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Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review

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Aims To provide systematic assessment of the safety and efficacy of autologous bone marrow-derived stem cell (BMSC) transplantation in acute myocardial infarction (AMI) based on clinical evidence.

Methods and results The search strategy included MEDLINE, EMBASE, the Cochrane Library, and Current Controlled Trials Register through to August 2007 for randomized controlled trials of BMSC treatment for AMI. Thirteen trials (14 comparisons) with a total of 811 participants were included. Data were analysed using a random effects model. Overall, stem cell therapy improved left ventricular ejection fraction (LVEF) by 2.99% [95% confidence interval (CI), 1.26–4.72%, $P = 0.0007$], significantly reduced left ventricular end-systolic volume (LVESV) by 4.74 mL (95% CI, −7.84 to −1.64 mL, $P = 0.003$), and myocardial lesion area by 3.51% (95% CI, −5.91 to −1.11%, $P = 0.004$) compared with controls. Subgroup analysis revealed that there was statistical significant difference in LEVF in favour of BMSCs when cells were infused within 7 days following AMI and when the BMSC dose administered was higher than 10^8 BMSCs. In addition, there were trends in favour of benefit for most clinical outcomes examined, although it should be acknowledged that the 95%CI included no significant difference.

Conclusion Stem cell treatment for AMI still holds promise. Clinically, these data suggest that improvement over conventional therapy can be achieved. Further, adequately powered trials using optimal dosing, longer term outcome assessments, more reliable, and more patient-centred outcomes are required.

Keywords Stem cells • Myocardial infarction • Bone marrow • Systematic review • Randomized clinical trials

Introduction

Acute myocardial infarction (AMI) is the major cause of congestive heart failure and subsequent mortality in developed countries. Unlike many other tissues in the human body, heart tissue has a diminished ability to repair itself adequately after myocardial infarction (MI). Pharmacological agents have successfully been used to increase the life expectancy of patients who have suffered MI. More recently, primary angioplasty, which has been shown to decrease early mortality by a half, has become the treatment of choice in those centres where the service is available.[1] Primary percutaneous coronary intervention (PCI) restores the normal flow in infarct-related arteries in >90% of the patients who have suffered MI.[2,3] Early reperfusion of the occluded artery after MI has raised life expectancy and improved long-term prognosis of patients with AMI. However, preventing the progression of the disease and development of congestive heart failure is still a challenge. Alternative therapies for chronic myocardial dysfunction such as stem/progenitor cell transplantation are presently being investigated to complement the current thrombolytic therapies and primary angioplasty. The rationale for cell therapy to be administered after MI is derived from the assumption that given the insufficient regeneration in the injured heart tissue, those cells may be able to replace or repair damaged vascular and cardiac tissue. Thus, this has resulted in a number of clinical trials worldwide.

The first Phase I clinical trials using bone marrow stem/progenitor cell therapy for MI were carried out over 5 years ago.[4–8]

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Although not designed to test the efficacy of the intervention, the initial trials indicated a promising improvement in a number of clinical outcomes and cardiac function, and suggested the intervention was safe. Preclinical experimental studies indicated that bone marrow mononuclear cells could contribute to the revascularization of ischaemic regions in the infarcted myocardium.[9,10] In both experimental and clinical studies, the mechanism of action of the new intervention remains unclear and is probably multifactorial (for review, see Mathur and Martin[11]). It has been proposed that stem or other more mature cells within the graft may exert a paracrine effect,[12] serve as a reservoir for vascular progenitors and cardiomyocytes,[13] or as support for endogenous cardiac stem cells.[14] More experimental studies may be required to address this question. Recently, randomized controlled trials (RCTs) have suggested that the initial global benefits observed in cardiac function might be very small and that the effect of cell therapy may be restricted to infarct-related regions.[15,16] It is those divergent outcomes that prompted us to undertake a meta-analysis of recent RCTs, the results of which we present here.

Methods

Search strategy

Randomized controlled trials, in which cells harvested from the bone marrow or from the peripheral blood after bone marrow mobilization and referred to here as bone marrow-derived stem cells (BMSCs), were administered as treatment for AMI, were identified from Medline (1950–2007), Embase (1974–2007), the Cochrane Library (issue 04/2006), CINAHL (1982–2007), Current Controlled Trials Register, and the UK National Research Register through to 31 August 2007. The search terms used for the retrieval of relevant studies are shown in the supplementary tables (see Supplementary material online, *Tables S1–S4*). Sensitive RCT search strategies based on those devised by Robinson and Dickersin[17] were used on Medline, Embase, and Cinahl combined with subject-specific text and index terms to capture the topic of interest. Conference abstracts of the American Heart Association (2004–2006), International Society of Stem Cell Research (2004–2007), the databases ISI Proceedings, KoreaMed, IndMed and LILACS, and the reference lists of identified studies and relevant review articles were searched for additional studies. There was no restriction by year of publication, language, or publication status applied.

Inclusion criteria

Trials that met the following criteria were eligible for inclusion in this study: (i) RCTs, (ii) participants with a clinical diagnosis of AMI, (iii) the intervention consisted of any autologous BMSCs freshly isolated without restriction by dose or administration route, (iv) in the comparator arm participants did not receive BMSC (e.g. control media or plasma), and (v) co-interventions were allowed provided they were equally applied to each treatment arm. Trials were excluded on the basis of BMSCs cultured *in vitro* for longer than 24 h prior to infusion, as this may result in enrichment of a particular progenitor cell population.

