differences in survival or adverse events over 3 years[6]. The SCIENCE II pilot study examined the use of adipose tissue-derived mesenchymal stromal cells administered intramyocardially compared to placebo in 30 patients with non-ischemic HF with EF<40%. After 6 months, significant improvement in left ventricular function, NYHA class, and 6-minute walk test was observed in the MSC group compared to placebo[10].

Autologous bone marrow-derived mesenchymal stromal cells

The MSC-HF trial conducted intramyocardial bone marrow-derived mesenchymal stromal cells or placebo administration in 60 patients with ischemic HF. A 12-month follow-up

showed significant improvement in left ventricular systolic function, increased myocardial mass, and decreased scar mass. Unfortunately, the change in echocardiographic parameters was not reflected in the improvement in quality of life, as there was no improvement in NYHA class or 6-minute walk test. There was also no difference in survival at 4-year follow-up[2]. In the CCTRN CONCERT-HF trial, 125 patients with ischaemic HF were treated with a trans endocardial injection of bone marrow-derived mesenchymal stromal cells in combination with or without c-kit positive cardiac cells. A 12-month follow-up showed improvement in quality of life in both groups, but no changes in LV systolic function, scar mass, or 6-minute walk test[3]. Soetisna et al (2021) conducted transseptal and trans epicardial bone marrow-derived mesenchymal stromal cells therapy in combination with CABG or CABG alone in a group of 26 patients with ischemic HF. After 6 months, significant improvements in left ventricular function, wall motion score index increased VEGF levels, and reduced scar mass were observed in the cell/CABG group compared to CABG alone[4]. The REGENERATE-AMI trial compared the safety and efficiency of intracoronary bone marrow-derived mesenchymal stromal cells injection in a group of 85 patients with ischemic HF with a follow up of 5 years. No improvement in cardiac function and similar odds of cardiac events were found between groups[8]. Soetisna et al (2020), evaluated the efficacy of transseptal and trans epicardial bone marrow-derived mesenchymal stromal cells administration in combination with CABG compared to CABG alone in a group of 30 patients with ischemic HF. A 6 months follow-up revealed improved left ventricular function, reduced scar mass, and improved 6-minute walk test compared to the CABG group[11].

Human umbilical cord-derived mesenchymal stromal cells

In the last 5 years, only one randomized clinical study using these cells in the treatment of HF has been published. He et al (2020) compared the effectiveness of human umbilical cord-derived mesenchymal stromal cells administered intramyocardially on a collagen scaffold or alone in a group of 50 patients with ischemic HF. After 12 months, a greater reduction in scar mass was observed in the group treated with cells on collagen carrier compared to cells alone or placebo[9].

Cardiac progenitor cells

Animal studies have shown the efficacy of c-kit positive cardiac cells in treating HF in rats[15]. Two randomized clinical trials with this cell type were conducted between 2020 and 2025. The CCTRN CONCERT-HF trial [3] was discussed above. The ALLSTAR trial

compared the effectiveness of intracoronary cardiosphere-derived cells therapy vs placebo in a group of 134 patients with ischemic HF. After 6 months, there was an improvement in left ventricular systolic function and a decrease in NT-proBNP levels compared to placebo, but no differences in scar mass were found between groups[7].

The table below summarizes key information on the course and outcomes of randomized clinical trials for the treatment of heart failure with stem cells from 2020 to 2025.

Study; Reference	**Type of cells used**	**Method of cell implantation**	**Study population**	**Results**
the SCIENCE trial; [1]	Allogeneic adipose tissue-derived mesenchymal stromal cells	Intramyocardial injection	133	No significant change in LVESV, LVEDV, LVEF, 6MWT or NYHA class between the groups at 6 month follow-up
The MSC-HF trial; [2]	Autologous bone marrow-derived mesenchymal stromal cells	Intramyocardial injection	60	Significant reduction of LVESV, improvement in LVEF and myocardial mass, reduction of scar tissue mass in MSC group compared to placebo at 12 months follow-up. No significant differences between groups in improvements in NYHA class, 6MWT. No significant difference in survival between groups in 4 years follow-up
The CCTRN CONCERT-HF trial; [3]	Autologous bone marrow-derived mesenchymal stromal cells and c-kit positive cardiac cells alone or in	Trans endocardial injection	125	No significant difference in LVEF, LVESV, LVEDV, scar size 6MWT between groups. Reduction of adverse cardiac events was observed in the CPCs group. Improved quality of life score was observed both in MSCs and MSCs+

