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Stem cell therapy for chronic ischaemic heart disease and congestive heart failure (Review)

Fisher SA, Doree C, Mathur A, Taggart DP, Martin-Rendon E

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[Intervention Review]

Stem cell therapy for chronic ischaemic heart disease and congestive heart failure

Sheila A Fisher[1], Carolyn Doree[1], Anthony Mathur[2], David P Taggart[3], Enca Martin-Rendon[4]

[1]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [2]Department of Clinical Pharmacology, William Harvey Research Institute, London, UK. [3]Oxford Heart Centre, John Radcliffe Hospital, Oxford, UK. [4]Systematic Review Initiative, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

Contact address: Enca Martin-Rendon, Systematic Review Initiative, Radcliffe Department of Medicine, University of Oxford, Oxford, UK. enca.rendon@ndcls.ox.ac.uk.

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ABSTRACT

Background

A promising approach to the treatment of chronic ischaemic heart disease and congestive heart failure is the use of stem cells. The last decade has seen a plethora of randomised controlled trials developed worldwide, which have generated conflicting results.

Objectives

The critical evaluation of clinical evidence on the safety and efficacy of autologous adult bone marrow-derived stem/progenitor cells as a treatment for chronic ischaemic heart disease and congestive heart failure.

Search methods

We searched CENTRAL in the Cochrane Library, MEDLINE, Embase, CINAHL, LILACS, and four ongoing trial databases for relevant trials up to 14 December 2015.

Selection criteria

Eligible studies were randomised controlled trials comparing autologous adult stem/progenitor cells with no cells in people with chronic ischaemic heart disease and congestive heart failure. We included co-interventions, such as primary angioplasty, surgery, or administration of stem cell mobilising agents, when administered to treatment and control arms equally.

Data collection and analysis

Two review authors independently screened all references for eligibility, assessed trial quality, and extracted data. We undertook a quantitative evaluation of data using random-effects meta-analyses. We evaluated heterogeneity using the I^2 statistic and explored substantial heterogeneity (I^2 greater than 50%) through subgroup analyses. We assessed the quality of the evidence using the GRADE approach. We created a 'Summary of findings' table using GRADEprofiler (GRADEpro), excluding studies with a high or unclear risk of selection bias. We focused our summary of findings on long-term follow-up of mortality, morbidity outcomes, and left ventricular ejection fraction measured by magnetic resonance imaging.

Main results

We included 38 randomised controlled trials involving 1907 participants (1114 cell therapy, 793 controls) in this review update. Twenty-three trials were at high or unclear risk of selection bias. Other sources of potential bias included lack of blinding of participants (12 trials) and full or partial commercial sponsorship (13 trials).

Cell therapy reduced the incidence of long-term mortality (≥ 12 months) (risk ratio (RR) 0.42, 95% confidence interval (CI) 0.21 to 0.87; participants = 491; studies = 9; I^2 = 0%; low-quality evidence). Periprocedural adverse events associated with the mapping or cell/placebo injection procedure were infrequent. Cell therapy was also associated with a long-term reduction in the incidence of non-fatal myocardial infarction (RR 0.38, 95% CI 0.15 to 0.97; participants = 345; studies = 5; I^2 = 0%; low-quality evidence) and incidence of arrhythmias (RR 0.42, 95% CI 0.18 to 0.99; participants = 82; studies = 1; low-quality evidence). However, we found no evidence that cell therapy affects the risk of rehospitalisation for heart failure (RR 0.63, 95% CI 0.36 to 1.09; participants = 375; studies = 6; I^2 = 0%; low-quality evidence) or composite incidence of mortality, non-fatal myocardial infarction, and/or rehospitalisation for heart failure (RR 0.64, 95% CI 0.38 to 1.08; participants = 141; studies = 3; I^2 = 0%; low-quality evidence), or long-term left ventricular ejection fraction when measured by magnetic resonance imaging (mean difference -1.60, 95% CI -8.70 to 5.50; participants = 25; studies = 1; low-quality evidence).

Authors' conclusions

This systematic review and meta-analysis found low-quality evidence that treatment with bone marrow-derived stem/progenitor cells reduces mortality and improves left ventricular ejection fraction over short- and long-term follow-up and may reduce the incidence of non-fatal myocardial infarction and improve New York Heart Association (NYHA) Functional Classification in people with chronic ischaemic heart disease and congestive heart failure. These findings should be interpreted with caution, as event rates were generally low, leading to a lack of precision.

PLAIN LANGUAGE SUMMARY

Stem cell treatment for chronic ischaemic heart disease and congestive heart failure

Review question

Are adult stem/progenitor cells derived from bone marrow safe and effective as a treatment for chronic ischaemic heart disease and heart failure?

Background

The current treatment for people suffering from heart disease and heart failure is drugs and, when possible, restoration of the blood supply in the heart (revascularisation) either by opening the arteries with a tiny balloon in a procedure called primary angioplasty (or percutaneous coronary intervention) or by heart surgery (or coronary artery bypass graft). Revascularisation has reduced the death rate associated with these conditions. In some people, heart disease and heart failure symptoms persist even after revascularisation. Recently, bone marrow stem/progenitor cells have been investigated as a new treatment for people with heart disease and heart failure, whether or not they also undergo revascularisation.

Search date

We searched electronic databases for relevant randomised controlled trials to December 2015.

Study characteristics

We included 38 randomised controlled trials involving more than 1900 participants in this review, with 14 trials of chronic ischaemic heart disease, 17 trials of ischaemic heart failure secondary to heart disease, and seven trials of refractory or intractable angina. The mean age of participants ranged from 55 to 70 years, and the proportion of male participants ranged from 51% to 100%.

Key results

Results indicated that treatment with bone marrow-derived cells can lead to a reduction in deaths in participants followed for at least 12 months. Adverse events occurring around the time of treatment were generally rare. Participants who received cell treatment also experienced fewer heart attacks and arrhythmias when compared to those who received no cells. However, cell therapy does not appear to reduce the risk of rehospitalisation for heart failure or the combined risk of death, non-fatal heart attack, or rehospitalisation, and did not result in any improvement over standard treatment in tests of heart function. These results suggest that cell therapy may be of benefit in people with chronic ischaemic heart disease or heart failure, or both.

Quality of the evidence

The quality of the evidence was low, as the number of included studies and participants is not currently high enough to draw robust conclusions. Thirteen studies received commercial funding, of which four were fully commercially sponsored, and 12 studies did not report

that participants were blinded to the treatment they received. Further research involving a larger number of participants is required to confirm our results.

Summary of findings for the main comparison. Bone marrow-derived cell therapy for people with chronic ischaemic heart disease and congestive heart failure

Bone marrow-derived cell therapy for people with chronic ischaemic heart disease and congestive heart failure

Patient or population: people with chronic ischaemic heart disease and congestive heart failure
Settings: hospitalisation
Intervention: bone marrow-derived cell therapy

Comparison: no cell therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)¶	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cell therapy	Bone marrow-derived cell therapy				
Mortality (all cause) Long-term follow-up (≥ 12 months)	**102 per 1000**	**43 per 1000** (21 to 89)	**RR 0.42** (0.21 to 0.87)	491 (9 studies)	⊕⊕⊝⊝ **low**[1,2]	The required information size of 1899 participants to detect a RRR of 35% has not been reached.
Periprocedural adverse events	See comment	See comment	Not estimable	1695 (34 studies)	See comment	Adverse events occurring during the mapping or cell/placebo injection procedure included ventricular tachycardia (7), ventricular fibrillation (1), atrial fibrillation (1), transient complete heart block (1), transient pulmonary oedema (3), thrombus on mapping catheter tip (1), visual disturbances (2), myocardial perforation (2), limited retrograde catheter-related dissection of the abdominal aorta (1).
Non-fatal myocardial infarction Long-term follow-up (≥ 12 months)	**83 per 1000**	**31 per 1000** (12 to 80)	**RR 0.38** (0.15 to 0.97)	345 (5 studies)	⊕⊕⊝⊝ **low**[2,3]	The required information size of 2383 participants to detect a RRR of 35% has not been reached.
Rehospitalisation due to heart failure	**155 per 1000**	**98 per 1000** (56 to 169)	**RR 0.63** (0.36 to 1.09)	375 (6 studies)	⊕⊕⊝⊝ **low**[2,4]	The required information size of 1193 participants to detect a RRR of 35% has not been reached.

Long-term follow-up (≥ 12 months)						
Arrhythmias Long-term follow-up (≥ 12 months)	**333 per 1000**	**140 per 1000** (60 to 330)	**RR 0.42** (0.18 to 0.99)	82 (1 study)	⊕⊕⊝⊝ **low**[5,6]	The required information size of 461 participants to detect a RRR of 35% has not been reached.
Composite MACE Long-term follow-up (≥ 12 months)	**350 per 1000**	**224 per 1000** (133 to 378)	**RR 0.64** (0.38 to 1.08)	141 (3 studies)	⊕⊕⊝⊝ **low**[7,8]	The required information size of 431 participants to detect a RRR of 35% has not been reached.
LVEF (%) measured by MRI Long-term follow-up (≥ 12 months)	-	The mean LVEF (%) measured by MRI in the intervention groups was **1.6 lower** (8.7 lower to 5.5 higher).	-	25 (1 study)	⊕⊕⊝⊝ **low**[6,7]	The required information size of 322 participants to detect a mean difference of 4% has not been reached.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

¶Only studies with a low risk of selection bias are included.
CI: confidence interval; **LVEF:** left ventricular ejection fraction; **MACE:** major adverse clinical events; **MD:** mean difference; **MRI:** magnetic resonance imaging; **NYHA:** New York Heart Assocation; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio; **RRR:** relative risk reduction

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Six trials received full or partial commercial funding, which could have resulted in a biased assessment of the intervention effect and were therefore deemed to have a high risk of bias. One trial was not blinded (high risk of performance bias) and had a high risk of attrition bias.
[2]The number of observed events was low, leading to imprecision.
[3]Four studies received full or partial commercial funding with a high risk of bias.
[4]Five trials received full or partial commercial funding with a high risk of bias.
[5]The included trial received partial commercial funding with a high risk of bias.
[6]Only one trial with a low number of observed events was included in the analysis, leading to imprecision.
[7]All three included trials received partial commercial funding with a high risk of bias.
[8]The number of included studies was low with a low number of observed events, leading to imprecision.

BACKGROUND

Description of the condition

Ischaemic heart disease (IHD) is a major health burden worldwide (BHF 2014). Survival following myocardial infarction (MI) has increased in recent years due to state-of-the-art revascularisation techniques such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) (Skinner 2011). In contrast, the number of people with congestive heart failure (CHF) is rapidly becoming an epidemic (Ambrosy 2014; Lloyd-Jones 2002). Preventing the progression of IHD and the development of CHF thus remains a challenge.

In IHD, there may be non-contractile scar tissue that has replaced damaged myocardium, which could cause further damage. The heart also may prevent the death of more cardiomyocytes by reducing the energy demands of contraction, resulting in non-contracting or hibernating myocardium. This typical physiological response to chronic hypoxic stress, which is identifiable by abnormalities in contractile function, can potentially be reversed by revascularisation of the hibernating myocardium in order to restore cardiac function (Taggart 2012). In some cases, revascularisation is not possible or may not be complete, and in cases with non-ischaemic cardiomyopathy revascularisation is not relevant and symptoms of chronic myocardial ischaemia, sometimes with refractory angina pectoris, are still present (Taggart 2012).

Alternative and complementary approaches in the treatment of CHF are being developed in the form of cell-based therapies for CHF. The rationale behind developing cell therapies as treatment for IHD is based on the notion that the heart has limited ability to repair itself following a major injury. Preclinical and clinical studies have suggested that cell therapies could potentially reverse left ventricular dysfunction in chronic IHD and CHF (Heldman 2014; Perin 2012a).

Description of the intervention

The procedure is currently as follows: either the bone marrow is harvested from the recipient, or bone marrow cells are mobilised into circulation by a growth factor stimulant (most commonly granulocyte colony-stimulating factor (G-CSF)) (Assmus 2006; Erbs 2005). In the former procedure, cells are usually collected (sometimes under general anaesthesia) from the pelvic bone using large suction needles. The stem/progenitor cells are thereafter separated from other bone marrow cells in sterile conditions (Assmus 2006). The bone marrow harvest and cell separation procedures may take several hours. In the G-CSF mobilisation procedure, mononuclear cells or progenitor cells are collected as a blood sample and then separated from other blood cells in sterile conditions (Erbs 2005). In both procedures, the cells are infused directly into the recipient's coronary arteries or heart (Ang 2008; Hamshere 2015). The first procedure delivers the cells to the coronary arteries via a special balloon-catheter during angioplasty (e.g. percutaneous coronary intervention) using a stop-flow technique (Ang 2008; Hamshere 2015). The latter procedure administers the cells into the heart muscle during an angioplasty-like procedure using electromechanical mapping and direct intramyocardial injection (e.g. NOGA system) or during cardiac surgery (e.g. coronary artery bypass grafting) (Ang 2008; Hamshere 2015), although this option may be limited by high costs associated with NOGA percutaneous procedure. The interval between the cell collection and their reinfusion varies; some are administered fresh, and others undergo some form of culture and expansion ex vivo that could take two to three weeks (Assmus 2006; Bartunek 2012; Mathiasen 2015).

A haematologist usually undertakes the collection of cells. A specialised technician or scientist undertakes the cell separation from the other bone marrow cells, and the cardiologist or cardiac surgeon peforms the infusion or intramyocardial injection of the cells.

Adverse effects associated with the administration of bone marrow or blood cells as a treatment for people with chronic IHD or CHF are infrequent and generally not serious (Behfar 2014). In those trials where G-CSF has been administered prior to the cell harvest, transient complications arising from the G-CSF treatment may occur. However, no long-term adverse effects have been reported.

This treatment is currently only available in research-associated facilities, but it is conceivable that, if long-term effectiveness is confirmed, it might become available to some or all people with chronic heart disease, since bone marrow and peripheral blood harvest is a standard procedure used in bone marrow transplantation. The costs may be high, depending on the procedures used, and currently relate to the costs of cell collection and cell processing (approximately a 10th of the overall cost of the trial). The potential for a large multicentre randomised controlled trial (RCT) is limited by funds and by discordant results from previous RCTs.

How the intervention might work

Clinical trials that have administered bone marrow-derived cells to people suffering from IHD or CHF have yielded divergent results, and therefore the mechanism of action of such therapies remains unclear. The selection of optimal cell type and the optimal patient cohort to be treated is thus a challenge. Although incorporation into blood vessels and direct generation of cardiomyocytes have been proposed as mechanisms of action (Beltrami 2003; Carr 2008; Martin-Rendon 2008a; Mathur 2004; Stuckey 2006; Yoon 2005), it is now accepted that a paracrine mechanism may be the major contribution to promoting cardiac repair and limit fibrosis in the damaged myocardium (Ibrahim 2016; Li 2012).

Why it is important to do this review

Cell therapies have the potential to become an exciting new form of treatment for many diseases. Heart disease is one of the clinical settings in which to address this new form of therapy, although the exact clinical role for cell therapy remains to be defined. Cell therapy as treatment for ischaemic heart disease is an experimental therapy that is not widely available and is not part of standard clinical practice. Currently, there are no clinical guidelines on the use of cell therapies for ischaemic heart disease and heart failure. Evidence from early trials and systematic reviews has suggested that cell therapy may result in some improvements over conventional therapy as measured by surrogate tests of heart function (Abdel-Latif 2007; Assmus 2006; Chen 2006; Jeevanantham 2012). More recent systematic reviews and meta-analyses have shown conflicting results (Afzal 2015; Fisher 2015b). A recent Cochrane review concluded that there is insufficient evidence for a beneficial effect of cell therapy

for people with acute myocardial infarction, with most evidence coming from small trials that showed no difference in clinically relevant outcomes (Fisher 2015a). However, there seems to be robust evidence to suggest that cell therapies have a beneficial effect on people with heart failure (Fisher 2016).

A Cochrane review of cell therapy for people with chronic IHD and CHF included 23 RCTs and found some evidence that bone marrow-derived cells improve left ventricular ejection fraction (LVEF), reduce the number of deaths and are associated with improved measures of performance in the long term (Fisher 2014). Since publication of the original review, several key new trials have been published (Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Jimenez-Quevedo 2011; Mathiasen 2015; Nasseri 2012; Patel 2015; Patila 2014; Santoso 2014; Trifunovic 2015; Wang 2014; Wang 2015). It is important to update the review with these new trials to re-evaluate and improve the quality of the available evidence.

OBJECTIVES

The critical evaluation of clinical evidence on the safety and efficacy of autologous adult bone marrow-derived stem/progenitor cells as a treatment for chronic IHD and CHF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Anyone with a clinical diagnosis of IHD or CHF, excluding people with acute myocardial infarction. We included studies evaluating both ischaemic and non-ischaemic disease only if data for the participants with ischaemic disease could be extracted separately.

Types of interventions

Studies involving the administration of autologous adult bone marrow-derived stem/progenitor cells on their own or in combination with co-interventions, such as cardiac surgery, as treatment for IHD or CHF.

Participants in the comparator treatment arm of the trial received either no intervention or a placebo (e.g. the medium in which the cells were suspended or plasma). Trials where co-interventions (e.g. CABG, PCI, G-CSF, extracorporal shockwave therapy) were additionally administered were eligible as long as the co-interventions were equal in both arms and administered to an equivalent proportion of participants.

In summary:

1. any autologous human adult bone marrow-derived stem/progenitor cells
2. any single dose
3. any method of stem/progenitor cell isolation
4. any route of administration
5. any co-intervention
6. repeated intervention or multiple doses

Types of outcome measures

Primary outcomes

1. Mortality
2. Periprocedural adverse events (defined as occurring at the time of bone marrow aspiration or administration of cell therapy (or placebo), or documented adverse events within 30 days of treatment)

Secondary outcomes

1. Morbidity: non-fatal MI, rehospitalisation for heart failure (HF), arrhythmias, composite measure of major adverse clinical events (MACE, mortality, non-fatal MI, and/or rehospitalisation for HF)
2. Health-related quality of life (QoL)
3. Performance status (e.g. New York Heart Association (NYHA) classification, Canadian Cardiovascular Society (CCS) class, exercise capacity)
4. Left ventricular ejection fraction (LVEF).

We divided beneficial outcomes into clinically based and surrogate outcomes. At the protocol stage of this review, we had intended to consider clinical and surrogate outcome data at 30 days, 6 months, and 12 months after baseline; however, this was not possible due to the variation in follow-up periods reported in individual studies. We therefore stratified outcome data into short term (up to 12 months) and long term (12 months or longer) follow-up. The scope of this version of the review was to assess the clinical benefit or harm of cell therapies in people with ischaemic heart disease and heart failure, and we have therefore focused on clinical outcomes. However, the surrogate outcome of LVEF is a standard, widely reported surrogate for cardiac function and has been retained as a reference point in other trials and systematic reviews of IHD. We have excluded surrogate outcomes other than LVEF reported in previous versions of this review, namely engraftment and survival of the infused cells, end-systolic volume, end-diastolic volume, wall motion score, and stroke volume index, in agreement with the Cochrane Heart Group. However, we consider that relevant surrogate outcomes such as left ventricular volumes may be more meaningful than LVEF, and as such, we will consider these surrogate outcomes in the next update of this review.

Search methods for identification of studies

Electronic searches

We updated and expanded the electronic database searches, originally run in March 2013 (see Appendix 1 for details), in June 2014, March 2015, and December 2015 (Appendix 2). We identified relevant studies from searching the following:

- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2015 Issue 11);
- MEDLINE (OvidSP, 1948 to 14 December 2015);
- Embase (OvidSP, 1974 to 14 December 2015);
- CINAHL (EBSCOHost, 1982 to 14 December 2015);
- PubMed (in process and epublications ahead of print only, on 14 December 2015);
- LILACS (1982 to 14 December 2015);
- IndMED (1986 to 14 December 2015);
- KoreaMed (1997 to 14 December 2015);

- PakMediNet (1995 to 14 December 2015);
- Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to 14 December 2015);
- four databases of ongoing trials on 14 December 2015:
  - ClinicalTrials.gov (clinicaltrials.gov/);
  - ISRCTN Register (www.isrctn.com/);
  - World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/);
  - HKU Clinical Trials Registry (www.hkuctr.com).

Searching other resources

We checked the reference lists of all identified eligible papers and relevant systematic reviews. We applied no language or date restrictions.

Data collection and analysis

Selection of studies

The Information Specialist (CD) conducted the electronic search for potentially relevant papers and removed references that were duplicates, clearly irrelevant, and/or included in previous search results. Two review authors (SF, EMR) independently screened all titles and abstracts identified by the review search strategy for relevance to the review question. We excluded studies that clearly did not meet the eligibility criteria at this stage. Two review authors (SF, EMR) independently assessed all other studies based on their full text for inclusion/exclusion using the criteria indicated above (type of studies, participants, interventions, and outcome measures). Disagreements were resolved through discussion.

Data extraction and management

Two review authors (SF, EMR) extracted data onto customised data extraction forms that were created and piloted specifically for this review and independently undertook data extraction for all eligible studies. Aside from details relating to the quality of the included studies, we extracted the following two groups of data.

1. Trial characteristics: place of publication, date of publication, population characteristics, setting, detailed nature of intervention, detailed nature of comparator, detailed nature of outcomes. A key purpose of these data was to explain clinical heterogeneity between included studies independently from analysis of the results.
2. Results of included studies for each of the main outcomes indicated in the review question. For dichotomous outcomes, we recorded the numbers of outcomes in treatment and control groups. For continuous outcomes, we recorded the mean and standard deviation. Where standard deviations of mean change from baseline values were not explicitly reported, where possible we calculated the standard deviation based on reported confidence intervals or P values as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we used these values in the analysis.

Disagreements between the review authors over data extraction were resolved by consensus. When disagreements regarding any of the above could not be resolved through discussion, we attempted to contact authors of the original trials to provide further details. One review author (SF) then transcribed the data into the systematic review computer software Review Manager 5 (Review Manager 2014).

Assessment of risk of bias in included studies

The two review authors (SF, EMR) independently undertaking the data extraction assessed the risk of bias for each trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For trials included in the previous version of this review, we re-evaluated the risk of bias in the context of the revised outcomes and long-term follow-up studies, and updated accordingly. Disagreements were resolved through discussion.

A study of trials published in Chinese medical journals that were described as randomised found that a high proportion of these trials did not adhere to accepted methodology for randomisation, and hence could not be deemed authentic RCTs (Wu 2009). It is now widely accepted that trials carried out in China may lack appropriate randomisation; we therefore deemed any Chinese studies for which methods of randomisation were not described and could not be clarified with trial authors to have a high risk of selection bias, and evaluated sensitivity to these trials through sensitivity analyses (see Sensitivity analysis section below).

Measures of treatment effect

We carried out separate analyses according to the duration of follow-up after treatment: short term (less than 12 months) and long term (equal to or greater than 12 months). We expressed dichotomous data for each arm in a particular study as a proportion or risk and the treatment effect as a risk ratio (RR) with 95% confidence intervals (CIs), calculated using Mantel-Haenszel methods. We expressed continuous data for each arm in a particular study as a mean and standard deviation, and the treatment effect as the mean difference (MD) if outcomes were measured in the same way across trials. For outcomes measured using different methods, we combined the treatment effect data and analysed them using the standardised mean difference (SMD).

Although we intended to analyse continuous outcomes as mean change from baseline, several studies only reported baseline and endpoint data. Where possible, we calculated the standard deviation of the mean change from baseline based on reported confidence intervals or P values, and used these values in the analysis. However, for several studies, insufficient information was reported to calculate the standard deviation. Since the mean difference based on the change from baseline can be assumed to address the same underlying intervention effects as an analysis based on final measures (i.e. the differences in mean final values will on average be the same as the differences in mean change scores), we combined studies reporting mean change from baseline values with those reporting endpoint values, but have presented mean change and endpoint values separately as well as in combined analyses for clarity, as suggested in the *Cochrane Handbook* (Higgins 2011). We did not conduct this pooling of studies by method of reporting of continuous measures for analyses of exercise capacity, since the assumption of consistent underlying effects does not hold for standardised mean differences.

Unit of analysis issues

Three published reports of trials randomised participants to one of two treatment arms, each with a comparator control group

(Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Mozid 2014_IC; Mozid 2014_IM); we have considered each of these studies as reporting two separate trials within one publication and treat them as such throughout this review. In the first trial (Heldman 2014_BMMNC; Heldman 2014_BM-MSC), exercise capacity, quality of life, and LVEF measures were reported pooled for both control groups; for these outcomes the pooled control data are used as the comparator for both intervention arms. In other studies in which there were multiple interventions in the same trial compared with a single control group, we combined the intervention trial arms for a single comparison with the comparator (control) arm to avoid double counting of participants and potential correlation of results. We thus pooled data across different methods of administration (intramyocardial/intracoronary) (Ang 2008), cell types (Assmus 2006), and cell doses (Losordo 2007; Losordo 2011). However, for subgroup and sensitivity analyses, where the two intervention arms were classified into different categories (e.g. type of cell, cell dose, route of administration of cells), we included results for each treatment arm in the corresponding group, with the control group included in both groups. In order to avoid unit of analysis issues, we treated cross-over trials as parallel trials and included them in the review up to the point of cross-over, i.e. first-phase data only.

In the analysis of quality of life outcomes, we converted Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores to negative values in order to include these in a meta-analysis with other measures on different scales using the standardised mean difference.

Dealing with missing data

We attempted to contact the authors of 27 studies (describing 30 independent trials) by email for clarification of methods (randomisation, allocation concealment, and blinding), potential overlapping of studies, and/or requests for additional data. We failed to establish contact with the authors of 16 studies (17 independent trials) by email (Ang 2008; Bartunek 2012; Erbs 2005; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Mathiasen 2015; Nasseri 2012; Patel 2015; Perin 2011; Perin 2012a; Perin 2012b; Pokushalov 2010; Santoso 2014; Tse 2007; Wang 2010; Yao 2008; Zhao 2008), and the authors of one study initially responded but did not reply to subsequent emails (Jimenez-Quevedo 2011).

We are grateful to the authors of 10 studies (12 independent trials) who responded to our emails as follows:

- Assmus 2006: results were reported for a pooled randomised cohort and a non-randomised pilot study cohort; the authors provided full clinical and surrogate outcome data for the randomised cohort alone, as well as details of the method of randomisation used;
- Assmus 2013: we received clarification of analysis sample sizes and confidence intervals for mean change in NYHA;
- Hendrikx 2006: we received left ventricular end-systolic volume (LVESV) and end-diastolic volume (LVEDV) data (as only LVESV/LVEDV index values were reported) (see previous version of this review);
- Hu 2011: the authors confirmed overlap of multiple publications and provided mean change from baseline data for exercise capacity, LVEF, and other surrogate outcome measures (see previous version of this review);
- Mozid 2014_IC; Mozid 2014_IM: results were reported pooled across intervention arms; the authors provided mortality, MI, rehospitalisation and arrhythmia rates, and mean NYHA and CCS baseline, follow-up, and change from baseline values separately for each randomised arm of the trial;
- Hamshere 2015_IC; Hamshere 2015_IM: this study was published in abstract form only with limited presentation of results. The authors kindly provided data for mortality, morbidity, NYHA class, and CCS class;
- Patel 2005: we received clarification of randomisation methods;
- Patila 2014: we received mean (rather than reported median) values for LVEF and NYHA class;
- Trifunovic 2015: LVEF data were reported graphically; the authors provided the actual data used to generate the graphs;
- Turan 2011: a discrepancy in brain natriuretic peptide data between papers was resolved; overlap of multiple publications was confirmed.

Assessment of reporting biases

Although we made every effort to identify unpublished studies, we assessed publication bias for the primary outcome of mortality using a funnel plot and with a formal test for publication bias using Egger's test for asymmetry (Egger 1987), implemented with the statistical software programme R v2.14.1 (R Core Team 2013). We accept that asymmetry, one cause of which may be publication bias, is difficult to detect with the small numbers of studies (i.e. fewer than 10) often encountered in systematic reviews.

Data synthesis

We undertook meta-analyses using Review Manager 5, employing random-effects models throughout due to the anticipated heterogeneity arising from differences in participant characteristics, interventions, and duration of follow-up (Review Manager 2014). This differs from the previous version of the review, in which fixed-effect models were used for meta-analyses in the first instance.

Although quantitative synthesis was the main method of analysis, we incorporated insights from a qualitative evaluation of studies for an overall interpretation of the data. We based conclusions on patterns of results identified across clearly tabulated results of included studies as well as summary measures, taking both direction and magnitude of any mean effect sizes from random-effects models into account.

We included all studies in the main analyses irrespective of risk of bias and performed sensitivity analyses for risk of selection, performance, and attrition bias as described in the Sensitivity analysis section below. Periprocedural adverse events were summarised for each trial in tabular form and evaluated descriptively. We made no formal evaluation of the frequency of periprocedural adverse events in each treatment group due to the differences in definition and reporting of periprocedural adverse events between studies.

Within each included trial, all participants were analysed in the treatment groups to which they had been randomised. We undertook an available-case analysis, including all participants who were randomised to treatment and were included in the analysis, irrespective of whether or not they had received their randomised treatment.

In two trials, no variation in NYHA class, in Trifunovic 2015, or CCS class, in Perin 2012b, between participants within the treatment group was observed (and hence the sample standard deviation was zero). For these outcomes, we estimated the standard deviation by that observed in the control group in order to incorporate these data into the meta-analysis.

We constructed 'Summary of findings' tables using GRADEpro GDT (GRADEpro GDT). We focused our summary of findings on long-term follow-up of the primary outcome of mortality, morbidity (non-fatal MI, rehospitalisation for HF, composite MACE, arrhythmias) and the surrogate outcome of LVEF measured by magnetic resonance imaging (MRI). We excluded studies with a high or unclear risk of selection bias from random sequence generation from the 'Summary of findings' tables and from summary results presented in the abstract. We made an assessment of the quality of the evidence based on study design limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias as described in the GRADE handbook (Schünemann 2013), with consideration of the optimal information size generated from trial sequential analysis (TSA).

Trial sequential analysis

Cumulative meta-analyses may result in type I errors due to an increased risk of random error arising from repeated testing of accumulating data (Borm 2009; Hu 2007; Lan 2003). Trial sequential analysis provides a method of adjusting the thresholds for statistical significance while maintaining the overall desired type I error rate (Wettersley 2008). These adjusted thresholds are known as trial sequential monitoring boundaries (TSMBs). If the cumulative Z-curve crosses the TSMB, then statistical significance has been reached whilst maintaining the overall type I error rate. Trial sequential analysis also provides a required information size, the meta-analysis information size needed to detect a statistically significant effect with overall desired power and type I error given a defined underlying model. We calculated the required information size for the outcomes of all-cause mortality (primary outcome), morbidity outcomes (non-fatal MI, rehospitalisation for HF, composite MACE, and arrhythmias), and LVEF at long-term follow-up using the TSA program (TSA 2011). For dichotomous outcomes, the required information size was based on a DerSimonian and Laird random-effects model for a relative risk reduction of 35% (equivalent to the reduced risk of mortality associated with PCI, Hartwell 2005, and less than that associated with CABG, Benedetto 2016). We acknowledge that this may be an overestimation of the effect of cell therapy, but as an arbitrary value it provides a benchmark comparison. Small treatment effects will require a larger information size. We assumed an incidence rate in the control group equal to that observed in our control data. For LVEF and NYHA class, we calculated the information size using a DerSimonian and Laird random-effects model with a model variance-based heterogeneity correction assuming an a priori absolute mean difference in change from baseline values of 4% (LVEF) or a mean difference of 1 (NYHA class). We excluded studies with a high or unclear risk of selection bias from random sequence generation from TSA. For outcomes demonstrating efficacy of cell therapy, cumulative Z-scores (i.e. the Z-statistics obtained after sequential inclusion of each trial) were constructed and assessed for significance against the trial sequential monitoring boundaries, calculated using the O'Brien-Fleming β-spending function for a reduced overall 5% type I error rate and 80% power.

Subgroup analysis and investigation of heterogeneity

A range of different methods (MRI, left ventricular angiography (LVA), single-photon emission computed tomography (SPECT), echocardiography, and radionuclide ventriculography (RNV)) were used to measure LVEF across studies, with several studies reporting LVEF as an outcome using more than one method of measurement. The limitations of some of these methods are well known (Arnesen 2007). Consistent with the previous version of this review, we subgrouped analyses of LVEF according to the measurement method used.

We assessed the percentage of variability in effect estimates due to heterogeneity using the I^2 statistic (Higgins 2002; Higgins 2003). We performed pre-planned subgroup analysis for mortality (primary outcome). For outcomes with substantial observed heterogeneity ($I^2 \geq 50\%$) in combined analyses (or separate analyses for outcomes reported as standardised mean difference) and a minimum of three studies in each subgroup, we investigated potential sources of heterogeneity by performing the subgroup analyses described below as exploratory analyses, and by visual inspection of forest plots with consideration of individual trial characteristics (Higgins 2003). Where possible, we based subgroup analyses on combined analyses of mean values at endpoint and mean change from baseline values, consistent with the main analyses as described in the Measures of treatment effectsection above. We performed subgroup analyses on all available trials irrespective of risk of bias.

Subgroup analysis considered the following factors:

1. mean dose of stem/progenitor cells administered (≤ 10^7, 10^7 to 10^8, or > 10^8);
2. route of cell administration (intramyocardial, intracoronary);
3. baseline cardiac function (mean baseline LVEF < 30%, 30% to 50%, or > 50%);
4. type of cell administered (mononuclear cells; circulating progenitor cells; haematopoietic progenitor cells; and mesenchymal stem cells);
5. participant diagnosis (chronic IHD; HF (secondary to IHD); intractable/refractory angina), classified in consultation with a clinical expert (AM);
6. use of co-interventions (PCI or CABG or shockwave administered or not administered).

We regarded the last three subgroup comparisons listed above as hypothesis-generating.

For trials with multiple active-intervention arms, in subgroup analyses where the intervention arms were stratified across the subgrouping strata, we used the single control group as the comparator in each subgroup.

Sensitivity analysis

For the outcomes of mortality, non-fatal MI, rehospitalisation for HF, composite major adverse clinical events, NYHA class, and LVEF measured by MRI, we assessed results for sensitivity to risk of selection bias (by excluding studies with a high or unclear risk of bias from random sequence generation). We also assessed the primary outcome of mortality for sensitivity to risk of attrition bias (by excluding studies with a high or unclear risk of attrition bias) and performance bias (by excluding studies with a high or unclear risk

of performance bias due to known lack of blinding of participants and clinicians).

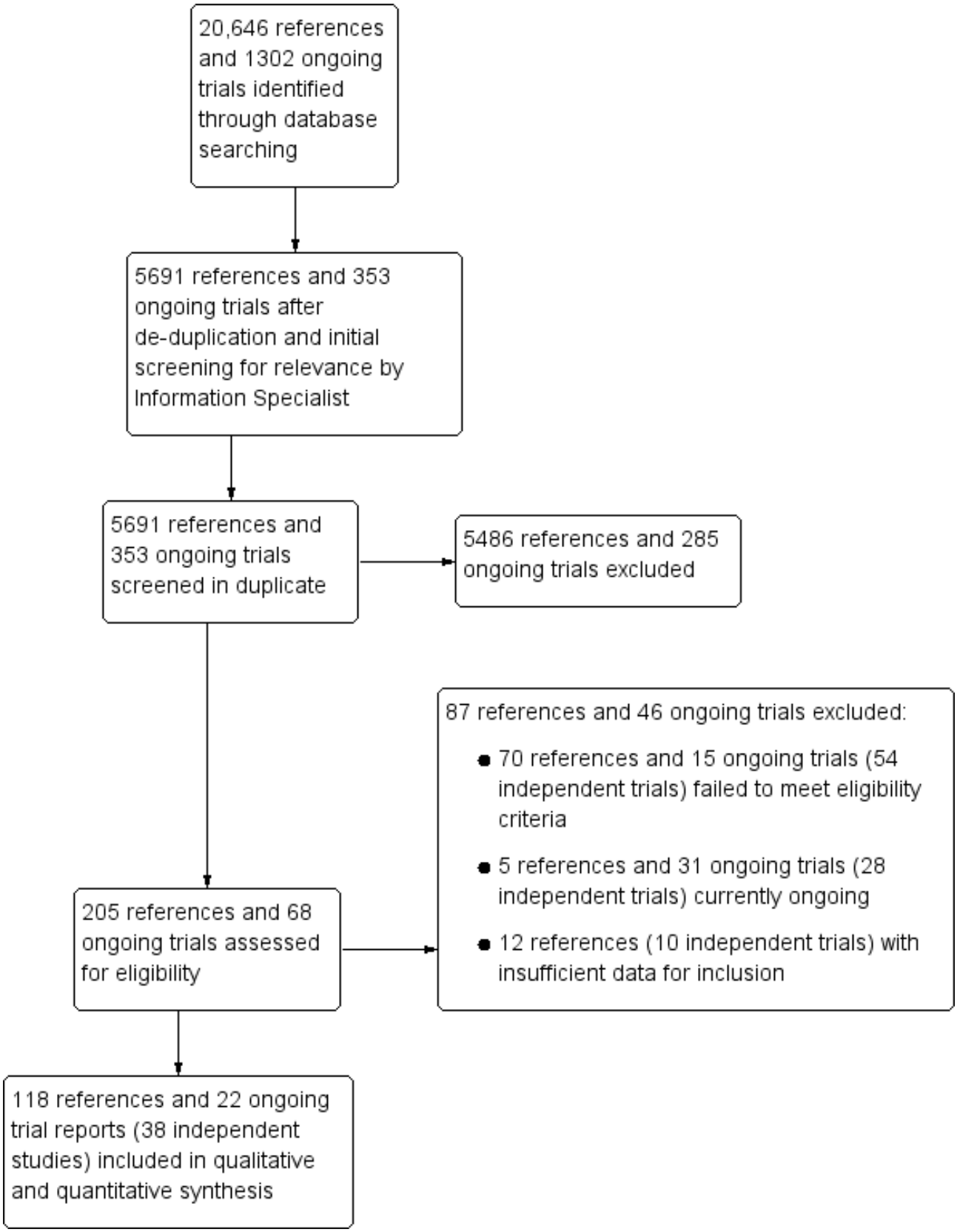
RESULTS

Description of studies

Results of the search

We identified a total of 20,646 references from the electronic database searches. De-duplication and removal of all clearly irrelevant references by the Information Specialist (CD) excluded 14,955 references. Initial screening of the remaining 5691 citations against inclusion criteria excluded a further 5486 references. Of the remaining 205 citations, we subsequently excluded 70 references (describing 54 independent studies), as they did not fully meet the inclusion criteria (see Excluded studies). Five further references described four independent study protocols (see Ongoing studies). Ten studies (12 references) were published in abstract form only, and although they appeared to meet the inclusion criteria, they did not contain sufficient data for inclusion; we have identified these as Studies awaiting classification. The remaining 118 citations describe a total of 38 independent RCTs (see Included studies). A summary of study classification is displayed in a PRISMA flow diagram (Figure 1).

Figure 1. PRISMA flow diagram.



Searching of ongoing trial databases identified 1302 trial records. De-duplication and removal of clearly irrelevant trials by the Information Specialist (CD) excluded 949 records. Of the remaining 353 records, 22 described included studies and 31 were ongoing trials that met the eligibility criteria and are shown in Ongoing studies.

Included studies

Thirty-eight studies met the inclusion criteria for this review, including a total of 1907 randomised participants (1114 bone marrow-derived stem/progenitor cells and 793 controls) who were assessed for the primary outcomes of the study. Sixteen independent trials are new to this review update (Bartunek 2012; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Jimenez-Quevedo 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Patel 2015; Patila 2014; Santoso 2014; Trifunovic 2015; Wang 2014; Wang 2015), representing an approximately 70% increase in the number of included participants from the previous version of the review. One study included in the original review was excluded in this update, as the co-intervention of G-CSF administered to the cell therapy group was not given to the control group (Kang 2006). See Table 1 for a summary of study participants.

The mean age of participants ranged from 55 to 70 years, and the proportion of men ranged from 50.9% to 100%. All trials were presented as full journal articles, with the exception of three trials that were published in the form of a conference abstract (Hamshere 2015_IC; Hamshere 2015_IM; Wang 2014), and two trials that reported additional long-term follow-up results in abstract form only (Assmus 2013; Patel 2005). Nine studies were multicentre trials (Bartunek 2012; Jimenez-Quevedo 2011; Losordo 2007; Losordo 2011; Patel 2015; Perin 2011; Perin 2012a; Santoso 2014; Tse 2007). Studies were based worldwide, including China (Chen 2006; Hu 2011; Wang 2009; Wang 2010; Wang 2014; Wang 2015; Yao 2008; Zhao 2008), Germany (Assmus 2006; Assmus 2013; Erbs 2005; Honold 2012; Nasseri 2012; Turan 2011), the United States (Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Losordo 2007; Losordo 2011; Perin 2011; Perin 2012a; Perin 2012b), the United Kingdom (Ang 2008; Hamshere 2015_IC; Hamshere 2015_IM; Mozid 2014_IC; Mozid 2014_IM), Spain (Jimenez-Quevedo 2011), Belgium (Hendrikx 2006), Denmark (Mathiasen 2015), the Netherlands (Van Ramshorst 2009), Finland (Patila 2014), Serbia (Trifunovic 2015), Russia (Pokushalov 2010), Argentina (Patel 2005), Hong Kong/Australia (Tse 2007), Indonesia/China (Santoso 2014), Belgium/Serbia/Switzerland (Bartunek 2012), and USA/Germany/India (Patel 2015). Two studies included publications in Chinese (Hu 2011; Wang 2009), which were translated into English for this review.

Fourteen studies included participants with chronic IHD (Ang 2008; Assmus 2006; Assmus 2013; Chen 2006; Erbs 2005; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hendrikx 2006; Honold 2012; Trifunovic 2015; Turan 2011; Wang 2014; Wang 2015; Yao 2008), normally defined as multivessel disease with persistent ischaemia and at least 30 days from the last MI. Seventeen studies included participants with CHF, defined as severe ischaemic HF and postinfarction HF (secondary to IHD) (Bartunek 2012; Hamshere 2015_IC; Hamshere 2015_IM; Hu 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Patel 2005; Patel 2015; Patila 2014; Perin 2011; Perin 2012a; Perin 2012b; Pokushalov 2010; Santoso 2014; Zhao 2008), and seven studies were of people with intractable or refractory angina (Jimenez-Quevedo 2011; Losordo 2007; Losordo 2011; Tse 2007; Van Ramshorst 2009; Wang 2009; Wang 2010). One trial also included people with non-ischaemic heart disease (Patel 2015), but reported results separately so that only participants with ischaemic disease are included in this review. All trials maintained participants with a standard set of drugs including aspirin, clopidogrel, heparin, blockers, statins, angiotensin converting enzyme (ACE) inhibitors, nitrates, and/or diuretics.

Duration of follow-up ranged from three months (Assmus 2006), four months (Hendrikx 2006), six months (Ang 2008; Jimenez-Quevedo 2011; Losordo 2007; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Perin 2011; Perin 2012a; Perin 2012b; Santoso 2014; Tse 2007; Van Ramshorst 2009; Wang 2009; Wang 2010; Wang 2014; Wang 2015; Yao 2008; Zhao 2008), 12 months (Chen 2006; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hu 2011; Losordo 2011; Patel 2015; Patila 2014; Pokushalov 2010; Turan 2011), 15 months (Erbs 2005), 24 months (Bartunek 2012) up to a median 45 (17) months (Assmus 2013), 60 months (Honold 2012; Trifunovic 2015), and 10 years (Patel 2005).

See Table 2 for a summary of study interventions. Twenty-seven trials isolated the stem cells by bone marrow aspiration and further separation of the mononuclear cells using density gradient centrifugation (Ang 2008; Assmus 2006; Assmus 2013; Bartunek 2012; Chen 2006; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hendrikx 2006; Hu 2011; Mathiasen 2015; Nasseri 2012; Patel 2005; Patila 2014; Perin 2011; Perin 2012a; Perin 2012b; Pokushalov 2010; Santoso 2014; Trifunovic 2015; Tse 2007; Turan 2011; Van Ramshorst 2009; Wang 2009; Wang 2010; Wang 2015; Yao 2008; Zhao 2008), and one trial isolated and concentrated the mononuclear cell fraction (Patel 2015). Three of these trials enriched the stem cell fraction in CD34-positive haematopoietic progenitors by magnetic separation (Patel 2005; Wang 2009; Wang 2010), whilst one trial enriched the stem cell fraction in CD133-positive cells (Nasseri 2012), and one trial in aldehyde dehydrogenase (ALDH)-positive haematopoietic progenitors (Perin 2012b). Three trials cultured the mononuclear cell population from bone marrow ex vivo to enrich in mesenchymal progenitors (Chen 2006; Heldman 2014_BM-MSC; Mathiasen 2015), whereas one trial cultured mononuclear cells and enriched them in cardiopoietic cells by exposure to cardiopoietic factors (Bartunek 2012). In one three-arm trial (Assmus 2006), bone marrow mononuclear cells were compared with circulating progenitor cells (CPCs), and with mononuclear cells isolated from venous peripheral blood. In the CPC arm, cells were isolated from peripheral blood by leukapheresis.

In five trials, bone marrow stem cells were mobilised into circulation with granulocyte colony-stimulating factor (G-CSF) and subsequently isolated from blood via leukapheresis (Erbs 2005; Honold 2012; Jimenez-Quevedo 2011; Losordo 2007; Losordo 2011). Whilst previous trials reported severe but transient complications associated with G-CSF treatment (Kang 2006), a recent pilot study demonstrated that G-CSF can be safely administered to people suffering from IHD as none of the participants in this trial experienced the type of adverse events previously associated with G-CSF treatment (Honold 2012). Two of these trials further enriched the stem cell population in CD34-positive progenitors by magnetic separation (Losordo 2007;

Losordo 2011). Four trials mobilised bone marrow cells into circulation with G-CSF and isolated bone marrow mononuclear cells by density gradient centrifugation (Hamshere 2015_IC; Hamshere 2015_IM; Mozid 2014_IC; Mozid 2014_IM). Finally, one study administered CD133-postive cells, but reported no details of cell isolation (Wang 2014).

All but six trials reported the mean (or median) dose of cells administered (Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Santoso 2014; Wang 2014). The mean dose of bone marrow mononuclear cells administered varied between 2 x 10^6 cells, in Perin 2011, and 8.4 x 10^8 cells, in Patila 2014, whilst bone marrow aspirate concentrate was administered at a mean dose of 3.7 x 10^9 cells (Patel 2015). Mesenchymal progenitor cells were administered at mean doses of between 5.0 x 10^6 cells, in Chen 2006, and 7.8 x 10^7 cells, in Mathiasen 2015, with one study administering 7.3 x 10^8 cardiopoietic cells (Bartunek 2012). Five studies that adminstered CD34-positive cells gave mean doses of between 5.0 x 10^4 cells, in Losordo 2007, and 5.6 x 10^7 cells, in Wang 2010, and included two dose escalation studies comparing 5.0 x 10^4 cells, 1.0 x 10^5 cells, and 5.0 x 10^5 cells or 1.0 x 10^5 cells and 5.0 x 10^5 cells (Losordo 2007; Losordo 2011). CD133-positive cells were administered at a median dose of 5.1 x 10^6 cells, in Nasseri 2012, or at doses of between 2 and 3 x 10^7 cells (Jimenez-Quevedo 2011). The doses of ALDH-positive cells averaged 2.96 x 10^6 cells (Perin 2012b). In the trial where bone marrow mononuclear cells were compared to CPCs, the mean dose of CPCs administered was between 2.9 x 10^6 cells, in Honold 2012, and 2.2 x 10^7 cells (Assmus 2006).

Thirteen trials administered the treatment via a coronary artery (intracoronarily (IC)) (Assmus 2006; Assmus 2013; Chen 2006; Erbs 2005; Hamshere 2015_IC; Honold 2012; Hu 2011; Mozid 2014_IC; Patel 2015; Turan 2011; Wang 2009; Wang 2010; Yao 2008), whilst 24 trials delivered the treatment intramyocardially (IM) (Bartunek 2012; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hendrikx 2006; Jimenez-Quevedo 2011; Losordo 2007; Losordo 2011; Mathiasen 2015; Mozid 2014_IM; Nasseri 2012; Patel 2005; Patila 2014; Perin 2011; Perin 2012a; Perin 2012b; Pokushalov 2010; Santoso 2014; Trifunovic 2015; Tse 2007; Van Ramshorst 2009; Wang 2014; Wang 2015; Zhao 2008). Of these 24 studies, 22 aided delivery of the treatment into the heart muscle using electromechanical mapping of the heart. The other two studies did not report whether the IM delivery of stem cells was aided in any other way (Hendrikx 2006; Zhao 2008). One trial included three treatment arms comparing IC and IM delivery of stem cells with control (Ang 2008).

Apart from G-CSF, 17 studies administered co-interventions. In nine studies, participants underwent coronary artery bypass graft (CABG) (Ang 2008; Hendrikx 2006; Hu 2011; Nasseri 2012; Patel 2005; Patila 2014; Trifunovic 2015; Wang 2015; Zhao 2008), and in seven studies, percutaneous coronary intervention (PCI) was administered to all participants (Chen 2006; Erbs 2005; Turan 2011; Wang 2009), or to a subset of participants (Assmus 2006; Honold 2012; Yao 2008). One study administered shockwave targeted to the left ventricular anterior wall at either high or low dose (Assmus 2013).

Twenty-five studies compared cell therapy with administration of a placebo consisting of a cell-free solution, either a heparin saline solution or a saline solution containing the participant's own serum (Assmus 2013; Erbs 2005; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hendrikx 2006; Hu 2011; Losordo 2007; Losordo 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Patila 2014; Perin 2012a; Perin 2012b; Santoso 2014; Tse 2007; Van Ramshorst 2009; Wang 2010; Wang 2014; Wang 2015; Yao 2008; Zhao 2008); two further studies used a simulated mock injection procedure for participants in the control arm, but without administering a placebo solution (Jimenez-Quevedo 2011; Perin 2011). The remaining 11 trials compared treatment to no treatment (Ang 2008; Assmus 2006; Bartunek 2012; Chen 2006; Honold 2012; Patel 2005; Patel 2015; Pokushalov 2010; Trifunovic 2015; Turan 2011; Wang 2009).

Three studies included multiple comparisons involving two or three intervention arms, including intracoronary versus intramyocardial cell administration (Ang 2008), mononuclear cells versus circulating progenitor cells (Assmus 2006), and high versus medium or low (Losordo 2007), or high versus low cell dose (Losordo 2011). We combined data for multiple intervention arms for the main analyses, although we used individual intervention trial arms for subgroup analyses where applicable. One three-arm trial was also a cross-over study (Assmus 2006); we have included only data up to the point of cross-over (three months) in this review.

One study described aortic cross-clamping during surgery with clamp times exceeding 25 to 30 minutes (Hendrikx 2006). Aortic cross-clamping isolates the systemic circulation during surgery but causes ischaemia. Although increasing times of aortic cross-clamping have been identified as a predictor of mortality, the effect of cross-clamping in this study was not as strong as might be expected. This may be due to the fact that the cause of cardiac damage is multifactorial, including coronary lesions.

All but one study published only in abstract form reported the primary clinical outcome of mortality (Wang 2014). All but three studies reported periprocedural adverse events (or lack of) (Hamshere 2015_IC; Hamshere 2015_IM; Wang 2014), and a fourth study reported adverse events for shockwave treatment but not for cell therapy (Assmus 2013). See the Characteristics of included studies tables for details of the included studies; see Table 3 for a summary of the reporting of outcomes considered in this review.

Studies awaiting classification

Ten independent studies (12 references) met the eligibility criteria for this review but reported insufficient data for inclusion; these studies are awaiting classification (see Characteristics of studies awaiting classification).

Ongoing studies

We identified 28 ongoing trials described in five references and 31 ongoing trial records; see Characteristics of ongoing studies for details.

Excluded studies

We excluded 54 studies (described by 70 references and 15 ongoing trial records) from the review following full-text assessment against the eligibility criteria (see Characteristics of excluded studies tables). In summary, we excluded studies for the following sequential reasons: 10 studies were of people with acute myocardial infarction (AMI); 16 studies were single-arm trials; seven

studies compared multiple interventions but with no control or placebo arm; eight studies did not randomise participants to treatment arm; two studies administered G-CSF to the intervention arm but not the comparator group; one study measured outcomes not relevant to this review; six studies were terminated or withdrawn; one study included non-bone marrow-derived cells; one study compared allogeneic cells with a control group; one study was a literature review; and one study was performed in animals.

Risk of bias in included studies

A summary of the risk of bias in individual studies is given below and in Figure 2. Further details of our assessment of risk of bias can been found in the Characteristics of included studies tables. We considered only five trials to have a low risk of bias across all domains (Jimenez-Quevedo 2011; Mathiasen 2015; Perin 2011; Perin 2012a; Van Ramshorst 2009).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

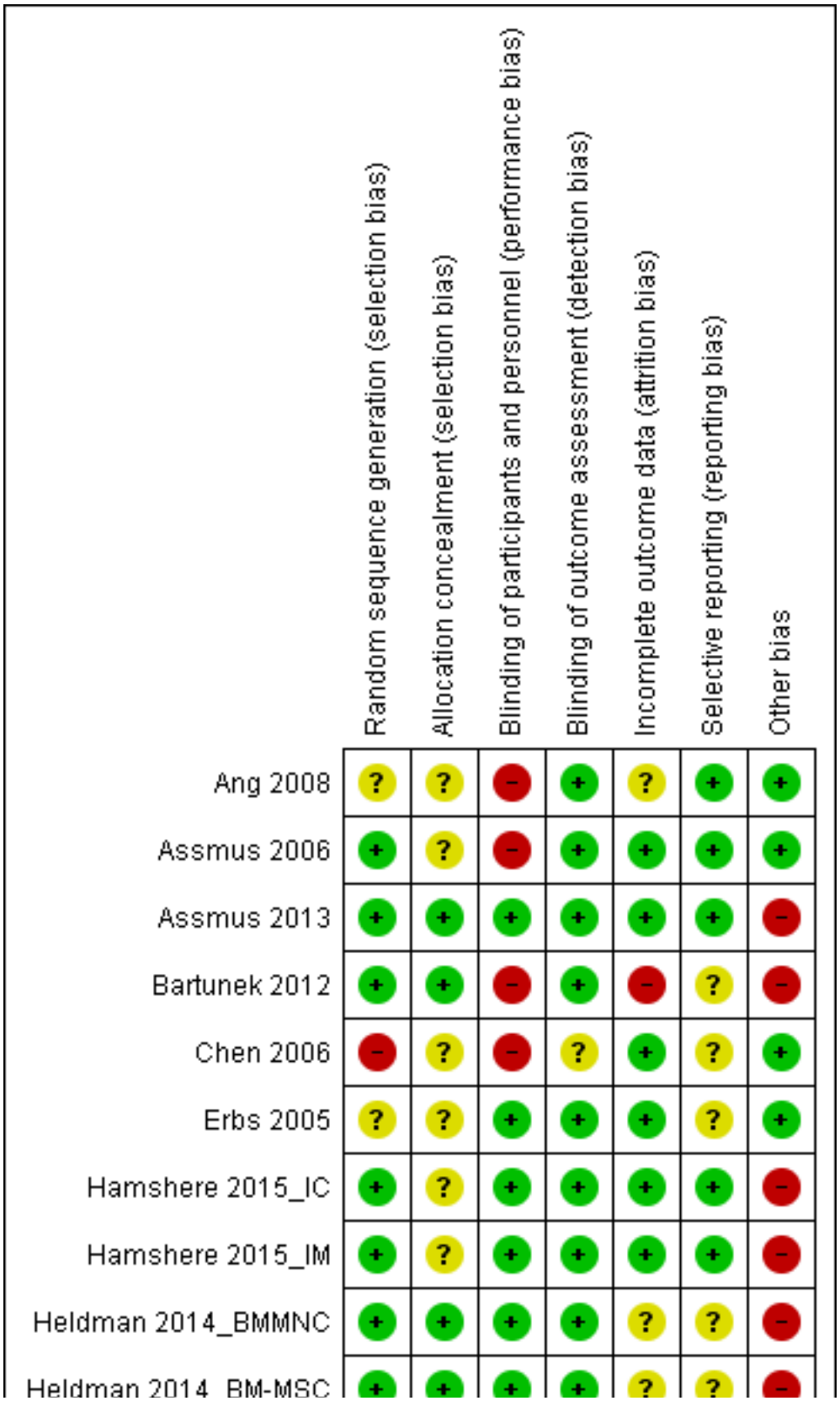


Figure 2. (Continued)

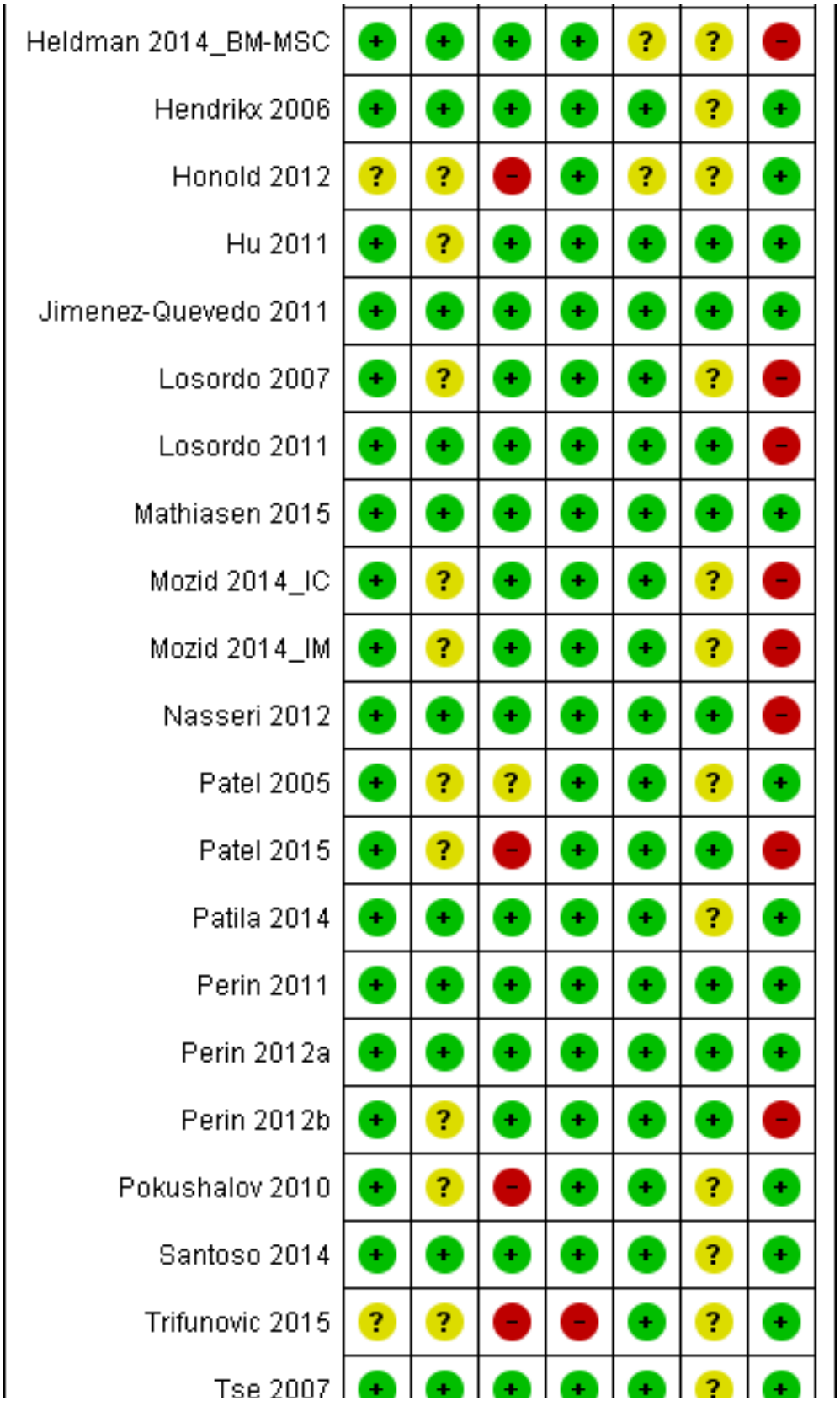
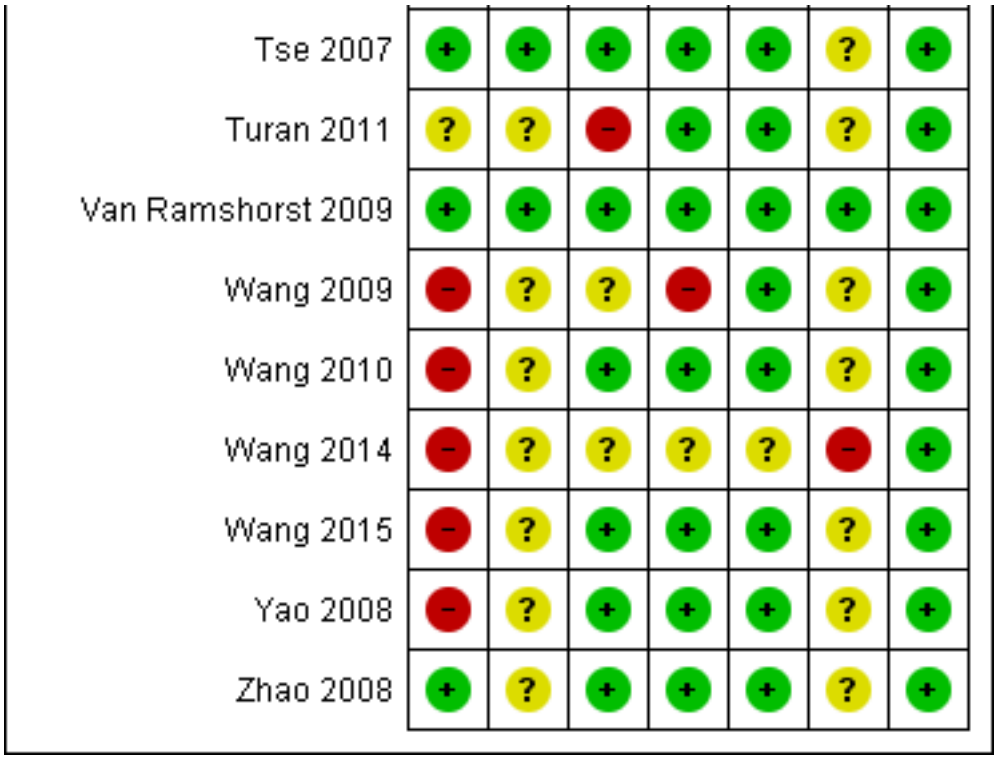


Figure 2. (Continued)



Allocation

Twenty-seven studies provided details of randomisation methods with a low risk of bias from random sequence generation. These methods included sequentially numbered, sealed envelopes (Hendrikx 2006; Patila 2014; Van Ramshorst 2009), simple randomisation table (Santoso 2014; Tse 2007), or randomisation codes generated electronically (Assmus 2006; Assmus 2013; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hu 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Patel 2015; Perin 2012a; Perin 2012b; Pokushalov 2010; Zhao 2008), by a study statistician (Losordo 2007; Perin 2011), by picking a coloured ball (Patel 2005), or via a centralised site-independent process (Bartunek 2012; Jimenez-Quevedo 2011; Losordo 2011; Nasseri 2012). Of these, 15 studies described appropriate methods of allocation concealment with a low risk of bias (Assmus 2013; Bartunek 2012; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hendrikx 2006; Jimenez-Quevedo 2011; Losordo 2011; Mathiasen 2015; Nasseri 2012; Patila 2014; Perin 2011; Perin 2012a; Santoso 2014; Tse 2007; Van Ramshorst 2009), whilst in 12 studies allocation concealment was unclear (Assmus 2006; Hamshere 2015_IC; Hamshere 2015_IM; Hu 2011; Losordo 2007; Mozid 2014_IC; Mozid 2014_IM; Patel 2005; Patel 2015; Perin 2012b; Pokushalov 2010; Zhao 2008).

We found five trials in which no description was given as to what methods were used to generate the random sequence to be at unclear risk of selection bias (Ang 2008; Erbs 2005; Honold 2012; Trifunovic 2015; Turan 2011). The method of generation of randomisation sequence was also not reported in six Chinese trials, which we deemed to have a high risk of bias (Chen 2006; Wang 2009; Wang 2010; Wang 2014; Wang 2015; Yao 2008).

Blinding

In 24 studies, participants randomised to the control group received a placebo injection (Assmus 2013; Erbs 2005; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hendrikx 2006; Hu 2011; Losordo 2007; Losordo 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Patila 2014; Perin 2012a; Perin 2012b; Santoso 2014; Tse 2007; Van Ramshorst 2009; Wang 2010; Wang 2015; Yao 2008; Zhao 2008), with all but one study reporting that the control group underwent bone marrow aspiration (Mathiasen 2015); we judged these trials to be at a low risk of performance bias. We deemed two additional trials to have a low risk of performance bias, as although no placebo was administered, participants in the control group underwent a sham procedure (Jimenez-Quevedo 2011; Perin 2011).

We considered nine trials in which no placebo was administered to have a high risk of performance bias (Ang 2008; Assmus 2006; Bartunek 2012; Chen 2006; Honold 2012; Patel 2015; Pokushalov 2010; Trifunovic 2015; Turan 2011). Two trials were reported as "double-blind" (Wang 2014), or as having blinded participants (Patel 2005), but no details of a placebo were given; a third trial reported no details of blinding (Wang 2009). We judged the risk of performance bias in these trials to be unclear.

We assessed two trials as having a high risk of detection bias: one was reported as an "open-label" trial with no details of blinding given (Trifunovic 2015), and one trial reported that outcome assessors were not blinded (Wang 2009). We judged two trials in which which blinding of outcome assessors was not reported as at unclear risk of detection bias (Chen 2006; Wang 2014). All other trials reported the blinding of outcome assessors.

Incomplete outcome data

One trial had a high risk of attrition bias (Bartunek 2012): 11 participants randomised to the cell therapy group were excluded from the analyses as they did not receive the study intervention. In the study report, these participants were analysed as part of the control group (although in this review they have been excluded). The risk of attrition bias was unclear in four studies in which some participants were excluded from the analyses without sufficient explanation (Ang 2008; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Honold 2012). We also attributed an unclear risk of attrition bias to one study reported in abstract form only (Wang 2014). In all other trials, any withdrawals or losses to follow-up were similar in both treatment arms with reasons for withdrawals fully documented.

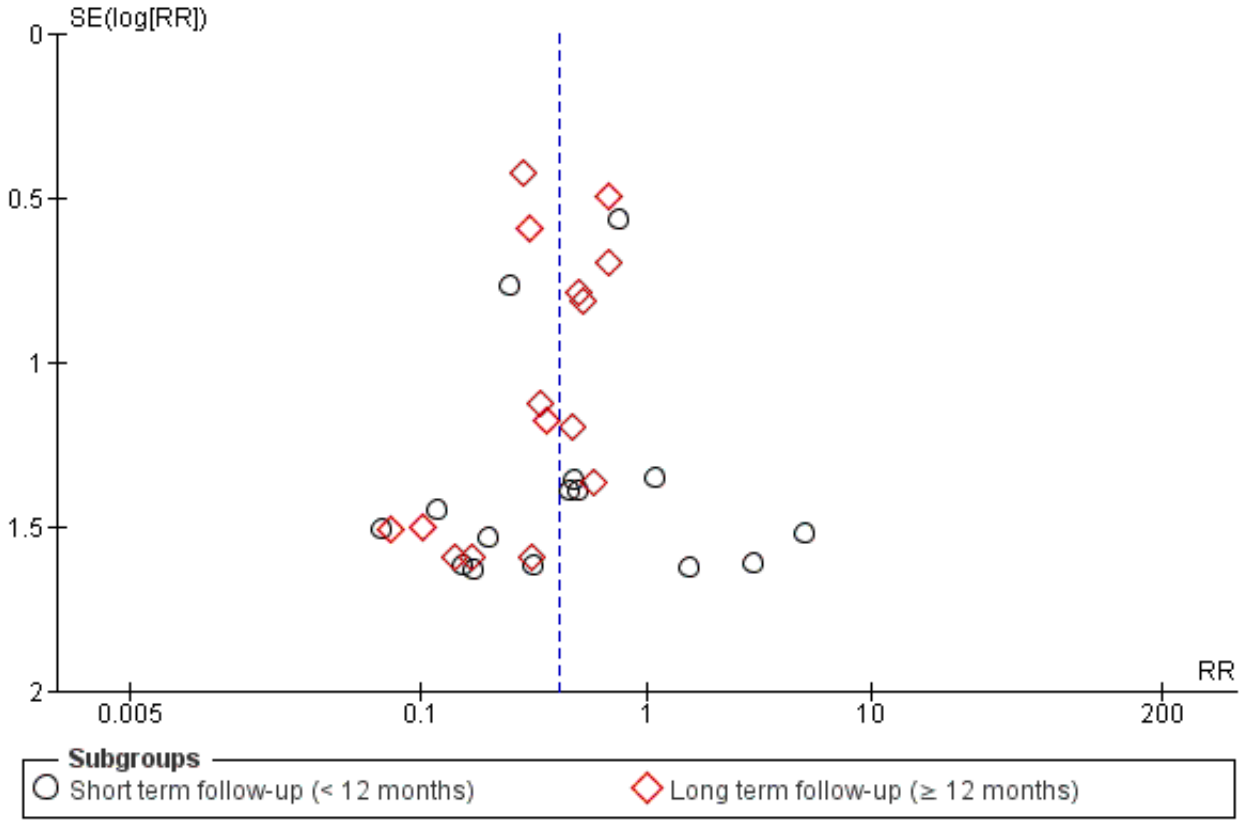
Selective reporting

We attributed a high risk of reporting bias to one study in which results have only been published as a conference abstract (Wang 2014). Twenty-two trials were prospectively registered on a clinical trial database. Of these, 13 studies reported all outcomes described in the the trial protocol, with a low risk of reporting bias (Ang 2008; Assmus 2006; Assmus 2013; Hu 2011; Jimenez-Quevedo 2011; Losordo 2011; Mathiasen 2015; Nasseri 2012; Patel 2015; Perin 2011; Perin 2012a; Perin 2012b; Van Ramshorst 2009), whilst in seven studies, we observed some differences between outcomes described in the study protocol and those reported. Specifically, three studies reported results for additional outcomes (Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Santoso 2014); two studies were a pilot study report of secondary outcomes only (Mozid 2014_IC; Mozid 2014_IM); one study failed to report six-month results as described in the protocol (Patila 2014); and in one study, different definitions of primary and secondary outcomes were reported in the study protocol and the publication of results (Bartunek 2012). We deemed the risk of reporting bias in these seven studies to be unclear. For two trials reported in abstract form only (Hamshere 2015_IC; Hamshere 2015_IM), we requested and obtained data for all outcomes presented in the trial protocol from the authors, therefore we judged these trials to be at low risk of reporting bias.

We identified no prospectively registered trial protocol for the remaining 15 trials, and although the results of all outcomes described in the methods were reported, we judged the risk of reporting bias to be unclear.

We identified no obvious asymmetry from a funnel plot for mortality (Figure 3). In a regression test for asymmetry (Egger's test), the model intercept was -0.02 (P = 0.90) at short-term follow-up and -0.004 (P = 0.98) at long-term follow-up, with no evidence of publication bias. However, of 28 identified ongoing trials, 11 trials (787 participants) were recorded as having been completed or were due to have been completed in advance of our search date, but we identified no publications for them and no study results were posted on the trial database. We therefore cannot rule out the possibility of publication bias.

Figure 3. Funnel plot of comparison: 1 Stem cells versus no stem cells, outcome: 1.1 Mortality.



Other potential sources of bias

Twenty-eight studies reported details of study funding or sponsorship (Ang 2008; Assmus 2006; Assmus 2013; Bartunek 2012; Erbs 2005; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hu 2011; Jimenez-Quevedo 2011; Losordo 2007; Losordo 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Patel 2015; Patila 2014; Perin 2011; Perin 2012a; Perin 2012b; Santoso 2014; Tse 2007; Van Ramshorst 2009; Wang 2015; Yao 2008; Zhao 2008. The majority of these studies were funded entirely by academic or healthcare research grants, or both and received no commercial sponsorship. Four studies acknowledged provision of equipment (Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Losordo 2007; Perin 2012a), and two studies acknowledged receipt of consultant fees, from Biosense Webster, in Tse 2007, and Cook Medical (Patel 2015). Four studies declared full commercial sponsorship: from Aldagen (Perin 2012b), Baxter Healthcare (Losordo 2011), Cardio3 BioSciences (Bartunek 2012), and Harvest Technologies (Patel 2015), and nine studies declared partial commercial funding: from Baxter Healthcare (Losordo 2007), Chugai Pharma UK and the Cordis Corporation (Hamshere 2015_IC; Hamshere 2015_IM; Mozid 2014_IC; Mozid 2014_IM), Miltenyi Biotec (Nasseri 2012), and BioCardia (Heldman 2014_BMMNC; Heldman 2014_BM-MSC), and an unrestricted grant from t2cure GmbH (Assmus 2013). We judged all 13 studies that received some degree of commercial funding to be at high risk of bias. The primary investigator in four included trials is also an author of this review (Hamshere 2015_IC; Hamshere 2015_IM; Mozid 2014_IC; Mozid 2014_IM).

Effects of interventions

See: **Summary of findings for the main comparison** Bone marrow-derived cell therapy for people with chronic ischaemic heart disease and congestive heart failure

An overview of results for the primary outcomes of mortality and periprocedural adverse events, and for morbidity outcomes (non-fatal MI, rehospitalisation for HF, arrhythmias, composite major adverse clinical events) and LVEF measured by MRI is given in Summary of findings for the main comparison. We excluded quality of life and performance status outcomes since different measures are likely to be used for different participant diagnoses, and therefore fewer trials are likely to have reported each of these outcomes.

In one study (Yao 2008), continuous measures were reported as mean +/- standard deviation. However, visual inspection of the data revealed that the standard deviations were considerably lower than might be expected for all continuous outcomes. This study also reported P values for statistical comparisons between the baseline and follow-up data using paired t-tests. However, we could not identify the reported significance values, either using the standard deviations provided, or based on an assumption that the values were in fact standard errors. We therefore could not verify or include continuous data from this study.

Primary outcomes

Mortality

All but one study included mortality as an outcome (Wang 2014), which was published in abstract form only (see Table 3; Table 4).

Of 33 studies that reported mortality rates during short-term follow-up (< 12 months), 15 trials reported deaths (Ang 2008; Assmus 2006; Assmus 2013; Hendrikx 2006; Hu 2011; Jimenez-Quevedo 2011; Losordo 2011; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Nasseri 2012; Perin 2012a; Pokushalov 2010; Van Ramshorst 2009; Zhao 2008), whilst the remaining 18 trials reported no deaths. In all trials, over short-term follow-up, the mortality rate of 1.6% (15/963) in participants who received cell therapy was lower than that observed in participants who received no cells (4.0%, 27/674) (risk ratio (RR) 0.48, 95% confidence interval (CI) 0.26 to 0.87; participants = 1637; studies = 33; I^2 = 0%) (Analysis 1.1). However, in the subset of trials with a low risk of selection bias, the effect of cell therapy on short-term mortality was no longer seen (RR 0.69, 95% CI 0.32 to 1.50; participants = 744; studies = 14; I^2 = 0%) (Analysis 8.1). Similarly, no effect of cell therapy on short-term mortality was shown when studies with a high or unclear risk of performance bias were excluded (RR 0.58, 95% CI 0.29 to 1.16; participants = 1216; studies = 25; I^2 = 0%) (Analysis 9.1). However, results appeared to be robust to attrition bias (RR 0.48, 95% CI 0.26 to 0.89; participants = 1449; studies = 28; I^2 = 0%) (Analysis 10.1).

Seven studies reported reasons for short-term mortality in participants who had received cell therapy, which included perforated oesophageal ulcer complicated by mediastinitis seven days postoperatively (Hendrikx 2006), cardiogenic shock (Jimenez-Quevedo 2011), death on day 158 shortly after surgery for intestinal ischaemia (Mathiasen 2015), pump failure leading to death on day 29 after therapy (Perin 2012a), myocardial ischaemia leading to acute HF at 2.5 months (Van Ramshorst 2009), ventricular fibrillation five hours postoperatively leading to death on day three (Zhao 2008), and cerebral vessel accident during six-month follow-up (Zhao 2008). Cause of death in one study was not specified in detail but reported as "cardiac" in four participants and "non-cardiac" in one participant (Assmus 2013). In participants who did not receive cell therapy, reasons for short-term mortality included multiple organ failure secondary to low cardiac output syndrome (Hendrikx 2006), fatal MI at 3.5 months (Jimenez-Quevedo 2011), death during injection (Losordo 2007), terminal HF at day 182 (Mathiasen 2015), pneumonia, mediastinitis and sepsis with death on day 22 (Nasseri 2012), candida sepsis on day 8 after left ventricular failure (Nasseri 2012), and death reported as "cardiac" (five participants) or "non-cardiac" (one participant) (Assmus 2013).

Of the 21 studies reporting mortality over long-term follow-up (≥ 12 months), 15 studies reported deaths (Assmus 2013; Bartunek 2012; Chen 2006; Erbs 2005; Heldman 2014_BM-MSC; Honold 2012; Hu 2011; Losordo 2011; Nasseri 2012; Patel 2005; Patel 2015; Pokushalov 2010; Santoso 2014; Trifunovic 2015; Tse 2007), with a mortality rate of 4.8% (28/587) in participants who received cell therapy compared with 15.4% (65/423) in those who received no cells. Meta-analysis of all available trials showed that cell therapy reduced the risk of long-term mortality (RR 0.38, 95% CI 0.25 to 0.58; participants = 1010; studies = 21; I^2 = 0%) (Analysis 1.1). Sensitivity analyses restricted to those trials with a low risk of bias from randomisation sequence generation and allocation concealment showed that the reduced risk of mortality at long-term follow-up in participants who received cell therapy was robust to selection bias (RR 0.42, 95% CI 0.21 to 0.87; participants = 491; studies = 9; I^2 = 0%; low-quality evidence) (Analysis 8.1). Similarly, analysis of the subset of trials that blinded participants and clinicians showed that the effect of cell therapy on long-term mortality was robust

to performance bias (RR 0.43, 95% CI 0.21 to 0.86; participants = 624; studies = 13; I^2 = 0%) (Analysis 9.1). The effect of cell therapy also remained when trials with a high or unclear risk of attrition bias were excluded (RR 0.39, 95% CI 0.25 to 0.60; participants = 883; studies = 17; I^2 = 0%) (Analysis 10.1).

Eleven studies reported reasons for mortality at long-term follow-up. In participants who received cell therapy, reported causes of death were sepsis after elective cardiac transplant at 21 months (Bartunek 2012), lung cancer at seven months (Hu 2011), cerebrovascular haemorrhage at six years (Trifunovic 2015), pulmonary malignancy at six years (Trifunovic 2015), HF or sudden cardiac death, or both at 31 months (Nasseri 2012), cardiac death on day 239 (Heldman 2014_BM-MSC), "sudden death" (Chen 2006), and death due to cardiac (three participants) or non-cardiac causes (two participants) (Patel 2015). Reported deaths in participants who did not receive cell therapy were due to ventricular fibrillation, sudden death, and HF (two participants) (Chen 2006), angina followed by sudden death secondary to AMI (Erbs 2005), progressive HF (Honold 2012), AMI (Tse 2007), HF deterioration (Bartunek 2012), sudden cardiac death (Bartunek 2012; Santoso 2014), systemic infection (Hu 2011), gastrointestinal bleeding (Hu 2011), cardiac death on day 115 (Heldman 2014_BM-MSC), HF and/or sudden cardiac death at 34 months (Nasseri 2012), "cardiac" death (Patel 2015), gastrointestinal bleeding from carcinoma of the colon (Santoso 2014), and cardiac events in four participants (Trifunovic 2015).

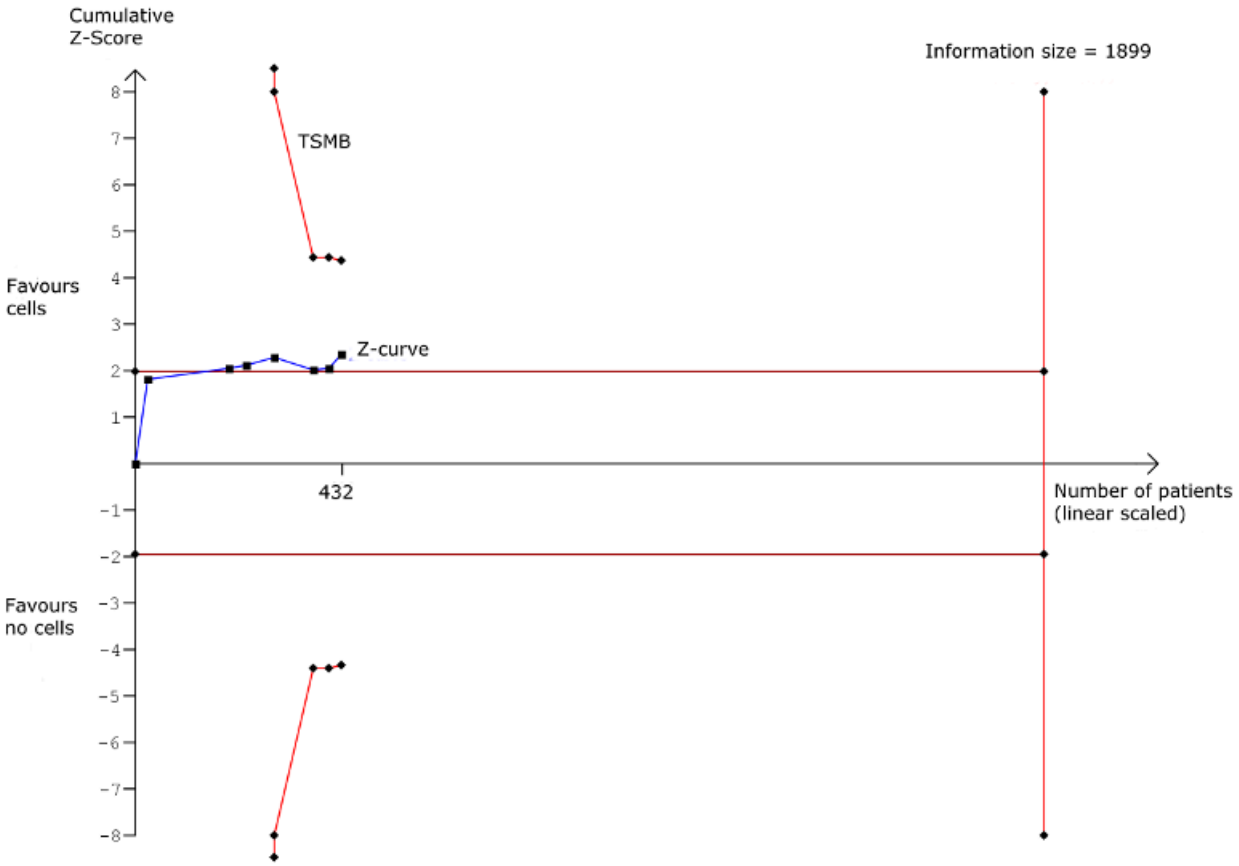
Subgroup analyses

Although primary analyses of mortality showed no evidence for heterogeneity, values of I^2 are known to be underestimated, especially when there are few events or a limited number of studies included in a meta-analysis (Huedo-Medina 2006; Ioannidis 2007). We therefore performed prespecified subgroup analyses on the primary outcome of mortality as described in the Methods section. Tests for differences between subgroups revealed no differences in mortality between treatment groups, either at short-term or long-term follow-up when participants were grouped according to cell dose (test for subgroup differences, short term: P = 0.23 (Analysis 2.1); long term: P = 0.29 (Analysis 2.2)), baseline cardiac function (short term: P = 0.13 (Analysis 3.1); long term: P = 0.35 (Analysis 3.2)), route of cell administration (short term: P = 0.90 (Analysis 4.1); long term: P = 0.12 (Analysis 4.2)), cell type (short term: P = 0.89 (Analysis 5.1); long term: P = 0.65 (Analysis 5.2)), participant diagnosis (short term: P = 0.57 (Analysis 6.1); long term: P = 0.29 (Analysis 6.2)), or use of co-interventions (short term: P = 0.15 (Analysis 7.1); long term: P = 0.37 (Analysis 7.2)). Notably, subgroup analysis by participant diagnosis revealed a lower risk of long-term mortality associated with cell therapy in participants irrespective of diagnosis: chronic ischaemic heart disease (CIHD) (RR 0.52, 95% CI 0.27 to 0.99; participants = 389; studies = 9; I^2 = 0%), HF secondary to IHD (RR 0.33, 95% CI 0.19 to 0.58; participants = 401; studies = 9; I^2 = 0%), and refractory angina (RR 0.11, 95% CI 0.01 to 0.91; participants = 220; studies = 3; I^2 = 0%) (Analysis 6.2), and irrespective of whether co-interventions were used (co-interventions: RR 0.47, 95% CI 0.26 to 0.88; participants = 312; studies = 6; I^2 = 0%; no co-interventions: RR 0.32, 95% CI 0.19 to 0.56; participants = 698; studies = 15; I^2 = 0%) (Analysis 7.2).

Trial sequential analyses

In trial sequential analysis of long-term mortality, the cumulative Z-curve crossed both the conventional threshold but not the adjusted trial sequential monitoring boundary, which may be indicative of an inflated type I error rate (see Figure 4). Furthermore, the existing evidence, based on a total of 432 participants, falls considerably short of the required information size of 1899, suggesting that the apparent beneficial effect of cell therapy on long-term mortality based on the existing evidence lacks robustness.

Figure 4. Trial sequential analysis: Mortality at long-term follow-up (≥ 12 months). TSMB = trial sequential monitoring boundary; horizontal red lines indicate conventional significance threshold.



Periprocedural adverse events

A summary of periprocedural adverse events in each study is included in Table 5. All but three studies reported periprocedural adverse events (or lack of) (Hamshere 2015_IC; Hamshere 2015_IM; Wang 2014), and a fourth study reported adverse events for shockwave treatment but not cell therapy (Assmus 2013).

