Special Article

Phase 3 DREAM-HF Trial of Mesenchymal Precursor Cells in Chronic Heart Failure

A Review of Biological Plausibility and Implementation of Flexible Clinical Trial Design

Kenneth M. Borow, Alex Yaroshinsky, Barry Greenberg,* Emerson C. Perin*

Abstract: **Advanced heart failure (HF) is a progressive disease characterized by recurrent hospitalizations and high risk of mortality. Indeed, outcomes in late stages of HF approximate those seen in patients with various aggressive malignancies. Clinical trials assessing beneficial outcomes of new treatments in patients with cancer have used innovative approaches to measure impact on total disease burden or surrogates to assess treatment efficacy. Although most cardiovascular outcomes trials continue to use time-to-first event analyses to assess the primary efficacy end point, such analyses do not adequately reflect the impact of new treatments on the totality of the chronic disease burden. Consequently, patient enrichment and other strategies for ongoing clinical trial design, as well as new statistical methodologies, are important considerations, particularly when studying a population with advanced chronic HF. The DREAM-HF trial (Double-Blind Randomized Assessment of Clinical Events With Allogeneic Mesenchymal Precursor Cells in Advanced Heart Failure) is an ongoing, randomized, sham-controlled phase 3 study of the efficacy and safety of mesenchymal precursor cells as immunotherapy in patients with advanced chronic HF with reduced ejection fraction. Mesenchymal precursor cells have a unique multimodal mechanism of action that is believed to result in polarization of proinflammatory type 1 macrophages in the heart to an anti-inflammatory type 2 macrophage state, inhibition of maladaptive adverse left ventricular remodeling, reversal of cardiac and peripheral endothelial dysfunction, and recovery of deranged vasculature. The objective of DREAM-HF is to confirm earlier phase 2 results and evaluate whether mesenchymal precursor cells will reduce the rate of nonfatal recurrent HF-related major adverse cardiac events while delaying or preventing progression of HF to terminal cardiac events.**

DREAM-HF is an example of an ongoing contemporary events-driven cardiovascular cell–based immunotherapy study that has utilized the concepts of baseline disease enrichment, prognostic enrichment, and predictive enrichment to improve its efficiency by using accumulating data from within as well as external to the trial. Adaptive enrichment designs and strategies are important components of a rational approach to achieve clinical research objectives in shorter clinical trial timelines and with increased cost-effectiveness without compromising ethical standards or the overall statistical integrity of the study. The DREAM-HF trial also presents an alternative approach to traditional composite time-to-first event primary efficacy end points. Statistical methodologies such as the joint frailty model provide opportunities to expand the scope of events-driven HF with reduced ejection fraction clinical trials to utilize time to recurrent nonfatal HF-related major adverse cardiac events as the primary efficacy end point without compromising the integrity of the statistical analyses for terminal cardiac events. In advanced chronic HF with reduced ejection fraction studies, the joint frailty model is utilized to reflect characteristics of the high-risk patient population with important unmet therapeutic needs. In some cases, use of the joint frailty model may substantially reduce sample size requirements. In addition, using an end point that is acceptable to the Food and Drug Administration and the European Medicines Agency, such as recurrent nonfatal HF-related major adverse cardiac events, enables generation of clinically relevant pharmacoeconomic data while providing comprehensive views of the patient's overall cardiovascular disease burden. The major goal of this review is to provide lessons learned from the ongoing DREAM-HF trial that relate to biologic plausibility and flexible clinical trial design and are potentially applicable to other development programs of innovative therapies for patients with advanced cardiovascular disease.

Clinical Trial Registration: **URL: https://www.clinicaltrials.gov. Unique identifier: NCT02032004.** (***Circ Res*****. 2019;125:265-281. DOI: 10.1161/CIRCRESAHA.119.314951.)**

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From the Borow Consulting Group, LLC, Bryn Mawr, PA (K.M.B.); Vital Systems, Inc, Rolling Meadows, IL (A.Y.); University of California, San Diego School of Medicine, La Jolla (B.G.); Advanced Heart Failure Treatment Program, Sulpizio Cardiovascular Center, University of California, San Diego Healthcare System, La Jolla (B.G.); and Stem Cell Center and Adult Cardiology, Texas Heart Institute, Houston (E.C.P.).

*B.G. and E.C.P. share senior coauthorship of this article.

Correspondence to Kenneth M. Borow, MD, Borow Consulting Group, LLC, 407 Wyntre Lea Dr, Bryn Mawr, PA 19010. Email kborow@gmail.com

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
Ang-2	angiopoietin-2
Ang-1	angiopoietin-1
ARB	angiotensin receptor blocker
CF-LVAD	continuous-flow left ventricular assist device
CHAMPION	Cardiomems Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients
CHARM-Added	Effects of Candesartan in Patients With Chronic Heart Failure and Reduced Left Ventricular Systolic Function Taking Angiotensin-Converting Enzyme Inhibitors
CUPID-2	Calcium Upregulation by Percutaneous Administration of Gene Therapy in Patients With Cardiac Disease
DREAM-HF	Double-Blind Randomized Assessment of Clinical Events With Allogeneic Mesenchymal Precursor Cells in Advanced Heart Failure
EMPHASIS-HF	Comparison of Outcomes in Patients in NYHA Class II Heart Failure When Treated With Eplerenone or Placebo in Addition to Standard Heart Failure Medicines
eNOS	endothelial NO synthase
FDA	Food and Drug Administration
HF	heart failure
HF-MACE	heart failure–related major adverse cardiac event
HFrEF	heart failure with reduced ejection fraction
IL	interleukin
INF-γ	interferon-γ
JFM	joint frailty model
LV	left ventricle
LVAD	left ventricular assist device
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
M1	type 1 macrophage
M2	type 2 macrophage
MOA	mechanism of action
MPC	mesenchymal precursor cell
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PARADIGM-HF	Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure
PARAGON	Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction
SDF-1	stromal cell-derived factor-1
SHIFT	Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial
TCE	terminal cardiac event
TNF-α	tumor necrosis factor-α
TTFE	time-to-first event
ValHeFT	Valsartan Heart Failure Trial
VEGF	vascular endothelial growth factor

During the past decade, numerous clinical trials evaluating novel drug therapies have been conducted in patients with advanced chronic heart failure (HF) with reduced ejection fraction (HFrEF). Despite progress made in reducing morbidity and mortality in patients with HF, those with advanced disease continue to experience an unfavorable clinical course characterized by frequent hospitalizations and premature death.[1] Although the PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) reported significant reduction in both cardiovascular death or hospitalization for HF and SHIFT (Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial) reported a reduction in hospitalization for HF,[2,3] a substantial unmet clinical need exists for improving outcomes for patients with more advanced levels of HFrEF.

Traditionally, biologic plausibility has been defined as evidence that a surrogate biochemical, anatomic and morphological, or pathophysiologic end point is causally related to a clinically relevant adverse outcome or is a regular finding associated with that outcome and that it is plausibly related to a common causal factor.[4–6] The persuasiveness of an end point in supporting the effectiveness of a drug (or biologic) is based on multiple factors.[7] Knowledge relating to mechanistic data from the bench can lead to new and successful targeted therapies at the bedside, and conversely, new clinical treatments can lead to mechanistic discoveries.[8]

Recently, our understanding that HFrEF has a strong inflammatory component has afforded an opportunity to reassess the evolving role of clinical trial design and patient enrichment strategies in the conduct of innovative phase 2 and phase 3 studies in cardiovascular cellular medicine. In particular, patient enrichment strategies can improve the efficiency of a clinical trial by allowing design specifications to be changed based on blinded accumulating data from the ongoing trial or information external to the trial.[9–12] These approaches are part of a rational strategy to achieve research objectives more efficiently by utilizing

1. knowledge gained from the ongoing study in a manner that maintains the validity and interpretability of the results and
2. newly acquired information that could not have been reasonably anticipated before trial start.

