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Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial)

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Aims Regenerative treatment with mesenchymal stromal cells (MSCs) has been promising in patients with ischaemic heart failure but needs confirmation in larger randomized trials. We aimed to study effects of intra-myocardial autologous bone marrow-derived MSC treatment in patients with severe ischaemic heart failure.

Methods and results The MSC-HF trial is a randomized, double-blind, placebo-controlled trial. Patients were randomized 2 : 1 to intra-myocardial injections of MSC or placebo, respectively. The primary endpoint was change in left ventricular end-systolic volume (LVESV), measured by magnetic resonance imaging or computed tomography at 6 months follow-up. Sixty patients aged 30–80 years with severe ischaemic heart failure, New York Heart Association (NYHA) classes II–III, left ventricular ejection fraction (LVEF) <45% and no further treatment options were randomized. Fifty-five patients completed the 6-month follow-up (37 MSCs vs. 18 placebo). At 6 months, LVESV was reduced in the MSC group: −7.6 (95% CI −11.8 to −3.4) mL ($P = 0.001$), and increased in the placebo group: 5.4 (95% CI −0.4 to 11.2) mL ($P = 0.07$). The difference between groups was 13.0 (95% CI 5.9–20.1) mL ($P = 0.001$). Compared with placebo, there were also significant improvements in LVEF of 6.2% ($P < 0.0001$), stroke volume of 18.4 mL ($P < 0.0001$), and myocardial mass of 5.7 g ($P = 0.001$). No differences were found in NYHA class, 6-min walking test and Kansas City cardiomyopathy questionnaire. No side effects were identified.

Conclusion Intra-myocardial injections of autologous culture expanded MSCs were safe and improved myocardial function in patients with severe ischaemic heart failure.

Study registration number NCT00644410 (ClinicalTrials.gov).

Keywords Mesenchymal stromal cell • Stem cell • Ischaemic heart disease • Heart failure • Clinical trial

Introduction

Stem cell therapy is an emerging treatment modality for cardiovascular disease. While many clinical trials have been conducted, the optimal cell source and delivery technique yet remain to be defined.[1] Most trials have been conducted in patients with acute myocardial infarction (AMI) using intra-coronary infusion of bone marrow (BM) mononuclear cells (MNCs).[2–4]

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Several cell sources have demonstrated promising results including mesenchymal stromal cells (MSCs). Mesenchymal stromal cells are multi-potent stem cells that can be isolated from BM.[5] Mesenchymal stromal cells seem to stimulate growth of new blood vessels and cardiomyocytes by paracrine activation of resident stem cells in the myocardium.[6–9]

The majority of clinical MSC trials conducted prior to the present trial have been in AMI patients.[2,3] The treatment was safe with improvements in ventricular function, exercise capacity, and clinical symptoms. Intra-myocardial injection of MSCs in patients with chronic ischaemic heart disease (IHD) and refractory angina has shown promising results.[1,10–14] In patients with chronic IHD and heart failure, two relatively small MSC studies have been conducted.[15,16] These studies used intra-myocardial delivery and reported a significant reduction in scar tissue and non-significant trends towards improved left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF). To confirm these promising results larger randomized trials are needed.

The aim of the present randomized double-blind placebo-controlled study was to evaluate the treatment effects of intra-myocardial injection of autologous MSCs in a larger group of patients with chronic ischaemic heart failure.

Methods

Study overview

The MSC-HF trial is a phase-two, single-centre, randomized, double-blind, placebo-controlled study performed at Rigshospitalet, Copenhagen University Hospital, Denmark.

The study protocol complied with the Declaration of Helsinki and was approved by the Danish National Ethical Committee (j.no: H-A-2008-043) and Danish Medicines Agency (j.no: 2612-3737). The trial was registered at clinicaltrials.gov (NCT00644410) in 2008.

Manufacturing of cells was performed according to manufacturer's authorization of tissue establishment and manufacturer's authorization regarding human medicinal products issued by The Danish Health and Medicines Authority.

Enrolment started in September 2008, with the first patient treated in April 2009 and the last patient in April 2013. The study data were monitored continuously during the study period by the regional Good Clinical Practice unit. The rationale for the study design and endpoints were previously reported.[17]

Patient population

Key inclusion criteria were patients aged 30–80 years with ischaemic heart failure deemed without further conventional revascularization options by the clinical heart team at Rigshospitalet. At time of inclusion the patients were on maximum tolerable medication with no changes in medication for 2 months. Patients had LVEF $\leq$ 45% and were New York Heart Association (NYHA) Classes II–III. Major exclusion criteria were acute coronary syndrome, stroke, or transitional cerebral ischaemia within 6 weeks, revascularization within 4 months, moderate or severe valvular disease, severe chronic pulmonary disease, morbid obesity, and history of cancer within 5 years. All patients provided written informed consent. For detailed inclusion and exclusion criteria, see Supplementary material online, *Table S1*.

