

Original Investigation

Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy

The TAC-HFT Randomized Trial

Alan W. Heldman, MD; Darcy L. DiFede, RN, BSN; Joel E. Fishman, MD, PhD; Juan P. Zambrano, MD; Barry H. Trachtenberg, MD; Vasileios Karantalis, MD; Muzammil Mushtaq, MD; Adam R. Williams, MD; Viky Y. Suncion, MD; Ian K. McNiece, PhD; Eduard Ghersin, MD; Victor Soto, MD; Gustavo Lopera, MD; Roberto Miki, MD; Howard Willens, MD; Robert Hendel, MD; Raul Mitrani, MD; Pradip Pattany, PhD; Gary Feigenbaum, MD; Behzad Oskouei, MD; John Byrnes, MD; Maureen H. Lowery, MD; Julio Sierra, MD; Mariesty V. Pujol, MBA; Cindy Delgado, MA; Phillip J. Gonzalez, CRC; Jose E. Rodriguez, RTMR; Luiza Lima Bagno, PhD; Didier Rouy, MD, PhD; Peter Altman, PhD; Cheryl Wong Po Foo, PhD; Jose da Silva, PhD; Erica Anderson, MA; Richard Schwarz, PhD; Adam Mendizabal, PhD; Joshua M. Hare, MD

IMPORTANCE Whether culture-expanded mesenchymal stem cells or whole bone marrow mononuclear cells are safe and effective in chronic ischemic cardiomyopathy is controversial.

OBJECTIVE To demonstrate the safety of transendocardial stem cell injection with autologous mesenchymal stem cells (MSCs) and bone marrow mononuclear cells (BMCs) in patients with ischemic cardiomyopathy.

DESIGN, SETTING, AND PATIENTS A phase 1 and 2 randomized, blinded, placebo-controlled study involving 65 patients with ischemic cardiomyopathy and left ventricular (LV) ejection fraction less than 50% (September 1, 2009-July 12, 2013). The study compared injection of MSCs (n=19) with placebo (n = 11) and BMCs (n = 19) with placebo (n = 10), with 1 year of follow-up.

INTERVENTIONS Injections in 10 LV sites with an infusion catheter.

MAIN OUTCOMES AND MEASURES Treatment-emergent 30-day serious adverse event rate defined as a composite of death, myocardial infarction, stroke, hospitalization for worsening heart failure, perforation, tamponade, or sustained ventricular arrhythmias.

RESULTS No patient had a treatment-emergent serious adverse events at day 30. The 1-year incidence of serious adverse events was 31.6% (95% CI, 12.6% to 56.6%) for MSCs, 31.6% (95% CI, 12.6%-56.6%) for BMCs, and 38.1% (95% CI, 18.1%-61.6%) for placebo. Over 1 year, the Minnesota Living With Heart Failure score improved with MSCs (−6.3; 95% CI, −15.0 to 2.4; repeated measures of variance, $P=.02$) and with BMCs (−8.2; 95% CI, −17.4 to 0.97; $P=.005$) but not with placebo (0.4; 95% CI, −9.45 to 10.25; $P=.38$). The 6-minute walk distance increased with MSCs only (repeated measures model, $P=.03$). Infarct size as a percentage of LV mass was reduced by MSCs (−18.9%; 95% CI, −30.4 to −7.4; within-group, $P=.004$) but not by BMCs (−7.0%; 95% CI, −15.7% to 1.7%; within-group, $P=.11$) or placebo (−5.2%; 95% CI, −16.8% to 6.5%; within-group, $P=.36$). Regional myocardial function as peak Eulerian circumferential strain at the site of injection improved with MSCs (−4.9; 95% CI, −13.3 to 3.5; within-group repeated measures, $P=.03$) but not BMCs (−2.1; 95% CI, −5.5 to 1.3; $P=.21$) or placebo (−0.03; 95% CI, −1.9 to 1.9; $P=.14$). Left ventricular chamber volume and ejection fraction did not change.

CONCLUSIONS AND RELEVANCE Transendocardial stem cell injection with MSCs or BMCs appeared to be safe for patients with chronic ischemic cardiomyopathy and LV dysfunction. Although the sample size and multiple comparisons preclude a definitive statement about safety and clinical effect, these results provide the basis for larger studies to provide definitive evidence about safety and to assess efficacy of this new therapeutic approach.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Joshua M. Hare, MD, Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine, Biomedical Research Bldg, Room 908, PO Box 016960 (R-125), Miami, FL 33101 (jhare@med.miami.edu).

Recent preclinical studies and clinical trials suggest that bone marrow-derived cell preparations, including mononuclear bone marrow cells¹⁻⁶ and mesenchymal stem cells,^{7,8} ameliorate left ventricular (LV) remodeling with acute^{4,7} myocardial infarction (MI) and chronic^{1-3,5,8,9} ischemic cardiomyopathy. An effective antiremodeling, proregenerative treatment for ischemic cardiomyopathy would address a major unmet need for many patients. By virtue of their greater differentiation potential,¹⁰ the culture-expanded mesenchymal stem cells constituent of bone marrow is speculated to have potential for forming ectopic tissue¹¹ or stimulating tumors¹² but could also have greater antifibrotic and proregenerative effects than bone marrow mononuclear cells.¹³ An unresolved issue is whether mesenchymal stem cells have similar safety and possibly greater efficacy than bone marrow mononuclear cells.⁸

To address these issues, we performed a phase 1 and 2 randomized, double-blind, placebo-controlled study of autologous culture-expanded mesenchymal stem cells vs autologous bone marrow mononuclear cells delivered by transcatheter stem cell injection (TESI) in patients with ischemic cardiomyopathy.¹⁴ The findings of the Transcatheter Autologous Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells in Ischemic Heart Failure Trial (TAC-HFT) have implications for the development of cell-based therapies for ischemic cardiomyopathy and possibly for other organs and diseases.

Methods

Study Design and Enrollment

The TAC-HFT study protocol, a phase 1 and 2, randomized, double-blind, placebo-controlled study of the safety and efficacy of the procedure, was conducted under the Investigational National Drug Application from the US Food and Drug Administration. The primary objective was to demonstrate the safety of mesenchymal stem cells and bone marrow mononuclear cells administered by TESI in patients with chronic MI and LV dysfunction. The secondary objective was to demonstrate the efficacy of autologous mesenchymal stem cells and bone marrow mononuclear cells in this context. Efficacy domains included myocardial scar size; regional function; LV size; viable tissue mass, shape, and global function; and patient quality of life and exercise capacity. A detailed description of the trial design was published.¹⁴

Patients were randomized at the University of Miami starting on September 1, 2009, with follow-up completed on July 12, 2013. This study had institutional review board approval from the University of Miami Miller School of Medicine, and all patients gave written informed consent. Sixty-five patients were randomized in a 1:1 ratio between the mesenchymal stem cell group and the bone marrow mononuclear cell group. Randomization between mesenchymal stem cell and bone marrow mononuclear cell groups was unblinded to preserve the advantage of a bone marrow mononuclear cell strategy, which allows use on the day of aspiration. Preparation¹⁴ of mesenchymal stem cells took 4 to 6 weeks after bone mar-

row aspiration,⁸ whereas the preparation of bone marrow mononuclear cells took 4 hours. To maintain a blinded assessment of cells vs placebo, patients were further randomized in a 2:1 ratio of cell therapy vs placebo. Preparation and administration of the study product was blinded to patients and investigators outside the cell-processing laboratory. An electronic data entry system was used for randomization and data collection.

