

# World Journal of *Transplantation*

*World J Transplant* 2021 May 18; 11(5): 138-146



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The WJT is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

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**NAME OF JOURNAL**

*World Journal of Transplantation*

**ISSN**

ISSN 2220-3230 (online)

**LAUNCH DATE**

December 24, 2011

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Maurizio Salvadori, Sami Akbulut, Vassilios Papalois

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3230/editorialboard.htm>

**PUBLICATION DATE**

May 18, 2021

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<https://www.wjgnet.com/bpg/gerinfo/208>

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

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## Transplantation of CD34+ cells for myocardial ischemia

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**Author contributions:** Matta A contributed to conception, design and writing of the report; Nader V contributed to conception and design of the report; Galinier M revised the paper; Roncalli J contributed to design and writing of the report and provided important intellectual contributions to the study.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

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**Manuscript source:** Invited manuscript

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### Abstract

CD34+ cells are multipotent hematopoietic stem cells also known as endothelial progenitor cells and are useful in regenerative medicine. Naturally, these cells are mobilized from the bone marrow into peripheral circulation in response to ischemic tissue injury. CD34+ cells are known for their high proliferative and differentiation capacities that play a crucial role in the repair process of myocardial damage. They have an important paracrine activity in secreting factors to stimulate vasculogenesis, reduce endothelial cells and cardiomyocytes apoptosis, remodel extracellular matrix and activate additional progenitor cells. Once they migrate to the target site, they enhance angiogenesis, neovascularization and tissue regeneration. Several trials have demonstrated the safety and efficacy of CD34+ cell therapy in different settings, such as peripheral limb ischemia, stroke and cardiovascular disease. Herein, we review the potential utility of CD34+ cell transplantation in acute myocardial infarction, refractory angina and ischemic heart failure.

**Key Words:** Cell therapy; Endothelial progenitor cells; Myocardial ischemia; Refractory angina; Heart failure; Coronary microvascular dysfunction

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**Core Tip:** CD34+ cells are mobilized from the bone marrow into the peripheral circulation in response to ischemic tissue injury. Once they migrate to the target site, they enhance angiogenesis, neovascularization and tissue regeneration. Safety and efficacy of CD34+ cell transplantation has been investigated in order to limit left ventricular dysfunction after acute myocardial infarction, refractory angina and heart failure.

**Specialty type:** Transplantation**Country/Territory of origin:** France**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**Received:** January 29, 2021**Peer-review started:** January 29, 2021**First decision:** February 25, 2021**Revised:** March 1, 2021**Accepted:** April 13, 2021**Article in press:** April 13, 2021**Published online:** May 18, 2021**P-Reviewer:** Zhao L**S-Editor:** Gao CC**L-Editor:** A**P-Editor:** Yuan YY**Citation:** Matta A, Nader V, Galinier M, Roncalli J. Transplantation of CD34+ cells for myocardial ischemia. *World J Transplant* 2021; 11(5): 138-146**URL:** <https://www.wjgnet.com/2220-3230/full/v11/i5/138.htm>**DOI:** <https://dx.doi.org/10.5500/wjt.v11.i5.138>

## INTRODUCTION

Ischemic heart disease or myocardial ischemia (MI) is a common disorder characterized by an imbalance between myocardial oxygen demand and supply. A wide spectrum of clinical manifestations ranging from chest discomfort to myocardial infarction is attributed to ischemic heart disease[1]. Conceptually, it is related to atherosclerotic coronary artery disease and considered the principal cause of death worldwide[2]. An epicardial coronary stenosis limits blood flow to a specific myocardial area, leading to ischemia, infarction and apoptosis[3]. In line with scientific development, microvascular dysfunction becomes responsible for a major part of MI[4]. It plays a crucial role by impairing the reactivity of coronary microcirculation in response to an increase in myocardial oxygen demand, which is equivalent to the effect of an obstructive plaque[4]. A large variety of therapeutic modalities targeting the pathophysiological patterns, consequences and underlying causes of MI are available.