Randomization, blinding, and endpoints

Patients were enrolled in a 2 : 1 randomization in blocks of six. The randomization list was computer generated by a person unrelated to the study group. The trial investigators, study nurses, and patients were blinded to treatment allocation. To maintain blinding, by making the MSC solution and placebo look-alike, a drop of the patient's blood was mixed into the syringe containing MSCs or placebo by the stem cell laboratory.

The primary endpoint was change in LVESV measured by magnetic resonance imaging (MRI) or computed tomography (CT) after 6 months. An absolute difference of 10 mL in LVESV (with assumed SD of 11.1 mL) yielded a statistical power of 90% when enrolling 60 patients.[17]

Secondary endpoints included left ventricular end-diastolic volume (LVEDV), LVEF, stroke volume (SV), cardiac output, left ventricular myocardial mass, wall thickness, wall thickening, scar volume, NYHA class, Canadian Cardiovascular Society (CCS) Class, 6-min walking test, weekly angina attacks and weekly use of nitroglycerine, biomarkers, the Seattle Angina Questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ), and safety. The detailed follow-up plan was previously published.[17]

Bone marrow cell preparation and culturing

The isolation and culture expansion of the MSCs from BM have previously been described in detail.[5,10] All patients were treated with the full amount of cells reached after two culture expansion passages. Release criteria were sterility, viability, and MSC morphology. Expansion for only two passages was chosen as a guarantor of preserved primary cell features overriding total number of cells. Minimal criteria for defining MSCs according to The International Society for Cellular Therapy position statement were applied. The culture media was tested for bacteria, yeast, and mycoplasma 1 week before and on the day of treatment.

Cell transplantation

Left ventricular mapping was performed with the NOGA-XP system and intra-myocardial injections with Myostar injection catheters (Biologics Delivery Systems Group, Johnson & Johnson, USA).[18] Ten to 15 injections of 0.2 mL MSC or placebo (phosphate-buffered saline) solution were made into viable myocardium (unipolar voltage $>$6 mV) in the border zone of an area of scar tissue (unipolar voltage $<$6 mV).

Magnetic resonance imaging and computed tomography imaging

Patients had cardiac MRI scans if they were without contraindications for MRI and otherwise cardiac CT scans at baseline and after 6 months. The cardiac MRI (1.5T AvantoMagnetom; Siemens, Germany) protocol included LV short-axis cine images and late enhancement images using gadolinium (Gadovist, Bayer Healthcare, Germany) as previously described.[17] For cardiac CT (Aquillion, Toshiba, Japan), the R–R interval was covered and multi-segmental image reconstruction was done. No heart rate modulating drugs were given prior to cardiac CT.

All image data were analysed with the cvi[42] post-processing tool (Circle Cardiovascular Imaging, Canada). Endo- and epicardial borders were traced manually in end-diastole and end-systole and the mitral plane was set to define the basal border of the LV. Analyses were performed by two experienced physicians blinded to treatment allocation.

Statistics

Statistical analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS 20 (SPSS Inc., Chicago, IL, USA). For normal distributed continuous data comparison within groups was done with paired *t*-test and comparison between groups with unpaired *t*-test. Mann–Whitney *U*-test was used for between group comparisons of continuous non-normal distributed data. Categorical data were compared using Pearson's

