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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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 preoperative 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 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%.[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 improve further 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 cells.[6–9]

The vast majority of clinical trials have used autologous stem cells, an attractive approach because 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 (ie, age, diabetes mellitus, and smoking) may impair the potential of autologous stem cells.[11–13] 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.

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Allogeneic cell therapy enables preparatory production of potent 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.[14–17] Features of allogeneic and autologous cell sources are summarized in Table 1.

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Nonstandard Abbreviations and Acronyms	
CI	confidence interval
EDV	end-diastolic volume
ESV	end-systolic volume
LVEF	left ventricular ejection fraction
MSC	mesenchymal stem cell

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.[18] 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 cells modified to enhance cell function.

Results were screened independently by 2 researchers (S.J. and J.E.). 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 end points, mortality, cell characteristics, quality parameters, and general study information were extracted. The primary functional end point was LVEF, and the secondary end points 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 because baseline data and change from baseline were 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.[19] Included parameters for quality were reporting of 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

	Advantage	Disadvantage
Autologous	No immunologic issues	Cell exposure to risk factors
		Restricted (immediate) availability
Allogeneic	Production of potent cell lines	Immunologic issues
	Immediate availability	

Statistics

For LVEF, a raw difference in mean analysis was performed.[20] Data are reported as an absolute difference in mean LVEF at follow-up between treated and control groups, with 95% confidence interval (CI) or 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.[21] Trim and fill is a nonparametric 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.[22]

Where different treatment groups were reported within the same study (ie, 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, and 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 following 9 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 ($<10^7$, 10^7–10^8, 10^8–10^9, and $>10^9$), 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

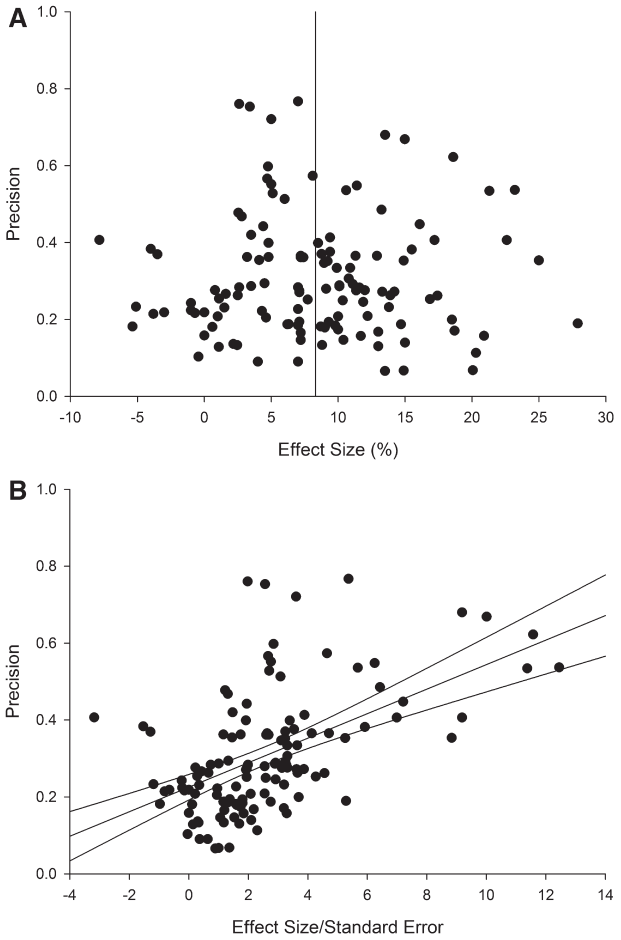

Figure 1. Publication bias. Funnel plot (**A**) and Egger regression (**B**) of left ventricular ejection fraction, showing potential evidence for publication bias.

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 (τ2=31.4; I^2=79%). We used meta-regression to explore

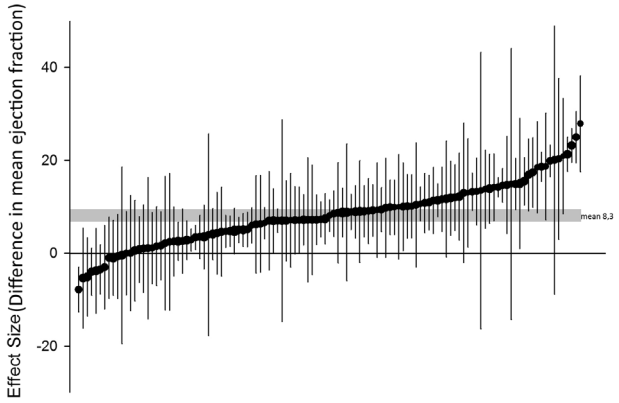

Figure 2. Timber plot. Timber plot of differences in mean left ventricular ejection fraction (LVEF) between treated and placebo animal. The vertical error bars represent the 95% confidence intervals of individual studies. The gray bar represents the 95% confidence interval of the mean difference in LVEF.

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; τ2=13.7; 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

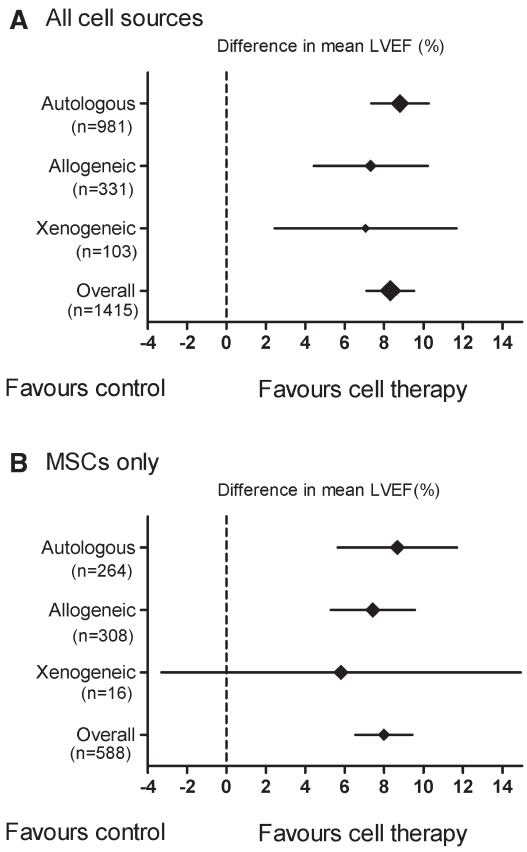

Figure 3. Comparison of cell source. Effect size and 95% confidence intervals of different cell sources based on meta-regression, for meta-regression of all cell types (**A**) and for mesenchymal stem cells (MSCs) alone (**B**). LVEF indicates left ventricular ejection fraction.

occlusion models compared with 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 *single-photon emission computed tomography* (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 *single-photon emission computed tomography*, without any differences between methods (*P*=0.2). For total quality score and for randomization and allocation concealment, no statistically significant differences between groups were observed (Table 2; Online Figure IIB).

