Supplementary

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 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).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 sanciclo 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).tn.	6795

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

SCOPUS Searched March 8, 2022 Results = 1568

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

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 sti0529 or "t 1580" or t1580 or verkazia or vekacia) 67,609
#5 cr=59865-13-3 28,691
#6 #4 OR #5 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
#10 #8 Not #9 1,154,443
#11 #7 Not #10 656

Cochrane Library Searched March 8, 2022
(Cochrane Database of Systematic Reviewes Results =0)
(Cochrane 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 damag* or necrosis or necrotic or hemorrhag* or haemorrhag*)):ti,ab,kw	2952
#5	((reperfus* or ir or hypoxi* ischemi*) NEAR/3 (free 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 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 sti0529 or "t 1580" or t1580 or verkazia 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 (invivo OR "in vivo"))	2916
#13	#11 NOT #12	46

PROSPERO Searched March 9, 2022

Line	Search for	Hits
#1	(ir or "hypox* ischemi*" or reperfus*) and (injur* or damag* or necros* or necrotic or hemorrhag* or haemorrhag* or "free radical*" or shock)	646
#2	("adi 628" or adi628 or equa or "cgc 1072" or cgc1072 or	

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	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 sti0529 or "t 1580" or t1580 or verkazia or vekacia)	236
#3	#1 and #2	8

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Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Mouse								
Boengler et al. 2010	50	7	10	61	12	7	1.5%	-11.00 [-20.89, -1.11]
Gomez et al. 2005	51	12	6	77	12	6	1.2%	-26.00 [-39.58, -12.42]
Gomez et al. 2008	35	14	8	58	15	9	1.2%	-23.00 [-36.79, -9.21]
Ikeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.8%	2.00 [-4.86, 8.86]
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	7	8	1.6%	-19.00 [-27.46, -10.54]
Ikeda et al. 2016 (2.5mg/kg)	49	10	8	51	7	8	1.6%	-2.00 [-10.46, 6.46]
Ikeda et al. 2016 (2.5mg/kg NP)	31	10	8	51	7	8	1.6%	-20.00 [-28.46, -11.54]
Ikeda et al. 2016 (25mg/kg)	32	10	8	51	7	8	1.6%	-19.00 [-27.46, -10.54]
Ikeda et al. 2021 (30min)	33	10	8	53	7	8	1.6%	-20.00 [-28.46, -11.54]
Ikeda et al. 2021 (60min)	65	6	8	72	4	8	1.9%	-7.00 [-12.00, -2.00]
Lim et al. 2007	32	7	6	48	10	6	1.5%	-16.00 [-25.77, -6.23]
Nikolaou et al. 2019	25.17	2.6	7	48	6	7	1.9%	-22.83 [-27.67, -17.99]
Rusinkevich et al. 2019	45	13	11	31	9	11	1.6%	14.00 [4.66, 23.34]
Youcef et al. 2015	13	5	6	35	8	6	1.7%	-22.00 [-29.55, -14.45]
Subtotal (95% CI)			**126**			**124**	**26.1%**	**-13.62 [-18.66, -8.58]**
Heterogeneity: $Tau^2 = 86.66$; $Chi^2 = 99.34$, df = 15 ($P < 0.00001$); $I^2 = 85\%$								
Test for overall effect: $Z = 5.29$ ($P < 0.00001$)								
Rat								
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 (before)	23.9	14.3	7	59.4	7.4	7	1.3%	-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	2.0%	-23.10 [-26.12, -20.08]
Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.0%	-11.30 [-15.38, -7.22]
Huang et al. 2014 (1mg/kg)	35.29	1.52	8	45	2.07	8	2.1%	-9.71 [-11.49, -7.93]
Huang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2.1%	-15.95 [-17.98, -13.92]
Huang et al. 2014 (5mg/kg)	26.9	1.86	8	45	2.07	8	2.1%	-18.10 [-20.03, -16.17]
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	1.8%	-19.60 [-25.60, -13.60]
Huhn et al. 2010	61	9	7	58	6	7	1.7%	3.00 [-5.01, 11.01]
Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.4%	-6.20 [-17.11, 4.71]
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]
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	1.6%	-22.60 [-31.17, -14.03]
Nagaoka et al. 2015	56	5	7	72	9	7	1.7%	-16.00 [-23.63, -8.37]
Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.6%	-19.90 [-29.05, -10.75]
Niemann et al. 2002 (10mg/kg)	23	28	4	58	12	4	0.5%	-35.00 [-64.85, -5.15]
Niemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.0%	-44.10 [-61.37, -26.83]
Niemann et al. 2002 (25mg/kg)	17	14.6	4	58	12	4	0.9%	-41.00 [-59.52, -22.48]
Niemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.5%	-23.00 [-51.06, 5.06]
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]
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	1.9%	-6.00 [-11.66, -0.34]
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	1.9%	-23.00 [-27.67, -18.33]
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.8%	-45.00 [-51.45, -38.55]
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.0%	-36.00 [-40.08, -31.92]
Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	1.9%	-18.50 [-23.62, -13.38]
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)			**217**			**218**	**49.7%**	**-19.01 [-22.32, -15.70]**
Heterogeneity: $Tau^2 = 67.70$; $Chi^2 = 360.41$, df = 32 ($P < 0.00001$); $I^2 = 91\%$								
Test for overall effect: $Z = 11.25$ ($P < 0.00001$)								
Rabbit								
Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	1.8%	-15.00 [-21.12, -8.88]
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Fancelli et al. 2014	32.6	14.1	8	57.3	18.1	8	1.0%	-24.70 [-40.60, -8.80]
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 [-18.92, -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]
Pagel & Krolikowski 2009	42	5	6	46	5	6	1.9%	-4.00 [-9.66, 1.66]
Ranji et al. 2009	39.1	4.4	6	53.4	4.7	7	1.9%	-14.30 [-19.25, -9.35]
Wang et al. 2006	25	3	7	44	4	7	2.0%	-19.00 [-22.70, -15.30]
Subtotal (95% CI)			**83**			**91**	**16.7%**	**-17.47 [-21.81, -13.13]**
Heterogeneity: $Tau^2 = 33.60$; $Chi^2 = 40.20$, df = 9 ($P < 0.00001$); $I^2 = 78\%$								
Test for overall effect: $Z = 7.89$ ($P < 0.00001$)								
Pig								
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]
Skyschally et al. 2010	25	6	4	35	6	4	1.7%	-10.00 [-18.32, -1.68]
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.0%	-7.60 [-11.16, -4.04]
Subtotal (95% CI)			**55**			**57**	**7.5%**	**-4.77 [-10.19, 0.65]**
Heterogeneity: $Tau^2 = 17.13$; $Chi^2 = 7.72$, df = 4 ($P = 0.10$); $I^2 = 48\%$								
Test for overall effect: $Z = 1.73$ ($P = 0.08$)								
Total (95% CI)			**481**			**490**	**100.0%**	**-16.30 [-18.59, -14.01]**
Heterogeneity: $Tau^2 = 64.71$; $Chi^2 = 556.12$, df = 63 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: $Z = 13.93$ ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 20.69$, df = 3 ($P = 0.0001$), $I^2 = 85.5\%$								