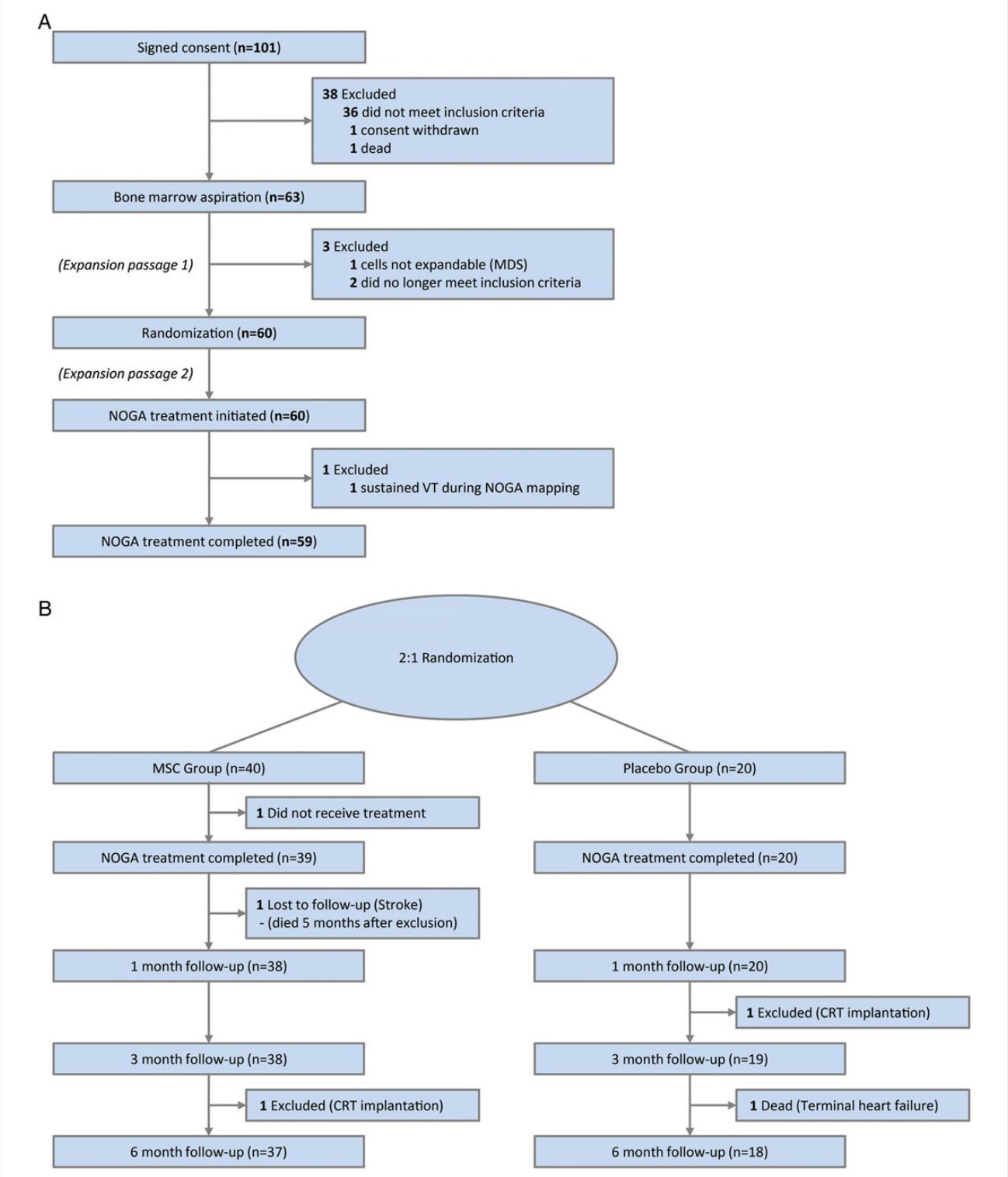

Figure 1 Clinical trial design: (*A*) pre-treatment period and (*B*) follow-up period. MDS, myelodysplastic syndrome; VT, ventricular tachycardia; CRT, cardiac resynchronization therapy.

χ^2 or Fisher's exact test as appropriate. One-way Anova was used to compare dose–response group differences. For follow-up data with more than two time-points, we used repeated measures with autoregressive covariance structure. For nominal repeated data, we used generalized estimating equations. The confidence interval for risk difference was constructed using the robust approximation of Miettinen

and Nurminen. All data were analysed as an *intention-to-treat analysis* including data from all randomized patients. Excluded patients were kept in their originally assigned group regardless of one patient not receiving treatment. Missing data were filled in using 'last observation carried forward'. A two-sided *P*-value of <0.05 was considered statistically significant.

Table 1 Baseline characteristics

Parameter	MSC ($n = 40$)	Placebo ($n = 20$)	*P*-value
Risk factors			
Age (years)	66.1 ± 7.7	64.2 ± 10.6	0.44
Male	36(90.0)	14(70.0)	0.07
Smoking			
Current	7(17.5)	1(5.0)	0.25
Former	26(65.0)	15(75.0)	0.43
Diabetes mellitus	15(37.5)	3(15.0)	0.07
BMI (kg/m^2)	29.8 ± 4.7	28.7 ± 5.3	0.44
eGFR (mL/min/1.73 m^2)	70.8 ± 25.2	74.3 ± 24.7	0.61
Cholesterol (mmol/L)	3.9 ± 0.8	4.1 ± 0.9	0.43
Systolic BP (mmHg)	114 ± 18	108 ± 9	0.08
Diastolic BP (mmHg)	59 ± 7	58 ± 10	0.92
Heart rate (bpm)	65 ± 12	67 ± 12	0.43
Cardiac history			
Years with IHD	12.9 ± 7.8	13.1 ± 8.5	0.95
Previous MI	35 (87.5)	19 (95.0)	0.65
Previous PCI	28 (70.0)	15 (75.0)	0.69
Previous CABG	26 (65.0)	10 (50.0)	0.26
ICD implant	11 (27.5)	8 (40.0)	0.33
CRT implant	1 (5.0)	1 (2.5)	1.00
CRT-D implant	13 (32.5)	5 (25.0)	0.55
Baseline endpoints			
NYHA Class II	11 (27.5)	5 (25.0)	0.84
NYHA Class III	29 (72.5)	15 (75.0)	0.84
ESV (mL)	195.1 (115.8)	200.6 (193.0)	0.33
EDV (mL)	277.0 (101.6)	282.8 (207.7)	0.55
SV (mL)	76.6 ± 20.1	74.2 ± 21.7	0.68
LVEF (%)	28.2 ± 9.3	25.1 ± 8.5	0.22
CO (L)	4.9 ± 1.1	4.9 ± 1.5	0.88
LV mass (g)	136.0 ± 47.9	131.4 ± 43.0	0.72
Scar mass (g)	19.2 ± 18.1	18.7 ± 10.3	0.96
6 min walking test (m)	401 ± 70	385 ± 81	0.43
NT-proBNP (pmol/L)	68.9 (114.7)	66.7 (116.1)	0.84
Medication			
ASA	36 (90.0)	16 (80.00)	0.42
Clopidogrel	15 (37.5)	3 (15)	0.07
VKA	9 (22.5)	6 (30.0)	0.54
ACE or ARB	37 (92.5)	18 (90.0)	1.00
β-Blocker	35 (87.5)	15 (75.0)	0.28
Calcium antagonist	11 (27.5)	3 (15.0)	0.35
Diuretic agent	33 (82.5)	16 (80.0)	1.00
Statins	36 (90.0)	18 (90.0)	1.00
Nitrate	23 (57.5)	9 (45.0)	0.36

