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Adult stem cell therapy and heart failure, 2000 to 2016: a systematic review

Patricia K. Nguyen, MD[*,1,2,3], **June-Wha Rhee, MD**[*,1,2], and **Joseph C. Wu, MD, PhD**[1,2,4]

[1]Stanford Cardiovascular Institute, Stanford University

[2]Department of Medicine, Division of Cardiovascular Medicine

[3]Veterans Affairs Palo Alto Health Care System

[4]Department of Radiology

Abstract

Importance—Stem cell therapy is a promising treatment strategy for patients with heart failure, which accounts for over 10% of deaths in the U.S. annually. Despite over a decade of research, further investigation is still needed to determine whether stem cell regenerative therapy is clinically effective and can be routinely implemented in clinical practice.

Objective—The purpose of this review is to describe the current progress in cardiac stem cell regenerative therapy using adult stem cells and highlight the merits and limitations of clinical trials performed to date.

Evidence Review—Information for this review was obtained through a search of PubMed and the Cochrane database for English language studies published between January 1, 2000 and April 20, 2016. Twenty-nine randomized clinical trials and 7 systematic reviews and meta-analyses were included in this review.

Findings—Although adult stem cells were once believed to have the ability to create new heart tissue or grow blood vessels, preclinical studies suggest instead that these cells release cardio-protective paracrine factors that activate endogenous pathways, leading to myocardial repair. Subsequent randomized controlled clinical trials, the majority of which used autologous bone marrow mononuclear cells, have found only a modest benefit in patients receiving stem cell therapy. The lack of a significant benefit may result from variations in trial methodology, discrepancies in reporting, and an over-reliance on surrogate endpoints.

Conclusions and Relevance—Although stem cell therapy for cardiovascular disease is not yet ready for routine clinical application, significant progress continues to be made. Physicians should be aware of the current status of this treatment so that they can better inform their patients who may be in search of alternative therapies.

Correspondence: Joseph Wu, MD, PhD, 265 Campus Drive, Rm G1120B, Stanford, CA 94305-5454, joewu@stanford.edu or Patricia Nguyen, MD, 300 Pasteur Drive, Stanford, CA 94305, pknguyen@stanford.edu.

*Drs. Patricia Nguyen and June-Wha Rhee contributed equally to this manuscript

Introduction

Heart failure (HF) is a devastating disease that causes significant morbidity and mortality, accounting for one in nine deaths in the US.[1] Patients who suffer from coronary artery disease (CAD), valvular heart disease, and other cardiac disorders are at risk of developing HF. Because therapeutic options for advanced HF remain limited to organ transplantation and left ventricular assist device (LVAD), there is a strong impetus to develop alternative treatment strategies. Stem cell regenerative medicine is a promising therapeutic strategy to repair or replace injured and nonviable myocardium. Effective clinical translation, however, remains challenging due to inconclusive study results regarding stem cell regenerative capacity and their ability to improve cardiac function.[2–6] Here we will review the proposed mechanisms of action for stem cell regenerative therapy, compare various stem cell sources, and discuss the merits and limitations of recently published adult stem cell clinical trials.

Proposed Mechanisms of Action to Improve Heart Function

Over the last decade, investigators have proposed three basic mechanisms to support the assertion that stem cell therapy can be used as an effective treatment for HF (Figure 1). Although it was once believed that adult stem cells could generate new cardiac tissue,[7,8] a process termed cardiogenesis, further investigation has revealed that few if any adult stem cells differentiate into cardiomyocytes and engraft into the myocardium.[9] The second proposed mechanism of action suggests that stem cells could generate vasculature via angiogenesis or vasculogenesis by activating endogenous endothelial progenitor cells (EPCs) or recruiting them from the vasculature. The existence of EPCs, however, remains controversial due to a lack of unique surface markers to identify these cells.[10] Moreover, only a subset of EPCs may be of true endothelial lineage capable of neovasculogenesis, and these populations are rare and likely of insufficient number to produce measureable improvement in heart function.[11]

While these two hypotheses remain controversial, mounting evidence now suggests that adult stem cells may exert paracrine effects by secreting cardio-protective factors. These secreted factors may stimulate vascular growth and remodeling, attenuate fibrosis, modulate inflammation, regulate cell differentiation and survival, and recruit resident stem or progenitor cells.[12,13] Activation of these pathways may blunt reperfusion injury or attenuate adverse remodeling in patients suffering from acute myocardial infarction (AMI) or HF, respectively. Interestingly, recent studies have shown that these factors may be clustered into extracellular membrane vesicles, including exosomes and microsomes, which can then transfer proteins, lipids, RNA, and microRNAs to mediate cardioprotection.[14,15] Although further studies are needed to confirm that these vesicles can substitute for stem cell therapy, delivering these vesicles rather than cells themselves may present a clinically attractive therapeutic option from a regulatory and commercial perspective.

