

CLINICAL RESEARCH

Clinical Trials

Cardiopoietic Stem Cell Therapy in Heart Failure

The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) Multicenter Randomized Trial With Lineage-Specified Biologics

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Objectives

This study sought to evaluate the feasibility and safety of autologous bone marrow–derived and cardiogenically oriented mesenchymal stem cell therapy and to probe for signs of efficacy in patients with chronic heart failure.

Background

In pre-clinical heart failure models, cardiopoietic stem cell therapy improves left ventricular function and blunts pathological remodeling.

Methods

The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) trial, a prospective, multicenter, randomized trial, was conducted in patients with heart failure of ischemic origin who received standard of care or standard of care plus lineage-specified stem cells. In the cell therapy arm, bone marrow was harvested and isolated mesenchymal stem cells were exposed to a cardiogenic cocktail. Derived cardiopoietic stem cells, meeting release criteria under Good Manufacturing Practice, were delivered by endomyocardial injections guided by left ventricular electromechanical mapping. Data acquisition and analysis were performed in blinded fashion. The primary endpoint was feasibility/safety at 2-year follow-up. Secondary endpoints included cardiac structure/function and measures of global clinical performance 6 months post-therapy.

Results

Mesenchymal stem cell cocktail–based priming was achieved for each patient with the dose attained in 75% and delivery without complications in 100% of cases. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic cell therapy. Left ventricular ejection fraction was improved by cell therapy (from $27.5 \pm 1.0\%$ to $34.5 \pm 1.1\%$) versus standard of care alone (from $27.8 \pm 2.0\%$ to $28.0 \pm 1.8\%$, $p < 0.0001$) and was associated with a reduction in left ventricular end-systolic volume (-24.8 ± 3.0 ml vs. -8.8 ± 3.9 ml, $p < 0.001$). Cell therapy also improved the 6-min walk distance ($+62 \pm 18$ m vs. -15 ± 20 m, $p < 0.01$) and provided a superior composite clinical score encompassing cardiac parameters in tandem with New York Heart Association functional class, quality of life, physical performance, hospitalization, and event-free survival.

Conclusions

The C-CURE trial implements the paradigm of lineage guidance in cell therapy. Cardiopoietic stem cell therapy was found feasible and safe with signs of benefit in chronic heart failure, meriting definitive clinical evaluation. (C-Cure Clinical Trial; NCT00810238) (J Am Coll Cardiol 2013;61:2329–38) © 2013 by the American College of Cardiology Foundation

Acute management of myocardial infarction has reduced early mortality, precipitating the unintended consequence of increased prevalence of chronic heart failure among survivors

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**Abbreviations
and Acronyms**

CI = confidence interval
ESV = end-systolic volume
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction

(1,2). As the myocardium has a limited intrinsic capacity to restore organ function after ischemic injury (3–5), multimodal treatments are used to alleviate symptoms and improve clinical status in heart failure. Current therapies target impaired contractility and hemodynamic decompensation without, however, treating the parenchymal loss that underlies the development and progression of disease (6). To address this unmet need, stem cell therapy is increasingly considered as a potential means to fortify innate mechanisms of regeneration (7–11). Stem cells traditionally isolated from bone marrow, a readily used source, demonstrate excellent safety in the clinical testing, yet patient-to-patient variability in repair outcome remains a recognized limitation necessitating further optimization (12–18).

By processing myocardial tissue excised during cardiac surgery or obtained by endovascular biopsy, it is now possible to derive resident stem cell populations (19,20). This advance provides the prospect of anatomically matching the regenerative cell source with the target organ. Such an approach is, however, hampered by the invasive nature of heart tissue sampling and the limited quantity of starting material. Orienting bone marrow stem cells for cardiac repair would eliminate the need for the patient to undergo myocardial harvest, rendering this accessible and renewable compartment an alternative to heart tissue. Recently, hallmark traits of cardiac development were successfully triggered within bone marrow-derived mesenchymal stem cells, establishing the first human scalable lineage-specified phenotype derived without heart tissue harvest (21–24). Pre-clinical testing demonstrated that cardiopoietic stem cells reliably repair the failing myocardium, providing the foundation for clinical translation (22).

The ensuing C-CURE clinical trial addressed the feasibility and safety of autologous bone marrow-derived cardiopoietic stem cell therapy and assessed the signs of efficacy

in patients with ischemic cardiomyopathy. This first-in-class biotherapeutics introduces a new strategy to optimize regenerative intervention in heart failure.

Methods

Study design and patient population. The multicenter C-CURE clinical trial was approved by competent authorities and ethics committees as a prospective, randomized, open, and parallel 2-arm study in a stable heart failure population with a history of myocardial infarction (Fig. 1). The primary study endpoint was feasibility and safety at 2-year follow-up. Secondary endpoints, assessed at 6 months, included cardiac structure and function in tandem with measures of global clinical performance. The defining inclusion criterion was chronic heart failure of ischemic origin with impaired left ventricular ejection fraction (LVEF) (15% to 40%) (Online Table 1). Key inclusion criteria were age (18 years of age and older and younger than 75 years of age), ischemic heart disease, and management according to guidelines. Patients with an ischemic event at least 2 months before recruitment were eligible. At least 2 months before enrollment, patients needed to be optimally managed and revascularized. If patients were not already fitted with an implantable cardioverter-defibrillator (ICD), one was provided. Major exclusion criteria were previous cell therapy, myocardial infarction or revascularization within 2 months before enrollment, ventricular aneurysm, and left ventricular wall thickness <5 mm in the target territory documented by echocardiography after patient consent and before randomization (Online Table 1). Patients with moderate to severe aortic valve disease or left ventricular thrombus were excluded, as were patients who received a biventricular pacemaker within 6 months. Patients having a biventricular pacemaker for >6 months and under stable pacing were permitted to join the study. Patients (N = 319) were screened at 9 clinical sites in Europe (Belgium, Serbia, and Switzerland). The trial was conducted from January 2009 to January 2012.

