

Autologous bone marrow stem cell therapy for patients undergoing coronary artery bypass grafting: A meta-analysis of 14 randomized controlled trials

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Abstract. Autologous bone marrow stem cell (BMSC) therapy is a novel option for regenerative therapy in patients with ischemic heart disease. The aim of the present meta-analysis was to evaluate the effectiveness of BMSCs combined with coronary artery bypass grafting (CABG). The PubMed, Cochrane Library, EMBASE and Web of Science databases were searched from inception to November 22, 2017 for randomized controlled trials on BMSC therapy combined with CABG. Finally, 14 trials with a total of 596 participants were included. Data were analyzed using a random-effects model. Compared with the control group, the BMSC therapy group exhibited an improvement in the left ventricular (LV) ejection fraction from baseline to follow-up [mean difference (MD)=4.36%; 95% confidence interval (CI): 1.90-6.81%; P<0.01]. Analysis of the pooled results revealed non-significant differences in the LV end-diastolic volume (MD=-6.27 ml; 95% CI: -22.34 to 9.80 ml; P=0.44), LV end-diastolic volume index (MD=-15.11 ml/m²; 95% CI: -31.53 to 1.30 ml/m²; P=0.07), LV end-systolic volume

(MD=-11.52 ml; 95% CI: -26.97 to 3.93 ml; P=0.14) and LV end-systolic volume index (MD=-16.56 ml/m²; 95% CI: -37.75 to 4.63 ml/m²; P=0.13) between the BMSC and CABG alone groups. Therefore, autologous BMSC therapy for patients undergoing CABG appears to be associated with an improvement in LV function compared with CABG alone.

Introduction

Ischemic heart disease (IHD) remains the leading cause of morbidity and mortality worldwide (1,2). Ischemic injury to the heart muscle often results in irreversible loss of myocardial tissue, with ensuing impairment of left ventricular (LV) function. In addition to medical treatment and surgical or interventional revascularization methods, there is currently a considerable number of studies on autologous bone marrow stem cell (BMSC) therapy in combination with coronary artery bypass grafting (CABG) in the treatment of IHD (3-16). BMSC therapy is aimed at repairing the damaged myocardium, preventing ventricular remodeling and improving overall cardiac function (17).

In clinical studies, the use of BMSCs is the most popular cardiac cell-based therapy. This may be due to the fact that BMSCs are easier to obtain compared with other stem cells (e.g., circulating stem cells and cardiac stem cells), and their preparation does not require prolonged *ex vivo* manipulation (18). Although recent studies demonstrated that catheter-based cell delivery (e.g., NOGA™ mapping) enables increased myocardial retention of cells, this method may not be feasible in certain patients with peripheral vascular disease (19). Therefore, injection of BMSCs is a good option for patients undergoing CABG.

However, the efficacy of CABG in combination with BMSC therapy remains controversial. It has been demonstrated that CABG combined with BMSC therapy is beneficial for cardiac function, without any adverse effects, and is therefore a safe and feasible adjunct therapy in clinical practice (3,4,13,16).

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However, other studies reported that CABG combined with BMSC therapy had no effect on global LV function and clinical symptoms (5,7).

Several previous meta-analyses on CABG combined with BMSC therapy either had certain methodological limitations or included an insufficient number of studies (20-22). In addition, since the publication of those meta-analyses, several new randomized controlled trials (RCTs) have been published (3,13,15). Hence, the present meta-analysis was performed to re-evaluate the effectiveness of CABG combined with BMSC therapy.

Materials and methods

Trial search. The PubMed, Cochrane Library, EMBASE and Web of Science databases were searched from inception to November 22, 2017, using the key words 'bone marrow cells OR s'tem cells' OR 'cell' OR 'progenitor cell' OR 'stem cell transplantation' OR 'cell transplantation' OR 'bone marrow transplantation' OR 'stromal cells' and 'coronary artery bypass' OR 'coronary artery bypass grafting' OR 'Myocardial Revascularization'. There were no language restrictions.

Inclusion criteria. Studies were included based on the following criteria: i) Participants with a clinical diagnosis of chronic IHD; ii) RCTs comparing CABG in combination with BMSC therapy and CABG alone for chronic IHD; iii) follow-up for at least 3 months after stem cell therapy.

Exclusion criteria. The exclusion criteria were as follows: i) Non-RCTs; ii) catheter-based stem cell injection methods; iii) stem cells derived from sources other than the bone marrow (e.g., c-kit⁺ cardiac stem cells); iv) participants with a clinical diagnosis of acute myocardial infarction; v) stem cell injection without CABG; and vi) studies with incomplete LV function data.

Risk of bias assessment. The methodological quality of the selected RCTs was independently assessed by 2 researchers (SW and LY) based on the Cochrane risk of bias criteria (23), and each quality item was rated as low-risk, high-risk or unclear-risk. The 7 items used to evaluate bias in each trial included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

