Similar Effect of Autologous and Allogeneic Cell Therapy for Ischemic Heart Disease: Systematic Review and Meta-Analysis of Large Animal Studies

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ABSTRACT

Rationale: In regenerative therapy for ischemic heart disease, use of both autologous and allogeneic stem cells have been investigated. Autologous cell can be applied without immunosuppression but availability is restricted and cells have been exposed to risk factors and aging. Allogeneic cell therapy enables pre-operative production of potent cell lines and immediate availability of cell products, allowing ‘off the shelf’ therapy. It is unknown which cell source is preferred with regard to improving cardiac function.

Objective: We performed a meta-analysis of pre-clinical data of cell therapy for ischemic heart disease.

Methods and Results: We conducted a systematic literature search to identify publications describing controlled pre-clinical trials of unmodified stem cell therapy in large animal models of myocardial ischemia. Data from 82 studies involving 1415 animals showed a significant improvement in mean left ventricular ejection fraction (LVEF) in treated compared to control animals (8.3 %, 95% CI 7.1 – 9.5, p <0.001). Meta-regression revealed a similar difference in LVEF in autologous (8.8% 95% CI 7.3 – 10.3 n= 981) and allogeneic (7.3% 95% CI 4.4 – 10.2 n= 331) (p=0.3) cell therapies.

Conclusions: Autologous and allogeneic cell therapy for ischemic heart disease show a similar improvement in LVEF in large animal models of myocardial ischemia, compared to placebo. These results are important for the design of future clinical trials.

Keywords: Autologous, allogeneic, cell therapy, cardiac repair, ischemic heart disease, animal model cardiovascular disease, meta-analysis, stem cell.

Nonstandard Abbreviations and Acronyms:
BMMNC    Bone marrow mononuclear cells
CAMARADES Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies
LAD      Left anterior descending coronary artery
LCX      Left circumflex coronary artery
LVEF     Left ventricular ejection fraction
MSC      Mesenchymal stem cell
INTRODUCTION

Stem cell therapy for ischemic heart disease has been of great interest for more than a decade. Clinical meta-analyses show that stem-cell therapy is associated with an improvement in left ventricular ejection fraction (LVEF) of 3-4%1-4. This is accompanied by an improvement in exercise capacity and quality of life. The increase in LVEF is promising, but effort should be put into strategies to further improve the magnitude of effect. The European Society of Cardiology urge researchers to focus on unsolved issues in cardiac repair strategies, including the type of cell used.5 Consequently, the field has shifted from bone marrow mononuclear cells to mesenchymal stem cells and more recently to cardiac stem cells6-9.

The vast majority of clinical trials have used autologous stem cells, an attractive approach since no immunologic problems are encountered.10 Two important drawbacks of autologous cell therapy are exposure of cells to the patient’s risk factors; and the limited availability. Patient’s lifelong exposure to risk factors contributing to ischemic heart disease (i.e. age, diabetes and smoking), may impair the potential of autologous stem cells.11-13 Restricted availability is present since selection and culturing of sufficient potent cells is cumbersome and time-consuming. This limitation is especially important in the acute setting of myocardial ischemia.

Allogeneic cell therapy enables preparatory production of potent cell lines, immediate availability and allows ‘off-the-shelf’ therapy. However, immunological matters have to be taken into account. Where immunosuppression is required this carries risk for the patient (opportunistic infections, risk for malignancies) and might affect the potential of stem cells.14-17 Features of allogeneic and autologous cell sources are summarized in Table 1.

To help inform the design of future clinical trials we set out to establish whether, in large animal models, allogeneic cell therapy is associated with the same magnitude of effect as autologous cell therapy. To do this end we carried out a meta-analysis of pre-clinical data.

METHODS

A meta-analysis was performed for safety and efficacy of stem cell therapy for cardiac repair in large animal models of myocardial ischemia. Differences in effect size for autologous and allogeneic stem cell were explored by meta-regression.