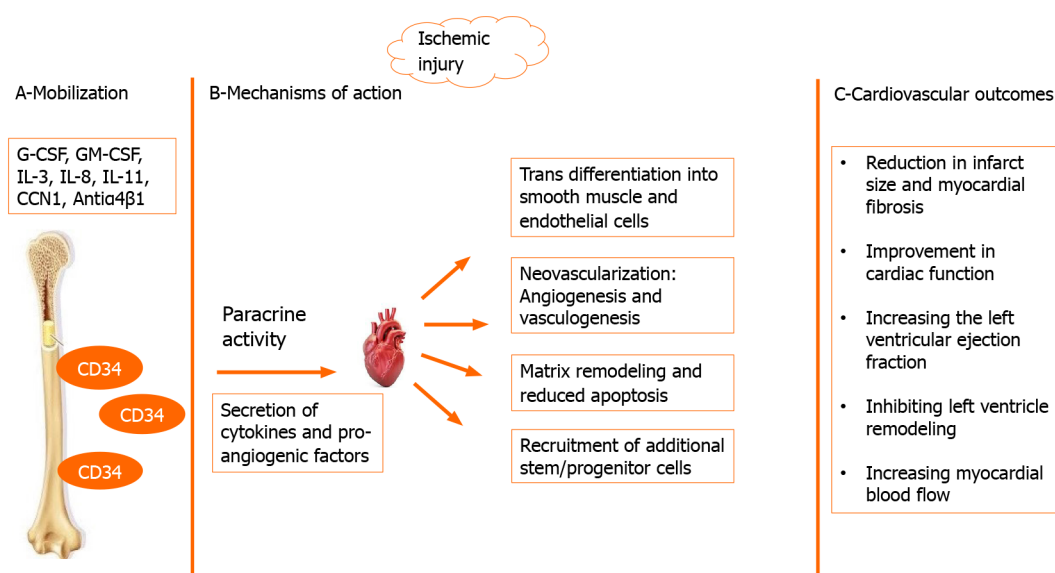
CD34+ cell implantation has emerged as a promising approach to overcome the main limitations of conventional therapies by combining optimal medical treatment and myocardial revascularization by percutaneous coronary intervention or coronary artery bypass graft. CD34+ cells are multipotent hematopoietic stem cells also known as endothelial progenitor cells and are useful in regenerative medicine for treating ischemic injuries[5]. These cells are easily mobilized from the bone marrow into peripheral circulation and characterized by their ability to promote neoangiogenesis and cardiomyocyte regeneration[6]. Previous published trials have reported the effectiveness of CD34+ cell implantation for treating ischemic vascular disease like ischemic stroke, peripheral limb ischemia and MI[7,8]. Herein, we focus on the utility of CD34+ cell administration in the settings of myocardial infarction, refractory angina and ischemic heart failure.

## MECHANISMS OF ACTION OF CD34+ CELLS

CD34+ cells are released into peripheral blood circulation in response to ischemic tissue injury. High circulating levels of CD34+ cells were detected after myocardial infarction[9]. These cells are known for their high proliferative and differentiation capacities that play a crucial role in the repair process after myocardial damage (Figure 1)[5]. Integrin antibodies, cysteine-rich angiogenic protein 61, stromal cell derived-factor 1 (SDF-1) and granulocyte colony stimulating factor were identified as agents incorporated in CD34+ cell mobilization from the bone marrow to peripheral circulation[10,11]. Then, an interaction between several factors (SDF-1, hepatocyte growth factor, vascular cell adhesion molecule, stem cell factor) and homing receptors such as CXCR4-chemokine receptor-4 is responsible for CD34+ cells traveling to ischemic tissue[12]. Once CD34+ cells migrate to the target site, they enhance angiogenesis, neovascularization and cardiac regeneration in two ways. First, CD34+ cells differentiate into smooth muscle cells and endothelial cells, which are the main structural components of internal vascular walls that lead to vascular re-endothelialization[13]. Second, they have an important paracrine role in secreting factors to stimulate vasculogenesis, reduce endothelial cell and cardiomyocyte apoptosis, remodel extracellular matrix and activate additional progenitor cells[5,13]. CD34+ cells produce angiogenic cytokines, such as interleukin-8, vascular epithelial growth factor and cytokine like 1[14]. A major part of their proangiogenic mechanism is mediated by producing exosomes (membrane-bound nanovesicles)[15]. These exosomes transfer proangiogenic microRNAs that may amplify the stem cell function and explain the angiogenic and therapeutic benefits associated with CD34+ stem cell therapy[15].