Data extraction. Two reviewers (SW and LY) independently extracted the following relevant data from each study: First author; year of publication; country of origin; study population, including treatment and control group; participant characteristics, including age and sex; follow-up time; type of stem cells; dose of stem cells; route of stem cell administration; outcome measurement method; LV ejection fraction (LVEF), including baseline (LVEF_{baseline}), follow-up (LVEF_{follow-up}), and LVEF change from baseline to follow-up for the treatment (LVEF_{BMSC change}) and control groups (LVEF_{control change}); LV end-diastolic volume (LVEDV), including baseline (LVEDV_{baseline}), follow-up (LVEDV_{follow-up}), and LVEDV change from baseline to follow-up for the treatment (LVEDV_{BMSC change}) and control

groups (LVEDV_{control change}); LV end-systolic volume (LVESV), including baseline (LVESV_{baseline}), follow-up (LVESV_{follow-up}), and LVESV change from baseline to follow-up for the treatment (LVESV_{BMSC change}) and control groups (LVESV_{control change}); LV end-diastolic volume index (LVEDVI), including baseline (LVEDVI_{baseline}), follow-up (LVEDVI_{follow-up}), and LVEDVI change from baseline to follow-up for the treatment (LVEDVI_{BMSC change}) and control groups (LVEDVI_{control change}); and LV end-systolic volume index (LVESVI), including baseline (LVESVI_{baseline}) and follow-up (LVESVI_{follow-up}), and LVESVI change from baseline to follow-up for the treatment (LVESVI_{BMSC change}) and control groups (LVESVI_{control change}). Any disagreements between the reviewers were resolved by reaching a consensus.

Statistical analysis. The statistical analysis software R, version 3.4.2 was used to analyze the data. A meta-analysis was performed to calculate the mean difference (MD) LVEF_{change} (MD LVEF_{change}=LVEF_{BMSC change}-LVEF_{control change}, LVEF_{BMSC change}=LVEF_{BMSC follow-up}-LVEF_{BMSC baseline}, LVEF_{control change}=LVEF_{control follow-up}-LVEF_{control baseline}), and similarly, the MD LVEDV_{change}, MD LVEDVI_{change}, MD LVESV_{change}, and MD LVESVI_{change}, as well as their 95% confidence intervals (CIs). The majority of the studies reported the mean and standard deviation (SD). In one study (3), LV volume and ejection fraction values were expressed as mean and standard error (SE). The SE was converted into the SD by applying the formula $SD=SE\sqrt{n}$, where n is the sample size. In two studies (4,7), the LV volume and ejection fraction values were expressed as the median and interquartile range. Median and interquartile range were converted into the mean and SD using the method introduced by Hozo *et al* (24).

In addition, the mean and SD of the LVEF_{BMSC change} and LVEF_{control change} were not directly reported by certain studies (3,5,6,9,10,12,13,15,16). The mean of the LVEF_{BMSC change} and LVEF_{control change} may be easily obtained by calculating the difference between the means of the LVEF_{baseline} and LVEF_{follow-up}. However, the SD of the LVEF_{BMSC change} and LVEF_{control change} may only be effectively calculated from the LVEF_{baseline} and LVEF_{follow-up} values if the value of the correlation coefficient (Corr) is known. Therefore, the SD of LVEF_{BMSC change} and LVEF_{control change} in the study by Hendrikx *et al* (11) were used to calculate the Corr values by using the following formula:

$$\text{Corr} = \frac{SD_{\text{baseline}}^2 + SD_{\text{follow-up}}^2 - SD_{\text{change}}^2}{2 \times SD_{\text{baseline}} \times SD_{\text{follow-up}}}$$

The calculation yielded Corr=0.6 for the BMSC and the control groups. The SD of LVEF_{BMSC change} and LVEF_{control change} was calculated by inputting these values in the following formula:

$$SD_{\text{change}} = \sqrt{SD_{\text{baseline}}^2 + SD_{\text{follow-up}}^2 - 2 \times \text{Corr} \times SD_{\text{baseline}} \times SD_{\text{follow-up}}}$$

The mean and SD of the LV volume change values were calculated in the same manner.

A random-effects model was used to pool the data, and statistical heterogeneity between summary data was evaluated using I² statistics. Egger's test was applied to examine publication bias. All tests were two-tailed and P<0.05 was considered to indicate a statistically significant difference.

Subgroup analysis. To evaluate whether the effectiveness of CABG combined with BMSC therapy in ischemic heart disease patients was influenced by the clinical characteristics, subgroup analyses were performed based on i) follow-up time (>6 or ≤ 6 months); ii) method to determine the outcome measure [echocardiography or cardiac magnetic resonance imaging (cMRI)]; iii) type of stem cells [bone marrow mononuclear cells (BMMNCs) or other selected cell populations (CD133⁺ and CD34⁺ cells)]; iv) route of injection [intramyocardial (IM) or intracoronary (IC)]; v) dose of stem cells [$\geq 10^8$ or $< 10^8$ cells (10^8 was the median number of BMSCs injected)]; vi) baseline LVEF ≤ 35 or $> 35\%$ (35% was the median LVEF at baseline in the included studies). Analyses were performed to evaluate whether the differences between the subgroups were statistically significant.

Sensitivity analysis. Sensitivity analysis was performed by excluding low-quality studies, trials recruiting participants with particular conditions or trials with characteristics different from the others. A sensitivity analysis of the primary outcome LVEF was performed.

Results

Search results. A total of 1,785 studies were identified from the electronic database search. Deduplication and removal of all clearly irrelevant studies excluded 151 articles. Initial screening of the remaining 1,627 studies against the inclusion criteria excluded a further 1,602 studies (animal experiments, case reports, meeting abstracts, insufficient data and reviews). In the remaining 23 studies, the full text was assessed for eligibility, subsequently excluding 9 studies: 2 studies used c-kit⁺ cardiac stem cells rather than BMSCs, 4 studies did not provide complete LV function data, 2 studies were replicated and no CABG was performed in 1 study. The final analysis included 14 independent RCTs. A flow chart depicting the study selection process is presented in Fig. 1.

