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Efficacy and Safety of Bone Marrow Cell Transplantation for Chronic Ischemic Heart Disease: A Meta-Analysis

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Background: Although bone marrow-derived cells (BMCs) have shown great therapeutic potential in patients with chronic ischemic heart disease (CIHD), the exact efficacy and safety of BMCs therapy is still not completely defined.





Material/Methods: We searched PubMed, OVID, EMBASE, the Cochrane Library, and ClinicalTrials.gov and finally identified 20 qualified trials in this meta-analysis. Assessment of efficacy was based on left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV) improvement, by weighted mean difference (WMD) with 95% confidence intervals (CIs). Results of all-cause death, ventricular arrhythmia, recurrent myocardial infarction, and cerebrovascular accident were pooled to assess safety. Subgroup analysis was performed by stratifying RCTs into 2 subgroups of those with revascularization and without revascularization.

Results: BMC transplantation significantly improved LVEF in patients with revascularization (3.35%, 95% CI 0.72% to 5.97%, $p=0.01$; $I^2=85%$) and without revascularization (3.05%, 95% CI 0.65% to 5.45%, $p=0.01$; $I^2=86%$). In patients without revascularization, BMC transplantation was associated with significantly decreased LVESV (-11.75 ml, 95% CI -17.81 ml to -5.69 ml, $p=0.0001$; $I^2=81%$), and LVEDV (-7.80 ml, 95% CI -15.31 ml to -0.29 ml, $p=0.04$; $I^2=39%$). Subgroup analysis showed that the route of transplantation, baseline LVEF, and type of cells delivered could influence the efficacy of BMC transplantation.

Conclusions: Autologous transplantation of BMCs was safe and effective for patients who were candidates for revascularization with CABG/PCI and those who were not. However, large clinical trials and long-term follow-up are required to confirm these benefits.

MeSH Keywords: **Mesenchymal Stromal Cells • Meta-Analysis • Myocardial Ischemia**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/892047>

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Background

Chronic ischemic heart disease (CIHD) is characterized as reduced blood supply to the heart muscle due to plaque building up along the inner walls of the arteries of the heart. If not properly treated, it can lead to end-stage heart failure [1]. CIHD is a major cause of morbidity and mortality in developed countries and in some of the emerging countries. Although the application of medical therapy and coronary artery revascularization techniques (e.g., coronary artery bypass grafting [CABG] and percutaneous coronary intervention [PCI]) have improved clinical outcomes, CIHD is still a leading cause of angina and congestive heart failure refractory to traditional therapies [2]. Optimal therapies for this disease should achieve clinical improvement of cardiac function by realizing myocardial regeneration and revascularization, without severe adverse effects. Therefore, stem/progenitor cells-based cell therapy has great potential due to the ability to self-renew and to differentiate into specialized cells [3].

Since 2001, transplantation of bone marrow-derived cells (BMCs), either by intracoronary or intramyocardial route, has been tested as a therapy for myocardial infarction and other ischemic heart disease [4] due to their multipotent, autologous origin and readily usable features [5]. A number of studies were launched to evaluate the effect of this therapy and some reported improved left ventricular ejection fraction (LVEF) and exercise capacity in patients with myocardial infarction or other coronary artery diseases [3,6]. Initial meta-analysis also demonstrated the safety and beneficial effects of intracoronary BMC therapy [7,8]. However, due to small sample size of the trials, the exact efficacy of BMC therapy for patients with CIHD is still unclear. Some studies even reported no significant benefits of BMC therapy compared with controls [9,10]. In addition, previous meta-analyses also found significant heterogeneity of trials included and conflicting results [11–13]. Thus, it is necessary to integrate results of the latest clinical trials to perform an updated meta-analysis. The aim of this meta-analysis was to make an updated assessment of efficacy and safety of autologous transplantation of BMCs for patients with CIHD.

Material and Methods

Search strategy

This meta-analysis generally followed the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies focusing on BMC transplantation in patients with CIHD were retrieved from PubMed, OVID, EMBASE, the Cochrane Library and ClinicalTrials.gov from January 2000 to April 2014. The subject terms and free-text terms used for

this study were: bone marrow cell, bone marrow mononuclear cell, stem cell, stromal cell, coronary artery disease, ischemic cardiomyopathy, ischemic heart disease, heart failure, myocardial ischemia, and myocardial infarction. Introduction and reference lists of included trials were manually searched to identify additional qualified studies. No language restriction was set when searching qualified studies.

