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REVIEW ARTICLE

Adult Stem Cell Therapy for Cardiac Repair in Patients After Acute Myocardial Infarction Leading to Ischemic Heart Failure: An Overview of Evidence from the Recent Clinical Trials

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Abstract: ***Background*:** Cardiovascular diseases (CVD) still represent the leading cause of mortality worldwide, despite the remarkable advances in interventional cardiology, cardiac surgery, and modern pharmacotherapy, particularly in the setting of acute myocardial infarction (AMI), chronic ischemic heart failure (HF), cardiomyopathy (CM), and the associated left ventricular (LV) dysfunction.

A significant loss of cardiomyocytes that underlies all of these conditions was previously considered irreversible. However, current evidence indicates that the human heart has some potential for repair, and over the past decade, many research studies have been exploring the use of stem cells (SCs) to facilitate restoration of myocardium. Consequently, the safety, feasibility, and effectiveness of SC therapy have been reported in many randomized clinical trials (RCTs), using different lineages of adult SCs. Nevertheless, the clinical benefits of SC therapy are not yet well established. In the near future, understanding of the complex interrelations between SCs, paracrine factors, genetic or epigenetic predispositions, and myocardial microenvironment, in the context of an individual patient, will be crucial for translation of this knowledge into practical development of successful, long-term regenerative SC therapeutic applications, in a growing population of patients suffering from previous myocardial infarction (MI) leading to chronic ischemic cardiomyopathy.

***Conclusion*:** This overview highlights the therapeutic potential of adult SCs in terms of their possible regenerative capacity, safety, and clinical outcomes, in patients with AMI, and/or subsequent HF (due to chronic ischemic cardiomyopathy). This review was based upon PubMed database search for trials on SC therapy, in patients with AMI and HF, and the main timeframe was set from 2006 to 2016.

Keywords: Adult stem cells (SCs), acute myocardial infarction (AMI), heart failure (HF), regeneration, randomized clinical trials (RCTs), cardiomyocytes.

1. INTRODUCTION

Cardiovascular (CV) events, as common consequences of ischemic heart disease (IHD), represent the leading cause of morbidity and mortality worldwide [1]. In spite of the remarkable advances in interventional cardiology, cardiac surgery, and pharmacotherapy, the prevalence of acute myocardial infarction (AMI), and chronic ischemic heart failure (HF) continues to increase [1]. In AMI, progressive loss of cardiomyocytes, secondary to apoptosis (programmed cell death), is a common feature underlying the HF [2]. Unfortunately, currently used standard invasive and non-invasive cardiac therapies are not able to successfully repair the damaged cardiac tissue post AMI, and thus, many patients develop HF, and dilated cardiomyopathy (CM) [2]. To fulfill a growing need for cardiac function restoration, in this patient population, some new strategies, including stem cell-based therapies, have emerged over the past decade [3]. Stem cells (SCs) are undifferentiated, self-renewing cells that possess a multi-lineage differentiation potential. The lineages of adult SCs, with some therapeutic potential for AMI and HF, have been classified as bone marrow derived cells (BMDCs) [3, 4], mesenchymal stem cells (MSCs) [3, 4], hematopoietic stem cells (HSCs) [3, 5], adipose derived stem cells (ADSCs) [3, 5], skeletal myoblasts (SMs) [3, 5], and cardiac stem cells (CSCs) [3, 5] (Table **1**). In patients post recent AMI, or with ischemic cardiomyopathy (CM), intracoronary (IC) or percutaneous intramyocardial (IM) delivery routes of SCs have usually been used [6, 7]. The safety of SC-based therapy has been demonstrated in several randomized controlled trials (RCTs), and in terms of efficacy, some beneficial effects of SC therapy (*e.g.*, improvement in left ventricular ejection fraction (LVEF)) have been demonstrated in the setting of AMI, HF and CM [2, 3, 5, 7, 8]. However, the clinical efficacy of SC-based therapy needs to be confirmed by future large-scale RCTs, in which the exact cell type, dose, time, and route of delivery have to be specified [7, 8]. In this overview, the SC regenerative capacity, therapeutic potential, main clinical

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Table 1. Stem cell types investigated for the use in cardiac repair: cell types, benefits, risks, and concerns.