Limited data from the literature describe a beneficial effect of autologous CD34+ cell therapy on endothelial dependent/independent microvascular dysfunction[16]. Previous trials have reported a significant improvement in coronary flow reserve[17,18]. Lastly, replicative efficiency of endothelial progenitor cells is inversely





**Figure 1 Role of CD34+ cells in ischemic myocardial repair.** A: In response to ischemic injury, several factors like granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin (IL)-3, IL-8, IL-11, cysteine-rich angiogenic protein 61 (CCN1) and integrin antibodies (Antic4β1) trigger mobilization of CD34+ cells from the bone marrow into peripheral circulation; B: Mechanisms of action of CD34+ cells on cardiomyocytes via paracrine activity are transdifferentiation into smooth muscle and endothelial cells, neovascularization, matrix remodeling, reduced apoptosis and recruitment of additional stem/progenitor cells; C: The main cardiovascular outcomes of CD34+ cells. G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; IL: Interleukin; CCN1: Cysteine-rich angiogenic protein 61.

correlated with age[19]. A decline in CD34+ cell function and in circulating number were associated with aging above 60 years[20,21] and type 2 diabetes mellitus[22,23].

## EFFICACY OF CD34+ CELL IMPLANTATION IN ISCHEMIC CARDIOVASCULAR DISEASE

### Myocardial infarction

Numerous trials have investigated the efficacy and safety of CD34+ cell therapy in the setting of acute myocardial infarction (AMI) (Table 1). In general, stimulation of angiogenesis and reduction in the infarct size, scar formation and myocardial fibrosis were commonly observed after CD34+ cell injection in the hibernating zone surrounding the infarcted myocardial area[24-34]. Inhibition of cardiomyocyte apoptosis and collagen deposition were reported by Kocher *et al*[24] in an animal model. An improvement in left ventricular function was associated with CD34+ cell transplantation after AMI in human and nonhuman trials[25,28,29,32]. Shintani *et al*[30] observed a synergistic effect while combining CD34+ cells and vascular epithelial growth factor 2 gene therapies in the management of AMI, which yielded better outcomes. Also, Mackie *et al*[33] showed that injection of genetically modified CD34+ cells expressing sonic hedgehog protein enhanced angiogenic potency of CD34+ cells in ischemic myocardial tissue. In parallel, the injection of CD34+ cells deficient in microRNA377 following AMI significantly promoted angiogenesis and reduced left ventricle remodeling and cardiac fibrosis when compared to regular cells[34]. It is known that ischemic pre-conditioning (IPC) is beneficial for MI. Subsequently, Kamota *et al*[35] have demonstrated that this positive outcome was linked to the released cardioprotective factors in the early phase of IPC and to the CD34+ cells mobilization in the late phase of IPC.

Findings from the BONAMI trial showed that a decreased number of CD34+ cells in smokers was negatively correlated to viability recovery measured by single-photon emission computerized tomography at 3 mo post-AMI[36,37]. This suggests that these cells play a significant role after AMI. Thus, the PreSERVE-AMI trial revealed the safety of intracoronary injection of autologous CD34+ cells in revascularized ST-segment elevated myocardial infarction patients with altered left ventricular ejection fraction[38]. Indeed, a reduction in post-AMI major adverse cardiovascular events and an improvement in left ventricular function at 6 mo after cell injection were observed[39]. We noticed that therapeutic results of CD34+ cell implantation were

