Published in final edited form as:

Am Heart J. 2020 February ; 220: 155–175. doi:10.1016/j.ahj.2019.09.005.

Meta-Analysis of Short- and Long-Term Efficacy of Mononuclear Cell Transplantation in Patients with Myocardial Infarction

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Abstract

Background—Mononuclear cells (MNCs) have been tested in clinical trials across multiple cardiovascular pathologies with mixed results. Major adverse cardiac events (MACE) and markers of cardiovascular capacity have been particularly challenging to interpret due to small size. This meta-analysis is aimed to assess the efficacy of MNC therapy in randomized clinical trials to identify the markers of efficiency that could influence future trial design.

Methods—PubMed, Embase, Cochrane library, and [ClinicalTrials.gov](https://clinicaltrials.gov) were searched from inception through November 8, 2018. Changes in left ventricular ejection fraction (LVEF) and infarct size (IS) from baseline to follow-up were selected as primary outcomes. Changes in the left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), BNP/NT-proBNP, 6-minute walk test (6MWT), NYHA class and MACE incidences were considered secondary outcomes.

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Conflicts of interest

All authors declared no conflicts of interest.

Results—In short-term follow-up, patients treated with MNCs demonstrated a significant increase in absolute LVEF of 2.21% (95% CI 1.59 to 2.83; $P < 0.001$; $I^2 = 32\%$) and 6.01% (95% CI 4.45 to 7.57; $P < 0.001$; $I^2 = 0\%$) in acute myocardial infarction (AMI) and ischemic cardiomyopathy (ICM) studies, respectively. This effect was sustained in long-term follow-up. MNC therapy significantly reduced LVESV; however, infarct size (IS), 6MWT, NYHA class, and MACE rates were comparable.

Conclusion—MNC therapy may convey a modest but sustained increase in LVEF in ICM patients, supporting further investigation. AMI trials, however, demonstrated minimal improvement in LVEF of unclear clinical significance, suggesting a limited role for MNC therapy in AMI.

Keywords

myocardial infarction; bone marrow mononuclear cells; cell therapy; clinical trial

Ischemic heart disease remains a leading cause of death worldwide despite remarkable advances in therapeutic approaches. In patients with myocardial infarction (MI) and chronic ischemic cardiomyopathy (ICM), progressive left ventricular (LV) dysfunction and cardiomyocyte death are major determinants of long-term prognosis; no therapeutic currently addresses this mechanism of disease progression¹. In hopes of solving this clinical need, mononuclear cells (MNCs), generally derived from human bone marrow, have been broadly tested in various forms of ischemic heart disease. Animal models demonstrated that long term engraftment of MNCs is weak, but therapeutic benefits are evident in the treated myocardium. This observation has led to the hypothesis that transplanted MNCs have paracrine effects that may convey pleiotropic effects, including anti-inflammatory, anti-fibrotic, and anti-apoptotic benefits to the ischemic myocardium².

Prior clinical experience with the harvest and therapeutic transplantation of autologous bone marrow for hematologic disorder made MNCs an attractive candidate for clinical trial as opposed to other subtypes of stem cells with less robust safety records. Experimental studies of MI have suggested that the MNCs improve LV function and attenuate LV remodeling³. Subsequent randomized clinical trials demonstrated that in the short term follow-up (≤ 6 months), MNCs delivered a modest but significant improvement in LV function in AMI patients^{4–8}. In contrast, other trials failed to show such benefit of MNCs compared to standard treatment^{9–12}. Furthermore, the data on LV function in the long term follow-up (> 6 months) are limited and contradictory.

To help clarify these conflicting results, we conducted a meta-analysis to evaluate the short (≤ 6 months) and long-term (> 6 months) effects of MNC therapy on LV function in patients with ischemic heart disease. In addition to the imaging outcomes, we also evaluated short- and long-term exercise tolerance and major adverse cardiac events (MACE).

Methods

Search strategy

The protocol for this study was prospectively registered with the PROSPERO database of systemic reviews (CRD42019126213). This research protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹³. Specifically, we performed a systematic search of relevant articles in the following databases: PubMed, Embase, the Cochrane library, and [ClinicalTrials.gov](https://www.clinicaltrials.gov), from inception through November 8, 2018. The search terms were used as follows: “mononuclear cell*”, “myocardial infarction”, “ischemic heart disease*”, “coronary artery disease*”, “coronary heart disease*”, and “clinical trial*”. We did not impose any language restrictions on our research. Also, we manually searched the reference lists of relevant articles.

Eligibility criteria

Eligible studies for the AMI or ICM groups in the present analysis were as follows: (1) RCTs; (2) transplanted cells were limited to the unsorted MNC cell type without using pretreated or engineered MNCs, but the cell dose, intervention timing or administration route were unrestricted; (3) patients with ST-segment elevation myocardial infarction (STEMI) and ischemic cardiomyopathy (ICM) with previous MI; (4) more than one month of follow-up were recorded.

Outcome measures

The primary outcomes were taken as changes in LVEF and IS from baseline to follow-up. Changes in the left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), BNP/NT-proBNP, 6-minute walk test (6MWT) time, NYHA class and the incidence of MACEs were considered the secondary outcomes. In several clinical trials, cardiac function was measured by more than one modality; magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) data were preferred over echocardiography and radionuclide angiography data.

Risk of bias

The study quality was assessed using a risk scale to evaluate the quality as low, unclear, or high risk as implemented in Review Manager (RevMan 5.3) software. Funnel plots were constructed to investigate possible publication bias, with Egger’s and Begg’s tests used to assess asymmetry.