Patient enrichment in a randomized placebo- or sham-controlled trial involves the prospective identification of a patient's baseline characteristics (eg, demographic, pathophysiologic, laboratory, historical, or genetic) that represent a high risk for important clinical outcomes so that there will be a sufficient number of events to assess the efficacy of an active intervention to delay or prevent.[12,13] This is common in studies of patients with advanced chronic HFrEF and is intended to increase study power in the 3 principal ways shown in Table 1.[14]

Advanced Chronic HFrEF: Unmet Clinical Needs and Impact on Health Economics

Current treatments for patients with chronic HFrEF including neurohormonal antagonists (eg, ACE [angiotensin-converting enzyme] inhibitor, ARBs [angiotensin receptor blockers], sacubitril/valsartan, aldosterone antagonists, and β-adrenergic receptor blockers), heart rate control, implantable cardioverter

Table 1. Patient Enrichment Strategies That Can Potentially Increase Study Power in Advanced Chronic HFrEF Clinical Trials

Patient Enrichment Strategies	
Baseline disease enrichment	Decreases heterogeneity (noise) with selection of an appropriate patient population at baseline that has clinically important HFrEF.
	Choose patients based on disease severity score (eg, NYHA class), quantitative cardiac volume characteristics (eg, LVESV), baseline biomarker level, or medical history.
Prognostic enrichment	Involves identifying a patient population with a high targeted outcome event rate (ie, high-risk patients or those with relatively severe disease).
	FDA encourages these strategies for cardiovascular diseases aiming to reduce the rate of death or serious events and delay progression of the disease's natural history.
	These strategies may increase the power in event-driven trials because of a higher rate of primary end point events.
Predictive enrichment	Involves identifying patients more likely to respond to treatment.
	Choose patients based on characteristics (eg, pathophysiology) or more empirical responses to the active agent seen in a similar trial population other than the current study.
	May potentially enhance the power of a clinical trial and has clear implications for how a drug or biologic agent will be used.

FDA indicates Food and Drug Administration; HFrEF, heart failure with reduced ejection fraction; LVESV, left ventricular end-systolic volume; and NYHA, New York Heart Association.

defibrillators, or cardiac resynchronization therapy devices have greatly benefited many patients with mild or moderate chronic HFrEF as manifested by[2,3,10,15,16]

- stabilized or improved left ventricular (LV) ejection fraction (LVEF) and LV volumes,
- decreased number and duration of HF hospitalizations, and
- reduced mortality even in the absence of significant improvement in LVEF
- improved quality of life.

However, the progressive response throughout the myocardium to neurohormonal activation, direct mechanical stretch, ventricular volume overload, and cardiac as well as systemic endothelial dysfunction, results in progressive maladaptive adverse LV remodeling and increased risk of clinical events over time despite optimal treatment with guideline-directed therapies.[17–25] The progression of chronic HF to advanced stages of disease is characterized by frequent hospitalizations, marked limitation of exercise capacity, poor quality of life, and hemodynamic impairment, which often lead to consideration of an LV assist device (LVAD) or heart transplantation.[17–25] While heart transplants can improve outcomes in end-stage HF patients, only ≈3300 transplants are performed in the United States each year.[26,27] The major limitation to the use of this procedure is the scarcity of donor hearts in conjunction with the time constraints associated with current myocardial preservation techniques.[15,26–28] As an alternative, LVADs have significantly improved survival and are increasingly used as destination therapy.[28,29] However, 12-month mortality rates are frequently high and nonsurgical major morbidity, including gastrointestinal bleeding, infection, and stroke, limits the use of these life-saving devices.[23,24,30,31]

HF is a major global health problem, and the overall prevalence of this disease continues to rise. One can estimate the size of the US HF population with advanced disease that could be helped by mesenchymal precursor cell (MPC) immunotherapy by considering the following: of the 6.5 million patients with HF in the United States, ≈3.25 million have HFrEF.[32,33] Of these, one could conservatively estimate that 5% to 10% are either on the verge of stage D HF (and are likely to develop it in the near future) or have reached stage D. This results in a population of ≈300 000 patients who remain symptomatic despite current medical therapies and are at high risk of both recurrent hospitalizations and death.[34–36] This defines the potential target population for MPC immunotherapy.

Progression of HFrEF occurs because of relentless inflammation, persistent neurohormonal activation, ongoing maladaptive adverse cardiac remodeling, and associated endothelial dysfunction and vascular abnormalities (Figure 1). Ultimately, the most effective treatment for end-stage HF is to prevent it from occurring. Clearly, newer more innovative therapeutic approaches are needed that can, at a minimum, delay or prevent progression to end-stage HF in patients with advanced chronic HFrEF.[24,25,37–39] A promising approach that is

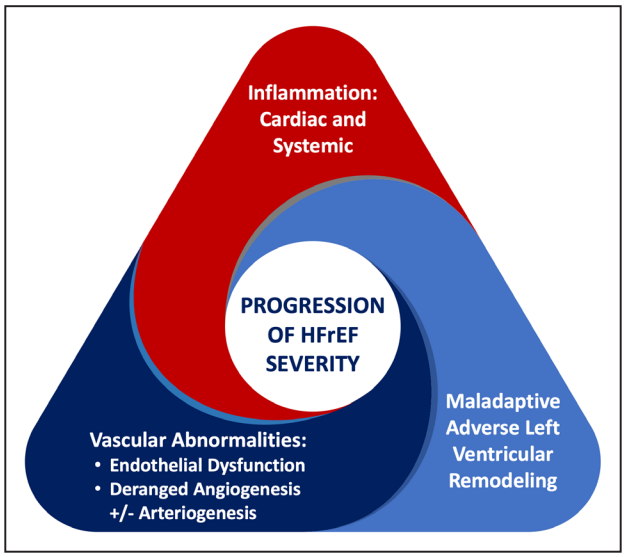

Figure 1. Relationships between multiple key factors that affect progression of heart failure with reduced ejection fraction (HFrEF) severity.

currently in phase 3 investigation involves a single-dose transendocardial administration of the immunotherapeutic agent MPCs in patients with advanced HFrEF.

MPCs in Advanced Chronic HFrEF Patients: Is There Biologic Plausibility?

Multiple pathophysiologic pathways are associated with the development and progression of advanced chronic HFrEF (Figure 1). Based on this background, the immunotherapeutic mechanisms of action (MOAs) of MPCs lend themselves well to the possibility of providing benefits to patients at high risk for end-stage HFrEF.

MPCs Targeting HFrEF and Inflammation

Background on HFrEF and Inflammation

Interest in the role of inflammation in HF has remained at a high level.[40–46] As in atherosclerosis, acute and chronic inflammation in HF is caused by a series of stress responses and leaves pathological memory in the organ.[40,44,47] This inflammation-initiated memory plays a key role in the pathogenesis of HF, leading to increased morbidity and mortality risk in patients with ischemic or nonischemic HF pathogenesis.[48,49] HF is associated with alterations in a wide array of cellular, autocrine, and paracrine signaling systems, many of which are involved in mediating inflammation and oxidative stress. For the past 25 years, HF models in animals and data collected in humans with HF have demonstrated that failing myocardium exhibits a characteristic profile of elevated levels of proinflammatory cytokines, including TNF-α (tumor necrosis factor-α), INF-γ (interferon-γ), IL (interleukin)-1b, and IL-6, and decreased levels of the anti-inflammatory cytokine IL-10.[43,50–55] Moreover, the development of maladaptive adverse LV remodeling in patients with progressive HF appears to be directly related to and temporally impacted by the degree of inflammation involving the acute site of ischemic injury, as well as the myocardium remote from that site.[40,45,51,54,55] Despite increased understanding of the relationship between inflammation and HF development/progression, targeting a single pathway of inflammation, such as TNF-α, in isolation has failed to improve the prognosis of HF in randomized controlled trials.[56] This strongly suggests that the complex pathophysiology associated with HFrEF will ultimately require innovative multitargeted therapeutic approaches if the natural history of the disease is to be significantly altered in a beneficial manner.

