REVIEWS

Stem Cell Therapy for Heart Disease

Shannon B. Puliafico, MSN, APRN, NP-C, PCCN[1,2], Marc S. Penn, MD, PhD, FACC[1,2,3,4], and Kevin H. Silver, MD, FACC, FSCAI, FASNC[1,2,3]

[1]Northeast Ohio Cardiovascular Specialists (NEOCS), Akron, OH, USA; [2]Summa Cardiovascular Institute, Summa Health System, Akron, OH, USA; [3]Summa Physician Incorporated, Summa Health System, Akron, OH, USA; [4]Northeast Ohio Medical University, Rootstown, OH, USA.

Coronary artery disease is the leading cause of death in Americans. After myocardial infarction, significant ventricular damage persists despite timely reperfusion and pharmacological management. Treatment is limited, as current modalities do not cure this damage. In the past decade, stem cell therapy has emerged as a promising therapeutic solution to restore myocardial function. Clinical trials have demonstrated safety and beneficial effects in patients suffering from acute myocardial infarction, heart failure, and dilated cardiomyopathy. These benefits include improved ventricular function, increased ejection fraction, and decreased infarct size. Mechanisms of therapy are still not clearly understood. However, it is believed that paracrine factors, including stromal cell-derived factor-1, contribute significantly to stem cell benefits. The purpose of this article is to provide medical professionals with an overview on stem cell therapy for the heart and to discuss potential future directions.

KEY WORDS: myocardial infarction; heart failure; ventricular function; stem cell; paracrine.
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Coronary artery disease (CAD) remains the top killer in the Western world, despite advancing medical technology. Annually, 935,000 Americans suffer from acute myocardial infarctions (AMI).[1] Arterial obstruction causes inadequate perfusion and cardiomyocyte death. If flow is not quickly reestablished, loss of cardiomyocytes can be massive.[2] Significant declines in CAD mortality rates are attributable to decreased AMI incidence coupled with improved survival from aggressive revascularization.[1]

AMI patients who previously might not have survived without percutaneous coronary intervention (PCI) are now living longer,[1] but with considerable left ventricular dysfunction.[3,4] Heart failure (HF) subsequently ensues, affecting 5.7 million Americans.[1,2,4,5] Despite advanced therapies, this is expected to increase to 9.6 million by 2030.[1] Left ventricular dysfunction ultimately affects contractility, worsening HF and increasing mortality.[3,6] HF confers poor prognosis; half of Americans with HF will die within five years after diagnosis.[1]

Treatment of HF, due to ischemic or non-ischemic causes, is limited; heart transplantation is the only strategy addressing cardiomyocyte loss. Prospects remain dismal, because current treatment modalities may compensate for, but not cure, the condition.[7] New approaches should alter the remodeling process, regenerate cardiomyocytes and repair infarcted myocardium.[6]

Historically, the heart was described as a terminally differentiated organ, incapable of regeneration. The discovery that myocardial injury induces cardiomyocyte proliferation challenged traditional belief.[8] Identification of cardiac stem cells (CSC) in the adult heart activated by AMI supported the argument.[8] AMI demands myocardial repair, causing resident CSC to reenter the cell cycle and circulating stem cells to move to the injury site. Early studies suggested that non-cardiac stem cells transdifferentiate into cardiomyocytes and repair damaged myocardium.[9,10] In 2001, bone marrow mononuclear cells (BMC) transplanted into mice repaired myocardial damage and improved cardiac function.[9] Later in 2001, autologous BMC were safely injected into a patient after AMI, reducing infarct size and increasing ejection fraction (EF).[11]

Preclinical studies showed that stem cell therapy benefits perfusion and ventricular function. Clinical trials demonstrated feasibility and safety with positive results.[12–14] Benefits cannot be explained solely by stem cells, and are likely associated with paracrine factors released into injured tissue. This review explores emerging clinical applications of stem cell therapy as a promising approach for restoring myocardial function in heart disease.

CELL TYPES

The optimal cell types for treating heart disease continue to be debated. Potentially, no one type is ideal and can be exclusively used. It is possible that different forms of heart disease may require different cell types.

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Embryonic stem cells (ESC) were considered favorable for their unlimited self-renewal and pluripotency.[15] Being allogeneic, there are concerns for immunological incompatibility and risk of teratoma formation.[7,16] Secondary to ethical, political and scientific challenges, no heart disease clinical trials used ESC.[16] Animal studies using ESC demonstrated cardiomyocyte differentiation and improved ventricular function.[17] These findings spurred development of ESC-like cells by reprogramming adult cells to become undifferentiated pluripotent cells for autologous transplantation, known as induced pluripotent stem cells (iPSC). Preclinical studies showed temporary benefits on remodeling and function, but teratoma concerns remain.[15]

A cell type infrequently used in heart disease is human umbilical cord-derived stem cells. These cells are abundant, easily obtained, and with lowered rejection risk.[18,19] A challenge is whether these can be used as an allogeneic source or whether systems for genotyping donor cells need development to achieve wide-spread use.

