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

Sanne Johanna Jansen of Lorkeers, Joep Egbert Coenraad Eding, Hanna Mikaela Vesterinen, Tycho Ids Gijbvert van der Spoel, Emily Shamiso Sena, Henricus Johannes Duckers, Pieter Adrianus Doevendans, Malcolm Robert Macleod, Steven Anton Jozef Chamuleau

Rationale: In regenerative therapy for ischemic heart disease, use of both autologous and allogeneic stem cells has 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 preparative production of pot 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 preclinical data of cell therapy for ischemic heart disease.

Methods and Results: We conducted a systematic literature search to identify publications describing controlled preclinical 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 in treated compared with control animals (8.3%, 95% confidence interval, 7.1–9.5; P<0.001). Meta-regression revealed a similar difference in left ventricular ejection fraction in autologous (8.8%, 95% confidence interval, 7.3–10.3; n=981) and allogeneic (7.3%, 95% confidence interval, 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 left ventricular ejection fraction in large animal models of myocardial ischemia, compared with placebo. These results are important for the design of future clinical trials. (Circ Res. 2015;116:80-86. DOI: 10.1161/CIRCRESAHA.116.304872.)

Key Words: allogeneic transplantation ■ autologous transplantation ■ meta-analysis ■ myocardial ischemia ■ stem cells ■ translational medical research

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% to 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 improve further the magnitude of effect. The European Society of Cardiology urge researchers to focus on unresolved issues in cardiac repair strategies, including the type of cell used. Consequently, the field has shifted from bone marrow mononuclear cells to mesenchymal stem cells and more recently to cardiac stem cells.

The vast majority of clinical trials have used autologous stem cells, an attractive approach because no immunologic problems are encountered. 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 (ie, age, diabetes mellitus, and smoking) may impair the potential of autologous stem cells. Restricted availability is present because selection and culturing of sufficient potent cells is cumbersome and time consuming. This limitation is especially important in the acute setting of myocardial ischemia.

Editorial, see p 12

Allogeneic cell therapy enables preparatory production of pot cell lines, immediate availability and allows off-the-shelf therapy. However, immunologic 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. 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 performed a meta-analysis of preclinical 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 cells were explored by meta-regression.

Methods for selection of studies are extensively described in van der Spoel et al. In brief, a systematic search was performed in the electronic databases PubMed and EMBASE on January 15th, 2013 (see Online Data Supplement 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, and pigs), use of stem cells, the use of a proper control group, and reporting of LVEF as outcome measure. Exclusion criteria were studies not published in full (eg, meeting abstracts) and the use of cell therapy is associated with the same magnitude of effect as xenogeneic cell therapy. For meta-regression, the number of covariates included was statistically limited to 10. Based on clinical interest, we explored the impact of the following parameters next to cell source: type of ischemia (permanent ischemia versus ischemia/reperfusion), infarct location (left circumflex coronary artery versus left anterior descending coronary artery), cell type (bone marrow mononuclear cells, mesenchymal stem cells [MSC], and cardiac stem cells), cell dose (<10^3, 10^3–10^4, 10^4–10^5, and >10^5), delivery method (intracoronary, intramyocardial injections, and transendocardial injections), timing of treatment (<1 day, 1–7 days, and >7 days), randomization, blinding of operator, and total quality score. All analyses were performed using Stata version 12 (StataCorp LP, TX, USA).

**Results**

The search identified 459 publications in PubMed and 168 in EMBASE. After merging, 595 unique publications were screened. After excluding 513 publications (Online 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 Online 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 end point 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 randomization, 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.

**Table 1. Features of Autologous and Allogeneic Cell Sources**

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

**Nonstandard Abbreviations and Acronyms**

- **CI**: confidence interval
- **EDV**: end-diastolic volume
- **ESV**: end-systolic volume
- **LVEF**: left ventricular ejection fraction
- **MSC**: mesenchymal stem cell

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for the treatment), blinded assessment of outcome, reporting of compliance with animal welfare regulations, and a statement of potential conflict of interest. Randomization 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 (Online 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 favor 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 Online Figure III for the timber plot of mortality.

