Preclinical systematic review & meta-analysis of cyclosporine for the treatment of myocardial ischemia-reperfusion injury

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Background: Though best known for its immunosuppressant effects, cyclosporine A (CsA) has also been studied as a treatment to mitigate ischemia-reperfusion injury (IRI) by its inhibition of the mitochondria permeability transition pore (mPTP). Despite numerous preclinical studies supporting its benefit in reducing infarct size following myocardial IRI, large randomized controlled clinical trials have been unable to show a beneficial effect. Exploring existing preclinical data can give us the opportunity to revisit some the assumptions that may have led to the failure of these studies to translate clinically. Herein, we present a systematic review of preclinical studies testing CsA to attenuate myocardial IRI (PROSPERO CRD42020159620).

Methods: We conducted a systematic search of health research databases Ovid MEDLINE, Ovid EMBASE, Web of Science BIOSIS, and Scopus, as well as Cochrane and PROSPERO systematic review databases, on March 9, 2022 for non-human *in vivo* animal studies of myocardial IRI, using CsA as a treatment that reported clinically relevant outcomes. Bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation's risk of bias tool and a modified Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies checklist. Sub-group meta-analyses were conducted to identify potential factors influencing outcomes.

Results: We identified 71 studies, 59 of which were studies of coronary occlusion. Overall, 75% of studies reported a clear positive effect of CsA in mitigating myocardial IRI by some clinically relevant parameter (e.g., infarct size). A meta-analysis including 43 coronary occlusion studies showed an overall reduction in infarct size with CsA treatment (16.09%; 95% CI: –18.50% to –13.67%). Subgroup meta-analyses identified species, age, timing of administration, and duration of ischemia as factors potentially affecting the efficacy of CsA in the setting of myocardial IRI.

Conclusions: Our systematic review and meta-analysis identifies questions that have yet to be answered by preclinical studies, highlighting important differences between these and clinical studies that should be addressed prior to proceeding with any further clinical studies using CsA to treat IRI in the heart or other

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organs. We also use the example of CsA to highlight general considerations for researchers attempting to translate animal studies into the clinical setting.

Keywords: Meta-analysis; systematic review; ischemia-reperfusion injury (IRI); preclinical models; cyclosporine A (CsA)

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Introduction

Cyclosporine A (CsA) was first isolated in 1970 at Sandoz laboratories from a fungus found in a Norwegian soil sample (1). Sandoz had been trying to identify novel antibiotic compounds, but, in screening this compound, discovered that it had the ability to neutralize cytotoxic T cell activity *in vitro* (2). Subsequent *in vivo* studies further demonstrated its ability to suppress both antibody- and cellmediated immunity (2). By the late 1970's, CsA had been shown to promote graft survival in animal models of heart and kidney transplantation (3,4). This quickly led to clinical trials, which found similar benefits in human transplant recipients (5). This, combined with its low toxicity, led to CsA become the immunosuppressant drug of choice in the early days of solid organ transplantation and enabled the expansion of transplant programs worldwide.

The immunosuppressant effect of CsA is a result of calcineurin inhibition (6). Calcineurin is a phosphatase, whose activation of certain transcription factors leads to the upregulation of interleukin-2 and other cytokines important for initiating the T cell response. A secondary effect of CsA on mitochondria membrane permeability was later described by researchers trying to understand the mechanism behind CsA nephrotoxicity (7). It was discovered that CsA can bind to cyclophilin D, part of the mitochondria permeability transition pore (mPTP), preventing its opening during times of increased oxidative stress, which could otherwise lead to mitochondrial swelling, disruption of the electron transport chain, and eventual rupture (8).

Researchers soon realized that this property of CsA could mitigate ischemia-reperfusion injury (IRI) caused by transient loss of blood flow to an organ or tissue. This was demonstrated in animal models involving various organs, including the heart and kidney (9,10). There was particular interest in using CsA to protect the myocardium from IRI following revascularization, such as after coronary artery thrombosis.

Despite promising studies in animals, attempts to translate findings into the clinical realm produced mixed results. An initial pilot randomized controlled trial (RCT) of 58 patients conducted across several hospital in France found that CsA given at 2.5 mg/kg at the onset of reperfusion in patients undergoing percutaneous coronary intervention (PCI) led to smaller infarct size and decreased creatinine kinase (CK) levels (11). However, the subsequent larger trial involving 970 patients failed to show any clinical benefit and found that CsA did not reduce the risk of adverse left ventricular remodeling at 1 year (12).

In order to better understand the failure of CsA to translate clinically, it is worthwhile to return to the preclinical studies that informed clinical trials. The purpose of this review is to summarize evidence in the preclinical literature for the benefit of CsA in IRI. In addition to elucidating possible reasons for the failure of preclinical studies to translate into the clinical realm, we sought to identify gaps that should be addressed before moving forward with any further clinical studies aiming to use CsA to mitigate IRI in the heart or other organs. Our search included models of IRI in any organ; however, in this article we will summarize only cardiac studies to allow for a more in-depth analysis. We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-618/rc).

Methods

Database & literature search strategies

The proposed systematic review was prospectively registered in the online international registry PROSPERO (www.crd.york.ac.uk/prospero/) with the unique ID CRD42020159620. Searches were conducted on March 9, 2022 by a health librarian/expert searcher (SC) of the health research databases Ovid MEDLINE, Ovid EMBASE, Web

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of Science BIOSIS, and Scopus, as well as the Cochrane Database of Systematic Reviews and the PROSPERO database of systematic review protocols. Keywords and controlled vocabulary (e.g., MeSH, EMTREE) were used to identify studies related to the concepts: "reperfusion injuries" and "cyclosporin". *In vitro* studies were excluded. No other limits were applied. Searches were adjusted appropriately for each database. Results were exported to Covidence review management software (www.covidence. org) and duplicates were automatically removed. A detailed search strategy is included in the Appendix 1.

Eligibility criteria

The primary aim of the review was to include all nonhuman in vivo animal studies of IRI, using CsA as a treatment. There was no exclusion of studies based on species, language, date of publication or type of publication (e.g., paper, brief communication, abstract). Nonexperimental publications, as well as in vitro and ex vivo (i.e., isolated perfused organs) studies were excluded. Studies were excluded if they did not have an appropriate control group for comparison (i.e., ischemia-reperfusion alone) or if CsA was used for another indication (e.g., at high doses to cause nephrotoxicity). Studies not reporting clinically relevant outcomes were also excluded. Clinically relevant outcomes were taken as routine serum biochemistry (e.g., troponin, creatinine, lactate, liver transaminases), infarct size, histological assessment of injury, organ function, and survival. Human studies were excluded last, with the intention for them to be analyzed separately if appropriate. Different publications presenting identical data (e.g., conference abstracts and full-length papers by the same authors) were excluded, however, publications presenting non-identical data from the same authors were included to minimize the risk of publication bias.

Studies were reviewed in two stages. First, a title and abstract review was conducted independently by two reviewers (JH and BAMG). This was followed by a full text review, applying the same inclusion/exclusion criteria. Conflicts were resolved by means of consensus between the two reviewers.

Data extraction

Data was retrieved from selected studies by a single reviewer (JH). Data extracted included animal characteristics (species, strain, sex, age, number per group), experimental

characteristics (dose of CsA, timing of drug administration, duration of ischemia, blood vessel occluded), and animal outcomes (infarct size, biochemical markers of injury, histological evidence of injury, markers of organ function, survival). Data was extracted manually from graphs if it was not listed explicitly.

Quality assessment

Bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) risk of bias tool, as well as a modified Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist (13,14). Though any type of publication was included in our review, only full-length articles were assessed for bias, as this was impractical for conference abstracts and brief reports due to their lack of detail.

Statistical analysis

Meta-analysis was conducted using RevMan 5 software (Cochrane). Only coronary occlusion studies reporting infarct size were included, as this was the most common study design and most common reported outcome. Results were reported as weighted mean differences since all studies used the same unit measure (percentage of area at risk). Results from abstracts were included in the analysis only if there were no subsequent full-length publications of the same study (to avoid duplication of results). Different treatment groups within the same study were treated separately. A random effects model was chosen due to the statistical and methodological heterogeneity of the studies. Subgroup meta-analyses were planned based on age, sex, species, dose, timing of administration, and ischemia duration, if appropriate.

Results

Study inclusion

The PRISMA diagram for the systematic review is presented in *Figure 1*. Our initial search yielded 2,070 unique records. At the abstract review phase, the kappa score between reviewers was 0.98, indicating almost perfect agreement. After abstract screening, 625 studies remained for full text review, 164 of which were ultimately included as preclinical studies. The full text of 67 studies could not be found despite extensive searching through online databases



Figure 1 PRISMA diagram for systematic review of preclinical studies of cyclosporin A for the treatment of IRI. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; IRI, ischemia-reperfusion injury.

and physical records. The majority of these were either conference abstracts (37/67) or from smaller, non-English language journals (12/67). The numbers of included studies were further broken down by organ. Given the high number of records identified, this article will deal with only cardiac IRI, which includes 71 total studies (see Appendix 1 for full list of included articles).

Risk of bias assessment

Risk of bias was assessed using SYRCLE's risk of bias tool, as well as a modified CAMARADES checklist. Using SYRCLE's tool, the majority of categories had either high or unclear risk of bias across studies (*Figure 2A*). The risk of bias being unclear was mainly due to studies lacking sufficient detail about procedures, such as randomization, allocation concealment, and handling of baseline characteristics. We found low risk of bias related to selective outcome reporting. Though no study had a prespecified protocol available, we did find that the majority of studies were consistent in reporting all outcomes described in the methods. We also found that studies were largely free of other important sources of bias, such as contamination, unit analysis error or the inappropriate influence of funders. Results from the CAMARADES checklist (*Figure 2B*) additionally highlighted other potential areas of bias, such as lack of sample size calculation, unclear conflicts of interest, and confirmation of ischemia.

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Figure 2 ROB assessment of full-length articles. (A) ROB assessment using the SYRCLE's risk of bias tool. (B) ROB assessment using a modified CAMARADES checklist. ROB, risk of bias; SYRCLE, Systematic Review Centre for Laboratory Animal Experimentation; CAMARADES, Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies.

Study characteristics

Of the 71 cardiac studies identified, 13 (18%) were conference abstracts, while 58 (82%) were full-length articles. The majority of cardiac studies (59/71, 83%) used a model of coronary artery occlusion, most commonly occlusion of the left anterior descending artery (36/59, 61%) (Appendix 1). Other models included cardiac arrest, cardiopulmonary bypass (CPB), hypoxia, and one study of CsA for the treatment of IRI in cardiac transplantation

(Appendix 1).

Studies employed a variety of animals, including mice, rats, rabbits, pigs, and sheep. However, rats were the most common animal, used in 42% of studies (30/71). CsA was most commonly administered as a single dose, intravenously or intraperitoneally, though several studies either pretreated the animal with CsA for several days prior or continued dosing CsA up to 24 hours post-ischemia. Doses ranged from 0.25 to 40 mg/kg, with 10 mg/kg being the most

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common, used in 51% (36/71) of studies. Regarding studies of myocardial IRI through coronary artery occlusion, the most common duration of ischemia was 30 minutes [59% (35/59) of studies], though ischemic times ranged from 5 to 90 minutes. The majority of studies administered CsA during the period of myocardial ischemia [58% (34/59)]. Fewer studies administered CsA prior to myocardial ischemia [22% (13/59)] or following reperfusion [i.e., postischemia; 12% (7/59)], while a minority administered CsA both before and after myocardial ischemia (multiple doses) or during and after myocardial ischemia (multiple doses or continuous infusion).

Study outcomes

Overall, 75% (53/71) of the studies reported a clear positive effect of CsA in mitigating myocardial IRI by some clinically relevant parameter, such as infarct size, serum troponin, or cardiac function parameters (e.g., cardiac output, cardiac index). However, some studies testing multiple doses reported no positive effect with the lowest tested dose. Coronary artery occlusion studies most commonly reported infarct size [reported in 93% (55/59) of studies], given as the percentage of the myocardium at risk. Of these, 80% (44/55) reported a reduction in infarct size with CsA. Serum troponin and/or CK or cardiac function parameters (e.g., cardiac output or cardiac index) were less commonly reported with coronary occlusion studies. Only 2 of the 4 studies testing CsA in cardiac arrest showed positive effects on cardiac parameters following resuscitation and only 2 of the studies testing CsA in CPB reported post-CPB cardiac output, with no observed benefit. Three studies of anoxia in a piglet model reported a positive effect of CsA in post-hypoxia cardiac function and troponin, though they were all published by the same group. A minority of studies (4%, 3/71) reported histologic findings exclusively.

Meta-analysis of coronary artery occlusion studies

Combining the results of all suitable coronary artery occlusion studies (43/59), we found an overall positive effect of CsA administration in reducing infarct size, with a combined reduction of 16.09% (95% CI: 13.67% to 18.50%) of infarct size as a percentage of the area at risk (*Figure 3*). Statistical heterogeneity between studies, however, was found to be high (I^2 =89%), suggesting this effect may be due to study differences rather than a true effect of the treatment. This is similarly reflected in the

funnel plot (*Figure 4*), whose asymmetry may be explained, in part, by statistical heterogeneity.

Subgroup analysis was undertaken to uncover the potential effects of various study differences. We performed meta-analyses grouping studies by species, sex, age, dose, and ischemia time. A similar overall effect was seen between mouse, rat, and rabbit studies (Appendix 1). However, the effect of CsA became non-significant (P=0.08) when considering only porcine studies (Figure 5A). The five porcine studies also had lower statistical heterogeneity $(I^2=48\%)$ compared to the other species subgroups. Similarly, the effect of CsA disappeared when considering studies that included only female animals (P=0.88), though this subgroup included only three studies (Appendix 1). Combining studies including older animals (rodents 20-24 months) likewise showed a non-significant effect (P=0.14), though this was not statistically different from the combined effect seen in studies containing young animals (P=0.48) (Figure 5B).

Studies administering CsA prior to ischemia showed a greater reduction in infarct size (22.86%; 95% CI: 17.73% to 27.98%) compared to those administering CsA during or after ischemia (Appendix 1). The test for subgroup differences was statistically significant (P=0.01). A subgroup meta-analysis of studies by dose likewise showed a greater reduction in infarct size with doses ≥ 12.5 mg/kg (22.36%; 95% CI: 17.26% to 27.46%), however this effect was not statistically different from other subgroups (P=0.09) (Appendix 1). The overall effect of CsA on infarct size reduction was lower in studies with ischemic times greater than 40 minutes (8.63%; 95% CI: 4.25% to 13.01%) compared to other studies (P=0.002), but still remained positive (P=0.0001) (Figure 5C, Appendix 1). Despite differences observed between subgroups, heterogeneity within most subgroups remained high ($I^2 > 70\%$).

Discussion

In this systematic review of preclinical studies administering CsA to mitigate myocardial IRI, we found that the majority of studies reported a clearly positive effect on various clinically relevant parameters. A meta-analysis of 43 studies utilizing coronary artery occlusion demonstrated an overall reduction in infarct size with the use of CsA (*Figure 3*). In stark contrast, several clinical studies have been conducted with weak or non-effective benefit (12,15). Understanding this discrepancy between positive results in small and large animals and negative results in clinical practice is vital.

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	Exp	eriment	al	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	1.8%	-15.00 [-21.12, -8.88]	
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]	
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]	
Boengler et al. 2010	50	11 10	10	61	12		1.5%	-11.00 [-20.89, -1.11]	
Choi et al. 2017 De Baulie et al. 2013 (befere)	30.10	11.18	4	54.17	13.5	4	1.0%	-18.01 [-35.19, -0.83]	
De Paulis et al. 2013 (belore)	23.9	14.5	7	59.4	7.4	7	1.3%	-35.50 [-47.43, -23.57]	
Eancelli et al. 2014	32.2	14 1	8	57 3	18.1	8	1.0%	-24 70 [-40 60 -8 80]	
Fand et al. 2014	24 4	33	12	47.5	4.2	12	2.0%	-23 10 [-26 12 -20 08]	-
Gomez et al. 2005	51	12	6	77	12	6	1.2%	-26 00 [-39 58 -12 42]	
Gomez et al. 2008	35	14	8	58	15	9	1.2%	-23.00 [-36.799.21]	
Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.0%	-11.30 [-15.38, -7.22]	-
Huang et al. 2014 (1mg/kg)	35.29	1.52	8	45	2.07	8	2.1%	-9.71 [-11.49, -7.93]	-
Huang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2.1%	-15.95 [-17.98, -13.92]	-
Huang et al. 2014 (5mg/kg)	26.9	1.86	8	45	2.07	8	2.1%	-18.10 [-20.03, -16.17]	-
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	1.8%	-19.60 [-25.60, -13.60]	
Huhn et al. 2010	61	9	7	58	6	7	1.7%	3.00 [-5.01, 11.01]	
Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]	
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.4%	-6.20 [-17.11, 4.71]	
lkeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]	
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]	
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.8%	2.00 [-4.86, 8.86]	
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	-	8	1.6%	-19.00 [-27.46, -10.54]	
Ikeda et al. 2016 (2.5mg/kg)	49	10	8	51	-	8	1.6%	-2.00 [-10.46, 6.46]	
Ikeda et al. 2016 (2.5mg/kg NP)	31	10	8	51	7	8	1.6%	-20.00 [-28.46, -11.54]	
Ikeda et al. 2016 (25mg/kg)	32	10	0	51	7	0	1.0%	-19.00 [-27.46, -10.54]	
Ikeda et al. 2021 (Somin)	55	10	0	23	4	0	1.0%	-20.00 [-20.40, -11.54]	
Kadeson et al. 2010	10	14	12	11	16	15	1.9%	8 00 [-12:00, -2:00]	
Karlsson et al. 2012	51	21	12	54	20	11	1.4%	-3 00 [-19 76 13 76]	
Kiss et al 2016	45.9	6.3	7	63.8	11.6	8	1.6%	-17 90 [-27 19 -8 61]	
Laudi et al. 2007 (12.5mg/kg)	30	21	4	57	16	4	0.6%	-27.00 [-52.87, -1.13]	
Laudi et al. 2007 (5mg/kg)	51	16	4	57	16	4	0.7%	-6.00 [-28.17, 16.17]	
Leshnower et al. 2008	39	10	12	60	8	15	1.8%	-21.00 [-27.96, -14.04]	
Lie et al. 2010	47.3	15.7	19	51.4	16.5	19	1.5%	-4.10 [-14.34, 6.14]	
Li et al. 2012	35.2	9.3	7	59.8	8.7	7	1.6%	-24.60 [-34.03, -15.17]	
Li et al. 2014	26.1	6.1	6	42.3	3.9	6	1.9%	-16.20 [-21.99, -10.41]	
Lim et al. 2007	32	7	6	48	10	6	1.5%	-16.00 [-25.77, -6.23]	
Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.4%	-2.30 [-13.62, 9.02]	
Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.6%	-22.60 [-31.17, -14.03]	
Matsubara et al. 2010 (after ischemia)	39.6	3.6	4	53.4	5	7	1.9%	-13.80 [-18.92, -8.68]	
Matsubara et al. 2010 (before ischemia)	39.1	4.2	6	53.4	5	7	1.9%	-14.30 [-19.30, -9.30]	
Nagaoka et al. 2015	56	5	7	72	9	7	1.7%	-16.00 [-23.63, -8.37]	
Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.6%	-19.90 [-29.05, -10.75]	
Niemann et al. 2002 (10mg/kg)	12.0	28	4	58	12	4	0.5%	-35.00 [-64.85, -5.15]	
Niemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.0%	-44.10 [-61.37, -26.83]	
Niemann et al. 2002 (25mg/kg)	25	14.0	4	50	12	4	0.9%	-41.00 [-09.02, -22.40]	
Nikolaou et al. 2002 (Sing/kg)	25 17	20	4 7	48	6	7	1 0%	-23.00 [-51.00, 5.00]	
Pagel & Krolikowski 2009	42	2.0	6	46	5	6	1.9%	-4 00 [-9 66 1 66]	
Ranii et al. 2009	39 1	44	6	53.4	47	7	1.9%	-14 30 [-19 25 -9 35]	
Rusinkevich et al. 2019	45	13	11	31	9	11	1.6%	14.00 [4.66, 23.34]	
Shintani-Ishida et al. 2012 (before ischemia)	28	18	6	55	13	6	0.9%	-27.00 [-44.77, -9.23]	
Shintani-Ishida et al. 2012 (during/after ischem)	16	13	6	55	13	6	1.1%	-39.00 [-53.71, -24.29]	
Skyschally et al. 2010	25	6	4	35	6	4	1.7%	-10.00 [-18.32, -1.68]	
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	1.9%	-6.00 [-11.66, -0.34]	
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	1.9%	-23.00 [-27.67, -18.33]	
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.8%	-45.00 [-51.45, -38.55]	
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.0%	-36.00 [-40.08, -31.92]	
Wang et al. 2006	25	3	7	44	4	7	2.0%	-19.00 [-22.70, -15.30]	
Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	1.9%	-18.50 [-23.62, -13.38]	
Youcef et al. 2015	13	5	6	35	8	6	1.7%	-22.00 [-29.55, -14.45]	
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.0%	-7.60 [-11.16, -4.04]	-
Zhu et al. 2013	51.1	10.4	8	55.4	10.9	8	1.5%	-4.30 [-14.74, 6.14]	
T. () (05% O)			40.1			100	100.001	10 00 1 10 70 11	▲
l otal (95% Cl)			481			490	100.0%	-16.30 [-18.59, -14.01]	
Heterogeneity: Tau ² = 64.71; Chi ² = 556.12, df =	63 (P < (0.00001)	; $ ^2 = 8$	9%					-50 -25 0 25 50
lest for overall effect: ∠ = 13.93 (P < 0.00001)									Favours [experimental] Favours [control]

Figure 3 Forrest plot showing the effect of CsA treatment on infarct size. CsA, cyclosporine A.

Importantly, subgroup meta-analyses suggest that the effect of CsA may differ based on species, sex, age, timing of administration, and ischemia duration.

The findings of these multiple studies contrast with clinical trials, which have shown mixed results at best. The largest trial, published by Cung *et al.* (12) in 2015, included 970 patients with presenting with anterior ST-elevation myocardial infarction (STEMI) undergoing

PCI randomized to receive 2.5 mg/kg of CsA or placebo immediately prior to reperfusion. They found that CsA conferred no benefit on multiple clinical parameters, including death, worsening heart failure, and left ventricular remodeling. The concurrently run trial (using the same dose), published by Ottani *et al.* (15) in 2016, which included 410 STEMI patients undergoing PCI, similarly found no difference in multiple cardiac-specific outcomes, Page 8 of 11

0 0 0 8 00 4 0 0 de 0 00 00 Standard error 8 0 0 C 0 0 0 0 12 0 C \cap 16 20 50 -25 0 25 -50 Mean difference (% area at risk)



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including ST-segment resolution, serum troponin, and left ventricular ejection fraction.