Data extraction

Two investigators independently screened all studies and extracted the data using customized data extraction forms. Disagreements were resolved by a third investigator. The following data were extracted: first author, publication date, country, sample size, patient baseline characteristics, baseline LVEF, functional modality, follow-up duration, cell origin, cell source, cell dose, cell condition, delivery route, timing from acute MI (AMI)-PCI (days) or diagnosis of ischemic cardiomyopathy (months) to MNC therapy, LV function and structural outcomes (LVEF, LVESV, LVEDV), regenerative outcome (IS), performance status (6MWT

and NYHA), clinical outcomes (MACEs, all-cause death, non-fatal MI, re-hospitalization for heart failure, revascularization and arrhythmia) and BNP/NT-proBNP. Clinical trials with multiple publications and sequential follow-up durations were considered as a single study. Studies with a follow-up duration of ≤ 6 months were included in short-term effects and > 6 months in long-term outcomes.

The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting, and editing of the paper and its final contents. No extramural funding was used to support this work.

Statistical analysis

Outcome data were analyzed using RevMan 5.3 (Cochran Tech, London, UK). Fixed effects models were preferred unless heterogeneity extended beyond the expected outcome by chance. For continuous data, MNC treatment effects were presented as weighted mean difference (WMD) with 95% confidence intervals (CI) if outcomes were measured in the same way. For dichotomous data, MNC treatment effects were presented as odds ratio (OR) with 95% CI. The I^2 statistic was used to examine the heterogeneity within the different subgroups. Heterogeneity was defined as low (25% to 50%), moderate (50% to 75%), or high (>75%)¹⁴. Subgroup analyses were conducted based on MI status (AMI or ICM) and the longer follow-up (> 6 months and 1 year or >1 year) after cell infusion. In studies reporting the mean±standard error, mean with 95% CI, or mean±SD at baseline and follow-up, changes in SD were calculated with a standardized formula. Sensitivity analysis, and Egger's and Begg's tests were conducted using Stata 12 (StataCorp LP, College Station, TX). A level of 5% was used to determine statistical significance in all analyses.

Results

Search results

The initial search identified 1,202 records. After the exclusion of duplicates, screening of title/abstract, and inclusion of eligible records from the reference lists of relevant articles, 118 articles were selected for full-text review. Forty-nine randomized placebo-controlled trials were included in the initial analysis. Two articles excluded due to serial publications (Lunde et al. 2006 and Hirsch et al. 2011) and four due to relatively late and/or wide injection range (Karpov et al. 2005, 7 to 21; Nair et al. 2015, 7 to 21; Ryabov et al. 2017, 8 to 32; Traverse et al. 2011, 15.5 to 20) during the analysis. Finally, forty-three studies were analyzed in this analysis. Figure 1 shows the flow diagram of studies selection.

Study characteristics

Of the 43 included studies, all were RCTs from North America, South America, Asia, and Europe. The number of evaluated patients who received MNCs ranged from 11 to 125 patients and from 6 to 125 patients for the control (vehicle placebo) group. Follow-up duration ranged from 3 to 96 months. The average participant age in the 49 trials ranged from 48 to 67 years. Most participants were male. The mean age, gender, and baseline LVEF were similar between the treatment and control groups. The main characteristics of the studies are summarized in Table I.

Intervention characteristics

Of the 43 studies, 35 evaluated MNCs treatment in AMI^{4, 9–11, 15, 165–8} (all STEMI patients)^{17–34, 35–41} and 8 in ICM with previous MI^{42–49}. All studies used autologous bone-marrow-derived MNCs and delivered MNCs into the infarcted-related artery by infusion or intramyocardial injection < 24h after the bone marrow aspiration. The routes of MNC administration were intracoronary (IC, 36 studies), intramyocardial (IM, 5 studies), and transendocardial (TESI, 2 studies). Timing of MNC administration for studies evaluating the treatment of AMI was < 12 days after PCI or > 3 months for ICM studies. MNC's doses ranged from 40 to $2,640 \times 10^6$. Details on cell characterization are reported in Table II.

Primary outcomes

Left ventricular ejection fraction—A total of 31 short-term studies (n = 2149 patients) and 19 long-term studies (n = 1160 patients) reported data on LVEF that could be included in the meta-analysis. For the short-term follow-up (duration ≤ 6 months), initially, thirty-one AMI studies and five ICM studies were analyzed. One AMI study Naseri et al. 2018 was excluded due to a difference in route of MNC administration by (intramyocardium). One ICM study was excluded, Perin et al. 2012, because of end-point heterogeneity. Patients treated with MNCs had a modest but significant increase in absolute LVEF of 2.21% in AMI studies (95% CI 1.59 to 2.83; $P < 0.001$; $I^2 = 32\%$, Figure 2A) but a more significant increase of 6.01% in ICM studies (95% CI 4.45 to 7.57; $P < 0.001$; $I^2 = 0\%$, Figure 2A). In analysis of the long-term follow-up, eighteen AMI studies and three ICM studies were examined. Two long-term studies (one AMI and one ICM) were subsequently excluded due to adding significant heterogeneity (Lamirault et al. 2017 and from Pätälä et al. 2014), and one long-term AMI study was subsequently excluded due to a difference in route (intramyocardial) of MNC administration (Naseri et al. 2018). A subgroup analysis was conducted in long-term studies for which both ≤ 1 year and > 1-year follow-up durations were available. In long-term AMI sub-analyses, LVEF increased significantly after MNC infusion at ≤ 1 year (3.68% increase, 95% CI 2.49 to 4.88; $P < 0.001$; $I^2 = 22\%$, Figure 3A), and this improvement was sustained in follow-up of > 1 year (2.09% increase, 95% CI 0.89 to 3.28; $P < 0.001$; $I^2 = 28\%$, Figure 3A). In long-term ICM studies, the analysis showed a similarly sustained and significant increase in LVEF of 6.25% in MNC-treated patients (95% CI 5.32 to 7.19; $P < 0.001$; $I^2 = 0\%$, Figure 3A).

