Meta-Analysis of Cell Therapy Trials for Patients with Heart Failure – An Update

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ABSTRACT

**Rationale:** Cell-based therapies are a promising intervention for the treatment of heart failure (HF) secondary to ischemic and non-ischemic cardiomyopathy. However, the clinical efficacy of such new treatment requires further evaluation.

**Objective:** To assess available clinical evidence on the safety and efficacy of cell-based therapies for HF.

**Methods and Results:** Electronic databases (CENTRAL, DARE, NHSEED & HTA, PubMed, MEDLINE, EMBASE, CINAHL, LILACS, KoreaMed, PakMediNet, IndMed and the Transfusion Evidence Library) were searched for relevant randomized controlled trials to June 2014. Trials of participants with HF and where the administration of any dose of autologous cells by any delivery route was compared to no intervention or placebo were eligible for inclusion. Primary outcomes were defined as mortality and rehospitalization due to HF. Secondary outcomes included performance status, quality of life, incidence of arrhythmias, brain natriuretic peptide levels, left ventricular ejection fraction, myocardial perfusion and adverse events. Thirty-one independent trials (1,521 participants) were included. The treatment significantly reduced the risk of mortality and rehospitalization due to HF. There was a significant improvement in favour of stem cell treatment in performance status and exercise capacity, left ventricular ejection fraction and quality of life. The treatment was also associated with a reduction of brain natriuretic peptide levels and no increase in the incidence of arrhythmias. However, there was considerable risk of performance, selection and reporting bias amongst the included trials.

**Conclusions:** This study shows evidence that autologous cell therapy may be beneficial for patients suffering from HF, but further evidence is required.

**Keywords:** Stem cells, cell therapy, heart failure, randomized controlled trials, ischemic cardiomyopathy, non-ischemic cardiomyopathy, meta-analysis.

**Nonstandard Abbreviations and Acronyms:**

<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
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<td>BMMNC</td>
<td>bone marrow derived mononuclear cells</td>
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<td>BNP</td>
<td>brain natriuretic peptide</td>
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<td>CABG</td>
<td>coronary artery bypass graft</td>
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<td>CI</td>
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<td>CSC</td>
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<td>HF</td>
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<td>ICM</td>
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<td>IHD</td>
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<td>LVAD</td>
<td>left ventricular assist device</td>
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<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>MLHFQ</td>
<td>Minnesota living with heart failure questionnaire</td>
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<td>MSC</td>
<td>mesenchymal stem cells</td>
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<td>NT-proBNP</td>
<td>N-terminal prohormone of brain natriuretic peptide</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>PBMNC</td>
<td>peripheral blood mononuclear cells</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>SM</td>
<td>skeletal myoblasts</td>
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INTRODUCTION

Heart failure (HF) remains a major cause of mortality worldwide. It is the cause of approximately 5% of the acute hospital admissions, accounting for 10% of the patients in hospital beds in Europe. In the USA, over five million people suffer from HF, costing the nation an estimated $32 billion every year. Importantly, the number of patients suffering from HF is steadily increasing, partially as a consequence of an aging population and partially because long-term survival has increased with recent advances in medical therapy and revascularization techniques (e.g., percutaneous coronary intervention and coronary artery bypass grafting). In ischemic cardiomyopathy, almost 90% of the patients suffering from occluded coronary arteries achieve patency following revascularization. However, in approximately 25-30% of the patients myocardial reperfusion fails facing much higher risk of developing ventricular remodelling, HF and death. Additionally, even in those achieving successful revascularization by bypass grafting, decreased survival and recurrence of ischemic symptoms can develop after several years due to restenosis of the vein grafts, progressing to HF. The prognosis of symptomatic HF is poor, with more than 50% of the patients dying in four years following diagnosis and approximately 40% of the patients being dead or readmitted to hospital with HF within the first year. HF is characterized by a massive loss of cardiomyocytes, followed by replacement with fibrotic tissue which results in ventricular remodelling and subsequently contractile dysfunction and organ failure. Current strategies for treating end-stage HF are based on replacing or supporting the failing heart by heart transplantation or left ventricular assist devices (LVAD). However, these strategies have limited long-term efficacy. Similarly to ischemic cardiomyopathy, non-ischemic dilated cardiomyopathy (DCM) can cause up to a third of the cases of HF. Management and treatment of DCM has improved significantly in the last decades as a result of optimal medical therapies. Artificial pacemakers or implantable cardioverter-defibrillators may be used in some patients to improve symptoms and reduce hospitalization, but heart transplantation is indicated in patients with advanced disease and refractory to medical therapy. Consequently, there is a clinical need for a complementary or alternative strategy to bring further attenuation or halt the progression of HF. There is also a challenge in developing new treatments that may combine the use of cell therapy with end-stage HF therapies to prevent the progression of the disease.

The rationale behind using stem and progenitor cells as treatment for heart disease is based on the notion that the heart has a limited ability to repair itself following a major injury. Recently, preclinical studies and clinical trials have suggested that stem and progenitor cells may have the potential to ameliorate left ventricular dysfunction following acute myocardial infarction (AMI), chronic ischemic and non-ischemic cardiomyopathy and heart failure. As stand-alone treatment for HF, cell therapies may be restricted, but their potential could be harnessed especially in combination with current advanced HF treatments. Taking the available clinical evidence together, we can conclude that cell-based therapy is safe, with very little treatment-related adverse events and no increase in major adverse cardiac events compared to placebo. However, there is substantial clinical heterogeneity in the design of the clinical trials and not all of them confirm the beneficial effect of these cells on both left ventricular function and clinically relevant outcomes.

Despite a number of challenges, cell therapy remains an exciting novel form of treatment for patients with HF. Recent systematic reviews and meta-analyses have reported benefits of cell therapies on left ventricular function, quality of life and exercise tolerance and even a promising reduction in the risk of mortality and rehospitalization due to worsening HF. Importantly, one of the more robust tools that modern evidence-based medicine possesses is randomized controlled trials (RCTs). It is therefore imperative that new interventions are evaluated through RCTs wherever possible. Additionally, they are the best at evaluating the cost-effectiveness of a new treatment. We have conducted a previous Cochrane review and meta-analysis including 23 RCTs of stem and progenitor cells as treatment for ischemic heart disease and heart failure. A summary of findings assessment from that study suggested that the quality of the evidence for the reduction in mortality and rehospitalization due to HF was relatively low and likely
to change with further research. This conclusion was mainly drawn from a combination of low number of events (deaths) from the contributing RCTs and discordant results from one particular study. During the last year, new clinical evidence has become available in the form of new trials of stem cells treatment for HF patients which have been completed and reported. In addition, previous meta-analyses have not included trials of cell therapy for DCM. Here we present a new systematic review and meta-analyses evaluating clinical evidence from RCTs of autologous stem and progenitor cells in patients with heart failure secondary to ischemic and non-ischemic cardiomyopathy. The present study includes 14 RCTs which were also included in our previous Cochrane review and 17 new RCTs: nine RCTs administered bone marrow-derived cells to patients with ischemic cardiomyopathy, five RCTs administered cells from tissues other than bone marrow to patients with ischemic cardiomyopathy and the remaining three RCTs administered bone marrow-derived cells to patients with non-ischemic cardiomyopathy (Online Figure I).

METHODS

Eligibility.
Trials were eligible for inclusion in the meta-analysis if they met all of the following inclusion criteria: (1) randomized or quasi-randomized controlled trials (RCTs), (2) participants presented with symptoms of HF according to the New York Heart Association (NYHA) classification (class II-IV) or clear evidence of LV dysfunction, (3) autologous cell therapy by any route of administration was compared with either no intervention or placebo as treatment for HF, (4) any co-interventions were applied equality in all trial arms. Trials published in any language other than English were excluded, as were trials presented as conference proceedings or published abstract alone.

Search strategy and study selection.
Trials were identified from searches to 23 June 2014 of CENTRAL (The Cochrane Library, 2014, Issue 5), DARE, NHSEED & HTA databases (The Cochrane Library 2014, Issue 2), PubMed (epublications only), MEDLINE (1946 onwards), EMBASE (1974 onwards), CINAHL (1982 onwards), LILACS (1982 onwards), KoreaMed (1997 onwards), PakMediNet (1995 onwards), IndMed (1985 onwards), and the Transfusion Evidence Library (1980 onwards). Searches were not limited by publication date. Detailed search strategies are available from the authors upon request. Two reviewers (SF, EMR) independently screened the titles and abstracts of all remaining references against the full eligibility criteria. The full text of papers was retrieved and screened for all those references for which a decision of eligibility could not be made from title and abstract alone. The reference lists of relevant systematic reviews identified through the search were also checked. Differences of opinion were resolved through discussion with a third reviewer (AM).

Data extraction.
Data were extracted onto customized data extractions forms by two reviewers (SF and EMR) independently; disagreements were resolved through discussion. The reviewers were not blinded to authorship, institutions, journals or the outcomes of trials. Trial details including study design (objectives, setting, methods of treatment allocation, randomization and blinding, statistical analyses, protocol violations and conflicts of interest), characteristics of participants (age, gender, inclusion and exclusion criteria, sample sizes), interventions (experimental and control interventions, description of intervention/comparator, timing of intervention, dosage/extent of intervention) and outcomes were recorded. The primary outcomes of this systematic review were (i) mortality and (ii) rehospitalization due to worsening HF, measured at short term (up to 12 months) and long term (12 months and over) follow-up. Secondary outcomes were (i) performance status (NYHA classification and exercise capacity); (ii) health-related quality of life (QoL) (e.g. MLHFQ score); (iii) incidence of arrhythmias; (iv) brain natriuretic peptide (BNP) levels; (v) left ventricular ejection fraction (LVEF); (vi) myocardial perfusion; (vii) adverse
events e.g. immunoreaction, procedure-related bleeding complications, other complications of surgery or implantation. Where multiple times of follow-up were reported, data were extracted for the longest possible duration of short term and long term follow-up. The authors of 18 trials were contacted for clarification of data including apparent discrepancies and/or insufficient detail in the reporting of methods or results 19, 22-25 or for mean and standard deviation values of outcomes where not explicitly reported 11, 19, 25, 30-36 or where reported graphically 9, 10, 37-39. Responses were obtained from authors of seven trials (see Acknowledgments section). Where possible, for results presented graphically and where actual data values were not forthcoming from study authors (four studies), mean and standard deviation values were estimated independently by two reviewers and the average values were used.

**Evaluation of risk of bias.**

Two review authors (SF and EMR) independently assessed all included trials for possible risk of bias and made explicit judgements about whether trials were at risk of bias according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions 40. We assessed the design, conduct and analysis of the trial using a three-point scale: yes (low risk of bias), no (high risk of bias), or unclear. Assessment of risk of bias for each trial included the following questions: (i) Was the allocation sequence adequately generated? (ii) Was allocation adequately concealed? (iii) Was knowledge of the allocated intervention adequately prevented (i.e. blinded) throughout the trial? (iv) Were incomplete outcome data adequately addressed for every outcome? (v) Were reports of the trial free of selective outcome reporting? (vi) Was the trial apparently free of other problems that could put it at risk of bias? Publication bias was assessed for the primary outcome of mortality using a funnel plot.

**Data analysis.**

Meta-analyses were performed using Revman v5.3 41. Meta-analyses were restricted to outcomes which were reported in at least three trials. Random effect models were used throughout due to the likely heterogeneity arising from the different cell types and clinical diagnoses. Where standard deviations were not explicitly reported, these were estimated where possible from reported p-values or confidence intervals (CI). For continuous outcomes, the mean change from baseline over the study follow-up period was the preferred measure of outcome; the mean value at endpoint was used where insufficient data were available to calculate the mean change from baseline. Dichotomous data are presented as relative risks (RRs) with 95% CI; continuous measures are presented as the mean difference (MD) with 95% CI between groups at follow-up.

For trials with more than two treatment arms and a single control or placebo group, multiple pairwise comparisons of treatment groups were avoided by pooling treatment groups across different cell types 30 or cell doses 42-44. For dichotomous variables, count data were summed across groups and for continuous variables, the mean and standard deviation of the combined group was calculated from the mean and standard deviations of each subgroup.

In the analysis of LVEF, several methods of measurement (magnetic resonance imaging (MRI), echocardiography, single-photon emission computed tomography (SPECT), left ventricular angiography) were described, with some trials reporting results for several methods. In the analysis of LVEF, in order to obtain the most reliable and comparable measurements, results were extracted according to the above order of preference, subject to full availability of the required data.