Methods for selection of studies are extensively described in van der Spoel et al.18 In brief, a systematic search was performed in the electronic databases Pubmed and Embase on January 15th 2013. (see Supplemental material for search strategy) Inclusion criteria were: reporting of an original study in English language peer reviewed journals, the use of large animal myocardial ischemia models (dogs, sheep, pigs), use of stem cells, the use of a proper control group and reporting of left ventricular ejection fraction (LVEF) as outcome measure. Exclusion criteria were studies not published in full (e.g. meeting abstracts) and the use of cells modified to enhance cell function.

Results were screened independently by two researchers (SJ and JE). Consensus of inclusion was achieved in all cases by discussion. Reference lists of included studies were checked for additional relevant publications.

Publication details including animal model, functional endpoints, mortality, cell characteristics, quality parameters, and general study information were extracted. The primary functional endpoint was LVEF and the secondary endpoints were left ventricular end diastolic volume (EDV), left ventricular end systolic volume (ESV) and safety, presented as mortality after cell therapy. Data were entered in the online
international database of the working group ‘Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies’ (CAMARADES).

For LVEF, data at the end of the experiment were extracted since baseline data and/or change from baseline was not reported in several studies. For safety, only mortality occurring after stem cell therapy was included in the database. Mortality during induction of myocardial infarction, and thus before actual treatment, was not included in this analysis.

Risk of bias for included articles was established based on the CAMARADES scoring system. Included parameters for quality were reporting of randomisation, allocation concealment (meaning blinding of the operator to the given therapy), blinded assessment of outcome, compliance with animal welfare regulations and statement of potential conflict of interest.

Statistics.
For LVEF a raw difference in mean analysis was performed. Data are reported as an absolute difference in mean LVEF at follow up between treated and control groups, with 95% confidence interval (CI) or standard error of means (SEM). Because of difference in animal size, and consequential difference in cardiac volumes, we performed a standardized difference in mean analysis for both ESV and EDV. Safety was evaluated by estimating the odds ratio of mortality in treated and control groups.

The presence of publication bias was evaluated using funnel plot and Egger regression and trim and fill was used to correct for this bias. Funnel plot asymmetry can be used to identify a preponderance of imprecise studies overstating treatment effects that is consistent with publication bias. Egger regression is a formal statistical test where in a symmetrical funnel plot the regression line and its 95% CIs for precision versus standardized effect size pass through the origin of the graph. Trim and fill is a non-parametric test which attempts to impute the theoretical ‘missing’ studies that cause funnel plot asymmetry and recalculates the overall treatment effect in absence of publication bias.

Where different treatment groups were reported within the same study (i.e. different cell types or cell numbers), the number of animals in the control group was divided by the number of treatment groups served. We assigned weight of studies based on inverse variance. We anticipated substantial heterogeneity and so used a random effects model.

Differences in effect size for cell source (autologous, allogeneic, xenogeneic) were explored by random effects meta-regression. For meta-regression the number of covariates included was statistically limited to 10. Based on clinical interest, we explored the impact of the the following 9 parameters next to cell source: type of ischemia (permanent ischemia vs. ischemia/reperfusion), infarct location (left circumflex coronary artery (LCX) vs. left anterior descending coronary artery (LAD)), cell type (bone marrow mononuclear cells (BMMNC), mesenchymal stem cells (MSC), cardiac stem cells (CSC), cell dose (<10⁷, 10⁷-10⁸, 10⁸-10⁹, >10⁹), delivery method (intracoronary, intramyocardial injections, transendocardial injections), timing of treatment (<1 day, 1-7 days, >7 days), randomisation, blinding of operator and total quality score.

All analyses were performed using Stata version 12 (StataCorp LP, Texas, USA).