	combination			CPCs group at 12 months follow-up.
Soetisna et al [4], 2021	Autologous bone marrow-derived stromal cells	Transseptal and trans epicardial accompanied by CABG	26	Significant increase in LVEF, WMSI and level of VEGF. Reduction of scar tissue mass compared to CABG alone. No significant difference in LVEDV at 6 months follow-up.
Kawamura et al [5], 2024	Allogeneic adipose-derived mesenchymal stromal cells	Spray transplantation during CABG procedure	6	Decrease in LVEDV, LVESV and increase in LVEF was observed in stem cell group compared to CABG alone at 6 months follow-up.
Qayyum et al [6], 2023	Allogeneic adipose-derived mesenchymal stromal cells	Intramyocardial injection	81	No significant differences in LVESV, LVEDV, LVEF, NYHA classification or 6MWT between the groups at 6 months follow-up. There was no statistical difference between groups in mortality or adverse effects at 3 years follow-up.
The ALLSTAR trial; [7]	Cardiosphere-derived cells	Intracoronary	134	Reduction in LVEDV, LVESV, NT-proBNP compared to placebo. No significant reduction of scar size at 6 months follow-up.
REGENERATE-AMI trial; [8]	Autologous bone marrow-derived cells	Intracoronary	85	No improvements in heart function in patients treated with cell therapy compared to placebo. Similar incidence for cardiac events between the groups at 5 years follow-up.
He et al [9], 2020	Human umbilical cord-derived mesenchymal	Intramyocardial grafting on collagen	50	Reduction in scar size in the collagen/cell group compared to cell and placebo group at 12 months

	stromal cells	scaffold or alone		follow-up
SCIENCE II pilot study; [10]	Allogeneic adipose-derived mesenchymal stromal cells	Intramyocardial injection	30	Significant improvement in LVEF, LVESV, LVEDV, NYHA class and 6MWT in MSC group compared to placebo at 6 month follow-up.
Soetisna et al [11], 2020	Autologous bone marrow-derived stromal cells	Trans epicardial and transseptal accompanied by CABG	30	Improvement in LVEF, 6MWT, reduction of scar tissue mass compared to CABG alone at 6 month follow-up. The adverse event incidence was similar between both groups.

LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; LVEDV, left ventricle end-diastolic volume; NYHA, New York Heart Association; 6MWT, 6-minute walk test; MSC, mesenchymal stromal cells; CPC, c-kit positive cardiac cells; WMSI, wall motion score index; CABG, coronary artery bypass grafting;

Adverse effects

All cited studies described the therapy as safe and without a high risk of adverse events, but there were individual cases worth noting. The most frequently reported serious cardiac adverse events associated with stem cell therapy were: ventricular tachycardia([1]; [2]; [3]; [6]), atrial fibrillation([5]; [6]) and acute myocardial infarction([6]; [7]).

THE CHALLENGES OF STEM CELL THERAPY

Stem cell medicine is a relatively young and still developing field. The cited studies indicate numerous challenges associated with this treatment model. The basic problem is choosing the right type of cell - individual types of stem cells have their advantages and disadvantages, but clinical studies do not provide consistent conclusions as to which type of cell is best for treating heart failure. Another, similarly complicated issue is the route of cell administration, there is also no clinical consensus and no direct advantage of one method of implantation. In addition to these problems, there are also technical challenges related to cell culture and storage, donor acquisition, as well as legal and ethical issues related to the process([1]-[11],[16],[17]).

CONCLUSION

Heart failure therapy using stem cells seems to be an effective and relatively safe method. In the last 5 years, promising results of randomized clinical trials have been reported related to the improvement of cardiac contractile function, as well as reduction of scar mass and improvement of quality of life. However, there is still a need for consistent data and guidelines regarding the selection of cell types and the method of their administration in specific clinical situations. There is also a lack of information about the influence of comorbidities on the course of stem cell therapy. In the future, there is a need to create systematic clinical guidelines for this process, as well as to develop efficient methods of obtaining and storing cells. This topic requires broader studies on larger groups of patients.