Several trials reported NT-proBNP values rather than BNP. However, the diagnostic performance of these measurements is comparable and there is no meaningful difference between the two, despite the differences in measurement scales 45. Therefore, the standardized MD (SMD) was used in order to allow analysis of these two comparable measurements on different scales. Where values of NT-proBNP were reported as pmol/L, these were converted to pg/mL using the conversion factor 0.118 45.
The $I^2$ statistic was used to quantify the amount of possible statistical heterogeneity, (where $I^2 > 30\%$ denotes moderate heterogeneity and $I^2 > 75\%$ denotes considerable heterogeneity) \cite{46, 47}. $P<0.05$ was considered statistically significant. Two-sided significance values are reported throughout.

Where sufficient trials were available for meta-analysis of subgroups, tests for differences between subgroups were carried out according to (i) route of administration (intramyocardial versus intracoronary); (ii) baseline cardiac function (mean baseline LVEF >30\% vs mean baseline LVEF >35\%); (iii) ischemic vs. non-ischemic HF and (iv) cell type (BMMNC, hematopoietic progenitor cells (CD34+, CD133+, ALDH+), mesenchymal stem cells (MSC), endothelial progenitor cells (EPC), skeletal myoblasts (SM) and cardiac stem cells (CSC)). Sensitivity analyses were used to assess the impact of risk of bias on significant results from meta-analyses, by excluding trials which had a high or unclear risk of selection bias, performance bias or attrition bias.

RESULTS

Search results.

Electronic database searches identified a total of 4265 records which were screened in duplicate, resulting in 129 potential studies for inclusion. Of these, 93 were subsequently excluded as they failed to meet the inclusion criteria, see PRISMA flow diagram for details (Figure 1).

Characteristics of the included trials.

The inclusion criteria were met by 36 full text articles \cite{9-11, 19-39, 42-44, 48-56} which described 31 independent trials with a total of 1521 randomized participants (cells: 882, no cells: 639). Two studies \cite{9, 29} randomized participants separately to two different cell intervention groups, each with a comparative placebo arm; in these studies the two groups were considered as independent trials unless results were reported for a combined control group, in which case the two intervention groups were combined for consistency and to avoid double counting of controls. The characteristics of the included trials are summarized in Table 1.

Three trials \cite{10, 48, 54} were of non-ischemic DCM; the remaining 28 trials were ischemic cardiomyopathy (ICM). The number of participants randomized to these trials ranged from 14 to 120 and the duration of follow-up ranged from three months to 60 months or over \cite{10, 39, 43, 52}. All trials administered standard medical therapy to all participants including aspirin, clopidogrel, heparin, blockers, statins, angiotensin converting enzyme (ACE) inhibitors, nitrates and/or diuretics. Nine trials had CABG as co-intervention \cite{23, 24, 31, 32, 34, 35, 42, 49, 53}; six had PCI \cite{26, 28-30, 52}; one trial used shock-wave as co-intervention \cite{22} and the remaining 15 trials treated patients with the standard medical care as above during cell administration.

Twenty-one trials isolated the BMMNC by bone marrow aspiration and further separation of the mononuclear cells using density gradient centrifugation \cite{9-11, 19, 22-26, 28-35, 52-54}. Of these, three trials enriched the cell population in either CD34+ \cite{10, 24} or CD133+ \cite{23} cells by magnetic cell separation, and one trial enriched in alcohol dehydrogenase (ALDH)-positive cells \cite{33}. Two trials treated patients with G-CSF prior to bone marrow aspiration \cite{29}. One trial mobilized the bone marrow cells into circulation using G-CSF and subsequently isolated the mononuclear cell fraction by leukopheresis \cite{48}. One trial obtained bone marrow-derived endothelial progenitor cells (BM-EPC) from BMMNC by culturing the cells under endothelial culture conditions for three days \cite{52}.

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Of the remaining eight trials, three obtained BM-MSC from BMMNC by culturing the cells under MSC conditions for at least seven days, one of which treated the BM-MSC with a cardiopoietic cocktail of cytokines prior to administration. One trial administered cardiac stem cells, obtained from a right atrial appendage biopsy followed by magnetic separation and culture of c-kit-positive cells. The remaining four trials isolated SM from muscle biopsies followed by culture of the cells ex vivo and identification of a SM population containing at least 50% of CD56-positive cells. Finally, one trial administered adipose-derived regenerative cells (ADRC) obtained by liposuction and followed by enzymatic digestion of the adipose tissue, cell separation and cell elution using commercially available devices. The cell dose ranged from $5 \times 10^5$ CSC to $8.4 \times 10^8$ BMMNC or $8.4 \times 10^8$ SM.

Fifteen trials compared cells with a placebo, generally consisting of a cell-free solution, either the participants own serum or a saline solution containing heparin. One trial used a mock injection procedure in the control arm instead of a cell-free solution. The remaining 15 trials compared treatment to no treatment.

Twelve trials delivered the cells via the coronary arteries (IC) while the remaining 19 trials injected the cells into the heart muscle (IM). All but four trials reported primary outcomes which included safety/feasibility, cardiac function (predominantly LVEF), efficacy and efficiency, QoL, six-minute walk test, myocardial perfusion and mortality.

Evaluation of risk of bias.

A summary of the risk of bias of included trials is shown in Figure 2; an assessment of the risk of bias of individual trials is shown in Online Table I and Online Figure II. One trial used a two-staged design whereby the first 13 patients were enrolled consecutively (first nine allocated to stem cell, followed by four allocated to placebo) and subsequent patients were randomized electronically; this trial was deemed to have a high risk of selection bias. In 11 trials, the method of randomization was not reported and the risk of bias was unclear, with the exception on one trial in which paired randomization matched for sex, age, LVEF and severe coronary artery lesions was used; this trial was considered to have a high risk of selection bias. Fourteen trials included a description of the method of randomization and allocation concealment which included computerized methods, sealed envelopes, a telephone interactive voice-response system, coloured ball selection, random number tables and site-independent randomization, and the risk of selection bias in these trials was low. In 14 trials, no method of allocation concealment was reported and therefore these trials were considered to have an unclear risk of selection bias due to poor allocation concealment.

The risk of performance bias was low in 16 trials, with patients and clinicians blinded to treatment. Nine trials reported a lack of blinding of clinicians and patients and therefore had a high risk of performance bias. In six trials, blinding was not reported and the risk of bias in these trials was unclear. The risk of detection bias was generally low; only four trials failed to report blinding of outcome assessors.

The risk of attrition bias was low in the majority of trials, with any withdrawals balanced between trial arms and reasons for withdrawal reported. Six trials were deemed to have a high risk of attrition bias due to an unbalanced number of withdrawals between trial arms, and in one case the number of randomized participants in each trial arm was not reported and therefore withdrawals could not be evaluated. In four trials, the risk of attrition bias was unclear as withdrawals, although explained, were unbalanced between trial arms.
All outcomes that were detailed in the trial registration or protocol were reported in nine trials \(^9, 11, 21-23, 25, 30, 33\) and had a low risk of reporting bias. In a further 14 trials \(^{19, 24, 26, 28, 31, 32, 37, 42, 44, 48, 50-53}\), all outcomes mentioned in the methods were reported in the results although it would be difficult to rule out selective reporting, and these trials were therefore considered to have an unclear risk of reporting bias. The risk of bias was also unclear in seven other trials in which either one pre-defined secondary outcome was not reported \(^{20, 34}\), one reported outcome was not included in the trial registration or protocol \(^{10, 35, 49}\), or in the case of two trials \(^{29}\), interim results of secondary outcomes only were presented. In one trial \(^{54}\), the list of pre-defined outcomes differed between two published reports and this trial was therefore considered to have a high risk of reporting bias. Visual assessment of a funnel plot of the primary outcome of mortality (Online Figure III) did not identify any notable asymmetry suggestive of publication bias, although given the relatively small size of the included trials, small study bias would not be detectable from a funnel plot.

Sources of study funding was reported in 23 trials including seven \(^{20, 21, 23, 33, 37, 42, 44}\) which reported commercial study sponsorship.

**Effect of interventions.**

**Mortality:** Mortality was reported in all but one trial \(^{48}\). Twenty-six trials \(^{9, 11, 19-21, 23-26, 28-31, 33-35, 37, 42, 44, 49, 51-54}\) including 1069 participants (643 treated vs. 426 controls) reported mortality as an outcome at short term follow-up. Thirteen trials \(^{9, 20, 24-26, 28, 33, 44, 49, 51-53}\) observed no deaths at follow-up. In 13 trials \(^{11, 19, 21, 23, 29-31, 34, 35, 37, 42, 54}\) in which deaths occurred in one or both trial arms, 22/416 deaths occurred in patients who received cells compared with 21/280 in those who did not (RR 0.71, 95% CI 0.34 to 1.46, \(p=0.35\)). Results were similar when one non-ischemic DCM trial was excluded from the analysis (RR 0.61, 95% CI 0.28 to 1.35, \(p=0.22\)).

Mortality at long term follow-up (\(\geq 12\) months) was reported in 17 trials \(^{9, 19-23, 26, 32, 36, 39, 43, 49-52, 55}\). Six trials reported no deaths \(^{9, 26, 32, 43, 49, 51}\), whilst the remaining 11 trials reported 38/355 deaths in patients who received cells compared with 73/307 in those who did not. Meta-analysis revealed a significant reduction in mortality associated with cell therapy (RR 0.48, 95% CI 0.34 to 0.69, \(p<0.0001\)) (Figure 3A). The results remained significant when only ischemic HF trials were included (RR 0.42, 95% CI 0.25 to 0.71, \(p=0.001\)).

Subgroup analysis showed no difference in the risk of mortality between trials grouped according to route of stem cell administration or baseline cardiac function at either short term or long term follow-up (\(p<0.1\) for all comparisons). Insufficient trials were available to evaluate differences according to cell type at short term follow-up. At long term follow-up, there was no evidence for a difference in the risk of mortality between trials which used BMMNC (8 trials) and those which used MSC (3 trials) \(p=0.92\).

**Rehospitalization due to worsening heart failure:** Eight trials \(^{11, 28-30, 37, 44, 52}\) (340 participants; 225 treated vs. 117 controls) reported rehospitalization due to worsening HF during short term follow-up. All were ischemic cardiomyopathy patients. Whilst two trials \(^{29, 52}\) reported no rehospitalization in either group, in the remaining five trials there were 12/191 patients requiring rehospitalization in the treated group compared to 9/99 in the control group, with no significant difference between groups (RR 0.59, 95% CI 0.25 to 1.41, \(p=0.24\)).

However, at long term follow-up, in seven trials \(^{9, 22, 32, 43, 49, 52}\) which reported rehospitalization as an outcome, five trials reported patients requiring rehospitalization (11/104 vs. 25/69) \(^{9, 22, 43, 49, 52}\) showed a significantly lower risk of rehospitalization due to HF in patients who received cell treatment than in those who did not (RR 0.39, 95% CI 0.22 to 0.70, \(p=0.002\)) (Figure 3B).
Arrhythmias: Seventeen trials (684 participants; 409 treated and 275 controls) reported arrhythmias as an outcome during short-term follow-up 19, 21, 24, 25, 28-30, 33-35, 37, 42, 44, 49, 50, 53; all were ischemic cardiomyopathy trials. Ten trials reported no arrhythmias in either group, whilst the remaining seven trials 29, 30, 33, 34, 37, 42, 44 reported 26/191 patients who experienced arrhythmias in the treated group compared to 9/113 patients in the control group. There was no significant difference between the groups (RR 1.45, 95% CI 0.72 to 2.92, p=0.29).

The results were similar during long-term follow-up where seven trials 19, 21, 22, 35, 43, 49, 51 (304 participants; 176 treated and 128 controls) reported arrhythmias. Three of these trials reported no cases of arrhythmias in either group, whereas the remaining four trials 22, 35, 43, 51 reported that 14/90 patients experienced arrhythmias in the treatment group and 22/82 patients in the control group. No significant differences were observed between treatment and control groups (RR 0.77, 95% CI 0.28 to 2.09, p=0.61).

NYHA functional class: A total of 23 trials, all of ischemic HF, reported NYHA functional class as an outcome during short-term follow-up 9, 11, 19-26, 29, 30, 34, 37, 42, 44, 49-52. However, four trials 9, 20, 42 reported NYHA class as the proportion of patients whose NYHA class improved or changed from baseline value, two trials 11, 44 reported summary results only, and in one trial of intracoronary administration of cells 29, only one control survived at follow-up and therefore no standard deviation could be calculated. Meta-analysis of the remaining 16 trials showed a significantly lower NYHA class at short term follow-up in patients who received stem cell treatment compared with those who did not (RR -0.47, 95% CI -0.89 to -0.06, p=0.03) (Figure 4A).