Randomization. In total, 48 patients were randomized through a site-independent centralized process after exclusion of 271 patients (of whom 249 did not meet inclusion/exclusion criteria, 17 refused to participate, and 5 provided consent after the recruitment cutoff date). Baseline data demonstrated similar distribution of age, sex, body mass index, prevalence of cardiovascular risk factors, and cardiac disease history in study groups (Table 1). No difference in medications or hemodynamics was observed. At the time of consent, 1 patient refused participation, and on randomization, 2 patients were excluded because they did not meet clinical inclusion criteria and no bone marrow was harvested, 2 were excluded because they did not meet bone marrow inclusion criteria and declined repeat bone marrow harvest, and 7 were excluded as quality control inclusion criteria were not met and declined repeat bone marrow harvest (Fig. 1). Patients in the control arm received standard of care comprising a beta-blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic with

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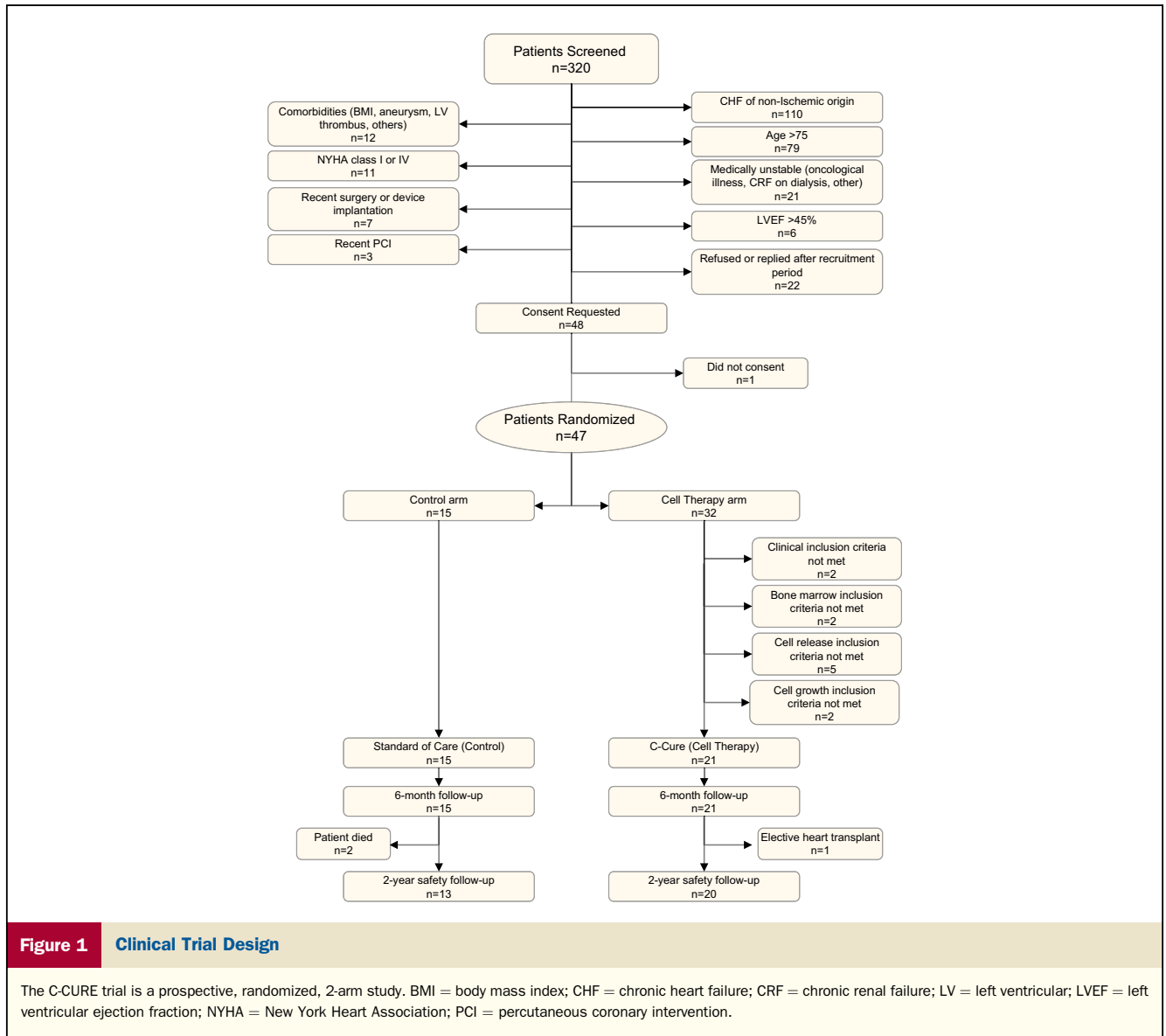


Figure 1 Clinical Trial Design

The C-CURE trial is a prospective, randomized, 2-arm study. BMI = body mass index; CHF = chronic heart failure; CRF = chronic renal failure; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

dosing and schedule tailored for maximal benefit and tolerability in accordance with practice guidelines for heart failure management (25). Patients in the cell therapy arm received, in addition to standard of care, bone marrow-derived cardiopoietic stem cells meeting quality release criteria. An independent centralized core laboratory masked to study arm assignment and chronology of clinical evaluation provided data analysis.

Cell production. Cell production consisted of mesenchymal stem cell isolation and expansion, lineage specification, and cardiopoietic cell expansion. Specifically, human bone marrow was harvested from the iliac crest with quality control ensuring temperature control and sterility during transportation between sites of collection and manufacturing. Abiding by Good Manufacturing Practice, bone marrow was cultured at 37°C/5% CO₂ in 175-cm² flasks to purify mesenchymal stem cells. Donor serology screening was

performed for human immunodeficiency virus types 1 and 2, syphilis, and hepatitis B and C. After 24 h, nonadherent bone marrow and cellular debris were discarded, and adherent mesenchymal stem cells were washed with phosphate-buffered saline solution. A 1-to-1 passage (P0) was performed to dissociate colony-forming units and allow for expansion for up to 6 days in a culture medium (high-glucose Dulbecco's Modified Eagle's Medium) supplemented with 5% human pooled platelet lysate media (Mayo Clinic Blood Bank) (26) to generate a monolayer whereby 50 × 10⁶ cells were obtained. Lineage specification was achieved by mesenchymal stem cell exposure to a cardiogenic cocktail regimen triggering expression and nuclear translocation of cardiac transcription factors (Online Fig. 1) while maintaining clonal proliferation (21,22,27). Passage P1 marked the start of cardiogenic cocktail treatment in which cells were cultured for 5 days in 5% platelet lysate-supplemented

Table 1 Patient Demographics, Cardiac History, and Medication Profile in Control and Cell Therapy Cohorts

