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

(((TTTLE-ABS-KEY ((reperfus* OR ir OR "Hypoxi* ischemi*") W/3 (injur* OR damag* OR necrosis OR necrotic OR hemorrhag* OR haemorrhag*))) OR (TTTLE-ABS-KEY ((reperfus* OR ir OR "Hypoxi* ischemi*") W/3 ("free radical*" OR "free oxygen radical*"))) OR (TTTLE-ABS-KEY (((hypox* OR hemorrhagi* OR haemorrhagi*))) AND (TTTLE-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 ((TTTLE-ABS-KEY((invitro OR "in vitro"))) AND (TTTLE-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	TS=((invitro or "in vitro") and (invivo or "in vivo"))	453,102
#1(J#8 Not #9	1,154,443
#1.	1 #/ Not #10	656
Coch	rane Library Searched March 8, 2022	
(Cocl	nrane Database of Systematic Reviewes Results =0)	
(Cocl	nrane Central Register of Controlled Trials Results =46)	
ID	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 i	nof" or cyclasol or cyclokat or cyclosporine or cyclosporin or	
"de 07	76" 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	is or restaysis or sanciclo or sanciclo or sandimmun or	
sandir	nmune or sandimun or sandimune or "sang 35" or sang35 or	
sango	rya 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	ro OR "in vivo"))	2916
#13	#11 NOT #12	46
PRO	SPERO Searched March 9, 2022	
Line	Search for	Hits
#1	(ir or "hypox* ischemi*" or reperfus*) and (iniur* or damag* or	
necro	s* or necrotic or hemorrhag* or haemorrhag* or "free radical*"	
or sh	ock)	646
#2	("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 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 (39%) CD1 Scheda et al. 2013 (during) 52.2 Scheda et al. 2013 (during) 52.2 For overall effect: Z = 5.29 (P < 0.00001) E4 37 Scheda et al. 2013 (during) 52.2 Farage at al. 2013 (during) 52.2 Scheda et al. 2013 (during) 52.2 Scheda et al. 2014 (Scheg/kg) 28.9 Using et al. 2014 (Img/kg) Sc.29 Scheda et al. 2015 (Scheg/kg) 51.5 Schet al. 2016 44	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 51 511 51 511 51 513 51 513 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
Mouse Boengler et al. 2010 50 Somez et al. 2005 51 Somez et al. 2006 35 keda et al. 2016 (10mg/kg) NP) 36 keda et al. 2016 (10mg/kg) NP) 32 keda et al. 2016 (25mg/kg) 49 32 keda et al. 2016 (2.5mg/kg) 49 32 keda et al. 2016 (2.5mg/kg) 32 32 keda et al. 2017 32 31 ocuref et al. 2017 32 31 Subtotal (95% CI) 45 fetrogeneity: Tau [*] = 86.66; Chi ² = 99.34, df = 15 (P < 0.00 rest for overall effect: Z = 5.29 (P < 0.00001) 52 iang et al. 2013 (briong) 52 33 tuang et al. 2014 (2.5mg/kg) 29.05 tuang et al. 2014 (2.5mg/kg) 29.05 tuang et al. 2014 (2.5mg/kg) 20.5 tuang et al. 2014 (2.5mg/kg) 30 uang et al. 2014 (2.5	7 12 14 7 7 7 10 10 10 10 6 7 2.6 13 5 0001); F 11.18 14.3 5.6 3.3 4.4 5 5 0001); F 11.18 14.3 5 8.3 8.9 6.3	7 1 24 77 77 77 70 00 00 00 00 00 00 00 00 00	61 77 57 58 51 51 51 51 51 51 51 51 51 51 51 51 51	12 15 7 7 7 7 7 7 7 7 7 4 10 6 9 8	7 9 8 8 8 8 8 8 8 8 8 8 8 8 7 11 6 124	1.5% 1.2% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.5% 1.9% 1.5% 1.9% 1.7% 26.1%	-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] -20.00 [-24.84, -16.45] -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 [-2.55, -14.45] -13.62 [-18.66, -8.58]	