Resident CSC were initially considered a prime cell choice because they differentiate into cardiomyocytes and demonstrate clonogenicity, self-renewal and cell cycle re-entry.[20] They increase in numbers and migration after ischemia,[2,21] and may be activated by transplanted cells.[22] However, CSC are limited by their small population and reduced effects with aging.[2,8] Moreover, their differentiation potential is low and inadequate to replace lost cardiomyocytes.[23] Clinical translation is challenged by small numbers obtained from biopsy, necessitating prolonged expansion in culture before delivery.

Adipose-derived stem cells (ASC) are an attractive option. Obtained from subcutaneous adipose tissue, ASC are a combination of endothelial progenitor cells (EPC), hematopoietic stem cells (HSC), and mesenchymal stem cells (MSC).[19] They differentiate into several cell lines, including cardiomyocytes.[2]

BMC are the most promising and dominate clinical studies, as they are easily obtained and cultured with differentiation capacity.[19] BMC contain a mixture of HSC, EPC, MSC, and multipotent adult progenitor cells (MAPC).[2] EPC encompass a cluster of cell types[24] that express CD34 and CD133 markers,[16] as well as growth factors that contribute to angiogenesis.[2] EPC are found in small amounts and are reduced in CAD patients.[16] MSC also differentiate into several cell types.[11] MSC and MAPC are considered optimal for allogeneic therapy due to nonimmunogenic and anti-inflammatory characteristics[25,26] Recent efforts use allogeneic BMC, with cells retrieved from healthy donors, cultured, and kept in stock. This allows for "off-the-shelf" treatment during AMI intervention.[27]

MODES OF DELIVERY

The best methods of stem cell delivery have not yet been determined. Peripheral intravenous infusion is an indirect method widely used in animal models with favorable outcomes.[19] It is simple and noninvasive, relying on post-AMI physiological signals to target cells towards damaged tissues.[28] Unfortunately, it is inefficient and impractical, as large cell numbers and infusions are necessary for sufficient amounts to reach infarct-related arteries,[29] due to confinement in the microvasculature and losses to other organs.[28,29]

Direct intramyocardial injection during coronary artery bypass graft (CABG) surgery easily allows stem cells to be placed into the targeted zone.[29] Suitable candidates include chronic ischemic HF patients, because chronically infarcted tissue does not release the necessary post-AMI physiological signals to attract and mobilize cells to the infarct zone.[19,28] However, only a small amount of cells survive more than three days,[30] because the microenvironment is problematic for cell survival secondary to inflammation and insufficient blood supply.[2,28] This is further complicated by mechanical leakage[2] and arrhythmia potential.[28]

Transendocardial injection is similar to the intramyocardial route, but uses a flexible catheter-based percutaneous technique across the aortic valve.[29] Injecting cells in and around the infarct zone[22] allows greater cell engraftment,[28] while using fewer cells.[22] Potential risks include myocardial perforation, AMI, and induction of ventricular arrhythmias.[23,28,29]

Intracoronary infusion into the infarct-related artery is the most popular in AMI trials.[19] Cells are injected via a catheter into the affected artery. Retrograde stem cell loss is prevented by a short balloon inflation.[19,29] Limitations include the complex cell preparation processes and reduced efficacy in CAD patients, secondary to atherosclerotic arteries,[27] reducing delivery to the target myocardium.[22] Temporary occlusion and decreased blood flow from the procedure increase the risk of microembolism, infarct, or restenosis.[22,28]

Building on the intracoronary approach is adventitial delivery. Cells are introduced using a balloon to temporarily occlude flow and a special catheter injects cells via a microneedle through the medial layer and into the adventitia of the infarct-related artery. By delivering directly into the adventitia, atherosclerosis issues are avoided.[27]

Ideal timing depends on cell types and microenvironment. Specific types may be more efficient in acute versus chronic injury[31] and environments may necessitate specific timing of administration for best results. It is suggested that optimal timing of therapy post-AMI is after the inflammatory response diminishes, but before scar formation.[31] Early administration during PCI has been proposed[32] to avoid post-AMI damage and prevent additional procedures. Physiological mechanisms at this time help cells migrate,[31,33] although the inflammatory microenvironment is unfavorable for cell survival.[12,31] Several stem cell administrations may be necessary for adequate therapy.