Stem Cell (SC) type	Tissue derived, Autologous, Adult [3, 5, 7, 38, 39, 53]	Reprogrammed, Autologous, Adult, Induced Pluripotent [3, 5, 7, 53]	Embryonic, Allogeneic [3]
Bone marrow derived cells (BMDC) [40-43, 53]	Tissue derived	Reprogrammed	Embryonic
Mononuclear/CD34+ Mesenchymal (MSCs) Hematopoietic (HSCs) Endothelial progenitor cells (EPCs) Multipotent adult progenitor cells (MAPCs)	Skeletal myoblasts (SMs) Adipose-derived stem cells (ADSCs) Resident cardiac stem cells (CSCs): c-kit+ CSCs, Cardiospheres, Cardiosphere-derived cells (CDCs)	Induced Pluripotent Stem cells (iPSs)	Embryonic stem cells (ESCs) Fetal cardiomyocytes Human umbilical cord-derived cells
Good safety Variable efficacy Limited replicative potential	Good safety Variable efficacy Limited replicative potential	Limited clinical data	Pluripotent (3 germ layers) High replicative potential Self-renewal Neoplastic potential (teratoma, teratocarcinoma) Immunological rejection Ethical concerns No trial evidence

outcomes, and safety concerns for patients with AMI and HF have been presented, based on the recently published medical literature, and the relevant data from the Clinical-Trials.Gov website. The main timeframe for this PubMed search was set from 2006 to 2016.

2. REPAIR MECHANISMS IN CARDIAC ISCHEMIA AND REPERFUSION MYOCARDIAL INJURY

It has been well established that in the IHD, lack of blood supply, caused by a thrombus (composed of atherogenic plaque and platelets), leads to insufficient oxygen and glucose delivery to myocardial cells, and to cell death (necrosis). This can be manifested as AMI, either transmural (involving the entire thickness of the ventricular wall, in the distribution of an obstructed coronary artery) or subendocardial (when the necrosis is limited to 30-50 % of the ventricular wall thickness) [9]. The loss of cardiomyocytes in AMI leads to a progressive left ventricle (LV) failure, characterized by LV dilatation, and reduced LV ejection fraction (LVEF) [9]. In consequence, many patients who survived AMI are at risk for chronic complications, secondary to the repair mechanisms generated by myocardial injury, and aimed at ventricular remodeling [9]. After an ischemic CV event, the reperfusion necessary for the restoration of blood flow and oxygen supply to the ischemic tissue causes the excessive production of reactive oxygen species (ROS) that in turn, aggravate cell damage and inflammatory processes [10]. In this way, the reperfusion injury often causes irreversible cardiac tissue damage, and cell death (apoptosis). Similar to ischemia, the reperfusion injury can cause myocardial hibernation that involves degeneration of cardiomyocytes, fibrosis, ventricular dysfunction, and inflammatory process [10].

3. CURRENT INSIGHTS INTO THE IMMUNE RESPONSE ACTIVATION BY ISCHEMIC MYOCARDIAL INJURY

It should be highlighted that AMI also activates the immune response that is responsible for: migration and aggregation of immune system cells, activation of the complement cascade, secretion of various cytokines (*e.g.*: interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor type-alpha (TNF-α)), increase in T and B lymphocyte populations, and production of free radicals [11]. In particular, the secretion of cytokines, and the expression of adhesion molecules (contributing to the progressive loss of hemodynamic functions) are crucial for the recruitment of progenitor cells from the bone marrow (BM) to the injured area of myocardium [11]. Moreover, homing of progenitor cells is an important physiological process, related to the replacement of cells (that are attracted to cytokines secreted by the damaged ischemic tissues) [11]. During this process, the stromal cell-derived factor-1 (SDF-1) and its specific receptor, CXCR-4, are the main molecules that allow the adhesion and transmigration of cells [12]. In AMI, especially within the infarct and peri-infarct areas, an increase in SDF-1 expression, followed by its reduction to baseline values, has been demonstrated over 4-7 day period [12]. It should be highlighted that the SDF-1 chemokine plays the main role in revascularization of ischemic tissue, and its regeneration (via the chemokine receptors: CXCR4 and CXCR7) that is essential to restoration of cardiac function [12]. In addition, in AMI, the SDF-1 also exerts its ef-

fects via activation of phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK). In this way, the SDF-1 activates the enzyme endothelial nitric oxide synthase (eNOS), and increases nitric oxide (NO) production [12]. Although the SDF-1/CXCR-4 axis is activated by physiological mechanisms (*e.g.*, replacement of cells in apoptotic processes), the SCs injections can positively impact the homing process, and augment myocardial repair [12].