Disclosure

Author's contribution

Conceptualization, I. Zydlewski; methodology, A. Nowik and M. Blecharczyk; software, M. Kosiński; check, M. Sękulski, M. Pacanowska and M. Mrozek; formal analysis, A. Nowik; investigation, P. Jakubiec; resources, M. Blecharczyk; data curation, M. Sękulski; writing - rough preparation, M. Pacanowska; writing - review and editing, P. Jakubiec, M. Kosiński; visualization, M. Mrozek; supervision, I. Zydlewski; project administration, I. Zydlewski;
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References:

1. Qayyum, A.A., van Klarenbosch, B., Frljak, S., Cerar, A., Poglajen, G., Traxler-Weidenauer, D., Nadrowski, P., Paitazoglou, C., Vrtovec, B., Bergmann, M.W., Chamuleau, S.A.J., Wojakowski, W., Gyöngyösi, M., Kraaijeveld, A., Hansen, K.S., Vrangbæk, K., Jørgensen, E., Helqvist, S., Joshi, F.R., Johansen, E.M., Follin, B., Juhl, M., Højgaard, L.D., Mathiasen, A.B., Ekblond, A., Haack-Sørensen, M., Kastrup, J. and (2023), Effect of allogeneic adipose tissue-

derived mesenchymal stromal cell treatment in chronic ischaemic heart failure with reduced ejection fraction – the SCIENCE trial. Eur J Heart Fail, 25: 576-587. https://doi.org/10.1002/ejhf.2772

2. Mathiasen, A.B., Qayyum, A.A., Jørgensen, E., Helqvist, S., Kofoed, K.F., Haack-Sørensen, M., Ekblond, A. and Kastrup, J. (2020), Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial. Eur J Heart Fail, 22: 884-892. https://doi.org/10.1002/ejhf.1700
3. Bolli, R., Mitrani, R.D., Hare, J.M., Pepine, C.J., Perin, E.C., Willerson, J.T., Traverse, J.H., Henry, T.D., Yang, P.C., Murphy, M.P., March, K.L., Schulman, I.H., Ikram, S., Lee, D.P., O'Brien, C., Lima, J.A., Ostovaneh, M.R., Ambale-Venkatesh, B., Lewis, G., Khan, A., Bacallao, K., Valasaki, K., Longsomboon, B., Gee, A.P., Richman, S., Taylor, D.A., Lai, D., Sayre, S.L., Bettencourt, J., Vojvodic, R.W., Cohen, M.L., Simpson, L., Aguilar, D., Loghin, C., Moyé, L., Ebert, R.F., Davis, B.R., Simari, R.D. and (2021), A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial. Eur J Heart Fail, 23: 661-674. https://doi.org/10.1002/ejhf.2178
4. Soetisna, T. W. (2021). CD133+ Stem Cell Therapy Effects on Myocardial Regeneration Through Increased Vascular Endothelial Growth Factor Correlate with Cardiac Magnetic Resonance Imaging Results in Coronary Artery Bypass Graft Surgery Patients with Low Ejection Fraction. *The Heart Surgery Forum*, *24*(4), E670-E674. https://doi.org/10.1532/hsf.3763
5. Kawamura, T., Yoshioka, D., Kawamura, A. *et al.* Safety and therapeutic potential of allogeneic adipose-derived stem cell spray transplantation in ischemic cardiomyopathy: a phase I clinical trial. *J Transl Med* **22**, 1091 (2024). https://doi.org/10.1186/s12967-024-05816-1
6. Qayyum, A. A., Mouridsen, M., Nilsson, B., Gustafsson, I., Schou, M., Nielsen, O. W., Hove, J. D., Mathiasen, A. B., Jørgensen, E., Helqvist, S., Joshi, F. R., Johansen, E. M., Follin, B., Juhl, M., Højgaard, L. D., Haack-Sørensen, M., Ekblond, A., and Kastrup, J. (2023) Danish phase II trial using adipose tissue derived mesenchymal stromal cells for patients with ischaemic heart failure. *ESC Heart Failure*, 10: 1170–1183. https://doi.org/10.1002/ehf2.14281
7. Raj R Makkar, Dean J Kereiakes, Frank Aguirre, Glenn Kowalchuk, Tarun Chakravarty, Konstantinos Malliaras, Gary S Francis, Thomas J Povsic, Richard Schatz, Jay H Traverse, Janice M Pogoda, Rachel R Smith, Linda Marbán, Deborah D Ascheim, Mohammad R Ostovaneh, João A C Lima, Anthony DeMaria, Eduardo Marbán, Timothy D Henry, Intracoronary ALLogeneic heart STem cells to Achieve myocardial Regeneration