An independent data and safety monitoring board was responsible for safety oversight.

Patient Population

Patients included in the study were aged 21 to 90 years and had ischemic cardiomyopathy with LV dysfunction resulting from chronic MI, as documented by confirmed coronary artery disease with a corresponding area of myocardial akinesis, dyskinesia, or severe hypokinesia and had LV ejection fraction of less than 50% within 6 months of screening while taking maximally tolerated doses of β -adrenergic blocking and angiotensin-converting enzyme or angiotensin II receptor blocking drugs and not during or recently after an ischemic event. Patients were eligible for TESI catheterization within 5 to 10 weeks of screening. Patients were excluded for noncardiac conditions limiting life expectancy to less than 1 year, glomerular filtration rate of less than 45 mL/min per 1.73 m², serious radiographic contrast allergy, clinical requirement for coronary revascularization, a life-threatening arrhythmia in the absence of an implanted defibrillator, or a diagnosis of a malignant cancer within 5 years of screening.

Study Procedures and Timeline

Baseline studies included chemistry and hematology laboratory tests, echocardiography, and computed tomography (CT) scans of chest, abdomen, and pelvis. Demographic and clinical variables were acquired by interview. Race and ethnicity were recorded as self-described. Cardiac imaging was done with magnetic resonance imaging (MRI) when possible; patients with an implanted device that precluded MRI underwent cardiac CT imaging instead.¹⁵ Most implanted pacemaker and defibrillator devices were not considered as contraindicating MRI, and these studies were performed as previously described.¹⁶ All patients underwent bone marrow aspiration from the iliac crest; mesenchymal stem cells were prepared in culture from the marrow aspirate, as described.^{8,17} Bone marrow mononuclear cells were prepared by centrifugation of whole bone marrow against a low-density gradient using Ficoll-Paque Premium ($d = 1.077$) according to the manufacturer's protocol (Mediatech Inc). Cells were collected at the interface.

Cells or vehicle placebo were delivered to 10 LV sites by TESI during retrograde left-heart catheterization using the Helical Infusion Catheter (Biocardia).^{2,14} Injections were targeted to encircle the border zone of a chronically infarcted myocardial territory, as delineated by MRI or CT imaging, echocardiography, and well-pacified biplane left ventriculography. Following TESI, patients were hospitalized for a minimum of 4 days and were seen at 2 weeks then monthly thereafter for 6 months and at 12 months for safety assessments including un-

dergoing clinical interview and physical examination for adverse events; CT of the chest, abdomen, and pelvis; and efficacy assessments including cardiac MRI or CT; being tested for exercise peak oxygen consumption and a 6-minute walk test; being evaluated for New York Heart Association (NYHA) class; and taking the Minnesota Living With Heart Failure questionnaire.

Study End Points

The primary end point was the incidence of any *treatment-emergent serious adverse events* 1 month after TESI, defined as the composite of death, nonfatal MI, stroke, hospitalization for worsening heart failure, cardiac perforation, pericardial tamponade, or sustained ventricular arrhythmias (>15 seconds or causing hemodynamic compromise). Additional safety assessments included clinical monitoring for adverse and serious adverse events and major adverse cardiac events (defined as the composite incidence of death, hospitalization for worsening heart failure, or nonfatal recurrent myocardial infarction), and surveillance testing including serial troponin and CK-MB; CT scans of the chest, abdomen, and pelvis to identify ectopic tissue formation; and 48-hour ambulatory electrocardiography, hematology, chemistry, urinalysis, spirometry, and serial echocardiography.

Prespecified secondary cardiac imaging end points were infarct size, regional wall motion at the sites of study agent injection, and measures of global LV size and function.^{8,14} Other prespecified secondary efficacy assessments included exercise peak oxygen consumption, a 6-minute walk test, NYHA class, and the Living With Heart Failure score.

MRI and CT Imaging

Cardiac MRI (General Electric 1.5T) with gadolinium contrast was performed at baseline and at 3, 6, and 12 months⁸ to measure global cardiac function (cine), regional function (tagged cine to measure peak negative Eulerian circumferential strain, a measure of local cardiac contraction^{8,18}), and infarct size (delayed myocardial gadolinium enhancement using 0.2 mmol/kg Magnevist, Bayer Healthcare) as previously described,⁸ and analyzed with Qmass MR 7.2 (Medis Inc), and Diagnosoft 2.71 (Diagnosoft Inc). Contrast-enhanced CT was performed at screening and at 12 months (128-slice Siemens AS+, Siemens Medical Solutions).^{18,19} Images were analyzed for global LV volumes, function, sphericity,²⁰ and infarct scar size¹⁹ (iNtuition software version .4.4.7.47; TeraRecon Inc). For CT assessment, early enhanced viability imaging¹⁹ used prospective electrocardiographic gating at 70% to 90% of the R-R interval and low tube voltage (100 kV) to minimize radiation exposure.

Statistical Analysis

The study was designed to estimate the confidence intervals of treatment-emergent serious adverse events at 30 days after undergoing TESI among both treatment groups vs placebo. The underlying rate of 30-day treatment-emergent adverse events was assumed to be 25% in each group. In this setting, the binomial 95% confidence interval is 6% to 44%. Rates of treatment-emergent, adverse, and serious adverse events were compared using the Fisher exact test at 30 days

and at 12 months. For continuous measures, normality of data was tested using the Shapiro-Wilk test, and the *t* test or non-parametric tests for differences between groups. Normally distributed efficacy parameters were tested with a repeated measures analysis of variance model using the entire data set including between-group comparisons as well as time and group × time interaction terms. Bonferroni correction was applied post hoc to test for within-group differences when the main effect was statistically significant. A 2-sided *P* value <.05 was considered statistically significant.²¹ For the prespecified secondary efficacy parameters, 6-minute walk test, Minnesota Living With Heart Failure score, and MI size, the data are presented with the placebo groups pooled together when no significant differences in baseline characteristics were detected between placebo groups. Analyses were conducted using the SAS System, version 9.3 (SAS Institute Inc), and conformed to the prespecified objectives of the trial. Imaging analyses combined MRI and CT data unless otherwise specified.

Results

Patient Population

A total of 65 patients were randomized. The 6 patients who did not receive TESI for protocol-specified reasons were not followed up once they were replaced by protocol-defined contingencies. Three patients who received the study intervention but did not complete the 1-year follow-up were evaluated for the 30-day safety assessment (Figure 1). The study population was predominantly male and white with a significant proportion of Hispanic participants (Table 1). Most patients had mild to moderate heart failure symptoms and impaired 6-minute walk test and Minnesota Living With Heart Failure scores.