MECHANISMS

The mechanism of therapy is not clearly understood. Some claim that transplanted cells differentiate into new cardiomyocytes, replacing necrotic cells.[9] Others suggest that transplanted cells fuse with existing cardiomyocytes.[34] Low engraftment and survival of transplanted cells,[16] in addition to limited differentiation, imply that observed improvements in outcomes cannot solely be due to regeneration.[35] Further, some effects are noted within one day, argued as a timeframe too brief for genuine regeneration.[16,32]

Improvements are mostly attributed to the effects of paracrine factors released from cells.[26,36,37] Promptly after transplantation into injured myocardium, stem cells express a variety of paracrine secretions, including cytokines, chemokines, and growth factors.[7] These appear to contribute to cardiac repair;[36] possibly through neo-vascularization, angiogenesis,[36] less inflammation,[32,36] smaller infarct size,[32,36,38] and decreased fibrosis.[36] Paracrine secretions contribute to enhanced cardiomyocyte survival by decreasing apoptosis,[32,36,38] while increasing cell proliferation[23] and mobilizing other stem cells to the infarct zone.[36] Moreover, paracrine activity encourages activation and migration of resident CSC[36,38] and may stimulate differentiation.[38]

Migration of cells to damaged areas after AMI is known as homing.[2,8,9,11,21] Successful homing permits better engraftment and survival.[11,21] This is regulated by the release of stem cell homing factors, which assist in directing cells.[33] One receiving considerable attention is stromal cell-derived factor-1 (SDF-1). Rapid ischemia up-regulates SDF-1 expression,[29,39] which binds to its receptor, CXC chemokine receptor type 4 (CXCR4), expressed on the surface of BMC.[29] Together, SDF-1 and CXCR4 are crucial in cell recruitment and homing.[33,40–42] SDF-1 regulates cell trafficking,[39] increases angiogenesis and cell survival,[40] and improves ventricular function.[41] SDF-1 is not naturally released in chronic ischemic myopthy,[33,37] although homing can be established if paracrine factors are released at a time remote from AMI.[33]

SDF-1 is expressed immediately post-AMI and declines after 4–7 days; a time when cells are considered most responsive to SDF-1.[33,41] CXCR4 is expressed 1–2 days after AMI, peaking on day 4.[42] Both cell responsiveness and CXCR4 expression occur when SDF-1 is decreasing. Such dyssynchrony explains why the heart has limited ability to repair itself. This has led to efforts to alter the timing of SDF-1 or CXCR4 expressions.[41] Moreover, it has been demonstrated that injection of SDF-1 alone provides similar benefit.[33]

ENGRAFTMENT AND SURVIVAL

Poor cell survival and incorporation into native tissue exists despite cell type or delivery. Cell death results from the ischemic environment into which cells are engrafted.[28] Inflammation and diminished vascular supply causes many cells to die within seven days after transplantation.[28,31] Mechanical leakage is unique to the heart because contractions squeeze out cells. Cell escape occurs when injected cells are no longer at the intended site of injury and instead are in extracardiac organs.[28]

There is increased interest in cell preconditioning and modification to alleviate these issues. Preconditioning involves shock, hypoxia, ischemia, and medications for the purpose of improving cell resistance to adverse stimuli. Cells can be modified to release factors to increase engraftment and survival.[28]

CLINICAL OUTCOMES

Acute Myocardial Infarction

There have been numerous AMI trials (Table 1).[27,43–65] Many demonstrated improvement in EF,[27,44–52,55,56,59,61] volumes,[27,43–45,47,48,50–52,59] wall motion,[43–45,47–49] and infarct size[43–45,47,54,61] when compared with conventional treatment. REPAIR-AMI showed decreased mortality, recurrent AMI, and HF re-hospitalizations,[51] with maintained improvement at two years.[52] REPAIR-AMI and TOPCARE-AMI confirmed that patients with decreased baseline EF showed more improvement.[44,45,51,52] Some trials did not show significant results,[57,60,63–65] while others demonstrated some benefits without EF changes.[43,53,54,62]

Heart Failure

Additionally, there have been multiple HF trials (Table 2).[66–86] Many demonstrated benefits in ventricular function noted by increased EF,[68–73,75,79,82,83] improved functional class,[75,78,80,82,83,86] reduced infarct size,[70,72,80,82–84] decreased mortality,[79] and acceptable safety outcomes.[66–69,75,78,80,82–84,86] SCIPIO was the first trial using autologous CSC in HF and showed improvement in EF, infarct size, viable tissue, and HF scores.[82] Two-year follow-up of the treated group showed an EF even higher than at 1-year follow-up without adverse effects.[83] STAR-Heart, the largest HF study, demonstrated improved ventricular function with significantly decreased mortality at 5 years.[79]

Some trials did not show significant results,[76,85] while others demonstrated benefits, but no effect on EF.[66,67,74,77,80,84,86] A highly anticipated trial, FOCUS-CCTRN, assessed BMC via transendocardial injection in chronic HF. However, results indicated no significant change in endpoints.[85]

Dilated Cardiomyopathy

There are few trials on dilated cardiomyopathy (DCM) (Table 3).[87,88] These two studies used the same cell type and delivery method. Both demonstrated improved EF.[87,88]