Discussion

This meta-analysis of 82 studies, including 1415 large animals, shows that (1) 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 EDV, and (3) cell therapy appears safe.

Autologous Versus 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 have been compared in the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) study.[25] Overall, both ESV and EDV decreased, and a nonsignificant 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.

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.[26,27] Cardiac repair by cell therapy is more often thought to act via paracrine signaling, rather than true regeneration by differentiation of transplanted cells.[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 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.[30] 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.[31] However, MSCs do interact with the immune system, play a role in immunomodulation,[32,33] and even elicit immune responses in vivo.[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 because only one study used immunosuppression.[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.

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.[35–38] Lees et al[35] 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,

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

Parameters					
Type of injury	Permanent (n=765)	Temporary (n=650)			
	9.8±0.8	6.2±1.2			*P*=0.004
Dose	<1E7 (n=109)	1E7-1E8 (n=626)	1E8-1E9 (n=604)	>1E9 (n=40)	
	4.8±2.4	8.6±0.9	8.3±1.3	12.3±3.5	NS
Time of administration	<1 d (n=452)	1–7 d (n=335)	>7 d (n=628)		
	7.7±1.6	8.5±1.8	8.3±1.9		NS
Cell type	BMMNC (n=248)	MSC (n=536)	CSC (n=64)		
	7.6±1.3	8.0±0.7	5.2±4.1		NS
Route of delivery	Intracoronary (n=355)	Surgical (n=610)	Transendocardial (n=264)		
	7.0±1.5	9.2±0.9	8.9±1.8		NS
Location of infarct	LAD (n=1128)	LCX (n=287)			
	8.8±0.7	6.3±1.5			NS
Blinding of operator	Nonblinded (n=685)	Blinded (n=730)			
	7.7±0.9	8.9±1.2			NS
Randomization	Nonrandomized (n=879)	Randomized (n=536)			
	9.3±1.0	7.7±1.3			NS

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.

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 al[38] 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 cysclosporin 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 (ie, stem cell biology, intrinsic repair mechanisms).

Oliveri et al[37] 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 hypoimmunogenic properties of MSCs and the absence of long-term engraftment.

Wang et al analyzed[39] 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.[40,41] Poor quality and in particular flaws in internal and external validity turn out to be significant predictors of outcome, affecting translation toward clinical practice.[35,40,42] The relative high effect size compared with clinical studies[1–4] 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 suggest that trim and fill may lack statistical power compared with Egger regression.[40] 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,[40,43] 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%.[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 preclinical trials upfront[46] 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

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.[18] 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.[18]

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.[1–4] 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.

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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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Supplemental material

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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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)

Figure I. Flow chart of excluded and included studies

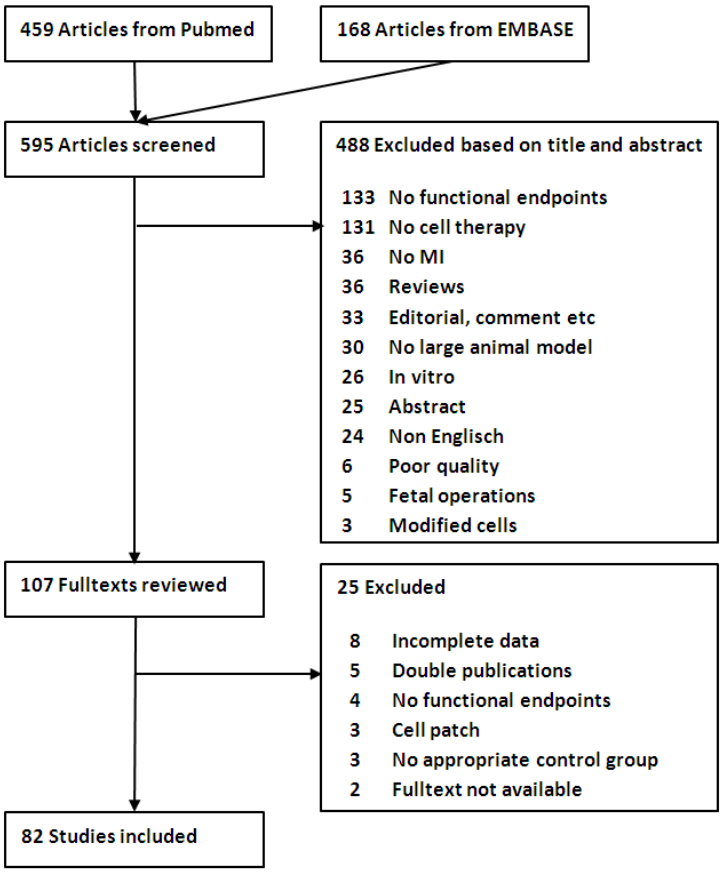


Table I Study characteristics of included studies

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 Peripherial 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.