Soengler et al. 2010 50 Somaz et al. 2005 51 Somaz et al. 2006 35 keda et al. 2016 (10mg/kg) NP) 36 keda et al. 2016 (10mg/kg) NP) 36 keda et al. 2016 (2.5mg/kg) 49 keda et al. 2016 (2.5mg/kg) 49 keda et al. 2016 (2.5mg/kg) 32 keda et al. 2016 (2.5mg/kg) 32 keda et al. 2011 (2.5mg/kg) 32 keda et al. 2017 (2.5mg/kg) 32 kikolaou et al. 2019 25.17 Vausinkevich et al. 2019 25.17 Vausinkevich et al. 2019 25.17 Vausinkevich et al. 2017 36.16 1 Soubotal (95% CI) 23.9 Veat for overail effect: Z = 5.29 (P < 0.00001)	7 12 14 7 7 7 10 10 10 10 10 10 10 10 10 10 10 10 10	7 1 2 4 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	6 61 6 77 8 58 5 51 6 53 7 2 6 48 7 48 7 48 7 55 6 55 7 55	12 15 7 7 7 7 7 7 7 7 4 10 6 9 8	7 6 9 8 8 8 8 8 8 8 8 8 8 8 8 7 11 6 124	1.5% 1.2% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.5% 1.9% 1.5% 1.9% 1.7% 26.1%	$\begin{array}{r} +11.00 \left[+20.89, -11.11 \right] \\ -26.00 \left[-39.58, -12.42 \right] \\ -23.00 \left[-36.79, -9.21 \right] \\ -15.00 \left[-21.86, -8.14 \right] \\ -10.00 \left[-21.86, -8.14 \right] \\ -2.00 \left[-43.68, -8.66 \right] \\ -19.00 \left[-27.46, -10.54 \right] \\ -2.00 \left[-24.66, -11.54 \right] \\ -20.00 \left[-28.46, -11.54 \right] \\ -7.00 \left[-23.46, -10.54 \right] \\ -7.00 \left[-23.46, -10.54 \right] \\ -7.00 \left[-23.46, -17.54 \right] \\ -2.200 \left[-28.36, -17.54 \right] \\ -2.201 \left[-29.55, -14.45 \right] \\ -13.62 \left[-18.66, -8.58 \right] \end{array}$	
Somez et al. 2005 51 Somez et al. 2006 35 Somez et al. 2016 (10mg/kg) MP) 36 keda et al. 2016 (10mg/kg) NP) 32 keda et al. 2016 (10mg/kg) NP) 32 keda et al. 2016 (2.5mg/kg) 49 keda et al. 2016 (2.5mg/kg) NP) 31 keda et al. 2016 (2.5mg/kg) NP) 31 keda et al. 2021 (80min) 65 jam et al. 2007 32 ikolaou et al. 2019 25.17 xusinkevich et al. 2019 45 fouce et al. 2015 13 Subtotal (95% CI) 45 teterogeneity: Tau" = 86.66; Chi" = 99.34, df = 15 (P < 0.00	12 14 7 7 10 10 10 10 10 10 10 10 10 10 10 10 0 6 13 5 5 0001); F	2 4 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	77 58 58 51 51 51 51 51 51 51 51 51 51	12 15 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	6 9 8 8 8 8 8 8 8 8 8 8 8 8 7 11 6 124	1.2% 1.2% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.6% 1.5% 1.9% 1.5% 1.9% 1.6%	$\begin{array}{r} -26.00 \left[-39.58, -12.42\right]\\ +23.00 \left[-36.79, -9.21\right]\\ +15.00 \left[-21.86, -8.14\right]\\ -15.00 \left[-27.46, -10.54\right]\\ +2.00 \left[-43.68, -8.61\right]\\ -2.000 \left[-72.46, -10.54\right]\\ +2.00 \left[-10.46, -6.46\right]\\ +20.00 \left[-28.46, -11.54\right]\\ +19.00 \left[-27.46, -10.54\right]\\ +20.00 \left[-28.46, -11.54\right]\\ -7.00 \left[-12.00, -2.00\right]\\ +16.00 \left[-25.77, -6.23\right]\\ +16.00 \left[-25.77, -6.23\right]\\ +22.20 \left[-29.55, -14.45\right]\\ +13.62 \left[-18.66, -8.58\right]\end{array}$	
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ss et al. 2016 (45.9%) uudi et al. 2007 (12.5mg/kg) 30 audi et al. 2007 (12.5mg/kg) 51 et al. 2012 35.2 et al. 2014 26.1 u et al. 2011 (old) 49.6 u et al. 2014 26.1 u et al. 2011 (young) 31.9 agaoka et al. 2015 56 azari et al. 2015 77.7 lemann et al. 2002 (15mg/kg) 13.9 lemann et al. 2002 (15mg/kg) 13.9 lemann et al. 2002 (15mg/kg) 35 initrani-lshida et al. 2012 (before ischemia) 28 initrani-lshida et al. 2012 (before ischemia) 28 initrani-lshida et al. 2012 (before ischemia) 16 quadrito et al. 1999 (0.5mg/kg) 29 uudrito et al. 1999 (0.5mg/kg) 29 iu et al. 2007 30.3 tu et al. 2013 51.1 ubtotal (95% C1) 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 accelli et al. 2014 32.6 atsubara et al. 2005 (after) 24 ancelli et al. 2014 32.6 atsubara et al. 2010 (before ischemia) 39.6 atsubara et al. 2010 (after ischemia) 39.6 atsubara et al. 2010 (before ischemia) 39.1 ang et al. 2009 42 anji et al. 2009 42 anji et al. 2006 25 ubtotal (95% C1) eterogeneity: Tau ² = 33.60; Chi ² = 40.20, df = 9 (P < 0.000 ast for overall effect: Z = 7.89 (P < 0.00001)	6.3	9	17.7	8.7	5	1.4%	-6.20 [-17.11, 4.71]	
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