Selection criteria

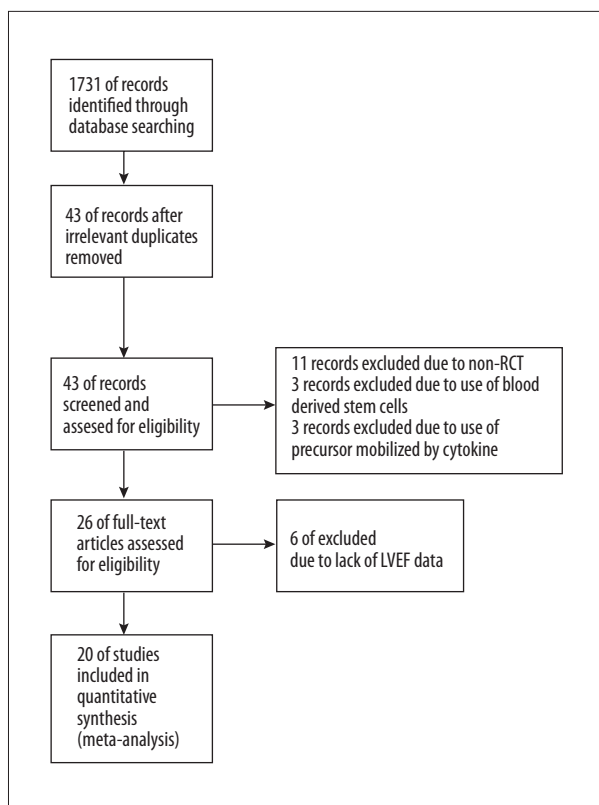
Studies included for meta-analysis had to meet all of the following criteria simultaneously: (1) randomized controlled trial (RCT) based on patients with chronic ischemic heart disease (CIHD); (2) cell therapy was autologous BMCs-based; (3) patients in the control arm received standard therapy; and (4) follow-up was at least 3 months. Exclusion criteria were: (1) studies provided patients cell precursors mobilized by cytokines due to the additional effect of cytokine myocardium and BMCs. In this study, CHID was defined as chronic coronary total occlusion, stable angina, refractory angina, myocardial ischemia, historical myocardial infarction, or patients with previous revascularization.

Data extraction

Two authors (CX and SZ) independently assessed eligibility of studies and extracted data from original studies. Disagreements and discrepancies were resolved through group discussion involving a third reviewer. The following information was extracted from original studies: first author, year of publication, number of patients recruited, basic information of patients (age, sex, and NYHA classification), clinical scenario, duration of follow-up, type and number of cells transplanted, route of delivery, and imaging modality. The outcomes of LV function and remodeling – primary endpoint-left ventricular ejection fraction (LVEF) and secondary endpoints-net changes in left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV) – were extracted for further meta-analysis. For studies that reported primary or secondary endpoints measured by various imaging modalities, MRI data was preferentially used due to superior accuracy. Data on the major adverse effects were extracted for assessing the safety of BMCs transplantation for CIHD patients.

Quality assessment

The methodological quality of included studies was assessed according to the method proposed by Juni et al. [14], in combination with modified Jadad score (7 point). The major quality components were: adequate method to generate randomized sequence, adequate method of allocation concealment, blinding of outcome assessors, loss of participant follow-up (%), and all patients treated in assigned group.



Supplement Figure 1. The search process.

Data analysis

RevMan 5.2 (Cochrane Collaboration) software was used for data analysis. To guarantee uniformity of outcomes, when multiple measurements of the change of primary and secondary endpoint from baseline to follow-up were available, 6-month data were obtained and used for further pooled analysis. If original data did not provide the changes in mean and SD form, the estimation method recommended by the Cochrane Handbook for Systematic Reviews of Interventions 16.1.3 was used (Version 5.1.0, the Cochrane Collaboration, 2011). Results are summarized in the form of weighted mean difference (WMD) with 95% confidence intervals (CIs). Heterogeneity between trials was assessed using chi-square test (χ^2) and I^2 statistics. $P < 0.1$ or $I^2 > 50\%$ suggests a substantial level of inconsistency [15]. Primary assessment was performed with a fixed model. If significant heterogeneity was identified, the source of heterogeneity was further analyzed. If no significant clinical heterogeneity was observed, the random effects model based on Mantel-Haenszel method was used to make estimates. Otherwise, descriptive analysis was performed. Funnel plots were used to explore possible publication bias. Subgroup analysis was also performed according to type of cells (BMMNCs or MCSs), the route of cell delivery (IM or IC), and above or below average LVEF level ($< 35.5\%$ or $\geq 35.5\%$). $P < 0.05$ was considered as statistically significant.

Results

Search results

The search process is described in Supplement Figure 1. Initial retrieval yielded 1731 references, among which 1688 were excluded after reviewing the title and/or abstract. The remaining 43 trials were reviewed in detail for assessing eligibility. Among them, 11 were excluded due to non-RCT, 3 were excluded due to use of precursors mobilized by cytokine, 3 were excluded due to use of blood-derived stem cells, and 6 were excluded because LVEF data was not reported. Finally, a total of 20 trials were included for meta-analysis [6,9,10,16–32].

Characteristics of included studies

The key characteristics of trials included are summarized in Supplement Table 1. All of the trials had relatively small sample size, with number of patients ranging from 14 to 109. A total of 453 patients were included in the cell therapy groups and 322 patients were included in the control groups. All trials recruited patients with CIHD, including chronic coronary total occlusion, refractory angina, ischemic heart failure, and chronic myocardial infarction. Twelve studies used PCI or CABG as the control method for revascularization and 8 studies recruited patients unsuitable for revascularization. The autologous BMCs, including both BMMNCs and MCSs, were delivered either directly through intramyocardial or intracoronary approach. Mean patient age in the intervention groups was 61.0 ± 3.3 and in the control groups was 61.2 ± 3.3 ($p = 0.88$), suggesting adequate match. Follow-up ranged from 3 to 12 months. The lowest and highest average number of cell delivered was 5×10^6 and 6.59×10^8 . The median LVEF of patients at baseline in the intervention group was 35.5%. A funnel plot for LVEF outcome was used to assess publication bias. The roughly symmetrical distribution pattern suggested there was no significant publication bias (Supplement Figure 2).