	Control	Cell Therapy	p Value
Age, yrs	59.5 ± 8.0	55.7 ± 10.4	0.82
Sex, M/F	22/2	20/1	0.63
Family history CAD	12 (50)	16 (73)	0.071
Smoking			
Former	18 (75)	10 (48)	0.059
Current	5 (21)	6 (28)	0.81
Arterial hypertension	13 (54)	10 (45)	0.66
Diabetes mellitus	8 (33)	4 (18)	0.28
On diet	3 (13)	1 (5)	0.36
NIDDM	2 (8)	2 (9)	0.89
IDDM	3 (13)	1 (5)	0.36
Hypercholesterolemia	24 (100)	17 (77)	0.025
On diet	1 (4)	0 (0)	0.34
On statins	13 (96)	17 (77)	0.053
Cardiac history			
ICD implant	8 (33)	11 (50)	0.20
CRT implant	2 (8)	1 (4.5)	0.63
PCI	21 (88)	18 (82)	0.86
CABG	8 (33)	5 (23)	0.48
Myocardial infarction	23 (96)	21 (100)	0.34
Q-wave	15 (86)	11 (73)	0.49
Other cardiac surgery	2 (8)	2 (9)	0.89
Sustained VT or VF	9 (38)	4 (18)	0.17
Atrial fibrillation	3 (13)	4 (18)	0.55
Medication profile			
ACE inhibitor	19 (79)	18 (82)	0.57
ATR1-blocker	4 (20)	3 (14)	0.83
Beta-blocker	19 (79)	20 (91)	0.11
Diuretic agent	19 (79)	18 (82)	0.57
Antiplatelet agent	23 (96)	20 (91)	0.92
Statins	23 (96)	18 (82)	0.23
Hypoglycemic agent	4 (17)	3 (14)	0.83
Antiarrhythmic agent	4 (20)	9 (41)	0.053
Calcium antagonist	1 (4)	3 (14)	0.23
Nitrate or molsidomine	7 (29)	3 (14)	0.23

Values are mean ± SD, n, or n (%).

ACE = angiotensin-converting enzyme; ATR1-blocker = angiotensin receptor-1 blocker; CABG = coronary artery bypass graft; CAD = coronary artery disease; CRT = cardiac resuscitation therapy; ICD = implantable cardioverter-defibrillator; IDDM = insulin-independent diabetes mellitus; M/F = male/female; NIDDM = noninsulin-dependent diabetes mellitus; PCI = percutaneous coronary intervention; VF = ventricular fibrillation; VT = ventricular tachycardia.

high-glucose Dulbecco's Modified Eagle's Medium containing cardiogenic growth factors (i.e., 2.5 ng/ml transforming growth factor-β, 5 ng/ml bone morphogenetic protein 4, 5 ng/ml activin A, 10 ng/ml fibroblast growth factor 2, 100 ng/ml cardiotrophin, and 1 U/ml α-thrombin, synergized by a diaminopyrimidine (100 nM 2-[(4-methoxyphenyl)amino]-4-pyrimidinyl). Cell density was 4,000 cells/cm² during mesenchymal stem cell culture and 1,500 cells/cm² during cardiopoietic induction. Passages P2 and P3 marked the end of cardiogenic cocktail treatment followed by expansion to yield 600 × 10⁶ to 1,200 × 10⁶ cells. Harvest involved final trypsinization, followed by concentration in a preservation solution (HypoThermosol-FRS, BioLifeSolutions, Bothell, Washington) for optimized storage and transportation within a biocompatible container.

Cells were centrally manufactured at a single accredited Good Manufacturing Practice facility supporting trial sites. Cell doses concentrated in the hypothermic preservation solution were cool-packaged in biocompatible containers fitted with a thermometer capable of real-time temperature monitoring to ensure environmental stability during transport. In parallel, cell aliquots were maintained in the central core facility under identical conditions with cellular viability confirmed immediately before administration. Cells packaged for transportation were transplanted within 72 h of derivation.

Release criteria. The initial step in release ensured that the stem cell yield obtained after cocktail exposure met the pre-specified dose range required for inclusion in the cell therapy arm, as documented for each patient (Online Fig. 2). Consistency and quality control were carried out under standard operating procedures to ensure purity, identity, and homogeneity, along with sterility (Online Table 2) (28). Purity assessment for each patient was documented by comparing mesenchymal stem cells after cocktail exposure with untreated counterparts using quantitative polymerase chain reaction analysis of CD34, FABP4, osteocalcin, Sox9, and Nestin corresponding to nonmesenchymal, adipose, osteoblast, chondrocyte, and neuronal progenitors, respectively, along with MYH7 indicating loss of multipotency (Online Fig. 3). Impurity threshold was set to detect 1 alternate cell lineage in 1,000,000 cells with a 2-fold gene induction. Release criteria for cell identity included quantitative polymerase chain reaction assessment with homogeneity validated by immunofluorescence documentation of MEF2c nuclear translocation in >140 cells for each patient (Online Figs. 4 to 10). The immunofluorescence threshold of release was set at a minimum of 85% cells, demonstrating a >2-fold induction of MEF2c in the nucleus versus cytosol, documented for each patient (Online Fig. 11). Negative controls included unguided mesenchymal stem cells demonstrating low nucleus/cytosol MEF2c ratio (Online Fig. 12). Sterility confirmation documented products as free of viable organisms, endotoxin, and mycoplasma. Production and release, conforming to imposed standards, required 4 to 6 weeks of processing.

Clinical protocol. Cardiopoietic stem cells were administered endoventricularly using the NOGA XP System with an 8-F Myostar catheter (Biologics Delivery Systems, Cordis Corporation, Hialeah, Florida) (29,30). Electromechanical mapping defined areas of viable and dysfunctional myocardium characterized by univoltage potential ≥4 mV and reduced longitudinal linear shortening. Cells were injected into mapped areas over 1 min per injection, with an average of 18 injections per patient (Fig. 2). Care was taken to spread injections homogeneously, avoiding apical region and scar. Patient follow-up was carried out per protocol. The ICD threshold to detect ventricular tachycardia was set for rates between 150 to 180 beats/min for fast ventricular tachycardia between 180 and 220 beats/min, and for ventricular fibrillation >220 beats/min. Two-dimensional transthoracic echocardiography was performed in accordance with American