Stem Cells Utilized in Clinical Trials For Heart Diseases

Although animal studies support the idea that the favorable effects observed from treatment with adult stem cells are attributable to paracrine effect,[13,16,17,] the exact mechanism of action in humans remains unclear. Despite this incomplete knowledge, ample clinical

experience has been accumulated from the numerous clinical trials using various adult stem cell populations, including bone marrow-derived mononuclear cells (BMMNCs), mesenchymal stem cells (MSCs), and stem cells isolated from cardiac tissue (Figure 1). The clinical translatability of each of these adult stem cell populations is discussed below.

Bone marrow mononuclear cells (BMMNCs)—The human bone marrow contains a small fraction of various stem cell populations, including hematopoietic stem cells (HSCs), EPCs, and MSCs, which can be isolated using a Ficoll density gradient centrifugation and purified to obtain a final product that is commonly known as BMMNCs.[18] Several studies have also used a magnetic separation device to isolate subpopulations of BMMNCs expressing CD34 or CD133 surface markers to further enhance efficacy.[19,20] Interestingly, recent studies have suggested that the reparative capabilities of these cells may also be dependent on the age as well as the health of the donor. Vrtovec et al. showed that $CD34^+$ cells obtained from younger patients had greater myocardial homing than those obtained from older patients, resulting in greater improvement in LVEF in the former.[21] The reparative capacity of BMMNCs may even decline post-MI, as shown by Cogle et al., who analyzed the bone marrow obtained from patients enrolled in the TIME, LateTIME, and FOCUS-CCTRN trials.[22] While all patients had a heterogeneous mixture of bone marrow cell subsets, bone marrow obtained from those patients post-MI had decreased angiogenic and vasculogenic capabilities. Patients with a higher number of $CD34^+$ had greater improvement in LVEF. Collectively, these studies support the notion that heterogeneity in cell number and viability can affect the therapeutic response of BMMNCS. Nevertheless, the relative abundance of stem cells in the bone marrow, low cost of isolation, and ease of procurement have allowed these cells to be used in more than 100 pre-clinical and clinical studies thus far,[23] making BMMNCs the most researched stem cell source.

Mesenchymal Stem Cells (MSCs)—Mesenchymal stem cells are mesoderm-derived stem cells that exist in various tissues, including the bone marrow, umbilical cord blood, adipose tissues, and muscles.[24] Although it remains unclear how biologically similar MSCs from various tissue sources are, both BM- and non-BM-derived (e.g., adipose tissue) MSCs, as well as “pre-conditioned” cardiopoietic MSCs, have been increasingly tested in cell therapy studies.[25,26] Isolation, expansion, and purification of MSCs, however, can be a long and tedious process, which may limit the large-scale production of these cells for clinical transplantation.

Cardiac-derived stem cells—While still controversial, several investigators have reported the existence of resident populations of cardiac progenitor cells in post-natal hearts, challenging the notion that the myocardium is terminally differentiated.[27,28] Isolated from adult heart tissue, c-kit-positive cardiac stem cells (CSCs) have been reported to differentiate into cardiomyocytes when transplanted into the heart after MI. Similarly, cells migrating out of cardiac tissue fragments to form spheres, commonly known as cardiosphere-derived cells (CDCs),[29] have been reported to give rise to cardiomyocytes *in vitro* and *in vivo* after transplantation. Isolation of CSCs and CDCs requires harvesting cardiac tissue via percutaneous endomyocardial biopsies or surgical extraction, followed by digestion,

expansion, and purification to the desired cell types, a process that can take over a month from the time of tissue sampling to generate a sufficient number of cells for therapy.[30]

Results from Clinical Trials

Over the last decade, researchers have evaluated the safety and efficacy of various stem cell populations in a number of clinical trials, with trials using autologous BMMNCs leading the charge (Table 1 and 2).[3,4,31,32] Although initial results were encouraging, subsequent large-scale randomized placebo controlled trials have shown only a modest benefit, as confirmed in recently published meta-analyses.[31,32] The following section summarizes a select list of clinical trials that have evaluated the safety and efficacy of transplanting adult stem cells in patients with CAD and HF. Due to space limitations, we are unable to detail the specifics of each trial and refer the reader to more comprehensive reviews of stem cell trials for further detail.[2,6,31–35]

Acute Myocardial Infarction—The use of stem cells at the time of AMI was supported by animal studies that suggested stem cell therapy could limit the extent of myocardial injury and potentially restore damaged myocardium.[36] The initial observation of improved ventricular function after AMI following BMMNC therapy led to the initiation of the BOne marrOw transfer to enhance ST-elevation infarct regeneration (BOOST) trial published in 2004,[37] which enrolled 60 patients randomized to receive intracoronary BMMNC therapy versus conventional medical therapy after percutaneous coronary intervention (PCI) for AMI. Although the study reported an improvement in left ventricular ejection fraction (LVEF) at 6 months following the BMMNC therapy, the observed benefit largely disappeared at 18 months except in those with significant infarct size (>60%) and depressed LVEF <50% at the time of therapy.[38] This study was then followed by The Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial,[39] the first double-blinded, randomized trial enrolling over 200 patients to receive placebo or autologous BMMNCs. A significantly greater increase in LVEF was reported in the cell therapy group versus control at 6 months (mean of 5.5% versus 3.0%, P = 0.01), with a mortality benefit and sustained LVEF improvement at the 2-year follow up. Similar to the BOOST trial, those with depressed LVEF <50% appeared to have derived the most benefit. Despite the initial encouraging results with BMMNC therapies, many subsequent studies utilizing BMMNCs did not find a significant benefit (Table 1).[20,40–46] Similarly, the most recent Cochrane Database Systematic Review published in 2015 that included 41 randomized controlled trials using BMMNCs and a total of 2,732 participants showed that cell treatment was safe but found no significant improvements in quality of life or LVEF in the short or long term. The mean difference in LVEF between the treated and control group was 2 – 5%, which was not considered clinically relevant given the inherent variability of imaging tests.[32]