Study characteristics. A total of 14 studies met the inclusion criteria for the present meta-analysis, including a total of 596 participants who were assessed for the primary outcomes of the study. The 'treatment group' (n=316) included participants who had received CABG combined with BMSC therapy, while the 'control group' (n=280) included patients who had only received CABG. The mean follow-up period was 11 months. The mean age of the participants ranged from 53.8 to 66.8 years, and the percentage of male patients ranged from 70 to 100%. A total of 5 studies were performed in China, 2 in Germany and 1 each in the USA, UK, Canada, Serbia, Finland, France and Belgium; the Canadian study was a multicenter trial (15 patients in Montreal and 18 in Toronto) (3). The baseline characteristics of the included studies are summarized in Table I.

Risk of bias assessment. Of the 14 studies, 9 (64.2%) adequately generated their randomisation sequence, 5 (35%) concealed allocation, 7 (50%) blinded participants and personnel, 6 (42.9%) blinded outcome assessment and 6 studies had a low risk of bias regarding selective reporting. All of the studies had a low risk of bias regarding missing outcome data. The detailed information on risk of bias is provided in Figs. 2 and 3.

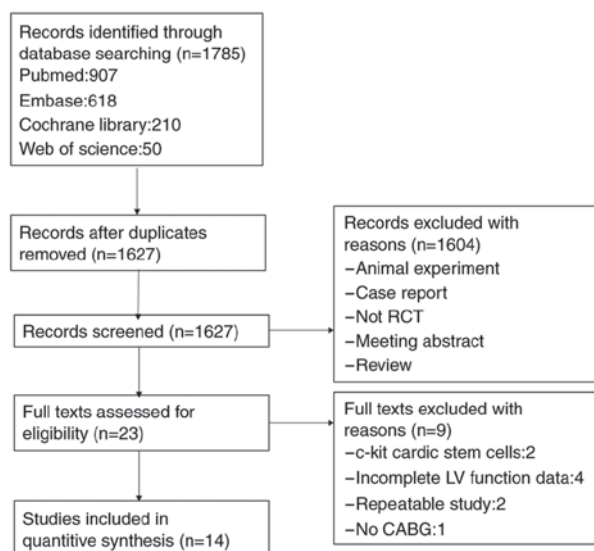


Figure 1. Flow diagram of included studies. RCT, randomized controlled trial; CABG, coronary artery bypass grafting; LV, left ventricle.

LVEF_{change}. All 14 studies, including a total of 537 participants, reported on the change in LVEF after the treatment. In the treatment group, the mean change in the LVEF from baseline to follow-up was 8.46%. In the control group, the mean change in the LVEF from baseline to follow-up was 4.22%. The difference in the change of the LVEF between the treatment and control groups was statistically significant (MD=4.36%; 95% CI: 1.90-6.81%; P<0.01; Fig. 4).

LVEDV_{change}. A total of 7 studies with 224 participants reported on the change in LVEDV after the treatment. There was no significant difference in the overall change of LVEDV from baseline to follow-up between the treatment and control groups (MD=-6.27 ml; 95% CI: -22.34 to 9.80 ml; P=0.44; Fig. 5).

LVEDVI_{change}. A total of 4 studies with 159 participants reported on the change in LVEDVI after the treatment. There was no significant difference in the overall change of LVEDVI from baseline to follow-up between the treatment and control groups (MD=-15.11 ml/m²; 95% CI: -31.53 to 1.30 ml/m²; P=0.07; Fig. 6).

LVESV_{change}. A total of 5 studies with 156 participants reported a change in LVESV after the treatment. There was no significant difference in the overall change of LVESV from baseline to follow-up between the treatment and control groups (MD=-11.52 ml; 95% CI: -26.97 to 3.93 ml; P=0.14; Fig. 7).

LVESVI_{change}. A total of 4 studies with 159 participants reported a change in LVESVI after the treatment. There was no significant difference in the overall change of LVESVI from baseline to follow-up between the treatment and control groups (MD=-16.56 ml/m²; 95% CI: -37.75 to 4.63 ml/m²; P=0.13; Fig. 8).

Publication bias. To exclude potential publication bias, funnel plots (Fig. 9) and Egger's test for publication bias was performed. No publication bias was evident for the 14 studies

Table I. Information on included studies, including cohorts, treatment and outcome measures.