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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 aggel & Krolikowski 2009 42 anji et al. 2010 (after ischemia) 39.1 aggel & 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 (25mg/kg) 17 iemann et al. 2002 (15mg/kg) 35 hintani-Shida et al. 2012 (during/after ischem) 16 quadrito et al. 1999 (0.25mg/kg) 29 quadrito et al. 1999 (0.15mg/kg) 20 guadrito et al. 1999 (0.15mg/kg) 29 quadrito et al. 1999 (0.15mg/kg) 20 stabuara et al. 2017 20.3 rgaud et al. 2005 (after) 24 rgaud et al. 2005 (before)	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]	
bit al. 2011 (young) 51.5 aganka et al. 2015 56 azari et al. 2015 17.7 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 hintani-Ishida et al. 2012 (before ischemia) 28 quadrito et al. 1999 (0.5mg/kg) 46 quadrito et al. 1999 (0.5mg/kg) 16 ie & Yu 2007 30.3 tu et al. 2013 51.1 ubtotal (5% CI) 16 eterogeneity: Tau ² = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	80	0	54.5	7.4	7	1.6%	-22 60 [21 17 -14 02]	
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]	
iemann et al. 2002 (5mg/kg) 35 hintani-Ishida et al. 2012 (before ischemia) 28 hintani-Ishida et al. 2012 (burng/after ischem) 16 quadrito et al. 1999 (0.5mg/kg) 46 quadrito et al. 1999 (0.5mg/kg) 46 quadrito et al. 1999 (0.5mg/kg) 46 quadrito et al. 1999 (0.5mg/kg) 16 quadrito et al. 1999 (10.5mg/kg) 16 two text 2013 51.1 ubtotal (95% CI) eterogeneity: Tau [±] = 67.70; Chi ² = 360.41, df = 32 (P < 0.0	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 (10,7kg, 30min ischemia) 12 quadrito et al. 1999 (11,7kg, 30min ischemia) 16 le & Yu 2007 30.3 hu et al. 2013 51.1 ubtotal (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 ancelli et al. 2005 (after) 24 ancelli et al. 2014 32.6 eshnower et al. 2010 (after ischemia) 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 < 0.00001)	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 ie & Yu 2007 30.3 butotal (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) 39.1 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 < 0.0001)	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 Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State Bit State 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)								
gaud et al. 2005 (after) 24 gaud et al. 2005 (before) 24 incelli et al. 2015 (before) 24 incelli et al. 2016 (before) 24 stubara et al. 2010 (after ischemia) 39.6 atsubara et al. 2010 (before ischemia) 39.1 agel & Krolikowski 2009 42 anji et al. 2006 25 ubtotal (95% CI) 25 ster or overall effect: Z = 7.89 (P < 0.0001)	9.8	8 1	37.7	8.9	18	1.8%	-15.00 [-21.12, -8.88]	
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 vall. 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 (schemia) 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%						
sation 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 [-18.321.68]	
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	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	0	59.4	10.4	0	1.5%	-35.50 [-47.43, -23.57]	
Fancelli et al. 2014	32.6	14.1	8	57.3	18.1	8	1.3%	-24.70 [-40.60, -8.80]	
Laudi et al. 2007 (12.5mg/kg)	50	21	4	57	10	4	0.7%	-27.00 [-52.87, -1.13]	and the second sec
Ladur et al. 2007 (Shigrkg)	20	10	4	57	0	15	1.0%	-0.00 [-20.17, 10.17]	
Mateubara et al. 2000 (hefore icchemia)	30 1	4.2	6	53.4	5	15	2.0%	-21.00 [-27.96, -14.04]	-
Nagaoka et al. 2015	56	4.2	7	72	9	7	1 0%	-16.00 [-23.63 -8.37]	
Niemann et al. 2002 (10mo/ko)	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); I	^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]	T S
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	354	1.6%	-4.30 [-14.74, 6.14]	
Hotorogonoity: Tous = 07.79 ; Chiz = 242.50 df =	20 /B < 1	00004	200	4.0/		234	50.576	-15.02 [-16.79, -11.25]	•
Test for overall effect: Z = 7.80 (P < 0.00001)	50 (P < 1	0.00001	, - = 9	1 70					
After Ischemia									