4. ADULT STEM CELLS (SCS) AND THEIR EFFECTS ON INJURED CARDIAC TISSUE

The endogenous repair capacity of the heart is insufficient to compensate for the loss of cardiomyocytes post AMI, and in advanced HF. Therefore, in order to increase the regenerative capacity, and to reduce adverse LV remodeling, enhancement of endogenous repair processes, by using SCs would offer a valuable therapeutic tool [13]. Autologous adult SCs, intrinsic to specific tissues, are capable of self-renewal and producing mature differentiated cells, which can be integrated into a cardiac tissue, and perform specialized functions. At present, adult SCs that have been studied in human trials, among patients with AMI and HF, include BMDCs [3, 4], MSCs [3, 4], HSCs [3, 5], ADSCs [3, 5], SMs [3, 5], and CSCs [3, 5] (Table **1**). BMDCs are isolated from the iliac crest, harvested *ex vivo*, enriched (via centrifugation), and injected to the heart via IC or IM route. These procedures are usually performed 4 to 7 days post AMI. MSCs represent a heterogeneous group of cells, that promote cell engraftment, and are involved in paracrine mechanisms for cardiac repair and remodeling (associated with inflammatory control) [14]. SMs, obtained via thigh muscle biopsy, and delivered to patients, might cause some complications (*e.g.*, cardiac arrhythmias). In face of current availability of safer SCs sources, SM trials are not a priority [15]. Recently discovered, clonogenic and self-replicating endogenous cardiac stem cells (CSCs) have been isolated and cultured from a human heart [3, 16]. The CSCs have the capacity to differentiate into endothelial cells, smooth muscle myocytes and cardiomyocytes. Although CSCs are insufficient for a complete repair of the myocardium after injury, they can be activated by extracardiac SCs, delivered by IC or IM method [3, 16]. Furthermore, cardiosphere-derived progenitor cells can reduce adverse remodeling of the heart, leading to improvement of cardiac structure and function after MI [17]. It should be highlighted that in attempt to repair the injured cardiac tissue, in addition to the application of above mentioned SC types, the importance of induced pluripotent stem cells (iPSCs) (which have embryonic stem cell-like characteristics, and offer a remarkable opportunity for derivation of autologous pluripotent cells from adult somatic tissues) has recently emerged [18]. Also, it can be expected that nuclear reprogramming strategies, aimed at achieving the most optimal blend of pluripotency and myocardial tissue-specific properties, will be helpful in cardiac regeneration post AMI [19]. Additional, detailed resources, including SC phenotypes, and therapy end points, with various SC types, as well as their safety, and feasibility (based on published clinical studies, in patients with AMI and/or previous MI leading to chronic ischemic cardiomyopathy) are provided in the following references: 38, 39, and 53.

5. THE ROLE OF STEM CELLS IN ANGIOGENESIS

Both EPCs and iPSCs have been used to stimulate angiogenesis by the expression of growth factors (*e.g.*: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), and angiopoietin-1 (Angpt-1)) via local paracrine pathways, in response to myocardial ischemia [20]. In addition, EPCs and iPSCs can play the role of precursor cells for angiogenesis, by delivering therapeutic genes that encode angiogenic factors, such as VEGF, Angpt-1, and SDF-1/CXCR-4 [21]. Therefore, angiogenesis in patients post AMI can be accomplished via the incorporation of vascular progenitor cells into the capillaries, or by the delivery of growth factors and cytokines that accelerate angiogenesis by stimulating the mature endothelial cells [20]. This includes genetic modification of SCs prior to their transplantation (*e.g.*: cell transduction with prosurvival genes), and pretreatment of cells with specific molecules (*e.g.*, eNOS), to promote angiogenesis. In addition, paracrine factors released from SCs and progenitor cells can improve cardiac function by decreasing the apoptosis of cardiomyocytes, or by stimulating cardiosphere-derived cells to increase cardiomyogenesis [6, 20].