NYHA functional class after long-term follow-up was reported as an outcome in 13 trials 9, 19, 21, 26, 32, 39, 43, 49-52. Four of those trials were excluded from the meta-analysis: two trials 9 reported NYHA class as a proportion of patients whose NYHA class changed from baseline value, one trial 39 reported control values graphically with no clear detail of measure of variation and one trial 49 did not report data from the control group at long-term follow-up. Meta-analysis of the remaining nine trials showed a significantly lower NYHA class in patients who received cell treatment compared with those who did not (RR -0.70, 95% CI -1.12 to -0.28, p=0.001) (Figure 4B). These results were confirmed when meta-analysis was restricted to ischemic HF trails (RR -0.72; 95% CI -1.17 to -0.26; p=0.002; I^2=94%).

Considerable statistical heterogeneity was observed at both short term and long term follow-up (short term: I^2=97%, long term: I^2=93%). There was no evidence for a difference in NYHA class between trials grouped according to route of cell administration at either short term or long term follow-up. In the comparison of cell types, there was no evidence for a difference in NYHA class between BMMNC and hematopoietic progenitor cells at short-term follow-up (p=0.71). Insufficient trials were available to evaluate differences between cell types at long term follow-up. When trials were grouped according to baseline cardiac function, there was no difference in NYHA class at short term follow-up. However, at long term follow-up, there was some evidence of a difference between trials with mean baseline LVEF <30% (4 trials, MD -1.01, 95% CI -1.45 to -0.58, p=0.00001) and those with mean baseline LVEF >35% (3 trials, MD -0.32, 95% CI -0.74 to 0.10, p=0.14) (test for subgroup differences, p=0.03). However, residual heterogeneity remained in both groups (I^2=84%, I^2=70% respectively).

Left ventricular ejection fraction: LVEF was reported in a total of 23 trials after short-term follow-up 11, 19, 20, 22-26, 28, 30, 31, 33-35, 37, 42, 44, 48-50, 52-54. One trial 42 reported median values of LVEF and therefore could not be included in the meta-analysis; another trial 44 reported only summary results. Seven trials (all of ischemic cardiomyopathy) 11, 22, 28, 30, 31, 35, 55 reported mean change from baseline values; the remaining 14 trials did not report sufficient data to enable calculation of the mean change standard deviation. Meta-analysis revealed a significant difference in mean change from baseline values in favour of cell therapy (MD 2.06%, 95% CI 1.10% to 3.01%, p=0.00001) (Figure 5A). This significant improvement was reflected in 20 trials which reported LVEF values at follow-up (MD 4.66%, 95% CI 2.99% to 6.33%, p<0.00001) (Figure 5A).
This effect remained when two non-ischemic HF trials \(^{48,54}\) were excluded (MD 4.48%, 95% CI 2.70% to 6.26%, \(p<0.00001\)).

Twelve trials \(^{9,19,21,26,32,36,39,43,50,52,55}\) reported LVEF after long-term follow-up although one trial \(^{21}\) only reported summary results with no data. One trial \(^{39}\) only reported control values graphically with no clear detail of measure of variation, and was therefore excluded from the analysis. In another study contributing two trials \(^{9}\) in which results were reported for the two control groups combined, results for the two intervention groups were also combined for meta-analysis. In four trials that reported mean change in LVEF from baseline values \(^{9,19,32,36}\), meta-analysis showed no significant difference in mean change from baseline values between groups (MD 1.26%, 95% CI -3.08% to 5.59%, \(p=0.57\)). However, in eight trials \(^{19,26,32,36,43,50,52,55}\) that reported LVEF values at time of follow-up, meta-analysis showed significant difference in mean change from baseline values in favour of cell treatment (MD 4.02%, 95% CI 1.09% to 6.96%, \(p=0.007\)) (Figure 5B). These results were also confirmed in ischemic HF trials only (MD 3.57%, 95% CI 0.30% to 6.84%, \(p=0.03\)).

Moderate statistical heterogeneity was observed at short term follow-up for endpoint analysis \((I^2=61\%)\) and at long term for both mean change from baseline and endpoint analyses \((I^2=69\%\mbox{ for both analyses})\). There was no evidence for a difference in LVEF measured at follow-up between trials grouped according to route of cell administration or baseline cardiac function at either short term or long term follow-up. In the comparison of cell types, there was no evidence for a difference in LVEF between BMMNC and hematopoietic progenitor cells at short-term follow-up \((p=0.75)\). Insufficient trials were available to evaluate differences between cell types at long term follow-up.

**BNP/NT-proBNP:** At short term follow-up, four trials reported NT-proBNP \(^{22,29,52}\) and five trials reported BNP \(^{19,26,35,44,48}\). However, in one trial of intracoronary administration of cells \(^{29}\), only one control survived at follow-up and therefore no standard deviation could be calculated; in another trial \(^{35}\), median values were reported and in a third trial \(^{44}\), no standard deviations were reported. In a combined analysis of BNP and NT-proBNP, the remaining six trials showed a significant difference in measurements taken at follow-up in favour of cell therapy \((SMD -0.72 \mbox{ pg/mL}, 95\% \mbox{ CI} -1.41 \mbox{ to} -0.02, p=0.04)\) (Figure 6A).

Four trials reported NT-proBNP \(^{39,52}\) or BNP \(^{26,32}\), although one trial \(^{39}\) only reported control values graphically with no clear detail of measure of variation, and was therefore excluded from the analysis. Meta-analysis of the remaining three trials showed no significant difference between groups in measurements taken at long term follow-up \((SMD -0.01 \mbox{ pg/mL}, 95\% \mbox{ CI} -1.59 \mbox{ to} 1.57, p=0.99)\).

Considerable statistical heterogeneity was observed at both short term and long term follow-up \((I^2=84\%, I^2=92\% \mbox{ respectively})\).

**Exercise capacity:** Exercise capacity at short term follow-up was reported in 10 trials, eight of which measured exercise using a six-minute walk distance test \(^{9,19,20,23,35,37,44}\). Other methods of measuring exercise capacity were use of a treadmill test \(^{30}\) and a bicycle ergometer. \(^{52}\) Meta-analysis of four trials \(^{19,20,35,37}\) which reported values at the time of follow-up showed a significantly better exercise capacity in patients who received cell treatment than those who did not \((MD 65.18 \mbox{ m}, 95\% \mbox{ CI} 9.86 \mbox{ to} 120.5, p=0.02)\) with considerable heterogeneity across trials \((I^2=80\%)\) (Figure 6B). Meta-analysis of mean change from baseline values at short term follow-up was not possible as two trials reported in one study \(^{9}\) pooled controls from each trial, and in a third trial \(^{23}\) it was unclear whether mean or median values were reported. Seven trials \(^{9,19,21,39,50,52}\) reported exercise capacity at long term follow-up, although differences in the methods of measurement and reporting prohibited meta-analysis of these trials.
Maximum oxygen volume: Maximum oxygen volume (MVO$_2$) was reported in nine trials $^{9, 11, 21, 23, 25, 33, 48, 52}$, although two trials reported in one study $^9$ only reported brief summary results. In meta-analysis of the remaining seven trials there was no significant difference in MVO$_2$ measured at short term follow-up (MD 0.27 mL/min/kg, 95% CI -0.29 to 0.83, p=0.35) (Figure 6C). Four trials $^9, 21, 52$ reported MVO$_2$ at long term follow-up with insufficient data to perform meta-analysis.

Quality of life (QoL): Eleven trials $^9, 19, 20, 23, 25, 37, 42, 44, 49, 51$ reported QoL measures at short term follow-up, with all but one trial $^42$ reporting MLHFQ values. Two trials reported in one study $^9$ reported maximum values (as mean change from baseline) during the study follow-up period; these results were excluded to avoid potential bias. Mean change from baseline values were also reported in two other trials $^{23, 44}$ although in one trial $^{52}$ it was unclear whether mean or median values were reported. One trial $^{20}$ reported the percentage of patients who improved from baseline score. Meta-analysis of the five trials which reported MLHFQ at time of short term follow-up $^{19, 25, 37, 49, 51}$ showed a significant difference between treatment and control groups, demonstrating a significantly better quality of life at short term follow-up in patients who received cell therapy than those who did not (MD -19.6, 95% CI -30.3 to -9.0, p=0.0003) (Figure 6D). Moderate heterogeneity was observed across trials ($I^2=61\%$).

Seven trials $^9, 19, 48, 49, 51, 55$ reported QoL at long term follow-up, although meta-analysis was prohibited by differences in measurement and reporting methods between trials.

Myocardial perfusion: Myocardial perfusion was reported as an outcome at short term follow-up in 10 trials $^{11, 19, 21, 23, 25, 28, 33, 34, 50, 53}$. However, different methods were used across trials including % reversible defects $^{11, 50}$, % perfusion defect $^{28}$, proportion of LV myocardial segments with a perfusion deficit $^{23}$, summed stress, rest and/or difference scores $^{19, 21, 33}$, left ventricular/infarcted area segmental resting scores $^{34}$ and Technetium (99mTc) sestamibi (MIBI) uptake at rest $^{53}$, and therefore meta-analysis could not be performed. Of the 10 trials, four $^{23, 34, 50, 53}$ found significant differences between treatment groups at short term follow-up, whereas three $^{11, 28, 33}$ found no significant differences between groups and three $^{19, 21, 25}$ only reported changes over time within treatment groups. Only three trials $^{19, 21, 50}$ reported myocardial perfusion at long term follow-up and the different methods of reporting precluded meta-analysis of these trials.

Adverse events: Peri-procedural adverse events reported in patients who received cell therapy are summarized in Online Table II. Peri-procedural adverse events were infrequent and generally related to the interventional procedure rather than the cells themselves, with the exception of arrhythmias reported in six trials $^{10, 11, 20, 29, 34, 91}$ including one patient with severely depressed LV function (LVEF 22%) who experienced refractory ventricular fibrillation followed by death on day 3 $^{34}$. In addition, two patients experienced peri-procedural myocardial infarction $^{21, 30}$ and one patient who died on postoperative day 7 because of a cardiac unrelated cause (perforated esophageal ulcer complicated by mediastinitis) $^{31}$.

Adverse events reported at short and long term follow-up in patients who received cell therapy as well as those who received no cells are summarized in Online Table III. With the exception of mortality and rehospitalization due to worsening HF (reported above), meta-analysis of adverse events reported at short and long term follow-up was not possible due to disparities in the types of adverse events reported and whether reported episodically or by the number of patients affected.

Sensitivity analysis

An evaluation of the effect of risk of bias on the significant outcomes of long term mortality and NYHA functional class and LVEF at short and long term follow-up (measured at time of follow-up) was undertaken with sensitivity analyses, excluding those trials with a high or unclear risk of bias due to randomization methods (allocation), withdrawals or exclusions (attrition bias) and lack of blinding of participants and clinicians (performance bias) (see Online Table I and Online Figure II). When meta-
analysis was restricted to those trials reporting appropriate randomization methods, the reduction in the risk of mortality associated with stem cell therapy remained significant (7 trials, RR 0.43, 95% CI 0.25 to 0.74 p=0.002); similar results were found when only trials with a low risk of attrition bias were included (7 trials; RR 0.41, 95% CI 0.27 to 0.64, p<0.0001). NYHA class and LVEF were similarly robust to both selection and attrition bias, with the exception of LVEF at long term follow-up (data not shown). However, when only those trials where both clinicians and patients were blinded to treatment, i.e. trials with a low risk of performance bias were included, the beneficial effect of stem cell therapy on risk of mortality at long term follow-up (5 trials, RR 0.62, 95% CI 0.29 to 1.35, p=0.23) and on NYHA class and LVEF at both short term (NYHA class: 7 trials, MD -0.31, 95% CI 0.77 to 0.16, p=0.19; LVEF: 7 trials, MD 3.20, 95% CI -1.07 to 7.47, p=0.14) and long term (NYHA class: 3 trials, MD -0.25, 95% CI -0.65 to 0.14, p=0.21; LVEF: 3 trials, MD 1.86, 95% CI -1.84 to 5.56, p=0.32) follow-up no longer reached statistical significance.

DISCUSSION

Cell therapies have the potential to be developed as treatment for HF 16-18, but safety and clinical efficacy require further evaluation. The present study is the most comprehensive systematic review and meta-analysis to date of stem cell trials for HF, with 31 included RCTs and a total of 1,521 participants. The included trials recruited patients who have been diagnosed with HF and compared the active intervention (cells) with placebo or control (no cells). This systematic review and meta-analysis evaluated, for the first time, clinical data on stem cell treatment for non-ischemic DCM. However, the contribution of ischemic HF trials to the main results of the meta-analyses is stronger as only three RCTs on cell therapy and non-ischemic DCM were eligible for inclusion in this study. Overall, autologous cell-based therapies have been shown to be safe as treatment for HF, with minimal major intervention-related adverse effects and no increase in the incidence of arrhythmias.

The main findings of this systematic review and meta-analyses are: (i) stem cell treatment is associated with a significant reduction of mortality and rehospitalization due to worsening HF during long-term follow up, (ii) stem cell treatment significantly, but moderately, improves global LVEF, (iii) HF symptoms, measured by NHYA functional class and BNP/NT-proBNP levels, are significantly improved by stem cell treatment, and (iv) the treatment improves exercise capacity and QoL.