Data extraction

The details extracted were the study and patient population characteristics, the nature of the intervention and comparator, outcomes assessed, and study quality. The latter used criteria were adapted from Juni *et al.*,[18] principal components of which are generation of random sequence, concealment of treatment allocation schedule, adequacy of follow-up, and blinding of outcome assessment. Eligibility screening, data extraction, and assessment of methodological quality were undertaken independently by two reviewers. When several methods were used for outcome assessment [e.g. echocardiography, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), or left ventricular (LV) angiography], MRI data were preferentially included in the analysis.

Statistical analysis

Outcome data were analysed quantitatively using RevMan 4.2. Summary results are presented as weighted mean difference (WMD) with 95% confidence interval (CI). Where significance tests were used, these tests were two-sided. Meta-analysis was undertaken using both fixed and random effects models, the latter being preferred when heterogeneity beyond that expected by chance alone was encountered. Heterogeneity was examined using the I^2 statistic and the χ^2 test. The values of $I^2 > 50\%$ were considered to indicate a substantial level of heterogeneity.[19] Potential reasons for observed heterogeneity were explored, with particular emphasis placed on clinical, treatment, and outcome measurement differences between the included studies. These were the administration of any co-intervention (e.g. G-CSF), the timing of BMSC infusion from onset of AMI, and the dose of BMSC infused. Funnel plots were plotted to investigate possible publication bias with Egger's and Begg's tests being used to assess asymmetry.

Results

Characteristics of included studies

The initial search identified 573 citations (*Figure 1*), of which 495 referred to editorials, animal experiments, or reviews, and 78 were examined in more detail. Forty-three of the 78 citations were RCTs. Twelve studies were excluded for not fulfilling all the inclusion criteria, 13 are still ongoing, five are awaiting translation from their original language or assessment, and 13 studies were eligible for inclusion. A Funnel plot was used to assess the

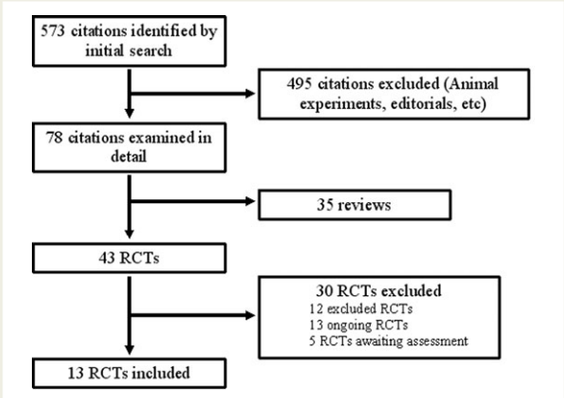

Figure 1 Flow diagram of studies included in this review. RCTs, randomized controlled trials.

possible publication bias using LVEF outcome data (see Supplementary material online, *Figure S1*). Neither the Egger's nor the Begg's test for Funnel plot asymmetry was statistically significant, suggesting that any apparent asymmetry in the plot could be explained by chance.

The 13 published RCTs included in this study represent 14 treatment comparisons. They compared PCI + BMSC with PCI + control in 811 patients (see *Table 1* for further characteristics of the studies). One trial was a three-arm comparison,[20] having 22 patients assessed in each arm. The two treatment arms compared different doses of BMSC administered, and were referred to as low dose (LD) and high dose (HD). This trial was stratified by dose to be included in the meta-analysis (see *Table 1*). Stratifying the analyses by intervention dose led to double-counting of the control group. Therefore, all results were re-analysed dividing the number of observations by the number of strata. These analyses indicated that the corrections led to only very small changes in the summary measures. Therefore, for simplicity, the original versions of the graphs with double-counting of control groups are presented.

The sample size in each trial was relatively small, ranging from 20 to 204 participants. Twelve trials isolated cells directly from the bone marrow by aspiration, while two trials[21,22] mobilized cells into circulation by administering G-CSF and subsequently isolated the cells from peripheral blood, with both grouped as BMSC in this paper. All trials used PCI as the primary intervention to treat AMI. The follow-up duration was 3–6 months in all of them. Only three trials conducted long-term follow-up for >12 months,[16,23,24] but only one study[16] presented appropriate outcome data, precluding from statistical analysis. For the purpose of this review, only the 3–6 month follow-up data have been analysed. There was a considerable heterogeneity in the method used for outcome measurement: MRI, echocardiography, LV angiography, and SPECT. Two trials used multiple methods to measure the outcomes. One of these[25] measured LVEF by three methods such as MRI, SPECT, and echocardiography. The other trial[26] measured LVEF by LV angiography and MRI. When available, the MRI data have been preferentially used in the analysis.

Methodological quality assessment of included studies

All trials randomized the participants, but only seven of them reported details of the randomization process used[8,15,16,21,23,25,27,28] (*Table 2*). These were permuted block randomization stratified according to center,[25] computerized randomization lists,[15,23] and sequentially numbered sealed envelopes provided by another institution. All seven used methods concealed treatment allocation adequately. All trials blinded outcome assessors to treatment allocation except one.[21] In all trials, at least 81% (ranging from 81 to 92%) of randomized patients were analysed by their randomized treatment arm. A power calculation to determine the number of patients required to show a difference between treatment groups on their primary outcome (LVEF) was undertaken in four trials.[8,15,16,23,25]

Relative risks of clinical outcomes

Clinical outcomes such as mortality, morbidity, adverse events, quality of life, and requirement for re-operation were assessed (*Table 3*). Overall, there were trends in favour of BMSC treatment for all clinical outcomes. Nevertheless, the 95% CI included no significant differences between the trial arms in mortality and morbidity. These results indicate that BMSC treatment may be safe for patients with AMI. Adverse events were not always reported in full detail, precluding from statistical analysis. Only two trials reported data on quality of life,[29,30] and another one reported the need for re-operation.[8,16]