6. DELIVERY OF STEM CELLS TO THE HEART

In the cardiac catheterization laboratory, a standard percutaneous coronary angioplasty (PCA) is used with IC infusion of SCs, several times with balloon inflation. Such a procedure allows necessary time interval for the SCs to interact with the microcirculation of injured myocardium. A precise location of specific cardiac areas of intervention can be accomplished via an electromechanical mapping system (Noga XP cardiac navigation system), which maps the ischemic, infarcted, or scarred myocardial site. According to the recent studies, injecting the SCs directly into the myocardium may increase myocardial retention of cells. The NOGA XP system is equipped with a catheter, which is designed to guide and deliver transendocardial injections *via* a transfemoral or brachial (*e.g.*, in case of anatomical difficulties) approach, without a guidewire [21]. This allows to identify the endothelium adjacent to nonviable myocardium, and subsequent, more precise injections of SCs. Also, in case of hibernating myocardium, direct injection of SCs into the damaged area can salvage the myocardium, and improve angiogenesis [21].

7. OUTCOMES OF STEM CELL THERAPY IN AMI AND HF, BASED ON RECENT CLINICAL TRIALS

Two particular groups of patients, for whom the restoration of contractile function is the main clinical objective: early post-MI cases, and late, end-stage ischemic HF, represent a high priority populations, for whom the delivery of SCs with contractile potential would have the most beneficial impact. Human research has been limited to IHD, post-AMI, and HF, as illustrated by the most relevant RCTs (Table **2**).

As mentioned before, cardiosphere-derived cells (CSCs) are intrinsic to the heart, express a distinctive profile of antigens (*e.g.*: $CD105^+$, and $CD45^+$), and promote cardiac regeneration after ischemic injury [3, 22]. According to the first-in-human CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction) trial, the

Table 2. Recent clinical trials using adult stem cells for improving cardiac repair of the ischemic myocardium.

Trial name, Phase, Identifier, Author, Year [Reference Number]	Primary Outcome or Main Clinical Effects	Cell Type, Origin, Route Of Delivery	Patient status, or Trial Inclusion Criteria	Sample Size (n) Follow-up (Years/Months)
CADUCEUS Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction Phase 1, NCT00893360 Makkar *et al.*, 2012 [22]	Improved LVF ΔLVEF 5.4% (MRI NS), >viable tissue 22.6g <scar mass12g	Autologous CDC Heart IC	Recent MI;<30 d, LVEF 25-45%	25 1 year
SCIPIO Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy Phase 1, NCT00474461 Bolli *et al*., 2011 [16]	Improved LVF ΔLVEF >12.0% 3-D ECHO >12.1% MRI >viable cardiac tissue 12,2% <scar mass 15,7g	Autologous c-kit+ CDC Heart IC	ICM No option	16 2 years
TOPCARE-AMI Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction Phase 3, RCT NCT00289822 Assmus *et al*., 2006 [13]	Improved LVEF	Progenitor cells BMSC IC	healed MI	75 3 months
Cardio 133 Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic IHD Phase 3, RCT, NCT00462774 Stamm *et al*., 2007 [23]	Improved LVEF, IM delivery of BMSC with CABG is safe and provides beneficial effects	BMMNC (CD133+) BM IM CABG	IHD	40 3 years
POSEIDON Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis Phase 1,2, RCT, NCT01218828 Hare *et al.,* 2012 [24]	No ΔLVEF ↓Infarct size	MSC BM IM Transendo-cardial	ICM, no option LVEF 20-50%	30 13 months
MAGIC Myoblast Autologous Grafting in Ischemic Cardiomyopathy Phase 2, RCT, NCT00102128 Menasche *et al*., 2008 [15]	No ΔLVEF No ΔLVEDV No ΔLVESV	Autologous SM Heart IM CABG	LVEF <35% AMI	97 6 months
REPAIR-AMI Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction Phase 3, RCT, NCT00279175 Schächinger *et al*., 2006 [25]	Improved LVEF	MSC BM IC	AMI	204 4 months
IMPACT-CABG IMPlantation of Autologous CD133+ sTem Cells in Patients Undergoing Coronary Artery Bypass Grafting Phase 1, NCT01467232 Noiseux *et al*., 2026 [46]	Improved segmental myocardial perfusion, more favorable LV remodeling	Selected autologous CD133(+) & CD133(-) CD34(+) progenitor cells CABG IM	Chronic ICM	24 28 months
REGENERATE-AMI Phase 2, RCT, NCT00765453 Choudry *et al*., 2016 [47]	Improved LVEF, greater myocardial salvage index	Autologous BMSCs IC (in 24 hours of reperfusion therapy, PPCI)	AMI	100 12 months