In progressive chronic HFrEF, the immune system is involved in proinflammatory processes.[42,43,46,55] Traditionally, intracardiac macrophages, denoted as type 1 macrophage (M1), have been implicated in tissue remodeling and HF. These macrophages, which have been considered major drivers of myocardial inflammation, are the principal source of the proinflammatory cytokines TNF-α, IL-6, and IL-1β, which negatively affect disease outcomes in HF models.[55,57–60] Consistent with a pathological role for M1 macrophages, their abundance in the heart is associated with worsened LV systolic dysfunction and adverse LV remodeling.[46,61] Alternatively, tissue macrophages can be polarized to an anti-inflammatory type 2 macrophage (M2) phenotype by various cytokines. These M2 macrophages preferentially secrete the anti-inflammatory cytokine IL-10, help repair the heart, and reduce adverse interstitial fibrosis.[42] As such, IL-10 appears to be a major cardioprotective factor against progression of myocardial dysfunction and worsening HF. This suggests that strategies leading to the selective expansion of cellular subsets that produce IL-10 in the failing heart may protect against inflammation-mediated adverse LV remodeling, fibrosis, and contractile dysfunction.[46]

MPC Effects on Inflammation in HFrEF

MPCs may represent a novel immunotherapeutic approach reducing inflammation and treating chronic HFrEF. These cells are immunoselected from healthy adult bone marrow using an anti–STRO (stromal precursor antigen)-3 monoclonal antibody and are expanded in culture and cryopreserved to generate the final product. MPCs are characterized by a hypoimmunogeneic phenotype and do not stimulate clinically significant immune responses after allogeneic transplantation in humans.[62–65] Data from studies in large animal models of myocardial infarction–induced ischemic cardiomyopathy and doxorubicin-induced nonischemic cardiomyopathy provide evidence of the bioactivity of MPCs in the injured heart.[66–69] In these animal studies in which the cells were delivered by intramyocardial injection, data showed that MPCs attenuated LV dysfunction, mitigated adverse LV remodeling, and augmented myocardial neovascularization.[66–69]

Nonclinical in vivo and in vitro studies have shown that the positive effects of MPCs are attributable, at least in part, to the secretion of soluble molecules with trophic and proangiogenic activities.[66,67] Notably, MPCs express an array of surface receptor soluble factors that bind proinflammatory cytokines (eg, TNF-α, IL-1, IL-6, and IL-17).[67] When placed into an inflammatory local microenvironment (such as the failing heart), MPCs are activated by the presence of proinflammatory cytokines resulting in the release of multiple anti-inflammatory factors.[66,67] Several of these factors have been shown to mediate polarization of proinflammatory M1 macrophages to an anti-inflammatory M2 phenotype, resulting directly and indirectly in reduced inflammation and reversal of endothelial dysfunction (Figure 2).

The in vivo effects of MPCs on systemic inflammation were assessed in sheep with collagen-induced arthritis—an animal model characterized by local joint inflammation, systemic inflammatory changes, and endothelial dysfunction in coronary and peripheral vascular beds. Arthritic sheep were randomized to intravenous treatment with either 150 million allogeneic MPCs or placebo on day 1 after arthritis induction.[70] The most striking effect of MPC treatment on plasma cytokine levels was in the response of anti-inflammatory IL-10. Plasma levels of IL-10 spiked significantly in sheep treated with MPCs one day after cell treatment with a mean concentration of over 600 ng/mL in the MPC-treated sheep compared with 100 ng/mL in control animals suggesting activation of either a significant number of anti-inflammatory M2 macrophages or polarization of proinflammatory macrophages (M1) into anti-inflammatory macrophages (M2). Plasma IL-6 levels in control sheep peaked in the 2 days after induction of arthritis. This response was blunted by 50% with MPC

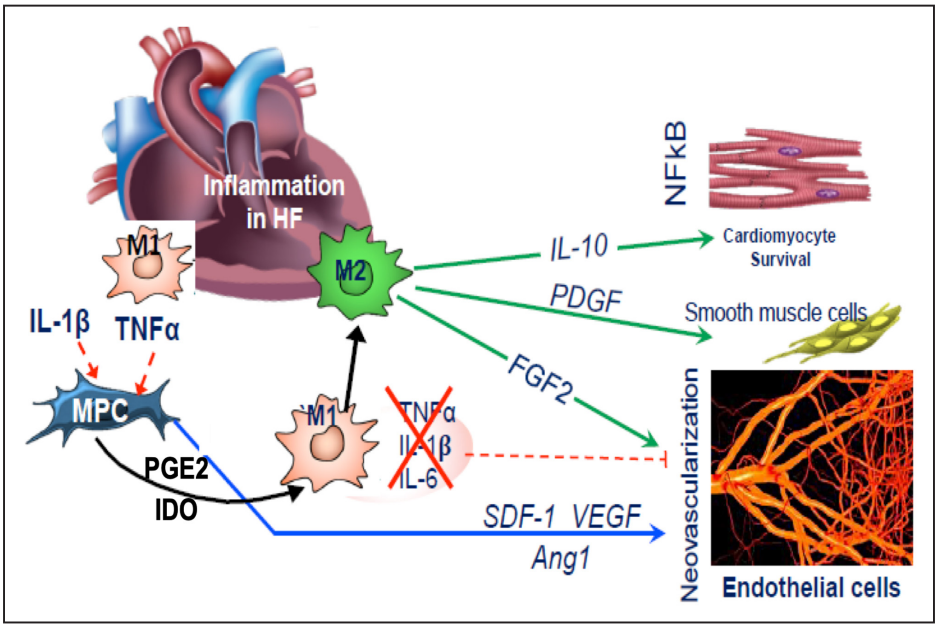

Figure 2. Proposed key components of the mesenchymal precursor cell mechanisms of action in chronic heart failure (HF). Ang-1 indicates angiopoietin-1; FGF2, fibroblast growth factor 2; IDO, indoleamine dioxygenase; IL, interleukin; M1, macrophage (type 1); M2, macrophage (type 2); MPC, mesenchymal precursor cell; NF-κB, nuclear factor κB; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; SDF-1, stromal cell-derived factor-1; TNF-α, tumor necrosis factor-α; and VEGF, vascular endothelial growth factor.

administration. Plasma fibrinogen and serum amyloid-A (biomarkers of systemic inflammatory response) were also significantly reduced in the MPC group. In the inflamed joints, there was a marked reduction in inflammatory macrophages and significantly reduced levels of the proinflammatory cytokines TNF-α and IL-6.[70,71]

Clinical studies support the concept that injecting MPCs into the LV wall of the failing HFrEF heart reduces inflammation, reverses endothelial dysfunction, and improves clinical outcomes.[63,72,73] Using these cells as an add-on treatment to standard-of-care medical and other therapies in patients with progressive chronic HFrEF may provide an opportunity to delay or prevent progression to more severe advanced or end-stage HFrEF.

MPCs Targeting HFrEF and Adverse LV Remodeling

Background on HFrEF and Maladaptive Adverse LV Remodeling

HF is the final common pathway in a pathological continuum of clinical, biological, and cellular events that leads to progressive maladaptive adverse ventricular remodeling.[74–77] In patients with HFrEF, ventricular dilatation with ischemia at the local tissue level and derangements in molecular biodynamics and signaling pathways lead to cellular and genomic responses that result in progressive maladaptive adverse LV remodeling.[78–80] For example, the LV remodeling process after an acute myocardial infarction begins with necrosis, inflammation, and thinning of the affected heart wall.[81–83] Ultimately, the overloaded surviving cardiomyocytes, especially in the remote (noninfarcted) myocardium, participate in the inflammatory processes initiated by the infarction resulting in the progressive involvement of the entire LV in the post-MI ventricular remodeling process.[41,45,84]

For years, LVEF has been the most commonly used surrogate parameter for diagnosis and management of patients with HF. However, LVEF is a misunderstood and overrated estimate of LV contractile state because of its high dependence on preload and afterload and because of the various methods used to acquire the data.[85–88] As the HF state progresses, more physiologically appropriate measurements of LV function include increased LV end-systolic volume (LVESV) and LVESV index (reflecting diminished contractile performance and augmented ventricular afterload) and increased LV end-diastolic volume (LVEDV; reflecting elongated fiber length [ie, preload]).[74–77,85] These structural changes have important impact on the integral of LV systolic wall stress [$\dot{O}$]—a major determinant of tissue level myocardial oxygen demand and metabolism—and hence, myocardial oxygen consumption. Overall, these LV structural changes are the basis for much of the patient's worsening symptoms and signs that manifest as pulmonary venous hypertension, decreased cardiac output, renal hypoperfusion with sodium and water retention, and neuroendocrine and metabolic derangements.[89–92]