First author (year)	Country	Sample size (n)	T (n)	C (n)	Follow-up (months)	Age (years)		Sex, male, n (%)		Treatment		Route of cell administration	Treatment of control group	Method for determining outcome measure (Refs.)
						Treatment	Control	Treatment	Control	Type of stem cells	Dose of stem cells			
Qi (2016)	China	42	24	18	12	57.88±8.52	56.56±9.09	23 (95.8%)	17 (94.4%)	CABG+BMMNC	13.28±9.41x10 ⁷	IC	CABG only	Echocardiography (15)
Noiseux (2016)	Canada	41	19	14	6	66.40±6.50	63.1±7.2	17 (89.5%)	13 (92.9%)	CABG+CD133+	6.5±3.1x10 ⁶	IM	CABG+Placebo	cMRI (3)
Wang (2015)	China	90	45	45	6	61.4±7.45	62.9±6.93	37 (82.0%)	35 (78.0%)	CABG+BMC	5.21±0.44x10 ⁸	IM	CABG+saline	Echocardiography (13)
Trifunović (2015)	Serbia	30	15	15	60	53.8±10.1	60±6.8	14 (93.3%)	14 (93.3%)	CABG+BMMNC	70.7±32.4x10 ⁶	IM	CABG only	Echocardiography (6)
Pättilä (2014)	Finland	39	20	19	12	65±4	64±3	19 (95.0%)	18 (94.7%)	CABG+BMMNC	8.4±2.08x10 ⁸	IM	CABG+Placebo	cMRI (7)
Nasseri (2014)	Germany	60	30	30	6	61.9±7.3	62.7±10.6	28 (93.3%)	29 (96.7%)	CABG+CD133+	5.1±1.017x10 ⁶	IM	CABG+Placebo	cMRI (5)
Lu (2013)	China	50	25	25	12	58.0±7.8	57.0±8.3	22 (88.0%)	24 (96.0%)	CABG+BMMNC	13.38±8.14x10 ⁷	IM	CABG only	cMRI (16)
Maureira (2012)	France	14	7	7	6	58±10	57±10	7 (100.0%)	6 (85.7%)	CABG+BMMNC	3.42±0.41x10 ⁸	IM	CABG only	cMRI (8)
Hu (2011)	China	60	31	29	6	56.61±9.72	58.27±8.86	None reported	None reported	CABG+BMMNC	13.17±10.66x10 ⁷	IC	CABG only	cMRI (4)
Zhao (2008)	China	36	18	18	6	60.3±10.4	59.1±15.7	15 (83.3%)	15 (83.3%)	CABG+BMMNC	6.59±5.12x10 ⁸	IM	CABG only	Echocardiography (14)
Ang (2008)	UK	62	42	20	6	63.4±8.69	61.3±8.3	34 (81.0%)	18 (90.0%)	CABG+BMC	9.95±6.61x10 ⁷	IM+IC	CABG only	cMRI (9)
Stamm (2007)	Germany	40	20	20	6	62±10.2	63.5±8.4	15 (75.0%)	16 (80.0%)	CABG+CD133+	5.8±20.6x10 ⁶	IM	CABG only	Echocardiography (10)
Hendrikx (2006)	Belgium	20	10	10	4	63.2±8.5	66.8±9.2	10 (100.0%)	7 (70.0%)	CABG+BMC	60.25±31.35x10 ⁶	IM	CABG only	cMRI (11)
Patel (2005)	USA	20	10	10	6	64.8±7.1	63.6±5.2	8 (80.0%)	8 (80.0%)	CABG+CD34+	Median 22x10 ⁶	IM	CABG only	Echocardiography (12)

Values are expressed as the mean ± standard deviation. CABG, coronary artery bypass grafting; BMMNC, bone marrow mononuclear cell; BMC, bone marrow cell; IC, intracoronary; IM, intramyocardial; cMRI, cardiac magnetic resonance imaging; T, treatment group; C, control group.

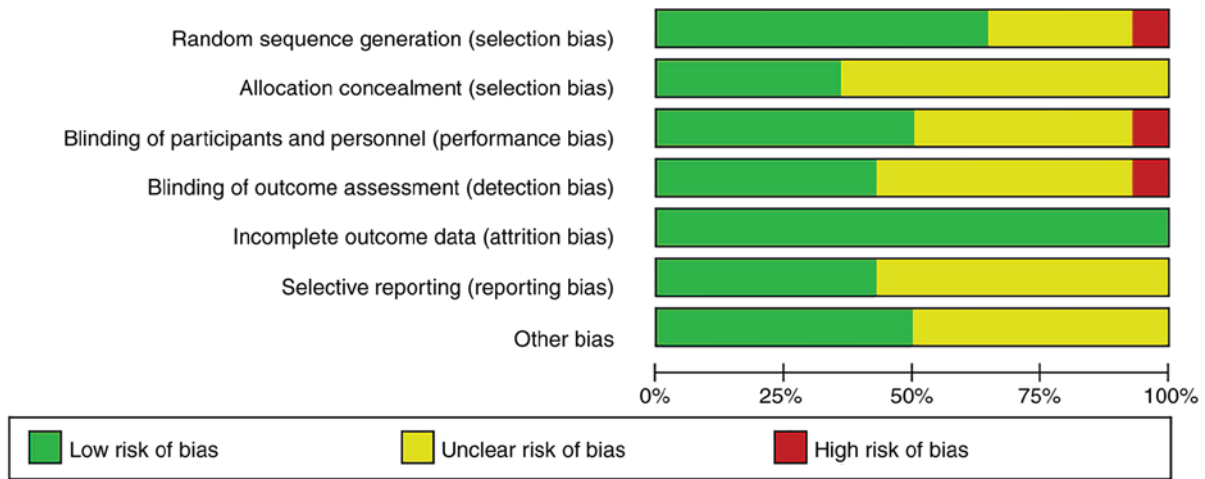


Figure 2. Risk of bias graph. The authors' judgement regarding each risk of bias item is presented as percentages across all included studies.