Values are mean ± SD, *n* (%), or median (inter-quartile range).
BMI, body mass index, eGFR, estimated glomerular filtration rate; BP, blood pressure; IHD, ischaemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; NYHA, New York Heart Association; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; ASA, acetylsalicylic acid; VKA, vitamin K antagonist; ACE, angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers.

Results

Patients

Sixty patients were randomized and 59 of these were treated successfully (*Figure 1A*). Baseline characteristics were similar between the study groups (*Table 1*).

Mesenchymal stromal cells

Mesenchymal stromal cells were successfully culture expanded under good manufacturing practice conditions for 46.9 ± 10.5 days. Patients were treated with the number of cells reached after two passages, resulting in a mean of 77.5 ± 67.9 × 10^6 (inter-quartile range 53.8 × 10^6) MSCs. There were no contaminations with bacteria, yeast, or mycoplasma. All cultures had normal MSC morphology and cell viability was 90.0 ± 7.1%.

Serious adverse events

There were two serious adverse events (SAEs) related to the NOGA procedure. One patient with a history of episodic ventricular tachycardia (VT) developed VT during the NOGA mapping procedure. The patient reverted to sinus rhythm by his implantable cardioverter-defibrillator (ICD) unit and the procedure was cancelled (see *Figure 1*). Another patient experienced double-vision and dizziness during the injection procedure. Cerebral-CT afterwards was normal, but the incident was diagnosed as a minor stroke by the neurologist. The patient was without sequelae and completed follow-up.

Two patients were excluded due to implantation of a cardiac resynchronization therapy device during follow-up. One patient from the treatment group suffered a stroke 12 days after treatment. This patient was reported dead 158 days after MSC treatment shortly after surgery for intestinal ischemia. Finally, one patient in the placebo group died from terminal heart failure 182 days after treatment. All SAEs are listed in *Table 2*. There were significantly more hospitalizations for angina and pneumonia in the placebo group compared with the MSC group (both $P = 0.03$). Otherwise there were no significant differences between the groups.

Cardiac imaging

Twenty patients were MRI scanned (17 also with the late gadolinium contrast protocol) and 38 were scanned with CT. Two patients, both with known chronic nephropathy, had too high creatinine levels at 6 months follow-up and therefore echocardiographic measurements (baseline and follow-up) were used for these patients (Supplementary material online, *Table S2*). Imaging analyses for all patients were done using the same imaging modality at baseline and 6 months follow-up. All imaging results are depicted in *Figure 2* and *Table 3*.

At 6 months follow-up, the primary endpoint, LVESV, was significantly reduced in the MSC group and not in the placebo group.

Table 2 Serious adverse events

Serious adverse event	MSC ($n = 40$)	Placebo ($n = 20$)	*P*-value	RD (%)	RD 95% CI	
					Lower	Upper
Death	1 (2.5)	1 (5.0)	1.00	−2.5	−21.6	8.9
Hospitalizations						
MI	0 (0.0)	0 (0.0)	1.00	0.0	0.0	0.0
PCI or CABG	0 (0.0)	0 (0.0)	1.00	0.0	0.0	0.0
Stroke or TCI	2 (5.0)	1 (5.0)	1.00	0.0	−19.4	12.7
Heart failure worsening	6 (15.0)	2 (10.0)	0.71	5.0	−17.0	21.7
Angina worsening	0 (0.0)	3 (15.0)	0.03	−15.0	−36.2	−5.2
Orthostatic syncope	0 (0.0)	1 (5.0)	0.33	−5.0	−23.8	4.2
Atrial fibrillation	1 (2.5)	0 (0)	1.00	2.5	−14.0	13.0
VT/VF	2 (2.5)	1 (5.0)	1.00	0.0	−19.4	12.7
ICD implantation	1 (2.5)	0 (0.0)	1.00	2.5	−14.0	13.0
CRT/CRT-D implantation[a]	1 (2.5)	1 (5.0)	1.00	−2.5	−21.6	8.9
ICD/CRT pocket revision	0 (0.0)	1 (5.0)	0.33	−5.0	−23.8	4.2
ICD/CRT electrode reposition	0 (0.0)	1 (5.0)	0.33	−5.0	−23.8	4.2
Cancer	0 (0.0)	0 (0.0)	1.00	0.0	0.0	0.0
Pneumonia	0 (0.0)	3 (15.0)	0.03	−15.0	−36.2	−5.2
Gallbladder infection	0 (0.0)	1 (5.0)	0.33	−5.0	−23.8	4.2
Observation for headache	0 (0.0)	1 (5.0)	0.33	−5.0	−23.8	4.2

