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ORIGINAL INVESTIGATIONS

Randomized Trial of Targeted Transendocardial Mesenchymal Precursor Cell Therapy in Patients With Heart Failure

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ABSTRACT

BACKGROUND Mesenchymal precursor cells (MPCs) are allogeneic, immunoselected cells with anti-inflammatory properties that could improve outcomes in heart failure with reduced ejection fraction (HFrEF).

OBJECTIVES This study assessed the efficacy and safety of MPCs in patients with high-risk HFrEF.

METHODS This randomized, double-blind, multicenter study evaluated a single transendocardial administration procedure of MPCs or sham-control in 565 intention-to-treat patients with HFrEF on guideline-directed therapies. The primary endpoint was time-to-recurrent events caused by decompensated HFrEF or successfully resuscitated symptomatic ventricular arrhythmias. Hierarchical secondary endpoints included components of the primary endpoint, time-to-first terminal cardiac events, and all-cause death. Separate and composite major adverse cardiovascular events analyses were performed for myocardial infarction or stroke or cardiovascular death. Baseline and 12-month echocardiography was performed. Baseline plasma high-sensitivity C-reactive protein levels were evaluated for disease severity.

RESULTS The primary endpoint was similar between treatment groups (HR: 1.17; 95% CI: 0.81-1.69; $P = 0.41$) as were terminal cardiac events and secondary endpoints. Compared with control subjects, MPCs increased left ventricular ejection fraction from baseline to 12 months, especially in patients with inflammation. MPCs decreased the risk of myocardial infarction or stroke by 58% (HR: 0.42; 95% CI: 0.23-0.76) and the risk of 3-point major adverse cardiovascular events by 28% (HR: 0.72; 95% CI: 0.51-1.03) in the analysis population (n = 537), and by 75% (HR: 0.25; 95% CI: 0.09-0.66) and 38% (HR: 0.62; 95% CI: 0.39-1.00), respectively, in patients with inflammation (baseline high-sensitivity C-reactive protein ≥2 mg/L).

CONCLUSIONS The primary and secondary endpoints of the trial were negative. Positive signals in prespecified, and post hoc exploratory analyses suggest MPCs may improve outcomes, especially in patients with inflammation. (J Am Coll Cardiol 2023;81:849-863) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

GDMT = guideline-directed medical therapy

HFrEF = heart failure with reduced ejection fraction

hsCRP = high-sensitivity C-reactive protein

ITT = intention-to-treat

LVEDV = Left ventricular end diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

MPC = mesenchymal precursor cell

NYHA = New York Heart Association

TCE = terminal cardiac event

Despite advances in therapy, morbidity and mortality for patients with heart failure with reduced ejection fraction (HFrEF) remain high. Most guideline-directed medical therapy (GDMT) recommended for this population targets neurohormonal pathways that are activated in patients with HFrEF. However, inflammation plays a pivotal role in the initiation and progression of heart failure. Acute and chronic inflammation in heart failure initiate multiple pathophysiological pathways, factors, and processes that lead to an increased risk of morbidity and mortality.[1,2] This underlying inflammation in conjunction with neurohormonal activation contributes to a constellation of clinical manifestations that drive disease progression. Historically, maladaptive changes have been the focus of pharmacological therapies for HFrEF. In a parallel fashion, atherosclerosis is mediated by immune and inflammatory processes that can lead to myocardial infarction (MI) and stroke. However, efforts to improve outcomes resulting from both heart failure and atherosclerosis through cardiac cell therapy as well as anti-inflammatory interventions have met with little success in either condition.[3-5]

SEE PAGE 864

Mesenchymal precursor cells (MPCs) are allogeneic STRO-1/STRO-3-positive cells that are immunoselected from human bone marrow mononuclear cell populations obtained from young adult donors. These cells have immunomodulatory properties and express surface markers for proinflammatory cytokines produced by activated macrophages and T cells. Results from preclinical studies suggest that MPCs and mesenchymal stromal cells may reduce macrophage-dependent inflammation and improve microvascular blood flow via the release of multiple critical angiogenic factors that act in concert to induce microvascular capillary networks in ischemic tissues. In addition, release of these factors reduces proinflammatory cytokines resulting in increased endothelial nitric oxide synthase activity, nitric oxide bioavailability, and reversal of endothelial dysfunction. These effects have the potential to improve myocardial perfusion and contractility while reversing cardiac and systemic endothelial dysfunction. Thus, MPCs appear to target many of the pathological factors that contribute to clinical events in patients with HFrEF.[6-12] Furthermore, results from a phase 2 dose-finding study suggested that MPCs may reduce major adverse cardiovascular events (MACE) associated with HFrEF.[13]

The DREAM-HF (Double-Blind Randomized Assessment of Clinical Events With Allogeneic Mesenchymal Precursor Cells in Heart Failure) trial was designed to assess the efficacy and safety of MPCs in patients with high-risk HFrEF.

METHODS

TRIAL DESIGN AND PARTICIPANTS. The DREAM-HF trial was a phase 3, multinational, randomized, double-blind, sham-controlled clinical trial in patients with New York Heart Association (NYHA) functional class II or III HFrEF of ischemic or nonischemic etiology.[7,14] The primary objective was to examine the effect of MPCs on recurrent, nonfatal decompensated heart failure events or life-threatening ventricular arrhythmias in patients with HFrEF. Secondary objectives included assessing the effects of MPCs on prespecified clinical events and on left ventricular systolic function and volumes. Exploratory objectives included studying the association of baseline plasma levels of the biomarker high-sensitivity C-reactive protein (hsCRP) with disease severity and clinical outcomes.

We enrolled patients (18-80 years of age) with high-risk but stable HFrEF who were treated with optimal GDMT and previous coronary revascularization when appropriate. Randomization occurred at 51 study sites across North America (Supplemental Table 1). Key inclusion criteria included left ventricular ejection fraction (LVEF) ≤40% by 2-dimensional echocardiogram or ≤35% by multigated acquisition scan, which was acquired within 42 days before study intervention. The study population was enriched at enrollment to target patients with more severe

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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disease by the presence of 1 or more of the following: 1) at least 1 heart failure hospitalization between 1 and 9 months before screening; 2) at least 1 outpatient urgent care heart failure visit requiring intravenous diuretic, vasodilator, and/or positive inotropic therapy between 1 and 9 months before screening; and/or 3) plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) >1,000 or >1,200 pg/mL for patients with atrial fibrillation. Key exclusion criteria included patients who were candidates for coronary revascularization, who had NYHA functional class I or IV symptoms, and who had an acute MI or unstable angina within 1 month of screening. Patients listed as heart transplant candidates were eligible for the study if they met all inclusion criteria without having any exclusion criteria. All inclusion and exclusion criteria are presented in Supplemental Table 2.

In mid-2017, we confirmed in a treatment-blind manner that patients with baseline NYHA functional class III heart failure had relatively high cardiac and cardiovascular mortality rates. Thus, a U.S. Food and Drug Administration–reviewed protocol amendment was instituted to enrich and replenish this subgroup in the trial population. Initiated in late 2017, this amendment ensured future enrollment of only NYHA functional class III patients but did not change eligibility criteria for the trial (beyond enrolling only NYHA functional class III patients). All patients with baseline NYHA functional class II HFrEF who were randomized before the protocol adaptation were followed to study completion and were included in the final data analyses. The hypotheses being tested in the trial and the primary endpoint of the trial were unchanged.

