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RESEARCH ARTICLE

Mesenchymal precursor cells reduce mortality and major morbidity in ischaemic heart failure with inflammation: DREAM-HF

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Aims Progressive heart failure with reduced ejection fraction (HFrEF) is adversely affected by alterations in the myocardial balance between bone marrow-derived pro-inflammatory cardiac macrophages and embryo-derived reparative cardiac resident macrophages. Mesenchymal precursor cells (MPCs) may restore this balance and improve clinical outcomes when inflammation is present. The purpose was to (i) identify risk factors for cardiovascular death (CVD) in control patients with HFrEF in the DREAM-HF trial, and (ii) determine if MPCs improve major clinical outcomes (CVD, myocardial infarction [MI], stroke) in high-risk patients with ischaemic HFrEF and inflammation.

Methods and results Cause-specific regression analyses were used to identify CVD risk factors in DREAM-HF control patients. Aalen–Johansen cumulative incidence curves were used to examine CVD, 2-point major adverse cardiovascular events (MACE) (MI or stroke), and 3-point MACE (CVD or MI or stroke) by treatment group in ischaemic vs non-ischaemic HFrEF and in patients with or without baseline inflammation. In control DREAM-HF patients, factors portending the greatest risk for CVD were inflammation (baseline plasma high-sensitivity C-reactive protein $\geq$2 mg/L; $p = 0.003$) and ischaemic HFrEF aetiology ($p = 0.097$), with increased CVD risk of 61% and 38%, respectively. Over 30-month mean follow-up, MPCs reduced 2-point and 3-point MACE by 88% ($p = 0.005$) and 52% ($p = 0.018$), respectively, in patients with ischaemic HFrEF and inflammation compared to controls.

Conclusion Ischaemic aetiology and inflammation were identified as major risk factors for MACE in control DREAM-HF patients. A single intramyocardial MPC administration produced the most significant, sustained reduction in 2-point and 3-point MACE in patients with ischaemic HFrEF and inflammation.

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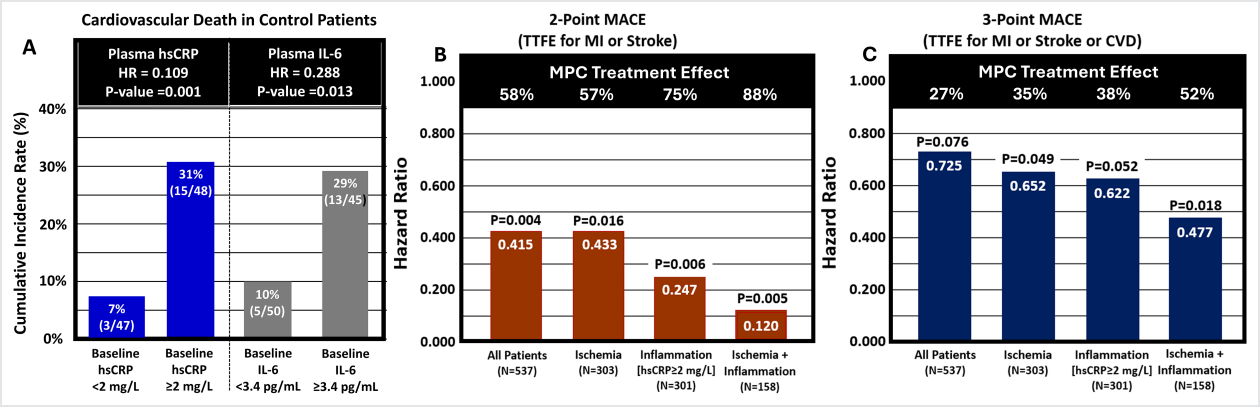
Graphical Abstract



(*A*) The cumulative incidence rate for cardiovascular death (CVD) was higher in the same control patients when analysed using baseline inflammatory plasma biomarkers high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L (*left panel*) and interleukin (IL)-6 ≥ 3.4 pg/ml (*right panel*). The effect of mesenchymal precursor cells (MPCs) on (*B*) 2-point major adverse cardiovascular events (MACE) (myocardial infarction [MI] or stroke) and (*C*) 3-point MACE (MI or stroke or CVD) in all patients with heart failure with reduced ejection fraction in the DREAM-HF trial and in the subgroups of patients with ischaemia, inflammation, and ischaemia and inflammation. The greatest beneficial effect was seen in patients with both ischaemia and inflammation. TTFE, time-to-first event.

Keywords Heart failure with reduced ejection fraction • Mesenchymal precursor cells • High-sensitivity C-reactive protein • Cardiovascular death • 2-point MACE • 3-point MACE

Introduction

Mesenchymal precursor cells (MPCs) are well-characterized allogeneic STRO-1/STRO-3+ cells with immunomodulatory properties that are derived from human bone marrow mononuclear cell populations. MPCs express surface markers for pro-inflammatory cytokines such as interleukin (IL)-6, IL-1, tumour necrosis factor-α, and interferon-γ that are produced by activated macrophages and T cells. Binding of these cytokines to the surface receptors on MPCs activates the cells, which then exert anti-inflammatory, immunomodulatory, vascular regulating, anti-fibrotic, and pro-angiogenic effects.[1–7] MPCs have been shown to reduce myocardial fibrosis, induce angiogenesis, increase cardiomyocyte cycling, and reverse myocardial dysfunction in small and large animal models of heart failure after either ischaemia or anthracycline toxicity.[5,7]