Because only a very small fraction of BMMNCs are actually stem cells (e.g., ~2–4% HSCs/EPCs and <0.01% MSCs), several studies have utilized a more select subgroup of BMMNCs, namely, $CD34^+$ cells and MSCs, to eliminate biological variability and augment efficacy by removing bystander cells. In a study comparing the effects of intracoronary

treatment with BMMNCs vs. BM-derived $CD34^+/CXCR4^+$ cells for patients after AMI with reduced LVEF <40%,[20] Tendera et al. found no significant differences in LVEF or in the incidence of major adverse cardiovascular events (MACE), including death, re-infarction, stroke, or target vessel revascularization, between the two groups. In 2004, Chen et al. reported the first randomized trial delivering autologous MSCs via intracoronary injection in patients after AMI, finding a significant improvement in LVEF following cell therapy.[47] Subsequently, Hare et al. administered intravenous allogeneic MSCs vs. placebo to AMI patients approximately 7–10 days after PCI, and found similar adverse event rates between the two groups, but also a trend toward improved LVEF and functional capacity in the treatment group.[48] Despite a previous preclinical study reporting a high risk of micro-infarction from intracoronary delivery,[49] available randomized placebo-controlled human studies have shown no significant adverse events after intracoronary or intravenous delivery of MSCs.[34]

After these encouraging initial results with BM-derived MSCs, investigators then turned their attention to the application of MSCs from adipose tissue and the umbilical cord. In 2004, Vulliet et al. randomized 14 patients with anterior AMI to receive intracoronary infusion of adipose-derived MSCs versus placebo (APOLLO) and showed that the treatment was safe with a trend towards a small reduction in infarct size.[49] Further information on the efficacy and safety of these cells in patients with acute MI will be available after the release of findings from a multicenter, prospective, randomized, placebo-controlled phase IIb/III clinical sponsored by Cytori Therapeutics (ADVANCE study, NCT01216995). More recently, Gao et al. reported that intracoronary infusion of MSCs derived from umbilical cord obtained from healthy donors after full term birth resulted in a significant improvement in LVEF, LV volumes, and perfusion compared to controls at 18 months.[25] It should be emphasized, however, that given the limited number of studies performed using MSCs and the relatively small sample size in each study, definitive conclusions regarding the efficacy of this cell population cannot be made at the present. Additional studies with larger sample sizes using MSCs are needed to validate these findings.

Finally, in a recent study CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dysfunction (CADUCEUS) trial, Makkar et al. reported the first randomized, phase I trial evaluating the therapeutic effects of CDCs in the treatment of AMI.[30] Patients with recent AMI and LVEF 25–45% were randomized to receive CDC therapy (n=23) or standard therapy (n = 8). Varying doses of CDCs were injected via intracoronary infusion approximately at 65 days after AMI. Results at 6 and 12 months of follow up showed that no patients died or developed cardiac tumors. However, at 12 months, one patients suffered a non-ST elevation MI and another patient required coronary vascularization.[50] Although there was a significant decrease in scar size, increase in viability, and improvement in regional wall function after CDC treatment, there were no significant improvements in global systolic function or quality of life assessments. Subsequent studies such as the REgenerative CardiOsphere iNjection to STRengthen dysfUnCTional Hearts (RECONSTRUCT) trial and the ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration (ALLSTAR) trial are underway to evaluate the efficacy of autologous and allogenic CSCs, respectively, in treating AMI.

Chronic Ischemia with Intractable Angina—Patients with intractable angina due to ischemia that is otherwise not amenable to revascularization may also benefit from therapy with stem cells. Losordo et al. published the first Phase I/IIa trial evaluating the safety and efficacy of intramyocardial transplantation of autologous $CD34^+$ stem cells in 24 patients with intractable angina.[51] Although results were not significant due to a small sample size, improvements in angina and exercise time were noted in the treatment group without safety issues. Importantly, in a follow-up study that included a larger sample of patients (n=167),[52] the cell therapy group reported less frequent angina with improved exercise tolerance. Cardiac enzyme elevation, however, was reported in both the control and treatment after cell mobilization with G-CSF. More recently, Wang et al. reported similar efficacy results with the use of an intracoronary method for delivering EPCs.[53]