The trial conformed to the Declaration of Helsinki and was approved by the Institutional Review Board at each study center. The study is registered at clinicaltrials.gov (NCT02032004). The trial was sponsored by Mesoblast, Inc. Written informed consent was obtained for all patients. All amendments to the study are described in the Supplemental Appendix. An independent data and safety monitoring committee oversaw the trial conduct. Clinical outcomes including all prespecified clinical events and all deaths were prospectively adjudicated by an independent blinded Clinical Endpoint Committee at Brigham and Women's Hospital in Boston, Massachusetts, USA, using prespecified causal categories and criteria (Supplemental Table 3).

RANDOMIZATION AND MASKING. Patients were randomly assigned in a 1:1 ratio with computer-generated randomization using interactive response technology to receive either transendocardial injections of MPCs or a sham control procedure (control group). Patients who underwent the control procedure did not receive any placebo transendocardial injections. Randomization was stratified by NYHA functional class II or III, the presence of ischemic vs nonischemic cardiomyopathy, and geographic region (United States vs outside of the United States) to ensure that there was a balance between MPC and control patients within each group.

Blinding of the study was achieved by creating a "firewall" between an unblinded team that performed the MPC/sham catheterization procedure and a team blinded to patient treatment assignment that conducted all other aspects of the study. Blinding of the patient to treatment (MPC or control) assignment included conscious sedation, arterial access, and left ventricular angiography of all patients, and adherence to a written script in control patients over a similar timeframe as required for cell treatment.

PROCEDURES. Left ventriculography was performed in all randomized patients who underwent the index cardiac catheterization and had at least 1 catheter placed across the aortic valve. Patients in the control group had the pigtail angiography catheter removed, and no other catheter was placed in the left ventricle. Patients who were randomized to MPCs were expected to undergo cardiac mapping and transendocardial delivery of cells. The location for cell delivery was identified by left ventricular electrical mapping of viable but electrically abnormal myocardium using the NOGA Cardiac Navigational System in combination with the NogaStar Mapping Catheter (Johnson and Johnson). The MyoStar injection catheter was used to deliver approximately 150 million MPCs in 15 to 20 injection sites (in 0.2 mL volume containing 8-10 million MPCs).

After the index cardiac catheterization (day 0) in MPC and control patients, study site visits were conducted on day 10 and at months 1, 3, 6, and 12 (and every 6 months thereafter) for follow-up assessments (Supplemental Table 4). Telephone contact was made at prespecified time points throughout the study.

MESENCHYMAL PRECURSOR CELLS. Allogeneic MPCs derived from the bone marrow of 3 healthy adult donors were used in the study. In brief, MPCs are isolated from bone marrow mononuclear cells using a monoclonal antibody against STRO-3 and magnetic bead-based cell separation technology. Immunoselected cells are culture expanded using proprietary techniques and stored in liquid nitrogen until use. The final cell product must pass a panel of quality control release tests before use in humans. Cell procurement, processing, cryopreservation, and storage procedures are performed under cGMP conditions.

ENDPOINTS. The primary endpoint was time to recurrent nonfatal hospitalization or urgent care events caused by decompensated heart failure or successfully resuscitated high-grade symptomatic ventricular arrhythmias. This endpoint was analyzed using a joint frailty model that takes into account terminal cardiac events (TCE) defined as left ventricular assist device implantation, heart transplant, placement of an artificial heart, or cardiac death.[15] These events all resulted in the native left ventricle no longer providing the predominant (or any) source of cardiac output to the patient's vital organs.

Data for all endpoints were recorded throughout the trial. All events were captured as they occurred from the time of initial treatment to the last patient at the last visit. Hierarchical secondary endpoints included components of the primary endpoint as well as time-to-all-cause death. Other prespecified efficacy and safety endpoints included MIs (nonfatal or fatal), strokes (nonfatal or fatal), or mortality (cardiac death, cardiovascular death, and all-cause death). An exploratory post hoc 3-point MACE composite for time-to-first event for MI or stroke or cardiovascular death was evaluated. For the 3-point MACE, we defined the occurrence of a first-event MI or stroke as the day of onset of the MI or stroke and not the day of subsequent cardiovascular death.

To assess inflammation as a predictor of risk of MI or stroke or cardiovascular death, we performed prespecified subgroup analyses based on baseline plasma levels of hsCRP using hsCRP ≥2 mg/L as an indicator of important inflammation. This threshold was based on the analysis of the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial and previous evidence showing that elevated CRP levels are associated with inflammation and adverse outcomes in cardiovascular diseases.[2,7,16-21] Additionally, the study included prespecified secondary efficacy measures and endpoints related to left ventricular function (LVEF, left ventricular end-systolic volume [LVESV], and left ventricular end-diastolic volume [LVEDV]). These measurements were assessed for serial changes from baseline using echocardiographic imaging.

STATISTICAL ANALYSIS. This was an events-driven study using the intention-to-treat (ITT) population as the primary analysis data set. A supportive analysis data set was denoted as the analysis population (defined as all patients who underwent the index cardiac catheterization and had at least 1 catheter cross the aortic value). For these patients, the analyses were performed according to treatment group based on the randomization designation. The safety population was defined as all treated patients and analyzed according to the actual treatment each patient received regardless of randomization (MPC or control).

We based the ITT population sample size on Monte-Carlo simulations for 600 patients with an estimated total of 531 recurrent nonfatal decompensated heart failure events requiring hospitalization or urgent care treatment or successfully resuscitated cardiac death events. These recurrent nonfatal decompensated heart failure events provided approximately 93.5% power (with 91.4% for the low limit of 95% CI for the powers from all the simulations) at the 0.05 2-sided (0.025 1-sided) significance level to detect at least a 40% risk reduction (HR: 0.6) in recurrent nonfatal decompensated heart failure adjusted for TCEs. For patients with a TCE, events that occurred after the TCE were censored for primary analysis purposes.

The primary endpoint analysis was performed using the joint frailty model. This model simultaneously analyzes recurrent events and an associated time to first terminal cardiac event taking into account the relationship between the 2 processes (see Supplemental Appendix for details).