RESULTS

The search identified 459 publications in PubMed and 168 in EMBASE. After merging, 595 unique publications were screened. After excluding 513 publications (Supplemental material figure I) 82 articles could be included in our analysis. No additional studies could be added by screening the reference list of...
included studies. The 82 articles contained 125 groups for comparisons of the primary outcome (67 comparisons for EDV, 59 for ESV and 74 for mortality). A total of 1415 animals were included, 832 in treatment groups and 583 control animals. The vast majority investigated cell therapy in pigs (67 studies, n=1141) (dogs 5 studies, 64 animals; sheep 10 studies, 210 animals). See supplemental material table I for specific characteristics per included study (including first author, year of publication, animal species, number of animals, location of infarct, type of injury, cell type, dose, cell source, delivery method, timing of treatment and method of endpoint assessment, LVEF of control and treatment group and effect size).

Risk of bias in included studies.

Visual inspection of the funnel plot suggests symmetry. (figure 1A). However, using Egger regression the 95% CIs of the regression line do not pass through the origin, suggesting asymmetry of the funnel plot, consistent with potential publication bias. (figure 1b) Where we tried to correct for publication bias using trim and fill, this test did not identify any theoretical missing studies.

Internal validity was examined by scoring studies for randomisation, allocation concealment (meaning blinding of the operator for the treatment), blinded assessment of outcome, reporting of compliance with animal welfare regulations and a statement of potential conflict of interest. Randomisation was reported in 61%, allocation concealment in 11%, blinded assessment of outcome in 42%, compliance with animal welfare regulations in 74% and a statement of conflict of interest was reported in 4% of the included studies (supplemental material Figure II). The total quality score is the total number of positive scored parameters, with a minimum of 0 and a maximum score of 5. The median quality score was 2.

Meta-analysis.

Overall, treatment showed an absolute difference in LVEF between treated and control animals of 8.3% (95% CI 7.1 – 9.5% SEM 0.6 p < 0.0001) in favour of cell treated animals. (Figure 2) Increased LVEF can be explained by a significant decrease in EDV (standardized difference in mean 0.60, 95%CI 0.32 - 0.90% SEM 0.14). There is no significant difference in ESV for treated and control animals (standardized difference in mean 0.76 95% CI 0.44 -1.1% SEM 0.16). Cell therapy did not lead to increased therapy-related mortality. Odds ratio for mortality is 1.1 (95% CI 0.7 – 1.6). See supplemental material figure III for the timber plot of mortality.

Observed heterogeneity for the primary endpoint LVEF was higher than would be expected from sampling error alone (tau^2 = 31.4, I^2 = 79%). We used meta-regression to explore potential contributions to this heterogeneity of parameters chosen a priori (type of ischemia, infarct location, cell type, cell dose, delivery method, timing of treatment, randomisation, blinding of operator and total quality score).

Cell source.

Autologous cells were compared to allogeneic and xenogeneic cell sources. Of 125 comparisons, 85 groups received autologous cells, 30 received allogeneic and the remaining 10 comparison groups received xenogeneic cells. No significant difference in effect size was found between different cell sources by meta-regression. Subgroup analyses revealed mean difference in LVEF for autologous cells 8.8 (95% CI 7.3 – 10.3), for allogeneic 7.3 (95% CI 4.4 – 10.2) and 7.1 (95% CI 2.4 – 11.7) for xenogeneic cell therapy (differences not significant) (Figure 3A). Cell source had also no impact on ESV or EDV.

In most cases (25 out of 30 comparisons, 300 out of 352 animals) the allogeneic cells used were MSCs. Only one study using allogeneic cells, used immunosuppression. For studies using xenogeneic cells, 8 out of 10 used immunosuppression, which is too few to perform meta-regression. Cyclosporin was
the immunosuppressant of choice (doses ranging from 5 to 500 mg/kg/day). One group added methylprednisolone (125 mg/day).24

Because of the abundance of studies using MSCs in the allogeneic group (300 out of 352 animals), a post hoc regression analysis was performed to explore differences in cell source for MSCs alone. As with the overall analysis no effect of cell source on effect size by MSCs was seen for LVEF (autologous 8.6% (95% CI 5.6 – 11.7); allogeneic 7.4% (95% CI 5.3 – 9.6) and xenogeneic 5.8% (95% CI -3.3 – 14.9); p=0,4; tau² = 13.7; I² = 64% (Figure 3B)) and for ESV and EDV.