There are notable differences between these trials and the preclinical studies identified by our search, such as animal age, health, CsA dose, duration of ischemia, and timing of dose, as well as species differences (i.e., humans versus research animals) that could potentially explain the discrepancies in outcomes. Animal age was not commonly reported for rabbits or pigs, but most rodent studies used animals between 8 and 12 weeks old, which is roughly equivalent to a young adult or even adolescent human (16). In both of the large RCTs testing CsA in reperfusion following STEMI, the average age of patients was close to 60 (12,15). Only three studies were identified that used older animals (rodents aged 20–24 months), two of which



Figure 5 Combined effect of CsA on infarct size for coronary occlusion studies of different subgroups compared with the combined effect from all coronary occlusion studies (for which the subgroup variables were known). (A) Effect of CsA on infarct size in studies using porcine models. (B) Effect of CsA on infarct size in studies using old animals. (C) Effect of CsA on infarct size in studies in which duration of ischemia was greater than 40 minutes. CsA, cyclosporine A.

showed no effect of CsA on infarct size (17-19). While Cung et al. (12) did include a subgroup analysis of patients older and younger than 75, which showed no difference in clinical outcomes, patients in the younger group were still quite a bit older, relative to the animals used in preclinical studies. Furthermore, the animals used in these studies were typically disease free. Only one study was identified that tested the ability of CsA to reduce infarct size in a comorbid animal (pre-diabetic, obese Zucker rats) and found no effect on infarct size (20). In contrast, participants in the clinical trials by Cung et al. and Ottani et al. were often co-morbid, with type 2 diabetes and hypertension being common, as well as being overweight (12,15). While young, healthy animals may be appropriate for initial investigations, moving toward an animal model that is more representative of the clinical population to which the intervention would likely be applied should be considered prior to proceeding with costly clinical trials.

Our meta-analysis of subgroups divided by species suggested that CsA could be less effective in pigs (Figure 4). This is somewhat confounded by the fact that all of the pig studies used mixed sex or female only animals. However, it does highlight the importance of considering species differences when interpreting preclinical studies. For pharmacological interventions, particular attention should be paid to the specific pathways of metabolism for the drug of interest. CsA is metabolised by the cytochrome P450-3A family of enzymes (21). Not only does the kinetic activity of cytochrome P450 (CYP450) enzymes differ between animals and humans, it appears that there is no one animal whose CYP450 enzymatic activity best matches that of humans across multiple metabolites (22). This does not even take into consideration differences between individuals, which is likely more pronounced in human populations than the inbred animal strains used for most biomedical research. Seeing a consistent effect across a variety of species and strains increases confidence that the intervention will work in human studies.

Grouping studies by duration of ischemia, we found that the effect of CsA in reducing infarct size was significantly reduced for ischemic times longer than 40 minutes. Average ischemic times in the studies by Cung *et al.* and Ottani *et al.* were 4.5 and 3 hours, respectively (12,15). In both studies, more than 80% of patients had no flow through the occluded vessel [i.e., thrombolysis in myocardial infarction (TIMI) score of 0], as was the case in all but one of the animal studies identified. In clinical practice, it is rare to have ischemia of such short duration in acute coronary thrombosis, given the time that is taken for patients to present, diagnosis to occur, and treatment to be initiated. Though a target of 90 minutes from presentation to PCI is recommended by the American Heart Association, shorter time to reperfusion (e.g., less than 60 minutes) has been shown to be associated with decreased mortality (23). Similarly, we did find a significant difference between subgroups divided by timing of administration, with dosing prior to ischemia being more effective at reducing infarct size. This is relevant, as it would be impossible to administer CsA prior to unexpected ischemia as occurs in the setting of myocardial infarction (MI), but CsA could be given prior to known periods of ischemia, such as during cardiac surgery or transplantation.

It is worth noting that our subgroup meta-analysis did not suggest an effect based on dose. All clinical trials of CsA have used doses of 2.5 mg/kg, while preclinical studies tended to use higher doses (with 10 mg/kg being most common). The overall effect from studies using doses of 12.5 mg/kg or more showed greater reduction in infarct size, however, this was not significantly different from other subgroups. This was true even after eliminating studies using nanoparticle formulations, which tended to show greater benefit with lower doses (24,25). It may be that for this particular drug the effect on mitochondria is not gradational, but rather exhibits more of a threshold effect, below which it is ineffective (or at least a very narrow range in which increased doses will result in increased effect).

As alluded to previously, the goal of this systematic review is largely hypothesis generating. The suggestions gleaned from meta-analyses of subgroups should be understood within certain limitations. An important caveat for interpreting the results of the meta-analyses is the high degree of statistical heterogeneity observed between studies, which remained largely unchanged despite grouping studies according to several different methodological considerations. It does not appear that the heterogeneity can be entirely explained by dose, timing of administration, duration of ischemia or species (though the heterogeneity for porcine studies was low). It may be a result of a combination of these factors. Methodology is another consideration to explain heterogeneity in results, especially given the high degree of variation in their results compared to others. The majority of studies purported to be measuring infarct size by injecting Evans blue dye, which is a well-established technique, though may lead to variability

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in unskilled hands. Particularly with preclinical studies, there is always the concern for publication bias, which can contribute to heterogeneity. As well, selective reporting of results (i.e., omitting negative results) could also be a factor and is not easily detectable in preclinical studies.

Another important limitation is the high risk for bias seen in these studies. Animal studies are typically far less diligent in following standard practices that are commonly used to minimize bias in clinical trials (e.g., randomization, allocation concealment, blinding during analysis) (26). They are also less detailed in their description of methods taken to minimize bias. For instance, while several studies indicated that they randomized animals, they did not include sufficient detail to judge whether this was properly done (e.g., using a random number table or generator, as opposed to assigning every other animal to a group). It is important to encourage the implementation of these biasreducing methods in preclinical studies, as this will, not only increase confidence in study results, but reduce the chance of obtaining false positive results.

We would like to acknowledge a systematic review posing a similar question, published by Lim *et al.* in 2012 (27). They similarly found an overall positive effect, while commenting on several discrepancies, such as between species. In addition to updating and broadening the search results, which resulted in the addition of 23 studies for meta-analysis, we have added extended subgroup metaanalyses. As well, we now have the opportunity to interpret the findings of our systematic review and meta-analysis in light of the data from several large clinical trials.

Overall, our systematic review identified multiple preclinical studies that tested CsA for the treatment of myocardial IRI. Their indication of an overwhelmingly positive effect is in contrast with the results from clinical studies. Our meta-analysis identified several factors that potentially contributed to these discrepancies. It may not be worthwhile to further explore these in animal studies of myocardial ischemia, given that the clinical trials have already been conducted. However, our findings highlight the potential pitfalls of translating the results of preclinical studies that should be considered prior to initiating clinical trials.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm. amegroups.com/article/view/10.21037/atm-22-618/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1

Detailed Search Methods

Ovid MEDLINE(R) ALL <1946 to March 08, 2022>

#	Search Statement	Results
1	exp Reperfusion Injury/	46662
2	(((reperfus* or IR or hypoxi* ischemi*) adj3 (injur* or damag* or necrosis or necrotic or hemorrhag* or haemorrhag* or (free adj2 radical*))) or ((hypox* or hemorrhagic) adj3 shock)).mp. or exp Shock, Hemorrhagic/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	81057
3	1 or 2	81955
4	exp Cyclosporine/ or cyclosporin.ti,ab. or cyclosporine.ti,ab.	57197
5	("csa neural" or csaneoral or "cya nof" or "ol 27 400" or "ol 27400" or sandimmun).ti,ab.	344
6	("adi 628" or adi628 or equa or "cgc 1072" or cgc1072 or ciclomulsion or cicloral or cipol or consupren or cyclasol or cyclokat or "de 076" or de076 or deximune or equoral or gengraf or ikervis or iminoral or implanta or imusporin or "lx 201" or lx201 or "c2 03" or mc203 or "mtd 202" or mtd202 or neoral or neuro-stat or neurostat or "nm 0133" or "nm 133" or nm0133 or "nm133" or "nova 22007" or nova22007 or ol27400 or "olo 400" or olo500 or "opph 088" or opph088 or opsisporin or "otx 101" or otx101 or "p 3072" or p3072 or padciclo or papilock or pulminiq or restasis or restaysis or sanciclo or sanciclo or sandimune or sandimune or "sang 35" or sang35 or sangcya or "sp 14019" or "sti 0529" or sti0529 or "t 1580" or t1580 or verkazia or vekacia).ti,ab.	1418
7	4 or 5 or 6	57371
8	3 and 7	698
9	(invitro or "in vitro").mp. or Invitro Techniques/	1622947
10	9 not (invivo or "in vivo").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1144101
11	8 not 10	624
12	remove duplicates from 11	624

Embase <1974 to 2022 March 04>

#	Search Statement	Results
1	(((reperfus* or ir or hypoxi* ischemi*) adj3 (injur* or damag* or necrosis or necrotic or hemorrhag* or haemorrhag* or (free adj2 radical*))) or ((hypox* or hemorrhagic) adj3 shock)).mp. or exp hemorrhagic shock/	106648
2	exp reperfusion injury/	65519
3	1 or 2	106790
4	exp Cyclosporine/ or cyclosporin.ti,ab. or cyclosporine.ti,ab.	84079
5	("csa neural" or csaneoral or "cya nof" or neural or "ol 27 400" or "ol 27400" or sandimmun).tn.	2547
6	("adi 628" or adi628 or equa or "cgc 1072" or cgc1072 or ciclomulsion or cicloral or cipol or consupren or cyclasol or cyclokat or "de 076" or de076 or deximune or equoral or gengraf or ikervis or iminoral or implanta or imusporin or "lx 201" or lx201 or "c2 03" or mc203 or "mtd 202" or mtd202 or neoral or neuro-stat or neurostat or "nm 0133" or "nm 133" or nm0133 or "nm133" or "nova 22007" or nova22007 or ol27400 or "olo 400" or olo500 or "opph 088" or opph088 or opsisporin or "otx 101" or otx101 or "p 3072" or p3072 or padciclo or papilock or pulminiq or restasis or restaysis or sanciclo or sandimune or sandimune or sandimune or "sang 35" or sang25 or sangcya or "sp 14019" or "sti	6795

0529" or sti0529 or "t 1580" or t1580 or verkazia or vekacia).tn.

7	4 or 5 or 6	87630
8	3 and 7	978
9	(invitro or "in vitro").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	2257265
10	9 not (invivo or "in vivo").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1598454
11	8 not 10	920
12	remove duplicates from 11	904

SCOPUS Searched March 8, 2022 Results = 1568

(((TITLE-ABS-KEY ((reperfus* OR ir OR "Hypoxi* ischemi*") W/3 (injur* OR damag* OR necrosis OR necrotic OR hemorrhag* OR haemorrhag*))) OR (TITLE-ABS-KEY ((reperfus* OR ir OR "Hypoxi* ischemi*") W/3 ("free radical*" OR "free oxygen radical*"))) OR (TITLE-ABS-KEY (((hypox* OR hemorrhagi* OR haemorrhagi*))) AND (TITLE-ABS-KEY ("adi 628" OR adi628 OR equa OR "cgc 1072" OR cgc1072 OR ciclomulsion OR cicloral OR cipol OR consupren OR "csa neural" OR "cya nof" OR cyclasol OR cyclokat OR cyclosporine OR cyclosporin OR "de 076" OR de076 OR deximune OR equoral OR gengraf OR ikervis OR iminoral OR implanta OR imusporin OR "lx 201" OR lx201 OR "c2 03" OR mc203 OR "mtd 202" OR mtd202 OR neoral OR neuro-stat OR neurostat OR "nm 0133" OR "nm 133" OR nm0133 OR "nm133" OR "nova 22007" OR nova22007 OR "ol 27 400" OR "ol 27400" OR ol27400 OR "olo 400" OR olo500 OR "opph 088" OR opph088 OR opsisporin OR "otx 101" OR otx101 OR "p 3072" OR p3072 OR padciclo OR papilock OR pulminiq OR restasis OR restaysis OR sanciclo OR sanciclo OR sandimmune OR sandimune OR sandimune OR "sang 35" OR sang35 OR sangcya OR "sp 14019" OR "sti 0529" OR sti0529 OR "t 1580" OR t1580 OR verkazia OR vekacia))) AND NOT ((TITLE-ABS-KEY (invitro OR "in vitro")) AND NOT ((TITLE-ABS-KEY (invitro OR "in vitro"))))))

WOS BIOSIS Searched March 9, 2022 Results

Indexes=BIOSIS Previews Timespan=All years

#1 TS= (((reperfus* or ir or "Hypoxi* ischemi*") Near/3 (injur* or	
damag* or necrosis or necrotic or hemorrhag* or haemorrhag*)))	
OR TS= ((reperfus* or ir or "Hypoxi* ischemi*") Near/3	
("free radical*" or "free oxygen radical*"))	59,219
#2 DS=Reperfusion Injury	36,628
#3 #1 or #2	59,219
#4 TS=("adi 628" or adi628 or equa or "cgc 1072" or cgc1072 or	
ciclomulsion or cicloral or cipol or consupren or "csa neural"	
or "cya nof" or cyclasol or cyclokat or cyclosporine or cyclosporin	
or "de 076" or de076 or deximune or equoral or gengraf or ikervis	
or iminoral or implanta or imusporin or "lx 201" or lx201 or "c2 03"	
or mc203 or "mtd 202" or mtd202 or neoral or neuro-stat or	
neurostat or "nm 0133" or "nm 133" or nm0133 or "nm133" or	
"nova 22007" or nova22007 or "ol 27 400" or "ol 27400" or ol27400	
or "olo 400" or olo500 or "opph 088" or opph088 or opsisporin or	
"otx 101" or otx101 or "p 3072" or p3072 or padciclo or papilock	
or pulminiq or restasis or restaysis or sanciclo or sanciclo or	
sandimmun or sandimmune or sandimun or sandimune or	
"sang 35" or sang35 or sangcya or "sp 14019" or "sti 0529"	

or sti #5 #6	0529 or "t 1580" or t1580 or verkazia or vekacia) cr=59865-13-3 #4 OR #5	67,609 28,691 68,460
#7	#3 AND #6	691
#8	ts=(invitro or "in vitro")	1,607,545
#9 #1(1 S=((invitro or in vitro) and (invivo or in vivo))	455,102
#1(#7 Not #9	1,154,445
#11	#/ INOL #10	030
Coch	rane Library Searched March 8, 2022	
(Cocl	nrane Database of Systematic Reviewes Results =0)	
(Cocl	nrane Central Register of Controlled Trials Results =46)	
ÌD	Search	Hits
#1	MeSH descriptor: [Reperfusion Injury] this term only	606
#2	MeSH descriptor: [Shock, Hemorrhagic] this term only	113
#3	(((hypox* or hemorrhagic) Near/3 shock)):ti,ab,kw	387
#4	((reperfus* or ir or "hypoxi* ischemi*") NEAR/3 (injur* or	
dama	g* or necrosis or necrotic or hemorrhag* or haemorrhag*)):ti,ab,kw	2952
#5	((reperfus* or ir or hypoxi* ischemi*) NEAR/3	
(free l	NEAR/2 radical*)):ti,ab,kw	61
#6	#1 or #2 or #3 or #4 or #5	3357
# 7	MeSH descriptor: [Cyclosporine] this term only	2826
#8	(("adi 628" or adi628 or equa or "cgc 1072" or cgc1072 or	
ciclo	nulsion or cicloral or cipol or consupren or "csa neural" or	
"cya 1	nof" or cyclasol or cyclokat or cyclosporine or cyclosporin or	
"de 07	'6" or de076 or deximune or equoral or gengraf or ikervis or	
imino	ral or implanta or imusporin or "lx 201" or lx201 or "c2 03" or	
mc202	3 or "mtd 202" or mtd202 or neoral or neuro-stat or neurostat	
or "nr	n 0133" or "nm 133" or nm0133 or "nm133" or "nova 22007"	
or not	va22007 or "ol 27 400" or "ol 27400" or ol27400 or "olo 400"	
or old	o500 or "opph 088" or opph088 or opsisporin or "otx 101" or	
otx10	1 or "p 3072" or p3072 or padciclo or papilock or pulminiq or	
restas	s or restaysis or sanciclo or sanciclo or sandimmun or	
sandir	nmune or sandimun or sandimune or "sang 35" or sang35 or	
sango	ya or "sp 14019" or "sti 0529" or sti0529 or "t 1580" or t1580	
or ve	rkazia or vekacia)):ti,ab,kw	7709
#10	#7 or #8	7709
#11	#6 and #10	46
#12	(exvivo OR "ex vivo") NOT ((exvivo OR "ex vivo") AND	
(inviv	o OR "in vivo"))	2916
#13	#11 NOT #12	46
PRO	SPFRO Searched March 9 2022	
Line	Search for	Hite
#1	(ir or "hypox" ischemi"" or reperfus") and (injur" or damage or	11100
necro	s* or necrotic or hemorrhag* or haemorrhag* or "free radical*"	
or sh	pck)	646
#2	("adi 628" or adi628 or equa or "cgc 1072" or cgc1072 or	
	1 0 0	

ciclomulsion or cicloral or cipol or consupren or "csa neural" or "cya nof" or cyclasol or cyclokat or cyclosporine or cyclosporin or "de 076" or de076 or deximune or equoral or gengraf or ikervis or iminoral or implanta or imusporin or "lx 201" or lx201 or "c2 03" or mc203 or "mtd 202" or mtd202 or neoral or neuro-stat or neurostat or "nm 0133" or "nm 133" or nm0133 or "nm133" or "nova 22007" or nova22007 or "ol 27 400" or "ol 27400" or ol27400 or "olo 400" or olo500 or "opph 088" or opph088 or opsisporin or "otx 101" or otx101 or "p 3072" or p3072 or padciclo or papilock or pulminiq or restasis or restaysis or sanciclo or sancimun or sandimmune or sandimun or sandimune or "sang 35" or sang35 or sangcya or "sp 14019" or "sti 0529" or sti0529 or "t 1580" or t1580 or verkazia or vekacia)