Abnormalities in tissue fibrosis, angiogenesis, and cardiomyocyte apoptosis in the setting of myocardial ischaemia may result from alterations in the myocardial balance between bone marrow-derived pro-inflammatory cardiac macrophages and embryo-derived reparative cardiac resident macrophages.[8–14] MPCs appear to elicit favourable cardiac effects by restoring the balance between anti-inflammatory cardiac resident macrophages and pro-inflammatory bone marrow-derived monocytes that infiltrate the damaged, inflamed heart. Consequently, MPCs may improve clinical outcomes in high-risk patients with heart failure with reduced ejection fraction (HFrEF) and inflammation by mechanisms that differ from and are complementary to agents that target neurohormonal imbalances and congestion, providing a disease-modifying approach not achievable with traditional guideline-directed medical therapy (GDMT) alone.

Mesenchymal precursor cells have been evaluated in the largest cell therapy trial for heart failure to date—the randomized, sham-controlled DREAM-HF trial—in which a single transendocardial administration of MPCs in high-risk patients with chronic HFrEF on GDMT improved clinical outcomes, especially in those with high levels of baseline inflammation.[15] Specifically, MPCs reduced the risk of 2-point major adverse cardiovascular events (MACE; stroke or myocardial infarction [MI]) by 58% and 3-point MACE (stroke or MI or cardiovascular death) by 27% over the 30-month mean follow-up period.

In the current subgroup analyses of the DREAM-HF trial population, we have identified ischaemia and cardiac inflammation as major risk factors for MACE in control patients with HFrEF and examined the effects of MPCs on major clinical outcomes (2-point and 3-point MACE) in patients with HFrEF with ischaemia and inflammation.

Methods

Patients and trial design

The DREAM-HF trial was a prospective, randomized, sham-controlled trial in which a total of 565 patients with chronic HFrEF were enrolled

and randomized 1:1 to an intra-myocardial administration of MPCs or a sham control procedure (MPC, $n = 283$; control, $n = 282$). The cells used in the DREAM-HF study were immunoselected from the bone marrow of healthy donors and expanded in culture using proprietary techniques.[15] The analysis population in the DREAM-HF trial comprised 537 patients: 265 randomized to MPC treatment plus GDMT and 272 to the control group (GDMT alone).[15] All patients in the analysis population underwent cardiac catheterization with the passage of at least one catheter across the aortic valve. There were 301 patients with baseline inflammation (high-sensitivity C-reactive protein [hsCRP] ≥2 mg/L), which is 56% of the analysis population, and 303 patients who had an ischaemic aetiology of HFrEF (58% of the population; online supplementary *Figure S1*). The analysis population is further described in the online supplementary material. The cell-treated group underwent NOGA electrical mapping followed by injections of 150 million MPCs (15–20 transendocardial injections) targeted to viable but dysfunctional myocardium. This dose was based on findings from a previous MPC dose-ranging study in patients with chronic HFrEF.[16] Control patients underwent sham-scripted NOGA mapping and sham-scripted cell injections in the cardiac catheterization laboratory. Patients and follow-up physicians (after the catheterization laboratory procedure) were blinded to treatment randomization. Once treated, all patients continued GDMT throughout the study period. The mean follow-up was 30 months (maximum, 66 months). Vital status (alive or dead) was established for 100% of the randomized patients. The DREAM-HF trial conformed to the Declaration of Helsinki and was approved by the Institutional Review Board at each participating study centre.

Online supplementary *Table S1* shows the demographics and baseline characteristics for all 537 patients in the analysis population and for those with an ischaemic ($n = 303$) or non-ischaemic ($n = 234$) HFrEF aetiology. The major observed clinical differences between the ischaemic and non-ischaemic groups were for previous MI, previous stroke, and history of coronary artery revascularization; there was also evidence for greater use of antiplatelet agents and statins in the ischaemic group.

Statistical methods

Cause-specific Cox regression and Aalen–Johansen cumulative incidence function methods were used for all time-to-event analyses. For time to cardiovascular death and time to 3-point MACE (cardiovascular death or MI or stroke), non-cardiovascular deaths were considered as competing risk. For time to 2-point MACE (MI or stroke), all deaths other than fatal MI or fatal stroke events were considered competing risk. Gray's test for equality of cumulative incidence functions and cause-specific hazard ratios (HR) are presented. The above-mentioned analyses were performed for all patients and for pre-specified subgroups, which included but were not limited to baseline New York Heart Association (NYHA) functional class, sex, baseline inflammatory biomarkers (including hsCRP <2 vs. ≥2 mg/L), and the presence of macrovascular disease (ischaemic HFrEF aetiology: yes or no).

An ischaemic aetiology of chronic HFrEF was determined by the study site's principal investigator based on a well-documented clinical history of MI, stroke and/or coronary artery revascularization. In the ischaemic patient population, 97% of the MPC-treated patients and 99% of the control patients fulfilled these predefined criteria for myocardial ischaemia (online supplementary *Table S2*).