Seven studies reported adverse events associated with the administration of G-CSF. The most common reactions were bone or muscular pain (Honold 2012; Jimenez-Quevedo 2011; Losordo 2011; Mozid 2014_IC; Mozid 2014_IM), headache (Erbs 2005; Honold 2012), and pyrexia (Erbs 2005; Mozid 2014_IC; Mozid 2014_IM). Two studies reported increased frequency or severity of angina, or both associated with G-CSF administration (Losordo 2007; Losordo 2011), and one study reported that two participants developed CHF (Losordo 2011).

Reactions associated with bone marrow aspiration were rare: only two studies reported participants with haematomas at the bone marrow harvest site (Patel 2005; Patel 2015). Adverse events during the mapping or injection procedure included ventricular tachycardia in seven participants (three cell therapy (Bartunek 2012; Mathiasen 2015; Perin 2012a), three placebo (Losordo 2007; Perin 2012b), one unknown (Mozid 2014_IM)); ventricular fibrillation in one control participant (Perin 2012b); atrial fibrillation in one participant (Mozid 2014_IM); and the development of transient complete heart block periprocedure requiring temporary pacing only in one participant (Mozid 2014_IM).

Three cell therapy participants experienced transient pulmonary oedema during injection of cells (Chen 2006); a thrombus was observed in one participant on mapping catheter tip as removed (Losordo 2011); and two participants experienced visual disturbances: one reported double vision and dizziness during the injection procedure (Mathiasen 2015), and one participant with pre-existing ophthalmic migraines experienced blurred vision after the intervention (Bartunek 2012). Two participants experienced a myocardial perforation: one with haemothorax (successfully treated) (Losordo 2011), and one resulting in cardiac tamponade followed by death (Losordo 2011). One participant experienced a limited retrograde catheter-related dissection of the abdominal aorta (Perin 2012a).

Serious early postoperative adverse events were rare. In the cell therapy group, one participant died on postoperative day 7 from a perforated oesophageal ulcer complicated my mediastinitis (Hendrikx 2006); one participant developed refractory ventricular fibrillation five hours postoperatively and died on day 3 (Zhao 2008); and one death was reported within 30 days of treatment (cause of death not reported but not considered to be related to cell therapy) (Ang 2008). Postprocedural transient left bundle

branch block (resolved in 24 hours) was seen in one participant (Perin 2011); in-hospital MI occurred in one participant (Assmus 2006); one participant suffered a stroke on postoperative day 12 (Mathiasen 2015); and one participant developed ventricular fibrillation on day 5 but was successfully resuscitated (Zhao 2008). In the control group, one participant died on day 5 from multiorgan failure secondary to low cardiac output syndrome (Hendrikx 2006); one participant died on day 8 after developing *Candida* sepsis following left ventricular failure (Nasseri 2012); one participant died on day 22, no reason given (Nasseri 2012); one participant died from suspected acute left ventricular failure six days after discharge (Mozid 2014_IM); and one participant died within 30 days of treatment with no reason given (Ang 2008). Postprocedural transient left bundle branch block (resolved in 24 hours) was seen in one participant (Perin 2011); one participant developed a pericardial effusion two days after the procedure, and pericardiocentesis was performed (Van Ramshorst 2009); and ventricular arrhythmia was detected during monitoring in one participant (Assmus 2006). Transient fever but no sepsis occurred in one control participant (Perin 2011). One study reported that two participants (unclear which treatment arm) experienced neurological complications but recovered (Hu 2011).

We made no formal comparisons of periprocedural adverse events due to differences in the definition and reporting of adverse events between studies. We acknowledge that there may be a risk of reporting bias for this outcome, as few studies clearly defined periprocedural events.

Secondary outcomes

Morbidity

(a) Non-fatal myocardial infarction

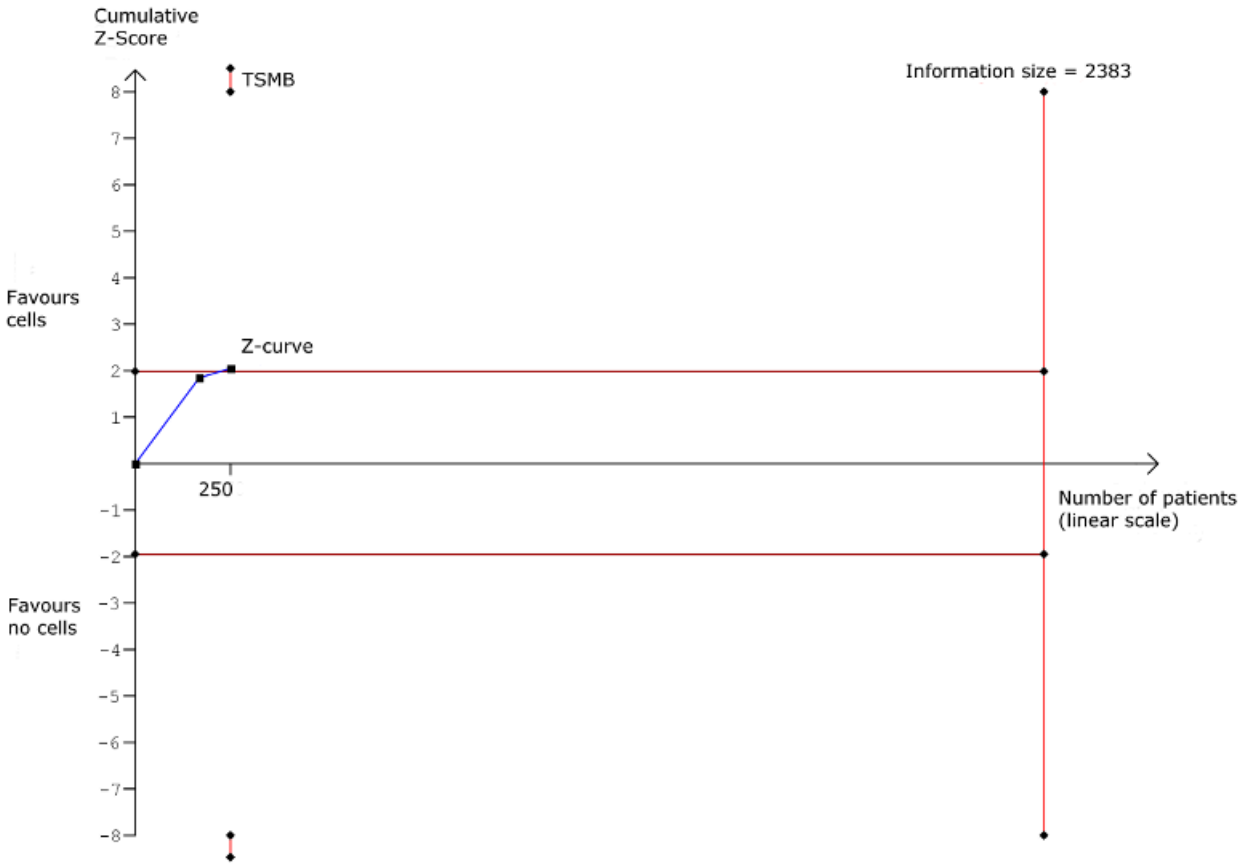
Twenty studies reported infarction as an outcome at short-term follow-up (see Table 3; Table 4) (Ang 2008; Assmus 2006; Hamshere 2015_IC; Hamshere 2015_IM; Honold 2012; Hu 2011; Jimenez-Quevedo 2011; Losordo 2007; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Perin 2011; Perin 2012a; Perin 2012b; Tse 2007; Van Ramshorst 2009; Wang 2009; Wang 2010; Yao 2008; Zhao 2008). There was no evidence of a difference in the risk of non-fatal MI between participants who received cell therapy and those who did not (RR 0.60, 95% CI 0.17 to 2.15; participants = 881; studies = 20; I^2 = 0%) (Analysis 1.2), consistent with findings when studies were restricted to those with a low risk of selection bias (RR 0.50, 95% CI 0.05 to 4.58; participants = 288; studies = 6; I^2 = 0%) (Analysis 8.2).

Of the nine studies reporting infarction as an outcome at long-term follow-up (Assmus 2013; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Honold 2012; Losordo 2007; Losordo 2011; Patila 2014), meta-analysis showed that cell therapy was associated with a lower risk of non-fatal MI at long-term follow-up (RR 0.40, 95% CI 0.17 to 0.93; participants = 461; studies = 9; I^2 = 0%) (Analysis 1.2). Sensitivity analysis showed that the effect of cell therapy was robust to risk of selection bias (RR 0.38, 95% CI 0.15 to 0.97; participants = 345; studies = 5; I^2 = 0%) (Analysis 8.2).

Trial sequential analysis

Trial sequential analysis applied to non-fatal MI at long-term follow-up (Figure 5) showed that the cumulative Z-curve crossed conventional significance thresholds but not the adjusted trial sequential monitoring boundaries, which may be indicative of an inflated type I error rate. Furthermore, the existing evidence falls considerably short of the required information size of 2383, suggesting that the apparent beneficial effect of cell therapy on non-fatal MI at long-term follow-up based on existing evidence lacks robustness.

Figure 5. Trial sequential analysis: Non-fatal myocardial infarction at long-term follow-up (≥ 12 months). TSMB = trial sequential monitoring boundary; horizontal red lines indicate conventional significance threshold.



(b) Rehospitalisation due to heart failure

Ten studies reported hospital readmission for HF at short-term follow-up (see Table 3; Table 4) (Assmus 2006; Assmus 2013; Hamshere 2015_IC; Hamshere 2015_IM; Honold 2012; Mathiasen 2015; Mozid 2014_IC; Mozid 2014_IM; Perin 2012a; Yao 2008). In participants who received cell therapy, 21/297 (7.0%) were rehospitalised for HF compared with 22/185 (11.9%) who did not, with no evidence of a difference between groups (RR 0.63, 95% CI 0.36 to 1.12; participants = 482; studies = 10; I^2 = 0%) (Analysis 1.3).

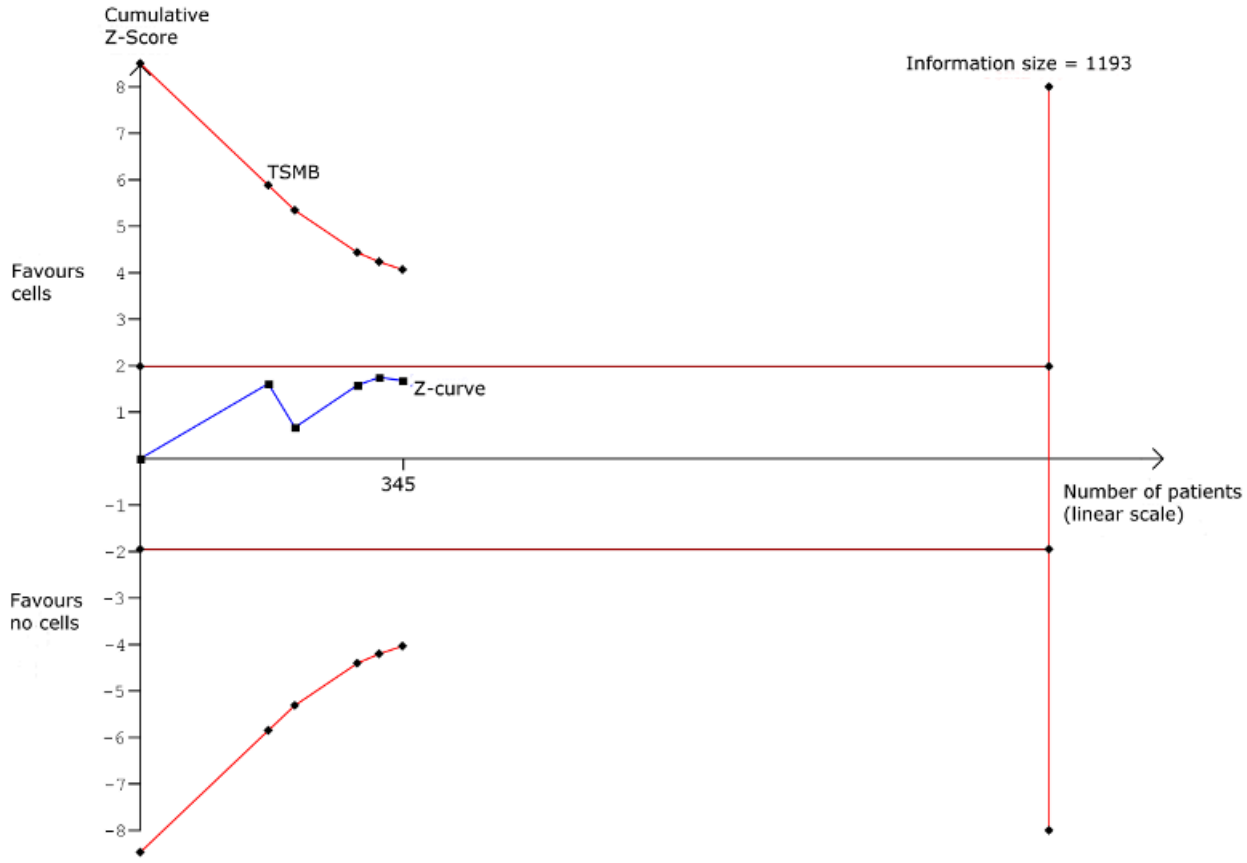
Of the 10 studies reporting this outcome at long-term follow-up (Assmus 2013; Bartunek 2012; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Honold 2012; Losordo 2011; Patel 2015; Patila 2014), incidences of rehospitalisation occurred in 21/302 participants (7.0%) who received cell therapy compared with 26/193 (13.5%) who did not (RR 0.62, 95% CI 0.36 to 1.04; participants = 495; studies = 10; I^2 = 0%) (Analysis 1.3).

In trials with a low risk of selection bias, sensitivity analysis showed no effect of cell therapy on rehospitalisation due to heart failure at either short-term (RR 0.65, 95% CI 0.32 to 1.32; participants = 234; studies = 3; I^2 = 15%) or long-term follow-up (RR 0.63, 95% CI 0.36 to 1.09; participants = 375; studies = 6; I^2 = 0%) (Analysis 8.3).

Trial sequential analysis

Trial sequential analysis applied to rehospitalisation due to HF at long-term follow-up (Figure 6) showed that the cumulative Z-curve crossed neither the conventional significance thresholds nor the adjusted trial sequential monitoring boundaries. The existing evidence from 345 participants falls considerably short of the required information size of 1193 to draw reliable conclusions about the effect of cell therapy on rehospitalisation for HF.

Figure 6. Trial sequential analysis: Rehospitalisation due to heart failure at long-term follow-up (≥ 12 months). TSMB = trial sequential monitoring boundary; horizontal red lines indicate conventional significance threshold.



(c) Incidence of arrhythmias

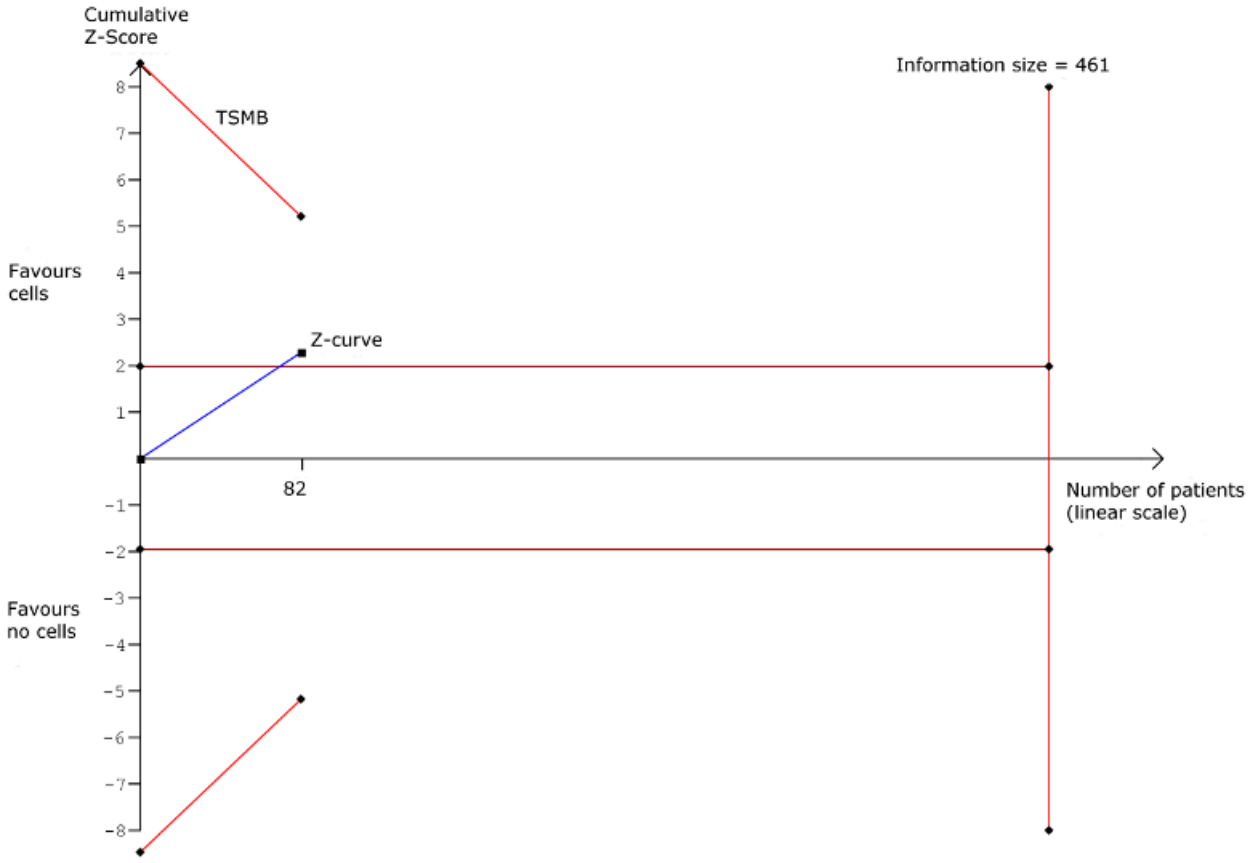
Twenty-four studies reported arrhythmias as an outcome at short-term follow-up (see Table 3; Table 4), although one study reported arrhythmias as the number of cumulative events rather than incidence (Wang 2015), and another included nine participants in the control group who were randomised to the treatment arm (Bartunek 2012), and was therefore excluded from the analysis. In trials that defined arrhythmia, the majority reported ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation); two trials reported incidences of atrial fibrillation (Hu 2011; Mathiasen 2015). In the remaining 22 studies, 11 reported incidences of arrhythmias (Assmus 2006; Hamshere 2015_IC; Hamshere 2015_IM; Jimenez-Quevedo 2011; Losordo 2007; Mathiasen 2015; Mozid 2014_IM; Perin 2012b; Santoso 2014; Wang 2010; Zhao 2008). Arrhythmias occurred in 11/550 participants (2.0%) who received cell therapy compared with 12/409 (2.9%) who did not (RR 0.70, 95% CI 0.33 to 1.45; participants = 959; studies = 22; I^2 = 0%) (Analysis 1.4). In trials with a low risk of selection bias, sensitivity analysis showed no effect of cell therapy on incidence of arrhythmias at short-term follow-up (RR 0.77, 95% CI 0.18 to 3.21; participants = 224; studies = 6; I^2 = 0%) (Analysis 8.4).

Of five studies reporting incidences of arrhythmia at long-term follow-up (Assmus 2013; Hamshere 2015_IC; Hamshere 2015_IM; Hu 2011; Losordo 2007), 8/199 participants (4.0%) in the cell therapy group experienced arrhythmias compared with 16/164 (9.8%) in the control group (RR 0.46, 95% CI 0.22 to 0.97; participants = 363; studies = 7; I^2 = 0%) (Analysis 1.4); this finding occurred in one study with a low risk of selection bias (RR 0.42, 95% CI 0.18 to 0.99; participants = 82; studies = 1; I^2 = 0%) (Analysis 8.3).

Trial sequential analysis

Trial sequential analysis applied to incidence of arrhythmias at long-term follow-up (Figure 7) showed that the cumulative Z-curve from a single trial with a low risk of selection bias crossed the conventional significance thresholds but not the adjusted trial sequential monitoring boundaries. The evidence from this single trial of 82 participants falls considerably short of the required information size of 461 to draw reliable conclusions about the effect of cell therapy on incidence of arrhythmias.

Figure 7. Trial sequential analysis: Arrhythmias at long-term follow-up (≥ 12 months). TSMB = trial sequential monitoring boundary; horizontal red lines indicate conventional significance threshold.



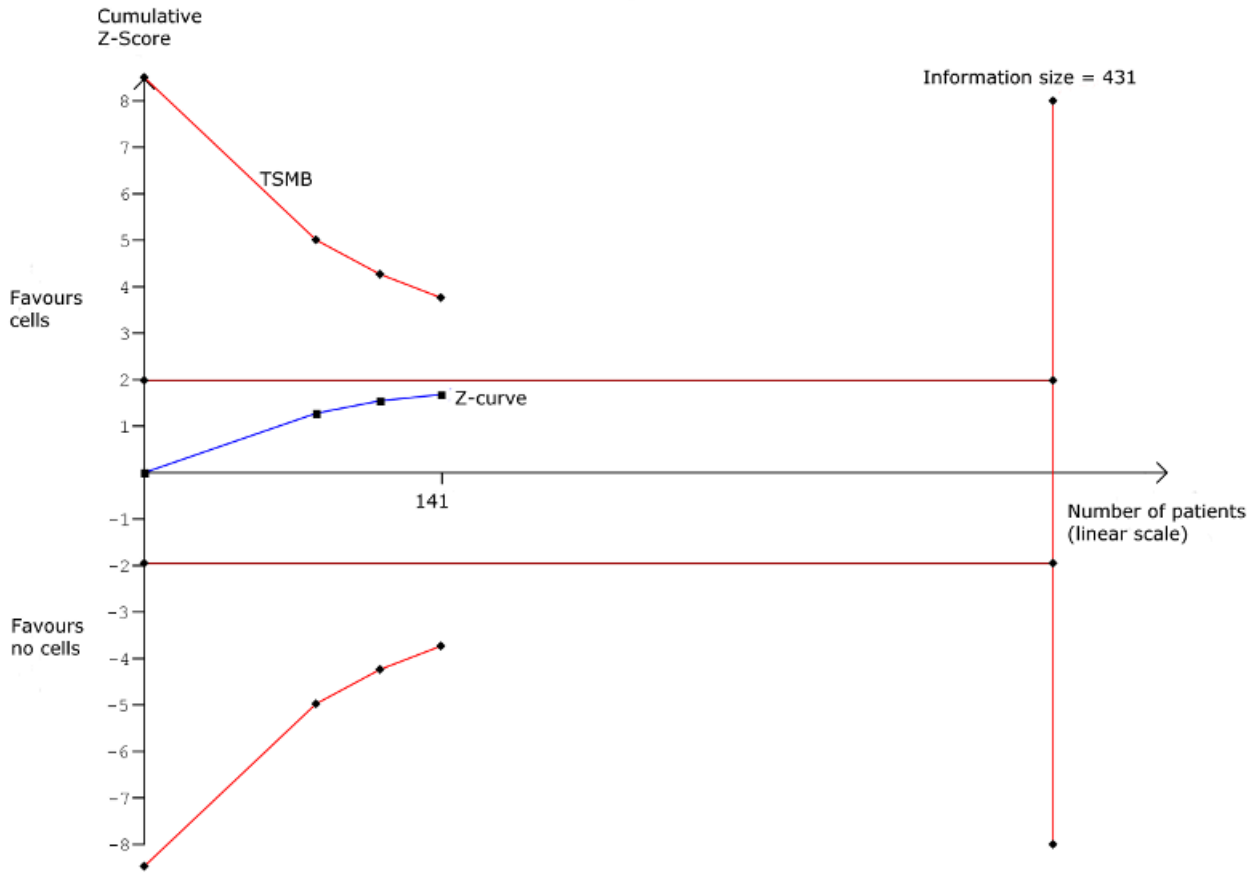
(d) Composite measure of mortality, non-fatal MI, and rehospitalisation for HF

Nine studies reported composite measures of major adverse clinical events, defined here as mortality, non-fatal MI, and rehospitalisation for HF (see Table 3; Table 4), of which seven reported the composite of mortality, non-fatal MI, and rehospitalisation for HF (Assmus 2006; Assmus 2013; Hamshere 2015_IC; Hamshere 2015_IM; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hu 2011; Mozid 2014_IC; Mozid 2014_IM). One study defined composite major adverse clinical events (MACE) as cardiovascular death, non-fatal MI, ischaemic stroke, need for revascularisation, and procedure-related complications (Jimenez-Quevedo 2011), and another reported the composite of death, MI, urgent revascularisation, worsening HF, and acute coronary syndrome (Losordo 2011); we excluded these studies from analyses. There was no evidence of a difference between treatment arms at either short-term (RR 0.51, 95% CI 0.18 to 1.42; participants = 288; studies = 8; I^2 = 0%) or long-term follow-up (RR 0.68, 95% CI 0.41 to 1.12; participants = 201; studies = 5; I^2 = 0%) (Analysis 1.5). These findings were consistent with those from sensitivity analyses of studies with a low risk of selection bias at long-term follow-up (RR 0.64, 95% CI 0.38 to 1.08; participants = 141; studies = 3; I^2 = 0%) (Analysis 8.5). No studies at low risk of selection bias reported this outcome.

Trial sequential analysis

Trial sequential analysis applied to the composite measure of MACE at long-term follow-up (Figure 8) showed that the cumulative Z-curve crossed neither the conventional significance thresholds nor the adjusted trial sequential monitoring boundaries. The existing evidence from 141 participants falls considerably short of the required information size of 431 to draw reliable conclusions about the effect of cell therapy on rehospitalisation for HF.

Figure 8. Trial sequential analysis: Composite MACE at long-term follow-up (≥ 12 months). TSMB = trial sequential monitoring boundary; horizontal red lines indicate conventional significance threshold.



Quality of life

(a) Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Seven studies reported MLHFQ scores as a measure of quality of life (Bartunek 2012; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Nasseri 2012; Patel 2015; Perin 2011; Pokushalov 2010), although one study reported results graphically as the percentage of participants showing improvement or deterioration (Bartunek 2012), another reported summary results only (Patel 2015), and in a third study, it was unclear whether mean or median values were reported (Nasseri 2012) (see Table 3; Table 6).

At short-term follow-up, two studies reported MLHFQ values at endpoint (Perin 2011; Pokushalov 2010), and two reported mean change from baseline values (Heldman 2014_BMMNC; Heldman 2014_BM-MSC). Combined analysis showed that quality of life measured by the MLHFQ was higher in participants who had received cell therapy than in those who had not (mean difference (MD) -18.96, 95% CI -31.97 to -5.94; participants = 197; studies = 4; I^2 = 68%) (Analysis 1.6). All but one of these studies also reported MLHFQ at long-term follow-up (Perin 2011), but there was insufficient evidence to show that the difference observed at short-term follow-up was maintained over long-term follow-up (MD -17.80, 95% CI -39.87 to 4.26; participants = 151; studies = 3; I^2 = 93%) (Analysis 1.7).

The number of studies reporting this outcome precluded further investigation of the substantial observed heterogeneity at both short-term and long-term follow-up through subgroup analyses.

(b) Seattle Angina Questionnaire (SAQ)

Five studies reported quality of life measured by the SAQ (Jimenez-Quevedo 2011; Losordo 2007; Losordo 2011; Mathiasen 2015; Van Ramshorst 2009), although two studies presented results graphically (Losordo 2007; Mathiasen 2015), and one reported median values (Jimenez-Quevedo 2011) (see Table 3; Table 6). Evidence from two studies that reported mean change from baseline values found a higher quality of life associated with cell therapy (MD 9.34, 95% CI 2.62 to 16.07; participants = 211; studies = 2; I^2 = 16%) (Analysis 1.8) (Losordo 2011; Van Ramshorst 2009). A single study reporting mean change in SAQ values from baseline at long-term follow-up found no difference between treatment arms (Losordo 2011).

Other reported measures of quality of life included the 36-Item Short Form Health Survey (SF-36) physical and mental scores (Perin 2011), SF-36 (eight dimensions) (Patila 2014), and the Kansas City Cardiomyopathy Questionnaire (Mathiasen 2015).

(c) Angina frequency

Seven studies measured angina frequency, which has been shown to be strongly associated with health-related quality of life outcomes in people with chronic heart disease (Arnold 2014), and can therefore be considered a surrogate measure of quality of life. Angina frequency was reported as the number of episodes per day (Pokushalov 2010), per week (Losordo 2007; Losordo 2011; Mathiasen 2015; Wang 2009; Wang 2010), or per month (Jimenez-Quevedo 2011) (see Table 3; Table 6). One study reported median values at endpoint (Jimenez-Quevedo 2011), and another reported results graphically (Mathiasen 2015). Meta-analysis of four studies reporting angina frequency at follow-up showed that participants who received cell therapy experienced fewer episodes of angina per week than the control group (MD -6.96, 95% CI -11.99 to -1.93; participants = 396; studies = 4; I^2 = 44%), although we observed no difference in three studies reporting mean change from baseline values (MD -1.77, 95% CI -14.61 to 11.08; participants = 167; studies = 3; I^2 = 76%) (Analysis 1.9). There were insufficient studies to explore potential reasons for the substantial observed heterogeneity through subgroup analyses.

Only one study reported angina frequency at long-term follow-up; this study reported fewer angina episodes associated with cell therapy (Pokushalov 2010).

Performance status

(a) New York Heart Association (NYHA) classification

Twenty-three studies reported NYHA classification at short-term follow-up (see Table 3; Table 6). Two studies reported results graphically (Bartunek 2012; Mathiasen 2015); one study reported the number of participants in NYHA class III or IV (Ang 2008); two studies only reported summary results (Santoso 2014; Wang 2014); and in one study there was only one participant in the control group (Mozid 2014_IC); we have therefore excluded these studies from meta-analysis. In 17 studies reporting mean NYHA class at short-term follow-up (Assmus 2006; Assmus 2013; Chen 2006; Hamshere 2015_IC; Hamshere 2015_IM; Honold 2012; Mozid 2014_IM; Nasseri 2012; Patel 2005; Perin 2011; Perin 2012a; Perin 2012b; Pokushalov 2010; Trifunovic 2015; Tse 2007; Turan 2011; Zhao 2008), combined meta-analysis of mean change from baseline and endpoint values showed cell therapy to be associated with a lower NYHA classification (MD -0.44, 95% CI -0.84 to -0.05; participants = 741; studies = 17; I^2 = 97%). This was also demonstrated in the analysis of endpoint values only (MD -0.42, 95% CI -0.84 to -0.00; participants = 658; studies = 16; I^2 = 97%), but not in four studies that reported mean change from baseline values (MD -0.56, 95% CI -1.49 to 0.36; participants = 239; studies = 4; I^2 = 95%) (Analysis 1.10). Sensitivity analysis omitting those studies with a high or unclear risk of selection bias indicated that the difference in NYHA class between treatment groups in favour of cell therapy may be subject to selection bias (MD -0.26, 95% CI -0.59 to 0.07; participants = 277; studies = 5; I^2 = 79%) (Analysis 8.6).

Eleven studies reported NYHA class at long-term follow-up, although two studies only reported the number of participants who improved or worsened (Heldman 2014_BMMNC; Heldman 2014_BM-MSC). Meta-analysis of nine studies showed that a lower NYHA class was associated with cell therapy (MD -0.81, 95% CI -1.23 to -0.39; participants = 346; studies = 9; I^2 = 93%) (Analysis 1.11) (Chen 2006; Hamshere 2015_IC; Hamshere 2015_IM; Honold 2012; Patel 2015; Patila 2014; Pokushalov 2010; Trifunovic 2015; Turan 2011). This improvement in NYHA class associated with cell therapy was demonstrated in one study with a low risk of selection bias (MD -2.20, 95% CI -2.70 to -1.70; participants = 39; studies = 1; I^2 = 0%) (Analysis 8.7).

Subgroup analyses

In view of the high level of heterogeneity across studies measuring NYHA class at both short- and long-term follow-up, we conducted exploratory subgroup analyses. At short-term follow-up, tests for subgroup differences showed no difference in the effect of cell therapy on NYHA class between studies grouped according to cell dose (P = 0.69) (Analysis 2.3), baseline cardiac function (P = 0.86) (Analysis 3.3), route of cell administration (P = 0.75) (Analysis 4.3), cell type (P = 0.95) (Analysis 5.3), participant diagnosis (P = 0.91) (Analysis 6.3), or use of co-interventions (P = 0.62) (Analysis 7.3). Visual inspection of forest plots revealed two study outliers at short-term follow-up (Patel 2005; Pokushalov 2010); however, substantial heterogeneity (I^2 = 80%) remained when these two studies were omitted from the analysis.

At long-term follow-up, the number of studies reporting NYHA classification precluded subgroup analysis by cell dose or cell type. We observed no differences from tests of subgroup differences when participants were grouped according to baseline cardiac function (P = 0.51) (Analysis 3.4), route of cell administration (P = 0.21) (Analysis 4.4), or participant diagnosis (P = 0.41) (Analysis 6.4). Of note, the mean NYHA class was significantly lower both in participants with CIHD (MD -0.66, 95% CI -0.91 to -0.42; participants = 105; studies = 3; I^2 = 0%) and participants with HF secondary to IHD (MD -0.92, 95% CI -1.47 to -0.37; participants = 241; studies = 6; I^2 = 93%) when compared to the respective control groups (Analysis 6.4).

Trial sequential analysis

Trial sequential analysis of NYHA class at short-term follow-up showed that the cumulative Z-curve did not cross the threshold for significance despite exceeding the information size of 522 participants required to detect a mean difference in NYHA class of 1. However, the required information size to detect a small difference would be substantially higher (e.g. 2025 participants would be required to detect a mean difference in NYHA class between groups of 0.5). Over long-term follow-up, the cumulative Z-curve crossed the adjusted trials sequential monitoring boundaries, although the required information size of 380 to detect a difference between groups of 1 was not reached. Further evidence is required before this result can been considered robust.

(b) Canadian Cardiovascular Society (CCS) angina classification

Twenty studies reported CCS angina classification (see Table 3; Table 6). However, mean values at follow-up or as change from baseline values were not available in seven studies: one reported median values (Jimenez-Quevedo 2011); one reported results graphically (Mathiasen 2015); one reported the number of participants with CCS class greater than 2 (Ang 2008); one reported the percentage of participants who changed CCS class (Losordo 2011); two reported results pooled across multiple trial arms (Mozid 2014_IC; Mozid 2014_IM); and one reported summary results only (Patel 2015).

At short-term follow-up, combined meta-analysis of 13 studies found no difference in mean CCS class at follow-up between participants who had received cell therapy and those who had not (MD -0.43, 95% CI -0.92 to 0.06; participants = 608; studies = 13; I^2 = 94%) (Analysis 1.12). Similarly, there was no difference between treatment arms at long-term follow-up in three studies (all of which reported mean CCS class at endpoint) (MD -0.58, 95% CI -2.04 to 0.88; participants = 142; studies = 3; I^2 = 99%) (Analysis 1.13).

Subgroup analyses

We observed substantial heterogeneity at short- and long-term follow-up. Exploratory subgroup analyses of CCS class at short-term follow-up revealed no differences between studies grouped according to cell dose (P = 0.64) (Analysis 2.4), baseline cardiac function (P = 0.82) (Analysis 3.5), route of cell administration (P = 0.50) (Analysis 4.5), cell type (P = 0.79) (Analysis 5.4), or participant diagnosis (P = 0.27) (Analysis 6.5). Although we observed no difference in CCS class between treatment groups at short-term follow-up overall, subgroup analysis showed that in five studies of refractory angina (Losordo 2007; Tse 2007; Van Ramshorst 2009; Wang 2009; Wang 2010), a higher CCS class was observed in participants who had received cell therapy compared with those who had not (MD -0.78, 95% CI -1.44 to -0.11; participants = 245; studies = 5; I^2 = 74%) (Analysis 6.5).

(c) Exercise capacity

Twenty-one studies reported exercise capacity (see Table 3; Table 6). Measures of exercise capacity included an exercise tolerance test measured as metabolic equivalents, in Chen 2006 and Jimenez-Quevedo 2011, or as time in minutes (Losordo 2007; Wang 2009; Wang 2010), seconds (Losordo 2011), log seconds (Tse 2007), or unspecified (Jimenez-Quevedo 2011); a bicycle test measured as maximum O_2 update, in Erbs 2005 and Honold 2012, or by workload (Van Ramshorst 2009); and by a five-minute, in Wang 2014, or six-minute walk test measured as distance (Bartunek 2012; Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hu 2011; Mathiasen 2015; Nasseri 2012; Perin 2012a; Pokushalov 2010; Santoso 2014; Trifunovic 2015). All but five trials reported either mean values at follow-up or mean change from baseline values. One study reported data as median values (Jimenez-Quevedo 2011); one reported results graphically (Mathiasen 2015); two reported summary descriptive results only (Santoso 2014; Wang 2014); and in one study it was unclear whether mean or median values were reported (Nasseri 2012).

We have described results for exercise capacity using the standardised mean difference, allowing outcomes of different measurement scales to be combined in a meta-analysis. This method of analysis does not allow mean change from baseline and endpoint data to be combined, and we therefore have presented separate analyses of mean change from baseline and endpoint data.

In 11 studies that reported exercise capacity as mean values at follow-up (Bartunek 2012; Chen 2006; Erbs 2005; Honold 2012; Hu 2011; Perin 2012a; Pokushalov 2010; Trifunovic 2015; Tse 2007; Van Ramshorst 2009; Wang 2010), participants who received cell therapy showed a greater exercise capacity than those who did not (standardised mean difference (SMD) 0.56, 95% CI 0.19 to 0.93; participants = 563; studies = 11; I^2 = 75%). Similarly, meta-analysis of nine studies with mean change from baseline values showed greater performance levels associated with cell therapy (SMD 0.33, 95% CI 0.05 to 0.61; participants = 535; studies = 9; I^2 = 52%) (Analysis 1.14) (Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Hu 2011; Losordo 2007; Losordo 2011; Tse 2007; Van Ramshorst 2009; Wang 2009; Wang 2010).

We also saw the difference in performance levels between participants who had received cell therapy and the control group at long-term follow-up, in five studies that reported mean values at endpoint (SMD 1.14, 95% CI 0.04 to 2.25; participants = 178; studies = 5; I^2 = 89%) (Chen 2006; Erbs 2005; Honold 2012; Pokushalov 2010; Trifunovic 2015), and in three studies with mean change from baseline values (SMD 0.34, 95% CI 0.07 to 0.62; participants = 227; studies = 3; I^2 = 0%) (Analysis 1.15) (Heldman 2014_BMMNC; Heldman 2014_BM-MSC; Losordo 2011).

Subgroup analyses

We investigated the substantial observed heterogeneity at short-term follow-up through exploratory subgroup analysis. Tests for subgroup differences found no differences in measures of exercise performance at follow-up between studies grouped according to cell dose (P = 0.72) (Analysis 2.5), baseline cardiac function (P = 0.31) (Analysis 3.6), route of cell administration (P = 0.21) (Analysis 4.6), or participant diagnosis (P = 0.40) (Analysis 6.6). The number of studies reporting exercise capacity was insufficient to perform subgroup analysis according to the type of cells infused.

Left ventricular ejection fraction (LVEF)

In order to limit possible heterogeneity, we have subgrouped trials reporting LVEF by the method of measurement. Results are shown in forest plots for the combined analyses of mean change from baseline and endpoint values as well as separately, as described in the Methods section. Baseline LVEF values for each trial are given in Table 7 for each method of measurement reported. One study measured LVEF by either single-photon emission computed tomography (SPECT) or echocardiography and was therefore excluded from the analyses (Patel 2005).

(a) Magnetic resonance imaging (MRI)

Fifteen studies reported LVEF measured by MRI at short-term follow-up, although two studies reported summary results only (Hamshere 2015_IC; Hamshere 2015_IM), and we excluded one study, Yao 2008, from analysis due to data inconsistencies as described above (Ang 2008; Assmus 2013; Erbs 2005; Hendrikx 2006; Honold 2012; Hu 2011; Mathiasen 2015; Nasseri 2012; Santoso 2014; Tse 2007; Van Ramshorst 2009; Wang 2014). Meta-analysis showed that cell therapy was associated with improved LVEF at short-term follow-up (MD 2.92, 95% CI 1.03 to 4.82; participants = 439; studies = 12; I^2 = 64%). This was also demonstrated in separate analyses of nine studies with mean change from baseline data (MD 4.05, 95% CI 2.55 to 5.55; participants = 308; studies = 9; I^2 = 33%), but not in 10 studies that reported mean LVEF values at follow-up (MD 3.01, 95% CI -0.05 to 6.07; participants = 352; studies = 10; I^2 = 59%) (Analysis 1.16).

Sensitivity analysis excluding studies with a high or unclear risk of selection bias confirmed the improved LVEF observed in participants who had received cell therapy compared with those who had not (MD 2.92, 95% CI 0.67 to 5.17; participants = 249; studies = 7; I^2 = 63%) (Analysis 8.8).

Six studies reported LVEF measured by MRI at long-term follow-up, although two reported results graphically (Heldman 2014_BMMNC; Heldman 2014_BM-MSC). Meta-analysis of the remaining four studies showed cell therapy to be associated with higher LVEF values (combined analysis: MD 4.38, 95% CI 0.82 to 7.93; participants = 110; studies = 4; I^2 = 17%) (Erbs 2005; Honold 2012; Hu 2011; Patila 2014), although this was not demonstrated in separate analyses of mean LVEF at endpoint and mean change from baseline values (Analysis 1.17), and was not found in one study with a low risk of selection bias (MD -1.60, 95% CI -8.70 to 5.50; participants = 25; studies = 1; I^2 = 0%) (Analysis 8.9).

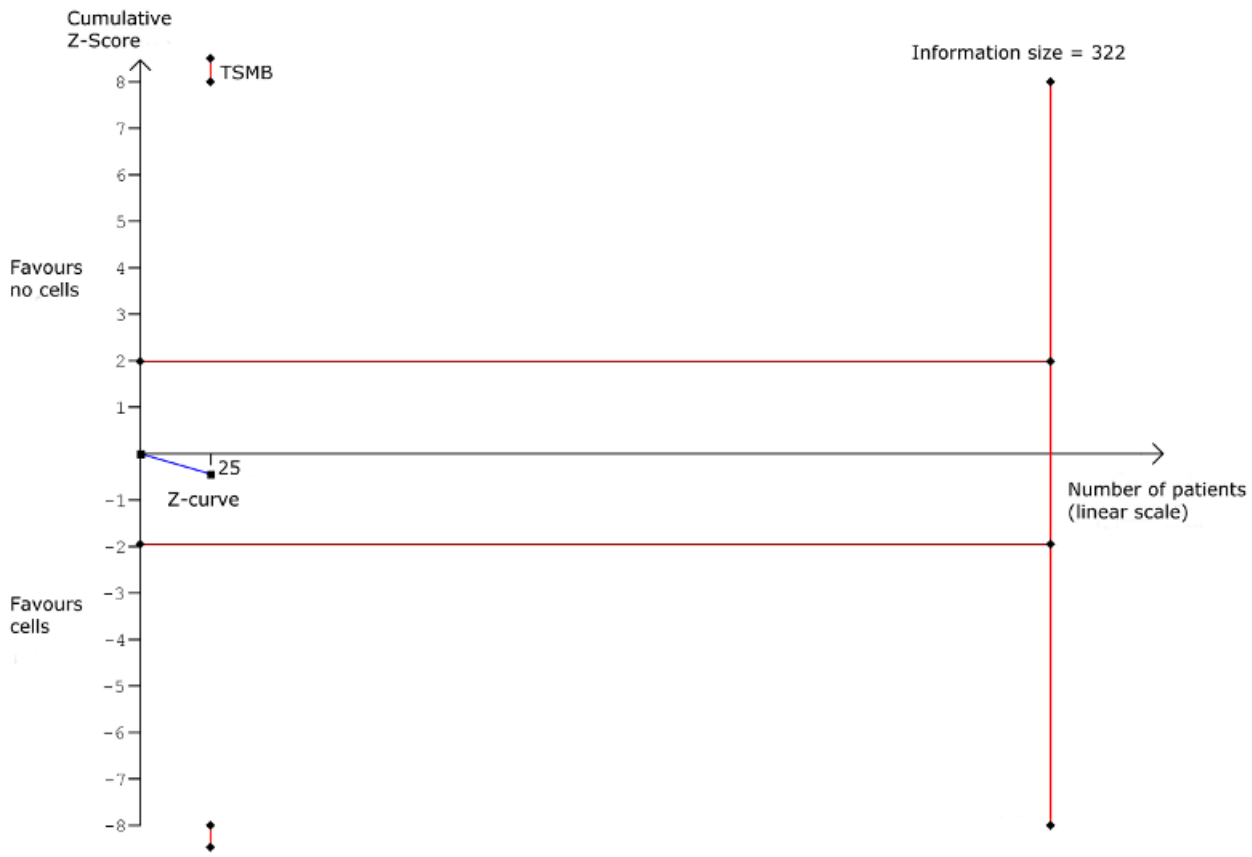
Subgroup analyses

In view of the substantial heterogeneity observed at short-term follow-up, we performed exploratory subgroup analyses. Tests for subgroup differences revealed no differences between subgroups defined by cell dose (P = 0.08) (Analysis 2.6), baseline cardiac function (P = 0.38) (Analysis 3.7), route of cell administration (P = 0.46) (Analysis 4.7), cell type (P = 0.95) (Analysis 6.7), or use of co-interventions (P = 0.42) (Analysis 7.4).

Trial sequential analysis

Trial sequential analysis of LVEF at long-term follow-up based on evidence from a single trial with low risk of selection bias showed that the cumulative Z-curve crossed neither the conventional threshold nor the adjusted trials sequential monitoring boundaries (Figure 9). The available evidence from 25 participants falls considerably short of the required information size of 322 participants.

Figure 9. Trial sequential analysis: Left ventricular ejection fraction measured by MRI at long-term follow-up (≥ 12 months). TSMB = trial sequential monitoring boundary; horizontal red lines indicate conventional significance threshold.



(b) Echocardiography

Twelve studies reported LVEF measured by echocardiography at short-term follow-up, although one reported median values (Jimenez-Quevedo 2011), and two studies, Nasseri 2012 and Patel 2015, reported results graphically (Bartunek 2012; Jimenez-Quevedo 2011; Nasseri 2012; Patel 2015; Perin 2011; Perin 2012a; Perin 2012b; Pokushalov 2010; Trifunovic 2015; Van Ramshorst 2009; Wang 2015; Zhao 2008). Meta-analysis of nine studies showed cell therapy to be associated with LVEF (combined analysis: MD 5.71, 95% CI 4.29 to 7.13; participants = 470; studies = 9; I^2 = 28%) (Analysis 1.18). This was also observed in separate analyses of mean LVEF values at follow-up (MD 5.16, 95% CI 2.87 to 7.44; participants = 388; studies = 8; I^2 = 64%) and mean change from baseline values (MD 3.47, 95% CI 1.59 to 5.34; participants = 161; studies = 3; I^2 = 0%) (Analysis 1.18).

At long-term follow-up, five studies reported LVEF measured by echocardiography, although one reported results graphically (Patel 2015), and one did not report any measures of variation (Patel 2005). Meta-analysis of three studies showed that the improvement in LVEF associated with cell therapy extended to long-term follow-up (MD 7.96, 95% CI 6.39 to 9.54; participants = 154; studies = 3; I^2 = 6%) (Analysis 1.19).

(c) Single-photon emission computed tomography (SPECT)

Five studies reported LVEF measured by SPECT at short-term follow-up (Chen 2006; Jimenez-Quevedo 2011; Patel 2015; Perin 2011; Van Ramshorst 2009), although one study reported median values (Jimenez-Quevedo 2011). Meta-analysis of the remaining four studies showed cell therapy to be associated with improved LVEF when measured by SPECT (MD 5.22, 95% CI 2.60 to 7.85; participants = 145; studies = 4; I^2 = 0%) (Analysis 1.20). Only two studies reported LVEF measured by SPECT at long-term follow-up (Chen 2006; Van Ramshorst 2009): we observed no difference in LVEF between participants who had received cell therapy and controls (MD 0.28, 95% CI -2.48 to 3.03; participants = 88; studies = 2; I^2 = 0%) (Analysis 1.21).

(d) Left ventricular (LV) angiography

Seven studies reported LVEF measured by LV angiography (Assmus 2006; Assmus 2013; Honold 2012; Jimenez-Quevedo 2011; Perin 2011; Perin 2012b; Turan 2011), although one study reported median values (Jimenez-Quevedo 2011). Meta-analysis showed that cell therapy improved LVEF at short-term follow-up (MD 2.00, 95% CI 0.53 to 3.46; participants = 250; studies = 6; I^2 = 33%). We observed this result in separate analysis of both mean LVEF at follow-up (MD 3.18, 95% CI 0.39 to 5.97; participants = 265; studies = 6; I^2 = 7%) and mean change in LVEF from baseline (MD 1.72, 95% CI 0.50 to 2.95; participants = 181; studies = 4; I^2 = 18%) (Analysis 1.22). Only one study reported LVEF measured by LV angiography at long-term follow-up (Turan 2011): this study found higher LVEF values at long-term follow-up in participants who had received cell therapy compared with those who had not (MD 6.00, 95% CI 0.81 to 11.19; participants = 49; studies = 1; I^2 = 0%) (Analysis 1.23).

DISCUSSION

Mortality rates following MI have decreased in recent years due to state-of-the-art revascularisation procedures and optimal medical care (Hartwell 2005). Consequently, the incidence of HF secondary to IHD is increasing. RCTs involving the administration of cell therapies as adjunctive therapies to revascularisation for patients with chronic IHD and HF have developed over the last 15 years (for review see Afzal 2015; Fisher 2014; Jeevanantham 2012). We have updated the original version of this review (Fisher 2014), incorporating data from 15 new trials to increase the quality of available evidence and draw more robust conclusions.

Trials compared cell therapy to no cells (control or placebo) and administered standard primary interventions consisting of medical therapy only or medical therapy and revascularisation (PCI or CABG) or shockwave. Included participants were diagnosed with chronic IHD, generally including chronic symptoms of ischaemia that persisted for at least 30 days since the last MI, HF secondary to IHD, or refractory angina. Cell type and dose administered and route of administration are detailed in Table 2. All trials reported short-term follow-up of between three and six months, and 17 trials reported follow-up of 12 months and longer. We defined mortality and adverse events as primary outcomes and morbidity, composite measure of mortality, non-fatal MI, and rehospitalisation for HF; performance status; health-related quality of life measures; and LVEF as secondary outcomes.

Summary of main results

This update includes 38 RCTs with a total of 1907 participants (1114 cell therapy, 793 no cell therapy). We have drawn the main conclusions of this version of the review from those studies with a low risk of selection bias; they are as follows.

1. We found low-quality evidence that cell therapy reduces the risk of all-cause mortality at long-term follow-up in people with CIHD, HF secondary to IHD, and refractory angina. However, trial sequential analysis showed that this result may be subject to an inflated type I error rate. The available evidence has not met the overall number of participants required to draw robust conclusions (the information size); a further large trial of around 1899 participants is required before this result can be considered robust and conclusive.
2. Periprocedural adverse events were infrequent, and serious adverse events were rare.
3. Analysis of morbidity produced low-quality evidence that cell therapy may reduce the risk of both non-fatal MI and arrhythmias at long-term follow-up. However, as for mortality, these findings may be subject to an inflated type I error rate. Trial sequential analysis showed that the available evidence has not met the number of participants (2383 for non-fatal MI and 461 for arrhythmias) required to draw robust conclusions. The current evidence does not support a beneficial effect of cell therapy on rehospitalisation for HF or morbidity defined as a composite measure of mortality, non-fatal MI, and rehospitalisation for HF.
4. In studies with a low risk of selection bias, we found no effect of cell therapy for either mortality or morbidity outcomes at short-term follow-up.
5. Cell therapy is associated with an improvement in LVEF measured by MRI at short-term follow-up, but not at long-term follow-up. Trial sequential analysis of LVEF at long-term follow-up showed that the evidence is not robust, as the meta-analysis did not reach the required information size of 322 participants.
6. Quality of life and performance status outcomes were infrequently reported, often with different measures used for different participant diagnoses, and with limitations in reporting (e.g. different summary measures reported, results reported graphically), minimising the data available for formal meta-analysis, therefore results should be interpreted with caution.
7. Subgroup analyses found no evidence for differences in the effect of cell therapy between subgroups when studies were grouped according to cell dose, route of cell administration, cell type, participant diagnosis, or use of co-interventions. Notably, cell therapy was effective on long-term mortality irrespective of participant diagnosis (CIHD, HF secondary to IHD, refractory angina) and irrespective of whether co-interventions were used.

Overall completeness and applicability of evidence

We found low-quality evidence that cell therapy is associated with a reduced risk of mortality over long-term follow-up, although more evidence is required before this finding can been considered robust. The number of studies reporting morbidity outcomes was

generally low. There was evidence that cell therapy reduces the risk of non-fatal MI and arrhythmias during long-term follow-up, but meta-analyses were underpowered due to the number of included studies (and participants), as well as the low number of observed events. Composite measures of mortality and morbidity are infrequently reported, despite the increased statistical power obtained from such measures.

We detected no differences between different cell types, doses, or routes of administration. This contrasts with a recent systematic review that found evidence of greater efficacy associated with more than 50 million cells in a combined analysis of trials of both AMI and IHD (Afzal 2015), although it should be said that the subgroup analyses performed here were considerably underpowered to detect subgroup effects, with few studies in each group. Notably, subgroup analysis by participant diagnosis showed that cell therapy appears to reduce the risk of long-term mortality in people with the following diagnoses: chronic IHD, HF secondary to IHD, and refractory angina, and is also effective both in people who are given co-interventions (PCI, CABG, or shockwave) and in those who receive no such co-interventions.

We have included trial sequential analysis in the present update of this systematic review. We acknowledge that the assumption of a relative risk reduction in mortality of 35% is arbitrary and only compares with the effect size associated with revascularisation using PCI. This may indeed seem optimistic, considering the expectation that cell therapies may have a more modest effect. However, if we consider a relative risk reduction in mortality of 25% as an acceptable clinically relevant effect (Yusuf 2002), clearly the required meta-analysis information size will increase.

This systematic review and meta-analysis aimed at evaluating the clinical effect of cell therapies in IHD and HF because these outcomes are more likely to be free of risk of performance bias. However, this review also reports changes in LVEF as a surrogate for heart function. Although a great majority of included trials report LVEF as an outcome measure, its use as surrogate for heart function is questionable in the setting of heart failure. Changes in LV volumes (LVESV and LVEDV) may be more meaningful measures to assess the effect of these therapies on heart function. Future trials and future updates of this systematic review should report changes in LV volume in preference to LVEF.

Quality of the evidence

Although the summary of findings is promising, we deemed the quality of the available evidence as low for all outcomes. The included studies were small: only three studies included more than 100 participants in total, and the majority were considerably smaller, leading to a risk of small-study bias and spuriously inflated effect sizes. Furthermore, where pooling of trial results was possible, meta-analytical findings were based on small numbers of events (e.g. 93 deaths out of 1010 participants, 22 non-fatal MIs out of 461 participants, 47 rehospitalisations for HF out of 495 participants over long-term follow-up), with the composite measure of mortality, non-fatal MI, and rehospitalisation for HF reported in only five studies.

We have conducted subgroup analyses as defined in the protocol of the review. However, results from subgroup analyses should be considered with caution, as the number of studies in each subgroup and the number of events were reduced even further.

The GRADE approach aims to evaluate the quality of the evidence for each major outcome. It also takes into consideration results from the trial sequential analyses (see Summary of findings for the main comparison). For the outcomes of mortality, morbidity, and LVEF, we deemed the quality of the evidence as generally low due to imprecision, as the required information size had not been reached. We further downgraded quality due to the risk of bias from a lack of blinding, a high attrition rate, and commercial sponsorship of some studies.

Overall, the results of this systematic review should be interpreted with caution, as it appears that for most outcomes the meta-analyses were underpowered to detect the expected treatment effect. Larger, adequately powered studies are needed to confirm these results. As suggested by trial sequential analyses, a further trial of approximately 700 participants with long-term mortality data may be needed to reach the required information size of 1899 participants based on a relative risk reduction of 35%. Similarly, the number of participants with long-term follow-up of LVEF measured by MRI (currently only 25 participants in one study with a low risk of selection bias) falls considerably short of the information size required to detect an improvement in LVEF of 4% (322 participants).

Potential biases in the review process

This systematic review was based on a comprehensive search strategy. We undertook formal tests for publication bias for the primary outcome of mortality and found no evidence of asymmetry, but we accept that the possibility of publication and reporting bias cannot be ruled out completely. There was a risk of small-study bias, as all included studies were small (as discussed above), which could lead to spurious inflated results.

Risk of bias was present in the included trials, as summarised in Figure 2. We assessed the robustness of results for outcomes that showed evidence of a beneficial effect of cell therapy through sensitivity analyses, restricting analyses to those studies with a low risk of selection, performance, and attrition bias. Our summary of findings and conclusions are based only on those studies with a low risk of selection bias.

The reporting and analysis of multiple outcomes considered in this review could increase the likelihood of observing type I (false positives) or type II (false negatives) random errors due to multiple testing. In order to reduce the chance of observing random errors, we have applied trial sequential analysis to major outcome measures and have reported the information size required to give robust and conclusive findings.

Finally, although the review authors have limited the selection of studies to those administering bone marrow-derived cells, variation remains in the type of cells utilised among the various clinical trials (e.g. bone marrow mononuclear cells, bone marrow mesenchymal stromal cells), which may be a potential source of bias.

Agreements and disagreements with other studies or reviews

In this Cochrane review update we have focused on the outcomes of mortality and periprocedural adverse events. Our results suggest that cell therapy may reduce the risk of long-term mortality in people with IHD and congestive HF and that there are no major adverse events associated with the treatment. This is in

agreement with the original version of the review, Fisher 2014, and other previous systematic reviews (Fisher 2015b; Wen 2011; Xu 2014). However, our data is discordant with results obtained in systematic reviews and meta-analysis where cell therapies have been administered to people with AMI (de Jong 2014; Delewi 2014; Fisher 2015a; Gyöngyösi 2015). This suggests that people with chronic IHD or HF, or both may benefit more from such treatments than AMI patients.

The efficacy of cell therapy in reducing LVEF is consistent with the findings of a recent review of 11 systematic reviews of cell therapy, which reported that the mean difference in change from baseline LVEF between treatment groups (random-effects) ranged from 2.6% to 5.6% across the included systematic reviews, and that meta-analytical results were broadly similar irrespective of how follow-up was defined and which patient population was studied (Harvey 2015). However, in a recent trial sequential analysis of HF trials (Fisher 2016), no difference in LVEF was observed between treatment arms, and the available evidence led us to reject the hypothesis of a mean difference in change from baseline LVEF of 4% between treatment arms in this patient cohort.

These apparently conflicting results are certainly intriguing. Could the effect of cell therapy be reduced in the presence of co-interventions? Of the eight trials included in the trial sequential analysis of LVEF (Fisher 2016), all but two (accounting for over 70% of the analysed participants) administered co-interventions (CABG: 4 trials, PCI: 1 trial, shockwave: 1 trial), whereas in the current review, these co-interventions were only administered in 11 out of 39 studies (28.5% of participants). Meta-analyses of people with HF with no option for revascularisation and refractory angina have reported significantly improved LVEF associated with cell therapy (Fisher 2013; Khan 2016). Here, we found no evidence for subgroup differences in the effect of cell therapy on outcomes between studies that administered co-interventions and those that did not, although the subgroup analyses here were considerably underpowered, and it is worth noting that the estimated effect size for both mortality and LVEF was smaller in participants who had received co-interventions. We regard this possible explanation as hypothesis-generating, and potential differences in the efficacy of cell therapy between studies that administer co-interventions and those that do not should be considered in the design of future trials and systematic reviews.

Limitations of the review

Our conclusions are based on evidence that is of low quality due to the lack of precision for the majority of reported outcomes and possible small-study bias, as well as risk of bias due to lack of blinding, high levels of attrition, and commercially funded trials. The information size derived from trial sequential analyses for key outcomes showed that meta-analyses are currently considerably underpowered, and further large randomised trials are needed before findings can been considered to be robust and conclusive.

The aim of this review was to assess the effect of cell therapies on main clinical outcomes, because these are less likely to be affected by risk of performance bias (blinding). We have assessed all-cause mortality. Our predefined outcomes did not include cardiac-related mortality; this will be considered as an outcome in future updates of the review.

We have summarised any periprocedural adverse events reported in individual studies descriptively and concluded that serious periprocedural adverse events are rare. A formal assessment of cumulative adverse events related to cell therapy, both periprocedurally and over long-term follow-up, is beyond the scope of this review.

In summary, the results of this review may be clinically relevant, but the evidence for the reduction in the number of deaths with cell treatment relative to controls needs to be confirmed in larger clinical trials. To this end, the first Phase II/III and Phase III clinical trials for severe IHD (NCT00362388; NCT00747708; NCT01727063), HF (NCT01768702), and refractory angina are currently ongoing (NCT01508910). Research should also focus on a better understanding of the best types of cells to use and why some people respond to treatment and others do not.

AUTHORS' CONCLUSIONS

Implications for practice

This review and meta-analysis provides evidence for a reduction in all-cause mortality at both short- and long-term follow-up (12 months and over) when cell therapy is administered to people with chronic ischaemic heart disease or congestive heart failure. However, we deemed the quality of evidence as low, and results need to be confirmed in larger, appropriately powered randomised clinical trials with appropriate generation and concealment of allocation sequence and blinding of participants, clinicians, and outcome assessors before cell-based treatment for these patients can be developed as clinical practice.

Implications for research

The results of this systematic review should be confirmed in large, adequately powered randomised controlled trials assessing the clinical relevance of the treatment. All future clinical trials should be prospectively registered and conducted appropriately to minimise the risk of bias in all domains (e.g. appropriate methods of randomisation, blinding, and reporting). It is important that published trials include all variables and outcomes and that deviations from the protocol are well documented and reported. Outcome measures should be standardised (e.g. quality of life outcome measures). In order to detect meaningful effects on mortality or hospitalisation due to worsening heart failure, trials should include follow-up of longer than six months, as 20% of people diagnosed with heart failure die in the first year, and up to 50% in the five years following diagnosis (Go 2014). These meta-analyses are underpowered to detect clinically relevant treatment effects on mortality (e.g. relative risk reduction in mortality lower than 35%). Currently, the number of participants included in these meta-analyses falls considerably short of the required information size, suggesting that double or triple that number may be required. Future research should also focus on a better understanding of the cell therapies used (e.g. mononuclear cells, circulating progenitor cells, mesenchymal stem cells, or haematopoietic progenitor cells) and their mechanism of action, particularly in the presence of co-interventions. Additionally, patient-dependent outcomes need to be more thoroughly investigated to ascertain and distinguish between responders and non-responders, and to be able to tailor autologous, allogeneic, or modified cell therapies to each patient group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ang 2008

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: British Heart Foundation (grant PG04050) *Study setting*: Leicester, UK *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: Intramyocardial BMSC (IM): 21; intracoronary BMSC (IC): 21; Controls: 21 *Number (N) of participants analysed (primary outcome) in each arm*: 17 IM, 16 IC, 15 C
Participants	*Description*: Chronic IHD (aged 18 to 80 years; presence of at least 1 chronic, irreversible myocardial scar; elective cardiac surgery).

Ang 2008 *(Continued)*

	Age distribution (SD) in each arm: IM: 64.7 (8.7) years; IC: 62.1 (8.7) years; Controls: 61.3 (8.3) years. *Sex (% male) in each arm*: IM: 71.4%; IC: 90.5%; Controls: 90%. *Number of diseased vessels*: n/r (multivessel). *Time from symptom onset to initial treatment*: At least 6 weeks. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arms*: BMSC-IM or BMSC-IC *Type of stem cells*: Mononuclear cells administered intramyocardially (IM) or intracoronarily (IC) *Summary of stem cell isolation and type and route of delivery*: Bone marrow aspiration followed by density gradient centrifugation to enrich in mononuclear cells, infused via the coronary artery (IC) or injected into the myocardium (IM) *Dose of stem cells*: 8.6 (5.6) x 10^7 cells (IM); 11.5 (73) x 10^7 cells (IC) *Timing of stem cell procedure*: Concomitant to CABG *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration; no placebo or sham procedure) *Co-intervention:* CABG
Outcomes	*Primary outcome*: Improvement in contractile function of treated scar areas at 6 months. *Secondary outcomes*: Global left ventricular functions at 6 months (infarct size, global end-diastolic volume and end-systolic volume, and improvement in stroke volume and LVEF). *Additional outcomes:* Postoperative complications, troponin I levels within 24 hours of surgery, and clinical evaluation (assessment of functional status and adverse events). *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: MRI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was administered; participants and clinicians were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians treating the participants during the postoperative period and the investigators performing the examinations and interpreting the results were blind to which group participants had been assigned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 controls (2/21) were excluded from analysis of mortality and morbidity (1x withdrawal before surgery, 1x deemed unsuitable for follow-up). 12 participants were lost to follow-up (4 IM, 4 IC, 3 controls), and 2 died within 30 days. MRI was performed in 33 participants, of which 4 were “not suitable for accu-

Ang 2008 *(Continued)*

		rate analysis". However, MRI results were only reported for 25 participants; this discrepancy was unexplained.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00560742) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Assmus 2006

Methods	*Type of study*: Cross-over RCT *Type of publication*: Full paper *Source of funding*: Supported by the Deutsche ForschungsGemeinschaft (FOR 501-1: WA 146/2-1), Fondation Leducq Transatlantic Network of Excellence for Cardiac Regeneration, European Union European Vascular Genomics Network (LSHM-CT-2003-503254), and Alfried Krupp Stiftung. *Study setting*: Frankfurt, Germany *Number of centres*: 1 *Length of follow-up*: 3 months *Number (N) of participants randomised to each arm*: BMSC: 28; CPC: 24; Controls: 23 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 24; CPC: 19, Controls: 18
Participants	*Description*: Chronic IHD (aged 18 to 80 years; MI at least 3 months previously; well-demarcated region of left ventricular dysfunction and a patent infarct-related artery). *Age distribution in each arm*: BMSC: 59 ± 12 years; CPC: 54 ± 12 years; Controls: 61 ± 9 years. *Sex (% male) in each arm*: BMSC: 89%; CPC: 79%; Controls: 100%. *Number of diseased vessels*: BMSC: 1 (n = 7), 2 (n = 13), 3 (n = 8); CPC: 1 (n = 7), 2 (n = 4), 3 (n = 12); Controls: 1 (n = 2), 2 (n = 9), 3 (n = 12). *Time from symptom onset to initial treatment*: Previous MI at least 3 months earlier. 100% participants with previous MI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC or CPC *Type of stem cells*: Mononuclear cells or circulating progenitor cells *Summary of stem cell isolation and type and route of delivery*: BMSC: 50 mL of bone marrow aspirate was obtained under local anaesthesia on the morning of cell transplantation. Mononuclear cells were isolated by Ficoll-gradient centrifugation. CPC: Mononuclear cell fraction was isolated by Ficoll-gradient centrifugation of 270 mL of venous blood and cultured for 3 days ex vivo. Cells were delivered intracoronarily in both arms of the trial. *Dose of stem cells*: BMSC arm: 2.05 ± 1.1 x 10^8 mononuclear cells. On average less than 1% were CD34-positive cells. CPC arm: 2.2 ± 1.1 x 10^7 mononuclear cells. No measure of CD34-positive cells in this fraction. *Timing of stem cell procedure*: At least 3 months after last MI. In some cases concomitant PCI. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration; no placebo or sham procedure) *Co-intervention:* Standard medical therapy; PCI (in 27% of participants)
Outcomes	*Primary outcome*: Change in global left ventricular function (measured by quantitative left ventricular angiography). *Secondary outcomes*: 1. Quantitative parameters of regional left ventricular function of the target area 2. Changes in left ventricular volumes

Assmus 2006 *(Continued)*

3. Functional status as assessed by NYHA classification
4. Event-free survival (defined as freedom from death, MI, stroke, or rehospitalisation for worsening HF) after 4 months' follow-up

Outcome assessment points: Baseline and 3 months.
Method(s) of outcome measurement: LV angiography and MRI

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using computerised simple random allocation with known N. No blockwise randomisation was performed.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was administered; participants and clinicians were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quantitative analysis of angiograms and MRI images was performed by an investigator who was blinded to the individual participant's treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis of mortality and morbidity. 14 participants (4x cell therapy, 5x CPC, 5x controls) were excluded from MRI/angiography and functional status at follow-up, with reasons given for all exclusions.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00289822) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Assmus 2013

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper; abstract (long-term follow-up) *Source of funding*: Supported by an unrestricted grant to the Goethe University Frankfurt from t2cure GmbH. *Study setting*: Langen, Germany *Number of centres*: 1 *Length of follow-up*: 45.7 (17) months *Number (N) of participants randomised to each arm*: BMSC: 43 (22 LD (low-dose shockwave), 21 HD (high-dose shockwave)); Controls: 39 (20 LD, 19 HD) *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 41 (21 LD, 20 HD); Controls: 38 (19 LD, 19 HD)
Participants	*Description*: Chronic ischaemic HF (aged 18 to 80 years; anterior MI occurring 3 months or more prior to inclusion and stable chronic postinfarction HF defined by LVEF less than 50% or symptoms of NYHA class II or greater; a patent vessel supplying the target region).

Assmus 2013 *(Continued)*

	Age distribution in each arm: BMSC: 65 (12) (LD), 58 (11) (HD); Controls: 60 (10) (LD), 63 (10) (HD). *Sex (% male) in each arm*: BMSC: 77% (LD), 86% (HD); Controls: 80% (LD), 90% (HD). *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: Not reported. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* 50 mL of bone marrow was aspirated into heparin-containing syringes from the iliac crest under local anaesthesia. Mononuclear cells were isolated and enriched with the use of Ficoll-Hypaque centrifugation procedures. The cell suspension consisted of a heterogeneous cell population including hematopoietic, mesenchymal, and other progenitor cells. The cells were suspended in 10 mL of X-VIVO 10 medium, including 2 mL of the participant's own serum. *Dose of stem cells*: 123 (69) x 10^6 (HD), 150 (77) x 10^6 (LD). *Timing of stem cell procedure*: 24 hours following shockwave. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; 10 mL of X-VIVO 10 medium, including 2 mL of the participant's own serum). *Co-intervention:* Shockwave (HD or LD)
Outcomes	*Primary outcome*: Improvement in global LVEF on quantitative LV angiography at 4 months' follow-up. *Secondary outcomes*: 1. Global LV volumes, regional LV function, and late enhancement volume measured by MRI at 4 months and 1 year 2. NYHA class at 4 months 3. NT BNP levels at 4 months 4. Major adverse clinical events (death, model of death, rehospitalisation for worsening HF, recurrent MI, ventricular tachycardia, revascularisation, and stroke) at 4 months 5. Quality of life at 4 months *Outcome assessment points*: Baseline, 4 months, and mean 45.7 (17) months (clinical outcomes only). *Method(s) of outcome measurement*: LV angiography; MRI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a simple random allocation using a computer list with known N. No blockwise randomisation was performed.
Allocation concealment (selection bias)	Low risk	Randomisation codes were generated at the cell-processing centre for the entire study cohort.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was reported as double-blind. All participants underwent BM aspiration, and the control group received a placebo. Participants were blinded; blinding of clinicians was not specifically reported.

Assmus 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded for the intracoronary infusion of the study medication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity. All participants were included in angiography analyses on an intention-to-treat basis. MRI was performed in a subset of participants (15 cell therapy and 12 controls).
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00326989) were reported.
Other bias	High risk	Supported by an unrestricted grant from t2cure GmbH. No other sources of bias were reported or identified.

Bartunek 2012

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Cardio3 BioSciences *Study setting*: Belgium, Serbia, Switzerland *Number of centres*: 9 (Belgium, Serbia, Switzerland) *Length of follow-up*: 2 years *Number (N) of participants randomised to each arm*: BMSC: 32; Controls: 15 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 21; Controls: 15
Participants	*Description*: IHD (aged 18 to 75 years; stable HF population with a history of MI; baseline LVEF 15% to 40%; ischaemic event at least 2 months prior to recruitment; optimally managed and revascularised). *Age distribution in each arm*: BMSC: 55.3 (SE 10.4) years; Controls: 58.7 (SE 8.2) years *Sex (% male) in each arm*: BMSC: 90.5%; Controls: 86.7% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: time from infarction to cell delivery, mean 1540 (range 192 to 7515) days. *Statistically significant baseline imbalances between the groups*? None
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Cardiopoietic cells (mesenchymal stem cells) *Summary of stem cell isolation and type and route of delivery:* Human BM was harvested from the iliac crest, cultured at 37°C/5% CO_2 in 175 cm^2 flasks to purify MSCs. After 24 h, nonadherent BM and cellular debris were discarded, and adherent MSCs were washed with PBS solution. A 1-to-1 passage was performed to dissociate colony-forming units and allow for expansion for up to 6 days in a culture medium supplemented with 5% human pooled platelet lysate media to generate a monolayer whereby 50 x 10^6 cells were obtained. Lineage specification was achieved by MSC exposure to a cardiogenic cocktail regimen triggering expression and nuclear translocation of cardiac transcription factors while maintaining clonal proliferation. Passage P1 marked the start of cardiogenic cocktail treatment in which cells were cultured for 5 days in 5% platelet lysate-supplemented high glucose medium containing cardiogenic growth factors (TGF-b, BMP-4, Activin A, FGF-2, cardiotrophin, a-thrombin, diaminopyrimidine). Cell density was 4000 cells/cm^2 during MSC culture and 1500 cells/cm^2 during cardiopoietic induction. Passage P2/P3 marked the end of the cardiogenic cocktail treatment followed by expansion to yield 600 to 1200 x 10^6 cells. Harvest involved trypsinisation and concentration in a preservation solution. Cells were centrally manufactured in a GMP facility. Cells packaged for transportation were transplanted within 72 h of derivation.

Bartunek 2012 *(Continued)*

	Dose of stem cells: mean 733 x 10^6 (range 605 x 1168 x 10^6) cells *Timing of stem cell procedure*: BM harvest - 24 hrs - (P0) (up to 6 days) - P1 (5 days cell culture) - 4 to 6 weeks. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration; no placebo or sham procedure) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcome*: Changes in LVEF at 6 months Note: Main study publication reports primary endpoint as feasibility and safety at 2-year follow-up (Bartunek 2012). *Secondary outcomes*: 1. 6-min walking distance (6 months, 1 and 2 years) 2. Quality of life (6 months, 1 and 2 years) 3. All-cause mortality (at each follow-up) 4. Cardiovascular events (at each follow-up) Note: Main study publication reports secondary endpoints as including cardiac structure and function (Bartunek 2012). *Outcome assessment points*: Baseline, 6 months, and 2 years (clinical outcomes only). *Method(s) of outcome measurement*: Echocardiography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted through a site-independent, centralised process after exclusion of participants that did not meet the inclusion criteria.
Allocation concealment (selection bias)	Low risk	Allocation concealment was not fully described, but randomisation was conducted in a site-independent manner through a centralised process.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was administered; neither participants nor clinicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent core laboratory masked to study arm assignment and chronology of clinical evaluation provided data analysis.
Incomplete outcome data (attrition bias) All outcomes	High risk	11 participants in the cell therapy group were excluded from analysis (2x clinical inclusion criteira not met; 2x BM inclusion criteria not met; 5x cell release inclusion criteria not met; 2x cell growth inclusion criteria not met). In primary analyses described in the paper, these participants were analysed as part of the control group (although they are excluded from analysis in the results of this review). All other randomised participants were included in all analyses.
Selective reporting (reporting bias)	Unclear risk	The study protocol (NCT00810238) defined the primary outcome as change in LVEF at 6 months, whereas the study publication defined the primary outcome as feasibility and safety at 2 years. Follow-up of exercise capacity and quality

Bartunek 2012 *(Continued)*

		of life at 1 and 2 years was also defined as an outcome according to the trial protocol but was not reported. All other outcomes described in the trial protocol were reported in results.
Other bias	High risk	This study received commercial funding from Cardio3 BioSciences, although the authors reported that they had no relationships relevant to the contents of the paper to disclose. No other sources of bias were reported or identified.

Chen 2006

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Not reported *Study setting*: China *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 24; Controls: 24 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 22; Controls: 23
Participants	*Description*: Severe ischaemic HF (isolated, chronic, total, or subtotal occluded LAD due to previous anterior wall infarction untreated by either thrombolysis or primary PCI; reversible perfusion defect detectable by SPECT; LVEF < 40%). *Age distribution in each arm*: BMSC: 59.3 ± 6.8 years; Controls: 57.8 ± 7.2 years. *Sex (% male) in each arm*: BMSC: 88%; Controls: 92%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: 14 days following successful PCI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mesenchymal stem cells *Summary of stem cell isolation and type and route of delivery:* 60 mL of autologous bone marrow were aspirated under local anaesthesia from the ilium of all participants during the morning of the 8th day after the PCI procedure and then cultured for 7 days. BM mesenchymal stem cells were harvested and washed 3 to 4 times with heparinised saline. 2 hours before transplantation, the stem cell suspension was mixed with heparin, filtered, and prepared for implantation. Cell viability was > 92%. *Dose of stem cells*: 5 x 10^6 cells *Timing of stem cell procedure*: 14 days following successful PCI and 7 days after bone marrow aspiration. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no placebo). *Co-intervention:* PCI
Outcomes	*Primary outcome*: None reported. *Secondary outcomes*: Reversible defects, metabolic equivalents, exercise, LVEF, NYHA, mortality. *Outcome assessment points*: Baseline and 12 months. *Method(s) of outcome measurement*: SPECT

Chen 2006 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This Chinese trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was used; neither participants nor clinicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 cell therapy participants and 1 control were excluded from all analyses due to failed PCI. All remaining participants were included in the analysis of mortality and morbidity; all surviving participants were included in the analysis of LVEF, NYHA class, and exercise tolerance at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Erbs 2005

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Supported by Heart Center Leipzig GmbH, University of Leipzig. *Study setting*: Leipzig, Germany *Number of centres*: 1 *Length of follow-up*: 15 months *Number (N) of participants randomised to each arm*: BMSC: 14; Controls: 14 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 12; Controls: 11
Participants	*Description*: Chronic total artery occlusion with clinical signs of myocardial ischaemia and local wall motion abnormalities. *Age distribution in each arm*: BMSC: 63 ± 7 years; Controls: 61 ± 9 years. *Sex (% male) in each arm*: BMSC: 71%; Controls: 86%. *Number of diseased vessels*: BMSC: 1 (n = 8), 2 (n = 4), 3 (n = 2); Control arm: 1 (n = 6), 2 (n = 5), 3 (n = 3). *Time from symptom onset to initial treatment*: Complete total obstruction defined as an obstruction of a native coronary artery for more than 30 days with no luminal continuity and with TIMI flow grade 0 or 1. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: G-CSF + BMSC *Type of stem cells*: Circulating progenitor cells

Erbs 2005 *(Continued)*

	Summary of stem cell isolation and type and route of delivery: All participants subcutaneously injected twice a day with filgrastim (G-CSF, 300 mcg) over 4 days to increase the amount of CPC in the blood. At day 4, 400 mL of venous blood were collected from all participants, MNC were purified and ex vivo-cultured for 4 days in endothelial-specific medium to select CPC. MNC were isolated from 400 mL of venous blood by density gradient centrifugation (Histopaque-1077). Immediately after isolation, total MNC were plated on gelatin-coated cell culture flasks with a cell density of 1 x 10^6 cells/cm^2. Cells were maintained for 4 days in endothelial basal medium supplemented with EGM SingleQuots and 10% human serum, collected from each individual participant. Additionally, the cell culture medium was supplemented with ascorbic acid (final concentration 75 ng/mL) and hydrocortisone (0.2 mcg/mL). After 4 days of culture, non-adherent cells were removed by a thorough washing with PBS, and the adherent cells were detached with trypsin/EDTA. The collected cells were washed twice with PBS containing 2 mmol/L EDTA and resuspended in a final volume of 20 mL physiological sodium chloride supplemented with 10% autologous participant serum. Cells were administered intracoronarily. *Dose of stem cells*: 69 ± 14 x 10^6 CPC (range 22 x 10^6 to 200 x 10^6). *Timing of stem cell procedure*: 10 ± 1 days following successful recanalisation. *G-CSF details*: 300 mg of G-CSF administered for 4 days to all participants. *Comparator arm*: G-CSF + placebo (BM aspiration; cell-free serum solution). *Co-intervention:* PCI
Outcomes	*Primary outcomes*: LV function *Secondary outcomes*: Assessment of coronary endothelial function, myocardial viability (number of myocardial segments with hibernation), regional wall motion, LV mass (myocardial mass; infarct size). Clinical outcomes, restenosis, coronary endothelium function, myocardial viability, number of hibernating segments in myocardium. *Outcome assessment points*: Baseline, 3 and 15 months. *Method(s) of outcome measurement*: MRI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	G-CSF was administered and blood was taken from all participants. Control participants received a placebo. Participants and clinicians were blinded to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Image analysis assessors remained blinded after the results at 3 months' follow-up. Other assessors were blinded to 3 months only.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 cell therapy participant and 2 controls were excluded from all analyses (1x reocclusion of target vessel, 2x withdrawal of consent). MRI was performed in 23 participants (12 cell therapy, 11 controls) at 3 months and 22 participants (12 cell therapy and 10 controls) at 15 months.

Erbs 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Hamshere 2015_IC

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: National Institute of Health Research (UK), Heart Cells Foundation, Barts and The London Charity, Chugai Pharma UK, and Cordis Corporation *Study setting*: London, UK *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 15; Controls: 15 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 15; Controls: 15
Participants	*Description*: Advanced HF (NYHA class II-IV; optimal medical therapy and device therapy with no further treatment options). *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: G-CSF + BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* 50 mL BM was obtained from the posterior iliac crest. The BMSC fraction was obtained from the BM samples, and cells were resuspended in 10 mL autologous serum. All samples were maintained at room temperature for the entire procedure. Following arterial access, a weight-adjusted (70 IU/kg) bolus dose of unfractionated heparin was administered. A coronary angiogram was performed to expose the largest possible area of the left ventricle to the injectate via the intact coronary circulation. The total 10 mL volume of injectate was divided equally and injected down patent coronary arteries or grafts, or both through an over-the-wire balloon catheter (Medtronic, Galway, Ireland). The balloon was inflated at low pressure to occlude blood flow, while the appropriate volume of injectate was delivered distally over 3 minutes. This procedure was repeated in the remaining target vessels. *Dose of stem cells*: n/r *Timing of stem cell procedure*: n/r *G-CSF details*: 10 ug/kg/day for 5 days *Comparator arm*: G-CSF + placebo (BM aspiration; 10 mL autologous serum) *Co-intervention:* standard medical therapy
Outcomes	*Primary outcomes*: Change in global LVEF from baseline (12 months) *Secondary outcomes*: Change in quality of life (6 and 12 months), NT-proBNP (6 months); major adverse cardiac events (12 months), change in NYHA class (12 months), change in CCS class (12 months).

Hamshere 2015_IC *(Continued)*

	Outcome assessment points: Baseline, 6 and 12 months. *Method(s) of outcome measurement*: NYHA class; MRI, computed tomography
Notes	Outcome data for this trial were obtained directly from the study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were enrolled in a 1:1 computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants received G-CSF, underwent bone marrow aspiration, and received a placebo infusion. Blinding of clinicians was not specifically reported, but the trial was described as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The endpoints of NYHA and CCS classifications were measured by an investigator blinded to the participant's treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	Information for all outcomes requested from the authors was provided.
Other bias	High risk	Partially sponsored by Chugai Pharma UK and the Cordis Corporation. The primary investigator of this trial is an author of this Cochrane review. No other sources of bias were reported or identified.

Hamshere 2015_IM

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: National Institute of Health Research (UK), Heart Cells Foundation, Barts and The London Charity, Chugai Pharma UK, and Cordis Corporation *Study setting*: London, UK *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 15; Controls: 15 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 15; Controls: 15
Participants	*Description*: Advanced HF (NYHA class II-IV; optimal medical therapy and device therapy with no further treatment options). *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r

Hamshere 2015_IM *(Continued)*

	Statistically significant baseline imbalances between the groups? None.
Interventions	*Intervention arm*: G-CSF + BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* 50 mL BM was obtained from the posterior iliac crest. The BMSC fraction was obtained from the BM samples and cells were resuspended in 10 mL autologous serum. All samples were maintained at room temperature for the entire procedure. After femoral arterial access, a weight-adjusted (70 IU/kg) bolus dose of heparin was administered. Participants underwent left ventricular electromechanical mapping using NOGA XP Cardiac Navigation System (Biologics Delivery Systems Group, Cordis Corporation, CA, USA) and direct intramyocardial injection with a MyoStar injection catheter. The number of sampling points for the mapping procedure varied between 86 and 110. The target areas for injection were the border zones around the scar tissue based on voltage criteria obtained using the NOGA map (areas greater than 6.9 mV). Areas of the myocardium with a wall thickness of < 5 mm were avoided. The total 2 mL volume of injectate was divided and delivered equally to 10 target areas at approximately 1-centimetre intervals. *Dose of stem cells*: n/r *Timing of stem cell procedure*: n/r *G-CSF details*: 10 ug/kg/day for 5 days *Comparator arm*: G-CSF + placebo (BM aspiration; 2 mL autologous serum) *Co-intervention:* standard medical therapy
Outcomes	*Primary outcomes*: Change in global LVEF from baseline (12 months) *Secondary outcomes*: Change in quality of life (6 and 12 months), NT-proBNP (6 months); major adverse cardiac events (12 months), change in NYHA class (12 months), change in CCS class (12 months). *Outcome assessment points*: Baseline, 6 and 12 months. *Method(s) of outcome measurement*: NYHA class; MRI, computed tomography
Notes	Outcome data for this trial were obtained directly from the study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were enrolled in a 1:1 computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants received G-CSF, underwent bone marrow aspiration, and received a placebo infusion. Blinding of clinicians was not specifically reported, but the trial was described as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The endpoints of NYHA and CCS classifications were measured by an investigator blinded to the participant's treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity on an intention-to-treat basis.

Hamshere 2015_IM *(Continued)*

Selective reporting (reporting bias)	Low risk	Information for all outcomes requested from the authors was provided.
Other bias	High risk	Partially sponsored by Chugai Pharma UK and the Cordis Corporation. The primary investigator of this trial is an author of this Cochrane review. No other sources of bias were reported or identified.