Mean differences in cardiac parameters

Mean change from baseline in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), myocardial lesion area, and LVEF were also assessed. Compared with controls, the infusion of BMSC also reduced LVEDV by 2.47 mL (95% CI, −5.65 to 0.71, $P = 0.13$, *Figure 2*), but this difference was not statistically significant. However, BMSC treatment significantly reduced LVESV by 4.74 mL (95% CI, −7.84 to −1.64 mL, $P = 0.003$, *Figure 3*), myocardial lesion area by 3.51% (95% CI, −5.91 to −1.11%, $P = 0.004$, *Figure 4*), and improved LVEF by 2.99% (95% CI, 1.26–4.72%, $P = 0.0007$, *Figure 5*). Statistical heterogeneity was either negligible or very low for LVEDV ($I^2 = 0\%$), LVESV ($I^2 = 2.4\%$), and myocardial lesion area ($I^2 = 0\%$). However, a considerable degree of heterogeneity was observed in the LVEF comparisons ($I^2 = 63.6\%$). Since LVEF was the primary outcome measured for all trials, we explored the statistical heterogeneity further by conducting planned subgroup analysis.

Subgroup analysis

The significance of (i) the use of G-CSF as co-intervention, (ii) the timing of the BMSC infusion following AMI, and (iii) the stem cell dose administered on LVEF was examined (*Table 4*). The timing of BMSC infusion was divided into two groups: within 7 days and >7 days (see *Table 1*). The dose of BMSC administered was standardized and grouped by order of magnitude (ranging from 1×10^7 to 2.46×10^9 BMSC, see *Table 1*).

Treating the participants with G-CSF to mobilize bone marrow cells prior to intracoronary infusion of BMSC did not change the outcome compared with isolating BMSC directly from bone marrow aspirates. There was a statistically significant difference in LVEF in favour of BMSC when the treatment was administered within 7 days following AMI. However, this significant difference was even greater when the treatment was administered later than 7 days after AMI. Finally, statistically significant differences in LEVF in favour of the treatment were observed only when the BMSC dose administered was higher than 10^8 BMSC (*Table 4* and *Figure 6*). These data suggest that the timing of BMSC infusion and the dose of BMSC administered may be two of the factors that could contribute to the clinical and statistical heterogeneity observed among the studies included in this systematic review.

Table I Characteristics of studies included in this review

Author (year)	Number of patients assessed	Baseline LVEF (SD)	Demographics	Primary intervention	Co-intervention: SC and mean dose (SD)	Comparator arm	Time of SC administration from onset of AMI[a]	Study duration
Ge (2006)[27]	10 in SC arm	53.8 (9.2)%	Mean age (SD): 58 (11) years in SC arm/59 (8) years in control arm	PCI	BMSC aspiration	Not reported	Within 7 days	6 months
	10 in control arm	58.2 (7.5)%	Male: 90%		4×10^7 MNC			
Huang (2006)[26]	20 in SC arm	44.5 (7.1)%	Mean age (SD): 57.3 (10.1) years in SC arm/56.7 (9.2) years in control arm	PCI	BMSC aspiration	Heparanised saline	Within 7 days	6 months
	20 in control arm	43.4 (6.7)%	Male: 67.5%		1.8 (4.2) $\times 10^8$ MNC			
Janssens (2006)[15]	33 in SC arm	48.5 (7.2)%	Mean age (SD): 55.8 (11) years in SC arm/57.9 (10) years in control arm	PCI	BMSC aspiration	Saline and 5% autologous serum	Within 7 days	4 months
	34 in control arm	46.9 (10.7)%	Male: 82%		1.7 (0.72) $\times 10^8$ MNC			
Kang (2006)[21]	25 in SC arm	52.0 (9.9)%	Mean age (SD): 60.0 (10.6) years in SC arm/59.4 (12.3) years in control arm	PCI	BMSC mobilization with G-CSF	No placebo or G-CSF	>7 days	6 months
	25 in control arm	53.2 (13.3)%	Male: 80%		1–2 $\times 10^9$ MNC			
Karpov (2005)[29]	10 in SC arm	Not reported	Mean age (SD): 55.2 (8.6) years in SC arm/52.1 (3.2) years in control arm	PCI	BMSC aspiration	Control	>7 days	6 months
	10 in control arm	Not reported	Male: 81%		88.5 (49.2) $\times 10^6$ MNC			
Li (2007)[22]	35 in SC arm	50.0 (8.2)%	Mean age (SD): 60 (12) years in SC arm/58 (7) years in control arm	PCI	BMSC mobilization with G-CSF	Not reported	>7 days	6 months
	23 in control arm	51.0 (8.1)%	Male: 80%		7.25 (7.33) $\times 10^7$ MNC			
Lunde (2006)[25]	50 in SC arm	54.8 (13.6)%	Mean age (SD): 58.1 (8.5) years in SC arm/56.7 (9.6) years in control arm	PCI	BMSC aspiration	Heparanized plasma	Within 7 days	6 months
	50 in control arm	53.6 (11.6)%	Male: 84%		0.68 $\times 10^8$ MNC			