An assessment of the risk of bias in the included trials revealed that performance bias, selection bias and reporting bias contributed the highest risk of bias. Performance bias was considerable as only 52% of the included trials reported blinding of participants and clinicians. Selection bias was also considerable as only 45% of the trials reported the methods of allocation concealment. Finally, 29% of the trials detailed all outcomes measured in the trial registration or protocol whilst in the remaining 71% selective reporting bias will be difficult to rule out. This systematic review and meta-analysis does not find evidence of publication bias amongst the included trials; however, due to the relatively small size of the included trials this cannot be completely ruled out.

The effect of risk of bias on the significant results was assessed through sensitivity analyses which will be more stringent than the primary analyses. The conclusion that lower mortality, lower NYHA class and improved LVEF were associated with cell therapy was robust to inadequate or unreported methods of randomization and to possible attrition bias. However, when trials were restricted to those in which both clinicians and participants were blinded, these significant results were no longer apparent. A consequence of such stringent sensitivity analysis is a substantial reduction in the number of trials included in meta-analyses and hence reduced power to detect a significant effect; this issue can only be resolved through future well-powered and appropriately blinded studies.
A recent study identified a high number of reporting discrepancies in trials of heart disease and concluded that such discrepancies in reporting can lead to bias. However, many of the discrepancies reported by Nowbar and colleagues were in fact a direct consequence of a single misreported sample size or other error, many of which we previously resolved through communication with individual trial authors in our previous systematic review. The same protocol has been adhered to in the present study (see the Acknowledgments section). Further, a large number of discrepancies identified by Nowbar and colleagues originated from non-randomized studies and these are not included in our systematic review. Clearly, any discrepancies in reporting can be suggestive of reporting bias and will affect the validity of conclusions that can be drawn. Our experience is that innocuous errors do occur and can often be resolved through communication with study authors.

We have identified 11 previous independent systematic reviews and meta-analyses that have evaluated stem cell therapies for HF. Seven of these included mortality as an outcome, of which five showed no increased in the risk of death following stem cell treatment whilst two observed a significant reduction in the risk of mortality associated with stem cell treatment. One notable difference between the latter two systematic reviews is that in our own previous study we included RCTs for chronic ischemic heart disease and HF (including refractory angina), whereas Jeevanantham and colleagues combined both randomized and non-randomized trials for chronic ischemic heart disease and acute myocardial infarction. In our previous study, the evidence for a beneficial effect of cell therapy on mortality was drawn from very few deaths from the contributing RCTs and notably discordant results from one trial of severe HF. Compared to our previous Cochrane review, the quality of evidence has increased. The present study includes 31 RCTs for HF, 14 of which were also included in our previous Cochrane systematic review and meta-analysis. Importantly, there is a substantial number of new trials included here: nine trials which administered BMNNC, four which used SM, one trial which administered CSC and three trials in which the participants presented HF secondary to non-ischemic DCM. Additionally, the 95% confidence intervals of the RR for the major outcomes have been reduced (Online Table IV). However, these results should be considered with caution as the clinical settings for which the treatment is evaluated differ between these two reviews. None of the included studies is a Phase III trial and therefore they were not designed to detect differences in clinical outcomes such as mortality. The present study has greater statistical power than previous systematic reviews and meta-analyses, improving the robustness of the evidence and confirming previous results. It has also greater statistical power than the included studies.

In agreement with previous studies, the present study shows that stem cell treatment improves patients’ QoL (measured by MLHFQ) and exercise capacity (measured by six-minute walk distance). Cheng et al. and Kandala et al. reported an improvement in NYHA class in favour of stem cell treatment but no significant differences inrehospitalization due to HF. The latter was also observed in a meta-analysis by Jiang et al. By contrast, Fisher et al. reported improved NYHA class and significant decrease inrehospitalization due to HF and Jeevanantham et al. confirmed a significant reduction in the incidence of HF in favour of stem cell treatment.

Rehospitalization due to worsening HF, NYHA functional class and levels of BNP/NT-proBNP are all surrogates for HF. In this study, we found significant effects with all of these measures, indicative of amelioration of HF symptoms. Here, the relative risk of rehospitalization due to HF is reduced to approximately 0.40. Although promising, the number of RCTs contributing to this data is relatively small (five RCTs) with a total of 242 participants included in the meta-analysis.

Of 11 previous systematic reviews and meta-analyses, all but one demonstrated a moderate but significant improvement in LVEF in favour of stem cell treatment that ranged from 2.8% to 5.4%. The present study is largely in agreement with previous meta-analyses, although improvement in global LVEF has not been consistently shown in cell therapy trials. The significant reduction in the risk of mortality...
and rehospitalization due to HF may be difficult to explain alongside the slight improvement in global LVEF: this question remains unresolved.

Alternative surrogate outcomes have been used to evaluate the efficacy of stem cell therapies. Reduction of scar size is highly predictive of mortality, HF and LV remodelling. Stem cell therapies have been shown to reduce scar size significantly in a previous systematic review and meta-analysis in patients with AMI. It is therefore tempting to suggest that in trials for HF scar size could also be measured as a surrogate outcome to predict clinical efficacy.

Trials included in this study have administered a variety of cell types, BMMNC being the most common therapy. However, there is no current evidence to support that other cell types, such as SM, MSC or MSC-like cells or CSC do not have similar therapeutic potential. There are only two studies amongst the included RCTs that included different types of cells: BMMNC and BM-MSC and BMMNC and CPC. The number of participants randomized to each arm of these trials is small. Interestingly, Heldman et al. showed that BM-MSC performed better than BMMNC at improving six-minute walk distance and reducing scar mass, thus confirming their regenerative and anti-fibrotic effect. However, a comparison side by side has not been done yet at a large scale.

If we accept the mechanistic shift that is emerging in the field, most cell therapies seem to be exerting their beneficial effect in a paracrine manner and most probably promoting endogenous repair and regeneration. Repair and regeneration seem to involve tissue remodelling and reduction of scar size. This may explain the discrepancy between the relatively low number of cells administered and the sustained efficacy of the treatment. Cells may be acting as factories that produce an array of growth factors, cytokines and modulators of extracellular matrix deposition that are required only temporarily. Although the limitations of cell delivery and cell engraftment have been recognized before, cells may not be needed to engraft long-term whilst still exerting their long-lasting therapeutic benefit.

In conclusion, we show that cell therapies may have a clinical benefit for patients with HF, as they appear to significantly reduce mortality and rehospitalization in the long-term. Although promising, these results need to be confirmed in larger appropriately randomized clinical trials in which both clinicians and participants are blinded. However, if confirmed, such a reduction in rehospitalization may mean a real long-term cost saving in the management of HF for any health care system.
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DISCLOSURES
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<th>RCT ID</th>
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<th>Cell type</th>
<th>Cell dose</th>
<th>Methods of cell isolation</th>
<th>Route of delivery</th>
<th>Comparator arm</th>
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<td>ICM</td>
<td>PCI</td>
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<td>BMMNC: 205 (110) x10^6 cells CPC: 22 (11) x10^7 cells</td>
<td>BMMNC: Density gradient centrifugation CPC: Density gradient centrifugation and 3 days in culture</td>
<td>IC</td>
<td>Control</td>
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<td>Change in LVEF (by LV angio)</td>
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<td>BMMNC</td>
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<td>Density gradient centrifugation</td>
<td>IC</td>
<td>Shock-wave</td>
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<td>IM</td>
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<td>BM-MSC: 32 Control:15</td>
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<td>2 years</td>
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<td>SM:12 Control:11 Safety and feasibility 12 months</td>
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<td>CABG</td>
<td>CD34: 10</td>
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<td>Follow-Up</td>
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<td>Placebo</td>
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<td>18</td>
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ADRCs, adipose tissue-derived regenerative cells; ALDH, alcohol dehydrogenase; BM, bone marrow; BM-EPC, bone marrow-derived endothelial progenitor cells; BMMNC, bone marrow mononuclear cells; BM-MSC, bone marrow-derived mesenchymal stem cells; CABG, coronary artery bypass graft; CSC, cardiac stem cells; Echo, echocardiography; G-CSF, granulocyte colony stimulating factor; HSC, hemopoietic stem cells; IC, intracoronary; ICM, ischemic cardiomyopathy; ID, identifier; IM, intramyocardial; LV angio, left ventricular angiography; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NICM, non-ischemic dilated cardiomyopathy; PBMMNC, peripheral blood mononuclear cells; PCI, percutaneous coronary intervention; QoL, quality of life; RCT, randomized controlled trial; RVEF, right ventricular ejection fraction; SM, skeletal myoblast; SPECT, single-photon emission computed tomography; TX, transplantation.
FIGURE LEGENDS

Figure 1: PRISMA flow diagram used in the study selection.

Figure 2: Cochrane risk of bias. Summary of the risk of bias from all included trials expressed as percentage.

Figure 3: Effect of cell treatment on primary outcomes during long-term follow-up (≥ 12 months), (A) Risk ratio (RR) of mortality and (B) risk ratio of rehospitalization due to worsening heart failure.

Figure 4: Effect of cell treatment on heart failure symptoms measured by NYHA functional class. (A) Mean difference (MD) in NYHA class from baseline in short-term follow-up (< 12 months) and (B) mean difference in NYHA class in long-term follow-up (≥ 12 months).

Figure 5: Changes in left ventricular ejection fraction (LVEF) following cell treatment compared to control. Mean difference in LVEF during (A) short-term (< 12 months) and (B) long-term (≥ 12 months) follow-ups.

Figure 6: Effect of cell treatment on secondary outcomes. Mean difference at end of study in (A) brain natriuretic peptide/ N-terminal prohormone of the brain natriuretic peptide (BNP/NT-proBNP), (B) exercise capacity measured by six-minute walk distance, (C) maximum oxygen volume and (D) quality of life (QoL).
Novelty and Significance

What Is Known?

- Cell-based therapies have emerged as potential and exciting new interventions to treat heart failure (HF).
- Clinical trials and meta-analyses have shown mixed results, which warrants further evaluation of their safety and clinical efficacy.

What New Information Does This Article Contribute?

- This meta-analysis is the most comprehensive to date and includes cell therapy trials to treat HF secondary to ischemic and non-ischemic cardiomyopathy.
- In these settings, cell therapies seem to have a long term clinical benefit significantly reducing the risk of death and rehospitalization due to worsening HF.

Cell therapies have been developed as new treatments for heart disease. However, the available clinical evidence has shown divergent results. Previous meta-analysis have evaluated the effect of cell therapies in patients suffering from acute myocardial infarction (AMI) and HF due to ischemic cardiomyopathy. Although the treatment seems safe, the clinical efficacy is not clear. Cell therapies significantly improve left ventricular ejection fraction in AMI and HF patients compared to control (or placebo). However, whilst there is not enough evidence to show that cell therapies reduce the number of deaths following AMI, results show a reduction in the risk of death and rehospitalization due to worsening HF in HF patients. The present study includes 17 new trials compared to previous meta-analysis and assesses the effect of cell therapies in HF secondary to both ischemic and, for the first time, non-ischemic cardiomyopathy. Thirty-one randomized controlled trials (RCTs), with 1,521 participants, were included in this study. Overall, cell therapies have a long term beneficial effect reducing the number of deaths and the risk of rehospitalization compared to control. These promising results need confirming in larger RCTs where the risk of bias, such as reporting bias and blinding of clinicians and participants, is reduced.
Figure 1

4265 records identified through database searching

4265 records screened independently by two reviewers

4136 records excluded

93 papers excluded:
- 22 systematic reviews
- 20 literature reviews or commentaries
- 8 trials with no control or placebo group
- 7 non-randomised trials of heart failure
- 12 trials of AMI
- 11 trials of ischaemic heart disease but not HF
- 9 trial protocols
- 1 trial involving allogenic stem cells
- 1 gene therapy trial
- 2 analytical methodology studies

129 papers fully assessed against eligibility criteria

36 papers describing 31 independent trials included in meta-analysis
### (A) Mortality

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Heterogeneity: Tau² = 0.00; Chisq = 4.38, df = 10 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.97 (P < 0.0001)

### (B) Rehospitalisation

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Heterogeneity: Tau² = 0.00; Chisq = 1.79, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 3.17 (P = 0.002)
### (A) NYHA class <12 months

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<td><strong>-0.47 [-0.89, -0.06]</strong></td>
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Heterogeneity: Tau² = 0.67; Chi² = 454.86, df = 15 (P < 0.00001), I² = 97%
Test for overall effect: Z = 2.22 (P = 0.03)