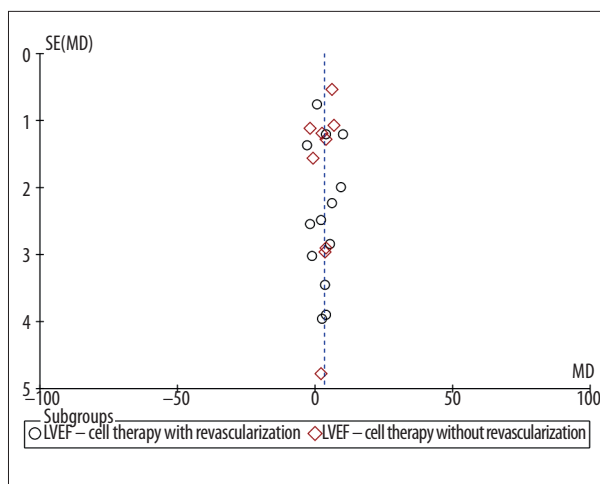
Quality assessment

Methodological quality of the 20 studies included is summarized in Supplement Table 2. Generally, the quality of trials included was good. According to the modified Jadad score, 14 out of 20 studies scored 5 or above, which suggests relatively high quality. There was no significant difference in patient characteristics between cell therapy and standard therapy groups. All of the trials were randomized, but 6 studies did not report the method of generating a randomized sequence and 6 did not give concealing allocation method. Eighteen studies had both blinded patients and practitioners and 2 studies had only blinded patients. All these studies had blinded assessors of outcome measurement. Eighteen studies had loss of follow-up rate under 15% and 2 were over this level.

Supplement Table 1. Characteristics of included studies.

Study	Country	Sample size (I/C)	Average age (I/C)	NYHA classification	Duration (Mo)	Gender (male%) (I/C)	Revascularization	Baseline LVEF (mean SD)	Clinical scenario	Route of transplantation (no.)	No. of cells	Cell type	Imaging modality
Ang et al., 2008	UK	42/20	IM: 64.7/61.3; IC: 62.1/61.3	N.A.	6	86/14	CABG	25.4 (8.1) IM 28.5 (6.5) IC	R-CIHD	IM(21)/ IC(21)	85±56×10 ⁶ IM 115±73×10 ⁶ IC	BMMNC	MRI
Assmus et al., 2006	Germany	35/23	60/61	1–3	3	93/7	PCI	41 (11)	R-CIHD	IC	205±110×10 ⁶	BMMNC	LVG
Chen et al., 2006	China	22/23	N.A.	N.A.	12	N.A.	PCI	26 (6)	R-CIHD	IC	5×10 ⁶	MSC	Echo (EF)
Heldman et al., 2013	US	MSC: 22/11 BMMNC: 22/10	MSC: 57.1/60.0 BMMNC: 61.1/61.3	1-3	12	MSC: 94.7/90.9 BMMNC: 89.5/100	N.A.	35.9 (8.2) BMMNC 35.7 (9.0) MSC	N-CIHD	IM	≥100×10 ⁶	BMMNC/ MSC	MRI
Hendrikk et al., 2006	Belgium	10/10	63.2/66.8	N.A.	4	100/70	CABG	42.9 (10.3)	R-CIHD	IM	60.25± 31.35×10 ⁶	BMMNC	MRI
Lu et al., 2013	China	25/25	57/58	2–3	12	96/88	CABG	23.4 (7.1)	R-CIHD	IC	13.38±8.14×10 ⁷	BMMNC	MRI
Maureira et al., 2012	France	7/7	58/57	I: 2.1 (mean) C: 1.9 (mean)	6	100/86	CABG	41 (8)	R-CIHD	IM	≥300×10 ⁶	BMMNC	MRI
Patel et al., 2005	Argentina	10/10	64.8/63.6	I: 3.5 C: 3.4	6	80/80	CABG	29.4 (3.6)	R-CIHD	IM	22×10 ⁶ (median)	CD34+ BMC	Echo
Perin et al., 2011	America	20/10	60.5/56.3	I: 2.3 C: 2.6	6	80/50	N.A.	37.5 (8.2)	N-CIHD	IM	30×10 ⁶	BMMNC	LVG
Perin et al., 2012a	America	61/31	63.95/62.32	1-3	6	92/98	N.A.	32.43 (9.23)	N-CIHD	IM	100×10 ⁶	BMMNC	Echo
Perin et al., 2012b	America	10/10	58.2/57.8	I: 2.5 C: 2.6	6	90/80	N.A.	36.1(10.9)	N-CIHD	IM	0.29×10 ⁷	ALDHbr BMC	Echo/ LVG
Pokushalov et al., 2010	Russia	55/54	61/62	I: 3.3 C: 3.5	12	48/46	N.A.	27.8 (3.4)	N-CIHD	IM	41±16×10 ⁶	BMMNC	Echo
Stamm et al., 2007	Germany	22/21	62/63.5	2–3	6	75/80	CABG	37.4 (8.4)	R-CIHD	IM	5.86×10 ⁶ (median)	CD133+ BMC	Echo
Tse et al., 2007	China & Australia	19/9	65.2/68.9	I: 2–4 C: 2–3	6	79/88	N.A.	45.7 (8.3)	N-CIHD	IM	1.67±0.34×10 ⁷ low 4.20±2.80×10 ⁷ high	BMMNC	MRI
van Ramshorst et al., 2009	Netherlands	25/25	64/62	N.A.	3	92/80	N.A.	56 (12)	N-CIHD	IM	98±6×10 ⁶	BMMNC	MRI
Yao et al., 2008	China	24/23	54.8/56.3	1–3	6	96/96	PCI	44.3 (5.5)	R-CIHD	IC	180×10 ⁶	BMMNC	MRI
Zhao et al., 2008	China	18/18	60.3/59.1	3–4	6	83.3/83.3	CABG	35.80 (7.28)	R-CIHD	IM	6.59±5.12×10 ⁸	BMMNC	Echo
Bartunek et al., 2013	Belgium/ Serbia	21/15	55.7/59.5	2–3	6	95.2/91.7	N.A.	27.5 (2)	N-CIHD	IM	>600×10 ⁶	MSC	Echo
Nasseri et al., 2014	Germany	30/30	61.9/62.7	1–4	6	93.3/96.7	CABG	27 (6)	R-CIHD	IM	11.7×10 ⁶	CD133+ BMC	MRI
Pättilä et al., 2014	Finland	20/19	65/64	2–3	12	95/94.7	CABG	37.2 (4)	R-CIHD	IM	8.4×10 ⁶ (median)	BMMNC	MRI