In patients with HFrEF, beneficial reverse LV remodeling initiated by pharmacological and device interventional therapies, as measured by LV volume changes, have been shown to have important prognostic significance.[77,93–95] These benefits have been reported for randomized clinical studies of ACE inhibitor,[2,96,97] ARBs,[2,98] β-adrenergic receptor blockers,[99,100] ivabradine,[3,101] and cardiac resynchronization therapy in which reverse remodeling predicts improved clinical outcomes and reduction in arrhythmic events.[102,103] Importantly, LVESV and LVESV index have been shown to be powerful predictors of subsequent cardiovascular-related morbidity and mortality in patients with HFrEF who are treated with an array of drug, biologic, or device therapies.[73,77,93,94,104–109] Beneficial LV remodeling in HFrEF patients would be expected to mitigate the

demand-supply mismatch in myocardial oxygen consumption requirements thereby reducing local tissue ischemia.[110–112] The potential net result would be improved overall LV systolic and diastolic performance, decreased pulmonary congestion, increased exercise capacity, and potentially reduced morbidity and mortality.[113,114]

MPC Effects on Maladaptive Adverse LV Remodeling in HFrEF

In preclinical studies using various models of LV systolic dysfunction, MPCs prevented progression of maladaptive adverse LV remodeling, induced cardiac arteriogenesis, and reduced cardiac fibrosis.[66,67,115,116] Moreover, in a sheep model of myocardial ischemia and LV systolic dysfunction, high-dose MPCs (225 million cells) improved LV performance, reversed adverse LV remodeling, and stimulated neovascularization.[117] Allogeneic MPCs also provided cardioprotective benefits in sheep with doxorubicin-induced nonischemic cardiomyopathy.[66] In these studies, the control groups showed progressive enlargement of LVESV and LVEDV, whereas MPC-treated animals showed either no change or decreases in LVESV and LVEDV.

Based on these preclinical and animal data, a phase 2 feasibility, safety-and-dose finding study of immunoselected allogeneic MPCs was conducted in patients with New York Heart Association (NYHA) class II or III chronic HFrEF (LVEF<40%). Over a 36 month follow-up, HF-related major adverse cardiac events (HF-MACE; hospitalization for decompensated HF, successfully resuscitated ventricular fibrillation, or cardiac death) were significantly reduced (P=0.026) in the 150-million MPC group (0/15, 0%) versus controls (5/15, 33%; Figure 3A, left). The 25-million and 75-million MPC–treated groups had significantly worse outcomes than the 150-million MPC group and did not differ from the control group. HF-MACE occurred only in patients with baseline LVESV >100 mL—a surrogate for LV contractile state that is >3 SDs above the mean value for normal subjects.[63,118–120] Figure 3A (right) shows HF-MACE data over 36 months for the 18 patients with baseline LVESV >100 mL (7 control patients and 11 150-million MPC–treated patients). HF-MACE was significantly less for patients treated with 150-million MPCs than for control patients when analyzed by time-to-first event (TTFE; P=0.007) or recurrent events with allowance for multiple events per patient (P<0.001). Adverse events were similar across groups. No clinically symptomatic immune responses were noted.

Figure 3B shows the change from baseline to month 6 for LVESV and LVEDV.[63,73] The left includes all patients in the control and 150-million groups. MPC treatments resulted in beneficial LV remodeling whether analyzed as absolute or control-corrected change from baseline. In the right, which includes only data from patients with baseline LVESV >100 mL, MPCs at the 150-million dose demonstrated enhanced therapeutic benefit on LV remodeling. These data were characterized by statistically significant increases in LVESV and LVEDV for the control group compared with modest reductions in the MPC patients.[73] For the baseline LVESV >100 mL patients, 71% of the control group had either died by 6 months post the index cardiac catheterization or had nominal increases in LVESV and LVEDV (month 6 minus baseline). In contrast, the MPC group had no cardiac deaths at month 6. Similar statistical results were evident when LVESV index (normalized to body size) was analyzed instead of LVESV. These data show that especially in the control group, maladaptive adverse LV remodeling would be expected to increase the integral of LV systolic wall stress and myocardial tissue demand at the local tissue level resulting in increased local myocardial ischemia.

MPCs Targeting HFrEF With Abnormal Coronary and Systemic Vasculature

Background on HFrEF and Vascular Abnormalities (Endothelial Dysfunction and Deranged Angiogenesis/Arteriogenesis)

In the pathophysiology of HF, generalized endothelial dysfunction plays a pivotal role particularly in the cardiac, muscular, pulmonary, renal, and endothelial vasculatures.[43,49,121–123] Dysregulation of communication between cardiac endothelial cells and cardiomyocytes has been implicated in the development of structural and functional abnormalities in the heart.[121–123] Restoring endothelium-related signaling pathways is an emerging approach to mitigating HF progression.[121–123] This concept is supported by numerous studies that assessed peripheral microvascular endothelial dysfunction and demonstrated that HF-related clinical events in patients with HFrEF are independently related to abnormalities in endothelial function.[49,122–127]

The endothelium produces multiple important factors, particularly NO, that help regulate vascular tone, cardiomyocyte contractility, and tissue perfusion.[128,129] Imbalanced production and decreased release of NO results in endothelial dysfunction leading to vascular dysregulation, increased vascular stiffness and resistance, increased cardiac afterload, increased levels of oxidative stress, and neuroendocrine activation.[123,124,128–131] In addition, NO modulates cardiac function through its inotropic, lusitropic, and chronotropic effects.[128,129] The net result of a systemic deficit in NO is decreased local tissue perfusion and multiorgan dysfunction.[124]

The inflammatory state seen in chronic HF results in the downregulation of eNOS (endothelial NO synthase) expression, uncoupling of eNOS, increased production of reactive oxygen species, and increased plasma levels of Ang-2 (angiopoietin-2), all of which lead to reduced NO availability and ultimately endothelial dysfunction.[123,132,133] This process, which is directly initiated by the proinflammatory cytokines TNF-α, IL-1β, and IL-6, affects the vascular endothelium in the heart and peripheral tissues. Ultimately, a prolonged state of attenuated NO activity and endothelial dysfunction is associated with HFrEF progression.[123,132,133]

Derangements in angiogenesis and arteriogenesis (the formation of new capillaries and arterioles, respectively) also contribute to HF progression. Specifically, this complex process requires coordination between endothelial cells and other vascular cells, particularly pericytes and smooth muscle cells.[134–136] While VEGF (vascular endothelial growth factor) controls the early phases of new blood vessel formation, the angiopoietins and the Tie-2 (tyrosine-protein kinase receptor) receptor are importantly involved in controlling the maturation and stability of blood vessels.[134] The interaction between VEGF and Ang-1 (angiopoietin-1) plays an essential and complementary role in vascular development, angiogenesis, and arteriogenesis.[137–139]