Table 1. Acute Myocardial Infarction (AMI) Major Clinical Trials

Study	Patients (treated/ control)	Cell Type	Route	Time Post-AMI	Imaging Technique	Follow-Up (months)	Outcomes in Treated Group
Strauer[43]	10/10	BMC	IC	5–9 days	LV angiogram, DSE	3	Improved infarct size, volumes & wall motion, safety outcomes, No difference in EF
TOPCARE-AMI[44,45]	29 vs. 30	BMC vs. EPC	IC	< 5 days	LV angiogram, Cardiac MRI	4 & 12	Improved EF by 8 %, infarct size, volumes & wall motion, + safety outcomes
BOOST[46]	30/30	BMC	IC	4–8 days	Cardiac MRI	6 & 18	Transient improved EF by 6.7 %, + safety outcomes
Chen[47]	34/35	MSC	IC	18 days	LV angiogram, Echo	6	Improved EF by 18 %, infarct size, wall motion & LVEDV, + safety outcomes
Fernandez-Aviles[48]	20/13	BMC	IC	12–20 days	Cardiac MRI, LV angiogram	6	Improved EF by 5.8 %, volumes & wall motion, + safety outcomes
Bartunek[49]	19/16	BMC ($CD133^+$)	IC	10–12 days	LV angiogram, SPECT	4	Improved EF by 7 % & wall motion
Ruan[50]	9/11	BMC	IC	< 7 days	Echo	6	Improved EF by 6 %, volumes & + safety outcomes
REPAIR-AMI[51,52]	102/102	BMC	IC	3–7 days	LV angiogram, Cardiac MRI	4, 12 & 24	Improved EF by 5.5 %, volumes & mortality, + safety outcomes
ASTAMI[53]	47/50	BMC	IC	4–7 days	SPECT, Echo, Cardiac MRI	12	+ safety outcomes, no difference in EF
Janssens[54]	33/34	BMC	IC	< 1 day	Cardiac MRI	4	Improved infarct size, No difference in EF, + safety outcomes
Fincell[55]	40/40	BMC	IC	2–6 days	LV angiogram, IVUS, Echo,	6	Improved EF by 7 %, + safety outcomes
Krause[56]	20/0	BMC	Trans-endocardial	10.5 days	Echo, EMM, LV angiogram	6 & 12	Improved electromechanical parameters, Improved EF by 6.8 %, + safety outcomes
REGENT[57]	80 vs. 80/ 40	BMC vs. $CD34^+CXCR4^+$	IC	7 days	LV angiogram, Cardiac MRI	6	No difference in EF or volumes
MYSTAR[58]	60	BMC	IM vs. IC	3–6 weeks vs. 3–4 months	LV angiogram	9–12	Improved EF but no significant difference between groups
Hare[59]	53	MSC (allogeneic)	IV	1–10 days	Echo, Cardiac MRI	12	Improved EF by 5.2 % & volumes, Decreased arrhythmias, + safety outcomes
LateTIME[60]	58/29	BMC	IC	2–3 weeks	Cardiac MRI	6	No difference in EF or volumes
Penn[27]	19/6	MAPC (allogeneic)	Adventitial	2–5 days	Echo	4	Significant improved EF by 12.6 % & volumes, + safety outcomes
APOLLO[61]	9/4	ASC	IC	< 1 day	Cardiac MRI, SPECT	6	Improved EF by 4 %, scar formation, & perfusion defect, + safety outcomes
Osiris[62]	110/110	MSC (allogeneic)	IV	< 7 days	Cardiac MRI	6	Decreased hypertrophy, arrhythmias & re-hospitalizations, + safety outcomes (No mention of EF)
TIME[63,64]	43/24 vs. 36/17	BMC	IC	3 vs. 7 days	Cardiac MRI	6	No difference in EF or effect on LV function
SWISS-AMI[65]	59 vs. 49/ 60	BMC	IC	1 week vs. 4 weeks	Cardiac MRI	Ongoing	No effect on LV function at 4 months

BMC bone marrow-derived cells; IC intracoronary; LV left ventricular; DSE dobutamine stress echocardiogram; EF ejection fraction; EPC endothelial progenitor cells; MRI magnetic resonance imaging; + positive; MSC mesenchymal stem cells; Echo echocardiogram; LVEDV left ventricular end-diastolic volume; SPECT single photon emission computed tomography; IVUS intravascular ultrasound; EMM electromechanical mapping; CXCR4 CXC chemokine receptor type-4; IM intramuscular; IV intravenous; MAPC multipotent adult progenitor cells; ASC adipose-derived stem cells

Cell Type Comparisons

ASC had favorable results in APOLLO and PRECISE. Both trials demonstrated the efficacy of ASC in AMI and left ventricular dysfunction in settings of marked myocardial ischemia.[61,80] Landmark, large-scale trials using BMC showed benefits in neovascularization, ventricular function and remodeling.[12–14] The ACT-34 study demonstrated that EPC mobilization, isolation and injection significantly improved recurrent angina.[81]