Heldman 2014_BM-MSC

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Partially funded by the Interdisciplinary Stem Cell Institute, Miller School of Medicine, BioCardia, and grant U54HL081028 from the National Heart, Lung, and Blood Institute Specialized Centers for Cell-Based Therapy. Helical infusion catheters were provided by BioCardia Inc and one trial investigator (J. Hare) was supported by grants from the National Institutes of Health. *Study setting*: Florida, USA *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BM-MSC: 22; Controls: 11 *Number (N) of participants analysed (primary outcome) in each arm*: BM-MSC: 19; Controls: 11
Participants	*Description*: Chronic MI and LV dysfunction (aged 21 to 90 years; ischaemic cardiomyopathy with LV dysfunction resulting from chronic MI, as documented by confirmed coronary artery disease with a corresponding area of myocardial akinesis, dyskinesis, or severe hypokinesis and had LVEF < 50% within 6 months of screening while taking maximally tolerated doses of beta-adrenergic blocking and angiotensin-converting enzyme or angiotensin II receptor blocking drugs and not during or recently after an ischaemic event). *Age distribution in each arm*: BM-MSC: 57.1 (10.6) years; Controls: 60.0 (12.0) years *Sex (% male) in each arm*: BM-MSC: 94.7%; Controls: 90.9% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? Significantly higher baseline stroke volume in participants who had received MSC compared with placebo.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mesenchymal stem cells *Summary of stem cell isolation and type and route of delivery:* All participants had bone marrow harvested. MSC were cultured from bone marrow aspirates. Delivery was by injection at 10 LV sites using TESI during left heart catheterisation using the helical infusion catheter (BioCardia). Injections were targeted to encircle the border zone of a chronically infarcted myocardial territory and defined by MRI and CT imaging, echocardiography, and well-pacified biplane left ventriculography. *Dose of stem cells*: n/r *Timing of stem cell procedure*: 4 to 6 weeks from BM aspiration to cell administration. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; vehicle placebo) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes:*

Heldman 2014_BM-MSC *(Continued)*

Incidence of treatment-emergent serious adverse events (defined as composite of death, non-fatal MI, stroke, hospitalisation for worsening HF, cardiac perforation, pericardial tamponade, ventricular arrhythmias > 15 sec, or with haemodynamic compromise or atrial fibrillation) at 1 month

Secondary outcomes:

1. Serial troponin values (every 12 hours for the first 48 hours postcatheterisation)
2. Serial creatine kinase values (every 12 hours for the first 48 hours postcatheterisation)
3. Incidence of major adverse cardiac events (MACE) (defined as the composite incidence of (1) death, (2) hospitalisation for HF, or (3) non-fatal recurrent MI) at 12 months
4. Ectopic tissue formation (12 months)
5. Number of deaths at 12 months
6. Change from baseline in distance walked in 6 minutes (12 months)
7. Change from baseline in the MLHFQ total score (12 months)
8. Change from baseline in scar mass as a fraction of left ventricle mass by cardiac MRI or CT (12 months)

Additional outcomes:

Infarct size, regional wall motion at the sites of study agent injection, global LV size and function, exercise peak O_2 consumption, NYHA class, quality of life measured at 3 and 6 months
Outcome assessment points: Baseline, 3 and 6 months (quality of life only), 12 months
Method(s) of outcome measurement: MRI

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An electronic data entry system was used for randomisation. Participants were randomised to the MSC or BMMNC group, and further randomised within groups to cell therapy or placebo.
Allocation concealment (selection bias)	Low risk	Participants were randomised (unblinded) to the MSC or BMMNC group. Participants were further randomised (blinded) within groups to cell therapy or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM harvest, and control participants received a placebo. Neither participants nor clinicians were aware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Preparation and administration of the study product was blinded to investigators outside the cell-processing laboratory.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 cell therapy participants were excluded from the analysis of mortality and morbidity (2x withdrew consent, 1x cell-processing failure). MRI analysis included 16 cell therapy participants and 17 controls (BMSC and MSC control groups combined); missing data were unexplained.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the trial protocol (NCT00768066) were reported; some additional outcomes were reported in the publication of results.
Other bias	High risk	Received partial funding from BioCardia. No other sources of bias were reported or identified.

Heldman 2014_BMMNC

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Partially funded by the Interdisciplinary Stem Cell Institute, Miller School of Medicine, BioCardia, and grant U54HL081028 from the National Heart, Lung, and Blood Institute Specialized Centers for Cell-Based Therapy. Helical infusion catheters were provided by BioCardia Inc and one trial investigator (J. Hare) was supported by grants from the National Institutes of Health. *Study setting*: Florida, USA *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 22; Controls: 10 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 19; Controls: 10
Participants	*Description*: Chronic MI and LV dysfunction (aged 21 to 90 years; ischaemic cardiomyopathy with LV dysfunction resulting from chronic MI, as documented by confirmed coronary artery disease with a corresponding area of myocardial akinesis, dyskinesis, or severe hypokinesis and had LVEF < 50% within 6 months of screening while taking maximally tolerated doses of beta-adrenergic blocking and angiotensin-converting enzyme or angiotensin II receptor blocking drugs and not during or recently after an ischaemic event). *Age distribution in each arm*: BMSC: 61.1 (8.4) years; Controls: 61.3 (9.0) years *Sex (% male) in each arm*: BMSC: 89.5%; Controls: 100% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* All participants underwent BM aspiration from the iliac crest. BMMNC were prepared by centrifugation of whole BM against a low-density gradient using Ficoll-Paque PREMIUM according to manufacturer's protocol. Cells were collected at the interface. Delivery was by injection at 10 LV sites using TESI during left heart catheterisation using the helical infusion catheter (BioCardia). Injections were targeted to encircle the border zone of a chronically infarcted myocardial territory and defined by MRI and CT imaging, echocardiography, and well-pacified biplane left ventriculography. *Dose of stem cells*: n/r *Timing of stem cell procedure*: 4 to 6 weeks from BM aspiration to cell administration. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; vehicle placebo) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes:* Incidence of treatment-emergent serious adverse events (defined as composite of death, non-fatal MI, stroke, hospitalisation for worsening HF, cardiac perforation, pericardial tamponade, ventricular arrhythmias > 15 sec, or with haemodynamic compromise or atrial fibrillation) at 1 month *Secondary outcomes*: 1. Serial troponin values (every 12 hours for the first 48 hours postcatheterisation) 2. Serial creatine kinase values (every 12 hours for the first 48 hours postcatheterisation) 3. Incidence of the major adverse cardiac events (MACE) (defined as the composite incidence of (1) death, (2) hospitalisation for HF, or (3) non-fatal recurrent MI) at 12 months 4. Ectopic tissue formation (12 months)

Heldman 2014_BMMNC *(Continued)*

5. Number of deaths at 12 months
6. Change from baseline in distance walked in 6 minutes (12 months)
7. Change from baseline in MLHFQ total score (12 months)
8. Change from baseline in scar mass as a fraction of left ventricle mass by cardiac MRI or CT (12 months)

Additional outcomes:

Infarct size, regional wall motion at the sites of study agent injection, global LV size and function, exercise peak O_2 consumption, NYHA class, quality of life measured at 3 and 6 months
Outcome assessment points: Baseline, 3 and 6 months (quality of life only), 12 months
Method(s) of outcome measurement: MRI

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An electronic data entry system was used for randomisation. Participants were randomised to the MSC or BMMNC group, and further randomised within groups to cell therapy or placebo.
Allocation concealment (selection bias)	Low risk	Participants were randomised (unblinded) to the MSC or BMMNC group. Participants were further randomised (blinded) within groups to cell therapy or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM harvest, and control participants received a placebo. Neither participants nor clinicians were aware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Preparation and administration of the study product was blinded to investigators outside the cell-processing laboratory.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 cell therapy participants were excluded from the analysis of mortality and morbidity (2x withdrew consent, 1x ineligible before BM aspiration). MRI analysis included 16 cell therapy participants and 17 controls (BMSC and MSC control groups combined); missing data were unexplained.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the trial protocol (NCT00768066) were reported; some additional outcomes were reported in the publication of results.
Other bias	High risk	Received partial funding from BioCardia. No other sources of bias were reported or identified.

Hendrikx 2006

Methods

Type of study: Parallel RCT
Type of publication: Full paper
Source of funding: Not reported

Study setting: Hasselt, Belgium
Number of centres: 1
Length of follow-up: 4 months
Number (N) of participants randomised to each arm: BMSC: 11; Controls: 12

Hendrikx 2006 *(Continued)*

	Number (N) of participants analysed (primary outcome) in each arm: BMSC: 10; Controls: 10
Participants	*Description*: Elective CABG surgery; transmural MI on ECG and akinesia or dyskinesia in part of the left ventricle as shown by angiography. *Age distribution in each arm*: BMSC: 63.2 ± 8.5 years; Controls: 66.8 ± 9.2 years. *Sex (% male) in each arm*: BMSC: 100%; Controls: 70%. *Number of diseased vessels*: BMSC: 1 (n = 0), 2 (n = 2), 3 (n = 8); Controls: 1 (n = 1), 2 (n = 2), 3 (n = 7). *Time from symptom onset to initial treatment*: BMSC arm: 217 (162) days and control arm: 213 (145) days between occurrence of MI and time of CABG (and treatment). *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: 40 mL of bone marrow was aspirated under local anaesthesia from the participant's iliac crest, the day before surgery. BMSC were immediately isolated by density gradient centrifugation using Lymphoprep. Isolated cells were washed twice with saline and subsequently resuspended in X-VIVO 15 medium (Cambrex) supplemented with 2% autologous serum. This cell suspension was transferred to Teflon bags at a concentration of approximately 1 x 10^6 cells/mL for overnight cultivation. The next day cells were harvested and washed 3 times before finally being suspended in 10 mL heparinised saline. 10 mL of cell suspension were injected into the border zone of the infarct with 29-gauge myoinjector syringes containing 0.5 mL of cell suspension. Multiple punctures were performed with prevent needles to make injections parallel to the epicardium and avoid delivery of cells into the ventricular cavity. *Dose of stem cells*: 60.25 (31.35) x 10^6 cells with > 95% viability and over 73% recovery. Containing 1.42% (0.99%) CD34-positive cells and 76.37 (44.47) CFU-GM/10^5 mononuclear cells. *Timing of stem cell procedure*: Approximately 24 hours following bone marrow aspiration; 217 (162) days post-AMI. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; heparinised saline) *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Global LVEF change and regional wall-thickening changes in the infarct area. *Secondary outcomes*: Changes in metabolic activity measured by thallium scintigraphy. *Outcome assessment points*: Baseline, postoperative (9 to 14 days), and 4 months *Method(s) of outcome measurement*: MRI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (1:1) was carried out using sequentially numbered, sealed envelopes.
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both treatment groups underwent BM aspiration: the BM group had bone marrow isolated the day before surgery from the iliac crest, and the control group had bone marrow aspirated from the sternum during the operation.

Hendrikx 2006 *(Continued)*

		Controls received a placebo. Both participants and the surgeon were unaware of whether cells or only saline was injected.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cardiac MR images were analysed by an investigator blinded to treatment assignment. For thallium scintigraphy, 2 investigators independently analysed data and were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity. 3 participants (1x cell therapy and 1x control) were excluded from MRI analysis (2x death, 1x acute psychiatric illness).
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Honold 2012

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Not reported *Study setting*: Frankfurt/Main, Germany *Number of centres*: 1 *Length of follow-up*: 60 months *Number (N) of participants randomised to each arm*: BMSC: 23; Controls: 10 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 23; Controls: 9
Participants	*Description*: Coronary artery disease (aged > 18 years; previous MI at least 3 months prior to cell therapy and well demarcated LV regional wall motion abnormality; receiving constant state-of-the-art pharmacotherapy for at least 3 months prior to enrolment). *Age distribution in each arm*: BMSC: 53.4 ± 12.3 years; Controls: 58.8 ± 7.3 years. *Sex (% male) in each arm*: BMSC: 82%; Controls: 100%. *Number of diseased vessels*: BMSC: 1 (n = 10), 2 (n = 6), 3 (n = 6); Controls: 1 (n = 4), 2 (n = 2), 3 (n = 4). *Time from symptom onset to initial treatment*: At least 3 months from previous MI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: G-CSF + BMSC *Type of stem cells*: Circulating progenitor cells. *Summary of stem cell isolation and type and route of delivery*: G-CSF was administered to the participants for 5 days. 270 mL of peripheral blood was drawn. Mononuclear cells were isolated using a Ficoll gradient centrifugation, and cells were resuspended in X-VIVO 15 medium with 1 ng/mL carrier-free human recombinant VEGF, atorvastatin, and 20% human serum drawn from each individual participant. Cells were cultured ex vivo for 4 days to enrich in endothelial progenitor cells (uptake of LDL). *Dose of stem cells*: 29 ± 12 x 10^6. *Timing of stem cell procedure*: % days following G-SCF administration and 4 days following bone marrow aspiration and cell culture. *G-CSF details*: 5 ug/kg/day (first 12 participants) or 10 ug/kg/day (20 participants) for 5 days. *Comparator arm*: G-CSF + control (no BM aspiration, no placebo) *Co-intervention:* Standard medical therapy; PCI (in 33% of participants)
Outcomes	*Primary outcomes*:

Honold 2012 *(Continued)*

	Safety and efficacy. *Secondary outcomes*: Global and regional LV function and volumes after 3 months, determined by both LV angiography and MRI. Clinical parameters like functional NYHA class, cardiopulmonary exercise testing, and NT-proBNP serum levels were obtained during a 5-year follow-up period. *Outcome assessment points*: Baseline and 3, 12, 60 months *Method(s) of outcome measurement*: MRI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of clinicians and participants was not specifically reported, but no placebo was administered to the control group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	MRI independent observers were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All randomised participants were included in the analysis of mortality and morbidity, although 1 participant randomised to (but who did not receive) cell therapy was analysed in the control group. Angiography was carried out at follow-up in 26 participants (21 cell therapy, 5 controls). MRI was performed in a subset of participants (9 cell therapy, 4 controls).
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Hu 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Key project in the National Science and Technology Pillar programme during the 11th 5-year plan period (2006BAJ01A09), basic scientific research fund of the National Scientific Institute 2009-2011. *Study setting*: Beijing, China *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 31; Controls: 29 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 31; Controls: 28

Hu 2011 *(Continued)*

Participants	*Description*: Chronic HF (aged 18 to 75 years; at least 3 months since last MI; severe ischaemic cardiomyopathy with LVEF < 30% by MRI and suitable for CABG; no evidence of surviving myocardium in the infarct area, as shown by SPECT and LV angiography; without LV aneurysm or valvular diseases requiring surgical intervention). *Age distribution in each arm*: BMSC: 56.6 ± 9.7 years; Controls: 58.3 ± 8.9 years. *Sex (% male) in each arm*: 93.3% (both arms pooled). *Number of diseased vessels*: BMSC: 3; Controls: 3. *Time from symptom onset to initial treatment*: At least 3 months from last MI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: After anaesthesia but before CABG, 60 mL of BM was aspirated from the participant's iliac crest and diluted with normal saline solution. The mononuclear cells were isolated using Ficoll density gradient centrifugation according to good manufacturing practice regulations and resuspended in 10 mL of saline solution. The cell suspension was filtered by a 70-micrometre cell strainer before transplantation. The cells were counted under a light microscope, and the viability was assessed by trypan blue dye. The final suspension of BMMNC contained 10^7 mL MNC. Cells were delivered via the grafted vessel (saphenous vein graft). *Dose of stem cells*: Mean 13.17 ± 10.66 x 10^7. *Timing of stem cell procedure*: Within 24 hours and during CABG. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; mixture of 8 mL of saline solution and 2 mL of the participant's own serum) *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Changes in LVEF from baseline to 6 months' follow-up. *Secondary outcomes:* None reported. *Additional outcomes*: LVEDV index (MRI; echocardiograpy); LVESV index (MRI); wall motion score index (echocardiography); perfusion score (SPECT), 6-min walking test, and BNP value. *Outcome assessment points*: Baseline, 6 and 12 months *Method(s) of outcome measurement*: MRI; echocardiography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation table was generated by statistical software.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias)	Low risk	All participants underwent BM harvest, and control participants received a placebo. The study processes were blinded to surgeons and participants.

Hu 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study processes were blinded to investigators who were responsible for participant assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis of mortality and morbidity; 1 control participant did not attend follow-up at 6 months. MRI at 12 months included 25 participants in each group. Echocardiography at 12 months included 42 participants (24 cell therapy and 18 controls); missing data were explained.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00395811) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Jimenez-Quevedo 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Funded by an independent research grant from the Spanish National Ministry of Health and Social Policy (Direccion general de Terapias Avanzadas y Transplante) and an unrestricted grant from Mutua Madrileña Foundation. *Study setting*: Spain *Number of centres*: 3 (Madrid, Barcelona, Logrono) *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 19; Controls: 9 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 19; Controls: 9
Participants	*Description*: Refractory angina (CCS class II-IV; optimal medical therapy; not suitable for surgical/percutaneous revascularisation; and with reversible perfusion defect measured by SPECT). *Age distribution in each arm*: BMSC: median 70 years; Controls: median 58.2 years *Sex (% male) in each arm*: BMSC: 78.9%; Controls: 100% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r (no AMI within preceding 3 months) *Statistically significant baseline imbalances between the groups*? Median age significantly higher in treated group.
Interventions	*Intervention arm*: G-CSF; BMSC *Type of stem cells*: CD133+ progenitor cells from mobilised peripheral blood *Summary of stem cell isolation and type and route of delivery:* All participants underwent leukapheresis to isolate the mononuclear fraction from the peripheral blood. Only those participants allocated to the cell group CD133+ PC were isolated by immunomagnetic selection with CliniMACS cell separation system (Miltenyi Biotec, Bergisch-Gladback, Germany). Sterility tests (Gram stain and culture) were performed on the final cell preparation. The cells were suspended in normal saline and concentrated in 3 mL for the injection. *Dose of stem cells*: 20 to 30 × 10^6 cells *Timing of stem cell procedure*: At last 5 days after G-CSF. *G-CSF details:* 5 µg/kg per 12 hours for 4 days *Comparator arm*: Control (BM aspiration; sham procedure but no placebo administered)

Jimenez-Quevedo 2011 *(Continued)*

	Co-intervention: Standard medical therapy
Outcomes	*Primary outcomes:* Major adverse cardiac and cerebrovascular events, defined as cardiovascular death, non-fatal MI, ischaemic stroke, need for revascularisation, or procedure-related complications (pericardial effusion/cardiac tamponade, vascular complications, and sustained ventricular arrhythmias) at 6, 12, and 24 months. *Secondary outcomes:* Efficacy of the transendocardial injection of PC CD133+ assessed by means of the following variables: the change in the myocardial perfusion defect as measured by SPECT, symptom-limited treadmill test, quality of life, CCS angina classification, and antianginal medication requirement. *Outcome assessment points*: Baseline, 6 months *Method(s) of outcome measurement*: Echocardiography, SPECT, LV angiography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A centralised telephone randomisation was performed using a computer-generated code before the index procedure.
Allocation concealment (selection bias)	Low risk	Randomisation was performed using a centralised telephone procedure.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both groups were treated with G-CSF, underwent an apheresis and electromechanical mapping; however, transendocardial injections were not performed in the control group but were simulated to keep the participant and all the investigators except the 2 operators who performed the injections blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A blinded investigator analysed angiograms with the use of a computer-based system. All the analyses were centralised in an independent core laboratory blinded to the randomisation. All investigators except 2 operators who performed the injections were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis of all outcomes on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00694642) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Losordo 2007

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Supported in part by National Institutes of Health grants and by a grant from Baxter Healthcare. Biosense Webster provided the mapping and injection catheters for this study at no extra cost. *Study setting*: USA *Number of centres*: n/r (multicentre)

Losordo 2007 *(Continued)*

	Length of follow-up: 6 months *Number (N) of participants randomised to each arm*: BMSC-high dose (HD): 6; BMSC-medium dose (MD): 6; BMSC-low dose (LD): 6; and Controls: 6 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC-HD: 6; BMSC-MD: 6; BMSC-LD: 6; and Controls: 6
Participants	*Description*: Chronic refractory angina (aged > 21 years; CCS class III–IV; optimal medical therapy; not suitable for revascularisation; ischaemia on nuclear perfusion imaging, to complete at least 1 minute but no more than 6 mins of a standard Bruce protocol, and to experience angina/angina equivalent during the baseline exercise test). *Age distribution in each arm*: Mean 62.4 (range 48 to 84 years) for all groups. *Sex (% male) in each arm*: 80% for all arms. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: Not reported, not applicable. *Statistically significant baseline imbalances between the groups*? None reported.
Interventions	*Intervention arm*: G-CSF, BMSC at low dose, medium dose, or high dose. *Type of stem cells*: CD34+ cells from mobilised peripheral blood. *Summary of stem cell isolation and type and route of delivery*: Leukoapheresis was performed on the 5th day for collection of mononuclear cells. The cells were stored overnight at 4°C, and the following morning the CD34+ fraction was purified on a commercially available device (Isolex 300i, Baxter Healthcare) according to manufacturer's instructions. Cells were then subjected to testing and were required to meet lot-release criteria. Once passed, the participants underwent NOGA electromechanical mapping and intramyocardial injection of CD34+ cells suspended in saline plus 5% autologous serum, versus cell diluent using the NOGA MyoStar catheter. The dose was divided into 10 injections of 0.2 mL per injection. *Dose of stem cells*: 5 x 10^4 CD34 cells/kg (LD); 1 x 10^5 CD34 cells/kg (MD); 5 x 10^5 CD34 cells/kg (HD). *Timing of stem cell procedure*: On day 6 following G-CSF administration and within 24 hours of cell isolation. *G-CSF details*: G-CSF was given to all participants at 5 µg/kg for 4 to 5 days. *Comparator arm*: G-CSF; placebo (BM aspiration; saline (0.9% sodium chloride) with 5% autologous plasma). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Not reported. *Secondary outcomes*: Safety analysis (AEs), efficacy (angina frequency, NTG use, exercise tolerance, CCS class, SPECT perfusion imaging, quality of life testing). *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: Angina frequency and CCS angina class
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation codes were established by the study statistician.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias)	Low risk	All participants were administered G-CSF prior to treatment and had CD34+ cells collected. Controls received a placebo solution in a syringe that was identical for all treatment arms.

Losordo 2007 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation codes were only revealed to the stem cell laboratory technician responsible for separating the cells into aliquots or preparing the placebo material.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	High risk	Partially funded by a grant from Baxter Healthcare. No other sources of bias were reported or identified.

Losordo 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Baxter Healthcare sponsored the study and was responsible for the conduct of the investigation, with oversight provided by the principal investigator and the scientific advisory board. *Study setting*: USA *Number of centres*: 26 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC-low dose (LD): 56; BMSC-high dose (HD): 56; Controls: 56 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC-LD: 55; BMSC-HD: 56; Controls: 56
Participants	*Description*: Chronic refractory angina (aged 21 to 80 years; CCS class III–IV; optimum medical management; not suitable for revascularisation; SPECT imaging to document the presence of reversible ischaemia; patients required to walk a minimum of 3 mins but no longer than 10 mins on a modified Bruce protocol exercise tolerance test and had to experience angina or their angina equivalent during exercise testing. *Age distribution in each arm*: BMSC-LD: 61.3 (9.1) years; BMSC-HD: 59.8 ± 9.2 years; Controls: 61.8 ± 8.5 years. *Sex (% male) in each arm*: BMSC-LD: 83.6%; BMSC-HD: 87.5%; Controls: 89.3%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: At least 40 days from previous MI. *Statistically significant baseline imbalances between the groups*? Cardiovascular risk factors (HTN, smoking, DM); angina episodes per week.
Interventions	*Intervention arm*: G-CSF, BMSC at low dose or high dose. *Type of stem cells*: CD34+ cells from mobilised peripheral blood. *Summary of stem cell isolation and type and route of delivery*: On day 5 leukapheresis was performed. The following day mononuclear cells were collected and CD34+ cells enriched using a commercially available device (Isolex 300im) magnetic cell separation system. Cell suspension with > 70% viability and > 50% CD34+ cells were given at 2 doses of body weight with a maximum of 100 kg. Cell suspension was diluted in saline (0.9% sodium chloride) with 5% autologous plasma. Cells were injected into the myocardium. The injection was performed by NOGA mapping and at 10 sites (0.2 cm^3/site) using a NOGA MyoStar catheter. *Dose of stem cells*: 1 x 10^5 CD34 cells/kg (LD) or 5 x 10^5 CD34 cells/kg (HD). *Timing of stem cell procedure*: At least 3 months following MI.

Losordo 2011 *(Continued)*

	G-CSF details: G-CSF was given to all participants at 5 µg/kg for 4 to 5 days. *Comparator arm*: G-CSF; placebo (BM aspiration; saline (0.9% sodium chloride) with 5% autologous plasma). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Angina frequency 6 months after treatment. *Secondary outcomes*: None reported in study protocol. *Additional outcomes:* Efficacy endpoints including exercise tolerance testing; use of antianginal medication; CCS functional class; health-related QOL (Seattle Angina Questionnaire, SF-36, Dyspnea Questionnaire, EQ-5D); combined rate of MACE, SPECT, cardiac MRI (in a substudy). Safety endpoints including adverse event reporting, chest X-ray, and echocardiology and laboratory screening. *Outcome assessment points*: Baseline, 6 and 12 months *Method(s) of outcome measurement*: CCS functional class
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to 1 of 3 treatment groups via a telephone call-in and an interactive voice-response system.
Allocation concealment (selection bias)	Low risk	The cell-processing laboratory at each centre was responsible for making the randomisation call and preparing the CD34+ cells or control injection accordingly.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were administered G-CSF prior to treatment and had CD34+ cells collected. Controls received a placebo solution in a syringe that was identical for both treatment arms.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent committee conducted the analysis. All study personnel remained blinded until the end of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in analyses at follow-up on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00300053) were reported.
Other bias	High risk	Baxter Healthcare sponsored the study and was responsible for the conduct of the investigation. No other sources of bias were reported or identified.

Mathiasen 2015

Methods	*Type of study*: Parallel RCT

Mathiasen 2015 *(Continued)*

	Type of publication: Full paper *Source of funding*: Supported by the Arvid Nilsson's Foundation, Aase and Ejnar Danielsen's Foundation, Agustinus Foundation, the Research Foundation at Rigshospitalet, Axel Muusfeldt Foundation, Eva and Henry Fraenkel's Foundation, Gangsted Foundation, Vera and Fleming Westerberg's Foundation, Jeppe and Ovita Juhl's Foundation, Sophus and Astrid Jacobsen Foundation. *Study setting*: Copenhagen, Denmark *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 40; Controls: 20 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 40; Controls: 20
Participants	*Description*: Severe ischaemic HF (aged 30 to 80 years; optimal medical therapy with no change in medication for 2 months; no revascularisation options, LVEF < 45%; NYHA class II-III). *Age distribution in each arm*: BMSC: 66.1 (7.7) years; Controls: 64.2 (10.6) years *Sex (% male) in each arm*: BMSC: 90%; Controls: 70% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mesenchymal stem cells *Summary of stem cell isolation and type and route of delivery:* A total of 50 mL bone marrow aspirate was obtained from the iliac crest by needle aspiration under local anaesthesia. The marrow sample was diluted 1:2 with PBS. MNC were harvested by gradient centrifugation on lymphoprep (density 1077 g/cm^3), then primary cell cultures were established by seeding 2 × 10^7 BMMNC using a T75 culture flask in complete medium (DMEM low glucose (1 g/L) with 25 mM HEPES and L-Glutamine, 1% penicillin/streptomycin and 10% fetal bovine serum). The cells were incubated at 37°C in humid air with 5% CO_2. The medium was changed 5 days after plating and subsequently every 3 or 4 days. After 2, 3, 4, and 5 weeks of cultivation, cells were harvested. Mesenchymal stromal cells were successfully culture expanded under good manufacturing practice conditions for 46.9 + 10.5 days. Participants were treated with the number of cells reached after 2 passages. *Dose of stem cells*: mean 77.5 (67.9) x 10e6 *Timing of stem cell procedure*: Mesenchymal stromal cells were successfully culture expanded under good manufacturing practice conditions for 46.9 (10.5) days following BM aspiration. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; PBS mixed with a drop of the participant's blood to maintain blinded appearance of placebo solution). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcome:* Changes in LVESV at 6 months' follow-up *Secondary outcome:* Clinical improvements at 6 and 12 months Note: the main study publication reports secondary outcomes as LVEDV, LVEF, SV, cardiac output, LV myocardial mass, wall thickness, wall thickening, scar volume, NYHA class, CCS class, 6MWT, weekly angina attacks and weekly use of nitroglycerine, biomarkers, the Seattle Angina Questionnaire and Kansas City Cardiomyopathy Questionnaire, and safety (Mathiasen 2015). *Outcome assessment points*: Baseline, 6 months *Method(s) of outcome measurement*: MRI; computed tomography
Notes	

Mathiasen 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were enrolled in a 2:1 computer-generated randomisation list blocks of 6.
Allocation concealment (selection bias)	Low risk	The randomisation list was generated by a person unrelated to the study group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial investigators, study nurses, and participants were blinded to treatment allocation. To maintain blinding, a drop of the participant's blood was mixed into the syringe containing MSC or placebo by the stem cell laboratory to make the MSC solution and placebo identical.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial investigators and experienced physicians who performed the MRI analyses were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in all analyses at follow-up on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00644410) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Mozid 2014_IC

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: National Institute of Health Research (UK), Heart Cells Foundation, Barts and The London Charity, Chugai Pharma UK, and Cordis Corporation. *Study setting*: London, UK *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 14; Controls: 2 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 14; Controls: 2
Participants	*Description*: Advanced HF (NYHA class II-IV; optimal medical therapy and device therapy with no further treatment options). *Age distribution in each arm*: Mean 70 (10) years *Sex (% male) in each arm*: 94% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: Duration since last MI: 11 (7) years *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: G-CSF + BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* 50 mL BM was obtained from the posterior iliac crest. The BMSC fraction was obtained from the BM samples, and cells were resuspended in 10 mL autologous serum. All samples were maintained at room temperature for the entire procedure.

Mozid 2014_IC *(Continued)*

	Following arterial access, a weight-adjusted (70 IU/kg) bolus dose of unfractionated heparin was administered. A coronary angiogram was performed to expose the largest possible area of the left ventricle to the injectate via the intact coronary circulation. The total 10 mL volume of injectate was divided equally and injected down patent coronary arteries or grafts, or both through an over-the-wire balloon catheter (Medtronic, Galway, Ireland). The balloon was inflated at low pressure to occlude blood flow, while the appropriate volume of injectate was delivered distally over 3 minutes. This procedure was repeated in the remaining target vessels. *Dose of stem cells*: Mean 8.6 (11.0) x 10^7 *Timing of stem cell procedure*: n/r *G-CSF details*: 10 ug/kg/day for 5 days *Comparator arm*: G-CSF + placebo (BM aspiration; 10 mL autologous serum) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: None (change in global LVEF from baseline (12 months) is a primary outcome in the main REGENERATE-IHD trial but not included in the pilot study) *Secondary outcomes*: Change in quality of life (6 and 12 months); NT-proBNP (6 months); major adverse cardiac events (12 months); change in NYHA class (12 months) *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: NYHA class; MRI, computed tomography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were enrolled in a 1:1 computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants received G-CSF, underwent bone marrow aspiration, and received a placebo infusion. Blinding of clinicians was not specifically reported, but the trial was described as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The endpoints of NYHA and CCS classifications were measured by an investigator blinded to the participant's treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity on an intention-to-treat basis.
Selective reporting (reporting bias)	Unclear risk	This is a pilot study report that only reports 6-month follow-up of the secondary outcomes described in the protocol (NCT00747708).
Other bias	High risk	Partially sponsored by Chugai Pharma UK and the Cordis Corporation. The primary investigator of this trial is an author of this Cochrane review. No other sources of bias were reported or identified.

Mozid 2014_IM

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: National Institute of Health Research (UK), Heart Cells Foundation, Barts and The London Charity, Chugai Pharma UK, and Cordis Corporation. *Study setting*: London, UK *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 10; Controls: 8 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 10; Controls: 8
Participants	*Description*: Advanced HF (NYHA class II-IV; optimal medical therapy and device therapy with no further treatment options). *Age distribution in each arm*: Mean 64 (9) years *Sex (% male) in each arm*: 100% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: Duration since last MI: 7 (5) years *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: G-CSF + BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* 50 mL BM was obtained from the posterior iliac crest. The BMSC fraction was obtained from the BM samples, and cells were resuspended in 10 mL autologous serum. All samples were maintained at room temperature for the entire procedure. After femoral arterial access, a weight-adjusted (70 IU/kg) bolus dose of heparin was administered. Participants underwent left ventricular electromechanical mapping using NOGA XP Cardiac Navigation System (Biologics Delivery Systems Group, Cordis Corporation, CA, USA) and direct intramyocardial injection with a MyoStar injection catheter. The number of sampling points for the mapping procedure varied between 86 and 110. The target areas for injection were the border zones around the scar tissue based on voltage criteria obtained using the NOGA map (areas greater than 6.9 mV). Areas of the myocardium with a wall thickness of < 5 mm were avoided. The total 2 mL volume of injectate was divided and delivered equally to 10 target areas at approximately 1-centimetre intervals. *Dose of stem cells*: Mean 5.2 (5.3) x 10^7 *Timing of stem cell procedure*: n/r *G-CSF details*: 10 ug/kg/day for 5 days *Comparator arm*: G-CSF + placebo (BM aspiration; 2 mL autologous serum) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: None (change in global LVEF from baseline (12 months) is a primary outcome in the main REGENERATE-IHD trial but not included in the pilot study) *Secondary outcomes*: Change in quality of life (6 and 12 months); NT-proBNP (6 months); major adverse cardiac events (12 months); change in NYHA class (12 months) *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: NYHA class; MRI, computed tomography
Notes	
Risk of bias	

Mozid 2014_IM *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were enrolled in a 1:1 computer-generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants received G-CSF, underwent bone marrow aspiration, and received a placebo infusion. Blinding of clinicians was not specifically reported, but the trial was described as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The endpoints of NYHA and CCS classifications were measured by an investigator blinded to the participant's treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity on an intention-to-treat basis.
Selective reporting (reporting bias)	Unclear risk	This is a pilot study report that only reports 6-month follow-up of the secondary outcomes described in the protocol (NCT00747708).
Other bias	High risk	Partially sponsored by Chugai Pharma UK and the Cordis Corporation. The primary investigator of this trial is an author of this Cochrane review. No other sources of bias were reported or identified.

Nasseri 2012

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Supported in part by Miltenyi Biotec and by the German Bundesministerium fur Bildung und Forschung. *Study setting*: Berlin, Germany *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 30; Controls: 30 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 28; Controls: 26
Participants	*Description*: Chronic IHD (indication for CABG surgery; reduced global LVEF by transthoracic echocardiography at rest (LVEF ≤ 35); presence of akinetic or hypokinetic and hypoperfused LV myocardium on MRI for defining the target area). *Age distribution in each arm*: BMSC: 61.9 (7.3) years; Controls: 62.7 (10.6) years *Sex (% male) in each arm*: BMSC: 93%; Controls: 97% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: Duration since last MI: BMSC: 2.6 months (range 17 days to 17.1 years); Controls: 1.5 months (range 14 days to 28.5 years). *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: CD133+ progenitor cells *Summary of stem cell isolation and type and route of delivery:* All participants underwent BM aspiration from the left posterior iliac crest with local anaesthesia and analgosedation. An average BM volume

Nasseri 2012 *(Continued)*

	of 196 +/- 28 mL was harvested and diluted with 20 mL saline solution containing 1000 U heparin. The BM solution was filtered, transferred into a plastic bag, and washed with PBS/EDTA solution containing 0.5% human serum albumin. This cell suspension was incubated with human IgG 5% as blocking reagent, labelled with 7.5mL reconstituted CD133 MicroBeads, murine anti-human CD133 monoclonal antibodies conjugated to superparamagnetic iron dextran particles. Then CD133+ cells were separated using the CliniMACS Magnetic Separation device. The enriched cell fraction was reconstituted with 13 mL saline containing 10% autologous serum. Samples were drawn for cell numbers, purity, viability, and proof of sterility. Finally, cells were aliquoted into 1-millilitre syringes and stored at 4°C without heparin. *Dose of stem cells*: Median 5.1 (IQR 3.0 to 9.1) x 10^6 CD133+ cells *Timing of stem cell procedure*: 36 hours after BM aspiration *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; isotonic sodium chloride solution containing 10% autologous serum) *Co-intervention:* CABG
Outcomes	*Primary outcomes*: LVEF at rest, measured 6 months' postoperatively by MRI. *Secondary outcomes*: 1. Change in LVEF compared with preoperatively and early postoperatively 2. Regional contractility in the area of interest 3. Physical exercise capacity determined by 6-minute walk test 4. Perfusion in the AOI 5. Change in LV dimensions 6. NYHA and CCS class 7. MLHFQ 8. Death, MI, or need for reintervention during follow-up *Post-hoc outcome:* Infarct scar size. *Outcome assessment points*: Baseline, 6 months *Method(s) of outcome measurement*: MRI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted in the cell preparation facility. Group allocation was performed according to a predefined non-block-wise 1:1 randomisation plan.
Allocation concealment (selection bias)	Low risk	The randomisation plan was accessible only to the external cell processing team that prepared the cell product or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent bone marrow aspiration. Syringes were prepared with either cells or placebo solution, and an ID number was added so that participants, the surgical team, and all investigators were unaware of treatment allocation.

Nasseri 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Syringes were prepared with either cells or placebo solution, and an ID number was added so that participants, the surgical team, and all investigators were unaware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity (3x cell therapy and 1x control were excluded from exercise testing). In MRI analysis, the number of withdrawals was low (treatment: 2/30 vs control: 4/30), and reasons for exclusion were given. 4 participants (3 cell therapy, 1 control) did not undergo exercise tests.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00462774) were reported. One post-hoc outcome was clearly defined as such.
Other bias	High risk	Supported in part by Miltenyi Biotec and the German Bundesministerium fur Bildung und Forshcung. Two authors received lecture fees from Miltenyi Biotec. No other sources of bias were reported or identified.

Patel 2005

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper (6 months); abstract (10 years) *Source of funding*: Not reported. *Study setting*: Rosario, Argentina *Number of centres*: 1 *Length of follow-up*: 10 years *Number (N) of participants randomised to each arm*: BMSC: 10, Controls: 10 (pilot study); BMSC: 25, Controls: 25 (long-term follow-up) *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 10, Control: 10 (pilot study); BMSC: 25, Controls: 25 (long-term follow-up)
Participants	*Description*: Ischaemic HF (LVEF < 35% by echocardiography and multiplanar cardiac catheterisation; NYHA class III or IV; requiring revascularisation, undergoing off-pump CABG). *Age distribution in each arm*: BMSC arm: 64.8 ± 7.1 years old; Control arm: 63.6 ± 5.2 years old (pilot study data). *Sex (% male) in each arm*: BMSC arm: 80%; Control arm: 80% (pilot study data). *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: At least 7 days after the last MI, all participants had history of MI and revascularisation by PCI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: CD34+ progenitor cells *Summary of stem cell isolation and type and route of delivery*: Bone marrow was harvested from the iliac bone in a sterile fashion after achievement of general anaesthesia. A special multihold harvest needle with a 60-millilitre syringe was designed to minimise the anaesthetic time. It was introduced into the iliac bone between both posterior iliac spines at both sides. 500 mL to 600 mL of BM with a minimal number of puncture sites was harvested. At least 250 mL BM must have been harvested to continue with the protocol. Harvested BM was placed in a blood bag with 10,000 U of heparin sulfate and 400 µm of lysine acetylsalicylate to avoid platelet clumping. The BM was filtered on a 500-micrometre filter followed by a 200-micrometre filter. The resulting solution was mixed with hydroethylstarch 6%. The supernatant was centrifuged at 400 g for 15 mins. The cellular pellet was resuspended in PBS. The cell solution was mixed 3:1 with a solution of 155 mmol/L ammonium chloride, 10 mmol/L potassium bicarbonate, and 0.1 mmol/L EDTA and set for 5 mins at room temperature. The solution was then centrifuged at 400 g for 10 mins. The pellet was washed with PBS and resuspended. The cell suspension was placed over Ficoll-Paque (1.077 density) 4:1 and centrifuged at 400 g for 30 mins. The upper layer was aspirated, leav-

Patel 2005 *(Continued)*

	ing the mononuclear cell layer at the interphase. The interphase cells were transferred to a new conical tube with PBS and centrifuged at 300 g for 10 mins. The supernatant was completely removed, and the cell pellet was resuspended in PBS. Cell counts were performed, and the magnetic labelling with Isolex 300i was performed to obtain an enriched product of at least 70% CD34+ cells. The resulting cell solution was resuspended in 30 mL of the participant's own plasma and 10,000 U of heparin sulphate. 30 mL of cell preparation was delivered in 1 mL aliquots over a 2-second period. The injections into the myocardium were spaced 1 cm apart and spaced to avoid coronary vessels. Injections were 3 mm to 5 mm in depth. *Dose of stem cells*: Median 22 x 10^6 CD34+ cells. *Timing of stem cell procedure*: At least 7 days following last MI. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration, no placebo) *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Not reported. *Secondary outcomes*: Global LVEF, LVEDV, NYHA class (6 months only), arrhythmias (6 months) only. *Outcome assessment points*: Baseline and 1, 3, and 6 months; 1, 5, and 10 years *Method(s) of outcome measurement*: SPECT; echocardiography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A person who did not participate in the trial had the choice of picking a coloured ball (red = BMSC arm; blue = control arm).
Allocation concealment (selection bias)	Unclear risk	The person undertaking the randomisation procedure did not participate in the trial.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Clinicians were not blinded. The authors report that participants were blinded, although the control group did not undergo bone marrow aspiration and no placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The reviewers of imaging studies (cardiologists) were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Patel 2015

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper

Patel 2015 *(Continued)*

	Source of funding: Funded by Harvest Technologies, Plymouth, MA. One study investigator (A. Patel) has "compensated honoraria" from Cook Medical Inc. *Study setting*: Utah and California, USA; Rostock and Berlin, Germany; and Grugoan, India *Number of centres*: 5 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 24; Controls: 6 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 22; Controls: 6
Participants	*Description*: CHF (aged > 18 years; LVEF < 40% by contrast echocardiography, NYHA class III or IV, stable with standard medical therapy for at least 1 month before screening, and a life expectancy of 6 months or longer). *Age distribution in each arm*: BMSC: 58.5 (12.7) years; Controls: 52.7 (8.5) years. *Sex (% male) in each arm*: BMSC: 91.7%; Controls: 100%. *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r (at least 7 days since last MI). *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Bone marrow cell concentrate *Summary of stem cell isolation and type and route of delivery:* Approximately 240 mL of bone marrow was aspirated from the posterior iliac crest. The samples was concentrated to a volume of 60 mL over 15 mins using the Harvest Bone Marrow Aspirate Concentrate System (from Harvest Technologies, Plymouth, MA). The concentrate comprised mononuclear cells. Retrograde delivery through the coronary sinus, accessed via the right femoral vein using a 7F 8 mm x 40 mm balloon catheter (Cook Medical Inc) under fluoroscopic guidance. The 60 mL of BM concentrate was infused continuously over a 5-minute period. The balloon was kept inflated for 10 min afterwards to allow the migration of cells into the cardiac tissue. *Dose of stem cells*: Mean 3.7 (0.9) x 10^9 nucleated cells. *Timing of stem cell procedure*: 29 (14) minutes from venous access. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration; no placebo) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Number of participants with adverse events as a measure of safety and tolerability (12 months) *Secondary outcomes*: To assess the effect of the infusion of bone marrow nucleated cells on the clinical course of angina as measured by QOL questionnaire, MLHFQ, NYHA and CCS classification, and SPECT (12 months) Assess the effect of the infusion of bone marrow nucleated cells on the clinical course of HF (12 months) *Outcome assessment points*: Baseline; 1, 3, 6, and 12 months *Method(s) of outcome measurement*: SPECT, NYHA class, CCS class, MLHFQ
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Electronic randomisation" was performed.

Patel 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was used; neither participants nor clinicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All imaging and follow-up information was blinded to the reviewers.
Incomplete outcome data (attrition bias) All outcomes	Low risk	With the exception of 2 early withdrawals with reasons clearly defined, all randomised participants were included in the analysis of mortality and morbidity on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT01299324) were reported.
Other bias	High risk	Commercially sponsored study (funded by Harvest Technologies). No other sources of bias were reported or identified.

Patila 2014

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Supported by the Heart Research Foundation, the Academy of Finland and government subsidies for medical research block grants. *Study setting*: Helsinki, Finland *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 20; Controls: 19 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 18; Controls: 17
Participants	*Description*: Ischaemic HF (aged 18 to 75 years; managed by optimal medical care; undergoing CABG; LVEF between 15% and 45%; NYHA class II-IV HF symptoms). *Age distribution in each arm*: BMSC: median 65 (IQR 57 to 73) years; Controls: median 64 (IQR 58 to 70) years. *Sex (% male) in each arm*: BMSC: 94.7%; Controls: 95% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* After anaesthesia induction, 100 mL of BM aspirated from each participant's posterior iliac crests was collected into a sterile bag containing heparin (final concentration 20 units/mL). The aliquots were filtered and density-gradient centrifuged (Ficoll-Paque PREMIUM; GE Healthcare Bio-Sciences AB; COBE 2991 Cell Processing Centrifuge) to obtain the mononuclear cell traction, according to standard methods. The cells were washed with medium 199 containing human serum albumin 0.5% and heparin (20 unit/mL) and finally suspended in 6 mL of the same medium. The cell suspension was divided into six 1-millilitre syringes for each participant in the treatment group. After BM aspiration, standard CABG operation was performed under cardiac arrest, cardiopulmonary bypass, cardioplegia protection, and mild hypothermia. After completion of by-

Patila 2014 *(Continued)*

	pass anastomoses, each participant received, under cardiac arrest, 15 to 20 0.2 mL injections into the infarction border area through a small 24G needle into sites chosen before surgery using imaging data. Injection procedure was carefully photographed during each surgery, and segments injected were specified in participants' documentation for analysis. *Dose of stem cells*: Median 8.4 (range 5.2 to 13.5) x 10^8 cells *Timing of stem cell procedure*: n/r *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; vehicle medium) *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Change in LVEF after 1-year follow-up measured by MRI (12 months) *Secondary outcomes*: Changes in any other cardiac parameters as measured by echocardiography, MRI, or PET ischaemia area (6 months; 1 year) Change in plasma concentrations of proBNP (6 months; 1 year) Primary hospitalisation or days stayed in hospital Correlation between pericardial fluid growth factor concentrations and left ventricular function improvement (up to 1 year) Correlation between autologous cardiac stem cell quality and left ventricular function improvement (6 months; 1 year) *Outcome assessment points*: Baseline, 1 week, 1 year. *Method(s) of outcome measurement*: MRI, PET
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Before examination, numbered randomisation envelopes were sealed by stem cell laboratory personnel blinded to other participants. After delivery of the BM harvest to the stem cell laboratory, randomisation of each participant was done at the time of operation.
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes were prepared by the stem cell laboratory before examinations.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent bone marrow aspiration, and the control group received a placebo. Syringes containing cell therapy or placebo were masked using a non-transparent tape.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	1 investigator analysed all MRI imaging data in a random order. Areas of scar and ischaemic myocardium were assessed by 2 study-blind, experienced nuclear medicine physicians.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity. The number of withdrawals from MRI analysis was low (treatment: 2/20 vs control: 2/19), and reasons for withdrawals were reported in detail.

Patila 2014 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the trial protocol (NCT00418418) were reported, although results were reported for 12 months only and not at 6 months as specified in the trial protocol.
Other bias	Low risk	No other sources of bias were reported or identified.

Perin 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: No extramural funding was used to support this work; the authors have no disclosures, no funding, and no relationship with industry to report. *Study setting*: Texas and Minneapolis, USA *Number of centres*: 2 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 20; Controls: 10 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 20; Controls: 10
Participants	*Description*: Ischaemic HF (functional class III or IV (angina) and/or HF symptoms (NYHA) on maximal medical therapy; chronic CAD with a reversible perfusion defect ≥ 7% (SPECT); LVEF < 40%; MVO_2 < 21 mL/kg/min; ineligible for percutaneous or surgical revascularisation). *Age distribution in each arm*: BMSC: 56.3 ± 8.6 years; Controls: 60.5 ± 6.4 years. *Sex (% male) in each arm*: BMSC: 50%; Controls: 80%. *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: 50 mL of BM was aspirated from the posterior iliac crest, approximately 4 hours before the cells were injected into the heart. Mononuclear cells were isolated using a density gradient centrifugation, washed in heparinised saline containing 5% human serum albumin and passed through a mesh. 3 x 10^7 cells were resuspended in 3 mL saline containing serum albumin (5%). 3 mL were preserved for further studies. 3 hours after bone marrow aspiration, participants underwent an electromechanical mapping to select myocardial segments for cell injection. Cells were injected into viable myocardium (> 6.9 mV unipolar voltage). Electromechanical maps comprised an average of 87 ± 16 points. Each injection of 2 million cells was delivered in a volume of 0.2 mL. Participants received an average of 15 cell injections in a mean of 6 ± 1 segments. *Dose of stem cells*: 2 x 10^6 cells. *Timing of stem cell procedure*: Within 24 hours of harvesting the bone marrow. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration; sham procedure performed but no placebo administered). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Safety of cell injections at 3 time points: i) early safety (periprocedural and up to 2 weeks); ii) 3 months; and iii) 6 months: major adverse events (hospitalisation, arrhythmia, exacerbation of CHF, acute coronary syndrome, MI, stroke, or death). *Secondary outcomes*: 1. CCS angina score (baseline, 3 months, 6 months) 2. NYHA classification (baseline, 3 months, 6 months)

Perin 2011 *(Continued)*

3. Myocardial oxygen consumption (baseline, 3 months, 6 months)
4. Ejection fraction measured by echocardiography (baseline, 3 months, 6 months)
5. Minute ventilation - CO_2 production relationship (VE/VCO_2 slope) (baseline, 3 months)
6. Wall motion score index measured by echocardiography (baseline, 3 months)
7. LVEF measured by SPECT (baseline, 3 months, 6 months)
8. LVEF measured by angiography (baseline, 6 months)
9. LVEDV and LVESV (baseline and 6 months)
10. Endocardial unipolar voltages (UPV) (baseline, 6 months)
11. Linear local shortening (baseline, 6 months)

Outcome assessment points: Baseline, 3 and 6 months
Method(s) of outcome measurement: Not applicable.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation tables were prepared by the statistical department.
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes were used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicians were not blinded, but participants received a simulated mock injection procedure (although it was unclear whether BM aspiration was undertaken in control group).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efficacy studies were read by an independent, blinded investigator. Blinding was maintained until the end of the assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00203203) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Perin 2012a

Methods

Type of study: Parallel RCT
Type of publication: Full paper
Source of funding: NHLBI under co-operative agreement 5 U01 HL087318-04. In part by NHLBI contracts N01-HB37164 and HHSN268201000008C awarded to the Molecular and Cellular Therapeutics Facility, University of Minnesota and NO1-HB-37163 and HHSN268201000007C awarded to the Cell Processing Facility, Baylor College of Medicine and National Center for Research Resources CTSA grant UL1 TR000064 awarded to the University of Florida. The CCTRN also acknowledges its industry partners, BioSafe, Biologics Delivery Systems Group, and Cordis Corporation for their contributions of equipment and technical support during the conduct of the trial. (Full details and conflict of interest declarations in the paper.)

Perin 2012a *(Continued)*

	Study setting: USA *Number of centres*: 5 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 61; Controls: 31 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 54; Controls: 28
Participants	*Description*: Chronic IHD (aged > 18 years; clinically stable coronary artery disease, LVEF ≤ 45%, limiting angina (CCS class II-IV) and/or CHF (NYHA class II-III), a perfusion defect by SPECT, and no revascularisation options while receiving guideline-based medical therapy). *Age distribution in each arm*: BMSC: 63.95 ± 10.90 years; Controls: 62.32 ± 8.25 years. *Sex (% male) in each arm*: BMSC: 86.89%; Controls: 93.65%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: Not reported. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: Approximately 80 mL to 100 mL of BM was aspirated from the iliac crest using standard techniques. The aspirate was processed using Ficoll with a closed, automated cell processing system (Sepax). Composition of CD34 and CD133 cells was determined by flow cytometry. Cells passed stipulated lot release criteria, included viability (> 70%) and sterility. The target dose was 100 x 10^6 total BMC. The BMC final product was suspended in normal saline containing 5% human serum albumin and adjusted to a concentration of 100 x 10^6 cells in 3 mL distributed into three 1-millilitre syringes. The placebo group received a cell-free suspension in the same volume. Mean (SD) volume of BM harvested was 93.7 (8.3) mL. Total dose of 100 x 10^6 contained an average of 2.6% of CD34 cells and 1.2% of CD133 cells. Cells were delivered by intramyocardial injection. The cell-containing or cell-free preparation was delivered to viable myocardial regions identified during electromechanical mapping of the LV endocardial surface (NOGA). *Dose of stem cells*: 100 x 10^6 BMSC. *Timing of stem cell procedure*: Within 12 hours of cell harvest. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; cell-free suspension in the same volume). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: 1. Change in LVESV (baseline, 6 months) 2. Change in maximal oxygen consumption (baseline, 6 months) 3. Change in reversible defect size on SPECT (baseline, 6 months) *Secondary outcomes*: 1. Regional wall motion by MRI (baseline, 6 months) 2. Regional blood flow improvement by MRI (baseline, 6 months) 3. Regional wall motion by echocardiography (baseline, 6 months) 4. Clinical improvement in CCS classification (baseline, 6 months) 5. Clinical improvement in NYHA classification (baseline, 6 months) 6. Number of participants with a decrease in antianginal medication (baseline, 6 months) 7. Exercise time and level (6MWT) (baseline, 6 months) 8. Serum BNP levels in participants with CHF (baseline, 6 months) 9. LV diastolic dimension measured by echocardiography (baseline, 6 months) 10. Incidence of a major adverse cardiac event (baseline, 6 months) 11. Reduction in fixed perfusion defect via SPECT (baseline, 6 months) *Outcome assessment points*: Baseline and 6 months

Perin 2012a *(Continued)*

	Method(s) of outcome measurement: Echocardiography and SPECT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated and used variable block sizes of 6 or 9, randomly selected and stratified by centre.
Allocation concealment (selection bias)	Low risk	Treatment assignment was masked to all but 1 designated cell-processing team member at each centre not involved in participant care.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM aspiration, and the control group received a placebo injection. All caregivers and participants were masked to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was described as “double-blind”. Major adverse clinical events were assessed by 2 independent cardiologists not affiliated with any clinical site and masked to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity outcomes. Reasons for loss to follow-up and withdrawals from echocardiography and SPECT analysis were given, with similar attrition rates in both treatment arms.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00824005) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Perin 2012b

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: "This work was supported solely by Aldagen, Inc, Durham, NC". *Study setting*: Texas, USA *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 10; Controls: 10 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 10; Controls: 10
Participants	*Description*: Advanced ischaemic HF (CCS class II-IV angina or NYHA class II-III HF; optimal medical therapy, LVEF < 45% by echocardiography; presence of a reversible perfusion defect on SPECT, ineligible for percutaneous or surgical revascularisation). *Age distribution in each arm*: BMSC: 58.2 ± 6.1 years; Controls: 57.8 ± 5.5 years. *Sex (% male) in each arm*: BMSC: 90%; Controls: 80%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: At least 1 month from the last MI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: ALDH+ cells

Perin 2012b *(Continued)*

	Summary of stem cell isolation and type and route of delivery: 100 mL (± 20) BM was harvested from the iliac crest under local anaesthesia unless institutional guidelines required general anaesthesia. Bone marrow cells were depleted of CD15 and glycophorin-A-expressing cells using immunomagnetic beads (EasySep). The cells were reacted with ALDH substrate and ALDH bright (+) cells were isolated using a cell sorter (MoFlo or FACSAria). After centrifugation, the cells were resuspended in 3.5 mL 5% pharmaceutical grade human serum albumin. The final products were transferred to a 3-millilitre fluorinated ethylene propylene bag with a needles entry port. ALDH (+) cells were administered intramyocardially via a NOGA MyoStar catheter. Cells comprised a mean of 0.74% (0.28%) of the nucleared BM cells in the unprocessed aspirates from participants (median 0.73%, range 0.35% to 1.16%). Cell injections were targeted at areas of the myocardium identified as ischaemic or SPECT and as viable by EMM. *Dose of stem cells*: 15 injections in a volume of 0.2 mL per injection. Mean number of nucleated cells administered to the treatment group was 2.94 ± 1.58 x 10^6 cells (median 2.78 x 10^6, range 0.53 to 5.42 x 10^6). When the total cell doses were corrected for the proportion of ALDH (+) cells in the cell product, the mean number of ALDH (+) cells administered to the cell treatment group was 2.37 ± 1.31 x 10^6 (median 2.27 x 10^6, range 0.35 to 4.42 x 10^6). *Timing of stem cell procedure*: Products manufactured at Aldagen were administered within 50 to 55 hours of BM aspiration, whereas those produced locally at the University of Texas were administered within 30 to 36 hours of aspiration. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; 5% albumin). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Safety (combined early and late adverse events) (baseline, 6 months) *Secondary outcomes*: 1. NYHA classification (baseline, 6 months) 2. CCS score (baseline, 6 months) 3. EF measured by echocardiography (baseline, 6 months) 4. LVESV; LVEDV (baseline, 6 months) 5. Wall motion score index measured by echocardiography (baseline, 6 months) 6. Myocardial oxygen consumption (baseline, 6 months) 7. Total severity score (stress, rest, and reversible) (baseline, 6 months) *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: SPECT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomised sequence was used.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Control participants underwent an identical bone marrow harvest procedure, including insertion of the needle, except that BM was not aspirated. Control participants received transendocardial injections of placebo solution instead of cell preparation. All personnel involved were blinded. Personnel involved in

Perin 2012b *(Continued)*

		the harvesting procedure acted independently of the study team, thus maintaining blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was described as "double-blind". Two blinded, independent echocardiologists reviewed the echocardiograms, and the average of the 2 readings was reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (NCT00314366) were reported.
Other bias	High risk	This work was supported solely by Aldagen Inc, Durham, NC. No other sources of bias were reported or identified.

Pokushalov 2010

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Not reported. *Study setting*: Russia *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 55; Controls: 54 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 49; Controls: 33 at the end of study
Participants	*Description*: Chronic MI and end-stage chronic HF (history of MI > 12 months before enrolment and fixed perfusion defect on technetium-99m tetrofosmin SPECT; clinical symptoms of HF; ineligible for revascularisation; LVEF < 35% as determined by 2-dimensional echocardiography). *Age distribution in each arm*: BMSC: 61 ± 9 years; Controls: 62 ± 5 years. *Sex (% male) in each arm*: BMSC: 87%; Controls: 85%. *Number of diseased vessels*: BMSC: 1 (n = 2), 2 (n = 1), 3 (n = 52); Controls: 1 (n = 3), 2 (n = 3), 3 (n = 48). *Time from symptom onset to initial treatment*: History of MI > 12 months before enrolment. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: On the day of surgery, BM was aspirated from the iliac crest under local anaesthesia by the standard technique. BMMNC were isolated by Ficoll density gradient centrifugation. 3 washing steps were performed, and the cells were resuspended in heparinised saline for further use. Cell viability was tested by trypan blue (exclusion method) and estimated at more than 98% for each transplant. Intramyocardial injection. Non-fluroscopic mapping with the NOGA system via femoral artery access and retrograde aortic approach using a 7-Fr NOGA-Star catheter. An area of interest located by technetium-99m tetrofosmin SPECT was delineated in detail by means of NOGA mapping, including ischaemic but viable myocardium. Immediately before injection, the catheter was positioned perpendicularly to endocardium with excellent loop stability and the extension of the needle to induce premature ventricular contraction. 10 successive intramyocardial injections (roughly 0.2 mL each) were administered into the infarction border zone. *Dose of stem cells*: 41 ± 16 x 10^6 BMSC, with 2.5 (1.6)% being CD34-positive cells. *Timing of stem cell procedure*: Within 24 hours after cell harvesting. *G-CSF details*: No G-CSF administered.

Pokushalov 2010 *(Continued)*

	Comparator arm: Control (no BM aspiration or placebo administration reported). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Efficacy of the intramyocardial injection of autologous bone marrow mononuclear cells, measured by change in myocardial perfusion defects at rest and under pharmacological stress. *Secondary outcomes*: Safety of the intramyocardial BMMNC therapy, quality of life, CCS angina class, NYHA functional class, LV functions, life-threatening arrhythmias, mortality between 2 groups, NOGA change in voltage assessed by NOGA follow-up endocardial mapping. *Outcome assessment points*: Baseline, 6 and 12 months *Method(s) of outcome measurement*: SPECT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using an electronic system.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was administered; participants and clinicians were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	SPECT imaging was carried out though consensus by 2 readers blinded to the type of study and clinical data. Other blinding was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes (other than deaths prior to follow-up).
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Santoso 2014

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Supported by the S.K. Yee Medical Foundation Grant (208207); Research Grant Council of Hong Kong: General Research Fund (no. HKU 780110M); the Collaborative Research Fund (HKU 8/CRF/09); and Theme Based Research Scheme (T12-705/11). *Study setting*: Jakarta (Indonesia) and Hong Kong (China) *Number of centres*: 2 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 19; Controls: 9 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 19; Controls: 9

Santoso 2014 *(Continued)*

Participants	*Description*: Advanced ischaemic HF (NYHA class III or IV; HF refractory to conventional medical therapy not eligible for conventional percutaneous or surgical revascularisation; existence of 1 or 2 coronary territories of viable, ischaemic myocardium as documented by dipyridamole single-photon emission computed tomographic perfusion study; and LVEF < 40% measured by transthoracic echocardiogram). *Age distribution in each arm*: BMSC: 58 (5.9) years; Controls: 60 (5.6) years *Sex (% male) in each arm*: BMSC: 95%; Controls: 100% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: At least 3 months since last MI. *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* On the day of the procedure, BMC were harvested from every participant by an experienced haematologist via posterior iliac crest puncture under local anaesthetic. A total of 80 mL to 100 mL of BM blood was aspirated, and an adequate trephine biopsy was performed. Mononuclear cells were isolated by Ficoll density gradient centrifugation. Bone marrow cells were washed twice in PBS, resuspended in PBS enriched with 10% autologous plasma to 100×10^6 mononuclear cells/mL, and returned directly to cardiac catheterisation laboratory for use. In the preparation for the control group, BM cells were not included in the final suspension, which comprised merely phosphate-buffered saline with 10% autologous plasma. Bone marrow suspensions were tested by flow cytometry (Elite, Beckman Coulter, Fullerton, CA, USA) with directly conjugated antibodies. Cells administered by electromechanical mapping and endocardial injection (e.g. NOGA system). *Dose of stem cells*: n/r *Timing of stem cell procedure*: At least 3 to 4 hours after BM harvest. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; PBS with 10% autologous plasma). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Change in LVEF from baseline to 6 months' follow-up measured by MRI *Secondary outcomes*: Changes in exercise duration and MVO_2 (treadmill modified Bruce protocol) (baseline and 6 months) Note: main study publication reports secondary endpoints as changes in NYHA classification, LVESV, LV infarct and peri-infarct ischaemic volume, and exercise performance (6MWT) (Santoso 2014). *Outcome assessment points*: Baseline, 6 months; mean 23 (8) months (mortality only) *Method(s) of outcome measurement*: MRI, NYHA, 6MWT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation codes were generated using a randomisation table; randomisation was constrained, stratified by study centre.
Allocation concealment (selection bias)	Low risk	Randomisation was conducted via a system of sealed and numbered envelopes provided to each investigation centre.

Santoso 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Bone marrow cells were harvested from all participants. The control group received an identical final suspension but without cells. After randomisation, participants were blinded to the study processes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After randomisation, investigators who were responsible for participant assessment were blinded to study processes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes on an intention-to-treat basis.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the trial protocol (NCT01150175) were reported; additional outcomes were reported in the publication of results.
Other bias	Low risk	No other sources of bias were reported or identified.

Trifunovic 2015

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: n/r *Study setting*: Belgrade, Serbia *Number of centres*: 1 *Length of follow-up*: median 5 years (IQR 2.5 to 7.5) *Number (N) of participants randomised to each arm*: BMSC: 15; Controls: 15 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 15; Controls: 15
Participants	*Description*: IHD (aged 35 to 72 years; scheduled for CABG surgery due to LAD occlusion or multivessel coronary disease; previous MI older than 30 days; established diagnosis of ischaemic cardiomyopathy with LVEF < 40% and in the NYHA III-IV functional class, full medical treatment for HF). *Age distribution in each arm*: BMSC: 53.8 (10.1) years; Controls: 60 (6.8) years. *Sex (% male) in each arm*: BMSC: 93.3%; Controls: 93.3% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: Duration since last MI, BMSC: mean 3.2 (range 6 to 12) months; Controls: mean 3.07 (range 6 to 12) months *Statistically significant baseline imbalances between the groups*? Significantly higher hypercholesterolaemia in BMSC group than in control group.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* Bone marrow was obtained by multiple aspirations from the posterior iliac crest in the amount of 150 mL, mixed with 25 mL of heparinised saline and transferred into a sterile bag. The BMMNC fraction was isolated by gradient centrifugation. All procedures from harvesting to cell injection were performed in a closed-circuit system using sterile connection equipment with a sterile plastic bag system designated for cell transplantation in preoperative conditions. After finishing revascularisation with LIMA to LAD and sufficient number of autovenous aortocoronary bypass grafts to achieve total targeted revascularisation (either “on pump” or “off pump”, and if “on pump” when heart resumed its function from cardiopulmonary bypass), intramyocardial injection of BMMNC was carried out with a 1-millilitre insulin syringe through a 27-gauge needle. Bone marrow mononuclear cells injection was targeted into the hypocontractile peri-infarcted viable myocardium visually identified and performed transepicardially in 30- to 45-degree manner by

Trifunovic 2015 *(Continued)*

	multiple injections (17.5 (3.8) injections) injecting 0.2 mL to 0.5 mL in each injection to a final volume of 5.7 (1.5) mL. *Dose of stem cells*: Mean 70.7 (32.4) x 10^6 cells *Timing of stem cell procedure*: n/r *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration, no placebo). *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Postoperative functional capacity and cardiac-related mortality in the median follow-up of 5 years. *Secondary outcomes*: Cardiovascular mortality, NYHA, 6MWT, LVEF, perfusion defect; BNP levels. *Outcome assessment points*: Baseline, 2 and 4 months, 1 year and subsequent years (clinical f/up); pre-operatively and 6 months and at 2-year intervals (SPECT) or at each follow-up visit (echocardiography); baseline, 6 months and yearly (exercise capacity). Median follow-up 5 years (range 2.5 to 7.5 years). *Method(s) of outcome measurement*: SPECT, echocardiography, 6MWT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial; no blinding was carried out.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The heart team consisting of an interventional cardiologist/radiologist, heart surgeon, and clinical cardiologist evaluated coronary angiography and all clinical and imaging data and made decisions on coronary revascularisation and stem cell implantation. This was an open-label trial; no blinding was reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Tse 2007

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: This study was partially supported by the Sun Chieh Yeh Heart Foundation Fund; S K Ye Medical Foundation Grant (project no 203217), and The Research Grants Council of Hong Kong (HKU 7357/02M). Two authors received consultant fee from Biosense Webster, CA, USA. All other authors declare that they have no conflict of interest. *Study setting*: Hong Kong (China) and Newcastle (Australia) *Number of centres*: 2 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 19; Controls: 9 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 19; Controls: 9
Participants	*Description*: Refractory angina (CCS class III or IV; no conventional percutaneous or surgical revascularisation option; ability to complete > 3 min but < 10 min of treadmill exercise using modified Bruce protocol, and 1 or 2 coronary territories of viable, ischaemic myocardium as documented by dipyridamole SPECT perfusion study). *Age distribution in each arm*: BMSC: 65.2 ± 8.3 years; Controls: 68.9 ± 6.3 years. *Sex (% male) in each arm*: BMSC: 79%; Controls: 88%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: Not reported. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: Bone marrow was harvested via posterior iliac crest puncture under local anaesthesia. A total of 40 mL of BM blood was aspirated, and an adequate trephine biopsy was performed. Bone marrow mononuclear cells were isolated by Ficoll density gradient centrifugation. Bone marrow cells were washed twice in phosphate-buffered saline, resuspended in phosphate-buffered saline enriched with 10% autologous plasma to either 1 or 2 x 10^7 MNC/mL and returned directly to cardiac catheterisation laboratory for use. Bone marrow suspensions were tested by flow cytometry with directly conjugated antibodies against CD34. Intramyocardial injection. Non-fluoroscopic LV electromechanical mapping (NOGA) to identify the foci of ischaemic myocardium. During the procedure, systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 250 to 300 s throughout the procedure. The targeted injection regions were selected by matching the area of ischaemic myocardium identified by SPECT. After completion of the LV electromechanical mapping, the mapping catheter was replaced by a modified mapping catheter incorporated with a 27G needle at the tip that could be used for direct endomyocardial injection. *Dose of stem cells*: 1.5 x 10^7 BMMNC. *Timing of stem cell procedure*: Within 3 to 4 hours from cell harvest. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; 8 to 12 injections of 0.1 mL of phosphate buffered saline with 10% autologous serum). *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Change from baseline in total exercise time on a modified Bruce protocol at 6 months' follow-up. *Secondary outcomes*: Changes in LVEF, NYHA, and CCS angina classification and sum of different scores on SPECT, global LVEF, LVEDV and LVESV by MRI. *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: SPECT and MRI
Notes	

Risk of bias

Tse 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a randomisation table and was constrained, stratified by the study centre.
Allocation concealment (selection bias)	Low risk	Sealed, numbered envelopes were provided by the study centre (centralised) to each investigational centre.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All randomised participants underwent BM aspiration, and the control group received a placebo injection. After randomisation, the study processes were blinded to participants. No details were given of the blinding of clinicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After randomisation, the study processes were blinded to study co-ordinators and investigators responsible for participants' assessment. Blinding was maintained until the end of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes on an intention-to-treat basis.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Turan 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Not reported *Study setting*: Germany *Number of centres*: 1 *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: BMSC: 38; Controls: 18 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 33; Controls: 16
Participants	*Description*: IHD (aged 18 to 80 years; documented MI at least 3 months previously; clear-cut demarcated region of left ventricular dysfunction with an open infarct-related coronary artery at the time of stem cell therapy). *Age distribution in each arm*: BMSC: 62 ± 10 years old; Controls: 60 ± 9 years old. *Sex (% male) in each arm*: BMSC: 52.6%; Controls: 55.6%. *Number of diseased vessels*: BMSC: 1.5 ± 0.5; Controls: 2.0 ± 0.6. *Time from symptom onset to initial treatment*: Transmural MI 28 ± 14 months before treatment. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC. *Type of stem cells*: Mononuclear cells. *Summary of stem cell isolation and type and route of delivery*: 120 mL bone marrow was aspirated from the participant's own iliac crest, mononuclear cells were isolated using Harvest BMAC System (Germany) (most likely by density gradient centrifugation) and concentrated into 20 mL of cell suspension. Cell transplantation was performed via the coronary artery using 4 fractional infusions parallel to balloon inflation over 2 to 4 mins of 5 mL cell suspension. Cells were infused directly into the infarcted

Turan 2011 *(Continued)*

	artery via an angioplasty balloon catheter that was inflated at a low pressure and was located within the previously stented coronary artery. Intracoronary infusion. This prevented back flow of cells and produced stop flow beyond the site of balloon inflation to facilitate high-pressure infiltration of cells into the infarcted zone with prolonged contact time for cellular migration. After undergoing arterial puncture, all participants received 7500 to 10,000 units of heparin. *Dose of stem cells*: 99 x 10^6 (± 25) mononuclear cells. *Timing of stem cell procedure*: Within 24 hours from cell harvest. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration; no placebo administered). *Co-intervention:* PCI
Outcomes	*Primary outcomes*: Change in global EF as well as the size of infarcted area measured by left ventriculography. *Secondary outcomes*: Functional activity of BMSC immediately pre-procedure and 3, 6, and 12 months after procedure; functional status assessed by NYHA classification and brain natriuretic peptide level in peripheral blood in both groups. *Outcome assessment points*: Baseline, 3 and 12 months *Method(s) of outcome measurement*: Left ventriculography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants in the control group did not undergo BM aspiration, and no placebo was administered. Blinding was not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Haemodynamic investigations and laboratory results were obtained independently by 2 investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of mortality and morbidity outcomes; 7 participants (5x cell therapy, 2x controls) were excluded from LVEF and functional capacity at follow-up due to restenosis.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Van Ramshorst 2009

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper

Van Ramshorst 2009 *(Continued)*

	Source of funding: This study is an academia-initiated exploratory Phase II study. No external sponsor was involved in study design, data collection, data analysis, data interpretation, or writing of the report. No external funding was applicable for this study. *Study setting*: Leiden, the Netherlands *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 25; Controls: 25 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 25; Controls: 25
Participants	*Description*: Severe angina (CCS class II-IV, myocardial ischaemia in at least 1 myocardial segment on Tc099m tetrofosmin SPECT, ineligible for CABG or PCI). *Age distribution in each arm*: BMSC: 64 ± 8 years; Controls: 62 ± 9 years. *Sex (% male) in each arm*: BMSC: 92%; Controls: 80%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: At least 6 months from the last MI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: Bone marrow was aspirated from the iliac crest under local anaesthesia and placed in a heparinised Hanks balanced salt solution. The MNC were isolated using Ficoll density gradient centrifugation, washed in phosphate-buffered saline with 0.5% human serum albumin and resuspended in phosphate-buffered saline with 0.5% human serum albumin. The final suspension of BMMNC contained 40 x 10^2 mL. The filtered bone marrow was checked for the presence of clots, and the BM cell population was analysed by fluorescence-activated cell sorting using anti-CD34 and anti-CD35 antibodies. Intramyocardial injection. During cell isolation and randomisation, a 3D electromechanical map of the LV was obtained using the NOGA system. The ischaemic regions on SPECT were visually matched with the 3D electromechanical map based on anatomical landmarks including LV long axis, position of apex, mitral valve area, aortic valve location, and basal inferoseptal point. Cross-referencing was also performed using fluoroscopic identification of anterior, septal, lateral, and inferior orientations. *Dose of stem cells*: The cell suspension contained 98 ± 6 x 10^6 BM cells with a cell viability of 98% (1%) and a CD34+ cell fraction of 2.4% (0.9%). *Timing of stem cell procedure*: Within 2 hours of BM aspiration. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; sodium chloride 0.9% with 0.5% human serum albumin). *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Change in myocardial perfusion (SPECT) at 3 months' follow-up relative to baseline. *Secondary outcomes*: 1. Angina frequency 2. CCS score 3. Quality of life 4. Exercise capacity 5. Change in LVEF at 3 months 6. Regional myocardial function on a segmental base at 3 months 7. Occurrence of arrhythmias 8. Pericardial effusion greater than 5 mm (echocardiography) 9. Myocardial damage 10. Severe inflammation

Van Ramshorst 2009 *(Continued)*

	Outcome assessment points: Baseline and 6 months *Method(s) of outcome measurement*: SPECT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using sequentially numbered, sealed envelopes provided by the Department of Medical Statistics and Bioinformatics. A block size of 4 was used without further stratification.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed envelopes were used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM aspiration, and the control group received a placebo injection; participants were unaware of group assignment. A blinded syringe with either cell suspension or placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, study co-ordinators, and investigators involved in participant assessments were unaware of group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the trial protocol (ISRCTN58194927) were reported.
Other bias	Low risk	No other sources of bias were reported or identified.

Wang 2009

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Not reported. *Study setting*: Beijing, China *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 16; Controls: 16 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 16; Controls: 16
Participants	*Description*: Angina (no AMI in the month prior to transplantation). *Age distribution in each arm*: BMSC: 60.6 years; Controls: 60 years. *Sex (% male) in each arm*: BMSC: 56.25%; Controls: 63.25%. *Number of diseased vessels*: Not reported. *Time from symptom onset to initial treatment*: At least 1 month from the last AMI. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC

Wang 2009 *(Continued)*

	Type of stem cells: CD34+ progenitor cells *Summary of stem cell isolation and type and route of delivery*: 150 mL of BM was aspirated from the iliac crest. CD34+ cells were enriched by a cell separation device under GMP conditions. CD34+ cells were re-suspended in normal saline and kept at room temperature. Cells were transported to the catheterisation lab. Cells were delivered using a microcatheter following PCI. *Dose of stem cells*: 1.0 - 6.1 x 10^6 CD34+ cells. *Timing of stem cell procedure*: Unclear, not reported. *G-CSF details*: No G-CSF administered. *Comparator arm*: Control (no BM aspiration, no placebo administered). *Co-intervention:* PCI
Outcomes	*Primary outcomes*: Not reported. *Secondary outcomes*: Myocardial perfusion defect area, wall motion, angina frequency change, nitrate triglycerine dose change, angina classification by CCS class. *Outcome assessment points*: Baseline and 6 months. *Method(s) of outcome measurement*: SPECT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This Chinese trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of clinicians and participants was not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Wang 2010

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Not reported. *Study setting*: China

Wang 2010 *(Continued)*

	Number of centres: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 56; Controls: 56 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 56; Controls: 56
Participants	*Description*: Intractable angina (aged > 30 years; diffuse triple-vessel disease; CCS class III or IV; optimal medical therapy and considered ineligible for revascularisation, no ischaemia or nuclear perfusion imaging according to the Bruce protocol; angina experienced during baseline exercise test). *Age distribution in each arm*: BMSC: 42 to 80 years; Controls: 43 to 80 years. *Sex (% male) in each arm*: BMSC: 51.79%; Controls: 50%. *Number of diseased vessels*: 3 *Time from symptom onset to initial treatment*: Not reported. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: CD34+ progenitor cells *Summary of stem cell isolation and type and route of delivery*: 120 mL to 150 mL bone marrow aspirates from the posterior iliac crest were obtained from all participants. CD34+ cells were isolated by labelling with the appropriate CD34 antibody and separating them magnetically using a CliniMACS (Miltenyi Biotec). CD34+ cells were resuspended in 15 mL of saline + human serum albumin. Only the saline + human serum albumin was infused in the control group, using the same protocol as in the BMSC group. The cells were infused into the coronary artery using a GE Innova 2000 DSA with 3000 units of heparin. Approximately 1 to 2 hours after cell separation, 10 mL of cells and 5 mL of saline were infused into the left coronary artery and right coronary artery separately by an over-the-wire balloon. *Dose of stem cells*: $5.6 \pm 2.3 \times 10^7$ CD34 cells. *Timing of stem cell procedure*: Within 2 hours of cell harvest. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; saline + human serum albumin) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: Safety (mortality and morbidities). *Secondary outcomes*: Arrythmias, angina frequency, nitroglycerine use, exercise tolerance, CCS class, perfusion effect or myocardial perfusion. *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: Treadmill test, CCS class
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This Chinese trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM aspiration, and the control group received a placebo injection. Participants were unaware of the treatment received. Blinding of clinicians was not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All researchers were unaware of the treatments.

Wang 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Wang 2014

Methods	*Type of study*: Parallel RCT *Type of publication*: Conference abstract *Source of funding*: Not reported. *Study setting*: Guangzhou, China *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 35; Controls: 35 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 35; Controls: 35
Participants	*Description*: Chronic IHD (impaired LV function: LVEF < 35%). *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r *Statistically significant baseline imbalances between the groups*? None reported.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: CD133+ progenitor cells *Summary of stem cell isolation and type and route of delivery:* Injection of cells into the non-transmural hypokinetic infract border zone. No further details reported. *Dose of stem cells*: n/r *Timing of stem cell procedure*: n/r *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration not reported; no further details) *Co-intervention:* Standard medical therapy
Outcomes	*Primary outcomes*: LVEF measured by cMRI. *Secondary outcomes*: 5-min walk test; NYHA, regional wall motion, scar mass, LVESV, LVEDV. *Outcome assessment points*: Baseline, 6 months *Method(s) of outcome measurement*: MRI, NYHA class, 5-min walk test
Notes	
Risk of bias	

Wang 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This Chinese trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was reported as "double-blind", but no details of blinding were reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was reported as "double-blind", but no details of blinding were reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals were reported in this conference abstract.
Selective reporting (reporting bias)	High risk	All outcomes mentioned in the methods were reported in the results, although selective reporting would be considered likely in this conference abstract. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Wang 2015

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Supported by funding from the Major Project of Clinical Advanced Technology from PLA (2010gxjs002 to H.W.) and funded in part by the National Natural Science Foundation of China (30960379 to J.H.) *Study setting*: Shenyang, China *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 45; Controls: 45 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 45; Controls: 45
Participants	*Description*: Chronic MI (multivessel disease; admitted for elective OPCAB surgery at least 4 weeks after a cardiac infarction). *Age distribution in each arm*: BMSC: 61.4 (7.45) years; Controls: 62.9 (6.93) years. *Sex (% male) in each arm*: BMSC: 82%; Controls: 78%. *Number of diseased vessels*: n/r (multivessel) *Time from symptom onset to initial treatment*: Duration since last MI, mean 18.2 (16.8) months (BMSC) or 20.1 (19.0) months (Controls). *Statistically significant baseline imbalances between the groups*? None.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery:* Bone marrow aspiration (100 mL) took place from the sternum of all participants. Bone marrow mononuclear cells were isolated by gradient centrifugation using Lymphoprep, washed twice with saline, and resuspended in 2 mL of heparinised

Wang 2015 *(Continued)*

	saline. The 2 mL suspension or an equivalent volume of saline was injected with 8 punctures from a 22-gauge Myjector syringe at the border zone of the infarct scar after finishing the revascularisation of the infarct-related area. In cases where the infarct border could not be visualised, the cells were injected in an area of myocardium that corresponded to the perfusion defect on SPECT or scintigraphy. The injections were made parallel to the epicardium to avoid leakage of cells or delivery into the ventricular cavity, and depth was controlled with a plate stabiliser. *Dose of stem cells*: mean 5.21 (0.44) x 10^8 cells *Timing of stem cell procedure*: n/r *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration, saline solution) *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Incidence of emergent adverse events within the follow-up period (6 months). *Secondary outcomes*: LVEF, wall motion score index, LVEDV/LVESV, LVEDD/LVESD, arrhythmias, atrial fibrillation, non-sustained ventricular tachycardia, ventricular premature beats, sustained ventricular tachycardia, troponin T levels. *Outcome assessment points*: Baseline, 6 months *Method(s) of outcome measurement*: Echocardiography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This Chinese trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM aspiration and received cells or a placebo injection. The surgeon performing the OPCAB and injections was unaware of whether the light-resistant syringe contained saline or BMC.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All preoperative baseline and follow-up echocardiography was performed by an experienced cardiologist blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Yao 2008

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: This work was supported by Shanghai Scientific Research Fund (06DJ14001), Program for Shanghai Outstanding Medical Academic Leader (LJ06008), and National Key Program (2006CB943704). *Study setting*: Shanghai, China *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 24; Controls: 23 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 24; Controls: 23
Participants	*Description*: IHD (aged < 75 years; history of transmural MI and revascularisation plus stent implantation at least 6 months earlier; patent infarct-related artery at the time of stem cell transplantation). *Age distribution in each arm*: BMSC: 54.8 ± 11.5 years; Controls: 56.3 ± 7.9 years. *Sex (% male) in each arm*: BMSC: 96%; Controls: 96%. *Number of diseased vessels*: BMSC: 1 (67%), 2 (29%), 3 (4%); Controls: 1 (70%), 2 (26%), 3 (4%). *Time from symptom onset to initial treatment*: At least 6 months from last MI. 13 ± 8 months before entry into study. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: Bone marrow (95 (20) mL) was collected under local anaesthesia from the posterior superior iliac spine. Bone marrow cells were isolated and enriched with the use of Ficoll-Hypaque gradient centrifugation procedures. Bone marrow aspirates were diluted with 0.9% sodium chloride (1:5), and mononuclear cells were isolated by density gradient centrifugation using Ficoll (800 g x 25 mins). Mononuclear cells were washed (800 g x 5 mins) 3 times with phosphate-buffered saline and then resuspended in 16 mL of heparin-treated plasma at a density of 2.4 (1.2 x 10^7) cells/mL at room temperature. Before intracoronary injection, the mononuclear cells were filtered (Falcon) and counted. These cells were used for therapy. To ensure that a certain % of stem cells was present in the infused MNC, a 1 mL suspension was subjected to FACS analysis after incubation with anti-human monoclonal antibodies: anti-human CD34 conjugated with FITC, or CD133 antibodies conjugated with APC. The FACS analysis revealed that 2.4% (0.9%) of BMC was positive for CD34, and 0.75% (0.2%) was positive for CD133. Intracoronary infusion. An over-the-wire angioplasty balloon catheter was inserted into the stent previously implanted during the acute reperfusion procedure. The balloon was inflated with low pressure (2 atm to 4 atm) to completely block blood flow for 2 mins; this was repeated 5 times. During each balloon inflation, 3 mL of BMC suspensions was infused distal to the occluding balloon into the infarct-related artery. *Dose of stem cells*: 7.2 x 10^7 cells. *Timing of stem cell procedure*: Within 6 hours after bone marrow puncture. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (0.9% sodium chloride containing heparin). Unclear whether BM aspiration was performed. *Co-intervention:* Standard medical therapy, PCI (in 30% of participants)
Outcomes	*Primary outcomes*: Improvement of LV function. *Secondary outcomes*: LVEF, LVED diameter, LVES diameter (echocardiography). LVEF, LVESV, LVEDV, infarct size (MRI). Myocardial perfusion (SPECT); mortality and morbidities. *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: Echocardiography, MRI, and SPECT
Notes	

Risk of bias

Yao 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This Chinese trial was described as randomised, but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM aspiration, and the control group received a placebo injection. Blinding of clinicians was not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors (MRI, echocardiography, SPECT) were blinded to the assigned therapy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

Zhao 2008

Methods	*Type of study*: Parallel RCT *Type of publication*: Full paper *Source of funding*: Shanghai Medical Development Research Fund, Grant Number 2000I-2D002 *Study setting*: Shanghai, China *Number of centres*: 1 *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: BMSC: 18; Controls: 18 *Number (N) of participants analysed (primary outcome) in each arm*: BMSC: 18; Controls: 18
Participants	*Description*: Ischaemic HF (aged 18 to 75 years; admitted for elective CABG; history of transmural old MI with akinesis or dyskinesis of the left ventricle shown by echocardiography; multivessel disease with a reversible perfusion defect detected by SPECT; LVEF less than 40%). *Age distribution in each arm*: BMSC: 60.3 ± 10.4 years; Controls: 59.1 ± 15.7 years. *Sex (% male) in each arm*: BMSC: 83.3%; Controls: 83.3%. *Number of diseased vessels*: multivessel, 2 or more *Time from symptom onset to initial treatment*: Not reported. *Statistically significant baseline imbalances between the groups*? No.
Interventions	*Intervention arm*: BMSC *Type of stem cells*: Mononuclear cells *Summary of stem cell isolation and type and route of delivery*: After heparinisation and median sternotomy, BM (about 30 mL) was aspirated from the sternum by a special suction appliance in both groups. The BMMNC were immediately isolated by density gradient centrifugation using Ficoll. Isolated cells were washed twice with heparinised saline and subsequently resuspended in 5 mL saline. The cells were counted and the viability was assessed by trypan blue dye exclusion. The cell suspension was fil-

Zhao 2008 *(Continued)*

	tered by a 70-micron cell strainer before transplantation. During CABG, intramyocardial injection in and around the infarct area at 10 points (approximately 0.5 mL per injection) with a 29-gauge syringe. *Dose of stem cells*: 6.59 ± 5.12 x 10^8 (cell viability 96.48% ± 3.10%). *Timing of stem cell procedure*: Within 24 hours following cell harvest. *G-CSF details*: No G-CSF administered. *Comparator arm*: Placebo (BM aspiration; saline). *Co-intervention:* CABG
Outcomes	*Primary outcomes*: Death, MI, and recurrence of HF. *Secondary outcomes*: Echo: infarction wall thickness; infarction wall motion velocity; LVEDD/LVESD; global LVEF; LV shortening fraction; mitral valve regurgitation. SPECT: LV SRS; infarcted area SRS; clinical parameters; NYHA, CCS classification; 24-hour Holter analysis. *Outcome assessment points*: Baseline and 6 months *Method(s) of outcome measurement*: Echocardiography and SPECT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computer-generated sequence of random numbers.
Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment was reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants underwent BM aspiration, and the control group received a placebo injection. Blinding of clinicians was not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The results were analysed by 2 independent, experienced observers; investigators (echocardiography, SPECT) were blinded to the randomisation scheme.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis of all outcomes at follow-up (other than deaths).
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the methods were reported in the results, although it would be difficult to rule out selective reporting. No prospectively registered or published trial protocol was identified.
Other bias	Low risk	No other sources of bias were reported or identified.