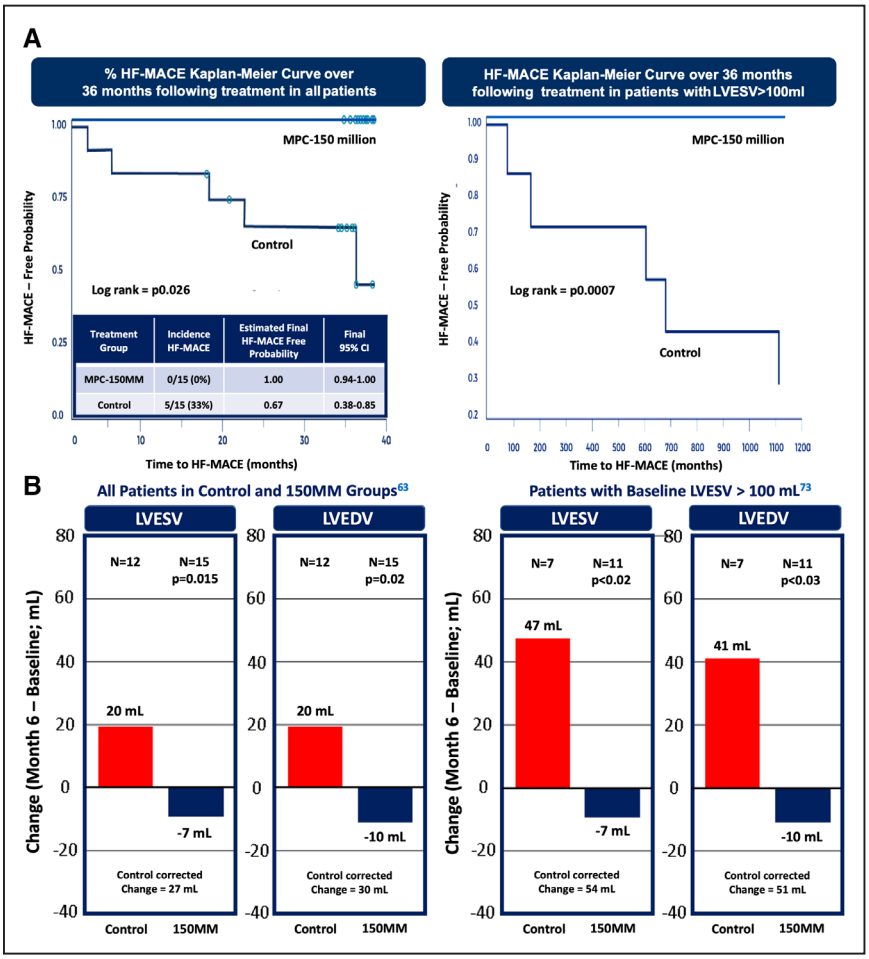

Figure 3. Phase 2 randomized dose-finding sham-controlled trial in New York Heart Association class II/III heart failure with reduced ejection fraction patients. A, The 150-million mesenchymal precursor cell group (MPC-150M) showed durable (36 mo) protection against heart failure–related major adverse cardiac events (HF-MACE) following single intracardiac injection. **Left**, All MPC-150M and control subjects.[63] **Right**, MPC-150M and control subjects enriched for baseline left ventricular end-systolic volume (LVESV) >100 mL.[73] **B**, Therapeutic benefit of MPCs on left ventricular remodeling at 6 mo enhanced in subjects with baseline LVESV >100 mL. LVEDV indicates left ventricular end-diastolic volume; and MPC, mesenchymal precursor cells.

Ang-1, which is produced by pericytes adjacent to endothelial cells, promotes structural stability and integrity of blood vessels. It also inhibits endothelial cell apoptosis promoting cell survival.[136,137,139–142] In contrast, Ang-2 produced by endothelial cells acts as a naturally occurring antagonist at the same surface receptor promoting vessel destabilization, growth, and inflammation.[140] Release of Ang-2 from endothelial cells after exposure to TNF-α and other proinflammatory mediators results in competitive inhibition of Ang-1 binding to Tie-2 surface receptors, thereby priming the endothelium for activation and vascular destabilization.[134,141–143] In addition, Ang-2 appears to act synergistically with VEGF to promote angiogenic sprouting and development of leaky, dysfunctional vasculature.[144] Circulating Ang-2 levels are elevated in patients with HF and correlate with a progressive decline in heart function.[145,146] Moreover, the degree of increase in Ang-2 serum levels predicts 1-year adverse clinical prognosis in patients with chronic HF due to LV systolic dysfunction.[147,148] Together, these data indicate that the inflammatory state and accompanying release of Ang-2 may directly contribute to HF progression through an abnormal vascular network in the failing heart and the peripheral tissues.

MPC Effects on Abnormal Coronary and Systemic Vasculature in HFrEF

Endothelial Dysfunction

The potential beneficial effects of MPCs on endothelial function were evaluated using the previously mentioned sheep model of collagen-induced arthritis and systemic inflammation.[70] A single intravenous administration of 150 million allogeneic MPCs resulted in reversal of eNOS-dependent endothelial dysfunction and vasodilatory abnormalities (as assessed by bradykinin or carbachol challenge) in coronary arteries and digital vascular beds. In contrast, no differences were seen between MPC-treated and MPC-untreated groups relative to the maximal response of coronary and peripheral arteries to the endothelium independent vasodilator sodium nitroprusside. The conclusion was that MPCs reversed inflammation-mediated endothelial dysfunction via an NO-dependent pathway.[70] This response was most likely due to increased eNOS enzyme activity and expression. In this sheep model, MPC-related improvements in myocardial and peripheral tissue endothelial function may have been achieved either indirectly through immunomodulation after interactions with various immune cell subsets or via direct secretion of proarteriogenic factors such as Ang-1.

Deranged Angiogenesis/Arteriogenesis

The proarteriogenic effects of MPCs are believed to be due to the integrated actions of at least 3 major factors secreted by MPCs, which are important in the development of the mature vascular tree: SDF-1 (stromal cell-derived factor-1), VEGF, and Ang-1.[66–68] These factors act in concert to support arteriogenesis in adult tissues where there are foci of microscopic ischemia such as in the failing heart. The release of each of

these factors by MPCs is enhanced by the action of proinflammatory cytokines such as TNF-α and IL-1β through their specific receptors on the MPCs.[67] The inflammatory milieu in the failing heart serves as a stimulus for MPCs to induce a mature vascular network. This angiogenic/arteriogenic ability of MPCs in the failing heart has been proposed to be an important component of the MOA by which MPCs may augment myocardial function. As noted previously, in small and large animal models of HF, administration of MPCs resulted in dose-dependent increases in cardiac arteriogenesis, a reduction in myocardial fibrosis, an increase in LV function, and improvement in survival outcome.[66,68,149]

The potential clinical benefit of MPC immunotherapy for reversing inflammation-related endothelial dysfunction and derangements of angiogenesis/arteriogenesis has recently been reported in end-stage HFrEF patients with a continuous-flow LVAD (CF-LVAD) who were randomized to MPCs or placebo sham control (LVAD-MPC Study No. 2).[72,150] MPC-treated patients were administered 150 million cells epicardially at the time of device implantation. These patients are believed to be characterized by an exceptionally high level of intracardiac inflammation due predominantly to activation of M1 cardiac macrophages.[151,152] In the overall study population of 159 patients, the primary end point (proportion of successful temporary weans from full CF-LVAD support) was not significantly different between MPC and control patients.[72,150] However, in a prespecified secondary analysis, MPCs significantly reduced the incidence of nonsurgical major mucosal bleeding events (predominantly gastrointestinal in origin)—a common and potentially fatal complication occurring in 20–40% of CF-LVAD–treated patients.[29,31,72,150,153,154] It is thought that inflammation in the heart in conjunction with diminished pulsatile blood flow to the splanchnic circulation (due to the abnormal blood flow characteristics of CF-LVADs) predisposed to bleeding events through multiple pathophysiologic pathways that are associated with increased serum levels of TNF-α and Ang-2.[70,137] The proposed interactions between multiple factors converge within the systemic vasculature causing angiodysplasia, vascular disruption, and destabilization resulting in major gastrointestinal bleeding. In the LVAD-MPC study No. 2, a single dose of 150 million MPCs at the time of CF-LVAD implantation resulted in a clinically meaningful 76% reduction in the rate of nonsurgical major mucosal bleeding events ($P<0.001$), as well as a 65% reduction in hospitalization rate for treatment of nonsurgical major gastrointestinal bleeding events or epistaxis when compared with placebo-treated patients ($P=0.03$).[72] At 6 months of follow-up in the subset of patients with an ischemic pathogenesis to their HFrEF, MPCs decreased the rate of nonsurgical major mucosal bleeding events by 85%. This LVAD-MPC clinical trial supports the biologic plausibility that direct local injection of MPCs into the failing heart results in stability and integrity of systemic vasculature, presumed improvement in endothelial function, significant reduction in clinically meaningful adverse outcomes, and a decrease in hospitalization for nonsurgical major mucosal bleeding events (predominantly gastrointestinal in origin).