Because bone marrow derived cells were all autologous, except for one study, no meta-regression for cell source could be performed for bone marrow derived cells alone.

Meta-regression for other parameters.

Meta-regression could be performed including all 125 comparisons per parameter, except for administration route (110) and dose (121). Meta-regression showed ‘myocardial infarction model’ to be the only significant predictor for a difference in LVEF (Table 2), with a the largest effect seen in permanent occlusion models compared to ischemia/reperfusion (difference in mean LVEF 9.8% (95% CI 8.3 – 11.4) and 6.2% (95% CI 3.8 – 8.6) respectively (p=0.004)). All other clinical parameters were no predictors for effect size.

We performed a post hoc subgroup analysis for method of outcome assessment. The majority of studies used echocardiography (n=62), MRI (n=35) or SPECT (n=9). The difference in LVEF between treated and untreated animals was 8.7% (95% CI 7.4 – 10.3) for echocardiography, 6.7% (95% CI 4.5 – 8.9) for MRI and 10.1% (95% CI 4.6 – 15.6) for SPECT, without any differences between methods (p=0.2).

For total quality score and for randomisation and allocation concealment, no statistically significant differences between groups were observed. (Table 2 and Supplemental material Figure IIB).

DISCUSSION

This meta-analysis of 82 studies, including 1415 large animals, shows that 1) autologous and allogeneic cell therapy for myocardial infarction exhibit similar effect size, 2) cell therapy provides an overall significant difference in mean LVEF of 8.3% and a significant decrease in EDV and 3) cell therapy appears safe.

Autologous vs. allogeneic cell therapy.

To the best of our knowledge, no direct comparative preclinical study of autologous and allogeneic cell therapy for myocardial ischemia has been reported. However, safety and efficacy of both autologous and allogeneic MSC therapy in ischemic cardiomyopathy has been compared in the POSEIDON study (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis).25 Overall, both end systolic and end diastolic volumes decreased and a non-significant decrease in LVEF of 2.0% was observed, without any difference between autologous and allogeneic cell sources. Authors concluded that both allogeneic and autologous cell therapy is safe and demonstrates potential regenerative activity. No increased antibody response was seen in patients receiving allogeneic MSCs.
Immunological issues are of great interest in allogeneic cell therapy for cardiac repair. Alloreactivity depends on presenting foreign peptides to T-cells by MHC-complexes on antigen-presenting cells. Immunosuppression (i.e. tacrolimus, cyclosporin, HLA matching) might be needed to improve cell engraftment over time.\textsuperscript{26,27} Cardiac repair by cell therapy is more often thought to act via paracrine signalling, rather than true regeneration by differentiation of transplanted cells.\textsuperscript{28,29} Prolonged presence of transplanted cells, and thus (sustained) immunosuppression, might not be essential for cardiac repair by paracrine effects. We hypothesize that the mechanism of action and the need for immunosuppression differs for various stages of disease, treatment goals and cell types.

MSCs are the most commonly used cell type in clinical and pre-clinical setting (pre-clinical see Figure 2), and are often regarded as the ideal and ‘universal’ cell type.\textsuperscript{30} In our analysis, 88\% of animals treated with allogeneic cells received MSCs (i.e. 300 of 352 see figure 3). None of them received immunosuppression. Immunosuppression for MSCs might be redundant, since these cells are considered by some to be ‘immuno privileged’.\textsuperscript{31} However, MSCs do interact with the immune system, play a role in immunomodulation\textsuperscript{32,33}, and even elicit immune responses in vivo.\textsuperscript{34} We performed a post hoc meta-regression of cell source for MSCs alone to establish whether there was any evidence of immune privileged properties for MSCs in cardiac repair. Interestingly, allogeneic MSCs appeared to be as effective as autologous MSCs, suggesting either that MSCs do not elicit an immune response, or that their mechanism of action does not require resistance to immune attack and clearance.