Analyses of inflammation as an underlying condition for high rates of cardiovascular death, 2-point MACE, and 3-point MACE

High-risk patients with chronic HFrEF frequently have elevated levels of IL-6 and other pro-inflammatory cytokines produced by bone-marrow derived macrophages (M1) and the inflamed myocardium. hsCRP, an acute phase reactant that is synthesized by the liver in response to inflammatory cytokines, has been validated as a biomarker of cardiovascular risk associated with inflammation.[17–20] High cardiac levels of IL-6 contribute to inflammation in chronic HFrEF. Moreover, this high concentration of IL-6 in the heart relates to high levels of hsCRP in the circulation because cardiac IL-6 can enter the venous system and travel to the liver where it stimulates the synthesis of C-reactive protein. These pro-inflammatory cytokines and acute phase reactants have been associated with cardiomyocyte apoptosis, reduced left ventricular systolic function, and endothelial dysfunction[15,19–23]

Since MPCs express cell surface receptors that respond to the binding of inflammatory cytokines by releasing paracrine immunomodulatory and pro-angiogenic factors, we examined the possibility that stratifying patients on the basis of high baseline hsCRP or IL-6 levels may identify MPC treatment responders.[6,7,15,24,25] In a subset of 195 NYHA class II patients who had baseline plasma measurements of IL-6 and hsCRP, we assessed whether elevated levels of IL-6 (at or above the study median value: 3.4 ng/dL) and hsCRP (≥2 mg/L) could be used to identify patients who were at high risk of cardiovascular death and who would respond to MPC administration. The objectives of these analyses were to determine if hsCRP and IL-6 plasma levels were (i) prognostic for risk of cardiovascular death in control patients, (ii) predictive of beneficial MPC treatment effects, and (iii) inter-related in the same patients.

Results

Inflammation and ischaemic aetiology portend greatest risk for cardiovascular death in control patients with HFrEF

Risk factors for cardiovascular death were evaluated for control patients by examining pre-specified baseline characteristics using univariate Cox regression analyses of cardiovascular death in control patients, adjusted for competing risk (non-cardiovascular deaths). These variables included hsCRP and history of myocardial ischaemia, diabetes, NYHA class, and MI (*Table 1*). Because baseline log(hsCRP) passed the significance threshold ($p = 0.069$), we further explored hsCRP subgroups (baseline hsCRP threshold values of ≥2 mg/L, ≥3 mg/L and ≥4 mg/L). In this analysis, the strongest prognostic risk factors for cardiovascular death in control patients were baseline plasma hsCRP ≥2 mg/L ($p = 0.003$) and ischaemic aetiology of HFrEF ($p = 0.097$) (*Table 1*). Analyses showed that using baseline plasma hsCRP ≥3 mg/L ($p = 0.008$) or baseline plasma hsCRP ≥4 mg/L ($p = 0.016$) did not provide additional prognostic benefit over that of baseline plasma hsCRP ≥2 mg/L. These findings led to subgroup analyses using established risk factors of baseline hsCRP ≥2 mg/L and myocardial ischaemic aetiology for chronic HFrEF.

Table 1 **Risk factors for cardiovascular death with competing risk for non-cardiovascular death in control patients (analysis population) using univariable Cox proportional hazard models for cardiovascular death**

Risk factor for CVD (absent [no] vs. present [yes])	Hazard ratio	95% confidence interval	*p*-value
Inflammatory biomarkers			
Baseline hsCRP ≥2 mg/L	0.376	0.200–0.716	0.003
Baseline hsCRP ≥3 mg/L	0.461	0.259–0.818	0.008
Baseline hsCRP ≥4 mg/L	0.498	0.283–0.877	0.016
Medical history			
Myocardial ischaemia	0.614	0.346–1.092	0.097
NYHA class IIIA (vs. class II)	0.724	0.416–1.260	0.254
Diabetes	0.827	0.484–0.1412	0.486
Prior myocardial infarction	0.963	0.562–1.650	0.892

CVD, cardiovascular death; hsCRP, high-sensitivity C-reactive protein; NYHA, New York Heart Association.