Values are *n* (%).
RD, risk difference; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TCI, transient cerebral ischaemia; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator.
[a]Both patients excluded afterwards (see *Figure 1B*).

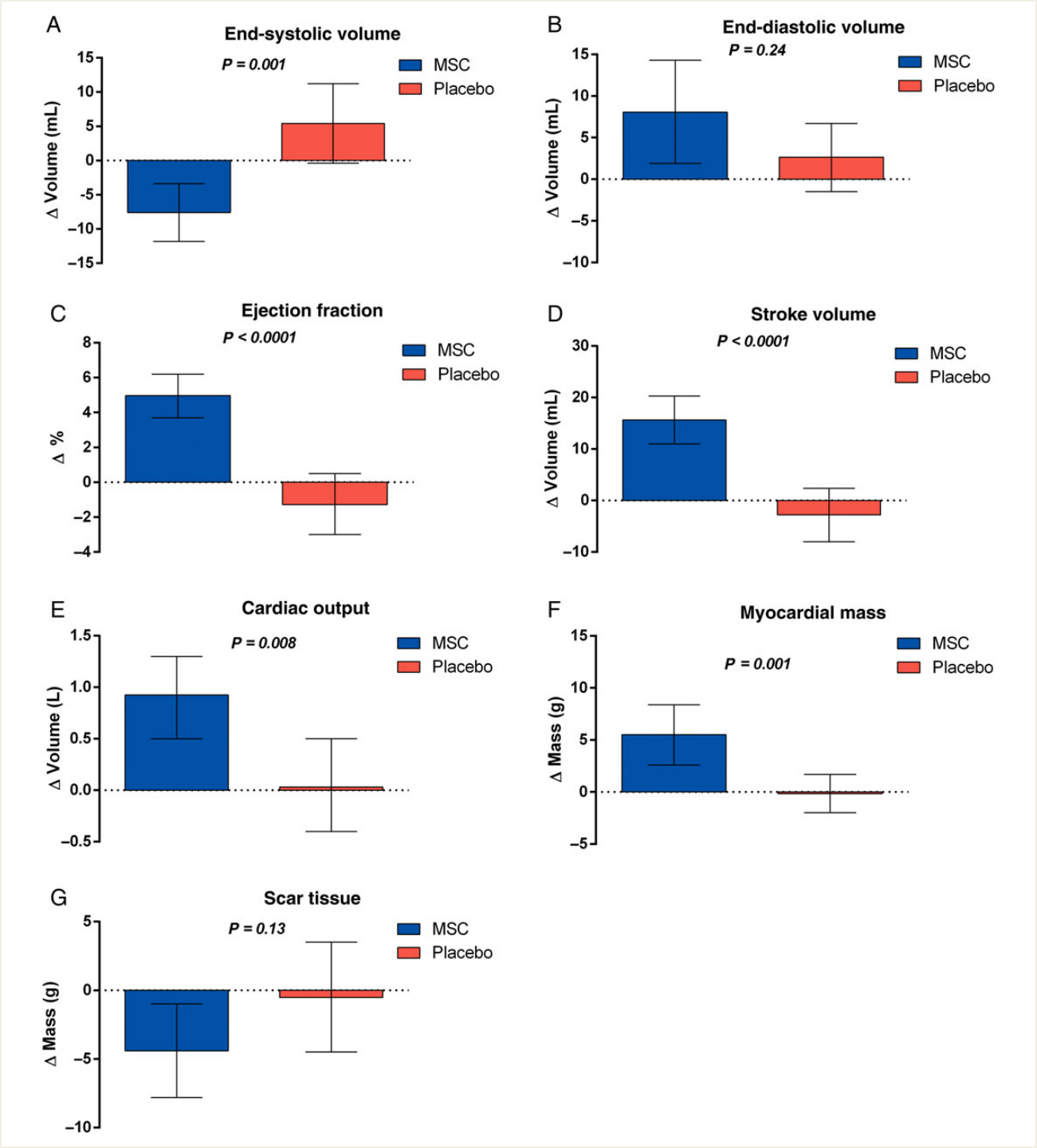

Figure 2 Imaging results: differences in imaging measurements between groups from baseline to 6-month follow-up. (*A*) End-systolic volume, (*B*) end-diastolic volume, (*C*) ejection fraction, (*D*) stroke volume, (*E*) cardiac output, (*F*) myocardial mass, (*G*) scar tissue (Paired *t*-test. Bar values are mean ± 95% confidence intervals.).