6MWT: 6-minute walk test
AEs: adverse events
ALDH: aldehyde dehydrogenase
AMI: acute myocardial infarction
AOI: area of interest
APC: allophycocyanin
BM: bone marrow
BMC: bone marrow cells
BMMNC: bone marrow mononuclear cells

BMSC: bone marrow stem cells
BNP: brain natriuretic peptide
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CCS: Canadian Cardiovascular Society
CCTRN: Cardiovascular Cell Therapy Research Network
CFU-GM: colony forming unit-granulocyte macrophage
CHF: congestive heart failure
cMRI: cardiovascular magnetic resonance imaging
CPC: circulating progenitor cells
CT: computed tomography
DM: diabetes mellitus
ECG: electrocardiogram
EDTA: ethylenediaminetetraacetic acid
EF: ejection fraction
EMM: electromechanical mapping
EPC: endothelial progenitor cells
FACS: fluorescence-activated cell sorting
FITC: fluorescein isothiocyanate
G-CSF: granulocyte colony-stimulating factor
GMP: good manufacturing practices
HF: heart failure
HTN: hypertension
IC: intracoronarily
IgG: immunoglobulin G
IHD: ischaemic heart disease
IM: intramyocardial
IQR: interquartile range
LAD: left anterior descending
LDL: low-density lipoprotein
LIMA: left internal mammary artery
LV: left ventricular
LVEDD: left ventricular end-diastolic diameter
LVEDV: left ventricular end-diastolic volume
LVEF: left ventricular ejection fraction
LVESD: left ventricular end-systolic diameter
LVESV: left ventricular end-systolic volume
MACE: major adverse clinical events
MI: myocardial infarction
MLHFQ: Minnesota Living with Heart Failure Questionnaire
MNC: mononuclear cells
MRI: magnetic resonance imaging
MSC: mesenchymal stem cells
MVO_2: myocardial oxygen consumption
NHLBI: National Heart, Lung, and Blood Institute
n/r: not reported
NTG: nitroglycerine
NT-proBNP: N-terminal pro b-type natriuretic peptide
NYHA: New York Heart Association
OPCAB: off-pump coronary artery bypass
PBS: phosphate-buffered saline
PBSC: peripheral blood stem cell
PC: progenitor cells
PCI: percutaneous coronary intervention
PET: positron emission tomography
QOL: quality of life
RCT: randomised controlled trial
SD: standard deviation
SE: standard error
SF-36: 13-Item Short Form Health Survey
SPECT: single-photon emission computed tomography
SRS: segmental resting score

SV: stroke volume
STEMI: ST elevation myocardial infarction
TIMI: Thrombolysis In Myocardial Infarction
VEGF: vascular endothelial growth factor

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ascheim 2014	RCT of allogeneic mesenchymal precursor cells.
Assmann 2014	Single-arm trial of CD133+ in ischaemic cardiomyopathy, no control arm included.
Beeres 2006	Single-arm substudy of BMMNC in refractory angina and chronic myocardial ischaemia, no control arm included.
Beeres 2007	Single-arm trial of BMMNC in chronic ischaemia, no control arm included.
Beeres 2007a	Single-arm trial of BMMNC in chronic myocardial infarction and severe left ventricular dysfunction, no control arm included.
Beeres 2007b	Review of imaging techniques for cardiac stem cell therapy.
Bittencourt 2008	Single-arm trial of BMSC in severe coronary artery disease, no control arm included.
Bolli 2011	RCT of cardiac stem cells in ischaemic cardiomyopathy, no BMSC administered.
Chang 2006	RCT of peripheral blood stem cells in AMI.
Charwat 2010	Randomised trial of early versus late administration of BMMNC in AMI.
Chen 2014	RCT of G-CSF-mobilised PBSC in heart failure; G-CSF was not administered to the control group.
Chin 2010	Single-arm trial of autologous MSC in end-stage dilated cardiomyopathy.
EUCTR2006-005628-17-ES	RCT of BMMNC in people with AMI.
EUCTR2009-017924-18-NL	A follow-on study of people with refractory angina and documented ischaemia who received bone marrow-derived cells in 2 previous trials, no control arm included.
Fuchs 2004	Single-arm trial of bone marrow cells in advanced ischaemic heart disease, no control arm included.
Gu 2011	Non-randomised trial of single or repeated infusion of PBSC and G-CSF compared with a control group in refractory ischaemic heart failure.
Haack-Sorensen 2013	A single-arm trial of autologous MSC in stable coronary artery disease and refractory angina, no control arm included.
Jimenez-Quevedo 2008	A comparison of outcomes in diabetic/non-diabetic patients with end-stage heart failure who received BMMNC in a previous trial.
Kang 2006	RCT of G-CSF-mobilised PBSC in people with acute and old myocardial infarction; G-CSF was not administered to the control group.
Kang 2006b	RCT of G-CSF-mobilised PBSC in people with acute myocardial infarction.

Study	Reason for exclusion
Karantalis 2014	RCT of autologous MSC in people undergoing CABG; trial suspended due to low accrual and no control participants included.
Koestering 2005	Non-randomised trial of BMMNC in chronic coronary artery disease.
Lai 2009	RCT of autologous MSC in people undergoing CABG; study of cardiac enzyme outcomes measured within 24 to 48 hours of treatment, which are not relevant to this review. No further publications have been identified.
Lee 2015	RCT of CD34+ in end-stage diffuse coronary artery disease comparing 2 cell doses, no control arm included.
Makkar 2011	RCT of cardiosphere-derived cells in AMI.
Mann 2015	A follow-on single-arm substudy of 3 previous cell therapy trials, no control group included.
Maroto 2010	RCT of BMMNC in sub-acute myocardial infarction (within 15 days).
Maureira 2012	Although this study was described as randomised, the 7 participants in each treatment arm (14 in total) were matched by age and sex.
Mocini 2006	Non-randomised study of BMSC in AMI.
Nagaya 2007	Non-randomised study of BMMSC for severe chronic heart failure.
NCT00285454	Study withdrawn prior to enrolment.
NCT00289822	Trial terminated (reason not given), no relevant publications identified.
NCT00362388	Trial terminated (reason not given), no relevant publications identified.
NCT01074099	Trial terminated due to pilot study resulting in changes to protocol and new study required.
NCT01337011	RCT of intramyocardial versus intracoronary administration of enriched CD133+ cells, no control arm included.
NCT01666132	Trial terminated after phase I due to slow recruitment.
NCT01693042	RCT of single versus repeated administration of BMMNC in chronic postinfarction HF, no control arm included.
NCT01721902	Trial terminated due to lack of recruitment, no relevant publications identified.
Perin 2003	Non-randomised controlled trial of BMMNC in chronic ischaemic heart failure.
Peruga 2009	Non-randomised trial of BMMNC in AMI.
Poglajen 2013	Single-arm trial of CD34+ cell in ischaemic cardiomyopathy.
Pokushalov 2011	Randomised cross-over trial of cardiac resynchronisation and BMMNC in ischaemic heart failure, no control arm included.
Premer 2014	Randomised trial of autologous versus allogeneic MSC in dilated cardiomyopathy.

Study	Reason for exclusion
Qin 2015	RCT of cardiosphere-derived cells for heart regeneration after myocardial infarction; no bone marrow-derived cells were administered.
Rivas-Plata 2010	Non-RCT of BMMNC in people with heart failure.
Shen 2007	Pre-clinical animal study of BMMSC after AMI.
Stamm 2007a	Non-randomised trial of CD133+ cells in chronic ischaemic heart disease.
Suncion 2014	A single-arm substudy of the POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial, no control arm.
Takehara 2012	A single-arm trial of autologous human cardiac-derived stem cells in ischaemic cardiomyopathy.
Tuma 2010	A comparison of outcomes in people with ischaemic and non-ischaemic heart failure who received CD34+ and MSC.
Tuma 2011	A single-arm trial of BMMNC in refractory angina.
Vicario 2004	A single-arm trial of autologous unfractionated bone marrow in refractory angina.
Vrtovec 2015	A comparison of the effects of CD34+ cell therapy in ischaemic and non-ischaemic HF, no control arm included.
Wang 2006	Non-randomised trial of BMMNC in AMI.

AMI: acute myocardial infarction
BMMNC: bone marrow mononuclear cells
BMMSC: bone marrow mesenchymal stem cells
BMSC: bone marrow stem cells
CABG: coronary artery bypass grafting
G-CSF: granulocyte colony-stimulating factor
MSC: mesenchymal stem cells
PBSC: peripheral blood stem cell
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ahmadi 2010

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: Tehran, Iran *Number of centres*: n/r *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: n/r *Number (N) of participants analysed (primary outcome) in each arm*: 10 (cell therapy), 10 (controls)
Participants	*Description*: Ischaemic cardiomyopathy and low global ejection fraction (< 35%) *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r

Ahmadi 2010 *(Continued)*

	Statistically significant baseline imbalances between the groups? n/r
Interventions	*Intervention arm*: CABG + intramyocardial mesenchymal/CD133+ stem cells *Type of cells:* Intramyocardial mesenchymal/CD133+ stem cells *Dose of cells*: n/r *Timing of stem cell procedure*: Bone marrow was harvested from iliac crest 2 weeks prior to surgery, and purified expanded mesenchymal/CD133+ stem/progenitor cells were injected in the ischaemic border zone of the heart during CABG. *Comparator arm*: CABG only
Outcomes	LV function, wall motion score index, mortality, morbidities *Outcome assessment points*: Baseline, 6 months *Method of measurement*: Echocardiography
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Ahmadi 2015

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: n/r *Number of centres*: n/r *Length of follow-up*: 35 months *Number (N) of participants randomised to each arm*: n/r (total 27) *Number (N) of participants analysed (primary outcome) in each arm*: n/r
Participants	*Description*: Severe ischaemic HF undergoing CABG *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r
Interventions	*Intervention arm 1*: CABG + BMMSC Intervention arm 2: CABG + recycling stem cells *Type of cells:* BMMNC *Dose of cells:* n/r *Timing of stem cell procedure*: Cells were injected in the border zone of the infarcted myocardium. *Comparator arm*: CABG

Ahmadi 2015 *(Continued)*

Outcomes	Morbidy, mortality, LVEF wall motion score index. *Outcome assessment points*: Baseline, 36 months *Method of measurement*: Echocardiography
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Cuzzola 2007

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: Italy *Number of centres*: n/r *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: n/r (total 37 randomised 1:1) *Number (N) of participants analysed (primary outcome) in each arm*: n/r (total 16)
Participants	*Description*: Ischaemic cardiomyopathy (acute transmural MI less than 6 months prior to admission and LVEF lower than 35%). *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: < 6 months prior to admission
Interventions	*Intervention arm*: CABG + BMMNC *Type of cells:* BMMNC *Dose of cells:* n/r *Timing of stem cell procedure*: Bone marrow mononuclear cells were isolated from bone marrow aspirates and injected intramyocardially during cardiac surgery (CABG). *Comparator arm*: CABG + placebo
Outcomes	Periprocedural adverse events, mortality, LVEF and LV volumes; flow cytometry measures *Outcome assessment points*: 6 and 12 months *Method of measurement*: Not reported.
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Grynberg 2008

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: Buenos Aires, Argentina *Number of centres*: n/r *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: n/r *Number (N) of participants analysed (primary outcome) in each arm*: 7 cell therapy, 8 controls
Participants	*Description*: Chronic MI with patent infarct-related artery, extensive necrosis, no development of ischaemia, and impaired ventricular function. *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: < 3 months
Interventions	*Intervention arm*: BMSC *Type of cells* CD34+ and CD133+ cells *Dose of cells:* 4 - 10 x 10^6 *Timing of stem cell procedure*: Bone marrow aspiration, with filter and cell processing to obtain CD34+ and CD133+, and latter intracoronary injection of this preparation through the infarct-related artery. *Comparator arm*: Control (optimal medical therapy)
Outcomes	Major cardiovascular events, rehospitalisation, target vessel revascularisation, LVEF, myocardial perfusion (summed rest score) *Outcome assessment points*: Baseline, 12 months *Method of measurement*: Radioisotopic ventriculography
Notes	Participants are from the chronic branch of the "RECUPERAR" study. To our knowledge, this trial has published in abstract form only with insufficient reporting of methodology to determine whether this substudy is randomised. Should further publications be identified confirming this, the study will be incorporated into future updates to this review.

Jie 2014

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: China *Number of centres*: n/r

Jie 2014 *(Continued)*

	Length of follow-up: 12 months *Number (N) of participants randomised to each arm*: n/r (110 in total) *Number (N) of participants analysed (primary outcome) in each arm*: 42x cell therapy (assumed 68 controls)
Participants	*Description*: Ischaemic HF with LVEF < 45% *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r
Interventions	*Intervention arm*: BMSC *Type of cells:* Mononuclear cells *Dose of cells:* 8.6 x 10^8 *Timing of stem cell procedure*: Cells or placebo were injected intraoperatively into the MI border area. *Comparator arm*: Placebo (no details)
Outcomes	Myocardial scar size, LVEF, cell viability, wall thickening *Outcome assessment points*: Baseline, 12 months *Method of measurement*: MRI, PET
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Kakuchaya 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: Moscow, Russia *Number of centres*: n/r *Length of follow-up*: 6 months *Number (N) of participants randomised to each arm*: n/r *Number (N) of participants analysed (primary outcome) in each arm*: n/r (total 50 participants)
Participants	*Description*: Chronic HF patients in NYHA class III-IV (24 participants with ischaemic dilated cardiomyopathy and 26 participants with idiopathic dilated cardiomyopathy) *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r

Kakuchaya 2011 *(Continued)*

	Time from symptom onset to initial treatment: n/r
Interventions	*Intervention arm*: BMSC *Type of cells:* CD133+ *Dose of cells: n/r* *Timing of stem cell procedure*: CD133+ were obtained by CliniMACS technology of magnetic separation. *Comparator arm*: Placebo
Outcomes	LVEF, LV volumes, LV mass *Outcome assessment points*: Baseline, 6 months *Method of measurement*: SPECT
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Minjie 2011

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: Beijing, China *Number of centres*: n/r *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: n/r *Number (N) of participants analysed (primary outcome) in each arm*: n/r (50 in total)
Participants	*Description*: Old MI *Age distribution in each arm*: total: 57.48 ± 7.98 years *Sex (% male) in each arm*: total: 94% *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r
Interventions	*Intervention arm*: CABG + BMSC *Type of cells:* BMMNC *Dose of cells:* n/r *Timing of stem cell procedure*: No details of cell isolation or cell delivery method reported. *Comparator arm*: CABG + placebo
Outcomes	LVEF, LV volumes, cardiac output, cardiac index, cardiac mass, infarct size *Outcome assessment points*: Baseline, 12 months

Minjie 2011 *(Continued)*

	Method of measurement: MRI
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Pourrajab 2013

Methods	*Type of study*: Controlled trial (unclear whether randomised) *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: Yazd, Iran *Number of centres*: n/r *Length of follow-up*: n/r *Number (N) of participants randomised to each arm*: n/r (15 recruited in total) *Number (N) of participants analysed (primary outcome) in each arm*: n/r
Participants	*Description*: Severe ischaemic cardiomyopathy requiring CABG *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r
Interventions	*Intervention arm*: CABG + BMSC *Type of cells:* BMSC *Dose of cells:* median 5 x 10^7 (SD 1 x 10^6) cells *Timing of stem cell procedure*: No details given. *Comparator arm*: CABG + placebo
Outcomes	Periprocedural adverse events, angina frequency, LVEF, LV volumes, wall motion *Outcome assessment points*: n/r *Method of measurement*: n/r
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Stefanelli 2015

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r

Stefanelli 2015 *(Continued)*

	Study setting: Modena, Italy *Number of centres*: n/r *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: 19x BMSC, 11x controls *Number (N) of participants analysed (primary outcome) in each arm*: 10x BMSC, controls n/r
Participants	*Description*: Ischaemic HF *Age distribution in each arm*: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r
Interventions	*Intervention arm*: LV restoration + BMSC *Type of cells:* BMMNC *Dose of cells:* 5 cm^3 to 8 cm^3 *Timing of stem cell procedure*: Mononuclear cells were derived from the sternal bone marrow and processed in a sterile mini-lab before injection by direct visualisation into the infarcted areas of the myocardium before LV reconstruction. *Comparator arm*: LV restoration only
Outcomes	Mortality, rehospitalisation, change in LVEF diameter, change in LVEF and NYHA, change in infarcted area *Outcome assessment points*: Baseline, 6 and 12 months *Method of measurement*: Echocardiography, PET
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

Zverev 2006

Methods	*Type of study*: Parallel RCT *Type of publication*: Abstract *Source of funding*: n/r *Study setting*: St Petersburg, Russia *Number of centres*: n/r *Length of follow-up*: 12 months *Number (N) of participants randomised to each arm*: 18x BMMSC, 38x BMMNC, 13x controls *Number (N) of participants analysed (primary outcome) in each arm*: 8x BMMSC, 38x BMMNC, 13x controls
Participants	*Description*: Non-acute IHD

Zverev 2006 *(Continued)*

	Age distribution in each arm: n/r *Sex (% male) in each arm*: n/r *Number of diseased vessels*: n/r *Time from symptom onset to initial treatment*: n/r
Interventions	*Intervention arm*: BMMSC or BMMNC *Type of cells:* BMMSC or BMMNC *Dose of cells:* 12 x 10^8 cells *Timing of stem cell procedure*: Mesenchymal stem cells were isolated from bone marrow and cultured in vitro. Bone marrow mononuclear cells were also isolated from bone marrow. Cells were delivered via the coronary artery. *Comparator arm*: Placebo
Outcomes	Angina episodes, nitroglycerine consumption, myocardial viability and perfusion, LVEF *Outcome assessment points*: Baseline, 6, 9, and 12 months *Method of measurement*: PET, SPECT, echocardiography
Notes	To our knowledge, this trial has published in abstract form only with insufficient data reporting for inclusion. Should further publications be identified, this study will be incorporated into future updates to this review.

AMI: acute myocardial infarction
BMMNC: bone marrow mononuclear cells
BMMSC: bone marrow mesenchymal stem cells
BMSC: bone marrow stem cells
BNP: brain natriuretic peptide
CABG: coronary artery bypass grafting
CCS: Canadian Cardiovascular Society
CPC: circulating progenitor cells
EPC: endothelial progenitor cells
G-CSF: granulocyte colony-stimulating factor
HF: heart failure
IC: intracoronary
IM: intramyocardial
LV: left ventricular
LVEF: left ventricular ejection fraction
LVEDV: left ventricular end-diastolic volume
LVESV: left ventricular end-systolic volume
MACE: major adverse clinical events
MI: myocardial infarction
MRI: magnetic resonance imaging
MSC: mesenchymal stem cells
MVO_2: myocardial oxygen consumption
NYHA: New York Heart Association
PCI: percutaneous coronary intervention
PET: positron emission tomography
RCT: randomised controlled trial
SD: standard deviation
SPECT: single-photon emission computed tomography

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2009-016364-36-NL

Trial name or title	Injection of autologous bone marrow cells into damaged myocardium of no-option patients with ischaemic heart failure: a randomised placebo controlled trial - cell therapy for ischaemic heart failure
Methods	A randomised, double-blind, cross-over, placebo-controlled trial
Participants	Ischaemic HF: 1. Ischaemic HF NYHA class III or IV despite optimal pharmacological and non-pharmacological therapy. 2. No candidate for (repeat) surgery (revascularisation, valve repair, or ventricular reconstruction). 3. No candidate for (repeat) percutaneous revascularisation. 4. Optimal resynchronisation therapy, or no candidate for resynchronisation therapy. 5. Male or female > 18 and < 75 years old. 6. Life expectancy more than 6 months. 7. Able to perform an exercise tolerance test prior to therapy. 8. Able and willing to undergo all the tests used in this protocol including the travelling involved. 9. Written informed consent.
Interventions	*Intervention arm:* Intracardiac administration of bone marrow mononuclear cells *Comparator arm:* Intracardiac administration of placebo
Outcomes	*Primary outcomes:* 1. Left ventricular global ejection fraction as assessed by gated SPECT. 2. LV regional wall motion by echocardiography. 3. FDG-SPECT for assessment of viability and hibernation. 4. Myocardial innervation imaging (MIBG-SPECT) for assessment of myocardial innervation. 5. Exercise capacity by bicycle exercise testing with VO_2 measurement. 6. Quality of life assessed using the MLHFQ. *Secondary outcomes:* Safety (incidence of arrhythmias via Holter monitoring, inflammation and myocardial damage)
Starting date	July 2010
Contact information	None identified.
Notes	*Planned enrolment:* 64 *Estimated completion date:* The status of this trial is "completed", but no publications have been identified.

ISRCTN71717097

Trial name or title	Bone-marrow derived stem cell transplantation in patients undergoing left ventricular restoration surgery for dilated ischaemic end-stage heart failure: a randomised blinded controlled trial (TransACT 2)
Methods	A double-blind, randomised, placebo-controlled trial
Participants	End-stage HF:

ISRCTN71717097 *(Continued)*

	1. Previous anterior MI (with evidence of large surgically excludible scar at cardiac MRI). 2. Significant LV dilation (LVESV index greater than or equal to 60 mL/m^2). 3. LVEF less than or equal to 35%. 4. NYHA class III/IV and 1 episode of CHF requiring medical attention. 5. Elective left ventricular restoration surgery indicated. 6. Elective CABG indicated to bypass stenoses or occlusions of coronary arteries. 7. Participant aged ≥ 16 and < 80 years old, either sex.
Interventions	*Intervention arm:* Surgical ventricular restoration and transplantation of autologous CD133+ *Comparator arm:* Surgical ventricular restoration and injection of placebo, i.e. autologous plasma
Outcomes	*Primary outcome*: Regional LV thickening of the 'affected' segments 6 months after surgery. *Secondary outcomes*: 1. Mid-term generic and cardiac-specific health status and quality of life, measured at baseline and 6 months' follow-up. 2. End-systolic volume and stroke volume quantified by cardiac MRI, measured at baseline (3 to 5 days postoperatively), and 6 months' follow-up. 3. Myocardial injury throughout the duration of the study by measuring troponin I levels (24 hours preoperatively; surgery; 4, 12, 24 hours postoperatively; 6 weeks' and 6 months' follow-up).
Starting date	August 2009
Contact information	University of Bristol, Bristol Royal Infirmary. Contact: Mr R Ascione (r.ascione@bristol.ac.uk)
Notes	*Planned enrolment*: 40 *Estimated completion date*: The status of this trial is "completed", but no publications have been identified.

ISRCTN75217135

Trial name or title	A pilot study to evaluate the efficacy of combined transplantation of progenitor cells and coronary artery bypass grafting (TOPCABG)
Methods	RCT
Participants	Participants undergoing CABG
Interventions	*Intervention arm:* Stem cells (5 participants) *Comparator arm:* Heparinised saline (5 participants)
Outcomes	*Primary outcome*: To show improvements in myocardial function, regional wall motion, and myocardial perfusion.
Starting date	January 2004
Contact information	Southampton University Hospitals NHS Trust, Level D, East Wing, Southampton General Hospital, Tremona Road, Southampton, UK SO16 6YD. Contact: Mr D Varghese (dvarghese@btinternet.com)
Notes	*Planned enrolment:* 10

ISRCTN75217135 *(Continued)*

	Estimated completion date: The status of this trial is "completed", but no publications have been identified.

NCT00690209

Trial name or title	Bypass surgery with stem cell therapy in chronic ischemic cardiopathy
Methods	A phase II, parallel, randomised, single-blind (participant) controlled study
Participants	IHD: 1. Aged 18 to 75 years. 2. Chronic IHD. 3. LVESV > 140 mL. 4. Poor global contractile function (LVEF < 40%). 5. Substantial amount of residual viability (> 30% of left ventricle).
Interventions	*Intervention arm:* Surgical revascularisation associated with autologous bone marrow-derived stem cells injection in viable territories. *Comparator arm:* Surgical revascularisation alone.
Outcomes	*Primary outcome*: Evolution of left ventricular volumes and contractility. *Secondary outcome*: Functional status.
Starting date	May 2008
Contact information	Departments of Cardiac Surgery, Cardiology and Radiology, University Hospital, Clermont-Ferrand, France (Principal Investigator: Dr J Lipiecki. Contact: Patrick Lacarin (placarin@chu-clermontferrand.fr)
Notes	*Planned enrolment:* 12 *Estimated completion date:* June 2011 The status of this trial is "completed", but no publications have been identified.

NCT00790764

Trial name or title	Phase II combination stem cell therapy for the treatment of severe coronary ischemia (CI)
Methods	A phase II, randomised, placebo-controlled, safety/efficacy study
Participants	Severe coronary ischaemia: 1. Age 18 to 80. 2. Men or women. 3. Angina pectoris: CCS class III or IV or symptoms consistent with angina equivalent (dyspnoea) CCS class III or IV (Functional Class). 4. Chronic coronary artery disease in at least 1 epicardial vessel with stenosis > 70% by coronary angiography within the last 6 months. 5. Stable medical therapy for at least 1 month. 6. Reversible perfusion defects by SPECT.

NCT00790764 *(Continued)*

	7. Not a candidate for coronary artery bypass surgery due to poor targets or small vessels and not a candidate for percutaneous intervention due to small vessels or unreachable coronary lesions due to complicated anatomy.
Interventions	Enrolled individuals (60) will be divided into 2 treatment groups for the infusion of the cell/placebo product: 1. *Intervention arm A:* 30 individuals, including patients and placebo controls, will receive the product by intracoronary infusion. 2. *Intervention arm B:* 30 individuals, including patients and placebo controls, will receive the product by transendocardial injections. In turn, each treatment group will consist of 2 subgroups of individuals that will receive the infusion of 1 of the 2 doses established of the cell product: 1. *In subgroup 1*, 10 individuals will receive the 'low dose' of the cell product, and 5 individuals will receive the placebo product. 2. *In subgroup 2*, 10 individuals will receive the 'high dose' of the cell product, and 5 individuals will receive the placebo product. For the cell product, proper aliquots of each cell type will be taken to fulfil the doses established for this protocol. The 2 aliquots will be mixed and resuspended to a final volume of 3 mL in the "final suspension medium", which consists of Dulbecco's Phosphate Buffered Saline, containing 5% HSA. For placebo, 3 mL of the "final suspension medium", which consists of Dulbecco's Phosphate Buffered Saline, containing 5% HSA will be transferred to a 5-millilitre syringe.
Outcomes	*Primary outcome*: Safety as measured by laboratory assessments, ECG, and temperature (2 weeks). *Secondary outcome*: Efficacy as measured by SPECT scan, MUGA scan, and 2D echocardiogram (6 months).
Starting date	November 2008
Contact information	TCA Cellular Therapy, Covington, LA, United States, 70433 (Principal Investigator: Dr Patrick Lacarin)
Notes	*Planned enrolment:* 60 *Estimated completion date*: November 2011 This study has suspended participant recruitment due to lack of funding.

NCT00820586

Trial name or title	Intramyocardial delivery of autologous bone marrow
Methods	A phase II, parallel, randomised, double-blind (participant, investigator), safety/efficacy study
Participants	Refractory angina: 1. Participants > 21 years old. 2. Participants with functional class (CCS) III or IV angina. 3. Participants with LVEF < 30%. 4. Attempted 'best' tolerated medical therapy. 5. Clinical signs and symptoms of myocardial ischaemia with reversible ischaemia on perfusion imaging. 6. Participant deemed to be a poor candidate or at high surgical risk.

NCT00820586 *(Continued)*

	7. Participant must be able to complete a minimum of 2 minutes but no more than 10 minutes exercise test (Bruce protocol). 8. Participant (or their legal guardian) understands the nature of the procedure and provides written consent prior to the procedure. 9. Participant is willing to comply with specified follow-up evaluations. 10. Participant must develop angina and a horizontal or down-sloping ST segment depression of < 1 mm during exercise, compared to pre-exercise ST segment, 80 ms from the J point or moderate angina with or without the above ST segment changes. Angiographic inclusion criteria: 1. Severe obstruction (lumen diameter stenosis > 70%) in a coronary or surgical conduit believed to be solely or partially responsible for angina and myocardial ischaemia. 2. At least 1 coronary or surgical conduit with < 70% diameter stenosis. 3. Poor candidate for PCI of treatment zone. 4. Poor candidates for surgical revascularisation procedures, such as inadequate target coronary anatomy or lack of potential surgical conduits.
Interventions	*Intervention arm:* Direct intramyocardial percutaneous delivery of autologous total bone marrow-derived total mononuclear cells or selected CD34+ bone marrow-derived cells. *Comparator arm:* Not specified.
Outcomes	*Primary outcome*: Incidence of MACE, defined as a combined endpoint of death, acute MI (Q wave and non-Q wave), revascularisation procedures (percutaneous or surgical), and periprocedural complications (i.e. left ventricular perforation with haemodynamic consequences requiring pericardiocentesis, and stroke) (1/3/6/12 months). *Secondary outcomes*: 1. Change in CCS angina classification score from baseline (12 months). 2. Changes in the quality of life, as assessed according to the Seattle Angina Questionnaire. 3. Change in exercise duration and exercise tolerance using standardised treadmill exercise testing from baseline (6/12 months). 4. Cumulative number of hospitalisations for coronary ischaemia and CHF (12 months). 5. SPECT changes in global and regional radionuclide perfusion at rest, peak stress, and redistribution from baseline (1/6/12 months). 6. Change in angiographic collateral score (6 months). 7. Change in global and regional myocardial contractility (assessed by echocardiography) from baseline (6/12 months).
Starting date	January 2009
Contact information	Antonio Colombo, Director of Invasive Cardiology Unit, IRCCS San Raffaele, Milan, Italy
Notes	*Planned enrolment:* 13 *Estimated completion date*: February 2012 This study has suspended participant recruitment due to lack of further funding support.

NCT00950274

Trial name or title	Intramyocardial transplantation of bone marrow stem cells in addition to coronary artery bypass graft (CABG) surgery (PERFECT)
Methods	A phase III, randomised, parallel, double-blind (participant, caregiver, investigator, outcomes assessor) efficacy study
Participants	Chronic ischaemic coronary artery disease: 1. Coronary artery disease after MI with indication for CABG surgery. 2. Currently reduced global LVEF assessed at site by cardiac MRI at rest (25% ≤ LVEF ≤ 50%). 3. Presence of a localised akinetic/hypokinetic/hypoperfused area of LV myocardium for defining the target area. 4. Informed consent of the participant. 5. Aged ≥ 18 and < 80 years. 6. Not pregnant and do not plan to become pregnant during the study. Women with childbearing potential must provide a negative pregnancy test within 1 to 7 days before operation and must be using oral or injectable contraception (non-childbearing potential is defined as postmenopausal for at least 1 year or surgical sterilisation or hysterectomy at least 3 months before study start).
Interventions	*Intervention arm:* Intramyocardial injection of 5 mL CD133+ cells (0.5 - 5 x 10^6 cells) suspended in physiological saline + 10% autologous serum intramyocardially during CABG surgery. *Comparator arm:* Intramyocardial injection of 5 mL of physiological saline + 10% autologous serum intramyocardially during CABG surgery.
Outcomes	*Primary outcome*: LVEF at rest, measured by MRI (6 months). *Secondary outcomes*: 1. Change in LVEF as assessed by MRI and echocardiography (early postoperatively and 6 months). 2. Regional contractility in the AOI/change in LVESD, LVEDD as assessed by echocardiography (early postoperatively (discharge), 6 months). 3. Physical exercise capacity determined by 6-minute walk test (early postoperatively (discharge), 6 months). 4. NYHA and CCS class (early postoperatively (discharge), 6 months). 5. MACE (cardiac death, MI, secondary intervention/reoperation, ventricular arrhythmia) (6 months). 6. QOL score: MLHFQ, SF-36, EQ-5D (3 months, 6 months).
Starting date	July 2009
Contact information	University of Rostock, Germany, 18057 (Principal Investigator: Dr G Steinhoff (gustav.steinhoff@med.uni-rostock.de))
Notes	*Planned enrolment:* 142 *Estimated completion date*: December 2013 The status of this trial is "terminated"; no further details are provided, and no publications have been identified.

NCT01033617

Trial name or title	IMPACT-CABG trial: IMPlantation of Autologous CD133+ sTem Cells in Patients Undergoing CABG (IMPACT-CABG)

NCT01033617 *(Continued)*

Methods	A phase II, parallel, randomised, double-blind (participant, caregiver, investigator, outcomes assessor), placebo-controlled safety/efficacy study
Participants	Myocardial infarct; HF: 1. Age ≥ 18 and ≤ 75 years. 2. People with severe chronic ischaemic cardiomyopathy manifested by CCS class II or greater angina or NYHA class II or greater, or both, and who have undergone diagnostic coronary angiography demonstrating ≥ 70% diameter narrowing of at least 2 major coronary arteries or branches or ≥ 50% diameter narrowing of the left main coronary artery. 3. A significant left ventricular systolic dysfunction evaluated by echocardiography or LV angiography (LVEF ≤ 45% but ≥ 25%) due to prior MI. This area of left ventricular dysfunction should be akinetic or severely hypokinetic, not dyskinetic or aneurysmal, when assessed by echocardiography or LV angiogram. This territory should be irrigated by 1 or a branch of the 3 major vascular territories (i.e. right coronary artery, left circumflex, or left anterior descending artery distribution) that will be bypassed during the surgical procedure. 4. No contraindications or exclusions (see below). 5. Willingness to participate and ability to provide informed consent.
Interventions	*Intervention arm:* Autologous CD133+ stem cells (total 2 mL with 10 to 15 injections) injected into the myocardium. *Comparator arm:* Placebo solution containing plasma injected into the myocardium.
Outcomes	*Primary outcomes*: 1. Freedom from MACE: cardiac death, myocardial infarct, repeat coronary bypass grafting or percutaneous intervention of bypassed artery (6 months). 2. Freedom from major arrhythmia: sustained ventricular tachycardia or survived sudden death (6 months). *Secondary outcomes*: 1. Regional myocardial perfusion and function assessed by magnetic resonance scans (6 months). 2. Device performance endpoint: feasibility to produce from 100 mL of bone marrow aspiration a final cell product that contains a target CD133+ cells higher than 0.5 million with a purity superior to 30% and a recovery superior to 10% (baseline). 3. Symptom severity and quality of life after CABG surgery (6 months).
Starting date	December 2009
Contact information	Centre de recherche du CHUM (CRCHUM), Montreal, Quebec, Canada, H2W 1T8 (Principal Investigators: Dr N Noiseux, Dr S Mansour, Dr D-C Roy). Contact: Nicolas Noiseux, MD, MSc, FRCSC, (noiseuxn@videotron.ca)
Notes	*Planned enrolment:* 20 *Estimated completion date:* July 2013 The recruitment status of this study is unknown because the information has not been recently verified.

NCT01214499

Trial name or title	Prospective, controlled and randomized clinical trial on cardiac cell regeneration with laser and autologous bone marrow stem cells, in patients with coronary disease and refractory angina

NCT01214499 *(Continued)*

Methods	A phase II, randomised, single-blind (outcome assessor), parallel safety/efficacy study
Participants	Coronary disease and refractory angina: 1. Aged > 18 years of age. 2. At least 1 area of myocardial ischaemia or chronic MI of the left ventricle demonstrated by any imaging technique not amenable to conventional revascularisation and angina refractory to medical treatment. 3. LVEF > 25% measured in the 6 months prior to the procedure. 4. Participants must be mentally competent to give consent for inclusion in the clinical trial.
Interventions	*Intervention arm:* Transmyocardial revascularisation with Holmium YAG laser plus the participant's own stem cells extracted from bone marrow. *Comparator arm:* Transmyocardial revascularisation with Holmium YAG laser.
Outcomes	*Primary outcome*: NYHA classification for angina (12 months). *Secondary outcomes*: 1. The demographic, intra-operative, and postoperative variables (12 months). 2. Percentage of ischaemic area (SPECT) and maximum effort capacity before the occurrence of the angina (12 months). 3. LVEF, LVESV, LVEDV will be examined through an echocardiogram and a pre- and postoperative cardiac magnetic resonance imaging study (12 months). 4. The EQ-5D (standardised instrument for use as a measure of health outcome) will be completed by the participant for the subjective assessment of quality of life (12 months).
Starting date	October 2010
Contact information	Cardiovascular Surgery Service, Hospital Universitario de La Princesa, Madrid, Spain, 28006 (Principal Investigator: Dr GR Copa (guillermo_reyes_copa@yahoo.es))
Notes	*Planned enrolment*: 20 *Estimated completion date:* October 2012 The recruitment status of this study is unknown because the information has not been recently verified.

NCT01267331

Trial name or title	Cell therapy in patients with chronic ischemic heart disease undergoing cardiac surgery
Methods	A phase I/II, randomised, double-blind (participant, caregiver), parallel safety/efficacy study
Participants	Severe, chronic ischaemic disease: 1. Aged between 18 and 75 years. 2. Scheduled to undergo CABG. 3. At least 3 months since last episode of MI. 4. Echocardiogram-assessed LVEF between 15% and 40% (Simpson's rule). 5. Abnormal wall motion of at least 1 segment due to prior MI shown by echocardiography or left ventriculography. 6. Abnormal myocardial perfusion in infarcted area by SPECT.

NCT01267331 *(Continued)*

	7. Willingness to participate and ability to provide written informed consent.
Interventions	*Intervention arm:* Direct intramyocardial injection of autologous bone marrow mononuclear cells during CABG. *Comparator arm:* Between 10 and 15 placebo injections consisting of saline and 5% HSA during CABG.
Outcomes	*Primary outcome:* Major adverse cardiac events (6 months) *Secondary outcomes*: Left ventricular function (global function, regional myocardial perfusion, and function assessed by magnetic resonance imaging and echocardiogram) (6 months)
Starting date	December 2010
Contact information	Chinese PLA General Hospital, Beijing, China (Principal Investigator: Dr C Gao (gaochq301@yahoo.com) and Dr L Zhang (drzhanglin@gmail.com))
Notes	*Planned enrolment:* 60 *Estimated completion date:* June 2013 The recruitment status of this study is unknown because the information has not been recently verified.

NCT01354678

Trial name or title	Intramyocardial Multiple Precision Injection of Bone Marrow Mononuclear Cells in Myocardial Ischemia (IMPI)
Methods	A phase I, parallel, randomised, double-blind (participant, caregiver, investigator) safety/efficacy study
Participants	Ischaemic HF: 1. Participants with coronary artery disease and HF NYHA class II-III. 2. MI > 6 months before the study. 3. LVEF < 35%. 4. Absence of indication to coronary revascularisation. 5. Optimal pharmacological therapy no less than 8 weeks. 6. Heart transplantation is contraindicated. 7. Participants with implantable cardioverter-defibrillator or cardiac resynchronisation therapy defibrillator. 8. Participants giving informed consent.
Interventions	*Intervention arm:* Intramyocardial multiple precision injection of bone marrow mononuclear cells. *Comparator arm:* Intramyocardial multiple precision injection with placebo.
Outcomes	*Primary outcome*: Change in global LVEF and regional wall motion score index (6/12 months). *Secondary outcomes*: Incidence of the major adverse cardiac events (6/12 months).
Starting date	May 2011

NCT01354678 *(Continued)*

Contact information	Almazov Federal Center of Heart, Blood and Endocrinology (Principal Investigator: Prof EV Shlyakhto). Contact: Prof DS Lebedev (lebedevdmitry@mail.ru); Prof OM Moiseeva (moiseeva@almazovcentre.ru)
Notes	*Planned enrolment:* 30 *Estimated completion date:* May 2015 This study is marked as ongoing but is not currently recruiting participants. First identified publication in Russian (Shlyakhto 2013) confirmed by translator as early report of safety in 1 participant.

NCT01467232

Trial name or title	IMPACT-CABG trial: IMPlantation of Autologous CD133+ sTem Cells in Patients Undergoing Coronary Artery Bypass Grafting
Methods	A phase II, randomised, parallel, double-blind (participant, caregiver, investigator, outcomes assessor) safety/efficacy study
Participants	Chronic ischaemic cardiomyopathy: 1. Age ≥ 18 and ≤ 75 years. 2. People with severe chronic ischaemic cardiomyopathy manifested by CCS class II or greater angina or NYHA class II or greater dyspnoea, or both, AND who have undergone diagnostic coronary angiography demonstrating ≥ 70% diameter narrowing of at least 2 major coronary arteries or branches or ≥ 50% diameter narrowing of the left main coronary artery. 3. Significant left ventricular systolic dysfunction evaluated by echocardiography or LV angiography (LVEF ≤ 45% but ≥ 25%) due to a prior MI. This area of left ventricular dysfunction should be akinetic or severely hypokinetic, not dyskinetic or aneurysmal, when assessed by echocardiography or LV angiogram. 4. No contraindications or exclusions. 5. Willingness to participate and ability to provide informed consent.
Interventions	*Intervention arm:* Autologous CD133+ stem cells injected into the mycardium. *Comparator arm:* Placebo (saline solution containing autologous plasma without CD133+).
Outcomes	*Primary outcomes*: 1. Freedom from major adverse cardiac event at 6 months (cardiac death, myocardial infarct, repeat coronary bypass grafting or percutaneous intervention of bypassed artery). 2. Freedom from major arrhythmia at 6 months (sustained ventricular tachycardia or survived sudden death). *Secondary outcomes*: 1. Regional myocardial perfusion and function assessed by magnetic resonance scans. 2. Global ventricular function assessed by echocardiographic measures of ejection fraction. 3. Relief of symptom severity after CABG surgery. 4. Device performance endpoint. 5. Feasibility to produce from 100 mL of bone marrow aspiration a final cell product that contains a target CD133+ cells higher than 0.5 million with a purity superior to 30% and a recovery superior to 10%. 6. Quality of life after CABG surgery.

NCT01467232 *(Continued)*

Starting date	September 2011
Contact information	Terrence M Yau, MD, Peter Munk Cardiac Center/University Health Network, Toronto, Ontario, Canada, M5G 2C4
Notes	*Planned enrolment:* 20 *Estimated completion date*: October 2015 This study is marked as completed, but no publications have been identified.

NCT01508910

Trial name or title	Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina (RENEW)
Methods	A phase III, randomised, parallel, double-blind (participant, investigator) safety/efficacy study
Participants	Refractory angina and chronic myocardial ischaemia: 1. Men or women aged 21 to 80 years at the time of signing the informed consent. 2. Participants with CCS class III or IV chronic refractory angina. 3. Participants without control of their angina symptoms despite maximal tolerated doses of antiangina drugs. Participants must be on optimal therapy for their angina and have been on a stable antianginal medication regimen for at least 4 weeks before signing the informed consent form. 4. Participants with obstructive coronary disease unsuitable for conventional revascularisation due to unsuitable anatomy or comorbidity as determined at the site and confirmed by an independent adjudication committee. 5. Participants must have evidence of inducible myocardial ischaemia. 6. Participants must experience angina episodes. 7. Participants must be able to complete 2 exercise tolerance tests on the treadmill within 3 weeks of randomisation. 8. If a woman of childbearing potential, she must not be pregnant and must agree to employ adequate birth control measures for the duration of the study.
Interventions	*Intervention arm:* Targeted intramyocardial delivery of 1 x 10^5 Auto-CD34+ cells after G-CSF mobilisation and apheresis. *Comparator arm:* Targeted intramyocardial delivery of placebo after G-CSF mobilisation and apheresis.
Outcomes	*Primary outcome*: Change from baseline in total exercise time on exercise tolerance test using the modified Bruce protocol (12 months). *Secondary outcomes*: 1. Angina frequency (episodes per week) (3/6/12 months). 2. Change from baseline in total exercise time on exercise tolerance test (6 months). 3. Incidence of MACE and other serious adverse events in all participants (24 months).
Starting date	April 2012
Contact information	Baxter Healthcare Corporation (Study Director: Dr A Nada). Contact: Lauren Davis, Clinical Project Manager (lauren.davis@ppdi.com)

NCT01508910 *(Continued)*

Notes	*Planned enrolment:* 291 *Estimated completion date:* June 2016 This study is marked as completed, but no publications have been identified.

NCT01615250

Trial name or title	Implantation of Peripheral Stem Cells in Patient With Ischemic Cardiomyopathy (ISCIC)
Methods	A phase I, randomised, parallel, open-label safety/efficacy study
Participants	Ischaemic cardiomyopathy: 1. People with ischaemic cardiomyopathy and HF NYHA class II-IV. 2. MI > 6 months before the study. 3. LVEF < 35%. 4. Absence of effect of coronary revascularisation during 6 months. 5. Optimal pharmacological therapy no less than 8 weeks. 6. Heart transplantation is contraindicated. 7. Participants with implantable cardioverter-defibrillator or cardiac resynchronisation therapy defibrillator. 8. Participants giving informed consent.
Interventions	*Intervention arm:* Intramyocardial implantation of peripheral mononuclear cells with CD34+ stem cells in participant with ischaemic cardiomyopathy after preparatory course of shockwave therapy. *Comparator arm:* Cardiospec shockwave therapy only.
Outcomes	*Primary outcomes:* Change in global LVEF and regional wall motion score index (6/12 months). *Secondary outcomes:* Incidence of MACE (6/12 months).
Starting date	January 2012
Contact information	Odessa Regional Clinical Hospital, Odessa, Ukraine, 65025 (Principal Investigator: Prof II Karpenko (arcard2@gmail.com))
Notes	*Planned enrolment:* 50 *Estimated completion date*: January 2016 The recruitment status of this study is unknown because the information has not been recently verified.

NCT01660581

Trial name or title	Intracardiac CD133+ cells in patients with no-option resistant angina (RegentVsel)
Methods	A phase II, randomised, parallel, double-blind (participant, investigator) efficacy study

NCT01660581 *(Continued)*

Participants	Stable angina: 1. Stable angina CCS II-IV despite maximum pharmacotherapy for at least 2 weeks since last medications change. 2. Presence of ≥ 1 myocardial segment with ischaemia features in Tc-99m SPECT. 3. Participants disqualified from revascularisation procedures by Heart Team. 4. Aged over 18 and less than 75 years old. 5. Person must provide written informed consent for participation in study.
Interventions	*Intervention arm:* Intramyocardial injection (electromechanical mapping based) of autological CD133+ cells, isolated from bone marrow. *Comparator arm:* Intramyocardial injection (electromechanical mapping based) of placebo (0.9% sodium chloride plus 0.5% solution of participant's serum).
Outcomes	*Primary outcome:* Myocardial perfusion change (4 months). *Secondary outcomes:* 1. Global and segmental contractility change and myocardial perfusion change (MRI: 4 months; echocardiography: 4/12 months). 2. Exercise tolerance (4/12 months). 3. Occurrence of symptomatic angina (1/4/6/12 months). 4. Quality of life (1/4/6/12 months). 5. Occurrence of ventricular arrhythmia (1/4/6/12 months). 6. Occurrence of in-stent restenosis and progression of atherosclerotic lesions in remained coronary artery segments (4 months).
Starting date	June 2012
Contact information	Samodzielny Publiczny Szpital Kliniczny nr 7 Śląskiego Uniwersytetu Medycznego w Katowicach Górnośląskie Centrum Medyczne im. prof. Leszka Gieca, Katowice-Ochojec, Silesian, Poland, 40-635 (Principal Investigator: Prof W Wojakowski (wojtek.wojakowski@gmail.com))
Notes	*Planned enrolment:* 60 *Estimated completion date*: June 2014 This study is currently recruiting participants.

NCT01720888

Trial name or title	Intracoronary autologous mesenchymal stem cells implantation in patients with ischemic dilated cardiomyopathy
Methods	A phase II, randomised, parallel, open-label efficacy study
Participants	Ischaemic dilated cardiomyopathy: 1. Aged between 35 and 75 years. 2. Diagnosed as having ischaemic cardiomyopathy confirmed by previous coronary angiogram showing significant coronary artery disease > 70% or history of previous MI. 3. Myocardial infarction event occurred 6 months or longer from time of screening. 4. Left ventricular ejection fraction of ≤ 40% by echocardiogram or cardiac MRI.

NCT01720888 *(Continued)*

Interventions	*Intervention arm:* Intracoronary implantation of autologous bone marrow-derived mesenchymal stem cells. *Comparator arm:* Control (optimal medical therapy).
Outcomes	*Primary outcome:* Change in LV ejection fraction as measured by echocardiogram and cardiac MRI after implantation (measured at 1, 3, 6, 9, and 12 months). *Secondary outcomes:* 1. Changes in functional status (12 months). 2. Improvement in other LV parameters as assessed by echocardiogram and cardiovascular magnetic resonance (1, 3, 6, 9, 12 months). 3. Resolution of scar tissue volume/area on cardiac MRI (6, 12 months). 4. Change in serum NT-proBNP level (1, 6, 12 months). 5. Freedom from major adverse cardiac events as defined by MI, hospitalisation for angina, MI or HF, or death (all-cause mortality) (1, 3, 6, 9, 12 months). *Other outcomes:* 1. No periprocedural complications (1, 3, 6, 9, 12 months). 2. Significant improvement in overall left ventricular function (12 months). 3. Resolution of scar tissue (6, 12 months). 4. Reduction of major adverse cardiac events (1, 3, 6, 9, 12 months).
Starting date	July 2012
Contact information	Oteh Maskon, MB Bch (Principal Investigator), UKM Medical Centre, Cheras, Kuala Lumpur, Malaysia, 56000
Notes	*Planned enrolment:* 80 *Estimated completion date:* December 2015 This study is ongoing but not recruiting participants.

NCT01727063

Trial name or title	Cell therapy in severe chronic ischemic heart disease (MiHeart)
Methods	A phase II/III, randomised, parallel, double-blind (participant, investigator) safety/efficacy study
Participants	Chronic IHD: 1. Symptoms of angina or angina equivalent. 2. Documented coronary artery disease (invasive angiography). 3. Documented myocardial ischaemia (stress echo, cardiac scintigraphy, or MRI). 4. Unsuitable for complete myocardial revascularisation (PCI or CABG) OR even if a complete procedure is feasible, it is anticipated that myocardial perfusion may not be restored due to poor distal beds.
Interventions	*Intervention arm:* Intramyocardial injection of autologous bone marrow-derived cells. *Comparator arm:* Saline injection.

NCT01727063 *(Continued)*

Outcomes	*Primary outcome*: Increase in myocardial perfusion assessed by MRI (1/6/12 months). *Secondary outcomes*: 1. Improvement in LV function assessed by MRI (1/6/12 months). 2. Improvement in angina functional class determined using the CCS classification (1/6/12 months).
Starting date	January 2006
Contact information	Heart Institute, Sao Paulo, SP, Brazil 05403-000 (Principal Investigator: Prof LHW Gowdak). Contact: Meyrielli A Vieira (meyri.vieira@incor.usp.br); Prof LHW Gowdak (luis.gowdak@incor.usp.br)
Notes	*Planned enrolment:* 200 *Estimated completion date:* July 2013 The recruitment status of this study is unknown because the information has not been recently verified.

NCT01758406

Trial name or title	Transplantation of autologous cardiac stem cells in ischemic heart failure
Methods	A phase II, randomised, parallel, double-blind (participant, investigator) safety/efficacy study
Participants	Ischaemic HF: 1. EF ≤ 40 (by echocardiography). 2. Not responding to standard therapies for HF for over 1 month. 3. NYHA class III or greater. 4. MI due to coronary artery atherosclerotic disease. 5. An area of regional dysfunction, i.e. hypokinetic, akinetic, or dyskinetic (echocardiography or MRI). 6. No HIV/viral hepatitis. 7. Normal liver function (SGPT < 3 times the upper reference range). 8. No or controlled diabetes (glycated haemoglobin < 8.5%). 9. Ability to provide informed consent and follow-up with protocol procedures.
Interventions	*Intervention arm:* Autologous cardiac stem cell intracoronary injection. *Comparator arm:* Placebo (no details).
Outcomes	*Primary outcomes:* Rate of mortality, arrhythmia, and hospitalisation at 18 months. *Secondary outcomes:* 1. Ejection fraction changes (18 months). 2. NT-proBNP changes (18 months). 3. NYHA functional class (18 months). 4. 6-minute walk test (18 months).
Starting date	December 2013

NCT01758406 *(Continued)*

Contact information	Hoda Madani, MD (Principal Investigator), Royan Institute, Tehran, Iran. Contact: Nasser Aghdami, MD, PhD +982123562000 ext 504 (nasser.aghdami@royaninstitute.org)
Notes	*Planned enrolment:* 50 *Estimated completion date:* December 2017 This study is currently recruiting participants.

NCT01768702

Trial name or title	Safety and efficacy of autologous cardiopoietic cells for treatment of ischemic heart failure (CHART-1)
Methods	A phase III, randomised, parallel, double-blind (participant, outcomes assessor) safety/efficacy study
Participants	Ischaemic HF: 1. Age ≥ 18 and < 80 years. 2. Systolic dysfunction with LVEF ≤ 30% as assessed by echocardiography. 3. Ischaemic HF without known need for revascularisation. 4. MLHFQ score > 30. 5. Ability to perform a 6-minute walk test > 100 m and ≤ 400 m. 6. History of hospitalisation for HF within 12 months prior to screening. 7. NYHA class III or IV despite optimal standard of care or INTERMACS class 4, 5, 6, or 7. 8. Use of ACE inhibitor and/or ARB and beta blocker for at least 3 months prior to screening visit, unless intolerant or contraindicated. 9. Stable dosing of ACE inhibitor, ARB, beta blocker, aldosterone blocker, and diuretics for at least 1 month prior to screening visit, defined as ≤ 50% change in total dose of each agent. 10. Willing and able to give written informed consent.
Interventions	*Intervention arm:* Injection of C3BS-CQR-1 cardiopoietic cells using the C-Cath injection catheter. *Comparator arm:* Mimic injection procedure through insertion of a sham catheter. No injection actually performed.
Outcomes	*Primary outcome:* Efficacy between groups post-index procedure: change between groups from baseline in a hierarchical composite outcome comprising, from most- to least-severe outcome, days to death from any cause, number of worsening of HF events, change in score for the MLHFQ (10-point deterioration, no meaningful change, 10-point improvement), change in 6-minute walk distance (40 m deterioration, no meaningful change, 40 m improvement), and change in LVESV (15 mL deterioration, no meaningful change, 15 mL improvement) and LVEF (4% absolute deterioration, no meaningful change, 4% absolute improvement) (39 weeks). *Secondary outcomes:* 1. Efficacy (time to all-cause mortality, time to worsening of HF, and time to aborted sudden death) and safety (number and cause of deaths and readmissions, number of cardiac transplantations, number of MIs, number of strokes, incidence of serious AEs and non-serious AEs) between groups post-index procedure (52/104 weeks). 2. Efficacy and safety between groups post-index procedure (time to all-cause mortality, time to cardiovascular mortality, and rate of worsening HF requiring outpatient IV therapy for HF or readmission for HF, and other) (39/52 weeks post-index).

NCT01768702 *(Continued)*

Starting date	November 2012
Contact information	Multicentre study: Cardio3 BioSciences (Study Chairs: Dr A Terzic, Mayo Clinic, Division of Cardiovascular Diseases, Rochester, MN, USA and Dr J Bartunek, OLV Ziekenhuiz Aalst, Belgium). Contact: Dr Christian Homsy (chomsy@c3bs.com)
Notes	*Planned enrolment:* 240 *Estimated completion date:* March 2017 This study is ongoing but not recruiting participants.

NCT02022514

Trial name or title	Intracoronary infusion of mononuclear cells autologous bone marrow in patients with chronic coronary occlusion and ventricular dysfunction, previously revascularized
Methods	Open-label randomised controlled trial
Participants	Chronic coronary artery occlusion: 1. People of both sexes with atherosclerotic coronary disease and chronic occlusions older than 3 months in which successful recanalisation was achieved, medicated stents implanted, and where it persists despite ventricular dysfunction. 2. Age between 18 and 80 years. 3. The baseline ventricular function recanalisation catheterisation (performed approximately 3 months earlier) should be less than 45% ejection fraction. 4. The ejection fraction of the person should remain below 45% in the MRI performed at 3 months of recanalisation.
Interventions	*Intervention arm:* Bone marrow mononuclear cells by intra-arterial administration. *Comparator arm:* Control (no placebo).
Outcomes	*Primary outcome:* Change in ejection fraction measured by MRI between inclusion and 6 months' follow-up. *Secondary outcomes:* 1. Changes in NYHA functional grade between groups. 2. Possible cardiac events during follow-up (death, MI, repeat revascularisation). 3. Need for hospitalisation or major arrhythmias. 4. Changes in global and segmental left ventricular function.
Starting date	November 2013
Contact information	None identified.
Notes	*Planned enrolment:* 66 *Estimated completion date:* May 2017 This study is currently recruiting participants.

NCT02059512

Trial name or title	Autologous bone marrow mononuclear cells in the combined treatment of coronary heart disease (TAMIS)
Methods	A phase III, randomised, parallel, single-blind (investigator) efficacy study
Participants	Coronary heart disease: 1. Men and women from 18 to 80 years. 2. People with angina pectoris III-IV functional class. 3. People signed informed consent.
Interventions	*Intervention arm 1:* Bone marrow mononuclear cells (intramyocardial). *Intervention arm 2:* Bone marrow mononuclear cells (intramyocardial and intracoronary). *Comparator arm:* Placebo (intramyocardial administration of 0.9% sodium chloride 0.2 mL).
Outcomes	*Primary outcome:* All-cause mortality associated with the progression of basic disease (60 months). *Secondary outcomes:* Quality of life (12 months). *Other outcomes:* 1. Percentage of functioning grafts in participants with implantation of autologous bone marrow mononuclear cells (60 months). 2. Estimation of efficiency: (i) assessment of myocardial perfusion and metabolism (before and after treatment); (ii) evaluation of systolic and diastolic myocardial function; (iii) speckle tracking echocardiography; (iv) patency of grafts within a specified time of treatment (angiography); (v) dependence and duration of positive clinical effect on the amount of injected cell material; (vi) evaluation of the quality of life (Minnesota questionnaire, Seattle questionnaire, SF-36 questionnaire).
Starting date	February 2013
Contact information	Alexander S Nemkov, MD, PhD (Principal Investigator), First Pavlov State Medical University of St Petersburg, St Petersburg, Russia, 197089 (nemk_as@mail.ru)
Notes	*Planned enrolment*: 100 *Estimated completion date:* February 2018 This study is ongoing but not recruiting participants.

NCT02317458

Trial name or title	Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-2) trial
Methods	A phase III, randomised, parallel, double-blind (participant, caregiver, investigator, outcomes assessor) safety/efficacy study
Participants	Advanced chronic ischaemic HF: 1. Age ≥ 18 and < 80 years.

NCT02317458 *(Continued)*

	2. Chronic HF, NYHA class II or greater, without need for revascularisation. 3. Systolic dysfunction with LVEF ≤ 35%. 4. Total MLHFQ score > 30. 5. 6-minute walk test distance > 100 m and < 400 m. 6. Hospitalisation or outpatient with intravenous therapy for HF within the previous 12 months. 7. Stable medical regimen, including ACE inhibitor or ARB, or both; beta blocker, aldosterone blocker and diuretic for at least 1 month. 8. Willing and able to give written informed consent.
Interventions	*Intervention arm:* BM-derived mesenchymal cardiopoietic cells (C3BR-CQR-1) using intramyocardial injection. *Comparator arm:* Control (standard of care with sham procedure).
Outcomes	*Primary outcome:* 6-minute walk test at 39 weeks' postprocedure. *Secondary outcomes:* None reported.
Starting date	December 2014
Contact information	Celyad (formerly named Cardio3 BioSciences)
Notes	*Planned enrolment*: 240 *Estimated completion date*: August 2018 This study is not yet open for participant recruitment.

NCT02362646

Trial name or title	Safety & efficacy of intramyocardial injection of mesenchymal precursor cells on myocardial function in LVAD recipients
Methods	A phase II, randomised, parallel, double-blind (participant, caregiver, investigator, outcomes assessor) safety/efficacy study
Participants	Left ventricular assist device recipients: 1. Age 18 years or older. 2. If the participant or partner is of childbearing potential, he or she must be willing to use adequate contraception (hormonal or barrier method or abstinence) from the time of screening and for a period of at least 16 weeks after procedure. 3. Female participants of childbearing potential must have a negative serum pregnancy test at screening. 4. Admitted to the clinical center at the time of randomisation. 5. Clinical indication and accepted candidate for implantation of an FDA-approved (US sites only) or Health Canada-approved (Canadian sites only) implantable, non-pulsatile LVAD as a bridge to transplantation or for destination therapy.
Interventions	*Intervention arm:* Mensenchymal precursor cells (intramyocardial injection).

NCT02362646 *(Continued)*

	Comparator arm: Placebo (50% Alpha-Minimum Essential Medium/42.5% ProFreeze NAO Freeze Medium/7.5% DMSO)
Outcomes	*Primary outcomes:* 1. Functional status (6 months). 2. Adverse events (12 months). *Secondary outcomes:* 1. Physiologic assessments (12 months). 2. Histopathological assessments of myocardial tissue (12 months). 3. Overall survival (12 months). 4. Change in quality of life (6, 12 months). 5. Hopkins Verbal Learning Test (3, 12 months). 6. Trail Making Tests A and B (3, 12 months). 7. Medical College of Georgia (MCG) complex figures (3, 12 months). 8. Digit span (3, 12 months). 9. Digit symbol substitution test (3, 12 months). 10. Controlled Oral Word Association Test (3, 12 months). 11. Length of hospital stay (12 months). 12. Hospitalisations (12 months). 13. Hospital costs (12 months). 14. Functional status (12 months).
Starting date	July 2015
Contact information	Michael Bowdish, MD (Principal Investigator), University of Southern California, Los Angeles, California, United States, 90033 (michael.bowdish@med.usc.edu); Joseph Woo, MD (Principal Investigator), Stanford University School of Medicine, Stanford, California, United States, 94305 (joswoo@stanford.edu)
Notes	*Planned enrolment:* 120 *Estimated completion date*: August 2016 This study is currently recruiting participants.

NCT02438306

Trial name or title	CardiAMP Heart Failure Trial
Methods	A phase III, randomised, parallel, double-blind (participant, outcome assessor) safety/efficacy study
Participants	Post-MI HF: 1. Older than 21 and younger than 90 years of age. 2. NYHA class II or III. 3. Diagnosis of chronic ischaemic left ventricular dysfunction secondary to MI. 4. Have an ejection fraction ≥ 20% and ≤ 40%. 5. On stable evidence-based medical and device therapy for HF or postinfarction left ventricular dysfunction, per the 2013 ACC/AHA heart failure guidelines, for at least 3 months prior to randomisation. 6. Cell potency assay score of 3, as determined by the Cell Analysis Core Lab results.

NCT02438306 *(Continued)*

	7. Provide written informed consent.
Interventions	*Intervention arm*: Autologous CardiAMP cell therapy. *Comparator arm*: Placement of an introducer and performance of LV gram only.
Outcomes	*Primary outcome*: Change in 6-minute walk distance at 12 months from baseline. *Secondary outcomes:* 1. Overall survival as a non-inferiority outcome (12 months). 2. Freedom from MACE (composite of all-cause death, hospitalisation for worsening HF, non-fatal MI, [LVAD], or heart transplantation) as a non-inferiority outcome (12 months). 3. Change in quality of life as measured by MLHFQ as a superiority outcome (12 months). 4. Time to first MACE as a superiority outcome (12 months). 5. Overall survival as a superiority outcome (12 months). 6. Survival at 2 years. 7. HF death (12 months). 8. Treatment-emergent serious adverse event at 30 days. 9. HF hospitalisation (12 months). 10. All-cause hospitalisation (12 months). 11. Days alive out of hospital (12 months). 12. Freedom from serious adverse events (12 months). 13. NYHA Functional Class (12 months). 14. 6-minute walk distance repeated measure analysis (12 months). 15. Echocardiographic measures of change in ejection fraction, left ventricular end-systolic and end-diastolic volumes, left ventricular end-systolic and end-diastolic dimensions, mitral regurgitation (composite) (baseline). 16. Technical success defined as successful delivery of ABM MNC, at the time of the procedure.
Starting date	January 2016
Contact information	Cheryl Wong Po Foo, BioCardia Inc (Email info@biocardia.com). Principal Investigators: Carl Pepine, University of Florida and Amish Raval, University of Wisconsin
Notes	*Planned enrolment:* 250 *Estimated completion date*: April 2019 This study is not yet open for participant recruitment.

NCT02462330

Trial name or title	Administration of mesenchymal stem cells in patients with chronic ischemic cardiomyopathy (MESAMI2)
Methods	A phase II, randomised, parallel, double-blind (participant, investigator) efficacy study
Participants	Chronic ischaemic cardiomyopathy and left ventricular dysfunction: 1. Aged 18 to 75 years. 2. Signed the informed consent. 3. Chronic, stable ischaemic cardiomyopathy for at least 1 month with a NYHA class II-IV or angina pectoris CCS class III or IV, or both.

NCT02462330 *(Continued)*

	4. Not a candidate for revascularisation by coronary artery bypass surgery or angioplasty. 5. Left ventricular function ≤ 45%. 6. Presence of ischaemia or myocardial viability on the myocardial perfusion imaging. 7. VO_2 max ≤ 20 mL/min/kg. 8. Optimal medical therapy. 9. Optimal interventional therapy (implantable cardioverter defibrillator, effort rehabilitation).
Interventions	*Intervention arm*: BMMSC (isolated and cultured during 17 ± 2 days by the French Blood Establishment; administered by intramyocardial injections of MSC using the electromechanical NOGA-XP system). *Comparator arm*: Human albumin 4%.
Outcomes	*Primary outcome:* Change in VO_2max (or peak VO_2) before injection and at 3 months' postinjection. *Secondary outcomes*: 1. Left ventricular viability (3 and 12 months). 2. Change in NYHA/CCS class (3 and 12 months). 3. Change on quality of life test score (3 and 12 months). 4. Change in VO_2max (or peak VO_2) at 3 and 12 months postinjection. 5. 6-minute walk test (3 and 12 months). 6. Volume of myocardium and measurement of ejection fraction (echocardiography) (3 and 12 months). 7. Myocardial perfusion imaging (3 and 12 months). *Other outcomes:* 1. Adverse event related to cell administration (12 months). 2. Complication related to cell administration (12 months). 3. Control of the implantable cardioverter defibrillator (12 months). 4. Analysis of major cardiovascular events (12 months).
Starting date	June 2015
Contact information	Jerome Roncalli, MD, PhD (Principal Investigator), Cardiology Department of Rangueil Hospital, Toulouse, France, 31059 (roncalli.j@chu-toulouse.fr)
Notes	*Planned enrolment:* 90 *Estimated completion date:* May 2017 This study is currently recruiting participants.

NCT02501811

Trial name or title	Combination of mesenchymal and c-kit+ cardiac stem cells as regenerative therapy for heart failure (CONCERT-HF)
Methods	A phase II, randomised, parallel, double-blind (participant, caregiver, investigator, outcomes assessor) safety/efficacy study
Participants	Ischaemic cardiomyopathy:

NCT02501811 *(Continued)*

	1. ≥ 21 and < 80 years of age. 2. Documented coronary artery disease with evidence of myocardial injury, LV dysfunction, and clinical evidence of HF. 3. "Detectable" area of myocardial injury defined as ≥ 5% LV involvement (infarct volume) and any subendocardial involvement by cMRI. 4. EF ≤ 40% by cMRI. 5. Receiving guideline-driven medical therapy for HF at stable and tolerated doses for ≥ 1 month prior to consent. For beta-blockade, "stable" is defined as no greater than a 50% reduction in dose or no more than a 100% increase in dose. 6. Candidate for cardiac catheterisation. 7. NYHA class II or III HF symptoms. 8. If a female of childbearing potential, be willing to use one form of birth control for the duration of the study, and undergo a pregnancy test at baseline and within 36 hours prior to injection.
Interventions	*Intervention arm 1*: 15 transendocardial injections of 0.4 mL BMMSC administered to the left ventricle via NOGA MyoStar injection catheter (single procedure) (target dose 150 million MSC). *Intervention arm 2*: 15 transendocardial injections of 0.4 mL cardiac stem cells (c-kit+ cells) administered to the left ventricle via NOGA MyoStar injection catheter (single procedure) (target dose 5 million CSC). *Intervention arm 3:* Combo: 15 transendocardial injections of 0.4 mL MSC administered to the left ventricle via NOGA MyoStar injection catheter (single procedure) and 15 transendocardial injections of 0.4 mL CSC administered to the left ventricle via NOGA MyoStar injection catheter (single procedure) (target dose 150 million MSC and 5 million CSC). *Comparator arm*: 15 transendocardial injections of 0.4 mL placebo (Plasma-Lyte A) administered to the left ventricle via NOGA MyoStar injection catheter (single procedure).
Outcomes	*Primary outcomes*: 1. Change in LVEF as measured by cMRI (12 months). 2. Change in global strain (HARP MRI) as measured by cMRI (12 months). 3. Change in regional strain (HARP MRI) as measured by cMRI (12 months). 4. Change in Left Ventricular End-Diastolic Volume Index (LVEDVI) as measured by cMRI (12 months). 5. Change in Left Ventricular End-Systolic Volume Index (LVESVI) as measured by cMRI (12 months). 6. Change in Left Ventricular Sphericity Index as measured by cMRI (12 months). 7. Change in infarct/scar volume (delayed enhancement MRI) as measured by cMRI (12 months). 8. Change in maximal oxygen consumption (VO_2 max) as measured by treadmill (12 months). 9. Change in exercise tolerance as measured by the 6-minute walk test (12 months). 10. Change in MLHFQ score (12 months). 11. Incidence rate of MACE (12 months). 12. Cumulative days alive and out of hospital (12 months). 13. Change in NT-proBNP as measured by blood draw (12 months). *Secondary outcomes:* 1. Change in LVEF as measured by cMRI (6 months). 2. Change in global strain (HARP MRI) as measured by cMRI (6 months). 3. Change in regional strain (HARP MRI) as measured by cMRI (6 months). 4. Change in Left Ventricular End-Diastolic Volume Index (LVEDVI) as measured by cMRI (6 months). 5. Change in Left Ventricular End-Systolic Volume Index (LVESVI) as measured by cMRI (6 months). 6. Change in Left Ventricular Sphericity Index as measured by cMRI (6 months). 7. Change in infarct/scar volume (delayed enhancement MRI) as measured by cMRI (6 months). 8. Change in maximal oxygen consumption (VO_2 max) as measured by treadmill (6 months). 9. Change in exercise tolerance as measured by the 6-minute walk test (6 months).

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	10.Change in MLHFQ score (6 months). 11.Incidence rate of MACE (6 months). 12.Cumulative days alive and out of hospital (6 months). 13.Change in NT-proBNP as measured by blood draw (6 months). *Other outcomes:* 1. Change in LVEF as measured by cMRI (6 to 12 months). 2. Change in global strain (HARP MRI) as measured by cMRI (6 to 12 months). 3. Change in regional strain (HARP MRI) as measured by cMRI (6 to 12 months). 4. Change in Left Ventricular End-Diastolic Volume Index (LVEDVI) as measured by cMRI (6 to 12 months). 5. Change in Left Ventricular End-Systolic Volume Index (LVESVI) as measured by cMRI (6 to 12 months). 6. Change in Left Ventricular Sphericity Index as measured by cMRI (6 to 12 months). 7. Change in infarct/scar volume (delayed enhancement MRI) as measured by cMRI (6 to 12 months). 8. Change in maximal oxygen consumption (VO_2 max) as measured by treadmill (6 to 12 months). 9. Change in exercise tolerance as measured by the 6-minute walk test (6 to 12 months). 10.Change in MLHFQ score (6 to 12 months). 11.The difference in the incident rate of MACE (6 to 12 months). 12.The difference in the cumulative days alive and out of hospital (6 to 12 months). 13.Change in NT-proBNP as measured by blood draw (6 to 12 months).
Starting date	October 2015
Contact information	The University of Texas Health Science Center, Houston, TX, United States; National Heart, Lung, and Blood Institute. Contact: Rachel Vojvodic, MPH (Rachel.W.Vojvodic@uth.tmc.edu); Lemuel Moye, MD, PhD (Lemmoye@msn.com)
Notes	*Planned enrolment*: 144 *Estimated completion date*: February 2019 This study is currently recruiting participants.

NCT02503280

Trial name or title	The Transendocardial Autologous Cells (hMSC or hMSC and hCSC) in Ischemic Heart Failure Trial (TAC-HFT II)
Methods	A phase I/II, randomised, parallel, single-blind (participant) safety/efficacy study
Participants	Chronic ischaemic left ventricular dysfunction and HF secondary to MI: 1. ≥ 21 and < 90 years of age. 2. Provide written informed consent. 3. Diagnosis of chronic ischaemic left ventricular dysfunction secondary to MI as defined by the following: Screening MRI must show an area of akinesis, dyskinesis, or severe hypokinesis associated with evidence of myocardial scarring based on delayed hyperenhancement following gadolinium infusion. 4. Been treated with appropriate maximal medical therapy for HF or postinfarction left ventricular dysfunction. For beta-blockade, the person must have been on a stable dose of a clinically appropriate beta-blocker for 3 months. For angiotensin-converting enzyme inhibition, the person must have been on a stable dose of a clinically appropriate agent for 1 month. 5. Candidate for cardiac catheterisation.

NCT02503280 *(Continued)*

	6. Ejection fraction ≤ 50% by gated blood pool scan, 2-dimensional echocardiogram, cardiac MRI, or left ventriculogram within the prior 6 months and not in the setting of a recent ischaemic event.
Interventions	*Treatment arm 1*: Autologous hMSC: 40 million cells/mL delivered in 0.5 mL injection volumes times 10 injections for a total of 2 x 10^8 (200 million) hMSC. *Treatment arm 2:* Autologous hMSC PLUS autologous c-kit hCSC: mixture of 39.8 million hMSC and 0.2 million c-kit hCSC/mL delivered in 0.5 mL injection volumes times 10 injections for a total of 1.99 x 10^8 (199 million) hMSC and 1 million c-kit hCSC. *Comparator arm*: Placebo (10 0.5 mL injections of phosphate-buffered saline and 1% human serum albumin).
Outcomes	*Primary outcomes*: 1. Incidence of any TE-SAEs 1 month postcatherisation. 2. Incidence (at 1 month postcatheterisation) of any TE-SAEs, defined as the composite of: death, non-fatal MI, stroke, hospitalisation for worsening HF, cardiac perforation, pericardial tamponade, sustained ventricular arrhythmias (characterised by ventricular arrhythmias lasting longer than 15 seconds or with haemodynamic compromise), or atrial fibrillation. *Secondary outcomes*: 1. Treatment emergent adverse event rates (6 and 12 months). 2. Ectopic tissue formation (6 and 12 months). 3. 48-hour ambulatory electrocardiogram recordings (6 and 12 months). 4. Urinalysis results changes postcatheterisation (6 and 12 months). 5. Clinical chemistry values postcatheterisation (6 and 12 months). 6. Pulmonary function - forced expiratory volume in 1 second (FEV1) results. 7. Serial troponin I values (every 12 hours for first 48 hours post-cardiac catheterisation). 8. Creatine kinase-MB values (every 12 hours for first 48 hours post-cardiac catheterisation). 9. Post-cardiac catheterisation echocardiogram (6 and 12 months). 10. MRI measures of infarct scar size (6 and 12 months). 11. Echocardiographic measures of infarct scar size (6 and 12 months). 12. Left regional and global ventricular function (6 and 12 months). 13. Global ventricular function (6 and 12 months). 14. Tissue perfusion measured by MRI (6 and 12 months). 15. Peak oxygen consumption (peak VO_2) (by treadmill determination) (6 and 12 months). 16. 6-minute walk test (6 and 12 months). 17. NYHA Functional Class (6 and 12 months). 18. MLHFQ (6 and 12 months). 19. Incidence of MACE (6 and 12 months). 20. Incidence of MACE, defined as the composite incidence of death, hospitalisation for worsening HF, or non-fatal recurrent MI (6 and 12 months).
Starting date	March 2020
Contact information	ISCI/University of Miami Miller School of Medicine, Miami, Florida, United States, 33136. Principal Investigator: Joshua M Hare, MD. Contact: Darcy L DiFede (DDIFEDE@MED.MIAMI.EDU)
Notes	*Planned enrolment*: 55 *Estimated completion date*: March 2030 This study is not yet open for participant recruitment.

NCT02504437

Trial name or title	Therapy of Preconditioned Autologous BMMSCs for Patients With Ischemic Heart Disease (TPAABPIHD)
Methods	A phase I/II, randomised, parallel, double-blind (participant, outcome assessor) safety/efficacy study
Participants	IHD: 1. Under 75 years of age. 2. Clinical diagnosis of AMI, chronic MI, and ischaemic cardiomyopathy. 3. NYHA grade III-IV, LVEF 25% to 50%. 4. No infection diseases including hepatitis B virus, hepatitis C virus, syphilis, and AIDS. 5. No psychiatric illnesses and speaking dysfunction. 6. Informed consent.
Interventions	*Intervention arm 1*: Autologous BMMSC with hypoxia pre-condition and endothelial pre-induction. *Intervention arm 2*: Autologous BMMSC without pre-condition. *Comparator*: Standard therapy without autologous BMMSC infusion.
Outcomes	*Primary outcome:* LVEF at 12 months. *Secondary outcomes*: None reported.
Starting date	November 2015
Contact information	Academy Military Medical Science, China; Sun Yat-sen University. Contact: Xuetao Pei, MD, PhD (AMMS0906@163.com); Junnian Zhou, PhD (zhoujunnian@scrm.org.cn)
Notes	*Planned enrolment:* 200 *Estimated completion date:* December 2017 This study is not yet open for participant recruitment.