AMI, Acute myocardial infarction; BM, bone marrow; BMMNC, bone marrow mononuclear cell; BMSC, bone marrow derived stem cells; CABG, coronary artery bypass graft surgery; CD, cardiac derived; CDCs, cardiac derived cells; Δ, change; ↓, decreased; d, day; 3-D, 3-Dimentional; ECHO, Echocardiography; FGF, fibroblast growth factor; g, gram; HF, Heart failure; IC, Intracoronary injection; ICM, Ischemic Cardiomyopathy;↑, increased; IM, Intramyocardial injection; IHD, Ischemic heart disease; LVF, Left ventricular function; LVEDV, Left ventricular end-diastolic volume; LVEF, Left ventricular ejection fraction; LVESV, Left ventricular end-systolic volume; MI, Myocardial infarction; MRI, Magnetic resonance imaging; MSC, Mesenchymal stem cells; NS, nonsignificant; PPCI, primary percutaneous intervention; RCT, randomized controlled trial; SM, Skeletal myoblasts

CDCs derived from both normal, and recently infarcted human hearts, have been capable of regenerating healthy heart tissue after MI. In addition, CDCs from advanced HF patients exhibited augmented potency in ameliorating ventricular dysfunction post-MI [22] (Table **2**).

The Stem Cell Infusion in Patients with Ischemic cardiOmyopathy (SCIPIO) trial studied autologous CSCs (c-kit +) for the treatment of HF, caused by IHD. The SCIPIO findings revealed that IC infusion of autologous CSCs is effective in improving LV systolic function, and decreasing infarct size in patients with HF post MI [16]. Similarly, positive results with regard to the moderate, but significant improvement in LVEF were reported in some other trials, such as TOPCARE-AMI [13], and a phase 3 study by Stamm, *et al*. [23]. Furthermore, in the POSEIDON trial [24], the infarct size was reduced, but there was no change in LVEF, according to the study report (Table **2**). Also, SMs, investigated in the MAGIC trial, revealed some disappointing results (*e.g*.: lack of beneficial effect on LVEF, and adverse events such as arrhythmias) [15]. The Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) study reported that BM-derived SC therapy was associated with improved LVEF, and a decrease in the combined outcome of recurrent MI, revascularization procedure, and CV mortality [25]. The ongoing study, the Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction (BAMI), NCT 01569178 [26], is a large-scale, open-label, multinational, multicenter, phase 3 RCT that aims to demonstrate that a single IC infusion of autologous BM-derived mononuclear cells is safe, and reduces all-cause mortality in patients with reduced LVEF (equal to, or below 45%), after successful reperfusion for AMI, as compared to a control group of patients receiving a standard medical care only [26].

In addition, three trials assessing clinical outcomes that are currently under way, are expected to shed some light on possible myocardial regeneration, in patients with chronic HF. They include: the CHART-1 (NCT 01768702, exploring IM injection of autologous cardiopoietic cells) [27], the REPEAT (NCT01693042, comparing single versus repeated IC infusion of autologous BM-derived cells) [28], and the trial applying IM injection of allogenic mesenchymal precursor cells (NCT02032004) [29].