### (B) NYHA class >12 months

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<tr>
<td>Dib 2009</td>
<td>1.7</td>
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<tr>
<td>Mennache 2008</td>
<td>1.75</td>
<td>0.5</td>
<td>4</td>
<td>2.67</td>
<td>0.58</td>
<td>3</td>
<td>3</td>
<td>-0.92 [-1.74, -0.10]</td>
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</tr>
<tr>
<td>Patla 2014</td>
<td>1.3</td>
<td>0.5</td>
<td>20</td>
<td>1.4</td>
<td>0.5</td>
<td>19</td>
<td>19</td>
<td>-0.10 [-0.41, 0.21]</td>
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</tr>
<tr>
<td>Perin 2014</td>
<td>1.55</td>
<td>0.95</td>
<td>18</td>
<td>1.67</td>
<td>0.52</td>
<td>6</td>
<td>6</td>
<td>-0.12 [-0.69, 0.46]</td>
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</tr>
<tr>
<td>Pokushalov 2010</td>
<td>2.5</td>
<td>0.1</td>
<td>48</td>
<td>3.9</td>
<td>0.1</td>
<td>33</td>
<td>33</td>
<td>-1.40 [-1.44, -1.36]</td>
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<tr>
<td>Seth 2006</td>
<td>2.40</td>
<td>0.95</td>
<td>29</td>
<td>3.05</td>
<td>0.76</td>
<td>26</td>
<td>26</td>
<td>-0.66 [-1.01, -0.11]</td>
<td></td>
</tr>
<tr>
<td>Turan 2011</td>
<td>1.6</td>
<td>0.6</td>
<td>33</td>
<td>2.3</td>
<td>0.6</td>
<td>16</td>
<td>16</td>
<td>-0.70 [-1.06, -0.34]</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>205</strong></td>
<td></td>
<td></td>
<td><strong>139</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>-0.70 [-1.12, -0.28]</strong></td>
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</tbody>
</table>

Heterogeneity: Tau² = 0.36; Chi² = 122.55, df = 8 (P < 0.00001), I² = 93%
Test for overall effect: Z = 3.24 (P = 0.001)
### (A) LVEF < 12 months

<table>
<thead>
<tr>
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<td>Weight</td>
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<td>Weight</td>
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#### 1.1.2 Mean change from baseline

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<td>Weight</td>
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#### 1.1.2 Mean at endpoint

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<td>Weight</td>
<td>IV, Random, 95% CI</td>
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#### Heterogeneity

- Tau²: 0.00; Chisq² = 5.69, df = 6 (P = 0.48); P = 0%

#### Test for overall effect: Z = 4.22 (P = 0.0001)

---

### (B) LVEF > 12 months

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<th>Cells</th>
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<td>Weight</td>
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<td>Weight</td>
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#### Mean change from baseline

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#### Mean at endpoint

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<td></td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
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</tbody>
</table>

#### Heterogeneity

- Tau²: 12.95; Chisq² = 47.51, df = 3 (P = 0.0032); P = 68%

#### Test for overall effect: Z = 5.47 (P = 0.0001)
Meta-Analysis of Cell Therapy Trials for Patients with Heart Failure - An Update
Sheila A Fisher, Carolyn Doree, Anthony Mathur and Enca Martin-Rendon

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Data Supplement (unedited) at:
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Supplemental Material

Meta-analysis of cell therapy trials for patients with heart failure – an update

First Author: S.A. Fisher

Running title: Meta-analyses of cell therapy trials

Sheila A Fisher (PhD) 1,2, Carolyn Doree (PhD) 1,2, Anthony Mathur (MD, DPhil) 3 and Enca Martin-Rendon (PhD) 2,4

(1) Systematic Review Group, NHS Blood and Transplant, Oxford, UK
(2) Nuffield Division of Clinical Laboratory Sciences, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
(3) William Harvey Research Institute, Queen Mary University of London, London, UK
(4) Stem Cell Research Laboratory, NHS Blood and Transplant, Oxford, UK

Supplemental material:

Online Figure I: Included trials in this study compared to Fisher et al., 2014

Online Table I: Cochrane risk of bias in individual studies

Online Figure II: Cochrane risk of bias summary

Online Figure III: Funnel plot representation of publication bias for the primary outcome (mortality)

Online Table II: Peri-procedural adverse events associated with cell therapy

Online Table III: Adverse events at short and long term follow-up

Online Table IV: Quality of evidence for major outcomes during long term follow-up (>12 months)
(*) Maureira 2012 was excluded in Fisher et al., 2014 but re-assessed as an RCT in the current study.

Online Figure I: Included trials in this study compared to Fisher et al., 2014
**Online Table I: Cochrane risk of bias in individual studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of patients and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmus 2006</td>
<td>L: Randomisation was performed using computerised simple random allocation with known N. No block-wise randomisation was performed.</td>
<td>U: No method of allocation concealment was reported.</td>
<td>H: Clinicians were not blinded. Blinding of patients was not reported.</td>
<td>L: Quantitative analysis of angiograms and MRI analysis was performed by an investigator who was blinded to the individual patients' treatment.</td>
<td>L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms.</td>
<td>L: All outcomes mentioned in the methods were reported in results and the trial registration protocol.</td>
<td>L: Supported by the Deutsche Forschungsgemeinschaft, The Foundation Leducq Transatlantic Network of excellence for Cardiac Regeneration, The European Union European Vascular Genomics Network and the Alfried Krupp Stiftung. No other sources of bias were identified.</td>
</tr>
<tr>
<td>Assmus 2013</td>
<td>L: Randomisation was performed by simple random allocation using a computer list. Patients were first randomised to shock-wave group before being randomised to receive cell treatment group.</td>
<td>L: Randomisation was performed in two steps for the entire study cohort at the cell processing centre.</td>
<td>L: Patients were blinded for the intracoronary infusion of the study medication. Investigators were blinded for the intracoronary infusion of the study medication.</td>
<td>L: The number of withdrawals was low and reasons for withdrawals were reported in detail.</td>
<td>L: All outcomes mentioned in the methods and trial registration protocol were reported in the results.</td>
<td>L: Supported by an unrestricted grant to the Goethe University Frankfurt from t2cure GmbH. No other sources of bias were identified.</td>
<td></td>
</tr>
<tr>
<td>Bartunek 2013</td>
<td>L: Randomisation was conducted through a site-independent centralized process after exclusion of patients that did not meet the inclusion criteria.</td>
<td>L: Allocation concealment was not fully described, but randomisation was conducted in a site-independent manner through a centralised process.</td>
<td>H: Patients and clinicians were not blinded.</td>
<td>L: An independent core laboratory masked to study arm assignment and chronology of clinical evaluation provided data analysis</td>
<td>H: The number of withdrawals was high and unbalanced (11/32 in the treatment group vs. 0/15 in the control group).</td>
<td>U: Follow-up of exercise capacity and quality of life at 1 and 2 years was also defined as an outcome according to the trial registration protocol but was not reported. All other outcomes mentioned in the methods were reported in results.</td>
<td>U: 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 identified.</td>
</tr>
<tr>
<td>Reference</td>
<td>Findings</td>
<td>Methodology</td>
<td>Additional Notes</td>
<td></td>
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</tr>
<tr>
<td>Fisher et al.</td>
<td>U: No method for generation of random sequences was reported.</td>
<td>U: No method of allocation concealment was reported.</td>
<td>U: Blinding of clinicians and patients was not reported.</td>
<td>U: Blinding of outcome assessors was not reported.</td>
<td>U: All outcomes mentioned in the methods were reported in results although MLHF scores were not reported in controls and no statistical comparison with controls was reported. It would be difficult to rule out further selective reporting as no study protocol was identified.</td>
<td>L: Study funding was not reported. No other sources of bias were identified.</td>
<td></td>
</tr>
<tr>
<td>Bocchi 2008</td>
<td>H: The number of individuals randomised to each treatment arm and whether there were any withdrawals is unclear</td>
<td>U: Blinding of clinicians and patients was not reported.</td>
<td>U: Blinding of outcome assessors was not reported.</td>
<td>U: All outcomes mentioned in the methods were reported in results although MLHF scores were not reported in controls and no statistical comparison with controls was reported. It would be difficult to rule out further selective reporting as no study protocol was identified.</td>
<td>L: Study funding was not reported. No other sources of bias were identified.</td>
<td></td>
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</tr>
<tr>
<td>Bolli 2011</td>
<td>H: The first stage of the trial enrolled patients consecutively (first 9 to treatment, last 4 to placebo). In the second stage, patients were randomised via a computer software programme using an adaptive block randomisation scheme and a block size of five.</td>
<td>H: The two investigators assigned the patients.</td>
<td>H: Patients and clinicians were not blinded.</td>
<td>L: All randomised patients were included in the analysis.</td>
<td>U: All outcomes mentioned in the methods were reported in results although MLHF scores were not reported in controls and no statistical comparison with controls was reported. It would be difficult to rule out further selective reporting as no study protocol was identified.</td>
<td>L: Supported by a University of Louisville Research Foundation and National Institute of Health. One patient randomised to receive cell therapy switched to the control group after refusing treatment.</td>
<td></td>
</tr>
<tr>
<td>Chen 2006</td>
<td>U: No method for generation of random sequences was reported.</td>
<td>U: No method of allocation concealment was reported.</td>
<td>H: Patients and clinicians were not blinded.</td>
<td>L: All randomised patients were included in the analysis.</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>L: Study funding was not reported. No other sources of bias were identified.</td>
<td></td>
</tr>
<tr>
<td>Dib 2009</td>
<td>L: Patients were assigned to treatment before the trial with a random block method.</td>
<td>L: The randomisation scheme was not revealed to the clinical centre to maintain impartiality during the patient recruitment process.</td>
<td>H: Patients and clinicians were not blinded.</td>
<td>L: All randomised patients were included in the analysis.</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>L: Study funding was not reported. No other sources of bias were identified.</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Allocation Concealment</td>
<td>Randomization</td>
<td>Blinding</td>
<td>Results Reporting</td>
<td>Funding</td>
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<tr>
<td>Fisher et al.</td>
<td>2011</td>
<td>U: No method for generation of random sequences was reported.</td>
<td>U: No method of allocation concealment was reported.</td>
<td>H: Patients and clinicians were not blinded.</td>
<td>L: Clinical parameters and analyses of functional outcome were collected and analysed by an independent clinical research organisation and independent core laboratories respectively, all blinded to the treatment of the individual patients.</td>
<td>U: Withdrawals were unbalanced between trial arms (treatment: 6/31 vs. control: 2/16) although reasons were given for withdrawals.</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
</tr>
<tr>
<td>Duckers</td>
<td>2011</td>
<td>L: An electronic data entry system was used for randomisation.</td>
<td>L: Patients were randomised (unblinded) to the MSC or BMMNC group. Patients were further randomised (blinded) within groups to cell therapy or placebo.</td>
<td>L: All patients had BM harvest. Preparation and administration of the study product was blinded to investigators outside the cell-processing laboratory; clinicians were unaware of treatment allocation.</td>
<td>L: Preparation and administration of the study product was blinded to investigators outside the cell-processing laboratory.</td>
<td>U: Withdrawals were unbalanced between trial arms (treatment: 3/19 vs. placebo: 0/10) although reasons were given for withdrawals.</td>
<td>L: All outcomes mentioned in the methods and trial registration protocol were reported in the results.</td>
</tr>
<tr>
<td>Heldman 2014 [BMSC]</td>
<td>L: An electronic data entry system was used for randomisation.</td>
<td>L: Patients were randomised (unblinded) to the MSC or BMMNC group. Patients were further randomised (blinded) within groups to cell therapy or placebo.</td>
<td>L: All patients had BM harvest. Preparation and administration of the study product was blinded to investigators outside the cell-processing laboratory; clinicians were unaware of treatment allocation.</td>
<td>L: Preparation and administration of the study product was blinded to investigators outside the cell-processing laboratory.</td>
<td>U: Withdrawals were unbalanced between trial arms (treatment: 3/22 vs. placebo: 0/11) although reasons were given for withdrawals.</td>
<td>L: All outcomes mentioned in the methods and trial registration protocol were reported in the results.</td>
<td>L: Partially funded by the Interdisciplinary Stem Cell Institute, Miller School of Medicine, Biocardia and the National Heart Lung and Blood Institutes Specialised Centre for Cell Therapy. No other sources of bias were identified.</td>
</tr>
<tr>
<td>Heldman 2014 [MSC]</td>
<td>L: 1:1 randomisation was carried out using sequentially numbered sealed envelopes</td>
<td>L: Sealed envelopes were used.</td>
<td>L: Both groups had bone marrow aspirated (bone marrow group on the day before surgery from the iliac crest, control group during the operation from the sternum). The surgeon conducting</td>
<td>L: Cardiac MR images were analysed by an investigator blinded to treatment assignment. For Thallium scintigraphy, two investigators independently analysed data,</td>
<td>L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms.</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>L: Study funding was not reported. No other sources of bias were identified.</td>
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<tr>
<td>Study</td>
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<td>surgery was unaware whether cells or only saline was injected.</td>
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<td>blinded to treatment assignment.</td>
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<td>Honold 2012</td>
<td>U: No method for generation of random sequences was reported.</td>
<td>U: No method of allocation concealment was reported.</td>
<td>U: Blinding of clinicians and patients was not reported.</td>
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<td>U: MRI independent observers were blinded; blinding was not reported for other outcomes.</td>
<td>L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>U: Study funding was not reported. One patient randomised to receive cell therapy switched to the control group after experiencing post-G-CSF bleeding.</td>
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<tr>
<td>Hu 2011</td>
<td>L: A randomisation table was generated by statistical software</td>
<td>U: No method of allocation concealment was reported.</td>
<td>L: The study processes were blinded to patients surgeons, patients, co-ordinators and investigators who were responsible for patient assessments.</td>
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<tr>
<td>L: The study processes were blinded to patients surgeons, patients, co-ordinators and investigators who were responsible for patient assessments.</td>
<td>L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms</td>
<td>U: All outcomes mentioned in the methods were reported in results; additional efficacy outcomes were reported but not mentioned in the trial registration protocol.</td>
<td>L: Key project in the National Science and Technology Pillar programme during the Eleventh 5-year plan period. Basic scientific research fund of the National Scientific Institute 2009-2011. No other sources of bias were identified.</td>
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<tr>
<td>Maureira 2012</td>
<td>U: The method of randomisation was not reported but patients were matched for (1) sex, (2) age older than 64 yrs, (3) EF less than 40% at MRI, (4) severe coronary artery lesions.</td>
<td>H: matched pairs randomisation used</td>
<td>H: Patients and clinicians were not blinded.</td>
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<tr>
<td>L: All randomised patients were included in the analysis</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>L: Supported by the French Ministry of Health. No other sources of bias were identified.</td>
<td>L: Supported by the French public grant and by Genzyme Corporation. The two study sponsors were involved in study design and</td>
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<tr>
<td>Menasche 2008</td>
<td>L: Treatment assignments were determined with the use of a computer generated randomisation list drawn up by the statistician.</td>
<td>L: Treatment assignments were allocated by each recruiting study site using a centralised telephone randomisation system after study</td>
<td>L: Patients were blinded to treatment assignment: all patients underwent muscle biopsy and a placebo was used.</td>
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<tr>
<td>L: Echocardiography readings were performed blinded to treatment group, timing, number and location of coronary bypasses, and sites of cell injections. All</td>
<td>L: Withdrawals were unbalanced between trial arms (high dose: 11/40 vs low dose: 6/39 vs placebo: 9/41); reasons were given for withdrawals prior</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>L: Supported jointly by a French public grant and by Genzyme Corporation. The two study sponsors were involved in study design and</td>
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</table>
Randomisation was stratified by centre, and involved blocking within each centre. Eligibility of patients was confirmed. ICD data were reviewed by an independent expert electrophysiologist blinded to treatment group. After discharge from hospital, a separate and blinded cardiology team provided all subsequent follow-up care. To treatment but there was some unexplained loss to follow-up. was identified. Data collection. They were not involved in interpretation of the data, writing of the article and decision to submit it for publication. No other sources of bias were identified.