#3 #1 and #2

236 8

Study or Subgroup Mean Mouse Sonnger et al. 2010 50 Sonnger et al. 2005 51 Sonnger et al. 2006 51 Sonnger et al. 2016 (10mg/kg) MP) 36 Scheda et al. 2016 (10mg/kg) MP) 36 Keda et al. 2016 (10mg/kg) MP) 32 Scheda et al. 2016 (2.5mg/kg) MP) 31 Keda et al. 2016 (2.5mg/kg) MP) 31 Scheda et al. 2016 (2.5mg/kg) MP) 32 Keda et al. 2016 (2.5mg/kg) MP) 32 Scheda et al. 2021 (60min) 65 Vasinkevich et al. 2019 25.17 Scheda et al. 2021 (60min) 65 Yasinkevich et al. 2019 25.17 Scheda et al. 2015 13 Substoal (35%) 10 Scheda et al. 2017 36.16 1 De Paulis et al. 2013 (before) 23.9 Scheda et al. 2013 51.5 Yuang et al. 2014 (10mg/kg) 25.22 Scheda et al. 2013 51.5 Yuang et al. 2014 (10mg/kg) 26.9 Scheda et al. 2016 44 Stores et al. 2013 51.5 Scheda et al. 2016 49 Yuang et al. 2014 (50mg/kg) 29.05 Scheda et al. 20	SD 7 12 14 7 7 7 7 10 10 10 10 10 10 10 10 10 0 10 0 10 0 10 0 10 0 10 0 10 1	D Tot 7 1 2 4 4 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	I Mean 0 611 777 588 51 51 51 51 51 51 51 51 52 488 31 35 55% 54.17	SD 12 15 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	Total 7 6 9 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 7 11 6 124	Weight 1.5% 1.2% 1.8% 1.8% 1.6% 1.6% 1.6% 1.5% 1.9% 1.5% 1.9% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.7% 26.1%	V, Random, 95% Cl -11.00 [-20.89, -1.11] -26.00 [-39.58, -12.42] -23.00 [-36.79, -9.21] -15.00 [-21.86, -8.14] -15.00 [-21.86, -8.14] -2.00 [-4.86, 8.86] -19.00 [-27.46, -10.54] -2.00 [-10.46, 6.46] -20.00 [-28.46, -11.54] -7.00 [-12.00, -2.00] -16.00 [-25.77, -6.23] -22.83 [-27.67, -17.99] 14.00 [4.66, 23.34] -22.00 [-3.55, -14.45] -13.62 [-18.66, -8.58]	IV, Random, 95% Cl
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udi et al. 2007 (12, Smg/kg) 30 udi et al. 2007 (12, Smg/kg) 51 et al. 2012 35.2 et al. 2014 26.1 u et al. 2011 (old) 49,6 u et al. 2011 (young) 31.9 agaoka et al. 2015 56 zara it et al. 2015 17.7 lemann et al. 2002 (15mg/kg) 13.9 iemann et al. 2002 (25mg/kg) 17 juadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (11mg/kg, 30min ischemia) 12 quadrito et al. 1999 (11mg/kg, 30min ischemia) 12 quadrito et al. 1999 (11mg/kg) 16 ex Yu 2007 30.3 u et al. 2013 51.1 ubtotal (95% CI) 51.1 eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	-	3	63.8	11.6	8	1.6%	-17.90 [-27.19, -8.61]	and the second se
uudi et al. 2007 (5mg/kg) 51 et al. 2012 35.2 et al. 2014 26.1 u et al. 2011 (young) 31.9 agaoka et al. 2015 56 azari et al. 2015 16 iemann et al. 2002 (15mg/kg) 23 iemann et al. 2002 (15mg/kg) 35 hintani-Ishida et al. 2012 (before ischemia) 28 initani-Ishida et al. 2012 (before ischemia) 28 quadrito et al. 1999 (0.5mg/kg) 46 quadrito et al. 1999 (0.5mg/kg) 19 quadrito et al. 1999 (0.5mg/kg) 16 e X Yu 2007 30.3 tu et al. 2017 22.7 riguud et al. 2005 (after) 24 ancelli effect: Z = 11.25 (P < 0.00001)	21	1	57	16	4	0.6%	-27.00 [-52.87, -1.13]	
et al. 2012 35.2 et al. 2014 26.1 u et al. 2011 (old) 49.6 u et al. 2011 (old) 49.6 u et al. 2011 (young) 31.9 agaoka et al. 2015 56 emann et al. 2015 17.7 emann et al. 2002 (15mg/kg) 13.9 emann et al. 2002 (15mg/kg) 25 mintani-Ishida et al. 2012 (during/after ischem) 16 guadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (15mg/kg) 29 quadrito et al. 2007 30.3 tu et al. 2013 51.1 ubtotal (95% CI) eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0 atsubara et al. 2005 (after) 24 ancelli et al. 2005 (after) 24 ancelli et al. 2005 (after) 24 ancelli et al. 2005 (after) 24 ansubara et al. 2005 (after) 24 angi et al. 2005 (after) 24 angi et al. 2009 39.1 (ang et al. 2009 39.1 (ang et al. 2006 25 butotal (95% CI) eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000) ast for overall effect: Z = 7.89 (P < 0.00001)	16	6	57	16	4	0.7%	-6.00 [-28.17, 16.17]	
et al. 2014 26.1 u et al. 2011 (young) 31.9 agaoka et al. 2015 56 azari et al. 2015 76 ermann et al. 2002 (10mg/kg) 23 iemann et al. 2002 (15mg/kg) 13.9 iemann et al. 2002 (25mg/kg) 13.9 iemann et al. 2002 (25mg/kg) 35 initani-Ishida et al. 2012 (before ischemia) 28 initani-Ishida et al. 2012 (before ischemia) 28 uquadrito et al. 1999 (10mg/kg, 30min ischemia) 12 uquadrito et al. 1999 (10mg/kg, 30min ischemia) 12 uquadrito et al. 1999 (10mg/kg, 30min ischemia) 12 iudicito et al. 1999 (10mg/kg) 16 le & Yu 2007 30.3 tu et al. 2013 51.1 ubtotal (35% CI) retorgeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0 est for overall effect: Z = 11.25 (P < 0.00001) Rabbit lexopoulos et al. 2017 22.7 rgaud et al. 2005 (after) 24 ancelli et al. 2014 32.6 atsubara et al. 2010 (after ischemia) 39.1 aggle & Krolikowski 2009 42 anji et al. 2010 (after ischemia) 39.1 aggle & Krolikowski 2009 42 anji et al. 2006 25 ubtotal (95% CI) eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 ats for overall effect: Z = 7.89 (P < 0.00001)	9.3	3	59.8	8.7	7	1.6%	-24.60 [-34.03, -15.17]	
u et al. 2011 (old) 49.6 u et al. 2011 (young) 31.9 agoka et al. 2015 56 azari et al. 2015 17.7 lemann et al. 2002 (15mg/kg) 13.9 lemann et al. 2002 (15mg/kg) 13.9 lemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (15mg/kg) 35 hintani-Ishida et al. 2012 (during/after ischem) 16 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.15mg/kg) 29 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg) 51.1 ubtotal (35% C1) 21.1 eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	6.1	1	42.3	3.9	6	1.9%	-16.20 [-21.9910.41]	
b cl ii. 2011 (young) 31.9 agaoka et al. 2015 56 azari et al. 2015 17.7 emann et al. 2002 (10mg/kg) 23 iemann et al. 2002 (15mg/kg) 13.9 iemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (25mg/kg) 35 inintani-Ishida et al. 2012 (before ischemia) 28 updrito et al. 1999 (0.5mg/kg) 46 updrito et al. 1999 (0.5mg/kg) 16 updrito et al. 1999 (10mg/kg) 16 stupdrito et al. 2013 51.1 ubtotal (95% CI) 16 estor overall effect: Z = 11.25 (P < 0.00001)	10.9	9	51 9	10.7	7	1.4%	-2 30 [-13 62 9 02]	
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agadak et al. 2015 bo azari et al. 2015 17.7 lemann et al. 2002 (15mg/kg) 13.9 iemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (25mg/kg) 28 hintani-Shida et al. 2012 (during/after ischem) 16 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (10mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg) 16 ie & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (95% CI) eterogeneity: Tau ^a = 67.70; Chi ^a = 360.41, df = 32 (P < 0.0	0.0		- 70		-	4 70/	10 00 1 00 00 0 000	
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iemann et al. 2002 (15mg/kg) 23 iemann et al. 2002 (15mg/kg) 17 iemann et al. 2002 (15mg/kg) 35 intnani-Ishida et al. 2012 (during/after ischem) 16 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.25mg/kg) 66 quadrito et al. 1999 (0.25mg/kg) 16 quadrito et al. 1999 (0.25mg/kg) 16 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg) 16 ie X 'u 2007 30.3 hu et al. 2013 51.1 ubtotal (95% Cl) 21 eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	14.4	4 1	37.6	8.7	13	1.6%	-19.90 [-29.05, -10.75]	
iemann et al. 2002 (15mg/kg) 13.9 iemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (25mg/kg) 35 inintani-Ishida et al. 2012 (before ischemia) 35 inintani-Ishida et al. 2012 (before ischemia) 28 quadrito et al. 1999 (0.25mg/kg) 46 quadrito et al. 1999 (0.5mg/kg) 29 quadrito et al. 1999 (0.5mg/kg) 16 ie & Yu 2007 30.3 ub et al. 2013 51.1 ubtotal (95% CI) 51.1 ubtotal (95% CI) 67.70; Chi ² = 360.41, df = 32 (P < 0.0	28	8	58	12	4	0.5%	-35.00 [-64.85, -5.15]	
lemann et al. 2002 (25mg/kg) 17 iemann et al. 2002 (5mg/kg) 35 intnani-Ishida et al. 2012 (before ischemia) 28 hintani-Ishida et al. 2012 (before ischemia) 28 uadrito et al. 1999 (0.25mg/kg) 46 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.15mg/kg) 29 quadrito et al. 1999 (0.15mg/kg) 29 quadrito et al. 1999 (0.15mg/kg) 16 ie & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (5% CI) 51.1 eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	12.9	9	58	12	4	1.0%	-44.10 [-61.37, -26.83]	
$\label{eq:second} \begin{array}{llllllllllllllllllllllllllllllllllll$	14.6	6	58	12	4	0.9%	-41.00 [-59.52, -22.48]	
$\label{eq:constraints} \begin{array}{llllllllllllllllllllllllllllllllllll$	26	6	58	12	4	0.5%	-23.00 [-51.06, 5.06]	
hintani-Ishida et al. 2012 (during/after ischem) 16 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg) 16 is & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (95% CI) eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	18	8	55	13	6	0.9%	-27 00 1-44 77 -9 231	
Initiation as the state of 2 (Gump/Rg) 16 quadrito et al. 1999 (0.25mg/Rg) 29 quadrito et al. 1999 (0.5mg/Rg) 29 quadrito et al. 1999 (0.5mg/Rg) 16 ie & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (5% CI) 16 left or overall effect: Z = 11.25 (P < 0.00001)	12	2	55	12	6	1 100	20.00 [52 74 24 20]	
quadrito et al. 1999 (0.25mg/kg) 46 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg) 16 is % Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (95% CI) eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0 est for overall effect: Z = 11.25 (P < 0.00001) Rabbit lexopoulos et al. 2017 22.7 rgaud et al. 2005 (after) 24 rgaud et al. 2005 (before) 24 ancelli et al. 2015 (before) 24 ancelli et al. 2016 (before ischemia) 39.6 latsubara et al. 2010 (ofter ischemia) 39.6 latsubara et al. 2010 (before ischemia) 39.1 /ang et al. 2009 39.1 /ang et al. 2005 (chi ² = 40.20, df = 9 (P < 0.000 est for overall effect: Z = 7.89 (P < 0.0001)	15	5	00	13	0	1.170	-39.00 [-53.71, -24.29]	10.00 M
quadrito et al. 1999 (10,5mg/kg) 29 quadrito et al. 1999 (10,5mg/kg) 12 quadrito et al. 1999 (10,5%g, 30min ischemia) 12 quadrito et al. 1999 (11,7%g, 30min ischemia) 16 le & Yu 2007 30,3 tubtotal (95% CI) eterogeneity: Tau [±] = 67.70; Chi ² = 360,41, df = 32 (P < 0.0 est for overall effect: Z = 11.25 (P < 0.00001) Rabbit lexopoulos et al. 2017 22.7 rgaud et al. 2005 (after) 24 argaud et al. 2005 (after) 24 ancelli et al. 2014 32.6 eshnower et al. 2010 (after ischemia) 39.1 agel & Krolikowski 2009 42 arji et al. 2006 25 ubtotal (95% CI) eterogeneity: Tau [±] = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 est for overall effect: Z = 7.89 (P < 0.00001)	5	5	52	D	0	1.9%	-6.00 [-11.66, -0.34]	
quadrito et al. 1999 (1mg/kg, 30min ischemia) 12 quadrito et al. 1999 (1mg/kg) 16 ie & Yu 2007 30,3 hu et al. 2013 51.1 ubtotal (95% CI) 51.1 eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	3	3	52	5	6	1.9%	-23.00 [-27.67, -18.33]	
quadrito et al. 1999 (1mg/kg) 16 ie & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (95% Cl) 51.1 eterogeneity: Tau [±] = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	4	4	57	7	6	1.8%	-45.00 [-51.45, -38.55]	
le & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (85% CI) eterogeneity: Tau" = 67.70; Chi ² = 360.41, df = 32 (P < 0.0 est for overall effect: Z = 11.25 (P < 0.00001) Rabbit lexopoulos et al. 2017 22.7 rgaud et al. 2005 (after) 24 ancelli et al. 2005 (after) 24 ancelli et al. 2005 (after) 24 ancelli et al. 2005 (after) 39.1 agel & Krolikowski 2009 42 anji et al. 2006 25 ubtotal (95% CI) eterogeneity: Tau" = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 est for overall effect: Z = 7.89 (P < 0.0001)	1	1	52	5	6	2.0%	-36.00 [-40.08, -31.92]	
hu et al. 2013 51.1 ubtotal (95% CI) derogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0 est for overall effect: Z = 11.25 (P < 0.00001) Rabbit lexopoulos et al. 2017 22.7 rgaud et al. 2005 (before) 24 ancelli et al. 2005 (before) 24 ancelli et al. 2014 32.6 eshnower et al. 2014 32.6 eshnower et al. 2010 (after ischemia) 39.6 latsubara et al. 2010 (after ischemia) 39.1 agel & Krolikowski 2009 42 anji et al. 2006 25 ubtotal (95% CI) eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 est for overall effect: Z = 7.89 (P < 0.00001)	2.7	7	48.8	5.8	6	1.9%	-18.50 [-23.62, -13.38]	
Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State	10.4	4	55.4	10.9	8	1.5%	-4 30 [-14 74 6 14]	
derogeneity: Tau* = 67.70; Chi² = 360.41, df = 32 (P < 0.0	10.1	21	00.1	10.0	218	49.7%	-19.01 [-22.32, -15.70]	•
Rabbit lexopoulos et al. 2017 22.7 rgaud et al. 2005 (after) 24 rgaud et al. 2005 (before) 24 ancelli et al. 2014 32.6 sehnower et al. 2014 39.1 atsubara et al. 2010 (before ischemia) 39.1 agel & Krolikowski 2009 42 anjit et al. 2006 25 ubtotal (95% CI) 25 eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000)	00001);)1); I² =	91%					
lexopoulos et al. 2017 22.7 rgaud et al. 2005 (after) 24 rgaud et al. 2005 (before) 24 ancelli et al. 2014 32.6 sshnower et al. 2010 39 latsubara et al. 2010 (after ischemia) 39.1 agel & Krolikowski 2009 42 anji et al. 2006 25 ubtotal (95% CI) 25 eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000)								
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graud et al. 2005 (before) 24 ancelli et al. 2014 32.6 sshnower et al. 2008 39 atsubara et al. 2010 (before ischemia) 39.6 atsubara et al. 2010 (before ischemia) 39.1 agel & Krolikowski 2009 42 anji et al. 2006 25 ubtotat (95% Cl) 25 eterogeneity: Tau ^a = 33.60; Chi ^a = 40.20, df = 9 (P < 0.000)	11	1	60	17	8	1.2%	-36.00 [-50 03 -21 97]	
glads tell. 2000 (bit of p) 24 aschnower et al. 2014 32,6 sshnower et al. 2010 (after ischemia) 39,1 atsubara et al. 2010 (before ischemia) 39,1 agel & Krolikowski 2009 42 anji et al. 2006 25 ubtotal (95% Cl) 25 eterogeneity: Tau ^a = 33.60; Chi ^a = 40.20, df = 9 (P < 0.000)	11	1	60	17	8	1.2%	-36 00 [-50 03 -21 07]	
atsocher vi dl. 2014 32.05 shnower et al. 2008 39 atsubara et al. 2010 (after ischemia) 39.6 atsubara et al. 2010 (before ischemia) 39.1 angi et al. 2009 42. angi et al. 2009 39.1 ang et al. 2006 25 ubtotal (95% Cl) 25 eterogeneity: Tau ² = 33.60; Ch) ² = 40.20, df = 9 (P < 0.000)	14.4		67.9	18 1	0	1.00	-24 70 1-40 60 -9 801	
sennower et al. 2008 39 atsubara et al. 2010 (after ischemia) 39.6 atsubara et al. 2010 (before ischemia) 39.1 agel & Krolikowski 2009 42 anji et al. 2006 39.1 ubtotal (95% CI) 25 ubtotal (95% CI) 36.6; Ch)² = 40.20, df = 9 (P < 0.000)	14.1		51.3	16.1	0	1.0%	-24.70 [-40.60, -8.80]	
atsubara et al. 2010 (after ischemia) 39.6 atsubara et al. 2010 (before ischemia) 39.1 agel & Krolikowski 2009 42 anji et al. 2009 39.1 ang et al. 2006 25 ubtotal (95% CI) 25 eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000	10	U 1	60	8	15	1.8%	-21.00 [-27.96, -14.04]	
latsubara et al. 2010 (before ischemia) 39.1 agel & Krollikowski 2009 42 anji et al. 2009 39.1 /ang et al. 2006 25 ubtotal (95% Cl) 25 eterogeneity: Tau ^a = 33.60; Chi ^a = 40.20, df = 9 (P < 0.000	3.6	6	53.4	5	7	1.9%	-13.80 [-18.92, -8.68]	
agel & Krolikowski 2009 42 anji et al. 2009 39.1 fang et al. 2006 25 ubtotal (95% Cl) 25 eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000	4.2	2	53.4	5	7	1.9%	-14.30 [-19.30, -9.30]	
anji et al. 2009 39.1 /ang et al. 2006 25 ubtotal (95% CI) eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 sst for overall effect: Z = 7.89 (P < 0.00001)	5	5	46	5	6	1.9%	-4.00 [-9.66, 1.66]	
fang et al. 2006 25 ubtotal (95% Cl) 25 eterogeneity: Tau ^a = 33.60; Chi ^a = 40.20, df = 9 (P < 0.000	4.4	4	53.4	4.7	7	1.9%	-14.30 [-19.25, -9.35]	
bbtotal (95% Cl) teterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 est for overall effect: Z = 7.89 (P < 0.0001)	3	3	44	4	7	2.0%	-19.00 [-22.70 -15.30]	
eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 sist for overall effect: Z = 7.89 (P < 0.00001)		8			91	16.7%	-17.47 [-21.81, -13.13]	•
est for overall effect: Z = 7.89 (P < 0.00001)	001); l²	; l ² = 7	%				[, []	
DI-								
Pig arisson et al. 2010. 40		4 4	44	16	15	1.49/	8 00 1.3 33 10 991	
alisson et al. 2010 49	14		41	10	10	1.4%	0.00 [-0.00, 19.00]	
ansson et al. 2012 51	14	1 1	54	20	11	1.0%	-3.00 [-19.76, 13.76]	
ie et al. 2010 47.3	14 21	7 1	51.4	16.5	19	1.5%	-4.10 [-14.34, 6.14]	
kyschally et al. 2010 25	14 21 15.7	6	35	6	4	1.7%	-10.00 [-18.32, -1.68]	
alewski et al. 2015 46.2	14 21 15.7 6	1	53.8	4.1	8	2.0%	-7.60 [-11.16, -4.04]	
ubtotal (95% CI)	14 21 15.7 6 3.1	5			57	7.5%	-4.77 [-10.19, 0.65]	•
leterogeneity: $Tau^2 = 17.13$; $Chi^2 = 7.72$, $df = 4$ (P = 0.10); Heat for overall effect: $T = 1.73$ (P = 0.08)	14 21 15.7 6 3.1	48%						
ss. to overall effect. 2 = 1.73 (P = 0.08)	14 21 15.7 6 3.1 ² = 48 ⁴				100	100 004	46 20 7 40 70 44 64	•
stai (95% CI)	14 21 15.7 6 3.1 ² = 48 ⁴				490	100.0%	-10.30 [-18.59, -14.01]	
eterogeneity: Tau ² = 64.71; Chi ² = 556.12, df = 63 (P < 0.0	14 21 15.7 6 3.1 ² = 48 ⁴	48	89%					50 25 0 05 50

Figure S1 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by species.

	Exp	eriment	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Male	00.7	0.0	40	07.7			1.00/	45 00 1 04 40 0 000	
Areaud at al. 2005 (after)	22.1	9.8	18	37.7	17	18	1.9%	-15.00 [-21.12, -8.88]	
Argaud et al. 2005 (alter)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]	
Choi et al. 2017	36.16	11.18	4	54.17	13.5	4	1.0%	-18.01 [-35.190.83]	
De Paulis et al. 2013 (before)	23.9	14.3	7	59.4	7.4	7	1.4%	-35.50 [-47.43, -23.57]	
De Paulis et al. 2013 (during)	52.2	5.6	7	59.4	7.4	7	1.8%	-7.20 [-14.07, -0.33]	
Fang et al. 2008	24.4	3.3	12	47.5	4.2	12	2.1%	-23.10 [-26.12, -20.08]	-
Gomez et al. 2005	51	12	6	77	12	6	1.3%	-26.00 [-39.58, -12.42]	
Gomez et al. 2008	35	14	8	58	15	9	1.2%	-23.00 [-36.79, -9.21]	
Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.0%	-11.30 [-15.38, -7.22]	-
Huang et al. 2014 (1mg/kg)	35.29	1.52	8	45	2.07	8	2.1%	-9.71 [-11.49, -7.93]	-
Huang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2.1%	-15.95 [-17.98, -13.92]	7
Huang et al. 2014 (5mg/kg)	26.9	1.86	8	45	2.07	8	2.1%	-18.10 [-20.03, -16.17]	T. I.
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	1.9%	-19.60 [-25.60, -13.60]	
Huhn et al. 2010	61	9	1	58	6	1	1.7%	3.00 [-5.01, 11.01]	
Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]	
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	0	1.5%	-6.20 [-17.11, 4.71]	
Ikeda et al. 2016 (10mg/kg NP)	30	7	0	51	7	0	1.070	-15.00 [-21.00, -0.14]	
Ikeda et al. 2016 (1mg/kg NF)	53	7	8	51	7	8	1.8%	2 00 [-4 86 8 86]	
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	7	8	1 7%	-19 00 [-27 46 -10 54]	
Ikeda et al. 2016 (2 5mg/kg)	49	10	8	51	7	8	1.7%	-2 00 [-10 46 6 46]	
Ikeda et al. 2016 (2.5mg/kg NP)	31	10	8	51	7	8	1.7%	-20.00 [-28,46, -11,54]	
Ikeda et al. 2016 (25mg/kg)	32	10	8	51	7	8	1.7%	-19.00 [-27.46, -10.54]	-
Ikeda et al. 2021 (30min)	33	10	8	53	7	8	1.7%	-20.00 [-28.46, -11.54]	
Ikeda et al. 2021 (60min)	65	6	8	72	4	8	2.0%	-7.00 [-12.00, -2.00]	
Kiss et al. 2016	45.9	6.3	7	63.8	11.6	8	1.6%	-17.90 [-27.19, -8.61]	
Laudi et al. 2007 (12.5mg/kg)	30	21	4	57	16	4	0.6%	-27.00 [-52.87, -1.13]	
Laudi et al. 2007 (5mg/kg)	51	16	4	57	16	4	0.7%	-6.00 [-28.17, 16.17]	
Leshnower et al. 2008	39	10	12	60	8	15	1.8%	-21.00 [-27.96, -14.04]	
Li et al. 2012	35.2	9.3	7	59.8	8.7	7	1.6%	-24.60 [-34.03, -15.17]	
Li et al. 2014	26.1	6.1	6	42.3	3.9	6	1.9%	-16.20 [-21.99, -10.41]	
Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.4%	-2.30 [-13.62, 9.02]	
Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.7%	-22.60 [-31.17, -14.03]	
Matsubara et al. 2010 (after ischemia)	39.6	3.6	4	53.4	5	7	2.0%	-13.80 [-18.92, -8.68]	
Matsubara et al. 2010 (before ischemia)	39.1	4.2	6	53.4	5	7	2.0%	-14.30 [-19.30, -9.30]	
Nagaoka et al. 2015	56	5	1	72	9	1	1.8%	-16.00 [-23.63, -8.37]	
Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.6%	-19.90 [-29.05, -10.75]	
Niemann et al. 2002 (10mg/kg)	120	12.0	4	58	12	4	1.0%	-35.00 [-64.85, -5.15]	
Niemann et al. 2002 (T5mg/kg)	13.9	14.0	4	50	12	4	0.0%	-44.10[-01.37, -20.03]	
Niemann et al. 2002 (25mg/kg)	25	14.0	4	50	12	4	0.9%	-41.00[=09.02, =22.40]	
Nikolaou et al. 2002 (Sing/kg)	25 17	26	7	48	6	7	2.0%	-22 83 [-27 67 -17 99]	
Pagel & Krolikowski 2009	42	5	6	46	5	6	1.9%	-4 00 [-9 66 1 66]	
Rusinkevich et al. 2019	45	13	11	31	9	11	1.6%	14.00 [4.66, 23.34]	
Shintani-Ishida et al. 2012 (before ischemia)	28	18	6	55	13	6	1.0%	-27.00 [-44.77, -9.23]	
Shintani-Ishida et al. 2012 (during/after ischem)	16	13	6	55	13	6	1.2%	-39.00 [-53.71, -24.29]	
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	1.9%	-6.00 [-11.66, -0.34]	
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	2.0%	-23.00 [-27.67, -18.33]	
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.9%	-45.00 [-51.45, -38.55]	
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.0%	-36.00 [-40.08, -31.92]	-
Wang et al. 2006	25	3	7	44	4	7	2.1%	-19.00 [-22.70, -15.30]	-
Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	2.0%	-18.50 [-23.62, -13.38]	
Youcef et al. 2015	13	5	6	35	8	6	1.8%	-22.00 [-29.55, -14.45]	
Zhu et al. 2013	51.1	10.4	8	55.4	10.9	8	1.5%	-4.30 [-14.74, 6.14]	
Subtotal (95% CI)			396	1000		405	89.1%	-17.43 [-19.91, -14.95]	•
Heterogeneity: $Tau^2 = 65.59$; $Chi^2 = 506.53$, $df =$ Test for overall effect: $Z = 13.78$ (P < 0.00001)	54 (P < (0.00001)); ² = 8!	9%					
Female									
Karlsson et al. 2010	49	14	12	41	16	15	1 4%	8.00 [-3.33, 19.33]	
Karlsson et al. 2012	51	21	12	54	20	11	1.0%	-3.00 [-19 76 13 76]	
Lie et al. 2010	47.3	15.7	19	51.4	16.5	19	1.5%	-4.10 [-14.34, 6.14]	
Subtotal (95% CI)			43			45	4.0%	0.62 [-7.48, 8.72]	+
Heterogeneity: Tau ² = 12.51; Chi ² = 2.63, df = 2 (Test for overall effect: $Z = 0.15$ (P = 0.88)	P = 0.27); I² = 24	1%						
mixed Boengler et al. 2010	50	7	10	61	12	7	1.6%	-11.00 (-20.89 -1.11)	
Lim et al. 2007	32	7	6	48	10	6	1.6%	-16.00 [-25.776.23]	<u> </u>
Skyschally et al. 2010	25	6	4	35	6	4	1.7%	-10.00 [-18.32, -1.68]	
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.1%	-7.60 [-11.16, -4.04]	
Subtotal (95% CI)			28			25	6.9%	-8.98 [-11.94, -6.02]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 2.78, df = 3 (P Test for overall effect: $Z = 5.94$ (P < 0.00001)	9 = 0.43);	l ² = 0%							
Total (05% CI)			467			475	100.0%	46 26 1.49 64 42 041	
Heterogeneity: Tau ² = 66.34: Chi ² = 554.60 df =	61 (P < 0	0.000011	407	9%		4/5	100.0%	-10.50 [-10.01, -13.31]	
Test for overall effect: Z = 13.56 (P < 0.00001)	arte et			- 10					-50 -25 0 25 50
Test for subgroup differences: Chi2 = 30.14, df =	2 (P < 0.	00001).	² = 93.	4%					Favours [experimental] Favours [control]

Figure S2 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by sex.