8. META-ANALYSES OF RECENT TRIALS ON STEM CELLS USE FOR MYOCARDIAL INFARCTION AND HEART FAILURE, AND THE REASONS FOR DIFFICULTIES WITH INTERPRETING OF THEIR RESULTS

Human trials that have investigated the use of SCs for cardiac regeneration post AMI, and in HF have usually been statistically underpowered, have used surrogate outcome measures, have applied different SC types, and open-label designs in various patient population that can be sources of concern. In order to overcome at least some of these limitations, recently several meta-analyses have been published (Table **3**) [30-36], addressing problems related to heterogeneous study designs. Although meta-analyses can successfully overcome limitations in statistical power, their results must be interpreted with caution. This is due to the fact that the biological activity of various types of SC therapy can differ significantly, depending on the SC origin, the microenvironment of the cardiac tissue, methods of SC preparation, and SC administration techniques. In contrast to previous meta-analyses, the meta-Analysis of Cell-based CaRdiac stUdiEs (ACCRUE meta-analysis) by Gyongyosi *et al*. [36], presents unique evidence, based on individual patient data (IPD). In the ACCRUE meta-analysis, 12 rigorously designed RCTs were included, assessing patients, undergoing SC therapy, using different cell products (*e.g*.: CD 133 enriched BM cells, CD34/CXCR4 enriched BM cells, and cardiosphere-derived cardiac cells) at various time points after AMI. The reports of the ACCRUE meta-analysis indicate that SC therapy does not impact myocardial contraction or LV remodeling, and has no effect on clinical outcomes in patients with AMI. However, the analyzed time period was rather short (*e.g*.: from 24 hours post AMI to 3 months after AMI), and thus a longer follow - up would be necessary to assess impact of SC therapy on cardiac outcomes in this setting. In summary, the results of several meta-analyses (Table **3**) [30-35], reported the safety of SC therapy in patients with AMI and chronic HF, and indicated that the IC delivery of BM cell therapy can lead to moderate improvement of LVEF, decrease in early CV mortality, and reduction of recurrent AMI [37]. In addition, IM delivery route of SCs might offer beneficial effects in case of hibernating myocardium. Furthermore, it should be emphasized that the method and timing of SCs injection, the volume of delivery, and the application of specific SC types and cell-enrichment modalities represent key factors in achieving the therapeutic goals [37]. Finally, whether or not SC therapy is related to reduced overall mortality, lower rehospitalization rates, improvement of patient quality of life, and HF-specific symptoms and biomarkers, need to be evaluated in further clinical trials. Until then, SC therapy in AMI and HF should be considered as a promising, but still an experimental approach.

9. INSIGHTS FROM CLINICAL APPLICATIONS OF $CD133^+$ AND $CD34^+$ ENDOTHELIAL PROGENITOR CELLS (EPC) IN REPAIR OF THE ISCHEMIC MYOCARDIUM

The haematopoietic stem cells (HSCs) are present in the bone marrow (BM), and have the capacity to differentiate into myeloid and lymphoid cell lineages. The endothelial progenitor cells (EPCs) are found in peripheral blood, and they have the potential to differentiate into endothelial cells, resulting in neovascularisation in response to ischemic damage. CD133 and CD34, which are proteins of trans-membrane cell surface receptors, represent surface markers of both HSCs and EPCs [28]. Since baseline levels of circulating stem/progenitor cells are low, their therapeutic use is limited, and thus, a selection of some SC populations from total mononuclear circulating cells increases their capacity for cardiac repair (*e.g*., some SCs types can be mobilized from the BM into the circulation to be isolated and enriched) [29]. CD133 and CD34 (*e.g*., expressed on immature HSCs) are commonly used as single markers for the enrichment of HSCs. In addition, the CD133 protein has been found on tissue-specific SCs, cancer SCs, and cardiomyogenic pluripotent cells [38-40]. In view of the

Table 3. Meta-analyses of recent randomized controlled trials on stem cells use for acute myocardial infarction and heart failure.