Safety

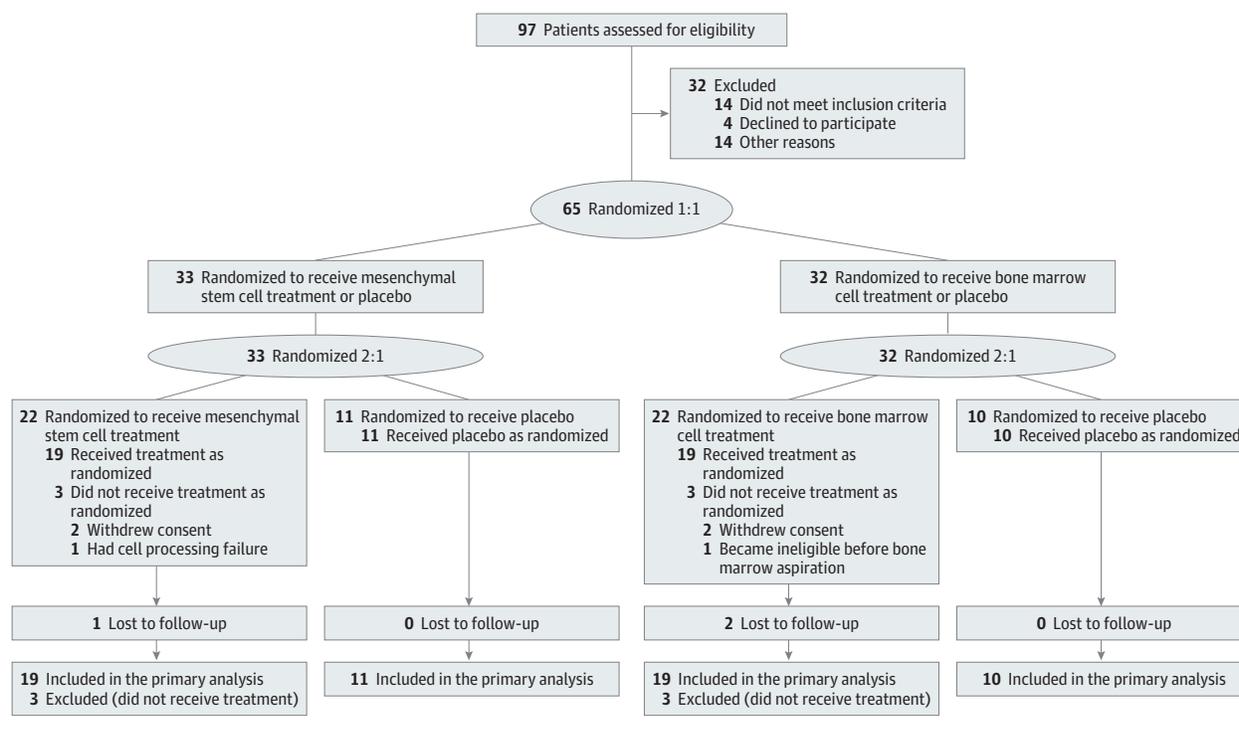
There were no treatment-emergent serious adverse events among any of the patients who underwent TESI in any of the cell groups; corresponding 95% CIs ranged from 0.0% to 17.7% (Table 2). Furthermore, the 30-day adverse event rate did not significantly differ by group: 31.6% (95% CI, 12.6%-56.6%) among those in the mesenchymal stem cell group vs 27.3% (95% CI, 6.0%-61.0%) in the respective placebo group and 36.8% (95% CI, 16.3%-61.6%) in the bone marrow group vs 30.0% (95% CI, 6.7%-65.3%) in the respective placebo group (Table 2). Serious adverse events were similarly infrequent among all patients who received TESI resulting in an overall incidence at 30 days of 11.9% (95% CI, 4.9%-22.9%).

The TESI procedure was technically successful in all patients. No patient had significant postprocedural pericardial effusion. The myocardial biomarkers (CK-MB and serum troponin I) showed small transient increases (Table 2). Patients with implanted cardiac rhythm devices experienced no complications related to MRI.

Long-term Adverse Events

Two patients in the mesenchymal stem cell/placebo group died of cardiac events during the study period: the first died 239 days after receiving transcatheter stem cell injection and the sec-

Figure 1. Study Flow Chart



ond, 115 days after receiving placebo. The 12-month adverse and serious adverse event incidence was similar among all groups (eTable 1 in the Supplement).

Rehospitalization and Major Cardiac Adverse Events

Six patients (31.6%; 95% CI, 12.6%-56.6%) in the mesenchymal stem cell group were rehospitalized during the 12-month study period, 5 (26.3%; 95% CI, 9.2%-51.2%) in the bone marrow group, and 5 (23.8%; 95% CI, 8.2%-47.2%) in the placebo groups ($P = .85$). The 12-month incidence of major adverse cardiac events was 1 (5.3%; 95% CI, 0.0%-26.0%) in the mesenchymal stem cell group, 0 (0.0%; 95% CI, 0.0%-17.7%) in the bone marrow group, and 2 (9.5%; 95% CI, 1.2%-30.4%) in the placebo groups ($P = .77$; eTable 1 in the Supplement).

Ectopic Tissue Formation

All patients underwent 12-month CT scans of chest, abdomen, and pelvis; no ectopic tissue formation was detected.

Functional Status, Quality of Life, and Pulmonary Function

Patient functional status and quality of life were monitored serially. In a repeated measures model, the 6-minute walk test increased in the mesenchymal stem cell group but not in the bone marrow or placebo groups ($P = .03$; Figure 2). The mean change from baseline in distance walked in the mesenchymal stem cell group at 6 months was 28.2 m (95% CI, 10.8 to 45.5 m; $P = .005$) and at 12 months, 32.6 m (95% CI, -4.6 to 69.7; $P = .12$). Among the bone marrow mononuclear cell group, the mean change from baseline in distance walked at 6 months was -25.7 m (95% CI, -74.1 to 22.6 m; $P = .21$) and

at 12 months, 16.9 m (95% CI, -14.2 to 48.0 m; $P = .30$), whereas the placebo group mean change from baseline at 6 months was 21.6 m (95% CI, 1.4 to 41.8 m; $P = .02$) and at 12 months, 6.3 m (95% CI, -31.4 to 44.0 m; $P = .70$). When changes in 6-minute walk test were evaluated relative to changes in their respective placebo group at 12 months, the distance walked in 6 minutes did not differ in the mesenchymal stem cell group (-5.24 m; 95% CI, -62.68 to 52.21; $P = .85$) or in the bone marrow group (45.55 m; 95% CI, -11.0 to 102.1; $P = .11$). Neither peak oxygen consumption nor spirometric forced expiration volume in the first second of expiration changed with cell therapy.

The NYHA class improved at 12 months compared with baseline in 6 patients (35.3%) in the mesenchymal stem cell group, 9 patients (52.9%) in the bone marrow group, and 7 patients (43.8%) in the placebo group or did not change in 7 patients (41.2%) in the mesenchymal stem cell group, 6 patients (35.3%) in the bone marrow group, and 8 patients (50.0%) in the placebo group. Four patients in the mesenchymal stem cell group, 2 in the bone marrow group, and 1 in the placebo group had worsened NYHA class scores at 12 months compared with baseline ($P = .47$).