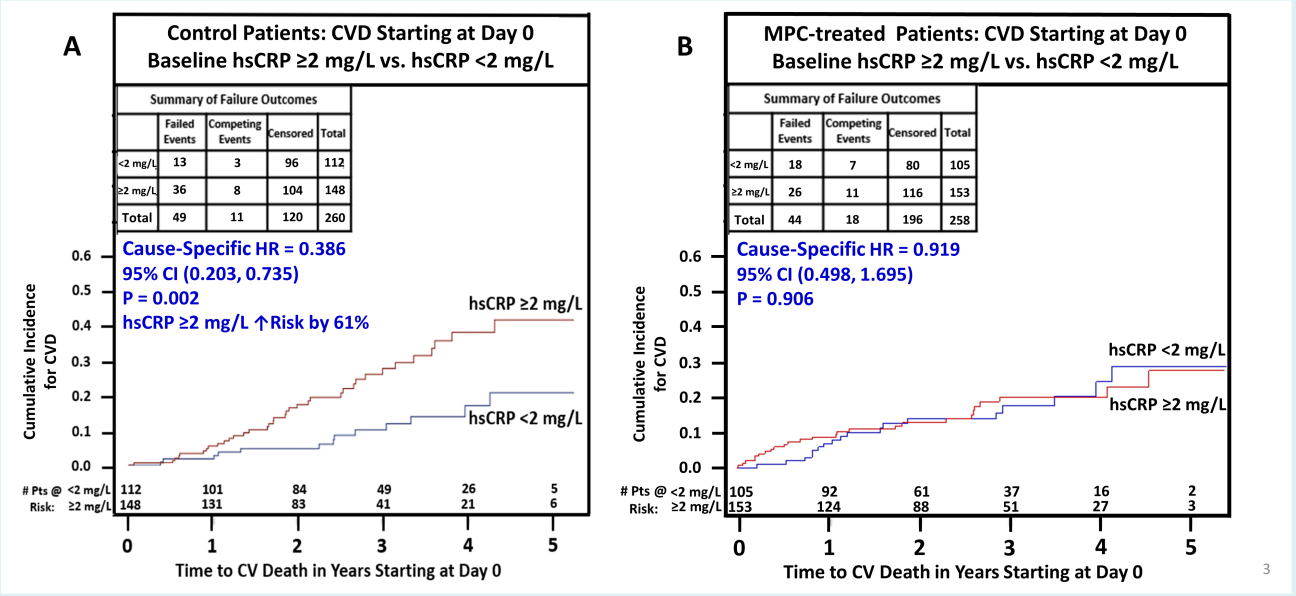


Figure 1 Aalen–Johansen cumulative incidence function curves for cardiovascular death (CVD) in (*A*) control and (*B*) mesenchymal precursor cell (MPC)-treated patients. Aalen–Johansen cumulative incidence function curves show that the risk of CVD was higher in heart failure with reduced ejection fraction (HFrEF) control patients with baseline high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L than in those with hsCRP <2 mg/L (*A*; $p = 0.002$). In MPC-treated patients with HFrEF, CVD incidence in those with baseline hsCRP ≥2 mg/L was reduced to a level similar to that seen in MPC-treated patients with baseline hsCRP <2 mg/L and in control patients with baseline hsCRP <2 mg/L.CI, confidence interval; HR, hazard ratio.

The risk of cardiovascular death (mean follow-up, 30 months) in control patients ($n = 260$) with baseline hsCRP ≥2 mg/L was higher than in those with baseline hsCRP <2 mg/L ($p = 0.002$; *Figure 1A*). In contrast, in MPC-treated patients ($n = 258$), the incidence of cardiovascular death in patients with baseline hsCRP ≥2 mg/L was reduced to a level similar to that seen in MPC-treated patients with baseline hsCRP <2 mg/L (*Figure 1B*) as well as control patients with baseline hsCRP <2 mg/L (*Figure 1A*).

High-sensitivity C-reactive protein and interleukin-6 as risk factors for cardiovascular death and predictors of mesenchymal precursor cell treatment effect on cardiovascular death

To compare hsCRP and IL-6 as potential biomarkers for the risk of cardiovascular death in HFrEF control patients, we evaluated cardiovascular rates in the 195 control or MPC-treated patients