The difference between groups was 13.0 ± 12.9 mL ($P = 0.001$). Compared with placebo, we also found significant improvements in LVEF (6.2 ± 3.8%, $P < 0.0001$), SV (18.4 ± 13.6 mL, $P < 0.0001$), cardiac output (0.9 ± 1.2 L, $P = 0.008$), and myocardial mass (5.7 ± 7.7 g, $P = 0.001$). Changes in LVEDV did not differ significantly between groups (5.4 ± 16.7 mL, $P = 0.24$). While we did find a significant decrease in amount of scar tissue in the MSC group the difference between groups were not significant (3.9 ± 4.7 g, $P = 0.13$). For wall thickness and wall thickening, see Supplementary material online, Data.

Table 3 Imaging results

	MSC group				Placebo group				Group difference (treatment effect)			
	Difference	95% Confidence interval		P-value	Difference	95% Confidence interval		P-value	Difference	95% Confidence interval		P-value
		Lower	Upper			Lower	Upper			Lower	Upper	
LVESV (mL)	−7.6 ± 13.2	−11.8	−3.4	0.001	5.4 ± 12.5	−0.4	11.2	0.07	13.0 ± 12.9	5.9	20.1	0.001
LVEDV (mL)	8.1 ± 19.4	1.9	14.3	0.012	2.6 ± 8.7	−1.5	6.7	0.19	5.4 ± 16.7	−3.7	14.6	0.24
LVEF (%)	5.0 ± 3.8	3.7	6.2	<0.0001	−1.3 ± 3.7	−3.0	0.5	0.14	6.2 ± 3.8	4.2	8.3	<0.0001
SV (mL)	15.6 ± 14.6	11.0	20.3	<0.0001	−2.8 ± 11.2	−8.0	2.4	0.28	18.4 ± 13.6	11.0	25.8	<0.0001
CO (L)	0.9 ± 1.3	0.5	1.3	<0.0001	0.03 ± 1.0	−0.4	0.5	0.89	0.9 ± 1.2	0.2	1.5	0.008
LV Mass (g)	5.5 ± 9.0[1]	2.6	8.4	<0.0001	−0.2 ± 3.9	−2.0	1.7	0.86	5.7 ± 7.7	2.3	9.1	0.001
Scar Mass (g)	−4.4 ± 5.1[2]	−7.8	−1.0	0.017	−0.5 ± 3.8	−4.5	3.5	0.76	3.9 ± 4.7	−1.2	9.0	0.13

Values are mean ± SD.
LV, left ventricle; LVESV, LV end-systolic volume; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; SV, stroke volume; CO, cardiac output.

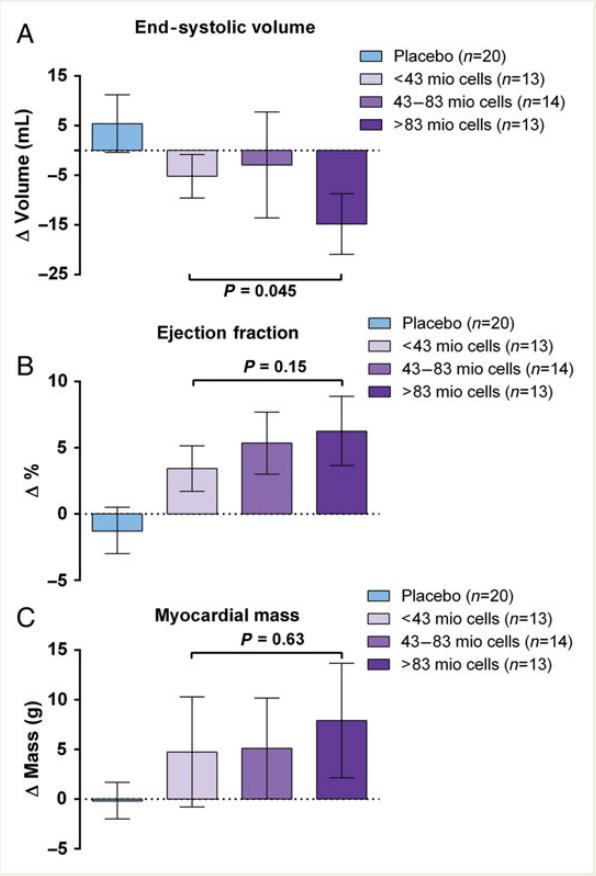

Figure 3 Dose–response effects: (*A*) end-systolic volume, (*B*) ejection fraction, (*C*) mean myocardial mass. *P*-values represent the differences between subgroups of the mesenchymal stromal cell group (One-way ANOVA. Bar values are mean ± 95% confidence intervals.).