	Exp	eriment	al	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
Before Ischemia									
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.4%	-36.00 [-50.03, -21.97]	
Boengler et al. 2010	50	7	10	61	12	7	1.7%	-11.00 [-20.89, -1.11]	
De Paulis et al. 2013 (before)	23.9	14.3	1	59.4	10.4	1	1.5%	-35.50 [-47.43, -23.57]	
Fancelli et al. 2014	32.0	14.1	8	57.3	18.1	8	1.3%	-24.70 [-40.60, -8.80]	
Laudi et al. 2007 (12.5mg/kg)	30	21	4	57	10	4	0.7%	-27.00 [-52.87, -1.13]	and the second sec
Ladur et al. 2007 (Singrkg)	20	10	10	57	0	15	1.0%	-0.00 [-20.17, 10.17]	
Mateubara et al. 2000	39 1	4.2	6	53.4	5	15	2.0%	-21.00 [-27.96, -14.04]	
Naraoka et al. 2015	56	4.2	7	72	9	7	1 0%	-16.00 [-23.63 -8.37]	
Niemann et al. 2002 (10mg/kg)	23	28	4	58	12	4	0.6%	-35 00 [-64 85 -5 15]	
Niemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.2%	-44.10[-61.37, -26.83]	
Niemann et al. 2002 (25mg/kg)	17	14.6	4	58	12	4	1.1%	-41.00 [-59.52 -22.48]	
Niemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.7%	-23.00 [-51.06, 5.06]	
Ranji et al. 2009	39.1	4.4	6	53.4	4.7	7	2.0%	-14.30 [-19.25, -9.35]	+
Shintani-Ishida et al. 2012 (before ischemia)	28	18	6	55	13	6	1.1%	-27.00 [-44.77, -9.23]	
Subtotal (95% CI)			94			96	20.0%	-22.86 [-27.98, -17.73]	•
Heterogeneity: Tau ² = 52.18; Chi ² = 40.85, df = 1 Test for overall effect: Z = 8.74 (P < 0.00001)	4 (P = 0.	0002); P	^z = 66%	6					
During Ischemia									
Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	2.0%	-15.00 [-21.12, -8.88]	
Choi et al. 2017	36.16	11.18	4	54.17	13.5	4	1.2%	-18.01 [-35.19, -0.83]	
De Paulis et al. 2013 (during)	52.2	5.6	7	59.4	7.4	7	1.9%	-7.20 [-14.07, -0.33]	
Fang et al. 2008	24.4	3.3	12	47.5	4.2	12	2.1%	-23.10 [-26.12, -20.08]	-
Gomez et al. 2008	35	14	8	58	15	9	1.4%	-23.00 [-36.79, -9.21]	
Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.1%	-11.30 [-15.38, -7.22]	-
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	2.0%	-19.60 [-25.60, -13.60]	-
Huhn et al. 2010	61	9	7	58	6	7	1.8%	3.00 [-5.01, 11.01]	
Hurt et al. 2016	49	5	6	61	5	6	2.0%	-12.00 [-17.66, -6.34]	-
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.6%	-6.20 [-17.11, 4.71]	
Karlsson et al. 2010	49	14	12	41	16	15	1.6%	8.00 [-3.33, 19.33]	
Karlsson et al. 2012	51	21	12	54	20	11	1.2%	-3.00 [-19.76, 13.76]	
Kiss et al. 2016	45.9	6.3	7	63.8	11.6	8	1.7%	-17.90 [-27.19, -8.61]	
Lie et al. 2010	47.3	15.7	19	51.4	16.5	19	1.7%	-4.10 [-14.34, 6.14]	
Li et al. 2012	35.2	9.3	7	59.8	8.7	7	1.7%	-24.60 [-34.03, -15.17]	
Li et al. 2014	26.1	6.1	6	42.3	3.9	6	2.0%	-16.20 [-21.99, -10.41]	
Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.6%	-2.30 [-13.62, 9.02]	
Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.8%	-22.60 [-31.17, -14.03]	
Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.7%	-19.90 [-29.05, -10.75]	
Nikolaou et al. 2019	25.17	2.6	7	48	6	7	2.0%	-22.83 [-27.67, -17.99]	
Pagel & Krolikowski 2009	42	5	6	46	5	6	2.0%	-4.00 [-9.66, 1.66]	
Skyschally et al. 2010	25	6	4	35	6	4	1.8%	-10.00 [-18.32, -1.68]	
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	2.0%	-6.00 [-11.66, -0.34]	
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	2.0%	-23.00 [-27.67, -18.33]	
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.9%	-45.00 [-51.45, -38.55]	
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.1%	-36.00 [-40.08, -31.92]	-
Wang et al. 2006	25	3	7	44	4	7	2.1%	-19.00 [-22.70, -15.30]	
Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	2.0%	-18.50 [-23.62, -13.38]	
Youcef et al. 2015	13	5	6	35	8	6	1.9%	-22.00 [-29.55, -14.45]	
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.1%	-7.60 [-11.16, -4.04]	
Zhu et al. 2013	51.1	10.4	250	55.4	10.9	254	1.6%	-4.30 [-14.74, 6.14]	A T
Heterogeneity: Tau ² = 97.78; Chi ² = 342.59, df =	30 (P < 0	0.00001)	; l ² = 9	1%		234	50.5%	-15.02 [-16.79, -11.25]	
After Ischemia									
Argaud et al. 2005 (after)	24	11	8	60	17	8	1 4%	-36.00 [-50 03 -21 97]	
Ikeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1 9%	-15 00 [-21 86 -8 14]	
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.9%	-15.00 [-21.86, -8.14]	
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.9%	2.00 [-4.86, 8.86]	
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	7	8	1.8%	-19.00 [-27.4610.54]	
Ikeda et al. 2016 (2.5mg/kg)	49	10	8	51	7	8	1.8%	-2.00 [-10.46. 6 46]	
Ikeda et al. 2016 (2.5mg/kg NP)	31	10	8	51	7	8	1.8%	-20.00 [-28.4611 54]	
Ikeda et al. 2016 (25mg/kg)	32	10	8	51	7	8	1.8%	-19.00 [-27.46, -10.54]	
Ikeda et al. 2021 (30min)	33	10	8	53	7	8	1.8%	-20.00 [-28.4611.54]	
Ikeda et al. 2021 (60min)	65	6	8	72	4	8	2.0%	-7.00 [-12.00, -2.00]	+
Lim et al. 2007	32	7	6	48	10	6	1.7%	-16.00 [-25.77, -6.23]	
Matsubara et al. 2010 (after ischemia)	39.6	3.6	4	53.4	5	7	2.0%	-13.80 [-18.92, -8.68]	+
Rusinkevich et al. 2019 Subtotal (95% CI)	45	13	11 101	31	9	11 104	1.7% 23.5%	14.00 [4.66, 23.34] -12.36 [-17.81, -6.91]	• -
Heterogeneity: Tau ² = 82.89; Chi ² = 80.53, df = 1 Test for overall effect: $Z = 4.45$ (P < 0.00001)	12 (P < 0.	00001);	l² = 85	%					
Total (95% CI)			445			454	100.0%	-16.12 [-18.87, -13.37]	•
Heterogeneity: Tau ² = 91.35; Chi ² = 492.88, df =	58 (P < 0	0.00001)	; l ² = 8	8%					-100 -50 0 50 100
Test for overall effect: Z = 11.47 (P < 0.00001) Test for subgroup differences: Chi ² = 8.71, df = 2	2 (P = 0.0	1), ² = 7	7.0%						Favours [experimental] Favours [control]

Figure S3 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by timing of treatment.