Table 1 Summary of clinical studies of CD34+ cell therapy

Disease	Ref.	Model	Delivery route	Results
Myocardial infarction	Kocher <i>et al</i> [24]	Animal	Intravenous	(+) Angiogenesis; (-) Cardiomyocyte apoptosis, collagen deposition, scar formation
	Kawamoto <i>et al</i> [25]	Human	Intramyocardial	(+) Angiogenesis, cardiac function; (-) Myocardial fibrosis
	Botta <i>et al</i> [26]	Animal	Intramyocardial	(+) Cardiac function; (+) Cardiac hemodynamics with CD34+ KDR+ subset
	Brenner <i>et al</i> [27]	Animal	Intracavitary of LV	(+) LV function
	Ott <i>et al</i> [28]	Animal	Intramyocardial	(+) LVEF
	Yoshioka <i>et al</i> [29]	Human	Intracardiac	(+) Blood flow; (+) Cardiac function
	Shintani <i>et al</i> [30]	Animal	Intramyocardial	(+) Capillary density; (-) Myocardial infarct size
	Zhang <i>et al</i> [31]	Animal	Intracoronary	(+) Cardiac repair, therapeutic benefits
	Wang <i>et al</i> [32]	Animal	Intramyocardial	(+) Angiogenesis, cardiac function
	Mackie <i>et al</i> [33]	Animal	Intramyocardial	(+) Capillary density; (-) Ventricular dilation, infarct size, cardiac function alteration
	Joladarashi <i>et al</i> [34]	Animal	Intramyocardial	(+) Angiogenesis; (-) LV remodeling and cardiac fibrosis with CD34 deficient microRNA 377
	Quyyumi <i>et al</i> [38]	Human	Intracoronary	(+) LVEF; (-) Infarct size and MACE
	Quyyumi <i>et al</i> [40]	Human	Intracoronary	(+) Infarcted area perfusion
Refractory angina	Losordo <i>et al</i> [43]	Human	Intramyocardial	(+) Exercise tolerance; (-) Angina frequency, 12 mo mortality
	Henry <i>et al</i> [45]	Human	Intramyocardial	(-) Angina frequency at 2 yr
	Povsic <i>et al</i> [46]	Human	Intramyocardial	(-) Angina frequency
	Wang <i>et al</i> [47]	Human	Intramyocardial	(+) Myocardial perfusion by PET; (-) Angina frequency
	Lee <i>et al</i> [48]	Human	Intracoronary	(+) LVEF; (-) Angina frequency
Heart failure (dilated cardiomyopathy)	Johnson <i>et al</i> [49]	Human	Intramyocardial	(-) Mortality, cardiac admissions, hospital visits, health care costs
	Vrtovec <i>et al</i> [50]	Human	Intracoronary	(+) LVEF, 6MWD; (-) NT-proBNP, mortality
	Lezaic <i>et al</i> [51]	Human	Intracoronary	(+) Myocardial perfusion, LVEF, 6MWD
	Bervar <i>et al</i> [53]	Human	Transendocardial	(+) 6MWD, diastolic function; (-) NT-proBNP
	Poglajen <i>et al</i> [54]	Human	Transendocardial	(+) 6MWD, LVEF; (-) NT-proBNP
Coronary microvascular dysfunction	Erbs <i>et al</i> [17]	Human	Intracoronary	(+) CFR
	Schächinger <i>et al</i> [18]	Human	Intracoronary	(+) CFR

6MWD: 6-min walk distance; CFR: Coronary flow reserve; KDR: Vascular endothelial growth factor receptor 2; LV: Left ventricle; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiovascular events; NT-proBNP: N-terminal pro brain natriuretic peptide; PET: Positron emission tomography.

dose-dependent[6,38–41]. Greater improvement was associated with higher doses with a threshold dose of over 10 million cells, particularly in the setting of myocardial infarction[40,41].

Subsequently, it was relevant to develop new delivery systems to allow the administration of higher numbers of CD34+ cells. The main purpose of the EXCELLENT trial (ClinicalTrials.gov Identifier: NCT02669810) was to evaluate the safety, tolerance and efficacy of intramyocardial injections of ProtheraCytes (autologous peripheral blood-CD34+ stem cells after automated *ex vivo* expansion with the StemXpand<sup>®</sup> machine) in patients with AMI and decreased ejection fraction. In this ongoing trial, ProtheraCytes are currently reinjected using the BioCardia Helix biotherapeutic delivery system introduced through the femoral artery and guided towards the infarcted myocardium, thus avoiding surgical access.

### Refractory angina

Intramyocardial injection of autologous CD34+ cells for the treatment of patients with refractory angina (Table 1) despite optimal medical therapy and no alternative therapeutic options has been studied considerably. Losordo *et al*[42] first showed the safety and favorable effectiveness of CD34+ cell therapy in these patients. The major positive effects included decreased frequency of weekly angina episodes and nitroglycerine use and improved Canadian Cardiovascular Society classification, exercise tolerance and quality of life[43,44]. Data from the ACT34-CMI study showed sustained efficacy of a single intramyocardial CD34+ cell injection for up to 2 years, with a significant reduction in deaths and major adverse cardiovascular events compared to those treated by placebo[45].