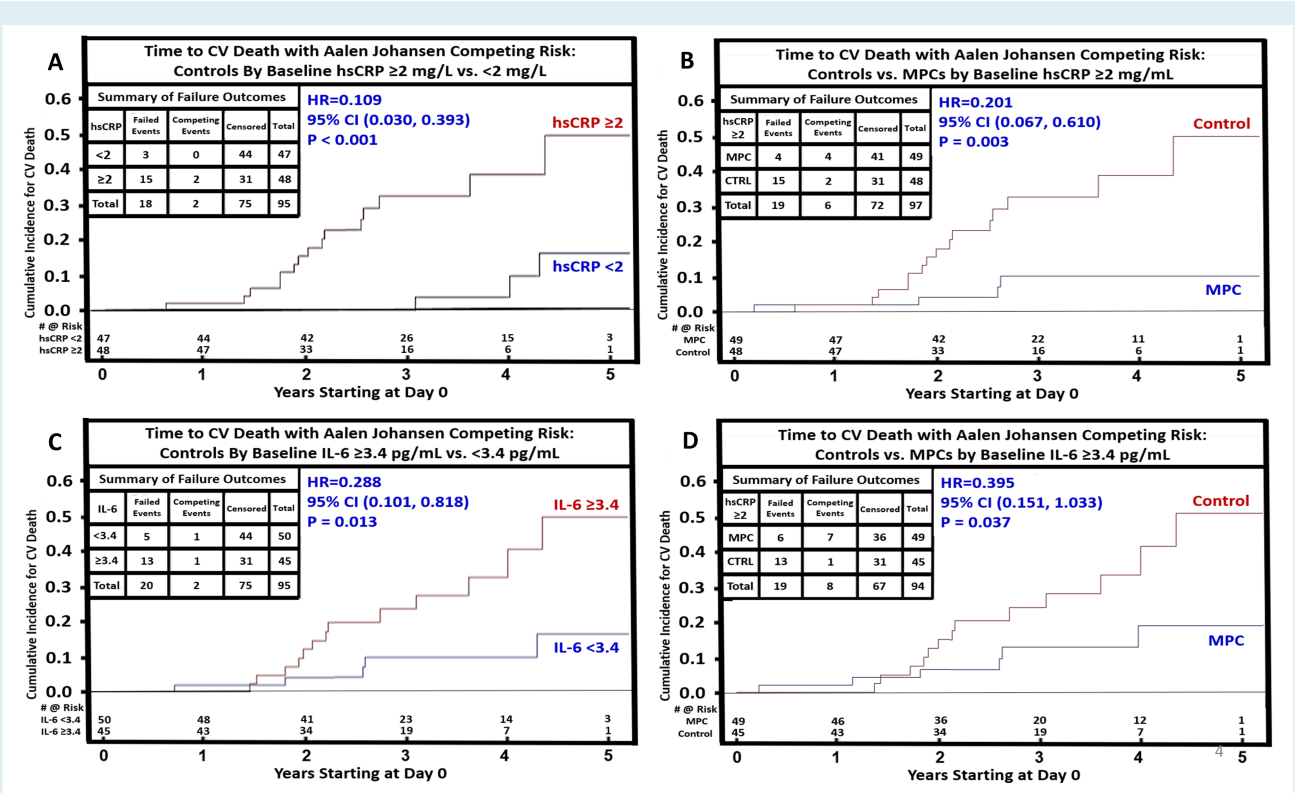


Figure 2 Aalen–Johansen competing risk analyses for time to cardiovascular (CV) death in control and mesenchymal precursor cell (MPC)-treated same patients by high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6). In control patients, CV death rates were significantly higher in those with elevated levels of the inflammatory biomarkers hsCRP (*A*) or IL-6 (*C*) than the rates seen in control patients with low levels of the biomarkers. CV death risk in MPC-treated patients was significantly reduced in heart failure with reduced ejection fraction patients with baseline plasma hsCRP ≥2 mg/L (*B*) and in those with plasma IL-6 ≥ 3.4 pg/mL (*D*) when compared with controls. CI, confidence interval; HR, hazard ratio.

who had paired baseline plasma samples of hsCRP and IL-6 levels. Patients were stratified on the basis of hsCRP <2 mg/L or ≥2 mg/L (*Figure 2A,B*) or plasma IL-6 below or above the median value (<3.4 pg/ml vs ≥3.4 pg/ml) (*Figure 2C,D*). Over a mean follow-up of 30 months, control patients who had elevated inflammatory biomarkers, whether defined by hsCRP or IL-6 levels, had cardiovascular death rates significantly higher than the rate seen in control patients with low inflammation levels ($p < 0.001$ and $p = 0.013$; *Figure 2A,C*, respectively). Thus, high levels of either plasma hsCRP or plasma IL-6 were similarly prognostic for a high cardiovascular death rate in control patients with HFrEF.

Using the same baseline plasma samples, we compared hsCRP and IL-6 as predictors of the treatment effect of MPCs on cardiovascular death. After MPC treatment, the risk of cardiovascular death compared to controls was reduced by 80% in HFrEF patients with baseline plasma hsCRP ≥2 mg/L (*Figure 2B*) and by 60% in patients with plasma IL-6 ≥3.4 pg/ml (*Figure 2D*). Thus, MPC treatment significantly lowered the risk of cardiovascular death in HFrEF patients with inflammation regardless of whether hsCRP or IL-6 was used as the biomarker of inflammation. Together, these results suggest that high plasma levels of hsCRP and IL-6 can be used interchangeably as markers of both disease activity and response to MPC treatment.

We analysed the four combinations of high and low baseline hsCRP and IL-6 for predicting cardiovascular death in control and MPC-treated patients (online supplementary *Figure S2*). In control patients, the Gray's test for equality of cumulative incidence functions showed that both inflammatory biomarkers, but especially high hsCRP levels, were highly predictive of cardiovascular death ($p = 0.0034$). In contrast, in MPC-treated patients, the Gray's test showed overlapping data ($p = 0.706$). These results support those shown in *Figure 2*.

Mesenchymal precursor cells reduce 2-point and 3-point MACE in ischaemic HFrEF

Because ischaemic HFrEF aetiology was identified as prognostic for high risk of cardiovascular death in control patients, we examined the effects of MPCs on 2-point MACE and 3-point MACE in a pre-specified subgroup analysis of patients in the DREAM-HF trial with ischaemic HFrEF. The analysis populations were all patients with ischaemic HFrEF ($n = 303$) and all patients with non-ischaemic HFrEF ($n = 234$). In patients with ischaemic disease, MPC treatment reduced the risk of 2-point MACE by 57% (HR 0.433, $p = 0.016$; *Figure 3A*) and 3-point MACE by 35%