Bady of Subgraph Bady of Subgraph Dir Hall Mark B0 Tetal Mark B0		Exp	erimenta	al .	C	ontrol			Mean Difference	Mean Difference
atmp3	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Genes at d. 2011 100 101 <td>≤1mg/kg</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>5.00</td>	≤1mg/kg									5.00
Hang at Δ 201 (https:) 52.0 12.0 8 40.0 21.0 8 12.0 <td>Gross et al. 2013</td> <td>51.5</td> <td>3.4</td> <td>8</td> <td>62.8</td> <td>4.8</td> <td>8</td> <td>2.0%</td> <td>-11.30 [-15.38, -7.22]</td> <td></td>	Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.0%	-11.30 [-15.38, -7.22]	
Intern at 0.201 (https://pi.schild.com/pi	Huang et al. 2014 (1mg/kg)	35.29	1.52	8	45	2.07	8	2.1%	-9.71 [-11.49, -7.93]	-
Intern at	Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.8%	2.00 [-4.86, 8.86]	
Data Like 2021 (Dime) 33 0 8 32 7 8 10% 20.12 (Like, 1.13) Scandbris of Li 1990 (Semplag) 28 6 6.2 6 10% 20.12 (Like, 1.13) Scandbris of Li 1990 (Semplag) 28 6 6.2 6 6.9 6 10% 20.01 (Like, 1.13) Scandbris of Li 1991 (Semplag) 28 6 6.2 6 6.9 6.0 10% 20.01 (Like, 1.13) Scandbris of Li 1991 (Semplag) 27 1.9 7.1 7.2 1.7 1.5 1.6 4.00 (Like, 1.4, 1.13) 1.0	Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	7	8	1.6%	-19.00 [-27.46, -10.54]	
Deck Has, 201 (DBM) Deck Has, 201 (DBM) Saudhi ed. 1990 (Tryle, 3.000) 2. Saudhi ed. 1990 (Tryle, 4.000) 2. Saudhi ed. 1990 (Tryle, 4.000) 3. Saudhi ed	Ikeda et al. 2021 (30min)	33	10	8	53	7	8	1.6%	-20.00 [-28.46, -11.54]	
Substitution Substitution<	Ikeda et al. 2021 (60min)	65	6	8	72	4	8	1.9%	-7.00 [-12.00, -2.00]	
Samable at 1999 (rungs 3) on tachenia 1 4 4 6 27 7 2 6 194 400 (54.4), 48.69 Market at 1999 (rungs 3) on tachenia 1 4 7 7 7 7 8 19 4 100 (54.4), 48.69 Market at 2016 (rungs 3) on tachenia 1 4 9 4 0.000 (1 7 8 127), 48.69 40.00, 51.42, 48.69 Market at 2016 (rungs 3) on tachenia 1 4 9 4 0.000 (1 7 8 127), 48.69 40.00, 51.12, 48.69 Angeoda at 200 (rungs 3) on tachenia 1 4 9 4 0.000 (1 7 8 127), 48.69 40.00, 51.12, 48.69 Angeoda at 200 (rungs 3) on tachenia 1 4 9 4 0.000 (1 7 8 127), 48.69 40.00, 51.12, 48.69 Market at 2016 (rungs 3) 0 24 11 8 0 0 17 8 127, 48.69 40.00, 51.12, 48.69 Angeoda at 2016 (rungs 3) 0 24 11 8 0 0 17 8 127, 48.69 40.00, 51.12, 48.69 Angeoda at 2016 (rungs 3) 0 24 11 0 0 17 8 127, 48.69 40.00, 51.12, 48.69 Angeoda at 2016 (rungs 3) 0 24 11 0 0 17 8 127, 48.69 40.00, 51.12, 48.69 Market at 2016 (rungs 3) 0 1 1 10, 47.20 (rungs 4) 0 0 17 8 127, 48.69 40.00, 51.12, 50.00, 51.17, 10.00 Market at 2016 (rungs 3) 0 1 1 10, 47.20 (rungs 4) 0 10 10 17 18 127, 48.69 40.00, 51.17, 10.00 Market at 2016 (rungs 3) 0 1 1 10, 47.10 (rungs 4) 0 10 10 17 18 127, 48.10 (rungs 4) 0 10 10 17 18 127, 48.10 (rungs 4) 0 10 10 17 18 127, 48.10 (rungs 4) 0 10 10 17 18 127, 11.00 (rungs 4) 0 10 10 17 18 127, 11.00 (rungs 4) 0 10 10 17 18 127, 11.00 (rungs 4) 0 10 10 17 18 127, 11.00 (rungs 4) 0 10 10 17 18 127, 11.00 (rungs 4) 0 10 10 17 18 127, 11.00 (rungs 4) 0 10 10 10 17 11 10 10 10 10 11 10 10 10 10 11 10 10	Squadrito et al. 1999 (0.25mg/kg)	40	3	6	52	5	6	1.9%	-0.00[-11.00, -0.34]	
Subjection (Single) 10 1 0 10	Squadrito et al. 1999 (0.5mg/kg) Squadrito et al. 1999 (1mg/kg. 30min ischemia)	12	3	6	57	5	6	1.9%	-23.00 [-27.07, -10.33]	
Balance of Str. 01 1/2 2/2 1/2	Squadrito et al. 1999 (Tmg/kg, Somin Ischemia) Squadrito et al. 1999 (Tmg/kg)	16	-	6	52	5	6	2.0%	-45.00 [-51.45, -38.55]	
Hearograms, Tar # 164.1; C# = 207 72, C# = 0 + 0.0001; P = 075 To rear Hear 2 - 20 P < 0.0001; P = 075 Append at 2.000 [cm/s] 2.0m/s] Append at 2.000 [cm/s] 2.0m/s] Append at 2.000 [cm/s] 2.0m/s] 4.000 [cm/s] 2.0m/s] 4.000 [cm/s] 2.0m/s] 4.000 [cm/s] 4.000 [cm/s] 4.00	Subtotal (95% CI)	10	S	72			72	18.7%	-17.47 [-25.45, -9.49]	•
The formula dist. 2 = 4.29 (P = 0.001) 2.5mg/hg Amogenetic at 30 (017) 2.27 9.8 16 977 6 177 6 124, 34.0 (017) 3.28 (160) 3.24 11 8 6 0 17 8 124, 34.0 (010), 24.9 11 8 6 0 17 8 124, 34.0 (010), 24.9 17 Amogenetic at 30 (010) 1.24 3.40 (010), 24.9 11 8 6 0 17 8 124, 34.0 (010), 24.9 17 4.25 3.40 (010), 24.9 11 8 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Heterogeneity: Tau ² = 156.83; Chi ² = 277.72, df =	9 (P < 0	.00001);	² = 9	7%					
Lamps of a 2001 2.7 8 9 77 8 1.2% 45.00 (±1.12, 4.8.8) Appared 14 2.00 (±1.0) 2.01 (±1.0) </td <td>Test for overall effect: Z = 4.29 (P < 0.0001)</td> <td></td> <td>84.9 3 S S</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Test for overall effect: Z = 4.29 (P < 0.0001)		84.9 3 S S							
$ \begin{array}{c} 2.5mplng \\ \hline The set of t$										
Alexpendent et al. 2017 Page 4 et al. 2028 Page 4 et al. 2018 Page 4 et al. 2018 P	2.5mg/kg									100
Angued et 2005 (drom) 24 11 6 0 60 77 6 12% 4300 (500, 24.97) Hard et 2005 (Gromphy) 20 2 2 6 6 61 6 6 19% 12% 4300 (500, 24.97) Hard et 2016 (Gromphy) 20 2 2 6 6 61 6 6 19% 12% 4300 (500, 24.97) Hard et 2016 (Gromphy) 20 2 2 6 6 61 6 6 19% 12% 4300 (504, 440) Hard et 2016 (Gromphy) 20 2 2 5 6 6 1 5 7 8 10% 4200 (24.4.11.54) Hercegoenty, Tar = 3.25; (CP - 7 (P - 0.000)); P = 77K Tent or cover affects = 2.59 (P - 0.0000); P = 77K Hard et 2016 (Gromphy) 20 2 2 5 6 4 3 5 7 8 12% 14% 150 (2500, 16.77) Hard et 200 (Gromphy) 10 3 10 7 9 14 4 13 77 6 5 4 5 9 15% 120 (17, 16.30) Hard et 200 (17, 16.30) 10 16 4 57 7 19 154 5 10 177 Hard et 200 (17, 16.70) Hard et 200 (17, 17, 14 11) 27 15 10 4 4 57 7 15 4 40 17 17, 14.80 (230, 14.577) Hard et 200 (17, 16.70) Hard et 200 (17, 17, 14 11) 27 15 4 10 (2306, 11.577) Hard et 200 (17, 16.70) Hard et 200 (1	Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	1.8%	-15.00 [-21.12, -8.88]	
$ \begin{array}{c} \label{eq:approx} at 2.205 (pellow) \\ \mbox{approx} at 2.255 (pellow) \\ \mbox} at 2.255 (p$	Argaud et al. 2005 (after)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]	
Hang at 2014 (2.5mg/s) 2010 2.00 8 4 42 207 8 2.114, $+5.56$ ($+7.78$, -3.50 (-7.84 , -7.84 (-7.84) (-7.84 , -7.84 (-7.84) (-7.84 (-7.84) (-7.84 (-7.84) (-7.84 (-7.84) (-7.84 (-7.84) (-7.84 (-7.84) (-7.84 (-7.84 (-7.84) (-7.84 (-7.84 (-7.84 (-7.84) (-7.84 (-7.84 (-7.84 (-7.84) (-7.84 ($-$	Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]	
$ \begin{aligned} & \operatorname{het} \operatorname{res} $	Huang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2.1%	-15.95 [-17.98, -13.92]	-
$ \begin{aligned} & \text{lade at at 2016 (2-5mg/kg)} & 49 & 10 & 6 & 51 & 7 & 6 & 168 & -2.00 (1-04.4, 6.48) \\ & \text{made at at 2016 (2-5mg/kg)} & 31 & 10 & 21 & 12 & 12 & 12 & 108 & -2.00 (1-04.4, 6.48) \\ & \text{made at at 2016 (2-5mg/kg)} & 31 & 10 & 21 & 12 & 108 & -2.00 (3-40, 4.48) \\ & \text{made at at 2016 (3-5mg/kg)} & 20 & 108 & 6 & 12 & 108 & -2.00 & -2.10 & -2.00$	Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]	
$ \begin{aligned} \begin{aligned} & \text{hads, at all 2016 } (2.5mg/s) (2.5m$	Ikeda et al. 2016 (2.5mg/kg)	49	10	8	51	7	8	1.6%	-2.00 [-10.46, 6.46]	
Martisson all, 2012 5 21 2 8 20 11 1.07 3.00 (45.76, 13.78) Hendergoweity, Time 25 (2014) 2.25 4.25 (2014) 2.25 (4.15.35 (2.17, 4.16)) 1.00 </td <td>Ikeda et al. 2016 (2.5mg/kg NP)</td> <td>31</td> <td>10</td> <td>8</td> <td>51</td> <td>7</td> <td>8</td> <td>1.6%</td> <td>-20.00 [-28.46, -11.54]</td> <td></td>	Ikeda et al. 2016 (2.5mg/kg NP)	31	10	8	51	7	8	1.6%	-20.00 [-28.46, -11.54]	
a table (197) c 100	Karlsson et al. 2012	51	21	12	54	20	11	1.0%	-3.00 [-19.76, 13.76]	
Heterogenerity: Tur ² - 38.25; CP = 31.05, df = 7 / P < 0.0001; F = 7/% Terms for a constraints, 2 - 5.90 / P < 0.0001; F = 7/% Hann et al. 2016 (mp/kg) 15.93 / 15.8 / 7 / 9 5.14 / 6 9 12.% - 18.10 (2.0.03, -16.17) Hann et al. 2016 (mp/kg) 15.93 / 15.8 / 7 / 9 5.14 / 6 9 12.% - 18.10 (2.0.03, -16.17) Hann et al. 2017 (mp/kg) 15.1 / 16.4 / 7 / 16.4 / 7 / 16.4 / 0.7% - 4.00 (2.41, 7.16.17) Load et al. 2017 (mp/kg) 15.1 / 16.4 / 15.7 / 16.4 / 15.7 / 16.4 / 0.7% - 4.00 (2.41, 7.16.17) Load et al. 2017 (mp/kg) 15.1 / 16.4 / 15.7 / 16.4 / 15.7 / 16.4 / 15.8 / 16.0 / 20.03, -16.17) Haterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 5.4 + 1.1 / et al. 9 / 2 0.0001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 6.8 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9 + C / P = 0.00001; P = 6/% Heterogenerity: Tur ² - 8.9	Subtotal (95% CI)			76			15	12.4%	-16.35 [-21.70, -11.00]	-
Test more manue. 2 - 2. of V 0.00001) Singkg Haang et al. 2016 (mg/kg) 26.9 1.86 6 2.07 8 2.11% 16.10 [2.00.3], 16.10] Hain et al. 2010 61 9 7 56.6 7 1.74 3.00 [2.50, 11.01] Hain et al. 2010 61 9 7 56.6 7 7 16.8 24.00 [2.30, 11.01] List al. 2012 52.9 3 7 56.6 7 7 16.8 24.00 [2.30, 15.07] Meman et al. 2002 (5mg/kg) 35 22.6 6 6 1.94 4.00 [2.30, 15.07] Niemsen et al. 2002 (5mg/kg) 35 28.6 6.7 7 1.65 -1.100 [2.20.8, -1.61] Banegore et al. 2010 50 7 10 61 1.2 7 1.55 -1.100 [2.20.8, -1.61] Cols et al. 2017 35.6 1.8 7.54 7.4 7 1.55 -1.100 [2.20.8, -1.61] De Pallie et al. 2016 (5mg/kg) 36 7 54.4 7 1.55 -1.00 [2.20.8, -1.51] 0.50 De Palie et al. 2016 (5mg/kg) 28	Test for everall effect: 7 = 5 00 /D = 0 000001	(P < 0.0	001); I ² =	11%						
Isophig Intervent Interv	Test for overall effect: ∠ = 5.99 (P < 0.00001)									
$\begin{aligned} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	5mg/kg									
$ \begin{array}{c} \mbox{transmits} transmits$	Huang et al. 2014 (Smolke)	26.0	1 90		45	2.07		2 40/	-18 10 [-20 02 46 47	-
$ \begin{array}{c} \label{eq:constraint} & 1 & 0 & 7 & 1 & 0 & 7 & 1 & 2 & 0 & 7 & 1 & 7 & 0 & 0 & 0 & 0 & 0 & 0 \\ \label{constraint} \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Hubn et al. 2008	20.9	7.7	0	40 51 A	2.07	0	1.8%	-10.10 [*20.03, -10.17]	
$ \begin{array}{c} \label{eq:second} \operatorname{second} $	Hubn et al. 2010	64	9	7	58	6	7	1 7%	3 00 [-5 01 11 01]	
$ \begin{array}{c} \mbox{left} rel 2007 complex () & [-1] + [-$	Hwang et al. 2018	11.5	89	5	17.7	87	5	1.4%	-6 20 [-17 11 4 71]	
$ \begin{array}{c} \mbox{Lines} 1 = 1 \\ \$	Laudi et al. 2007 (5mg/kg)	51	16	4	57	16	4	0.7%	-6.00 [-28.17 16.17]	
$\begin{aligned} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	Listal 2012	35.2	9.3	7	59.8	8.7	7	1.6%	-24.60 [-34.0315.17]	
Nerman et al. 2002 (Employ) Page & Kolkowski 2009 Page & Kolkowsk	Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.6%	-19.90 [-29.0510.75]	
Pagel & Acolkovski 200 ² 42 5 6 4 5 6 59xchahy et al. 201 50xchahy e	Niemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.5%	-23.00 [-51.06, 5.06]	
Superhaps etal. 2010 25 6 4 35 6 4 17.% $-1000[-18.22, 1.68]$ Heterogenetic: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.0001); P = 64% Test for versal field: 2 4.30 (P < 0.00001); P = 64% Test for versal field: 2 4.30 (P < 0.00001); P = 64% Test for versal field: 2 4.30 (P < 0.00001); P = 64% Test for versal field: 2 4.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.00001); P = 64% Test for versal field: 2 4 1.30 (P < 0.	Pagel & Krolikowski 2009	42	5	6	46	5	6	1.9%	-4.00 [-9.66, 1.66]	
Subtal (95% C) $C1 = 55.94$; $Ch^{2} = 55.81$; $Ch^{2} = 55.81$; $d^{2} = 9(^{2} < 0.0000)$; $F = 64\%$ Test for overall effect: $Z = 4.30$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 4.30$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 4.30$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 4.30$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 4.30$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 8.59$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.69$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.60$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.00$ ($P < 0.0000$); $F = 64\%$ Test for overall effect: $Z = 7.00$ ($P < 0.0000$); $F = 70\%$ Test for overall effect: $Z = 7.00$ ($P < 0.0000$); $F = 70\%$ Test for overall effect: $Z = 7.00$ ($P < 0.0000$); $F = 70\%$ Test for overall effect: $Z = 7.00$ ($P < 0.0000$); $F = 70\%$ Test for overall effect: $Z = 7.00$ ($P < 0.0000$);	Skyschally et al. 2010	25	6	4	35	6	4	1.7%	-10.00 [-18.32, -1.68]	
Heterogeneity: Tar $^{2} = 58.45$, (c) $^{2} = 6.45$, (c) $^{2} = 0.0000$); $^{2} = 64\%$ Test for overall effect: 2 = 4.30 (P < 0.0000); 10mgkg Beengler tal. 2020 (0 of 11, 13, 4, 54.17, 13, 5, 4, 10\%, -11.00 (-20.89, -1.11) Cols et al. 2013 (below) 2.25, 14, 3, 7, 59, 4, 74, 7, 1, 3%, 4, 55.014, 74, 2, 23.07 De Paular stal. 2013 (below) 2.25, 14, 3, 7, 59, 4, 74, 7, 1, 3%, 4, 55.014, 74, 2, 23.07 De Paular stal. 2013 (below) 2.25, 14, 3, 7, 59, 4, 74, 7, 1, 3%, 4, 55.014, 74, 2, 23.07 De Paular stal. 2016 (froms/ga MP) 36, 7, 84, 15, 7, 94, 17, 7, 12%, 42.00 (106, 48.00) Frag et al. 2006 35, 14, 8, 8, 15, 9, 12, 42, 2006, -24.00, -4.000, -4.000 Erang et al. 2006 1, 35, 7, 84, 15, 7, 84, 15, 7, 84, 15, 7, 84, 15, 7, 96, 127, 98, 81, 14, 15, 14, 14, 15, 14, 14, 15, 14, 14, 14, 14, 14, 14, 14, 14, 14, 14	Subtotal (95% CI)			67			67	14.9%	-12.57 [-18.29, -6.84]	•
Test for overall effect: $Z = 4.30 (P < 0.0001)$ 10 mg/kg Benefiter at 2010 50 7 10 61 12 7 1.5% -11.00 (20.89, -1.11) Choi et al. 2017 36.16 11.18 4 54.17 135 4 1.0% -18.01 (25.19, -0.83) De Paulis et al. 2013 (during) 22 5.6 7 594 7.4 7 1 7.8% -32.01 (4.07, -0.33) Panell et al. 2013 (during) 22 5.6 7 594 7.4 7 1 8% -32.01 (-2.01, -2.00, -0.80) Fang et al. 2013 (during) 52 2 1.6 1 8 57.1 16 1 8 10.9 -2.47.0 (-0.6, -8.6) Fang et al. 2016 (10mg/kg) 54 7 8 51 7 8 14.9% -50.01 (-2.66, -8.14) Hecta et al. 2016 (10mg/kg) PP 38 7 8 5 11 7 8 1.8% -50.01 (-2.66, -8.14) Hecta et al. 2016 (10mg/kg) PP 38 7 8 5 11 7 8 1.8% -50.01 (-2.66, -8.14) Hecta et al. 2016 (10mg/kg) PP 38 7 8 5 11 7 8 1.8% -50.01 (-2.66, -8.14) Hecta et al. 2016 (10mg/kg) PP 38 7 7 63 511 7 8 1.8% -50.01 (-2.16, -8.14) Hecta et al. 2010 47.3 15.7 19 51.1 16 51 19 (-0.7, 7.16, -2.00, -0.14) Heteragenetic tal. 2019 (10mg/kg) P3 7 51.9 10.7 7 1.4% -2.30 (-1.362, 9.02) Hun et al. 2007 32 7 6 4.48 10 6 1.9% -51.00 (-2.2.6, -8.14) Heteragenetic tal. 2019 45.3 11 31 11 9 11 1.4% +2.30 (-1.362, 9.02) Hun et al. 2007 32 7 6 4.48 5 7 2.9 7 1.7% +1.60.0 (-2.3.6, -8.5.16) Hundra et al. 2002 (10mg/kg) P3 35 7 5.19 10.7 7 1.4% +2.30 (-1.362, 9.02) Hun et al. 2007 32 7 6 4.48 5 7 1.9% +2.30 (-1.362, 9.02) Hun et al. 2007 32 7 6 4.48 5 7 1.9% +2.30 (-1.362, 9.02) Hun et al. 2001 (-2.7, -1.5.3) Hun et al. 2002 (10mg/kg) 23 28 4 55 8 12 4 6.05 *3.50.0 (-4.6, -5.16) Hun et al. 2005 5 3.7 7 4.44 5 1.0 8.04 (-2.3.4) Hun et al. 2005 5 3.0 7 4.44 5 1.0 8.04 (-2.3.4) Hun et al. 2005 5 3.0 7 4.44 5 1.0 8.04 (-2.3.4) Hun et al. 2005 5 3.0 7 1.2 6 7.70 (-1.16, -4.06) Hun et al. 2005 5 1.1 2 6 7.77 12 6 1.2% +2.80 (-3.958, -1.42) Hun et al. 2010 (40m et al.min et al. 2012 (40mg/kg) P3 0.0 12 6 0.8 15 1.7 8 1.6% +1.00 (-2.3.6, -3.5.4) Hun et al. 2010 (40mg/kg) 3.0 11 2.60 8 15 1.7 8 1.6% +1.00 (-2.3.6, -3.6.4) Hun et al. 2010 (40mg/kg) 3.0 11 2.60 8 15 1.7 8 1.6% +1.80 (-2.3.6, -1.6.4) Hun et al. 2010 (40mg/kg) 3.0 11 2.60 8 15 1.8% +2.00 (-3.9.	Heterogeneity: Tau ² = 58.94; Chi ² = 54.81, df = 9	(P < 0.0	0001); l²	= 84%						22
	Test for overall effect: Z = 4.30 (P < 0.0001)									
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $										
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Choi et al. 2017 30.16 11.8 4 54.17 13.5 4 10% -18.01 (55190.83) De Paulis et al. 2013 (during) 522 56 7 59.4 7.4 7 18% -7.20 [+4.07.4.3, -23.57] De Paulis et al. 2013 (during) 522 56 7 59.4 7.4 7 1.8% -7.20 [+4.07.4.3, -23.57] Fancill et al. 2016 24.4 3.3 12 47.5 4.2 12 20% -2.310 [26.12, -2.006] T Fang et al. 2008 24.4 3.3 12 47.5 4.2 12 20% -2.310 [26.12, -2.006] T Read et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -1.500 [21.66, -2.14] Read et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -1.500 [21.66, -2.14] Read et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -1.500 [21.66, -2.14] Read et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -1.500 [21.66, -2.14] Read et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -1.500 [21.66, -2.14] Read et al. 2016 (10mg/kg) 32 7 6 44 10 6 1.5% -1.600 [22.57, -2.23] Let al. 2014 261 16 16 42.3 32 6 1.5% -4.00 [24.58, -8.14] Let al. 2011 (ad) 2.32 7 6 44 510 6 1.5% -4.600 [24.58, -8.07] Herein and the all of the al	Boengler et al. 2010	50	7	10	61	12	7	1.5%	-11.00 [-20.89, -1.11]	
De Paulis et al. 2013 (before) 23.9 14.3 7 694 7.4 7 1.3% -35.50 [47.4, 2.3.57] Pancelli et al. 2014 (Jung) 52.2 5.6 7 594 7.4 7 1.3% -35.20 [47.4, 2.3.57] Pancelli et al. 2014 32.6 14.1 6 57.3 16.1 8 10.0% -24.70 [4.6.6, 4.6.80] Fancelli et al. 2016 (Ilomg) 36 24.4 3.3 12 4.75 4.2 12 2.0% -23.10 [4.6.7, 0.3.3] Gomez et al. 2008 35 14 8 58 15 9 12.4% -23.00 [4.5.6, 8.41] likeda et al. 2016 (Ilomg) 36 7 8 51 7 8 18% -15.00 [24.8, 8.41] likeda et al. 2016 (Ilomg) 49 14 12 41 16 15 14% 8.00 [3.03, 13.9.3] Krasson et al. 2016 45.9 6.3 7 6.3 7 18 18 15 14% 8.00 [23.8, 14.6] Lie et al. 2016 (1lomg) 49 14 12 41 16 15 14% 8.00 [23.8, 14.6] Lie et al. 2010 47.3 15.7 19 15.4 16.5 11.8 8 1.6% -17.00 [24.78, -8.41] Lie et al. 2011 42.5 1 6.1 6 42.3 3.9 6 1.9% -16.00 [24.87, -8.21] Lie et al. 2010 45.1 6.1 6 42.3 3.9 6 1.9% -16.00 [24.87, -8.21] Lie et al. 2011 42.5 1 6.1 6 42.3 1.8 16.1 9 1.5% -4.10 [-14.34, 6.14] Lie et al. 2011 42.5 1 6.1 6 42.3 1.8 16 1.5% -16.00 [24.87, -9.21] Lie et al. 2011 42.5 1 7 2.6 7 48 6 7 1.9% -22.00 [24.87, -14.91] Nagaoka et al. 2020 7 3.2 24 7 6 48 50 1 1.5% -16.00 [24.8, -3.7] Nickloave et al. 2019 25.17 2.6 7 48 6 7 1.9% -22.80 [24.39, -10.41] Hieroscience et al. 2002 (1lomg) 3.3 9 4.5 12 4 7 7 1.5% -22.00 [24.85, -13.8] Touce et al. 2015 5 1.3 5 6 35 8 6 1.7% -22.00 [24.85, -13.8] Touce et al. 2015 1.3 5 6 35 8 4 1.2 2.00 7 1.0.5 (14.8, -14.4) Heterogeneity: Tau" = 63.10; Ch ² = 152.44, gf = 24 (P < 0.00001); P = 84% Test for versal factor = 152.44, gf = 24 (P < 0.00001); P = 84% Test for versal factor = 152.04, gf = 10 (P < 0.00001); P = 84% Test for versal factor = 12.000 (22.70, -14.02, -13.8] Heterogeneity: Tau" = 63.10; Ch ² = 50, P < 0.00001; P = 85% To 14.2007 (12.5mg/kg) 3.0 21 4 55 11.0 4 0.9% -43.00 (27.76, -14.02] Heterogeneity: Tau" = 64.71; Ch ² = 56.12, df = 10 (P = 0.00001); P = 89% Test for versal et al. 2005 (25.9, 61.0, 00001) Total (95%, C1) 4.96; C1 4.96; C12, df = 63, (P < 0.00001); P = 89% Test for versal et al. 2010 (during ider is	Choi et al. 2017	36.16	11.18	4	54.17	13.5	4	1.0%	-18.01 [-35.19, -0.83]	
De Paulis et al. 2013 (during) 52.2 5.8 7 594 7.4 7 1 8.% -7.20 (-14.07, -9.33) Fang et al. 2006 24.4 3.3 12 47.5 4.2 12 20% -23.10 (-26.12, -20.08) Fang et al. 2006 24.4 3.3 12 47.5 4.2 12 20% -23.10 (-26.12, -20.08) Red at al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -15.00 (-24.8, -3.14) Red at al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -15.00 (-24.8, -3.14) Red at al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -15.00 (-24.8, -3.14) Red at al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -15.00 (-24.8, -3.14) Let al. 2010 49 14 12 41 16 15 1.4% 8.00 (-23.3, -23.1) Let al. 2010 47.3 15.7 19 51.4 16.5 19 1.5% -4.10 (-14.8, -14.4) Let al. 2011 (abd) 42.5 16.1 6 42.5 3.8 61 1.6 61 5.9% -4.20 (-21.9, -10.41) Let al. 2014 25.1 61.7 6 42.5 3.9 6 1.9% -16.20 (-21.9, -10.41) Let al. 2014 25.1 61.7 14% -22.30 (-21.9, -10.41) Let al. 2014 25.1 7 26 7 6 48 10 6 1.5% -16.00 (-23.7, -2.23) Let al. 2014 25.1 7 26 7 14.5% -22.80 (-21.9, -10.41) Let al. 2017 (abd) 43.6 16.3 7 7 15.1 9 1.7 14.5% -22.30 (-3.17.3, -2.3) Let al. 2015 (abg/kg) 52 53 7 4.5 7 7 1 6.5% -22.30 (-3.17.3, -10.67) Negative at al. 2015 25.3 7 44 6 10 7 14.5% -22.30 (-3.17.3, -2.3) Red Na 2015 00mg/kg) 52 53 7 4.44 6 7 19.5% -22.30 (-3.17.3, -2.3) Paulabouch at al. 2015 42.5 3.3 7 44 4 7 2.0% -10.00 (-27.6, -13.83) To al. 2015 32 5.7 2.6 7 4.8 5.8 6 1.9% -16.20 (-23.6, -5.53) To al. 2015 42.5 3.1 3 5.6 43.5 4.1 6.2 (-24.7, -25.0) (-1.16, -4.04) Paulabouch at al. 2015 42.5 3.1 3 5.6 4.5 3.8 4.1 6 2.0% -7.7.00 (-23.6, -1.3.83) To al. 2005 51 12 6 77 12 6 1.2% -26.00 (-39.68, -1.3.84) Paulabouch at al. 2015 42.2 3.1 8 5.1 7 8.4 7 1.9% -3.30 (-1.4.7, -4.54) Paulabouch at al. 2016 (-24.0.9% -1.0.00 (-27.4, -1.0.54) Lad et al. 2007 (12.5mg/kg) 30 21 4 57 16 4 0.6% -27.00 (-23.8, -1.4.45) To al. 2005 51 12 6 77 12 6 1.2% -26.00 (-39.6, -1.3.8) To al. 2006 39 10 12 6 77 19% -43.30 (-3.2.9, -3.5) To al. 2006 39 10 12 6 77 19% -43.00 (-27.4, -1.0.54) Lad et al. 2007 (12.5mg/kg) 13.9 12.9 4 58 12 4 1.0% +1.4.30 (-16.2, -3.68) To al. 2005 51 12 6 77 12 6 1.2% -26.00 (De Paulis et al. 2013 (before)	23.9	14.3	7	59.4	7.4	7	1.3%	-35.50 [-47.43, -23.57]	
Fancelli ral. 2014 32.6 14.1 8 57.3 16.1 8 10.7 $-24.70 (\pm 0.60, \pm 0.80)$ Gamez et al. 2006 24.4 3.3 12 7.7 4.2 12 0% $-23.10 (\pm 0.62, 12, 20.06)$ Gamez et al. 2006 (10mg/kg) 36 7 8 51 7 8 18% $\pm 15.00 (\pm 2.46, \pm 0.21)$ liked at al. 2016 (10mg/kg) 46 7 8 51 7 8 1.8% $\pm 15.00 (\pm 2.46, \pm 0.41)$ liked at al. 2016 (10mg/kg) 49 14 12 41 16 15 14% $\pm 0.00 (\pm 3.30, \pm 0.41)$ Krasson et al. 2016 (45.9 6.3 7 6.3 11.8 8 16% $\pm 17.00 (\pm 2.46, \pm 0.41)$ Lie et al. 2010 47.3 15.7 19 15.4 16.5 19 15% $\pm 1.00 (\pm 3.46, \pm 0.41)$ Lie et al. 2010 47.3 15.7 19 15.4 16.5 19 15% $\pm 1.00 (\pm 2.46, \pm 0.01)$ Lie et al. 2010 47.3 15.7 19 5.45 7.4 47 16 15% $\pm 6.00 (\pm 0.28, 77, \pm 0.23)$ Lie et al. 2010 47.3 15.7 19 5.45 7.4 7 16% $\pm 22.60 (\pm 3.17, \pm 1.40)$ Nagaoke tal. 2020 32 7 6 48 10 6 15% $\pm 6.00 (\pm 2.87, \pi, \pm 2.3)$ Nakawe et al. 2021 (10mg/kg) 31.9 6.9 7 5.45 7.4 7 16% $\pm 22.60 (\pm 3.17, \pm 1.40)$ Nagaoke tal. 2021 (10mg/kg) 23 12 8 45 8 12 4 0.5% $\pm 35.00 (\pm 3.46, 5.45)$ Nickloave et al. 2019 25.17 2.6 7 48 6 7 1.9% $\pm 22.60 (\pm 3.46, 5.45)$ Nickloave et al. 2019 45 13 11 11 11 16% $\pm 1.00 (\pm 2.36, 2.13, 30)$ To use at al. 2015 5 13 5 6 35 8 6 1.7% $\pm 20.00 (\pm 3.46, 5.45)$ Nickloave et al. 2019 45 13 11 10 4 8 55.4 10.9 8 1.5% $\pm 3.00 (\pm 3.28, 2.13, 30)$ To use at al. 2015 5 13 5 6 35 8 4 6 1.7% $\pm 20.00 (\pm 3.28, 2.13, 30)$ The derogeneity: Tau" ± 3.010 Ch ² ± 152.44 ($\pm 2.4 (P < 0.00001$); $\mu = 84\%$ Tast for varial factor ± 12.016 51 12 6 77 12 6 1.2% $\pm 20.00 (\pm 3.06, \pm 3.146)$ Heterogeneity: Tau" ± 3.010 (Ch ² ± 152.44 ($\pm 2.4 (P < 0.00001$); $\mu = 8.4\%$ Tast for varial factor ± 1.2008 39 10 12 6 77 112 6 1.2% $\pm 20.00 (\pm 3.08, \pm 1.242)$ Heterogeneity: Tau" ± 3.010 (Ch ² $\pm 2.4 (P < 0.00001$); $\mu = 8.4\%$ Tast for varial factor ± 1.2016 55 11 26 77 12 6 1.2% $\pm 2.00 (\pm 3.06, \pm 3.00)$ Heterogeneity: Tau" ± 3.010 (Ch ² $\pm 2.4 (P < 0.00001$); $\mu = 8.4\%$ Tast for varial factor ± 3.000 (Ch ² $\pm 3.46, \pm 3.46, \pm 5.74, \pm 5.46, \pm 5.$	De Paulis et al. 2013 (during)	52.2	5.6	7	59.4	7.4	7	1.8%	-7.20 [-14.07, -0.33]	