We were unable to perform post-hoc analysis on immunosuppression within the allogeneic subgroup, since only one study used immunosuppression.\textsuperscript{23} In this study, allogeneic PMultistem cells were surgically injected in a model of acute myocardial infarction, with and without cyclosporin immunosuppression. LVEF was significantly increased after cell therapy and this effect was independent of the presence of cyclosporin; further, cyclosporin did not increase cell engraftment. The authors speculated that rejection mechanisms may have limited activity in these models, or that apoptosis of some transplanted cells might itself have immunosuppressive consequences.

Non-cardiac meta-analyses of stem cell therapy.

Four meta-analyses concerning stem cell therapy in animal models in other areas of medicine are found in literature.\textsuperscript{35–38} Lees et al. conducted a meta-analysis of pre-clinical data for stem cell therapy for experimental stroke (119 studies, 2704 animals).\textsuperscript{35} In contrast to our analysis, differences in effect size between cell sources are observed. For functional outcome efficacy was higher for allogeneic cells, but autologous cells did better for infarct volume. Immunosuppression by cyclosporin had a positive effect on functional outcome, but not on infarct volume. The need for sustained survival of cells and the requirement of integration of transplanted cells in experimental stroke is questioned in this paper as well.

In the meta-analysis of Antonic et al. about cell transplantation in traumatic spinal cord injury, only one of the included 156 articles used autologous stem cells.\textsuperscript{38} Overall, allogeneic cells improve motor and sensory outcomes. Any kind of immunosuppression significantly decreased efficacy, where cyclosporin combined with methylprednisolone performed even worse than cyclosporine alone. Authors suggest that in their analysis, the beneficial effect of immunosuppressants is outweighed by other factors (i.e. stem cell biology, intrinsic repair mechanisms).

Oliveri et al. investigated the locomotor recovery by MSCs in rat models of traumatic spinal cord injury.\textsuperscript{37} In this meta-analysis of 83 studies including 15668 rats, 57\% of studies used non-autologous cells. In these studies 28\% of cells were administered in combination with immunosuppression, predominantly cyclosporin. Cell source was a significant predictor for improved outcome as autologous and allogeneic cells performed better than xenogeneic and syngeneic cells. These differences are not further discussed by the authors. Immunosuppressive status in allogeneic or xenogeneic cell therapy, was no significant predictor.
for locomotor outcome. Authors describe the anti-inflammatory, immunomodulatory and anti-apoptotic properties of MSCs. The lack of contribution of immunosuppression is explained by the hypo-immunogenic properties of MSCs and the absence of long-term engraftment.

Wang et al. analysed 21 pre-clinical studies, including 382 animals, concerning MSC therapy for renal impairment, but did not address differences in cell source and immunological issues.39

Translatability of pre-clinical studies.

Large animal models are generally used in medicine for development and validation of new therapies, but their usefulness has been questioned. The CAMARADES working group aims to provide evidence to inform translational medicine and investigates the translatability of in vivo studies using systematic approaches, including meta-analyses.40,41 Poor quality and in particular flaws in internal and external validity turn out to be significant predictors of outcome, affecting translation towards clinical practice.35,40,42 The relative high effect size compared to clinical studies1–4 and the dominance of positive studies might imply presence of flaws in validity or presence of publication bias against negative results.

In our assessment of publication bias, Egger regression suggests asymmetry in the funnel plot, but trim and fill did not identify missing studies. This is consistent with previous data that suggests trim and fill may lack statistical power compared to Egger regression.40 Further, asymmetry in the funnel plot may be caused by other factors than publication bias which is a limitation of these methods.