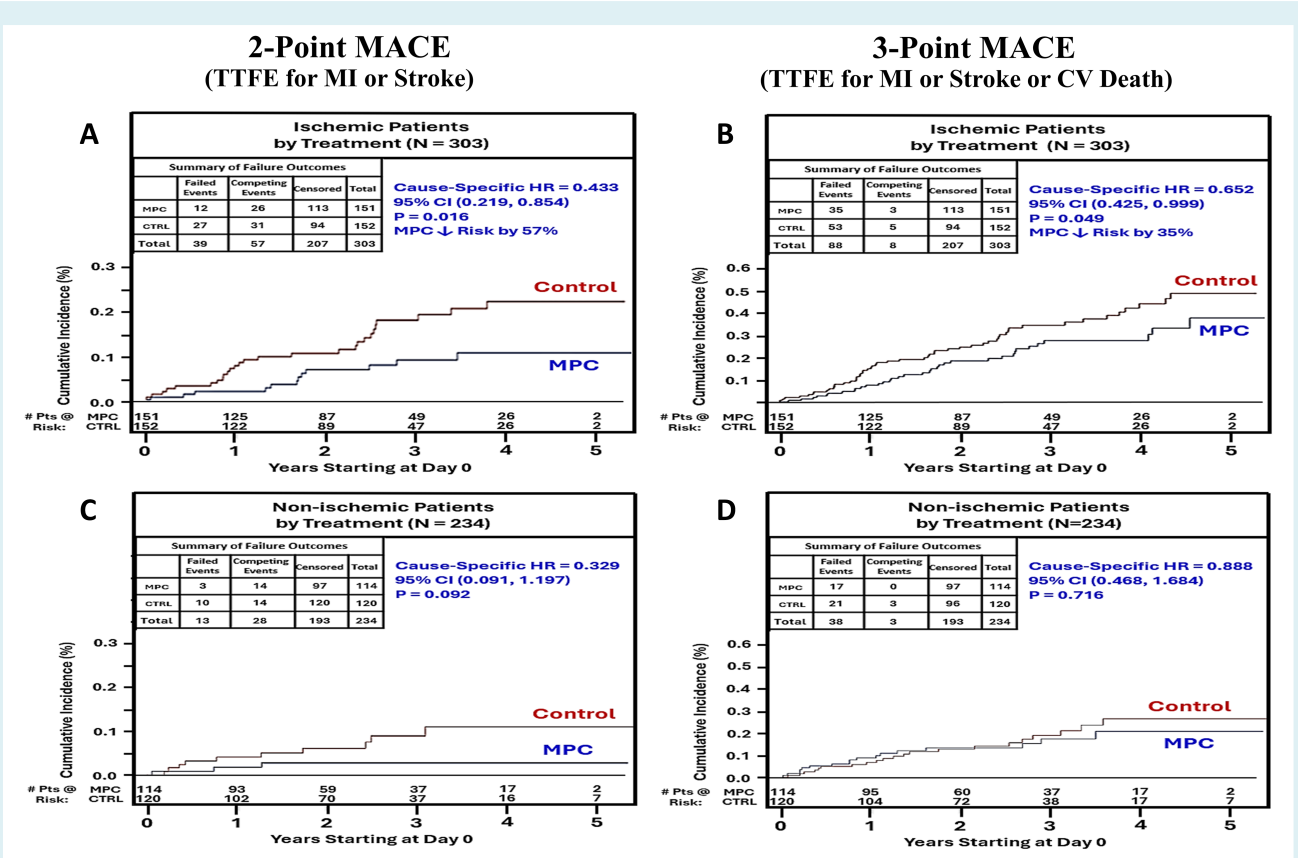


Figure 3 Aalen–Johansen cumulative incidence function curves for 2-point major adverse cardiovascular events (MACE) and 3-point MACE in patients with ischaemic and non-ischaemic heart failure with reduced ejection fraction (HFrEF). Mesenchymal precursor cell (MPC) treatment reduced the risk of 2-point MACE (time-to-first event for myocardial infarction [MI] or stroke) in patients with ischaemic HFrEF by 57% (*A*) and the risk of 3-point MACE (time-to-first event [TTFE] for cardiovascular [CV] death or MI or stroke) by 35% (*B*) compared to ischaemic control patients but had no effect on time to either 2-point MACE (*C*) or 3-point MACE (*D*) in patients with non-ischaemic HFrEF. CI, confidence interval; HR, hazard ratio.

(HR 0.652, $p = 0.049$; *Figure 3B*) compared with control patients. In contrast, MPC treatment had no effect on time to either 2-point (*Figure 3C*) or 3-point MACE (*Figure 3D*) in the non-ischaemic group.

Mesenchymal precursor cells reduce the risk of 2-point MACE and 3-point MACE in ischaemic HFrEF with inflammation

We next examined whether the presence of inflammation provided an additional predictive benefit of MPC treatment response in ischaemic HFrEF. For this analysis of patients with ischaemic HFrEF, our population comprised 158 patients with high levels of baseline inflammation and 131 with low levels. In patients with both ischaemia and inflammation, MPC treatment resulted in an 88% reduction in 2-point MACE risk (*Figure 4A*; HR 0.120, $p = 0.005$) and a 52% reduction in 3-point MACE risk (*Figure 4C*; HR 0.477, $p = 0.018$). However, in patients who had ischaemia without concomitant inflammation, MPC treatment did not reduce the risk of 2-point MACE (*Figure 4B*; HR 0.756, $p = 0.496$) or 3-point MACE (*Figure 4D*; HR 0.901, $p = 0.753$). Finally, we analysed the time to 2-point (online supplementary *Figure S3*) and 3-point MACE (online supplementary *Figure S4*) in patients with non-iscahemic HFrEF grouped by high ($n = 143$) and low ($n = 86$) baseline inflammation levels. MPCs had no effect on 2-point or 3-point MACE in any group of patients without ischaemia. These results demonstrate that inflammation must be present for MPC administration to provide MACE treatment benefits in patients with ischaemic HFrEF.

In summary, the *Graphical Abstract* shows the MPC treatment effect on 2-point and 3-point MACE for all patients in the analysis population ($n = 537$), those with ischaemic HFrEF ($n = 303$), those with inflammation ($n = 301$), and those with both ischaemic HFrEF and inflammation ($n = 158$). A single intramyocardial injection of MPCs produced the most significant and sustained reduction in risk of 2-point and 3-point MACE in patients with HFrEF of ischaemic aetiology accompanied by baseline inflammation.