The mean (SD) Minnesota Living With Heart Failure score at baseline was 28.4 (22.8) for the mesenchymal stem cell group, 29.5 (25.8) for the bone marrow group, and 33.3 (24.5) for the placebo group. The score improved in both treatment groups but not in the placebo group (Figure 3). The improved score was greatest at 5 months, with a mean reduction of 11.6 (95% CI, -23.7 to 0.5; $P = .006$) in the mesenchymal stem cell group and 15.80 (95% CI, -28.6 to -3.0; $P = .04$) in the bone marrow group, whereas the reduction in the placebo group was 4.6 (95%

Table 1. Baseline Characteristics

	No. (%) of Patients ^a			
	Mesenchymal Stem Cell		Mononuclear Bone Marrow Cells	
	Mesenchymal Stem Cell (n = 19)	Placebo (n = 11)	Bone Marrow (n = 19)	Placebo (n = 10)
Men	18 (94.7)	10 (90.9)	17 (89.5)	10 (100.0)
Hispanic or Latino ethnicity	7 (36.8)	4 (36.4)	10 (45.5)	5 (50.0)
White race	16 (84.2)	10 (90.9)	10 (52.6)	10 (100.0)
Age, mean (SD), y	57.1 (10.6)	60.0 (12.0)	61.1 (8.4)	61.3 (9.0)
Qualifying ejection fraction, mean (SD), %	35.8 (8.5)	31.6 (10.0)	36.3 (11.1)	34.4 (9.5)
History				
Coronary interventions	19 (100.0)	10 (90.9)	18 (94.7)	10 (100.0)
Atrial/ventricular arrhythmia	5 (26.3)	3 (27.3)	4 (21.1)	3 (20.0)
Hypertension	12 (63.2)	6 (54.5)	12 (63.2)	10 (100.0)
Diabetes	3 (15.8)	3 (27.3)	4 (21.1)	4 (40.0)
Congestive heart failure	11 (57.9)	7 (63.6)	16 (84.2)	9 (90.9)
Smoking	14 (73.7)	9 (81.8)	10 (52.6)	7 (70.0)
New York Heart Association class				
I	5 (26.3)	2 (20.0)	5 (26.3)	2 (25.0)
II	12 (63.2)	5 (50.0)	10 (52.6)	5 (62.5)
III	2 (10.5)	3 (30.0)	4 (21.1)	1 (12.5)
Six-minute walk test, mean (SD), m	415.3 (67.9)	388.5 (69.0)	399.6 (95.0)	387.8 (47.8)
Peak $\dot{V}O_2$, mean (SD), mL/kg/min	18.8 (3.8)	14.5 (4.5)	17.3 (4.4)	14.6 (7.0)
Predicted FEV ₁ , mean (SD), %	86.2 (15.7)	77.0 (14.2)	83.2 (23.2)	81.4 (25.8)
MLHF total score, mean (SD)	28.4 (22.8)	18.9 (15.0)	29.5 (25.8)	44.9 (24.9)
Device				
AICD	10 (52.6)	4 (36.4)	10 (52.6)	4 (40.0)
BiV	1 (5.3)	2 (18.2)	1 (5.3)	1 (10.0)
None	8 (42.1)	5 (42.5)	8 (42.1)	5 (50.0)
Imaging modality				
MRI	13 (68.4)	8 (72.7)	13 (68.4)	7 (70.0)
CT	6 (31.6)	3 (27.3)	6 (31.6)	3 (30.0)
Time since first MI, mean (SD), y	10.0 (10.1)	9.9 (7.9)	7.7 (7.2)	15.1 (8.6)
Cardiac imaging parameters, mean (SD)				
LV ejection fraction, %	35.7 (9.0)	28.1 (9.8)	35.9 (8.2)	36.2 (7.4)
End-diastolic volume, mL	283.2 (85.1)	261.0 (87.5)	254.9 (107.5)	237.6 (65.1)
End-systolic volume, mL	186.9 (75.6)	189.9 (75.6)	170.3 (92.5)	153.9 (52.6)
Stroke volume, mL	96.4 (18.9)	71.1 (24.9)	84.6 (19.1)	83.8 (21.5)
End-diastolic sphericity index	0.49 (0.08)	0.49 (0.11)	0.45 (0.10)	0.46 (0.08)
Scar mass, g	26.6 (16.1)	23.2 (14.3)	23.5 (16.7)	22.7 (14.6)
Scar size as % of LV mass, %	25.9 (11.3)	27.5 (16.5)	25.5 (8.4)	23.0 (9.2)
Viable tissue mass, g	145.1 (78.3)	123.6 (62.9)	143.6 (76.0)	146.3 (80.6)
Medications preinjection				
ACE inhibitors	11 (57.9)	8 (72.7)	11 (57.9)	6 (60.0)
Angiotensin II blockers	4 (21.1)	0 (0.0)	6 (31.6)	2 (20.0)
β-Blockers	17 (89.5)	11 (100.0)	17 (89.5)	9 (90.0)
Diuretic	12 (63.2)	6 (54.5)	14 (73.7)	6 (60.0)

Abbreviations: ACE, angiotensin-converting enzyme; AICD, automatic implanted cardioverter-defibrillator; BiV, biventricular pacing; CT, computed tomography; FEV₁, forced expiratory volume in the first second; LV, left ventricle; MI, myocardial infarction; MLHF, Minnesota Living With Heart Failure questionnaire; MRI, magnetic resonance imaging.

^a No statistically significant differences between groups with the exception of stroke volume ($P = .03$).

CI, -20.1 to 10.7; $P = .69$). When evaluating the changes in the Minnesota Living With Heart Failure score against the respective placebo group at 6 months, the mean difference between the mesenchymal stem cell group and the placebo group was -14.55 (95% CI, -31.1 to 2.01; $P = .08$) and the mean difference between the bone marrow group and the placebo group was

6.63 (95% CI, -15.68 to 28.95; $P = .54$). Over 1 year, the mesenchymal stem cell group score improved from baseline in a repeated measures analysis of variance model (-6.3; 95% CI, -15.0 to 2.4; $P = .02$) as did the bone marrow cell group score (-8.2; 95% CI, -17.4 to 0.97; $P = .005$), but the placebo group score did not improve (0.4; 95% CI, -9.45 to 10.25; $P = .38$; Figure 3).