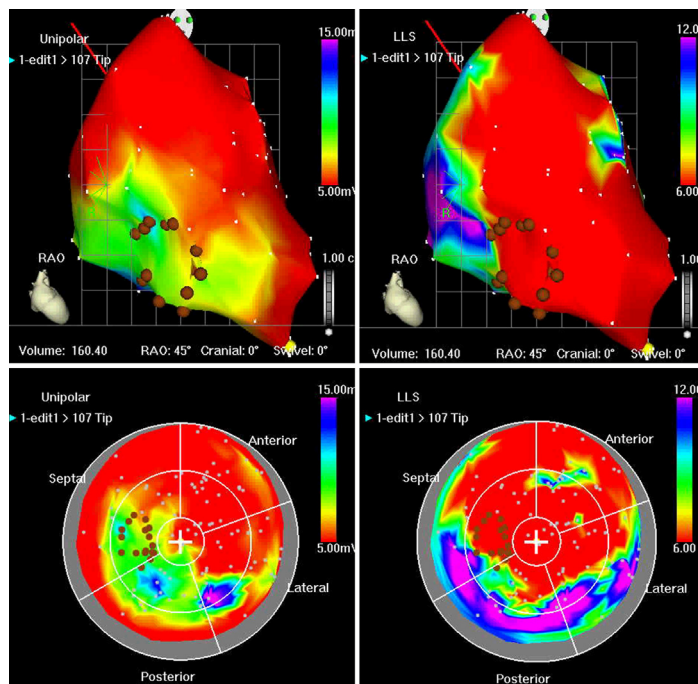


Figure 2 Intramyocardial Navigation and Mapping for Cell Delivery

Endomyocardial delivery of bone marrow–derived cardiopoietic stem cells using NOGA electromechanical guidance in the first patient enrolled in the C-CURE trial. Upper color coded panels show a right anterior oblique projection of unipolar voltage (left) and linear local shortening (LLS) maps (right). (Lower left and right) A bulls-eye view of electrical and mechanical maps. Cells were delivered (brown dots) into areas of dysfunctional yet viable myocardium characterized by a voltage >4 mV (green color on the unipolar map) with reduced LLS (red color on the LLS map).

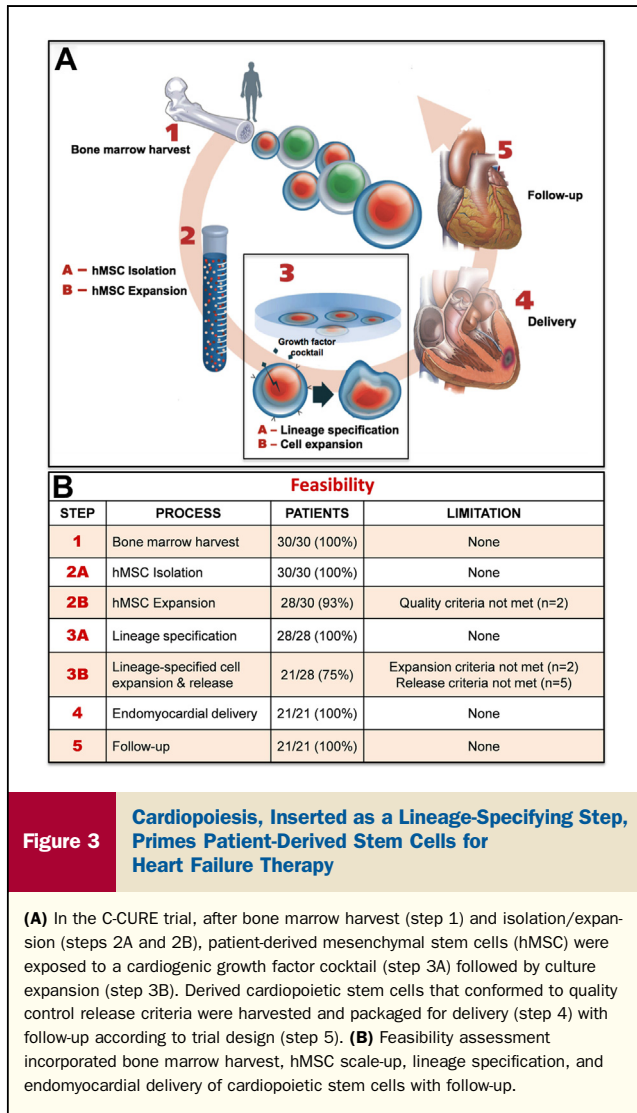
Society of Echocardiography guidelines. Left ventricular dimensions were measured from parasternal long- or short-axis views in tandem with apical 4-chamber, long-axis, and 2-chamber views. Electrocardiographic gating allowed left ventricular volumetric measurements at end-diastole and end-systole. LVEF was calculated using the biplane summation of disks method (31). A 6-min walk test, a parameter of exercise capacity, was performed according to American Thoracic Society guidelines, recording the distance walked in a 6-min period along a >30 -m track (32). Spiroergometry was performed per site practice.

Data analysis. Data were recorded using case report forms, and accuracy was verified by medical monitors with source documentation. Feasibility of intervention incorporated assessment of cell expansion, manufacturing, and phenotype release, in addition to catheter-based delivery. Safety was assessed from ICD monitoring of cardiac arrhythmia, and recording of adverse events was reviewed by an independent data and safety monitoring board. Efficacy signs included left ventricular structure/function and clinical performance. A composite clinical score (33) was created in an exploratory fashion to discern the impact on heart failure, and integrated New York Heart Association functional class, quality of life, exercise and peak oxygen capacity, left ventricular dimension, and ejection fraction, along with hospitalization and mortality. For each parameter, a score of +1, 0, or –1 was

given for improvement, no change, or deterioration, respectively. Thresholds were set as change of 10 ml in left ventricular end-diastolic/end-systolic volume (ESV), 5 g/m^2 in left ventricular mass index, 5% in ejection fraction, 20 m in 6-min walking distance, 2 ml/kg/min VO_2max , 10 points in Minnesota Living With Heart Failure Questionnaire, 1 functional class in New York Heart Association classification, and presence/absence of hospitalization and mortality. Baseline parameters and efficacy parameters were compared using the chi-square or Fisher exact test, as appropriate. Composite clinical score was compared using independent Student *t* tests; $p < 0.05$ was considered statistically significant. Data in text are presented with 95% confidence intervals and in figures as mean \pm SE unless otherwise indicated.

Results

Feasibility. Bone marrow harvest and mesenchymal stem cell isolation was achieved in 100% of cases (Fig. 3, steps 1 and 2A). Initial mesenchymal stem cell expansion was attained with a 93% success rate ($n = 28$) (Fig. 3, step 2B). Guidance of mesenchymal stem cells was successful in all lots passing initial expansion (Fig. 3, step 3A). Manufacturing according to predefined release criteria for cell yield and purity produced cardiopoietic stem cells at a dose $>600 \times 10^6$ cells with 75% success ($n = 21$) (Fig. 3, step 3B). All lots passed karyotype



evaluation. Cardiopoietic stem cells were successfully delivered by endoventricular injections, under electromechanical guidance, in all patients receiving cell therapy (Figs. 2 and 3B, step 4).