To evaluate a possible dose–response effect, we divided the MSC group into one-thirds based on the received cell numbers. For LVESV, there was a significantly higher reduction in the group of patients receiving most cells compared with the lower dose groups ($P = 0.045$). For LVEF and mean myocardial mass, there was a non-significant tendency towards larger improvements with higher cell numbers (*Figure 3*).

Functional status and quality of life

There were significant improvements in NYHA class in both groups with a trend towards more improvement in the MSC group ($P = 0.16$). In the 6-min walking test, we observed significant improvements in both groups with no differences between groups ($P = 0.77$). In the KCCQ quality-of-life score, we found significant improvements in the MSC group and not in the placebo group. However, there were no differences between groups ($P = 0.50$). The KCCQ overall summary score improved in both groups, with no differences between groups ($P = 0.67$) (*Figure 4*). For additional functional data, see Supplementary material online, Data and *Figure S1*.

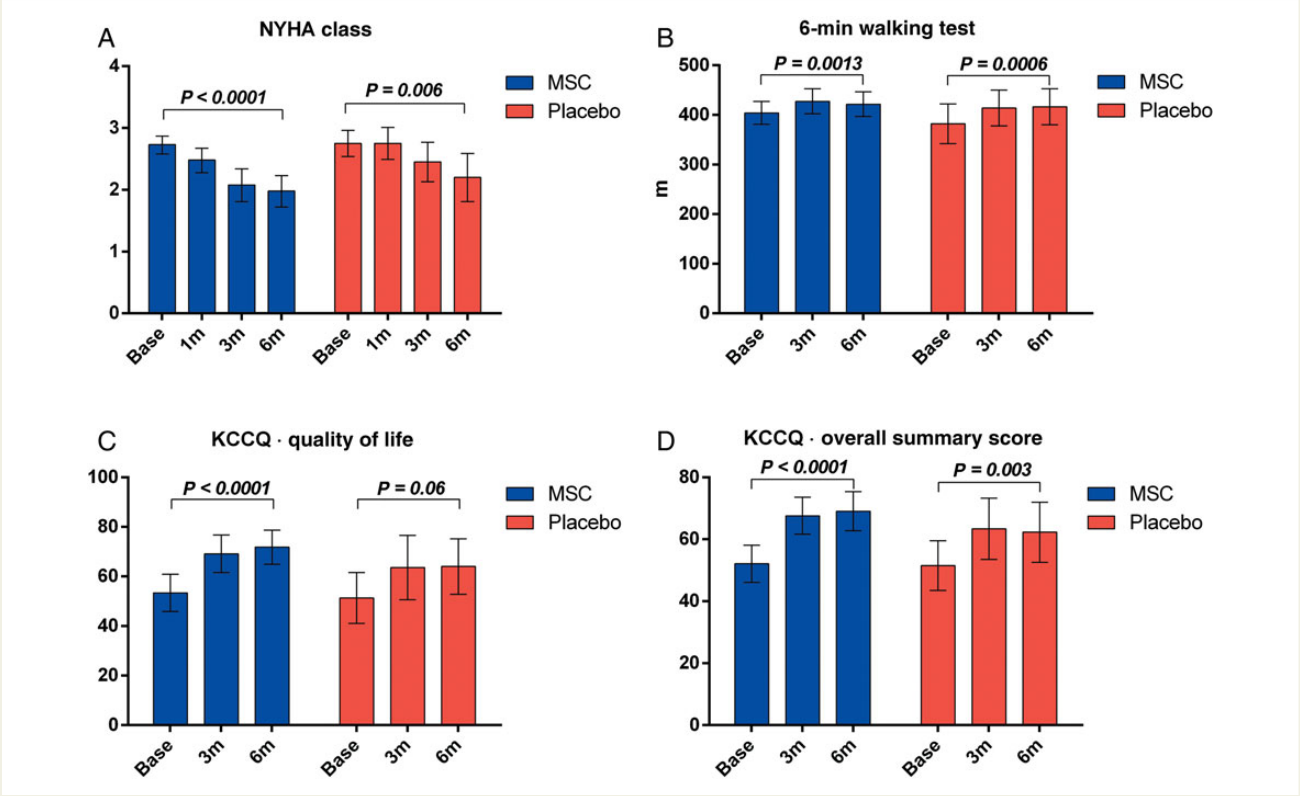

Figure 4 Functional status and quality of life: (*A*) New York Heart Association class, (*B*) 6-min walking test, (*C*) Kansas City Cardiomyopathy Questionnaire—quality-of-life score, and (*D*) Kansas City Cardiomyopathy Questionnaire—overall summary score. *P*-values represent difference between baseline and follow-up visits (*A*: general estimation equations, *B*–*D*: repeated measures analysis. Bar values are mean ± 95% CI.). NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Biomarkers

See Supplementary material online, Data and *Figures S2* and *S3*.