Ischemic Cardiomyopathy—The initial proposed mechanism of cardiogenesis made ischemic cardiomyopathy an attractive indication for adult stem cell therapy to replace the significant cardiomyocyte loss that occurs. A pilot study in 2003 by Perin et al. randomized 27 patients with ICM to receive transendocardial injection of BMMNCs or placebo.[54] At 4 months, there was a significant improvement in LVEF in patients with cell therapy versus placebo (29% vs. 20%; P=0.003) without an increase in serious adverse events. This study validated the safety of transendocardial injection of BMMNCs, leading to two large trials of BMMNC-based therapy for ICM. In the first trial, the Transplantation Of Progenitor Cells And REcovery of LV function in patients with Chronic ischemic Heart Disease (TOPCARE-CHD) study, Assmus et al. randomized ICM patients to intracoronary infusion of BMMNCs vs. “circulating progenitor cells (CPCs)” derived from peripheral blood vs. placebo and found that transplantation of BMMNCs, as opposed to CPCs or placebo, resulted in a modest but significant improvement in LVEF at 3 months.[55] These results, however, were not replicated in a second study sponsored by the National Heart, Lung, and Blood Institute (NHLBI), First Mononuclear Cells injected in the United States conducted by the Cardiovascular Cell Therapy Research Network (FOCUS-CCTRN),[56] which did not show a significant improvement in LVEF at 6 months following transendocardial delivery of BMMNCs for treating ICM patients with LVEF <45%. Consistent with these findings, a recent Cochrane meta-analysis review that included 23 randomized control trials and 1,255 participants found no short-term benefits (<12 months) associated with treatment with autologous BMMNCs.[31] Longer-term results (≥12 months), however, showed that autologous BMMNCs reduced the incidence of mortality (RR=0.28, 95% CI 0.14–0.53, p=0.0001) and HF re-hospitalization (RR 0.26, 95% CI 0.07–0.94, P=0.04).

Several studies have compared the efficacy of BMMNCs versus MSCs. In 2014, Heldman et al. reported a phase I/II study on the transendocardial delivery of BMMNCs versus BM-derived autologous MSCs versus placebo for ICM patients with LVEF <50%.[57] Although small in size, significant improvements in HF symptoms, infarct size, and regional myocardial function were observed in patients treated with MSCs. Because BM-derived MSCs require significant preparation time, Hare et al. conducted a study comparing the safety and efficacy of using allogenic instead of autologous MSCs in a non-placebo controlled, randomized, dose-escalating trial (POSEIDON).[26] While treatment with both cell types resulted in reduction in the infarct size, only autologous MSCs led to improved quality

of life score and 6-minute walk test. Ascheim et al. also reported the use of allogenic MSCs for patients with advanced HF randomized to myocardial injections of MSC versus placebo at the time of LVAD implantation.[58] Although imaging surrogates for improvement failed to reach statistical significance, the study demonstrated no increase in incidence of HLA antibodies to indicate immunologic reactions. Recently, Perin et al. reported improvement in exercise tolerance with higher peak VO_2 but not in in LVEF for 27 ICM patients receiving adipose-derived MSCs, suggesting that the injected MSCs may promote angiogenesis through its paracrine effects.[59] Taken together, these studies support the safety of BMMNCs and MSCs in ICM patients and suggest that MSCs may be more beneficial than BMMNCs. It should be noted, however, that three patients with ICM enrolled in one of two sister trials sponsored by Cytori Inc. (ATHENA I and II: NCT01556022 and NCT02052427) developed reversible, cerebrovascular events after receiving intramyocardial injection of adipose derived stem cells in one of two sister randomized, controlled trials evaluating the safety and efficacy of these cells delivered through intra-myocardial injection in patients with ICM.

With the introduction of potential residential cardiac progenitor cells, the use of CSCs for ICM was studied in the Stem Cell Infusion in Patients with Ischemic cardiOmyopathy (SCIPIO) trial.[60] In this phase I trial, CSCs were isolated from the right atrial appendage at the time of coronary artery bypass graft surgery. The cultured CSCs were then delivered to the patients via intracoronary injection at a later time (mean of 113 days after surgery). Published findings indicate that patients had improved LVEF, regional contractility, and HF symptoms when treated with CSCs versus no treatment.

Non-ischemic Cardiomyopathy—Limited but increasing research effort has been made to evaluate the safety and efficacy of cell therapy for treating non-ischemic cardiomyopathy (NICM). One of the largest studies to date on cell therapy for NICM randomized 110 patients with dilated cardiomyopathy in a 1:1 ratio to receive intracoronary infusion of autologous peripheral $CD34^+$ cells or no therapy.[21] In this study, $CD34^+$ cells mobilized by G-CSF were injected into the coronary artery territory with the greatest perfusion defect as identified by myocardial scintigraphy. At 1 year and 5 years, the treatment group showed a significant improvement in LVEF and 6-minute walk distance.[21]

Limitations of Adult Stem Cell Trials Performed To Date

As discussed above and outlined in Table 1 and 2, there are significant differences in the reported benefit between the early randomized controlled trials compared to more recent randomized controlled trials using adult stem cells. The reasons for these differences in efficacy remain unclear, but may be partially due to variations in trial design and methodology, including differences in the chosen cell source, dosing or concentration, the route of administration, timing of delivery, and clinical characteristics of patients recruited in the trial (Figure 2). Furthermore, the lack of standardized protocols limits our ability to evaluate the relative effectiveness of these approaches and most importantly the optimal cell source for each. While a handful of studies performed head-to-head comparisons of efficacy between two different cell types or among multiple doses,[48,52] additional studies are needed to identify the optimal strategy for clinical application.