In order to take the dose of MNC administration into consideration, we did subgroup analyses of the dosage in AMI studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs), “high” (H, ≥ 600 million MNCs) dose subgroups. For the short-term AMI studies, the VL dose group exhibited a significant increase in LVEF of 3.03% (95% CI 1.45 to 2.65; $P < 0.001$; $I^2 = 35\%$, Figure 2B), the L dose group had a 1.93% increase (95% CI 1.16 to 2.70; $P < 0.001$; $I^2 = 15\%$, Figure 2B), and the M dose group had a 3.08% increase (95% CI 1.61 to 4.56; $P < 0.001$; $I^2 = 0\%$, Figure 2B); whereas the H dose group did not (WMD −1.93%, 95% CI −6.42 to 2.56; $P = 0.40$; $I^2 = 0\%$, Figure 2B). Two studies were excluded due to the high heterogeneity (Wöhrle et al. 2010 in the M dose and Meyer et al. 2009 in the H dose). In long-term AMI sub-analyses, LVEF increased significantly after relatively lower doses of MNC infusion at ≤ 1 year, with a 2.57% increase

in the VL dose (95% CI 0.67 to 4.48; $P = 0.008$; $I^2 = 0\%$, Figure 3B), 3.44% increase in the L dose (95% CI 1.42 to 5.45; $P < 0.001$; $I^2 = 0\%$, Figure 3B) and 4.31% increase in the M dose (95% CI 1.61 to 7.02; $P < 0.001$; $I^2 = 0\%$, Figure 3B) and this improvement was observed in follow-up of > 1 year in the L dose (3.93% increase, 95% CI 2.06 to 5.80; $P < 0.001$; $I^2 = 0\%$, Figure 3B) but did not in the H dose (WMD 1.56%, 95% CI -3.06 to 6.18; $P = 0.51$; $I^2 = 0\%$, Figure 3B). One study from Turan et al. 2012 at 1 year in the VL dose and two studies from Delewi et al. 2015 and Traverse et al. 2018 in follow-up of > 1 year in the L dose were excluded due to the high heterogeneity. However, there were not sufficient numbers of ICM studies to do the similar dose subgroup analyses.

For the timing of administration, the timing of MNC injection was < 12 days in the AMI studies included in this analysis. For routes of MNC administration, all AMI studies included in meta-analyses investigated IC as a route of delivery after excluding one study using IM delivery. Of four short-term ICM studies, three investigated the IM route of delivery, and one studied the IC, but no heterogeneity was found when pooling these studies together. Besides, there was no heterogeneity in two long-term ICM studies.

To test whether our results were being unduly influenced by underpowered trials, we performed subgroup analyses where we only included studies with enough patients to offer $> 90\%$ statistical power based on the effect sizes calculated in our meta-analysis. For short-term outcomes, thirteen AMI studies (sample size > 37 in MNC) and three ICM studies (sample size > 17 in MNC) were analyzed for the efficacy of MNC treatment on LVEF difference. In AMI trials, we found that the measured effect of MNC therapy was attenuated showing a statistically significant but clinically trivial increase in LVEF of 1.89% in AMI studies (95% CI 1.08 to 2.70; $P < 0.001$; $I^2 = 39\%$, Figure 2C). ICM trials, however, showed a greater improvement in LVEF of 5.76% (95% CI 4.14 to 7.38; $P < 0.001$; $I^2 = 0\%$, Figure 2C). For the long-term follow-up, five AMI studies 1 year (sample size > 23 in MNC), six AMI studies > 1 year (sample size > 26 in MNC) and two ICM studies (sample size > 18 in MNC) were examined to assess the efficacy of MNC therapy for improving LVEF. LVEF increased significantly after MNC infusion at 1 year (2.68% increase, 95% CI 1.15 to 4.21; $P < 0.001$; $I^2 = 0\%$, Figure 3D), and this improvement was sustained in the follow-up of > 1 year (2.06% increase, 95% CI 0.86 to 3.26; $P < 0.001$; $I^2 = 39\%$, Figure 3D). In long-term ICM studies, the result of the analysis was the same, as shown in Figure A.

Infarct size.—Eight AMI studies ($n = 547$ patients) were examined to assess the short-term efficacy of MNCs therapy for reducing infarct size (IS). A trend toward a reduction in IS of 1.67% of LV mass was observed, but this difference was not statistically significant (95% CI -3.79 to 0.45; $P = 0.12$; $I^2 = 51\%$, Figure 4A). Similarly, no significant difference in IS was observed after longer (> 1 year) follow-up after infusion of MNCs in AMI studies (WMD -2.52% , 95% CI -7.33 to 2.30; $P = 0.31$; $I^2 = 83\%$, Figure 5A) or ICM studies (WMD -11.01% , 95% CI -26.96 to 4.94; $P = 0.18$; $I^2 = 78\%$, Figure 5A).

We performed subgroup analyses to assess the influence of dose on the therapeutic efficacy of MNCs in the reduction of IS in AMI short-term studies (Figure 4B). No significant difference in IS was observed in different dose groups with no heterogeneity after excluding two studies from Choudry et al. 2016 and Turan et al. 2012 in the VL dose. However, there

was a significant reduction in IS in follow-up of 1 year in the VL dose (5.55% decrease, 95% CI -10.45 to -0.65; $P = 0.03$; $I^2 = 55\%$, Figure 5B) after excluding one heterogeneous study from Choudry et al. 2016, indicating that the lower dose of MNC therapy may have favorable effects.

All AMI studies used IC as a route of delivery. The timing of MNC injection was < 12 days in included AMI studies. No short-term ICM study was available, and just two long-term ICM studies investigated the IS, which makes it challenging to make a comparison.