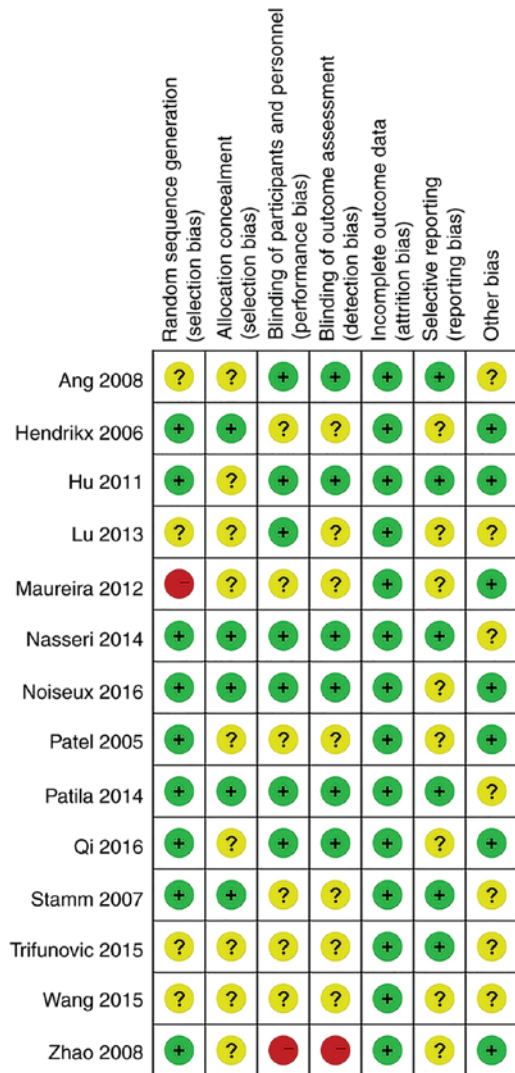


Figure 3. Risk of bias summary: Authors' judgement regarding each risk of bias item for each of the studies included.

Subgroup analysis. The subgroup analysis did not reveal any significant differences within subgroups based on follow-up period, type of stem cells, route of cell administration, dose of stem cells and baseline LVEF (Table II). However, the measurement method for the LVEF (echocardiography or cMRI) affected the effectiveness of CABG combined with BMSC injection in IHD patients ($P < 0.01$; Table II).

Sensitivity analysis. A sensitivity analysis, in which the trials with relatively low-quality data by Maureira *et al* (8) and Zhao *et al* (14) were excluded, indicated that the results were not markedly affected by the exclusion [$LVEF_{change}$ (MD=4.01%; 95% CI: 1.47-6.56%; $P < 0.01$)].

Discussion

The present meta-analysis demonstrated that BMSC therapy may improve cardiac function during CABG in patients with IHD. The change of LVEF from baseline to follow-up in the treatment group (CABG + BMSCs) increased by 4.36% compared with that in the control group (CABG alone). The $LVESV_{change}$ and $LVEDV_{change}$ were reduced in the treatment group, but the difference from the control group was not statistically significant. Sensitivity analyses that excluded low-quality studies and studies that only included patients with particular medical conditions did not alter these results. Furthermore, these results were generally consistent, regardless of the follow-up time, type of stem cells, route of cell injection (IM or IC), dose of stem cells and baseline LVEF. However, the difference in the measurement method of LVEF (echocardiography or cMRI) affected the results ($P < 0.0001$).

At present, the mechanisms of the efficacy of BMSC therapy in patients undergoing CABG remains elusive, and it may be multifactorial. Certain studies suggested that BMSCs may exert their beneficial effect by paracrine stimulation, cell fusion and transdifferentiation (25-28). Rota *et al* (29) demonstrated in rats that c-kit⁺ BMSCs engraft in proximity to the infarcted myocardium and differentiate into cells of the cardiogenic lineage, forming functionally competent cardiomyocytes and vascular structures. In addition, the effect of certain cytokines,

included in the LVEF meta-analysis (Egger's test $P = 0.48$ for the MD of $LVEF_{change}$).

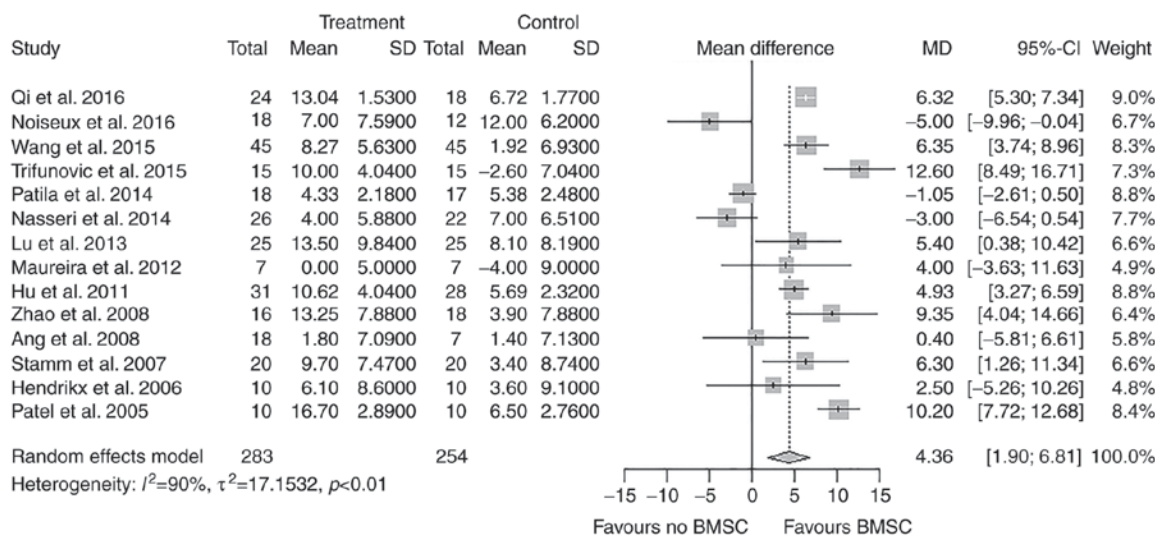


Figure 4. Forest plot of the difference in the change from baseline in the left ventricular ejection fraction between the treatment and control groups. Grey boxes represent the weight of the study; diamonds indicate the combined results of the effect size of each study; the data-points represent the mean difference value; horizontal lines represent the 95% CI; CI, confidence interval; MD, mean difference; SD, standard deviation; BMSC, bone marrow stem cell.