Publication bias is a serious problem in both clinical and pre-clinical studies,40,43 and impedes transition from pre-clinical towards clinical studies, by skewing the expected effect size. It is known from pre-clinical studies in stroke, that publication bias causes an relative overestimation of effect size of 31.1%.40 Largest contributors to publication bias are authors or researchers not willing to put effort in publishing negative results and editors who tend to select papers that are most exciting.44,45 Therefore, we call for registration of pre-clinical trials upfront46 and for tendency of editors to accept neutral or negative results for publication.

Flaws in internal and external validity can partly be solved by randomisation and blinding. In the current analysis, the quality of included studies was considered low. However, the reported prevalence of randomisation and blinding are substantially higher than observed in most other systematic reviews of preclinical data, but we consider this still not to be of sufficient quality to be robust. Interestingly, randomisation and blinding were no significant predictors for effect size, nor was total quality score. (Supplemental material figure IIB) This may be a limitation of using reported study quality as a proxy for how experiments were performed; too few studies detail the methods used to blind or randomise to allow detailed analysis of their susceptibility to bias. It is entirely plausible that some studies were performed in a blinded and randomised manner but this was not explicitly stated by the authors, or the vice versa. We believe that providing empirical evidence of the poor reporting of measures to reduce the risk of bias will encourage the field to report both the performance of these measures and also details of the methods used. By adding 30 new studies, we are able to reproduce the significant increase in LVEF we found in the previous meta-analysis.18 The slight increase in effect size (7.3% in the previous analysis, 8.3% in this analysis) might imply that pre-clinical research is improving and focusing on the right issues. Based on statistics, the number of parameters included in the current meta-regression was limited to 10. Therefore we were not able to analyse other relevant issues, like animal species or duration of follow up. Fortunately, we included several parameters in the sensitivity analysis in the previous analysis where we showed no difference in animal species and duration of follow up.18
Limitation.

In this meta-analysis we used the best available evidence to assess differences in the effects of autologous and allogeneic cell therapy for myocardial infarction. This exploration of the literature is a post-hoc analysis of the data and as such is considered hypothesis generating rather than confirmatory.

We identified a number of limitations in the preclinical studies included in this review, and subsequently this meta-analysis should be interpreted with caution. LVEF is considered the golden standard outcome measure and the reporting of other outcomes was less robust. Infarct size, for example, was reported in a small subset of studies, and the methods used to assess infarct size and the units in which they were presented differed greatly between these studies. Therefore, we were unable to include infarct size as one of the outcome parameters. In addition, the reporting of mortality appears to be less rigorous in preclinical studies compared to clinical studies; mortality was reported in only 74 of the 125 comparisons included. Studies that did report mortality did not show a difference between treatment groups, but this may be an artefact of limited reporting.

A notable feature of these animal data is the limited generalisability to humans in a clinical setting. Patients suffering from ischemic heart disease are usually old, and exposed to several risk factors, in contrast to the young healthy animals often used to model the disease. This might explain the larger effect size in our analysis, compared to that reported in clinical data. Moreover, the lack of exposure of autologous cells to risk factors in a preclinical setting is discordant to the autologous cells of a patient in a clinical setting. Therefore, we hypothesise a greater difference in effect sizes between pre-clinical and clinical studies where autologous cell therapy is used compared to allogeneic cell therapy.

We are unable to provide empirical evidence of the added value of immunosuppression in allogeneic cell therapy, as almost all allogeneic studies were performed without immunosuppression. However, LVEF is improved by allogeneic cell therapy compared to placebo, suggesting that allogeneic cell therapy can be performed without immunosuppression.

Conclusion.

In pre-clinical studies of cell therapy for cardiac repair, allogeneic cells are associated with a similar magnitude of effect as autologous cells. The majority of these allogeneic cells were MSCs. Based on the logistical and practical advantages of allogeneic cell sources and our data presented here, we support future clinical trials of MSCs for cardiac repair to focus on allogeneic cell therapy, without the use of immunosuppressive therapy.