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.4%	-36.00 [-50.03, -21.97]	
lkeda 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 [-27.46, -10.54]	
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 [-28.46, -11.54]	
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 [-28.46, -11.54]	
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	45	13	11	31	9	11	1.7%	14.00 [4.66, 23.34]	· · ·
Subtotal (95% CI)			101			104	23.5%	-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)	2 (P < 0.	.00001);	l² = 85	%					
Total (95% CI)			445			454	100.0%	-16 12 [-18 87 -13 27]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Tau2 = 01 25: Chi2 = 402 00 4f -	58 (D -	00004	12 - 0	8%		404	100.076	-10.12 [-10.01, -13.37]	
Test for overall effect: $7 = 11.47 (P < 0.00001)$	JOIPSI		8	U 70					-100 -50 0 50 100
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 100 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 <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 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 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.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/pi.schild.com/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 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 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 8 0 0 17 8 127, 48.69 40.00, 51.12, 48.69 Market at 2016 (rungs 3) 0 24 11 0 0 17 8 127, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 17.18, 48.69 40.00, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.17, 19.19 40.00, 18.20, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00, 18.19 40.00,	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 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 10 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 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 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) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±1.0) 2.01 (±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 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 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 13% 42.00 (50.4.9.47) Hard et 2016 (Gromphy) 20 2 2 6 6 61 6 6 13% 42.00 (50.4.9.47) Hard et 2016 (Gromphy) 20 2 2 6 6 61 6 6 13% 42.00 (50.4.9.47) Hard et 2016 (Gromphy) 20 2 2 6 6 61 6 6 13% 42.00 (50.4.9.47) Hard et 2016 (Gromphy) 20 2 2 6 1 6 6 1 5 7 8 12% 52.00 (23.4.4.11.64) Hercogeney, Tar = 3.25; (CP - 7 (P - 0.000)); P = 77K Tar = 1 200 (23.4.11.64) Hercogeney, Tar = 2.59; (P - 0.0000); P = 77K Hard et 200 (Gromphy) 20 2 2 5 6 4 35 6 2 15% - 18.00 (23.4.11.64) Hercogeney, Tar = 3.25; (CP - 19) (P - 0.0000); P = 77K Hard et 200 (Gromphy) 10 3 10 7 7 9 514 5 7 11 7 7 14 10 2205, 11.017 Hercogeney, Tar = 3.25; (CP - 19) (P - 0.0000); P = 77K Hercogeney, Tar = 3.25; (CP - 19) (P - 0.0000); P = 77K Hard et 200 (Gromphy) 10 4 5 7 7 9 514 5 7 11 54% - 1400 (23.0.5.11.67) Hercogeney, Tar = 3.25; (CP - 19) (P - 0.0000); P = 7K Hard et 200 (Gromphy) 10 7 14 10 77 4 10 77 4 400 (23.0.5.17) Hercogeney, Tar = 3.24; (CP - 19) (P - 0.0000); P = 7K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 7K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 7K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 7K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 7K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 5K Tormely dt 2010 2 5 6 7 7 59 7 7 1 15 7 7 14 10 7 24 7 133, 4551 (FA, 7.33) Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 5K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 5K Hercogeney, Tar = 3.44; (CP - 2.48; dF = 9) (P - 0.0000); P = 5K Hercogeney, Tar = 4.43; (CP - 2.48; dF = 9) (P - 0.0000); P = 5K Hercogeney, Tar = 4.43; (CP - 2.48; dF = 9) (P - 0.0000); P = 5K Hercogeney, Tar = 4.44; (CP - 2.44; (CP - 2.44; P - 0.0000); P = 5K Hercogeney, Tar = 4.44; (CP - 2.44; (CP - 2.44; P - 0.0000); P = 5K Hercogeney, Tar = 4.44; (CP - 2.44; (CP - 0	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 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -3.50 (-7.84 , -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 (-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 (-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 (-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 (-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 (-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 (-7.8	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 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -2.00 & -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 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 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 / 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 / 7 / 16.4 / 13. 27.6 / 16.4 / 0.7% - 4.00 (2.41, 7.16.17) 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 16.2 / 1	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 (Smg/kg) 35 22.6 6 6 1.94 4.00 [2.30, 15.07] Niemsen et al. 2002 (Smg/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] De Palle et al. 2010 50 7 50.4 7.4 7 1.83 -1.550 [4.73.4.2.57] -1.510 Ook et al. 2010 50.5 7.5 54.7 7 1.55 -1.100 [2.20.8, -1.51] -1.55 -1.554.5.0 -1.554.5.0 -1.554.5	Test for everall effect: 7 = 5 00 /D = 0 000001	(P < 0.0	001); I ² =	11%						
Isophig Interpret Interp	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] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-1] + [-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, 15, 20, 26, 8, -8, 14, 14, 14, 15, 14, 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 (10-2.2.7, -1.5.3) Hun et al. 2005 5 3.7 7 4.44 5 1.9 8 1 5 1.8% +2.00 (-3.6, -5.14) Hun et al. 2005 5 3.7 7 4.44 5 1.0 8.4 1.05 (-2.3.6, -3.5.16) Hun et al. 2005 5 3.7 7 4.44 5 1.9 8.4 1.00 (-2.2.6, -1.43) Hun et al. 2005 5 3.7 7 4.44 5 1.9 8.4 1.80 (-2.3.6, -3.5.16) Hun et al. 2019 (10mg/kg) 7 32 1.0 8 5.1 7 8 1.6% +1.00 (-2.3.6, -3.5.16) Hun et al. 2010 (10mg/kg) 7 5.1 12 6 77 12 6 1.2% +2.80 (-3.5.8, -5.14) Hun et al. 2010 (10mg/kg) 7 5.1 12 6 77 12 6 1.2% +2.80 (-3.5.8, -5.14) Hun et al. 2010 (10mg/kg) 7 5.1 12 6 77 12 6 1.2% +2.80 (-3.5.8, -5.14) Hun et al. 2010 (10mg/kg) 7 5.1 12 6	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 $										
Beengler tal. 2010 50 7 10 61 12 7 15% -110 (2288111 7 15% 42173.54 425173.54 43530 (2437.43 , 2357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 43577 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 4357 437 437 4357 437 437 4357 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 437 4	10mg/kg									10 million (1997)
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 12.5, 07, 14.45, Ch ² = 32.67, df = 10 (P = 0.00001); P = 89% Test for versal fact = 2.80, P < 0.00001; P = 80% Test for versal fact = 2.80, P < 0.00001; P = 80% Test for versal fact = 2.80, P < 0.00001; P = 80% Test for versal fact = 2.80, P < 0.00001; P = 80% Test for versal fact = 2.10, P	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 15.5% -22.80 (-3.17.3, -10.67) Negative at al. 2015 12 6 7 7 12 6 1.2% -26.00 (-3.17.3, -2.3) Prove at al. 2005 25.5 13 10.7 7 12.6 1.2% -26.00 (-3.17.3, -2.3) Prove at al. 2005 35.1 10.7 4.46 5.3 4.10 2.20 (-23.6, -5.15) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.18.46) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.18.46) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.13) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.14.46) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.13) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.13) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.14.46) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.0) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.0) Prove at al. 2005 51 12 6 77 19% +4.3.0 (-4.7, -2.3) Prove at al. 2005 51 12 6 77 19% +1.4.30 (-3.2, -3.68) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.0) Prove at al. 2005 51 12 6 77 12 6 1.2% -26.00 (-3.9, -3.0)	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% $-23.10 (\pm 26.12, \pm 20.06)$ Gamez et al. 2006 (10mg/kg) 36 7 8 51 7 8 18% $\pm 15.00 (\pm 28.6, \pm 0.41)$ liked at al. 2016 (10mg/kg) 46 7 8 51 7 8 1.8% $\pm 15.00 (\pm 28.6, \pm 0.41)$ liked at al. 2016 (10mg/kg) 49 14 12 41 16 15 14% $\pm 0.00 (\pm 28.77, \pm 2.31)$ Let ral. 2010 47.3 15.7 19 15.4 16.5 19 15.% $\pm 1.00 (\pm 23.62, \pm 0.02)$ Let ral. 2010 47.3 15.7 19 15.4 16.5 19 15.% $\pm 1.00 (\pm 23.62, \pm 0.02)$ Let ral. 2010 47.3 15.7 19 5.45 7.4 47 16 15.5% $\pm 0.00 (\pm 28.77, \pm 2.31)$ Let ral. 2011 (young) 31.9 6.9 7 5.19 10.7 7 14.% $\pm 2.30 (\pm 38.29, 0.02)$ Lue ral. 2017 (young) 31.9 6.9 7 5.45 7.4 7 16% $\pm 2.26 (\pm 31.77, \pm 0.41)$ Lue ral. 2017 (young) 31.9 6.9 7 5.45 7.4 7 16% $\pm 2.26 (\pm 31.77, \pm 0.41)$ Micana rat. 2020 (10mg/kg) 23 28 4 56 12 4 7 1.7% $\pm 0.00 (\pm 28.77, \pm 2.31)$ Nicana rat. 2015 56 5 7 72 9 7 1.7% $\pm 0.00 (\pm 28.67, \pm 0.32)$ Nicana rat. 2016 25.73 7 44 6 7 1.9% $\pm 2.26 (\pm 31.47, \pm 1.46)$ Nicana rat. 2019 25.17 2.6 7 48 6 7 1.9% $\pm 2.26 (\pm 31.47, \pm 1.46)$ Nicana rat. 2019 45 13 11 10 11 6% $\pm 1.00 (\pm 23.62, \pm 1.38)$ Tue rat. 2017 33 5 6 35 8 6 1.7% $\pm 2.00 (\pm 23.62, \pm 1.38)$ Tue rat. 2017 33 2.7 6 48 5.5.8 10.9 8 1.5% $\pm 3.00 (\pm 23.62, \pm 1.38)$ Tue rat. 2017 33 2.7 6 48 5.5.8 10.9 8 1.5% $\pm 3.00 (\pm 0.23.62, \pm 1.38)$ Tue rat. 2015 41.2015 43 2.2 10 8 51 7 12 6 1.9% $\pm 0.00 (\pm 23.62, \pm 1.38)$ Tue rat. 2017 33 5 1 12 6 77 12 6 1.2% $\pm 0.00 (\pm 0.23.62, \pm 1.38)$ Tue rat. 2017 41.6 (4 2.23.1 8 55.4 10.9 8 1.5% $\pm 3.00 (\pm 3.14.6, \pm 4.20)$ Autorist rat. 2016 (2.67.07.40) 39 10 12 6 0 8 15 7 7 18 4.00 (\pm 23.62, \pm 1.38) Tue rat. 2017 41.6 (-1.60.2000)1) $\pm 12.50mg/kg$ Gomez et al. 2005 51 12 6 77 12 6 1.2% $\pm 0.00 (\pm 27.66, \pm 1.06, 2)$ Nemann rat. 2006 (1.90.0% (\pm 0.00001)) $\pm 12.50mg/kg$ 13.9 10.1 2 6 7 11.9 4 10.0 4 10.0 (\pm 3.7, \pm 2.38) Nemann rat. 2006 (2.5 3.4 5 7 1.9% $\pm 3.30 (\pm 3.4, 5, 7 1.9% \pm 3.30 (\pm 3.4, 5, 7 1.4, 5, 1.4, 5, 1.4, 5, 1.4, 5, 1.4, 5, 1.4, 5, 1.4, 5, 1.$	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) Exet al. 2015 13 5 6 25 7 12 6 77 12 6 1.2% -26.00 (1.59.5, -14.45] Exet answer et al. 2015 11 10.4 8 55.4 10.9 202 39.1% -14.45 (-18.08, -10.82] Exet al. 2016 (2.5mg/kg) 30 01 2 6 0 8 15 7 8 1.6% -10.00 (2.2.70, -15.30] Exet al. 2016 (2.5mg/kg) 30 01 2 6 0 8 15 7 8 1.6% -10.00 (2.2.70, -15.30] Exet al. 2016 (2.5mg/kg) 30 01 2 6 0 8 15 7 19% -14.30 (-18.59, -14.02] Exet al. 2016 (2.5mg/kg) 30 01 2 6 0 8 15 7 8 1.6% -7.00 (1.2.47.6, -14.45] Heterogeneity: Tau' = 6.1.0, Chi = 152.44, df = 24 (P < 0.00001): F = 84% Test for overall effect: 2 = 7.80 (P < 0.00001): F = 84% Test for overall effect: 2 = 7.80 (P < 0.00001): F = 70% Test for overall effect: 2 = 7.80 (P < 0.00001): F = 70% Test for overall effect: 2 = 7.80 (P < 0.00001): F = 70% Te	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 \\$	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 [-3.56, -14.45] Zalewski et al. 2015 46.2 3.1 8 53.8 4.1 8 2.0% -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. 