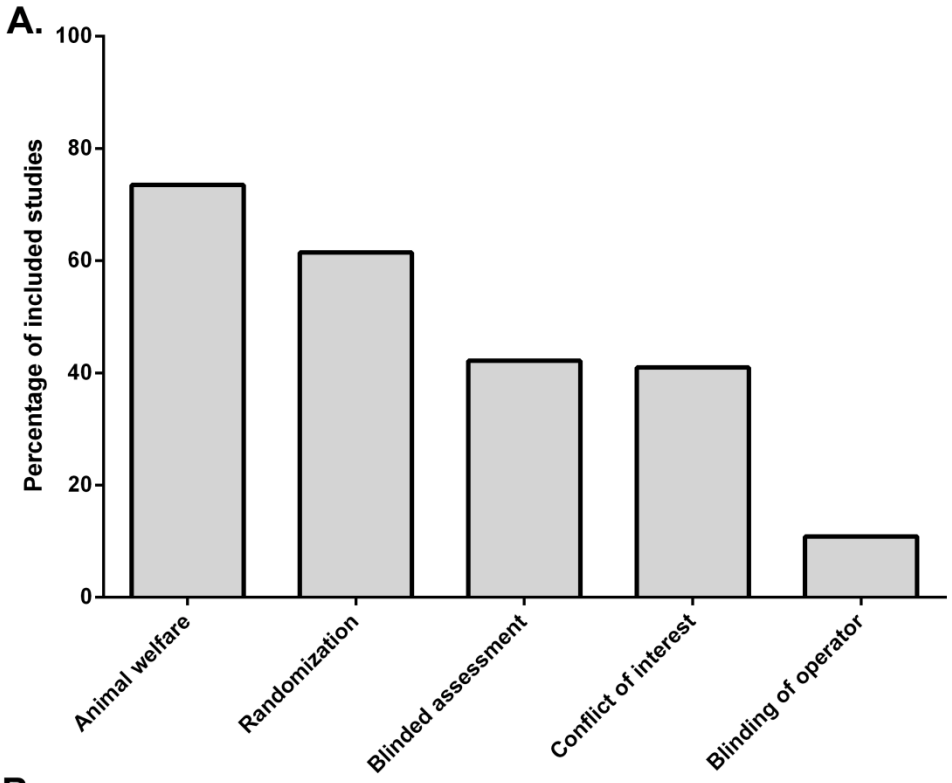
First author	Year	Animal	N (control)	N (treatment)	Location	Type of ischemia	Cell type	Dose	Cell source	Delivery route	Timing of treatment (days)	Endpoint assessment	Quality score	EDV(ml) control	EDV(ml) treatment	EDV Effect Size (ml)	ESV(ml) control	ESV(ml) treatment	ESV Effect Size (ml)	EF(%) control	EF(%) treatment	Effect Size
Bel	2003	Sheep	9	9	LCX	Permanent	BMMNC	4,2E+08	Autologous	Intramyocardial	21	Epicardial echocardiography	2	52.7 ± 13.2	57 ± 20.1	4.3 ± 8.02	34.1 ± 8.4	40.6 ± 17.2	6.5 ± 6.38	31 ± 3	30 ± 12	-1 ± 4,12
Bourahla	2010	Sheep	9	10	LAD	Permanent	Mesothelial cells	8,0E+07	Autologous	Intramyocardial	21	Epicardial echocardiography	3	69 ± 2.6	36.1 ± 2.4	-32.9 ± 1.44				35,8 ± 3,5	57,1 ± 2,8	21,3 ± 1,87
				9			Skeletal myoblast	8,2E+07							36.1 ± 2.4	-32.9 ± 1.46					59 ± 2,6	23,2 ± 1,86
Brasselet	2005	Sheep	7	7	LAD	Permanent	Skeletal myoblast	2,4E+08	Autologous	Transvenous	14	Echocardiography	3							39,7 ± 3,7	51,1 ± 3,1	11,4 ± 1,82
Chachques	2004	Sheep	5	6	LAD	Permanent	Skeletal myoblast	7,0E+07	Autologous	Intramyocardial	21	Echocardiography	1	74.4 ± 11.2	57 ± 11.1	-17.4 ± 6.75	44.6 ± 5.6	32.8 ± 8.8	-11.8 ± 4.38	39,8 ± 3,6	43,3 ± 4,3	3,5 ± 2,38
Chen	2009	Pig	6	7	LCX	Permanent	MSC	4,0E+07	Allogeneic	Intramyocardial	42	Echocardiography	4							43,8 ± 4,82	39,8 ± 4,53	-4 ± 2,61
Dixon	2009	Sheep	14	8	LAD	Permanent	MSC	4,5E+08	Allogeneic	Intramyocardial	≤1	Echocardiography	3	102.8 ± 29.9	98.4 ± 22.6	4.4 ± 17.87				13,7 ± 3,4	20,8 ± 9,1	7,1 ± 3,70
				10				2,3E+08							94 ± 14.5	-8.8 ± 16.63					20,9 ± 6,6	7,2 ± 2,77
				7				7,5E+07							84.6 ± 14.3	-18.2 ± 16.84					23,6 ± ,3	9,9 ± 3,00
				7				2,5E+07							85 ± 20.9	-17.8 ± 17.83					23,8 ± 7,9	10,1 ± 3,50
Doyle	2008	Pig	9	9	LCX	Ischemia/Reperfusion	EPC	3,0E+07	Autologous	Intracoronary	2	MRI	2	73.7 ± 12.15	73.5 ± 13.65	-0.2 ± 6.09	37.1 ± 12	27.3 ± 17.25	-9.8 ± 7.00	57,7 ± 12	66,5 ± 19,05	8,8 ± 7,50
Dubois	2010	Pig	7	7	LCX	Ischemia/Reperfusion	EPC	3,4E+07	Autologous	Intracoronary	7	MRI	5	81 ± 17	76 ± 24	-5 ± 12.84	42 ± 14	40 ± 16	-2 ± 9.62	48 ± 7	49 ± 8	1 ± 4,81
				7			MSC	1,0E+07	Allogeneic						85 ± 22	4 ± 12.32		48 ± 16	6 ± 9.62		45 ± 7	-3 ± 4,58
Gavira	2006	Pig	4	6	LAD	Permanent	Skeletal myoblast	4,0E+08	Autologous	Transendocardial	56	Echocardiography	2	64.7 ± 44.4	57.9 ± 48.5	-6.8 ± 37.12	32.2 ± 18.9	25.9 ± 31.6	-6.3 ± 18.58	49,5 ± 18,2	63 ± 19,8	13,5 ± 15,20
				6						Intramyocardial					58.9 ± 40.9	-5.8 ± 35.56		19.3 ± 10.3	-12.9 ± 14.01		64,4 ± 18,4	14,9 ± 14,90
Gavira	2010	Pig	5	5	LCX	Permanent	Skeletal myoblast	3,4E+08	Autologous	Transendocardial	56	Echocardiography	3							37,7 ± 5,9	56,2 ± 4,6	18,5 ± 5,01
				5				6,2E+08													56,4 ± 8,2	18,7 ± 5,86
				5				1,2E+09													65,6 ± 5,9	27,9 ± 5,28
Ghodsizad	2009	Pig	5	5	LCX	Permanent	USSC	1,3E+07	Xenogeneic	Intramyocardial	≤1	TEE	3	77 ± 4	26 ± 2	-51 ± 2	56 ± 4	12 ± 2	-44 ± 2	27 ± 6	52 ± 2	25 ± 2,83
Ghostine	2002	Sheep	8	8	LCX	Permanent	Skeletal myoblast	4,2E+08	Autologous	Intramyocardial	14	Echocardiography	3	105 ± 47	72 ± 27	-.3 ± 19.16				33 ± 11	48 ± 17	15 ± 7,16
Graham	2010	Pig	4	7	LAD	Ischemia/Reperfusion	BMMNC	1,3E+07	Autologous	Intracoronary	7	MRI	4							31,9 ± 6,8	34,5 ± 2,5	2,6 ± 3,53