Procedural safety. The elapsed period between time of infarction and cell delivery was on average 1,540 days with a minimum of 192 days and a maximum of 7,515 days. The mean number of delivered cells was 733×10^6 (dose range, $605 \times 1,168 \times 10^6$ cells extrapolated from pre-clinical experience) administered in 9 to 26 injections in 4.5 to 12.7 ml. Femoral access was typically used. In 1 patient, brachial access was required due to tortuosity of lower limb arteries (34). In 1 patient, the procedure was accompanied by ventricular tachycardia resolved by cardioversion. An additional patient with pre-existing ophthalmic migraines experienced blurred vision after intervention (Table 2). Overall, cell delivery was well tolerated without relevant complications.

Adverse events. No subject was discontinued from the study due to an adverse event. There was no evidence of systemic toxicity induced by cardiopoietic stem cells. There was no

evidence of uncontrolled tissue growth determined by serial echocardiography. Cell administration was well tolerated with no difference in cardiac or noncardiac events between study groups (Table 2). In the control group, 2 patients died at 18 and 20 months post-randomization due to heart failure deterioration and sudden cardiac death, respectively (Table 2). In the cell therapy group, in 1 patient who underwent elective cardiac transplantation at 21 months post-randomization, post-operative sepsis developed, and the patient died (Table 2). Throughout the 24-month follow-up period, no event was reported with a definite or probable relationship to cell therapy. A possible relationship to cell administration was reported in a patient with ventricular tachycardia documented before study enrollment who had recurrence presenting with slow monomorphic episodes at 98 and 182 days after cell delivery that resolved on cardioversion. Per protocol, ICD programming was applied in 14 control and 12 cell-treated patients. In controls, ICD programming was personalized in 4 patients from study initiation, and in the other 6, programming was changed on follow-up at the discretion of the treating cardiologist or due to arrhythmia. In the cell therapy group, 1 patient had personalized ICD programming at study start, whereas in 8, programming was changed by the treating cardiologists. Serial ICD readings revealed a comparable incidence of newly occurring ventricular tachycardia and ventricular fibrillation in either group over the 2-year observation period (Table 2).

Efficacy signs. Cardiac function, assessed in each individual by echocardiography at 6 months (Fig. 4A), demonstrated a 7% increase in the LVEF with cell therapy from 27.5% (95% confidence interval [CI]: 25.5% to 29.5%) to 34.5% (95% CI: 32.5% to 36.6%) ($n = 21$, $p < 0.0001$) (Fig. 4B). The LVEF was unchanged from 27.8% (95% CI: 25.8% to 29.8%) to 28.0% (95% CI: 26.1% to 30.6%) in the control group ($n = 15$) (Figs. 4A and 4B). Cell therapy significantly reduced the ESV by -24.8 ± 3.0 ml (95% CI: -30.7 ml to -18.9 ml) compared with -8.8 ± 3.9 ml (95% CI: -16.4 ml to -1.2 ml) in the control group ($p < 0.001$) (Fig. 4C). Reduction in left ventricular end-diastolic volume was -18 ml (95% CI: -25.5 ml to -10.5 ml) versus -9 ml (95% CI: -15.0 ml to -3.6 ml) in the cell therapy group versus the control group, respectively (Fig. 4C). The percentage of change in the LVEF, at 6 months, as a function of the ESV (Fig. 4D) or end-diastolic volume (Fig. 4E) percentage of change indicated that cardiopoietic cell therapy extended the therapeutic benefit of standard of care for cardiac function and structure (35). The 6-min walk test, an index of cardiovascular performance, significantly improved from 394 m (95% CI: 346 m to 442 m) to 456 m (95% CI: 391 m to 521 m) in cell-treated patients, whereas it decreased from 419 m (95% CI: 382 m to 456 m) to 404 m (95% CI: 350 m to 458 m) in the control group ($p < 0.01$), with a difference of 77 m favoring cell therapy at 6 months (Fig. 5A). The Minnesota Living With Heart Failure Questionnaire (36), a measure of health-related quality of life, improved with cell therapy albeit without reaching significance compared with the control group (Fig. 5B). To assess the percentage of patients who demonstrated

Table 2 Safety Evaluation

Cardiac Adverse Events						
Timing Group	Prior Control	Prior Cell Rx	Post Control	Post Cell Rx	New Event Control	New Event Cell Rx
Death	0 (0%)	0 (0%)	2 (8%)	0 (0%)	2 (8%)	0 (0%)
Elective transplant	0 (0%)	0 (0%)	0 (0%)	1 (5%)*	0 (0%)	1 (5%)*
Cardiac disorder	2 (8%)	5 (24%)	15 (62%)	16 (76%)	13 (54%)	11 (52%)
SV arrhythmia	1 (4%)	3 (14%)	7 (29%)	9 (43%)	6 (25%)	6 (28%)
Ventricular fibrillation	0 (0%)	0 (0%)	1 (4%)	1 (5%)	1 (4%)	1 (5%)
Ventricular tachycardia	1 (4%)	2 (10%)	8 (33%)	6 (20%)	7 (29%)	4 (19%)

Medical Adverse Events				
	Control	Cell Therapy	Relation to Cell Therapy	p Value
Gastrointestinal disorders	1 (4.2%)	2 (9.6%)	Not related	0.47
Upper abdominal pain	1 (4.2%)	1 (4.8%)		
Inguinal hernia		1 (4.8%)		
Retroperitoneal hematoma				
General disorders	5 (21%)		Not applicable	0.026
Chest pain	2 (8.4%)			
Fatigue	1 (4.2%)			
General deterioration	1 (4.2%)			
Pyrexia	1 (4.2%)			
Hepatobiliary disorder	0	1 (4.8%)	Not related	0.28
Cholecystitis		1 (4.8%)		
Nervous system disorder	1 (4.2%)	1 (4.8%)	Possible	0.92
Blurred vision	1 (4.2%)	1 (4.8%)		
Subdural hematoma				
Musculoskeletal disorder	1 (4.2%)			0.34
Intervertebral disk hernia	1 (4.2%)			
Respiratory, thoracic and mediastinal disorder	3 (12.6%)	5 (24%)	Not related	0.32
Bronchial irritation	1 (4.2%)	1 (4.8%)	Not related	
Pulmonary Edema	1 (4.2%)	1 (4.8%)	Not related	
COPD	1 (4.2%)	1 (4.8%)	Not related	
Cough		1 (4.8%)	Not related	
Dyspnea		1 (4.8%)		
Hemoptysis				
Surgical and medical procedures	1 (4.2%)	1 (4.8%)	Not related	0.92
Cholecystectomy	1 (4.2%)	1 (4.8%)	Not related	
Knee arthroplasty				
Peripheral vascular disorder	1 (4.2%)		Not applicable	0.34
Claudication	1 (4.2%)			

Analysis revealed no statistical significance between groups ($p > 0.05$). *Death resulted as a complication following elective heart transplantation.

improvement or deterioration for each monitored endpoint, the impact of standard of care versus standard of care plus cardiopoietic stem cells was quantified on left ventricular structure and function, quality of life, exercise capacity, peak oxygen uptake, New York Heart Association functional class, along with heart failure-related hospitalization and cardiac mortality (Fig. 5C, Online Table 3). The improvement achieved with standard of care alone was most affected with the addition of cell therapy for the LVEF, ESV, and the 6-min walk (Fig. 5C, Online Table 3). Post-hoc analysis, including a composite clinical score integrating outcome measures (33), corroborated the benefit of cell therapy (Online Fig. 13).