One-year results from the largest trial using allogeneic MSC post-AMI showed ventricular benefit, with significant decreases in HF and re-hospitalizations in the treated group.[62] POSEIDON was the first trial to compare safety and efficacy of allogeneic and autologous MSC in HF. Results indicated ventricular improvement, but no significant change in EF in either group. The allogeneic group demonstrated acceptable safety outcomes.[86]

Table 2. Heart Failure (HF) Major Clinical Trials

Study	Patients (treated/ control)	Cell Type	Route	Time Post-MI	Imaging Technique	Follow-Up (months)	Outcomes in Treated Group
Tse[66]	8/0	BMC	Transendocardial	Not reported	SPECT	3	Decreased angina, + safety outcomes, No change in EF
Fuchs[67]	10/0	BMC	Transendocardial	Not reported	SPECT	3	Decreased angina, + safety outcomes, No change in EF
Perin[68]	14/7	BMC	Transendocardial	Not reported	Echo, SPECT	4	Improved EF by 9 % & volumes, + safety outcomes
Stamm[69]	12/0	BMC enriched for $CD133^+$	IM with CABG	1–4 months	SPECT	10	Improved EF by 9 %, Improved perfusion, + safety outcomes
Erbs[70]	13/13	G-CSF mobilized EPC	IC	>7 months	Cardiac MRI	3	Improved EF by 14 % & infarct size
Patel[71]	10/10	BMC enriched for $CD34^+$	IM with CABG	Not reported	Echo, SPECT, LV angiogram	6	Improved EF by 16 %
IACT[72]	18/18	BMC	IC	5 months–8.5 years	LV angiogram	3	Improved EF by 15 % & infarct size
TOPCARE-CHD[73]	28 vs. 24/23	BMC vs. EPC	IC	> 3 months	LV angiogram	3	Improved EF by 2.9 % in BMC group
Hendrikx[74]	10/10	BMC	IM with CABG	2–12 months	Cardiac MRI	4	Improved contractile function, No difference in EF
PROTECT-CAD[75]	19/9	BMC	Transendocardial	Not reported	Cardiac MRI, SPECT	6	Improved EF by 5.4 %, Improved functional class, + safety outcomes
Ang[76]	21 vs. 21/20	BMC	IM vs. IC	> 6 weeks	DSE, Cardiac MRI	6	No difference in EF or scar size
Yao[77]	24/23	BMC	IC	> 4 months	Echo, Cardiac MRI, SPECT	6	Improved diastolic function, No change in EF
CAuSMIC[78]	12/11	SMB	Transendocardial	> 1 month	Echo, Questionnaire	12	Improved viability & functional class, + safety outcomes (EF not studied)
STAR-Heart[79]	191/200	BMC	IC	5–11 years	LV angiogram	5 years	Improved EF by 7.4 %, Decreased mortality
PRECISE[80]	21/6	ASC	Transendocardial	Not reported	MRI, SPECT, Echo	18	Improved infarct size & functional capacity, + safety outcomes, No increase in EF
ACT-34[81]	167/0	CD34+	IM	Not reported	ETT, SPECT, Questionnaire	12	Improved angina frequency & exercise tolerance (EF not studied)
SCIPIO[82,83]	20/13	CSC	IC	Not reported	Echo, Cardiac MRI, Questionnaire	Ongoing	Improved EF by 8.1 % at 1 year & 12.9 % at 2 years, Decreased scar size, Improved functional class, + safety outcomes
CADUCEUS[84]	17/8	CDC	IC	1.5–3 months	Cardiac MRI	6	Improved scar size and contractility, + safety outcomes, No difference in EF
FOCUS-CCTRN[85]	61/31	BMC	Transendocardial	Not reported	SPECT	Ongoing	No difference in LVESV at 6 months (EF was not a pre-specified endpoint)
POSEIDON[86]	15 vs. 15	MSC Allogeneic vs. Autologous	Transendocardial	0.2–32 years	Cardiac CT	13	+ safety outcomes, Improved functional class & ventricular remodeling, No change in EF

HF heart failure; BMC bone marrow-derived cells; SPECT single photon emission computed tomography; + positive; EF ejection fraction; Echo echocardiogram; IM intramuscular; CABG coronary artery bypass graft; G-CSF granulocyte colony stimulating factor; EPC endothelial progenitor cells; IC intracoronary; MRI Magnetic Resonance Imaging; LV left ventricular; DSE dobutamine stress echocardiogram; SMB skeletal myoblasts; ASC adipose-derived stem cells; ETT exercise tolerance testing; CSC cardiac stem cells; CDC cardiosphere-derived cells; MSC mesenchymal stem cells; CT computed tomography