<p>| Mozid 2014 | U | No method for generation of random sequences was reported. | U | No method of allocation concealment was reported. | L | Patients were blinded by use of a placebo; blinding of clinicians was not reported but the trial was described as 'double-blind'. | L | The endpoints of NYHA and CCS classifications were measured by an investigator blinded to the patient’s treatment assignment. | L | Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms | U | This is an interim report which only reports six month follow-up of the secondary outcomes described in the protocol. | L | Supported by the National Institute of Health Research. No other sources of bias were identified. |
| Mozid 2014 | U | No method for generation of random sequences was reported. | U | No method of allocation concealment was reported. | L | Patients were blinded by use of a placebo; blinding of clinicians was not reported but the trial was described as 'double-blind'. | L | The endpoints of NYHA and CCS classifications were measured by an investigator blinded to the patient’s treatment assignment. | L | Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms | U | This is an interim report which only reports six month follow-up of the secondary outcomes described in the protocol. | L | Supported by the National Institute of Health Research. No other sources of bias were identified. |
| Nasseri 2014 | L | Randomisation was conducted in the cell preparation facility. Group allocation was performed according to a pre-defined non-block-wise 1:1 randomisation plan that was accessible only to the external cell processing team which prepared the cell product or placebo. | L | Group allocation was performed according to a pre-defined, non-block-wise 1:1 randomisation plan that was accessible only to the external cell processing team which prepared the cell product or placebo. | L | The patient, surgical team and all investigators performing diagnostic tests were unaware of the therapy assignment of a given patient. Syringes filled with CD133 or placebo were indistinguishable. All patients had bone marrow | L | The external cell processing team prepared the syringes with either cells or placebo solution and added an ID number, so that patients, surgical team and all investigators were unaware of treatment allocation. | H | Withdrawals were unbalanced between trial arms (treatment: 2/30 vs control: 4/30) and included some unexplained loss to follow-up. | L | All outcomes mentioned in the methods were reported in results and the trial registration protocol. | H | Supported in part by Miltenyi Biotec and by the German Bundesministerium fur Bildung und Forschung. Two authors received lecture fees from Miltenyi Biotec. No other sources of bias were identified. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>L:</th>
<th>U:</th>
<th>L:</th>
<th>L:</th>
<th>U:</th>
<th>L:</th>
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</thead>
<tbody>
<tr>
<td>Fisher et al.</td>
<td>cells or placebo solution and added an ID number, so that patients, surgical team and all investigators were unaware of treatment allocation.</td>
<td>aspiration..</td>
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<tr>
<td>Patel 2005</td>
<td>A person who did not participate in the trial had the choice of picking a coloured ball (red = BMSC arm; blue = control arm).</td>
<td></td>
<td>The clinicians were not blinded, but the study was blinded for the patients</td>
<td>The study was blinded for reviewers of the imaging studies (cardiologists)</td>
<td>All randomised patients were included at follow-up.</td>
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</tr>
<tr>
<td>Perin 2011</td>
<td>Numbered sealed envelopes were used</td>
<td></td>
<td>Clinicians were not blinded, but patients received a simulated mock injection procedure (although unclear whether BM aspiration undertaken in control group).</td>
<td>Efficacy studies were read by an independent blinded investigator. Blinding was maintained until the end of the assessment</td>
<td>All randomised patients were included at follow-up.</td>
<td></td>
</tr>
<tr>
<td>Patila 2014</td>
<td>Before examination, numbered randomisation envelopes were sealed by stem-cell laboratory personnel blinded to other patients. After delivery of the BM harvest to the stem cell laboratory, randomisation of each patient was done at the time of operation</td>
<td>Numbered sealed envelopes were prepared by the stem cell laboratory before examinations.</td>
<td>Syringes containing treatment of placebo were masked using a non-transparent tape. Treatments were masked by covering syringes with non-transparent tape. All patients had bone marrow aspiration and CABG</td>
<td>One investigator analysed all MRI imaging data in a random order. Areas of scar and ischemic myocardium were assessed by two study-blind, experienced nuclear medicine physicians.</td>
<td>All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>Supported by the Heart Research Foundation, the Academy of Finland and government subsidies for medical research block grants. No other sources of bias were identified.</td>
</tr>
</tbody>
</table>

8
Fisher et al.  

| Perin 2012a |  
| L: Randomisation was computer generated and used variable block sizes of 6 or 9, randomly selected and stratified by centre. | L: Treatment assignment was masked to all but 1 designated cell processing team member at each centre not involved in patient care. | L: All caregivers and patients were masked to treatment. | L: Double-blind study: "MACEs were assessed by 2 independent cardiologists not affiliated with any clinical site and masked to treatment assignment" | L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms | L: All outcomes mentioned in the methods were reported in results and the published protocol. | L: Funded by NHLBI which had a role in the design and conduct of the study and had a minimal role in the collection, management, analysis or interpretation of the data and preparation, review or approval of the manuscript. No other sources of bias were identified. |

| Perin 2012b |  
| L: Computer generated randomised sequence | L: Computer generated randomised sequence | L: Placebo used; all personnel involved were blinded. Personnel involved in the harvesting procedure acted independently of the study team, thus maintaining blinding. Control patients underwent an identical bone marrow harvest procedure, including insertion of the needle, except that BM was not aspirated. Control patients received transendocardial injections of placebo solution instead of cell preparation. | L: Double blinded trial. "two blinded, independent echocardiologists reviewed the echocardiograms" and the average of the two readings was reported | L: All randomised patients were included at follow-up. | L: All outcomes mentioned in the methods were reported in results and the trial registration protocol. |  |

| Perin 2014 |  
| L: An interactive voice response system was used for treatment assignments and randomisation. A designated hospital staff member who was not involved in patient care made the randomisation call to the interactive voice response system. | L: A designated hospital staff member who was not involved in patient care made the randomisation call to the interactive voice response system. | L: Syringes were prepared by a cell processing technician; syringes containing ADRCs and placebo were visually indistinguishable. Patients and investigators were blinded to treatment assignments. | L: All personnel at the core laboratories and evaluating patient status were blinded to treatment assignments. | L: All randomised patients were included in the analysis | L: All outcomes mentioned in the methods were reported in results and the trial registration protocol. | U: Supported by Cytori Therapeutics Inc, San Diego, CA although study authors were solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the manuscript, and the final decision to submit the manuscript for publication. |

<p>| U: This work was supported solely by Aldagen, Inc, Durham, NC. The authors stated that they were solely responsible for the design, conduct, analyses and drafting of the manuscript. No other sources of bias were identified. |  |  |  |  |  |  |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>L: Randomisation was carried out using an interactive voice response system</th>
<th>U: No method of allocation concealment was reported.</th>
<th>U: Blinding of clinicians and patients was not reported.</th>
<th>L: SPECT imaging done by consensus of two readers blinded to the type of the study (baseline or follow-up) and clinical data; other blinding not reported.</th>
<th>L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms.</th>
<th>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</th>
<th>L: Study funding was not reported. No other sources of bias were identified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pokushalov 2010</td>
<td>L: Randomisation was carried out using an electronic system</td>
<td>U: Blinding of clinicians and patients was not reported.</td>
<td>L: SPECT imaging done by consensus of two readers blinded to the type of the study (baseline or follow-up) and clinical data; other blinding not reported.</td>
<td>L: Reasons for loss to follow-up and withdrawals were given, attrition rates were similar in both treatment arms.</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>L: Study funding was not reported. No other sources of bias were identified.</td>
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</tr>
<tr>
<td>Povsic 2011</td>
<td>L: Although the method of randomisation was not reported, randomisation was carried out using an interactive voice response system</td>
<td>L: Randomisation was carried out using an interactive voice response system</td>
<td>L: Patients were blinded by use of a placebo; clinicians were blinded to treatment assignment.</td>
<td>L: A separate blinded investigator was responsible for all patient contact and follow-up. Multiple-gated acquisition and echocardiography images were blindly assessed by a core facility, and blood levels were assessed at a central laboratory.</td>
<td>U: Reasons for withdrawals were given but it was unclear in which group these participants had been randomised.</td>
<td>U: All outcomes mentioned in the methods were reported in results; although it would be difficult to rule out selective reporting as no study protocol was identified.</td>
<td>H: Commercially sponsored by Bioheart Inc. (Sunrise, Florida). No other sources of bias were identified.</td>
</tr>
<tr>
<td>Seth 2006</td>
<td>U: No method for generation of random sequences was reported.</td>
<td>U: No method of allocation concealment was reported.</td>
<td>H: Patients and clinicians were not blinded.</td>
<td>L: LV function assessment was performed offline by the modified Simpson method by 2 observers blinded to the underlying treatment.</td>
<td>H: Withdrawals were unbalanced between trial arms (treatment: 4/45 vs control: 0/40) and included some unexplained loss to follow-up.</td>
<td>H: The defined outcomes differed between the initial follow-up reports. No study protocol was identified.</td>
<td>L: Supported by the research funds of the All India Institute of Medical Sciences under the Stem Cell Research Program. No other sources of bias were identified.</td>
</tr>
<tr>
<td>Study</td>
<td>Allocation Concealment</td>
<td>Randomisation</td>
<td>Blinding</td>
<td>Outcome Assessors</td>
<td>Attrition</td>
<td>Reporting</td>
<td>Funding/Conflict of Interest</td>
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<td>Turan 2011</td>
<td>U: No method for</td>
<td>U: Not reported</td>
<td>H:</td>
<td>L: All randomised</td>
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<td>U: All outcomes</td>
<td>L: Study funding not</td>
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<td></td>
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<td>clinicians, no</td>
<td>patients</td>
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<td>sequences was reported.</td>
<td>no placebo given</td>
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<td>methods were</td>
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<td>Vrtovec 2011</td>
<td>U: No method for</td>
<td>U: No method</td>
<td>H:</td>
<td>L: Echocardiography</td>
<td>L:</td>
<td>U: All outcomes</td>
<td>L: This work was supported</td>
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<td></td>
<td>generation of random</td>
<td>of allocation</td>
<td>patients</td>
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<td>L:</td>
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<td>L:</td>
<td>methods were</td>
<td>Republic of Slovenia,</td>
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<td>Tertiary Care Scientific</td>
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<td>and timing of the</td>
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<td>although it would</td>
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<td>L:</td>
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<td></td>
<td>sequences was reported.</td>
<td>concealment</td>
<td>of clinicians and</td>
<td>SPECT) were</td>
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<td>methods were</td>
<td>Program for Shanghai</td>
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<td>was reported.</td>
<td>patients was</td>
<td>blinded to the</td>
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<td>reported in results;</td>
<td>Outstanding Medical Academic</td>
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<td>assigned therapy.</td>
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<td>Leader and National Key</td>
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<td>L:</td>
<td>rule out selective</td>
<td>of bias were identified.</td>
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<tr>
<td>Zhao 2008</td>
<td>L: Randomisation was</td>
<td>U: No method</td>
<td>U:</td>
<td>L: The results</td>
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<td>U: NYHA class was</td>
<td>L: Supported by Shanghai</td>
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<td>achieved by using a</td>
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<td>L:</td>
<td>measured at 6</td>
<td>Medical Development Research</td>
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<td></td>
<td>sequence of random</td>
<td>concealment</td>
<td>of clinicians</td>
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<td>months but not</td>
<td>Fund. No other sources of</td>
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<td>was reported.</td>
<td>and patients</td>
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<td>L:</td>
<td>reported. All other</td>
<td>bias were identified.</td>
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<td>investigators (Echo,</td>
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<td>the methods were</td>
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<td>scheme</td>
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<td>rule out selective</td>
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</tbody>
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11
as no study protocol was identified.
Online Figure II: Cochrane risk of bias summary. Red, high risk of bias; yellow, unclear risk of bias; green, low risk of bias.
Online Figure III: Funnel plot representation of publication bias for the primary outcome (mortality)
Online Table II – Peri-procedural adverse events associated with cell therapy