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DISCLOSURES
No conflicts of interest to report.
REFERENCES


**TABLE 1.** Features of autologous and allogeneic cell sources.

<table>
<thead>
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<th>Advantage</th>
<th>Disadvantage</th>
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<tr>
<td><strong>Autologous</strong></td>
<td>• No immunological issues</td>
</tr>
<tr>
<td>• Cell exposure to risk factors</td>
<td>• Restricted (immediate) availability</td>
</tr>
<tr>
<td>• Restricted (immediate) availability</td>
<td></td>
</tr>
<tr>
<td><strong>Allogeneic</strong></td>
<td>• Production of potent cell lines</td>
</tr>
<tr>
<td>• Immediate availability</td>
<td>• Immunological issues</td>
</tr>
</tbody>
</table>

|
TABLE 2. Results from meta-regression of parameters other than cell source.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Permanent (n=765)</th>
<th>Temporary (n=650)</th>
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<tr>
<td><strong>Type of injury</strong></td>
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<td>Permanent (n=765)</td>
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<td>Temporary (n=650)</td>
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<td><strong>Dose</strong></td>
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<td>&lt; 1E7 (n=109)</td>
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<td>1E7 - 1E8 (n=626)</td>
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<td>8.3 ± 1.3</td>
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<td>1E8 - 1E9 (n=604)</td>
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<td>&gt; 1E9 (n=40)</td>
<td>12.3 ± 3.5</td>
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<td>NS</td>
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<td><strong>Time of administration</strong></td>
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<td>&lt; 1 day (n=452)</td>
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<td>8.5 ± 1.8</td>
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<td>1-7 days (n=335)</td>
<td>8.5 ± 1.8</td>
<td>8.3 ± 1.9</td>
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<td>&gt; 7 days (n=628)</td>
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<td>BMMNC (n=248)</td>
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<tr>
<td>MSC (n=536)</td>
<td>8.0 ± 0.7</td>
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<tr>
<td>CSC (n=64)</td>
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<td><strong>Route of delivery</strong></td>
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<td>Intracoronary (n=355)</td>
<td>7.0 ± 1.5</td>
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<td><strong>Location of infarct</strong></td>
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<td>LAD (n=1128)</td>
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<td>6.3 ± 1.5</td>
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<td>LCX (n=287)</td>
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<td>Non randomized (n=879)</td>
<td>9.3 ± 1.0</td>
<td>7.7 ± 1.3</td>
<td>NS</td>
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<td>Randomized (n=536)</td>
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Data presented as difference in mean LVEF (mean ± SEM) between treated and placebo per subgroup. BMMNC Bone marrow mononuclear cells, MSC Mesenchymal stem cells, CSC Cardiac stem cells, LAD Left anterior descending coronary artery, LCX Left circumflex coronary artery. NS Not significant.
FIGURE LEGENDS

**Figure 1.** Publication bias. Funnel plot (a) and Egger regression (b) of left ventricular ejection fraction, showing potential evidence for publication bias.

**Figure 2:** Timber plot. Timber plot of differences in mean left ventricular ejection fraction (LVEF) between treated and placebo animal. The vertical error bars represents the 95% confidence intervals of individual studies. The gray bar represents the 95% confidence interval of the mean difference in LVEF.

**Figure 3:** Comparison of cell source. Effect size and 95% confidence intervals of different cell sources based on meta-regression, for Meta-regression of all celltypes (A) and for mesenchymal stem cells alone (B).
Novelty and Significance

What Is Known?

- Cell therapy has emerged as a potential treatment for enhancing cardiac regeneration after myocardial infarction.

- Both autologous and allogeneic cell types have been used in clinical and pre-clinical studies to promote cardiac regeneration.

What New Information Does This Article Contribute?

- In large animal models of myocardial infarction, cell therapy was associated with an 8.3% change in the ejection fraction in comparison with placebo.