Observed heterogeneity for the primary end point LVEF was higher than would be expected from sampling error alone (\(\tau^2=31.4; \hat{I}^2=79\%\)). 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, randomization, blinding of operator, and total quality score).

**Cell Source**

Autologous cells were compared with 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 of 30 comparisons, 300 of 352 animals), the allogeneic cells used were MSCs. Only one study using allogeneic cells used immunosuppression.\(^{23}\) For studies using xenogeneic cells, 8 of 10 used immunosuppression, which is too few to perform meta-regression. Cyclosporin was the immunosuppressant of choice (doses ranging from 5–500 mg/kg per day). One group added methylprednisolone (125 mg/d).\(^{24}\)

Because of the abundance of studies using MSCs in the allogeneic group (300 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 to 14.9]; \(P=0.4; \tau^2=13.7; \hat{I}^2=64\%\); 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 the largest effect seen in permanent...
To the best of our knowledge, no direct comparative preclinical study of autologous and allogeneic cell therapy for myocardial infarction exhibits similar effect size, (2) cell therapy provides an overall significant difference in mean LVEF of 8.3% and a significant decrease in ESV and EDV, and (3) cell therapy appears safe. 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.

Immunologic issues are of great interest in allogeneic cell therapy for cardiac repair. Alloreactivity depends on presenting foreign peptides to T cells by MHC (major histocompatibility complex) complexes on antigen-presenting cells. Immunosuppression (ie, tacrolimus, cyclosporin, HLA [human leukocyte antigen] matching) might be needed to improve cell engraftment over time. Cardiac repair by cell therapy is more often thought to act via paracrine signaling, rather than true regeneration by differentiation of transplanted cells. 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 differ for various stages of disease, treatment goals, and cell types.

MSCs are the most commonly used cell type in clinical and preclinical setting (preclinical see Figure 2) and are often regarded as the ideal and universal cell type. In our analysis, 88% of animals treated with allogeneic cells received MSCs (ie, 300 of 352, see Figure 3). None of them received immunosuppression. Immunosuppression for MSCs might be redundant because these cells are considered by some to be immunoprivileged. However, MSCs do interact with the immune system, play a role in immunomodulation, and even elicit immune responses in vivo. 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 because only one study used immunosuppression. 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.

**Noncardiac 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. Lees et al conducted a meta-analysis of preclinical data for stem cell therapy for experimental stroke (119 studies, 2704 animals). 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 are questioned in this article as well.

In the meta-analysis of Antonic et al38 about cell transplantation in traumatic spinal cord injury, only one of the included 156 articles used autologous stem cells. Overall, allogeneic cells improve motor and sensory outcomes. Any kind of immunosuppression significantly decreased efficacy, where cyclosporin had a positive effect on functional outcome but not on infarct volume. Immunosuppression by cyclosporin alone. Authors suggest that in their analysis, the beneficial effect of immunosuppressants is outweighed by other factors (ie, stem cell biology, intrinsic repair mechanisms).

Oliveiri et al37 investigated the locomotor recovery by MSCs in rat models of traumatic spinal cord injury. In this meta-analysis of 83 studies including 15668 rats, 57% of studies used nonautologous 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 not significant predictor for locomotor outcome. Authors describe the anti-inflammatory, immunomodulatory, and antiapoptotic properties of MSCs. The lack of contribution of immunosuppression is explained by the hypoinmunogenic properties of MSCs and the absence of long-term engraftment.

Wang et al analyzed 21 preclinical studies, including 382 animals, concerning MSC therapy for renal impairment, but did not address differences in cell source and immunologic issues.

Translatability of Preclinical 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. Poor quality and in particular flaws in internal and external validity turn out to be significant predictors of outcome, affecting translation toward clinical practice. The relative high effect size compared with clinical studies 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 suggest that trim and fill may lack statistical power compared with Egger regression. Furthermore, 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 preclinical studies, and impedes transition from preclinical toward clinical studies, by skewing the expected effect size. It is known from preclinical studies in stroke that publication bias causes an relative overestimation of effect size of 31.1%. 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. Therefore, we call for registration of preclinical trials upfront and for tendency of editors to accept neutral or negative results for publication.