Fang et al. 2006 244 3.3 12 47.5 4.2 12 2.0% -23.10 (2.81, 2.2.008) Gome et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -15.00 (2.1.6.6.8.14) likeds et al. 2016 (10mg/kg) 36 7 8 51 7 8 1.8% -15.00 (2.1.6.6.8.14) Kartsson tal. 2010 49 14 12 41 16 15 1.4% 8.00 (3.3.3) (1.3.9.33) Kiss et al. 2016 45.9 6.3 7 6.38 11.6 8 1.6% -15.00 (2.1.6.6.8.14) Lie et al. 2016 47.3 15.7 19 51.4 10.5 19 15.% -4.10 (1.4.3.6.14) Lie et al. 2016 47.3 15.7 19 51.4 10.5 19 15.% -4.10 (1.4.3.6.14) Lie et al. 2011 (0.01) 49 14 12 41 16 5 1.9% -15.00 (2.1.6.8.14) Lie et al. 2010 47.3 15.7 19 51.9 10.7 1 4.4% -5.00 (2.3.7.6.23) Lie et al. 2011 (0.01) 49.6 10.9 7 54.5 7.4 7 1 16% -22.00 (3.1.7.6.23) Lie et al. 2011 (0.01) 49.6 10.9 7 54.5 7.4 7 7 16.% -22.00 (3.1.7.6.23) Lie et al. 2011 (0.01) 49.6 15.9 7 7 2 9 7 1.7% -16.00 (2.3.7.8.5.7.16) Kinolaou et al. 2019 5 15 15 7 7 2 9 7 1.7% -16.00 (2.3.7.8.5.7.16) Nikolaou et al. 2019 25.1 7 2.6 7 19% -0.25 31.27.67, -7.30] Wang et al. 2002 25 3 7 6 48 6.5 8 6 1.9% -45.00 (2.2.7.6, -1.5.0) Wang et al. 2019 25.1 7 2.6 7 7 12 6 1.9% -16.00 (2.2.7.6, -1.5.0) Wang et al. 2015 13 5 6 5 7 7 12 6 1.9% -7.60 (1.1.6, 4.04) Amageta et al. 2015 13 5 6 5 8 7 14 7 2.0% -10.00 (2.2.70, -1.5.0) Fu et al. 2015 13 5 6 25 8 6 1.9% -45.00 (2.2.76, -1.7.30) Exercise 2.2.00 (2.2.55, -1.4.4.5] Exercise 4.2.013 5.1 1 0.4 8 55.4 1.0 2 0 20 3 3.1% -14.4.5 (-14.04) Exercise 4.2.010 (2.0.7.0); Fi = 84% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 84% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 84% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 84% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 84% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 84% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 85% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 85% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 85% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 85% Test for overall effect: 2 = 7.80 (P < 0.00001); Fi = 70% Test for overall effect:	Fancelli et al. 2014	32.6	14.1	8	57.3	18.1	8	1.0%	-24.70 [-40.60, -8.80]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Fang et al. 2008	24.4	3.3	12	47.5	4.2	12	2.0%	-23.10 [-26.12, -20.08]	
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Gomez et al. 2008	35	14	8	58	15	9	1.2%	-23.00 [-36.79, -9.21]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	lkeda et al. 2016 (10mg/kg)	30	2	8	51	7	0	1.8%	-15.00 [-21.86, -8.14]	
$ \begin{array}{c} \text{Rulesoft if if is 2010} & 1 = 1 \\ \text{Res of it 2016} & 4 = 5 \\ \text{Le st it 2010} & 47.3 \\ \text{Le st it 2011} & 50.6 \\ \text{Res of it 2010} & 51.9 \\ \text{Res of it 2010} & 51.1 \\ \text{Res of it 2010} & 5$	Kedeson at al. 2016 (Tomgrkg NP)	30	14	12	31	16	15	1.0%	-15.00 [-21.00, -0.14]	
$\begin{aligned} & \text{Nos of al. 2010} & \text{Les of al. 2011} & L$	Kansson et al. 2010	43	6.3	7	63.8	116	10	1.476	17 00 [-3.33, 19.33]	
$ \begin{array}{c} Let al. 2016 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2016 \\ Li et al. 2019 \\ Li et al. 2016 \\ 202 \\ Li et al. 2018 \\ Li et al. 2019 \\ Voucef et al. 2019 \\ Voucef et al. 2019 \\ Voucef et al. 2015 \\ Li et al. 2018 \\ Li et al. 2016 \\ Li et al. 2016 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2016 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2017 \\ Li et al. 2018 \\ Li et al. 2018 \\ Li et al. 2018 \\ Li et al. 2019 \\ Li et al. 2018 \\$	Lie et al 2010	47.3	15.7	19	51.4	18.5	19	1 5%	-4 10 [-14 34 6 14]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Lietal 2014	26.1	61	6	42.3	3.9	6	1.9%	-16 20 [-21 99 -10 41]	
Lu et al. 2011 (old) 49.6 10.9 7 51.9 10.7 7 1.4% -2.30 [-13.62, 9.02] Lu et al. 2011 (young) 31.9 8.9 7 54.5 7.4 7 1.6% -22.00 [-3.17, 1-4.03] Magaoka et al. 2015 56 5 7 72 9 7 1.7% -16.00 [-2.36, 8.37] Niemann et al. 2020 (Ung/kg) 23 28 4 58 12 4 0.5% -35.00 [-4.85, 5.15] Wang et al. 2019 25.17 2.6 7 4.8 6 7 1.9% -22.8] 2.7.7, 7.17.99] Rusinkevich et al. 2019 45 13 11 31 9 11 1.6% 41.00 [4.66, 23.34] Wang et al. 2016 25 3 7 44 4 7 2.0% -19.00 [-22.02, -15.30] Tale avoid et al. 2015 13 5 6 35 8 6 1.9% -28.00 [-23.62, -13.38] Youcef et al. 2015 46.2 3.1 1 0.4 8 55.4 10.9 8 1.5% -4.30 [-14.74, 6.14] Zalewski et al. 2015 51 13 5 6 35 8 6 1.9% -7.60 [-11.6, -4.04] Zhu et al. 2013 51.1 10.4 8 55.4 10.9 8 1.5% -4.30 [-14.74, 6.14] Zhu et al. 2015 51 12 6 77 12 6 1.2% -26.00 [-39.58, -12.42] Ikeda et al. 2016 (Z6mg/kg) 32 10 8 51 7 8 1.6% -19.00 [-27.60, -11.6] Heterogeneily: Tau ² = 63.10; Chi ² = 152.44, df = 24 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001) $\ge 12.5mg/kg$ Gomez et al. 2016 (Z6mg/kg) 30 21 4 57 7 16 4 0.5% -43.00 [-39.58, -12.42] Ikeda et al. 2016 (Z6mg/kg) 39 10 12 60 8 15 1.8% -19.00 [-27.60, -11.04] Matsubara et al. 2010 (dofre ischemia) 39.6 3.6 4 53.4 5 7 1.9% -14.30 [-18.29, -8.88] Miemann et al. 2010 (dofre ischemia) 39.1 4.2 6 53.4 4.7 7 1.9% -14.30 [-13.0, -9.30] Niemann et al. 2002 (Z6mg/kg) 13.9 12.9 4 58 12 4 1.0% 44.10.16 [-53.7, -26.33] Miemann et al. 2002 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.71, -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.71, -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.71, -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.71, -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.71, -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.71, -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -	Lim et al. 2007	32	7	6	48	10	6	1.5%	-16.00 [-25.77, -6.23]	
Lu et al. 2011 (young) 31.9 6.9 7 54.5 7.4 7 1 6% -2260 ($\frac{5}{24}$, 17, 44.03] Nagaoka et al. 2021 ($\frac{5}{26}$, 17, 26 7 48 6 7 1.9% -16.00 ($\frac{23.63}{2.63, 6.37}$) Nicheave et al. 2019 25.17 2.6 7 48 6 7 1.9% -228 ($\frac{27.67}{2.76, 17.98}$] Wang et al. 2006 25 3 7 44 4 7 2.0% -19.00 ($\frac{22.70}{2.70, 15.30}$) Wang et al. 2006 25 3 7 44 4 7 2.0% -19.00 ($\frac{22.70}{2.70, 15.30}$) Wang et al. 2007 30.3 2.7 6 48.8 5.8 6 1.7% -22.00 ($\frac{23.52}{2.63, 2.13.38}$] Youcef et al. 2015 46.2 3.1 8 53.8 4.1 8 2.0% -7.60 ($\frac{11.16}{2.44, 4.65}$) Heterogeneity: Tau ² = 63.10; Ch ² = 152.44, df = 24 ($P < 0.00001$); $P = 84\%$ Test for overall effect: Z = 7.80 ($P < 0.00001$); $P = 84\%$ Test for overall effect: Z = 7.80 ($P < 0.00001$); $P = 84\%$ Naturbuare et al. 2016 ($\frac{25mg}{kg}$) 30 21 4 57 16 4 0.5% -32.100 ($\frac{27.46}{2.70, 61.43, 6.143}$] Nemann et al. 2007 ($\frac{12.5mg}{kg}$) 30 21 4 4 57 16 4 0.5% -27.00 ($\frac{12.85}{2.270, 61.404}$] Matsubare et al. 2016 ($\frac{12.5mg}{kg}$) 30 21 4 4 57 16 4 0.5% -27.00 ($\frac{14.92}{2.00, 61.47, 6.154}$] Laudi et al. 2007 ($\frac{12.5mg}{kg}$) 30 21 4 4 57 16 4 0.5% -27.00 ($\frac{14.92}{2.20, 61.404}$] Niemann et al. 2001 ($\frac{16.95}{2.50, 91.43}$) 13.9 112.9 4 58 12 4 1.0% +41.00 ($\frac{13.7}{2.70, 61.404}$] Niemann et al. 2002 ($\frac{15mg}{kg}$) 13.9 12.9 4 58 12 4 1.0% +41.00 ($\frac{13.7}{2.50, 82.37, 1.42.28}$] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{14.77}{2.02, 62.37, 1.42.28}$] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{14.77}{2.70, 62.37, 1.42.28}$] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{14.77}{2.70, 62.37, 1.42.28}$] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{14.17, 6.73, 22.88}{1.1, 1.43, 6.43, 52.72, 24.84, 1.77}$ Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{14.17, 6.28, 7.74, 6.77, 22.83}{1.1, 1.43, 6.43, 52.77, 42.72.85}$] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 (Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.4%	-2.30 [-13.62, 9.02]	
$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.6%	-22.60 [-31.17, -14.03]	
Niemann et al. 2002 (10mg/kg) 23 28 4 56 12 4 0.5% -35.00 [-64.85, -5.15] Nikolaou et al. 2019 25.17 2.5 7 48 6 7 1.5% -22.83 [27.67, -17.99] Wang et al. 2006 25 3 7 44 4 7 2.0% [-22.80, 164.62, 23.9] Youcef et al. 2019 30.3 2.7 6 48.8 5.8 6 1.5% +0.90 [-22.70, -15.30] Youcef et al. 2015 13 5 6 35 8 6 1.7% +22.80 [-23.62, -13.38] Youcef et al. 2015 46.2 3.1 8 53.8 4.1 8 2.0% -7.60 [-11.16, 4.04] Zalewski et al. 2015 46.2 3.1 8 53.8 4.1 8 2.0% -7.60 [-11.16, 4.04] Subtotal (95% CI) 200 202 39.1% -14.45 [-18.08, -10.82] Heterogeneity: Tau ² = 63.10; Chi ² = 152.44, df = 24 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 44% Test for overall effect: Z = 7.80 (P < 0.00001); P = 44% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0.00001); P = 89% Test for overall effect: Z = 8.59 (P < 0	Nagaoka et al. 2015	56	5	7	72	9	7	1.7%	-16.00 [-23.63, -8.37]	
Nikolaou et al. 2019 25.17 2.6 7 48 6 7 1.9% -22.83 [$\cdot 27.67, -17.99$] Rusinkevich et al. 2019 45 13 11 31 9 11 1.6% 4.400 [4.66, 23.34] Wang et al. 2006 25 3 7 44 4 7 2.0% -18.00 [22.70, 15.30] Xie & Yu 2007 30.3 2.7 6 48.8 5.8 6 1.3% +10.00 [24.66, 23.34] Youcef et al. 2015 46.2 3.1 8 5.8 6 1.3% +4.400 [14.66, 23.34] Zhu et al. 2013 51.1 10.4 8 55.4 10.9 8 1.5% +4.30 [-14.74, 6.14] Zhu et al. 2013 51.1 10.4 8 55.4 10.9 8 1.5% +4.30 [-14.74, 6.14] Subtotal (95% cl) 200 202 39.1% +14.45 [-18.06, -10.62]	Niemann et al. 2002 (10mg/kg)	23	28	4	58	12	4	0.5%	-35.00 [-64.85, -5.15]	·
Rusinkevich et al. 2019 45 13 11 31 9 11 1.8% 1.4.00 (4.66, 23.3.4) Wang et al. 2006 25 3 7 44 4 7 2.0% -19.00 (-22.70, -15.30) Youcef et al. 2015 13 5 6 35 8 6 1.7% -22.00 (-25.55, -14.45) Zalewski et al. 2015 46.2 31.8 8.53.8 4.1 8 2.0% -7.60 (-11.61, -0.4) Zalewski et al. 2015 46.2 31.8 8.55.4 10.9 8 1.5% -4.30 (-14.74, 6.14) Zub et al. 2013 51.1 10.4 8 55.4 10.9 8 1.5% -4.30 (-14.74, 6.14) Subtotal (95% CI) Tall * 6 77 12 6 1.2% -26.00 (-39.58, -12.42) - Lead ot al. 2007 (12.5mg/kg) 30 21 4 57 1.6% -13.00 (-27.46, -10.64) - Matsubara et al. 2010 (before ischemia) 39.6 3.6 4 53.4 5 7 1.9% -13.80 (-18.92, -6.8] - - - - -	Nikolaou et al. 2019	25.17	2.6	7	48	6	7	1.9%	-22.83 [-27.67, -17.99]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Rusinkevich et al. 2019	45	13	11	31	9	11	1.6%	14.00 [4.66, 23.34]	
Xie & Yu 2007 30.3 2.7 6 48.8 5.8 6 1.9% -18.50 [-23.62, -13.38] Youcef et al. 2015 13 5 6 35 8 6 1.9% -18.50 [-23.62, -13.38] Zalewski et al. 2015 46.2 3.1 8 53.8 4.1 8 2.0% -7.60 [-11.16, -4.04] Zhu et al. 2013 51.1 10.4 8 55.4 10.9 8 1.5% -4.30 [-14.74, 6.14] Zhu et al. 2013 51.1 10.4 8 55.4 10.9 8 1.5% -4.30 [-14.74, 6.14] Heterogeneity: Tau ² = 63.10; Ch ² = 152.44, df = 24 (P < 0.00001); P = 84% Test for overall effect: $Z = 7.80$ (P < 0.00001) $\ge 12.5mg/kg$ Gomez et al. 2005 51 12 6 77 12 6 1.2% -26.00 [-39.58, -12.42] Leading et al. 2016 (25mg/kg) 32 10 8 51 7 8 1.6% -19.00 [-27.46, -10.54] Laudi et al. 2007 (12.5mg/kg) 30 21 4 57 16 4 0.6% -27.00 [-52.87, -1.13] Leshnower et al. 2008 39 10 12 60 8 15 1.8% -21.00 [-52.68, -14.04] Matsubara et al. 2010 (after ischemia) 39.6 3.6 4 53.4 5 7 1.9% -13.80 [-18.92, -8.68] Matsubara et al. 2010 (bafter ischemia) 39.1 4.2 6 53.4 4.5 7 1.9% -14.30 [-19.25, -9.35] Niemann et al. 2002 (25mg/kg) 13.9 12.9 4 58 12 4 0.9% 4-10.0 [-59.52, -22.48] Matsubara et al. 2012 (bafter ischemia) 39.1 4.4 6 53.4 4.7 7 1.9% -41.30 [-19.25, -9.35] Niemann et al. 2002 (25mg/kg) 17 14.6 4 58 12 4 0.9% 4-10.0 [-59.52, -22.48] Matsubara et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18 6 55 13 6 0.9% -27.00 [-4.77, -8.23] Shintani-Ishida et al. 2012 (bafter ischemia) 28 18	Wang et al. 2006	25	3	7	44	4	7	2.0%	-19.00 [-22.70, -15.30]	
Youcef et al. 2015 13 5 6 35 8 6 17% $-22.00 [-29.55, -14.45]$ Zalewski et al. 2015 46.2 3.1 8 53.8 4.1 8 2.0% $-7.60 [-11.16, -4.04]$ Zule value of al. 2013 51.1 10.4 8 654 10.9 8 1.5% $-4.30 [-47.46, 1.4]$ Subtotal (95% CI) 200 202 39.1% $-14.45 [-18.08, -10.82]$ Heterogeneity: Tau ² = 63.10; Ch ² = 152.44, df = 24 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001) $\ge 12.5mg/kg$ Gomez et al. 2005 51 12 6 77 12 6 1.2% $-26.00 [-39.58, -12.42]$ Ikeda et al. 2016 (Z5mg/kg) 32 10 8 51 7 8 1.6% $-9.00 [-27.46, -10.54]$ Laudi et al. 2007 (12.5mg/kg) 30 21 4 4 57 16 4 0.6% $-27.00 [-52.57, -1.13]$ Leshnower et al. 2008 39 10 12 60 8 15 1.8% $-21.00 [-27.96, -14.04]$ Matsubara et al. 2010 (after ischemia) 39.6 3.6 4 53.4 5 7 1.9% $-13.80 [-18.29, -68.8]$ Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 1.0% $-41.00 [-59.52, -22.48]$ Niemann et al. 2002 (25mg/kg) 13.9 12.9 4 58 12 4 0.9% $-41.00 [-59.52, -22.48]$ Niemann et al. 2002 (25mg/kg) 13 9 12.9 4 58 12 4 0.9% $-27.00 [-52.5, -9.35]$ Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% $-27.00 [-54.77, -22.28]$ Shintani-Ishida et al. 2012 (during/after ischem) 16 13 6 55 13 6 1.1% $-39.00 [-53.71, -24.29]$ Shintani-Ishida et al. 2012 (during/after ischem) 16 13 6 55 13 6 1.1% $-39.00 [-53.71, -24.29]$ Heterogeneity: Tau ² = 41.49; Ch ² = 32.87, df = 10 (P = 0.0003); P = 70% Test for overall effect: Z = 3.59 (P < 0.00001) Total (95% CI) 481 490 100.0% $-16.30 [-18.59, -14.01]$ Heterogeneity: Tau ² = 44.71; Ch ² = 556.12, df = 63 (P < 0.00001); P = 89% Test for overall effect: Z = 13.93 (P < 0.00001)	Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	1.9%	-18.50 [-23.62, -13.38]	
$ \begin{array}{c} \text{Zalewski et al. 2015} & 46.2 & 3.1 & 8 & 53.8 & 4.1 & 8 & 2.0\% & 7.60 [+11, f6, -4.04] \\ \text{Zhu et al. 2013} & 51.1 & 10.4 & 8 & 55.4 & 10.9 & 8 & 1.5\% & -4.30 [-14.74, 6, 14] \\ \text{Zhu et al. 2013} & 51.1 & 10.4 & 8 & 55.4 & 10.9 & 8 & 1.5\% & -4.30 [-14.74, 6, 14] \\ \text{Heterogeneity: Tau2} = 63.10; \text{Chi2} = 152.44, \text{ df} = 24 (P < 0.00001); P = 84\% \\ \text{Test for overall effect: Z = 7.80 (P < 0.00001)} \\ \\ \hline \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Youcef et al. 2015	13	5	6	35	8	6	1.7%	-22.00 [-29.55, -14.45]	
Zhu etal. 2013 51.1 10.4 8 65.4 10.9 8 1.5% -4.30 [-14.74, 6, 14] Subtotal (95% Cl) 200 202 39.1% -14.45 [-18.08, -10.82] Heterogeneity: Tau ² = 63.10; Chi ² = 152.44, df = 24 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001) ≥12.5mg/kg Gomez et al. 2005 51 12 6 77 12 6 1.2% -26.00 [-39.58, -12.42] Ikeda et al. 2016 (25mg/kg) 32 10 8 51 7 8 1.6% -19.00 [-27.46, -10.54] Laudi et al. 2007 (12.5mg/kg) 30 21 4 57 16 4 0.6% -27.00 [-28.87, -1.13] Leshnower et al. 2008 39 10 12 60 8 15 1.8% -21.00 [-27.96, -14.04] Matsubara et al. 2010 (after ischemia) 39.6 3.6 4 53.4 5 7 1.9% -14.80 [-18.92, -8.68] Matsubara et al. 2010 (after ischemia) 39.1 4.2 6 53.4 5 7 1.9% -14.30 [-18.92, -8.68] Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 1.0% -41.00 [-59.52, -22.48] Niemann et al. 2002 (25mg/kg) 13.9 12.9 4 58 12 4 0.9% -41.00 [-59.52, -22.48] Niemann et al. 2002 (25mg/kg) 13.9 12.9 4 558 12 4 0.9% -41.00 [-59.52, -22.48] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 1.1% -30.00 [-37.42.29] Subtotal (95% Cl) 481 490 100.0% -16.30 [-18.59, -14.01] Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 10 (P = 0.0003); P = 70% Test for overall effect: Z = 13.93 (P < 0.00001) Total (95% Cl) 481 490 100.0% -16.30 [-18.59, -14.01] Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 63 (P < 0.00001); F = 89% Test for overall effect: Z = 13.93 (P < 0.00001)	Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.0%	-7.60 [-11.16, -4.04]	
Subtotial (95% CI) 200 202 39.1% -14.45 [-18.08, -10.82] Heterogeneity: Tau ² = 63.10; Ch ² = 152.44, df = 24 (P < 0.00001); P = 84% Test for overall effect: Z = 7.80 (P < 0.00001) $\geq 12.5mg/kg$ Gomez et al. 2005 51 12 6 77 12 6 1.2% -26.00 [-39.58, -12.42] Laudi et al. 2016 (25mg/kg) 32 10 8 51 7 8 1.6% -19.00 [-27.46, -10.54] Laudi et al. 2007 (12.5mg/kg) 30 21 4 4 57 16 4 0.6% -27.00 [-25.87, -1.13] Leshnower et al. 2008 39 10 12 60 8 15 1.8% -21.00 [-27.96, -14.04] Matsubara et al. 2010 (after ischemia) 39.6 3.6 4 53.4 5 7 1.9% -13.80 [-18.29, -6.68] Matsubara et al. 2010 (after ischemia) 39.1 4.2 6 6 53.4 5 7 1.9% -13.80 [-19.25, -9.35] Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 1.0% -41.00 [-59.52, -22.48] Niemann et al. 2002 (25mg/kg) 13.9 12.9 4 58 12 4 0.9% -41.00 [-59.52, -22.48] Niemann et al. 2002 (25mg/kg) 13.9 12.9 4 55 13 6 0.9% -27.00 [-4.77, -9.23] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Shintani-Ishida et al. 2012 (before ischemia) 16 13 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Heterogeneity: Tau ² = 41.49; Ch ² = 32.87, df = 10 (P = 0.0003); P = 70% Test for overall effect: Z = 3.59 (P < 0.00001) Total (95% CI) 481 490 100.0% -16.30 [-18.59, -14.01] +50 -25 0 25 50 Test for overall effect: Z = 13.93 (P < 0.00001); P = 89%	Zhu et al. 2013	51.1	10.4	8	55.4	10.9	8	1.5%	-4.30 [-14.74, 6.14]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Subtotal (95% CI)		0000	200			202	39.1%	-14.45 [-18.08, -10.82]	▼
iest for overall effect: $z = r, su (r^{2} < 0.00001)$ ≥12.5mg/kg Gomez et al. 2005 51 12 6 77 12 6 1.2% s26.00 [-39.58, -12.42] Ikeda et al. 2016 (25mg/kg) 32 10 8 51 7 8 1.6% s20.00 [-39.58, -12.42] Leadi et al. 2007 (12.5mg/kg) 30 21 4 57 16 4 0.6% s27.00 [-52.87, -1.13] Leshnower et al. 2008 39 10 12 60 8 15 7 1.9% s24.668] Matsubara et al. 2010 (before ischemia) 39.1 4.2 6 53.4 5 7 1.9% s1.80 [-19.30, -9.30] Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 0.9% s2.22.48] Ranji et al. 2009 39.1 4.4 6 53.4 5 7 1.9% s2.22.48] 5 Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% s2.22.48]	Heterogeneity: Tau ² = 63.10; Chi ² = 152.44, df =	24 (P < 0	1.00001);	1 ² = 8/	1%					
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	rest for overall effect: Z = 7.80 (P < 0.00001)									
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	>12.5mg/kg									
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Gomez et al. 2005	54	12	6	77	12	6	1.3%	-26 00 [-39 58 -12 42]	
Laudi et al. 2007 (12.5mg/kg) 30 21 4 57 16 4 0.6% -27.00 [52.87, -1.13] Leshnower et al. 2008 39 10 12 60 8 15 1.8% -27.00 [52.87, -1.13] Matsubara et al. 2010 (lafter ischemia) 39.6 3.6 4 53.4 5 7 1.9% -13.80 [18.92, -8.68] Matsubara et al. 2010 (before ischemia) 39.1 4.2 6 53.4 5 7 1.9% -14.30 [-19.30, -9.30] Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 1.0% 44.10 [-59.52, -22.48] Niemann et al. 2002 (25mg/kg) 17 14.6 4 58 12 4 0.9% -41.00 [59.52, -22.48] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Shintani-Ishida et al. 2012 (before ischemia) 16 13 65 51 3 6 1.1% -30.00 [-53.71, -24.29] Subtotal (95% Cl) 66 74 14.9% -22.36 [-27.46, -17.26] Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 10 (P = 0.0003); P = 70% Test for overall effect: Z = 8.59 (P < 0.00001) Total (95% Cl) 481 490 100.0% -16.30 [-18.59, -14.01] +50 -25 0 25 50 Test for overall effect: Z = 13.93 (P < 0.00001); F = 89%	Ikeda et al. 2016 (25mo/ko)	32	10	8	51	7	8	1.6%	-19.00 [-27.46 -10.54]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Laudi et al. 2007 (12.5mg/kg)	30	21	4	57	16	4	0.6%	-27.00 [-52.871.13]	
Matsubara et al. 2010 (after ischemia) 39.6 3.6 4 53.4 5 7 1.9% -13.80 [-18.92, -8.68] Matsubara et al. 2010 (before ischemia) 39.1 4.2 6 53.4 5 7 1.9% -13.80 [-18.92, -8.68] Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 0.9% -41.00 [-51.37, -26.83] Niemann et al. 2002 (25mg/kg) 17 14.6 4 58 12 4 0.9% -41.00 [-55.52, -22.48] Ranji et al. 2009 39.1 4.4 6 53.4 4.7 7 1.9% -14.30 [-19.25, -9.35] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Subtotal (95% CI) 66 74 14.9% -22.36 [-27.46, -17.26] - - Heterogeneity: Tau² = 41.49; Chi² = 32.87, df = 10 (P = 0.00001); F² = 89% 490 100.0% -16.30 [-18.59, -14.01] - - - - - - - - - - - - - - -	Leshnower et al. 2008	39	10	12	60	8	15	1.8%	-21.00 [-27.9614.04]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Matsubara et al. 2010 (after ischemia)	39.6	3.6	4	53.4	5	7	1.9%	-13.80 [-18.92, -8.68]	
Niemann et al. 2002 (15mg/kg) 13.9 12.9 4 58 12 4 1.0% -44.10 [-61.37, -26.83] Niemann et al. 2002 (25mg/kg) 17 14.6 4 58 12 4 0.9% -41.00 [-59.52, -22.48] Ranji et al. 2009 39.1 4.4 6 53.4 7 1.9% -41.00 [-59.52, -22.48] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Shintani-Ishida et al. 2012 (during/after ischem) 16 13 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Valutotat (95% Cl) 66 74 14.9% -22.36 [-27.46, -17.26] -44.10 [-61.37, -26.30 [-27.46, -17.26] Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 10 (P = 0.0003); P = 70% 70% -44.10 [-61.30 [-18.59, -14.01] -50 -25 0 25 50 Test for overall effect: Z = 13.93 (P < 0.00001)	Matsubara et al. 2010 (before ischemia)	39.1	4.2	6	53.4	5	7	1.9%	-14.30 [-19.30, -9.30]	
Niemann et al. 2002 (25mg/kg) 17 14.6 4 58 12 4 0.9% -41.00 [-59.52, -22.48] Ranji et al. 2009 39.1 4.4 6 53.4 4.7 7 1.9% -14.30 [-19.25, -9.35] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Shintani-Ishida et al. 2012 (buring/after ischem) 16 13 6 55 13 6 1.1% -30.00 [-53.71, -24.29] Subtotal (95% CI) 66 74 14.9% -22.36 [-27.46, -17.26] - Heterogeneity: Tau² = 41.49; Ch² = 32.87, df = 10 (P = 0.0003); P = 70% 70% - <td< td=""><td>Niemann et al. 2002 (15mg/kg)</td><td>13.9</td><td>12.9</td><td>4</td><td>58</td><td>12</td><td>4</td><td>1.0%</td><td>-44.10 [-61.37, -26.83]</td><td></td></td<>	Niemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.0%	-44.10 [-61.37, -26.83]	
Ranji et al. 2009 39.1 4.4 6 53.4 4.7 7 1.9% -14.30 [-19.25, -9.35] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Shintani-Ishida et al. 2012 (during/after ischem) 16 13 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Subtotal (95% Cl) 66 74 14.9% -22.36 [-27.46, -17.26] Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 10 (P = 0.0003); l ² = 70% Test for overall effect: Z = 8.59 (P < 0.00001) Test for overall effect: Z = 13.93 (P < 0.00001); l ² = 89% Test for overall effect: Z = 13.93 (P < 0.00001)	Niemann et al. 2002 (25mg/kg)	17	14.6	4	58	12	4	0.9%	-41.00 [-59.52, -22.48]	
Shintani-Ishida et al. 2012 (before ischermia) 28 18 6 55 13 6 0.9% -27.00 [-44.77, -9.23] Shintani-Ishida et al. 2012 (during/after ischerm) 16 13 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Shintani-Ishida et al. 2012 (during/after ischerm) 16 13 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 10 (P = 0.0003); P = 70% 74 14.9% -22.36 [-27.46, -17.26] Test for overall effect: Z = 8.59 (P < 0.00001)	Ranji et al. 2009	39.1	4.4	6	53.4	4.7	7	1.9%	-14.30 [-19.25, -9.35]	
Shintani-Ishida et al. 2012 (during/after ischem) 16 13 6 55 13 6 1.1% -39.00 [-53.71, -24.29] Subtotal (95% CI) 66 74 14.9% -22.36 [-27.46, -17.26] Heterogeneity: Tau ² = 41.49; Ch ² = 32.87, df = 10 (P = 0.0003); P = 70% Test for overall effect: Z = 8.59 (P < 0.00001) Heterogeneity: Tau ² = 64.71; Ch ² = 556.12, df = 63 (P < 0.00001); P = 89% Test for overall effect: Z = 13.93 (P < 0.00001) Favours [control]	Shintani-Ishida et al. 2012 (before ischemia)	28	18	6	55	13	6	0.9%	-27.00 [-44.77, -9.23]	
Subtotal (95% Cl) 66 74 14.9% -22.36 [-27.46, -17.26] Heterogeneity: Tau" = 41.49; Chi² = 32.87, df = 10 (P = 0.0003); I² = 70% 70% Test for overall effect: Z = 8.59 (P < 0.00001)	Shintani-Ishida et al. 2012 (during/after ischem)	16	13	6	55	13	6	1.1%	-39.00 [-53.71, -24.29]	
Heterogeneity: Tau ² = 41.49; Ch ² = 32.87, df = 10 (P = 0.0003); P = 70% Test for overall effect: Z = 8.59 (P < 0.00001) Total (95% Cl) 481 490 100.0% -16.30 [-18.59, -14.01] Heterogeneity: Tau ² = 64.71; Ch ² = 556.12, df = 63 (P < 0.00001); P = 89% Test for overall effect: Z = 13.93 (P < 0.00001) Fer stor overall effect: Z = 13.93 (P < 0.00001) Fer stor overall effect: Z = 13.93 (P < 0.00001)	Subtotal (95% CI)			66			74	14.9%	-22.36 [-27.46, -17.26]	•
Test for overall effect: Z = 8.59 (P < 0.00001)	Heterogeneity: Tau ² = 41.49; Chi ² = 32.87, df = 1	0 (P = 0.	0003); l²	= 70%						22
Total (95% CI) 481 490 100.0% -16.30 [-18.59, -14.01] Heterogeneity: Tau ² = 64.71; Chi ² = 556.12, df = 63 (P < 0.00001); I ² = 89% -50 -25 0 25 50 Test for overall effect: Z = 13.93 (P < 0.00001)	Test for overall effect: Z = 8.59 (P < 0.00001)									
Iotal (195% CI) 481 490 100.0% -16.30 [-18.59, -14.01] Heterogeneity: Tau ² = 64.71; Chi ² = 556.12, df = 63 (P < 0.00001); P = 89%	and the second and the second s			45.5						
Heterogeneity: Tau" = 54.71; Chi ² = 556,12, df = 63 (P < 0.00001); I ² = 89% Test for overall effect: Z = 13.93 (P < 0.00001) Favours [experimental] Favours [control]	Total (95% CI)			481			490	100.0%	-16.30 [-18.59, -14.01]	
Test for overall effect: Z = 13.93 (P < 0.00001) Favours (experimental) Favours (control)	Heterogeneity: Tau ² = 64.71; Chi ² = 556.12, df =	63 (P < (.00001);	² = 8	9%					-50 -25 0 25 50
The first factor $O(2 - 0.45) = 0.45 = 0.00$	Test for overall effect: Z = 13.93 (P < 0.00001)	(D		0.001						Favours [experimental] Favours [control]