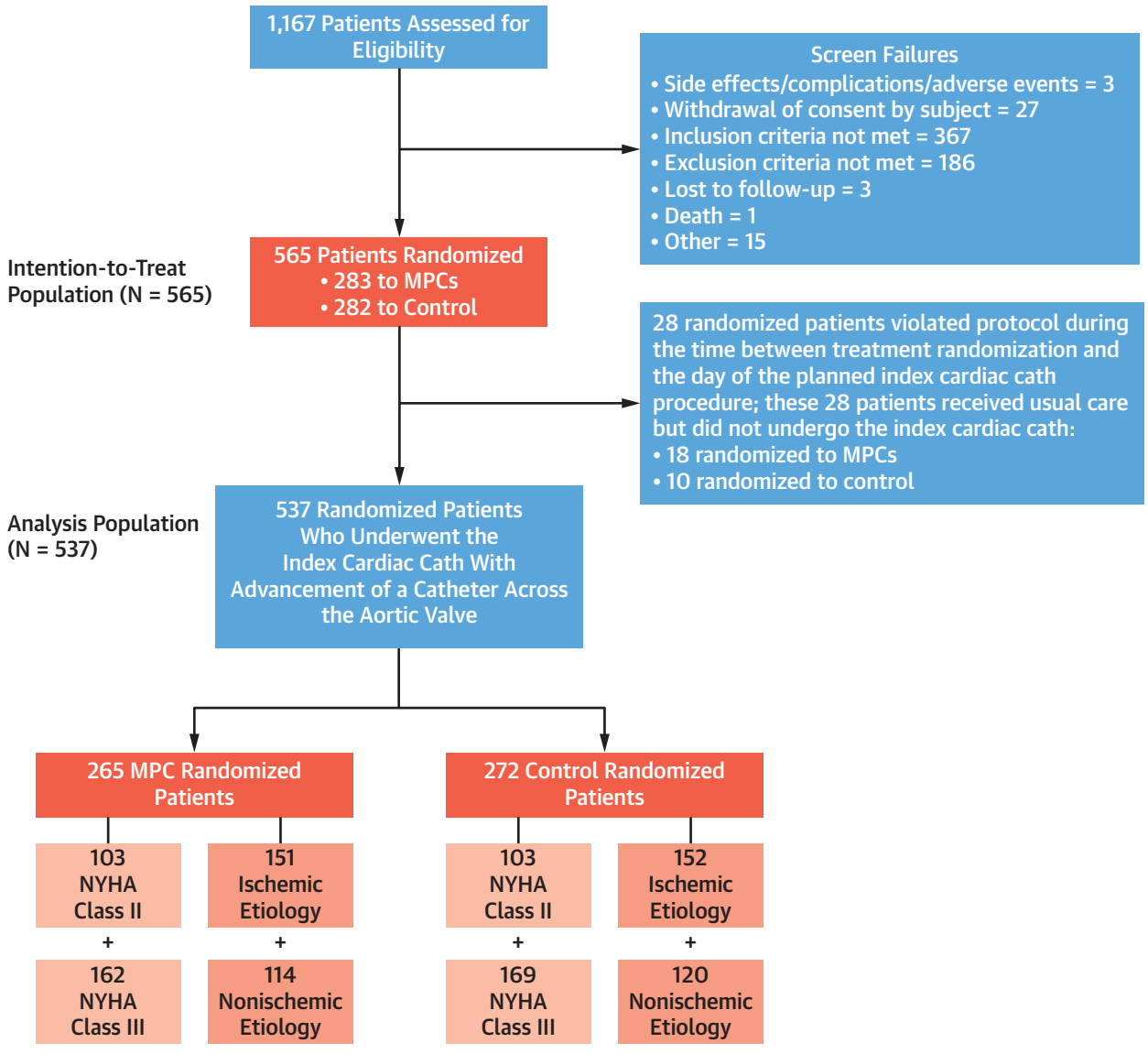
Secondary time-to-event endpoints were analyzed using Cox proportional hazards model with treatment as the main effect adjusting for baseline covariates of NYHA functional class (class II vs class III), presence of ischemic vs nonischemic etiology for cardiomyopathy per baseline case report form designation, and geographic region (the United States vs outside of the United States). Events after the first TCE were censored for the analyses.

Analyses were repeated for subgroups, which included but were not limited to baseline NYHA functional class, sex and other baseline characteristics, hsCRP (<2 mg/L vs ≥2 mg/L), and NT-proBNP (≤1,000 ng/mL vs >1,000 ng/mL).

Prespecified analyses of time to cardiac death, cardiovascular death, MI (nonfatal or fatal), stroke (nonfatal or fatal), and a composite of MI or stroke were performed. Post hoc exploratory analyses of time-to-first event for a 3-point MACE were performed.

For time to 3-point MACE and time to MI or stroke, all deaths other than the event of interest (ie, fatal MI, fatal stroke, or cardiovascular death for corresponding analyses) were considered competing risk events. We confirmed proportional hazards assumptions using the supremum test.[22] We created Aalen-Johansen cumulative incidence curves and calculated cause-specific HRs with 95% Wald confidence limits. These analyses were repeated for patients with or without

FIGURE 1 **Enrollment and Randomization**



The intention-to-treat (ITT) population includes all randomized patients (n = 565). The analysis population includes all randomized patients who underwent the index cardiac catheterization with advancement of a catheter across the aortic valve (n = 537). MPC = mesenchymal precursor cell; NYHA = New York Heart Association.

baseline systemic inflammation (hsCRP ≥2 and <2 mg/L). The interaction terms were not significant for the hsCRP covariate in all analyses. However, these subgroups are clinically important and were examined for exploratory purposes.

To assess the relative contributions of individual components of the TTFE composite 3-point MACE, we performed special competing risk analyses where for all 3 MACE components, the 2 other components were assumed as competing risk events to be counted as a MACE. Aalen-Johansen cumulative incidence function plots were created for all treated patients (n = 537) and for the hsCRP subgroups.

Echocardiographic data were acquired at baseline and 6 and 12 months after the index cardiac catheterization procedure. These data were analyzed for evidence of improved left ventricular systolic function and change from baseline for LVESV and LVEDV. Echocardiographic variables were analyzed using a mixed model for repeated measures methodology

TABLE 1 Demographic and Patient Characteristics at Baseline in the Intention-to-Treat Population (N = 565)

	MPCs (n = 283)	Control (n = 282)
Age, y[a]	62.7 ± 10.9	62.6 ± 10.4
Sex		
Male	222 (78.4)	221 (78.4)
Female	61 (21.6)	61 (21.6)
Race		
White	213 (75.3)	218 (77.3)
Black	59 (20.8)	51 (18.1)
Asian	3 (1.1)	4 (1.4)
American Indian or Alaskan Native	1 (0.4)	3 (1.1)
Native Hawaiian or other Pacific Islander	1 (0.4)	2 (0.7)
Other	6 (2.1)	4 (1.4)
Ethnicity		
Hispanic or Latino	18 (6.4)	17 (6.0)
Not Hispanic or Latino	265 (93.6)	265 (94.0)
Region		
United States	267 (94.3)	268 (95.0)
Outside the United States (Canada)	16 (5.7)	14 (5.0)
Body mass index, kg/m^2	30.5 ± 6.8	29.7 ± 6.3
Systolic blood pressure, mm Hg	121.0 ± 19.6	120.5 ± 19.3
Diastolic blood pressure, mm Hg	73.0 ± 11.8	72.2 ± 12.2
Pulse rate, beats/min	71.3 ± 11.4	72.6 ± 12.2
Cardiomyopathy etiology		
Ischemic	161 (56.9)	158 (56.0)
Nonischemic	122 (43.1)	122 (44.0)
NHYA functional class		
II	108 (38.2)	104 (36.9)
III	175 (61.8)	178 (63.1)
History of hypertension	233 (82.3)	222 (78.7)
History of diabetes	124 (43.8)	120 (42.6)
History of atrial fibrillation	111 (39.2)	109 (38.7)
Alcohol use		
None	178 (62.9)	181 (64.2)
Still consumes	105 (37.1)	101 (35.8)
Tobacco use		
Never	103 (36.4)	113 (40.1)
Current smoker	22 (7.8)	23 (8.2)
Ex-smoker	158 (55.8)	146 (51.8)
Years since heart failure diagnosis		
<1 y	14 (4.9)	14 (5.0)
≥1 to 5 y	113 (39.9)	101 (35.8)
≥5 y	156 (55.1)	167 (59.2)
Mean ± SD	7.5 ± 6.83	7.6 ± 6.83
Previous myocardial infarction	151 (53.4)	144 (51.1)
Previous stroke	32 (11.3)	19 (6.7)
Past peripheral artery disease	10 (3.5)	8 (2.8)
Coronary revascularization	164 (58.0)	156 (55.3)
Coronary artery bypass grafting	81 (28.6)	83 (29.4)
Percutaneous coronary intervention	137 (48.4)	124 (44.0)
Cardiac devices[b]	241 (85.2)	239 (84.8)
A-ICD	133 (47.0)	124 (44.0)
CRT device	108 (38.2)	115 (40.8)
CRT-P	3 (1.1)	0 (0.0)
Other CRT	2 (0.7)	9 (0.4)
CRT-D	103 (36.4)	114 (40.4)

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including treatment, visit, and treatment by visit as fixed factors; patient as a random factor; and covariates for the baseline value of the endpoint being analyzed, baseline NHYA functional class, country, and etiology of cardiomyopathy. Compound symmetry variance-covariance structure was used. Treatment differences for LVEF, LVESV, and LVEDV were calculated from comparisons of least squares means (LSM) of change from baseline at 6 and 12 months. The prespecified analyses did not include imputation for missing data. A sensitivity analysis was performed using the worst observation carried forward approach for missing data before the 12-month visit.