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 (Zsmg/kg) 32 10 8 51 7 8 1.6% -19.00 [-27.66, -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 (Zsmg/kg) 30 21 4 57 7 16 4 0.5% -43.00 [-39.58, -12.42] Ikeda et al. 2016 (Zsmg/kg) 39 10 12 60 8 15 1.8% -19.00 [-27.66, -11.6] Matsubara et al. 2010 (Lsmg/kg) 39 10 12 60 8 15 1.8% -21.00 [-27.96, -14.04] Matsubara et al. 2010 (Lsmg/kg) 13.9 12.9 4 58 12 4 1.0% 44.10 [-58.27, -28.8] Miemann et al. 2002 (Zsmg/kg) 13.9 12.9 4 58 12 4 1.0% 44.10 [-58.2, -28.8] Tal. 44.6 6 53.4 4.7 7 1.9% -14.30 [-13.9, -9.30] Niemann et al. 2002 (before ischemia) 39.6 55 13 6 0.9% -27.00 [-53.7], -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.7], -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.7], -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.7], -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.7], -24.28] Shintani-Ishida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 [-53.7], -24.28] Shintani-Ishida et al. 2012 (before ischemia)	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 7 12 6 7 17, 4 6 0.5% -35.00 ($\frac{2}{26.3}$, 6.8.7] Nikolaou et al. 2019 25.17 2.6 7 48 6 7 1.9% -228 ($\frac{2}{276}$, 17.39] Wang et al. 2006 25 3 7 44 4 7 2.0% -18.00 ($\frac{2}{23.63}$, 6.3.7] Wang et al. 2006 25 3 7 44 4 7 2.0% -18.00 ($\frac{2}{23.63}$, 26.3.7] Wang et al. 2006 25 3 7 44 4 7 2.0% -18.00 ($\frac{2}{23.63}$, 26.3.7] Wang et al. 2007 30.3 2.7 6 48.8 5.8 6 1.7% +22.00 ($\frac{2}{23.63}$, 26.3.7] 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] Zalewski 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] Zalewski 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 5 46.2 3.1 8 53.8 4.1 8 2.0% -7.60 (-11.16, -4.04] Zalewski et al. 2015 ($\frac{2}{27.80}$, 18, 1 0.0 8 15 7 8 1.5% -4.200 ($\frac{2}{23.85}$, 14.46] Gonze et al. 2005 5 51 12 6 77 12 6 1.2% -26.00 ($\frac{3}{39.58}$, 12.42] Eachnows et al. 2006 ($\frac{3}{27.66}$, 13, 200 202 39.1% -14.45 ($\frac{1}{18.96}$, -10.54] Laudi et al. 2007 ($\frac{1}{25.69}$, 14, 24 ($\frac{1}{24.00}$, 40.54 5 7 1.9% -14.30 ($\frac{1}{18.29}$, -8.68] Matsubara et al. 2001 ($\frac{1}{26.67}$, 13, 24 6 53.4 5 7 1.9% -14.30 ($\frac{1}{19.29}$, -4.68] Niemann et al. 2001 ($\frac{1}{26.67}$, 14.4 6 53.4 4.7 7 1.9% -14.30 ($\frac{1}{19.25}$, -9.35] Niemann et al. 2002 ($\frac{1}{25.69}$, 14, 4 6 53.4 4.7 7 1.9% -14.30 ($\frac{1}{19.25}$, -9.35] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{1}{44.77}$, -2.28] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{1}{44.77}$, -2.28] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{1}{44.77}$, -2.28] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -27.00 ($\frac{1}{44.77}$, -2.28] Shintani-Istida et al. 2012 (before ischemia) 28 18 6 55 13 6 0.9% -7.70 (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; 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 = 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 = 86% 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 3.9.1% +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% -18.00 (-27.46, -10.64) - Matsubara et al. 2010 (before ischemia) 39.6 3.6 4 53.4 5 7 1.9% -1.380 (-18.92, -6.81) - - - - - <td< td=""><td>Nikolaou et al. 2019</td><td>25.17</td><td>2.6</td><td>7</td><td>48</td><td>6</td><td>7</td><td>1.9%</td><td>-22.83 [-27.67, -17.99]</td><td></td></td<>	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, -6.23] 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% $-27.00 [-44.77, -9.23]$ Shintani-Ishida et al. 2012 (during/after ischem) 16 13 6 55 13 6 1.1% $-39.00 [-53.71, -24.29]$ 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 = 47.1; 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 = 556, 12, df = 63 (P < 0.00001); P = 