The incomplete RENEW phase III trial, which enrolled 112 of the 444 planned patients, failed to show a significant difference in total exercise time between the three study groups (CD34+ cells, placebo and conventional therapy) at 3, 6 and 12 mo[46]. However, it did confirm the findings from previous studies concerning the safety and efficacy of intramyocardial CD34+ cell therapy on angina frequency[47]. The efficacy and safety of intracoronary administration of CD34+ cells for refractory angina were evaluated in patients unsuitable for revascularization strategies with diffuse obstructive coronary artery disease[47,48]. A reduction in weekly angina frequency without significant adverse events were observed. A recently published study by Johnson *et al*[49] showed a significant reduction in mortality, cardiac-related admissions, hospital visits, coronary interventions and health care costs in the 12 mo following intramyocardial administration of CD34+ cells compared to the year before their injection.

### Heart failure

CD34+ cell therapy was investigated in ischemic and non-ischemic dilated cardiomyopathy (DCM) (Table 1). Improvement in the 6-min walk test, left ventricular ejection fraction, N-terminal pro brain natriuretic peptide level and resting myocardial perfusion were observed after intracoronary injection of autologous CD34+ cells in patients with non-ischemic DCM and reduced ejection fraction[50-52]. Similar results with improvement in diastolic function were found by Bervar *et al*[53] after transendocardial CD34+ cell delivery in non-ischemic heart failure patients. Also, a significant decrease in the prevalence of heart failure and total mortality rate without a difference in the prevalence of sudden cardiac death were observed at 5 years after CD34+ cell transplantation therapy[50].

In patients with ischemic cardiomyopathy and left ventricular ejection fraction below 40%, Poglajen *et al*[54] observed significant amelioration in left ventricular ejection fraction, 6-min walk test and N-terminal pro brain natriuretic peptide levels after transendocardial injection of CD34+ cells into hibernating myocardium, while no change in these parameters was observed after optimal medical treatment. It is noteworthy that greater clinical improvement was associated with higher delivered doses and extended injections[54]. Comparing delivery routes of CD34+ cells in DCM patients, a significantly better response was correlated with transendocardial administration than with intracoronary injections[55]. However, CD34+ cell transplantation was not beneficial in diabetic patients with non-ischemic DCM as shown by a small study sample size[56].

### Coronary microvascular dysfunction

Currently, coronary microvascular dysfunction (CMD) is a hot topic in cardiology. It plays a pivotal role in the pathophysiology of myocardial infarction with nonobstructive coronary artery disease, which accounts for 10% of acute coronary syndromes[57]. While therapeutic options are limited, the role of CD34+ cell therapy remains unclear in CMD, and available data are scarce in the literature (Table 1)[16]. Otherwise, reduced circulating levels of CD34+ cells were detected in the presence of coronary endothelial dysfunction even in the absence of atherosclerotic disease[58,59]. REPAIR-AMI and TOPCARE-AMI trials reported potential benefits of intracoronary injection of autologous CD34+ cells on CMD by revealing a normalization of coronary flow reserve in the studied AMI population[17,18]. Additionally, two ongoing trials are investigating the safety and efficacy of CD34+ cell therapy in patients with CMD (CLBS14 trial, ClinicalTrials.gov Identifier: NCT03508609; CD34 trial, ClinicalTrials.gov Identifier: NCT03471611).



## CONCLUSION

Regenerative medicine is a promising therapeutic approach for acquired cardiovascular disease, and routine use of stem cell therapy would be an ultimate goal of this area. Several clinical trials support the safety and efficacy of autologous CD34+ cell transplantation in AMI, refractory angina and systolic heart failure. Administration of genetically modified CD34+ sonic hedgehog+ microRNA377- cells amplifies the angiogenic target. Intramyocardial injection is likely the preferred delivery route, and a threshold dose over 10 million cells is desirable at least in the setting of AMI. Future studies investigating the tolerability and efficacy of allogenic CD34+ cells from youthful donors into elderly and diabetic recipients are warranted. Moving beyond clinical trials and translation of preliminary data into clinical practice after establishing a standardized procedure for CD34+ cell transplantation may revolutionize the management and overall prognosis of ischemic cardiovascular disease.

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