I – Intervention; C – control; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; N.A. – not available; R-CIHD – revascularizable chronic ischemic heart disease; IM – intramyocardial; IC – intracoronary; CABG – coronary artery bypass grafting; BMC – bone marrow cell; BMMNC – bone marrow mononuclear cell; ALDHbr – with a high level of aldehyde dehydrogenase activity; MRI – magnetic resonance imaging; Echo – echocardiography; LVG – left ventriculography.



Supplement Figure 2. Funnel plot of publication bias.

Efficacy of BMC transplantation

The primary and secondary outcome (LVEF, LVEDV, and LVESV) were pooled. Compared with standard treatment, BMC transplantation significantly improved LVEF in patients with revascularization (3.35%, 95%CI 0.72% to 5.97%, $p=0.01$; $I^2=85%$) and in patients without revascularization (3.05%, 95% CI 0.65% to 5.45%, $p=0.01$; $I^2=86%$). LVEF improvement was similar in these 2 groups ($p=0.87$) (Figure 1). LVESV and LVEDV are 2 important indicators of LV remodeling. Compared with control, BMC transplantation was associated with moderately decreased LVESV in patients with revascularization (-5.88 ml, 95% CI, -12.66 ml to 0.91 ml, $p=0.09$; $I^2=51%$) and significantly decreased in patients without revascularization (-11.75 ml, 95% CI -17.81 ml to -5.69 ml, $p=0.0001$; $I^2=81%$) (Figure 2). No significant difference in LVESV decrease was observed between

Supplement Table 2. Methodological quality of 20 studies included.

Study	Adequate method to generate randomized sequence	Adequate method of allocation concealment	Blinding of outcome assessors	Loss of participant follow-up (%)	All patients treated in assigned group	Jadad Score
Ang et al., 2008	N	N	Y	3.3	Y	3
Assmus et al., 2006	N	N	Y	12	Y	3
Chen et al., 2006	N	N	N	13.3	Y	1
Bartunek et al., 2013	Y	Y	Y	0	Y	7
Hendriks et al., 2006	Y	Y	Y	13	Y	6
Heldman et al., 2013	Y	Y	Y	4.6	Y	6
Lu et al., 2013	N	N	Y	16.7	Y	3
Maureira et al., 2012	Y	Y	N	0	Y	5
Nasseri et al., 2014	Y	Y	Y	10	Y	6
Patel et al., 2005	Y	Y	Y	0	Y	7
Pättilä et al., 2014	Y	Y	Y	0	Y	7
Perin et al., 2011	Y	Y	Y	0	Y	7
Perin et al., 2012a	Y	Y	Y	4.7	Y	6
Perin et al., 2012b	Y	Y	Y	0	Y	6
Pokushalov et al., 2010	Y	Y	Y	24.8	Y	6
Stamm et al., 2007	N	N	Y	7	Y	3
Tse et al., 2007	Y	Y	Y	3.6	Y	6
van Ramshorst et al., 2009	Y	Y	Y	2	Y	6
Yao et al., 2008	N	N	Y	0	Y	3
Zhao et al., 2008	Y	Y	Y	5.6	Y	6