Table 2. Safety Summary by 30-Days After Transendocardial Stem Cell Injection

	Mesenchymal Stem Cell Treatment Group		Mononuclear Bone Marrow Cells Treatment Group	
	Mesenchymal Stem Cell (n = 19)	Placebo (n = 11)	Bone Marrow (n = 19)	Placebo (n = 10)
Incidence of treatment-emergent serious adverse events, No. (%) [95% CI] ^a	0 [0.0-17.7]	0 [0.0-28.5]	0 [0.0-17.7]	0 [0.0-30.9]
Adverse events				
No.	8	4	10	4
No./patient, median (range)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)
Incidence, No. (%) [95% CI] ^a	6 (31.6) [12.6-56.6]	3 (27.3) [6.0-61.0]	7 (36.8) [16.3-61.6]	3 (30.0) [6.7-65.3]
Incidence system organ class, No. (%) [95% CI] ^a				
Cardiac disorders	2 (10.5) [1.3-33.1]	2 (18.2) [2.3-51.8]	1 (5.3) [0.1-26.0]	1 (10.0) [0.3-44.5]
Gastrointestinal disorders	1 (5.3) [0.1-26.0]	0	0	0
General disorders and administration site conditions	3 (15.8) [3.4-39.6]	1 (9.1) [0.2-41.2]	2 (10.5) [1.3-33.1]	0
Infections and infestations	0	0	1 (5.3) [0.1-26.0]	1 (10.0) [0.3-44.5]
Injury, poisoning, and procedural complications	0	0	0	0
Investigations	0	0	0	1 (10.0) [0.3-44.5]
Musculoskeletal and connective tissue disorders	0	0	1 (5.3) [0.1-26.0]	0
Nervous system disorders	0	0	3 (15.8) [3.4-39.6]	1 (10.0) [0.3-44.5]
Respiratory, thoracic, and mediastinal disorders	0	1 (9.1) [0.2-41.2]	0	0
Skin and subcutaneous tissue disorders	2 (10.5) [1.3-33.1]	0	1 (5.3) [0.1-26.0]	0
Serious adverse events				
No.	2	2	2	1
No./patient, median (range)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Incidence, No. (%) [95% CI] ^a	2 (10.5) [1.3-33.1]	2 (18.2) [2.3-51.8]	2 (10.5) [1.3-33.1]	1 (10.0) [0.3-44.5]
Incidence by system organ class, No. (%) [95% CI] ^a				
Cardiac disorders ^b	2 (10.5) [1.3-33.1]	2 (18.2) [2.3-51.8]	0	1 (10.0) [0.3-44.5]
General disorders and administration site conditions	0	0	1 (5.3) [0.1-26.0]	0
Musculoskeletal and connective tissue disorders	0	0	1 (5.3) [0.1-26.0]	0
Adverse events, No. (%) [95% CI] ^a				
Major cardiac	0	0	0	0
Deaths	0	0	0	0
Ectopic tissue formation	0	0	0	0
Creatine kinase MB, mean (95% CI), ng/mL ^c				
Baseline	1.61 (1.21-2.02)	1.32 (0.94-1.71)	1.36 (0.80-1.91)	1.96 (1.04-2.87)
12 h	3.75 (2.70-4.80)	2.85 (1.54-4.15)	2.98 (2.17-3.79)	6.14 (1.80-10.48)
24 h	2.19 (1.64-2.74)	2.08 (0.88-3.28)	1.73 (1.23-2.24)	3.78 (0.62-6.94)
36 h	1.38 (1.11-1.66)	1.19 (0.73-1.65)	1.28 (0.98-1.59)	2.11 (0.90-3.32)
48 h	1.05 (0.84-1.27)	0.87 (0.62-1.12)	1.03 (0.79-1.26)	1.91 (0.79-3.04)
Serum troponin I, mean (95% CI), ng/mL ^c				
Baseline	0.06 (0.02-0.10)	0.04 (0.03-0.05)	0.06 (0.02-0.11)	0.17 (0.03-0.48)
12 h	0.82 (0.47-1.17)	0.66 (0.21-1.12)	1.03 (0.06-1.99)	1.33 (0.36-2.29)
24 h	0.60 (0.29-0.91)	0.34 (0.05-0.63)	0.45 (0.04-0.86)	0.52 (0.03-1.00)
36 h	0.39 (0.16-0.62)	0.25 (0.03-0.46)	0.29 (0.01-0.57)	0.38 (0.04-0.72)
48 h	0.31 (0.08-0.54)	0.11 (0.02-0.20)	0.25 (0.01-0.49)	0.34 (0.00-0.68)

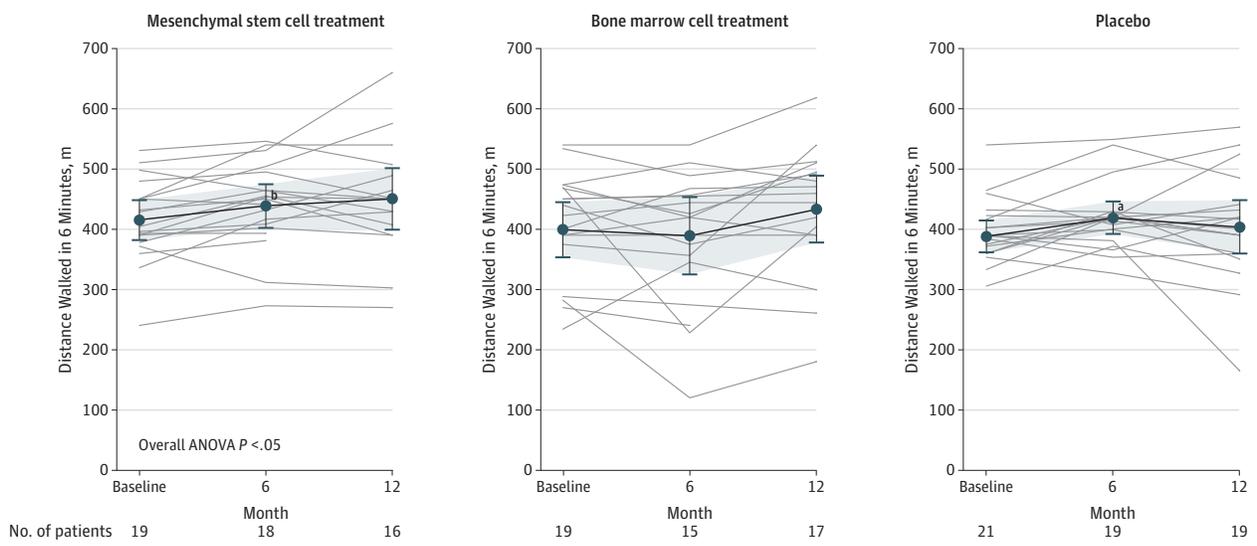
^a 95% confidence interval was estimated using the exact binomial proportion.

^b Major adverse cardiac event are defined as the composite incidence of (1) death, (2) hospitalization for worsening heart failure, or (3) nonfatal recurrent

myocardial infarction; serious adverse events and adverse events are categorized according to MedDRA by system organ class.

^c No statistically significant difference was noted among any parameter.

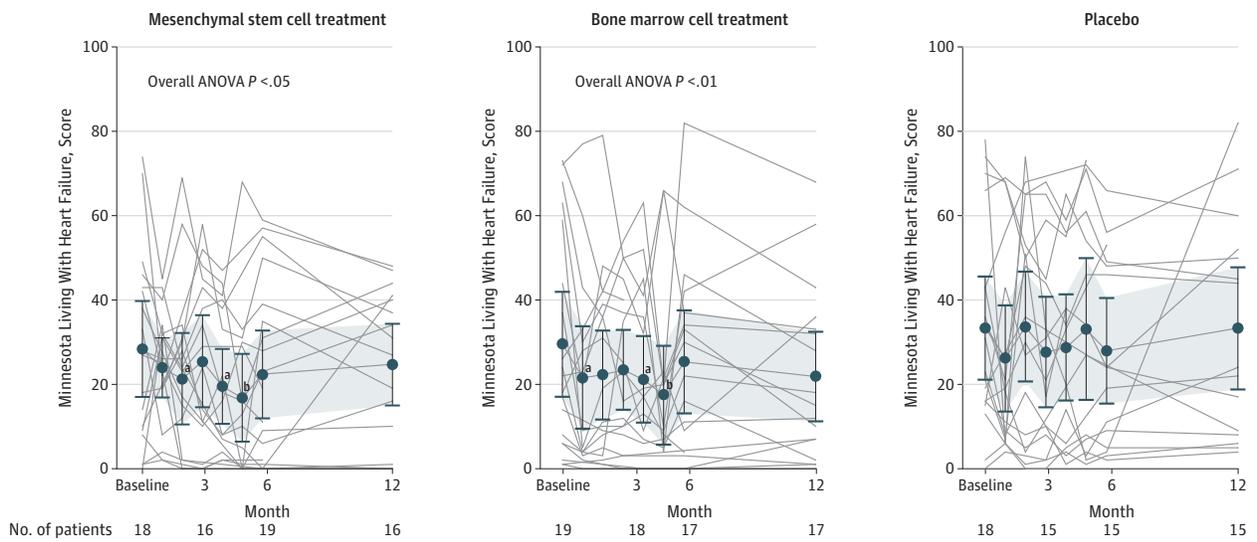
Figure 2. Impact of Transcatheter Stem Cell Injection of Mesenchymal Stem Cells, Bone Marrow Cells, or Placebo on the 6-Minute Walk Distance



Patients in the mesenchymal stem cell group exhibited a significant increase in 6-minute walk distance when 6-month and 12-month time points were compared to baseline in a repeated measures model ($P = .03$). No significant difference was observed for patients in the bone marrow cell group ($P = .73$) or in

the placebo group ($P = .25$). Data markers represent means; error bars, 95% CIs. Analysis of variance (ANOVA) was conducted with repeated measures. ^a Within group, $P < .05$. ^b Within group, $P < .01$.