Secondary outcomes

Safety—In AMI studies, there was no significant difference in the incidence of MACE event whether the follow-up was 6 months (OR 0.68, 95% CI 0.34 to 1.36; $P = 0.27$; $I^2 = 24\%$, Figure 6) after excluding one study from Traverse et al. 2011 due to late timing of MNCs administration; 1 year (OR 1.20, 95% CI 0.64 to 2.23; $P = 0.57$; $I^2 = 0\%$) or > 1 year (OR 0.93, 95% CI 0.52 to 1.67; $P = 0.80$; $I^2 = 0\%$) after MNCs administration when excluding two heterogeneous AMI studies (Huang et al. 2015 and Schächinger et al. 2006) and one wide range of timing from Ryabov et al. 201 (Figure 7). Only one study from Heldman et al. 2014 was analyzed in ICM without a difference between treatment and control (Figure 7). No inherent confounders were found in these analyses. These findings indicated that unsorted MNC treatment is safe for patients with MI.

Performance status—Three ICM studies ($n = 192$ patients) and no AMI study included reported the results of the 6MWT in the 6 months follow-up period. There was no significant difference in 6MWT in ICM studies between the MNC and control groups (3 studies, WMD 39.96, 95% CI -50.22 to 130.14; $P = 0.39$; $I^2 = 96\%$, Figure 8). In the long-term effect of MNCs therapy, two ICM studies showed no difference in 6MWT (2 studies, WMD 94.07, 95% CI -67.02 to 255.16; $P = 0.25$; $I^2 = 98\%$, Figure 9).

With regard to NYHA class, two ICM studies evaluated the short-term effect of MNC therapy (2 studies, OR 10.54, 95% CI 1.12 to 98.86; $P = 0.04$; $I^2 = 76\%$). Four studies (2 AMI and 2 ICM studies) reported improved NYHA class during a follow-up > 6 months after MNC infusion. No significant difference was observed in long-term NYHA class (2 AMI studies, OR 1.02, 95% CI 0.34 to 3.04; $P = 0.97$; $I^2 = 23\%$, Figure 10; and 2 ICM studies, OR 4.99, 95% CI 0.46 to 54.04; $P = 0.19$; $I^2 = 85\%$, Figure 11).

The heterogeneity among the analyses of performance status was high; however, there were not sufficient numbers of studies to do a subgroup analysis.

Other secondary outcomes

Mean changes in LVESV, LVEDV, BNP/NT-proBNP from baseline were assessed. Compared to the controls, infusion of MNCs led to a significant decrease in LVESV of 4.20ml (95% CI -5.78 to -2.63; $P < 0.001$; $I^2 = 48\%$, Figure 12A) after 6 months of follow-up, as well as after long-term > 6 months and 1 year follow-up (WMD -9.28, 95% CI -13.65 to -4.90; $P < 0.001$; $I^2 = 44\%$, Figure 13A) when excluding one significantly heterogeneous study from Yao et al. 2009 and > 1 year follow-up (WMD -6.21, 95% CI -9.78 to -2.63; $P < 0.001$; $I^2 = 0\%$, Figure 13A) in AMI studies. Also, the efficacy of MNC

in the reduction of LVESV was analyzed in ICM studies, with one short-term study from Pokushalov et al. favoring MNC treatment (Figure 12A) as well as three long-term studies (WMD -31.27 , 95% CI -42.91 to -19.63 ; $P < 0.001$; $I^2 = 11\%$, Figure 13A). No significant decrease in LVEDV was observed in patients treated with MNCs compared to controls regardless of whether the follow-up period was ≤ 6 months (Figure 14) or > 6 months in both AMI studies and ICM studies (Figure 15).

To clarify whether the dose influences volume changes, subgroup analyses were performed. For the short-term AMI studies, significant improvements were seen in both L dose (WMD -6.6 , 95% CI -9.11 to -4.10 ; $P < 0.001$; $I^2 = 9\%$, Figure 12B) and M dose (WMD -9.51 , 95% CI -14.33 to -4.68 ; $P < 0.001$; $I^2 = 0\%$, Figure 12B), but did not in the VL dose (WMD -0.94 , 95% CI -6.08 to 4.19 ; $P = 0.72$; $I^2 = 0\%$, Figure 12B) and in the H dose (WMD -1.0 , 95% CI -18.48 to 16.48 ; $P = 0.91$; $I^2 = 0\%$, Figure 12B) after excluding three heterogeneous studies. In the long-term AMI studies, the improvement effect in LVESV was sustained in the L dose (WMD -19.37 , 95% CI -32.41 to -6.33 ; $P = 0.004$; $I^2 = 0\%$, Figure 13B) as well as in the M dose (WMD -13.23 , 95% CI -20.53 to -5.93 ; $P < 0.001$; $I^2 = 0\%$, Figure 13B). Also, we did subgroup analyses for studies with statistical power. The results were stable, and the trend was similar, as shown in Figure 12A and 13A (Figure 12C and 13D). No significant difference was found in LVEDV changes in AMI studies when comparing the different doses of administration (Figure 14–15). For the route of delivery, all AMI studies were analyzed based on the IC delivery and timing of administration < 12 days relative to the timing of MI. Too few ICM studies were available to allow for independent analyses of dose.

A significant reduction in BNP was observed after < 6 months of follow-up (579.18 pg/ml [95% CI -723.47 to -434.89 ; $P < 0.001$; $I^2 = 0\%$; Figure 16]) and a significant reduction in NT-proBNP was seen after > 6 months of follow-up (SMD -0.35 95% CI -0.64 to -0.05 ; $P = 0.02$; $I^2 = 0\%$, Figure 17) in AMI studies.

Risk of bias assessment

The methodological quality of the enrolled studies was assessed using key indicators, as shown in Table III. All studies reported the method of randomization, and at least 29% of randomized patients were analyzed concerning the outcomes of the blinded analysis. No visually apparent asymmetry was present in the funnel plot of LVEF (Figure 18).