Gyöngyösi	2008	Pig	6	6	LAD	Ischemia/Reperfusion	MSC	7,1E+06	Autologous	Transendocardial	1,625	MRI	1	88 ± 7.7	80 ± 4.4	-8 ± 3.62	49.72 ± 3.8	43.3 ± 2.7	-6.42 ± 1.90	43,5 ± 2,3	46,9 ± 2,3	3,4 ± 1,33
Hagikura	2009	Pig	5	5	LAD	Permanent	PBMNC	5,0E+06	Autologous	Coronary venous	≤1	PV loop	1				45.6 ± 12.6	48 ± 2.7	2.4 ± 5.76	24,64 ± 4,4	16,81 ± 3,3	-7,83 ± 2,46
Haider	2004	Pig	6	5	LCX	Permanent	Skeletal myoblast	3,0E+08	Xenogeneic	Intramyocardial	21	SPECT	3							31 ± 11,17	40,8 ± 6,62	9,8 ± 5,44
Halkos	2008	Pig	10	8	LAD	Ischemia/Reperfusion	MSC	3,7E+08	Allogeneic	Intravenous	≤1	Left ventriculography	4							44 ± 10,1	54,4 ± 11,3	10,4 ± 6,82
				8				1,1E+08													51,2 ± 6,85	7,2 ± 6,04
				7				3,9E+07													51,2 ± 10,6	7,2 ± 6,83
Hamamoto	2009	Sheep	10	6	LAD	Permanent	MSC	4,5E+08	Allogeneic	Intramyocardial	≤1	Echocardiography	2	102.8 ± 25.3	98.4 ± 19.6	-4.4 ± 17.89	89 ± 23.7	77.8 ± 20.6	-11.2 ± 17.19	13,7 ± 2,8	20,8 ± 7,8	7,1 ± 3,64
				8				2,3E+08							94 ± 13	8.8 ± 16.65		74.1 ± 9.9	-14.9 ± 15.39		20,9 ± 5,9	7,2 ± 2,74
				5				7,5E+07							84.6 ± 12.1	-18.2 ± 16.89		64.5 ± 9.2	-24.5 ± 15.54		23,6 ± 5,4	9,9 ± 3,00
				6				2,5E+07							85 ± 19.4	17.4 ± 17.85		65 ± 18.1	-24 ± 16.71		23,8 ± 7,3	10,1 ± 3,47
Hashemi	2008	Pig	7	8	LAD	Ischemia/Reperfusion	MSC	2,0E+07	Allogeneic	Transendocardial	3	MRI	2	175.77 ± 39.62	195.41 ± 43.42	19.64 ± 30.14	118.87 ± 29.46	129.33 ± 35.87	10.46 ± 23.08	32,04 ± 10,72	34,21 ± 6,17	2,17 ± 7,35
				8				2,4E+08							187.7 ± 20.86	11.93 ± 26.97		124.19 ± 23.7	5.32 ± 21.02		34,5 ± 7,65	2,46 ± 7,52
				8				4,4E+08							163.8 ± 31.2	-11.97 ± 28.19		110.18 ± 26.33	-8.69 ± 21.42		33,12 ± 9,44	1,08 ± 7,77
He	2005	Dog	5	6	LAD	Permanent	Skeletal myoblast	5,4E+08	Autologous	Transendocardial	33,4	Echocardiography	2							40 ± 1	47 ± 3	7 ± 1,30
				3	5	LAD			3,6E+08			Intramyocardial									40 ± 3	46 ± 2	6 ± 1,95
Jameel	2010	Pig	7	7	LAD	Permanent	MSC	5,0E+07	Allogeneic	Intramyocardial	≤1	MRI	3	22.2 ± 4.8	16.9 ± 1.8	-5.3 ± 1.94	14.1 ± 2.5	8.9 ± 2.3	-5.2 ± 1.28	35,7 ± 5	51,2 ± 4,8	15,5 ± 2,62
Jaussaud	2012	Pig	4	8	LCX	Permanent	MSC	0,0E+00	Xenogeneic	Intramyocardial	30	Echocardiography	3							48,395 ± 6,58	53,004 ± 10,21	4,609 ± 4,88
Jiang	2010	Pig	6	5	LAD	Ischemia/Reperfusion	BMSC	1,0E+07	Allogeneic	Intracoronary	≤1	MRI	2	63.3 ± 5.34	60.72 ± 6.12	-2.58 ± 3.50	35.15 ± 2.95	30.76 ± 4.32	-4.39 ± 2.28	44,39 ± 3,22	49,5 ± 3,05	5,11 ± 1,89
Jiang	2011	Pig	7	6	LAD	Ischemia/Reperfusion	MSC	1,0E+07	Autologous	Intracoronary	≤1	MRI	2	59.89 ± 5.15	59.05 ± 6.01	-0.84 ± 3.13	33.41 ± 2.22	30.1 ± 2.11	-3.31 ± 1.20	44,06 ± 3,04	48,82 ± 2,98	4,76 ± 1,67
Johnston	2009	Pig	7	7	LAD	Ischemia/Reperfusion	CDC	1,0E+07	Autologous	Intracoronary	28	MRI	3	58.6 ± 11.4	49.6 ± 11.4	-9 ± 6.09	37.5 ± 11.4	31.8 ± 11.6	-5.7 ± 6.14	37 ± 9,2	37,6 ± 11,4	0,6 ± 5,54
Kawamoto	2003	Pig	9	7	LCX	Permanent	EPC	1,0E+07	Autologous	Transendocardial	28	Echocardiography	1							33 ± 6	45 ± 6	12 ± 3,63
				8			PBMNC														33,8 ± 6,4	0,8 ± 3,62
Kim	2005	Pig	8	8	LAD	Permanent	USSC	1,0E+08	Xenogeneic	Intramyocardial	28	Echocardiography	2							51,1 ± 4,9	55,2 ± 6,3	4,1 ± 2,82
Ko	2011	Pig	6	6	LAD	Permanent	BMMNC	3,0E+07	Autologous	Intramyocardial	≤1	MRI	4	58.56 ± 3.66	51.84 ± 2.16	-6.72 ± 1.73	40.26 ± 5.49	25.92 ± 4.32	-14.34 ± 2.85	30,6 ± 5,2	45,5 ± 4,6	14,9 ± 2,83