Discrepancies in reporting have also been recently identified as another potential source of inconsistency. Nowbar et al. performed a recent meta-analysis of 49 trials to determine if the number of discrepancies in trial design, methods and results was associated with improvement in LVEF.[61] They found a positive relationship between the number of discrepancies and improvement in LVEF, raising questions about the validity of earlier studies. Results from this study emphasize the need to adhere to rigorous standards in conducting and reporting future stem cell clinical trials.

Another possible source of difference in reported efficacy is the over-reliance on surrogate imaging endpoints, which have inherent inter- and intra-observer variability. Earlier trials have relied on imaging endpoints such as changes in LVEF, infarct size, and perfusion abnormalities because they are more easily measured, require smaller sample size and shorter follow-up. Surrogate endpoints, however, are generally limited by their degree of correlation with MACE, which casts significant doubt as to the clinical relevance of the outcomes observed. Even the most well-studied surrogate endpoint (i.e., global LVEF) does not consistently parallel survival.[62] Surrogate endpoints are also not accepted as primary endpoints by the US Food and Drug Administration for Phase III trials.

More recently, stem cell trials in AMI and HF have incorporated more definitive endpoints such as the incidence of death, infarction, HF, and arrhythmias,[31,32] but these were low-frequency events, resulting in inadequate power to detect significant differences. To address this limitation, European investigators have begun recruiting for the effect of intracoronary reinfusion of Bone marrow-derived mononuclear cells on all-cause mortality in Acute Myocardial Infarction (BAMI: NCT01569178) study, the largest stem cell trial using BMMNCs to date. The trial is recruiting 3,000 patients with AMI and LVEF <45% and is powered to detect a 25% decrease in 2-year all cause mortality after treatment. Results from this trial will help us determine whether further investment in BMMNCs is warranted.

Conclusion

In the past two decades, researchers have achieved significant milestones toward their goal of bringing stem cell regenerative medicine to the bedside. First, evidence suggests the benefit of adult stem cell therapy is likely mediated by the release of cardio-protective factors that activate endogenous pathways to repair the myocardium rather than *de novo* cardiomyocyte or blood vessel formation. Second, safe delivery of cells has been demonstrated in both preclinical and clinical trials, although the question of clinical efficacy of adult stem cell therapies remains elusive. Future research efforts should focus on developing new strategies to expand our knowledge of stem cell biology, following the fate of stem cells post-delivery, and designing larger trials using clinically meaningful endpoints rather than surrogate endpoints to better investigate their therapeutic potential.

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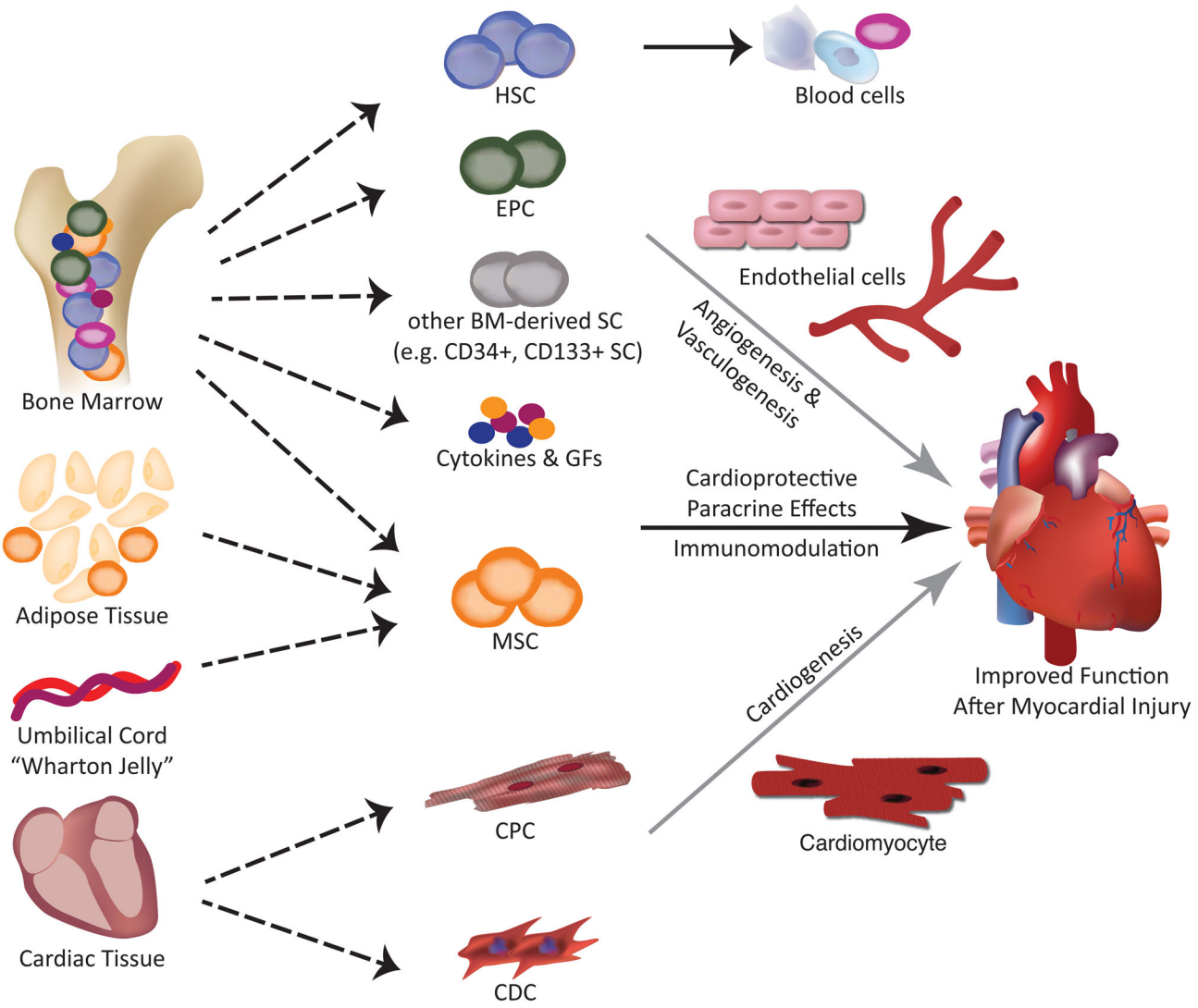