Author Year of publication [Reference number]	Patient diagnosis, Route of stem cells delivery	Main clinical findings	Number of trials, Number of patients	Follow-up time (months)
Zhang *et al*. 2008 [30]	AMI, (4-7 days post MI) IC	↑LVEF (4.6%), ↓LVESV, ↓CE, ↓rest/UA	7 660	3-18
Brunskill *et al*. 2009 [31]	AMI/IHD, IM/IC	IM delivery > IC delivery ↑LVEF (5.9%)	21 1091	3-6
Jeevanantham *et al*. 2012 [32]	AMI/IHD, IM/IC	↑LVEF (4.0%), ↓ scar size (-4.0%) ↓LVESV (-8.9 mL), ↓LVEDV (-5.2 mL)	50 2625	variable
Delewi *et al*. http://onlinelibrary.wiley.com/doi/10.1002/clc.22381/full - clc22381-bib-00532013 [33]	AMI, IC	↑LVEF (3.9%), ↓scar size NS, ↓LVESV (-9.4 mL), ↓recur AMI ↓rehosp HF, UA	26 1710	6-12
Fisher *et al*. 2014 [34]	IHD/HF, IC	Mortality ↓, ↑LVEF (2.6%)	23 1255	variable
Tian *et al*. 2014 [35]	IHD IM	↑LVEF (4.9%), ↓LVESV (-10.7 mL)	11 492	6-12
Gyöngyösi *et al*. 2015 [36]	AMI (based on individual patient data, at different time post AMI (*e.g.*: from 24 hours to 3 months after AMI).	no impact on LV remodeling, or myocardial contraction, no significant effect on clinical outcomes in AMI	12 1252	6

AMI, acute myocardial infarction; CE, cardiac events; HF, heart failure; IC, intracoronary injection; IHD, ischemic heart disease; IM, intramyocardial injection; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; mL, milliliter; rehosp, rehospitalization; recur, recurrent; rest, restenosis; UA, unstable angina.

potent angiogenesis-inducing capacity of BM-derived cells, the CD133+ cell subpopulation can be therapeutically helpful for patients with myocardial ischemia [38]. This concept has been investigated in several clinical studies. For instance, an intracoronary infusion of selected $CD133^+$ cells (that are more immature and less lineage-determined than $CD34^+$ cells) in patients with recent AMI was evaluated in a small clinical trial that showed improved LVEF after 4 months [41]. Unfortunately, more coronary events (*e.g.*, stent occlusion), and adverse remodeling of the MI-related artery were noted after $CD133^+$ cell delivery. Although transepicardial injection of $CD133^+$ cells into the MI area, during revascularization procedures, in patients post MI was considered safe and feasible, these findings need to be interpreted with caution, due to the lack of a control group, and a small study sample.

$CD34^+$ cells that represent a cell population enriched for early EPCs have also been explored in clinical trials. For instance, an intramyocardial injection of $CD34^+$ progenitors was evaluated in patients with coronary artery disease (CAD) and refractory angina, and showed a positive trend (based to the ACT34-CMI trial, NCT 21737787) [42]. Similarly, an improvement in local perfusion and LV remodeling, upon intracoronary SCs delivery with CD133+ or CD34+ cell types has been reported in patients with prior anterior MI. In particular, it was determined that intracoronary infusion of selected CD133(+) and CD133(-) CD34(+) progenitor cells to a previously infarcted and nonviable anterior wall is safe, and results in improvement in segmental myocardial perfusion, as well as in favorable LV remodeling [43]. Moreover, it should be highlighted that the injection of CD34+ cells into the peri-infarct area, during CABG surgery, in patients with ischemic cardiomyopathy led to better contractile function, comparing to CABG alone [44].Furthermore, the use of a novel population of HSCs, known as aldehyde dehydrogenase-bright (ALDHbr) cells, resulted in reduced LV end-systolic volume, and in improved maximal oxygen consumption [45].

The recently published trial, IMPACT-CABG (IMPlantation of Autologous CD133+ sTem Cells in Patients Undergo-

ing Coronary Artery Bypass Grafting), NCT01467232 (Table **2**), assessed the safety, feasibility and efficacy of intramyocardial delivery of selected autologous CD133+ BM SCs at the time of CABG surgery, in patients with chronic ischemic cardiomyopathy [46]. The findings of this RCT have shown that such a therapy is a possible option to repopulate the injured myocardium, to treat HF and to restore cardiac function. Another recent RCT, REGENERATE-AMI trial, NCT00765453 (Table **2**), aimed to determine the effect of intracoronary autologous BMCs on LV function, when delivered within 24 hours of successful reperfusion therapy The results of this trial have revealed that the early infusion of intracoronary BMCs, following primary percutaneous intervention (PPCI) in patients with AMI and regional wall motion abnormality leads to a small improvement in LVEF, compared with placebo, and it can contribute to infarct remodeling and myocardial salvage [47].