Discussion

The C-CURE clinical trial assessed cardiopoietic stem cell intervention as an adjunct to chronic heart failure

management. This is the first application of guided stem cells for targeted regeneration of a failing organ. Lineage priming of bone marrow stem cells from patients with ischemic heart failure was shown to be feasible. Administration of derived autologous cardiopoietic stem cells into the hibernating myocardium of patients with heart failure was safe. The study demonstrated consistent improvement of the LVEF with cardiopoietic stem cell therapy compared with standard of care. By introducing lineage guidance into the cell therapy protocol, the C-CURE trial provides initial clinical evidence of a new approach to cardiovascular regenerative medicine.

To date, clinical studies have used bone marrow stem cells in their native lineage-unspecified state, as unfractionated or purified cell products largely in the setting of acute or subacute myocardial infarction (9–18,35,37–40). The

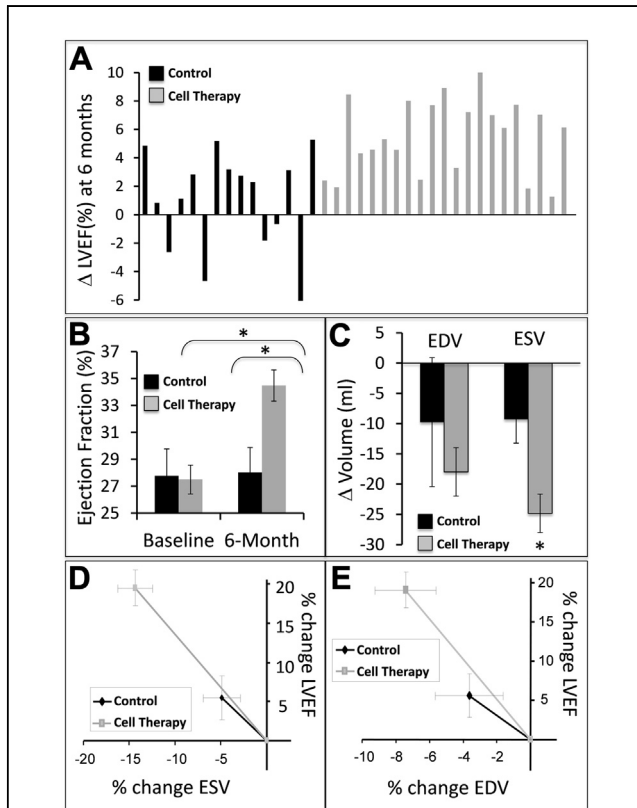


Figure 4 Impact of Cardiopoietic Stem Cell Therapy on Cardiac Function and Structure at 6-Month Follow-Up

(A) Changes in left ventricular ejection fraction (Δ LVEF) for each patient. Control group includes patients who received standard of care alone. The cell therapy group includes patients who received standard of care plus cardiopoietic stem cells. (B) Median values for LVEF before and 6 months after treatment. (C) Changes in left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV). (D, E) Impact of cardiopoietic stem cell therapy (Cell Therapy) on left ventricular remodeling compared with standard-of-care alone (Control). Changes in LVEF are plotted against changes in left ventricular ESV (D) and EDV (E). Change reflects the difference between parameters measured before and 6 months after therapy.

molecular substrate of advanced heart failure requires distinct regenerative strategies adequate to restore parenchymal integrity and prevent progressive remodeling (41,42). Human bone marrow stem cells are a desirable source for organ repair due to accessibility for harvest, propensity to propagate in culture, favorable biological profile, and extensive clinical experience (43–45). However, when derived from heart failure patients, bone marrow mesenchymal stem cells demonstrate latent plasticity with variable spontaneous capacity to instigate regeneration (22,46,47). Recent studies have used excised heart tissue, obtained at the time of cardiac bypass or by endomyocardial biopsy, to anatomically match the stem cell source to the target organ of repair (19,20). The rationale for the present clinical study is based on pre-clinical evidence that pre-emptive guidance optimizes repair potency despite a noncardiac source of stem cell derivation (22).

Induction of the cardiopoietic stem cell state is intended to ensure the regenerative benefit of mesenchymal stem cells

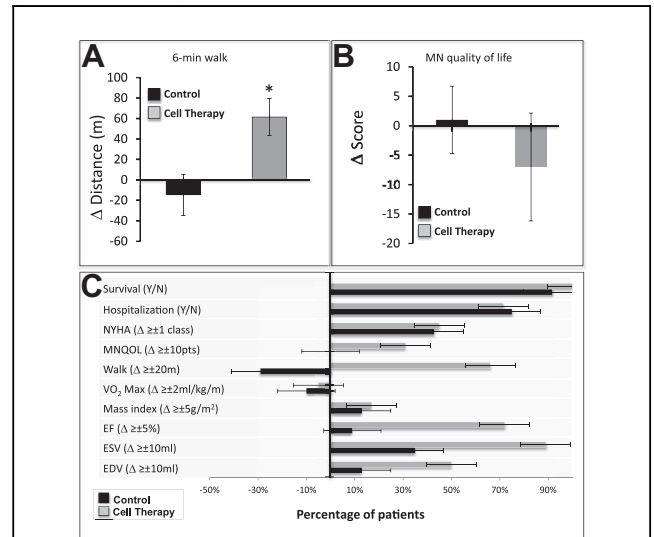


Figure 5 Global Benefit of Cardiopoietic Stem Cell Therapy

(A) Change (Δ) in 6-min walk distance. (B) Change (Δ) in the Minnesota (MN) Living With Heart Failure (HF) Questionnaire score. (C) Percentage of patients showing improvement or deterioration in left ventricular end-diastolic volume (EDV), left ventricular end-systolic volume (ESV), left ventricular ejection mass index (Mass Index), peak oxygen uptake (VO_2 Max); 6-min walk test (Walk); Minnesota Living with Heart Failure Questionnaire (MNQOL); New York Heart Association (NYHA) functional class, along with heart failure–related hospitalization (Hospitalization) and cardiac mortality (Survival) with standard of care (Control) versus those receiving standard of care plus cardiopoietic stem cells (Cell Therapy). Change reflects difference between parameters measured before and 6 months after therapy.