Figure 1. Schematic of the proposed mechanism of action of stem cell therapy

The figure illustrates the theoretical mechanisms of action of various stem cell populations proposed in the literature. Although stem cells can potentially repair the injured myocardium by increasing angiogenesis, releasing factors that reduce cell death or modulate the immune system (e.g., paracrine activation), and/or creating new heart tissue, thus far only paracrine activation has been proven while the other hypotheses remain controversial. Stem cell sources include: 1) the bone marrow which contains the most diverse group of cells (e.g., HSCs, EPCs, MSCs, and specific stromal cell subpopulations) and factors (e.g., cytokine and growth factors) that can potentially regenerate the myocardium; 2) other sources of MSCs such as adipose tissue and the umbilical cord; and 3) cardiac tissue that may contain cardiac progenitor cells or cardiospheres. HSCs: hematopoietic stem cells, EPCs: endothelial progenitor cells, BM: bone marrow, SCs: stem cells, GFs: growth factors, MSCs: mesenchymal stem cells, CSCs: cardiac stem cells, CDCs: cardiosphere-derived cells.

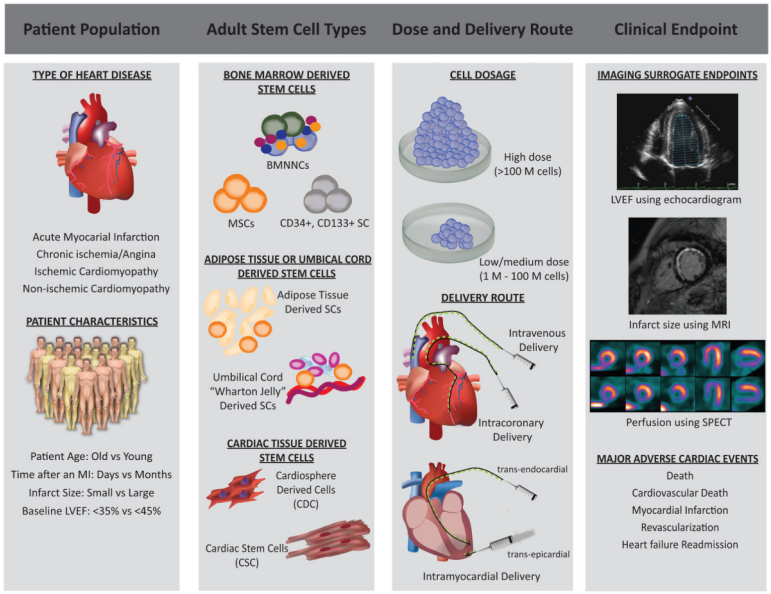

Figure 2. Overview of the various patient cohorts, cell types, doses, routes of delivery, and clinical endpoints used in adult stem cell trials

A significant difference in efficacy has been observed in earlier randomized, controlled trials versus later randomized, controlled trials, which may be partially explained by variations in patient cohorts, cell types, doses, routes of delivery, and clinical endpoints evaluated in adult stem cell trials. Trials have been conducted in patients with various cardiac diseases including AMI, chronic ischemia/angina, ischemic CM, and non-ischemic CM. Within each cohort, certain patient characteristics may also affect efficacy such as transplanting bone marrow acquired from young versus old patients, delivering cells to patients immediately versus weeks/months post MI, and treating patients who have suffered small versus large infarct or who have mild (<45%) versus significant (<35%) impairment in LVEF. Various adult stem cell types have also been evaluated, including bone-marrow derived cells (e.g., BMMNCs, $CD34^+$ or $CD133^+$ cells, and MSCs) and adipose/umbilical derived SCs, as well as stem cells derived from cardiac tissue (e.g., CSCs and CDCs). These cells have been delivered in multiple doses and with different delivery approaches. Finally, most studies have used surrogate endpoints like LVEF, infarct size, and perfusion defects, which do not always correlate with more definite endpoints such as death, myocardial infarction, revascularization, heart failure readmission, and other major adverse cardiovascular events (MACE).