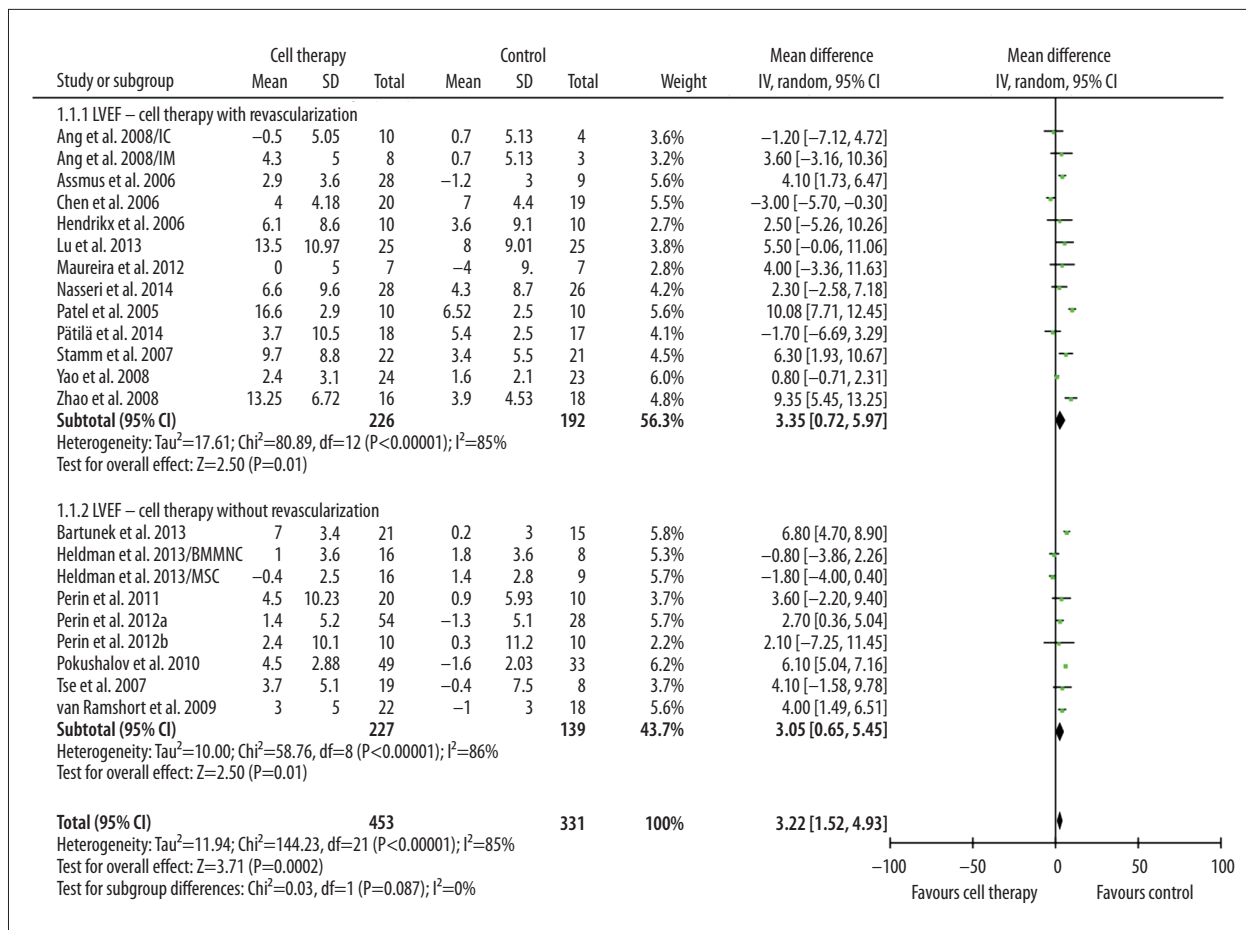


Figure 1. Meta-analysis of LVEF improvement after therapy.

these 2 groups ($p=0.21$) (Figure 2). In addition, a significant trend of decreased LVEDV was only observed in patients receiving only cell therapy (-7.80 ml, 95% CI -15.31 ml to -0.29 ml, $p=0.04$; $I^2=39\%$), but not in patients receiving combination of cell therapy and revascularization (-7.30 , 95% CI -17.68 ml to 3.09 ml, $p=0.17$; $I^2=57\%$). However, the difference between these 2 groups was not significant ($p=0.94$) (Figure 3).

Subgroup analysis

Due to significant heterogeneity observed within groups with or without revascularization, subgroup analysis was performed to explore whether the type of revascularization intervention (CABG or PCI), the type of cell delivered, and the level of baseline LVEF influenced the efficacy of cell therapy. Table 1 summarizes the results of subgroup analysis. Compared with LVEF improvement in intracoronary route (1.00%, 95% CI -0.11% to 2.10%), the improvement in intramyocardial delivery was significantly higher (4.77%, 95% CI 4.11% to 5.44%) ($p<0.00001$) (Table 1). However, no significant difference was observed in LVESV and LVEDV ($p=0.68$ and $p=0.64$, respectively). When comparing the effect of cell therapy transplanted on LV function

improvement, it was observed LVEF improvement was significantly higher in the BMMNCs group (4.33%, 95% CI 3.69% to 4.96%) than in the MCSs group (1.32%, 95% CI -0.00% to 2.65%) ($p<0.00001$) (Table 1). However, LVESV decrease was more evident in the MCSs group (-15.69 ml, 95% CI -17.87 ml to -13.52 ml) than in the BMMNCs group (-8.51 ml, 95% CI -14.28 ml to -2.74 ml) ($p=0.02$). The median LVEF of patients in 20 trials was 35.5%. LVEF increase was significantly higher in the group with higher than average LVEF (5.11%, 95% CI 4.36% to 5.86%) than the group with lower than average LVEF (1.93%, 95% CI, 1.05% to 2.81%) ($p<0.00001$). Changes in LVESV and LVEDV were similar in these 2 groups ($p=0.23$ and $p=0.32$, respectively) (Table 1).