RESULTS

From March 3, 2014, to January 31, 2019, we screened 1,167 patients for eligibility, of whom 565 were randomized to the ITT population to undergo either cardiac mapping and transendocardial delivery of MPCs (n = 283) or sham mapping and sham cell-delivery procedures (n = 282) (**Figure 1**); 28 randomized patients did not undergo the day 0 cardiac catheterization procedure because of post-randomization disqualifying events. The analysis population comprised the resulting 537 patients, and 265 were randomized to MPC treatment and 272 to the control group (**Figure 1**). All patients in the analysis population proceeded to cardiac catheterization and underwent passage of at least 1 catheter across the aortic valve. Of those randomized to MPC treatment, 98.5% received at least 1 injection of cells, and 94% of those injected with cells received the prespecified 15 to 20 transendocardial injections (Supplemental Figure 1).

For all randomized patients, baseline demographics and characteristics were comparable for the MPC and control groups (**Table 1**). The mean time since HFrEF diagnosis was 7.5 years. An ischemic HFrEF etiology was present in 319 (56%) patients. NYHA functional class III patients (n = 353) had higher NT-proBNP and baseline plasma hsCRP values with a lower 6-minute walk time distance than did the NYHA functional class II patients (n = 212). Patients were followed for a mean of 30 months (maximum 66 months). Vital status (alive or dead) at the end of the trial was established for all randomized patients (n = 565).

In the ITT population (n = 565), we found no significant between-group differences in the primary endpoint of time to recurrent decompensated heart failure-related events. **Figure 2** displays the mean cumulative rate of recurrent nonfatal decompensated

heart failure events per 100 patients (ITT: HR: 1.17; 95% CI: 0.81-1.69; $P = 0.406$). Supplemental Figure 2 shows the components of the primary endpoint by number and rate of events. The key secondary composite TCE endpoint did not differ between MPC and control patients (Supplemental Figure 3). The prespecified hierarchically ranked secondary outcomes, including all-cause death, were not different between the treatment groups (Supplemental Figure 3); results are presented only as HR and 95% CI because the primary endpoint did not achieve conventional statistical significance.

Prespecified analyses for serial echocardiographic LVEF and left ventricular volumes were performed on all patients in the analysis population who qualified for echocardiograms (n = 532) and on subgroups based on baseline hsCRP levels ≥2 mg/L vs <2 mg/L. Compared with control subjects, all echocardiography-qualifying patients treated with MPCs showed a small but statistically significant beneficial effect on the LSM change from baseline for LVEF at 12 months ($P = 0.041$) (**Figure 3**, left upper panel) that was driven by the effect of MPCs in patients with hsCRP ≥2 mg/L (n = 298; $P = 0.008$) (**Figure 3**, middle upper panel). MPCs showed no effect on LSM change from baseline for LVEF at 12 months in patients with baseline hsCRP <2 mg/L (**Figure 3**, upper right panel). **Figure 3** also shows the LSM of change from baseline for LVESV and LVEDV at 12 months in all treated patients and in those with baseline hsCRP ≥2 and <2 mg/L. The mean absolute values for LVEF and left ventricular volumes at baseline and 12 months are shown in Supplemental Figure 4.

In a prespecified assessment of the analysis population (n = 537), MPCs decreased the risk of occurrence of TTFE for MI (nonfatal or fatal) or stroke (nonfatal or fatal) by 58% compared with control patients (cause-specific HR: 0.415; 95% CI: 0.228-0.756) (**Figure 4**, top panel). Compared with control subjects, MPCs decreased the incidence of MI alone by 67% and stroke alone by 56% (Supplemental Figures 5 and 6, respectively). Using a prespecified indicator of baseline systemic inflammation (plasma hsCRP ≥2 mg/L), we performed analyses on the effects of MPCs on clinical outcomes in patients with and without elevated inflammation.[19] In patients with baseline hsCRP ≥2 mg/L (n = 301), MPCs reduced the risk of TTFE for MI or stroke by 75% (cause-specific HR: 0.247; 95% CI: 0.092-0.662) (**Figure 4**, bottom left panel). Patients with baseline hsCRP <2 mg/L had a smaller benefit from MPCs (43% risk reduction; cause-specific HR: 0.573; 95% CI: 0.255-1.285) (**Figure 4**, bottom right panel).

TABLE 1 Continued

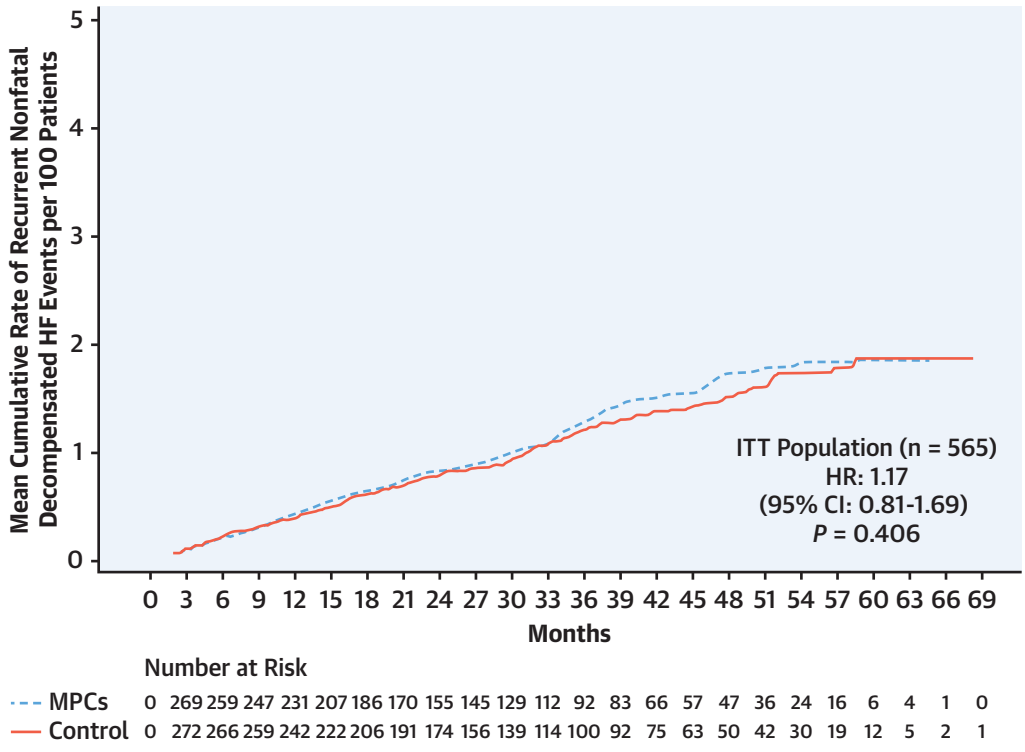
	MPCs (n = 283)	Control (n = 282)
Any type of defibrillator (AICD or CRT-D)	236 (83.4)	238 (84.8)
Cardiovascular medications		
All RAAS medications	239 (84.5)	237 (84.0)
ACE Inhibitors	128 (45.2)	109 (38.6)
ARBs	67 (23.7)	60 (21.3)
ARNi	71 (25.1)	54 (19.1)
Mineralocorticoid receptor agonists	167 (59.0)	173 (61.3)
Diuretic agents	276 (97.5)	272 (96.5)
Beta-blockers	270 (95.4)	274 (97.2)
Digitalis	83 (29.3)	64 (22.7)
Oral anticoagulants	64 (22.6)	60 (21.3)
Anti-platelet agents	205 (72.4)	188 (66.7)
SGLT-2 inhibitors	3 (1.1)	5 (1.8)
Statins	196 (69.3)	188 (66.7)
Echocardiographic imaging		
LVEF, %	28.6 ± 6.7	28.6 ± 6.9
LVESV, mL	149.8 ± 59.2	149.9 ± 65.8
LVEDV, mL	206.8 ± 68.6	206.4 ± 77.1
6-minute walk time distance, m	337 ± 84	346 ± 89
Biomarkers		
NT-proBNP, ng/L	2,305 ± 2,853	2,287 ± 2,976
hsCRP, mg/L	4.7 ± 7.3	6.1 ± 10.7
Laboratory measurements		
Sodium, mEq/L	139.8 ± 3.2	139.3 ± 3.0
Potassium, mEq/L	4.5 ± 0.5	4.5 ± 0.5
Chloride, mEq/L	98.9 ± 4.1	98.8 ± 3.9
Fasting glucose, mmol/L	6.7 ± 2.8	6.3 ± 2.2
Creatinine, μmol/L	108.9 ± 33.5	104.4 ± 31.6
BUN, mg/dL	8.7 ± 4.1	8.6 ± 3.9
Complete blood count		
Hemoglobin, g/dL	134.8 ± 17.0	135.7 ± 15.0
Hematocrit, %	41.5 ± 5.2	41.6 ± 4.5
WBC, K/cu mm	7.5 ± 2.2	7.5 ± 2.2
Platelet count, K/cu mm	205.3 ± 55.0	211.2 ± 56.2