Table 1

Published Stem Cell Clinical Trials for Ischemic Heart Disease

STUDY NAME	YEAR	DISEASE	TRIAL DESIGN	# OF PTS	CELLS USED	CELL HARVESTING	DELIVERY	MEAN F/U	LVEF	OTHER RESULTS
Acute MI										
TOPCARE-AMI[63]	2002	Acute MI s/p PCI	non-randomized, matched control	31	autologous BMMNCs/PBSCs	BM iliac crest	IC	4 mo	↑	improved perfusion + viability
Chen et al.[47]	2004	Acute MI s/p PCI	Randomized, DB, PC	69	autologous BMMNCs	BM iliac crest	IC	6 mo	↑	improved perfusion
BOOST[37]	2004	STEMI s/p PCI	randomized, open-label, single-center	60	autologous BMMNCs	BM iliac crest	IC	18 mo	→	no sig improvement
LEUVEN-AMI[46]	2006	STEMI s/p PCI, LV dysfunction	Randomized, DB, PC	67	autologous BMMNCs	BM iliac crest	IC	4 mo	→	decreased infarct size, NS
REPAIR-AMI[39]	2006	Acute MI s/p PCI, LVEF <45%	Randomized, DB, PC	204	autologous BMMNCs	BM iliac crest	IC	1 yr	↑	decreased LVEF, improved regional infarct contractility, improved MACE
ASTAMI[40]	2006	Ant STEMI	randomized, open-label, single-center	97	autologous BMMNCs	BM iliac crest	IC	6 mo	→	improved exercise capacity
FINCELL[64]	2008	STEMI s/p thrombolysis + PCI	Randomized, DB, PC	80	autologous BMMNCs	BM iliac crest	IC	6 mo	↑	
Hare et al.[65]	2009	Acute MI s/p PCI	Randomized, DB, PC, dose-escalating	53 *	hMSCs	n/a	IC	6 mo	↑	improved symptoms
MYSTAR[66]	2009	STEMI s/p PCI, LVEF <45%	SB, no-placebo	60	autologous BMMNCs	BM iliac crest	IC & TEN	1 year	↑	improved infarct size, viability, perfusion
REGENT[20]	2009	ant STEMI s/p PCI, LVEF <40%	Randomized, DB, PC	200	autologous BMMNCs UNSEL or SEL (CD34+CXCR4+)	BM iliac crest	IC	6 mo	→	no sig improvement
Cao et al.[67]	2009	STEMI s/p PCI	Randomized, DB, PC	86	autologous BMMNCs	BM iliac crest	IC	4 yr	↑	no diff in viability
BONAMI[68]	2011	STEMI s/p PCI, LVEF <45%	Randomized, DB, PC	101	autologous BMMNCs	BM iliac crest	IC	3 mo	→	trend to improved viability
HEBE[45]	2011	Acute MI s/p PCI	multicenter, randomized, 3-arm open trial	200	autologous BMMNCs	BM iliac crest or peripheral blood	IC	1yr	→	no significant improvement
LATE-TIME[41]	2011	Acute MI s/p PCI, LVEF <45%	Randomized, DB, PC	87	autologous BMMNCs	BM iliac crest	IC	6 mo	→	no significant diff in LVEF, infarct size, wall motion
TIME[42]	2012	anterior STEMI s/p PCI, LV dysfunction	Randomized, DB, PC	120	autologous BMMNCs	BM iliac crest	IC	1yr	→	no significant improvement
APOLLO[69]	2012	STEMI s/p PCI	Randomized, DB, PC	14	autologous ADSCs	liposuction	IC	6 mo	↗	improved perfusion & scar formation
CADUCEUS[30]	2012	AMI s/p PCI, LVEF <45%	Randomized, no placebo	25	autologous CDCs	Endomyocardial Bx	IC	6 mo	→	reductions in scar, increases in viable mass and regional contractility
SWISS-AMI[43]	2013	Acute MI s/p PCI	randomized, 3-arm trial, DB, PC	192	autologous BMMNCs	BM iliac crest	IC	1 yr	→	no significant improvement
Gao et al.[25]	2015	STEMI s/p PCI	Randomized, DB, PC	116 *	Allogenic WJMSCs	Allogenic	IC	18 mo	↑	Improved LVEF, LV volumes and perfusion
TECAM[44]	2015	STEMI s/p PCI	randomized, open-label, SB, PC	120	autologous BMMNCs, G-CSFs, both	Autologous	IC	12 mo	→	no significant improvement
Chronic Ischemia with Refractory Angina										
Losordo et al.[51]	2007	intractable angina, ischemia	Randomized, DB, PC	24	peripheral CD34+ after G-CSF × 5d	peripheral blood	TE	6 mo	n/a	significant improvement in angina
Ramshorst et al.[70]	2009	severe angina, ischemia, LVEF >35%	Randomized, DB, PC	50	BMMNCs	BM iliac crest	TE	6 mo	↑	significant improvement in perfusion and angina
ACT34-CMI[52]	2011	refractory angina, ischemia	Randomized, DB, PC	167	peripheral CD34+ after G-CSF × 5d	peripheral blood	TE	3/6 mo	n/a	Improvement in angina and exercise