Safety of BMC transplantation

Major adverse cardiovascular events reported in original studies were pooled to assess the safety of BMC transplantation (Table 2). Generally, compared with control, BMC transplantation had a similar risk ratio in ventricular arrhythmia, recurrent myocardial infarction, and cerebrovascular accident as control in subgroups both with and without revascularization. However,

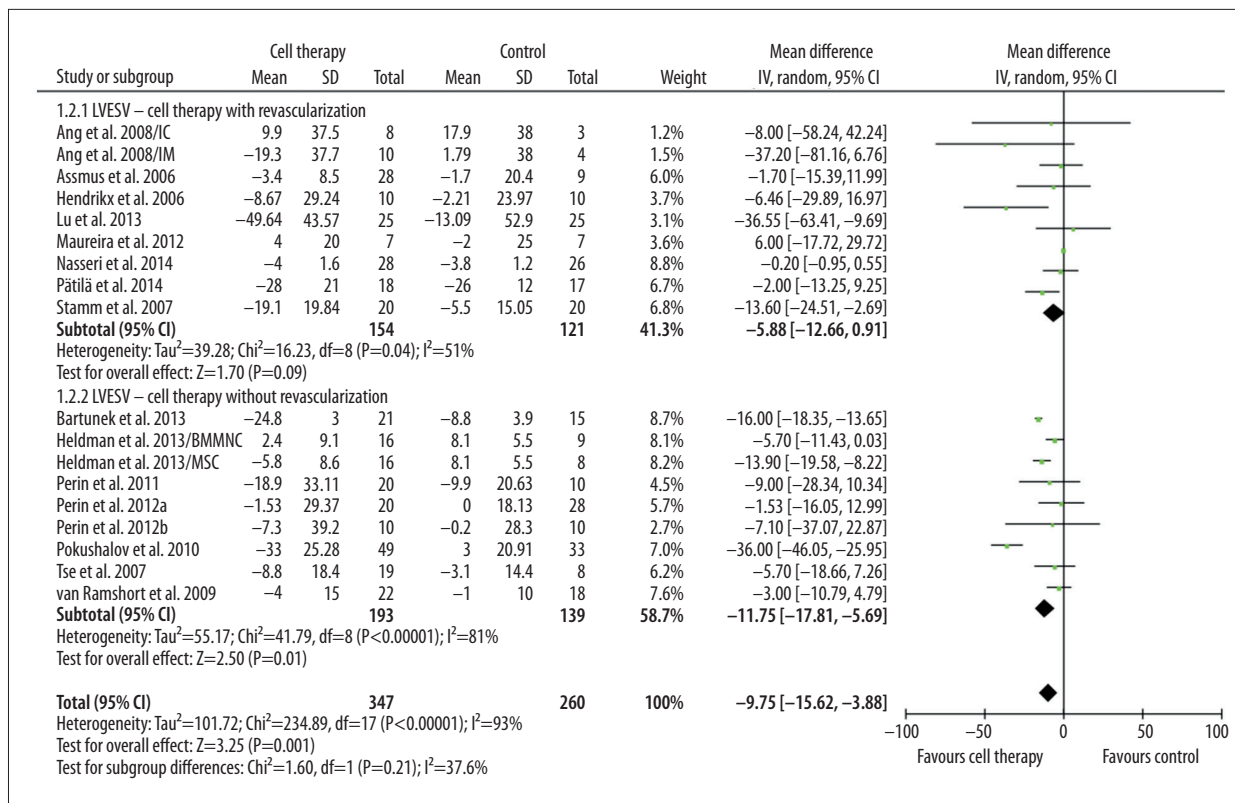


Figure 2. Meta-analysis of LVESV improvement after therapy.