Lee	2011	Pig	9	9	LAD	Ischemia/Reperfusion	CDC	1,0E+07	Autologous	Intramyocardial	28	Echocardiography	4	66.1 ± 12.9 *	65 ± 10.7 *	-1.1 ± 21.15	40.5 ± 11.8 *	34.7 ± 7.2 *	-5.8 ± 18.17	40 ± 7 *	47 ± 5 *	7 ± 11,09
				5			CSph								56.2 ± 7.8 *	-9.9 ± 19.84		31.8 ± 5.6 *	-8.7 ± 17.60		44 ± 5 *	4 ± 11,09
Leu	2011	Pig	6	6 *a*	LAD	Permanent	BMMNC	3,0E+07	Autologous	Intramyocardial	≤1	Echocardiography	2							45,2 ± 4	58,1 ± 3,6	12,9 ± 2,74
				6 *b*																	50 ± 3,7	4,8 ± 2,76
Li C.	2008	Pig	7	9	LAD	Ischemia/Reperfusion	BMMNC	3,5E+08	Autologous	Intracoronary	≤1	Echocardiography	2							59 ± 7	66 ± 7	7 ± 3,53
Li C.	2010	Pig	7	7	LAD	Ischemia/Reperfusion	EPC	1,2E+07	Autologous	Intracoronary	≤1	Echocardiography	1							59 ± 7	69 ± 8	10 ± 4,81
				9			BMMNC	3,5E+08												59 ± 7	66 ± 7	7 ± 4,41
Li S.	2008	Pig	10	10	LAD	Ischemia/Reperfusion	BMMNC	4,7E+07	Autologous	Intracoronary	≤1	Echocardiography	0							61,7 ± 3,91	64,5 ± 3,89	2,8 ± 2,14
				10			MSC	6,2E+05													64,25 ± 3,65	2,55 ± 2,10
Lim	2006	Pig	12	12	LAD	Ischemia/Reperfusion	MSC	1,0E+07	Allogeneic	Intracoronary	3	SPECT	1	66.5 ± 8.3	71.6 ± 3.7	-5.1 ± 2.62	42.7 ± 7.2	42.4 ± 6.7	-0.3 ± 2.84	36 ± 5,4	40,8 ± 6,8	4,8 ± 2,51
Lin	2010	Pig	8	8	LAD	Permanent	BMMNC	1,0E+08	Autologous	Intramyocardial	≤1	Echocardiography	4	147.5 ± 7 *	115 ± 5.7 *	-32.5 ± 9.03	103 ± 7 *	58.7 ± 2.4 *	-44.3 ± 7.4	45,2 ± 1,8 *	52,6 ± 2,1 *	7,4 ± 2,77
Lu	2012	Pig	8	8	LAD	Ischemia/Reperfusion	MSC	1,0E+08	Autologous	Coronary venous	7	Echocardiography	3							35,833 ± 7,5	47,708 ± 8,75	11,875 ± 4,07
Lu	2012	Pig	5	6	LAD	Ischemia/Reperfusion	MSC	3,0E+07	Autologous	Intracoronary	7	MRI	4	66.2 ± 5.2	64.6 ± 7.5	-1.6 ± 3.84	37.3 ± 7.6	32.9 ± 10.2	-4.4 ± 5.38	43,9 ± 7,6	50,1 ± 10,1	6,2 ± 5,34
Luan	2010	Pig	6	6	LAD	Permanent	MSC	2,0E+07	Autologous	Myocardial tunnels	≤1	SPECT	3	167.5 ± 4.5 *	149.8 ± 4.4 *	-17.7 ± 6.29	83.3 ± 7.6 *	61.5 ± 2.6 *	-21.8 ± 8.03	50,2 ± 5,3 *	58,9 ± 1,5 *	8,7 ± 5,51
Mäkelä	2007	Pig	7	7	LCX	Ischemia/Reperfusion	BMMNC	1,0E+08	Autologous	Intramyocardial	≤1	Echocardiography	4							61,2 ± 8,55	73,4 ± 9,36	12,2 ± 4,79
Makkar	2005	Pig	8	8	LAD	Permanent	MSC	2,0E+08	Allogeneic	Intramyocardial	28	Echocardiography	2							40 ± 13	49 ± 9	9 ± 5,59
Mazo	2012	Pig	9	7	LAD	Ischemia/Reperfusion	ADSC	2,1E+08	Autologous	Transendocardial	2	Echocardiography	4	86.16 ± 23.82	69.78 ± 19.38	-16.38 ± 10.80				55,79 ± 6,39	64,73 ± 5,14	8,94 ± 2,88
McConnell	2005	Sheep	6	5	LCX	Permanent	Skeletal myoblast	3,0E+08	Autologous	Intramyocardial	14	PV loop	1							28 ± 2 *	27 ± 4 *	-1 ± 4,47
Medicetty	2011	Pig	7	6	LAD	Ischemia/Reperfusion	MAPC	2,0E+08	Allogeneic	Transcoronary	2	Echocardiography	2				85.3 ± 7.5 *	90.0 ± 4.3 *	4.7 ± 11.45	30,8 ± 2,9 *	32,3 ± 1,4 *	1,5 ± 4,33
				6				2,0E+07									76.9 ± 10.6 *	-8.4 ± 15.00		37,1 ± 3,4 *	6,3 ± 5,33
Memon	2005	Dog	4	4	LAD	Permanent	Skeletal myoblast	1,0E+08	Autologous	Intramyocardial	14	Echocardiography	1							34,4 ± 5,4	47,4 ± 7,4	13 ± 5,96
				4			BMMNC	1,0E+08													55,3 ± 8,6	20,9 ± 6,35
				4			BMMNC	3,0E+06													44,4 ± 6,7	10 ± 5,75
Ménard	2005	Sheep	9	9	LCX	Permanent	ESC	3,0E+07	Xenogeneic	Intramyocardial	14	Epicardial echo	2							38,9 ± 7,3	42,4 ± 7,5	3,5 ± 3,49
Messas	2006	Sheep	7	6	LCX	Permanent	Skeletal myoblast	2,5E+08	Autologous	Intramyocardial	56	3D Echocardiography	3	111 ± 10.1	102.3 ± 12.5	-8.7 ± 6.37	75.4 ± 10.8	63.0 ± 7.1	-12.4 ± 5.01	33 ± 2,6	38 ± 2,4	5 ± 1,39