* Only a handful of trials use MSCs and these trials include only a small number of patients; thus, their conclusions may not be statistically significant.

Abbreviation: MI: myocardial infarction, SB: single-blinded, DB: double-blinded, PC: placebo-controlled, BM: bone marrow, BMMNCs: bone marrow derived mononuclear cells, MSCs: mesenchymal stem cells, ADSCs: adipose-derived stem cells, CDCs: cardiosphere-derived cells, IC: intracoronary, TEN: trans-endocardial, SM: skeletal myoblasts, TEP: transepicardial, AR: arrhythmogenicity

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Table 2

Published Stem Cell Clinical Trials for Heart Failure

STUDY NAME	YR	DISEASE	TRIAL DESIGN	# OF PTS	CELLS USED	CELL HARVESTING	DELIVERY	MEAN F/U	LV EF	OTHER RESULS	ADVERSE EVENTS
Menasche et al[71]	2003	ICM, LVEF <35%, WMA, pre-CABG	non-randomized	10	Autologous SM	skeletal muscle bx	TEP	10.9 mo	↑	N/A	AR
Perin et al[54]	2003	ICM, LVEF < 40%, ischemia	non-randomized, open-label	21	Autologous BMMNCs	BM iliac crest	TEN	4 mo	↑	improved perfusion	none
TOPCARE -CHD[55]	2006	Sub-acute MI with WMA	randomized, open-label, single-center	75	Autologous BMMNCs/PBSCs	BM iliac crest	IC	3 mo	↑	improved regional contractility	none
MAGIC[72]	2008	ICM, LVEF <35%, WMA, pre-CABG	randomized, DB, PC	97	Autologous SM	skeletal muscle bx from thigh	TEP	6 mo	→	no diff in MACE	AR
SCIPIO[60]	2011	ICM, LVEF <40, pre-CABG	open-label, randomized	56	Autologous CSCs	right atrial appendage	IC	4mo/12 mo	↑	decreased infarct size	none
FOCUS-CCTRN[73]	2012	ICM, LVEF <45%	multicenter, randomized, DB, PC	92	Autologous BMMNCs	BM iliac crest	TEN	6 mo	→	no significant diff in LVEF, infarct size, wall motion	none
POSEIDON[48]	2012	ICM, LVEF <40	randomized, NO placebo controlled	30	Autologous and Allogenic hMSCs *	EMBX	TEN	30d/1 yr	↗	Autologous MSC improved 6 min walk test, infarct size. Allogenic MSC reduced LVEDV and infarct size	none
C-CURE[74]	2013	ICM with LVEF <40%, NYHA >=2	randomized, DB, PC	36	Autologous Cardiopoietic hMSCs *	BM iliac crest	TEN	2 yr	↑	safe, improved LVEF, LVESV, symptoms	none
CELLWAVE[75]	2013	ICM with LVEF <50% + NYHA>=2	randomized, DB, PC	103	Autologous BMMNCs	BM iliac crest	SW/IC	4 mo	↑	Improved LVEF, regional wall thickening, and MACE	none
PRECISE[59]	2014	ICM with LVEF <45%, NYHA >=2	randomized, DB, PC	27	Autologous ADRCs	liposuction	TEN	36 mo	↑	N/A	none
TAC-HFT[57]	2014	ICM, LVEF <50%	randomized, DB, PC	59	Autologous BMMNC and MSCs	BM iliac crest	TEN	30 d	→	MSC - improved functional capacity, infarct size. BMNC improved functional capacity.	none
Vrtovec et al.[21]	2013	NICM (DCM)	randomized, DB, PC	110	peripheral CD34+ after G-CSF × 5d	peripheral blood	IC	5yr	↑	improved LVEF, 6min walk distance, and decreased NT-proBNP. No diff mortality	none

* Only a handful of trials use MSCs and these trials include only a small number of patients; thus, their conclusions may not be statistically significant.

Abbreviation: MI: myocardial infarction, SB: single-blinded, DB: double-blinded, PC: placebo-controlled, BM: bone marrow, BMMNCs: bone marrow derived mononuclear cells, MSCs: mesenchymal stem cells, ADSCs: adipose-derived stem cells, CDCs: cardiosphere-derived cells, IC: intracoronary, TEN: trans-endocardial, SM: skeletal myoblasts, TEP: transepicardial, AR: arrhythmogenicity