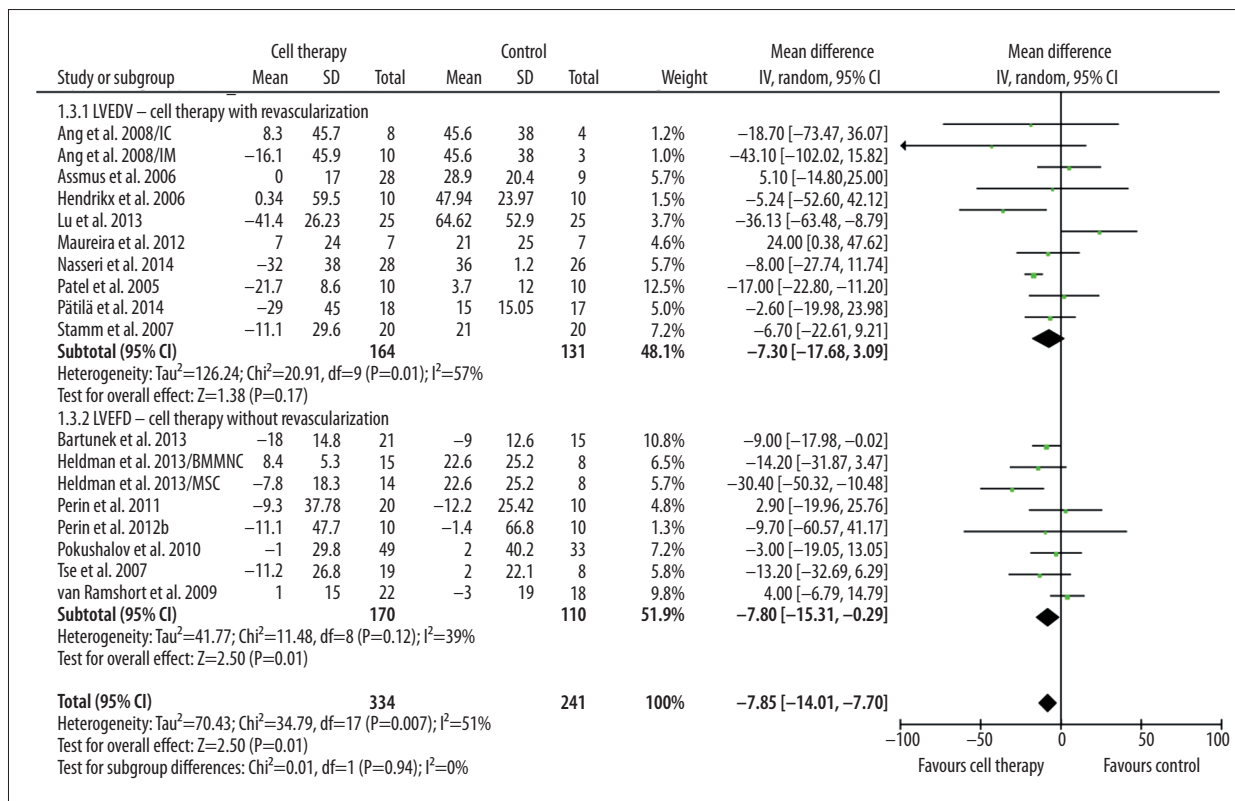


Figure 3. Meta-analysis of LVEDV improvement after therapy.

Table 1. Subgroup analysis of factors influencing efficacy of cell therapy.

Outcome	No. trials	Difference in mean [95% CI]	P	P-H	I ²	No. trials	Difference in mean (95% CI)	P	P-H	I ²	Group Comparison P value
IM						IC					
LVEF	17	4.77 [4.11, 5.44]	<0.00001	<0.00001	83%	5	1.00 [-0.11, 2.10]	0.08	0.001	78%	<0.00001
LVESV	13	-9.38 [-15.60, -3.17]	0.003	<0.00001	94%	3	-14.74 [-39.79, 10.31]	0.25	0.08	61%	0.68
LVEDV	15	-7.40 [-13.74, -1.06]	0.02	0.01	52%	3	-14.86 [-45.13, 15.41]	0.34	0.05	66%	0.64
BMMNC						MCS					
LVEF	18	4.33 [3.69, 4.96]	<0.00001	<0.00001	79%	3	1.32 [-0.00, 2.65]	0.05	<0.00001	95%	<0.0001
LVESV	15	-8.51 [-14.28, -2.74]	0.004	<0.00001	78%	2	-15.69 [-17.87, -13.52]	<0.00001	0.5	0%	0.02
LVEDV	15	-9.40 [-13.30, -5.50]	<0.00001	0.01	51%	2	-12.62 [-20.81, -4.43]	0.003	0.05	73%	0.49
Baseline LVEF <35.5%						Baseline LVEF ≥35.5%					
LVEF	9	5.11 [4.36, 5.86]	<0.00001	<0.00001	88%	11	1.93 [1.05, 2.81]	<0.00001	<0.00001	73%	<0.00001
LVESV	7	-14.34 [-24.60, -4.09]	0.006	<0.00001	97%	9	-7.89 [-11.23, -4.56]	0.001	<0.00001	93%	0.24
LVEDV	8	-12.96 [-17.24, -8.67]	0.001	0.16	32%	8	-3.81 [-10.00, 2.39]	0.34	0.03	54%	0.32

P – p value; P-H – P value of Q for heterogeneity test; I² >50%, high heterogeneity; Random effects model was used when P value of Q for heterogeneity test P-H >0.1 or I² >50%; otherwise, fixed effect model was used.

Table 2. Safety analysis of BMC transplantation.