Figure 3. Impact of Transcatheter Stem Cell Injection of Mesenchymal Stem Cells, Bone Marrow Cells, or Placebo on Minnesota Living With Heart Failure Score



Minnesota Living With Heart Failure questionnaire score improved in a repeated measures analysis of variance compared with baseline for the mesenchymal stem cell group ($P = .02$) and the bone marrow group ($P = .005$) but not the placebo group ($P = .38$). Repeated measures analyses of variance for model P values: treatment group, $P = .29$; time, $P = .01$; treatment group \times time, $P = .71$.

Data markers represent means; error bars, 95% CIs. Analysis of variance (ANOVA) was conducted with repeated measures. ^a Within-group, $P < .05$. ^b Within-group, $P < .01$.

Myocardial Infarct Size and Regional and Global Function

Infarct scar was assessed by cardiac MRI or CT^{18,22} and was expressed as absolute values of myocardial scar mass and as percentage of LV mass (scar size/LV mass). Both mesenchymal stem cells and bone marrow mononuclear cells reduced absolute scar mass but only mesenchymal stem cells reduced scar

size as a percentage of the LV mass. Scar mass as a fraction of LV mass decreased 18.9% (95% CI, -30.4% to -7.4%; within-group $P = .004$; Figure 4) 12 months after mesenchymal stem cells while remaining unchanged with bone marrow mononuclear cells (-7.0%; 95% CI, -15.7% to 1.7%; within-group $P = .11$), and placebo (-5.2%; 95% CI, -16.8% to 6.5%; within-

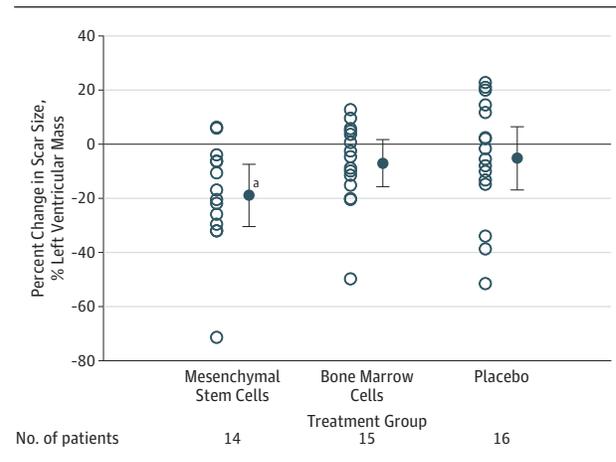
group $P = .36$). The change in scar mass as a fraction of LV mass relative to their respective placebo was -17.67% (95% CI, -35.85% to 0.51% ; $P = .06$) in the mesenchymal stem cell group and 2.1% (95% CI, -15.4% to 19.6% ; $P = .80$) in the bone marrow group.

Furthermore, at 12-month, viable tissue mass significantly increased only in the mesenchymal stem cell group (eFigure 1 in the Supplement) with a mean change of 8.4% (95% CI, 3.1% to 13.7% ; within-group $P = .005$) but not in the bone marrow group (3.4% ; 95% CI, -1.5% to 8.3% ; within-group $P = .16$), or in the placebo group (-1.1% ; 95% CI, -8.0% to 5.8% ; within-group $P = .73$). In an exploratory comparison analysis, the increase in viable tissue mass with mesenchymal stem cells differed significantly from the change in placebo (9.4% ; 95% CI, -0.4% to 19.3% ; $P = .05$; eFigure 1 in the Supplement), but there was no difference between the bone marrow and placebo groups (1.87% ; 95% CI, -3.64% to 12.73% ; $P = .26$). When considering patients studied with serial cardiac MRI, patients in the mesenchymal stem cell group exhibited a progressive, time-dependent decrease in scar mass as a fraction of LV mass ($P < .001$, Figure 5 and Figure 6).

The mean absolute mass of myocardial scar before injection was 26.6 g (95% CI, $18.6\text{--}34.6\text{ g}$) at baseline and 14.0 g (95% CI, $9.9\text{--}18.1\text{ g}$) at 12 months, corresponding to a 32.9% reduction (95% CI, -44.9% to -20.9% ; $P < .001$) in the mesenchymal stem cell group. Scar mass also decreased 23.1% in the bone marrow group (95% CI, -36.4% to -9.7% ; $P = .002$) and 15.3% in the placebo group (95% CI, -29.3% to -1.27% ; $P = .04$). Scar mass differed significantly at 12 months relative to their respective placebo cohort in the mesenchymal stem cell group

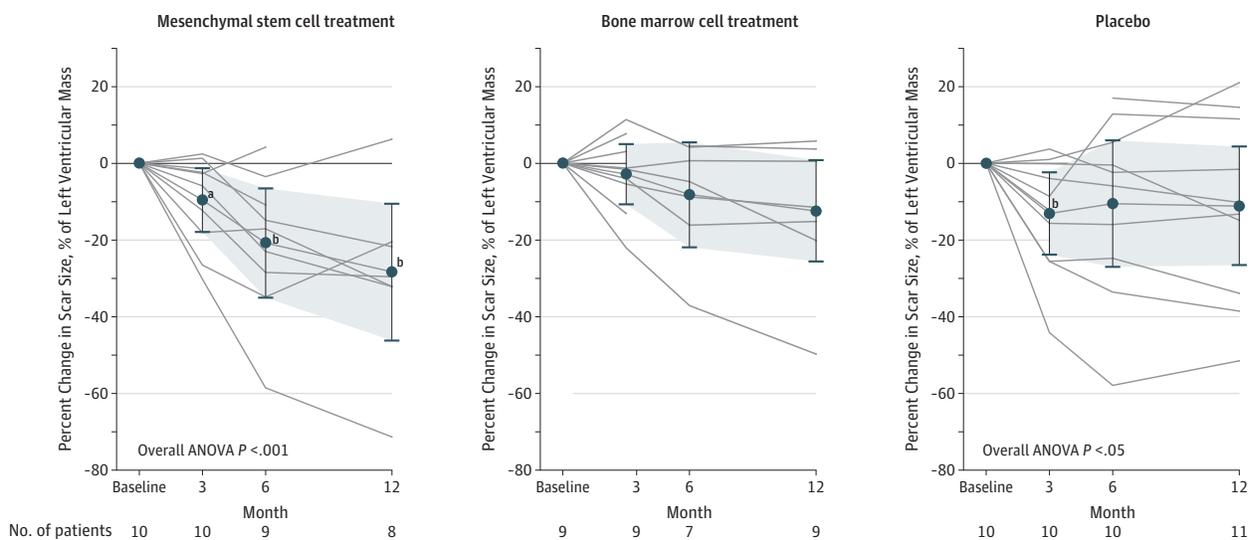
(-29.98 g ; 95% CI, -48.35 to -11.13 g ; $P = .003$) but not in the bone marrow group (4.58 g ; 95% CI, -18.43 to 27.58 g ; $P = .68$). End-diastolic volume, end-systolic volume, LV ejection fraction, or end-diastolic sphericity index did not significantly change in within-group or between-group comparisons (eFigure 1 in the Supplement).