derived from patients with heart failure. Cardiopoiesis is promoted through replication of natural cues decoded from endoderm-mediated cardiogenic guidance of the mesoderm (21,22,48–50). A set of recombinant factors here converted mesenchymal stem cells from patients with ischemic heart failure to yield a Good Manufacturing Practice grade, scalable biologics meeting pre-set quality control release criteria. Repeat manufacturing runs were imposed when the stem cell proliferative capacity was insufficient to derive the target dose. The inability to grow a critical mass of cells in and of itself has been suggested to be an outcome prognosticator (51). However, post-hoc analysis of data from patients not meeting cell quality inclusion criteria did not support this premise. Rather, in this study, bone marrow harvest, specimen anticoagulation, and/or cryopreservation were noted on retrospective quality review to compromise starting material and ultimate cell yield in line with previous studies (52). In this way, the quality standards pre-imposed in this study ensured that cells released for delivery into patients were adherent to a phenotype associated with repair benefit (22).

From time of delivery and through follow-up, cardiopoietic stem cell transplantation demonstrated a safety profile equivalent to standard of care. Endomyocardial delivery was associated acutely with a transient increase in cardiac enzymes, remaining within values previously reported with myocardial injections (29). Corroborating pre-clinical

findings (22), no long-term evidence of uncontrolled tissue growth or proarrhythmic risk was associated with exposure to cardiopoietic stem cells. Prospective, 2-year surveillance confirmed clinical safety.

Although not powered as a therapeutic efficacy trial, a benefit for left ventricular function was documented here with cardiopoietic stem cell treatment. Although in principle, varying cell doses and injection numbers could confound interpretation, pre-clinical data showed no dose dependence on outcome within the range used here. Improved LVEF, as observed at 6 months in the present study, is a powerful predictor of beneficial cardiovascular outcome in heart failure (53,54), and was here associated with a reduced ESV, consistent with reversal of pathological remodeling (35).

Study limitations. The present study was limited in assessing the change in myocardial regeneration or perfusion because modalities, such as magnetic resonance imaging and single-photon emission computed tomography, were precluded due to incompatibility with patient population or unavailability at all participating sites. A composite score comprising, in addition to changes in cardiac structure and function, quality of life and clinical endpoints improved with cardiopoietic stem cell therapy beyond standard of care alone. These data collectively highlight the potential of lineage-specified stem cells to meet the regenerative requirements of ischemic heart failure, particularly in select patients in whom revascularization, resynchronization, and pharmacotherapy failed to restore pump function. In this initial clinical experience, procurement and delivery of cardiopoietic stem cells, as well as safety and efficacy profiles, showed equivalence across distinct socioeconomic and health care settings, an early indicator that this new therapy can potentially reach broader populations in need. Ultimately, the rigor of comparative effectiveness outcome analysis (55) will be needed to inform on the value of introducing a personalized regenerative strategy in heart failure management.

Conclusions

Organ failure is a major global challenge with the aging of the population and the shortage of donor organs (56–58). The past decade realized translation of stem cell-based technology to formulate an emergent clinical trial experience (59–61). The present C-CURE trial introduces a potential new treatment for heart failure using readily accessible bone marrow mesenchymal stem cells lineage specified to upgrade cardioregenerative aptitude. This trial is the first to capture the benefit of lineage specification without the need for harvesting heart tissue as a stem cell source. This novel class of stem cells was optimized in proof-of-concept pre-clinical studies establishing superior benefit compared with unspecified stem cells (22). Clinical translation of cardiopoietic stem cell therapy, performed here in patients with ischemic heart failure, demonstrates that insertion of a lineage guidance step does not alter the feasibility and safety established with naïve bone marrow stem cell therapy, yet confers a favorable

impact on myocardial remodeling, LVEF, and global wellness beyond what has been reported in heart failure with unguided bone marrow stem cells or as compared head-to-head in this trial with standard of care alone. The C-CURE trial thus advances the paradigm of lineage specification in stem cell therapy, providing a rationale for further clinical validation.

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REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2–220.
2. Kovacic JC, Fuster V. From treating complex coronary artery disease to promoting cardiovascular health: therapeutic transitions and challenges, 2010–2020. *Clin Pharmacol Ther* 2011;90:509–18.
3. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science* 2009;324:98–102.
4. Kajstura J, Urbaneck K, Perl S, et al. Cardiomyogenesis in the adult human heart. *Circ Res* 2010;107:305–15.
5. Smart N, Bollini S, Dubé KN, et al. De novo cardiomyocytes from within the activated adult heart after injury. *Nature* 2011;474:640–4.
6. McMurray JJ. Systolic heart failure. *N Engl J Med* 2010;362:228–38.
7. Dimmeler S, Zeiher AM, Schneider MD. Unchain my heart: the scientific foundations of cardiac repair. *J Clin Invest* 2005;115:572–83.
8. Segers VF, Lee RT. Stem-cell therapy for cardiac disease. *Nature* 2008;451:937–42.
9. Janssens S. Stem cells in the treatment of heart disease. *Annu Rev Med* 2010;61:287–300.
10. Wollert KC, Drexler H. Cell therapy for the treatment of coronary heart disease: a critical appraisal. *Nat Rev Cardiol* 2010;7:204–15.
11. Mozdil AM, Arnous S, Sammut EC, Mathur A. Stem cell therapy for heart diseases. *Br Med Bull* 2011;98:143–59.
12. Assmus B, Honold J, Schächinger V, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med* 2006;355:1222–32.