ABM MNC: autologous bone marrow mononuclear cell
ACE: angiotensin converting enzyme
AEs: adverse events
ACC/AHA: American College of Cardiology/American Heart Association
AICD: automatic implantable cardioverter defibrillator
AMI: acute myocardial infarction
AOI:
ARB: angiotensin receptor blocker
AST: aspartate transaminase
BMAC: bone marrow aspirate concentrate
BMMNC: bone marrow mononuclear cells
BMMSC: bone marrow mesenchymal stem cells
BMSC: bone marrow stem cells
BNP: brain natriuretic peptide
CABG: coronary artery bypass grafting
CCS: Canadian Cardiovascular Society
CHF: congestive heart failure
CMR: cardiac magnetic resonance
cMRI: cardiovascular magnetic resonance imaging
CPC: circulating progenitor cells
CSC: cardiac stem cells
DMSO: dimethyl sulfoxide

ECG: electrocardiogram
EDTA: ethylene-diamine-tetraacetic acid
EF: ejection fraction
EPC: endothelial progenitor cells
FDA: US Food and Drug Administration
G-CSF: granulocyte-colony stimulating factor
HARP: harmonic phase
HcG: human chorionic gonadotrophin
hCSC: human cardiac stem cells
HF: heart failure
hMSC: human mesenchymal stem cells
HSA: human serum albumin
IC: intracoronary
IHD: ischaemic heart disease
IM: intramuscular
INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support
IV: intravenous
LV: left ventricular
LVAD: left ventricular assist device
LVEDD: left ventricular end-diastolic diameter
LVEDV: left ventricular end-diastolic volume
LVEF: left ventricular ejection fraction
LVESD: left ventricular end-systolic diameter
LVESV: left ventricular end-systolic volume
MACE: major adverse clinical events
MI: myocardial infarction
MLHFQ: Minnesota Living with Heart Failure Questionnaire
MRI: magnetic resonance imaging
MSC: mesenchymal stem cells
MUGA: multigated radionuclide angiography
MVO_2: myocardial oxygen consumption
NT-proBNP: N-terminal pro b-type natriuretic peptide
NYHA: New York Heart Association
PCI: percutaneous coronary intervention
QOL: quality of life
PET: positron emission tomography
RCT: randomised controlled trial
SF-36: 13-Item Short Form Health Survey
SGOT: serum aspartic aminotransferase
SGPT: serum glutamate pyruvate transaminase
SPECT: single-photon emission computed tomography
TE-SAEs: treatment emergent serious adverse events

DATA AND ANALYSES

Comparison 1. Cells versus no cells

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause)	37		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Short term follow-up (< 12 months)	33	1637	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.26, 0.87]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 Long term follow-up (≥ 12 months)	21	1010	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.25, 0.58]
2 Non-fatal myocardial infarction	25		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Short term follow-up (< 12 months)	20	881	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.17, 2.15]
2.2 Long term follow-up (≥ 12 months)	9	461	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.93]
3 Rehospitalisation due to heart failure	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Short term follow-up (< 12 months)	10	482	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.12]
3.2 Long term follow-up (≥ 12 months)	10	495	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.36, 1.04]
4 Arrhythmias	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Short term follow-up (< 12 months)	22	959	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.33, 1.45]
4.2 Long term follow-up (≥ 12 months)	7	363	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.22, 0.97]
5 Composite MACE	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Short term follow-up (< 12 months)	8	288	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.18, 1.42]
5.2 Long term follow-up (≥ 12 months)	5	201	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.12]
6 MLHFQ: short term follow-up (< 12 months)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Mean value at endpoint	2	125	Mean Difference (IV, Random, 95% CI)	-29.52 [-33.76, -25.27]
6.2 Mean change from baseline	2	72	Mean Difference (IV, Random, 95% CI)	-9.07 [-22.09, 3.95]
6.3 Combined	4	197	Mean Difference (IV, Random, 95% CI)	-18.96 [-31.97, -5.94]
7 MLHFQ: long term follow-up (≥ 12 months)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Mean value at endpoint	1	82	Mean Difference (IV, Random, 95% CI)	-36.5 [-42.21, -30.79]
7.2 Mean change from baseline	2	69	Mean Difference (IV, Random, 95% CI)	-7.63 [-16.35, 1.09]
7.3 Combined	3	151	Mean Difference (IV, Random, 95% CI)	-17.80 [-39.87, 4.26]
8 Seattle Angina Questionnaire: short term follow-up (< 12 months)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Mean value at endpoint	1	49	Mean Difference (IV, Random, 95% CI)	5.0 [-3.21, 13.21]
8.2 Mean change from baseline	2	211	Mean Difference (IV, Random, 95% CI)	9.34 [2.62, 16.07]
8.3 Combined	2	211	Mean Difference (IV, Random, 95% CI)	9.34 [2.62, 16.07]
9 Angina episodes per week: short term follow-up (< 12 months)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Mean value at endpoint	4	396	Mean Difference (IV, Random, 95% CI)	-6.96 [-11.99, -1.93]
9.2 Mean change from baseline	3	167	Mean Difference (IV, Random, 95% CI)	-1.77 [-14.61, 11.08]
9.3 Combined	5	428	Mean Difference (IV, Random, 95% CI)	-5.11 [-11.30, 1.09]
10 NYHA classification: short-term follow-up (< 12 months)	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Mean value at endpoint	16	658	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.84, -0.00]
10.2 Mean change from baseline	4	239	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.49, 0.36]
10.3 Combined	17	741	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.84, -0.05]
11 NYHA classification: long term follow-up (≥ 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Mean value at endpoint	9	346	Mean Difference (IV, Random, 95% CI)	-0.57 [-1.03, -0.10]
11.2 Mean change from baseline	1	39	Mean Difference (IV, Random, 95% CI)	-2.2 [-2.70, -1.70]

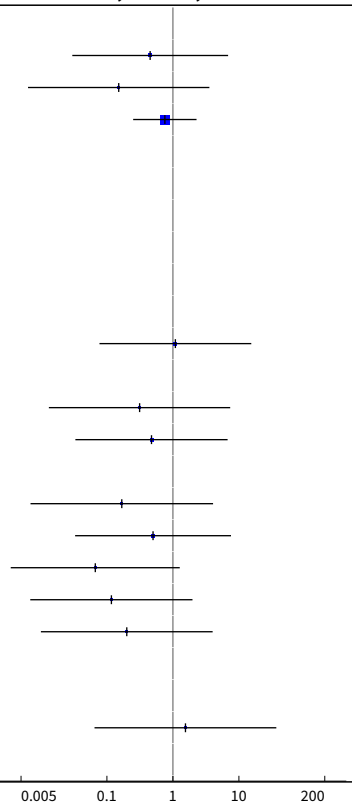
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Combined	9	346	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.23, -0.39]
12 CCS class: short term follow-up (< 12 months)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Mean value at endpoint	10	486	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.82, 0.18]
12.2 Mean change from baseline	6	318	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.40, 0.17]
12.3 Combined	13	608	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.92, 0.06]
13 CCS class: long term follow-up (≥ 12 months)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 Mean value at endpoint	3	142	Mean Difference (IV, Random, 95% CI)	-0.58 [-2.04, 0.88]
14 Exercise capacity: short term follow-up (< 12 months)	16		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Mean value at endpoint	11	563	Std. Mean Difference (IV, Random, 95% CI)	0.56 [0.19, 0.93]
14.2 Mean change from baseline	9	535	Std. Mean Difference (IV, Random, 95% CI)	0.33 [0.05, 0.61]
15 Exercise capacity: long term follow-up (≥ 12 months)	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 Mean value at endpoint	5	178	Std. Mean Difference (IV, Random, 95% CI)	1.14 [0.04, 2.25]
15.2 Mean change from baseline	3	227	Std. Mean Difference (IV, Random, 95% CI)	0.34 [0.07, 0.62]
16 LVEF (%) measured by MRI: short term follow-up (< 12 months)	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Mean value at endpoint	10	352	Mean Difference (IV, Random, 95% CI)	3.01 [-0.05, 6.07]
16.2 Mean change from baseline	9	308	Mean Difference (IV, Random, 95% CI)	4.05 [2.55, 5.55]
16.3 Combined	12	439	Mean Difference (IV, Random, 95% CI)	2.92 [1.03, 4.82]
17 LVEF (%) measured by MRI: long term follow-up (≥ 12 months)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

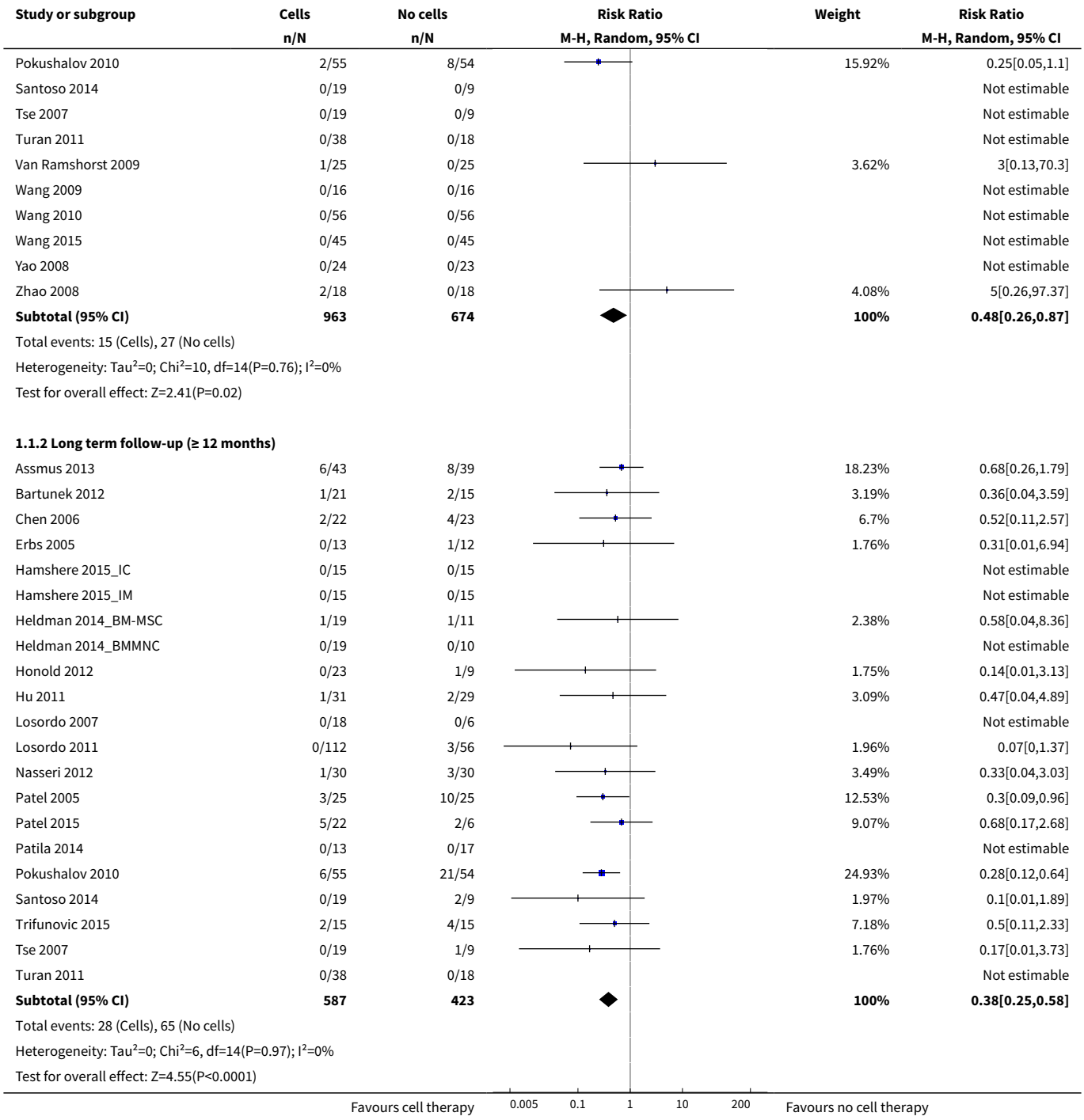
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Mean value at endpoint	4	110	Mean Difference (IV, Random, 95% CI)	2.37 [-1.54, 6.29]
17.2 Mean change from baseline	3	97	Mean Difference (IV, Random, 95% CI)	3.83 [-0.42, 8.08]
17.3 Combined	4	110	Mean Difference (IV, Random, 95% CI)	4.38 [0.82, 7.93]
18 LVEF (%) measured by echocardiography: short term follow-up (< 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Mean value at endpoint	8	388	Mean Difference (IV, Random, 95% CI)	5.16 [2.87, 7.44]
18.2 Mean change from baseline	3	161	Mean Difference (IV, Random, 95% CI)	3.47 [1.59, 5.34]
18.3 Combined	9	470	Mean Difference (IV, Random, 95% CI)	5.71 [4.29, 7.13]
19 LVEF (%) measured by echocardiography: long term follow-up (≥ 12 months)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Mean value at endpoint	3	154	Mean Difference (IV, Random, 95% CI)	7.69 [6.47, 8.92]
19.2 Mean change from baseline	1	82	Mean Difference (IV, Random, 95% CI)	6.1 [-1.27, 13.47]
19.3 Combined	3	154	Mean Difference (IV, Random, 95% CI)	7.96 [6.39, 9.54]
20 LVEF (%) measured by SPECT: short term follow-up (< 12 months)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Mean value at endpoint	4	145	Mean Difference (IV, Random, 95% CI)	2.41 [-2.65, 7.46]
20.2 Mean change from baseline	1	30	Mean Difference (IV, Random, 95% CI)	-2.3 [-17.33, 12.73]
20.3 Combined	4	145	Mean Difference (IV, Random, 95% CI)	5.22 [2.60, 7.85]
21 LVEF (%) measured by SPECT: long term follow-up (≥ 12 months)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Mean value at endpoint	2	88	Mean Difference (IV, Random, 95% CI)	0.37 [-2.30, 3.04]
21.2 Mean change from baseline	1	49	Mean Difference (IV, Random, 95% CI)	4.0 [-6.48, 14.48]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
21.3 Combined	2	88	Mean Difference (IV, Random, 95% CI)	0.28 [-2.48, 3.03]
22 LVEF (%) measured by LV angiography: short term follow-up (< 12 months)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 Mean value at endpoint	6	265	Mean Difference (IV, Random, 95% CI)	3.18 [0.39, 5.97]
22.2 Mean change from baseline	4	181	Mean Difference (IV, Random, 95% CI)	1.72 [0.50, 2.95]
22.3 Combined	6	250	Mean Difference (IV, Random, 95% CI)	2.00 [0.53, 3.46]
23 LVEF (%) measured by LV angiography: long term follow-up (≥ 12 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1 Mean value at endpoint	1	49	Mean Difference (IV, Random, 95% CI)	6.0 [0.81, 11.19]

Analysis 1.1. Comparison 1 Cells versus no cells, Outcome 1 Mortality (all-cause).

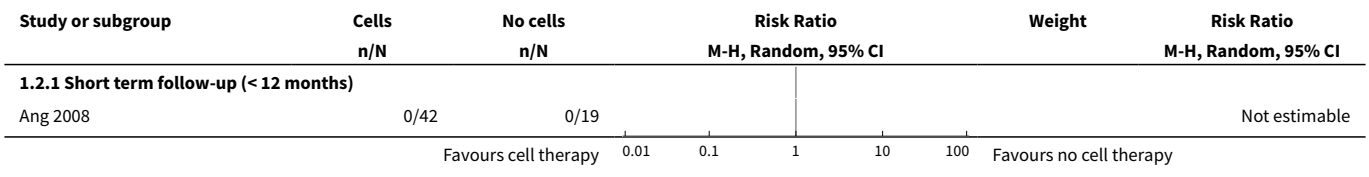
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short term follow-up (< 12 months)					
Ang 2008	1/42	1/19		4.87%	0.45[0.03,6.86]
Assmus 2006	0/52	1/23		3.59%	0.15[0.01,3.57]
Assmus 2013	5/43	6/39		29.47%	0.76[0.25,2.28]
Bartunek 2012	0/21	0/15			Not estimable
Erbs 2005	0/13	0/12			Not estimable
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hendrikx 2006	1/11	1/12		5.13%	1.09[0.08,15.41]
Honold 2012	0/23	0/9			Not estimable
Hu 2011	0/31	1/29		3.6%	0.31[0.01,7.38]
Jimenez-Quevedo 2011	1/19	1/9		5.1%	0.47[0.03,6.74]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		3.55%	0.17[0.01,4.06]
Mathiasen 2015	1/40	1/20		4.86%	0.5[0.03,7.59]
Mozid 2014_IC	0/14	1/2		4.13%	0.07[0,1.27]
Mozid 2014_IM	0/10	3/8		4.49%	0.12[0.01,1.98]
Nasseri 2012	0/30	2/30		4.01%	0.2[0.01,4]
Patel 2005	0/10	0/10			Not estimable
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		3.58%	1.55[0.06,36.94]
Perin 2012b	0/10	0/10			Not estimable



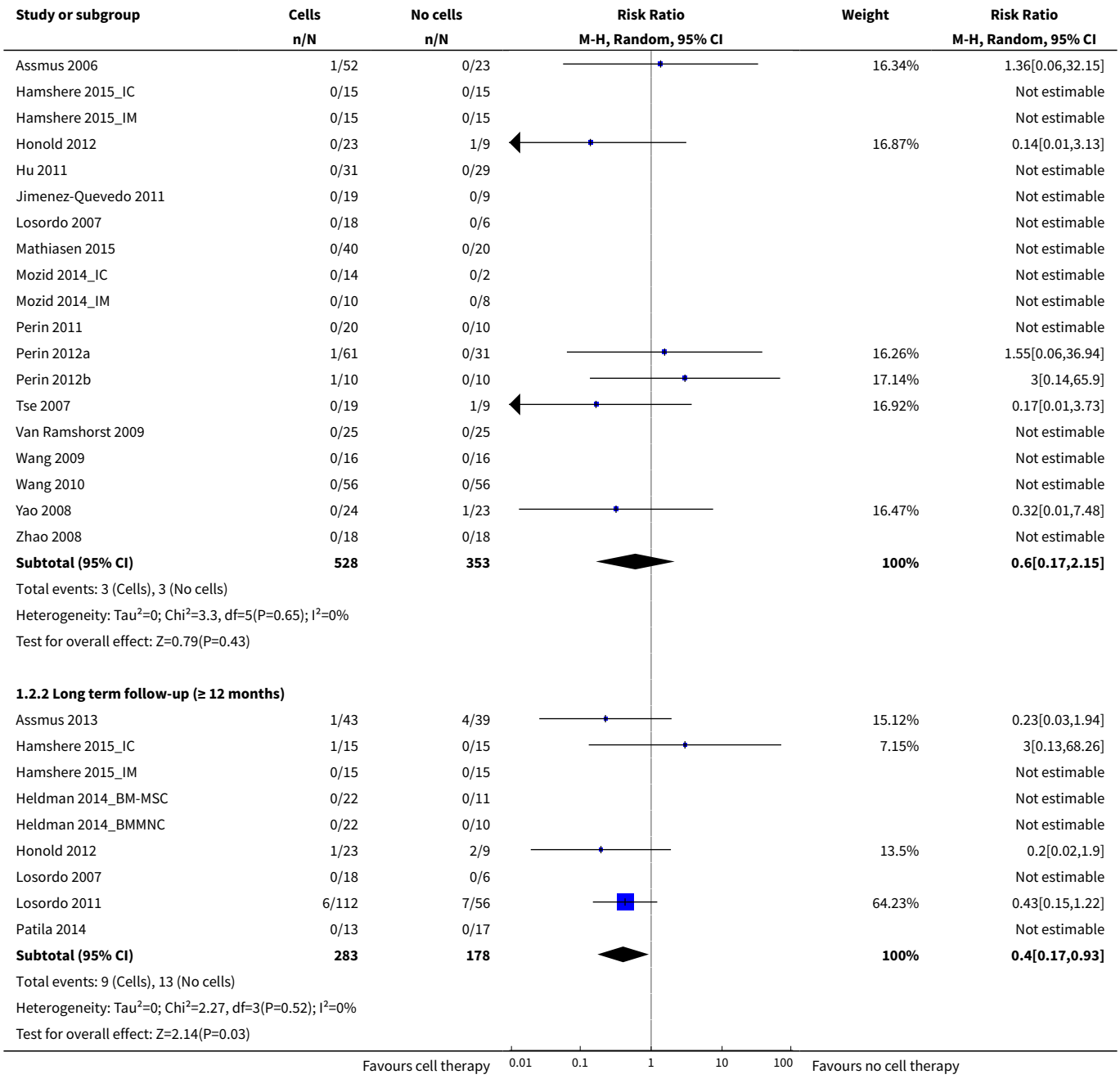


Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pokushalov 2010	2/55	8/54		15.92%	0.25[0.05,1.1]
Santoso 2014	0/19	0/9			Not estimable
Tse 2007	0/19	0/9			Not estimable
Turan 2011	0/38	0/18			Not estimable
Van Ramshorst 2009	1/25	0/25		3.62%	3[0.13,70.3]
Wang 2009	0/16	0/16			Not estimable
Wang 2010	0/56	0/56			Not estimable
Wang 2015	0/45	0/45			Not estimable
Yao 2008	0/24	0/23			Not estimable
Zhao 2008	2/18	0/18		4.08%	5[0.26,97.37]
Subtotal (95% CI)	**963**	**674**		**100%**	**0.48[0.26,0.87]**
Total events: 15 (Cells), 27 (No cells)					
Heterogeneity: Tau²=0; Chi²=10, df=14(P=0.76); I²=0%					
Test for overall effect: Z=2.41(P=0.02)					
1.1.2 Long term follow-up (≥ 12 months)					
Assmus 2013	6/43	8/39		18.23%	0.68[0.26,1.79]
Bartunek 2012	1/21	2/15		3.19%	0.36[0.04,3.59]
Chen 2006	2/22	4/23		6.7%	0.52[0.11,2.57]
Erbs 2005	0/13	1/12		1.76%	0.31[0.01,6.94]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BM-MSC	1/19	1/11		2.38%	0.58[0.04,8.36]
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Honold 2012	0/23	1/9		1.75%	0.14[0.01,3.13]
Hu 2011	1/31	2/29		3.09%	0.47[0.04,4.89]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	3/56		1.96%	0.07[0,1.37]
Nasseri 2012	1/30	3/30		3.49%	0.33[0.04,3.03]
Patel 2005	3/25	10/25		12.53%	0.3[0.09,0.96]
Patel 2015	5/22	2/6		9.07%	0.68[0.17,2.68]
Patila 2014	0/13	0/17			Not estimable
Pokushalov 2010	6/55	21/54		24.93%	0.28[0.12,0.64]
Santoso 2014	0/19	2/9		1.97%	0.1[0.01,1.89]
Trifunovic 2015	2/15	4/15		7.18%	0.5[0.11,2.33]
Tse 2007	0/19	1/9		1.76%	0.17[0.01,3.73]
Turan 2011	0/38	0/18			Not estimable
Subtotal (95% CI)	**587**	**423**		**100%**	**0.38[0.25,0.58]**
Total events: 28 (Cells), 65 (No cells)					
Heterogeneity: Tau²=0; Chi²=6, df=14(P=0.97); I²=0%					
Test for overall effect: Z=4.55(P<0.0001)					

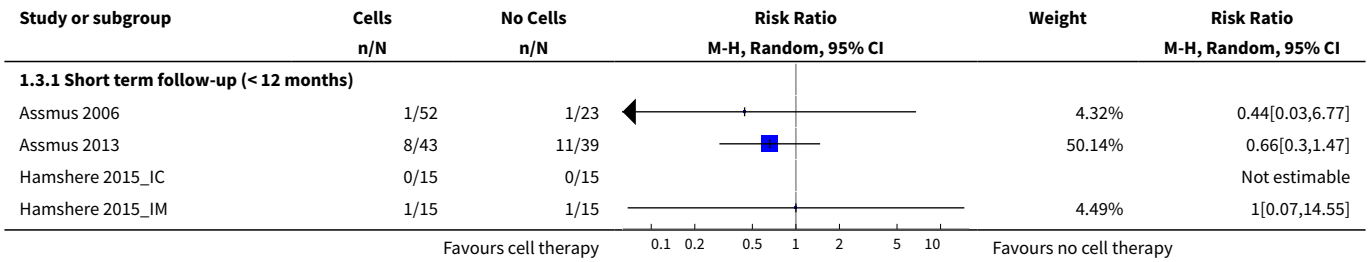
Analysis 1.2. Comparison 1 Cells versus no cells, Outcome 2 Non-fatal myocardial infarction.



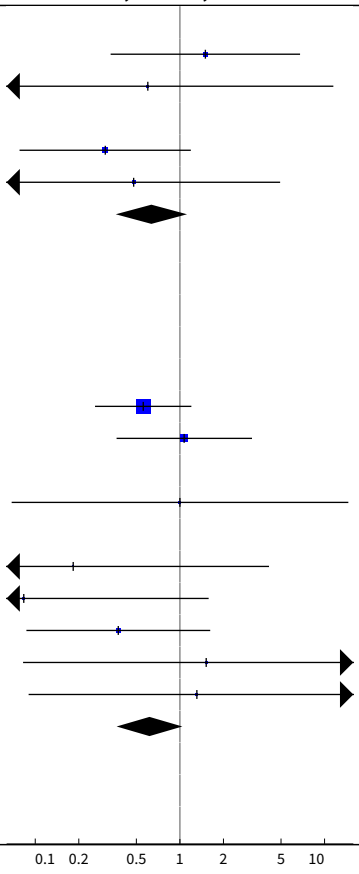
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Short term follow-up (< 12 months)					
Ang 2008	0/42	0/19			Not estimable



Analysis 1.3. Comparison 1 Cells versus no cells, Outcome 3 Rehospitalisation due to heart failure.

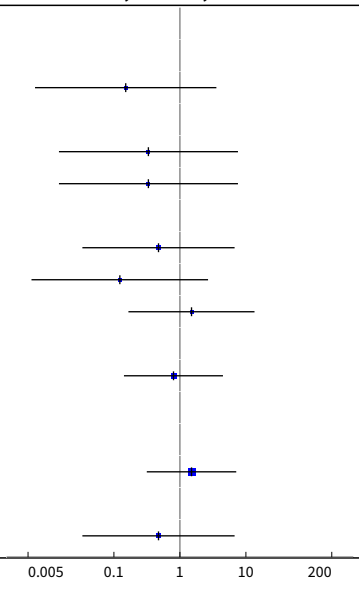


Study or subgroup	Cells n/N	No Cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Honold 2012	0/23	0/9			Not estimable
Mathiasen 2015	6/40	2/20		14.15%	1.5[0.33,6.77]
Mozid 2014_IC	1/14	0/2		3.69%	0.6[0.03,11.47]
Mozid 2014_IM	0/10	0/8			Not estimable
Perin 2012a	3/61	5/31		17.28%	0.3[0.08,1.19]
Yao 2008	1/24	2/23		5.92%	0.48[0.05,4.93]
Subtotal (95% CI)	**297**	**185**		**100%**	**0.63[0.36,1.12]**
Total events: 21 (Cells), 22 (No Cells)					
Heterogeneity: Tau²=0; Chi²=2.6, df=6(P=0.86); I²=0%					
Test for overall effect: Z=1.57(P=0.12)					
1.3.2 Long term follow-up (≥ 12 months)					
Assmus 2013	8/43	13/39		46.67%	0.56[0.26,1.2]
Bartunek 2012	6/21	4/15		23.62%	1.07[0.36,3.15]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	1/15	1/15		3.83%	1[0.07,14.55]
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	1/10		2.83%	0.18[0.01,4.13]
Honold 2012	0/23	2/9		3.16%	0.08[0,1.58]
Losordo 2011	3/112	4/56		12.83%	0.38[0.09,1.62]
Patel 2015	2/22	0/6		3.23%	1.52[0.08,28.11]
Patila 2014	1/13	1/17		3.83%	1.31[0.09,19]
Subtotal (95% CI)	**302**	**193**		**100%**	**0.62[0.36,1.04]**
Total events: 21 (Cells), 26 (No Cells)					
Heterogeneity: Tau²=0; Chi²=4.71, df=7(P=0.7); I²=0%					
Test for overall effect: Z=1.81(P=0.07)					

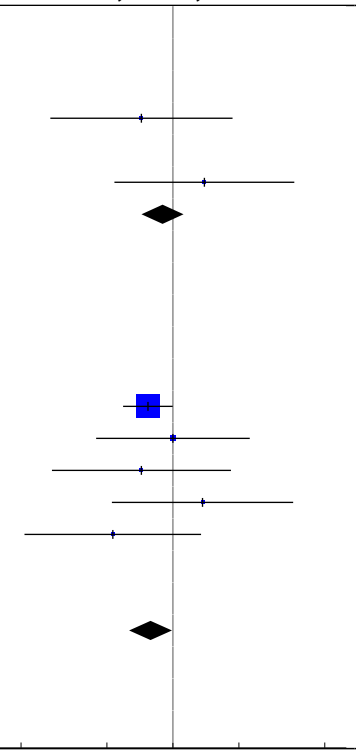


Analysis 1.4. Comparison 1 Cells versus no cells, Outcome 4 Arrhythmias.

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Short term follow-up (< 12 months)					
Ang 2008	0/42	0/19			Not estimable
Assmus 2006	0/52	1/23		5.41%	0.15[0.01,3.57]
Chen 2006	0/22	0/23			Not estimable
Hamshere 2015_IC	0/15	1/15		5.54%	0.33[0.01,7.58]
Hamshere 2015_IM	0/15	1/15		5.54%	0.33[0.01,7.58]
Hu 2011	0/31	0/29			Not estimable
Jimenez-Quevedo 2011	1/19	1/9		7.67%	0.47[0.03,6.74]
Losordo 2007	0/18	1/6		5.7%	0.12[0.01,2.67]
Mathiasen 2015	3/40	1/20		11.19%	1.5[0.17,13.52]
Mozid 2014_IC	0/14	0/2			Not estimable
Mozid 2014_IM	2/10	2/8		18.18%	0.8[0.14,4.49]
Patel 2005	0/10	0/10			Not estimable
Perin 2011	0/20	0/10			Not estimable
Perin 2012b	3/10	2/10		22.24%	1.5[0.32,7.14]
Pokushalov 2010	0/55	0/54			Not estimable
Santoso 2014	1/19	1/9		7.67%	0.47[0.03,6.74]

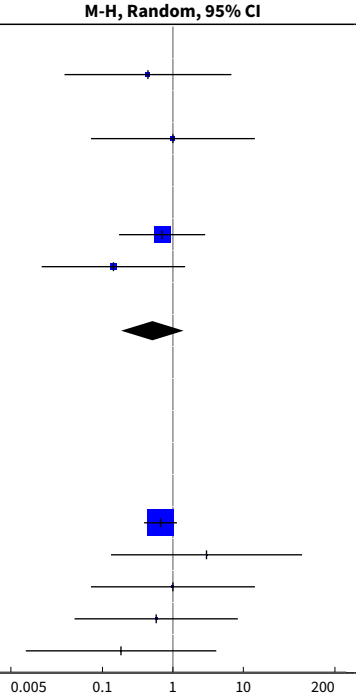


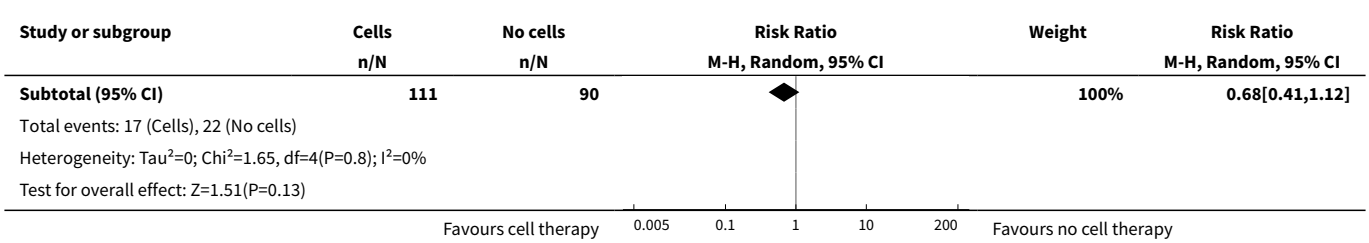
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Tse 2007	0/19	0/9			Not estimable
Van Ramshorst 2009	0/25	0/25			Not estimable
Wang 2009	0/16	0/16			Not estimable
Wang 2010	0/56	1/56		5.35%	0.33[0.01,8.01]
Yao 2008	0/24	0/23			Not estimable
Zhao 2008	1/18	0/18		5.5%	3[0.13,69.09]
Subtotal (95% CI)	**550**	**409**		**100%**	**0.7[0.33,1.45]**
Total events: 11 (Cells), 12 (No cells)					
Heterogeneity: Tau²=0; Chi²=5.18, df=10(P=0.88); I²=0%					
Test for overall effect: Z=0.96(P=0.34)					
1.4.2 Long term follow-up (≥ 12 months)					
Assmus 2013	6/43	13/39		74.93%	0.42[0.18,0.99]
Hamshere 2015_IC	1/15	1/15		7.82%	1[0.07,14.55]
Hamshere 2015_IM	0/15	1/15		5.74%	0.33[0.01,7.58]
Hu 2011	1/31	0/29		5.61%	2.81[0.12,66.4]
Losordo 2007	0/18	1/6		5.9%	0.12[0.01,2.67]
Patel 2015	0/22	0/6			Not estimable
Pokushalov 2010	0/55	0/54			Not estimable
Subtotal (95% CI)	**199**	**164**		**100%**	**0.46[0.22,0.97]**
Total events: 8 (Cells), 16 (No cells)					
Heterogeneity: Tau²=0; Chi²=2.38, df=4(P=0.67); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					



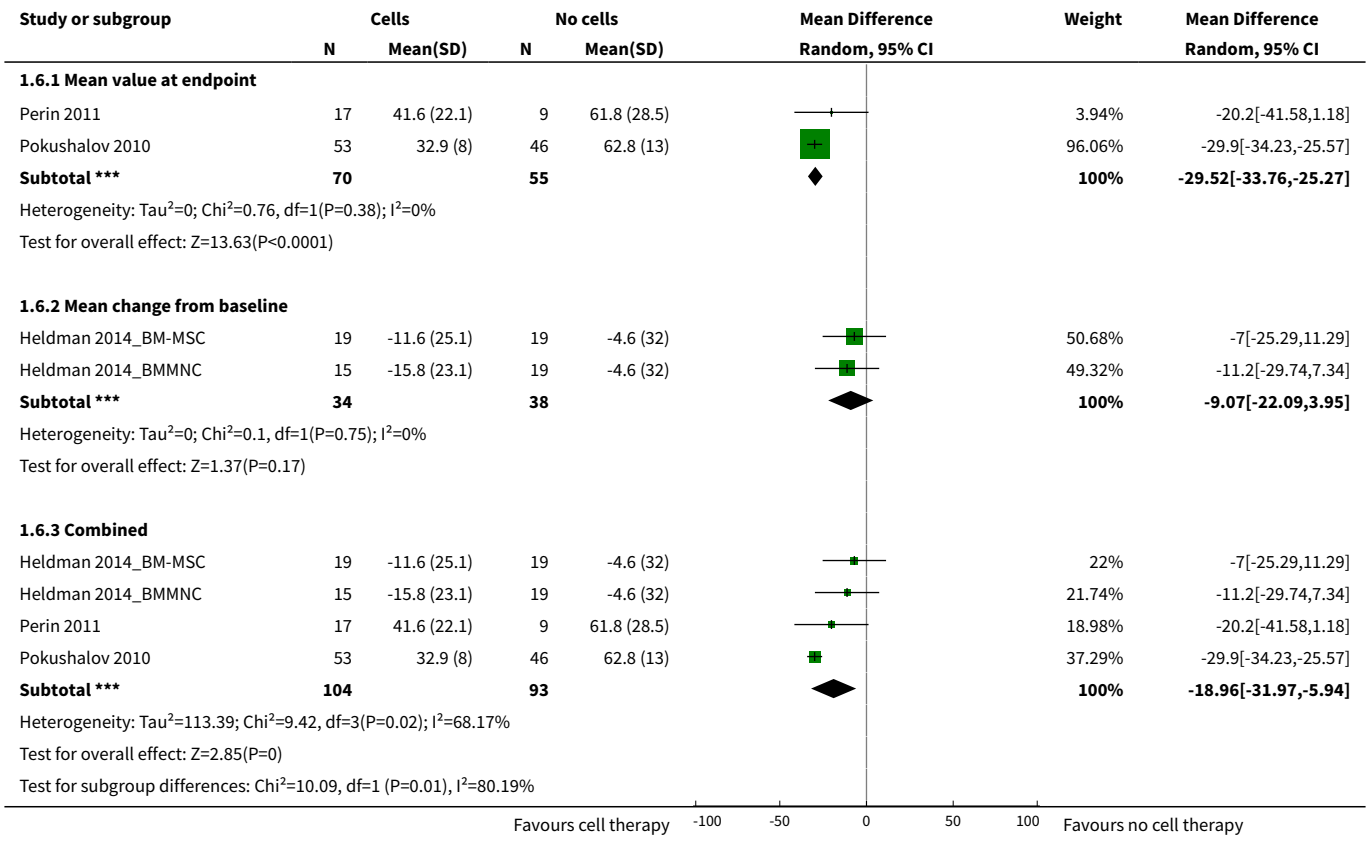
Analysis 1.5. Comparison 1 Cells versus no cells, Outcome 5 Composite MACE.

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Short term follow-up (< 12 months)					
Assmus 2006	1/52	1/23		14%	0.44[0.03,6.77]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	1/15	1/15		14.53%	1[0.07,14.55]
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hu 2011	3/31	4/29		52.49%	0.7[0.17,2.87]
Mozid 2014_IC	1/14	1/2		18.98%	0.14[0.01,1.49]
Mozid 2014_IM	0/10	0/8			Not estimable
Subtotal (95% CI)	**175**	**113**		**100%**	**0.51[0.18,1.42]**
Total events: 6 (Cells), 7 (No cells)					
Heterogeneity: Tau²=0; Chi²=1.64, df=3(P=0.65); I²=0%					
Test for overall effect: Z=1.29(P=0.2)					
1.5.2 Long term follow-up (≥ 12 months)					
Assmus 2013	14/43	19/39		87.71%	0.67[0.39,1.14]
Hamshere 2015_IC	1/15	0/15		2.59%	3[0.13,68.26]
Hamshere 2015_IM	1/15	1/15		3.53%	1[0.07,14.55]
Heldman 2014_BM-MSC	1/19	1/11		3.55%	0.58[0.04,8.36]
Heldman 2014_BMMNC	0/19	1/10		2.61%	0.18[0.01,4.13]

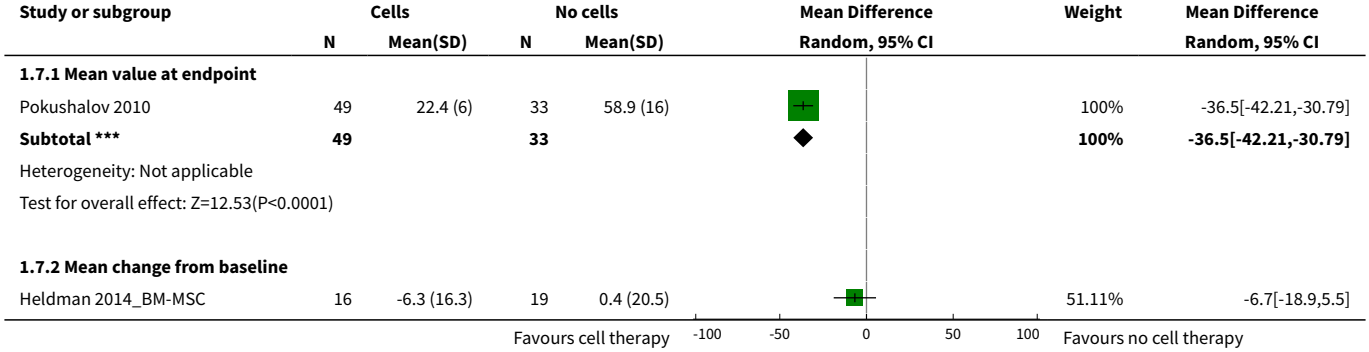


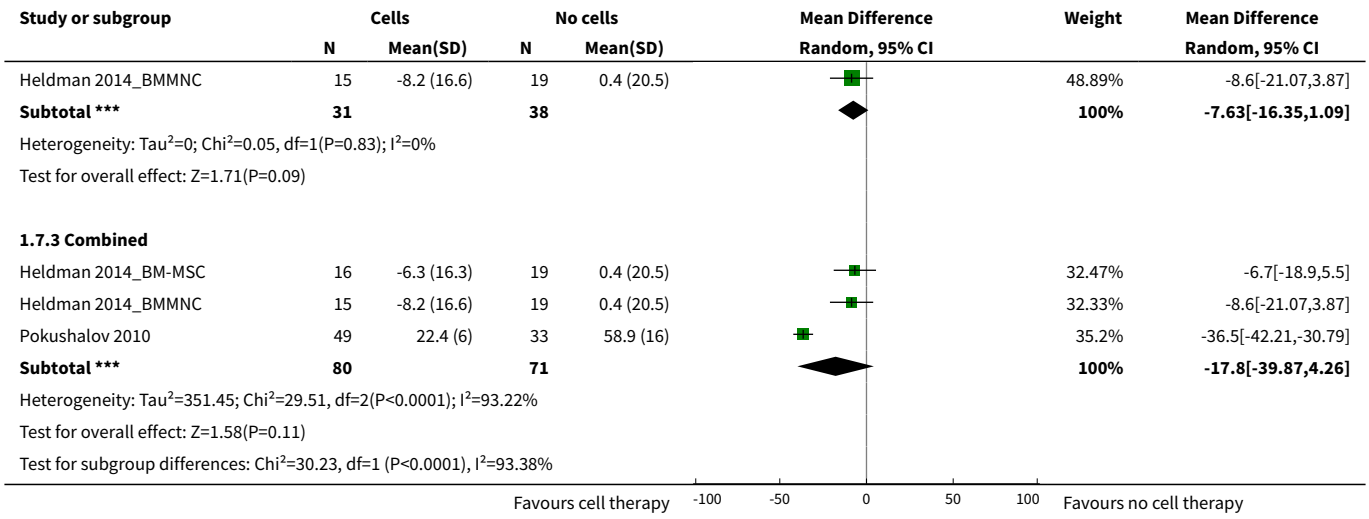


Analysis 1.6. Comparison 1 Cells versus no cells, Outcome 6 MLHFQ: short term follow-up (< 12 months).

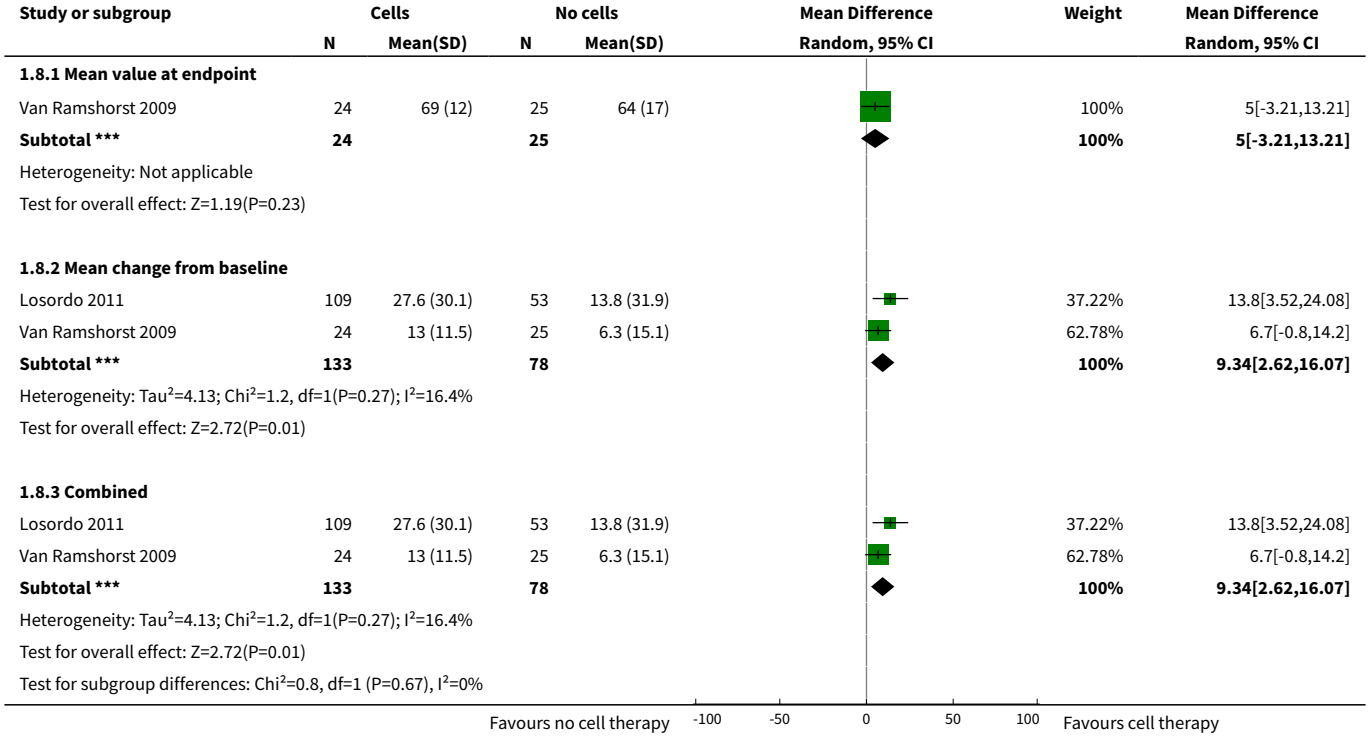


Analysis 1.7. Comparison 1 Cells versus no cells, Outcome 7 MLHFQ: long term follow-up (≥ 12 months).



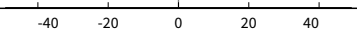


Analysis 1.8. Comparison 1 Cells versus no cells, Outcome 8 Seattle Angina Questionnaire: short term follow-up (< 12 months).



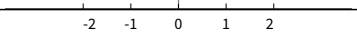
Analysis 1.9. Comparison 1 Cells versus no cells, Outcome 9 Angina episodes per week: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 Mean value at endpoint							
Losordo 2007	17	8.6 (10.3)	6	16 (19.3)		8.25%	-7.4[-23.6,8.8]
Losordo 2011	109	7.6 (8.1)	53	10.9 (8.7)		48.87%	-3.3[-6.09,-0.51]
Pokushalov 2010	53	7 (10.5)	46	19.6 (32.2)		18.26%	-12.6[-22.33,-2.87]
Wang 2010	56	5.6 (15.7)	56	15.5 (24.7)		24.62%	-9.9[-17.57,-2.23]
Subtotal ***	**235**		**161**			**100%**	**-6.96[-11.99,-1.93]**
Heterogeneity: Tau^2=11.44; Chi^2=5.37, df=3(P=0.15); I^2=44.18%							
Test for overall effect: Z=2.71(P=0.01)							
1.9.2 Mean change from baseline							
Losordo 2007	17	12.6 (18.2)	6	-4.5 (20.1)		23.86%	17.1[-1.16,35.36]
Wang 2009	16	-5.6 (9.3)	16	-2 (16.3)		37.29%	-3.6[-12.8,5.6]
Wang 2010	56	-14.6 (29.9)	56	-3 (8.9)		38.85%	-11.6[-19.77,-3.43]
Subtotal ***	**89**		**78**			**100%**	**-1.77[-14.61,11.08]**
Heterogeneity: Tau^2=93.21; Chi^2=8.19, df=2(P=0.02); I^2=75.57%							
Test for overall effect: Z=0.27(P=0.79)							
1.9.3 Combined							
Losordo 2007	17	12.6 (18.2)	6	-4.5 (20.1)		8.6%	17.1[-1.16,35.36]
Losordo 2011	109	7.6 (8.1)	53	10.9 (8.7)		31.95%	-3.3[-6.09,-0.51]
Pokushalov 2010	53	7 (10.5)	46	19.6 (32.2)		18.54%	-12.6[-22.33,-2.87]
Wang 2009	16	-5.6 (9.3)	16	-2 (16.3)		19.49%	-3.6[-12.8,5.6]
Wang 2010	56	-14.6 (29.9)	56	-3 (8.9)		21.42%	-11.6[-19.77,-3.43]
Subtotal ***	**251**		**177**			**100%**	**-5.11[-11.3,1.09]**
Heterogeneity: Tau^2=29.21; Chi^2=11.65, df=4(P=0.02); I^2=65.68%							
Test for overall effect: Z=1.62(P=0.11)							

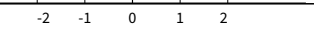


Analysis 1.10. Comparison 1 Cells versus no cells, Outcome 10 NYHA classification: short-term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.10.1 Mean value at endpoint							
Assmus 2006	43	2 (0.7)	18	2.1 (0.9)		6.13%	-0.14[-0.61,0.33]
Assmus 2013	43	2 (0.7)	39	2.2 (0.8)		6.41%	-0.2[-0.51,0.11]
Chen 2006	22	1.3 (0.7)	23	2.5 (0.6)		6.3%	-1.2[-1.58,-0.82]
Hamshere 2015_IC	15	2.2 (0.6)	15	2.2 (0.6)		6.24%	0[-0.42,0.42]
Hamshere 2015_IM	15	2 (0.6)	15	1.8 (0.4)		6.35%	0.2[-0.15,0.55]
Honold 2012	21	1.7 (0.7)	10	1.6 (0.7)		6%	0.11[-0.42,0.64]
Mozid 2014_IM	10	2.2 (0.4)	5	2.5 (0.6)		5.82%	-0.3[-0.91,0.31]
Nasseri 2012	28	2 (0.7)	26	1.5 (0.7)		6.32%	0.54[0.17,0.91]
Patel 2005	10	0.7 (0.8)	10	2.7 (0.7)		5.72%	-2[-2.66,-1.34]
Perin 2011	20	1.8 (0.2)	10	2.4 (0.3)		6.54%	-0.6[-0.81,-0.39]
Perin 2012b	10	2.3 (0.5)	10	2.1 (0.3)		6.33%	0.2[-0.16,0.56]
Pokushalov 2010	53	2.3 (0.2)	46	3.8 (0.1)		6.63%	-1.5[-1.56,-1.44]
Trifunovic 2015	15	1 (0.6)	15	1.3 (0.6)		6.22%	-0.27[-0.69,0.15]



Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Tse 2007	19	2 (0.4)	9	2.3 (0.5)		6.31%	-0.38[-0.75,-0.01]
Turan 2011	33	1.6 (0.5)	16	2.1 (0.7)		6.29%	-0.5[-0.88,-0.12]
Zhao 2008	16	1.5 (0.5)	18	2.3 (0.5)		6.38%	-0.8[-1.13,-0.47]
Subtotal ***	**373**		**285**			**100%**	**-0.42[-0.84,-0]**
Heterogeneity: Tau^2=0.69; Chi^2=512.53, df=15(P<0.0001); I^2=97.07%							
Test for overall effect: Z=1.98(P=0.05)							
1.10.2 Mean change from baseline							
Assmus 2013	42	-0.3 (0.7)	38	0.1 (1)		25.29%	-0.45[-0.82,-0.08]
Nasseri 2012	28	-0.5 (1)	26	-1 (0.7)		24.76%	0.48[0.02,0.94]
Patel 2005	10	-2.8 (0.4)	10	-0.7 (0.7)		24.53%	-2.1[-2.59,-1.61]
Perin 2012a	55	-0.3 (0.9)	30	-0.1 (0.7)		25.42%	-0.2[-0.55,0.15]
Subtotal ***	**135**		**104**			**100%**	**-0.56[-1.49,0.36]**
Heterogeneity: Tau^2=0.84; Chi^2=61.48, df=3(P<0.0001); I^2=95.12%							
Test for overall effect: Z=1.19(P=0.23)							
1.10.3 Combined							
Assmus 2006	43	2 (0.7)	18	2.1 (0.9)		5.75%	-0.14[-0.61,0.33]
Assmus 2013	42	-0.3 (0.7)	38	0.1 (1)		5.94%	-0.45[-0.82,-0.08]
Chen 2006	22	1.3 (0.7)	23	2.5 (0.6)		5.92%	-1.2[-1.58,-0.82]
Hamshere 2015_IC	15	2.2 (0.6)	15	2.2 (0.6)		5.86%	0[-0.42,0.42]
Hamshere 2015_IM	15	2 (0.6)	15	1.8 (0.4)		5.97%	0.2[-0.15,0.55]
Honold 2012	21	1.7 (0.7)	10	1.6 (0.7)		5.62%	0.11[-0.42,0.64]
Mozid 2014_IM	10	2.2 (0.4)	5	2.5 (0.6)		5.44%	-0.3[-0.91,0.31]
Nasseri 2012	28	-0.5 (1)	26	-1 (0.7)		5.78%	0.48[0.02,0.94]
Patel 2005	10	-2.8 (0.4)	10	-0.7 (0.7)		5.71%	-2.1[-2.59,-1.61]
Perin 2011	20	1.8 (0.2)	10	2.4 (0.3)		6.16%	-0.6[-0.81,-0.39]
Perin 2012a	55	-0.3 (0.9)	30	-0.1 (0.7)		5.98%	-0.2[-0.55,0.15]
Perin 2012b	10	2.3 (0.5)	10	2.1 (0.3)		5.95%	0.2[-0.16,0.56]
Pokushalov 2010	53	2.3 (0.2)	46	3.8 (0.1)		6.26%	-1.5[-1.56,-1.44]
Trifunovic 2015	15	1 (0.6)	15	1.3 (0.6)		5.84%	-0.27[-0.69,0.15]
Tse 2007	19	2 (0.4)	9	2.3 (0.5)		5.93%	-0.38[-0.75,-0.01]
Turan 2011	33	1.6 (0.5)	16	2.1 (0.7)		5.91%	-0.5[-0.88,-0.12]
Zhao 2008	16	1.5 (0.5)	18	2.3 (0.5)		6%	-0.8[-1.13,-0.47]
Subtotal ***	**427**		**314**			**100%**	**-0.44[-0.84,-0.05]**
Heterogeneity: Tau^2=0.64; Chi^2=495.64, df=16(P<0.0001); I^2=96.77%							
Test for overall effect: Z=2.21(P=0.03)							

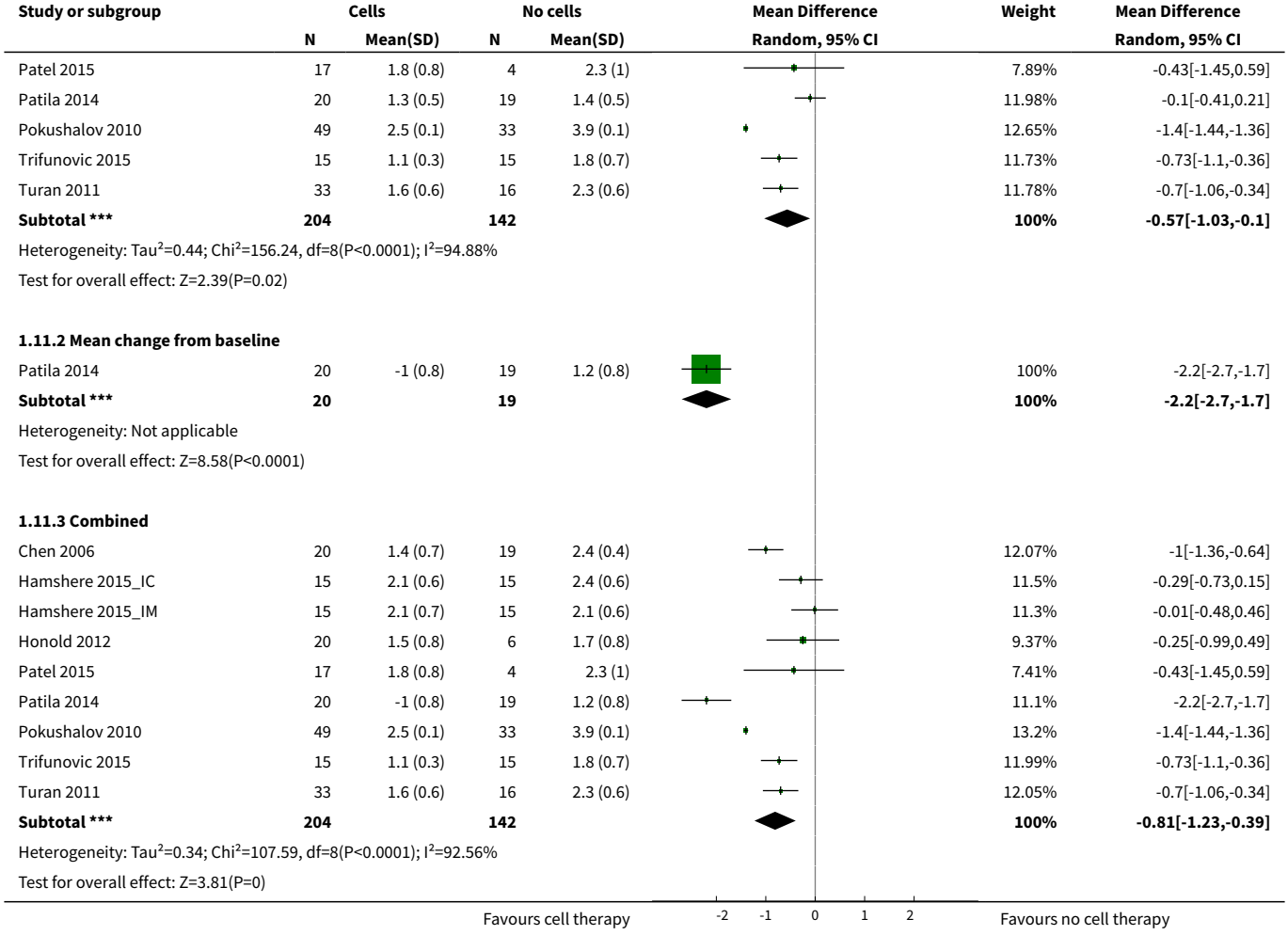


Favours cell therapy — Favours no cell therapy

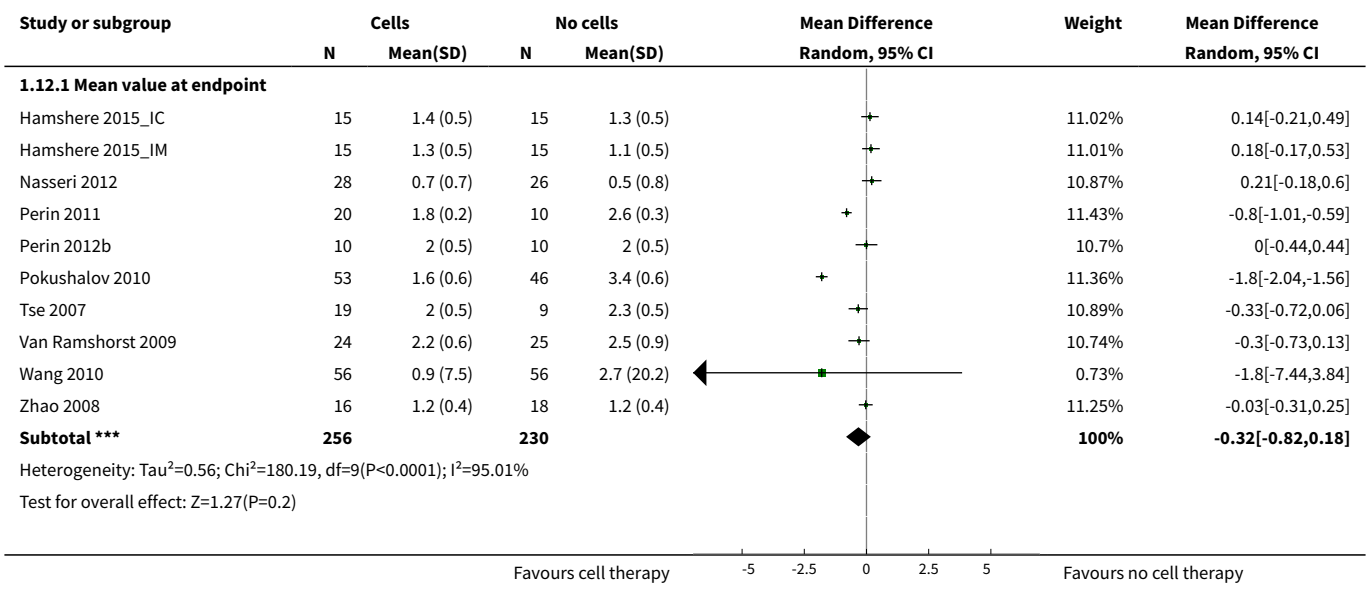
Analysis 1.11. Comparison 1 Cells versus no cells, Outcome 11 NYHA classification: long term follow-up (≥ 12 months).

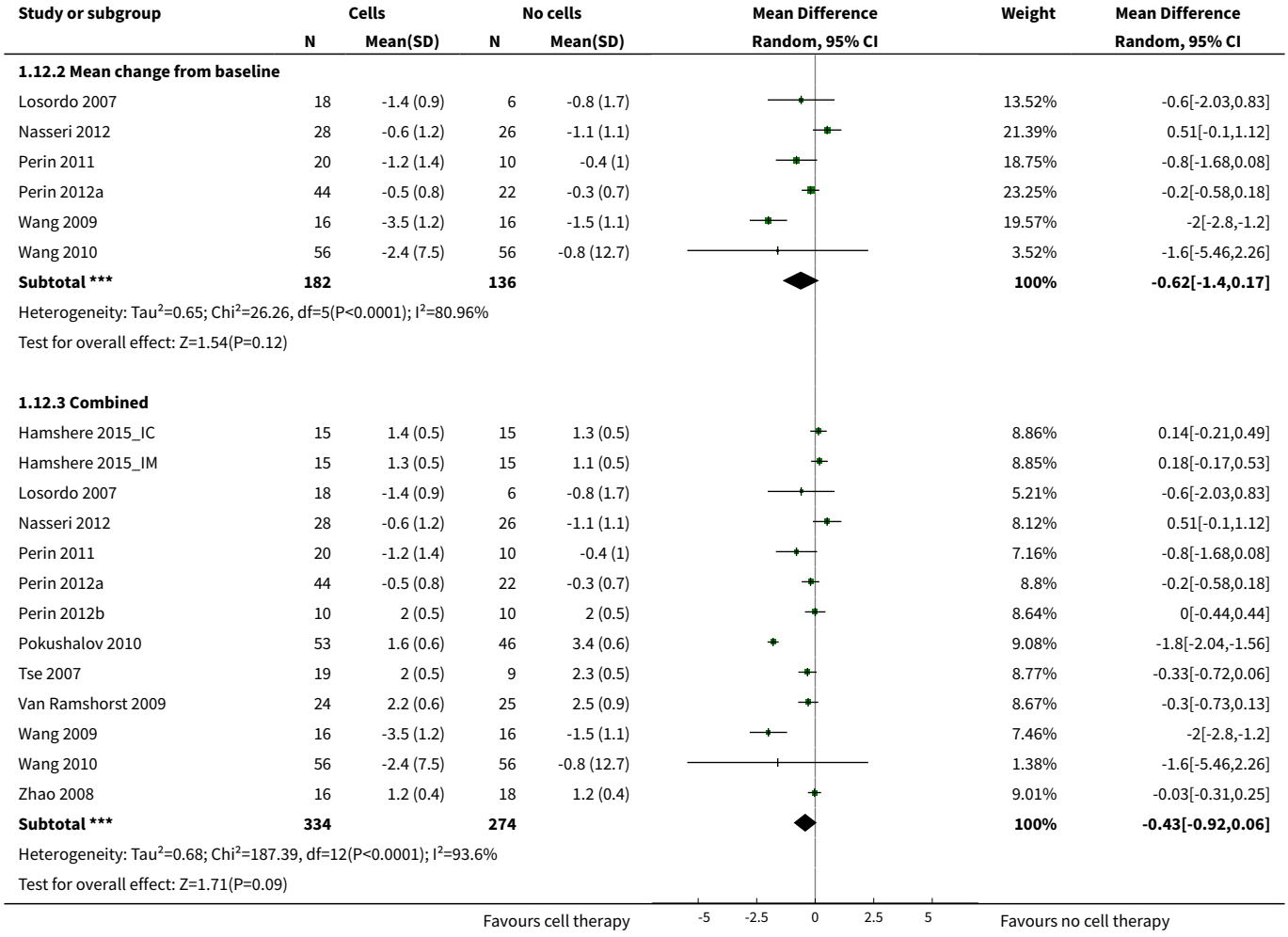
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Mean value at endpoint							
Chen 2006	20	1.4 (0.7)	19	2.4 (0.4)		11.79%	-1[-1.36,-0.64]
Hamshere 2015_IC	15	2.1 (0.6)	15	2.4 (0.6)		11.36%	-0.29[-0.73,0.15]
Hamshere 2015_IM	15	2.1 (0.7)	15	2.1 (0.6)		11.2%	-0.01[-0.48,0.46]
Honold 2012	20	1.5 (0.8)	6	1.7 (0.8)		9.62%	-0.25[-0.99,0.49]

Favours cell therapy — Favours no cell therapy

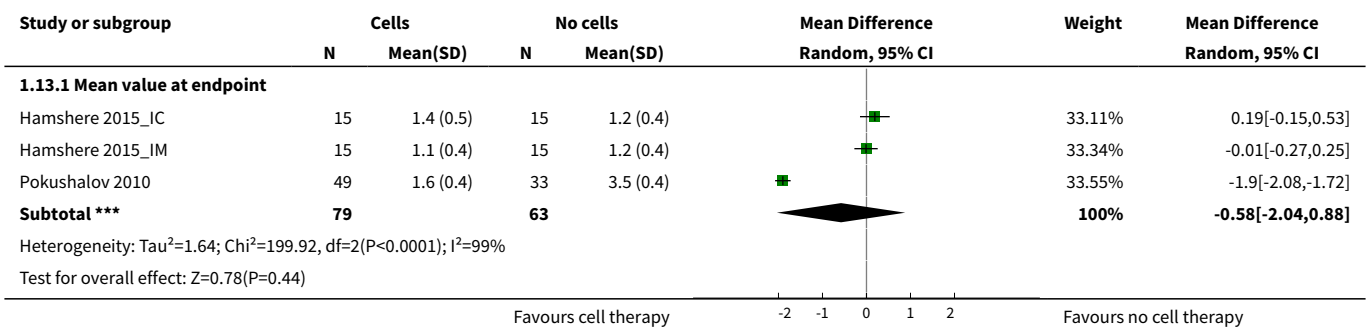


Analysis 1.12. Comparison 1 Cells versus no cells, Outcome 12 CCS class: short term follow-up (< 12 months).



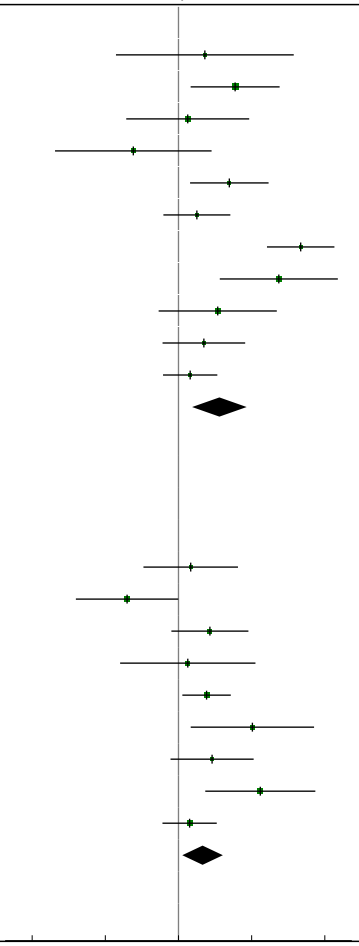


Analysis 1.13. Comparison 1 Cells versus no cells, Outcome 13 CCS class: long term follow-up (≥ 12 months).



Analysis 1.14. Comparison 1 Cells versus no cells, Outcome 14 Exercise capacity: short term follow-up (< 12 months).

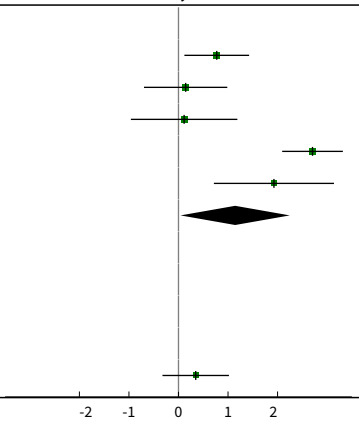
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.14.1 Mean value at endpoint							
Bartunek 2012	21	456 (142.8)	3	404 (97.5)		5.5%	0.36[-0.85,1.58]
Chen 2006	22	7 (3)	23	5 (2)		9.77%	0.77[0.17,1.38]
Erbs 2005	12	23.1 (5.8)	10	22.4 (4.7)		7.91%	0.13[-0.71,0.97]
Honold 2012	12	376 (198)	5	501 (175)		6.33%	-0.62[-1.69,0.45]
Hu 2011	30	491 (47)	27	451 (66)		10.37%	0.69[0.16,1.23]
Perin 2012a	51	184 (407)	29	80 (415)		11.01%	0.25[-0.21,0.71]
Pokushalov 2010	53	325 (81)	46	211 (48)		10.99%	1.67[1.21,2.13]
Trifunovic 2015	15	435 (90)	15	315 (80)		8.16%	1.37[0.56,2.18]
Tse 2007	19	6.1 (0.5)	9	5.7 (0.7)		8.16%	0.54[-0.27,1.34]
Van Ramshorst 2009	24	116 (32)	25	103 (41)		10.13%	0.35[-0.22,0.91]
Wang 2010	56	8.9 (9.7)	56	6.8 (15.7)		11.68%	0.16[-0.21,0.53]
Subtotal ***	**315**		**248**			**100%**	**0.56[0.19,0.93]**
Heterogeneity: Tau^2=0.27; Chi^2=39.4, df=10(P<0.0001); I^2=74.62%							
Test for overall effect: Z=2.94(P=0)							
1.14.2 Mean change from baseline							
Heldman 2014_BM-MSC	18	28.2 (34.9)	19	21.6 (41.9)		10.25%	0.17[-0.48,0.81]
Heldman 2014_BMMNC	15	-25.7 (87.3)	19	21.6 (41.9)		9.34%	-0.7[-1.4,-0]
Hu 2011	30	44 (39)	27	16 (84)		12.6%	0.43[-0.1,0.96]
Losordo 2007	18	0.5 (1.3)	6	0.3 (2.1)		6.47%	0.13[-0.8,1.05]
Losordo 2011	109	124.4 (153)	53	69 (122)		17.36%	0.38[0.05,0.71]
Tse 2007	19	0.1 (0.3)	9	-0.2 (0.5)		7.37%	1.01[0.17,1.85]
Van Ramshorst 2009	24	9 (15.7)	25	2 (14.3)		11.72%	0.46[-0.11,1.03]
Wang 2009	16	2.4 (1)	16	0.8 (1.7)		8.56%	1.12[0.37,1.87]
Wang 2010	56	4.5 (9.7)	56	2.5 (15.7)		16.33%	0.15[-0.22,0.52]
Subtotal ***	**305**		**230**			**100%**	**0.33[0.05,0.61]**
Heterogeneity: Tau^2=0.09; Chi^2=16.81, df=8(P=0.03); I^2=52.41%							
Test for overall effect: Z=2.33(P=0.02)							



Favours no cell therapy — Favours cell therapy

Analysis 1.15. Comparison 1 Cells versus no cells, Outcome 15 Exercise capacity: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.15.1 Mean value at endpoint							
Chen 2006	20	7 (2)	19	5 (3)		21.3%	0.77[0.12,1.43]
Erbs 2005	12	22.6 (7.9)	10	21.6 (4.7)		20.3%	0.14[-0.7,0.99]
Honold 2012	10	19 (19)	5	17 (8.9)		18.89%	0.11[-0.96,1.19]
Pokushalov 2010	49	359 (69)	33	196 (42)		21.49%	2.71[2.09,3.32]
Trifunovic 2015	15	520 (79)	5	343 (114)		18.01%	1.93[0.71,3.14]
Subtotal ***	**106**		**72**			**100%**	**1.14[0.04,2.25]**
Heterogeneity: Tau^2=1.38; Chi^2=35.67, df=4(P<0.0001); I^2=88.79%							
Test for overall effect: Z=2.03(P=0.04)							
1.15.2 Mean change from baseline							
Heldman 2014_BM-MSC	16	32.6 (69.7)	19	6.1 (78.2)		16.79%	0.35[-0.32,1.02]



Favours no cell therapy — Favours cell therapy

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Heldman 2014_BMMNC	17	16.9 (60.5)	19	6.1 (78.2)		17.58%	0.15[-0.51,0.81]
Losordo 2011	106	121.5 (166.8)	50	58 (146)		65.63%	0.39[0.05,0.73]
Subtotal ***	**139**		**88**			**100%**	**0.34[0.07,0.62]**
Heterogeneity: Tau²=0; Chi²=0.42, df=2(P=0.81); I²=0%							
Test for overall effect: Z=2.45(P=0.01)							

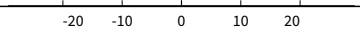
Favours no cell therapy -2 -1 0 1 2 Favours cell therapy

Analysis 1.16. Comparison 1 Cells versus no cells, Outcome 16 LVEF (%) measured by MRI: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.16.1 Mean value at endpoint							
Ang 2008	18	28.6 (8.4)	7	22.3 (5.8)		11.03%	6.3[0.51,12.09]
Erbs 2005	12	57.7 (10.9)	11	55.8 (8.8)		8.04%	1.9[-6.17,9.97]
Hendrikx 2006	10	48.9 (9.5)	10	43.1 (10.9)		7.1%	5.8[-3.16,14.76]
Honold 2012	9	32.8 (13.1)	4	25.3 (0.5)		7.49%	7.5[-1.07,16.07]
Hu 2011	31	36.5 (11.8)	28	32.3 (10.3)		11.26%	4.2[-1.44,9.84]
Nasseri 2012	26	31 (7)	22	33 (8)		13.42%	-2[-6.29,2.29]
Santoso 2014	19	25.7 (9.5)	9	29.4 (11.1)		7.66%	-3.7[-12.12,4.72]
Tse 2007	18	55.6 (8.8)	8	45.3 (8.2)		9.34%	10.3[3.31,17.29]
Van Ramshorst 2009	22	59 (11)	18	53 (10)		9.97%	6[-0.52,12.52]
Wang 2014	35	33 (7)	35	35 (8)		14.69%	-2[-5.52,1.52]
Subtotal ***	**200**		**152**			**100%**	**3.01[-0.05,6.07]**
Heterogeneity: Tau²=13.33; Chi²=21.88, df=9(P=0.01); I²=58.87%							
Test for overall effect: Z=1.93(P=0.05)							
1.16.2 Mean change from baseline							
Ang 2008	18	2.1 (4.8)	7	0.7 (4.2)		10.85%	1.4[-2.42,5.22]
Assmus 2013	15	1.9 (3.6)	12	-1.1 (3.5)		16.83%	3[0.31,5.69]
Erbs 2005	12	6.7 (6.2)	11	0 (4.6)		8.71%	6.7[2.26,11.14]
Hendrikx 2006	10	6.1 (8.6)	10	3.6 (9.1)		3.39%	2.5[-5.26,10.26]
Hu 2011	31	13 (10.3)	28	7.6 (8.7)		7.58%	5.4[0.55,10.25]
Mathiasen 2015	40	5 (3.8)	20	-1.3 (3.7)		22.18%	6.3[4.3,8.3]
Santoso 2014	19	1.9 (5.5)	9	2.6 (7.2)		6.54%	-0.7[-6.01,4.61]
Tse 2007	18	3.7 (5.1)	8	-0.4 (7.5)		5.81%	4.1[-1.61,9.81]
Van Ramshorst 2009	22	3 (5)	18	-1 (3)		18.12%	4[1.49,6.51]
Subtotal ***	**185**		**123**			**100%**	**4.05[2.55,5.55]**
Heterogeneity: Tau²=1.59; Chi²=11.92, df=8(P=0.15); I²=32.88%							
Test for overall effect: Z=5.29(P<0.0001)							
1.16.3 Combined							
Ang 2008	18	2.1 (4.8)	7	0.7 (4.2)		9.23%	1.4[-2.42,5.22]
Assmus 2013	15	1.9 (3.6)	12	-1.1 (3.5)		11.39%	3[0.31,5.69]
Erbs 2005	12	6.7 (6.2)	11	0 (4.6)		8.17%	6.7[2.26,11.14]
Hendrikx 2006	10	6.1 (8.6)	10	3.6 (9.1)		4.25%	2.5[-5.26,10.26]
Honold 2012	9	32.8 (13.1)	4	25.3 (0.5)		3.68%	7.5[-1.07,16.07]
Hu 2011	31	13 (10.3)	28	7.6 (8.7)		7.51%	5.4[0.55,10.25]

Favours no cell therapy -20 -10 0 10 20 Favours cell therapy

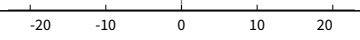
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Mathiasen 2015	40	5 (3.8)	20	-1.3 (3.7)		12.68%	6.3[4.3,8.3]
Nasseri 2012	26	31 (7)	22	33 (8)		8.41%	-2[-6.29,2.29]
Santoso 2014	19	1.9 (5.5)	9	2.6 (7.2)		6.84%	-0.7[-6.01,4.61]
Tse 2007	18	3.7 (5.1)	8	-0.4 (7.5)		6.32%	4.1[-1.61,9.81]
Van Ramshorst 2009	22	3 (5)	18	-1 (3)		11.74%	4[1.49,6.51]
Wang 2014	35	33 (7)	35	35 (8)		9.79%	-2[-5.52,1.52]
Subtotal * **	**255**		**184**			**100%**	**2.92[1.03,4.82]**
Heterogeneity: Tau²=6.33; Chi²=30.55, df=11(P=0); I²=63.99%							
Test for overall effect: Z=3.02(P=0)							



Favours no cell therapy — Favours cell therapy

Analysis 1.17. Comparison 1 Cells versus no cells, Outcome 17 LVEF (%) measured by MRI: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.17.1 Mean value at endpoint							
Erbs 2005	12	59 (10.9)	10	57.9 (8.7)		22.83%	1.1[-7.09,9.29]
Honold 2012	9	32.3 (10.9)	4	24.5 (7.5)		14.63%	7.8[-2.43,18.03]
Hu 2011	25	36.9 (12.3)	25	33 (10.2)		39.05%	3.9[-2.36,10.16]
Patila 2014	11	42.4 (9.1)	14	44.7 (11.5)		23.49%	-2.3[-10.38,5.78]
Subtotal * **	**57**		**53**			**100%**	**2.37[-1.54,6.29]**
Heterogeneity: Tau²=0; Chi²=2.69, df=3(P=0.44); I²=0%							
Test for overall effect: Z=1.19(P=0.23)							
1.17.2 Mean change from baseline							
Erbs 2005	12	8 (9.1)	10	2.1 (2.7)		36.56%	5.9[0.49,11.31]
Hu 2011	25	13.5 (10.3)	25	8 (8.6)		37.82%	5.5[0.24,10.76]
Patila 2014	11	3.7 (9.7)	14	5.3 (8)		25.62%	-1.6[-8.7,5.5]
Subtotal * **	**48**		**49**			**100%**	**3.83[-0.42,8.08]**
Heterogeneity: Tau²=5.23; Chi²=3.17, df=2(P=0.2); I²=36.95%							
Test for overall effect: Z=1.76(P=0.08)							
1.17.3 Combined							
Erbs 2005	12	8 (9.1)	10	2.1 (2.7)		33.04%	5.9[0.49,11.31]
Honold 2012	9	32.3 (10.9)	4	24.5 (7.5)		11.13%	7.8[-2.43,18.03]
Hu 2011	25	13.5 (10.3)	25	8 (8.6)		34.53%	5.5[0.24,10.76]
Patila 2014	11	3.7 (9.7)	14	5.3 (8)		21.3%	-1.6[-8.7,5.5]
Subtotal * **	**57**		**53**			**100%**	**4.38[0.82,7.93]**
Heterogeneity: Tau²=2.34; Chi²=3.63, df=3(P=0.3); I²=17.33%							
Test for overall effect: Z=2.41(P=0.02)							



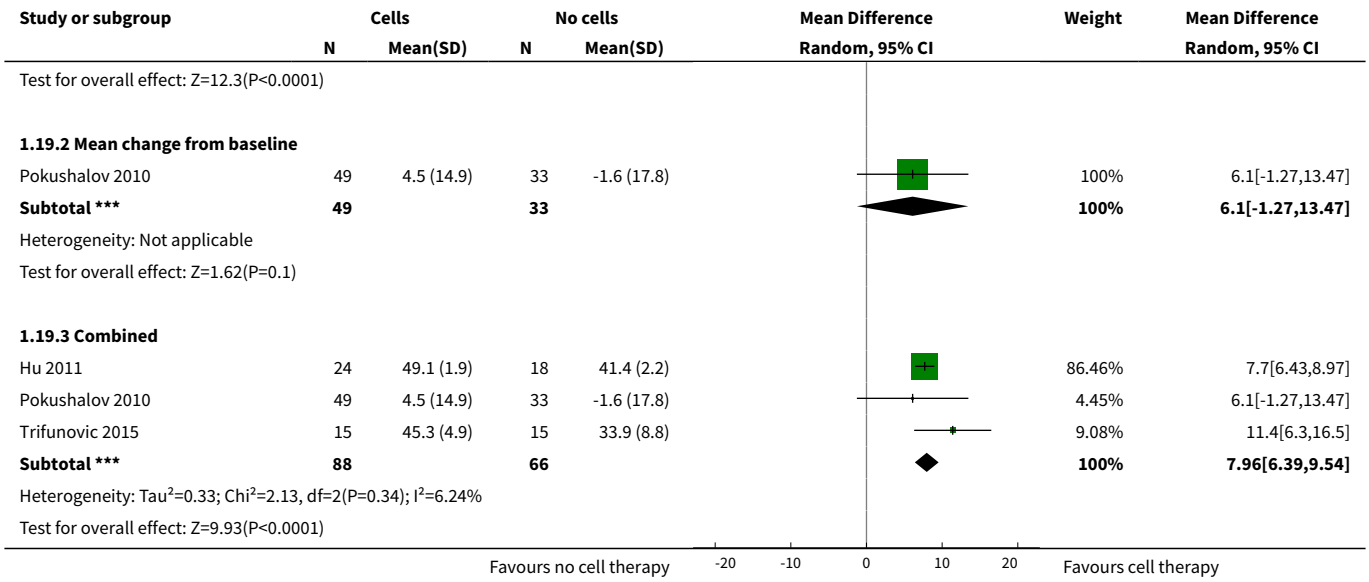
Favours no cell therapy — Favours cell therapy

Analysis 1.18. Comparison 1 Cells versus no cells, Outcome 18 LVEF (%) measured by echocardiography: short term follow-up (< 12 months).

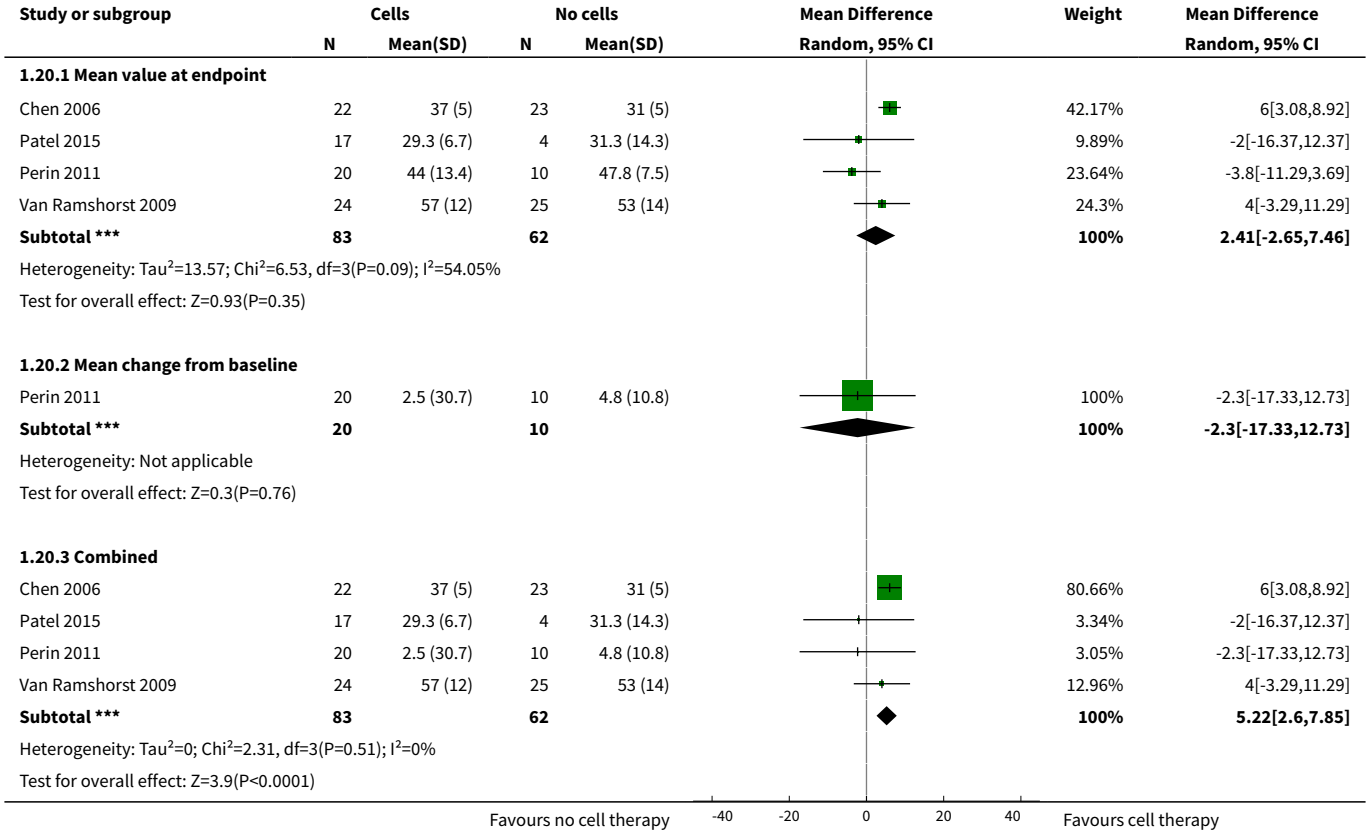
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.18.1 Mean value at endpoint							
Bartunek 2012	21	34.5 (4.5)	15	28 (4.1)		16.14%	6.5[3.67,9.33]
Perin 2011	20	40 (5.4)	10	42 (5.4)		12.69%	-2[-6.1,2.1]
Perin 2012b	10	36 (11.3)	10	34 (9.3)		4.89%	2[-7.07,11.07]
Pokushalov 2010	53	32.8 (6.2)	46	26.2 (6.1)		17.28%	6.6[4.17,9.03]
Trifunovic 2015	15	44.8 (5.5)	15	37.7 (7.4)		11.32%	7.1[2.43,11.77]
Van Ramshorst 2009	24	54 (7)	25	51 (7)		13.15%	3[-0.92,6.92]
Wang 2015	45	47.6 (6.3)	45	40.1 (7.4)		16.12%	7.5[4.66,10.34]
Zhao 2008	16	49.1 (9.7)	18	40.6 (8.4)		8.42%	8.5[2.36,14.64]
Subtotal ***	**204**		**184**			**100%**	**5.16[2.87,7.44]**
Heterogeneity: Tau^2=6.32; Chi^2=19.52, df=7(P=0.01); I^2=64.13%							
Test for overall effect: Z=4.43(P<0.0001)							
1.18.2 Mean change from baseline							
Perin 2011	20	3 (37.9)	10	3 (8)		1.17%	0[-17.33,17.33]
Perin 2012a	54	1.4 (5.2)	28	-1.3 (5.1)		64%	2.7[0.36,5.04]
Van Ramshorst 2009	24	4 (4)	25	-1 (7)		34.83%	5[1.82,8.18]
Subtotal ***	**98**		**63**			**100%**	**3.47[1.59,5.34]**
Heterogeneity: Tau^2=0; Chi^2=1.46, df=2(P=0.48); I^2=0%							
Test for overall effect: Z=3.63(P=0)							
1.18.3 Combined							
Bartunek 2012	21	34.5 (4.5)	15	28 (4.1)		15.95%	6.5[3.67,9.33]
Perin 2011	20	3 (37.9)	10	3 (8)		0.66%	0[-17.33,17.33]
Perin 2012a	54	1.4 (5.2)	28	-1.3 (5.1)		19.91%	2.7[0.36,5.04]
Perin 2012b	10	36 (11.3)	10	34 (9.3)		2.32%	2[-7.07,11.07]
Pokushalov 2010	53	32.8 (6.2)	46	26.2 (6.1)		19.15%	6.6[4.17,9.03]
Trifunovic 2015	15	44.8 (5.5)	15	37.7 (7.4)		7.64%	7.1[2.43,11.77]
Van Ramshorst 2009	24	4 (4)	25	-1 (7)		13.7%	5[1.82,8.18]
Wang 2015	45	47.6 (6.3)	45	40.1 (7.4)		15.88%	7.5[4.66,10.34]
Zhao 2008	16	49.1 (9.7)	18	40.6 (8.4)		4.77%	8.5[2.36,14.64]
Subtotal ***	**258**		**212**			**100%**	**5.71[4.29,7.13]**
Heterogeneity: Tau^2=1.21; Chi^2=11.04, df=8(P=0.2); I^2=27.54%							
Test for overall effect: Z=7.87(P<0.0001)							

Analysis 1.19. Comparison 1 Cells versus no cells, Outcome 19 LVEF (%) measured by echocardiography: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.19.1 Mean value at endpoint							
Hu 2011	24	49.1 (1.9)	18	41.4 (2.2)		58.82%	7.7[6.43,8.97]
Pokushalov 2010	49	32.3 (4.1)	33	25.2 (4.1)		35.61%	7.1[5.29,8.91]
Trifunovic 2015	15	45.3 (4.9)	15	33.9 (8.8)		5.58%	11.4[6.3,16.5]
Subtotal ***	**88**		**66**			**100%**	**7.69[6.47,8.92]**
Heterogeneity: Tau^2=0.25; Chi^2=2.44, df=2(P=0.3); I^2=18.03%							

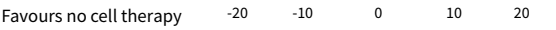


Analysis 1.20. Comparison 1 Cells versus no cells, Outcome 20 LVEF (%) measured by SPECT: short term follow-up (< 12 months).



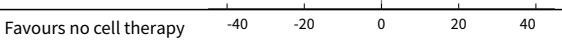
Analysis 1.21. Comparison 1 Cells versus no cells, Outcome 21 LVEF (%) measured by SPECT: long term follow-up (≥ 12 months).