First author	Year	Animal	N (control)	N (treatment)	Location	Type of ischemia	Cell type	Dose	Cell source	Delivery route	Timing of treatment (days)	Endpoint assessment	Quality score	EDV(ml) control	EDV(ml) treatment	EDV Effect Size (ml)	ESV(ml) control	ESV(ml) treatment	ESV Effect Size (ml)	EF(%) control	EF(%) treatment	Effect Size
Moelker	2006	Pig	10	10	LCX	Ischemia/Reperfusion	BMMNC	5,0E+08	Autologous	Intracoronary	7	MRI	3	128 ± 23.3	133.8 ± 26.2	5.8 ± 13.31	70 ± 20	66 ± 12	-4 ± 9.72	47,2 ± 8,9	43,4 ± 7,7	-3,8 ± 4,67
				10			Bone marrow	5,0E+08							116.4 ± 14.5	-11.6 ± 11.38		78	8 ± 10.95		42,1 ± 5,1	-5,1 ± 4,29
Moelker	2007	Pig	6	6	LCX	Ischemia/Reperfusion	USSC	1,0E+08	Xenogeneic	Intracoronary	7	MRI	2	124.4 ± 8.9	151.1 ± 11.1	26.7 ± 5.81	66.1 ± 7	87 ± 10.4	20.9 ± 5.12	45,2 ± 6,1	41,7 ± 2,6	-3,5 ± 2,71
Niccoli-Asabella	2011	Pig	4	7	LAD	Permanent	BMSC	5,0E+07	Autologous	Intramyocardial	≤1	SPECT	2	9825 ± 1.7	87.7 ± 6.9	-10.55 ± 2.74	6.75 ± 3.3	43 ± 2.6	-20.75 ± 1.92	32,3 ± 2,6	50,9 ± 2,5	18,6 ± 1,61
Pätilä	2009	Pig	6	9	LCX	Permanent	Skeletal myoblast	2,0E+06	Autologous	Intramyocardial	14	MRI	2	102.54 ± 55.85	130.73 ± 94.77	28.19 ± 38.96	49.22 ± 38.7	63.16 ± 53.5	13.94 ± 23.83	52,45 ± 20,62	52,01 ± 14,4	-0,44 ± 9,69
Peng	2011	Pig	5	5	LAD	Ischemia/Reperfusion	MSC	1,6E+08	Autologous	Intracoronary	7	Echocardiography	4	69.89 ± 7.64	46.31 ± 6.18	-23.58 ± 4.39	19.68 ± 3.29	11.84 ± 2.96	-7.84 ± 1.98	68,63 ± 5,62	79,98 ± 5,86	11,35 ± 3,63
Perin	2008	Dog	6	5	LAD	Ischemia/Reperfusion	MSC	1,0E+08	Autologous	Intracoronary	7	Echocardiography	2							35,5 ± 3,3	36,6 ± 7,7	1,1 ± 3,94
				6						Transendocardial											48,8 ± 7,7	13,3 ± 3,68
Price	2006	Pig	8	7	LAD	Ischemia/Reperfusion	MSC	3,2E+08	Allogeneic	Intravenous	≤1	Left ventriculography	2							44 ± 4	49 ± 3	5 ± 1,81
Qi	2008	Pig	6	7 *c*	LAD	Ischemia/Reperfusion	MSC	1,0E+08	Autologous	Intracoronary	5	MRI	1							41,87 ± 2,45	56,85 ± 1,29	14,98 ± 1,50
				7 *d*										112.33 ± 3.93	102.5 ± 4.6	-9.83 ± 2.37	62.5 ± 1.05	46.67 ± 3.88	15.83 ± 1.53		51,2 ± 10,4	7,0 ± 5,4
Qian	2007	Pig	6	6	LAD	Ischemia/Reperfusion	BMMNC	1,0E+09	Autologous	Intracoronary	7	MRI	1	66.7 ± 5.3	63.3 ± 7.8	-3.4 ± 3.85	38.5 ± 7.3	31.5 ± 10.3	-7 ± 5.15	44,2 ± 8,2	51,2 ± 10,4	7,0 ± 5,41
Quevedo	2009	Pig	4	6	LAD	Ischemia/Reperfusion	MSC	2,0E+08	Allogeneic	Transendocardial	84	MRI	2							32,2 ± 4,7	41,3 ± 6,6	9,1 ± 3,58
Rigol	2010	Pig	4	6	LAD	Ischemia/Reperfusion	ADSC	2,3E+07	Autologous	Transendocardial	7	Intracardiac echo	1	34.1 ± 5.9	38.4 ± 13.9	4.3 ± 6.40	16.6 ± 3.2	17.7 ± 2.9	1.1 ± 1.99	51 ± 8	51 ± 12	0 ± 6,32
			4	5				1,6E+07		Intracoronary				27.3 ± 3.9	32 ± 4.8	4.7 ± 2.90	13.8 ± 1.3	16.2 ± 2.7	2.4 ± 1.37	49 ± 2	49 ± 10	0 ± 4,58
Sato	2011	Pig	5	8	LAD	Permanent	MSC	1,0E+07	Autologous	Intraventricular vein	28	Left ventriculography	3	30.8 ± 10.9	35.1 ± 13.6	4.3 ± 6.85				40,3 ± 6,8	44,6 ± 9,4	4,3 ± 4,50
Schneider	2009	Pig	8	6	LCX	Permanent	BMMNC	1,7E+07	Autologous	Transendocardial	14	Echocardiography	3	63.6 ± 8.3	59.3 ± 4.8	-4.3 ± 5.45	40.00 ± 8.10	34.51 ± 4.68	-5.49 ± 5.32	37,1 ± 2,4	41,8 ± 2,4	4,7 ± 1,77
				4			MSC	unknown	Allogeneic						57.7 ± 13.6	-5.9 ± 8.49		30.18 ± 13.29	9.83 ± 8.29		47,7 ± 2,3	10,6 ± 1,87
				5			MSC	unknown	Autologous						58.2 ± 10.2	-5.4 ± 6.83		31.89 ± 9.99	-8.11 ± 6.67		45,2 ± 2,1	8,1 ± 1,74
Schuleri	2008	Pig	6	9	LAD	Ischemia/Reperfusion	MSC	2,0E+08	Autologous	Transendocardial	2	MRI	3							30,2 ± 2	39,4 ± 7,8	9,2 ± 2,84
Schuleri	2009	Pig	6	6	LAD	Ischemia/Reperfusion	MSC	2,0E+08	Autologous	Intramyocardial	111	MRI	4							34,6 ± 12,5	54,9 ± 12,5	20,3 ± 8,84
Schuleri	2011	Pig	8	8	LAD	Ischemia/Reperfusion	MSC	2,0E+08	Autologous	Intramyocardial	84	MRI	2	65.1 ± 2.8 *	53.5 ± 4.6 *	-11.6 ± 5.24	48.3 ± 3.7 *	36.4 ± 4.1 *	-11.9 ± 5.52	27,8 ± 1,9 *	41,7 ± 3,3 *	13,9 ± 3,81
Sheu	2009	Pig	6	6 *b*	LAD	Permanent	BMMNC	3,0E+07	Autologous	Intramyocardial	≤1	Echocardiography	2							46,8 ± 4	50,0 ± 3,7	3,2 ± 2,76
				6 *a*																	58,1 ± 3,6	11,3 ± 2,74
Silva	2005	Dog	6	6	LAD	Permanent	MSC	1,0E+08	Allogeneic	Intramyocardial	30	Echocardiography	2							28,16 ± 13,22 *	48,22 ± 6,53 *	20,06 ± 14,74