In summary, MPC immunotherapy appears to be an excellent candidate for meeting the large unmet clinical needs in patients with advanced chronic HFrEF at high risk for end-stage HFrEF. The multiple MOAs of MPCs align well with the pathophysiologic factors that account for the causal pathway for disease progression in patients with advanced chronic HFrEF. The likelihood that MPCs are biologically plausible agents with beneficial therapeutic effects on multiple interrelated causal pathways and clinical outcomes associated with disease progression in HFrEF is supported by 2 already completed phase 2 clinical trials:

- MPC dose-finding study in patients with advanced chronic HFrEF and
- MPCs as add-on therapy at the time of LVAD implantation.

In the next section, the ongoing phase 3 DREAM-HF trial (Double-Blind Randomized Assessment of Clinical Events With Allogeneic Mesenchymal Precursor Cells in Advanced Heart Failure) is used as an example of how flexible clinical trial design strategies can help keep a multiyear cardiovascular outcomes trial in cellular medicine both functionally efficient and contemporary from a clinical and regulatory perspective.

DREAM-HF Trial: Key Phase III Trial Design Aspects for Evaluation of MPCs in Patients With Chronic HFrEF

Original Trial Design

Overview

The DREAM-HF trial (MSB-MPC-CHF001; http://www.clinicaltrials.gov; unique identifier: NCT02032004) enrolled patients with advanced but stable chronic HFrEF who have been treated with what the investigators considered to be optimal medical therapy and coronary revascularization interventions. If administration of MPCs to these patients could reverse maladaptive adverse cardiac remodeling and endothelial dysfunction, as suggested in previous animal and clinical studies, then this therapy could conceivably reduce HF-MACE in this group with important unmet clinical needs.[63,70,72,73,150] Thus, the DREAM-HF trial is designed in conjunction with adaptive enrichment designs and strategies to test the hypothesis that MPCs can safely delay or prevent progression to worsening HF. Paramount to the value of this approach would be the robust demonstration that clinical research objectives can be achieved with shorter clinical trial timelines and increased cost-effectiveness without compromising ethics, statistical rigor, or regulatory standards.

The DREAM-HF population comprises patients with chronic HFrEF due to either an ischemic or nonischemic pathogenesis who fulfilled all of the following study entry criteria:

- optimal medical therapies with the best possible coronary revascularization,
- episode of documented decompensated HF within 1 to 9 months before initiation of screening or elevated plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide; >1000 pg/mL; >1200 pg/mL if atrial fibrillation),
- low ejection fraction (<40% by echo or <35% by multigated acquisition scan), and
- baseline NYHA class II or III chronic HFrEF.

A recent hospitalization or elevated NT-proBNP was included in the entry requirements for DREAM-HF to enrich the population with patients who would contribute to the trial's

clinical end points. In addition, these chronic HFrEF patients would be expected to have endothelial dysfunction involving the coronary arteries or systemic vasculature, conditions that would further contribute to the patients' morbidity, exercise intolerance, and mortality.[124–127,155,156]

Randomization and Study Treatment Delivery

Patients are randomly assigned in a 1:1 ratio to MPC or sham control treatment and subsequently undergo a single index cardiac catheterization procedure. During that procedure, the MPC-treated group undergoes cardiac mapping and transendocardial delivery of MPCs into viable myocardium. Patients in the control group undergo a scripted sham cardiac mapping and cell delivery procedure that mimics the actual cell delivery process. All cardiac catheterization procedures are performed at trained injection centers by unblinded interventional cardiology teams who are not involved with the blinded clinical follow-up and assessment of the subsequent HF-MACE and other study results.

Evolution of the DREAM-HF Trial's Primary Efficacy End Point

The DREAM-HF trial was designed from its inception as an events-driven study. The intent-to-treat population includes all patients randomly assigned to treatment (active or sham). In this population, analyses will be based on the treatment to which patients were randomly assigned regardless of which treatment they actually received. The safety population includes all patients in the intent-to-treat population who underwent the day 0 index cardiac catheterization and in whom the interventional cardiologist was able to advance a catheter across the aortic valve and into the LV chamber. In this population, treatment (active or control sham) will be based on the treatment patients actually received regardless of the treatment to which they were randomly assigned.

The original primary efficacy end point was defined as a traditional composite based on TTFE analysis. This composite consisted of the following prespecified positively adjudicated HF-MACE:

1. cardiac death or
2. hospitalization for decompensated HF or
3. successful resuscitation of documented ventricular fibrillation.

Inherent in the TTFE primary end point methodology is the convention that once a patient experiences one of the end point's component events, all other forward-looking events contained in the composite end point are censored. This approach, however, has major limitations:

- Recurrent HF hospitalizations and terminal cardiac events (TCEs), defined as cardiac death, heart transplant, or LVAD implantation, are not independent.
- Patients with prior HF hospitalization are more likely to be readmitted for decompensated HF events. Therefore, in the TTFE analysis, the HF hospitalization is a masking event for subsequent decompensated HF admission(s), as well as subsequent TCE.
- Death and HF hospitalization are assumed to have equal importance and to occur independently of each other. However, clinically, this is not the case.
- TTFE analyses ignore the fact that across a study, patients have different risks of TCEs and decompensated HF hospitalizations because of between-patient variability in the severity of their underlying clinical frailty.
- With this approach, ≈60% of recurrent nonfatal HF hospitalization events would be ignored in the TTFE analysis. Ultimately, ≤80% of TCEs could be masked when a decompensated HF hospitalization or successfully resuscitated ventricular fibrillation event occurs before a TCE. Figure 4 illustrates how a recurrent events analysis provides a more comprehensive assessment of a patient's HFrEF-related healthcare journey.

At the time that DREAM-HF was being initiated, there was growing recognition of the benefits of strategies that capture recurrent nonfatal HF-MACE in studies focused on patients with advanced chronic HFrEF. This alternative statistical approach (which may be implemented using various statistical recurrent event models) appeared to address many of the inherent limitations of the traditional TTFE methodology.[157,158] Extensive discussions were conducted with the Food and Drug Administration (FDA) on modifying the study's primary efficacy end point from a TTFE composite to one using recurrent events with the analysis based on the joint frailty model (JFM). The recurrent nonfatal HF-MACEs were defined as follows:

1. hospitalization or urgent care for decompensated HF and
2. successfully resuscitated high-grade symptomatic ventricular arrhythmias (eg, ventricular fibrillation)

The TCEs were defined as cardiac death, LVAD implantation, heart transplant, or placement of an artificial heart. Only the first TCE was taken into account in the primary and key secondary analysis.

This modification was ultimately supported by the FDA at a time when <10% of the estimated planned randomized patients had been enrolled into the trial and only 3.2% of the prespecified number of primary TTFE end points had occurred. Importantly, according to the adaptive design FDA guidance, since blinding was unequivocally maintained, this primary end point modification did not impact study integrity.[159]

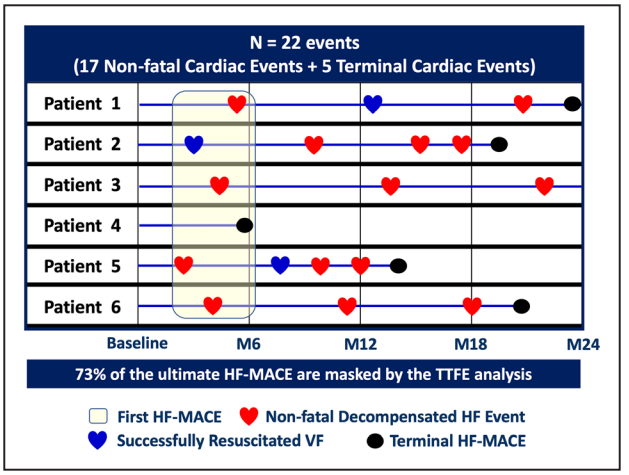

Figure 4. Illustrative example of recurrent events analysis for assessment of patients' comprehensive healthcare journey. HF indicates heart failure; HF-MACE, heart failure–related major adverse cardiac events; TTFE, time-to-first event; and VF, ventricular fibrillation.