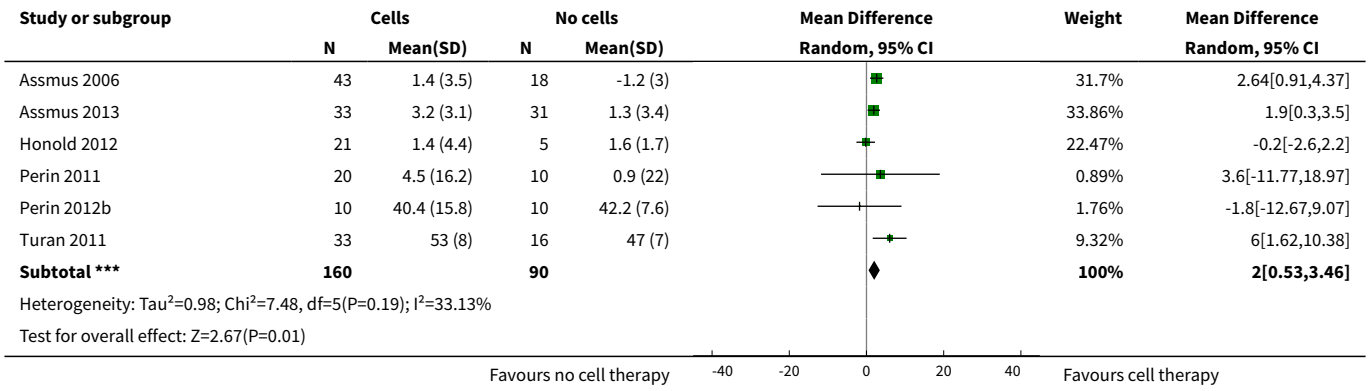
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.21.1 Mean value at endpoint							
Chen 2006	20	30 (4)	19	30 (5)		87.64%	0[-2.85,2.85]
Van Ramshorst 2009	24	56 (12)	25	53 (15)		12.36%	3[-4.59,10.59]
Subtotal ***	**44**		**44**			**100%**	**0.37[-2.3,3.04]**
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%							
Test for overall effect: Z=0.27(P=0.79)							
1.21.2 Mean change from baseline							
Van Ramshorst 2009	24	3 (5.2)	25	-1 (26.2)		100%	4[-6.48,14.48]
Subtotal ***	**24**		**25**			**100%**	**4[-6.48,14.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.75(P=0.45)							
1.21.3 Combined							
Chen 2006	20	30 (4)	19	30 (5)		93.11%	0[-2.85,2.85]
Van Ramshorst 2009	24	3 (5.2)	25	-1 (26.2)		6.89%	4[-6.48,14.48]
Subtotal ***	**44**		**44**			**100%**	**0.28[-2.48,3.03]**
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%							
Test for overall effect: Z=0.2(P=0.84)							



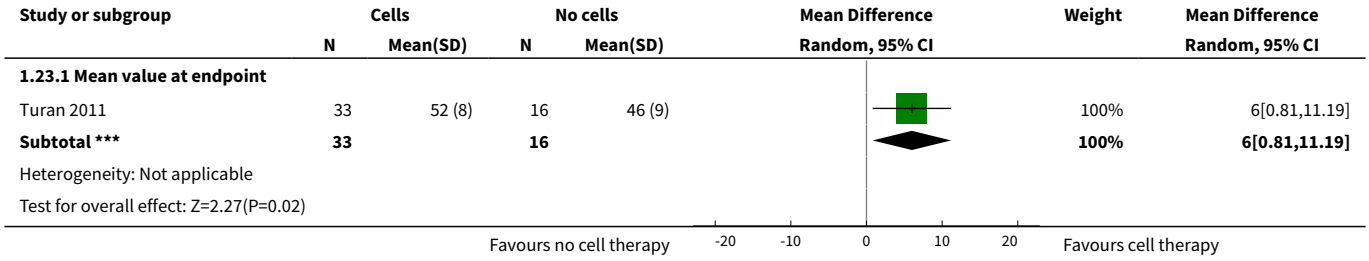
Analysis 1.22. Comparison 1 Cells versus no cells, Outcome 22 LVEF (%) measured by LV angiography: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.22.1 Mean value at endpoint							
Assmus 2006	43	41.2 (10.1)	18	42 (13)		15.96%	-0.8[-7.52,5.92]
Assmus 2013	41	37.8 (12.6)	38	32.1 (12.6)		22.56%	5.7[0.14,11.26]
Honold 2012	21	38.9 (13.3)	5	39.2 (7.4)		9.98%	-0.3[-8.93,8.33]
Perin 2011	20	42 (14.4)	10	40.9 (8.5)		10.94%	1.1[-7.12,9.32]
Perin 2012b	10	40.4 (15.8)	10	42.2 (7.6)		6.4%	-1.8[-12.67,9.07]
Turan 2011	33	53 (8)	16	47 (7)		34.17%	6[1.62,10.38]
Subtotal ***	**168**		**97**			**100%**	**3.18[0.39,5.97]**
Heterogeneity: Tau^2=0.93; Chi^2=5.39, df=5(P=0.37); I^2=7.27%							
Test for overall effect: Z=2.24(P=0.03)							
1.22.2 Mean change from baseline							
Assmus 2006	43	1.4 (3.5)	18	-1.2 (3)		36.61%	2.64[0.91,4.37]
Assmus 2013	33	3.2 (3.1)	31	1.3 (3.4)		40.94%	1.9[0.3,3.5]
Honold 2012	21	1.4 (4.4)	5	1.6 (1.7)		21.81%	-0.2[-2.6,2.2]
Perin 2011	20	4.5 (16.2)	10	0.9 (22)		0.63%	3.6[-11.77,18.97]
Subtotal ***	**117**		**64**			**100%**	**1.72[0.5,2.95]**
Heterogeneity: Tau^2=0.29; Chi^2=3.64, df=3(P=0.3); I^2=17.61%							
Test for overall effect: Z=2.76(P=0.01)							
1.22.3 Combined							





Analysis 1.23. Comparison 1 Cells versus no cells, Outcome 23 LVEF (%) measured by LV angiography: long term follow-up (≥ 12 months).



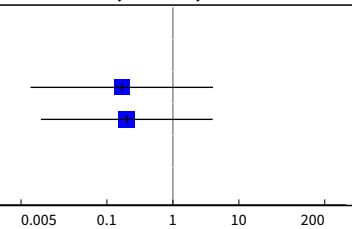
Comparison 2. Cell dose: subgroup analysis

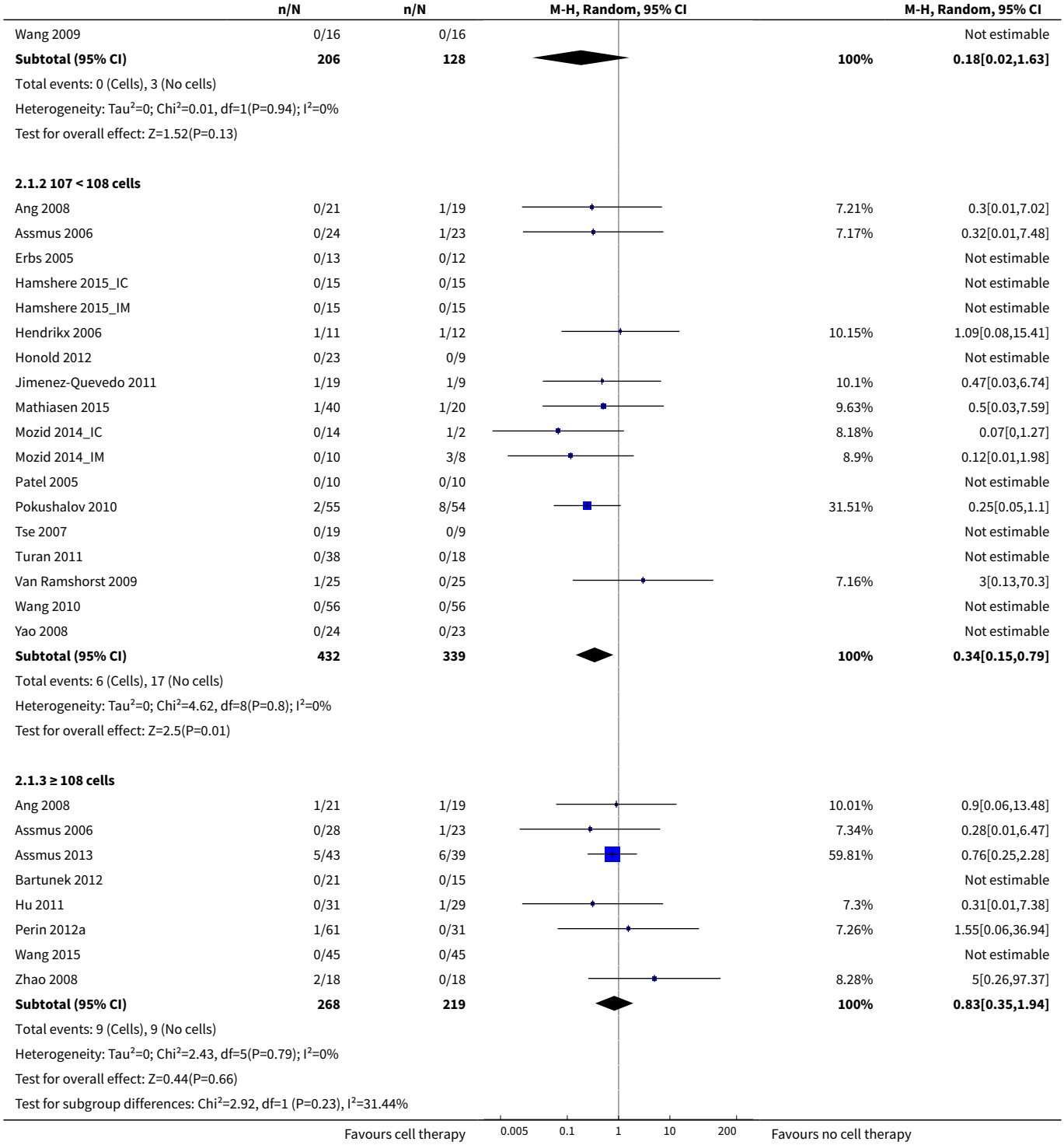
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause): short term follow-up (< 12 months)	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 < 10^7 cells	6	334	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.02, 1.63]
1.2 10^7 < 10^8 cells	18	771	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.15, 0.79]
1.3 ≥ 10^8 cells	8	487	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.35, 1.94]
2 Mortality (all-cause): long term follow-up (≥ 12 months)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 < 10^7 cells	4	297	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.10, 1.09]
2.2 10^7 < 10^8 cells	7	330	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.17, 0.53]
2.3 ≥ 10^8 cells	5	236	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.30, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 NYHA classification: short term follow-up (< 12 months)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 < 10^7 cells	4	149	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.94, 0.36]
3.2 10^7 < 10^8 cells	8	309	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.22, -0.08]
3.3 ≥ 10^8 cells	4	241	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.72, -0.11]
4 CCS class: short term follow-up (< 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 < 10^7 cells	4	288	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.92, 0.19]
4.2 10^7 < 10^8 cells	5	160	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.40, 0.32]
5 Exercise capacity: short term follow-up (< 12 months)	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 10^7 < 10^8 cells	7	357	Std. Mean Difference (IV, Random, 95% CI)	0.56 [-0.03, 1.14]
5.2 ≥ 10^8 cells	3	161	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.10, 0.77]
6 LVEF (%) measured by MRI: short term follow-up (< 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 10^7 < 10^8 cells	7	199	Mean Difference (IV, Random, 95% CI)	5.23 [3.91, 6.54]
6.2 ≥ 10^8 cells	3	101	Mean Difference (IV, Random, 95% CI)	2.37 [-0.92, 5.66]

Analysis 2.1. Comparison 2 Cell dose: subgroup analysis, Outcome 1 Mortality (all-cause): short term follow-up (< 12 months).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 < 107 cells					
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		46.94%	0.17[0.01,4.06]
Nasseri 2012	0/30	2/30		53.06%	0.2[0.01,4]
Perin 2011	0/20	0/10			Not estimable
Perin 2012b	0/10	0/10			Not estimable



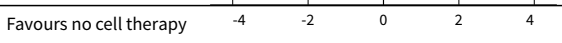


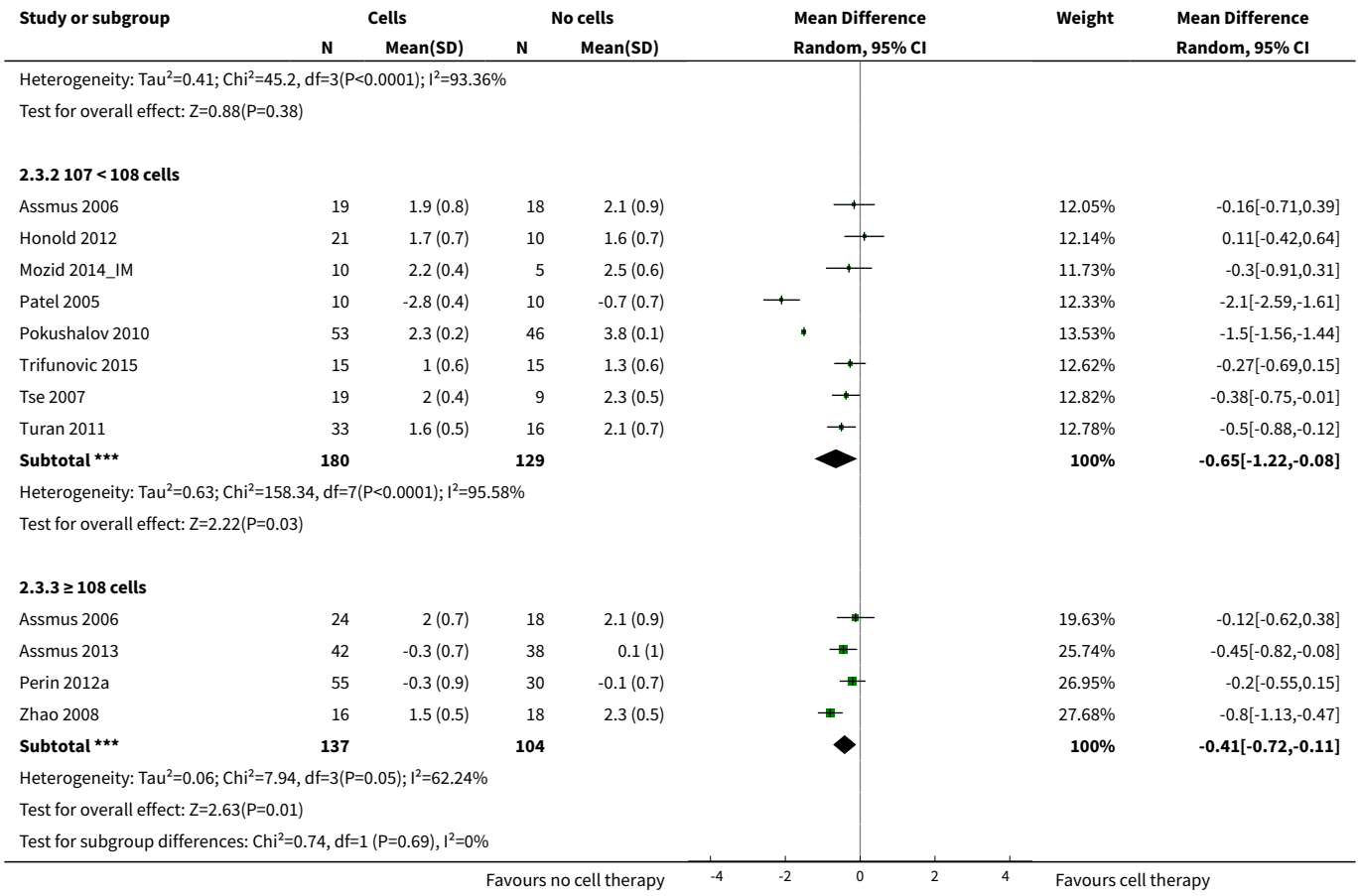
Analysis 2.2. Comparison 2 Cell dose: subgroup analysis, Outcome 2 Mortality (all-cause): long term follow-up (≥ 12 months).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 < 107 cells					
Chen 2006	2/22	4/23		55.11%	0.52[0.11,2.57]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	3/56		16.13%	0.07[0,1.37]
Nasseri 2012	1/30	3/30		28.76%	0.33[0.04,3.03]
Subtotal (95% CI)	**182**	**115**		**100%**	**0.33[0.1,1.09]**
Total events: 3 (Cells), 10 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=1.39, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=1.82(P=0.07)					
2.2.2 107 < 108 cells					
Erbs 2005	0/13	1/12		3.52%	0.31[0.01,6.94]
Honold 2012	0/23	1/9		3.51%	0.14[0.01,3.13]
Patel 2005	3/25	10/25		25.11%	0.3[0.09,0.96]
Pokushalov 2010	6/55	21/54		49.95%	0.28[0.12,0.64]
Trifunovic 2015	2/15	4/15		14.38%	0.5[0.11,2.33]
Tse 2007	0/19	1/9		3.52%	0.17[0.01,3.73]
Turan 2011	0/38	0/18			Not estimable
Subtotal (95% CI)	**188**	**142**		**100%**	**0.3[0.17,0.53]**
Total events: 11 (Cells), 38 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=0.82, df=5(P=0.98); I^2=0%					
Test for overall effect: Z=4.07(P<0.0001)					
2.2.3 ≥ 108 cells					
Assmus 2013	6/43	8/39		54.28%	0.68[0.26,1.79]
Bartunek 2012	1/21	2/15		9.51%	0.36[0.04,3.59]
Hu 2011	1/31	2/29		9.19%	0.47[0.04,4.89]
Patel 2015	5/22	2/6		27.01%	0.68[0.17,2.68]
Patila 2014	0/13	0/17			Not estimable
Subtotal (95% CI)	**130**	**106**		**100%**	**0.62[0.3,1.26]**
Total events: 13 (Cells), 14 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=3(P=0.95); I^2=0%					
Test for overall effect: Z=1.32(P=0.19)					
Test for subgroup differences: Chi^2=2.5, df=1 (P=0.29), I^2=19.91%					

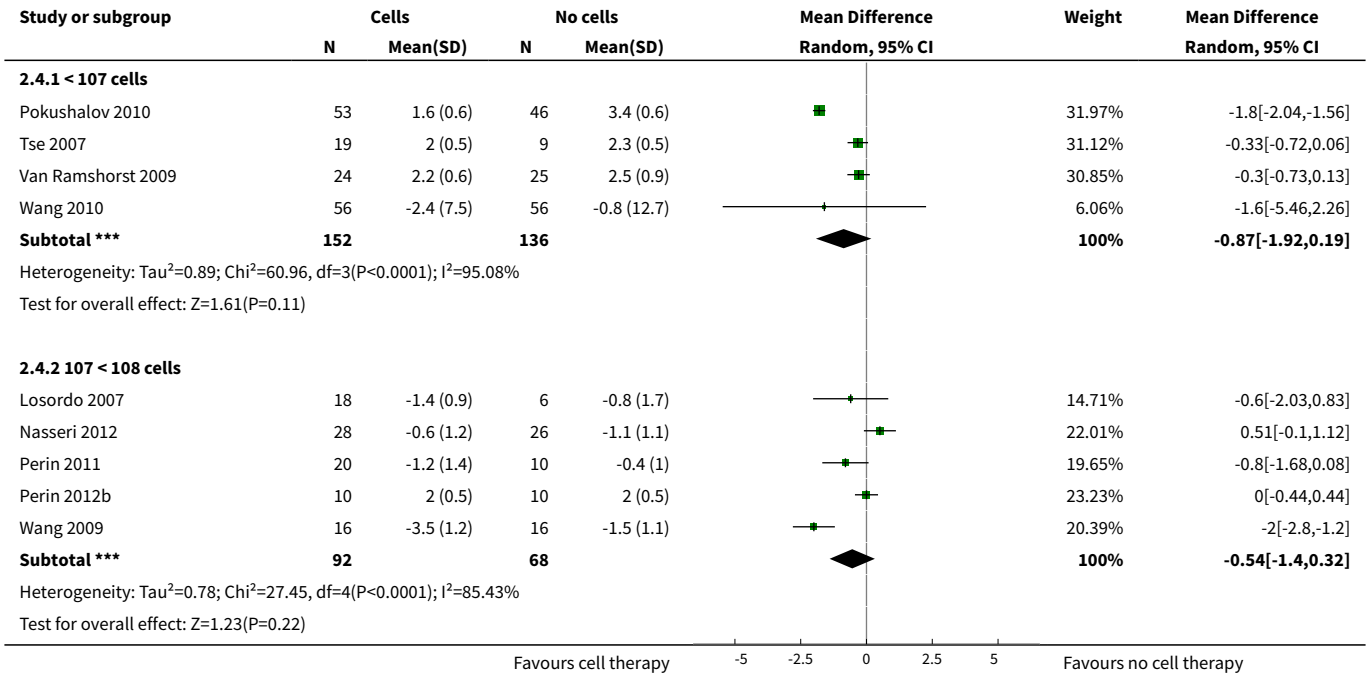
Analysis 2.3. Comparison 2 Cell dose: subgroup analysis, Outcome 3 NYHA classification: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.3.1 < 107 cells							
Chen 2006	22	1.3 (0.7)	23	2.5 (0.6)		24.77%	-1.2[-1.58,-0.82]
Nasseri 2012	28	-0.5 (1)	26	-1 (0.7)		23.89%	0.48[0.02,0.94]
Perin 2011	20	1.8 (0.2)	10	2.4 (0.3)		26.36%	-0.6[-0.81,-0.39]
Perin 2012b	10	2.3 (0.5)	10	2.1 (0.3)		24.99%	0.2[-0.16,0.56]
Subtotal ***	**80**		**69**			**100%**	**-0.29[-0.94,0.36]**

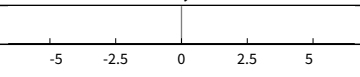




Analysis 2.4. Comparison 2 Cell dose: subgroup analysis, Outcome 4 CCS class: short term follow-up (< 12 months).

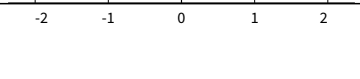


Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=0.22, df=1 (P=0.64), I²=0%							



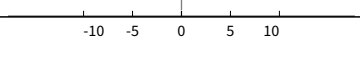
Analysis 2.5. Comparison 2 Cell dose: subgroup analysis, Outcome 5 Exercise capacity: short term follow-up (< 12 months).

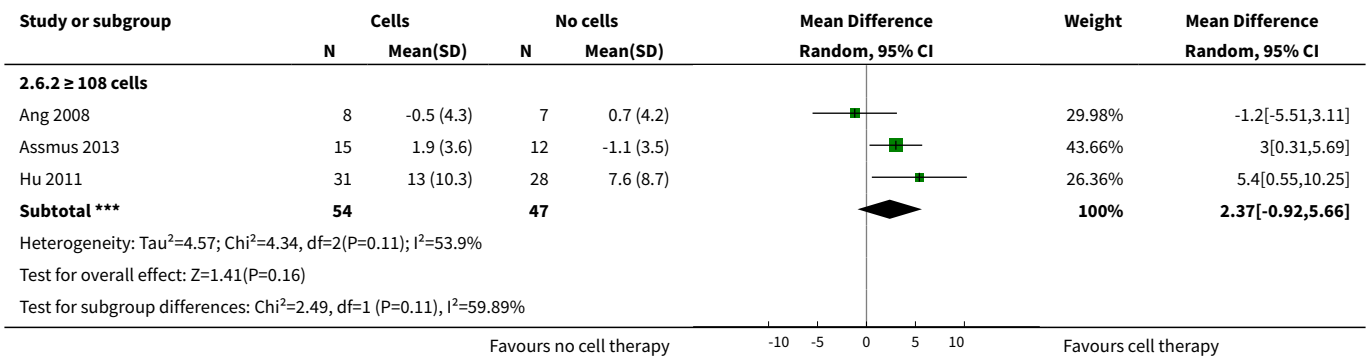
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.5.1 107 < 108 cells							
Erbs 2005	12	23.1 (5.8)	10	22.4 (4.7)		13.19%	0.13[-0.71,0.97]
Honold 2012	12	376 (198)	5	501 (175)		11.3%	-0.62[-1.69,0.45]
Pokushalov 2010	53	325 (81)	46	211 (48)		16.25%	1.67[1.21,2.13]
Trifunovic 2015	15	435 (90)	15	315 (80)		13.47%	1.37[0.56,2.18]
Tse 2007	19	6.1 (0.5)	9	5.7 (0.7)		13.47%	0.54[-0.27,1.34]
Van Ramshorst 2009	24	116 (32)	25	103 (41)		15.48%	0.35[-0.22,0.91]
Wang 2010	56	8.9 (9.7)	56	6.8 (15.7)		16.84%	0.16[-0.21,0.53]
Subtotal ***	**191**		**166**			**100%**	**0.56[-0.03,1.14]**
Heterogeneity: Tau²=0.5; Chi²=36.6, df=6(P<0.0001); I²=83.61%							
Test for overall effect: Z=1.85(P=0.06)							
2.5.2 ≥ 108 cells							
Bartunek 2012	21	456 (142.8)	3	404 (97.5)		7.59%	0.36[-0.85,1.58]
Hu 2011	30	491 (47)	27	451 (66)		38.92%	0.69[0.16,1.23]
Perin 2012a	51	184 (407)	29	80 (415)		53.49%	0.25[-0.21,0.71]
Subtotal ***	**102**		**59**			**100%**	**0.43[0.1,0.77]**
Heterogeneity: Tau²=0; Chi²=1.53, df=2(P=0.46); I²=0%							
Test for overall effect: Z=2.53(P=0.01)							
Test for subgroup differences: Chi²=0.13, df=1 (P=0.72), I²=0%							



Analysis 2.6. Comparison 2 Cell dose: subgroup analysis, Outcome 6 LVEF (%) measured by MRI: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.6.1 107 < 108 cells							
Ang 2008	10	4.3 (4.3)	7	0.7 (4.2)		10.28%	3.6[-0.5,7.7]
Erbs 2005	12	6.7 (6.2)	11	0 (4.6)		8.76%	6.7[2.26,11.14]
Hendrikx 2006	10	6.1 (8.6)	10	3.6 (9.1)		2.87%	2.5[-5.26,10.26]
Honold 2012	9	32.8 (13.1)	4	25.3 (0.5)		2.35%	7.5[-1.07,16.07]
Mathiasen 2015	40	5 (3.8)	20	-1.3 (3.7)		42.98%	6.3[4.3,8.3]
Tse 2007	18	3.7 (5.1)	8	-0.4 (7.5)		5.3%	4.1[-1.61,9.81]
Van Ramshorst 2009	22	3 (5)	18	-1 (3)		27.46%	4[1.49,6.51]
Subtotal ***	**121**		**78**			**100%**	**5.23[3.91,6.54]**
Heterogeneity: Tau²=0; Chi²=3.94, df=6(P=0.68); I²=0%							
Test for overall effect: Z=7.8(P<0.0001)							





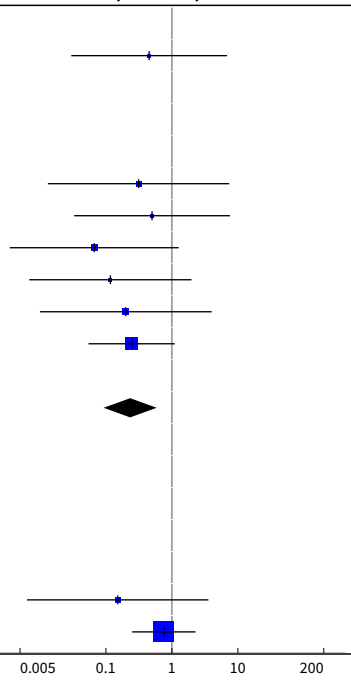
Comparison 3. Baseline cardiac function: subgroup analysis

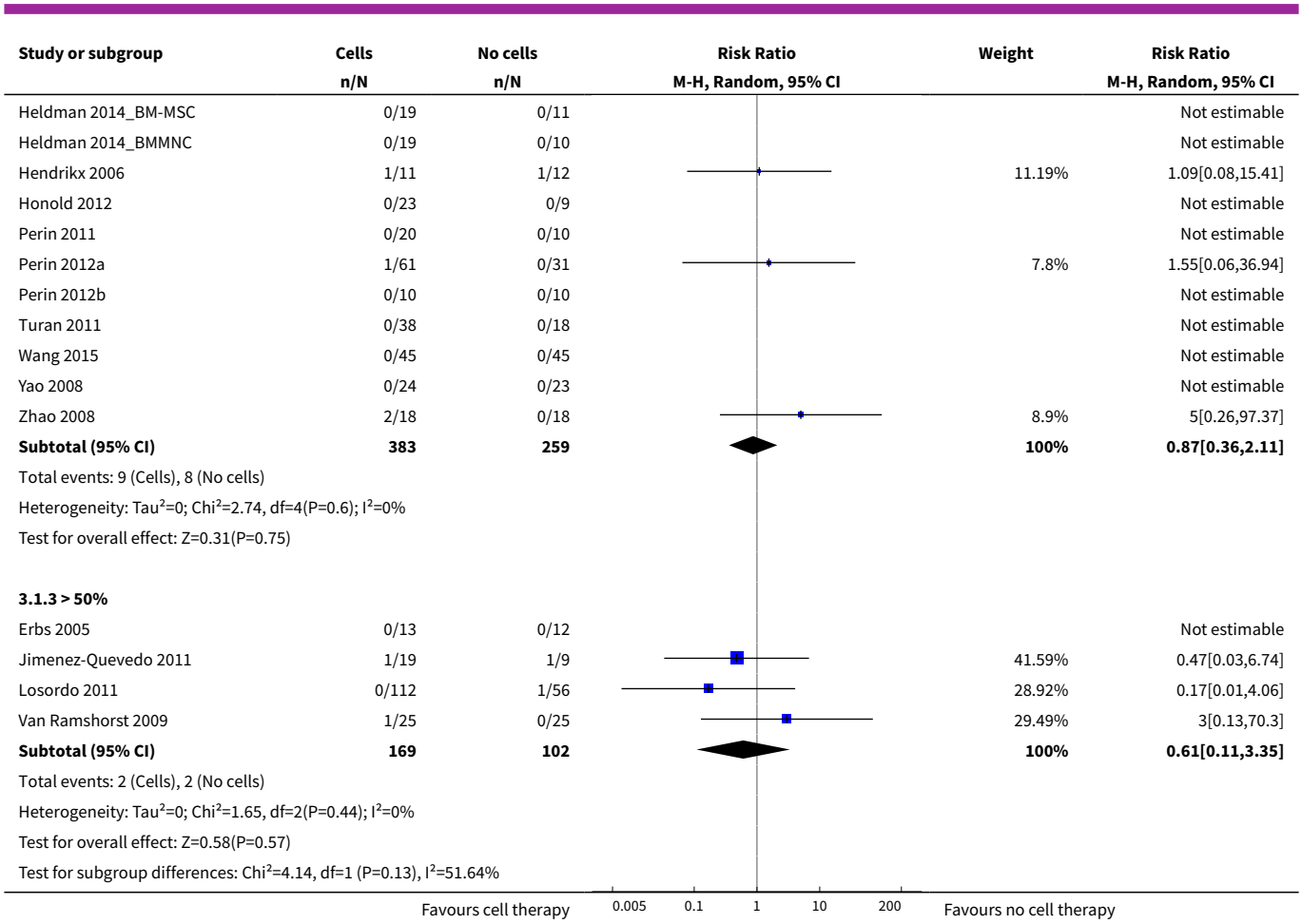
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause): short term follow-up (< 12 months)	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 < 30%	11	508	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.09, 0.59]
1.2 30 - 50%	13	642	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.36, 2.11]
1.3 > 50%	4	271	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.11, 3.35]
2 Mortality (all-cause): long term follow-up (≥ 12 months)	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 < 30%	9	426	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.20, 0.64]
2.2 30 - 50%	7	289	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.21]
3 NYHA classification: short term follow-up (< 12 months)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 < 30%	6	273	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.22, 0.43]
3.2 30 - 50%	9	420	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.54, -0.10]
4 NYHA classification: long term follow-up (≥ 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 < 30%	5	202	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.28, -0.04]
4.2 30 - 50%	4	144	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.72, -0.25]
5 CCS class: short term follow-up (< 12 months)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 < 30%	4	213	Mean Difference (IV, Random, 95% CI)	-0.25 [-1.47, 0.97]
5.2 30 - 50%	4	150	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.31, 0.09]
6 Exercise capacity: short term follow-up (< 12 months)	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 < 30%	4	225	Std. Mean Difference (IV, Random, 95% CI)	0.96 [0.37, 1.56]
6.2 30 - 50%	3	127	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.57, 1.33]
7 LVEF (%) measured by MRI: short term follow-up (< 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 < 30%	6	290	Mean Difference (IV, Random, 95% CI)	1.54 [-1.96, 5.03]
7.2 30 - 50%	3	60	Mean Difference (IV, Random, 95% CI)	3.31 [0.88, 5.75]

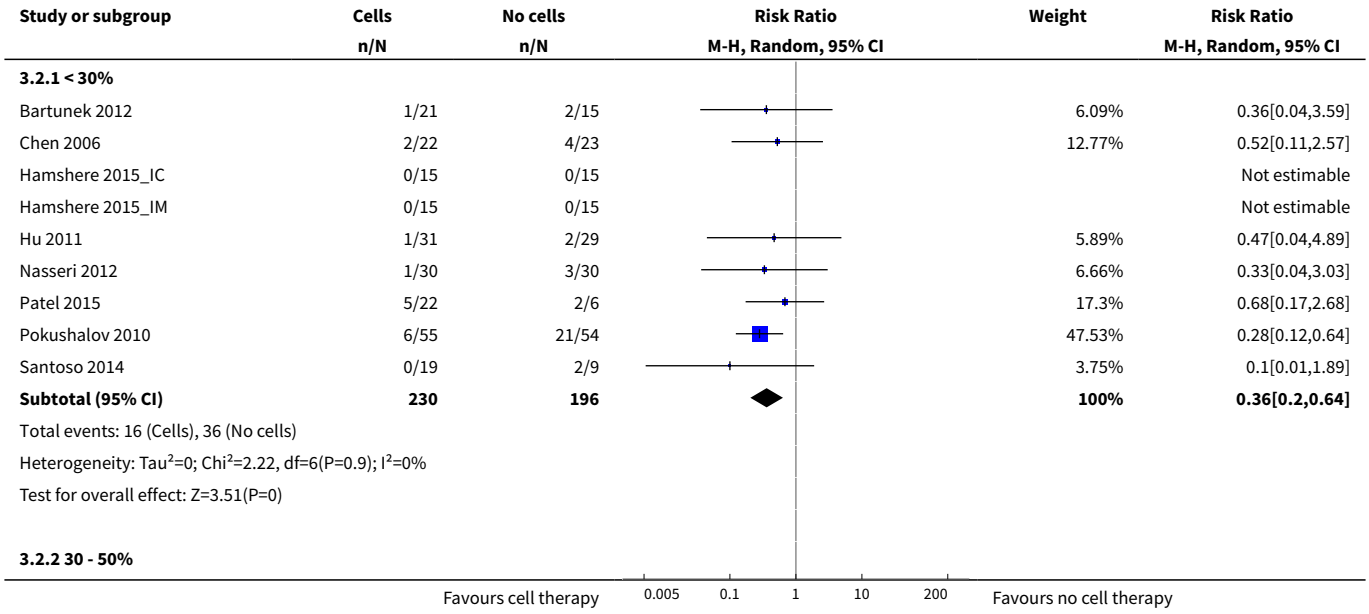
Analysis 3.1. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 1 Mortality (all-cause): short term follow-up (< 12 months).

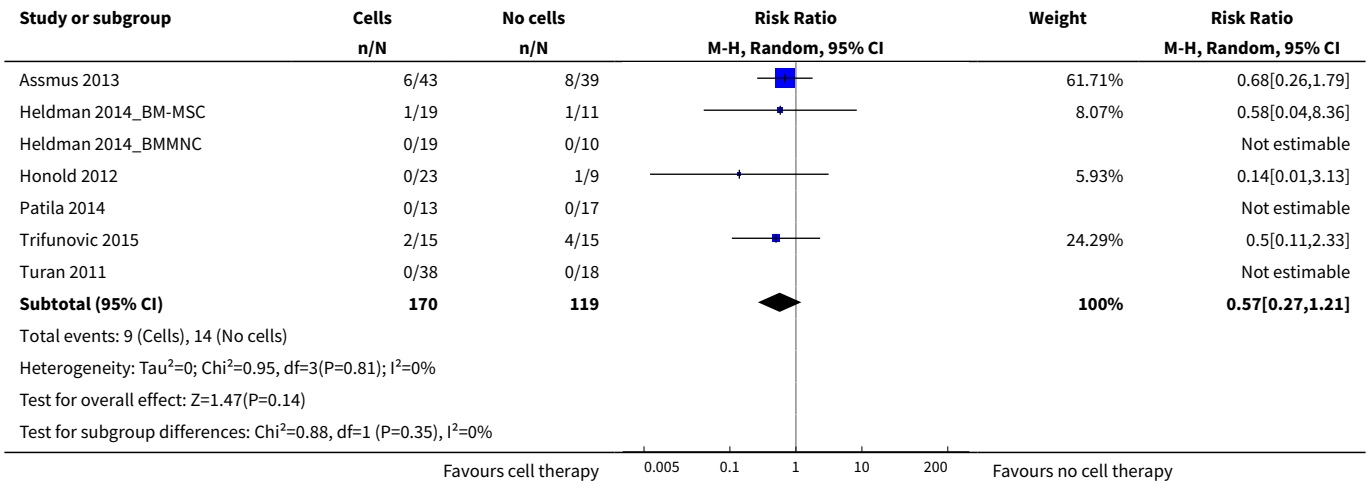
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 < 30%					
Ang 2008	1/42	1/19		11.62%	0.45[0.03,6.86]
Bartunek 2012	0/21	0/15			Not estimable
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Hu 2011	0/31	1/29		8.59%	0.31[0.01,7.38]
Mathiasen 2015	1/40	1/20		11.61%	0.5[0.03,7.59]
Mozid 2014_IC	0/14	1/2		9.86%	0.07[0,1.27]
Mozid 2014_IM	0/10	3/8		10.73%	0.12[0.01,1.98]
Nasseri 2012	0/30	2/30		9.57%	0.2[0.01,4]
Pokushalov 2010	2/55	8/54		38%	0.25[0.05,1.1]
Santoso 2014	0/19	0/9			Not estimable
Subtotal (95% CI)	**292**	**216**		**100%**	**0.23[0.09,0.59]**
Total events: 4 (Cells), 17 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=1.5, df=6(P=0.96); I^2=0%					
Test for overall effect: Z=3.08(P=0)					
3.1.2 30 - 50%					
Assmus 2006	0/52	1/23		7.84%	0.15[0.01,3.57]
Assmus 2013	5/43	6/39		64.28%	0.76[0.25,2.28]



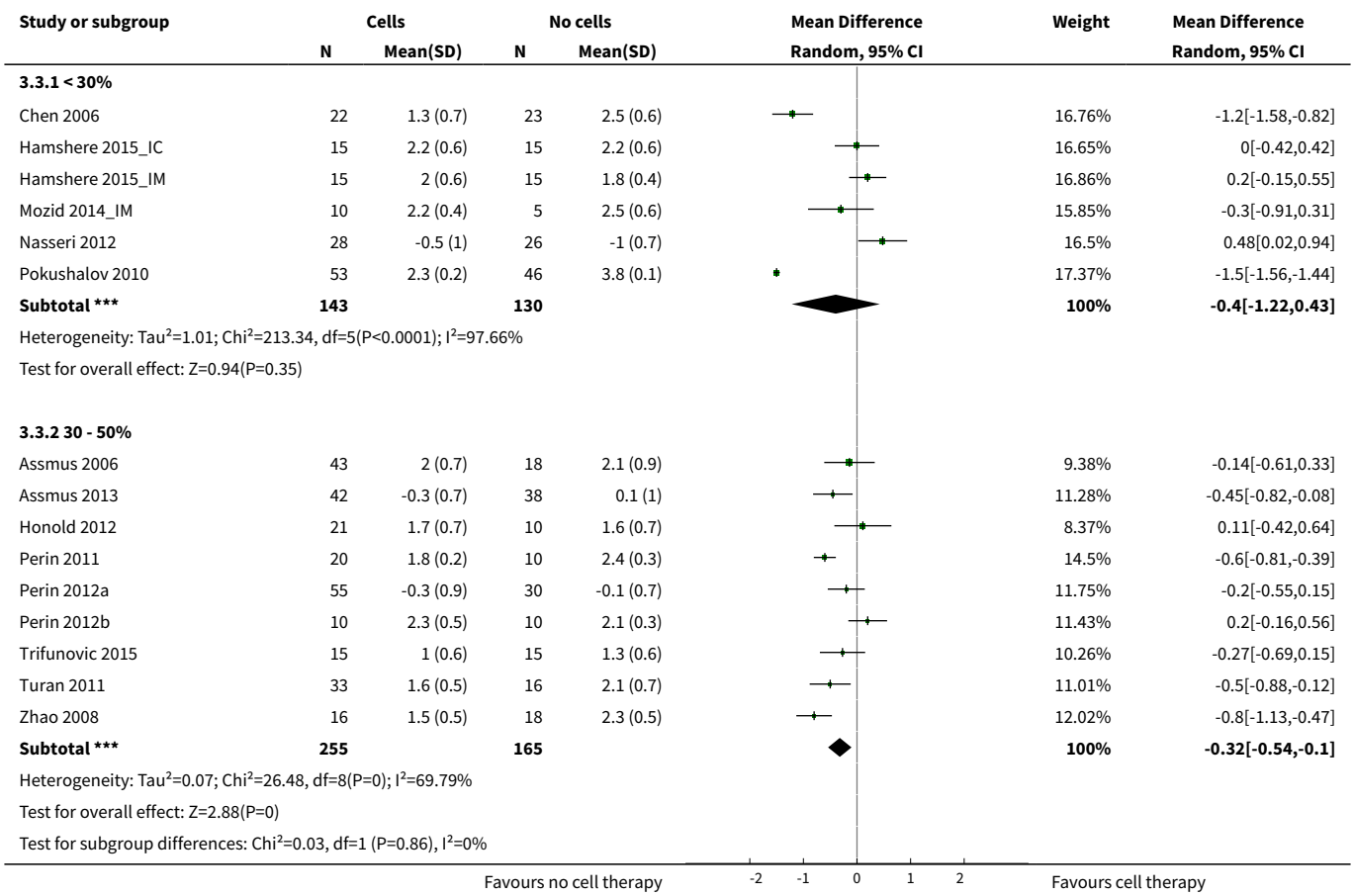


Analysis 3.2. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 2 Mortality (all-cause): long term follow-up (≥ 12 months).



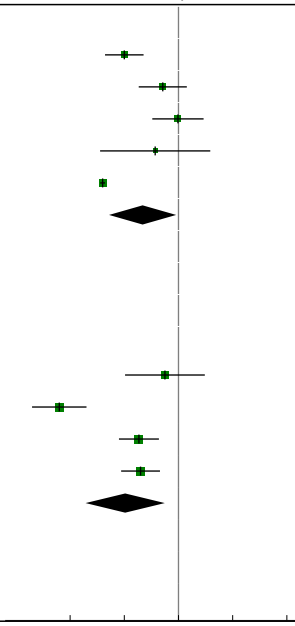


Analysis 3.3. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 3 NYHA classification: short term follow-up (< 12 months).



Analysis 3.4. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 4 NYHA classification: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.4.1 < 30%							
Chen 2006	20	1.4 (0.7)	19	2.4 (0.4)		21.51%	-1[-1.36,-0.64]
Hamshere 2015_IC	15	2.1 (0.6)	15	2.4 (0.6)		20.7%	-0.29[-0.73,0.15]
Hamshere 2015_IM	15	2.1 (0.7)	15	2.1 (0.6)		20.4%	-0.01[-0.48,0.46]
Patel 2015	17	1.8 (0.8)	4	2.3 (1)		14.27%	-0.43[-1.45,0.59]
Pokushalov 2010	49	2.5 (0.1)	33	3.9 (0.1)		23.13%	-1.4[-1.44,-1.36]
Subtotal ***	**116**		**86**			**100%**	**-0.66[-1.28,-0.04]**
Heterogeneity: Tau^2=0.43; Chi^2=63.7, df=4(P<0.0001); I^2=93.72%							
Test for overall effect: Z=2.09(P=0.04)							
3.4.2 30 - 50%							
Honold 2012	20	1.5 (0.8)	6	1.7 (0.8)		22.02%	-0.25[-0.99,0.49]
Patila 2014	20	-1 (0.8)	19	1.2 (0.8)		25%	-2.2[-2.7,-1.7]
Trifunovic 2015	15	1.1 (0.3)	15	1.8 (0.7)		26.44%	-0.73[-1.1,-0.36]
Turan 2011	33	1.6 (0.6)	16	2.3 (0.6)		26.54%	-0.7[-1.06,-0.34]
Subtotal ***	**88**		**56**			**100%**	**-0.98[-1.72,-0.25]**
Heterogeneity: Tau^2=0.49; Chi^2=30.5, df=3(P<0.0001); I^2=90.17%							
Test for overall effect: Z=2.64(P=0.01)							
Test for subgroup differences: Chi^2=0.43, df=1 (P=0.51), I^2=0%							



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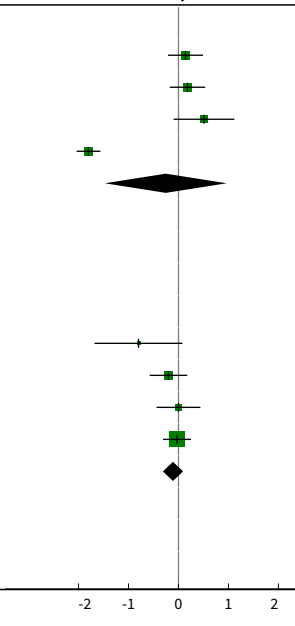
Analysis 3.5. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 5 CCS class: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.5.1 < 30%							
Hamshere 2015_IC	15	1.4 (0.5)	15	1.3 (0.5)		25.18%	0.14[-0.21,0.49]
Hamshere 2015_IM	15	1.3 (0.5)	15	1.1 (0.5)		25.17%	0.18[-0.17,0.53]
Nasseri 2012	28	-0.6 (1.2)	26	-1.1 (1.1)		24.17%	0.51[-0.1,1.12]
Pokushalov 2010	53	1.6 (0.6)	46	3.4 (0.6)		25.47%	-1.8[-2.04,-1.56]
Subtotal ***	**111**		**102**			**100%**	**-0.25[-1.47,0.97]**
Heterogeneity: Tau^2=1.51; Chi^2=143.01, df=3(P<0.0001); I^2=97.9%							
Test for overall effect: Z=0.41(P=0.68)							
3.5.2 30 - 50%							
Perin 2011	20	-1.2 (1.4)	10	-0.4 (1)		5.21%	-0.8[-1.68,0.08]
Perin 2012a	44	-0.5 (0.8)	22	-0.3 (0.7)		27.2%	-0.2[-0.58,0.18]
Perin 2012b	10	2 (0.5)	10	2 (0.5)		20.32%	0[-0.44,0.44]
Zhao 2008	16	1.2 (0.4)	18	1.2 (0.4)		47.27%	-0.03[-0.31,0.25]
Subtotal ***	**90**		**60**			**100%**	**-0.11[-0.31,0.09]**
Heterogeneity: Tau^2=0; Chi^2=3.14, df=3(P=0.37); I^2=4.52%							
Test for overall effect: Z=1.07(P=0.28)							
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%							



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Analysis 3.6. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 6 Exercise capacity: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.6.1 < 30%							
Bartunek 2012	21	456 (142.8)	3	404 (97.5)		14.56%	0.36[-0.85,1.58]
Chen 2006	22	7 (3)	23	5 (2)		26.7%	0.77[0.17,1.38]
Hu 2011	30	491 (47)	27	451 (66)		28.45%	0.69[0.16,1.23]
Pokushalov 2010	53	325 (81)	46	211 (48)		30.29%	1.67[1.21,2.13]
Subtotal ***	**126**		**99**			**100%**	**0.96[0.37,1.56]**
Heterogeneity: Tau^2=0.25; Chi^2=10.6, df=3(P=0.01); I^2=71.69%							
Test for overall effect: Z=3.17(P=0)							
3.6.2 30 - 50%							
Honold 2012	12	376 (198)	5	501 (175)		27.86%	-0.62[-1.69,0.45]
Perin 2012a	51	184 (407)	29	80 (415)		39.24%	0.25[-0.21,0.71]
Trifunovic 2015	15	435 (90)	15	315 (80)		32.9%	1.37[0.56,2.18]
Subtotal ***	**78**		**49**			**100%**	**0.38[-0.57,1.33]**
Heterogeneity: Tau^2=0.54; Chi^2=9.44, df=2(P=0.01); I^2=78.82%							
Test for overall effect: Z=0.78(P=0.43)							
Test for subgroup differences: Chi^2=1.05, df=1 (P=0.31), I^2=4.72%							

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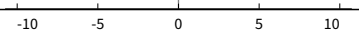
Analysis 3.7. Comparison 3 Baseline cardiac function: subgroup analysis, Outcome 7 LVEF (%) measured by MRI: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.7.1 < 30%							
Ang 2008	18	2.1 (4.8)	7	0.7 (4.2)		17%	1.4[-2.42,5.22]
Hu 2011	31	13 (10.3)	28	7.6 (8.7)		15.12%	5.4[0.55,10.25]
Mathiasen 2015	40	5 (3.8)	20	-1.3 (3.7)		19.93%	6.3[4.3,8.3]
Nasseri 2012	26	31 (7)	22	33 (8)		16.14%	-2[-6.29,2.29]
Santoso 2014	19	1.9 (5.5)	9	2.6 (7.2)		14.29%	-0.7[-6.01,4.61]
Wang 2014	35	33 (7)	35	35 (8)		17.53%	-2[-5.52,1.52]
Subtotal ***	**169**		**121**			**100%**	**1.54[-1.96,5.03]**
Heterogeneity: Tau^2=14.93; Chi^2=26.85, df=5(P<0.0001); I^2=81.38%							
Test for overall effect: Z=0.86(P=0.39)							
3.7.2 30 - 50%							
Assmus 2013	15	1.9 (3.6)	12	-1.1 (3.5)		82.05%	3[0.31,5.69]
Hendrikx 2006	10	6.1 (8.6)	10	3.6 (9.1)		9.86%	2.5[-5.26,10.26]
Honold 2012	9	32.8 (13.1)	4	25.3 (0.5)		8.08%	7.5[-1.07,16.07]
Subtotal ***	**34**		**26**			**100%**	**3.31[0.88,5.75]**
Heterogeneity: Tau^2=0; Chi^2=1.01, df=2(P=0.6); I^2=0%							
Test for overall effect: Z=2.67(P=0.01)							
Test for subgroup differences: Chi^2=0.67, df=1 (P=0.41), I^2=0%							



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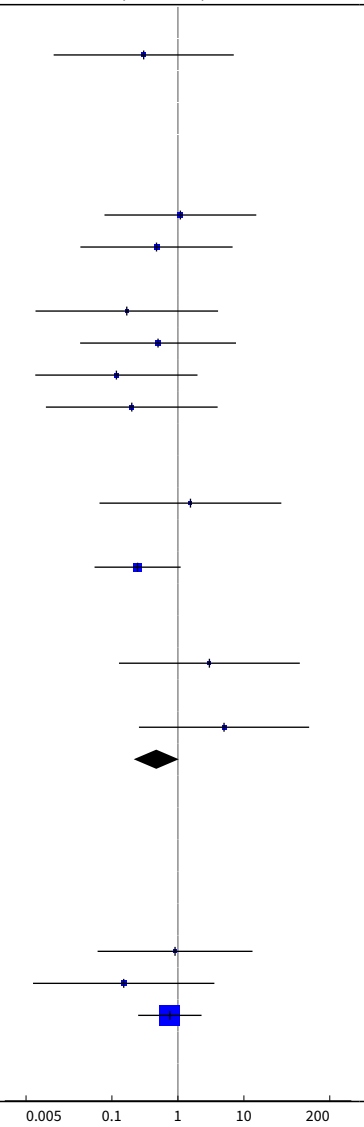
Comparison 4. Route of cell administration: subgroup analysis

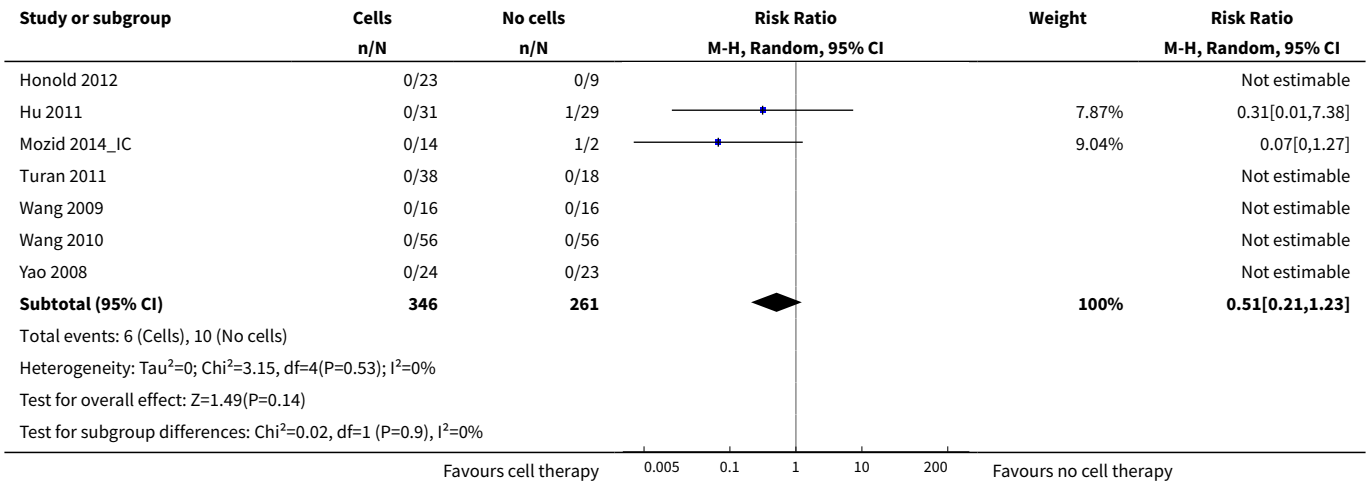
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause): short term follow-up (< 12 months)	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Intramyocardial	22	1049	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.21, 1.03]
1.2 Intracoronary	12	607	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.21, 1.23]
2 Mortality (all-cause): long term follow-up (≥ 12 months)	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Intramyocardial	13	652	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.17, 0.50]
2.2 Intracoronary	8	358	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.30, 1.09]
3 NYHA classification: short term follow-up (< 12 months)	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Intramyocardial	11	445	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.99, 0.03]
3.2 Intracoronary	6	296	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.76, 0.00]
4 NYHA classification: long term follow-up (≥ 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Intramyocardial	4	181	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.76, -0.41]
4.2 Intracoronary	5	165	Mean Difference (IV, Random, 95% CI)	-0.61 [-0.92, -0.30]
5 CCS class: short term follow-up (< 12 months)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Intramyocardial	10	434	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.87, 0.22]
5.2 Intracoronary	3	174	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.87, 0.86]
6 Exercise capacity: short term follow-up (< 12 months)	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Intramyocardial	6	310	Std. Mean Difference (IV, Random, 95% CI)	0.78 [0.19, 1.36]
6.2 Intracoronary	5	253	Std. Mean Difference (IV, Random, 95% CI)	0.33 [-0.06, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 LVEF (%) measured by MRI: short term follow-up (< 12 months)	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Intramyocardial	8	309	Mean Difference (IV, Random, 95% CI)	2.18 [-0.41, 4.77]
7.2 Intracoronary	5	137	Mean Difference (IV, Random, 95% CI)	3.72 [0.86, 6.57]

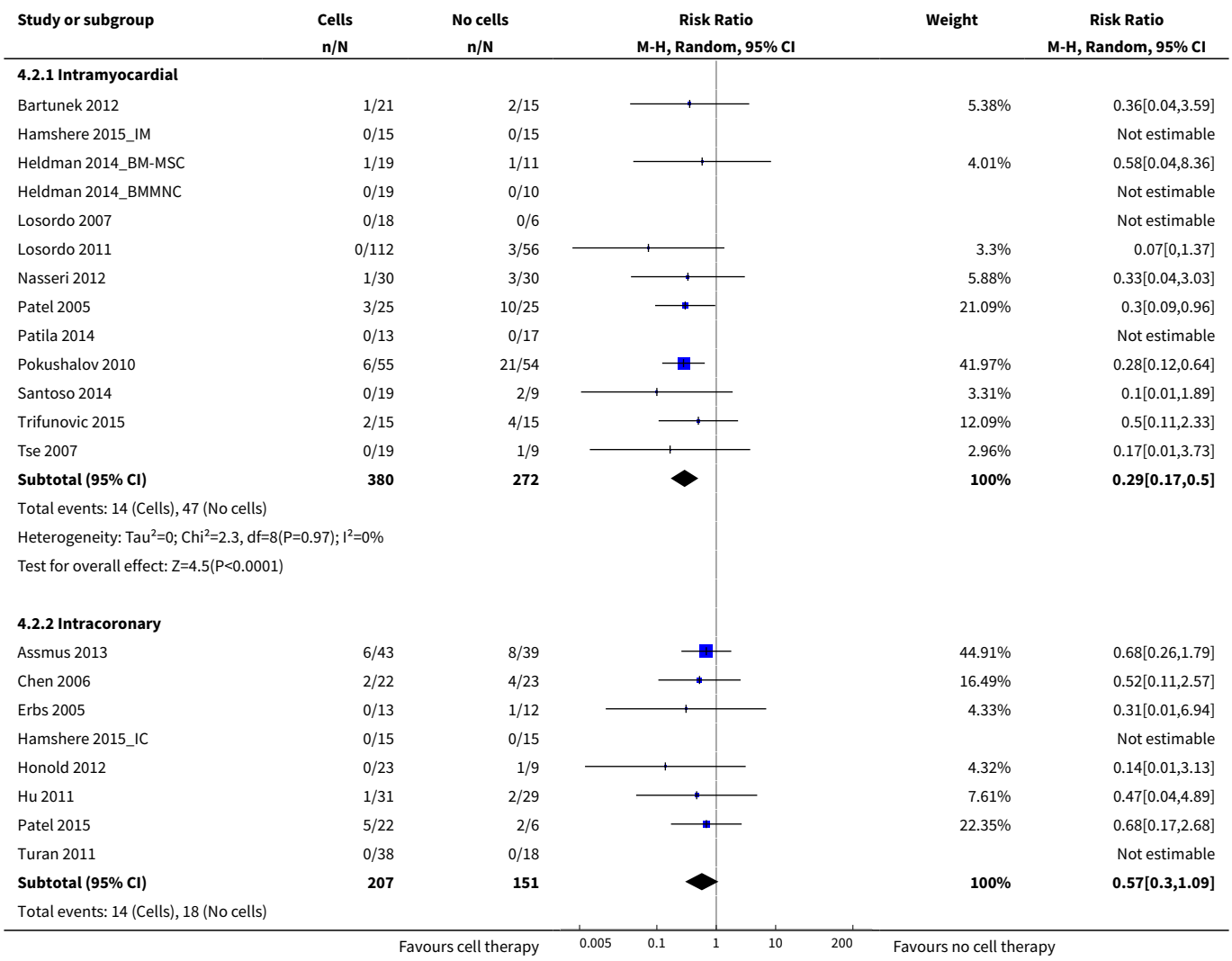
Analysis 4.1. Comparison 4 Route of cell administration: subgroup analysis, Outcome 1 Mortality (all-cause): short term follow-up (< 12 months).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Intramyocardial					
Ang 2008	0/21	1/19		6.28%	0.3[0.01,7.02]
Bartunek 2012	0/21	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hendrikx 2006	1/11	1/12		8.85%	1.09[0.08,15.41]
Jimenez-Quevedo 2011	1/19	1/9		8.8%	0.47[0.03,6.74]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		6.12%	0.17[0.01,4.06]
Mathiasen 2015	1/40	1/20		8.39%	0.5[0.03,7.59]
Mozid 2014_IM	0/10	3/8		7.75%	0.12[0.01,1.98]
Nasseri 2012	0/30	2/30		6.92%	0.2[0.01,4]
Patel 2005	0/10	0/10			Not estimable
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		6.17%	1.55[0.06,36.94]
Perin 2012b	0/10	0/10			Not estimable
Pokushalov 2010	2/55	8/54		27.46%	0.25[0.05,1.1]
Santoso 2014	0/19	0/9			Not estimable
Tse 2007	0/19	0/9			Not estimable
Van Ramshorst 2009	1/25	0/25		6.24%	3[0.13,70.3]
Wang 2015	0/45	0/45			Not estimable
Zhao 2008	2/18	0/18		7.04%	5[0.26,97.37]
Subtotal (95% CI)	**617**	**432**		**100%**	**0.47[0.21,1.03]**
Total events: 9 (Cells), 18 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=7.13, df=10(P=0.71); I^2=0%					
Test for overall effect: Z=1.88(P=0.06)					
4.1.2 Intracoronary					
Ang 2008	1/21	1/19		10.78%	0.9[0.06,13.48]
Assmus 2006	0/52	1/23		7.86%	0.15[0.01,3.57]
Assmus 2013	5/43	6/39		64.45%	0.76[0.25,2.28]
Erbs 2005	0/13	0/12			Not estimable
Hamshere 2015_IC	0/15	0/15			Not estimable

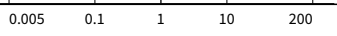




Analysis 4.2. Comparison 4 Route of cell administration: subgroup analysis, Outcome 2 Mortality (all-cause): long term follow-up (≥ 12 months).



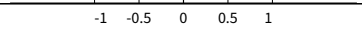
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=1.19, df=5(P=0.95); I²=0%					
Test for overall effect: Z=1.69(P=0.09)					
Test for subgroup differences: Chi²=2.44, df=1 (P=0.12), I²=59.1%					



Favours cell therapy — Favours no cell therapy

Analysis 4.3. Comparison 4 Route of cell administration: subgroup analysis, Outcome 3 NYHA classification: short term follow-up (< 12 months).

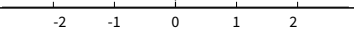
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.3.1 Intramyocardial							
Hamshere 2015_IM	15	2 (0.6)	15	1.8 (0.4)		9.18%	0.2[-0.15,0.55]
Mozid 2014_IM	10	2.2 (0.4)	5	2.5 (0.6)		8.42%	-0.3[-0.91,0.31]
Nasseri 2012	28	-0.5 (1)	26	-1 (0.7)		8.9%	0.48[0.02,0.94]
Patel 2005	10	-2.8 (0.4)	10	-0.7 (0.7)		8.81%	-2.1[-2.59,-1.61]
Perin 2011	20	1.8 (0.2)	10	2.4 (0.3)		9.44%	-0.6[-0.81,-0.39]
Perin 2012a	55	-0.3 (0.9)	30	-0.1 (0.7)		9.19%	-0.2[-0.55,0.15]
Perin 2012b	10	2.3 (0.5)	10	2.1 (0.3)		9.15%	0.2[-0.16,0.56]
Pokushalov 2010	53	2.3 (0.2)	46	3.8 (0.1)		9.58%	-1.5[-1.56,-1.44]
Trifunovic 2015	15	1 (0.6)	15	1.3 (0.6)		9%	-0.27[-0.69,0.15]
Tse 2007	19	2 (0.4)	9	2.3 (0.5)		9.12%	-0.38[-0.75,-0.01]
Zhao 2008	16	1.5 (0.5)	18	2.3 (0.5)		9.22%	-0.8[-1.13,-0.47]
Subtotal ***	**251**		**194**			**100%**	**-0.48[-0.99,0.03]**
Heterogeneity: Tau²=0.7; Chi²=391.54, df=10(P<0.0001); I²=97.45%							
Test for overall effect: Z=1.86(P=0.06)							
4.3.2 Intracoronary							
Assmus 2006	43	2 (0.7)	18	2.1 (0.9)		15.94%	-0.14[-0.61,0.33]
Assmus 2013	42	-0.3 (0.7)	38	0.1 (1)		17.56%	-0.45[-0.82,-0.08]
Chen 2006	22	1.3 (0.7)	23	2.5 (0.6)		17.36%	-1.2[-1.58,-0.82]
Hamshere 2015_IC	15	2.2 (0.6)	15	2.2 (0.6)		16.84%	0[-0.42,0.42]
Honold 2012	21	1.7 (0.7)	10	1.6 (0.7)		14.95%	0.11[-0.42,0.64]
Turan 2011	33	1.6 (0.5)	16	2.1 (0.7)		17.34%	-0.5[-0.88,-0.12]
Subtotal ***	**176**		**120**			**100%**	**-0.38[-0.76,0]**
Heterogeneity: Tau²=0.18; Chi²=25.31, df=5(P=0); I²=80.24%							
Test for overall effect: Z=1.94(P=0.05)							
Test for subgroup differences: Chi²=0.1, df=1 (P=0.75), I²=0%							



Favours no cell therapy — Favours cell therapy

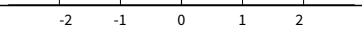
Analysis 4.4. Comparison 4 Route of cell administration: subgroup analysis, Outcome 4 NYHA classification: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.4.1 Intramyocardial							
Hamshere 2015_IM	15	2.1 (0.7)	15	2.1 (0.6)		24.01%	-0.01[-0.48,0.46]
Patila 2014	20	-1 (0.8)	19	1.2 (0.8)		23.66%	-2.2[-2.7,-1.7]



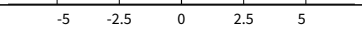
Favours no cell therapy — Favours cell therapy

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pokushalov 2010	49	2.5 (0.1)	33	3.9 (0.1)		27.17%	-1.4[-1.44,-1.36]
Trifunovic 2015	15	1.1 (0.3)	15	1.8 (0.7)		25.17%	-0.73[-1.1,-0.36]
Subtotal ***	**99**		**82**			**100%**	**-1.09[-1.76,-0.41]**
Heterogeneity: Tau²=0.44; Chi²=55.13, df=3(P<0.0001); I²=94.56%							
Test for overall effect: Z=3.15(P=0)							
4.4.2 Intracoronary							
Chen 2006	20	1.4 (0.7)	19	2.4 (0.4)		28.23%	-1[-1.36,-0.64]
Hamshere 2015_IC	15	2.1 (0.6)	15	2.4 (0.6)		23.36%	-0.29[-0.73,0.15]
Honold 2012	20	1.5 (0.8)	6	1.7 (0.8)		12.67%	-0.25[-0.99,0.49]
Patel 2015	17	1.8 (0.8)	4	2.3 (1)		7.67%	-0.43[-1.45,0.59]
Turan 2011	33	1.6 (0.6)	16	2.3 (0.6)		28.07%	-0.7[-1.06,-0.34]
Subtotal ***	**105**		**60**			**100%**	**-0.61[-0.92,-0.3]**
Heterogeneity: Tau²=0.06; Chi²=7.62, df=4(P=0.11); I²=47.48%							
Test for overall effect: Z=3.88(P=0)							
Test for subgroup differences: Chi²=1.57, df=1 (P=0.21), I²=36.33%							



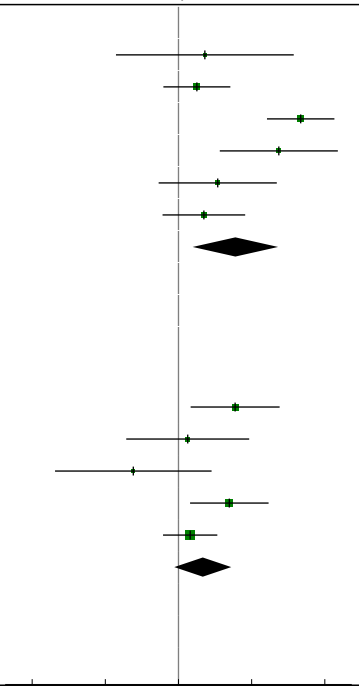
Analysis 4.5. Comparison 4 Route of cell administration: subgroup analysis, Outcome 5 CCS class: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.5.1 Intramyocardial							
Hamshere 2015_IM	15	1.3 (0.5)	15	1.1 (0.5)		10.74%	0.18[-0.17,0.53]
Losordo 2007	18	-1.4 (0.9)	6	-0.8 (1.7)		6.36%	-0.6[-2.03,0.83]
Nasseri 2012	28	-0.6 (1.2)	26	-1.1 (1.1)		9.88%	0.51[-0.1,1.12]
Perin 2011	20	-1.2 (1.4)	10	-0.4 (1)		8.71%	-0.8[-1.68,0.08]
Perin 2012a	44	-0.5 (0.8)	22	-0.3 (0.7)		10.68%	-0.2[-0.58,0.18]
Perin 2012b	10	2 (0.5)	10	2 (0.5)		10.49%	0[-0.44,0.44]
Pokushalov 2010	53	1.6 (0.6)	46	3.4 (0.6)		11.02%	-1.8[-2.04,-1.56]
Tse 2007	19	2 (0.5)	9	2.3 (0.5)		10.65%	-0.33[-0.72,0.06]
Van Ramshorst 2009	24	2.2 (0.6)	25	2.5 (0.9)		10.53%	-0.3[-0.73,0.13]
Zhao 2008	16	1.2 (0.4)	18	1.2 (0.4)		10.93%	-0.03[-0.31,0.25]
Subtotal ***	**247**		**187**			**100%**	**-0.33[-0.87,0.22]**
Heterogeneity: Tau²=0.69; Chi²=160.38, df=9(P<0.0001); I²=94.39%							
Test for overall effect: Z=1.18(P=0.24)							
4.5.2 Intracoronary							
Hamshere 2015_IC	15	1.4 (0.5)	15	1.3 (0.5)		43.66%	0.14[-0.21,0.49]
Wang 2009	16	-3.5 (1.2)	16	-1.5 (1.1)		41.03%	-2[-2.8,-1.2]
Wang 2010	56	-2.4 (7.5)	56	-0.8 (12.7)		15.31%	-1.6[-5.46,2.26]
Subtotal ***	**87**		**87**			**100%**	**-1[-2.87,0.86]**
Heterogeneity: Tau²=2.05; Chi²=23.66, df=2(P<0.0001); I²=91.55%							
Test for overall effect: Z=1.05(P=0.29)							
Test for subgroup differences: Chi²=0.46, df=1 (P=0.5), I²=0%							



Analysis 4.6. Comparison 4 Route of cell administration: subgroup analysis, Outcome 6 Exercise capacity: short term follow-up (< 12 months).

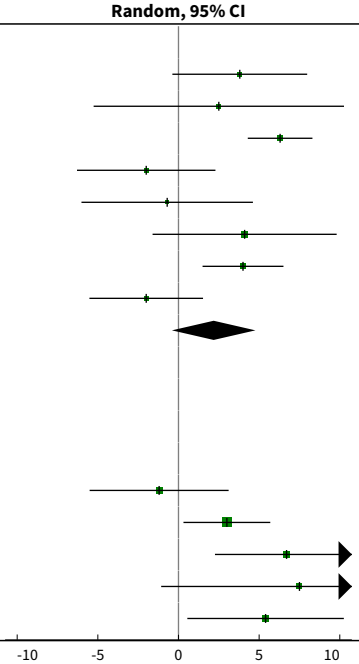
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
4.6.1 Intramyocardial							
Bartunek 2012	21	456 (142.8)	3	404 (97.5)		11.33%	0.36[-0.85,1.58]
Perin 2012a	51	184 (407)	29	80 (415)		19.55%	0.25[-0.21,0.71]
Pokushalov 2010	53	325 (81)	46	211 (48)		19.52%	1.67[1.21,2.13]
Trifunovic 2015	15	435 (90)	15	315 (80)		15.61%	1.37[0.56,2.18]
Tse 2007	19	6.1 (0.5)	9	5.7 (0.7)		15.6%	0.54[-0.27,1.34]
Van Ramshorst 2009	24	116 (32)	25	103 (41)		18.4%	0.35[-0.22,0.91]
Subtotal ***	**183**		**127**			**100%**	**0.78[0.19,1.36]**
Heterogeneity: Tau^2=0.4; Chi^2=24.53, df=5(P=0); I^2=79.61%							
Test for overall effect: Z=2.61(P=0.01)							
4.6.2 Intracoronary							
Chen 2006	22	7 (3)	23	5 (2)		20.98%	0.77[0.17,1.38]
Erbs 2005	12	23.1 (5.8)	10	22.4 (4.7)		14.32%	0.13[-0.71,0.97]
Honold 2012	12	376 (198)	5	501 (175)		10.12%	-0.62[-1.69,0.45]
Hu 2011	30	491 (47)	27	451 (66)		23.66%	0.69[0.16,1.23]
Wang 2010	56	8.9 (9.7)	56	6.8 (15.7)		30.91%	0.16[-0.21,0.53]
Subtotal ***	**132**		**121**			**100%**	**0.33[-0.06,0.72]**
Heterogeneity: Tau^2=0.09; Chi^2=7.87, df=4(P=0.1); I^2=49.18%							
Test for overall effect: Z=1.67(P=0.09)							
Test for subgroup differences: Chi^2=1.55, df=1 (P=0.21), I^2=35.36%							



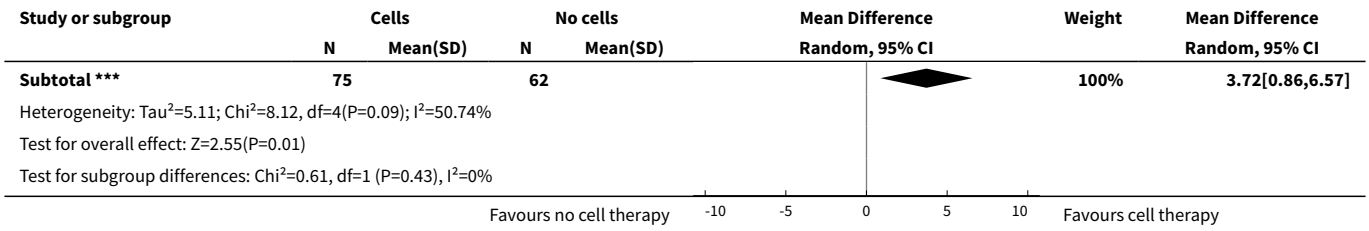
Favours no cell therapy — Favours cell therapy

Analysis 4.7. Comparison 4 Route of cell administration: subgroup analysis, Outcome 7 LVEF (%) measured by MRI: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.7.1 Intramyocardial							
Ang 2008	10	4.5 (4.5)	7	0.7 (4.2)		12.72%	3.8[-0.38,7.98]
Hendrikx 2006	10	6.1 (8.6)	10	3.6 (9.1)		7.03%	2.5[-5.26,10.26]
Mathiasen 2015	40	5 (3.8)	20	-1.3 (3.7)		17.08%	6.3[4.3,8.3]
Nasseri 2012	26	31 (7)	22	33 (8)		12.5%	-2[-6.29,2.29]
Santoso 2014	19	1.9 (5.5)	9	2.6 (7.2)		10.56%	-0.7[-6.01,4.61]
Tse 2007	18	3.7 (5.1)	8	-0.4 (7.5)		9.89%	4.1[-1.61,9.81]
Van Ramshorst 2009	22	3 (5)	18	-1 (3)		16.14%	4[1.49,6.51]
Wang 2014	35	33 (7)	35	35 (8)		14.07%	-2[-5.52,1.52]
Subtotal ***	**180**		**129**			**100%**	**2.18[-0.41,4.77]**
Heterogeneity: Tau^2=9.19; Chi^2=25.81, df=7(P=0); I^2=72.87%							
Test for overall effect: Z=1.65(P=0.1)							
4.7.2 Intracoronary							
Ang 2008	8	-0.5 (4.3)	7	0.7 (4.2)		21.33%	-1.2[-5.51,3.11]
Assmus 2013	15	1.9 (3.6)	12	-1.1 (3.5)		30.33%	3[0.31,5.69]
Erbs 2005	12	6.7 (6.2)	11	0 (4.6)		20.72%	6.7[2.26,11.14]
Honold 2012	9	32.8 (13.1)	4	25.3 (0.5)		8.75%	7.5[-1.07,16.07]
Hu 2011	31	13 (10.3)	28	7.6 (8.7)		18.88%	5.4[0.55,10.25]



Favours no cell therapy — Favours cell therapy

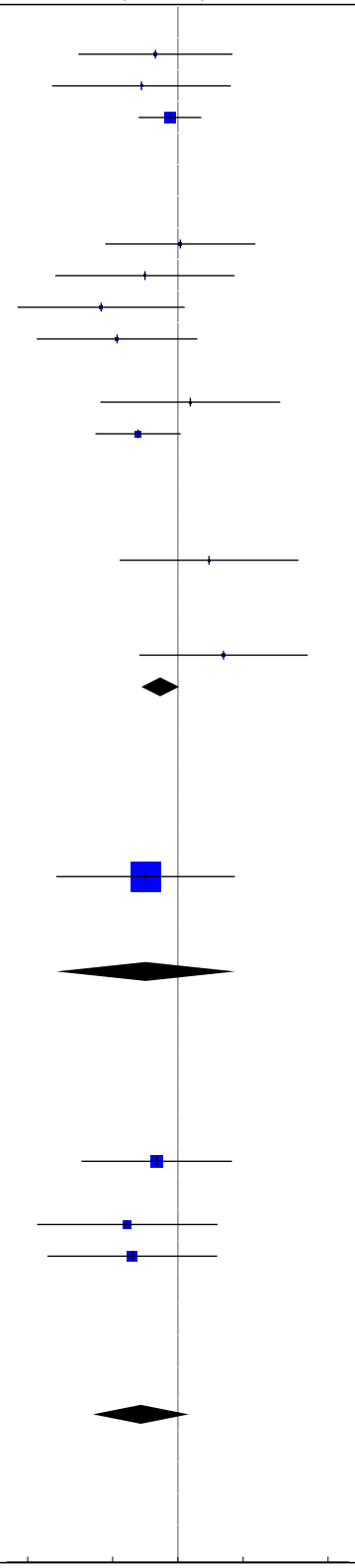


Comparison 5. Cell type: subgroup analysis

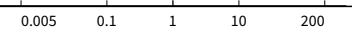
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause): short term follow-up (< 12 months)	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mononuclear cells	20	966	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.04]
1.2 Circulating progenitor cells	3	104	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.48]
1.3 Haematopoietic progenitor cells	8	464	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.05, 1.46]
1.4 Mesenchymal stem cells	3	126	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.03, 7.59]
2 Mortality (all-cause): long term follow-up (≥ 12 months)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mononuclear cells	12	540	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.70]
2.2 Haematopoietic progenitor cells	4	302	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.10, 0.69]
2.3 Mesenchymal stem cells	3	111	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.15, 1.57]
3 NYHA classification: short term follow-up (< 12 months)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Mononuclear cells	12	547	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.86, 0.02]
3.2 Haematopoietic progenitor cells	3	94	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.95, 1.02]
4 CCS class: short term follow-up (< 12 months)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Mononuclear cells	8	366	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.99, 0.21]
4.2 Haematopoietic progenitor cells	5	242	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.55, 0.46]

Analysis 5.1. Comparison 5 Cell type: subgroup analysis, Outcome 1 Mortality (all-cause): short term follow-up (< 12 months).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Mononuclear cells					
Ang 2008	1/42	1/19		5.9%	0.45[0.03,6.86]
Assmus 2006	0/28	1/23		4.38%	0.28[0.01,6.47]
Assmus 2013	5/43	6/39		35.72%	0.76[0.25,2.28]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hendrikx 2006	1/11	1/12		6.22%	1.09[0.08,15.41]
Hu 2011	0/31	1/29		4.36%	0.31[0.01,7.38]
Mozid 2014_IC	0/14	1/2		5.01%	0.07[0,1.27]
Mozid 2014_IM	0/10	3/8		5.45%	0.12[0.01,1.98]
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		4.33%	1.55[0.06,36.94]
Pokushalov 2010	2/55	8/54		19.3%	0.25[0.05,1.1]
Santoso 2014	0/19	0/9			Not estimable
Tse 2007	0/19	0/9			Not estimable
Turan 2011	0/38	0/18			Not estimable
Van Ramshorst 2009	1/25	0/25		4.38%	3[0.13,70.3]
Wang 2015	0/45	0/45			Not estimable
Yao 2008	0/24	0/23			Not estimable
Zhao 2008	2/18	0/18		4.95%	5[0.26,97.37]
Subtotal (95% CI)	**552**	**414**		**100%**	**0.54[0.28,1.04]**
Total events: 13 (Cells), 22 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=8.76, df=10(P=0.55); I^2=0%					
Test for overall effect: Z=1.86(P=0.06)					
5.1.2 Circulating progenitor cells					
Assmus 2006	0/24	1/23		100%	0.32[0.01,7.48]
Erbs 2005	0/13	0/12			Not estimable
Honold 2012	0/23	0/9			Not estimable
Subtotal (95% CI)	**60**	**44**		**100%**	**0.32[0.01,7.48]**
Total events: 0 (Cells), 1 (No cells)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
5.1.3 Haematopoietic progenitor cells					
Jimenez-Quevedo 2011	1/19	1/9		40.29%	0.47[0.03,6.74]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		28.02%	0.17[0.01,4.06]
Nasseri 2012	0/30	2/30		31.68%	0.2[0.01,4]
Patel 2005	0/10	0/10			Not estimable
Perin 2012b	0/10	0/10			Not estimable
Wang 2009	0/16	0/16			Not estimable
Wang 2010	0/56	0/56			Not estimable
Subtotal (95% CI)	**271**	**193**		**100%**	**0.27[0.05,1.46]**
Total events: 1 (Cells), 4 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=2(P=0.86); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					

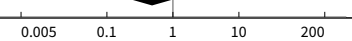


Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.4 Mesenchymal stem cells					
Bartunek 2012	0/21	0/15			Not estimable
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Mathiasen 2015	1/40	1/20		100%	0.5[0.03,7.59]
Subtotal (95% CI)	**80**	**46**		**100%**	**0.5[0.03,7.59]**
Total events: 1 (Cells), 1 (No cells)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.62)					
Test for subgroup differences: Chi^2=0.62, df=1 (P=0.89), I^2=0%					

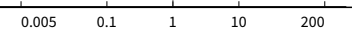


Analysis 5.2. Comparison 5 Cell type: subgroup analysis, Outcome 2 Mortality (all-cause): long term follow-up (≥ 12 months).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Mononuclear cells					
Assmus 2013	6/43	8/39		27.53%	0.68[0.26,1.79]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hu 2011	1/31	2/29		4.66%	0.47[0.04,4.89]
Patel 2015	5/22	2/6		13.7%	0.68[0.17,2.68]
Patila 2014	0/13	0/17			Not estimable
Pokushalov 2010	6/55	21/54		37.64%	0.28[0.12,0.64]
Santoso 2014	0/19	2/9		2.97%	0.1[0.01,1.89]
Trifunovic 2015	2/15	4/15		10.84%	0.5[0.11,2.33]
Tse 2007	0/19	1/9		2.66%	0.17[0.01,3.73]
Turan 2011	0/38	0/18			Not estimable
Subtotal (95% CI)	**304**	**236**		**100%**	**0.42[0.25,0.7]**
Total events: 20 (Cells), 40 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=3.73, df=6(P=0.71); I^2=0%					
Test for overall effect: Z=3.34(P=0)					
5.2.2 Haematopoietic progenitor cells					
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	3/56		10.9%	0.07[0,1.37]
Nasseri 2012	1/30	3/30		19.43%	0.33[0.04,3.03]
Patel 2005	3/25	10/25		69.67%	0.3[0.09,0.96]
Subtotal (95% CI)	**185**	**117**		**100%**	**0.26[0.1,0.69]**
Total events: 4 (Cells), 16 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=2.7(P=0.01)					
5.2.3 Mesenchymal stem cells					
Bartunek 2012	1/21	2/15		26.02%	0.36[0.04,3.59]
Chen 2006	2/22	4/23		54.55%	0.52[0.11,2.57]
Heldman 2014_BM-MSC	1/19	1/11		19.43%	0.58[0.04,8.36]
Subtotal (95% CI)	**62**	**49**		**100%**	**0.48[0.15,1.57]**



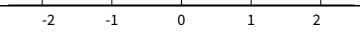
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 4 (Cells), 7 (No cells)					
Heterogeneity: Tau²=0; Chi²=0.09, df=2(P=0.95); I²=0%					
Test for overall effect: Z=1.21(P=0.23)					
Test for subgroup differences: Chi²=0.86, df=1 (P=0.65), I²=0%					



Favours cell therapy — Favours no cell therapy

Analysis 5.3. Comparison 5 Cell type: subgroup analysis, Outcome 3 NYHA classification: short term follow-up (< 12 months).