- In these models, both autologous and allogeneic cell therapy were associated with a similar magnitude of effect.

Stem cell therapy has emerged as a novel modality for the potential treatment of ischemic heart disease. In pre-clinical and clinical studies, both autologous and allogeneic cells have been investigated for cardiac regeneration. Both cell sources have their advantages and disadvantages with regard to logistics (immediate and sufficient availability) and immunological issues. In this systematic review and meta-analysis, we summarize data on cell therapy in large animal models of myocardial ischemia. We have analysed data from 82 studies including almost 1500 large animals and found that in comparison with controls, cell therapy was associated with a significant improvement in cardiac function. Our analysis suggests that allogeneic cells are as potent as autologous cells for improving cardiac function in ischemic heart disease. These findings could inform the design of future clinical trials.
A. All cell sources

Difference in mean LVEF (%)

- Autologous (n=981)
- Allogeneic (n=331)
- Xenogeneic (n=103)
- Overall (n=1415)

Favours control Favours cell therapy

B. MSCs only

Difference in mean LVEF (%)

- Autologous (n=264)
- Allogeneic (n=308)
- Xenogeneic (n=16)
- Overall (n=588)

Favours control Favours cell therapy
Similar Effect of Autologous and Allogeneic Cell Therapy for Ischemic Heart Disease: Systematic Review and Meta-Analysis of Large Animal Studies
Sanne J Jansen_of_Lorkeers, Joep E Eding, Hanna M Vesterinen, Tycho I van der Spoel, Emily S Sena, Henricus J Duckers, Pieter A Doevendans, Malcolm R Macleod and Steven A Chamuleau

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Similar effect of autologous and allogeneic cell therapy for ischemic heart disease:

Systematic review and meta-analysis of large animal studies

S.J. Jansen of Lorkeers¹, J.E.C. Eding¹, H.M. Vesterinen², T.I.G. van der Spoel¹, E.S. Sena², H.J. Duckers¹, P.A. Doevendans¹, M.R. Macleod², S.A.J. Chamuleau¹.

¹ Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
² Centre for clinical brain sciences, University of Edinburgh, Edinburgh, United Kingdom
Detailed methods

Search used in electronic databases:

((pig OR porcine OR dog OR canine OR sheep OR ovine)

AND

(stem cells OR progenitor cells OR bone marrow))

AND

(myocardial infarction OR heart failure OR coronary artery disease OR cardiac repair OR myocardial regeneration)
Table I Study characteristics of included studies

LAD Left anterior descending coronary artery, LCX Left circumflex coronary artery, BMMNC Bone marrow mononuclear cell, MSC Mesenchymal stem cell, EPC Endothelial progenitor cell, USSC Unrestricted somatic stem cell, PBMC Peripheral blood mononuclear cell, BMSC Bone marrow stromal cell, CDC Cardiac stem cell, CSph Cardiosphere derived cell, ADSC Adipose derived stem cell.

EDV (ml), ESV (ml) and EF(%) for control and treated groups is presented as mean ± SD. Effect size is presented as mean ± SEM. Quality score out of 5. * = Mean ± SEM. Subgroups: a Infarct related artery, b non-Infarct related artery, c unlabeld cells, d labelled, e GFP labelled, f dual labelled, g Cyclosporin treated animals, h Rentrop score 0, i Rentrop score 2, j Rentrop score 1.
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<td>Dose</td>
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*Note: ESV and EDV values are calculated based on the provided data.*
Figure II: Quality of included studies.

A. Quality of included studies presented as percentage of studies reporting individual parameters.

B. Bubble plot of the meta-regression for total quality score (out of 5), where each study is plotted against its quality score. Larger bubbles represent more precise studies, based on inverse standard error.
Figure III: Mortality.

Timber plot of odds ratio of mortality in cell treated and placebo animals per study. Vertical error bars represent 95% confidence intervals of individual studies. The gray bar represents the 95% confidence interval of the mean odds ratio.
Reference list


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