Figure S4 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by dose.

	Exp	eriment	al	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
20-Somma	51	12	6	77	12	6	1 29/	26 00 1 20 59 12 421	
Juhn et al. 2008	31.8	77	0	51.4	5	9	1 0%	-20.00 [-35.30, -12.42]	
Juhn et al. 2000	61	0	7	58	6	7	1 7%	3 00 [-5 01 11 01]	
keda et al. 2021 (30min)	33	10	8	53	7	8	1 7%	-20 00 [-28 46 -11 54]	
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	1.9%	-6.00 [-11.66 -0.34]	
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	2.0%	-23 00 [-27 67 -18 33]	_
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.9%	-45.00 [-51.45, -38.55]	
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.1%	-36 00 [-40 08 -31 92]	
Subtotal (95% CI)	10		54	02	°,	54	14.5%	-21.62 [-32.08, -11.15]	•
Heterogeneity: Tau ² = 213.52; Chi ² = 159.61, df = Fest for overall effect: Z = 4.05 (P < 0.0001)	7 (P < 0	0.00001)	; l² = 9	6%				•	
: 30-40min									
reaud at al. 2005 (aftar)	24	11	8	60	17	8	1 2%	-36 00 [-50 03 -21 07]	
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36 00 [-50 03 -21 97]	
Boengler et al. 2010	50	7	10	61	12	7	1.6%	-11.00 [-20.89 -1.11]	
choi et al. 2017	36.16	11 18	4	54 17	13.5	4	1.0%	-18 01 [-35 19 -0 83]	
e Paulis et al. 2013 (before)	23.9	14.3	7	59.4	7.4	7	1.4%	-35.50 [-47.4323.57]	
e Paulis et al. 2013 (during)	52.2	5.6	7	59.4	74	7	1.8%	-7 20 [-14 07 -0 33]	
ancelli et al. 2014	32.6	14.1	8	57.3	18 1	8	1 1%	-24 70 [-40 60 -8 80]	
and at al. 2014	24.4	33	12	47.5	4.2	12	2 1%	-23 10 [-26 12 -20 08]	-
ins et al. 2003	51.5	3.4	12	62.8	4.2	8	2 1%	-11 30 [-15 38 -7 22]	
luang et al. 2014 (1mg/kg)	35 20	1.52	8	45	2.07	8	2 2%	-9 71 [-11 49 -7 92]	-
luang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2 2%	-15.95 [-17.98 -13.92]	-
luana et al. 2014 (5malka)	28.0	1.86	0	45	2.07	9	2 20/	-18 10 [-20 03 -16 17]	-
furt at al 2016	40	5	6	61	5	6	1 0%	-12 00 [-17 66 -6 24]	
keda et al. 2016 (10mg/kg)	43	7	0	64	7	0	1 90/	-15.00 [-17.00, -0.34]	
(eda et al. 2016 (10mg/kg ND)	30	7	0	51	7	0	1.0%	-15.00 [-21.00, -0.14]	
(eda et al. 2016 (1mg/kg NP)	50	7	0	51	7	0	1.0%	2 00 [4 99 9 99]	
reda et al. 2016 (1mg/kg)	23	10	0	51	7	0	1.0%	2.00 [-4.00, 0.06]	
veda et al. 2016 (111g/kg/NP)	32	10	0	51	7	0	1.7%	-13.00 [-27.40, -10.34]	
keda et al. 2016 (2.5mg/kg)	49	10	0	51	-	0	1.7%	-2.00 [-10.46, 6.46]	
(eda et al. 2016 (2.5mg/kg NP)	31	10	0	51	4	0	1.770	-20.00 [-28.46, -11.54]	
Keda et al. 2016 (25mg/kg)	32	10	8	51		8	1.7%	-19.00 [-27.46, -10.54]	
uss et al. 2016	45.9	6.3	1	63.8	11.6	8	1.6%	-17.90 [-27.19, -8.61]	
audi et al. 2007 (12.5mg/kg)	30	21	4	57	16	4	0.6%	-27.00 [-52.87, -1.13]	
audi et al. 2007 (5mg/kg)	51	16	4	5/	16	4	0.7%	-6.00 [-28.17, 16.17]	
eshnower et al. 2008	39	10	12	60	8	15	1.8%	-21.00 [-27.96, -14.04]	and the second
. et al. 2012	35.2	9.3	1	59.8	8.7	1	1.6%	-24.60 [-34.03, -15.17]	
.i et al. 2014	26.1	6.1	0	42.3	3.9	0	1.9%	-16.20 [-21.99, -10.41]	
im et al. 2007	32	100	0	48	10	6	1.6%	-16.00 [-25.77, -6.23]	
iu et al. 2011 (old)	49.6	10.9	1	51.9	10.7	1	1.4%	-2.30 [-13.62, 9.02]	
iu et al. 2011 (young)	31.9	8.9	1	54.5	7.4	1	1.7%	-22.60 [-31.17, -14.03]	
Aatsubara et al. 2010 (atter ischemia)	39.6	3.6	4	53.4	5	4	2.0%	-13.80 [-18.92, -8.68]	
Aatsubara et al. 2010 (before ischemia)	39.1	4.2	6	53.4	5	7	2.0%	-14.30 [-19.30, -9.30]	
Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.6%	-19.90 [-29.05, -10.75]	
Niemann et al. 2002 (10mg/kg)	23	28	4	58	12	4	0.5%	-35.00 [-64.85, -5.15]	
Nemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.0%	-44.10 [-61.37, -26.83]	
viemann et al. 2002 (25mg/kg)	17	14.6	4	58	12	4	0.9%	-41.00 [-59.52, -22.48]	
liemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.5%	-23.00 [-51.06, 5.06]	
likolaou et al. 2019	25.17	2.6	7	48	6	7	2.0%	-22.83 [-27.67, -17.99]	
agel & Krolikowski 2009	42	5	6	46	5	6	1.9%	-4.00 [-9.66, 1.66]	
canji et al. 2009	39.1	4.4	6	53.4	4.7	7	2.0%	-14.30 [-19.25, -9.35]	
inintani-Ishida et al. 2012 (before ischemia)	28	18	6	55	13	6	0.9%	-27.00 [-44.77, -9.23]	
shintani-Ishida et al. 2012 (during/after ischem)	16	13	6	55	13	6	1.1%	-39.00 [-53.71, -24.29]	
Vang et al. 2006	25	3	7	44	4	7	2.1%	-19.00 [-22.70, -15.30]	
Ge & Yu 2007	30.3	2.7	6	48.8	5.8	6	2.0%	-18.50 [-23.62, -13.38]	
roucer et al. 2015	13	5	6	35	8	6	1.8%	-22.00 [-29.55, -14.45]	
chu et al. 2013 Subtotal (95% CI)	51.1	10.4	245	55.4	10.9	224	1.5%	-4.30 [-14.74, 6.14]	
Heterogeneity: Tau ² = 32.92; Chi ² = 235.08, df = 4 Fest for overall effect: Z = 15.62 (P < 0.00001)	44 (P < 0	0.00001)	; l ² = 8	1%		321	71.176	-17.12 [-19.27, -14.97]	•
>40min									
lexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	1.9%	-15.00 [-21.12, -8.88]	
Gomez et al. 2008	35	14	8	58	15	9	1.2%	-23.00 [-36.79, -9.21]	
Iwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.5%	-6.20 [-17.11, 4.71]	
keda et al. 2021 (60min)	65	6	8	72	4	8	2.0%	-7.00 [-12.00, -2.00]	
Carlsson et al. 2010	49	14	12	41	16	15	1.4%	8.00 [-3.33, 19.33]	+
arlsson et al. 2012	51	21	12	54	20	11	1.0%	-3.00 [-19.76, 13.76]	
ie et al. 2010	47.3	15.7	19	51.4	16.5	19	1.5%	-4.10 [-14.34, 6.14]	
lagaoka et al. 2015	56	5	7	72	9	7	1.8%	-16.00 [-23.63, -8.37]	
Rusinkevich et al. 2019	45	13	11	31	9	11		Not estimable	
Skyschally et al. 2010	25	6	4	35	6	4		Not estimable	
alewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.1%	-7.60 [-11.16, -4.04]	
Subtotal (95% CI) leterogeneity: Tau ² = 24.62; Chi ² = 22.31, df = 8 ast for overall effect: 7 = 3.86 (P = 0.0001)	(P = 0.0	04); l² =	97 64%			100	14.4%	-8.63 [-13.01, -4.25]	•
est for overall effect. 2 = 5.00 (P = 0.0001)									
otal (95% CI)			466			475	100.0%	-16.87 [-19.14, -14.60]	•
leterogeneity: Tau ² = 60.48; Chi ² = 515.51, df = 6	61 (P < 0	0.00001)	; l ² = 8	8%					-50 -25 0 25 5
est for overall effect: Z = 14.57 (P < 0.00001)									Favours [experimental] Favours [control]

Figure S5 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by duration of ischemia.

Timing of dose	Species (strain, sex, age, n = control/ experimental group)	Dose (mg/kg; route)	Duration of Ischemia (min; artery ligated)	Infarct Size (%AAR ±SEM)	Additional Clinically Relevant Outcomes
Before ischemia					
Boengler et al. (2010)	mouse (C57Bl/6, ♂/♀, 8 wk, 7/10)	10 (IV)	30 (LAD)	61±5% vs. 50±2% (P<0.05)	NR
Arteaga <i>et al.</i> (1992)	rat (Wistar, ♀, NR, 5/9)	20 (IV)	5 (LCA)	NR	 CK 2728U/L vs. 801U/L* Interstitial edema & loss of striation of myocardial in control group on histology
Niemann <i>et al.</i> (2002)	rat (Sprague-Dawley, ♂, 6 mo, 4/4/4/4)	5 ×3 (PO)	30 (LCA)	58±6% vs. 35±13% (P>0.03)	NR
		10 ×3 (PO)		<i>vs.</i> 23±14% (P<0.03)	
		15 ×3 (PO)		<i>vs.</i> 13.9±6.5% (P<0.03)	
		25 ×3 (PO)		<i>vs.</i> 17.0±7.3% (P>0.03)	
Laudi <i>et al.</i> (2007)	rat (Sprague-Dawley, ♂, 8–10 wk, 4/4/4)	5 ×3 (PO)	30 (LAD)	57±8% vs. 51±8% [†]	 LVEF 55.0±7.3% vs. 45.5±8.1% (ns) 14 d survival 16.0% vs. 31.6% (ns)
		12.5 ×3 (PO)		<i>v</i> s. 30±10% [†]	 LVEF 55.0±7.3% vs. 54.0±11.3% (ns) 14 d survival 16.0% vs. 55.6% (P=0.017)
Shintani-Ishida et al. (2012)	rat (Sprague-Dawley, ♂, 8 wk, 6/6)	25 (IP)	30 (LAD)	55±5% vs. 28±7% (P<0.05)	NR
De Paulis <i>et al.</i> (2013)	rat (Wistar, ♂, NR, 6–8/6–8)	10 (IV)	30 (LAD)	59.4±2.8% vs. 23.9±5.4% (P<0.05)	NR
Nagaoka <i>et al.</i> (2015)	rat (Sprague-Dawley, ♂, NR, 7/7)	10 (IV)	45 (LAD)	72±4% vs. 56±2% (P<0.05)	NR
Argaud <i>et al.</i> (2005)	rabbit (New Zealand white, ♂, NR, 8/8)	2.5 (IV)	30 (left marginal)	60±6% vs. 24±4% (P<0.0001)	NR
Ranji <i>et al.</i> (2007) [‡]	rabbit (NR, NR, NR, 5/5)	NR	30 (NR)	55.9±1.7% vs. 39.7±2.1% (P<0.05)	NR
Leshnower et al. (2008)	rabbit (New Zealand white, ♂, NR, 15/12)	25 (IV)	30 (left marginal)	60±2% vs. 39±3% (P<0.001)	• 53±12% vs. 20±7% disrupted mitochondria on EM
Ranji <i>et al.</i> (2009)	rabbit (New Zealand white, NR, NR, 7/6)	25 (IV)	30 (left marginal)	53.4±1.8% vs. 39.1±1.8% (P<0.0001)	• 53.31±12% vs. 19.71±7% disrupted mitochondria on EM
Matsubara et al. (2010)	rabbit (New Zealand white, ♂, NR, 7/6)	25 (IV)	30 (left marginal)	53.4±1.9% vs. 39.1±1.7% (P<0.001)	• 53±16% vs. 20±9% disrupted mitochondria on EM
Fancelli <i>et al.</i> (2014)	rabbit (New Zealand white, NR, NR, 8/8)	10 (IV)	30 (LAD)	57.3±6.4% vs. 32.6±5.0% (P<0.01)	NR
Before/after ischemia					
Gomez <i>et al.</i> (2004) [‡]	mouse (NR, NR, NR, 6/6)	40 ×3 (IP)	25 (NR)	72±4% vs. 56±4% (P<0.05)	NR
Gomez <i>et al.</i> (2005)	mouse (C57Bl/6, NR, 8–10 wk, 6/6)	40 ×3 (IP)	25 (LAD)	77±5% vs. 51±5% (P<0.01)	NR
He <i>et al.</i> (2010)	rat (Sprague-Dawley, ♂, NR, 10/10	2 x2 (IP)	30 (LAD)	NR	 Tnl 12.38±0.66 ng/mL vs. 9.26±0.56 ng/mL (P<0.01) CK-MB 123.22±2.10 U/L vs. 100.87±2.23 U/L (P<0.01)
During ischemia					
Gomez <i>et al.</i> (2007) [‡]	mouse (NR, NR, NR, 9/9)	10 (IV)	60 (NR)	56±5% vs. 36%* (P<0.05)	NR
Gomez <i>et al.</i> (2008)	mouse (C57Bl/6, ♂, 8–10 wk, 9/8)	10 (IV)	60 (LAD)	58±5% vs. 35±5% (P<0.05)	NR
Youcef et al. (2015)	mouse (C57BI/6, ♂, 22 mo, 5–7/5–7)	10 (IV)	30 (LAD)	35±3% vs. 13±2% (P<0.05)	NR
Nikolaou <i>et al.</i> (2019)	mouse (C57BI/6, ♂, 8–12 wk, 7/7)	10 (IV)	30 (LAD)	48±2% vs. 25.17±1.0% (P<0.0001)	NR
Squadrito <i>et al.</i> (1999)	rat (Sprague-Dawley, ♂, NR, 6/6/6/6/6/6, NR)	0.25 (IV)	20 (LCA)	52±2% vs. 46±2% (P>0.05)	NR
		0.5 (IV)		<i>vs.</i> 29±1% (P<0.05)	
		1 (IV)		<i>vs.</i> 16±0% (P<0.005)	
		1 (IV)	30 (LCA)	57±3% vs. 12±2% (P<0.01)	