Values are mean ± SD or n (%). Percentages are based on the number of patients in the treatment group. Baseline was defined as the last nonmissing assessment, including unscheduled assessments, before the day 0 study intervention. [a]Age was calculated relative to the date of informed consent. [b]Excludes stand-alone cardiac pacemaker.

ACE = angiotensin-converting enzyme; ARNi = angiotensin receptor-neprilysin inhibitor; BUN = blood urea nitrogen; CRT = cardiac resynchronization therapy; hsCRP = high-sensitivity C-reactive protein; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; MPC = mesenchymal precursor cells; NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system; SGLT = sodium-glucose cotransporter; WBC = white blood cell.

In an exploratory post hoc evaluation in the analysis population, MPCs substantially decreased the risk of TTFE for the composite 3-point MACE by 27% compared with control subjects (cause-specific HR: 0.725; 95% CI: 0.509-1.034) (**Figure 5**, top panel). In patients with high levels of baseline inflammation (hsCRP ≥2 mg/L), MPCs decreased the risk of TTFE of the composite MACE by 38% (cause-specific HR: 0.622; 95% CI: 0.385-1.005) (**Figure 5**, bottom left panel). Patients with baseline hsCRP <2 mg/L showed

FIGURE 2 Primary Endpoint for the Intention-to-Treat Population



The primary endpoint for the intention-to-treat population is shown as the mean cumulative rate of recurrent nonfatal decompensated heart failure events per 100 patients. HR, 95% CI, and *P* value were calculated from a Cox regression model. HF = heart failure; other abbreviations as in Figure 1.

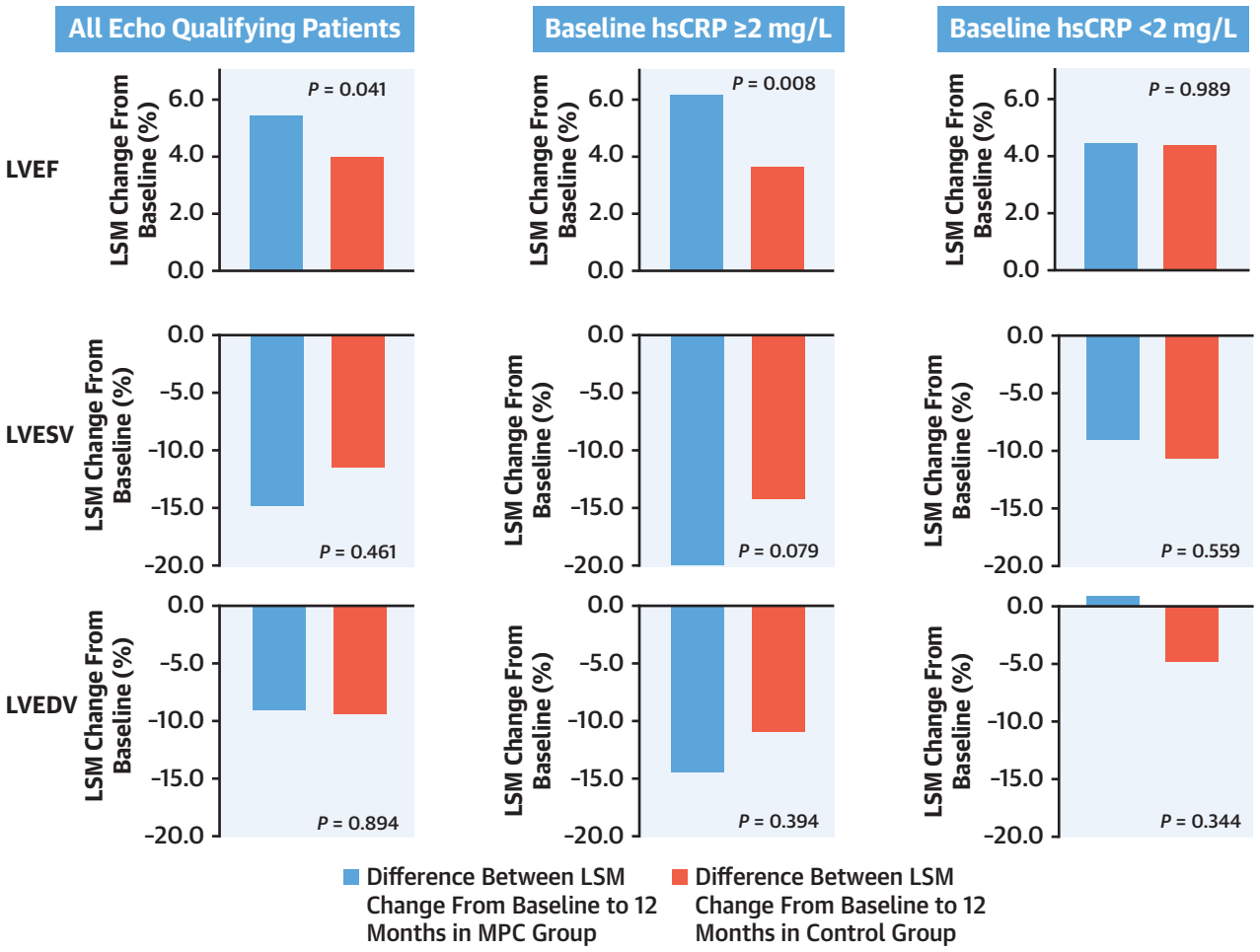
minimal MPC treatment effect (cause-specific HR: 0.863; 95% CI: 0,493-1.509) (Figure 5, bottom right panel). Using Aalen-Johansen cumulative incidence curves for time-to-first event of the individual components of the 3-point MACE when the other 2 components were considered competing risk events, we showed that each of the individual components of the composite 3-point MACE (MI, stroke, and cardiovascular death) contributed to the MPC treatment effect, especially in the high-risk prespecified subgroup with baseline systemic inflammation (Supplemental Figures 5 to 7). Proportional hazards assumptions were confirmed for these analyses (Supplemental Figure 8).