Cell Delivery Comparisons

Intravenous delivery has been shown to be safe in AMI with fewer arrhythmias and improved ventricular function.[59,62] Intracoronary delivery has been used in AMI,[43–55,58,61] HF,[70,72,73,77,79,82–84] and DCM[87,88] trials with safety and efficacy demonstrated. The majority showed improved EF in the treated groups.[44–52,55,61,70,72,73,79,82,83,87,88] Intramyocardial delivery was studied mostly in HF trials, with benefits and safety noted.[69,71,74,81] Results were mixed in terms of EF improvement. Transendocardial delivery was demonstrated as safe and beneficial after AMI[56] with mixed results in the highlighted HF trials, as only two showed improved EF.[68,75] While others demonstrated no effect on EF, there were still benefits.[66,67,78,80,85,86] Using allogeneic multipotent cells via adventitial delivery, Penn et al.[27] demonstrated a significant EF increase compared to results witnessed in other trials. There were no adverse effects or signs of infarction.

Timing Comparisons

Multiple trials showed positive results when administration is within 1 week of an AMI.[27,44–46,50,51,55,59,61,62] However,

Table 3. Dilated Cardiomyopathy (DCM) Major Clinical Trials

Study	Patients (treated/control)	Cell Type	Delivery	Imaging Technique	Follow-Up (months)	Outcomes in Treated Group
ABCD[87]	24/20	BMC	IC	LV angiogram	6	Improved EF by 5.4 % & ESV, Improved functional class
TOPCARE-DCM[88]	33/0	BMC	IC	LV angiogram	3	Improved EF by 2.2 %

BMC bone marrow-derived cells; IC intracoronary; LV left ventricular; EF ejection fraction; ESV end-systolic volumes

few studies have primarily assessed optimal timing. LateTIME showed negative results at 2–3 weeks.[60] MYSTAR showed short-term increased EF, but no significant differences between treatment at 3–6 weeks and 3–4 months.[58] TIME, comparing BMC delivered on day 3 and day 7 after AMI, aimed to determine optimal timing.[63] Results showed no significant recovery benefit on ventricular function in either timing group.[64] SWISS-AMI assessed BMC delivery at 1 week versus 3–4 weeks after AMI. Although not yet published, announced results revealed no improvement in ventricular function in either timing group compared with a control group at 4 months.[65]

Benefits and Safety

Tables 1, 2 and 3 show that various cell types have been shown to improve cardiac function. There were less re-infarctions, death, or HF hospitalizations in cell treated groups.[13] The EF increase is modest, sometimes transient, and less than expected compared to animal models (Figs. 1a