Discussion

DREAM-HF is the largest clinical trial to date of cell therapy in patients with high-risk chronic HFrEF. Its long mean follow-up of

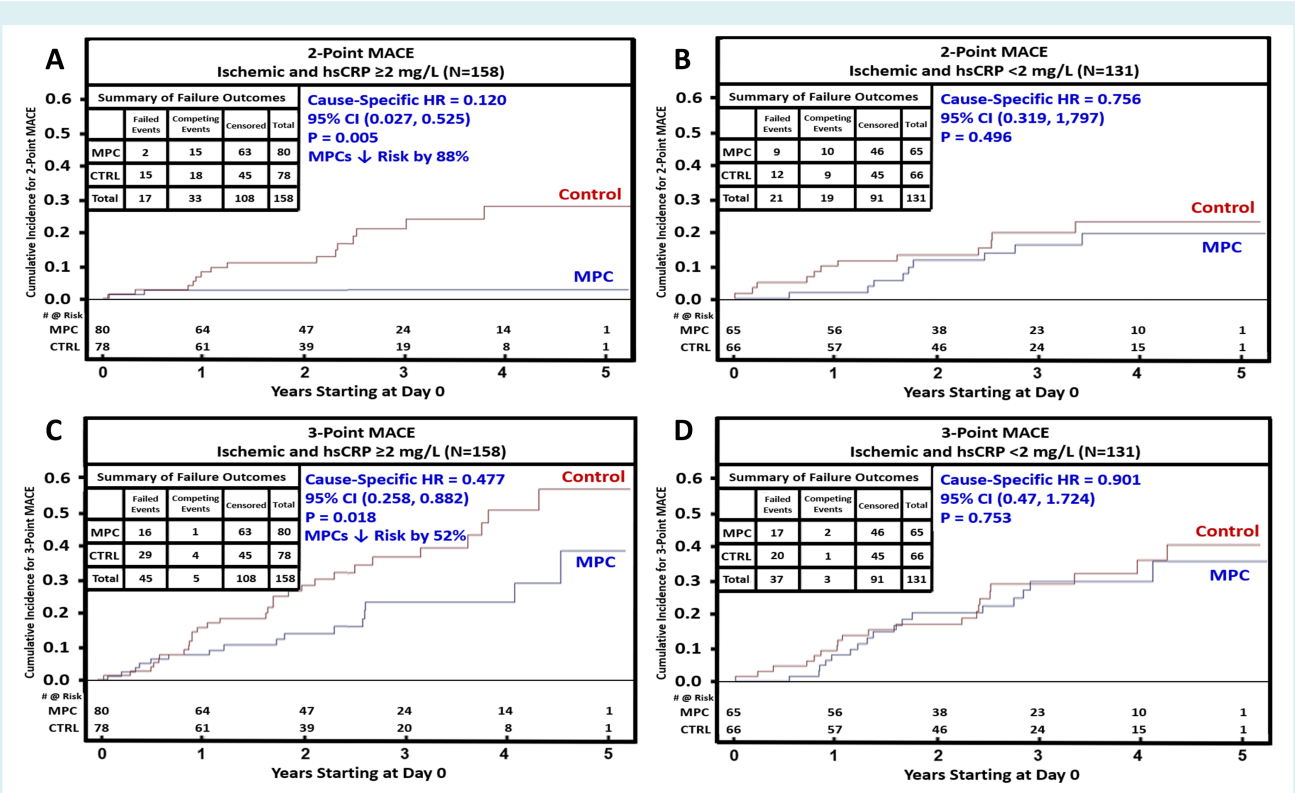


Figure 4 Aalen–Johansen cumulative incidence function curves for 2-point and 3-point major adverse cardiovascular events (MACE) in ischaemic heart failure with reduced ejection fraction (HFrEF) with and without inflammation. Mesenchymal precursor cells (MPCs) reduced the risk of 2-point MACE in patients with ischaemic HFrEF *only* in the presence of inflammation (high-sensitivity C-reactive protein [hs-CRP] ≥2 mg/L; *A*) and not in patients without inflammation (hs-CRP <2 mg/L; *B*). Similar results were seen with 3-point MACE (*C* and *D*, respectively). CI, confidence interval; HR, hazard ratio.

30 months (maximum, 66 months) after a single intramyocardial administration of allogeneic MPCs provides new insights into which high-risk patient subgroups are most likely to benefit from this therapy. In the DREAM-HF trial, hsCRP demonstrated prognostic value for cardiovascular death and predictive value for response to MPC therapy.[15] Here, our analysis of pre-specified risk factors for cardiovascular mortality and major morbidity (MI and stroke) in control patients in DREAM-HF further identified ischaemic aetiology in addition to inflammation as the two factors that provided the greatest prognostic risk for cardiovascular death. Critically, the most significant impact of MPC administration on cardiovascular mortality and major morbidity was observed in those patients with both ischaemia and inflammation.