Meluzin (LD) (2006)[20]	22 in SC arm	42 (SEM 2)%	Mean age (SD): 55 (2) years in SC arm/55 (2) years in control arm	PCI	BMSC aspiration	Cell suspension media	Within 7 days	3 months
	22 in control arm	42 (SEM 2)%	Male: 88.5%		1×10^7 MNC			
Meluzin (HD) (2006)[20]	22 in SC arm	41 (SEM 2)%	Mean age (SD): 55 (5) years in SC arm/55 (2) years in control arm	PCI	BMSC aspiration	Cell suspension media	Within 7 days	3 months
	22 in control arm	42 (SEM 2)%	Male: 95.5%		1×10^8 MNC			
Meyer (2006)[8,16]	30 in SC arm	50.0 (10.0)%	Mean age (SD): 53.4 (14.8) years in SC arm/ 59.2 (13.5) years in control arm	PCI	BMSC aspiration	Heparanised plasma	Within 7 days	6 months
	30 in control arm	51.3 (9.3)%	Male: 70%		2.46 (0.94) $\times 10^9$ MNC			
Penicka (2006)[24]	14 in SC arm	39.0 (6)%	Not reported	PCI	BMSC aspiration	Not reported	Within 7 days	4 months
	10 in control arm	39.0 (4)%			26.4×10^8 MNC			
Ruan (2005)[36]	9 in SC arm	53.4 (8.92)%	Mean age (SD): 61 (8) years in SC arm/ 58 (6) years in control arm	PCI	BMSC aspiration	Diluted serum	Within 7 days	6 months
	11 in control arm	53.5 (5.84)%	Male: 94.5%		No reported dose			
Schachinger (2006)[23]	95 in SC arm	48.3 (9.2)%	Mean age (SD): 55 (11) years in SC arm/ 57 (11) years in control arm	PCI	BMSC aspiration	X-vivo media and 20% autologous serum	Within 5 days	4 months
	92 in control arm	46.9 (10.4)%	Male: 82%		2.36 (1.74) $\times 10^8$ MNC			
Suarez de Lezo (2006)[28]	10 in SC arm	37.0 (5)%	Mean age (SD): 52 (12) years in SC arm/55 (11) years in control arm	PCI	BMSC aspiration	Saline containing 0.1% heparin	>7 days	3 months
	10 in control arm	39.0 (6)%	Male: 75%		9×10^8 MNC			

LD, low dose; HD, high dose; SD, standard deviation; PCI, percutaneous coronary intervention; SC, stem cells; BMSC, bone marrow stem cells; MNC, mononuclear cells; AMI, acute myocardial infarction.
[a]Time of SC administration grouped into 'within 7 days' and '>7 days'.

Table 2 Methodological quality assessment of included studies

Study ID	Method to generate randomized sequence	Method of allocation concealment	Blinding of outcome assessors	Loss of participant follow-up (%)	All patients treated in assigned group
Ge (2006)	A	A	A	0	Y
Huang (2006)	B	B	A	0	Y
Janssens (2006)	A	A	A	11	Y
Kang (2006)	A	B	C	10.5	Y
Karpov (2005)	B	B	A	0	Y
Li (2007)	B	B	A	17	Y
Lunde (2006)	A	A	A	1	Y
Meluzin (LD) (2006)	B	B	A	10.5	Y
Meluzin (HD) (2006)	B	B	A	10.5	Y
Meyer (2006)	A	A	A	8	Y
Penicka (2007)	B	B	A	18	Y
Ruan (2006)	B	B	A	0	Y
Schachinger (2006)	A	A	A	8.5	Y
Suarez de Lezo (2007)	A	A	A	0	Y

A, adequate; B, unclear or not reported in the published data; C, inadequate; Y, yes.[18]

Table 3 Summary of clinical outcomes

Outcome	No. of trials	Time point measure[a]	Relative risk (95% CI)	*P*-value
Mortality	5	1–12 months	0.62 (0.22, 1.76)	0.37
Morbidity				
Re-infarction	7[b]	<30 days (1)	0.33 (0.01, 7.81)	0.49
		1–4 months (4)	0.61 (0.12, 2.96)	0.54
		12 months (1)	0.08 (0.00, 1.37)	0.08
Arrhythmias	1	Not known	0.57 (0.21, 1.53)	NA
Restenosis	7[b]	6 months (5)	1.10 (0.68, 1.80)	0.69
		12 months (1)	0.34 (0.01, 8.13)	0.51
Re-admission	4[b]	1–6 months (2)	0.61 (0.25, 1.52)	0.29
		12 months (1)	0.15 (0.01, 2.78)	0.2
Revascularization	6[b]	1–6 months (2)	0.55 (0.19, 1.62)	0.28
		12 months (1)	0.71 (0.42, 1.20)	0.2
Adverse events	5[c]	Not reported in all studies	NA	NA
Quality of life	2	21 day–6 months	Not measured	NA
Re-operation	1	12 months	0.61 (0.39, 0.95)	NA

NA, not applicable.
[a]Number of trials that measured the outcome at each time point is in brackets.
[b]One study did not report the time point at which the outcome was measured.
[c]Adverse events not always reported in full details to allow statistical analysis.