(ALLSTAR): a randomized, placebo-controlled, double-blinded trial, *European Heart Journal*, Volume 41, Issue 36, 21 September 2020, Pages 3451–3458, https://doi.org/10.1093/eurheartj/ehaa541

8. Mathur, A., Sim, D.S., Choudry, F., Veerapen, J., Colicchia, M., Turlejski, T., Hussain, M., Hamshere, S., Locca, D., Rakhit, R., Crake, T., Kastrup, J., Agrawal, S., Jones, D. A., and Martin, J. (2022) Five-year follow-up of intracoronary autologous cell therapy in acute myocardial infarction: the REGENERATE-AMI trial. *ESC Heart Failure*, 9: 1152–1159 https://doi.org/10.1002/ehf2.13786
9. He X, Wang Q, Zhao Y, et al. Effect of Intramyocardial Grafting Collagen Scaffold With Mesenchymal Stromal Cells in Patients With Chronic Ischemic Heart Disease: A Randomized Clinical Trial. *JAMA Netw Open.* 2020;3(9):e2016236. doi:10.1001/jamanetworkopen.2020.16236
10. Qayyum, A.A., Frljak, S., Juhl, M., Poglajen, G., Zemljičl, G., Cerar, A., Litman, T., Ekblond, A., Haack-Sørensen, M., Højgaard, L. D., Kastrup, J., and Vrtovec, B. (2024) Mesenchymal stromal cells to treat patients with non-ischaemic heart failure: Results from SCIENCE II pilot study. *ESC Heart Failure*, 11: 3882–3891. https://doi.org/10.1002/ehf2.14925
11. Soetisna TW, Sukmawan R, Setianto B, et al. Combined transepicardial and transseptal implantation of autologous CD 133+ bone marrow cells during bypass grafting improves cardiac function in patients with low ejection fraction. *J Card Surg*. 2020; 35: 740–746. https://doi.org/10.1111/jocs.14454
12. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, Fonarow GC, Heidenreich P, Ho JE, Hsich E, Ibrahim NE, Jones LM, Khan SS, Khazanie P, Koelling T, Krumholz HM, Khush KK, Lee C, Morris AA, Page RL 2nd, Pandey A, Piano MR, Stehlik J, Stevenson LW, Teerlink JR, Vaduganathan M, Ziaeian B; Writing Committee Members. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. J Card Fail. 2023 Oct;29(10):1412-1451. doi: 10.1016/j.cardfail.2023.07.006. Epub 2023 Sep 26. PMID: 37797885; PMCID: PMC10864030.
13. Liu, Z., Tang, Y., Lü, S., Zhou, J., Du, Z., Duan, C., Li, Z. and Wang, C. (2013), The tumourigenicity of iPS cells and their differentiated derivates. J. Cell. Mol. Med., 17: 782-791. https://doi.org/10.1111/jcmm.12062
14. Mazo, M., Planat-Bénard, V., Abizanda, G., Pelacho, B., Léobon, B., Gavira, J.J., Peñuelas, I., Cemborain, A., Pénicaud, L., Laharrague, P., Joffre, C., Boisson, M., Ecay, M., Collantes, M., Barba, J., Casteilla, L. and Prósper, F. (2008), Transplantation of adipose derived stromal cells is associated with functional improvement in a rat model of chronic myocardial infarction. European Journal of Heart Failure, 10: 454-462. https://doi.org/10.1016/j.ejheart.2008.03.017