Discussion

In this meta-analysis, we found that autologous bone marrow-derived MNCs infusion after MI is associated with a modest but statistically significant improvement in LVEF and a reduction in LVESV in both short and long-term follow-up. In sub-analysis, ICM studies showed more favorable results than AMI studies in LVEF improvement and LVESV reduction. Relatively lower doses of MNCs administration seem to be more effective than the extremely high dose. There was a favorable trend toward reduced IS, but without changes in LVEDV, 6MWT, NYHA class, or MACE rate. Additionally, we found a reduction in BNP or NT-proBNP levels after MNCs treatment in AMI studies.

A previous meta-analysis by Delewi *et al.*⁵⁰ in 2013 involving 24 studies and 1546 subjects demonstrated that intracoronary bone marrow cell infusion leads to a moderate increase in LVEF and a decrease in LVESV at 6 months that persisted at the 12 months follow-up. Consistent with their results, our meta-analysis indicates that MNCs may be an effective therapy for improving cardiac function, as shown by an increase in LVEF and a reduction in LVESV, in patients with MI after 1 year of follow-up. A large number of studies included in our analysis allowed us to demonstrate persistent favorable effects on LVEF and LVESV after 12 months. Admittedly, the effect of MNC infusion on LVEF and LVESV appears modest, and some would say clinically insignificant, but it should be noted that the standard treatment such as direct revascularization (PCI) or standard therapy also had little effect on LVEF and LVESV in seminal trials^{51–53}. For example, PCI was approved for the treatment of AMI based on studies showing a modest increase in LVEF from baseline to 13 months. Given that both LVEF and LVESV are powerful predictors of cardiac outcomes in patients with AMI following PCI reperfusion and subsequent secondary prevention⁵⁴, these long-term benefits support the use of MNC therapy.

In the further sub-analysis, ICM studies showed more favorable results than AMI studies in LVEF improvement and LVESV reduction, which may be due to the different routes of MNC delivery or inherent differences in the underlying pathology. In AMI studies, IC was the most popular route of MNC delivery and only one study investigated the IM route of delivery; however, IM and TESI are the main routes of MNC delivery in ICM studies. A prior meta-analysis conducted by Kanelidis *et al.*⁵⁵ demonstrated that the way of delivery modulates the efficacy of mesenchymal stem cell therapy in preclinical and clinical studies with TESI and IM providing more favorable results. Considering the small number of ICM clinical trials, a comparison for the route of delivery is currently not possible. Future studies are needed to test the optimal route of MNC administration.

Importantly, the results of our study demonstrate that MACE tended to be less common in the MNC group at 12 months of follow-up, suggesting the MNC infusion may improve clinical outcomes after MI. However, this favorable effect was no longer significant after 12 months. More extensive randomized trials with primary clinical endpoints, such as the BAM1 trial, should elucidate whether MNC therapy decreases MACE after acute MI⁵⁶.

The main limitation of this analysis is the clinical heterogeneity across trials, particularly with regard to cell dosage, the timing of infusion, and imaging modalities. However, the overall end-point heterogeneity was not high, and no significant publication bias was seen in this meta-analysis. Another limitation is the smaller number of patients available for analysis of performance status and functional biomarkers. There was a trend toward beneficial effects of MNC therapy on these variables, but the strength of our statistical analysis is very limited by the small sample size.

Conclusion

In summary, we demonstrate that, after MI, MNC therapy may deliver a modest increase in LVEF and reduction in LVESV at 6 months that is sustained after 12 months of follow-up. ICM studies appear to be more promising than AMI studies in LVEF improvement and

LVESV reduction, which may be due to the different routes of MNC delivery. Relatively lower doses of MNCs administered exhibited more favorable outcomes than the highest dose. Meta-analyses cannot be used to make conclusions regarding the efficacy of a therapy. These results suggest that further investigation is warranted and well-designed, adequately powered RCTs using optimized delivery, and doses may prove MNCs to be valuable therapeutic modality in ischemic heart disease.

Acknowledgments

We gratefully acknowledge the valuable contribution of Junle Dong, MD, for his help with Data preparation.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Number 81700278, DY), and by the State Scholarship Fund (China, NO.201808110124, DY). National Institute of Health (NIH/NHLBI) UM-1 L12026 (PY), NIH/NHLBI 1K24 HL130553K (PY), NIH/NHLBI HL078825 (PY) and UM1 HL113530 (RB).

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Figure 1.
Flow diagram of studies included in this analysis. MI myocardial infarction, MNCs mononuclear cells.

Figure 2A.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of left ventricular ejection fraction (LVEF) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 2B.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of left ventricular ejection fraction (LVEF) based on dose in the short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs), “high” (H, 600 million MNCs) dose subgroups.

Figure 2C.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of left ventricular ejection fraction (LVEF) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies with a relatively strong power (p-AMI) and chronic ischemic cardiomyopathy (ICM) studies with a relatively strong power (p-AMI).

Figure 3A.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of left ventricular ejection fraction (LVEF) based on the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 3B.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of left ventricular ejection fraction (LVEF) based on dose in the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs), “high” (H, 600 million MNCs) dose subgroups.

Figure 3C.

Grouped plot of mean with error bars of mononuclear cells (MNCs) therapy on the improvement of left ventricular ejection fraction (LVEF) based on dose changes in short- and long-term follow-up of duration in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs), “high” (H, 600 million MNCs) dose subgroups.

Figure 3D.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of left ventricular ejection fraction (LVEF) based on the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies with a relatively strong power (p-AMI) and chronic ischemic cardiomyopathy (ICM) studies with a relatively strong power (p-AMI).

Figure 4A.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of infarct size (IS) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies.

Figure 4B.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of infarct size (IS) based on dose in the short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs) dose subgroups.