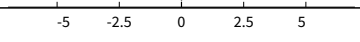
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.3.1 Mononuclear cells							
Assmus 2006	19	2 (0.8)	18	2.1 (0.9)		7.83%	-0.12[-0.67,0.43]
Assmus 2013	42	-0.3 (0.7)	38	0.1 (1)		8.38%	-0.45[-0.82,-0.08]
Hamshere 2015_IC	15	2.2 (0.6)	15	2.2 (0.6)		8.26%	0[-0.42,0.42]
Hamshere 2015_IM	15	2 (0.6)	15	1.8 (0.4)		8.44%	0.2[-0.15,0.55]
Mozid 2014_IM	10	2.2 (0.4)	5	2.5 (0.6)		7.6%	-0.3[-0.91,0.31]
Perin 2011	20	1.8 (0.2)	10	2.4 (0.3)		8.73%	-0.6[-0.81,-0.39]
Perin 2012a	55	-0.3 (0.9)	30	-0.1 (0.7)		8.44%	-0.2[-0.55,0.15]
Pokushalov 2010	53	2.3 (0.2)	46	3.8 (0.1)		8.88%	-1.5[-1.56,-1.44]
Trifunovic 2015	15	1 (0.6)	15	1.3 (0.6)		8.23%	-0.27[-0.69,0.15]
Tse 2007	19	2 (0.4)	9	2.3 (0.5)		8.37%	-0.38[-0.75,-0.01]
Turan 2011	33	1.6 (0.5)	16	2.1 (0.7)		8.35%	-0.5[-0.88,-0.12]
Zhao 2008	16	1.5 (0.5)	18	2.3 (0.5)		8.48%	-0.8[-1.13,-0.47]
Subtotal ***	**312**		**235**			**100%**	**-0.42[-0.86,0.02]**
Heterogeneity: Tau²=0.58; Chi²=345.96, df=11(P<0.0001); I²=96.82%							
Test for overall effect: Z=1.85(P=0.06)							
5.3.2 Haematopoietic progenitor cells							
Nasseri 2012	28	-0.5 (1)	26	-1 (0.7)		33.25%	0.48[0.02,0.94]
Patel 2005	10	-2.8 (0.4)	10	-0.7 (0.7)		33.1%	-2.1[-2.59,-1.61]
Perin 2012b	10	2.3 (0.5)	10	2.1 (0.3)		33.65%	0.2[-0.16,0.56]
Subtotal ***	**48**		**46**			**100%**	**-0.47[-1.95,1.02]**
Heterogeneity: Tau²=1.67; Chi²=70.38, df=2(P<0.0001); I²=97.16%							
Test for overall effect: Z=0.62(P=0.54)							
Test for subgroup differences: Chi²=0, df=1 (P=0.95), I²=0%							



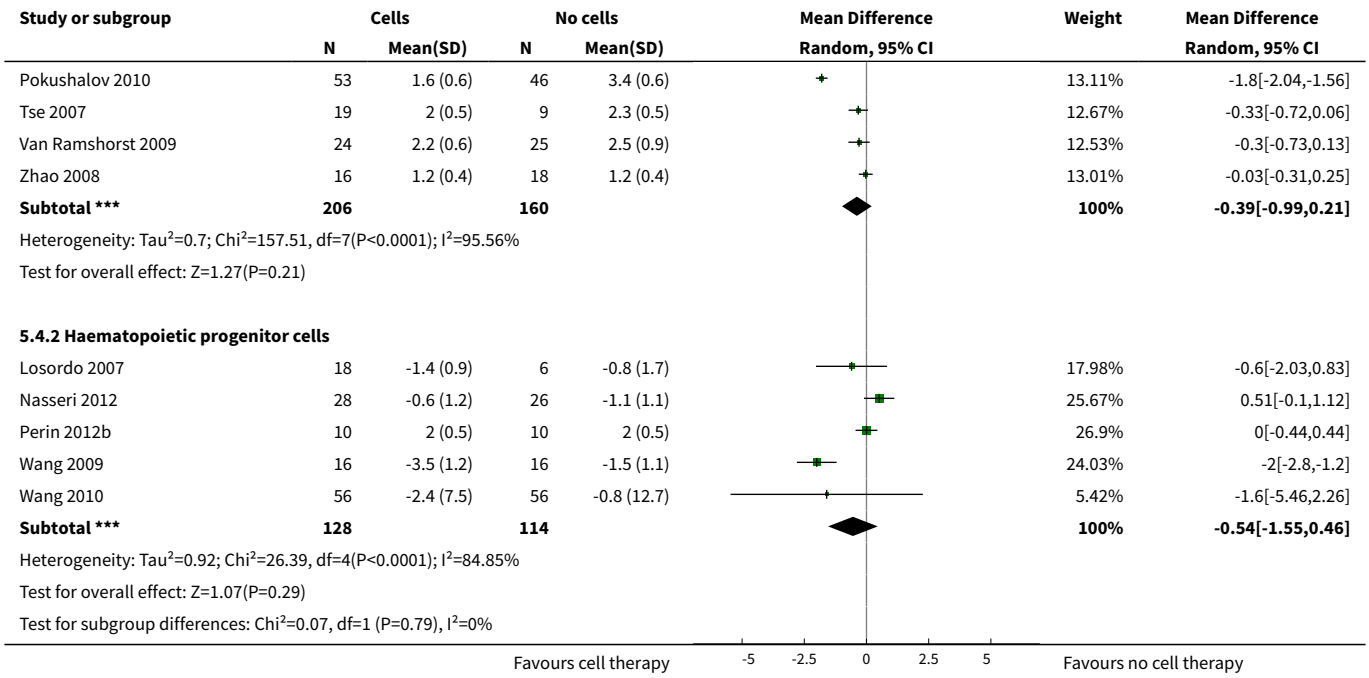
Favours no cell therapy — Favours cell therapy

Analysis 5.4. Comparison 5 Cell type: subgroup analysis, Outcome 4 CCS class: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.4.1 Mononuclear cells							
Hamshere 2015_IC	15	1.4 (0.5)	15	1.3 (0.5)		12.8%	0.14[-0.21,0.49]
Hamshere 2015_IM	15	1.3 (0.5)	15	1.1 (0.5)		12.79%	0.18[-0.17,0.53]
Perin 2011	20	-1.2 (1.4)	10	-0.4 (1)		10.39%	-0.8[-1.68,0.08]
Perin 2012a	44	-0.5 (0.8)	22	-0.3 (0.7)		12.71%	-0.2[-0.58,0.18]



Favours cell therapy — Favours no cell therapy



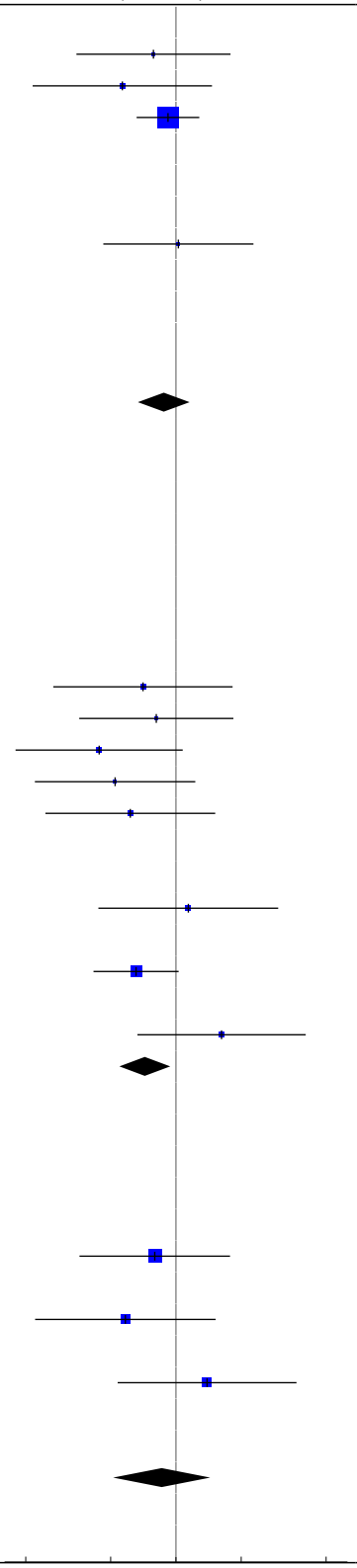
Comparison 6. Participant diagnosis: subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause): short term follow-up (< 12 months)	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Chronic IHD	11	550	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.26, 1.62]
1.2 HF (secondary to IHD)	15	645	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.82]
1.3 Refractory/intractable angina	7	442	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.11, 3.35]
2 Mortality (all-cause): long term follow-up (≥ 12 months)	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Chronic IHD	9	389	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.99]
2.2 HF (secondary to IHD)	9	401	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.19, 0.58]
2.3 Refractory/intractable angina	3	220	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.91]
3 NYHA classification: short term follow-up (< 12 months)	16		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Chronic IHD	6	296	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.78, -0.07]
3.2 HF (secondary to IHD)	10	417	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.02, 0.09]
4 NYHA classification: long term follow-up (≥ 12 months)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Chronic IHD	3	105	Mean Difference (IV, Random, 95% CI)	-0.66 [-0.91, -0.42]
4.2 HF (secondary to IHD)	6	241	Mean Difference (IV, Random, 95% CI)	-0.92 [-1.47, -0.37]
5 CCS class: short term follow-up (< 12 months)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 HF (secondary to IHD)	8	363	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.90, 0.40]
5.2 Refractory/intractable angina	5	245	Mean Difference (IV, Random, 95% CI)	-0.78 [-1.44, -0.11]
6 Exercise capacity: short term follow-up (< 12 months)	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Chronic IHD	4	114	Std. Mean Difference (IV, Random, 95% CI)	0.48 [-0.26, 1.22]
6.2 HF (secondary to IHD)	4	260	Std. Mean Difference (IV, Random, 95% CI)	0.79 [0.04, 1.53]
6.3 Refractory/intractable angina	3	189	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.03, 0.55]
7 LVEF (%) measured by MRI: short term follow-up (< 12 months)	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Chronic IHD	6	178	Mean Difference (IV, Random, 95% CI)	2.58 [-0.16, 5.31]
7.2 HF (secondary to IHD)	4	195	Mean Difference (IV, Random, 95% CI)	2.50 [-1.97, 6.97]

Analysis 6.1. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 1 Mortality (all-cause): short term follow-up (< 12 months).

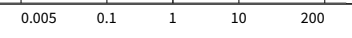
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Chronic IHD					
Ang 2008	1/42	1/19		11.31%	0.45[0.03,6.86]
Assmus 2006	0/52	1/23		8.34%	0.15[0.01,3.57]
Assmus 2013	5/43	6/39		68.44%	0.76[0.25,2.28]
Erbs 2005	0/13	0/12			Not estimable
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hendrikx 2006	1/11	1/12		11.91%	1.09[0.08,15.41]
Honold 2012	0/23	0/9			Not estimable
Turan 2011	0/38	0/18			Not estimable
Wang 2015	0/45	0/45			Not estimable
Yao 2008	0/24	0/23			Not estimable
Subtotal (95% CI)	**329**	**221**		**100%**	**0.65[0.26,1.62]**
Total events: 7 (Cells), 9 (No cells)					
Heterogeneity: Tau²=0; Chi²=1.11, df=3(P=0.77); I²=0%					
Test for overall effect: Z=0.92(P=0.36)					
6.1.2 HF (secondary to IHD)					
Bartunek 2012	0/21	0/15			Not estimable
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Hu 2011	0/31	1/29		8.06%	0.31[0.01,7.38]
Mathiasen 2015	1/40	1/20		10.89%	0.5[0.03,7.59]
Mozid 2014_IC	0/14	1/2		9.25%	0.07[0,1.27]
Mozid 2014_IM	0/10	3/8		10.06%	0.12[0.01,1.98]
Nasseri 2012	0/30	2/30		8.98%	0.2[0.01,4]
Patel 2005	0/10	0/10			Not estimable
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		8%	1.55[0.06,36.94]
Perin 2012b	0/10	0/10			Not estimable
Pokushalov 2010	2/55	8/54		35.63%	0.25[0.05,1.1]
Santoso 2014	0/19	0/9			Not estimable
Zhao 2008	2/18	0/18		9.14%	5[0.26,97.37]
Subtotal (95% CI)	**369**	**276**		**100%**	**0.33[0.14,0.82]**
Total events: 6 (Cells), 16 (No cells)					
Heterogeneity: Tau²=0; Chi²=6.18, df=7(P=0.52); I²=0%					
Test for overall effect: Z=2.4(P=0.02)					
6.1.3 Refractory/intractable angina					
Jimenez-Quevedo 2011	1/19	1/9		41.59%	0.47[0.03,6.74]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		28.92%	0.17[0.01,4.06]
Tse 2007	0/19	0/9			Not estimable
Van Ramshorst 2009	1/25	0/25		29.49%	3[0.13,70.3]
Wang 2009	0/16	0/16			Not estimable
Wang 2010	0/56	0/56			Not estimable
Subtotal (95% CI)	**265**	**177**		**100%**	**0.61[0.11,3.35]**
Total events: 2 (Cells), 2 (No cells)					
Heterogeneity: Tau²=0; Chi²=1.65, df=2(P=0.44); I²=0%					



Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.58(P=0.57)					
Test for subgroup differences: Chi²=1.13, df=1 (P=0.57), I²=0%					

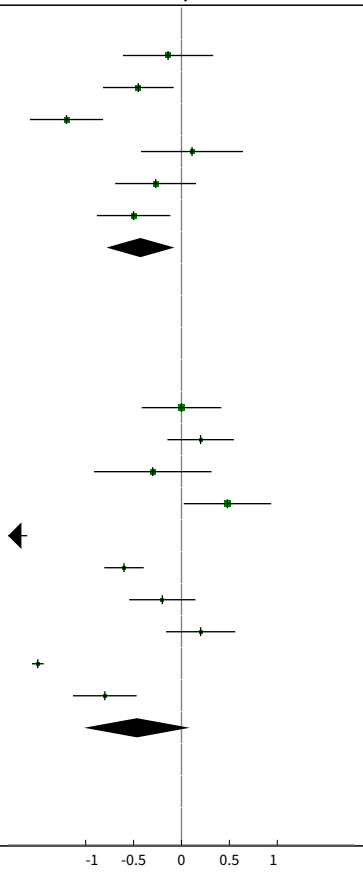
Analysis 6.2. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 2 Mortality (all-cause): long term follow-up (≥ 12 months).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Chronic IHD					
Assmus 2013	6/43	8/39		43.94%	0.68[0.26,1.79]
Chen 2006	2/22	4/23		16.14%	0.52[0.11,2.57]
Erbs 2005	0/13	1/12		4.24%	0.31[0.01,6.94]
Heldman 2014_BM-MSC	1/19	1/11		5.75%	0.58[0.04,8.36]
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Honold 2012	0/23	1/9		4.22%	0.14[0.01,3.13]
Nasseri 2012	1/30	3/30		8.42%	0.33[0.04,3.03]
Trifunovic 2015	2/15	4/15		17.3%	0.5[0.11,2.33]
Turan 2011	0/38	0/18			Not estimable
Subtotal (95% CI)	**222**	**167**		**100%**	**0.52[0.27,0.99]**
Total events: 12 (Cells), 22 (No cells)					
Heterogeneity: Tau²=0; Chi²=1.27, df=6(P=0.97); I²=0%					
Test for overall effect: Z=1.99(P=0.05)					
6.2.2 HF (secondary to IHD)					
Bartunek 2012	1/21	2/15		5.83%	0.36[0.04,3.59]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Hu 2011	1/31	2/29		5.64%	0.47[0.04,4.89]
Patel 2005	3/25	10/25		22.87%	0.3[0.09,0.96]
Patel 2015	5/22	2/6		16.56%	0.68[0.17,2.68]
Patila 2014	0/13	0/17			Not estimable
Pokushalov 2010	6/55	21/54		45.5%	0.28[0.12,0.64]
Santoso 2014	0/19	2/9		3.59%	0.1[0.01,1.89]
Subtotal (95% CI)	**216**	**185**		**100%**	**0.33[0.19,0.58]**
Total events: 16 (Cells), 39 (No cells)					
Heterogeneity: Tau²=0; Chi²=2.01, df=5(P=0.85); I²=0%					
Test for overall effect: Z=3.88(P=0)					
6.2.3 Refractory/intractable angina					
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	3/56		52.69%	0.07[0,1.37]
Tse 2007	0/19	1/9		47.31%	0.17[0.01,3.73]
Subtotal (95% CI)	**149**	**71**		**100%**	**0.11[0.01,0.91]**
Total events: 0 (Cells), 4 (No cells)					
Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi²=2.51, df=1 (P=0.29), I²=20.33%					



Analysis 6.3. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 3 NYHA classification: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.3.1 Chronic IHD							
Assmus 2006	43	2 (0.7)	18	2.1 (0.9)		15.83%	-0.14[-0.61,0.33]
Assmus 2013	42	-0.3 (0.7)	38	0.1 (1)		17.74%	-0.45[-0.82,-0.08]
Chen 2006	22	1.3 (0.7)	23	2.5 (0.6)		17.51%	-1.2[-1.58,-0.82]
Honold 2012	21	1.7 (0.7)	10	1.6 (0.7)		14.7%	0.11[-0.42,0.64]
Trifunovic 2015	15	1 (0.6)	15	1.3 (0.6)		16.75%	-0.27[-0.69,0.15]
Turan 2011	33	1.6 (0.5)	16	2.1 (0.7)		17.48%	-0.5[-0.88,-0.12]
Subtotal ***	**176**		**120**			**100%**	**-0.43[-0.78,-0.07]**
Heterogeneity: Tau²=0.15; Chi²=21.38, df=5(P=0); I²=76.61%							
Test for overall effect: Z=2.37(P=0.02)							
6.3.2 HF (secondary to IHD)							
Hamshere 2015_IC	15	2.2 (0.6)	15	2.2 (0.6)		9.92%	0[-0.42,0.42]
Hamshere 2015_IM	15	2 (0.6)	15	1.8 (0.4)		10.1%	0.2[-0.15,0.55]
Mozid 2014_IM	10	2.2 (0.4)	5	2.5 (0.6)		9.3%	-0.3[-0.91,0.31]
Nasseri 2012	28	-0.5 (1)	26	-1 (0.7)		9.81%	0.48[0.02,0.94]
Patel 2005	10	-2.8 (0.4)	10	-0.7 (0.7)		9.71%	-2.1[-2.59,-1.61]
Perin 2011	20	1.8 (0.2)	10	2.4 (0.3)		10.36%	-0.6[-0.81,-0.39]
Perin 2012a	55	-0.3 (0.9)	30	-0.1 (0.7)		10.1%	-0.2[-0.55,0.15]
Perin 2012b	10	2.3 (0.5)	10	2.1 (0.3)		10.06%	0.2[-0.16,0.56]
Pokushalov 2010	53	2.3 (0.2)	46	3.8 (0.1)		10.5%	-1.5[-1.56,-1.44]
Zhao 2008	16	1.5 (0.5)	18	2.3 (0.5)		10.13%	-0.8[-1.13,-0.47]
Subtotal ***	**232**		**185**			**100%**	**-0.47[-1.02,0.09]**
Heterogeneity: Tau²=0.75; Chi²=384.89, df=9(P<0.0001); I²=97.66%							
Test for overall effect: Z=1.65(P=0.1)							
Test for subgroup differences: Chi²=0.01, df=1 (P=0.91), I²=0%							



Analysis 6.4. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 4 NYHA classification: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.4.1 Chronic IHD							
Honold 2012	20	1.5 (0.8)	6	1.7 (0.8)		10.86%	-0.25[-0.99,0.49]
Trifunovic 2015	15	1.1 (0.3)	15	1.8 (0.7)		43.32%	-0.73[-1.1,-0.36]
Turan 2011	33	1.6 (0.6)	16	2.3 (0.6)		45.82%	-0.7[-1.06,-0.34]
Subtotal ***	**68**		**37**			**100%**	**-0.66[-0.91,-0.42]**
Heterogeneity: Tau²=0; Chi²=1.38, df=2(P=0.5); I²=0%							
Test for overall effect: Z=5.37(P<0.0001)							
6.4.2 HF (secondary to IHD)							
Chen 2006	20	1.4 (0.7)	19	2.4 (0.4)		17.95%	-1[-1.36,-0.64]
Hamshere 2015_IC	15	2.1 (0.6)	15	2.4 (0.6)		17.24%	-0.29[-0.73,0.15]
Hamshere 2015_IM	15	2.1 (0.7)	15	2.1 (0.6)		16.99%	-0.01[-0.48,0.46]

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Patel 2015	17	1.8 (0.8)	4	2.3 (1)		11.74%	-0.43[-1.45,0.59]
Patila 2014	20	-1 (0.8)	19	1.2 (0.8)		16.72%	-2.2[-2.7,-1.7]
Pokushalov 2010	49	2.5 (0.1)	33	3.9 (0.1)		19.36%	-1.4[-1.44,-1.36]
Subtotal * **	**136**		**105**			**100%**	**-0.92[-1.47,-0.37]**
Heterogeneity: Tau²=0.41; Chi²=74.11, df=5(P<0.0001); I²=93.25%							
Test for overall effect: Z=3.26(P=0)							
Test for subgroup differences: Chi²=0.69, df=1 (P=0.41), I²=0%							

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Analysis 6.5. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 5 CCS class: short term follow-up (< 12 months).

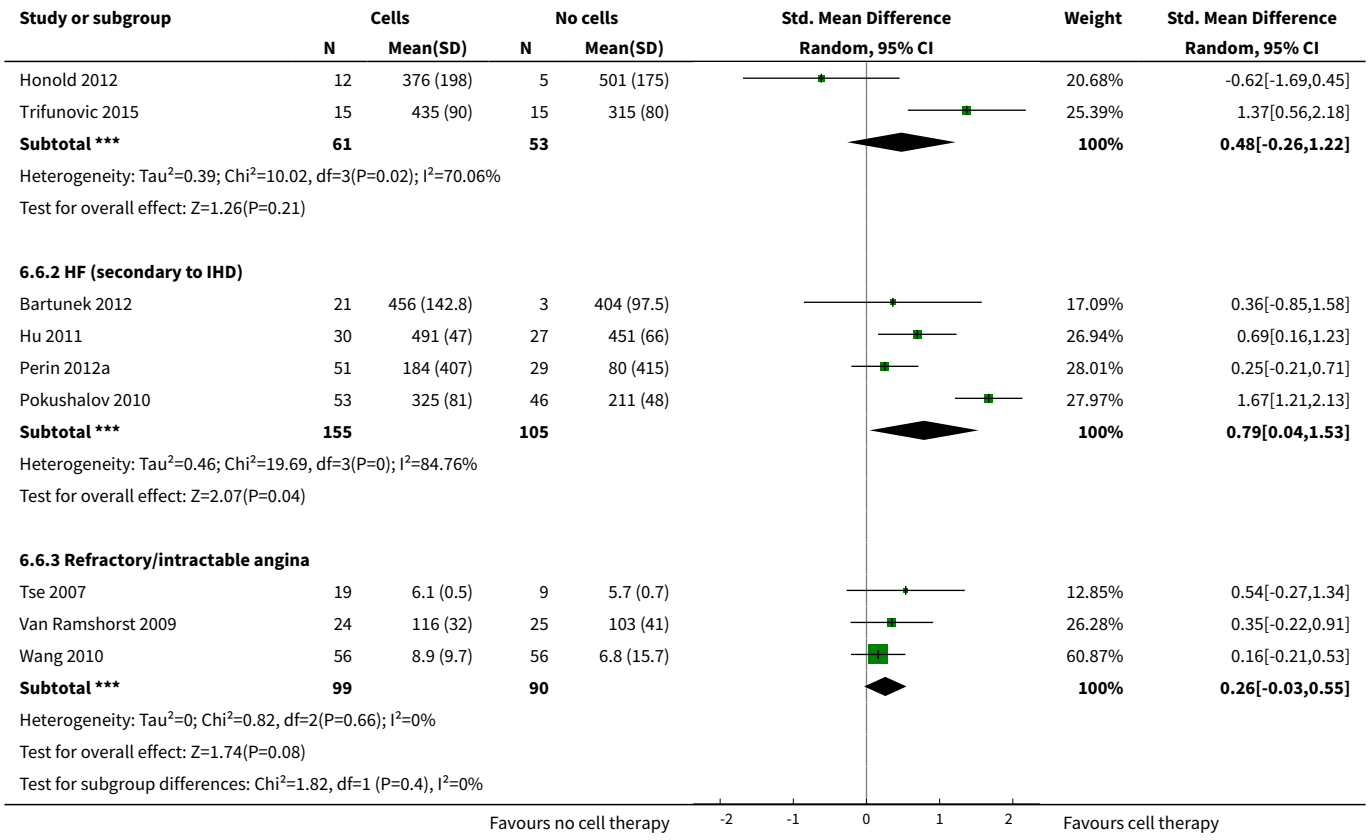
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.5.1 HF (secondary to IHD)							
Hamshere 2015_IC	15	1.4 (0.5)	15	1.3 (0.5)		12.86%	0.14[-0.21,0.49]
Hamshere 2015_IM	15	1.3 (0.5)	15	1.1 (0.5)		12.85%	0.18[-0.17,0.53]
Nasseri 2012	28	-0.6 (1.2)	26	-1.1 (1.1)		11.97%	0.51[-0.1,1.12]
Perin 2011	20	-1.2 (1.4)	10	-0.4 (1)		10.75%	-0.8[-1.68,0.08]
Perin 2012a	44	-0.5 (0.8)	22	-0.3 (0.7)		12.79%	-0.2[-0.58,0.18]
Perin 2012b	10	2 (0.5)	10	2 (0.5)		12.6%	0[-0.44,0.44]
Pokushalov 2010	53	1.6 (0.6)	46	3.4 (0.6)		13.13%	-1.8[-2.04,-1.56]
Zhao 2008	16	1.2 (0.4)	18	1.2 (0.4)		13.04%	-0.03[-0.31,0.25]
Subtotal * **	**201**		**162**			**100%**	**-0.25[-0.9,0.4]**
Heterogeneity: Tau²=0.83; Chi²=171.89, df=7(P<0.0001); I²=95.93%							
Test for overall effect: Z=0.75(P=0.45)							
6.5.2 Refractory/intractable angina							
Losordo 2007	18	-1.4 (0.9)	6	-0.8 (1.7)		13.35%	-0.6[-2.03,0.83]
Tse 2007	19	2 (0.5)	9	2.3 (0.5)		30.75%	-0.33[-0.72,0.06]
Van Ramshorst 2009	24	2.2 (0.6)	25	2.5 (0.9)		30.11%	-0.3[-0.73,0.13]
Wang 2009	16	-3.5 (1.2)	16	-1.5 (1.1)		23.04%	-2[-2.8,-1.2]
Wang 2010	56	-2.4 (7.5)	56	-0.8 (12.7)		2.74%	-1.6[-5.46,2.26]
Subtotal * **	**133**		**112**			**100%**	**-0.78[-1.44,-0.11]**
Heterogeneity: Tau²=0.34; Chi²=15.47, df=4(P=0); I²=74.15%							
Test for overall effect: Z=2.28(P=0.02)							
Test for subgroup differences: Chi²=1.23, df=1 (P=0.27), I²=18.48%							

Favours cell therapy -5 -2.5 0 2.5 5 Favours no cell therapy

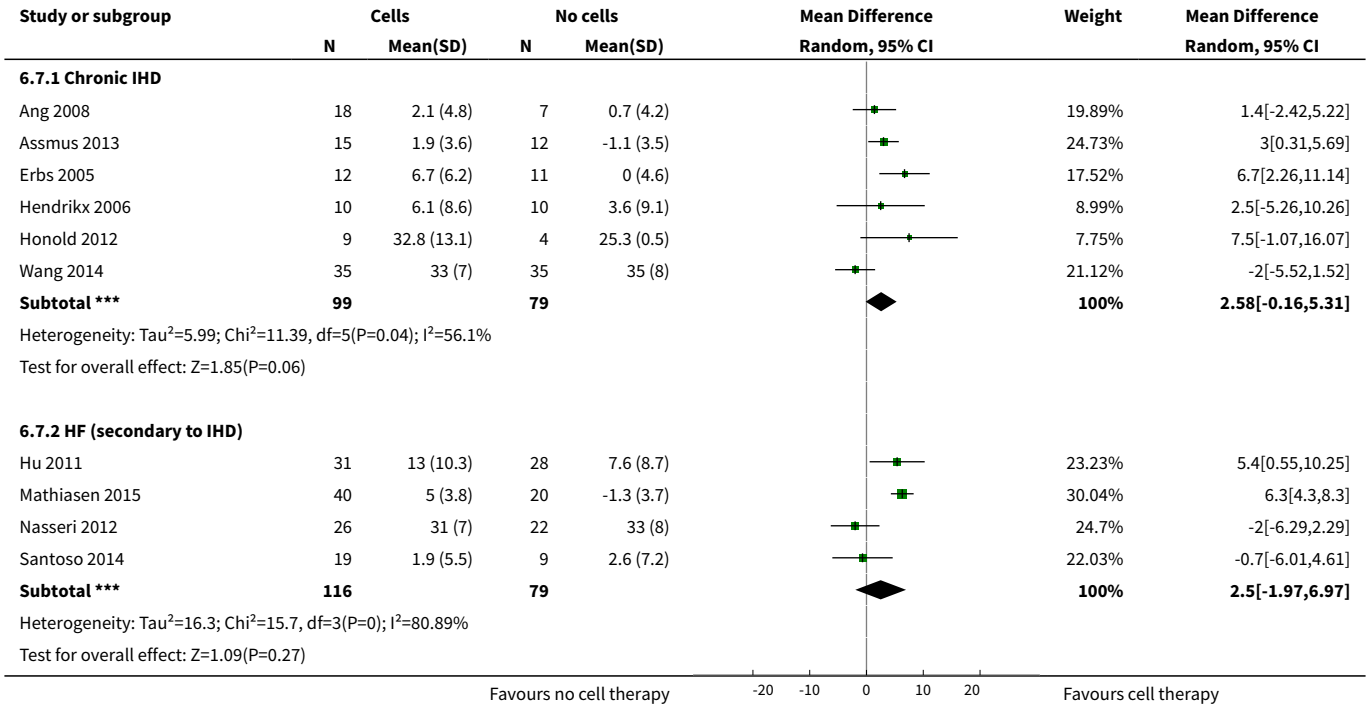
Analysis 6.6. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 6 Exercise capacity: short term follow-up (< 12 months).

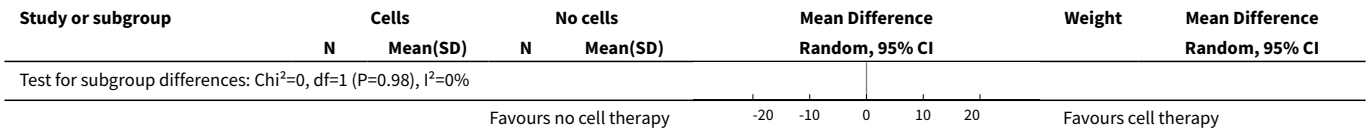
Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
6.6.1 Chronic IHD							
Chen 2006	22	7 (3)	23	5 (2)		29.17%	0.77[0.17,1.38]
Erbs 2005	12	23.1 (5.8)	10	22.4 (4.7)		24.76%	0.13[-0.71,0.97]

Favours no cell therapy -2 -1 0 1 2 Favours cell therapy



Analysis 6.7. Comparison 6 Participant diagnosis: subgroup analysis, Outcome 7 LVEF (%) measured by MRI: short term follow-up (< 12 months).

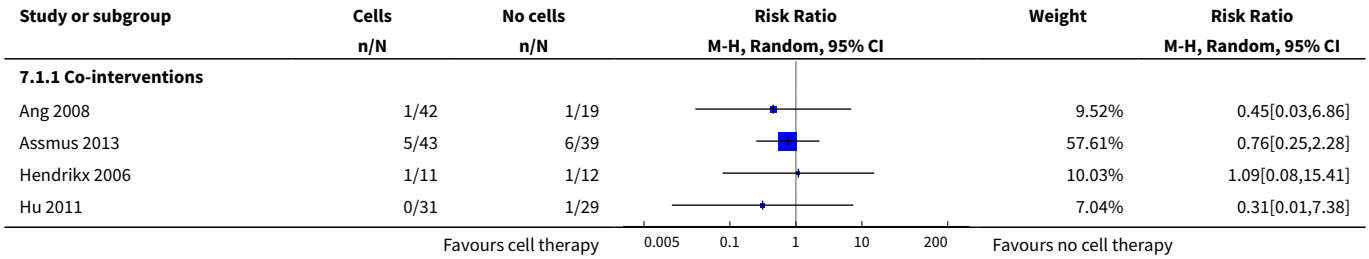


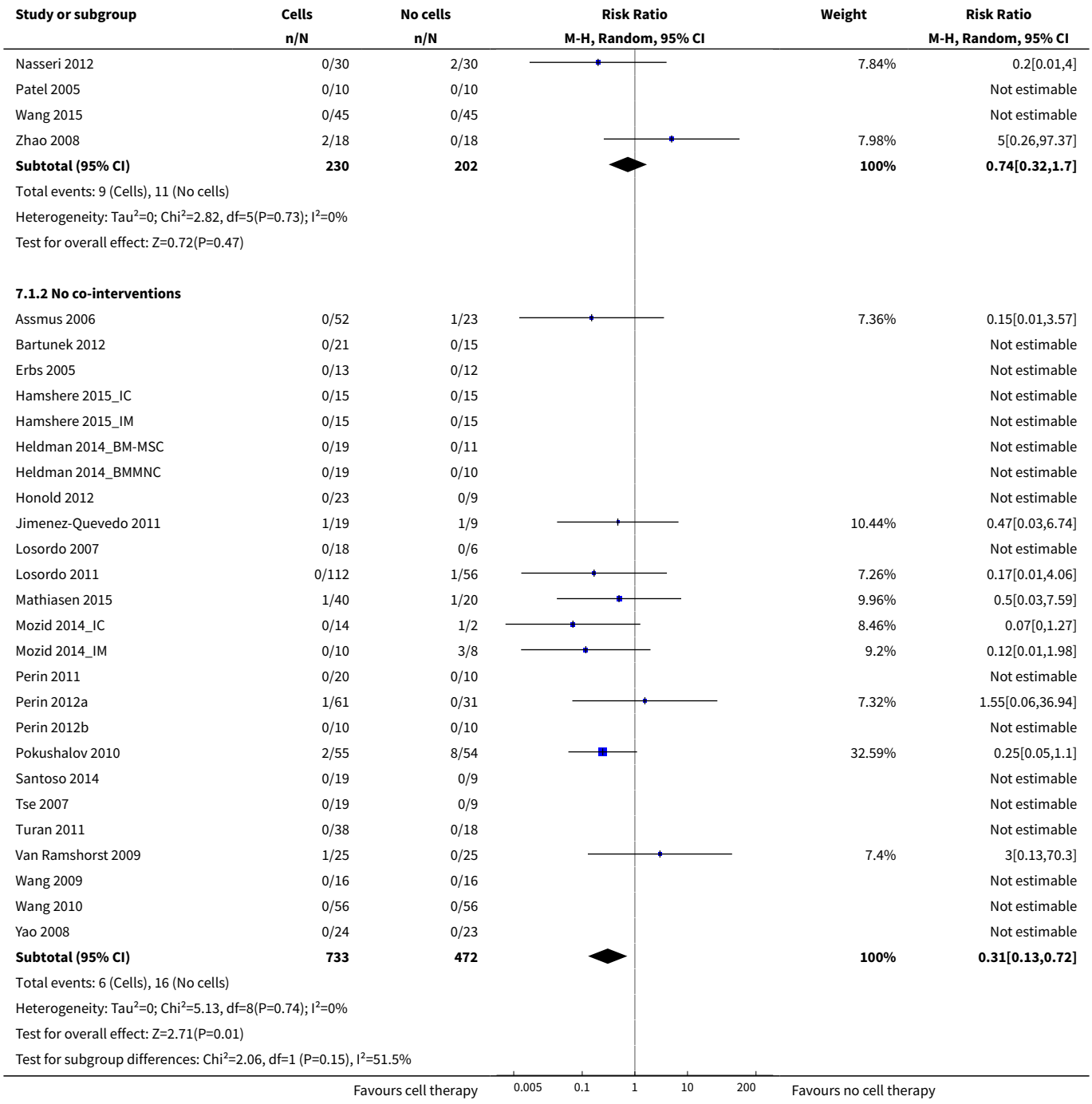


Comparison 7. Co-interventions: subgroup analysis

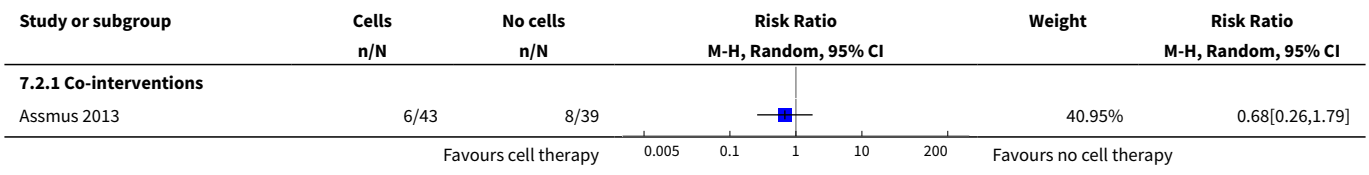
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mortality (all-cause): short term follow-up (< 12 months)	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Co-interventions	8	432	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.32, 1.70]
1.2 No co-interventions	25	1205	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.13, 0.72]
2 Mortality (all-cause): long term follow-up (≥ 12 months)	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Co-interventions	6	312	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.26, 0.88]
2.2 No co-interventions	15	698	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.19, 0.56]
3 NYHA classification: short term follow-up (< 12 months)	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Co-interventions	6	233	Mean Difference (IV, Random, 95% CI)	-0.57 [-1.20, 0.05]
3.2 No co-interventions	11	508	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.87, 0.13]
4 LVEF (%) measured by MRI: short term follow-up (< 12 months)	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Co-interventions	5	179	Mean Difference (IV, Random, 95% CI)	2.01 [-0.26, 4.29]
4.2 No co-interventions	7	260	Mean Difference (IV, Random, 95% CI)	3.55 [0.82, 6.27]

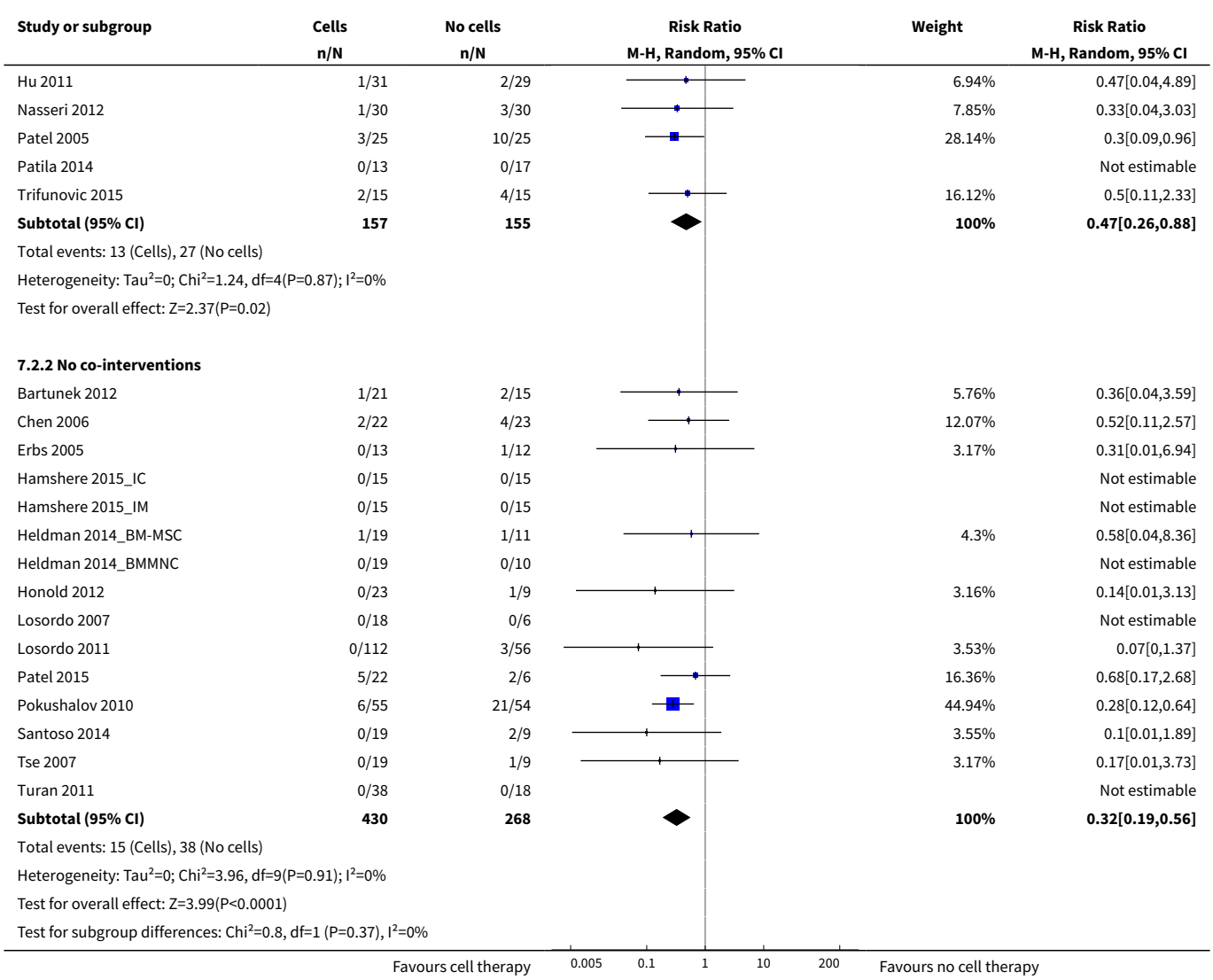
Analysis 7.1. Comparison 7 Co-interventions: subgroup analysis, Outcome 1 Mortality (all-cause): short term follow-up (< 12 months).



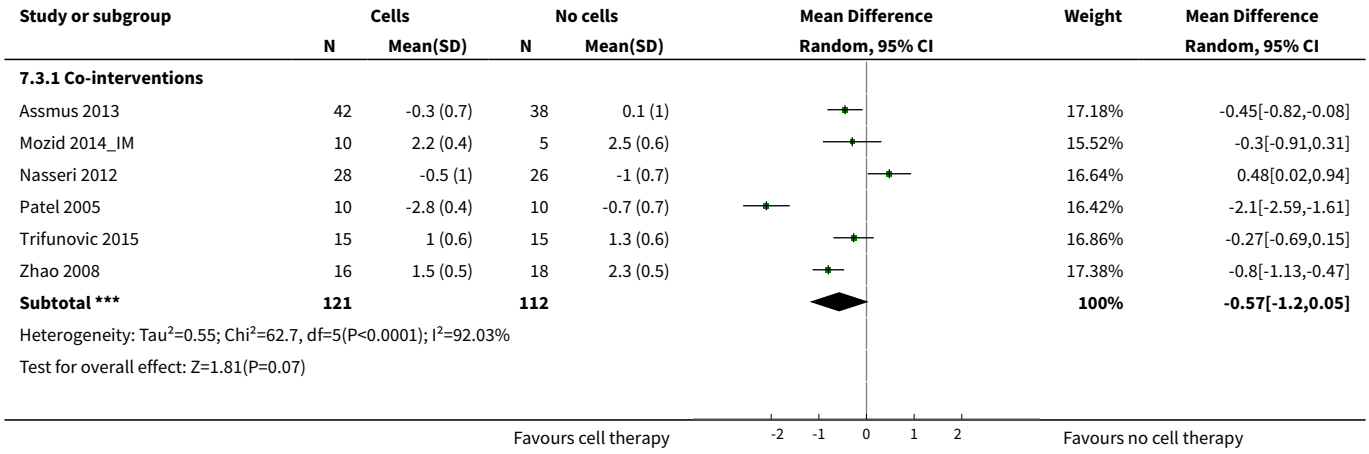


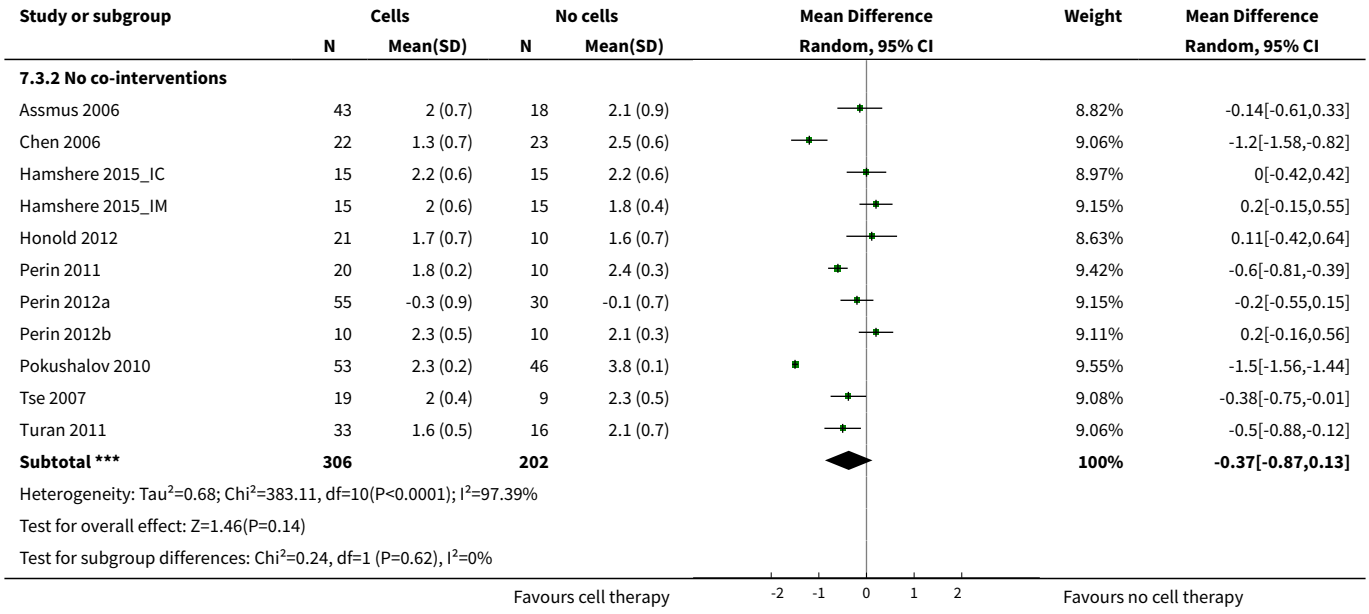
Analysis 7.2. Comparison 7 Co-interventions: subgroup analysis, Outcome 2 Mortality (all-cause): long term follow-up (≥ 12 months).



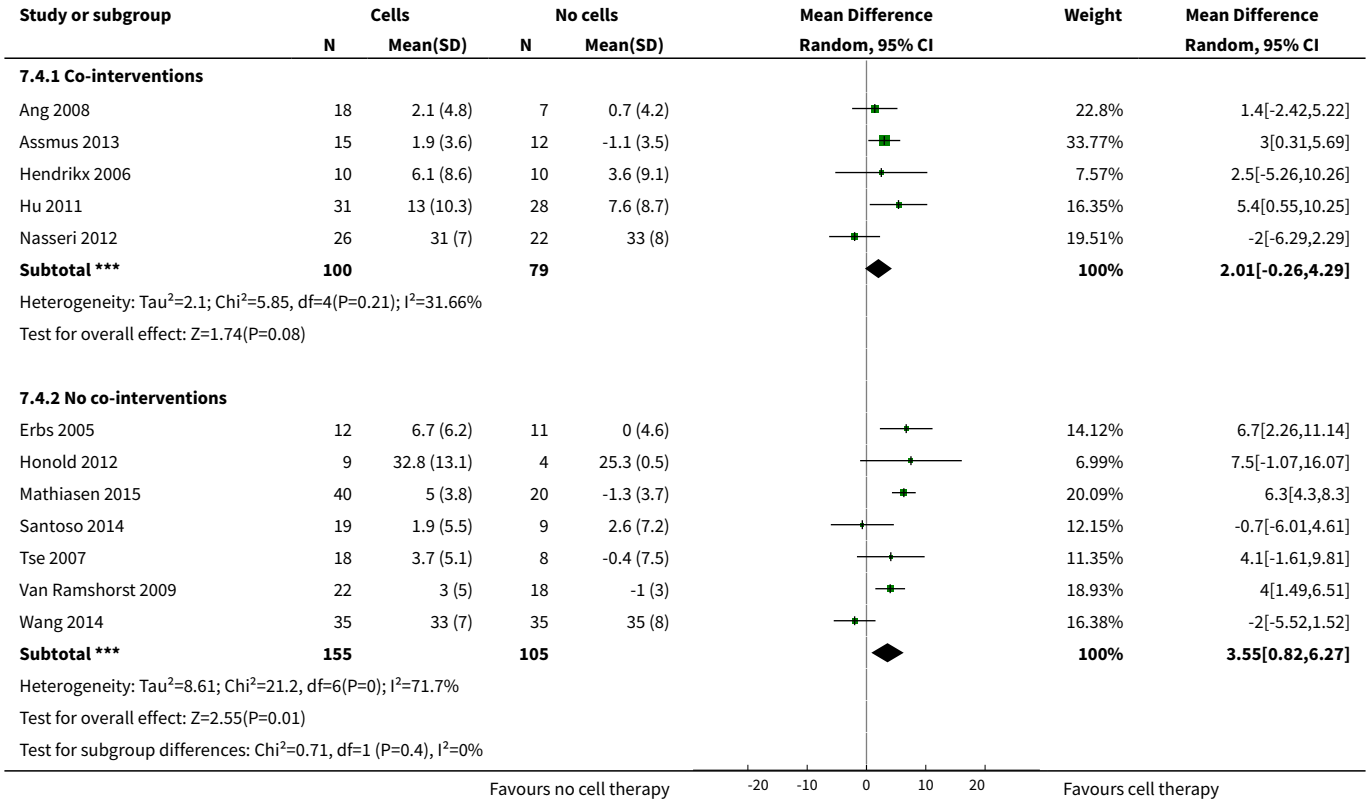


Analysis 7.3. Comparison 7 Co-interventions: subgroup analysis, Outcome 3 NYHA classification: short term follow-up (< 12 months).





Analysis 7.4. Comparison 7 Co-interventions: subgroup analysis, Outcome 4 LVEF (%) measured by MRI: short term follow-up (< 12 months).



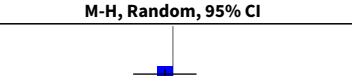
Comparison 8. Sensitivity analysis: excluding studies with high/unclear risk of selection bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause)	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Short term follow-up (< 12 months)	14	744	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.32, 1.50]
1.2 Long term follow-up (≥ 12 months)	9	491	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.21, 0.87]
2 Non-fatal myocardial infarction	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Short term follow-up (< 12 months)	6	288	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 4.58]
2.2 Long term follow-up (≥ 12 months)	5	345	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.15, 0.97]
3 Rehospitalisation due to heart failure	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Short term follow-up (< 12 months)	3	234	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.32, 1.32]
3.2 Long term follow-up (≥ 12 months)	6	375	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.09]
4 Arrhythmias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Short term follow-up (< 12 months)	6	224	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.18, 3.21]
4.2 Long term follow-up (≥ 12 months)	1	82	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.18, 0.99]
5 Composite MACE	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Short term follow-up (< 12 months)	2	59	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Long term follow-up (≥ 12 months)	3	141	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.38, 1.08]
6 NYHA classification: short term follow-up (< 12 months)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Combined	5	277	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.59, 0.07]
7 NYHA classification: long term follow-up (≥ 12 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Combined	1	39	Mean Difference (IV, Random, 95% CI)	-2.2 [-2.70, -1.70]

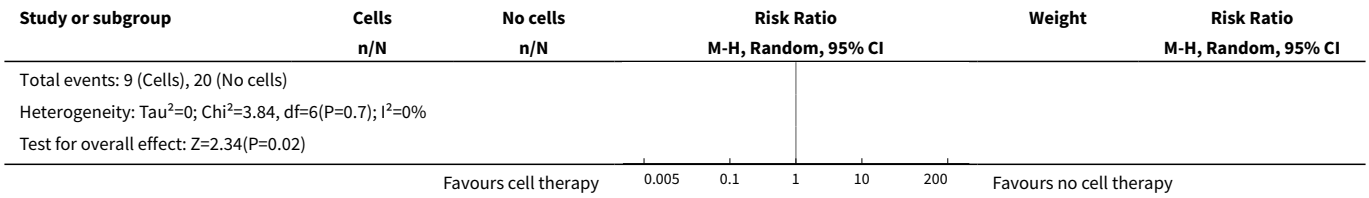
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 LVEF (%) measured by MRI: short term follow-up (< 12 months)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Combined	7	249	Mean Difference (IV, Random, 95% CI)	2.92 [0.67, 5.17]
9 LVEF (%) measured by MRI: long term follow-up (≥ 12 months)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Combined	1	25	Mean Difference (IV, Random, 95% CI)	-1.60 [-8.70, 5.50]

Analysis 8.1. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 1 Mortality (all-cause).

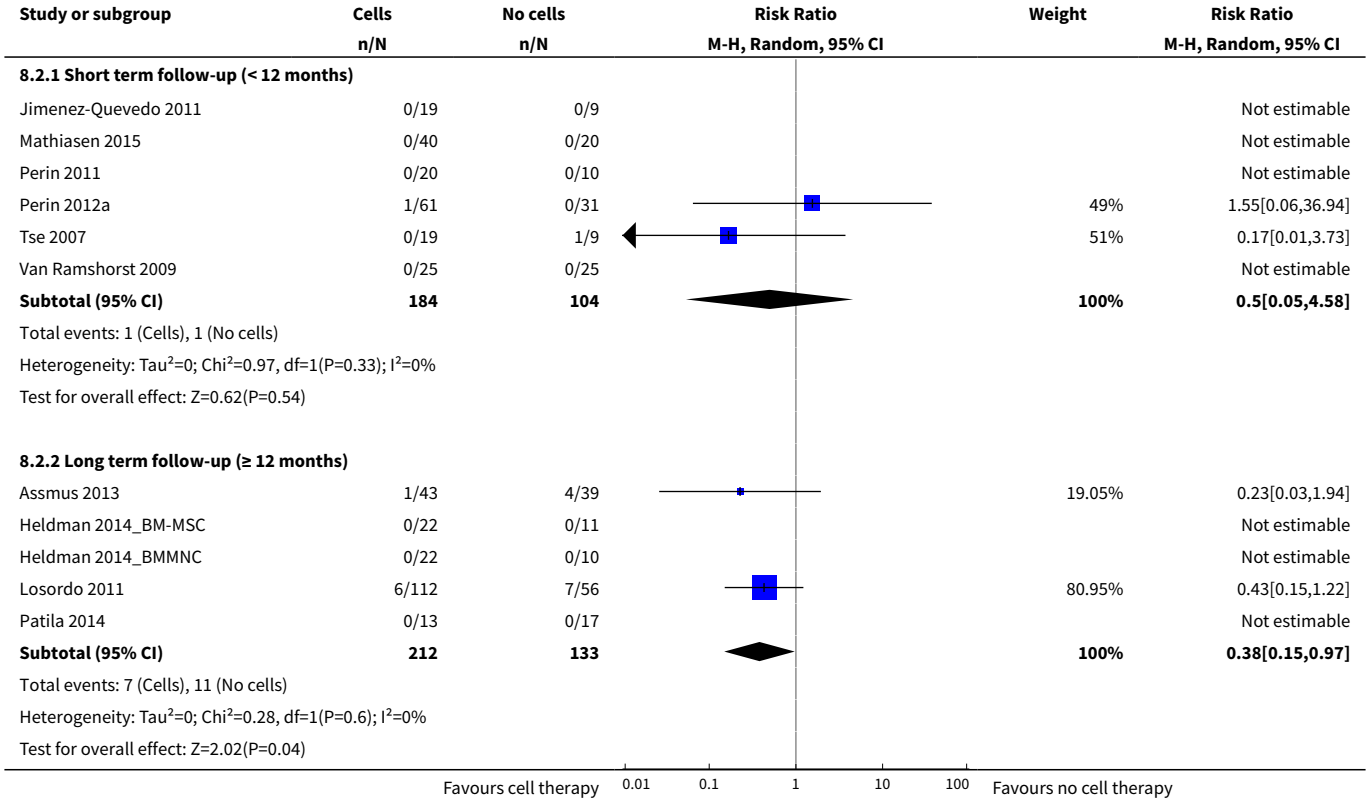
Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Short term follow-up (< 12 months)					
Assmus 2013	5/43	6/39		49.69%	0.76[0.25,2.28]
Bartunek 2012	0/21	0/15			Not estimable
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hendrikx 2006	1/11	1/12		8.65%	1.09[0.08,15.41]
Jimenez-Quevedo 2011	1/19	1/9		8.6%	0.47[0.03,6.74]
Losordo 2011	0/112	1/56		5.98%	0.17[0.01,4.06]
Mathiasen 2015	1/40	1/20		8.2%	0.5[0.03,7.59]
Nasseri 2012	0/30	2/30		6.76%	0.2[0.01,4]
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		6.03%	1.55[0.06,36.94]
Santoso 2014	0/19	0/9			Not estimable
Tse 2007	0/19	0/9			Not estimable
Van Ramshorst 2009	1/25	0/25		6.1%	3[0.13,70.3]
Subtotal (95% CI)	**458**	**286**		**100%**	**0.69[0.32,1.5]**
Total events: 10 (Cells), 12 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=2.77, df=7(P=0.91); I^2=0%					
Test for overall effect: Z=0.94(P=0.35)					
8.1.2 Long term follow-up (≥ 12 months)					
Assmus 2013	6/43	8/39		55.27%	0.68[0.26,1.79]
Bartunek 2012	1/21	2/15		9.68%	0.36[0.04,3.59]
Heldman 2014_BM-MSC	1/19	1/11		7.23%	0.58[0.04,8.36]
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Losordo 2011	0/112	3/56		5.94%	0.07[0,1.37]
Nasseri 2012	1/30	3/30		10.59%	0.33[0.04,3.03]
Patila 2014	0/13	0/17			Not estimable
Santoso 2014	0/19	2/9		5.96%	0.1[0.01,1.89]
Tse 2007	0/19	1/9		5.33%	0.17[0.01,3.73]
Subtotal (95% CI)	**295**	**196**		**100%**	**0.42[0.21,0.87]**



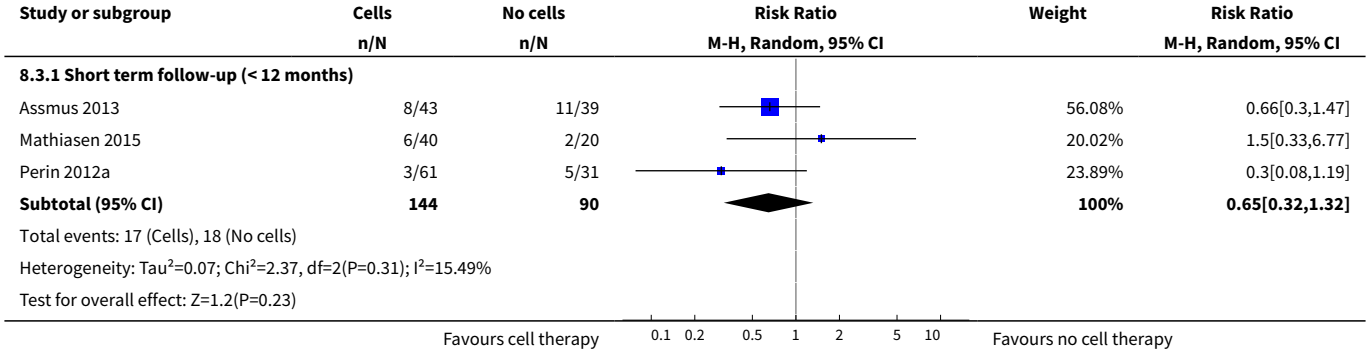
Favours cell therapy — Favours no cell therapy

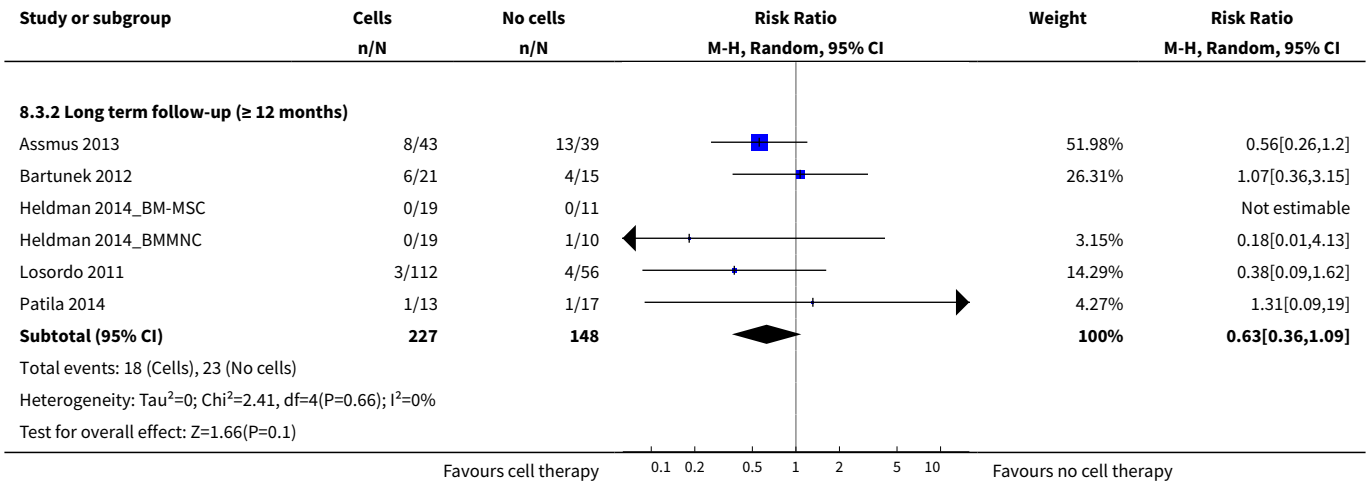


Analysis 8.2. Comparison 8 Sensitivity analysis: excluding studies with high/ unclear risk of selection bias, Outcome 2 Non-fatal myocardial infarction.

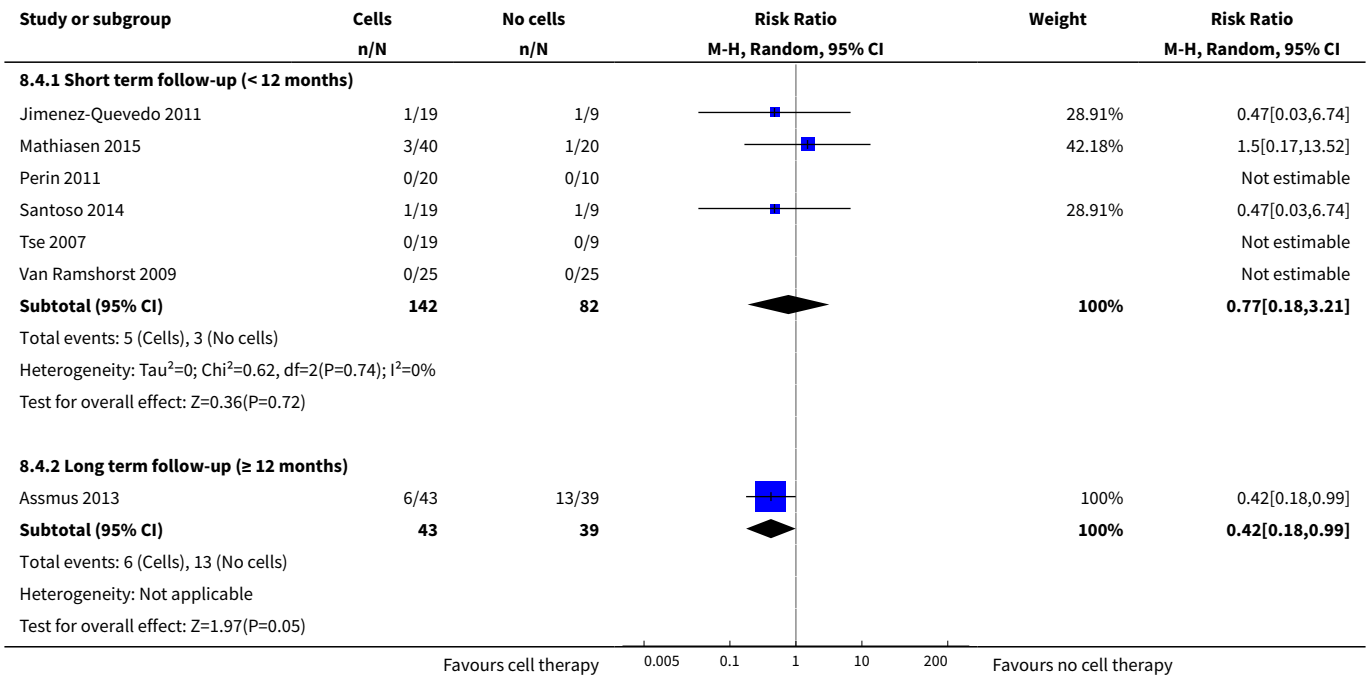


Analysis 8.3. Comparison 8 Sensitivity analysis: excluding studies with high/ unclear risk of selection bias, Outcome 3 Rehospitalisation due to heart failure.

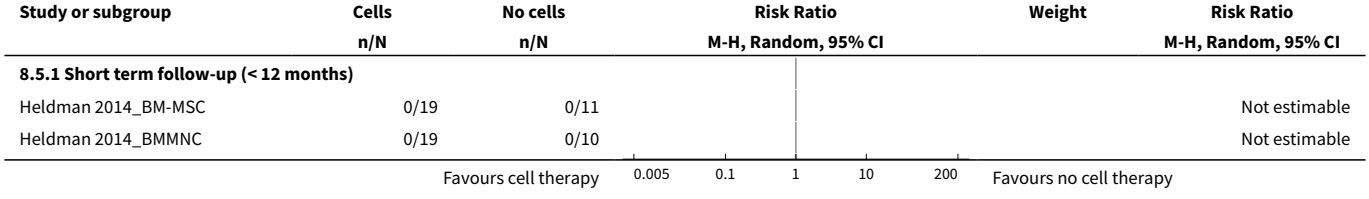


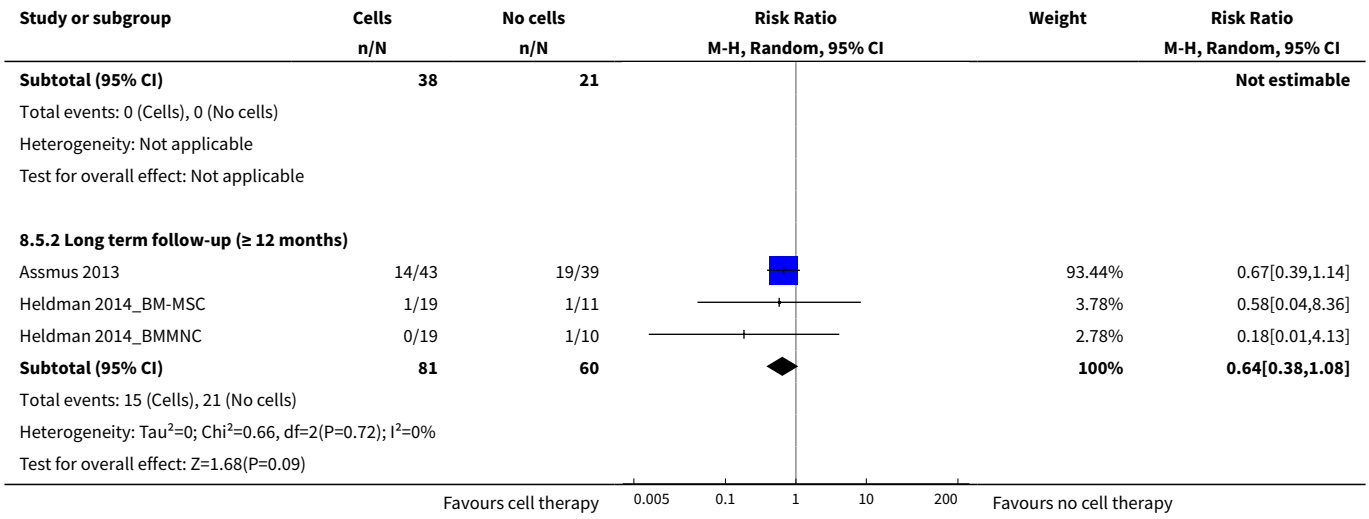


Analysis 8.4. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 4 Arrhythmias.

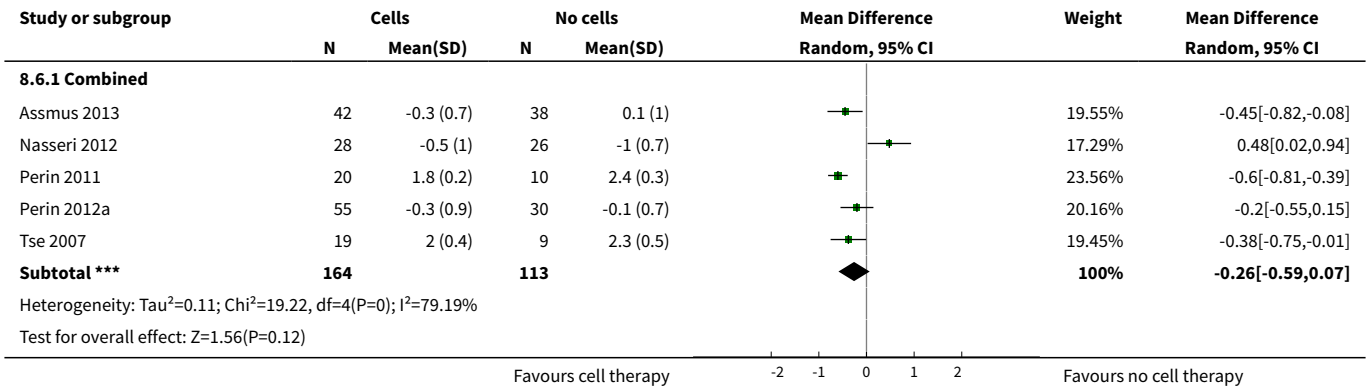


Analysis 8.5. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 5 Composite MACE.

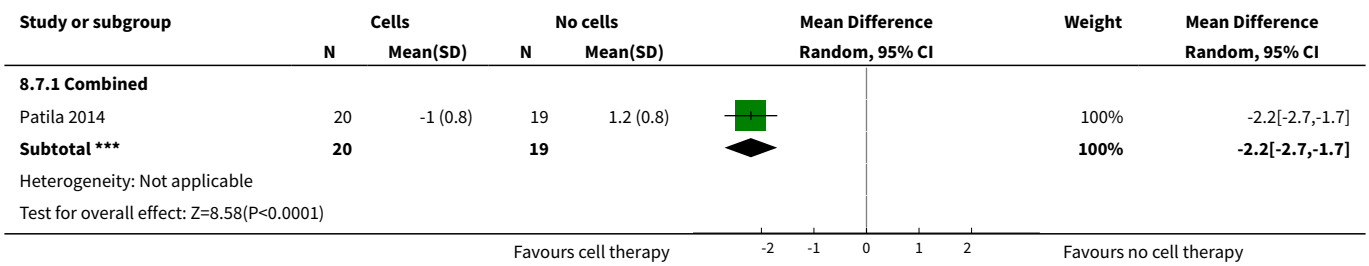




Analysis 8.6. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 6 NYHA classification: short term follow-up (< 12 months).

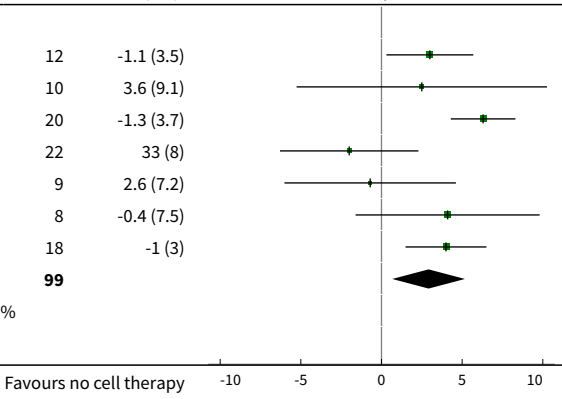


Analysis 8.7. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 7 NYHA classification: long term follow-up (≥ 12 months).



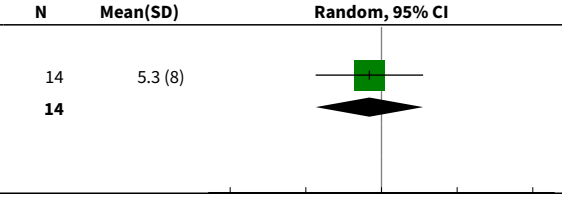
Analysis 8.8. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 8 LVEF (%) measured by MRI: short term follow-up (< 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.8.1 Combined							
Assmus 2013	15	1.9 (3.6)	12	-1.1 (3.5)		18.89%	3[0.31,5.69]
Hendrikx 2006	10	6.1 (8.6)	10	3.6 (9.1)		6.36%	2.5[-5.26,10.26]
Mathiasen 2015	40	5 (3.8)	20	-1.3 (3.7)		21.47%	6.3[4.3,8.3]
Nasseri 2012	26	31 (7)	22	33 (8)		13.35%	-2[-6.29,2.29]
Santoso 2014	19	1.9 (5.5)	9	2.6 (7.2)		10.61%	-0.7[-6.01,4.61]
Tse 2007	18	3.7 (5.1)	8	-0.4 (7.5)		9.73%	4.1[-1.61,9.81]
Van Ramshorst 2009	22	3 (5)	18	-1 (3)		19.59%	4[1.49,6.51]
Subtotal ***	**150**		**99**			**100%**	**2.92[0.67,5.17]**
Heterogeneity: Tau^2=5.12; Chi^2=16.21, df=6(P=0.01); I^2=62.99%							
Test for overall effect: Z=2.54(P=0.01)							



Analysis 8.9. Comparison 8 Sensitivity analysis: excluding studies with high/unclear risk of selection bias, Outcome 9 LVEF (%) measured by MRI: long term follow-up (≥ 12 months).

Study or subgroup	Cells N	Cells Mean(SD)	No cells N	No cells Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.9.1 Combined							
Patila 2014	11	3.7 (9.7)	14	5.3 (8)		100%	-1.6[-8.7,5.5]
Subtotal ***	**11**		**14**			**100%**	**-1.6[-8.7,5.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.44(P=0.66)							

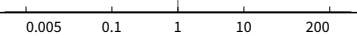


Comparison 9. Sensitivity analysis: excluding studies with high/unclear risk of performance bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause)	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Short term follow-up (< 12 months)	25	1216	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.29, 1.16]
1.2 Long term follow-up (≥ 12 months)	13	624	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.21, 0.86]

Analysis 9.1. Comparison 9 Sensitivity analysis: excluding studies with high/unclear risk of performance bias, Outcome 1 Mortality (all-cause).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 Short term follow-up (< 12 months)					
Assmus 2013	5/43	6/39		38.97%	0.76[0.25,2.28]
Erbs 2005	0/13	0/12			Not estimable
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BM-MSC	0/19	0/11			Not estimable
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hendrikx 2006	1/11	1/12		6.78%	1.09[0.08,15.41]
Hu 2011	0/31	1/29		4.76%	0.31[0.01,7.38]
Jimenez-Quevedo 2011	1/19	1/9		6.74%	0.47[0.03,6.74]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		4.69%	0.17[0.01,4.06]
Mathiasen 2015	1/40	1/20		6.43%	0.5[0.03,7.59]
Mozid 2014_IC	0/14	1/2		5.46%	0.07[0,1.27]
Mozid 2014_IM	0/10	3/8		5.94%	0.12[0.01,1.98]
Nasseri 2012	0/30	2/30		5.3%	0.2[0.01,4]
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		4.73%	1.55[0.06,36.94]
Perin 2012b	0/10	0/10			Not estimable
Santoso 2014	0/19	0/9			Not estimable
Tse 2007	0/19	0/9			Not estimable
Van Ramshorst 2009	1/25	0/25		4.78%	3[0.13,70.3]
Wang 2010	0/56	0/56			Not estimable
Wang 2015	0/45	0/45			Not estimable
Yao 2008	0/24	0/23			Not estimable
Zhao 2008	2/18	0/18		5.4%	5[0.26,97.37]
Subtotal (95% CI)	**706**	**510**		**100%**	**0.58[0.29,1.16]**
Total events: 12 (Cells), 17 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=8.42, df=11(P=0.68); I^2=0%					
Test for overall effect: Z=1.53(P=0.13)					
9.1.2 Long term follow-up (≥ 12 months)					
Assmus 2013	6/43	8/39		52.63%	0.68[0.26,1.79]
Erbs 2005	0/13	1/12		5.07%	0.31[0.01,6.94]
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Heldman 2014_BM-MSC	1/19	1/11		6.88%	0.58[0.04,8.36]
Heldman 2014_BMMNC	0/19	0/10			Not estimable
Hu 2011	1/31	2/29		8.91%	0.47[0.04,4.89]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	3/56		5.66%	0.07[0,1.37]
Nasseri 2012	1/30	3/30		10.09%	0.33[0.04,3.03]
Patila 2014	0/13	0/17			Not estimable
Santoso 2014	0/19	2/9		5.68%	0.1[0.01,1.89]
Tse 2007	0/19	1/9		5.08%	0.17[0.01,3.73]
Subtotal (95% CI)	**366**	**258**		**100%**	**0.43[0.21,0.86]**
Total events: 9 (Cells), 21 (No cells)					
Heterogeneity: Tau^2=0; Chi^2=3.86, df=7(P=0.8); I^2=0%					
Test for overall effect: Z=2.37(P=0.02)					



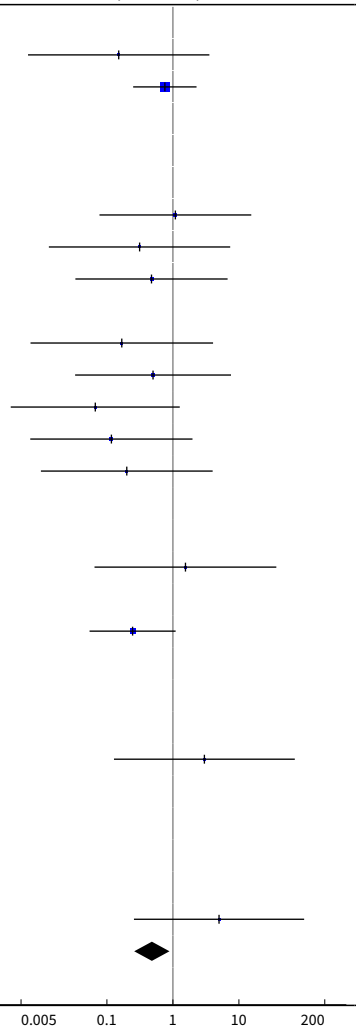
Favours cell therapy | Favours no cell therapy

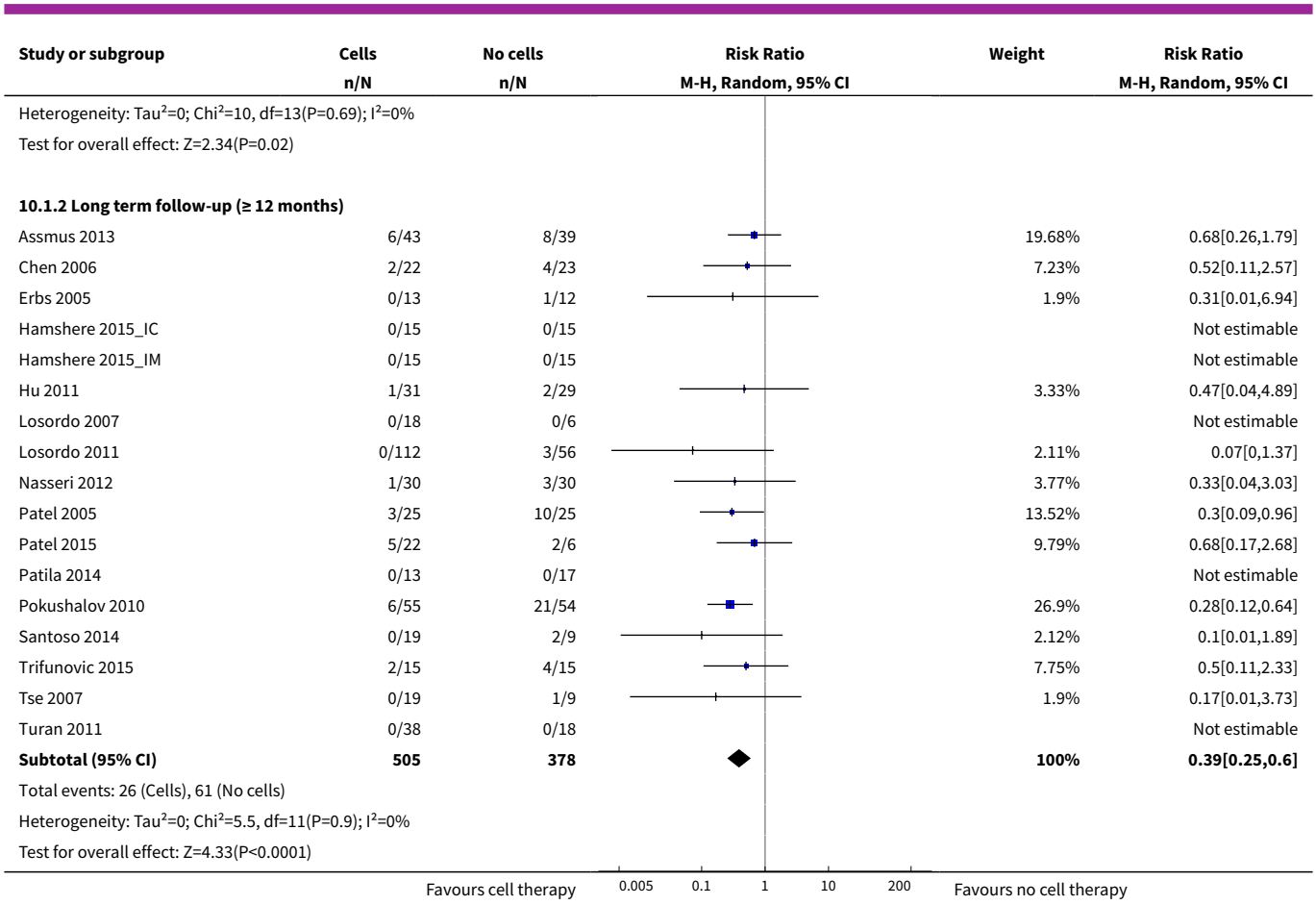
Comparison 10. Sensitivity analysis: excluding studies with high/unclear risk of attrition bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all-cause)	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Short term follow-up (< 12 months)	28	1449	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.26, 0.89]
1.2 Long term follow-up (≥ 12 months)	17	883	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.25, 0.60]

Analysis 10.1. Comparison 10 Sensitivity analysis: excluding studies with high/unclear risk of attrition bias, Outcome 1 Mortality (all-cause).