In patients with moderate-to-severe HFrEF, it is well established that recurrent nonfatal HF-MACEs are not independent (the occurrence of a nonfatal HF-MACE makes another nonfatal HF-MACE more likely to occur). Additionally, multiple recurrent nonfatal HF-MACEs increase the risk of a TCE.[160] A patient's susceptibility to recurrent nonfatal HF-MACEs and TCEs (patient frailty) may vary substantially among patients. Although multiple recurrent event models are available (eg, Poisson, negative binomial, Andersen-Gill), the JFM accounts for all of the above important population characteristics. In contrast, the Poisson, negative binomial, and Andersen-Gill models do not take into account a correlation between recurrent and terminal events. While recurrent HF hospitalizations increase the probability of death, this relationship is ignored in the abovementioned models and taken into account in the JFM (Table 2). Ignoring strong correlation between recurrent and terminal events leads to a substantial bias in treatment effect estimate.[161]

Specifically, the JFM analysis evaluates recurrent nonfatal HF-MACE in the presence of TCEs accounting for increased risk of nonfatal HF-MACEs and TCEs after the occurrence of a nonfatal HF-MACE.[157,158,161] This analysis takes into consideration that rates of recurrent nonfatal events are not constant over time. It acknowledges that recurrent nonfatal events within patient are accounted for as having less impact on the treatment effect than that patient's first nonfatal event because of between-event correlation. This prevents a single patient with a high number of recurrent nonfatal events from having a disproportionately large impact on that treatment arm's ultimate success. The JFM also accounts for the impact of random between-patient differences (frailties characterizing an individual patient's susceptibility to recurrent hospitalizations or TCEs) such that either increased frailty on placebo or decreased frailty on active treatment corresponds to greater treatment effect. The JFM also allows for consideration of differences in patient follow-up time due to TCEs. When TCEs occur early after the administration of a study product (either MPCs or sham control procedure), the follow-up time is shorter and the likelihood of recurrent nonfatal HF-MACE is lower. In the JFM analysis, a patient who dies early will likely have greater frailty impact, which will adversely affect the respective treatment effect estimate. As a result, a frail patient may lack nonfatal events because of early death but the absence of nonfatal HF events for that patients will not benefit the respective treatment arm. It is important and required by FDA to verify that improvement in recurrent HF hospitalizations is not at the expense of worsening TCEs. Accordingly, the following prespecified analyses will be performed to assess the beneficial active treatment effects that decrease the hazard ratio relative to controls:

- delayed or less frequent nonfatal HF-MACE (primary end point: analysis based on the JFM) and
- nonincreased, delayed, or lower TCE rate (key secondary end point: analysis based on TTFE).

Table 3 presents post hoc data from 3 well-known clinical trials conducted in patients with chronic HFrEF.

- The CHARM-Added trial (Effects of Candesartan in Patients With Chronic Heart Failure and Reduced Left Ventricular Systolic Function Taking Angiotensin-Converting Enzyme Inhibitors) enrolled patients with HFrEF who were stratified by ACE inhibitor (yes or no) and then randomized to candesartan versus placebo.[162] CHARM-Added followed 2548 patients for a median follow-up of 41 months. There were 649 cardiovascular deaths; 703 patients presented with a total of 1402 HF hospitalizations, of which 699 (49.9%) were repeat. The predefined primary end point for the trial was the composite of first HF hospitalization and cardiovascular death.
- ValHeFT (Valsartan Heart Failure Trial) randomized chronic HFrEF patients to either the ARB valsartan or placebo.[163] The study, which enrolled 2499 patients in the placebo arm and 2511 patients in the valsartan arm, had a mean duration of follow-up of 23 months. The primary analysis outcomes were all-cause mortality and TTFE of all-cause mortality and morbidity (cardiac arrest with resuscitation, hospitalization for HF, or receipt of intravenous inotropic or vasodilator therapy for at least 4 hours).
- The EMPHASIS-HF trial (Comparison of Outcomes in Patients in NYHA Class II Heart Failure When Treated With Eplerenone or Placebo in Addition to Standard Heart Failure Medicines) randomized chronic HFrEF patients with mild symptoms to either eplerenone or placebo.[164] A total of 2737 patients were randomized and followed for a median of 2.08 years. The primary analysis end point was cardiovascular death or HF hospitalization.

Table 2. Summary Comparison of Commonly Used Statistical Models for Analysis of Recurrent HF Major Adverse Cardiac Events

Statistical Model Name	Types of Events Assessed in the Statistical Model	Takes Into Account Correlation	
		Between Recurrent HF Events	Between Recurrent HF and Terminal Events
Poisson model	Treats terminal and recurrent HF events similarly. Does not allow subject-to-subject variability.	No	No
Negative binomial model	Treats all events similarly but accounts for different patient-specific event rates. As such, does handle some heterogeneity across subjects.	Yes	No
Joint frailty model	Treats terminal and recurrent HF events differently. Models correlation between recurrent and terminal events. Accounts for random between-patient differences.	Yes	Yes

HF indicates heart failure.

Table 3. Comparisons Using TTFE vs Recurrent Events Analyses: CHARM-Added, ValHeFT, and EMPHASIS-HF

CHARM-Added (candesartan vs SOC)
PH HR=0.83; *P*=0.003 TTFE for CV death or HF hospitalization
JFM HR=0.65; *P*<0.0001 recurrent events
ValHeFT (valsartan vs SOC)
PH HR=0.89; *P*=0.02 TTFE for CV death or HF hospitalization
JFM HR=0.77; *P*=0.0005 recurrent events
EMPHASIS-HF (eplerenone vs SOC)
PH HR=0.68; *P*<0.001 TTFE for all-cause death or HF hospitalization
JFM HR=0.53; *P*<0.0001 recurrent events

CHARM-Added indicates Effects of Candesartan in Patients With Chronic Heart Failure and Reduced Left Ventricular Systolic Function Taking Angiotensin-Converting Enzyme Inhibitors; CV, cardiovascular; EMPHASIS-HF, Comparison of Outcomes in Patients in New York Heart Association Class II Heart Failure When Treated With Eplerenone or Placebo in Addition to Standard Heart Failure Medicines; HF, heart failure; HR, hazard ratio; JFM, joint frailty model; PH, proportional hazard; SOC, standard of care; TTFE, time-to-first event; and ValHeFT, Valsartan Heart Failure Trial.

The table summarizes the statistical outcomes (post hoc analyses) based on traditional TTFE (proportional hazards) and recurrent event analyses (JFM or negative binomial).[161,165–167] It is important to note that interpretation of hazards is different for proportional hazards and these recurrent events models. In the proportional hazard analyses, the hazard ratio is based on the overall hazards for active versus placebo groups (marginal model), whereas in the JFM or negative binomial analyses, the hazards account for variable patient susceptibility to recurrent events (frailty). Accordingly, the respective hazard ratios from proportional hazard–based and JFM-based analyses are not directly comparable. The individual patients' hazards of recurrent events in the JFM are conditional on individual patients' frailties. Therefore, the risk of recurrent events for a patient is based on both observed event rates over time on study and individual patient's frailty, unlike in the proportional hazard model where patient's event hazard is calculated for an average patient without accounting for random between-patient differences. The hazard ratio from JFM is interpreted as the relative reduction of overall hazard of recurrent events in the treated versus placebo patients, which takes into account random between-patient differences and risk of correlated TCEs. With these caveats in mind, the use of JFM or other recurrent event models (such as negative binomial) frequently provides a greater power to detect treatment differences while often reducing study size requirements.