Adverse event rates were similar in MPC-treated and control patients (95.0% vs 96.7%, respectively). Serious adverse events were generally comparable in the 2 groups (control subjects: 191 of 276, 69.2%; MPCs: 170 of 261, 65.1%) (Supplemental Table 5). Adverse events related to intracardiac mapping or cell injection were rare. One patient with ITT randomization to the MPC group had a left ventricular perforation during mapping that resulted in the transendocardial cell injection procedure not being performed. MPC administration did not elicit immune-related responses in any patient. A low percentage of patients had a shift from negative at baseline to positive for HLA class I or HLA class II sensitivity during the study. There were no important differences in HLA responses against the allogeneic MPCs used in this trial.

DISCUSSION

DREAM-HF is the largest clinical trial of cell therapy in HFrEF to date. The primary endpoint of a reduction in recurrent nonfatal hospitalization or urgent care events because of decompensated heart failure or successfully resuscitated high-grade symptomatic ventricular arrhythmias and its associated key secondary endpoint (time-to-first TCE) were negative in our study. However, our findings suggest novel

FIGURE 3 Echocardiography Results of the LSM Change Analysis

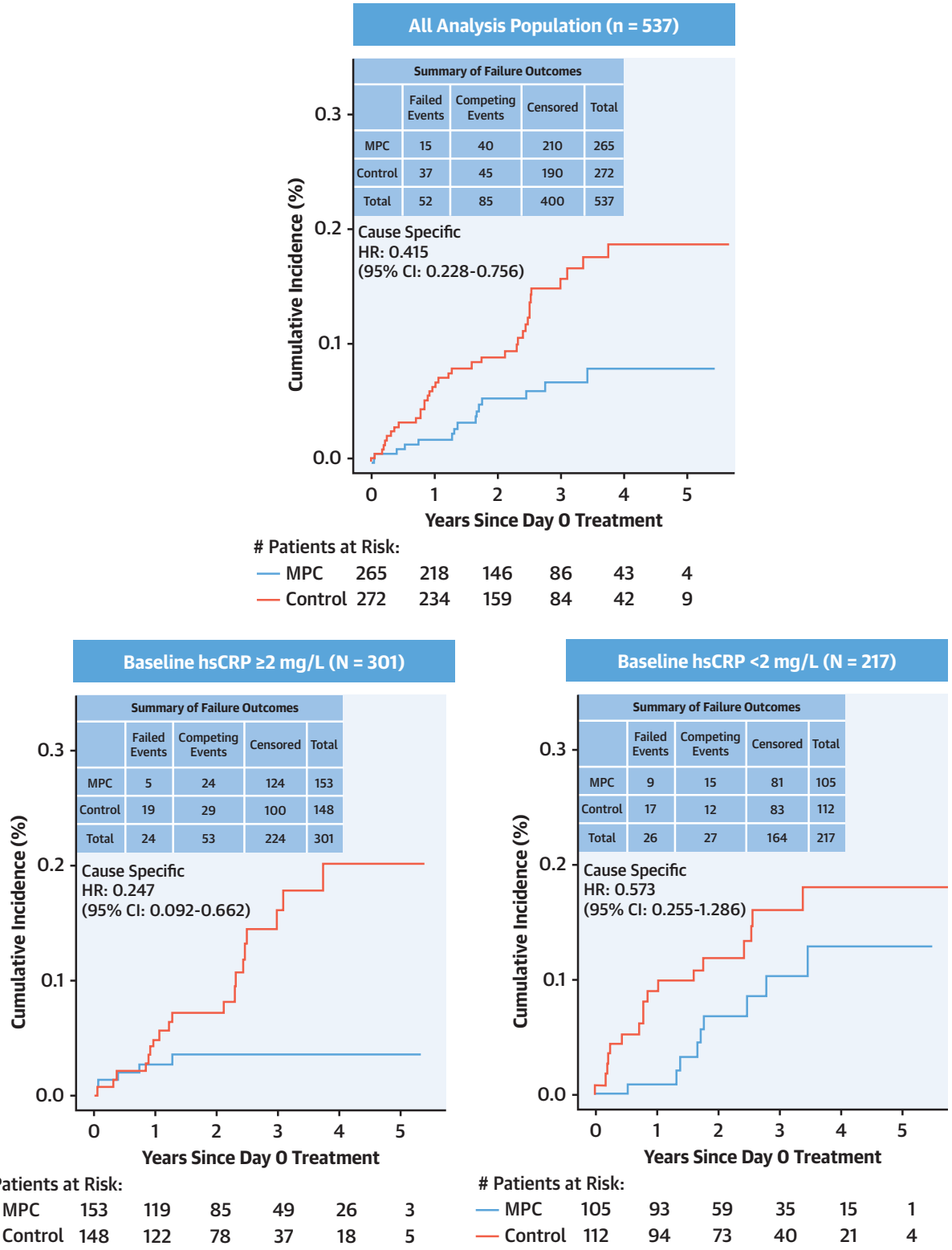


Serial echocardiographic least squares means (LSM) change from baseline at 12 months for left ventricular ejection fraction (LVEF) **(top)**, left ventricular end-systolic volume (LVESV) **(middle)**, and left ventricular end diastolic volume (LVEDV) **(bottom)** for all treated patients, for patients with baseline high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and for patients with baseline hsCRP <2 mg/L who qualified for echocardiography. All *P* values are based on the difference between the LSM change from baseline at 12 months for mesenchymal precursor cell (MPC) and control groups.

hypothesis-generating insights into how cardiac cell therapy using MPCs may have a significant benefit on the natural history of HFrEF. MPC therapy resulted in significant reductions in TTFE for MI or stroke over a mean follow-up of 30 months with the most benefit seen in patients with evidence of systemic inflammation (baseline hsCRP ≥2 mg/L). These findings raise the possibility that treating patients with HFrEF with MPCs may improve outcomes by targeting local cardiac and systemic inflammatory changes that cause macrovascular and microvascular abnormalities in patients with heart failure (**Central Illustration**).