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Intervention</th>
<th>No. patients</th>
<th>Periprocedural adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmus 2006</td>
<td>CPC</td>
<td>24</td>
<td>MI (1); local dissection of the coronary arterial wall angiographically visible after balloon inflation (3 in all study phases including additional cross-over phase).</td>
</tr>
<tr>
<td></td>
<td>BMMNC</td>
<td>28</td>
<td>No pre-hospital discharge adverse events</td>
</tr>
<tr>
<td>Assmus 2013</td>
<td>BMMNC + Shockwave</td>
<td>43</td>
<td>Only adverse events associated with shockwave therapy reported.</td>
</tr>
<tr>
<td>Bartunek 2013</td>
<td>BM-MSC-cardio</td>
<td>21</td>
<td>Brachial access required due to tortuosity of lower limb arteries (1), VT (1), blurred vision in patient with pre-existing ophthalmic migraines (1)</td>
</tr>
<tr>
<td>Bocchi 2008</td>
<td>BMMNC + G-CSF</td>
<td>8</td>
<td>None reported</td>
</tr>
<tr>
<td>Bolli 2011</td>
<td>CSC</td>
<td>16</td>
<td>Dissection of left internal mammary artery graft during balloon inflation (1), no other periprocedural adverse events observed</td>
</tr>
<tr>
<td>Chen 2006</td>
<td>BM-MSC</td>
<td>22</td>
<td>Pulmonary edema (3), no sustained arrhythmias monitored during the procedure</td>
</tr>
<tr>
<td>Dib 2009</td>
<td>SM</td>
<td>12</td>
<td>Sustained VT during NOGA mapping before cell administration (2)</td>
</tr>
<tr>
<td>Duckers 2011</td>
<td>SM</td>
<td>26</td>
<td>Dissection of the left main coronary artery, ascending and descending aorta upon dislocation of the injection catheter during injection (1)</td>
</tr>
<tr>
<td>Heldman 2014</td>
<td>BMMNC</td>
<td>19</td>
<td>No treatment-emergent SAE; no significant post-procedural pericardial effusion</td>
</tr>
<tr>
<td>Heldman 2014</td>
<td>MSC</td>
<td>19</td>
<td>No treatment-emergent SAE; no significant post-procedural pericardial effusion</td>
</tr>
<tr>
<td>Hendrikx 2006</td>
<td>BMMNC</td>
<td>10</td>
<td>One patient died on postoperative day 7 (perforated esophageal ulcer complicated by mediastinitis).</td>
</tr>
<tr>
<td>Honold</td>
<td>BM-EPC + G-CSF</td>
<td>22</td>
<td>Intracoronary infusions of CPC were performed without any procedural complications with no ischaemia-related ECG changes or Troponin T elevations recorded during further in-hospital course.</td>
</tr>
<tr>
<td>Hu 2011</td>
<td>BMMNC</td>
<td>31</td>
<td>AEs reported but unclear whether associated with BMMNC or placebo.</td>
</tr>
<tr>
<td>Maureira 2012</td>
<td>BMMNC</td>
<td>7</td>
<td>No perioperative MI or severe arrhythmia</td>
</tr>
<tr>
<td>Menasche 2008</td>
<td>SM</td>
<td>63</td>
<td>None reported</td>
</tr>
<tr>
<td>Mozid 2014 (IM)</td>
<td>BMMNC</td>
<td>14</td>
<td>AF (1), transient complete heart block (1), pulse-less VT (1). No deaths, MI or ICD discharges during peri-procedural period</td>
</tr>
<tr>
<td>Mozid 2014</td>
<td>BMMNC</td>
<td>10</td>
<td>No deaths, MI or ICD discharges during peri-procedural period</td>
</tr>
<tr>
<td>Study</td>
<td>Cell Type</td>
<td>Cell Source</td>
<td>Adverse Event(s)</td>
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<tr>
<td>-------</td>
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<tr>
<td>Nasseri 2014</td>
<td>CD133+</td>
<td>BM-MNC</td>
<td>None reported</td>
</tr>
<tr>
<td>Patel 2005</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>Hematoma at bone marrow harvest site (1)</td>
</tr>
<tr>
<td>Patila 2014</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>Subdural haematoma 1 month post-operatively (1)</td>
</tr>
<tr>
<td>Perin 2011</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>No major AE (perforation or arrhythmias) associated with cell injection procedures. Post-procedural transient left branch bundle block (1), non-significant pericardial effusion (1). No treated patients had fever or sepsis</td>
</tr>
<tr>
<td>Perin 2012a</td>
<td>ADRC</td>
<td>ADRC</td>
<td>Recurrent VT with hypotension; received small volume of cell product (1)</td>
</tr>
<tr>
<td>Perin 2012b</td>
<td>BM-MNC</td>
<td>BM-MNC</td>
<td>No major adverse cardiac events associated with injection procedures, including no perforations, no exacerbation of HF, no sustained VA</td>
</tr>
<tr>
<td>Perin 2014</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>Mild loculated pericardial effusion after injection (1), non-STEMI (1)</td>
</tr>
<tr>
<td>Pokushalov 2010</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>No patients developed periprocedural complications</td>
</tr>
<tr>
<td>Povsic 2011</td>
<td>SM</td>
<td>BM-MNC</td>
<td>None reported</td>
</tr>
<tr>
<td>Seth 2006</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>None reported</td>
</tr>
<tr>
<td>Turan 2011</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>No pre/post procedure adverse complications, no new electrocardiographic changes or significant elevations in CK or troponin, and no inflammatory response.</td>
</tr>
<tr>
<td>Vrtovec 2011</td>
<td>BM-MNC</td>
<td>BM-MNC</td>
<td>Non-sustained VT during procedure (2). No cases of distal coronary artery occlusion, acute cardiac dysfunction, or significant troponin leak occurred.</td>
</tr>
<tr>
<td>Yao 2008</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>No inflammatory response or myocardial reaction after cell therapy.</td>
</tr>
<tr>
<td>Zhao 2008</td>
<td>BMMNC</td>
<td>BM-MNC</td>
<td>Sporadic bouts of rapid AF were observed in both treatment groups. VF (1), VF followed by death at day 3 (1)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; AE, adverse event; ADRCs, adipose tissue-derived regenerative cells; AF, atrial fibrillation; ALDH, alcohol dehydrogenase; BM, bone marrow; BM-EPC, bone marrow-derived endothelial progenitor cells; BMMNC, bone marrow mononuclear cells; BM-MSC, bone marrow-derived mesenchymal stem cells; CABG, coronary artery bypass graft; CRT, cardiac resynchronisation therapy; CSC, cardiac stem cells; G-CSF, granulocyte colony stimulating factor; HF, heart failure; IC, intracoronary; ICD, implantable cardioverter defibrillator; IM, intramyocardial; LAD, left ventricular assist device; MI, myocardial infarction; MOF, multi-organ failure; PBMNC, peripheral blood mononuclear cells; SAE, serious adverse event; SM, skeletal myoblast; STEMI, ST-segment elevation myocardial infarction; VA, ventricular arrhythmia; VT, ventricular tachycardia.
# Online Table III: Adverse events at short and long term follow-up