Discussion

The present systematic review aimed to assess data from RCTs relevant to the clinical practice of stem cell therapy for AMI. The results presented here confirmed that autologous BMSCs may be safely administered to treat patients with AMI. Moreover, the relative risks of mortality and morbidity, measured by incidence of re-infarction, arrhythmias, restenosis, hospital re-admission, and target vessel revascularisation, were not significantly increased in participants who received BMSC treatment compared with controls. The pattern in favour of benefits across all clinical outcomes represents a very impressive feature, particularly because each

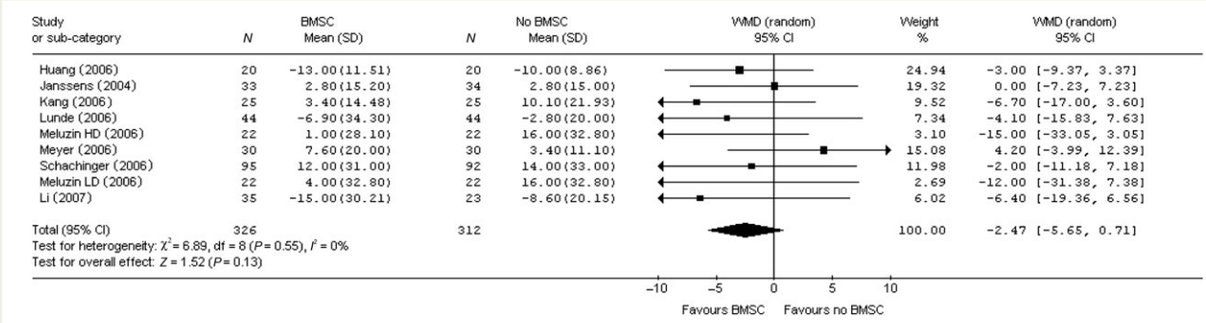

Figure 2 Forest plot of weighted mean difference [WMD, with 95% confidence interval (CI)] in left ventricular end-diastolic volume (LVEDV). Included studies measured LVEDV (in mL) in patients who received an infusion of BMSC compared with controls. LVEDV was reduced by 2.47 mL (95% CI, −5.65, 0.71) in favour of BMSC treatment. However, the difference was not statistically significant ($P = 0.13$).

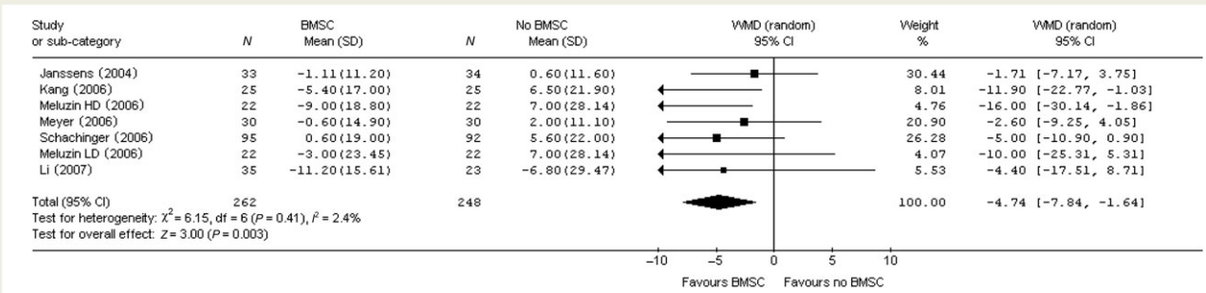

Figure 3 Forest plot of weighted mean difference [WMD, with 95% confidence interval (CI)] in left ventricular end-systolic volume (LVESV) in patients who received an infusion of BMSC compared with controls. LVESV (in mL) was significantly reduced by 4.74 mL (95% CI, −7.84, −1.64, $P = 0.003$) in favour of BMSC treatment.

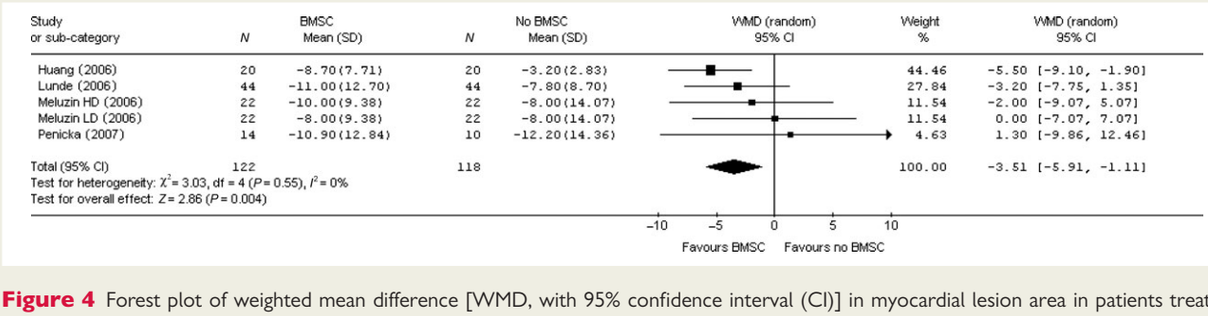

Figure 4 Forest plot of weighted mean difference [WMD, with 95% confidence interval (CI)] in myocardial lesion area in patients treated with BMSC compared with controls. Myocardial lesion area (%) was significantly reduced by 3.51% (95% CI, −5.91, −1.11, $P = 0.004$) in favour of BMSC treatment.

outcome received contribution from different studies. However, the CI is wide most probably because of the low number of studies and the low number of events in all outcomes. Caution in interpretation is also required because of the multiple comparisons being made in the review. Exercise capacity and quality of life were measured only in two trials.[29,30] Although this is a very small sample, there was a trend towards an improvement in exercise capacity in patients who had received BMSC compared with controls. Thus, future trials would need to incorporate more robust outcome measures that are patient centred.