In patients with ischaemic HFrEF and inflammation, MPC treatment on top of maximal medical therapy reduced the risk of 2-point MACE by 88% (HR 0.120; $p = 0.005$) and the risk of 3-point MACE by 52% (HR 0.477; $p = 0.018$) compared with maximal medical therapy alone. This suggests that MPCs alter the natural history of HFrEF in the highest risk patients by mechanisms that differ from but are synergistic to agents that target neurohormonal imbalances and congestion (i.e. GDMT). Furthermore, these findings indicate a central and synergistic role for ischaemia and cardiac inflammation in the mechanism by which MPCs provide long-term benefits in these patients. More specifically, our study supports a proposed mechanism in which inflammatory cytokines present in the myocardium bind to surface receptors on intramyocardially injected MPCs, activating the cells and ultimately resulting in tissue reparative responses and a sustained treatment effect. The relationships between inflammation and endothelial dysfunction, microvascular ischaemia, and HFrEF disease progression are well-established as is the relationship between ischaemic HFrEF aetiology and high mortality rates in patients with end-stage HFrEF treated with left ventricular assist device implantation.[26–28] Our results support the importance of cardiac inflammation in chronic HFrEF, as shown previously in the DREAM-HF trial.[15]

Since initiation of the DREAM-HF trial, the importance of inflammation for activating mesenchymal stromal cells in therapeutic settings has become much better understood, with optimal treatment benefit requiring *in vitro* or *in vivo* stimulation by macrophages and T cell-derived inflammatory cytokines.[29–33] Indeed, we have shown that MPCs are induced to secrete various immunomodulatory and survival factors in response to stimulation with inflammatory cytokines.[1–7] The pro-inflammatory cytokine IL-6 is particularly interesting in HFrEF patients with inflammation since

its soluble form travels via the venous circulation from the inflamed myocardium to the liver where hepatocytes are induced to synthesize C-reactive protein. Release of these factors by MPCs likely has major collaborative effects on pro-inflammatory and pro-reparative cardiac resident cell populations, which may be involved in the mechanism by which MPCs impart their sustained effects on mortality and major morbidity. Here, we show that inflammation is required to elicit the most beneficial MPC response in the DREAM-HF population. This finding is consistent with inflammatory cytokines present in the heart in HFrEF being responsible for initiating the MPC response, which results in the release of immunomodulatory and survival factors necessary for mediating prevention or reversal of cardiac dysfunction.

The sustained reduction in cardiovascular death and incidence of MI and stroke over 30 months of mean follow-up in the DREAM-HF trial deserves special attention. MPCs are efferocytosed and removed by tissue cardiac resident macrophages within days to weeks after their delivery into the heart. These long-term outcomes appear to involve MPC-induced modulation of critical cardiac resident cell populations. Embryo-derived CCR2-negative cardiac resident macrophages, which have a low replicative state and a long life span,[34] meet the criteria for such a candidate effector population because they are capable of efficient efferocytosis and mediate anti-inflammatory, pro-angiogenic, pro-reparative, and anti-fibrotic effects in the setting of cardiac ischaemia and inflammation.[13,34–38] It is attractive to speculate that intramyocardial administration of MPCs facilitates a coordinated response via cell surface receptors to pro-inflammatory cytokines from bone marrow-derived CCR2-positive macrophages in the inflamed heart.[31] The resulting release of immunomodulatory and survival factors such as stromal cell-derived factor-1 and macrophage colony-stimulating factor would restore the positive balance of reparative CCR2-negative cardiac resident macrophages to facilitate long-term disease resolution.[39,40] In the DREAM-HF trial, the sustained (mean of 30 months) beneficial effects of a single MPC administration on MACE in ischaemic patients with inflammation contrasts with GDMT, in which long-term medication adherence and persistence can be problematic, especially in patients with ischaemic heart disease.[41]

Study limitations

In the DREAM-HF trial, analyses of MPC treatment effects on cardiovascular death, non-fatal MI, non-fatal stroke, and 2-point MACE and the effect of an ischaemic HFrEF aetiology alone or with inflammation on these endpoints were pre-specified; however, the composite 3-point MACE endpoint was a post-hoc analysis. Accordingly, the data relating to 3-point MACE should be considered hypothesis generating and need to be confirmed in a clinical trial designed specifically to assess the effects of MPCs on this composite endpoint. Although patients in the DREAM-HF trial were receiving neurohormonal blockage, the use of sodium–glucose cotransporter 2 inhibitors had not yet been accepted as a pillar of therapy for patients with HFrEF.

Conclusions

The results of these analyses from the DREAM-HF trial indicate that a single intramyocardial injection of MPCs in patients with ischaemic HFrEF and active inflammation—the group at highest risk of disease progression—results in a sustained reduction in cardiovascular major morbidity and mortality as shown by 2-point and 3-point MACE analyses. Moreover, these findings suggest that disease progression in ischaemic patients is driven by inflammation and that MPC treatment has the potential to improve the natural history of chronic HFrEF in a complementary synergistic fashion to agents that predominantly improve neurohormonal and/or congestive symptoms.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: M.J. is a consultant for Mesoblast. K.M.B., O.R., J.H., and C.J. are employees of Mesoblast. K.M.B. is the Mesoblast Global Head of Cardiovascular Development, Mesoblast, Inc. E.R. is the Chief Medical Officer of Mesoblast, Ltd. H.S. served on the Clinical Endpoints Committee for the DREAM-HF trial. S.I. is the Chief Executive Officer of Mesoblast, Ltd, and is a major shareholder. All other authors have nothing to disclose.

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