Figure 4. Percent Change in Scar Size as a Percentage of Left Ventricular Mass



The 14 patients treated with mesenchymal stem cells (MSCs) exhibited a significant reduction in scar size ($P = .004$) as a percentage of left ventricular mass with no differences for the 15 patients treated with bone marrow cells or the 16 patients in the placebo group. The overall analysis of variance was $P = .13$. Data markers represent means; error bars, 95% CIs.
^a Within group, $P < .01$.

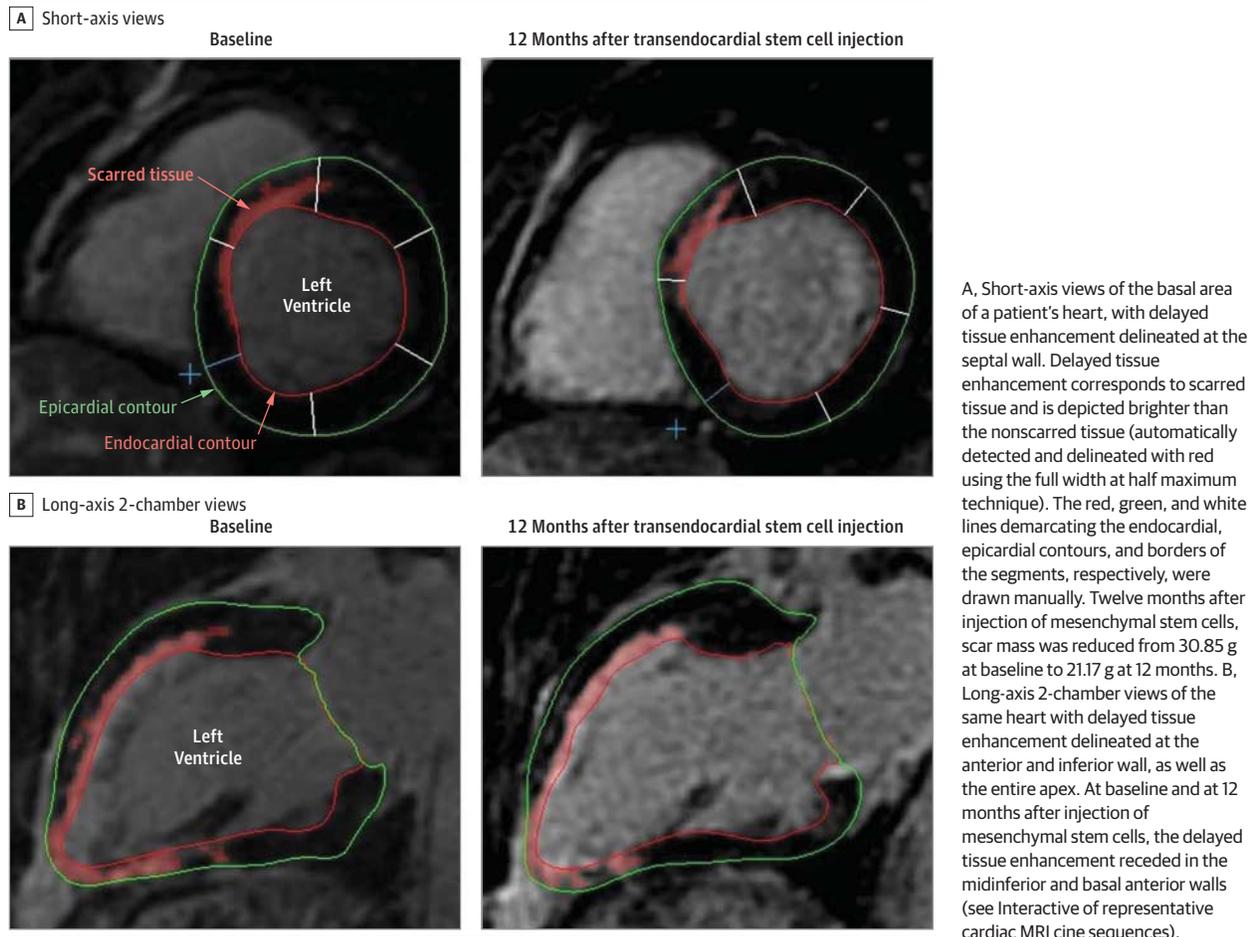
Figure 5. Impact of Transendocardial Stem Cell Injection of Mesenchymal Stem Cells, Bone Marrow Cells, or Placebo on the Scar Size



Significant reduction in scar size as the percentage of left ventricular mass for patients treated with mesenchymal stem cells (MSCs) and those in the placebo group who underwent serial magnetic resonance imaging. Repeated measures of analysis of variance model P values: treatment group, $P = .99$; time, $P = .007$; treatment group \times time, $P = .22$. Data markers represent means; error bars,

95% CIs. Analysis of variance (ANOVA) was conducted with repeated measures.
^a Within group, $P < .05$ vs baseline.
^b Within group, $P < .01$ vs baseline.

Figure 6. Cardiac Magnetic Resonance Images From a Representative Patient Before and 12 Months After Mesenchymal Stem Cell Injection



Regional Function

Regional myocardial function measured as peak Eulerian circumferential strain at the site of injection (Interactive of representative cardiac MRI cine sequences) was improved by mesenchymal stem cells with a mean absolute change from baseline at 12 months -4.9 (95% CI, -13.3 to 3.5 ; within-group repeated measures $P = .03$) for the mesenchymal stem cell group, -2.1 (95% CI, -5.5 to 1.3 ; within-group repeated measures $P = .21$) for the bone marrow group and -0.03 (95% CI, -1.9 to 1.9 ; within-group repeated measures $P = .14$) for the placebo group (eFigure 2 in the Supplement).

Discussion

Cell therapy offers promise for treating chronic ischemic heart disease,^{1-3,5,7,13,23-27} but safety and efficacy remain uncertain. The TAC-HFT study was designed to provide a rigorous placebo-controlled and double-blinded safety assessment using 2 leading candidates for cell therapy, bone marrow derived mesenchymal stem cells and fresh bone marrow mononuclear cells.¹⁴ Transendocardial injection of both cell types was not associated with an increased risk of adverse effects nor was

ectopic tissue formation detected, although the sample precludes any definitive statement about safety. We also show that mesenchymal stem cells exert regenerative and antifibrotic effects within the myocardium and that these effects are associated with improved functional capacity and quality of life. Ongoing exploration of cell-based therapy for ischemic cardiomyopathy is warranted.