Table S1 Summary of myocardial ischemia-reperfusion injury studies using temporary coronary artery ligation and testing cyclosporine A

Table S1 (continued)

Table S1 (continued)

Timing of dose	Species (strain, sex, age, n = control/ experimental group)	Dose (mg/kg; route)	Duration of Ischemia (min; artery ligated)	Infarct Size (%AAR ±SEM)	Additional Clinically Relevant Outcomes	
Xie & Yu (2007)	rat (Sprague-Dawley, ♂, NR, 6/6)	10 (IV)	30 (LAD)	48.8±2.2% vs. 30.3±1.1% (P<0.05) (%total LV area)	 Less vacuolar degeneration & no swelling of mitochondria in CsA group on EM 	
Fang et al. (2008)	rat (Sprague-Dawley, ♂, NR, 12/12)	10 (IV)	30 (LAD)	47.5±1.2% vs. 24.4±1.0% (P<0.01)	• 2.09±0.03 vs. 0.97±0.03 (P<0.01) mitochondria score on EM	
Huhn <i>et al.</i> (2008)	rat (Wistar, ♂, NR, 9/9)	5 (IV)	25 (LCA branch)	51.4±1.7% vs. 31.8±2.6% (P<0.05)	NR	
Huhn <i>et al.</i> (2010)	rat (Zucker obese, 3, 10 wk, 7/7)	5 (IV)	25 (LCA branch)	58±2% vs. 61±3% (P>0.05)	NR	
Liu <i>et al.</i> (2011)	rat (Fischer 344, ♂, 3–5 mo, 7/7)	10 (IV)	30 (LAD)	54.5±2.8% vs. 31.9±3.4% (<0.01)	NR	
	rat (Fischer 344, ♂, 20–24 mo, 7/7)			51.9±4.0% vs. 49.6±4.1% (>0.05)		
Li <i>et al.</i> (2012)	rat (Sprague-Dawley, ♂, NR, 7/7)	5 (IV)	30 (LAD)	59.8±3.3% vs. 35.2±3.5% (P<0.001)	• dP/dt _{max} 686 mmHg/s* vs. 1286±147 mmHg/s (P<0.001)	
De Paulis <i>et al.</i> (2013)	rat (Wistar, ♂, NR, 6–8/6–8)	10 (IV)	30 (LAD)	59.4±2.8% vs. 52.2±2.1% (P>0.05)		
Gross <i>et al.</i> (2013)	rat (Sprague-Dawley, ♂, NR, 6–10/6–10)	1 (IV)	30 (LAD)	62.8±1.7% vs. 51.5±1.2% (P<0.05)	NR	
Zhu <i>et al.</i> (2013)	rat (Fischer 344, ♂, 22–24 mo, 8/8)	10 (IV)	30 (LAD)	54±4% vs. 51±4% (P>0.05)	NR	
Li e <i>t al.</i> (2014)	rat (Sprague-Dawley, ♂, NR, 6/6)	10 (IP)	30 (LAD)	42.3±1.6% vs. 26.1±2.5% (P<0.05)	 CK-MB 692±22 U/L vs. 346±22 U/L (P<0.05) Decrease in vacuolar degeneration & lack of swelling in mitochondria on EM in CsA group 	
Choi <i>et al.</i> (2015) [‡]	rat (Sprague-Dawley, NR, NR, 4/4)	10 (NR)	35 (NR)	33.51±4.65% vs. 14.88±5.74% (P=0.3143)	NR	
Nazari <i>et al.</i> (2015)	rat (Wistar, ♂, NR, 13/13)	5 (IV)	30 (LAD)	37.6±2.4% vs. 17.7±4.0% (P<0.0001)	• CK-MB 279±29 U/L vs. 188±19 U/L (P>0.05)	
Hurt <i>et al.</i> (2016)	rat (Sprague-Dawley, ♂, 8–10 wk, 6/6)	2.5 (NR)	30 (LAD)	61±2% vs. 49±2% (P<0.01)	NR	
Kiss <i>et al.</i> (2016)	rat (Wistar, ♂, NR, 8/7)	10 (IV)	30 (LAD)	63.8±4.1% vs. 45.9±2.4% (P<0.05)	NR	
Choi <i>et al.</i> (2017)	rat (Sprague-Dawley, ♂, 8 wk, 4/4)	10 (IV)	35 (LAD)	54.17±6.75% <i>vs.</i> 36.16±5.59% (P=0.0041)	NR	
Hwang <i>et al.</i> (2018)	rat (Sprague-Dawley, ♂, 8 wk, 5/5)	5 (IP)	45 (LAD)	17.7±3.9% <i>vs.</i> 11.5±4.0% (P>0.05) (%total LV area)	 LVEF 47.2±1.7% vs. 48.2±1.7% at 3 d (P>0.999), 43.3±3.2% vs. 47.7±2.9% at 7 d (P=0.949), 44.6±1.9% vs. 46.7±3.0% at 14 d (P>0.999) 19±3% vs. 11±4% (P>0.05) area of necrotic myocardium & 64±3% 31±4% (P<0.05) necrotic cardiomyocytes on histology 	
Zhang <i>et al.</i> (2019) [§]	rat (Sprague-Dawley, ♂, NR, NR)	2.5 (IV)	30 (LAD)	46±5% vs. 36±4% (P>0.01)	 Tnl 350±30 ng/mL vs. 270±20 ng/mL (P<0.01) CK-MB 350±21 U/L vs. 320±21 U/L (P<0.01) 	
		2.5 (nanoparticle)		<i>vs.</i> 19±4% (P<0.01)	 Tnl 350±30 ng/mL vs. 210±10 ng/mL (P<0.01) CK-MB 350±21 U/L vs. 170±10 U/L (P<0.01) Near normal histological features compared to large area of necrosis, structural disarray & inflammatory infiltrate in control tissue 	
Krolikowski <i>et al.</i> (2005) [§]	rabbit (New Zealand white, ♂, NR, NR)	5 (IV)	30 (left marginal)	42±7% vs. 43±6% (P>0.05)	NR	
		10 (IV)		<i>vs.</i> 21±4% (P<0.05)		
Wang <i>et al.</i> (2006)	rabbit (New Zealand white, ♂, NR, 7-8/7-8)	10 (IV)	30 (LAD)	44±1% vs. 25±1% (P<0.05)	NR	
Pagel & Krolikowski (2009)	rabbit (New Zealand white, ♂, NR, 6/6)	5 (IV)	30 (LAD)	46±2% vs. 42±2% (P>0.05)	NR	
Paillard et al. (2009)	rabbit (New Zealand white, \mathcal{J} , NR, 8/8)	5 (IV)	30 (left marginal)	NR	 Preservation of myofibril organization & mitochondrial structure in CsA group on EM 	

Table S1 (continued)

Table S1 (continued)

Timing of dose	Species (strain, sex, age, n = control/ experimental group)	Dose (mg/kg; route)	Duration of Ischemia (min; artery ligated)	Infarct Size (%AAR ±SEM)	Additional Clinically Relevant Outcomes	
Alexopoulos et al. (2017)	rabbit (New Zealand white, ♂, NR, 18/18)	2.5 (IV)	40 (LCA or branch)	37.7±2.1% vs. 22.7±2.3% (P<0.05)	• Tnl 159.2±10.4 ng/mL vs. 101.7±10 ng/mL (P<0.05)	
Karlsson <i>et al.</i> (2010)	pig (Swedish Landrace, $\stackrel{\bigcirc}{,}$ NR, 15/12)	10 (IV)	45 (LAD)	41±4% vs. 49±4% (P>0.05)	NR	
Lie <i>et al.</i> (2010)	pig (mixed Danish Landrace/Yorkshire, \circleon , NR, 19/19)	10 (IV)	40 (LAD)	51.4±3.8% vs. 47.3±3.6% (P>0.05)	 TnT 6.4±0.7 ng/mL vs. 9.7±1.1 ng/mL (P>0.05) CO at 180 min after reperfusion 3.8±0.2 L/min vs. 3.8±0.2 L/min (P>0.05) 	
Skyschally et al. (2010)	pig (Göttinger minipigs, ♂/♀, NR, 4/4)	5 (IV)	90 (LAD hypoperfusion)	35±3 % vs. 25±3% (P<0.05)	 dP/dt_{max} at 120 min after reperfusion 1222±174 mmHg/s vs. 946±111 mmHg/s (P>0.05) 	
Karlsson <i>et al.</i> (2012)	pig (mixed Swedish/Pigham/Yorkshire, $\stackrel{\circ}{_{\!$	2.5 (IV)	40 (left marginal)	54±6% vs. 51±6% (P=0.75)	NR	
Zalewski <i>et al.</i> (2014) [‡]	pig (NR, NR, NR, 8/8)	NR	60 (NR)	54±1% vs. 44±2% (P=0.017)	• LVEF (%∆) –15.6±3.7% <i>vs.</i> –7.9±2.2% (P=0.015)	
Zalewski <i>et al.</i> (2015)	pig (NR, ♂/♀, NR, 8/8)	10 (IV)	60 (LAD)	53.8±1.4% vs. 46.2±1.1% (P=0.016)	 LVEF 38.9±2.0% vs. 46.3±1.2% (P<0.05) CO 42.9±2.3 mL/s vs. 42.6±2.7 mL/s (P>0.05) Increased edema with reduced myocyte density on histology in both groups 	
Kloner <i>et al.</i> (2011) [‡]	sheep (NR, NR, NR, NR)	NR	60 (NR)	<10% reduction (P>0.05)	NR	
During/after ischemia						
Shintani-Ishida et al. (2012)	rat (Sprague-Dawley, ♂, 8 wk, 6/6)	10 (IV)	30 (LAD)	55±5% vs. 16±5% (P<0.05)	NR	
After ischemia						
Lim <i>et al.</i> (2007)	mouse (B6Sv129F1, ♂/♀, 8–10 wk, 6/6)	10 (NR)	30 (LAD)	48±4% vs. 32±3% (P<0.05)	NR	
Horstkotte et al. (2011)	mouse (dtTomato, NR, NR, 6/6)	10 (IV)	90 (LAD)	NR	• dP/dt _{max} 19,000±3,000 mmHg/s <i>vs.</i> 18,000±4,000 mmHg/s (P>0.05)	
lkeda <i>et al.</i> (2016)	mouse (C57Bl/6, ♂, 10–12 wk, 8/8/8/8/8/8/8)	1 (IV) NR (left marginal)		51±3% vs. 53±3% (P>0.05)	• LVEF 33.0±2.0% vs. 32.0±2.6% (P>0.05)	
		1 (nanoparticle)		51±3% vs. 32±3% (P<0.001)	• LVEF 33.0±2.0% vs. 49.0±2.0% (<0.05)	
		2.5 (IV) 2.5 (nanoparticle) 10 (IV) 10 (nanoparticle)		51±3% vs. 49±3% (P>0.05)		
				51±3% vs. 31±3% (P<0.001)		
				51±3% vs. 36±3% (P<0.05)	• LVEF 33.0±2.0% vs. 43.2±2.0% (P<0.05)	
				51±3% vs. 36±3% (P<0.01)		
		25 (IV)		51±3% vs. 32±3% (P<0.01)		
Rusinkevich <i>et al.</i> (2019)	mouse (C57BI/6, ♂, 12–14 wk, 11/11)	10 x5 (IP)	90 (LAD)	31±3% <i>v</i> s. 45±4% (P<0.05) (%total LV area)	• LVEF 35±2% vs. 27±2% at 7 d (P<0.05); 35±2% vs. 28±2% at 14 d (P<0.05; 35±2% vs. 30±2% at 28 d (P>0.05)	
lkeda <i>et al.</i> (2021)	mouse (C57BI/6, ♂, 10–12 wk, 8–9/8–9/8–9/8–9	1 (nanoparticle)	30 (LAD) 60 (LAD)	53±2% vs. 33±3% (P<0.0001) 72±1% vs. 65±2% (P<0.001)	NR	
Argaud et al. (2005)	rabbit (New Zealand white, ♂, NR, 8/8)	2.5 (IV)	30 (left marginal)	60±6% vs. 24±4% (P<0.0001)	NR	
Matsubara <i>et al.</i> (2010)	rabbit (New Zealand white, ්, NR, 7/4)	25 (IV)	30 (left marginal)	53.4±1.9% vs. 39.6±1.8% (P<0.001)	• 53±16% vs. 18±7% disrupted mitochondria on EM	
Not reported						
lkeda <i>et al.</i> (2014) [‡]	mouse (NR, NR, NR, 8/8)	(nanoparticle)	NR	52±4% vs. 32±9% (P<0.05)	NR	
lkeda <i>et al.</i> (2015) [‡]	mouse (NR, NR, NR, NR)	1mg/kg (nanoparticle)	NR	52±4% vs. 32±6% (P<0.05)	NR	

Table S1 (continued)

Table S1 (continued)

Timing of dose	Species (strain, sex, age, n = control/ experimental group)	Dose (mg/kg; route)	Duration of Ischemia (min; artery ligated)	Infarct Size (%AAR ±SEM)	Additional Clinically Relevant Outcomes
lkeda <i>et al.</i> (2016) [‡]	mouse (NR, NR, NR, 8/8)	1mg/kg (nanoparticle)	30 (NR)	52±5% vs. 31±6% (P<0.05)	NR
Huang <i>et al.</i> (2014)	rat (Sprague-Dawley, ♂, NR, 8/8/8/8)	1 (NR)	30 (LAD)	45.00±0.73% vs. 35.29±0.54% (P<0.05)	 Tnl 12.98±0.46 ng/mL vs. 9.38±0.38 ng/mL (P<0.05) CK-MB 125.38±2.07 U/mL vs. 109.79±1.51 U/mL (P<0.05)
		2.5 (NR)		vs. 29.05±0.74% (P<0.05)	 Tnl 12.98±0.46 ng/mL vs. 8.53±0.30 ng/mL (P<0.05) CK-MB 125.38±2.07 U/mL vs. 99.83±0.46 U/mL (P<0.05)
		5 (NR)		vs. 26.90±0.66% (P<0.05)	 Tnl 12.98±0.46 ng/mL vs. 8.35±0.30 ng/mL (P<0.05) CK-MB 125.38±2.07 U/mL vs. 98.24±1.63 U/mL (P<0.05)
Gu <i>et al.</i> (2020) [‡]	rat (NR, NR, NR, 5/5)	2.5 (NR)	NR	46.8%* vs. 42.6%* (P=0.682)	NR

*, standard error not reported; [†], P value not reported; [‡], conference abstract; [§], results presented with standard deviation. CK-MB, creatinine kinase myocardial band; CO, cardiac output; CsA, cyclosporine A; EM, electron microscopy; IP, intraperitoneal; IV, intravenous; L, left; LAD, left anterior descending; LCA, left coronary artery; LV, left ventricle; LVEF, left ventricular ejection fraction; NR, not reported; ns, not significant; PO, per os; SEM, standard error of the mean; TnI, cardiac troponin I; TnT, cardiac troponin T.

	-,				
Model type	Species (strain, sex, age, n = control/ experimental group)	Dose (mg/kg; route)	Duration of Ischemia (min; method)	Cardiac Function (SEM)	Additional Clinically Relev
Cardiac arrest					
Before/during ischem	ia				
Ayoub <i>et al.</i> (2017)	rat (Sprague-Dawley, ♂, NR, 6/12)	10 (NR)	10 (electricity)	Cl 62 \pm 8 mL/min/kg vs. 63 \pm 4 mL/min/kg at 120 min (ns), 58 \pm 6 mL/min/kg vs. 59 \pm 3 mL/min/kg at 240 min (ns), 52 \pm 4 mL/min/kg vs. 46 \pm 5 mL/min/kg at 360 min (ns)	• Tnl 130±76 ng/mL vs. 2
During ischemia					
Huang et al. (2011)*	rat (Wistar, ♂, 8 wk, NR)	10 (IV)	8.5 (asphyxia)	CO 80.7±20.0 mL/min vs. 87.6±22.6 mL/min (P=0.58)	• 72 hr survival 16.7% vs.
Huang <i>et al.</i> (2012)	rat (Wistar, ♂, 8 wk, 10/10)	10 (IV)	8.5 (asphyxia)	CO 22 \pm 3 mL/min vs. 71 \pm 10 mL/min at 1 hr, 22 \pm 1 mL/min vs. 76 \pm 11 mL/min at 2 hr, 31 \pm 3 mL/min vs. 49 \pm 3 mL/min at 3 hr, 36 \pm 3 mL/min vs. 53 \pm 3 mL/min at 4 hr (P<0.01)	 Mitochondrial injury sco 72 hr survival 18.2% vs.
Cour <i>et al.</i> (2014)	rabbit (New Zealand white, NR, NR, 24/18)	5 (IV)	5–7 (asphyxia)	CO 60±6 mL/min vs. 90±6 mL/min (P<0.05)	• Tnl 34±10 ng/mL <i>vs.</i> 10 • Survival 67% <i>vs.</i> 89% [‡]
After ischemia					
Huang <i>et al.</i> (2012)	rat (Wistar, ♂, 8 wk, 10/10)	10 (IV)	8.5 (asphyxia)	CO 18 \pm 1 mL/min vs. 22 \pm 3 mL/min at 1 hr, 27 \pm 1 mL/min vs. 36 \pm 4 mL/min at 2 hr, 49 \pm 8 mL/min vs. 44 \pm 6 mL/min at 3 hr, 58 \pm 7 mL/min vs. 49 \pm 3 mL/min at 4 hr (P=0.690)	 Mitochondrial injury sco 72 hr survival 20% vs. 3
Cardiopulmonary bypa	SS				
Oka <i>et al.</i> (2008)	pig (NR, NR, 2 wk, 5/5)	10 (IV)	60 (cardioplegia)	NR	 Preservation of cristae a compared to controls o
Hoyer <i>et al.</i> (2016)*	pig (Landrace, NR, NR, 6/6)	1.2mg/L (cardioplegia)	90 (cardioplegia)	NR	No difference in cross s cell boundaries (P=0.36)
Hoyer <i>et al.</i> (2019)	pig (Landrace, NR, 4–5 mo, 10/10)	1.2mg/L (cardioplegia)	90 (cardioplegia)	CO 5.2±0.5 L/min vs. 4.7±0.4 L/min (ns)	NR
Hoyer <i>et al.</i> (2021)	pig (German Sattle, NR, NR, 10/10)	1.2mg/L (cardioplegia)	90 (cardioplegia)	CO 5.2±0.5 L/min vs. 4.7±0.4 L/min (ns)	 No difference in cross s edema (P=0.596), cellul of cell boundaries (P=0.
Hypoxia					
Gill <i>et al.</i> (2012)a	pig (NR, NR, 1–4 d, 8/8/8)	10 (IV, 5 min after reoxygenation)	120 (ventilation with FiO ² 0.11–0.15)	CI 62±5% vs. 95±4% of baseline (P<0.05)	• Lactate 6.1±0.4 mM <i>vs.</i> at 6 hr (P>0.05)
		10 (IV, 120 min after reoxygenation)		CI 62±5% vs. 79±6% of baseline (P=0.1)	• Lactate 6.1±0.4 mM vs. at 6 hr (P>0.05)
Gill <i>et al.</i> (2012)b	pig (mixed, NR, 1–4 d, 8/8/8/8)	2.5 (IV)	120 (ventilation with FiO ₂ 0.10–0.15)	CI 57±8% vs. 88±8% of baseline (P<0.05)	 Tnl 1.2±0.2 ng/mL vs. 0 Lactate 11.3±2.9 mM vs. 3.2±2.2 mM at 4 hr (P>0
		10 (IV)		<i>vs.</i> 100±7% of baseline (P<0.05)	 Tnl 1.2±0.2 ng/mL vs. 0 Lactate 11.3±2.9 mM vs. 3.1±1.0 mM at 4 hr (P>0
		25 (IV)		<i>vs.</i> 85±11% of baseline (P<0.05)	 Tnl 1.2±0.2 ng/mL vs. 1 Lactate 11.3±2.9 mM vs. 2.6±0.6 mM at 4 hr (P>0
Gill <i>et al.</i> (2013)	pig (mixed, NR, 1–4 d, 8/8)	10 (IV)	120 (ventilation with FiO₂ 0.10–0.15)	NR	• Tnl 1.2±0.2 ng/mL vs. 0
Cardiac transplantation	1				
Laudi <i>et al.</i> (2006)*	rat (Lewis, ♂, NR, 7/7/7/7)	12.5 x3 (PO)	NR	NR	• 28 d survival 75% vs. 1 transplant vs. 78% if ad

Table S2 Summary of myocardial ischemia-reperfusion injury studies testing cyclosporine A, using methods other than coronary artery occlusion

*, conference abstract; [†], results presented with standard deviation; [‡], P value not reported. CI, cardiac index; CO, cardiac output; CsA, cyclosporine A; EM, electron microscopy; FiO₂, fraction of inspired oxygen; IV, intravenous; NR, not reported; ns, not significant; PO, per os; TnI, cardiac troponin I; U/O, urine output.

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210±61 ng/mL (ns)
 58.3% (P=0.016)
ore 1.5±0.2 vs. 0.6±0.2 on EM (P<0.01)
 53.8% (P=0.046)
0±2 ng/mL (P<0.05)
ore 1.5±0.2 vs. 1.3±0.2 on EM (P>0.01)
30% (P=0.829)
architecture & intermembrane space in CsA-treated group
on EM
striation (P=0.917), eosinophil infiltration (P=0.661), loss of
62) or myocardial edema (P=0.998) on histology
striation (P=0.845), eosinophilia (P=0.510), myocardial
lar infiltration (P=0.279), visible bleeding (P=0.876) or loss
0.510) on histology
4.9±0.4 mM at 2 hr (P>0.05), 4.4±0.8 mM vs. 2.8±0.2 mM
. 7.0±0.7 mM at 2 hr (P>0.05), 4.4±0.8 mM vs. 4.2±0.9 mM
0.6±0.1 ng/mL (P<0.05)
/s. 11.3±3.3 mM at 30 min (P>0.05), 5.5±3.3 mM vs.
>0.05)
0.7±0.2 ng/mL (P<0.05)
/s. 11.7±4.3 mM at 30 min (P>0.05), 5.5±3.3 mM vs.
>0.05)
1.2±0.2 ng/mL (P>0.05)
/s. 11.8±1.8 mM at 30 min (P>0.05), 5.5±3.3 mM vs.
>0.05)
0.6±0.2 ng/mL (P<0.05)
```

100% if administered 3 d prior *vs.* 33% if administer day of dministered 3 d post-transplant (P=0.041)

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