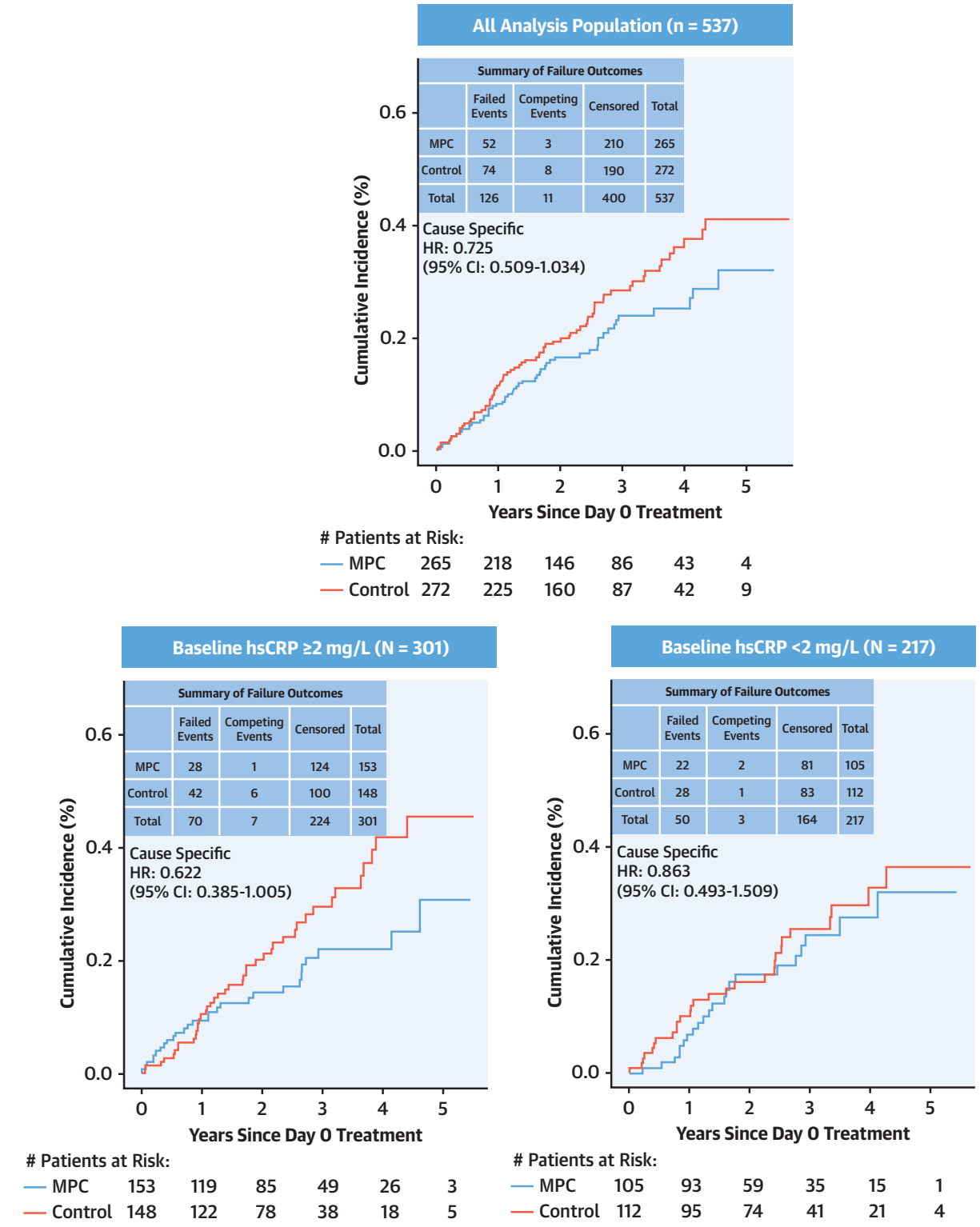
Historically, drug treatment of HFrEF has had disease-modifying effects that have predominantly been based on inhibiting the maladaptive effects of neurohormonal activation. Less attention has been paid to inflammatory factors that can also initiate and lead to progression of HFrEF. Although previous studies addressing inflammation in heart failure have failed to provide convincing evidence of benefit,[1,2,5] a subset analysis from the CANTOS trial showed that anti-inflammatory therapy targeting immune pathways could reduce cardiovascular events.[20] The primary endpoint in our study addressed events related to clinical heart failure symptoms and low

FIGURE 4 Risk of Myocardial Infarction or Stroke



The time-to-first-event data for myocardial infarction or stroke (nonfatal or fatal) are shown as Aalen-Johansen cumulative incidence function curves for all patients in the analysis population and for patients with or without baseline inflammation. The number of patients at risk at each year of follow-up and the cause-specific HRs with 95% Wald confidence limits are also presented. hsCRP = high-sensitivity C-reactive protein; MPC = mesenchymal precursor cell.

FIGURE 5 Risk of 3-Point MACE



The time-to-first-event data for the 3-point major adverse cardiovascular events (MACE) are shown as Aalen-Johansen cumulative incidence function curves for all patients in the analysis population and for patients with or without baseline inflammation. The number of patients at risk at each year of follow-up and cause-specific HRs with 95% Wald confidence limits are also presented. Abbreviations as in Figure 4.

cardiac output, which mostly involve noninflammatory aspects of the maladaptive compensatory pathways.[7,23-25] Moving forward in the field, separating endpoints related to congestive signs and symptoms from those relating to inflammation may become appropriate as more data regarding specific treatment of inflammation become available.

In the DREAM-HF trial, our results suggest that MPC treatment may have benefits in addition to those offered by concomitant GDMT. The mechanisms of action of MPC therapy appear to be directed predominantly toward altering the inflammatory environment within the heart and the vasculature once the cells are activated by local tissue cytokines.[6-12,26,27] We found that a single transendocardial administration procedure of MPCs resulted in a long-term 58% reduction in the prespecified MACE of MI or stroke. In the post hoc analysis of the composite 3-point MACE, MPC treatment showed a 27% risk reduction (cause-specific HR: 0.725; 95% CI: 0.509-1.034) in the analysis population. Our findings of a further risk reduction in patients with a greater degree of systemic inflammation suggest MPC therapy may provide clinical benefits via mechanisms that are different from but complementary to those of existing GDMT.

MPCs are a well-characterized STRO-1/STRO-3+ stem cell population with greater immunomodulatory activity than STRO-1-negative mesenchymal stromal cells.[28] Moreover, MPCs can bind the proinflammatory cytokines produced at high levels in the myocardium of patients with HFrEF, resulting in the release of factors that are anti-inflammatory and induce microvascular network formation (ie, neovascularization). In preclinical studies, MPCs reversed endothelial dysfunction within coronary arteries and peripheral arteries in the setting of systemic inflammation as well as induced angiogenesis and arteriogenesis within cardiac muscle in animal models of HFrEF.[6-12,28]

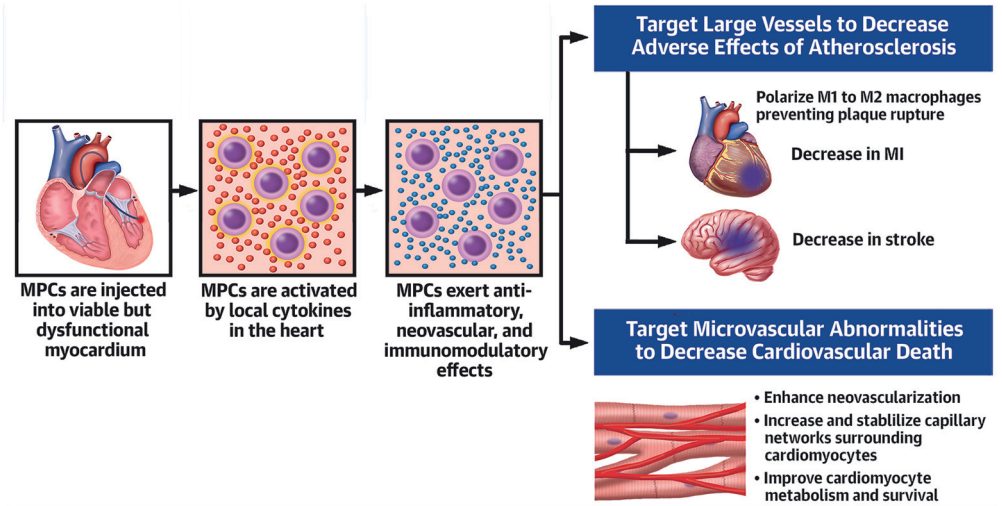
Atherosclerosis and heart failure have shared pathophysiological changes relating to inflammation. MI and stroke are common in patients with HFrEF, and when they occur, they adversely affect the clinical outcome.[29] Our results suggest that the anti-inflammatory effects of MPCs target these events and thus may contribute additionally to the benefits of GDMT. In a recent editorial, Braunwald[4] urged investigators to continue to move cardiac cell therapy forward into clinical practice, reminding us that current therapies, although improved, do not cure heart failure. He cites the safety of cell therapy and recent advances made in understanding cell selection and mechanisms, including the DREAM-HF trial,[14] as an urgent call for action in the field.[4]