Flaws in internal and external validity can partly be solved by randomization and blinding. In the current analysis, the quality of included studies was considered low. However, the reported prevalence of randomization and blinding is substantially higher.

Table 2. Results From Meta-Regression of Parameters Other Than Cell Source

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Permanent (n=765)</th>
<th>Temporary (n=650)</th>
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</thead>
<tbody>
<tr>
<td>Type of injury</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Permanent</td>
<td>9.8±0.8</td>
<td>6.2±1.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Temporary</td>
<td>1E8-1E9</td>
<td>8.3±1.3</td>
<td></td>
</tr>
<tr>
<td>Cell type</td>
<td></td>
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<tr>
<td>BMMNC (n=248)</td>
<td>7.6±1.3</td>
<td>8.0±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>MSC (n=536)</td>
<td>8.5±1.8</td>
<td>8.3±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>CSC (n=64)</td>
<td></td>
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<td></td>
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<tr>
<td>Route of delivery</td>
<td></td>
<td></td>
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<tr>
<td>Intracoronary (n=355)</td>
<td>7.0±1.5</td>
<td>9.2±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Transendocardial (n=264)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical (n=610)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Location of infarct</td>
<td></td>
<td></td>
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<tr>
<td>LAD (n=1128)</td>
<td>8.8±0.7</td>
<td>6.3±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>LCX (n=287)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blinding of operator</td>
<td></td>
<td></td>
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<tr>
<td>Nonblinded (n=685)</td>
<td>7.7±0.9</td>
<td>8.9±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Blinded (n=730)</td>
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<tr>
<td>Randomization</td>
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<tr>
<td>Nonrandomized (n=879)</td>
<td>9.3±1.0</td>
<td>7.7±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Randomized (n=536)</td>
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</table>

Data presented as difference in mean LVEF (mean±SEM) between treated and placebo per subgroup. BMMNC indicates bone marrow mononuclear cells; CSC, cardiac stem cells; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; MSC mesenchymal stem cells; and NS, not significant.
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, randomization and blinding were no significant predictors for effect size or was total quality score (Online 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 randomize to allow detailed analysis of their susceptibility to bias. It is entirely plausible that some studies were performed in a blinded and randomized manner, but this was not explicitly stated by the authors or the vice versa. We think 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. The slight increase in effect size (7.3% in the previous analysis, 8.3% in this analysis) might imply that preclinical 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 analyze 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.

Limitations
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 several 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 seems to be less rigorous in preclinical studies compared with 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 artifact of limited reporting.

A notable feature of these animal data is the limited generalizability to humans in a clinical setting. Patients having 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 with 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 hypothesize a greater difference in effect sizes between preclinical and clinical studies where autologous cell therapy is used compared with allogeneic cell therapy.

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

Conclusions
In preclinical 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.

Sources of Funding
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Disclosures
None.

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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 preclinical 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 therapies 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 preclinical 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 immunologic issues. In this systematic review and meta-analysis, we summarize data on cell therapy in large animal models of myocardial ischemia. We have analyzed data from 82 studies including >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.
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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

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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, PBMNC 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 unlabelled 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.
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Species</th>
<th>Treatment</th>
<th>Cell source</th>
<th>N (treatment)</th>
<th>N (control)</th>
<th>Cell source</th>
<th>Histological grade</th>
<th>Histological grade</th>
<th>Histological grade</th>
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<tr>
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<td>Makkar</td>
<td>Pig</td>
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<td>MSC</td>
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<td>9 ± 5.59</td>
<td>28 ± 3.62</td>
<td>54 ± 3.62</td>
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<td>2010</td>
<td>Luan</td>
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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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34. Lim SY, Kim YS, Ahn Y, Jeong MH, Hong MH, Joo SY, Nam K Il, Cho JG, Kang PM, Park JC. The effects of mesenchymal stem cells transduced with Akt in a porcine myocardial infarction model. *Cardiovascular research.* 2006;70:530–42.