15. Tang XL, Li Q, Rokosh G, Sanganalmath SK, Chen N, Ou Q, Stowers H, Hunt G, Bolli R. Long-Term Outcome of Administration of c-kit(POS) Cardiac Progenitor Cells After Acute Myocardial Infarction: Transplanted Cells Do not Become Cardiomyocytes, but Structural and Functional Improvement and Proliferation of Endogenous Cells Persist for at Least One Year. Circ Res. 2016 Apr 1;118(7):1091-105. doi: 10.1161/CIRCRESAHA.115.307647. Epub 2016 Feb 2. PMID: 26838790; PMCID: PMC4818175.Nair, N.,Gongora, E, Stem cell therapy in heart failure: Where do we stand today?,Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease,Volume 1866, Issue 4,2020,165489,ISSN 0925-4439,https://doi.org/10.1016/j.bbadis.2019.06.003.
16. Bhawnani N, Ethirajulu A, Alkasabera A, et al. (August 16, 2021) Effectiveness of Stem Cell Therapies in Improving Clinical Outcomes in Patients With Heart Failure. Cureus 13(8): e17236. doi: https://doi.org/10.7759/cureus.17236
17. Bhawnani N, Ethirajulu A, Alkasabera A, Onyali CB, Anim-Koranteng C, Shah HE, Mostafa JA. Effectiveness of Stem Cell Therapies in Improving Clinical Outcomes in Patients With Heart Failure. Cureus. 2021 Aug 16;13(8):e17236. doi: https://doi.org/10.7759/cureus.17236. PMID: 34540463; PMCID: PMC8447853.
18. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hülsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535. doi: https://doi.org/10.1002/ejhf.1236. Epub 2018 Jul 17. PMID: 29806100.
19. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hülsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535. doi: https://doi.org/10.1002/ejhf.1236. Epub 2018 Jul 17. PMID: 29806100.
20. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Ferguson JF, Generoso G, Ho JE, Kalani R, Khan SS, Kissela BM, Knutson KL, Levine DA, Lewis TT, Liu J, Loop MS, Ma J, Mussolino ME, Navaneethan SD, Perak AM, Poudel R, Rezk-Hanna M, Roth GA, Schroeder EB, Shah SH, Thacker EL, VanWagner LB, Virani SS, Voecks JH, Wang NY, Yaffe K, Martin SS. Heart Disease and Stroke Statistics-2022 Update:

A Report From the American Heart Association. Circulation. 2022 Feb 22;145(8):e153-e639. doi: https://doi.org/10.1161/CIR.0000000000001052. Epub 2022 Jan 26. Erratum in: Circulation. 2022 Sep 6;146(10):e141. doi: 10.1161/CIR.0000000000001074. PMID: 35078371.

21. Takahashi, K., Yamanaka, S.; Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors,Cell,Volume 126, Issue 4,2006,Pages 663-676,ISSN 0092-8674,https://doi.org/10.1016/j.cell.2006.07.024.
22. Takahashi, K., Tanabe, K. , Ohnuki, M. , Narita, M. , Ichisaka, T., Tomoda, K., Yamanaka, S. , Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors,Cell,Volume 131, Issue 5,2007,Pages 861-872,ISSN 0092-8674,https://doi.org/10.1016/j.cell.2007.11.019.
23. Ye L, Chang YH, Xiong Q, Zhang P, Zhang L, Somasundaram P, Lepley M, Swingen C, Su L, Wendel JS, Guo J, Jang A, Rosenbush D, Greder L, Dutton JR, Zhang J, Kamp TJ, Kaufman DS, Ge Y, Zhang J. Cardiac repair in a porcine model of acute myocardial infarction with human induced pluripotent stem cell-derived cardiovascular cells. Cell Stem Cell. 2014 Dec 4;15(6):750-61. doi: https://doi.org/10.1016/j.stem.2014.11.009. Erratum in: Cell Stem Cell. 2015 Jan 8;16(1):102. PMID: 25479750; PMCID: PMC4275050.
24. Tehzeeb J, Manzoor A, Ahmed MM. Is Stem Cell Therapy an Answer to Heart Failure: A Literature Search. Cureus. 2019 Oct 22;11(10):e5959. doi: https://doi.org/10.7759/cureus.5959. PMID: 31803548; PMCID: PMC6874291.
25. Rheault-Henry M, White I, Grover D, Atoui R. Stem cell therapy for heart failure: Medical breakthrough, or dead end? *World J Stem Cells* 2021; 13(4): 236-259 [PMID: PMC8080540 DOI: https://doi.org/10.4252/wjsc.v13.i4.236
26. Menasché P. Cell therapy trials for heart regeneration - lessons learned and future directions. Nat Rev Cardiol. 2018 Nov;15(11):659-671. doi: https://doi.org/10.1038/s41569-018-0013-0. PMID: 29743563.
27. Bruyneel AA, Sehgal A, Malandraki-Miller S, Carr C. Stem Cell Therapy for the Heart: Blind Alley or Magic Bullet? J Cardiovasc Transl Res. 2016 Dec;9(5-6):405-418. doi: https://doi.org/10.1007/s12265-016-9708-y. Epub 2016 Aug 19. PMID: 27542008; PMCID: PMC5153828.
28. Nakamura K, Murry CE. Function Follows Form - A Review of Cardiac Cell Therapy. Circ J. 2019 Nov 25;83(12):2399-2412. doi: https://doi.org/10.1253/circj.CJ-19-0567. Epub 2019 Nov 13. PMID: 31723070; PMCID: PMC7002039.