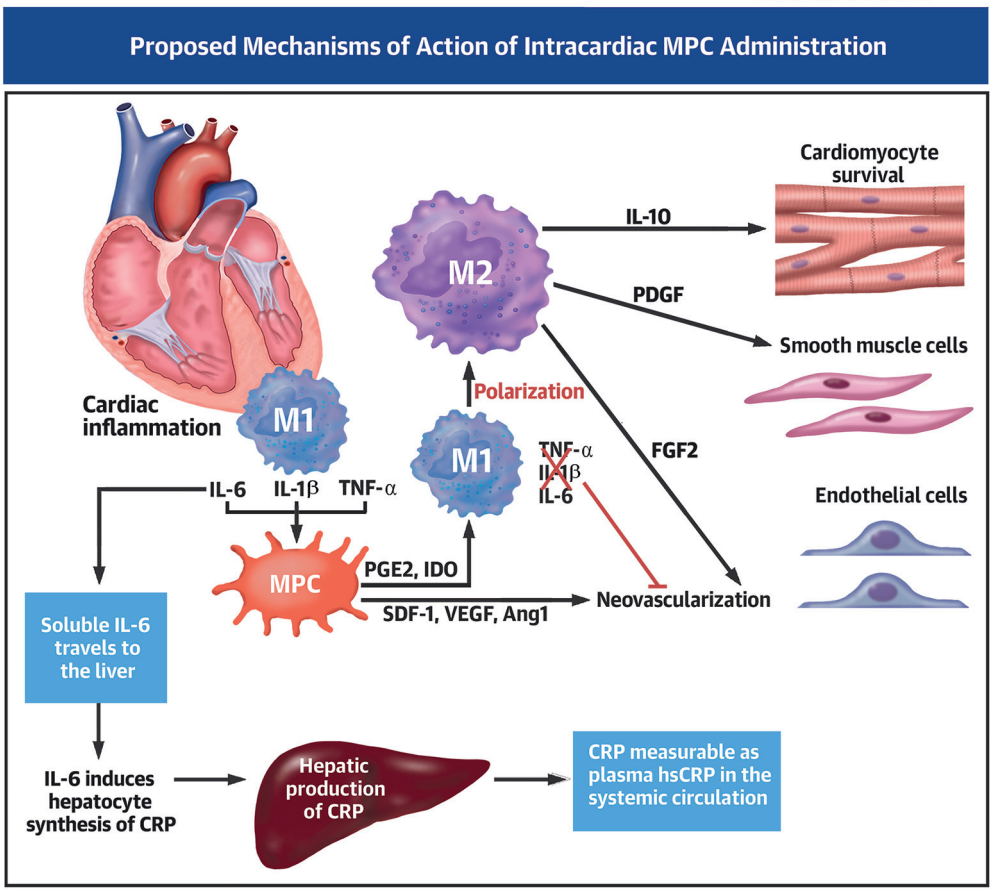
Elevated plasma levels of hsCRP portend worse outcomes in patients with HFrEF.[16-21] Our reduction in MI or stroke after a single intramyocardial administration of MPCs suggests that the immunomodulatory effects of the cells extend to the systemic vasculature. MPCs have been shown to polarize M1 proinflammatory macrophages to M2 anti-inflammatory macrophages in arteries with underlying atherosclerosis, thus potentially stabilizing atherosclerotic vulnerable plaque and preventing plaque rupture and thrombus formation.[9-12,26,27] In addition, microvascular neovascularization induced by mesenchymal lineage cells can form a functional vascular network that protects ischemic heart muscle against apoptosis and scar tissue replacement while improving myocardial energetics and function.[9-12] These beneficial effects may reduce cardiac mortality in patients with greater amounts of salvageable cardiac tissue at an earlier stage in the disease process.[30] Endothelium-controlled signaling pathways in the heart are crucial for homeostasis in local tissue and regulate cardiac function and vasomotor tone, adjust vascular permeability, and preserve blood fluidity. Thus, generalized endothelial dysfunction plays a significant role in the pathophysiology of heart failure. Dysregulation of the communication between cardiac endothelial cells and cardiomyocytes has been implicated in the development of cardiac structural and functional abnormalities.[31]

Consistency was observed between echocardiographic demonstration of the positive treatment effect of MPCs on LVEF at 12 months and the decrease in TTFE composite MACE over a mean follow-up of 30 months. The improvement in LVEF seems to be driven predominantly by reductions in LVESV (a measurement of LV contractile state). Improvement in early left ventricular systolic function appears to strongly support MPCs' proposed mechanisms of action, which include improvement in the cardiac microvasculature with subsequent translation to left ventricular systolic functional recovery and long-term reduction in MACE.

STUDY LIMITATIONS. The 30 days between randomization and the index cardiac catheterization resulted in 28 randomized patients becoming ineligible for the index procedure. These patients were included in the ITT population (not the analysis population); however, the 2 populations had no clinically meaningful differences in major outcomes. Second, we selected primary and secondary endpoints relating to the occurrence of decompensated heart failure events that are commonly used in heart failure clinical trials. Our findings show that these traditional endpoints

CENTRAL ILLUSTRATION **Transendocardial Administration of Mesenchymal Precursor Cells in Patients With Heart Failure With Reduced Ejection Fraction**





Perin EC, et al. J Am Coll Cardiol. 2023;81(9):849-863.

Potential mechanisms and clinical effects of mesenchymal precursor cells (MPCs) in patients with heart failure with reduced ejection fraction. MPCs may exert anti-inflammatory and immunomodulatory effects locally and systemically and reverse endothelial dysfunction to reduce nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death in patients with high levels of inflammation. Ang = angiopoietin; CRP = C-reactive protein; FGF = fibroblast growth factor; hsCRP = high-sensitivity C-reactive protein; IDO = indoleamine 2,3-dioxygenase; IL = interleukin; M = macrophage; PDGF = platelet-derived growth factor; PGE = prostaglandin E; SDF = stromal cell-derived factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

may not fully reveal the benefits or mechanisms of action of MPCs on MI, stroke, and cardiovascular death in patients with HFrEF. Finally, although analyses of the effects of MPCs on MI, stroke, and the components of the composite MACE were prespecified, the treatment effects on these endpoints and in subgroups based on hsCRP levels should be considered hypothesis generating and need to be confirmed in clinical trials designed specifically to assess the effects of MPCs on these events.

CONCLUSIONS

In the DREAM-HF trial, the primary and secondary endpoints were negative. However, MPCs showed positive signals in improving outcomes in prespecified and post hoc exploratory analyses. These hypothesis-generating findings may help identify patients most likely to benefit from MPC therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Transendocardial delivery of MPCs reduces MACE in patients with heart failure and systemic inflammation, but does not prevent hospitalization for decompensated heart failure or high-grade symptomatic ventricular arrhythmias.

TRANSLATIONAL OUTLOOK: Future trials should examine the immunomodulatory effects of MPCs on myocardial function and MACE in patients with HFrEF and systemic inflammation.

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KEY WORDS cell therapy, heart failure with reduced ejection fraction, major adverse cardiovascular events, mesenchymal precursor cells

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.