Study or subgroup	Cells n/N	No cells n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 Short term follow-up (< 12 months)					
Assmus 2006	0/52	1/23		3.78%	0.15[0.01,3.57]
Assmus 2013	5/43	6/39		30.98%	0.76[0.25,2.28]
Erbs 2005	0/13	0/12			Not estimable
Hamshere 2015_IC	0/15	0/15			Not estimable
Hamshere 2015_IM	0/15	0/15			Not estimable
Hendrikx 2006	1/11	1/12		5.39%	1.09[0.08,15.41]
Hu 2011	0/31	1/29		3.78%	0.31[0.01,7.38]
Jimenez-Quevedo 2011	1/19	1/9		5.36%	0.47[0.03,6.74]
Losordo 2007	0/18	0/6			Not estimable
Losordo 2011	0/112	1/56		3.73%	0.17[0.01,4.06]
Mathiasen 2015	1/40	1/20		5.11%	0.5[0.03,7.59]
Mozid 2014_IC	0/14	1/2		4.34%	0.07[0,1.27]
Mozid 2014_IM	0/10	3/8		4.72%	0.12[0.01,1.98]
Nasseri 2012	0/30	2/30		4.22%	0.2[0.01,4]
Patel 2005	0/10	0/10			Not estimable
Perin 2011	0/20	0/10			Not estimable
Perin 2012a	1/61	0/31		3.76%	1.55[0.06,36.94]
Perin 2012b	0/10	0/10			Not estimable
Pokushalov 2010	2/55	8/54		16.73%	0.25[0.05,1.1]
Santoso 2014	0/19	0/9			Not estimable
Tse 2007	0/19	0/9			Not estimable
Turan 2011	0/38	0/18			Not estimable
Van Ramshorst 2009	1/25	0/25		3.8%	3[0.13,70.3]
Wang 2009	0/16	0/16			Not estimable
Wang 2010	0/56	0/56			Not estimable
Wang 2015	0/45	0/45			Not estimable
Yao 2008	0/24	0/23			Not estimable
Zhao 2008	2/18	0/18		4.29%	5[0.26,97.37]
Subtotal (95% CI)	**839**	**610**		**100%**	**0.48[0.26,0.89]**
Total events: 14 (Cells), 26 (No cells)					





ADDITIONAL TABLES

Table 1. Characteristics of study participants

Study ID	Country of study	Patient population	Mean (SD) age of participants (years)	% Male	No. randomised participants receiving intervention	No. randomised participants receiving comparator	Mean duration of follow-up
Ang 2008	UK	CIHD (> 1 chronic myocardial scar; elective CABG)	BMMNC-IM: 64.7 (8.7) BMMNC-IC: 62.1 (8.7) Controls: 61.3 (8.3)	BMMNC-IM: 71.4% BMMNC-IC: 90.5% Controls: 90.0%	42 (21 IM, 21 IC)	21	6 months
Assmus 2006	Germany	CIHD (MI > 3 months; LV dysfunction)	BMMNC: 59 (12) CPC: 54 (12) Controls: 61 (9)	BMMNC: 89% CPC: 79% Controls: 100%	52 (28 MNC, 24 CPC)	23	3 months
Assmus 2013	Germany	CIHD (MI > 3 months; LVEF < 50%; NYHA class II or greater)	BMMNC-LDSW: 65 (12) BMMNC-HDSW: 58 (11) Controls-LDSW: 60 (10) Controls-HDSW: 63 (10)	BMMNC-LDSW: 77% BMMNC-HDSW: 86% Controls-LDSW: 80% Controls-HDSW: 90%	43 (22 LDSW, 21 HDSW)	39 (20 LDSW, 19 HDSW)	45.7 (17) months
Bartunek 2012	Belgium/ Serbia/ Switzerland	HF (LVEF 15% to 40%; ischaemic event > 2 months)	BM-MSC: 55.3 (SE 10.4) Controls: 58.7 (SE 8.2)	BM-MSC: 90.5% Controls: 86.7%	32	15	24 months
Chen 2006	China	CIHD (isolated, chronic LAD; LVEF < 40%)	BM-MSC: 59.3 (6.8) Controls: 57.8 (7.2)	BM-MSC: 88% Controls: 92%	24	24	12 months
Erbs 2005	Germany	CIHD (chronic total occlusion; myocardial ischaemia)	CPC: 63 (7) Controls: 61 (9)	CPC: 71% Controls: 86%	14	14	15 months

Table 1. Characteristics of study participants *(Continued)*

Hamshere 2015_IC	UK	HF (NYHA class II-IV; no revascularisation options)	BMMNC: n/r Controls: n/r	BMMNC: n/r Controls: n/r	15	15	12 months
Hamshere 2015_IM	UK	HF (NYHA class II-IV; no revascularisation options)	BMMNC: n/r Controls: n/r	BMMNC: n/r Controls: n/r	15	15	12 months
Heldman 2014_BMMNC	USA	CIHD (chronic MI; LV dysfunction)	BMMNC: 61.1 (8.4) Controls: 61.3 (9.0)	BMMNC: 89.5% Controls: 100%	22	10	12 months
Heldman 2014_BM-MSC	USA	CIHD (chronic MI; LV dysfunction)	BM-MSC: 57.1 (10.6) Controls: 60.0 (12.0)	BM-MSC: 94.7% Controls: 90.9%	22	11	12 months
Hendrikx 2006	Belgium	CIHD (transmural MI; LV dysfunction; elective CABG)	BMMNC: 63.2 (8.5) Controls: 66.8 (9.2)	BMMNC: 100% Controls: 70%	11	12	4 months
Honold 2012	Germany	CIHD (MI > 3 months; LV regional wall motion abnormality)	CPC: 53.4 (12.3) Controls: 58.8 (7.3)	CPC: 82% Controls: 100%	23	10	60 months
Hu 2011	China	HF (MI > 3 months; LVEF < 30%; elective CABG)	BMMNC: 56.6 (9.7) Controls: 58.3 (8.9)	BMMNC: 88% Controls: 96%	31	29	12 months
Jimenez-Quevedo 2011	Spain	Refractory angina (CCS class II-IV)	CD133+: median 70.0 Controls: median 58.2	CD133+: 78.9% Controls: 100%	19	9	6 months
Losordo 2007	USA	Refractory angina (CCS class III-IV)	CD34+/controls pooled: 62.4 (range 48 to 84)	CD34+/controls pooled: 80%	18 (6 LD, 6 MD 6, HD)	6	6 months

Table 1. Characteristics of study participants *(Continued)*

Losordo 2011	USA	Refractory angina (CCS class III-IV)	CD34+/LD: 61.3 (9.1) CD34+/HD: 59.8 (9.2) Controls: 61.8 (8.5)	CD34+/LD: 83.6% CD34+/HD: 87.5% Controls: 89.3%	112 (56 LD, 56 HD)	56	12 months
Mathiasen 2015	Denmark	HF (NYHA class II-III; LVEF < 45%; no revascularisation options)	BM-MSC: 66.1 (7.7) Controls: 64.2 (10.6)	BM-MSC: 90% Controls: 70%	40	20	6 months
Mozid 2014_IC	UK	HF (NYHA class II-IV; no revascularisation options)	BMMNC/controls pooled (16 participants): 70 (10)	BMMNC/controls pooled (16 participants): 94%	14	2	6 months
Mozid 2014_IM	UK	HF (NYHA class II-IV; no revascularisation options)	BMMNC/controls pooled (18 participants): 64 (9)	BMMNC/controls pooled (18 participants): 100%	10	8	6 months
Nasseri 2012	Germany	HF (LVEF < 35%; elective CABG)	CD133+: 61.9 (7.3) Controls: 62.7 (10.6)	CD133+: 93% Controls: 97%	30	30	6 months
Patel 2005	Argentina	HF (LVEF < 35%; NYHA class III-IV; elective CABG)	CD34+: 64.8 (7.1) Controls: 63.6 (5.2)	CD34+: 80% Controls: 80%	25	25	10 years
Patel 2015	USA/Germany/India	HF (LVEF < 40%; NYHA class III-IV)	BMAC: 58.5 (12.7) Controls: 52.7 (8.5)	BMAC: 91.7% Controls: 100%	24	6	12 months
Patila 2014	Finland	HF (LVEF 15% to 40%; NYHA class II-IV; elective CABG)	BMMNC: median 65 (range 57 to 73) Controls: median 64 (range 58 to 70)	BMMNC: 94.7% Controls: 95.0%	20	19	12 months
Perin 2011	USA	HF (angina/HF symptoms;	BMMNC: 56.3 (8.6)	BMMNC: 50%	20	10	6 months

Table 1. Characteristics of study participants *(Continued)*

		chronic CAD; LVEF < 40%; no revascularisation options)	Controls: 60.5 (6.4)	Controls: 80%			
Perin 2012a	USA	HF (CCS class II-IV or NYHA class II-III, or both; LVEF < 45%; no revascularisation options)	BMMNC: 64.0 (10.9) Controls: 62.3 (8.3)	BMMNC: 86.9% Controls: 93.7%	61	31	6 months
Perin 2012b	USA	HF (CCS class II-IV or NYHA class II-III, or both; LVEF < 45%; no revascularisation options)	ALDH+: 58.2 (6.1) Controls: 57.8 (5.5)	ALDH+: 90% Controls: 80%	10	10	6 months
Pokushalov 2010	Russia	HF (LVEF < 35%; no revascularisation options)	BMMNC: 61 (9) Controls: 62 (5)	BMMNC: 87% Controls: 85%	55	54	12 months
Santoso 2014	Indonesia/China	HF (NYHA class III-IV; LVEF < 40%; no revascularisation options)	BMMNC: 58 (5.9) Controls: 60 (5.6)	BMMNC: 95% Controls: 100%	19	9	6 months
Trifunovic 2015	Serbia	CIHD (MI < 30 days; LVEF < 40%; NYHA class III-IV; elective CABG)	BMMNC: 53.8 (10.1) Controls: 60.0 (6.8)	BMMNC: 93.3% Controls: 93.3%	15	15	Median 5 years (IQR 2.5 to 7.5)

Table 1. Characteristics of study participants *(Continued)*

Tse 2007	China/Australia	Refractory angina (CCS class III-IV)	BMMNC: 65.2 (8.3) Controls: 68.9 (6.3)	BMMNC: 79% Controls: 88%	19	9	6 months
Turan 2011	Germany	CIHD (MI > 3 months; LV dysfunction)	BMMNC: 62 (10) Controls: 60 (9)	BMMNC: 52.6% Controls: 55.6%	38	18	12 months
Van Ramshorst 2009	The Netherlands	Refractory angina (CCS class II-IV)	BMMNC: 64 (8) Controls: 62 (9)	BMMNC: 92% Controls: 80%	25	25	6 months
Wang 2009	China	Refractory angina (MI > 1 month)	CD34+: 60.6 (n/r) Controls: 60.0 (n/r)	CD34+: 56.3% Controls: 63.3%	16	16	6 months
Wang 2010	China	Refractory angina (CCS class III-IV)	CD34+: range 42 to 80 Controls: range 43 to 80	CD34+: 51.8% Controls: 50.0%	56	56	6 months
Wang 2014	China	CIHD (LVEF < 35%)	CD133+: n/r Controls: n/r	CD133+: n/r Controls: n/r	35	35	6 months
Wang 2015	China	CIHD (multivessel disease; MI > 4 weeks; elective CABG)	BMMNC: 61.4 (7.5) Controls: 62.9 (6.9)	BMMNC: 82% Controls: 78%	45	45	6 months
Yao 2008	China	CIHD (MI > 6 months)	BMMNC: 54.8 (11.5) Controls: 56.3 (7.9)	BMMNC: 96% Controls: 96%	24	23	6 months
Zhao 2008	China	HF (LVEF < 40%; elective CABG)	BMMNC: 60.3 (10.4) Controls: 59.1 (15.7)	BMMNC: 83.3% Controls: 83.3%	18	18	6 months

ALDH: aldehyde dehydrogenase
BMAC: bone marrow aspirate concentrate
BMMNC: bone marrow mononuclear cells
BM-MSC: bone marrow-derived mesenchymal stem cells
CABG: coronary artery bypass grafting
CCS: Canadian Cardiovascular Society

CIHD: chronic ischaemic heart disease
CPC: circulating progenitor cells
EF: ejection fraction
HD: high dose
HDSW: high dose shockwave
HF: heart failure
IC: intracoronary
IM: intramyocardial
IQR: interquartile range
LAD: left ventricular assist device
LD: low dose
LDSW: low dose shockwave
LV: left ventricular
LVEF: left ventricular ejection fraction
MD: medium dose
MI: myocardial infarction
MNC: mononuclear cells
n/r: not reported
NYHA: New York Heart Association
SD: standard deviation
SE: standard error
SW: shockwave

Table 2. Characteristics of study interventions

Study ID	Co-intervention	Intervention given by:	Route of cell administration	Intervention cell type	How are cells obtained?	What were they resuspended in?	Dose administered?	Comparator arm (placebo or control)
Ang 2008	CABG	Cardiothoracic surgeon	IC or IM	BMMNC	BM aspiration (**)	Autologous serum	IM: 84 (56) million cells IC: 115 (73) million cells	No additional therapy (control)
Assmus 2006	Standard medical therapy	Cardiologist	IC	BMMNC or CPC	BM aspiration (**) for BMMNC. Vein puncture, mononuclear cell isolation by gradient centrifugation and culture for 3 days for CPC	n/r	BMMNC: 205 (110) million cells CPC: 22 (11) million cells	No additional therapy (control)

Table 2. Characteristics of study interventions *(Continued)*

Assmus 2013	Shock-wave	Cardiolo-gist	IC	BMMNC	BM aspiration (**)	X-VIVO 10 medi-um and autologous serum	HDSW: 123 (69) mil-lion cells LDSW: 150 (77) mil-lion cells	Placebo (10 mL X-VIVO 10 medi-um and autologous serum)
Bartunek 2012	Standard medical therapy	Cardiolo-gist	IC	BM-MSC (car-diopoietic cells)	BM aspiration (**), culture for 6 days and exposure to cardiopoietic fac-tors	Preservation solu-tion (no details)	733 (range 605 to 1168) million cells	No additional therapy (control)
Chen 2006	Standard medical therapy	Cardiolo-gist	IC	BM-MSC	BM aspiration (**), culture for 7 days to select MSC	Heparinised saline	5 million cells	No additional therapy (control)
Erbs 2005	G-CSF	Cardiolo-gist	IC	CPC	G-CSF infusion for 4 days prior to vein puncture, mononu-clear cell isolation by gradient cen-trifugation and cul-ture for 3 days for CPC	Saline and 10% au-tologous serum	69 (14) million cells	Placebo (cell-free serum solu-tion)
Hamshere 2015_IC	G-CSF	Cardiolo-gist	IC	BMMNC	G-CSF infusion for 5 days and BM aspi-ration (**)	Autologous serum	n/r	Placebo (10 mL autologous serum)
Hamshere 2015_IM	G-CSF	Cardiolo-gist	IM	BMMNC	G-CSF infusion for 5 days and BM aspi-ration (**)	Autologous serum	n/r	Placebo (2 mL autologous serum)
Heldman 2014_BMM-NC	Standard medical therapy	Cardiolo-gist	IM	BMMNC	BM aspiration (**)	n/r	n/r	Placebo (vehicle medium)
Heldman 2014_BM-MSC	Standard medical therapy	Cardiolo-gist	IM	BM-MSC	BM aspiration (**), culture to select MSC	n/r	n/r	Placebo (vehicle medium)
Hendrikx 2006	CABG	Cardiotho-racic sur-geon	IM	BMMNC	BM aspiration (**)	Heparinised saline	60 (31) million cells	Placebo (heparinised saline)

Table 2. Characteristics of study interventions *(Continued)*

Honold 2012	G-CSF	Cardiologist	IC	CPC	G-CSF infusion for 5 days prior to vein puncture, mononuclear cell isolation by gradient centrifugation and culture for 4 days for CPC	n/r	29 (12) million cells	No additional therapy (control)
Hu 2011	CABG	Cardiothoracic surgeon	IC	BMMNC	BM aspiration (**)	Saline solution and 20% autologous serum	132 (107) million cells	Placebo (8 mL saline; 2 mL autologous serum)
Jimenez-Quevedo 2011	G-CSF	Cardiologist	IM	CD133+	G-CSF infusion for 5 days prior to leukapheresis, mononuclear cell isolation by gradient centrifugation immunomagnetic selection to isolate CD133+ cells	Normal saline solution	20 to 30 million cells	No additional therapy (control)
Losordo 2007	G-CSF	Cardiologist	IM	CD34+	G-CSF infusion for 5 days prior to leukapheresis, mononuclear cell isolation by gradient centrifugation immunomagnetic selection to isolate CD34+ cells	Saline solution and 5% autologous serum	LD: 0.05 million cells MD: 0.1 million cells HD: 0.5 million cells	Placebo (0.9% sodium chloride; 5% autologous plasma)
Losordo 2011	G-CSF	Cardiologist	IM	CD34+	G-CSF infusion for 5 days prior to leukapheresis, mononuclear cell isolation by gradient centrifugation immunomagnetic selection to isolate CD34+ cells	Saline solution and 5% autologous serum	LD: 0.1 million cells HD: 0.5 million cells	Placebo (0.9% sodium chloride; 5% autologous plasma)

Table 2. Characteristics of study interventions *(Continued)*

Mathiasen 2015	Standard medical therapy	Cardiologist	IM	BM-MSC	BM aspiration (**), culture for 14 to 35 days to select MSC	Phosphate buffered saline with a drop of the participant's blood	77.5 (68) million cells	Placebo (phosphate buffered saline mixed with drop of participant's blood)
Mozid 2014_IC	G-CSF	Cardiologist	IC	BMMNC	G-CSF infusion for 5 days and BM aspiration (**)	Autologous serum	86 (110) million cells	Placebo (10 mL autologous serum)
Mozid 2014_IM	G-CSF	Cardiologist	IM	BMMNC	G-CSF infusion for 5 days and BM aspiration (**)	Autologous serum	52 (53) million cells	Placebo (2 mL autologous serum)
Nasseri 2012	CABG	Cardiothoracic surgeon	IM	CD133+	BM aspiration (**), immunomagnetic selection to isolate CD133+ cells	Sodium chloride and 10% autologous serum	Median 5.1 million cells	Placebo (isotonic saline solution; 10% autologous serum)
Patel 2005	CABG	Cardiothoracic surgeon	IM	CD34+	BM aspiration (**), immunomagnetic selection to isolate CD34+ cells	Heparinised saline and autologous serum	Median 22 million cells	No additional therapy (control)
Patel 2015	Standard medical therapy	Cardiologist	IC	BMAC	BM aspiration (**) and concentration	Autologous serum	3700 (900) million cells	No additional therapy (control)
Patila 2014	CABG	Cardiothoracic surgeon	IM	BMMNC	BM aspiration (**)	Medium 199 containing albumin, heparin	Median 840 (range 52 to 135) million cells	Placebo (vehicle medium)
Perin 2011	Standard medical therapy	Cardiologist	IM	BMMNC	BM aspiration (**)	Saline containing 5% human serum albumin	2 million cells	No additional therapy (control)
Perin 2012a	Standard medical therapy	Cardiologist	IM	BMMNC	BM aspiration (**)	Saline containing 5% human serum albumin	100 million cells	Placebo (cell-free suspension in same volume)
Perin 2012b	Standard medical therapy	Cardiologist	IM	ALDH+	BM aspiration (**) and cell sorting	Pharmaceutical grade human serum albumin	2.4 (1.3) million cells	Placebo (5% pharmaceutical serum albumin)

Table 2. Characteristics of study interventions *(Continued)*

Pokushalov 2010	Standard medical therapy	Cardiologist	IM	BMMNC	BM aspiration (**)	Heparinised saline	41 (16) million cells	No additional therapy (control)
Santoso 2014	Standard medical therapy	Cardiologist	IM	BMMNC	BM aspiration (**)	Phosphate buffered saline with 10% autologous plasma	n/r	Placebo (phosphate buffered saline; 10% autologous plasma)
Trifunovic 2015	CABG	Cardiothoracic surgeon	IM	BMMNC	BM aspiration (**)	n/r	70.7 (32.4) million cells	No additional therapy (control)
Tse 2007	Standard medical therapy	Cardiologist	IM	BMMNC	BM aspiration (**)	Phosphate buffered saline with 10% autologous plasma	15 million cells	Placebo (8 - 12 x 0.1 mL phosphate buffered saline with 10% autologous serum)
Turan 2011	Standard medical therapy	Cardiologist	IC	BMMNC	BM aspiration (**)	n/r	99 (25) million cells	No additional therapy (control)
Van Ramshorst 2009	Standard medical therapy	Cardiologist	IM	BMMNC	BM aspiration (**)	Phosphate buffered saline with 0.5% human serum albumin	98 (6) million cells	Placebo (0.9% sodium chloride; 0.5% human serum albumin)
Wang 2009	Standard medical therapy	Cardiologist	IC	CD34+	BM aspiration (**), immunomagnetic selection to isolate CD34+ cells	Normal saline	Range 1.0 to 6.1 million cells	No additional therapy (control)
Wang 2010	Standard medical therapy	Cardiologist	IC	CD34+	BM aspiration (**), immunomagnetic selection to isolate CD34+ cells	Saline and human serum albumin	56 (23) million cells	Placebo (saline; human serum albumin)
Wang 2014	Standard medical therapy	Cardiologist	IM	CD133+	n/r	n/r	n/r	Placebo (n/r)
Wang 2015	CABG	Cardiothoracic surgeon	IM	BMMNC	BM aspiration (**)	Heparinised saline	521 (44) million cells	Placebo (saline solution)

Table 2. Characteristics of study interventions *(Continued)*

Yao 2008	Standard medical therapy	Cardiologist	IC	BMMNC	BM aspiration (**)	Heparinised saline	72 million cells	Placebo (0.9% sodium chloride containing heparin)
Zhao 2008	CABG	Cardiothoracic surgeon	IM	BMMNC	BM aspiration (**)	Heparinised saline	659 (512) million cells	Placebo (saline)

**BM aspiration - bone marrow aspiration and isolation of bone marrow mononuclear cells by gradient centrifugation.
ALDH: aldehyde dehydrogenase
BM: bone marrow
BMAC: bone marrow aspirate concentrate
BMMNC: bone marrow mononuclear cells
BM-MSC: bone marrow-derived mesenchymal stem cells
CABG: coronary artery bypass grafting
CPC: circulating progenitor cells
G-CSF: granulocyte colony-stimulating factor
HD: high dose
HDSW: high dose shockwave
IC: intracoronary
IM: intramyocardial
LD: low dose
LDSW: low dose shockwave
MD: medium dose
MSC: mesenchymal stem cells
n/r: not reported
SW: shockwave

Table 3. Summary of outcome reporting *(Continued)*

Study ID	Primary outcomes				Secondary outcomes																	
	All-cause mortality		Non-fatal MI		Hospital readmission for HF		Composite MACE[a]		Arrhythmias		NYHA class		CCS class		Angina frequency		Exercise tolerance		Quality of life		LVEF[b]	
	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT	ST	LT
Ang 2008	FR	NR	PR*	NR	NR	NR	NR	NR	PR*	NR	PR	NR	PR	NR	NR	NR	NR	NR	NR	NR	FR	NR
Assmus 2006	FR	NR	FR	NR	FR	NR	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FR	NR

Table 3. Summary of outcome reporting *(Continued)*

Assmus 2013	FR	FR	NR	FR	FR	FR	NR	FR	NR	FR	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FR	NR
Bartunek 2012	PR*	FR	NR	NR	NR	FR	NR	NR	PR	PR	PR	NR	NR	NR	NR	NR	FR	NR	PR	NR	FR	NR
Chen 2006	NR	FR	NR	NR	NR	NR	NR	NR	PR*	NR	FR	FR	NR	NR	NR	NR	FR	FR	NR	NR	FR	FR
Erbs 2005	PR*	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FR	FR	NR	NR	FR	FR
Hamshere 2015_IC	PR*	PR*	PR*	FR	PR*	PR*	PR*	FR	FR	FR	FR	FR	FR	FR	NR	NR	NR	NR	NR	NR	PR	PR
Hamshere 2015_IM	PR*	PR*	PR*	PR*	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	NR	NR	NR	NR	NR	NR	PR	PR
Heldman 2014_BMMNC	PR*	PR*	NR	PR*	NR	FR	PR*	FR	NR	NR	NR	PR	NR	NR	NR	NR	FR	FR	FR	FR	NR	PR
Heldman 2014_BM-MSC	PR*	FR	NR	PR*	NR	PR*	PR*	FR	NR	NR	NR	PR	NR	NR	NR	NR	FR	FR	FR	FR	NR	PR
Hendrikx 2006	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FR	NR
Honold 2012	PR*	FR	FR	FR	PR*	FR	NR	NR	NR	NR	FR	FR	NR	NR	NR	NR	FR	FR	NR	NR	FR	FR
Hu 2011	FR	FR	PR*	NR	NR	NR	FR	NR	PR*	FR	NR	NR	NR	NR	NR	NR	FR	NR	NR	NR	FR	FR
Jimenez-Quevedo 2011	FR	NR	PR*	NR	NR	NR	PR	NR	FR	NR	NR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR
Losordo 2007	PR*	PR*	PR*	PR*	NR	NR	NR	NR	FR	FR	NR	NR	FR	NR	FR	NR	FR	NR	PR	NR	NR	NR
Losordo 2011	FR	FR	NR	FR	NR	FR	NR	PR	NR	NR	NR	NR	PR	PR	FR	NR	FR	FR	FR	FR	NR	NR
Mathiasen 2015	FR	NR	PR*	NR	FR	NR	NR	NR	FR	NR	PR	NR	PR	NR	PR	NR	PR	NR	PR	NR	FR	NR
Mozid 2014_IC	FR	NR	PR*	NR	FR	NR	FR	NR	PR*	NR	FR	NR	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mozid 2014_IM	FR	NR	PR*	NR	PR*	NR	FR	NR	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nasseri 2012	FR	FR	NR	NR	NR	NR	NR	NR	NR	NR	FR	NR	FR	NR	NR	NR	PR	NR	PR	NR	FR	NR
Patel 2005	PR*	FR	NR	NR	NR	NR	NR	NR	PR*	NR	FR	NR	NR	NR	NR	NR	NR	NR	NR	NR	PR	PR
Patel 2015	NR	FR	NR	NR	NR	FR	NR	NR	NR	PR*	NR	FR	NR	PR	NR	NR	NR	NR	NR	PR	PR	PR

Table 3. Summary of outcome reporting *(Continued)*

Patila 2014	NR	PR*	NR	PR*	NR	FR	NR	NR	NR	NR	NR	FR	NR	NR	NR	NR	NR	NR	NR	PR	NR	FR
Perin 2011	PR*	NR	PR*	NR	NR	NR	NR	NR	PR*	NR	FR	NR	FR	NR	NR	NR	NR	NR	FR	NR	FR	NR
Perin 2012a	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR	FR	NR	FR	NR	NR	NR	FR	NR	NR	NR	FR	NR
Perin 2012b	PR*	NR	FR	NR	NR	NR	NR	NR	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR	NR	NR	FR	NR
Pokushalov 2010	FR	FR	NR	NR	NR	NR	NR	NR	PR*	PR*	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR	FR
Santoso 2014	PR*	FR	NR	NR	NR	NR	NR	NR	FR	NR	PR	NR	NR	NR	NR	NR	PR	NR	NR	NR	FR	NR
Trifunovic 2015	NR	FR	NR	NR	NR	NR	NR	NR	NR	NR	FR	FR	NR	NR	NR	NR	FR	FR	NR	NR	FR	FR
Tse 2007	PR*	FR	FR	NR	NR	NR	NR	NR	PR*	NR	FR	NR	FR	NR	NR	NR	FR	NR	NR	NR	FR	NR
Turan 2011	PR*	PR*	NR	NR	NR	NR	NR	NR	NR	NR	FR	FR	NR	NR	NR	NR	NR	NR	NR	NR	FR	FR
Van Ramshorst 2009	FR	NR	PR*	NR	NR	NR	NR	NR	PR*	NR	NR	NR	FR	NR	NR	NR	FR	NR	FR	NR	FR	FR
Wang 2009	PR*	NR	PR*	NR	NR	NR	NR	NR	PR*	NR	NR	NR	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR
Wang 2010	PR*	NR	PR*	NR	NR	NR	NR	NR	FR	NR	NR	NR	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR
Wang 2014	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	PR	NR	NR	NR	NR	NR	PR	NR	NR	NR	FR	NR
Wang 2015	PR*	NR	NR	NR	NR	NR	NR	NR	PR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FR	NR
Yao 2008	PR*	NR	FR	NR	FR	NR	NR	NR	PR*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	PR	NR
Zhao 2008	FR	NR	PR*	NR	NR	NR	NR	NR	FR	NR	FR	NR	FR	NR	NR	NR	NR	NR	NR	NR	FR	NR
Total (%) analysed[c]	1637 (85.8)	1010 (53.0)	881 (46.2)	461 (24.2)	482 (25.3)	495 (26.0)	288 (15.1)	201 (10.5)	959 (50.3)	363 (19.0)	741 (38.9)	346 (18.1)	608 (31.9)	142 (7.4)	428 (22.4)	82 (4.3)[d]	535 (28.1)	227 (11.9)	197 (10.3)[e]	151 (7.9)[e]	439 (23.0)[f]	110 (5.8)[f]

CCS: Canadian Cardiovascular Society; FR: full reporting, outcome included in analysis; HF: heart failure; LT: long-term follow-up (≥ 12 months); LVEF: left ventricular ejection fraction; MACE: major adverse clinical events; MI: myocardial infarction; NR: outcome not reported; NYHA: New York Heart Association; PR: partial reporting with insufficient information on outcome reported for inclusion in analysis; PR*: no incidence of outcome observed; ST: short-term follow-up (< 12 months)

[a]Composite measure of mortality, reinfarction, or rehospitalisation for heart failure.

[b]LVEF measured by any method.

[c]Total number of participants included in meta-analysis of outcome (% of total number of participants from all included studies).
[d]No meta-analysis was performed, as only one study reported values suitable for inclusion.
[e]Minnesota Living with Heart Failure Questionnaire.
[f]Total number analysed given for LVEF measured by magnetic resonance imaging.

Table 4. Clinical (dichotomous) outcomes *(Continued)*

Study ID	Number of analysed participants		All-cause mortality events			Non-fatal MI events			Hospital readmission for HF			Composite MACE[a]			Arrhythmia events		
	Cells	No cells	Cells	No cells	Length of follow-up	Cells	No cells	Length of follow-up	Cells	No cells	Length of follow-up	Cells	No cells	Length of follow-up	Cells	No cells	Length of follow-up
Ang 2008	42	19	1	1	6 mths[a]	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Assmus 2006	52	23	0	1	3 mths	1	0	3 mths	1	1	3 mths	1	1	3 mths	0	1	3 mths
Assmus 2013	43	39	6	8	45.7 (17) mths	1	4	45.7 (17) mths	8	13	45.7 (17) mths	14	19	45.7 (17) mths	6	13	45.7 (17) mths
Bartunek 2012	21	15	1	2	24 mths	n/r	n/r	n/r	6	4	24 mths	n/r	n/r	n/r	n/r	n/r	n/r
Chen 2006	22	23	2	4	12 mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Erbs 2005	13	12	0	1	15 mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Hamshere 2015_IC	15	15	0	0	12 mths	1	0	12 mths	0	0	12 mths	1	0	12 mths	1	1	12 mths
Hamshere 2015_IM	15	15	0	0	12 mths	0	0	12 mths	1	1	12 mths	1	1	12 mths	0	1	12 mths
Heldman 2014_BMMNC	19	10	0	0	12 mths	0	0	12 mths	0	1	12 mths	0	1	12 mths	n/r	n/r	n/r
Heldman 2014_BM-MSC	19	11	1	1	12 mths	0	0	12 mths	0	0	12 mths	1	1	12 mths	n/r	n/r	n/r

Table 4. Clinical (dichotomous) outcomes *(Continued)*

Hendrikx 2006	11	12	1	1	4 mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Honold 2012	23	9	0	1	60 mths	1	2	60 mths	0	2	60 mths	n/r	n/r	n/r	n/r	n/r	n/r
Hu 2011	31	29	1	2	12 mths	0	0	6 mths	n/r	n/r	n/r	3	4	6 mths	1	0	12 mths
Jimenez-Quevedo 2011	19	9	1	1	6 mths	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	1	1	6 mths
Losordo 2007	18	6	0	0	12 mths	0	0	12 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	1	12 mths
Losordo 2011	112	56	0	3	12 mths	6	7	12 mths	3	4	12 mths	n/r	n/r	n/r	n/r	n/r	n/r
Mathiasen 2015	40	20	1	1	6 mths	0	0	6 mths	6	2	6 mths	n/r	n/r	n/r	3	1	6 mths
Mozid 2014_IC	14	2	0	1	6 mths	0	0	6 mths	1	0	6 mths	1	1	6 mths	0	0	6 mths
Mozid 2014_IM	10	8	0	3	6 mths	0	0	6 mths	0	0	6 mths	0	3	6 mths	2	2	6 mths
Nasseri 2012	30	30	1	3	34 mths[b]	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Patel 2005	25	25	3	10	10 yrs	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Patel 2015	22	6	5	2	12 mths	n/r	n/r	n/r	2	0	12 mths	n/r	n/r	n/r	0	0	12 mths
Patila 2014	13[c]	17[c]	0	0	Median 60 mths	0	0	Median 60 mths	1	1	Median 60 mths	n/r	n/r	n/r	n/r	n/r	n/r
Perin 2011	20	10	0	0	6 mths	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Perin 2012a	61	31	1	0	6 mths	1	0	6 mths	3	5	6 mths	n/r	n/r	n/r	n/r	n/r	n/r
Perin 2012b	10	10	0	0	6 mths	1	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	3	2	6 mths
Pokushalov 2010	55	54	6	21	12 mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	0	0	12 mths

Table 4. Clinical (dichotomous) outcomes *(Continued)*

Santoso 2014	19	9	0	2	23 (8) mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	1	1	6 mths
Trifunovic 2015	15	15	2	4	Median 5 yrs	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Tse 2007	19	9	0	1	19 (9) mths	0	1	3 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Turan 2011	38	18	0	0	12 mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Van Ramshorst 2009	25	25	1	0	6 mths	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Wang 2009	16	16	0	0	6 mths	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	0	6 mths
Wang 2010	56	56	0	0	6 mths	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	0	1	6 mths[d]
Wang 2014	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Wang 2015	45	45	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r	n/r
Yao 2008	24	23	0	0	6 mths	0	1	6 mths	1	2	6 mths	n/r	n/r	n/r	0	0	6 mths
Zhao 2008	18	18	2	0	6 mths	0	0	6 mths	n/r	n/r	n/r	n/r	n/r	n/r	1	0	6 mths

HF: heart failure; MACE: major adverse clinical events; MI: myocardial infarction; n/r: not reported

[a]Ang 2008: participants followed up for six months; mortality reported as "death within 30 days of treatment".

[b]Nasseri 2012: deaths reported "beyond follow-up period" occurred at 31 and 34 months.

[c]Patila 2014: mortality rates reported in 20/19 participants at 12 months and 13/17 participants at 60 months.

[d]Wang 2010: values are for ventricular arrhythmia (atrial arrhythmia also reported but unclear whether any participant overlap).

Table 5. Periprocedural adverse events

Study ID	Periprocedural adverse events
Ang 2008	2 deaths (1 control, 1 intracoronary cell therapy) occurred within 30 days of treatment. Reasons were not given, but neither was considered to be related to cell therapy.
Assmus 2006	In-hospital events: MI occurred in 1 CPC participant and ventricular arrhythmia detected during monitoring in 1 control participant.
Assmus 2013	n/r (only safety of shockwave procedure reported)
Bartunek 2012	In the cell therapy group, 1 participant had ventricular tachycardia during procedure which was resolved by cardioversion, and 1 participant had blurred vision after intervention (participant had pre-existing ophthalmic migraines). Other reported adverse events (gastrointestinal, hepatobiliary, respiratory, thoracic, mediastinal, and peripheral vascular disorders) were not considered to be related to cell therapy.
Chen 2006	3 participants in cell therapy group experienced a transient episode of pulmonary oedema during the injection of stem cells. No sustained arrhythmias were monitored during the procedure.
Erbs 2005	1 cell therapy and 1 control participant reported headache, and 1 control participant developed fever during G-CSF stimulation. G-CSF resulted in comparable increases in serum C-reactive protein levels and blood leukocyte count in both CPC and control groups (returned to baseline values within 4 days after G-CSF). Neither G-CSF injection nor intracoronary transplantation of CPC caused any elevation in troponin T levels.
Hamshere 2015_IC	n/r
Hamshere 2015_IM	n/r
Heldman 2014_BMMNC	No participant had significant postprocedural pericardial effusion. Small transient increases in CK-MB and serum troponin I were observed. There were no treatment emergent serious adverse events among any of participants who received cell therapy.
Heldman 2014_BM-MSC	No participant had significant postprocedural pericardial effusion. Small transient increases in CK-MB and serum troponin I were observed. There were no treatment emergent serious adverse events among any of participants who received cell therapy.
Hendrikx 2006	1 cell therapy participant died on postoperative day 7 from a perforated oesophageal ulcer complicated by mediastinitis. 1 control participant died on the 5th postoperative day from multiorgan failure secondary to low cardiac output syndrome.
Honold 2012	Mild cephalgies and episodes of mild to moderate bone and muscular pain were reported during 5-day course of G-CSF. No participant developed chest pain episodes or clinical signs of decompensated HF. No novel ischaemia-related ECG changes were observed during G-CSF treatment and after intracoronary CPC infusion. Troponin T levels remained unchanged. Moreover, no specific G-CSF-mediated severe complications occurred. Intracoronary infusions were successfully performed without any procedural complications.
Hu 2011	2 participants (unclear which treatment arm) had neurological complications but recovered and were discharged. No participants had arrhythmia.
Jimenez-Quevedo 2011	G-CSF treatment was well tolerated, all participants presented bone pain as the only symptom. After cell injection, none of the participants had a significant rise in creatine phosphokinase, symptoms, ECG changes, or echocardiographic abnormalities.
Losordo 2007	13 participants reported transient increase in angina frequency after administration of G-CSF. There were no cardiac enzyme elevations, MIs, acute coronary syndromes, or deaths. 1 partici-

Table 5. Periprocedural adverse events *(Continued)*

	pant in the placebo group developed ventricular tachycardia during the mapping procedure. No arrhythmias were detected by implantable cardioverter defibrillator, LifeVest, or Holter monitoring in any participant during or after the injection procedure.
Losordo 2011	Administration of G-CSF was associated with bone pain (20.1%), angina (17.4%), CHF (2 participants), and 8 participants had troponin elevations consistent with non-STEMI. In 1 participant a thrombus was observed on the mapping catheter tip as it was removed. 2 participants experienced an apparent myocardial perforation during the injection procedure (1 resulted in haemothorax, which was successfully treated; 1 resulted in cardiac tamponade; this participant died after unsuccessful pericardiocentesis procedure). Elevated troponin levels were observed in 28% of participants at some point during the mobilisation and injection period, all of which were minor and subclinical except for those mentioned above.
Mathiasen 2015	1 participant with a history of episodic ventricular tachycardia developed ventricular tachycardia during the NOGA mapping procedure. Another participant experienced double vision and dizziness during the injection procedure; cerebral-CT afterwards was normal, but the incident was diagnosed as a minor stroke by the neurologist. 1 participant from the treatment group suffered a stroke 12 days after treatment.
Mozid 2014_IC	The most common side effects from G-CSF were bone pain (22%) and low grade pyrexia (65%) (reported in all G-CSF groups combined). Bleeding from the arterial access site did not differ significantly between the 2 intervention arms. All episodes were minor and resolved with conservative treatment within 24 h of the procedure. As expected, there were increases in troponin and creatine kinase levels postprocedure in both arms.
Mozid 2014_IM	The most common side effects from G-CSF were bone pain (22%) and low grade pyrexia (65%) (reported in all G-CSF groups combined). There were 3 cases of arrhythmia during the intramyocardial procedure that required treatment. Of these, 1 participant developed atrial fibrillation, which reverted to sinus rhythm within 24 h of the procedure. Another participant developed transient complete heart block periprocedure requiring temporary pacing only. The final participant suffered an episode of pulseless ventricular tachycardia following intramyocardial injection, which was successfully cardioverted with a single 200 J external defibrillation and remained haemodynamically stable afterwards. 1 participant died from suspected acute LV failure 6 days after discharge. Bleeding from the arterial access site did not differ significantly between the two intervention arms. All episodes were minor and resolved with conservative treatment within 24 h of the procedure. As expected, there were increases in troponin and creatine kinase levels postprocedure in both arms.
Nasseri 2012	2 participants in the placebo group died early postoperatively: 1 died on day 8 after developing *Candida* sepsis following LV failure despite intra-aortic balloon pump and catecholamine treatment and mechanical assist device implantation, and 1 died on day 22 (reason not given).
Patel 2005	1 participant in the OPCAB plus stem cell therapy group had a haematoma at the bone marrow harvest site. There were no other adverse events in either group (i.e. neurologic, haematologic, vascular, death, or infection events). No participants had any postoperative arrhythmias.
Patel 2015	5 participants who received BMAC experienced “non-serious adverse events possibly related to the procedure”. Procedure-related complications included haematomas at the catheterisation site and elevated serum creatinine levels.
Patila 2014	There were no differences between treatment groups in participants’ haemodynamics, arterial blood gases, systemic vein oxygen level, blood glucose, acid–base balance, lactate, haemoglobin, body temperature, and diuresis, as well as medications needed. Perioperative measures are reported in detail in Lehtinen 2014.
Perin 2011	No perforations or arrhythmias were associated with cell injection procedures. Postprocedural transient left bundle-branch block (resolved in 24 h) was seen in 1 treated and 1 control participant. 1 treated participant had non-significant pericardial effusion. No sustained ventricular arrhythmias were observed by Holter monitoring in any participant. Transient fever but no sepsis occurred in 1 control participant.

Table 5. Periprocedural adverse events *(Continued)*

Perin 2012a	1 participant experienced a limited retrograde catheter-related dissection of the abdominal aorta (withdrawn from study). 1 participant experienced recurrent ventricular tachycardia with hypotension (and received only a small volume of cell product).
Perin 2012b	No major adverse clinical cardiac events were associated with the cell injection procedures, including no perforations. Electromechanical mapping–related ventricular tachycardia occurred in 2 control participants, and ventricular fibrillation occurred in 1 control participant. No deaths occurred, and HF was not exacerbated in any participant. Holter monitoring showed no sustained ventricular arrhythmia in any participant.
Pokushalov 2010	No periprocedural complications occurred in participants who received cell therapy. 2-dimensional echocardiography did not reveal postprocedural pericardial effusion. Creatine kinase activity and peak troponin T level remained unaltered. No new periprocedural arrhythmias were recorded during 24 h of consecutive electrocardiographic monitoring. An implantable cardioverter defibrillator was implanted to 2 participants with ventricular tachycardia prior to cell injections.
Santoso 2014	There were no acute procedural-related complications, including stroke, transient ischaemic attack, ECG changes, sustained ventricular or atrial arrhythmias, and elevation of CPK-MB. There was also no echocardiographic evidence of pericardial effusion in any participant within the first 24 h of the procedure.
Trifunovic 2015	The early postoperative course was uneventful in both groups with no significant differences between them with regard to adverse side effects during hospital stay. There were no significant differences in cardiac-specific enzymes activities after the operation or the number of atrial fibrillation episodes or appearance of pericardial effusion between the groups.
Tse 2007	There were no acute procedure-related complications, including stroke, transient ischaemic attack, ECG changes, sustained ventricular or atrial arrhythmias, elevation of CPK-MB, or echocardiographic evidence of pericardial effusion within the first 24 h after the procedure.
Turan 2011	There was no inflammatory response or myocardial reaction (white blood cell count, C-reactive protein, CK, troponin) after cell therapy. There were no immediate pre- or postprocedure adverse complications, new electrocardiographic changes, or significant elevations in CK or troponin, and no inflammatory response was observed in participants with bone marrow cell transplant.
Van Ramshorst 2009	In the placebo group, a greater than 0.5-centimetre pericardial effusion was detected on 2-dimensional echocardiography in an asymptomatic participant 2 days after the injection procedure, and pericardiocentesis was subsequently performed.
Wang 2009	No periprocedural adverse events; cardiac proteins in normal range.
Wang 2010	No increase in angina frequency or usage of sublingual NTG was observed in participants of either group. There were no cardiac enzyme elevations, MIs, acute coronary syndromes, or deaths. No participants from either group developed ventricular tachycardia during the cell or saline infusion procedure. No arrhythmias were detected by Holter monitoring in any participant during or after the infusion process.
Wang 2014	n/r
Wang 2015	Predischarge arrhythmias were reported (as number of events) in both cell therapy and control participants.
Yao 2008	Intracoronary application of BMC was performed without any acute or long-term side effects. There was no inflammatory response or myocardial reaction (i.e. white blood cell count, C-reactive protein, and creatinine phosphokinase) after cell therapy.
Zhao 2008	In the perioperative period, sporadic ventricular premature beats and self terminating bouts of rapid atrial fibrillation were observed in both groups. However, 2 participants developed VF, and 1

Table 5. Periprocedural adverse events *(Continued)*

	died in the BMMNC group: 1 participant developed VF on the 5th day postoperatively but was successfully resuscitated and VF well-controlled, and the other developed refractory VF 5 hours' postoperatively with death on postoperative day 3. There were no ventricular arrhythmias in the control group.

AMI: acute myocardial infarction
BM: bone marrow
BMAC: bone marrow aspirate concentrate
BMC: bone marrow cells

BMMNC: bone marrow mononuclear cells
CHF: congestive heart failure
CK-MB: creatine kinase-MB
CPC: circulating progenitor cells
CPK-MB: creatine phosphokinase-MB
CT: computed tomography
ECG: electrocardiogram
G-CSF: granulocyte colony-stimulating factor
HF: heart failure
LV: left ventricular
MI: myocardial infarction
MSC: mesenchymal stem cells
non-STEMI: non-ST elevation myocardial infarction
n/r: not reported
NTG: nitroglycerine
OPCAB: off-pump coronary artery bypass
PCI: percutaneous coronary intervention
ULN: upper limit of normal
VF: ventricular fibrillation

Table 6. Quality of life and performance measures *(Continued)*

Study ID	No. analysed participants		Performance assessment	Mean follow-up		No. analysed participants		Quality of life assessment	Mean follow-up	
	Cells	No cells		ST	LT	Cells	No cells		ST	LT
Ang 2008	21	21	NYHA class (SR)[a]	6 mths	n/r	-	-	-	-	-
	21	21	CCS class (SR)[b]	6 mths	n/r	-	-	-	-	-
Assmus 2006	43	18	NYHA class (EP)	3 mths	n/r	-	-	-	-	-
Assmus 2013	43	39	NYHA class (EP/MC)	4 mths	n/r	-	-	-	-	-
Bartunek 2012	21	15	NYHA class (SR)[c]	6 mths	n/r	21	15	MLHFQ (SR)[c]	6 mths	n/r
	21	15	6MWT (distance) (EP)	6 mths	n/r	-	-	-	-	-
Chen 2006	22[d]	23[d]	NYHA class (EP)	6 mths	12 mths	-	-	-	-	-
	22[d]	23[d]	ETT (METs) (EP)	6 mths	12 mths	-	-	-	-	-
Erbs 2005	12	10	Bike test (max O_2 update) (EP)	3 mths	15 mths	-	-	-	-	-
Hamshere 2015_IC	15	15	NYHA class (EP)	6 mths	12 mths	-	-	-	-	-
	15	15	CCS class (EP)	6 mths	12 mths	-	-	-	-	-
Hamshere 2015_IM	15	15	NYHA class (EP)	6 mths	12 mths	-	-	-	-	-
	15	15	CCS class (EP)	6 mths	12 mths	-	-	-	-	-
Heldman 2014_BMMNC	17	16	NYHA class (SR)[e]	n/r	12 mths	15	19	MLHFQ (MC)	6 mths	12 mths
	15[f]	19[f]	6MWT (distance) (MC)	6 mths	12 mths	-	-	-	-	-
Heldman 2014_BM-MSC	17	16	NYHA class (SR)[e]	n/r	12 mths	19[g]	19[g]	MLHFQ (MC)	6 mths	12 mths

Table 6. Quality of life and performance measures *(Continued)*

	18[h]	19[h]	6MWT (distance) (MC)	6 mths	12 mths	-	-	-	-	-
Honold 2012	21[j]	10[j]	NYHA class (EP)	3 mths	60 mths	-	-	-	-	-
	12[k]	5[k]	Bike test (sec) (EP)	3 mths	12 mths	-	-	-	-	-
Hu 2011	30	27	6MWT (distance) (EP/MC)	6 mths	n/r	-	-	-	-	-
Jimenez-Quevedo 2011	19	9	CCS class (median)[m]	6 mths	n/r	n/r	n/r	SAQ (median)[m]	6 mths	n/r
	15	7	ETT (time; METs) (median)[m]	6 mths	n/r	19	9	Angina frequency (median)[n]	6 mths	n/r
Losordo 2007	18	6	CCS class (MC)	6 mths	n/r	18	6	SAQ (SR)[p]	6 mths	n/r
	18	6	ETT (time) (MC)	6 mths	n/r	17	6	Angina frequency (EP/MC)	6 mths	n/r
Losordo 2011	109[q]	53[q]	CCS class (SR)[r]	6 mths	12 mths	109[q]	53[q]	SAQ (MC)	6 mths	12 mths
	109[q]	53[q]	ETT (time) (MC)	6 mths	12 mths	109	53	Angina frequency (EP)	6 mths	n/r
Mathiasen 2015	40	40	NYHA class (SR)[s]	6 mths	n/r	40	40	KCCQ-QOL (SR)[s]	6 mths	n/r
	40	40	CCS class (SR)[s]	6 mths	n/r	40	40	SAQ (SR)[s]	6 mths	n/r
	40	40	6MWT (SR)[s]	6 mths	n/r	40	40	Angina frequency (SR)[s]	6 mths	n/r
Mozid 2014_IC	14	2	NYHA class (EP)	6 mths	n/r	-	-	-	-	-
	14	2	CCS class (SR)	6 mths	n/r	-	-	-	-	-
Mozid 2014_IM	10	8	NYHA class (EP)	6 mths	n/r	-	-	-	-	-
	10	8	CCS class (SR)	6 mths	n/r	-	-	-	-	-

Table 6. Quality of life and performance measures *(Continued)*

Nasseri 2012	28	26	NYHA class (EP/MC)[t]	6 mths	n/r	28	26	MLHFQ[u]	6 mths	n/r
	28	26	6MWT[u]	6 mths	n/r	-	-	-	-	-
	28	26	CCS class (EP/MC)[t]	6 mths	n/r	-	-	-	-	-
Patel 2005	10	10	NYHA class (EP/MC)[t]	6 mths	n/r	-	-	-	-	-
Patel 2015	17	4	NYHA class (EP)[t]	n/r	12 mths	17	4	MLHFQ (SR)	n/r	12 mths
	17	4	CCS class (SR)	n/r	12 mths	-	-	-	-	-
Patila 2014	20	19	NYHA class (EP/MC)	n/r	12 mths[v]	20	19	SF-36[w]	n/r	60 mths
Perin 2011	20	10	NYHA class (EP)	6 mths	n/r	17	9	MLHFQ (EP)	6 mths	n/r
	20	10	CCS class (EP/MC)	6 mths	n/r	13	10	SF-36 (physical/mental) (EP)	6 mths	n/r
Perin 2012a	55	30	NYHA class (MC)	6 mths	n/r	-	-	-	-	-
	44	22	CCS class (MC)	6 mths	n/r	-	-	-	-	-
	51	29	6MWT (distance) (EP)	6 mths	n/r	-	-	-	-	-
Perin 2012b	10	10	NYHA class (EP)	6 mths	n/r	-	-	-	-	-
	10	10	CCS class (EP)	6 mths	n/r	-	-	-	-	-
Pokushalov 2010	53[x]	46[x]	NYHA class (EP)	6 mths	12 mths	53[x]	46[x]	MLHFQ (EP)	6 mths	12 mths
	53[x]	46[x]	CCS class (EP)	6 mths	12 mths	53[x]	46[x]	Angina frequency (EP)	6 mths	12 mths
	53[x]	46[x]	6MWT (distance) (EP)	6 mths	12 mths	-	-	-	-	-
Santoso 2014	19	9	NYHA class (EP)[y]	6 mths	n/r	-	-	-	-	-

Table 6. Quality of life and performance measures *(Continued)*

	19	9	6MWT (distance) (EP)[y]	6 mths	n/r	-	-	-	-	-
Trifunovic 2015	15	15	NYHA class (EP)	6 mths	12 mths	-	-	-	-	-
	15	15	6MWT (distance) (EP)	6 mths	12 mths	-	-	-	-	-
Tse 2007	19	9	NYHA class (EP)[t]	6 mths	n/r	-	-	-	-	-
	19	9	CCS class (EP)[t]	6 mths	n/r	-	-	-	-	-
	19	9	Treadmill test (time; METs) (EP/MC)	6 mths	n/r	-	-	-	-	-
Turan 2011	33	16	NYHA class (EP)	6 mths	12 mths	-	-	-	-	-
Van Ramshorst 2009	24	25	CCS class (EP)	6 mths	n/r	24	25	SAQ (EP/MC)	6 mths	n/r
	24	25	Bike test (workload) (EP/MC)	6 mths	n/r	-	-	-	-	-
Wang 2009	16	16	CCS class (MC)	6 mths	n/r	16	16	Angina frequency (MC)	6 mths	n/r
	16	16	ETT (min) (MC)	6 mths	n/r	-	-	-	-	-
Wang 2010	56	56	CCS class (EP/MC)	6 mths	n/r	56	56	Angina frequency (EP/MC)	6 mths	n/r
	56	56	ETT (min) (EP/MC)	6 mths	n/r	-	-	-	-	-
Wang 2014	n/r	n/r	NYHA class (SR)	6 mths	n/r	-	-	-	-	-
	n/r	n/r	5MWT (distance) (SR)	6 mths	n/r	-	-	-	-	-
Zhao 2008	16	18	NYHA class (EP)	6 mths	n/r	-	-	-	-	-
	16	18	CCS class (EP)	6 mths	n/r	-	-	-	-	-

CCS: Canadian Cardiovascular Society; EP: endpoint; ETT: exercise tolerance test; KCCQ-QOL: Kansas City Cardiomyopathy Questionnaire – Quality of Life; LT: long term; MC: mean change from baseline; MET: metabolic equivalent test (mL/kg/min); MLHFQ: Minnesota Living with Heart Failure Questionnaire; n/r: not reported; NYHA: New York Heart Association; SAQ: Seattle Angina Questionnaire; SF-36: 36-Item Short Form Health Survey; SR: summary results; ST: short term; 5MWT: 5-minute walk test; 6MWT: 6-minute walk test

[a]Reported as number of participants in NYHA class III/IV.

[b]Reported as number of participants in CCS class II or greater.
[c]Reported graphically as percentage of participants showing improvement or deterioration.
[d]20/19 at 12 months.
[e]Reported as number who improved/did not change/deteriorated.
[f]17/19 at 12 months.
[g]16/19 at 12 months.
[h]16/19 at 12 months.
[j]20/6 at 5 years.
[k]10/5 at 12 months.
[m]Reported as median absolute difference with 95% confidence interval.
[n]Median time to onset of angina also reported.
[p]Results presented graphically.
[q]106/50 at 12 months.
[r]Reported as percentage of participants changed.
[s]Results presented graphically with P values for differences between groups.
[t]Calculated from frequency data.
[u]Unclear whether mean or median values are reported.
[v]Also reported: median values at 60 months.
[w]Reported graphically for each of eight components of SF-36 at 60 months.
[x]49/33 at 12 months.
[y]Reported as difference between groups at endpoint.

Table 7. Surrogate (continous) outcome: LVEF *(Continued)*

Study ID	No. randomised participants		No. analysed participants		Baseline LVEF: Mean (SD)		Mean follow-up of LVEF	
	Cells	No cells	Cells	No cells	Cells	No cells	ST	LT
Measured by MRI								
Ang 2008	42	21	18	7	IM: 25.4 (8.1) IC: 28.5 (6.5)	20.9 (8.9)	6 mths	-
Assmus 2013	43	39	15	12	n/r	n/r	4 mths	-
Erbs 2005	14	14	12[a]	11[a]	51.0 (12.1)	55.8 (12.4)	3 mths	15 mths

Table 7. Surrogate (continous) outcome: LVEF *(Continued)*

Hendrikx 2006	11	12	10	10	42.9 (10.3)	39.5 (5.5)	4 mths	-
Honold 2012	23	10	9	4	33.4 (SEM 12.7)	23.3 (SEM 7.2)	3 mths	12 mths
Hu 2011	31	29	31[b]	28[b]	23.5 (6.7)	24.8 (5.2)	6 mths	12 mths
Mathiasen 2015	40	20	40	20	28.2 (9.3)	25.1 (8.5)	6 mths	-
Nasseri 2012	30	30	26	22	27 (6)	26 (6)	6 mths	-
Patila 2014	20	19	18	7	37.1 (9.5)	38.5 (13.5)	-	60 mths
Santoso 2014	19	9	19	9	23.6 (8.4)	26.8 (8.8)	6 mths	-
Tse 2007	19	9	18	8	51.9 (8.5)	45.7 (8.3)	6 mths	-
Van Ramshorst 2009	25	25	22	18	56 (12)	54 (10)	6 mths	-
Wang 2014	35	35	35	35	29 (7)	28 (6)	6 mths	-
Measured by echocardiography								
Bartunek 2012	32	15	21	15	27.5 (95% CI 25.5, 29.5)	27.8 (95% CI 25.9, 29.8)	6 mths	-
Hu 2011	31	29	24	18	36.0 (1.2)	34.7 (1.4)	-	12 mths
Perin 2011	20	10	20	10	37.0 (10.6)	39.0 (9.1)	6 mths	-
Perin 2012a	61	31	54	28	34.7 (8.8)	32.3 (8.6)	6 mths	-
Perin 2012b	10	10	10	10	36.1 (10.9)	32.1 (10.6)	6 mths	-
Pokushalov 2010	55	54	53[c]	46[c]	27.8 (3.4)	26.8 (3.8)	6 mths	12 mths

Table 7. Surrogate (continous) outcome: LVEF *(Continued)*

Trifunovic 2015	15	15	15	15	35.3 (3.9)	36.5 (5.3)	6 mths	12 mths
Van Ramshorst 2009	25	25	24	25	50 (5)	52 (5)	6 mths	-
Wang 2015	45	45	45	45	39.3 (6.2)	38.2 (8.0)	6 mths	-
Zhao 2008	18	18	16	18	35.8 (7.3)	36.7 (9.2)	6 mths	-
Measured by SPECT								
Chen 2006	24	24	22[d]	23[d]	26 (6)	23 (8)	6 mths	12 mths
Perin 2011	20	10	20	10	41.5 (11.2)	43.0 (10.4)	6 mths	-
Van Ramshorst 2009	25	25	24	25	53 (12)	54 (12)	6 mths	12 mths
Measured by LV angiography								
Assmus 2006	52	23	43	18	BMMNC: 41 (11) CPC: 39 (10)	43 (13)	3 mths	-
Assmus 2013	43	39	41	38	LDSW: 37.2 (95% CI 31.7, 42.7) HDSW: 32.4 (95% CI 26.9, 37.9)	LDSW: 29.9 (95% CI 24.0, 35.7) HDSW: 32.3 (95% CI 26.5, 38.1)	4 mths	-
Honold 2012	23	10	21	5	37.5 (SEM 12.9)	37.6 (SEM 7.5)	3 mths	-
Perin 2011	20	10	20	10	37.5 (8.2)	40.0 (3.2)	6 mths	-

Table 7. Surrogate (continous) outcome: LVEF *(Continued)*

Perin 2012b	10	10	10	10	38.0 (17.5)	41.9 (11.8)	6 mths	-
Turan 2011	38	18	33	16	46 (10)	46 (10)	3 mths	12 mths

95% CI: 95% confidence interval; BMMNC: bone marrow mononuclear cells; CPC: circulating progenitor cells; HDSW: high-dose shockwave; IC: intracoronary; IM: intramyocardial; LDSW: low-dose shockwave; LT: long term; LV: left ventricular; LVEF: left ventricular ejection fraction; SD: standard deviation; SEM: standard error of the mean; SPECT: single-photon emission computed tomography; ST: short term

[a]12/10 at 15 months.

[b]25/25 at 12 months.

[c]20/19 at 12 months.

[d]49/33 at 12 months.

APPENDICES

Appendix 1. Search strategies (March 2013)

THE COCHRANE LIBRARY

#1 STEM CELL TRANSPLANTATION explode all trees (MeSH)
#2 HEMATOPOIETIC STEM CELL MOBILIZATION single term (MeSH)
#3 STEM CELLS explode all trees (MeSH)
#4 CELL TRANSPLANTATION single term (MeSH)
#5 haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or marrow NEAR cell* or stem cell* or progenitor cell* or precursor cell* or cell* therapy
#6 ((myoblast* or cell*) NEAR (transplant* or graft* or implant*))
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MYOCARDIAL ISCHEMIA explode all trees (MeSH)
#9 HEART FAILURE explode all trees (MeSH)
#10 HEART DISEASES single term (MeSH)
#11 (myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) NEAR (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*)
#12 heart disease* or coronary disease* or IHD or CIHD
#13 chronic myocardial dysfunction or angina or stenocardia
#14 (ischemi* or ischaemi*) NEAR (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)
#15 (artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) NEAR coronary
#16 (heart or cardiac or cardial or myocardium or myocardial) NEAR (repair* or reparation or improve* or regenerat*)
#17 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #7 AND #17
#19 (cellular NEXT cardiomyoplast*) or (cardiomyocyte* NEAR transplant*) or (intramyocardial* NEAR (transplant* or stem or bone marrow)) or (transendocardial* NEAR stem NEXT cell*) or (intracoronary NEAR progenitor NEXT cell*) or (transcoronary NEAR transplant*)
#20 #18 or #19

MEDLINE (Ovid)

1. CELL TRANSPLANTATION/
2. exp STEM CELL TRANSPLANTATION/
3. BONE MARROW TRANSPLANTATION//
4. exp STEM CELLS/
5. (haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or (marrow adj2 cell*) or stem cell* or progenitor cell* or precursor cell* or cell* therapy or bone marrow).ti,ab.
6. ((mesenchymal or stromal) AND marrow).ti,ab.
7. (cell*) adj3 (transplant* or graft* or implant*)).ti,ab
8. cell transplantation.jn. or cell stem cell.jn. or stem cell reviews.jn. or bone marrow transplantation.jn.
9. or/1-8
10. exp MYOCARDIAL ISCHEMIA/
11. exp HEART FAILURE/
12. HEART DISEASES/
13. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) adj2 (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*)).ti,ab.
14. (heart disease* or coronary disease* or IHD or CIHD).ti,ab.
15. (myocardial dysfunction or angina or stenocardia).ti,ab.
16. ((ischemi* or ischaemi*) adj2 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)).ti,ab.
17. ((end stage or endstage) adj cardiomyopath*).ti,ab.
18. ((artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) adj2 coronary).ti,ab.
19. ((heart or cardiac or cardial or myocardium or myocardial) adj3 (repair* or reparation or improve* or regenerat*)).ti,ab.
20. or/10-19
21. 9 and 20
22. ((cellular adj cardiomyoplast*) or (cardiomyocyte* adj5 transplant*) or (intramyocardial* adj6 (transplant* or stem or bone marrow)) or (transendocardial* adj5 stem adj cell*) or (intracoronary adj5 progenitor adj cell*) or (transcoronary adj3 transplant*)).mp.
23. 21 or 22

EMBASE (Ovid)

1. exp CELL THERAPY/
2. exp STEM CELL/
3. BONE MARROW CELL/
4. ((mesenchymal or stromal) AND marrow).ti,ab.
5. (haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or marrow adj2 cell* or stem cell* or progenitor cell* or precursor cell* or cell* therapy or bone marrow).ti,ab.
6. (cell* adj3 (transplant* or graft* or implant*)).ti,ab.
7. cell transplantation.jn. or cell stem cell.jn. or stem cell reviews.jn.
8. or/1-7
9. exp ISCHEMIC HEART DISEASE/
10. exp HEART FAILURE/
11. exp MYOCARDIAL DISEASE/
12. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) adj2 (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*).ti,ab.
13. (heart disease* or coronary disease* or IHD or CIHD).ti,ab.
14. (chronic myocardial dysfunction or angina or stenocardia).ti,ab.
15. ((ischemi* or ischaemi*) adj2 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)).ti,ab.
16. ((artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) adj2 coronary).ti,ab.
17. ((end stage or endstage) adj cardiomyopath*).ti,ab.
18. ((heart or cardiac or cardial or myocardium or myocardial) adj3 (repair* or reparation or improve* or regenerat*)).ti,ab.
19. or/9-18
20. 8 AND 19
21. ((cellular adj cardiomyoplast*) or (cardiomyocyte* adj5 transplant*) or (intramyocardial adj6 (transplant* or stem or bone marrow)) or (transendocardial adj5 stem adj cell*) or (intracoronary adj5 progenitor adj cell*) or (transcoronary adj3 transplant*)).mp.
22. 20 or 21

CINAHL (EBSCOhost)

S1 (MH "Cell Transplantation+")
S2 (MH "Stem Cells+")
S3 TI ((haematopoietic OR hematopoietic OR haematopoetic OR hematopoetic OR hemopoietic OR haemopoietic OR (marrow N2 cell*) OR "stem cell*" OR "progenitor cell*" OR "precursor cell*" OR "cell* therapy" OR "bone marrow")) OR AB ((haematopoietic OR hematopoietic OR haematopoetic OR hematopoetic OR hemopoietic OR haemopoietic OR (marrow N2 cell*) OR "stem cell*" OR "progenitor cell*" OR "precursor cell*" OR "cell* therapy" OR "bone marrow"))
S4 TX ((mesenchymal or stromal) AND marrow)
S5 TI (((cell* N3 transplant*) OR (cell* N3 graft*) OR (cell* N3 implant*))) OR AB (((cell* N3 transplant*) OR (cell* N3 graft*) OR (cell* N3 implant*)))
S6 S1 OR S2 OR S3 OR S4 OR S5
S7 (MH "Heart Diseases") OR (MH "Heart Failure+") OR (MH "Heart Valve Diseases+") OR (MH "Myocardial Diseases+") OR (MH "Myocardial Ischemia+")
S8 TI ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) N6 (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*)) OR AB ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) N6 (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*))
S9 TI (("heart disease*" or "coronary disease*" or IHD or CIHD)) AND AB (("heart disease*" or "coronary disease*" or IHD or CIHD))
S10 TI (("chronic myocardial dysfunction" OR angina OR stenocardia)) OR AB (("chronic myocardial dysfunction" OR angina OR stenocardia))
S11 TI (((ischemi* or ischaemi*) N5 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*))) OR AB (((ischemi* or ischaemi*) N5 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)))
S12 TI (((chronic or artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) AND coronary)) OR AB (((chronic or artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) AND coronary))
S13 TI (((heart or cardiac or cardial or myocardium or myocardial) AND (repair* or reparation or improve* or regenerat*))) OR AB (((heart or cardiac or cardial or myocardium or myocardial) AND (repair* or reparation or improve* or regenerat*)))
S14 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15 S6 AND S14
S16 TX (transplant* N5 (cardiomyocyte* or transcoronary)) or (cellular N2 cardiomyoplast*) or (intramyocardial* N6 (transplant* or stem or marrow)) or (transendocardial* N5 stem cell*) or (intracoronary N5 progenitor cell*)
S17 S15 OR S16

TRANSFUSION EVIDENCE LIBRARY (www.transfusionevidencelibrary.com)

("marrow cell*" OR "stem cell*" OR "progenitor cell*" OR "precursor cell*") AND (infarct* OR coronar* OR myocard* OR heart OR cardiac* OR cardiomyo* OR intramyocardial* OR ischemi* OR ischaemi* OR angina)

PubMed (epublications only)

(stem[TI] OR marrow[TI] OR progenitor[TI] OR precursor[TI] OR cell[TI] OR cells[TI]) AND (infarct*[TI] OR coronar*[TI] OR heart*[TI] OR myocard*[TI] OR cardial[TI] OR cardiac[TI] OR transmural*[TI] OR ischemia[TI] OR ischemic[TI] OR subendocardial[TI] OR cardiomyopath*[TI] OR angina[TI]) AND (random* OR blind* OR control group* OR controlled OR placebo OR trial) AND (publisher[sb] NOT pubstatusnihms)

LILACS

("marrow cell$" OR "stem cell$" OR "progenitor cell$" OR "precursor cell$") AND (infarct$ OR coronar$ OR myocard$ OR heart OR cardiac $ OR cardiomyo$ OR intramyocardial$ OR ischemi$ OR ischaemi$ OR angina) AND (random$ OR blind$ OR control$ OR placebo$ OR trial)

KoreaMed & PakMediNet

(stem or marrow or progenitor or precursor or cell or cells) AND random*

IndMed

((marrow OR stem OR progenitor OR precursor) AND (infarct$ OR coronar$ OR myocard$ OR heart OR cardiac$ OR cardiomyo$ OR intramyocardial$ OR ischemi$ OR ischaemi$) AND (random$ OR blind$ OR control$ OR placebo$ OR trial))

ISRCTN Register (Current Controlled Trials)

("stem cells" or "stem cell" or marrow or "progenitor cells" or "precursor cells") and (infarction or infarct or coronary or myocardial or heart or myocardium or cardial or transmural or ischemia or ischemic or subendocardial or cardiomyopathy OR angina)

ClinicalTrials.gov

Study Type: Intervention Studies
Conditions: heart failure
Search Terms: marrow OR stem OR progenitor OR precursor OR myoblast OR myocell OR mesenchymal OR stromal

WHO ICTRP

Title: marrow OR stem OR progenitor OR precursor OR myoblast OR myocell OR mesenchymal OR stromal
Condition: heart OR cardiac OR myocardial
Recruitment Status: ALL

Appendix 2. Search strategies (June 2014; March/December 2015)

CENTRAL, the Cochrane Library

#1 MeSH descriptor: [Stem Cell Transplantation] explode all trees
#2 MeSH descriptor: [Bone Marrow Cells] explode all trees
#3 MeSH descriptor: [Stem Cells] explode all trees
#4 MeSH descriptor: [Cell Transplantation] this term only
#5 MeSH descriptor: [Bone Marrow Transplantation] this term only
#6 MeSH descriptor: [Stromal Cells] explode all trees
#7 ((stem or haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or progenitor or precursor or bone marrow or mononuclear or "adipose tissue" or mesenchymal or stromal or autologous or allogeneic or allogenic or ALDH* or C-KIT*) next/2 cell*)
#8 "cell transplantation":so or "stem cell":so or "bone marrow transplantation":so
#9 (autologous next/3 transplant*) or "cell* therap*"
#10 ((cell* or myoblast*) near/3 (autologous or transplant* or autotransplant* or allotransplant* or graft* or implant*))
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 MeSH descriptor: [Heart Diseases] explode all trees
#13 ((ischemi* or ischaemi* or nonischemi* or nonischaemi*) near/2 (myocardium or myocardial or cardiomyopath* or heart or coronary or cardiac or cardial or subendocardial))
#14 ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) near/2 (failure* or decompensation or insufficien*))
#15 (IHD or CIHD or DCM or IDCM)
#16 ((myocardial near/3 dysfunction*) or stenocardia or angina*)
#17 ((end stage or endstage or dilated or idiopathic or congestive) near/2 cardiomyopath*)

#18 (arter* occlusion* or arter* disease* or arterioscleros* or atheroscleros*) near/2 coronary
#19 ((heart or cardiac or cardial or myocardium or myocardial) near/3 (repair* or reparation or improv* or regenerat*))
#20 (heart disease* or coronary disease* or cardiovascular disease*)
#21 ((end stage or endstage or dilated or idiopathic or congestive) near/2 cardiomyopath*)
#22 ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart or acute) near/3 (infarct* or postinfarct* or hypoxi* or anoxi*))
#23 heart attack* or coronary attack* or acute coronary syndrome* or AMI
#24 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 #11 and #24
#26 cellular cardiomyoplast* or ((cardiomyocyte* or cardiac cell*) near/6 transplant*) or ((intramyocardial* or intracoronary or transendocardial* or transcoronary) near/6 (transplant* or stem or bone marrow or marrow cell* or BMC* or stromal or mesenchymal or progenitor cell* or precursor cell*))
#27 #25 or #26 [Publication Year from 2014 to 2015]

MEDLINE (OvidSP)

1. exp STEM CELL TRANSPLANTATION/
2. BONE MARROW TRANSPLANTATION/
3. CELL TRANSPLANTATION/
4. exp STEM CELLS/
5. BONE MARROW CELLS/
6. exp STROMAL CELLS/
7. ((stem or haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or progenitor or precursor or bone marrow or mononuclear or adipose tissue or mesenchymal or stromal or autologous or allogeneic or allogenic or ALDH* or C-KIT*) adj2 cell*).ti,ab.
8. (cell transplantation or stem cell* or bone marrow transplantation).jn.
9. ((autologous adj3 transplant*) or cell* therap*).tw.
10. ((cell* or myoblast*) adj3 (autologous or transplant* or autotransplant* or allotransplant* or graft* or implant*)).ti,ab.
11. or/1-10
12. exp HEART DISEASES/
13. ((ischemi* or ischaemi* or nonischemi* or nonischaemi*) adj2 (myocardium or myocardial or cardiomyopath* or heart or coronary or cardiac or cardial or subendocardial)).ti,ab.
14. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) adj2 (failure* or decompensation or insufficien*)).ti,ab.
15. (IHD or CIHD or DCM or IDCM).ti,ab.
16. ((myocardial adj3 dysfunction*) or stenocardia or angina*).ti,ab.
17. ((arter* occlusion* or arter* disease* or arterioscleros* or atheroscleros*) adj2 coronary).ti,ab.
18. (heart disease* or coronary disease* or cardiovascular disease*).ti,ab.
19. ((end stage or endstage or dilated or idiopathic or congestive) adj2 cardiomyopath*).ti,ab.
20. ((heart or cardiac or cardial or myocardium or myocardial) adj3 (repair* or reparation or improv* or regenerat*)).ti,ab.
21. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart or acute) adj3 (infarct* or postinfarct* or hypoxi* or anoxi*)).ti,ab.
22. (heart attack* or coronary attack* or acute coronary syndrome* or AMI).ti,ab.
23. or/12-22
24. 11 and 23
25. (cellular cardiomyoplast* or ((cardiomyocyte* or cardiac cell*) adj6 transplant*) or ((intramyocardial* or intracoronary or transendocardial* or transcoronary) adj6 (transplant* or stem or bone marrow or marrow cell* or BMC* or stromal or mesenchymal or progenitor cell* or precursor cell*))).mp.
26. 24 or 25

Embase (OvidSP)

1. exp STEM CELL TRANSPLANTATION/
2. exp BONE MARROW TRANSPLANTATION/
3. exp STEM CELL/
4. BONE MARROW CELL/
5. exp STROMA CELLS/
6. ((stem or haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or progenitor or precursor or bone marrow or mononuclear or adipose tissue or mesenchymal or stromal or autologous or allogeneic or allogenic or ALDH* or C-KIT*) adj2 cell*).ti,ab.
7. (cell transplantation or stem cell* or bone marrow transplantation).jn.
8. ((autologous adj3 transplant*) or cell* therap*).tw.
9. ((cell* or myoblast*) adj3 (autologous or transplant* or autotransplant* or allotransplant* or graft* or implant*)).ti,ab.

10. or/1-9
11. exp ISCHEMIC HEART DISEASE/
12. exp HEART FAILURE/
13. exp MYOCARDIAL DISEASE/
14. ((ischemi* or ischaemi* or nonischemi* or nonischaemi*) adj2 (myocardium or myocardial or cardiomyopath* or heart or coronary or cardiac or cardial or subendocardial)).ti,ab.
15. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) adj2 (failure* or decompensation or insufficien*)).ti,ab.
16. (IHD or CIHD or DCM or IDCM).ti,ab.
17. ((myocardial adj3 dysfunction*) or stenocardia or angina*).ti,ab.
18. ((arter* occlusion* or arter* disease* or arterioscleros* or atheroscleros*) adj2 coronary).ti,ab.
19. (heart disease* or coronary disease* or cardiovascular disease*).ti,ab.
20. ((end stage or endstage or dilated or idiopathic or congestive) adj2 cardiomyopath*).ti,ab.
21. ((heart or cardiac or cardial or myocardium or myocardial) adj3 (repair* or reparation or improv* or regenerat*)).ti,ab.
22. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart or acute) adj3 (infarct* or postinfarct* or hypoxi* or anoxi*)).ti,ab.
23. (heart attack* or coronary attack* or acute coronary syndrome* or AMI).ti,ab.
24. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 10 and 24
26. (cellular cardiomyoplast* or ((cardiomyocyte* or cardiac cell*) adj6 transplant*) or ((intramyocardial* or intracoronary or transendocardial* or transcoronary) adj6 (transplant* or stem or bone marrow or marrow cell* or BMC* or stromal or mesenchymal or progenitor cell* or precursor cell*))).mp.
27. 25 or 26

PubMed (epublications)

#1 (stem[TI] OR haematopoietic[TI] OR hematopoietic[TI] OR haematopoetic[TI] OR hematopoetic[TI] OR hemopoietic[TI] OR haemopoietic[TI] OR progenitor[TI] OR precursor[TI] OR bone marrow[TI] OR mononuclear[TI] OR "adipose tissue"[TI] OR mesenchymal[TI] OR stromal[TI] OR autologous[TI] OR allogeneic[TI] OR allogenic[TI] OR ALDH*[TI] OR C-KIT*[TI]) AND cell*[TI]
#2 cell transplantation[TA] OR stem cell*[TA] OR bone marrow transplant*[TA]
#3 "autologous transplant*"[TI] OR "cell therapy"[TI] OR "cell therapies"[TI] OR "cellular therapy"[TI]
#4 (cell[TI] OR cells[TI] OR cellular[TI] OR myoblast*[TI]) AND (transplant[TI] OR transplantation[TI] OR transplants[TI] OR transplanting[TI] OR transplanted[TI] OR autotransplant*[TI] or allotransplant*[TI] or graft*[TI] or implant[TI] OR implants[TI] OR implantation[TI] OR implanted[TI])
#5 #1 OR #2 OR #3 OR #4
#6 (ischemi*[TI] OR ischaemi*[TI] OR nonischemi*[TI] OR nonischaemi*) AND (myocardium[TI] OR myocardial[TI] OR cardiomyopath*[TI] OR heart[TI] OR coronary[TI] OR cardiac[TI] OR cardial[TI] OR subendocardial[TI])
#7 (myocardial[TI] OR myocardium[TI] OR subendocardial[TI] OR transmural[TI] OR cardiac[TI] OR cardial[TI] OR coronary[TI] OR heart) AND (failure*[TI] OR decompensation[TI] OR insufficien*[TI])
#8 "myocardial dysfunction*"[TI] OR stenocardia[TI] OR angina*[TI] OR IHD[TI] OR CIHD[TI] OR DCM[TI] OR IDCM[TI] OR "heart disease"[TI] OR "coronary disease"[TI] OR "coronary artery disease"[TI] OR "cardiovascular disease"[TI]
#9 ("arterial occlusion*"[TI] OR "arterial disease*"[TI] OR arterioscleros*[TI] OR atheroscleros*[TI]) AND coronary[TI]
#10 ("end stage"[TI] OR endstage[TI] OR dilated[TI] OR idiopathic[TI] OR congestive[TI]) AND cardiomyopath*[TI]
#11 (heart[TI] OR cardiac[TI] OR cardial[TI] OR myocardium[TI] OR myocardial[TI]) AND (repair*[TI] OR reparation[TI] OR improv*[TI] OR regenerat*[TI])
#12 (myocardial[TI] OR myocardium [TI] OR subendocardial [TI] OR transmural [TI] OR cardiac [TI] OR cardial [TI] OR coronary [TI] OR heart [TI] OR acute[TI]) AND (infarct* [TI] OR postinfarct* [TI] OR hypoxi* [TI] OR anoxi*)
#13 heart attack* [TI] OR coronary attack* [TI] OR acute coronary syndrome* [TI] OR AMI[TI]
#14 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #5 AND #14
#16 (cellular cardiomyoplast* OR ((cardiomyocyte* OR cardiac cell*) AND transplant*) OR ((intramyocardial* OR intracoronary OR transendocardial* OR transcoronary) AND (transplant* OR stem OR bone marrow OR marrow cell* OR BMC* OR stromal OR mesenchymal OR progenitor cell* OR precursor cell*)))
#17 #15 OR #16
#18 (random* OR blind* OR control group* OR placebo OR controlled trial OR controlled study OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase) AND ((publisher[sb] OR inprocess[sb]) NOT pubstatusnihms)
#19 #17 AND #18

CINAHL (EBSCOhost)

S1 (MH "Cell Transplantation+")
S2 (MH "Stem Cells+")

S3 TI ((stem or haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or progenitor or precursor or bone marrow or mononuclear or adipose tissue or mesenchymal or stromal or autologous or allogeneic or allogenic or ALDH* or C-KIT*) N2 cell*) OR AB ((stem or haematopoietic or hematopoietic or haematopoetic or hematopoetic or hemopoietic or haemopoietic or progenitor or precursor or bone marrow or mononuclear or adipose tissue or mesenchymal or stromal or autologous or allogeneic or allogenic or ALDH* or C-KIT*) N2 cell)
S4 TX ((autologous N3 transplant*) or cell* therap*)
S5 TI ((cell* or myoblast*) N3 (autologous or transplant* or autotransplant* or allotransplant* or graft* or implant*)) OR AB ((cell* or myoblast*) N3 (autologous or transplant* or autotransplant* or allotransplant* or graft* or implant*))
S6 S1 OR S2 OR S3 OR S4 OR S5
S7 (MH "Heart Diseases+")
S8 TI ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart or acute) N3 (infarct* or postinfarct* or hypoxi* or anoxi*)) OR AB ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart or acute) N3 (infarct* or postinfarct* or hypoxi* or anoxi*))
S9 TI (("heart disease*" or "coronary disease*" or IHD or CIHD or DCM or IDCM)) AND AB (("heart disease*" or "coronary disease*" or IHD or CIHD or DCM or IDCM))
S10 TI (((myocardial N3 dysfunction) OR angina OR stenocardia)) OR AB (((myocardial N3 dysfunction) OR angina OR stenocardia))
S11 TI (((ischemi* or ischaemi* or nonischemi* or nonischaemi*) N5 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*))) OR AB (((ischemi* or ischaemi* or nonischemi* or nonischaemi*) N5 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)))
S12 TI (((arter* occlusion* or arter* disease* or arterioscleros* or atheroscleros*) N2 coronary)) OR AB (((arter* occlusion* or arter* disease* or arterioscleros* or atheroscleros*) N2 coronary))
S13 TI (((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) N2 (failure* or decompensation or insufficien*))) OR AB (((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) N2 (failure* or decompensation or insufficien*)))
S14 TI ((end stage or endstage or dilated or idiopathic or congestive) N2 cardiomyopath*) OR AB ((end stage or endstage or dilated or idiopathic or congestive) N2 cardiomyopath*)
S15 TI ((heart or cardiac or cardial or myocardium or myocardial) N3 (repair* or reparation or improv* or regenerat*)) OR AB ((heart or cardiac or cardial or myocardium or myocardial) N3 (repair* or reparation or improv* or regenerat*))
S16 TI (heart attack* or coronary attack* or acute coronary syndrome* or AMI) OR AB (heart attack* or coronary attack* or acute coronary syndrome* or AMI)
S17 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S18 S6 AND S17
S19 TI (cellular cardiomyoplast* or ((cardiomyocyte* or cardiac cell*) N6 transplant*) or ((intramyocardial* or intracoronary or transendocardial* or transcoronary) N6 (transplant* or stem or bone marrow or marrow cell* or BMC* or stromal or mesenchymal or progenitor cell* or precursor cell*))) OR AB (cellular cardiomyoplast* or ((cardiomyocyte* or cardiac cell*) N6 transplant*) or ((intramyocardial* or intracoronary or transendocardial* or transcoronary) N6 (transplant* or stem or bone marrow or marrow cell* or BMC* or stromal or mesenchymal or progenitor cell* or precursor cell*))
S20 S18 OR S19 {Limiters - Published Date: 20140101-20151214}

LILACS

(tw:((infarct OR infarction OR coronary OR myocardial OR heart OR cardiac OR cardiomyopathy OR myocardial OR subendocardial OR intramyocardial OR intracoronary OR ischemia OR ischemic OR nonischemic))) AND (tw:((bone marrow OR marrow cell OR marrow cells OR stem cell OR stem cells OR progenitor cells OR precursor cells OR cell therapy OR cellular therapy OR cell-based therapy OR mononuclear cells OR mesenchymal cells OR stromal cells))) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

IndMED

(bone marrow OR marrow cell OR marrow cells OR stem cell OR stem cells OR progenitor cell OR precursor cell OR cell therapy OR cellular therapy OR mesenchymal cells OR stromal cells) AND (infarct OR infarction OR coronary OR intracoronary OR myocardial OR heart OR cardiac OR congestive OR cardiomyopathy OR intramyocardial OR intracoronary OR ischemia OR ischemic OR ischaemia OR ischaemic OR nonischemic OR nonischaemic) AND (randomised OR randomly OR randomized OR blind OR blinded OR trial OR study OR control group)

KoreaMed [N.B. Search lines run separately: presented this way for brevity]

(stem [ALL] OR marrow [ALL] OR mesenchymal[ALL] OR stromal[ALL]) AND (myocardial [ALL] OR heart[ALL] OR cardiac[ALL] OR coronary[ALL] OR cardiomyopathy[ALL]) AND "Randomized Controlled Trial" [PT]

PakMediNet

Combinations of the following free text terms were used:
stem cell, stem cells, bone marrow, marrow cells, progenitor cells, precursor cells, mesenchymal cells, stromal cells
AND

myocardial infarction, heart attack, cardiac ischemia, coronary ischemia, myocardial ischemia, cardiomyopathy, heart failure, cardiac failure, angina, coronary artery disease

Web of Science CPCI-S

TI=("cardiac failure" OR "heart attack" OR "heart failure" OR "coronary disease" OR "cardiovascular disease" OR "coronary artery" OR "coronary arterial" OR "myocardial infarction" OR cardiomyopathy OR "heart disease" OR "heart diseases" OR "cardiac insufficiency" OR AMI OR IHD OR CIHD OR DCM OR IDCM OR "myocardial dysfunction" OR stenocardia OR angina) AND TI=("stem cell" OR "stem cells" OR "bone marrow" OR "marrow cells" OR "cellular therapy" OR "mesenchymal cells" OR "stromal cells" OR "cell transplant" OR "precursor cells" OR "progenitor cells" OR (c-kit* NEAR/5 cells) OR HSCT OR SCT OR MSC OR MSCs OR BMT OR BMC OR BMAC OR BMCs OR HST OR HSTs) AND TS=(randomised OR randomly OR randomized OR blind OR blinded OR trial OR study OR "control group" OR groups)

ClinicalTrials.gov

Search Terms: randomized OR randomised OR random OR randomly
Study Type: Intervention Studies
Condition: cardiac OR heart attack OR heart failure OR coronary OR myocardial OR cardiomyopathy OR heart disease OR angina
Intervention: stem cells OR bone marrow cells OR cellular therapy OR mesenchymal cells OR stromal cells OR cell transplant OR marrow transplant OR precursor cells OR progenitor cells OR HSCT OR SCT OR MSC OR MSCs OR BMT OR BMC OR BMAC OR BMCs OR HST OR HSTs

ISRCTN Register

(("marrow cell" OR "marrow cells" OR "stem cell" OR "stem cells" OR "progenitor cells" OR "precursor cells" OR "mesenchymal cells" OR "stromal cells") AND ("myocardial infarction" OR "heart attack" OR cardiomyopathy OR intramyocardial OR intracoronary))
OR
(("marrow cell" OR "marrow cells" OR "stem cell" OR "stem cells" OR "progenitor cells" OR "precursor cells" OR "mesenchymal cells" OR "stromal cells") AND ("cardiac ischemia" OR "coronary ischemia" OR "myocardial ischemia" OR "heart failure" OR "cardiac failure" OR congestive OR "coronary artery disease"))
OR
(("cell therapy" OR "cellular therapy" OR "cell transplant" OR "marrow transplant") AND ("myocardial infarction" OR "heart attack" OR cardiomyopathy OR intramyocardial OR intracoronary OR "cardiac ischemia" OR "coronary ischemia" OR "myocardial ischemia" OR "heart failure" OR "cardiac failure" OR congestive OR "coronary artery disease" OR angina))

WHO ICTRP Search Portal

Intervention OR Title: stem cells OR bone marrow cells OR cellular therapy OR mesenchymal cells OR stromal cells OR cell transplant OR marrow transplant OR precursor cells OR progenitor cells OR HSCT OR SCT OR MSC OR MSCs OR BMT OR BMC OR BMAC OR BMCs OR HST OR HSTs
Condition OR Title: cardiac OR heart OR coronary OR myocardial OR angina OR cardiomyopathy
Recruitment Status: ALL

Hong Kong Clinical Trials Registry

Combinations of the following free text terms were used:
stem cell, stem cells, bone marrow, marrow cells, progenitor cells, precursor cells, mesenchymal cells, stromal cells
AND
myocardial infarction, heart attack, cardiac ischemia, coronary ischemia, myocardial ischemia, cardiomyopathy, heart failure, cardiac failure, angina, coronary artery disease

WHAT'S NEW

Date	Event	Description
1 December 2016	New citation required and conclusions have changed	The original review has been updated to include 39 randomised controlled trials (1921 participants). The defined primary and secondary outcomes of the review have been revised in this version of the review and now focus on clinical outcomes.
5 May 2016	New search has been performed	The evidence is up-to-date to 14 December 2015.

CONTRIBUTIONS OF AUTHORS

Sheila A Fisher: methodology expert, eligibility screening, data extraction and quality assessment, data analysis, and preparation of the final report.

Carolyn Doree: Information Specialist, design and implementation of search strategies, initial eligibility screening and data verification, comments on the final report.

Anthony Mathur: clinical content expert (clinical cardiology), preparation of the final report.

David P Taggart: clinical content expert (cardiac surgery), comments on the final report.

Enca Martin-Rendon: scientific content expert, eligibility screening, data extraction and quality assessment, preparation of the final report. Corresponding author who takes the global responsibility of this review.

DECLARATIONS OF INTEREST

Professor Anthony Mathur was the chief investigator of four included studies (Hamshere 2015_IC; Hamshere 2015_IM; Mozid 2014_IC; Mozid 2014_IM), and is the lead investigator of the ongoing BAMI trial.

All other authors have no known conflicts of interest.

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- William Harvey Research Institute, UK.

External sources

- Oxford BRC, UK.

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- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Several outcomes listed in the protocol for this review, Martin-Rendon 2009, were based on those of a previous review of acute myocardial infarction, Clifford 2012a, and were not as relevant for ischaemic heart disease and congestive heart failure. In addition, the original outcomes of this review have been revised in this update, focusing on clinical outcomes. However, the surrogate outcome of left ventricular ejection fraction (LVEF) is a standard, widely reported marker for cardiac function and has been retained as a reference point in other trials and systematic reviews in acute myocardial infarction. Surrogate outcomes other than LVEF reported in previous versions of this review, namely engraftment and survival of the infused stem cells, left ventricular end-systolic volume, left ventricular end-diastolic volume, stroke volume index, and infarct size are no longer included. Our revised primary outcomes are (i) all-cause mortality and (ii) periprocedural adverse events. We have defined our secondary outcomes as morbidity (non-fatal myocardial infarction, rehospitalisation for heart failure, and arrhythmias), composite measure of mortality, non-fatal myocardial infarction, and rehospitalisation for heart failure; quality of life; performance measures; and LVEF.

In the protocol and previous versions of this review, we implemented fixed-effect models in the first instance. It is now clear that there are many potential sources of heterogeneity across trials, and in this version of the review we performed meta-analyses using random-effects models throughout.

At the protocol stage of this review, we had intended to consider clinical and surrogate outcome data at 30 days, six months, and 12 months after baseline, however this was not possible due to the variation in follow-up periods reported in individual studies. We therefore stratified outcome data into short-term (up to 12 months) and long-term (12 months or longer) follow-up.

Subgroup analyses by cell type and participant diagnosis are considered as hypothesis-generating. In this version of the review, we assessed co-interventions by subgroup analyses (considering the effect of cell therapy in participants who receive co-interventions as well as in those who do not) rather than by sensitivity analyses restricted to studies without co-interventions, as we considered the effect of cell therapy to be relevant in both subgroups.

INDEX TERMS

Medical Subject Headings (MeSH)

Adult Stem Cells [transplantation]; Arrhythmias, Cardiac [epidemiology]; Bone Marrow Cells [cytology]; Chronic Disease; Heart Failure [mortality] [*surgery]; Hospitalization [statistics & numerical data]; Myocardial Infarction [epidemiology]; Myocardial Ischemia [mortality] [*surgery]; Patient Readmission; Randomized Controlled Trials as Topic; Stem Cell Transplantation [adverse effects] [*methods] [mortality]; Stroke Volume [physiology]

MeSH check words

Humans