	Safety outcome	No. of trials	Pooled risk ratio	95%CI	P-H	I ²	P
With revascularization	All-cause of death	9	0.61	0.20–1.84	0.30	18%	0.38
	Ventricular arrhythmia	10	1.32	0.43–4.08	0.48	0%	0.63
	Recurrent myocardial infarction	7	2.88	0.12–67.29	–	–	0.51
	Cerebrovascular accident	7	2.14	0.66–7.00	0.27	24%	0.21
Without revascularization	All-cause of death	8	0.30	0.12–0.77	0.43	0%	0.01
	Ventricular arrhythmia	7	0.45	0.10–1.98	0.51	0%	0.29
	Recurrent myocardial infarction	4	0.33	0.06–1.80	0.19	41%	0.20
	Cerebrovascular accident	2	0.30	0.03–2.74	0.93	0%	0.29

P – p value; P-H – P value of Q for heterogeneity test; I² >50%, high heterogeneity; Random effects model was used when P value of Q for heterogeneity test P-H >0.1 or I² >50%; otherwise, fixed effect model was used; “–” – not applicable.

significantly lower risk of all-cause death was observed in the subgroup without revascularization (RR: 0.30, 95% CI: 0.12 to 0.77, $P=0.01$), but not in the subgroup with revascularization. No death directly related to BMC transplantation was reported in either subgroup.

Discussion

For patients with CIHD, the goal of cell therapy is to achieve coronary neovascularization- and myocardial regeneration-based cardiac structural and functional improvement. LV function impairment is an important indicator of disease prognosis. Although previous meta-analyses explored the therapeutic effects and adverse events of BMCs compared with standard therapy, due to significant heterogeneity, small number of original trials and inconsistency of the findings, it is quite necessary to add outcomes new trials for better understanding of BMCs therapy.

To date, there is no available meta-analysis that explored the efficacy of BMCs-based cell therapy between patients with revascularizable and non-revascularizable CIHD. This meta-analysis of 20 RCTs showed that autologous transplantation of BMCs was safe and effective both for patients who were candidates for revascularization with CABG/PCI and those who were not. Findings of this study also indicated that for patients with no option for revascularization, single administration of BMCs could provide compatible effect in improving LV function, including increased LVEF and decreased LVEDV and LVESV compared with patients who received a combination of cell therapy and revascularization. Subgroup analysis found that the route of transplantation, baseline LVEF, and type of cells delivered could influence the efficacy of cell therapy. We found that IM injection was more beneficial to improve LVEF compared with IC injection (4.77% vs. 1.00%, $p<0.00001$). This finding is consistent that of Brunskill et al., who found that cell therapy through IM injection was associated with better effect [33]. This difference might be related to the higher proportion of cells retained in the heart through IM injection than through the IC route, which was confirmed by an animal study [34] and 1 small RCT [26]. Previous studies reported that cell therapy had better effect in patients with lower baseline LVEF [13,33]. Subgroup analysis of this study also found that patients with lower than average baseline LVEF ($<35.5\%$) had better therapeutic outcome (more LVEF improvement) than those with higher than average baseline (5.11% vs. 1.93%, $p<0.00001$). Furthermore, this study found that transplantation of BMMNCs had better effect in improving LVEF than did MCSs. However, due to the small number of trials based on MCSs ($n=3$), the reliability of this finding should be confirmed in future RCTs. As to LVEDV and LVESV, no significant difference was observed between paired subgroups. Pooled safety

assessment found that cell therapy significantly decreased all-cause death in the subgroup without revascularization. Other major adverse events were similar between cell therapy and control group in both subgroups.

The mechanisms by which BMCs contribute to cardiac repair and function improvement are still not fully understood. A previous study observed that BMCs could differentiate to cardiomyocytes in infarcted areas of the heart [35]. However, this was proven to be a minor mechanism because the process of transdifferentiation occurs very rarely in this situation [36]. The role of BMCs in impaired heart tissue could be multifunctional and multifactorial. Previous studies found that BMCs and bone marrow progenitor cells could secrete a series of cytokines that activate endogenous cardiac repair, such as activating resident cardiac progenitor cells and stimulating cardiomyocyte cell-cycle re-entry [37,38]. In addition, BMCs were involved in the process of neovascularization, inhibiting apoptosis of myocardial cells, and reducing inflammation through paracrine production of cytokines and growth factors [36,39,40]. However, how these mechanisms interact with each other and whether other mechanisms are involved is not clear. The exact and detailed mechanism should be explored in future research.

This study has several limitations. As observed in previous meta-analyses, this study also found a considerable degree of between-study heterogeneity. The high level of heterogeneity is closely related to patient baseline characteristics of each trial, route of transplantation, type and number of cell delivered, and methodology used to measure LV functional indicators. For example, a recent study indicated that use of low-dose mesenchymal stem cells (approximately 20×10^6 cells) was associated with the best effect in LV volume and LVEF increase [41]. However, the number of cells transplanted ranged from 10^6 to 10^8 in trials included in this meta-analysis. Secondly, in subgroup analysis, few trials assessed the effect of PCI and MCSs, which resulted in incompatible pooled sample size and thus might impair the reliability of observed phenomenon. Thirdly, most of the trials included had short-term follow-up (less than 1 year). The medium to long-term effect of cell therapy is still not quite clear.

Conclusions

In conclusion, the results of this meta-analysis suggest that transplantation of BMCs is a safe and effective therapy to improve left ventricular function both for patients who were candidates for revascularization with CABG/PCI and those who were not. Large clinical trials and long-term follow-up are required to confirm the benefits.

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