Figure 5A.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of infarct size (IS) based on 1 year of follow-up duration in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 5B.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of infarct size (IS) based on dose in the 1 year of follow-up duration in acute myocardial infarction (AMI) studies with “very low” (VL, < 100 million MNCs) doses.

Figure 6.

Forest plot of odds ratio (OR, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of major adverse cardiac events (MACEs) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies.

Figure 7.

Forest plot of odds ratio (OR, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of major adverse cardiac events (MACEs) based on the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 8.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of 6-minute walk distance (6MWT) based on short-term follow-up (duration 6 months) in chronic ischemic cardiomyopathy (ICM) studies.

Figure 9.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of 6-minute walk distance (6MWT) based on long-term follow-up (duration > 6 months) in chronic ischemic cardiomyopathy (ICM) studies.

Figure 10.

Forest plot of odds ratio (OR, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of New York Heart Association (NYHA) functional classification based on short-term follow-up (duration 6 months) in chronic ischemic cardiomyopathy (ICM) studies.

Figure 11.

Forest plot of odds ratio (OR, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the improvement of New York Heart Association (NYHA) functional classification based on long-term follow-up (duration > 6 months) in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 12A.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-systolic volume (LVESV) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 12B.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-systolic volume (LVESV) based on dose in the short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs), “high” (H, 600 million MNCs million MNCs) dose subgroups.

Figure 12C.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-systolic volume (LVESV) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies with a relatively strong power (p-AMI) and chronic ischemic cardiomyopathy (ICM) studies.

Figure 13A.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-systolic volume (LVESV) based on the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 13B.

Forest plot of mean difference (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-systolic volume (LVESV) based on dose in the long-term follow-up of duration: > 6 months but ≤ 1 year in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs) dose subgroups.

Figure 13C.

Grouped plot of mean with error bars of mononuclear cells (MNCs) therapy on the reduction of left ventricular end-systolic volume (LVESV) based on dose changes in short- and long-term follow-up (≤ 1 year) of duration in acute myocardial infarction (AMI) studies by dividing the studies into “very low” (VL, < 100 million MNCs), “low” (L, 100 but < 300 million MNCs), “medium” (M, 300 but < 600 million MNCs), “high” (H, ≥ 600 million MNCs) dose subgroups.

Figure 13D.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-systolic volume (LVESV) based on the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies with a relatively strong power (p-AMI) and chronic ischemic cardiomyopathy (ICM) studies with a relatively strong power (p-AMI).

Figure 14.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-diastolic volume (LVEDV) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 15.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of left ventricular end-diastolic volume (LVEDV) based on the long-term follow-up of duration: > 6 months 1 year and > 1 year in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 16.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of brain natriuretic peptide (BNP) based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Figure 17.

Forest plot of (MD, with 95% confidence interval [CI]) of mononuclear cells (MNCs) or control on the reduction of N-terminal pro-B-type natriuretic peptide (NT-proBNP) based on long-term follow-up (duration > 6 months) in acute myocardial infarction (AMI) studies.

Figure 18.

Funnel plot for left ventricular ejection fraction outcome data of the included studies based on short-term follow-up (duration 6 months) in acute myocardial infarction (AMI) studies and chronic ischemic cardiomyopathy (ICM) studies.

Table I.

Characteristics of studies included in this analysis

Study	Country	Sample size		Mean age(yrs)		Male(%)		Baseline LVEF(%) mean(SD)		Tool	Follow-up Duration (month)
		MNC	CO	MNC	CO	MNC	CO	MNC	CO		
Beitnes et al. 2011 ⁹	Norway	50	50	58	57	84	84	45.7	46.9	Echo	3,6,12,36
Cao et al. 2009 ⁴	China	41	45	51	51	95	93	39	38.6	Echo	1,3,6,12,48
Choudry et al. 2016 ¹⁰	UK	55	45	56	57	85	91	47.8	48.9	MRI	3,12
Delewi et al. 2014 ¹¹	Netherlands	69	65	56	55	84	86	43.7	42.4	MRI	4,24
Duan et al. 2015 ⁴²	China	24	18	58	57	95	94	36.04	34.6	Echo	12
Ge et al. 2006 ¹⁵	China	10	10	58	59	80	10	56	58	Echo	6
Grajek et al. 2010 ¹⁶	Poland	31	14	51	50	87	86	50.32	50.84	Echo	3,6,12
Heldman et al. 2014 ⁴³	USA	19	10	61	61	89.5	100	35.9	36.2	MRI or CT	6,12
Hu et al. 2011 ⁴⁴	China	31	29	57	58	93	93	22.78	24.9	MRI	6
Hu et al. 2015 ¹⁷	China	11	14	61	61	81.8	64	56.9	57.	Echo	6,12
Huang et al. 2015 ⁵	China	27	25	60	59	93	88	44.7	43.5	Echo	6,12
Huikuri et al. 2008 ¹⁸	Finland	40	40	60	59	90	85	56	57	Echo or LV angio	6
Janssens et al. 2006 ¹⁹	Belgium	33	34	56	58	82	82	48.5	46.9	MRI	4
Jin et al. 2008 ²⁰	China	14	12	62	61	71	75	54.29	55.83	Echo	6,12
Lamirault et al. 2017 ²¹	France	52	49	56	55	81	90	38	40	Echo	3,12
Meluzín et al. 2006 ⁶	Czech	22	22	55	55	86	91	41	42	Echo or SPECT	3
Meyer et al. 2009 ²²	Germany	30	30	53	59	67	73	50.0	51.3	MRI	6,18,61
Naseri et al. 2018 ²³	Iran	30	26	56	55	90	89	39.64	39.64	SPECT	6,18
Nicolau et al. 2018 ²⁴	Brazil	66	55	59	59	93	93	44.66	42.3	MRI	6
Nogueira et al. 2009 ²⁵	Brazil	14	6	60	57	71	67	48.26	47.59	Echo	3,6
Panovsky et al. 2008 ²⁶	Czech	17	17	55	55	88	88	35	35	Echo or SPECT	3
Pätälä et al. 2014 ⁴⁵	Finland	20	19	65	64	95	95	37.2	36.4	MRI	12
Penicka et al. 2007 ²⁷	Czech	17	10	59	59	81	81	39	39	Echo	4
Perin et al. 2012 ⁴⁶	USA	61	31	64	62	87	93	32.43	30.19	Echo	6
Piepoli et al. 2010 ²⁸	Italy	19	19	63	67	68	68	38.9	38.4	Echo or SPECT	3,6,12
Plewka et al. 2009 ²⁹	Poland	38	18	56	56	68	78	35	33	Echo	6
Plewka et al. 2011 ³⁰	Poland	40	20	56	56	67	75	35	33	Echo	1,6,12,24
Pokushalov et al. 2010 ⁴⁷	USA	55	54	61	62	87	85	27.8	26.8	SPECT	3,6,12
Roncalli et al. 2011 ³¹	France	52	49	56	55	81	90	37	38.7	MRI	3
San Roman et al. 2015 ³²	Spain	30	31	54	57	97	90	49	47	MRI	12