Simioniuc	2011	Pig	7	7	LAD	Permanent	Placental MSC	1,0E+07	Xenogeneic	Intramyocardial	≤1	MRI	3	68.5 ± 4.5 *	75.58 ± 9.2 *	7.08 ± 10.24	24 ± 1.7 *	31.33 ± 7.6 *	7.33 ± 7.79	64,9 ± 1,5 *	59,5 ± 5,3 *	-5,36 ± 5,51
Thompson	2005	Pig	4	4	LAD	Permanent	BMMNC	3,0E+08	Autologous	Transvenous injections	28	Left ventriculography	2							34,3 ± 6,4	48,5 ± 3,6	14,2 ± 3,67
Tomita	2002	Pig	6	5	LAD	Permanent	BMSC	1,0E+08	Autologous	Intramyocardial	28	SPECT	2							37 ± 16	50 ± 9	13 ± 7,67
Valina	2007	Pig	7	7	LAD	Ischemia/Reperfusion	MSC	2,0E+06	Autologous	Intracoronary	≤1	SPECT	5							27,7 ± 6,3	29,3 ± 4,4	1,6 ± 3,76
				7			ADSC														30,2 ± 4,7	2,5 ± 3,81
Wang D.	2011	Pig	10	12	LAD	Ischemia/Reperfusion	MSC	3,0E+08	Allogeneic	Intracoronary	≤1	Left ventriculography	2							40,76 ± 6,48	49,52 ± 6,1	8,76 ± 2,70
Wang X.	2009	Pig	6	6	LAD	Ischemia/Reperfusion	MSC	5,0E+07	Allogeneic	Transcoronary	≤1	MRI	3							35,4 ± 3,2	46,3 ± 6,6	10,9 ± 2,99
Williams	2012	Pig	5	5	LAD	Ischemia/Reperfusion	CSC/MSC	2,0E+08	Xenogeneic	Intramyocardial	14	MRI	1	106.1 ± 21.17	95 ± 14.9	-11.1 ± 17.70	74.38 ± 20.52	53 ± 7.91	-21.38 ± 16.28	30 ± 4,61	43,8 ± 5,4	13,8 ± 4,31
				5			CSC	1,0E+06							109.2 ± 21.96	3.1 ± 19.11		67.2 ± 19.19	-7.18 ± 18.06		39,3 ± 8,36	9,3 ± 5,17
				5			MSC	2,0E+08							105.1 ± 23.99	-1 ± 19.60		67.4 ± 22.46	-6.98 ± 18.80		37,1 ± 8,32	7,1 ± 5,16
Wojakowski	2012	Pig	5	5	LAD	Ischemia/Reperfusion	BMMNC	unknown	Autologous	Intracoronary	≤1	Echocardiography	3							39,60 ± 0,57 *	52,84 ± 1,98 *	13,24 ± 2,06
Yang Y.	2009	Pig	6	6	LAD	Ischemia/Reperfusion	MSC	3,0E+07	Autologous	Intramyocardial	≤1	MRI	3	67.2 ± 6.6	65.2 ± 5.8	-2 ± 3.59	39.2 ± 7.3	38.5 ± 8.6	-0.7 ± 4.61	42 ± 7,1	41,3 ± 8,8	-0,7 ± 4,62
Yang Z.	2006	Pig	6	6	LAD	Permanent	MSC	5,0E+06	Autologous	Intracoronary	28	SPECT	1							30,3 ± 11,3	45 ± 6,6	14,7 ± 5,34
Yang Z.	2007	Pig	6	6	LAD	Permanent	BMSC	5,0E+06	Autologous	Intracoronary	28	SPECT	2							30,36 ± 2,76 *	47,78 ± 2,64 *	17,42 ± 3,82
Yang K.	2011	Pig	5	10 *e*	LAD	Ischemia/Reperfusion	MSC	1,4E+08	Autologous	Intracoronary	10,5	MRI	5	69.86 ± 7.64	48.68 ± 6.09	-21.18 ± 5.20	19.68 ± 3.29	13.47 ± 2.48	-6.21 ± 2.22	38,63 ± 5,62	46,35 ±5,61	7,72 ± 3,97
				10 *f*											46.31 ± 6.18	-23.55 ± 5.21		11.84 ± 2.96	-7.84 ± 2.28		48,98 ± 5,86	10,3 ± 4,01
Yi	2006	Pig	6	8	LAD		MSC	8,0E+07	Autologous	Transendocardial	28	Echocardiography	2							35,6 ± 10,4	47,3 ± 13,4	11,7 ± 6,36
Yokoyama	2006	Pig	5	6	LAD	Permanent	BMMNC	3,2E+09	Autologous	Coronary venous	≤1	PV loop	2	111.4 ± 7.1	95.6 ± 7.1	-12.8 ± 4.30				27,3 ± 3,3	36,7 ± 4,7	9,4 ± 2,42
				5							14			110.7 ± 8.6	101.4 ± 7.1	-9.3 ± 4.99				28,6 ± 3,6	37,1 ± 4,3	8,5 ± 2,51
Yu	2010	Pig	6	6	LAD	Permanent	MSC	1,0E+07	Autologous	Intracoronary	28	Echocardiography	1							35,94 ± 2,31 *	52,80 ± 3,21 *	16,86 ± 3,95
Zeng	2007	Pig	9	7	LAD	Permanent	pMultistemcell	5,0E+07	Allogeneic	Intramyocardial	≤1	MRI	3							30,4 ± 5,4	42,0 ± 6,5	11,6 ± 3,53
				6 *g*																	41,2 ± 5,0	10,8 ± 3,26
Zhang S.	2012	Pig	4	4 *h*	LAD	Permanent	EPC	5,0E+07	Autologous	Intramyocardial	28	Echocardiography	5	53.4 ± 5.2	42.8 ± 6.38	-10.6 ± 4.28	35.8 ± 5.8	26.3 ± 4.8	-9.5 ± 3.76	34,3 ± 4,5	38,8 ± 5,1	4,5 ± 3,40
			5	5 *i*							28			52.5 ± 3.8	41.7 ± 5.3	-10.8 ± 2.92	33.2 ± 5.4	25.3 ± 3.5	-7.9 ± 2.88	36,7 ± 1,7	39,3 ± 2,4	2,6 ± 1,32
			5	4 *h*							14			48.4 ± 4.6	37.4 ± 7.4	-11 ± 4.23	31.6 ± 1.8	23.6 ± 3.2	-8 ± 1.79	34,0 ± 3,0	45,1 ± 6,3	11,1 ± 3,42
			5	4 *i*							14			48.4 ± 8.4	29.1 ± 3.7	-19.3 ± 4.19	30.7 ± 6.8	13.7 ± 2.6	-17 ± 3.31	36,9 ± 3,6	53,0 ± 3,1	16,1 ± 2,23
			4	3 *h*							≤1			51.3 ± 3.9	40.6 ± 7.2	-10.7 ± 4.59	33.6 ± 1.5	24.9 ± 3	-8.7 ± 1.89	34,6 ± 1,1	39,0 ± 3,8	4,4 ± 2,26
			5	4 *i*							≤1			48.8 ± 7.6	36.1 ± 5.3	-12.7 ± 4.31	29.8 ± 3.1	20.1 ± 1.9	-9.7 ± 1.68	35,4 ± 1,7	44,8 ± 5,1	9,4 ± 2,66
Zhang S.	2007	Pig	5	5 *h*	LAD	Permanent	BMSC	5,0E+07	Autologous	Intracoronary	14	Echocardiography	2							41,4 ± 5,2	58,6 ± 1,8	17,2 ± 2,46
			5	5 *j*																43,8 ± 1,8	66,4 ± 5,2	22,6 ± 2,46