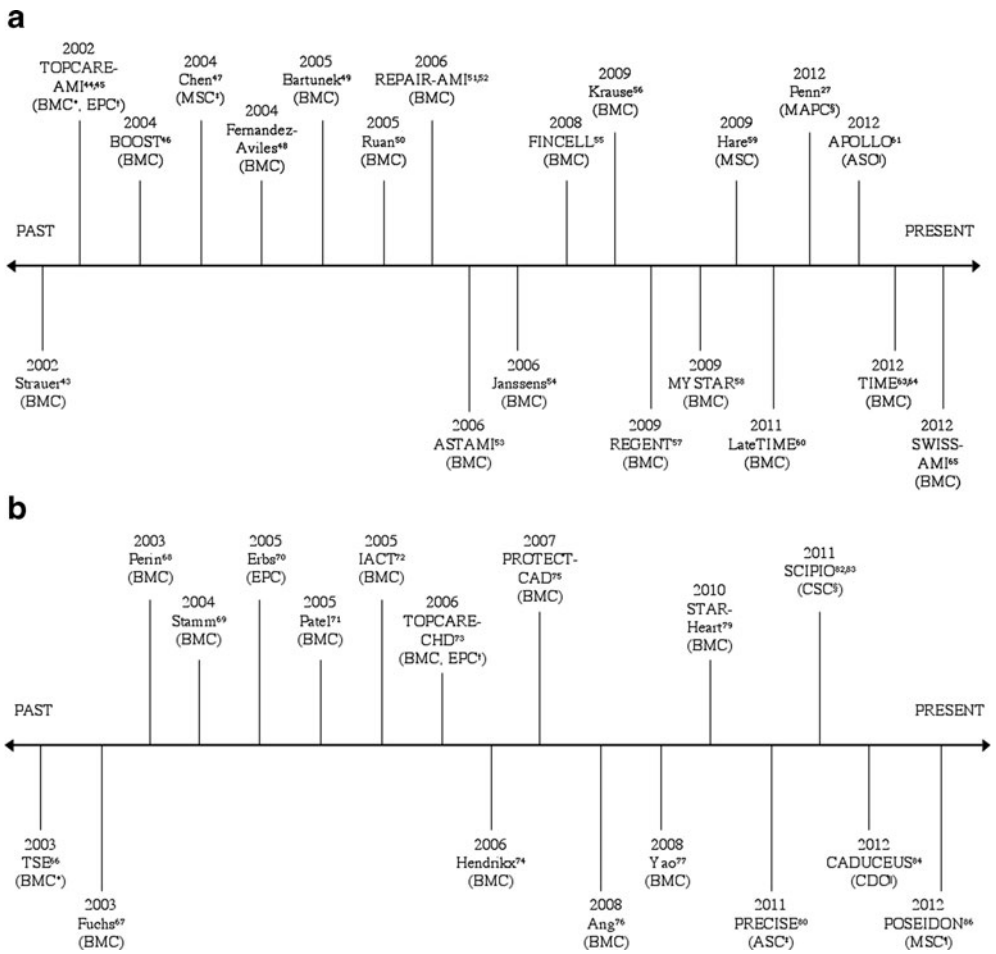

Figure 1. a Timeline of Major Positive and Negative Acute Myocardial Infarction Clinical Trials. b Timeline of Major Positive and Negative Heart Failure Clinical Trials. Trials above horizontal line represent positive trials that resulted in increased ejection fraction in treatment group over control group. Trials below horizontal line represent negative trials that resulted in unchanged or no difference in ejection fraction between treatment and control groups. Each trial is identified with the specific cell type used. *=Bone Marrow Derived Cells; †=Endothelial Progenitor Cells; ‡=Mesenchymal Stem Cells; §=Multipotent Adult Progenitor Cells; ‖=Adipose Derived Stem Cells.

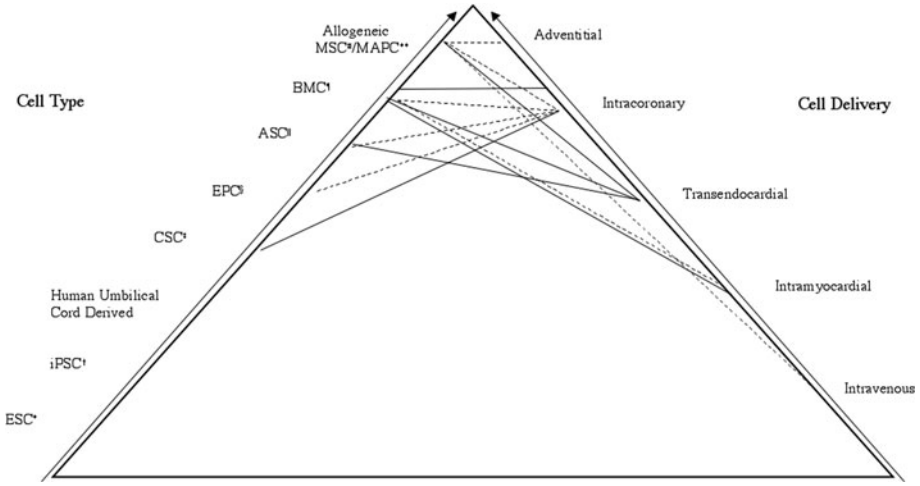

Figure 2. Clinical Approaches Displaying Cell Types and Deliveries. Lines connecting cell type and delivery method show which combinations have been used in major trials to date. Dashed lines represent acute myocardial infarction trials. Solid lines represent heart failure trials. Progression up the pyramid reveals the more promising and useful clinical approaches. *=Embryonic Stem Cells; †=induced Pluripotent Stem Cells; ‡=Cardiac Stem Cells; §=Endothelial Progenitor Cells; ‖=Adipose-derived Stem Cells; ¶=Bone Marrow Derived Cells; #=Mesenchymal Stem Cells; **=Multipotent Adult Progenitor Cells

and b).[12–14] Inconsistent results are attributable to the lack of standardization among trials in cell types used, dosages, delivery methods, timing, and follow-up.[7] Lastly, measured endpoints vary between studies.

Stem cell therapy has been reasonably safe. Inflammation, tumor formation, arrhythmias, and restenosis were not increased in the trials in which they were measured.[12–14] Use of adult allogeneic and autologous cells is considered to be without ethical concerns.[29] The only known contraindications for use of autologous cells include chronic infectious diseases, malignant solid tumors, and diseases of the bone marrow and stem cells.[11]