Study	Country	Sample size		Mean age(yrs)		Male(%)		Baseline LVEF(%) mean(SD)		Tool	Follow-up Duration (month)
		MNC	CO	MNC	CO	MNC	CO	MNC	CO		
Schächinger et al.2006 ⁷	Germany	101	10	55	57	82	82	47.5	46.7	LV angio	4,12
Silva et al. 2009 ³³	Brazil	14	6	60	57	71	67	40.96	40.14	RNV	3,6
Skalicka et al. 2012 ³⁴	Czech	17	10	61	54	71	100	39.2	39.4	Echo or SPECT	4,24
Sürder et al.2013 ³⁵	Switzerland	65	67	55	56	86.2	83.6	34.6	39.6	MRI	4
Sürder et al.2016 ³⁶	Switzerland	66	67	55	56	86	84	35	40	MRI	4,12
Tendera et al.2009 ³⁷	Poland	80	40	55	59	71	75	37	39	MRI	6
Traverse et al.2010 ³⁹	USA	30	10	53	58	83	60	49	48.6	Echo or MRI	3,6
Traverse et al. 2018 ³⁸	USA	58	27	56	56	88	86	45.9	46.9	MRI	6,12,24
Turan et al. 2012 ⁴⁰	Germany	42	20	61	60	67	70	43	45	LV angio	3,6,12
Wang et al. 2015 ⁴⁸	China	45	45	61	63	82	78	39.31	38.19	Echo	6
Wöhrle et al. 2010 ⁴¹	Germany	29	13	61	61	90	62	53.5	55.7	MRI	1,3,6
Yao et al. 2009 ⁸	China	12	12	52	53	83	92	32.5	32.3	MRI	6,12
Zhao et al. 2008 ⁴⁹	China	18	18	60	59	83	83	35.8	36.73	Echo	3,6

Abbreviations: MNC, mononuclear cell; CO, control; MRI, magnetic resonance image; CT, computed tomography; LV angio, left ventricular angiography; NA, not available; SPECT, single photon emission computed tomography.

Table II.

Characteristics of autologous BM-MNC cell therapy interventions

Study	Cell dose (million)	Time from aspiration to delivery	Delivery route	Timing from AMI-PCI (days) or ICM (months) to MNC therapy
Beitnes et al. 2011 ⁹	68	<24h	IC	AMI-PCI 5 to 8
Cao et al. 2009 ⁴	125	<24h	IC	AMI-PCI 7
Choudry et al. 2016 ¹⁰	60	5.5	IC	AMI-PCI<1
Delewi et al. 2015 ¹¹	296	6.3	IC	AMI-PCI 8
Duan et al. 2015 ⁴²	130	<24h	CABG-IC	MI-ICM>3
Ge et al. 2006 ¹⁵	40	<24h	IC	AMI-PCI <1
Grajek et al. 2010 ¹⁶	410	24h	IC	AMI-PCI 4 to 6
Heldman et al.2014 ⁴³	200	4h	TESI	MI-ICM>84
Hu et al. 2011 ⁴⁴	130	<24h	CABG-IC	MI-ICM>3
Hu et al. 2015 ¹⁷	100	24h	IC	AMI-PCI 3 to 5
Huang et al. 2015 ⁵	480	2h	IC	AMI-PCI <1
Huikuri et al. 2008 ¹⁸	402	6h	IC	AMI 2 to 6
Janssens et al. 2006 ¹⁹	300	4 to 6h	IC	AMI-PCI 1
Jinet al. 2008 ²⁰	63	<24h	IC	AMI-PCI<1
Lamirault et al.2017 ²¹	98	5h	IC	AMI-PCI 7 to 11
Meluzín et al. 2006 ⁶	100	20 to 21h	IC	AMI-PCI 5 to 9
Meyer et al.2009 ²²	2500	6 to 8h	IC	AMI-PCI 4 to 8
Naseri et al. 2018 ²³	564	24h	CABG-IM	CABG-IM
Nicolau et al. 2018 ²⁴	100	6h	IC	AMI-PCI 6 to 9
Nogueira et al. 2009 ²⁵	100	8.5h	IC	AMI-PCI 4 to 7
Panovsky et al. 2008 ²⁶	100	20 to 21h	IC	AMI-PCI 5 to 9
Pättilä et al. 2014 ⁴⁵	840	<24h	CABG-IM	MI-ICM
Penicka et al. 2007 ²⁷	2640	<24h	IC	AMI-PCI 4 to 11
Perin et al. 2012 ⁴⁶	100	12h	TESI	MI-ICM
Piepoli et al.2010 ²⁸	249	<24h	IC	AMI-PCI 4 to 7
Plewka et al. 2009 ²⁹	144	NA	IC	AMI-PCI 5 to 9
Plewka et al. 2011 ³⁰	144	2h	IC	AMI-PCI 7
Pokushalov et al. 2010 ⁴⁷	41	<24h	IM	MI-ICM>12
Roncalliet al. 2011 ³¹	98	5h	IC	AMI-PCI 7 to 11
San Roman et al. 2015 ³²	83	<24h	IC	AMI-PCI 3 to 5
Schächinger et al. 2006 ⁷	236	<24h	IC	AMI-PCI 3 to 7
Silva et al. 2009 ³³	93.69	8.5h	IC	AMI-PCI 4 to 7
Skalicka et al. 2012 ³⁴	2640	<24h	IC	AMI-PCI 4 to 11
Sürder et al.2013 ³⁵	160	<24h	IC	AMI-PCI 5 to 7
Sürder et al.2016 ³⁶	160	<24h	IC	AMI-PCI 5 to 7
Tendera et al.2009 ³⁷	178	>24h	IC	AMI-PCI 3 to 12