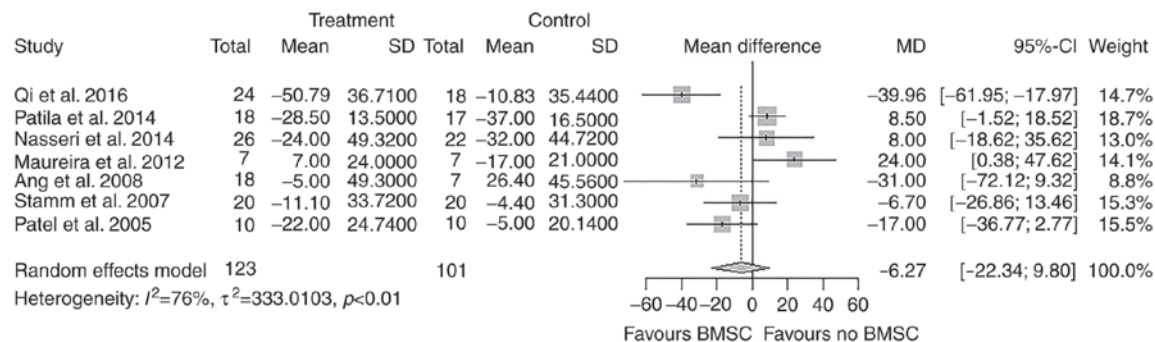


Figure 5. Forest plot of the difference in the change from baseline in left ventricular end-diastolic volume (ml) between the treatment group and control group. Grey boxes represent the weight of the study; diamonds indicate the combined results of the effect size of each study; the data-points represent the mean difference value; horizontal lines represent the 95% CI; CI, confidence interval; MD, mean difference; SD, standard deviation; BMSC, bone marrow stem cell.

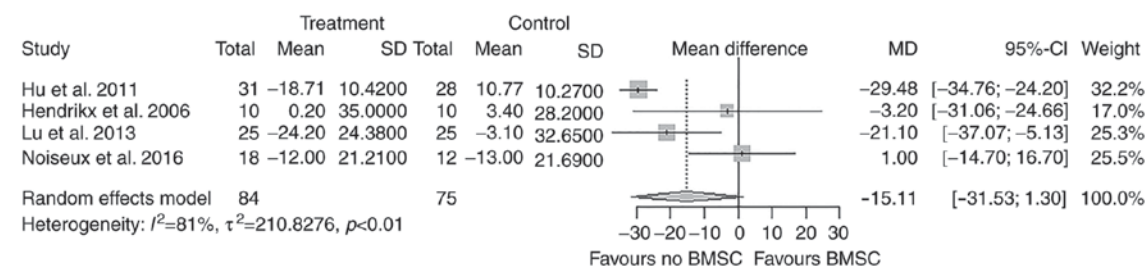


Figure 6. Forest plot of the difference in the change from baseline in the left ventricular end-diastolic volume index between the treatment group and the control group (ml/m²). Grey boxes represent the weight of the study; diamonds indicate the combined results of the effect size of each study; the data-points represent the mean difference value; horizontal lines represent the 95% CI; CI, confidence interval; MD, mean difference; SD, standard deviation; BMSC, bone marrow stem cell.

including vascular endothelial growth factor (VEGF), has been indicated to restore coronary vessels and myocytes via angiogenesis following experimental infarction. BMSCs express a number of cytokines, including VEGF, insulin-like growth factor and platelet-derived growth factor, which stimulate the regeneration and proliferation of residual normal myocytes and intrinsic myocardial stem cells (endogenous stem cells) for cell regeneration and fusion (30,31).

In the present meta-analysis, 10 studies provided short-term follow-up (≤ 6 months) and 4 studies reported long-term follow-up (> 6 months) data, but only 1 study provided 5-year follow-up data. There was no significant difference regarding the improvement in the LVEF between the short-term and long-term follow-up. A systematic review and meta-analysis by Jeevanantham *et al* (32) indicated that adult BMSC therapy improves the LVEF in patients with IHD compared with

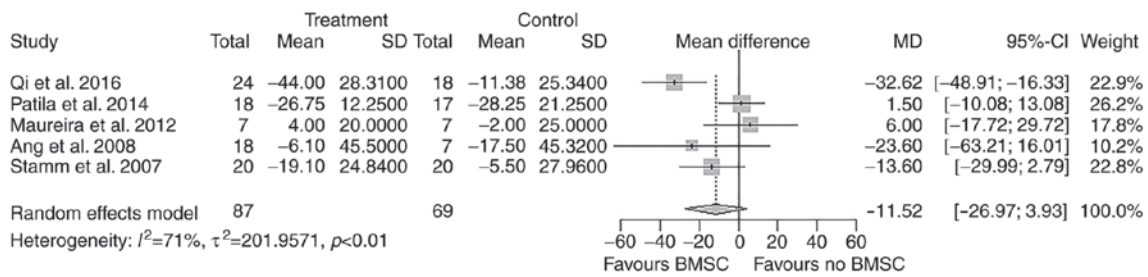


Figure 7. Forest plot of the difference in the change from baseline in the left ventricular end-systolic volume (ml) between the treatment group and the control group. Grey boxes represent the weight of the study; diamonds indicate the combined results of the effect size of each study; the data-points represent the mean difference value; horizontal lines represent the 95% CI; CI, confidence interval; MD, mean difference; SD, standard deviation; BMSC, bone marrow stem cell.