This systematic review is based on a comprehensive search strategy. Formal testing for publication bias has also been carried out using a funnel plot, and Egger's and Begg's tests for asymmetry were not statistically significant. Together these factors reduce, but

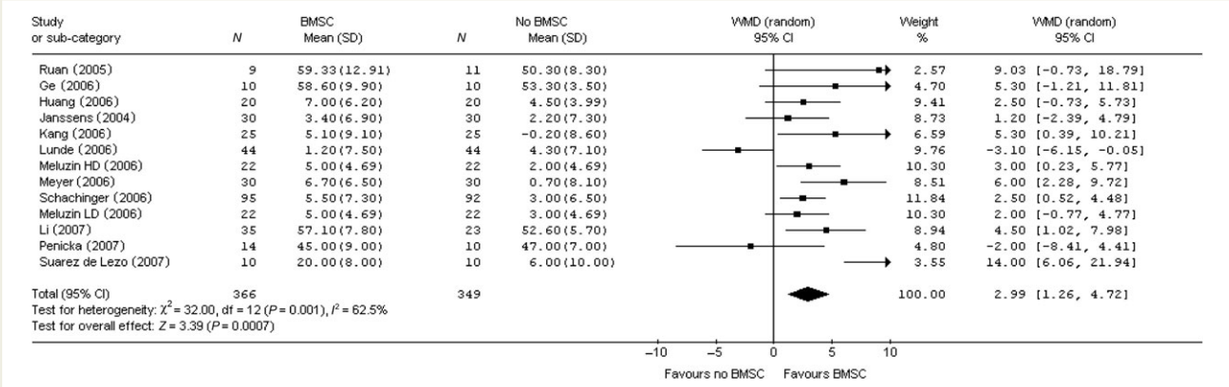

Figure 5 Forest plot of weighted mean difference [WMD, with 95% confidence interval (CI)] in left ventricular ejection fraction (LVEF) in patients treated with BMSC compared with controls. Infusion of BMSC significantly improved LVEF by 2.99% (95% CI, 1.26, 4.72, $P = 0.0007$) in favour of the treatment.

Table 4 Subgroup analysis determining the significance of G-CSF as co-intervention, timing of stem cell infusion following AMI, and stem cell dose administered on LVEF

Subgroup	Weighted mean difference (95% CI)	*P*-value
Co-intervention		
G-CSF	4.77 (1.93, 7.61)	0.001
No G-CSF	2.58 (0.60, 4.55)	0.01
Timing of BMSC infusion (range)		
Within 7 days (1–7 days)	1.99 (0.25, 3.73)	0.02
>7 days (7–21 days)	6.78 (2.24, 11.32)	0.003
BMSC dose administered[a]		
$<10^7$ cells	1.00 (−1.77, 3.77)	0.48
$<10^8$ cells	1.51 (−1.96, 4.98)	0.39
$<10^9$ cells	3.60 ((1.04, 6.16)	0.006
$<10^{10}$ cells	6.00 (2.28, 9.72)	0.002

AMI, acute myocardial infarction; BMSC, bone marrow stem cells; G-CSF, granulocyte colony stimulating factor; LVEF, left ventricular ejection fraction.
[a]Measured as MNC counts.

do not completely exclude the possibility of publication bias being present. The meta-analysis included 13 RCTs where BMSC + PCI were compared with PCI alone. The results have demonstrated that, at least up to 6 months follow-up, BMSC treatment leads to a moderate improvement of LV function, measured by a reduction in LVESV, LVEDV, and myocardial lesion area and a significant increase in LVEF (2.99%) over controls. Similar results were obtained in the CADILLAC[31] and ADMIRAL[32] trials, where thrombolytic therapy was administered in combination with PCI in AMI patients. In those studies, the average improvement in LVEF was 2.8 and 4.1%, respectively. Clinically, the moderate but significant difference in favour of BMSC treatment observed here could be important if prolonged long term. It suggests that improvement over regular therapy could still be achieved by turning BMSC therapy into a potential complementary therapy for MI, although this may involve either cellular therapy as described here or drug discovery approaches. The mechanism of action of BMSC treatment remains unclear and may be multifactorial. Although the majority of the data derive from experimental studies, this may be the case in humans as well. It has been suggested that BMSC therapy may exert their beneficial effect by activation of resident cardiac progenitor cells,[9,12,33–35] by a paracrine mechanism.[12] Most recently, Rota *et al.*[13] have demonstrated in mice that adult c-kit$^+$ BMSC implanted in the infarcted myocardium lose their haemopoietic phenotype over time and acquire the cardiogenic and endothelial lineages, forming functional cardiomyocytes and vascular structures.[13] In this instance, the cardiac niche may be crucial in modulating BMSC engraftment and fate. In addition, the production of cytokines (i.e. VEGF) or the presence of specific progenitor cell subsets enriched for endothelial, monocytic, or mesenchymal progenitors in the BMSC fraction may assist or contribute to revascularization, reduce inflammation, or affect cardiac remodelling. Moreover, this systematic analysis presents data in support of a correlation between the timing of BMSC infusion following AMI, the BMSC dose administered, and improvement of LVEF as a primary outcome. In the first instance, the significant improvement in LVEF observed when BMSCs were infused within the first 7 days post-AMI may be explained by increase in cytokines such as VEGF, HGF, and G-CSF in plasma during the first week following AMI.[37] It has previously been reported that VEGF presents two peaks of release during AMI, the first one in the acute phase (24–48 h) and the second in the subacute phase (7 days).[38] In our study, the improvement on LVEF was even greater when BMSC were infused later (>7 days), confirming the results of the REPAIR–AMI trial that suggested BMSC infusion to be more effective when infused >6 days following reperfusion.[23] Interestingly, very early time points, i.e. within 6 h of angioplasty, have not yet been studied.