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 [-53.71, -24.29] 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 (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% 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)	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 6 51 16 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 Test for overall effect: Z = 8.59 (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 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 0.00 = 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, ♂, 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* <i>vs.</i> 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 <i>et 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% vs. 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 <i>et al.</i> (2009)	rabbit (New Zealand white, $\vec{\circ}$, 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, $\stackrel{\circ}{_{ m o}}$, 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, $\stackrel{\bigcirc}{}$, 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, \mathcal{J}/\mathbb{Q} , NR, 4/4)	5 (IV)	90 (LAD hypoperfusion)	35±3 % vs. 25±3% (P<0.05)	 dP/dtmax 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, $\stackrel{\bigcirc}{}$, NR, 11/12)	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% vs. −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 <i>et al.</i> (2011)	mouse (dtTomato, NR, NR, 6/6)	10 (IV)	90 (LAD)	NR	 dP/dt_{max} 19,000±3,000 mmHg/s vs. 18,000±4,000 mmHg/s (P>0.05) 	
Ikeda et al. (2016)	mouse (C57BI/6, ♂, 10–12 wk, 8/8/8/8/8/8/8/8)	1 (IV) NR (left marginal) 1 (nanoparticle) 2.5 (IV)		51±3% vs. 53±3% (P>0.05)	• LVEF 33.0±2.0% vs. 32.0±2.6% (P>0.05)	
				51±3% vs. 32±3% (P<0.001)	• LVEF 33.0±2.0% vs. 49.0±2.0% (<0.05)	
				51±3% vs. 49±3% (P>0.05)		
		2.5 (nanoparticle)		51±3% vs. 31±3% (P<0.001)		
		10 (IV) 10 (nanoparticle)		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>vs</i> . 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)	
Ikeda e <i>t 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 <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	
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 et al. $(2014)^{\ddagger}$	mouse (NR, NR, NR, 8/8)	(nanoparticle)	NR	52±4% vs. 32±9% (P<0.05)	NR	
Ikeda <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 et al. (2014)	rat (Sprague-Dawley, ♂, NR, 8/8/8) 1 (NR) 30 (LAD) 45.00±0.73% vs. 35.29±		45.00±0.73% vs. 35.29±0.54% (P<0.05)	 5) • 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)		<i>vs</i> . 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 et al. (2017)	rat (Sprague-Dawley, ♂, NR, 6/12)	10 (NR)	10 (electricity)	Cl 62±8 mL/min/kg vs. 63±4 mL/min/kg at 120 min (ns), 58±6 mL/min/kg vs. 59± 3 mL/min/kg at 240 min (ns), 52±4 mL/min/kg vs. 46±5 mL/min/kg at 360 min (ns)	• Tnl 130±76 ng/mL vs. 2
During ischemia					
Huang <i>et al.</i> (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% <i>vs</i>
Huang et al. (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 vs. 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 e <i>t al.</i> (2012)b	pig (mixed, NR, 1–4 d, 8/8/8/8)	2.5 (IV)	120 (ventilation with FiO₂ 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 v: 3.2±2.2 mM at 4 hr (P>
		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 v: 3.1±1.0 mM at 4 hr (P>
		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>
Gill <i>et al.</i> (2013)	pig (mixed, NR, 1–4 d, 8/8)	10 (IV)	120 (ventilation with FiO ₂ 0.10–0.15)	NR	• Tnl 1.2±0.2 ng/mL vs. 0
Cardiac transplantation	I				
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 ac

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

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