An earlier RCT, NCT00400959**,** conducted by Colombo *et al*., aimed to assess the effect of intracoronary administration of CD133+ SCs on myocardial blood flow and function, in the setting of an acute ST-elevation myocardial infarction (STEMI) (which often causes ischemic damage, in spite of a timely performed PCI procedure, resulting in good recanalization, but incomplete reperfusion). The results of this RCT support the hypothesis that intracoronary delivery of BM-derived, but not peripheral blood-derived CD133+ SCs, 10-14 days after STEMI, may improve long-term perfusion. However, further, larger RCTs are needed to explore this subject [48]. In addition, the CELLWAVE trial, NCT00326989, demonstrated an improvement of local contractile function and scar size, among patients post AMI, when intracoronary BMCs infusion was combined with targeted shock wave delivery [49].

10. FUTURE TRIAL DESIGNS AND PERSPECTIVES IN STEM CELL THERAPY RESEARCH

The Task Force of the European Society of Cardiology (ESC) on SCs and repair of the heart, proposed criteria for designing further trials in this field [50] that include:

1. Large-scale, double-blind, controlled RCTs for the use of autologous BMDC in patients with AMI. The study candidates should present within 12 hours (h) of the onset of AMI, and receive necessary treatment (*e.g*., immediate revascularization, via primary angioplasty or fibrinolysis). In addition, some AMI patients presenting late (over 12 h post AMI), or those who fail to respond to standard therapy (*e.g*., candidates for 'rescue' angioplasty) should also be considered.
2. Double-blind, controlled RCTs for the use of autologous BMDC or SM in the treatment of ischemic HF. At some point, the role of autologous stem/progenitor cells in the treatment of cardiomyopathies (*e.g*., dilated cardiomyopathy) should also be explored.
3. A series of small trials to investigate safety issues, or to address the methodology to test specific hypotheses, generated during basic science experiments (*e.g*., trials exploring paracrine or autocrine mechanisms).
4. Trials to establish the risk - benefit ratio of the use of cytokines alone (*e.g*., G-CSF) or in conjunction with stem/progenitor cell therapy.

The ESC Task Force has also underscored the necessity for more multicentre studies with clinical outcome measures, major adverse cardiac events (MACEs), quality of life parameters, and economic benefits, as well as the standardization of the SC products [50].

In addition, tissue engineering strategies should elucidate ways, in which the cytokines, and various cell types within the myocardium might shape the homing, retention, maturation, survival, and integration of endogenous and exogenous SCs or PCs [5-7]. Furthermore, new types of SCs (*e.g*., cardiosphere-derived cells, or c-kit+ cardiac progenitor cells), the reprogramming adult cells (*e.g*., skin fibroblasts) to a pluripotent state (*e.g*., by retroviral transduction), cardiomyocyte dedifferentiation, in situ stimulation of endogenous cardiac stem cells, advances in SC delivery methods and techniques of myocardial imaging, as well as strategies to modulate the myocardial microenvironment, represent the examples of further research directions in this field [5-7, 51-53]. Finally, construction of "acellular", bioartificial hearts that can be repopulated with cardiac SCs or EPCs, displaying contractility, are also being investigated [52]. In summary, successful therapeutic strategies would modify both the SCs and the cardiac microenvironment, in order to enhance the efficacy of myocardial regeneration processes.

CONCLUSION

Recent research data suggest that the SC therapy can be an innovative treatment strategy for many patients with AMI, and/or subsequent HF (due to chronic ischemic cardiomyopathy). The safety of SC therapy has been demonstrated in many clinical trials, regardless of their design. The main issues that need to be resolved include indications for a specific SC type, dosage, route and time of administration, in various clinical scenarios of myocardial ischemia. Future efforts to explore the long-term efficacy of currently available methods, as well as investigating combination approaches, including the application of SCs, and paracrine factors, as well as designing of biomaterials hold promise to regenerate the ischemic myocardium. Unquestionably, further large-scale prospective RCTs, in the settings of AMI leading to ischemic HF, to establish the long-term effectiveness of SC therapy (*e.g*.: improving clinical outcomes, patient survival, and quality of life) are necessary prior to implementing the SC-based therapies in the clinical armamentarium.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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