Discussion

The MSC-HF trial is the largest randomized, double-blind, placebo-controlled clinical trial with intra-myocardial injection of autologous BM-derived MSCs in patients with ischaemic heart failure. We demonstrate significant improvements in LV systolic function in terms of LVESV, LVEF, SV, and cardiac output in patients receiving active treatment compared with placebo. We also report significant improvements in LV mass, wall thickness, and wall thickening in cell-treated patients compared with placebo. Left ventricular end-systolic volume and LVEF are powerful independent predictors of survival in chronic heart failure.[19–21] Therefore, the results of this trial suggest that autologous MSC transplantation might be beneficial to long-term survival in patients with severe heart failure. In addition, we found significantly reduced hospitalizations for angina worsening. This is in agreement with another MSC study treating patients with refractory angina.[12]

Number of cells injected had a significant impact on the primary endpoint, LVESV. Patients receiving the most cells had the greatest improvements. Moreover, LVEF and myocardial mass showed trends towards improvement with higher dose. Therefore, future trials should be designed to secure high cell numbers.

In the 6-min walking test (6MWT), we found increased walking distances in both groups, with no difference between groups. The limitation of the 6MWT is well known as most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test.[22,23] Measured maximal oxygen uptake during 6MWT may be a more optimal functional endpoint in future studies. NYHA class, CCS class, and quality of life improved in both groups with no difference between groups. These measurements are subjective by nature and demonstrate a placebo effect of the treatment.

NOGA injections of MSCs have previously shown to be safe.[10–12] In this study, there were two SAE's related to NOGA injections. This warrants continued focus on safety. Temporary elevations in the cardiac biomarkers TNT and CKMB post-injection were similar to findings in other trials (see online *Figures 2* and *3*).[18,24]

In the randomized double-blind TAC-HFT trial patients with chronic heart failure received intra-myocardial injections of MSCs ($n = 19$), MNCs ($n = 19$), or placebo ($n = 21$).[16] A non-significant trend towards reduced LVESV in the MSC group was found. The main finding of the trial was a significant 18.9% ($P < 0.001$) reduction in scar tissue in the MSC-treated group compared with placebo. Both these findings correlate with our study. In the randomized

POSEIDON trial, 30 chronic heart failure patients received intra-myocardial injections of autologous and allogeneic MSCs.[15] The study demonstrated significantly reduced scar tissue (33.2%, $P > 0.001$) and a tendency towards improved LVEF (1.96%, $P = 0.11$). No difference was seen between allogeneic and autologous MSCs. In the open-labelled randomized C-CURE trial, 21 chronic heart failure patients were treated with cardiopoietic stem cells and compared with 15 control patients receiving standard care.[25] The cells used were BM-derived MSCs exposed to a cytokine cocktail to engage the cells into cardiopoiesis.[26] This trial demonstrated significant improvements in LVEF (6.8%, $P < 0.0001$) and LVESV (16 mL, $P < 0.0001$) similar to the present study. In both the C-CURE and the TAC-HFT trial 6MWT improved in the cell-treated group but not in the placebo group. This is in contrast to the present trial. In the randomized double-blind PRECISE trial, 27 patients with chronic heart failure were treated with intra-myocardial injections of adipose-derived cells which share similarities to MSCs.[27] Improvements in myocardial mass in cell-treated patients compared with placebo correlates with the present study. In contrast, no differences were found in LVEF, LVESV, or LVEDV.

Other cell sources, than MSCs, have been evaluated in chronic heart failure patients. Intra-myocardial injections of MNCs were utilized in the double-blind randomized FOCUS-CCTRN trial in 92 patients.[28] There were no improvements in LVESV, but a significant improvement in LVEF (2.7%, $P = 0.03$). Intra-myocardial injection of MNCs was also evaluated in a randomized, double-blinded trial in 50 patients with chronic IHD and refractory angina without heart failure.[29] This trial reported significant improvements in myocardial perfusion and LVEF (4%, $P < 0.03$) after 3 months follow-up.

The mechanisms behind the regenerative capacity of MSCs are not fully understood. However, evidence accumulates suggesting secretion of cytokines and growth factors from the MSCs as the main mechanism.[6–9]

The study had several limitations. Only 17 patients in the MSC-HF trial were eligible for late gadolinium MRI and with more patients the differences in scar tissue mass might have been significant. In a patient group as severely diseased as in this study there will most certainly always be a placebo effect in regards to subjective endpoints. Also, the assessment of differences in SAE's is underpowered. The intention-to-treat analysis has pro and cons. Cons being that data from excluded patients were filled in using 'last observation carried forward' and also that the patient receiving no treatment was kept in the MSC group using this principle for all analyses.

In conclusion, the present study demonstrates that intra-myocardial MSC injection is a promising new treatment for patients with chronic ischaemic heart failure. The study confirms and extends the results from smaller open-labelled and randomized studies. The present encouraging results needs confirmation in larger clinical trials.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

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