Study	Cell dose (million)	Time from aspiration to delivery	Delivery route	Timing from AMI-PCI (days) or ICM (months) to MNC therapy
Traverse et al. 2010 ³⁹	100	<24h	IC	AMI-PCI 4 to 7
Traverse et al. 2018 ³⁸	146	9h	IC	AMI-PCI 3 to 7
Turan et al. 2012 ⁴⁰	96	<24h	IC	AMI 7
Wang et al. 2015 ⁴⁸	521	<24h	CABG-IM	MI-ICM>12
Wöhrle et al. 2010 ⁴¹	381	6h	IC	AMI-PCI 5 to 7
Yao et al. 2009 ⁸	190	3h	IC	AMI-PCI 3 to 7
Zhao et al. 2008 ⁴⁹	659	<24h	IM	MI-ICM>12

Abbreviations: MNC, mononuclear cell; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; ICM, ischemic cardiomyopathy; BM, bone marrow; Auto, autologous; IC, intracoronary; CABG, coronary artery bypass graft; TESI, transendocardial stem cell injection; IM, intramyocardial.

Table III.

Methodological quality assessment of included studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attention bias)	Selective reporting (reporting bias)
Beitnes et al. 2011 ⁹	L	L	U	U	L	L
Cao et al. 2009 ⁴	L	L	U	U	L	L
Choudry et al. 2016 ¹⁰	L	L	L	L	L	L
Delewi et al. 2014 ¹¹	L	L	U	U	L	L
Duan et al. 2015 ⁴²	L	L	L	L	L	L
Ge et al. 2006 ¹⁵	L	L	U	U	L	L
Grajek et al. 2010 ¹⁶	L	L	U	U	H	U
Heldman et al. 2014 ⁴³	L	L	L	L	L	L
Hu et al. 2011 ⁴⁴	L	L	L	L	L	L
Hu et al. 2015 ¹⁷	L	L	L	L	L	L
Huang et al. 2015 ⁵	L	L	H	H	L	L
Huikuri et al. 2008 ¹⁸	L	L	U	U	L	L
Janssens et al. 2006 ¹⁹	L	L	L	L	L	L
Jin et al. 2008 ²⁰	L	L	U	U	L	L
Lamirault et al. 2017 ²¹	L	L	U	U	L	L
Meluzín et al. 2006 ⁶	L	L	U	U	L	L
Meyer et al. 2009 ²²	L	L	U	U	L	L
Naseri et al. 2018 ²³	L	L	L	L	L	L
Nicolau et al. 2018 ²⁴	L	L	L	L	L	L
Nogueira et al. 2009 ²⁵	L	L	U	U	L	L
Panovsky et al. 2008 ²⁶	L	L	U	U	L	L
Pätilä et al. 2014 ⁴⁵	L	L	L	L	L	L
Penicka et al. 2007 ²⁷	L	L	U	U	H	U
Perin et al. 2012 ⁴⁶	L	L	L	L	L	L
Piepoli et al. 2010 ²⁸	L	L	U	U	L	L
Plewka et al. 2009 ²⁹	L	L	U	U	L	L
Plewka et al. 2011 ³⁰	L	L	U	U	L	L
Pokushalov et al. 2010 ⁴⁷	L	L	U	U	L	L
Roncalli et al. 2011 ³¹	L	L	U	U	L	L
San Roman et al. 2015 ³²	L	L	U	U	L	L
Schächinger et al. 2006 ⁷	L	L	U	U	L	L
Silva et al. 2009 ³³	L	L	H	H	L	L
Skalicka et al. 2012 ³⁴	L	L	U	U	L	L
Sürder et al. 2013 ³⁵	L	L	H	H	L	L
Sürder et al. 2016 ³⁶	L	L	H	H	L	L

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attention bias)	Selective reporting (reporting bias)
Tendera et al. 2009 ³⁷	L	L	U	U	L	L
Traverse et al. 2010 ³⁹	L	L	L	L	L	L
Traverse et al. 2018 ³⁸	L	L	L	L	L	L
Turan et al. 2012 ⁴⁰	L	L	U	U	L	L
Wang et al. 2015 ⁴⁸	L	L	U	U	L	L
Wöhrle et al. 2010 ⁴¹	L	L	L	L	L	L
Yao et al. 2009 ⁸	L	L	U	U	L	L
Zhao et al. 2008 ⁴⁹	L	L	U	U	L	L

Abbreviations: H, high risk; L, low risk; U, unclear risk (Cochrane Handbook for Systematic Reviews of Interventions, Version 5.3).