In general, regulatory authorities have accepted the use of recurrent events analyses for evaluation of cardiovascular outcomes trials' primary efficacy end points.[158,165–167] For example, discussions during the Cardiovascular Round Table Workshop sponsored by the European Society of Cardiology in 2015 emphasized that evaluations of recurrent events are particularly suitable for diseases where reductions in repeat hospitalizations are of interest.[166] In the area of HF, the FDA has been supportive of the prospective use of recurrent events methodologies as the primary end point for pivotal/late-stage trials of devices (CHAMPION [Cardiomems Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients]), gene therapies (CUPID-2 [Calcium Upregulation by Percutaneous Administration of Gene Therapy in Patients With Cardiac Disease]), drugs (PARAGON [Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction]), and biologics (DREAM-HF).

Adaptive Patient Enrichment Modifications to the DREAM-HF Trial Design

As noted previously, the DREAM-HF trial originally enrolled patients with chronic HFrEF who were designated at baseline as having either NYHA class II or III chronic HFrEF. Independent of baseline NYHA class, all randomized patients were required to have had either a recent clinically important decompensated HF event or high levels of the HF biomarker NT-proBNP. The baseline disease enrichment added by these criteria, both of which have been identified as increasing the risk of future events, was expected to result in rates of subsequent recurrent nonfatal HF-MACEs and TCEs that would be similar between the baseline NYHA class II and III populations. In addition, it was expected that these criteria would enrich for patients with baseline LVESV >100 mL.

To test this assumption, in early 2017, the DREAM-HF trial data were reviewed by an independent statistical consultant who was blinded to the treatment groups to assess the rate of TCEs for the entire study population and as stratified by baseline NYHA class (separately for class II and III patients). The mean follow-up time was similar for baseline class III and II patients (≈15.4 months) as were the number of patients in each subgroup (class III, 147 patients; class II, 123 patients; class III/II ratio, 1.19). The sponsor was provided blinded-to-treatment summaries of the results. Strikingly, the number of TCEs was 3.5-fold higher for baseline NYHA class III patients than for class II patients (*P*=0.0014 by Kaplan-Meier log-rank analysis). This significant excess of TCEs in the more vulnerable class III HF patients and their subsequent censoring of recurrent nonfatal HF-MACE from the trial are critical factors because the TCE-censored class III patients had a significantly higher rate of primary end point events before the time of censoring than did the TCE-censored class II patients. Over time, the expected result of disproportionately losing class III patients would be an important reduction in the number, as well as prolongation of the timing of future recurrent nonfatal HF-MACE. This is an example of how blinded data acquired during the conduct of a clinical events-driven trial can indicate an operational design problem that was not anticipated at the start of the study.

For these reasons, enrichment and replenishment of the trial with baseline NYHA class III patients was deemed necessary to determine whether MPC therapy could improve the defined efficacy end points. This was accomplished using an FDA-reviewed protocol amendment and revised statistical analysis plan that allowed for adaptive patient enrichment of baseline NYHA class III patients during the screening evaluation. Considering the previous data with MPCs that suggest that patients with the most advanced chronic HFrEF have the greatest beneficial response to therapy, this adaptation aligned

well with the suspected MOAs of the cells.[63,73] The net result of this enrichment for patients who may be more capable of responding to MPC therapy could be a better differentiation between MPC- and sham-treated patients because of enhanced alignment of the cells' immunomodulatory, anti-inflammatory, and proangiogenic effects (predictive enrichment).

It is important to emphasize that throughout the entire conduct of the DREAM-HF trial, the baseline NYHA class II and III patients were randomized separately for appropriate treatment balance. The patient enrichment and replenishment adaptation did not change eligibility criteria for the trial (beyond future enrollment of only baseline NYHA class III patients). All baseline NYHA class II patients who were randomized before the adaptation will be included in the final intent-to-treat analysis. Because all details of this patient adaptation were prespecified before the beginning of its implementation, this planned adaptation adhered to FDA recommendations.[159] Finally, the hypotheses being tested in the DREAM-HF trial and the primary end point were unchanged and continue as prespecified previously. Based on the specifics of this blinded adaptation, we believe that the type 1 error rate was not affected and no α-level adjustment will be required.

Discussion

Adaptive patient enrichment approaches are particularly helpful when they are applied to innovative clinical trials that address large unmet needs in patients with complex disease states such as advanced chronic HF. These strategic design methodologies can improve the efficiency of an ongoing events-driven trial by allowing design specifications to be changed based on accumulating blinded data from the trial itself or information from other recent studies.[12] In addition, they can help maximize net present value for the development sponsors.

The results of recent preclinical and clinical studies provide biologic rationale for the use of MPCs to treat patients with advanced chronic HFrEF. The MOAs of MPCs present multiple opportunities to interrupt 3 underlying causal pathways for progression of HFrEF by

- suppressing cardiac and systemic inflammation,
- stabilizing or reversing maladaptive adverse LV remodeling, and
- improving coronary and systemic vascular abnormalities relating to endothelial dysfunction and deranged angiogenesis/arteriogenesis.

The biologic plausibility analysis suggests that MPCs have therapeutic effects on multiple interrelated causal pathways and clinical outcomes associated with disease progression in HFrEF. This is supported by the phase 2 dose-finding clinical trial data in patients with advanced chronic HFrEF and by the statistically significant beneficial effects on nonsurgical major mucosal bleeding events (predominantly gastrointestinal in origin) and related hospitalization that occurred with intracardiac MPC injections at the time of CF-LVAD implantation in patients with end-stage HFrEF.

DREAM-HF is an ongoing phase 3 randomized, sham-controlled, events-driven clinical trial assessing the safety and efficacy of the direct intracardiac delivery of 150 million MPCs in an enriched patient population with late NYHA class II or III symptoms of chronic HFrEF. The study, which randomized its first patient in 2014, is designed to assess whether MPCs can reduce morbidity and mortality in this population. Despite the duration of the trial, the fact that study treatment was required only once (ie, at the time of the day 0 cardiac catheterization) has the added benefit that the many challenges associated with real-world medication adherence and persistence of most traditional therapies for chronic HFrEF are not confounding factors in DREAM-HF. Since the study initiation, several important decisions have been made in conjunction with the FDA and implemented in the trial to improve its feasibility and to enhance the relevance of the clinical outcomes data. Among these are concepts relating to baseline disease enrichment, prognostic enrichment, and predictive enrichment—all of which were used to improve the trial's efficiency by allowing design specifications to be changed based on new information obtained from sources either internal or external to the clinical trial. These adaptive patient enrichment strategies demonstrate how flexible clinical trial design can be used to keep a phase 3 multiyear cardiovascular outcomes trial in cellular medicine contemporary from a clinical and regulatory perspective while maintaining economic efficiency.

Finally, the DREAM-HF trial showcases, from a statistical and analytics perspective, the JFM, which evaluates recurrent nonfatal HF-MACE in the presence of TCEs, thereby accounting for increased risk of nonfatal HF-MACE and TCEs after the occurrence of a nonfatal HF-MACE. This innovative approach allows for integration of efficacy, safety, and pharmacoeconomic data into a comprehensive assessment of the patient's overall disease burden over time. This type of analysis is of increasing importance in today's evolving global regulatory environment. In particular, the use of recurrent event analysis in general and the JFM in particular may have major impact on the size of a trial. As all recurrent events occurring before a terminal event are taken into account, the size of a trial may potentially be reduced by ≤30% as compared with the respective TTFE analysis (based on currently available power simulations).

In conclusion, the potential value of adaptive enrichment designs and strategies as part of a rational approach to ongoing clinical trial design is the robust demonstration that clinical research objectives can be achieved with shorter clinical trial timelines and increased cost-effectiveness without compromising ethics, statistical rigor, or regulatory standards. The DREAM-HF trial, which evaluates a cellular immunotherapy product—MPCs—with high biologic plausibility for targeted beneficial effects in patients with advanced chronic HFrEF, represents the real-world translation back and forth between preclinical science and clinical research. It is potentially an important step on the cellular medicine pathway to meeting large unmet clinical needs in patients with advanced chronic HFrEF. Ultimately, the results of this study are expected to clarify the role of MPC immunotherapy as an adjunct to standard-of-care therapies in patients with advanced chronic HFrEF who are at high risk for disease progression to end-stage HF and poor clinical outcomes.

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