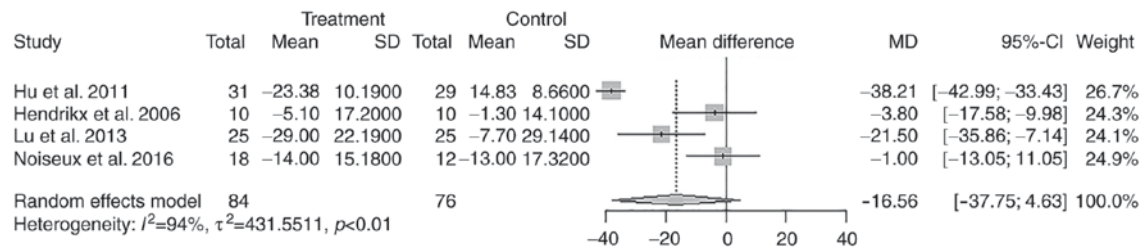


Figure 8. Forest plot of the difference in the change from baseline in the left ventricular end-systolic volume index between the treatment and control groups (ml/m²). Grey boxes represent the weight of the study; diamonds indicate the combined results of the effect size of each study; the data-points represent the mean difference value; horizontal lines represent the 95% CI; CI, confidence interval; MD, mean difference; SD, standard deviation; BMSC, bone marrow stem cell.

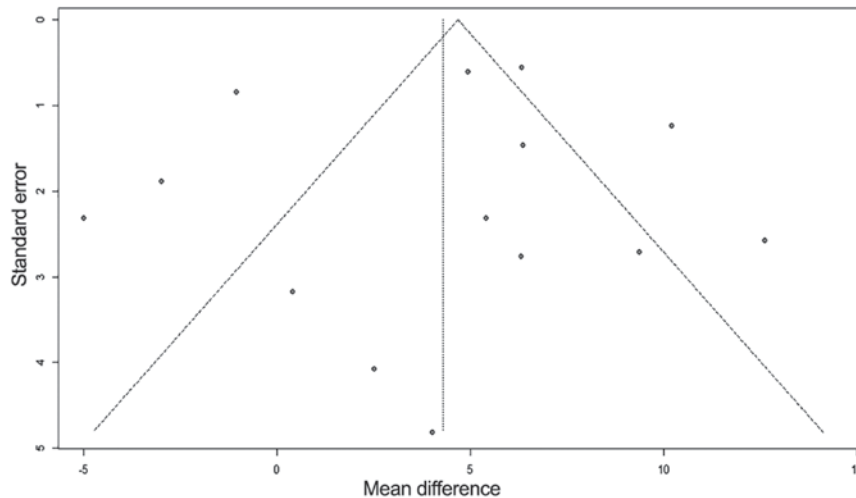


Figure 9. Funnel plot of the difference in the change from baseline in the left ventricular ejection fraction in treatment and control groups.

standard treatment, and these benefits persist at least beyond 24 months (32). Similarly, Nesteruk *et al* (33) indicated that the LVEF in the stem cell therapy group improved at 5 years compared with that in the CABG alone group. These data suggest that the benefits of BMSC therapy on cardiac function are not short-lived.

With regard to the methods for measuring the LVEF (echocardiography or cMRI), the subgroup analysis demonstrated that the choice of method affected the determined effectiveness of CABG combined with BMSC injection in IHD patients ($P<0.0001$). cMRI and echocardiography have important diagnostic value in assessing cardiac function, and perform similarly regarding the method of calculation in

the measurement of the cardiac ejection fraction. However, echocardiographic measurements may be affected by the ultrasonographer, whereas MRI is more reliable and accurate for measuring cardiac function.

Regarding the type of BMSC therapy, 2 of the 4 studies that included CD133⁺ or CD34⁺ cells in the meta-analysis had an unfavorable MD. However, only 1 of the 10 studies using BMMNCs/BMCs had an unfavorable MD. These results suggest that using BMMNCs/BMCs may lead to a more noticeable improvement in the LVEF compared with CD133⁺ or CD34⁺ cells. However, this result may be limited by the small sample size of the cohort treated with CD133⁺ or CD34⁺ cells, and accordingly, the conclusions may only be preliminary.

Table II. Subgroup analysis of LVEF change for each variable.

Variable	No. of trials	MD (95% CI)	P-value
Follow-up for examining LVEF (months)			
>6	4	5.61 (0.34-10.89)	0.56
≤6	10	3.81 (0.78-6.83)	
Method of measurement			
Echocardiography	6	8.26 (6.15-10.36)	<0.0001
cMRI	8	0.86 (-2.19-3.90)	
Type of stem cells			
BMMNC	7	5.73 (2.46-9.01)	0.42
CD133 ⁺ /CD34 ⁺	4	2.21 (-5.69-10.12)	
Route of cell administration			
IC	2	5.79 (4.46-7.11)	0.47
IM	11	4.35 (0.67-8.03)	
Amount of stem cells administered			
≥10 ⁸	7	4.84 (1.95-7.73)	0.69
<10 ⁸	7	3.56 (-1.96-9.08)	
Baseline LVEF (%)			
≤35	6	4.49 (1.65; 7.34)	0.97
>35	8	4.39 (0.10; 8.68)	

LVEF, left ventricular ejection fraction; cMRI, cardiac magnetic resonance imaging; BMMNC, bone marrow mononuclear cells; IC, intracoronary; IM, intramyocardial; MD, mean difference ('effect size' for the treatment vs. control group); CI, confidence interval.

Autologous cell preparations are medical products characterized by complexity in terms of differences in cell isolation protocols and storage of cell products, and the methods for assessing outcome may be inhomogeneous. These factors may affect the role of CD133⁺ or CD34⁺ cell therapy in improving cardiac function. Therefore, the function of CD133⁺ or CD34⁺ cells in improving LVEF and the underlying mechanisms and remain to be further elucidated.