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.



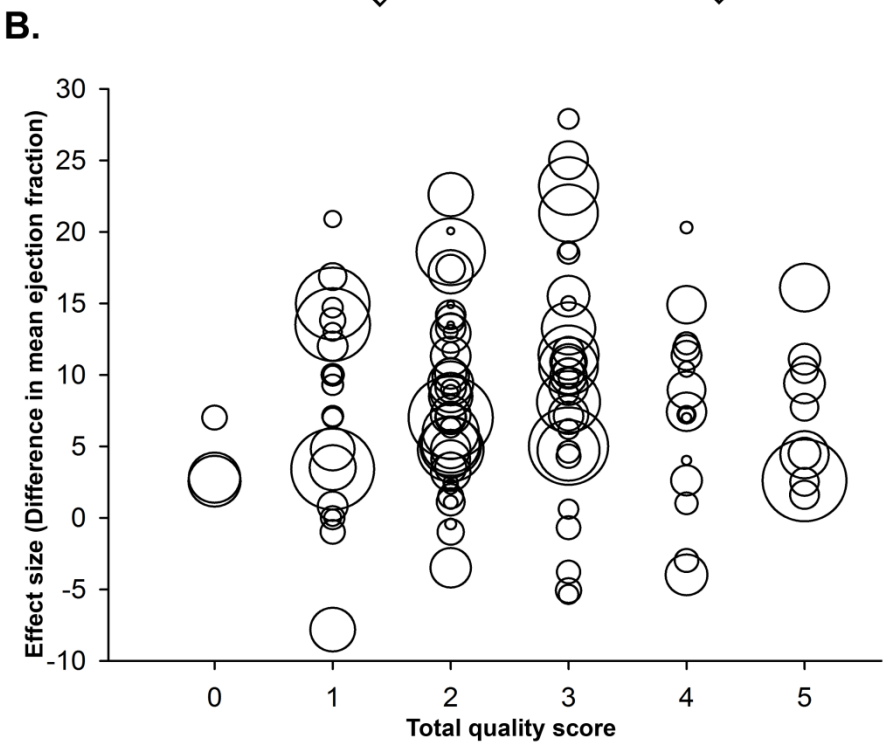
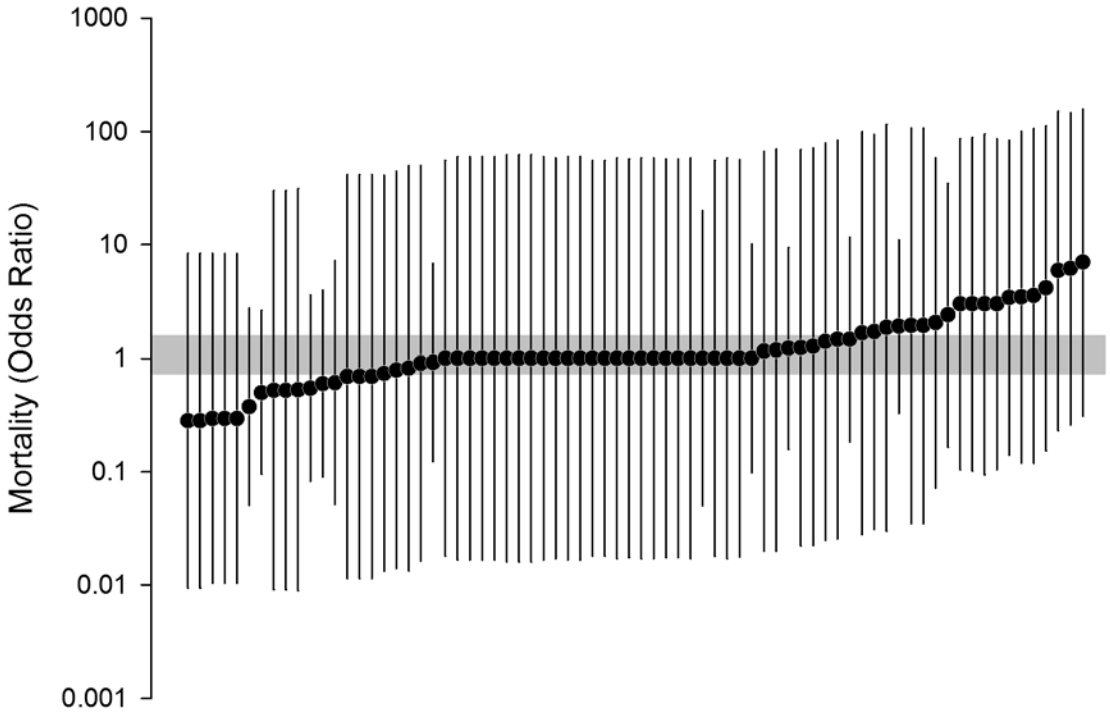


Figure III: Mortality.

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



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