Table 4. Major Ongoing Clinical Trials

Trial	Condition	Cell Type	Route	Time Post-MI	Outcomes
REGEN-AMI[89]	AMI	BMC	IC	< 6 h	Recruiting—Assessing safety & efficacy in anterior AMI
Allogeneic MPCs after AMI[90]	AMI	MPC (Allogeneic)	Transendocardial	2–10 days	Recruiting—Assessing safety & efficacy
Prochymal after AMI[91]	AMI	MPC (Allogeneic)	IV	< 7 days	Ongoing—Assessing LVESV
ADVANCE[92]	AMI	ASC	IC	> 1 day	Recruiting—Assessing safety & efficacy
BAMI[93]	AMI	BMC	IC	< 5 days	Not yet recruiting—Assessing safety and mortality reduction
ALLSTAR[94]	AMI	CDC (Allogeneic)	IC	1–12 months	Recruiting—Assessing safety and efficacy
REVITALIZE[95]	HF	MSC	IC	Not specified	Ongoing—Assessing safety & feasibility
PERFECT[96]	HF	BMC CD133+	Transendocardial with CABG	Not specified	Recruiting—Assessing efficacy
REGEN-IHD[97]	HF	BMC	G-CSF mobilization vs. IC vs. Transendocardial	Not specified	Ongoing—Comparing three different delivery routes
IMPACT-CABG[98]	HF	CD133+	Transendocardial with CABG	Not specified	Recruiting—Assessing efficacy
STOP-HF[99]	HF	JVS-100	Endomyocardial	Not specified	Ongoing—Assessing safety and efficacy
REGENERATE-DCM[100]	DCM	BMC+G-CSF	IC	Not applicable	Recruiting—Assessing efficacy & safety
Long-Term Evaluation of Patients Receiving BMC Administration for Heart Disease[101]	AMI, HF, DCM	BMC	IC	Not specified	Recruiting—Assessing long-term effects up to 10 years after transplantation

AMI acute myocardial infarction; BMC bone marrow-derived cells; IC intracoronary; MPC mesenchymal precursor cells; IV intravenous; LVESV left ventricular end-systolic volumes; ASC adipose-derived stem cells; CDC cardiosphere-derived cells; HF heart failure; MSC mesenchymal stem cells; CABG coronary artery bypass graft; G-CSF granulocyte colony stimulating factor; DCM dilated cardiomyopathy

Table 5. Abbreviations in Order They Appear in Text

CAD	Coronary artery disease
AMI	Acute myocardial infarction
PCI	Percutaneous coronary intervention
HF	Heart failure
EF	Ejection fraction
CSC	Cardiac stem cells
BMC	Bone marrow mononuclear cells
ESC	Embryonic stem cells
iPSC	Induced pluripotent stem cells
ASC	Adipose-derived stem cells
EPC	Endothelial progenitor cells
HSC	Hematopoietic progenitor stem cells
MSC	Mesenchymal stem cells
MAPC	Multipotent adult progenitor cells
CABG	Coronary artery bypass graft
SDF-1	Stromal cell-derived factor-1
CXCR4	CXC chemokine receptor type 4
DCM	Dilated cardiomyopathy

IMPLICATIONS FOR PRACTICE

Figure 2 displays lines connecting cell types and delivery methods showing combinations used in major trials to date. Arguably, progression up the pyramid reveals the more promising and useful approaches most likely to be applicable in practice. Clinicians should convey to patients that although stem cell therapy is novel, trials demonstrate benefits supplementing conventional treatment. It should be emphasized that therapy appears to be safe and without ethical concerns. Patients should be advised that optimal cell type and delivery have not yet been determined so there are a variety of different methods. Additional research and study participants are needed; primary care providers are essential in identifying and referring patients who may be suitable candidates.

FUTURE RESEARCH

Questions remain unanswered regarding optimal cell type, dosing, timing, and delivery. Future studies will focus on these areas. Ultimately, standardization of variables and procedure protocols will be necessary for adequate comparison. More effective treatment development will focus on better understanding of cellular therapy mechanisms. Increasing knowledge of engraftment and paracrine involvement will lead to advanced therapies that increase cell survival. Future therapy may deliver certain paracrine proteins instead of cells. Use of biomaterials and new imaging techniques will become increasingly important.

Selected ongoing AMI, HF, and DCM trials are listed in Table 4.[89–101] A trial with great potential is BAMI, delivering autologous BMC via intracoronary infusion 5 days post-AMI. This aims to determine whether there are mortality benefits to stem cell therapy shortly after AMI. It will be the largest trial using stem cells post-AMI, involving over 3,000 patients from 11 countries.[93] REGEN-IHD focuses on addressing the optimal delivery by comparing three different routes in HF.[97] STOP-HF uses endomyocardial injection of a DNA plasmid encoding SDF-1 to recruit stem cells to peri-infarct regions to improve ventricular function in HF patients.[99]

SUMMARY

Stem cell therapy is an exciting and revolutionary treatment for heart disease. Numerous clinical trials demonstrated improved ventricular function with positive safety outcomes. Although modest, benefits noted after cell transplantation have surpassed those with conventional treatment. If the next decade brings as much significant advancement as this past one, cell therapy may realistically become standard treatment for heart disease (Table 5).

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Corresponding Author: *Kevin H. Silver, MD, FACC, FSCAI, FASNC; Summa Physician Incorporated, Summa Health System, 95 Arch St. Suite 300, Akron, OH 44304, USA (e-mail: ksilver@neocs.org).*

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