Although cell therapy for acute MI has been extensively studied, the challenges of treating chronic infarction are mechanistically distinct. In acute MI, anti-inflammatory and other healing influences could be invoked, whereas in chronic infarction the regenerative and antifibrotic potential of stem cells may be required. Consistent with preclinical mechanistic studies^{18,28-33} and previous clinical studies, our data indicate biological activity of these cells in vivo after TESI. Dose and delivery are critical determinants of outcome. In the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis Pilot Study (POSEIDON) clinical trial of patients with ischemic cardiomyopathy, mesenchymal stem cells (both autologous and allogeneic) produced significant scar size reductions, with an inverse dose response; the effect of 20 million mesenchymal stem cells exceeded that of 200 million.¹⁹ Other studies have indicated

that infarct size reduction may be the predominant outcome of cell-based therapy.^{23,25,26,32,34}

Exploratory analyses of TAC-HFT data suggest that the efficacy of mesenchymal stem cells may possibly exceed that of bone marrow mononuclear cells, yet these findings are limited by small sample size; thus, conclusions are preliminary. Bone marrow mononuclear cells reduced absolute scar mass and improved the Minnesota Living With Heart Failure score, suggesting a possibility of efficacy. Interestingly, patients receiving placebo injections showed some evidence of scar reduction at 3 months, which did not further change over time; however, in neither the bone marrow mononuclear cell nor placebo groups did the scar as a percentage of LV mass decrease, suggesting that mechanisms other than myocardial regeneration may explain the improvements in these groups. Mesenchymal stem cells were associated with decreasing scar fraction and increasing viable myocardial mass, suggesting true myocardial regeneration. We detected correlation between scar reduction and improved Living With Heart Failure score functional status, and this was particularly evident in the mesenchymal stem cell group (eFigure 3A and 3B in the Supplement).

Although ejection fraction improvements have not been consistently shown in clinical trials of cell therapy,³⁵ it is important to note that scar size is highly predictive of ventricular arrhythmias, LV remodeling, heart failure, and mortality.^{36,37} Although our study was not powered for mortality outcomes, infarct size reductions are of a magnitude that might have the potential of a mortality benefit. Efficacy findings were detected in several clinical outcome measures, but definitive demonstration of the value of TESI remains for future trials, including in the sickest patients for whom cell therapy might answer an urgent unmet need.

Mechanistically, mesenchymal stem cells reduce tissue fibrosis by releasing antifibrotic matrix metalloproteinases¹³ and stimulate neovascularization^{13,30,38,39} and cardiomyocyte regeneration both primarily and by promoting endogenous stem cell proliferation.⁴⁰ The findings of the TAC-HFT trial are consistent with observations from animal models and support that these mechanisms are operative in the human heart.

This study used both cardiac MRI and multidetector CT scanning to evaluate heart function and infarct size. The sophisticated cardiac phenotyping of MRI can be repeated without accumulating radiation exposure and can be used in many patients with implanted devices,¹⁶ although artifact from intracardiac defibrillating leads may obscure parts of the heart.

Computed tomography also allows measurement of cardiac function and infarct size.^{18,41} Either cardiac MRI or CT were both performed at baseline and at 12 months; patients studied by MRI also had LV assessment at 3 and 6 months.¹³ With MRI, myocardial scar was determined from delayed enhanced images. With CT, we analyzed the early enhancement defect in accordance with the POSEIDON trial¹⁹; this may detect infarction as well as severe resting ischemia,⁴² but by excluding individuals with active ischemia, early enhancement defects in TAC-HFT reasonably measure scar size. Three-dimensional echocardiography could have offered a unified approach to measuring LV dimension in all patients but may not discern changes in infarct scar size.⁴³

Future refinements in cell-based therapy may lead to greater effectiveness of the approach. Cardiac stem cells exerted highly favorable effects in the Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy (SCIPIO) trial²³; tissue-derived cells and cell combinations³³ are both under development in patients with ischemic cardiomyopathy, and both autologous and allogeneic options are being evaluated.²⁷ This study and the POSEIDON¹⁹ trial highlight the importance of carefully delineating optimal delivery and dosing.

Limitations

Within-group efficacy improvements were detected by analyses of several outcome measures for mesenchymal stem cell and a few for bone marrow mononuclear cells, but these differences were not significant in most cases when compared across group with placebo. This in part reflects that the study was not powered to draw definitive efficacy comparisons between cell types. Multiple comparisons were conducted, further limiting the conclusions.²¹ Although, this and other studies support the safety of delivering cell-therapy by transendocardial injection, the sample size limits the strength of the conclusion, so larger studies are warranted (eFigure 3 in the Supplement).

Conclusions

In this preliminary study, TESI with autologous mesenchymal stem cells or bone marrow mononuclear cells appeared to be safe in patients with chronic ischemic cardiomyopathy and LV dysfunction. These results provide the basis for larger studies to provide definitive assessment of safety and to assess efficacy of this new therapeutic approach.

ARTICLE INFORMATION

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Author Affiliations: The Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine (Heldman, DiFede, Zambrano, Trachtenberg, Karantalis, Mushtaq, Williams, Suncion, McNiece, Soto, Lopera, Feigenbaum, Oskouei, Byrnes, Sierra, Pujol, Delgado, Gonzalez, Rodriguez, Bagno, da Silva, Schwarz, Hare); Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida (Heldman,

Zambrano, Trachtenberg, Mushtaq, McNiece, Soto, Lopera, Miki, Willens, Hendel, Mitrani, Feigenbaum, Oskouei, Byrnes, Lowery, Hare); Department of Radiology, University of Miami Miller School of Medicine, Miami, Florida (Fishman, Ghersin); Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida (Williams); Miami Veterans Affairs Healthcare System, Miami, Florida (Lopera); Biocardia Corporation, San Carlos, California (Rouy, Altman, Foo); EMMES Corporation, Rockville, Maryland (Anderson, Mendizabal); MD Anderson Cancer Center, Houston, Texas. (McNiece).

Author Contributions: Drs Hare and Heldman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Heldman, DiFede, Fishman, McNiece, Feigenbaum, Rouy, Altman, Schwarz, Mendizabal, Hare.

Acquisition of data: Heldman, DiFede, Fishman, Zambrano, Trachtenberg, Mushtaq, Williams, Suncion, Ghersin, Soto, Lopera, Willens, Mitrani, Pattany, Feigenbaum, Oskouei, Byrnes, Lowery, Sierra, Pujol, Delgado, Gonzalez, Rodriguez, Wong Po Foo, da Silva, Schwarz, Mendizabal, Hare.

Analysis and interpretation of data: Heldman, Fishman, Karantalis, Williams, Suncion, Ghersin, Soto, Lopera, Miki, Hendel, Feigenbaum, Oskouei, Bagno, Anderson, Mendizabal, Hare.

Drafting of the manuscript: Heldman, Difede, Fishman, Zambrano, Suncion, Miki, Delgado, Gonzalez, Bagno, Schwarz, Mendizabal, Hare.

Critical revision of the manuscript for important intellectual content: Heldman, Difede, Fishman, Trachtenberg, Karantalis, Mushtaq, Williams, Suncion, McNiece, Ghersin, Soto, Lopera, Willens, Hendel, Mitrani, Pattany, Feigenbaum, Oskouei, Byrnes, Lowery, Sierra, Pujol, Rodriguez, Rouy, Altman, Wong Po Foo, da Silva, Anderson, Schwarz, Mendizabal, Hare.

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Study supervision: Heldman, Difede, Zambrano, Fishman, Suncion, Lopera, Pattany, Hare.

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