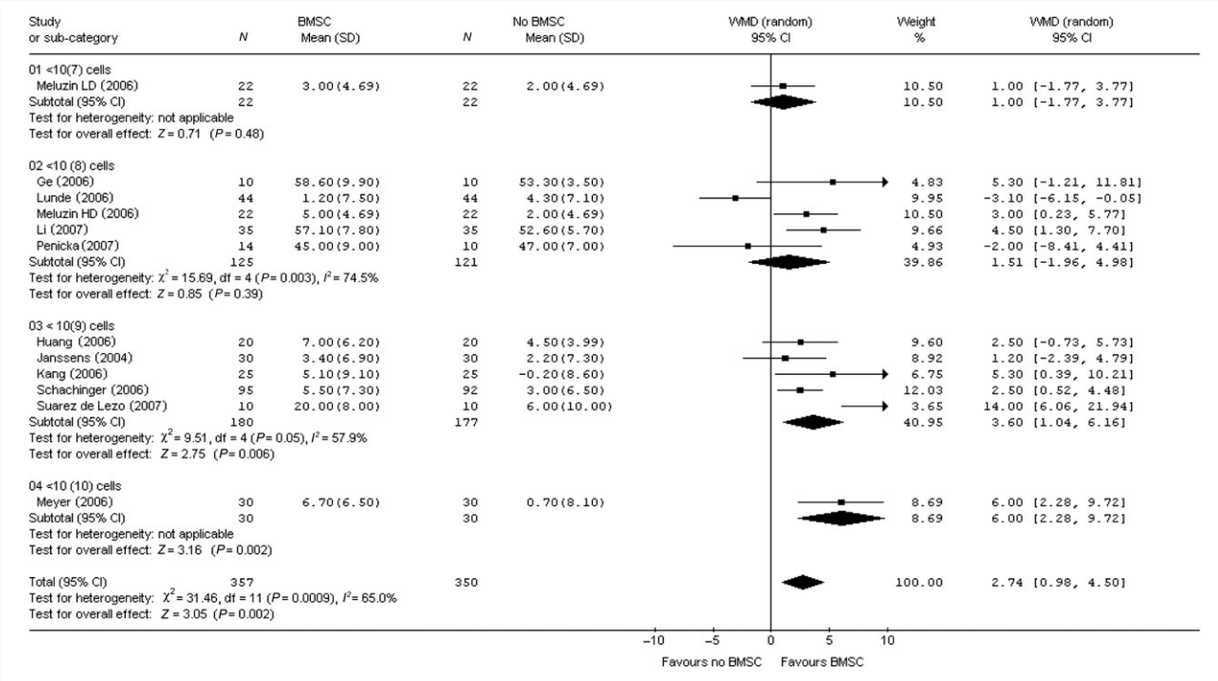

Figure 6 Forest plot of weighted mean difference [WMD, with 95% confidence interval (CI)] in left ventricular ejection fraction (LVEF) in patients who received different doses of bone marrow-derived stem cells (BMSCs) compared with controls. BMSC doses are grouped by order of magnitude (ranging from 1×10^7 to 2.46×10^9 mononuclear cell counts). Doses of BMSC higher than 10^8 cells significantly improved LVEF.

Therefore, the possibility exists that earlier intervention may lead to a significant improvement in cardiac function over what has been achieved to date.

In the second case, the effect on LEVF seemed to correlate positively with BMSC dose administered. The mean change in LVEF was statistically significant in favour of administering BMSC for studies using higher doses of BMSC,[15,16,21,23,26,28] but statistically significant in favour of no BMSC therapy for the lower doses of BMSC infused.[20,22,24,25,27] Taken together, these results suggest that significant effects on LVEF may only be achieved when infusing doses are higher than 10^8 BMSC. This is consistent with the idea that after MI, there are not enough endogenous BMSCs mobilized into circulation[16] or that home to the damaged heart within a sufficient time frame for the damaged cardiac tissue to be repaired, or that the factors that promote this improvement are dependent on cell number. Risk factors for coronary artery diseases that may precipitate AMI, such as diabetes, hypertension, and smoking, are contributors to the reduced mobilization of BMSC.[39] To date, there are few published trials that have followed BMSC engraftment or survival following intracoronary infusion.[29] In those studies, BMSCs have been found in the liver, the lungs, and the bone marrow, and only ~7% of the infused cells were present in the heart 24 h post-transplantation. Since adult BMSCs implanted in the infarcted myocardium have been shown to contribute to the regeneration of cardiac and vascular tissue,[13] one method to overcome the hurdle of BMSC recruitment to the damaged tissue might be to administer more cells or by other route (e.g. intramyocardially), to deliver multiple doses or specific cell subsets. However, the beneficial effect of BMSC to treat AMI may have limitations. It is possible that a threshold for cell number or cell type may exist. There are some indications that the effect of BMSCs on global LEVF may not persist long term,[16] and regional effects may be more important to maintain. Administering multiple doses over time or directly to the ischaemic region or using specific cell subset may prove more beneficial for sustained improvement in life expectancy and prevention of congestive heart failure. Limitations may come not from the number of cells but from the type of cells that engraft in the heart after transplantation. Differences in BMSC processing methods have been reported to affect cell viability and expression of surface receptors or adhesion molecules (e.g. CXCR4 or connexin 43) that play a crucial role in BMSC homing to and retention in the regions of damaged tissue.[13,40] Other factors such as type or extent of infarct may also affect efficacy. Should individual patient data be available for all the trials included in this study, it would be very interesting to compare mean changes in baseline LVEF between patients and according to the type of infarct. It has already been suggested that patients with lower baseline LVEF or larger infarcts are more likely to benefit from stem cell therapy.[15,23]