A total of 3 previous meta-analyses (20-22) have analyzed the effect of CABG in combination with BMSC therapy in patients with IHD. The present results differ from those of the previous meta-analyses in several aspects. In the meta-analysis study by Donndorf *et al* (22) reported that the improvement in the LVEF (MD of LVEF_{change} of 5.40%) tended to be more prominent; however, their study only included 6 trials (4 RCTs and 2 cohorts; Table III presents the studies that were included in previous meta-analyses) with a total of 179 patients, whereas the present study included 14 RCTs with a total of 596 participants. Therefore, the present results may be more reliable. The meta-analysis by Qin *et al* (20) indicated that BMSC therapy significantly improved the LVEF and reduced the LVEDV and LVESV; however, their study only indicated the MD of the post-treatment LVEF values between the BMSC and the CABG alone groups, whereas in the present meta-analysis, the MD of LVEF change from follow-up to baseline between the BMSC and CABG groups was calculated. Therefore, the present results may be more reliable. Ali-Hassan-Sayegh *et al* (21), who included 9 studies (6 RCTs and 3 cohorts) with a total of 335 patients, obtained similar results compared with the present meta-analysis for the

LVEF_{change} (MD=4.06%, 95% CI: 0.41 to 7.72%; P<0.01) and LVEDV_{change} (MD=7.06 ml, 95% CI: 8.58 to 22.7 ml; P=0.30). Our study demonstrated, with markedly narrower CIs, that CABG in combination with BMSC therapy may improve cardiac function. Compared with the previous meta-analysis studies, a large number of additional studies was included and more thorough analyses were performed. The addition of large RCTs provided more reliable estimates of the effects of CABG combined with BMSC therapy. Furthermore, the LVEDVI and LVESVI were only determined in 4 trials included in the present study (3,4,11,16). Although this is a small sample, these indexes are more reflective regarding the heart function compared with LVEDV and LVESV, as each individual's body surface area is different. In addition, the majority of the studies reported on the LVEDV and LVESV as clinical outcomes, so their data were extracted separately. This may be one of the reasons for the difference in LVEDV and LVESV not being statistically significant. Therefore, future meta-analyses must include more studies to obtain significant results.

The present meta-analysis was based on a comprehensive search strategy, including a systematic rigorous approach to the evaluation of RCTs investigating the effectiveness of BMSC therapy in combination with CABG in IHD patients. A detailed subgroup analysis was performed to explore differences in LVEF_{change}. Although the results of the present study appear promising regarding the efficacy of BMSC therapy, there were also certain limitations: First, there was significant heterogeneity in the present meta-analysis, which may be attributable to the dose and type of BMSC therapy, the timing

Table III. Comparison of studies included in the previous meta-analyses.

Study (years)	Meta-analysis by Qin <i>et al</i> (20)	Meta-analysis by Donndorf <i>et al</i> (22)	Meta-analysis by Ali-Hassan-Sayegh <i>et al</i> (21)	(Refs.)
Qi <i>et al</i> (2016)	No	No	No	(15)
Noiseux <i>et al</i> (2016)	No	No	No	(3)
Wang <i>et al</i> (2015)	No	No	No	(13)
Trifunović <i>et al</i> (2015)	No	No	No	(6)
Pätälä <i>et al</i> (2014)	No	No	No	(7)
Nasseri <i>et al</i> (2014)	No	No	Yes	(5)
Lu <i>et al</i> (2013)	Yes	No	No	(16)
Maureira <i>et al</i> (2012)	Yes	No	No	(8)
Hu <i>et al</i> (2011)	Yes	No	No	(4)
Zhao <i>et al</i> (2008)	Yes	Yes	Yes	(14)
Ang <i>et al</i> (2008)	Yes	No	Yes	(9)
Stamm <i>et al</i> (2007)	No	Yes	Yes	(10)
Hendrikx <i>et al</i> (2006)	Yes	Yes	Yes	(11)
Patel <i>et al</i> (2005)	No	Yes	Yes	(12)

Yes refers to the studies that were included in the present study that were also included in previous respective meta-analyses. No refers to the studies that were included in the present study, but were not included in the previous respective meta-analyses.

of CABG combined with BMSC therapy after myocardial ischemia, the baseline LVEF, method of cell processing and outcome measurement methods, and these factors may affect the efficacy of BMSC therapy. Furthermore, the CIs were relatively wide, most likely due to the small number of studies and the relatively sparse subjects in all outcomes. Finally, the follow-up was relatively short in most studies, and the sustained efficacy of BMSC therapy for patients undergoing CABG remains to be further demonstrated. The results of the present meta-analysis should be confirmed in large, adequately powered RCTs assessing the efficacy of BMSC therapy, and outcome measures should be standardised (e.g. LVEF, LVEDV and LVESV). Future research should also focus on the mechanisms of action of BMSC therapy to further confirm the results of meta-analyses in IHD patients.

In conclusion, based on the present evidence, autologous BMSC therapy for patients undergoing CABG appears to be associated with an improvement in LV function. This improvement is beyond that achieved by CABG alone. Therefore, BMSC therapy may be beneficial as an adjuvant therapy for patients undergoing CABG.

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Availability of data and materials

All the datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SW and LY analyzed the patient data and were the major contributors in the preparation of the manuscript. QB and AW analyzed part of the patient data. XS and YD performed the literature search and extracted the data. XD and XL were responsible for the statistical analysis. YZ, PY and KY made substantial contributions to the conception of the study. MZ and YC drafted the manuscript. All the authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests to disclose.

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