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Duration of follow-up</th>
<th>Trial arm</th>
<th>No patients analysed</th>
<th>Total no. adverse events / patients affected</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Short term follow-up</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Assmus 2006</td>
<td>3 months</td>
<td>CPC</td>
<td>24</td>
<td>5 / nr</td>
<td>MI (1), rehospitalisation for HF (1), infarct vessel revascularisation (2), syncope (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMMNC</td>
<td>28</td>
<td>3 / nr</td>
<td>infarct vessel revascularisation (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>23</td>
<td>4 / nr</td>
<td>Death, cause not reported (1), rehospitalisation for HF (1), cerebral infarction (1), VA (1)</td>
</tr>
<tr>
<td>Duckers 2011</td>
<td>6 months</td>
<td>SM</td>
<td>26</td>
<td>21 / 11</td>
<td>Cardiovascular (18), gastrointestinal (1), pulmonary (1), death due to HF/MOF (1)</td>
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<td></td>
<td></td>
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<td>14</td>
<td>23 / 5</td>
<td>Cardiovascular (18), gastrointestinal (3), urinary (2)</td>
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<td></td>
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<td>10</td>
<td>4 / 3</td>
<td>Cardiac (1), infections/infestations (1), investigations (1), nervous system (1)</td>
</tr>
<tr>
<td>Heldman 2014</td>
<td>30 days</td>
<td>BMMNC</td>
<td>19</td>
<td>9 / 7</td>
<td>Cardiac (1), general/site of administration (2), infections/infestations (1), musculoskeletal (1), nervous system (3), skin/subcutaneous tissue (1)</td>
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<td>Cardiac (1), infections/infestations (1), investigations (1), nervous system (1)</td>
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<td>MSC</td>
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<td>Cardiac (2), gastrointestinal (1), general/site of administration (3), skin/subcutaneous tissue (2)</td>
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<td>Cardiac (2), general/site of administration (1), respiratory/thoracic/mediastinal (1)</td>
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<td>Honold 2012</td>
<td>3 months</td>
<td>BM-EPC + G-CSF</td>
<td>22</td>
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<td>Target vessel revascularisation (1), non-target vessel revascularisation (1)</td>
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<td>G-CSF only</td>
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<td>2 / 2</td>
<td>Acute MI (1), target vessel revascularisation (1)</td>
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<tr>
<td>Hu 2011</td>
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<td>31</td>
<td>3 / nr</td>
<td>HF (3)</td>
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<td>Placebo</td>
<td>29</td>
<td>4 / nr</td>
<td>HF (3), death, cause not reported (1)</td>
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<tr>
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<td>6 months</td>
<td>BMMNC</td>
<td>7</td>
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<td>Ischaemic areas in CABG territories (3)</td>
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<td>Study</td>
<td>Duration</td>
<td>Treatment</td>
<td>n</td>
<td>AE / SAE</td>
<td>Adverse Events</td>
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<td>Menasche 2008</td>
<td>6 months</td>
<td>SM</td>
<td>63</td>
<td>nr / 28</td>
<td>MACE (including death, MI, congestive HF, resuscitated sudden death, stroke) (19), VA (9)</td>
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<td></td>
<td>34</td>
<td>nr / 9</td>
<td>MACE (including death, MI, congestive HF, resuscitated sudden death, stroke) (7), VA (2)</td>
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<tr>
<td>Mozid 2014 [IC]</td>
<td>6 months</td>
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<td>Rehospitalisation for HF (1)</td>
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<td>1 / 1</td>
<td>Death, cause not reported (1)</td>
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<td>Mozid 2014 [IM]</td>
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<td>Arrhythmia (2)</td>
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<td>8</td>
<td>5 / 5</td>
<td>Cardiac-related death (3), arrhythmia (2)</td>
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<tr>
<td>Nasseris 2014</td>
<td>6 months</td>
<td>CD133+</td>
<td>30</td>
<td>78 / 27</td>
<td>AE (78), SAE (12), see trial reported for details</td>
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<tr>
<td>Control</td>
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<td>88 / 29</td>
<td>AE (88), SAE (13), see trial reported for details</td>
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<td>Patel 2005</td>
<td>6 months</td>
<td>CD34+</td>
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<td>1 / 1</td>
<td>No AEs (neurologic, haematologic, vascular, infections)</td>
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<td>0 / 0</td>
<td>None</td>
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<td>Perin 2011</td>
<td>6 months</td>
<td>BMMNC</td>
<td>20</td>
<td>3 / 3</td>
<td>ICD discharge (1), congestive HF (2)</td>
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<td>10</td>
<td>3 / 3</td>
<td>Fever (2), congestive HF (1)</td>
</tr>
<tr>
<td>Perin 2012a</td>
<td>6 months</td>
<td>BMMNC</td>
<td>61</td>
<td>7 / nr</td>
<td>Death due to pump failure at day 29 (1), MI (1), rehospitalisation for HF (3), rehospitalisation for ACS (1), LAD (1)</td>
</tr>
<tr>
<td>Placebo</td>
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<td></td>
<td>31</td>
<td>7 / nr</td>
<td>Rehospitalisation for HF (5), heart transplant (1), LAD (1)</td>
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<td>Perin 2012b</td>
<td>6 months</td>
<td>ADLH+</td>
<td>10</td>
<td>9 / nr</td>
<td>Angina (5), MI (1), intracardiac thrombus (1), atrial arrhythmia (2)</td>
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<td>5 / nr</td>
<td>VT (2), VF (1), cerebrovascular (1), angina (1)</td>
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<td>Pokushalov 2010</td>
<td>6 months</td>
<td>BMMNC</td>
<td>55</td>
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<td>Death, cause not reported (2)</td>
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<td>54</td>
<td>8 / 8</td>
<td>Death, cause not reported (8)</td>
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<td>Povsic 2011</td>
<td>6 months</td>
<td>SM</td>
<td>14</td>
<td>15 / 10</td>
<td>Sustained VT (4), HF (2), respiratory failure (1), chest pain (4), non-cardiovascular AEs (4)</td>
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<td>Placebo</td>
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<td>6</td>
<td>8 / 4</td>
<td>Sustained VT (4), symptomatic bradycardia (1), HF (1), other cardiovascular AEs (1), non-cardiovascular AEs (1)</td>
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<tr>
<td>Seth 2006</td>
<td>6 months</td>
<td>BMMNC</td>
<td>24</td>
<td>4 / 4</td>
<td>Death due to HF (3), Sudden cardiac death (1)</td>
</tr>
<tr>
<td>Control</td>
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<td>20</td>
<td>2 / 2</td>
<td>Death, cause not reported (2)</td>
</tr>
<tr>
<td>Yao 2008</td>
<td>6 months</td>
<td>BMMNC</td>
<td>24</td>
<td>3 / nr</td>
<td>Rehospitalisation for HF (1), revascularisation (2)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>23</td>
<td>6 / nr</td>
<td>MI (1), rehospitalisation for HF (2), revascularisation (3)</td>
</tr>
<tr>
<td>Zhao 2008</td>
<td>6 months</td>
<td>BMMNC</td>
<td>18</td>
<td>1 / 1</td>
<td>Death due to cerebral vessel accident (1)</td>
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<tr>
<td>Study</td>
<td>Duration</td>
<td>Treatment</td>
<td>Survivors</td>
<td>Deaths</td>
<td>Outcomes</td>
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<td>-----------</td>
<td>-----------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Placebo</td>
<td>18</td>
<td>0 / 0</td>
<td>No deaths</td>
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<tr>
<td>Assmus 2013</td>
<td>&gt;5 years</td>
<td>BMMNC + Shockwave</td>
<td>43</td>
<td>20 / nr</td>
<td>Cardiac death (4), non-cardiac death (1), repeat acute MI (1), rehospitalisation for HF (9), VT (5)</td>
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<tr>
<td>Placebo + shockwave</td>
<td>39</td>
<td>46 / nr</td>
<td>Cardiac death (5), non-cardiac death (1), repeat acute MI (4), rehospitalisation for HF (20), VT (16)</td>
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<td></td>
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<tr>
<td>Bartunek 2013</td>
<td>24 months</td>
<td>BM-MSC-cardio</td>
<td>21</td>
<td>27 / nr</td>
<td>Elective transplant (1), SV arrhythmia (9), VF (1), VT (6), gastrointestinal (2), hepatobiliary (1), nervous system (1), respiratory/mediastinal (5), surgical/medical procedure (1)</td>
</tr>
<tr>
<td>Control</td>
<td>24</td>
<td>31 / nr</td>
<td>Cardiac death (2), SV arrhythmia (7), VF (1), VT (8), gastrointestinal (1), general disorders (5), nervous system (1), musculoskeletal (1), respiratory/thoracic/mediastinal (3), surgical/medical procedure (1), peripheral vascular disorder (1)</td>
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<tr>
<td>Bolli 2011</td>
<td>12 months</td>
<td>CSC</td>
<td>16</td>
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<td>Rehospitalisation for HF (1), rehospitalisation for angina (1)</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>3 / 3</td>
<td>Revascularisation (1), Rehospitalisation for angina (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen 2008</td>
<td>12 months</td>
<td>BM-MSC</td>
<td>22</td>
<td>2 / 2</td>
<td>Cardiac death (2)</td>
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<tr>
<td>Control</td>
<td>23</td>
<td>4 / 4</td>
<td>Cardiac death (4)</td>
<td></td>
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<tr>
<td>Dib 2009</td>
<td>12 months</td>
<td>SM</td>
<td>12</td>
<td>12 / nr</td>
<td>SAE (12) including sustained VT (2), perforated carcinoma (1)</td>
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<tr>
<td>Control</td>
<td>11</td>
<td>6 / nr</td>
<td>SAE (6) including sustained VT (1), CRT for worsening HF (1)</td>
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<tr>
<td>Heldman [BMMNC] 12 months</td>
<td>BMMNC</td>
<td>19</td>
<td>26 / 14</td>
<td>Cardiac (3), general/site of administration (7), infections/infestations (5), injury/poisoning/procedural complications (2), metabolic/nutritional (1), musculoskeletal (3), nervous system (4), skin/subcutaneous tissue (1)</td>
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<tr>
<td>Placebo</td>
<td>10</td>
<td>16 / 8</td>
<td>Cardiac (2), ear/labyrinth (1), gastrointestinal (1), general/site of administration (1), infections/infestations (2), injury/poisoning/procedural complications (1), investigations (2), nervous system (2), renal/urinary (1), respiratory (2), surgical/medical (1)</td>
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<tr>
<td>Heldman [MSC] 12 months</td>
<td>MSC</td>
<td>19</td>
<td>24 / 11</td>
<td>Blood/lymphatic (1), cardiac (4) cardiac-related death (1), ear/labyrinth (1), gastrointestinal (2), general/site of administration (5), infections/infestations (2), metabolic/nutritional (1), musculoskeletal (2),</td>
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<tr>
<td>Study</td>
<td>Duration</td>
<td>Treatment</td>
<td>Events</td>
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<td>------------------------------------------------------------------------</td>
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<tr>
<td>Fisher et al.</td>
<td></td>
<td></td>
<td>nervous system (1), reproductive/breast (1), respiratory/thoracic/mediastinal (1), skin/subcutaneous tissue (2)</td>
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</tr>
<tr>
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<td></td>
<td>Cardiac (3), cardiac-related death (1), eye (1), general/site of administration (1), infections/infestations (1), nervous system (1), respiratory/thoracic/mediastinal (2), surgical/medical procedure (1)</td>
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<td></td>
</tr>
<tr>
<td>Honold 2012</td>
<td>5 years</td>
<td>BM-EPC + G-CSF</td>
<td>Acute MI (2), target vessel revascularisation (4), non-target vessel revascularisation (5), syncope (1), ICD (9)</td>
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</tr>
<tr>
<td>G-CSF only</td>
<td>10</td>
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<td>Acute MI (1), target vessel revascularisation (2), hospitalisation for HF (2), ICD (4), cancer (1), death due to HF (1)</td>
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<tr>
<td>Hu 2011</td>
<td>12 months</td>
<td>BMMNC</td>
<td>Acute MI (2), target vessel revascularisation (4), non-target vessel revascularisation (5), syncope (1), ICD (9)</td>
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<tr>
<td>Placebo</td>
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<td>6 / nr</td>
<td>Death from systemic infection (1), Death from gastrointestinal bleeding (1), HF (3), AT (1)</td>
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<tr>
<td>Menasche 2008</td>
<td>&gt;5 years</td>
<td>BM-EPC + G-CSF</td>
<td>Acute MI (2), target vessel revascularisation (4), non-target vessel revascularisation (5), syncope (1), ICD (9)</td>
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<td>11 / 4</td>
<td>ICD (6), slow VT (1), rehospitalisation for HF (4)</td>
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<tr>
<td>Patila 2014</td>
<td>12 months</td>
<td>BMMNC</td>
<td>Pacemaker (1), ICD (1), cerebral infarction (1), subdural haematoma 1 month post-operatively (1)</td>
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<td>Placebo</td>
<td>19</td>
<td>2 / nr</td>
<td>Pacemaker (1), cerebral infarction (1)</td>
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<tr>
<td>Perin 2014</td>
<td>18 months</td>
<td>ADRC</td>
<td>Non-STEMI (1), death due to HF (1)</td>
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<td>Placebo</td>
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<td>3 / 3</td>
<td>Death due to choking (1), death due to end-stage renal failure (1), stroke (1)</td>
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<tr>
<td>Pokushalov 2010</td>
<td>12 months</td>
<td>BMMNC</td>
<td>Death, cause not reported (6)</td>
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<td>Death, cause not reported (21)</td>
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<td>Seth 2006</td>
<td>12 months</td>
<td>BMMNC</td>
<td>Death due to HF (3), Sudden cardiac death (1), Death, cause not reported (6)</td>
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</tr>
<tr>
<td>Control</td>
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<td>14 / 14</td>
<td>Death, cause not reported (14)</td>
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<tr>
<td>Vrtovek 2011</td>
<td>5 years</td>
<td>CD34+ + G-CSF</td>
<td>Death due to pump failure (3), sudden cardiac death (4), heart transplantation (4)</td>
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<td>24 / 24</td>
<td>Death due to pump failure (10), sudden cardiac death (9), heart transplantation (5)</td>
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</table>

ACS, acute coronary syndrome; AE, adverse event; ADRCs, adipose tissue-derived regenerative cells; AF, atrial fibrillation; ALDH, alcohol dehydrogenase; BM, bone marrow; BM-EPC, bone marrow-derived endothelial progenitor cells; BMMNC, bone marrow mononuclear cells; BM-MSC, bone marrow-derived...
mesenchymal stem cells; CABG, coronary artery bypass graft; CRT, cardiac resynchronisation therapy; CSC, cardiac stem cells; G-CSF, granulocyte colony stimulating factor; HF, heart failure; IC, intracoronary; ICD, implantable cardioverter defibrillator; IM, intramyocardial; LAD, left ventricular assist device; MI, myocardial infarction; MOF, multi-organ failure; PBMNC, peripheral blood mononuclear cells; SAE, serious adverse event; SM, skeletal myoblast; STEMI, ST-elevation myocardial infarction; VA, ventricular arrhythmia; VT, ventricular tachycardia.
Online Table IV: Quality of evidence for major outcomes during long term follow-up (>12 months)

<table>
<thead>
<tr>
<th>Fisher et al., 2014</th>
<th>This study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Outcome (follow-up)</strong></td>
<td><strong>Assumed risk</strong>*</td>
</tr>
<tr>
<td><strong>Mortality Long-term (&gt;12months)</strong></td>
<td>No cells</td>
</tr>
<tr>
<td></td>
<td>185 per 1000 (30 in 162)</td>
</tr>
<tr>
<td><strong>Re-hospitalization (&gt;12months)</strong></td>
<td>92 per 1000 (6 in 65)</td>
</tr>
</tbody>
</table>

CI, confidence intervals; RR, relative risk. (*) Relative numbers are given per 1000 participants (absolute numbers are in brackets).

(†) The risk estimates derived from Fisher et al., 2014 include three trials (mortality, 227 participants) and one trial (rehospitalization, 166 participants) of ischemic heart disease but not heart failure which were not included in the current study.