Recently, a meta-analysis on evidence of BMSC transplantation to treat patients with ischaemic heart diseases (IHDs) has been published.[41] Our study differs from that of Abdel-Latif *et al.*[41] in a number of ways. First, Abdel-Latif's study included RCTs and cohorts, whereas this review is concerned with RCTs only. Secondly, they took into consideration trials that treated patients with acute and chronic IHDs, including AMI and ischaemic

cardiomyopathies (ICM), whereas this study is focused on AMI. Thirdly, their analysis combined short-term (3–6 months) with long-term (18 months) outcome data without distinguishing the two. There is concern about how continuous data were dealt with in their meta-analysis, since differences in outcome measures would be expected at two such different time points. However, our results are globally in agreement with Abdel-Latif's in that BMSC treatment improves LEVF and reduces LVESV, LVEDV, and myocardial lesion area or scar size over controls.

Although this systematic review is optimistic concerning the efficacy of stem cell transplantation, larger sample size and further RCT evidence are required. This study has highlighted a number of issues. A considerable degree of heterogeneity has been observed among the included trials. This clinical and statistical heterogeneity relates to the dose and type of BMSCs infused, the timing between onset of AMI, primary intervention and infusion of BMSC, the media that participants in the comparator arm received, and the methodology involved in outcome measurements (for review see Arnesen *et al.*[42]). In addition, the field is lacking medium and long-term data. The sustained efficacy of BMSC treatment for AMI needs to be demonstrated too. Finally, the mechanism by which BMSCs may exert a beneficial effect in patients with AMI is still unclear. Although a great deal of experimental studies have been conducted, one of the most convincing ones by Rota *et al.*,[13] there is a clear call for investigating these issues further in appropriate animal models and in future clinical trials that should incorporate more robust measures and will require greater patient numbers. This is in agreement with the guidelines produced by the European Society of Cardiology task force for the design of future clinical trials.[43]

In summary, this study has evaluated RCT evidence for BMSC therapy after AMI. Although current trials are clinically diverse and are lacking long-term follow-up, this analysis suggests that the intervention might be clinically relevant.

Supplementary material

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

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CLINICAL VIGNETTE

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Acute proximal aortic dissection penetrating into left atrium with a hypermobile thrombus

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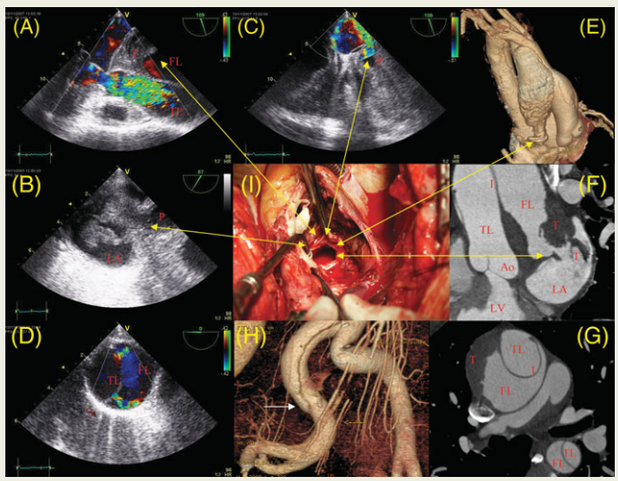

A 42-year old patient with suspected Marfan syndrome was admitted for examination of resting chest pain occurring intermittently for 1 week. Physical examination was completely normal with a normal blood pressure and present symmetrical upper extremities pulsation. ECG showed 2 mm ST-elevation in II, III, aVF, V_{4-6} leads. Selective coronarography was performed with a negative finding. On the basis of negative troponin test, myocardial infarction and myocarditis were excluded. Transthoracic echocardiography showed no pericardial effusion, but a spherical formation in left atrium (LA) adjacent to interatrial septum suspicious of myxoma. Subsequently transesophageal echocardiography (TEE) revealed a proximal aortic dissection. This finding was confirmed by a 64-slice CT angiography of aorta. Bentall procedure was successfully performed.

Panel A. Aortic dissection with a systolic flow in the true lumen (TL) of ascending aorta on TEE. A continual flow can be seen in the false lumen (FL) in which an intraluminal thrombus (T) is evident.

Panel B. A hypermobile double lobar thrombus connected to the penetration canal (P) heading to left atrial roof.

Panel C. Continuous turbulent jet heading from the aorto-left atrium fistula canal (P) to left atrial roof.

Panel D. Double intimal tear in descending aorta.

Panel E. A reconstructed three-dimensional CT image using volumetric rendering method. An evident aneurysmatic dissection of ascending aorta with a rupture of aortic adventitia and penetration into left atrium (arrow).

Panel F. An extensive thoracic aorta aneurysm dissection penetrating into left atrium. A tricuspid aortic valve (Ao), left ventricle (LV), and an intimal line (I) separating true aortic lumen (TL) from false lumen (FL) can also be noticed. Hypodense masses with an irregular margin lining the edges of a proximal part of a false lumen are thrombi (T) penetrating into the left atrium (LA).

Panel G. Short axis CT image of ascending and descending aorta.

Panel H. Distal part of dissection in area of right common iliac artery (white arrow).

Panel I. A view of a false lumen with a noticeable penetration opening into left atrium. The arrows are pointing towards its CT angiography and TEE correlates. The true aortic lumen is compressed by a suction tube.