13. Gersh BJ, Simari RD, Behfar A, Terzic CM, Terzic A. Cardiac cell repair therapy: a clinical perspective. *Mayo Clin Proc* 2009;84:876-92.
14. Mummery CL, Davis RP, Krieger JE. Challenges in using stem cells for cardiac repair. *Sci Transl Med* 2010;2:27ps17.
15. Chavakis E, Koyanagi M, Dimmeler S. Enhancing the outcome of cell therapy for cardiac repair: progress from bench to bedside and back. *Circulation* 2010;121:325-35.
16. Bartunek J, Vanderheyden M, Hill J, Terzic A. Cells as biologics for cardiac repair in ischaemic heart failure. *Heart* 2010;96:792-800.
17. Menasche P. Cardiac cell therapy: lessons from clinical trials. *J Mol Cell Cardiol* 2011;50:258-65.
18. Ptaszek LM, Mansour M, Ruskin JN, Chien KR. Towards regenerative therapy for cardiac disease. *Lancet* 2012;379:933-42.
19. Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet* 2011;378:1847-57.
20. Makkar RR, Smith RR, Cheng K, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet* 2012;379:895-904.
21. Behfar A, Terzic A. Derivation of a cardiopoietic population from human mesenchymal stem cells yields cardiac progeny. *Nat Clin Pract Cardiovasc Med* 2006;3 Suppl 1:S78-82.
22. Behfar A, Yamada S, Crespo-Diaz R, et al. Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. *J Am Coll Cardiol* 2010;56:721-34.
23. Marbán E, Malliaras K. Boot camp for mesenchymal stem cells. *J Am Coll Cardiol* 2010;56:735-7.
24. Mercola M, Ruiz-Lozano P, Schneider MD. Cardiac muscle regeneration: lessons from development. *Genes Dev* 2011;25:299-309.
25. Jessup M, Abraham WT, Casey DE, et al. ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009;53:1343-82.
26. Crespo-Diaz R, Behfar A, Butler GW, et al. Platelet lysate consisting of a natural repair proteome supports human mesenchymal stem cell proliferation and chromosomal stability. *Cell Transplant* 2011;20:797-811.
27. Behfar A, Faustino RS, Arrell DK, Dzeja PP, Perez-Terzic C, Terzic A. Guided stem cell cardiopoiesis: discovery and translation. *J Mol Cell Cardiol* 2008;45:523-9.
28. Nelson TJ, Behfar A, Terzic A. Stem cells: biologics for regeneration. *Clin Pharmacol Ther* 2008;84:620-3.
29. Bartunek J, Sherman W, Vanderheyden M, Fernandez-Aviles F, Wijns W, Terzic A. Delivery of biologics in cardiovascular regenerative medicine. *Clin Pharmacol Ther* 2009;85:548-52.
30. Psaltis PJ, Zannettino AC, Gronthos S, Worthley SG. Intramyocardial navigation and mapping for stem cell delivery. *J Cardiovasc Transl Res* 2010;3:135-46.
31. Gottdiener JS, Bednarz J, Devereux R, et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr* 2004;17:1086-119.
32. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111-7.
33. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;7:176-82.
34. Banovic M, Ostojic MC, Bartunek J, Nedeljkovic M, Beleslin B, Terzic A. Brachial approach to NOGA-guided procedures: electromechanical mapping and transendocardial stem-cell injections. *Tex Heart Inst J* 2011;38:179-82.
35. Hare JM, Traverse JH, Henry TD, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal) after acute myocardial infarction. *J Am Coll Cardiol* 2009;54:2277-86.
36. Rector TS. A conceptual model of quality of life in relation to heart failure. *J Cardiac Failure* 2005;11:173-6.
37. Traverse JH, Henry TD, Ellis SG, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA* 2011;306:2110-9.
38. Losordo DW, Henry TD, Davidson C, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res* 2011;109:428-36.
39. Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006;355:1210-21.
40. Traverse JH, Henry TD, Pepine CJ, et al. Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: The TIME randomized trial. *JAMA* 2012;308:2380-9.
41. Williams AR, Trachtenberg B, Velazquez DL, et al. Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. *Circ Res* 2011;108:792-6.
42. Malliaras K, Kreke M, Marbán E. The stuttering progress of cell therapy for heart disease. *Clin Pharmacol Ther* 2011;90:532-41.
43. Hatzistergos KE, Quevedo H, Oskoueï BN, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circ Res* 2010;107:913-22.
44. Lovell MJ, Mathur A. Cardiac stem cell therapy: progress from the bench to bedside. *Heart* 2010;96:1531-7.
45. Williams AR, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. *Circ Res* 2011;109:923-40.
46. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: The POSEIDON randomized trial. *JAMA* 2012;308:2369-79.
47. Marbán E, Malliaras K. Mixed results for bone marrow-derived cell therapy for ischemic heart disease. *JAMA* 2012;308:2405-6.
48. Epstein JA. Cardiac development and implications for heart disease. *N Engl J Med* 2010;363:1638-47.
49. Penn MS, Dong F, Klein S, Mayorga ME. Stem cells for myocardial regeneration. *Clin Pharmacol Ther* 2011;90:499-501.
50. Mohsin S, Siddiqi S, Collins B, Sussman MA. Empowering adult stem cells for myocardial regeneration. *Circ Res* 2011;109:1415-28.
51. Stolzing A, Jones E, McGonagle D, Scutt A. Age-related changes in human bone marrow-derived mesenchymal stem cells: consequences for cell therapies. *Mech Ageing Dev* 2008;129:163-73.
52. Lioznov M, Dellbrügger C, Sputtek A, Fehse B, Kröger N, Zander AR. Transportation and cryopreservation may impair haematopoietic stem cell function and engraftment of allogeneic PBSCs, but not BM. *Bone Marrow Transplant* 2008;42:121-8.
53. St John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation* 1997;96:3294-9.
54. Solomon SD, Anavekar N, Skali H, et al. Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;112:3738-44.
55. Terzic A, Nelson TJ. Regenerative medicine advancing health care 2020. *J Am Coll Cardiol* 2010;55:2254-7.
56. Badyal SF, Weiss DJ, Caplan A, Macchiarini P. Engineered whole organs and complex tissues. *Lancet* 2012;379:943-52.
57. Waldman SA, Terzic A. Cardiovascular health: the global challenge. *Clin Pharmacol Ther* 2011;90:483-5.
58. Terzic A, Waldman S. Chronic diseases: the emerging pandemic. *Clin Transl Sci* 2011;4:225-6.
59. Strauer BE, Steinhoff G. 10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart: from the methodological origin to clinical practice. *J Am Coll Cardiol* 2011;58:1095-104.
60. Perin EC, Willerson JT, Pepine CJ, et al. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. *JAMA* 2012;307:1717-26.
61. Brunt KR, Weisel RD, Li RK. Stem cells and regenerative medicine—future perspectives. *Can J Physiol Pharmacol* 2012;90:327-35.

Key Words: bone marrow ■ cardiopoiesis ■ ischemic cardiomyopathy ■ regenerative medicine ■ stem cells.

APPENDIX

For supplemental tables and figures, please see the online version of this article.