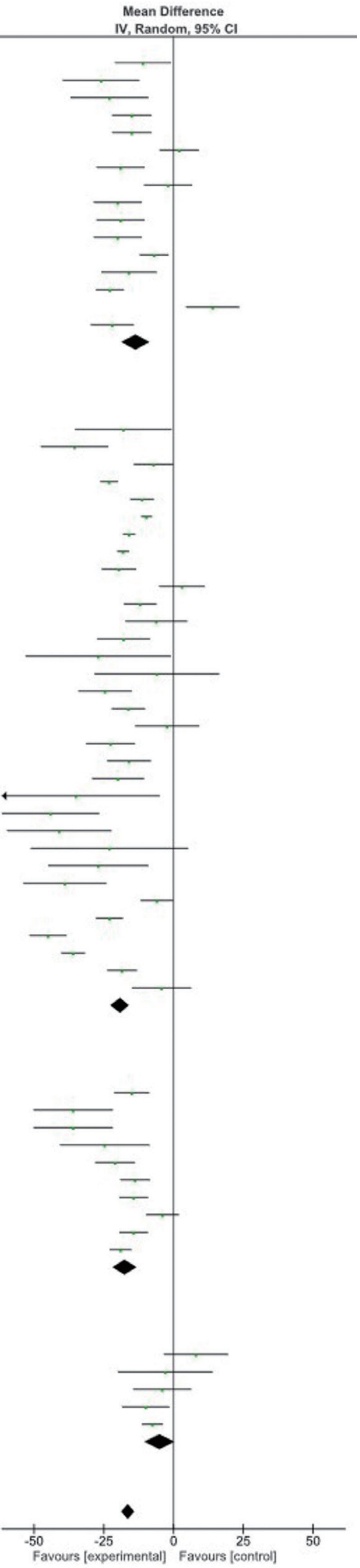

Figure S1 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by species.

 https://dx.doi.org/10.21037/atm-22-618

	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Male								
Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	1.9%	-15.00 [-21.12, -8.88]
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
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 (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]
Huang et al. 2014 (5mg/kg)	26.9	1.86	8	45	2.07	8	2.1%	-18.10 [-20.03, -16.17]
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	1.9%	-19.60 [-25.60, -13.60]
Huhn et al. 2010	61	9	7	58	6	7	1.7%	3.00 [-5.01, 11.01]
Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.5%	-6.20 [-17.11, 4.71]
Ikeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.8%	2.00 [-4.86, 8.86]
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	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	7	72	9	7	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)	23	28	4	58	12	4	0.5%	-35.00 [-64.85, -5.15]
Niemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.0%	-44.10 [-61.37, -26.83]
Niemann et al. 2002 (25mg/kg)	17	14.6	4	58	12	4	0.9%	-41.00 [-59.52, -22.48]
Niemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.5%	-23.00 [-51.06, 5.06]
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	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**			**405**	**89.1%**	**-17.43 [-19.91, -14.95]**
Heterogeneity: $\text{Tau}^2 = 65.59$; $\text{Chi}^2 = 506.53$, df = 54 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: $Z = 13.78$ ($P < 0.00001$)								
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: $\text{Tau}^2 = 12.51$; $\text{Chi}^2 = 2.63$, df = 2 ($P = 0.27$); $I^2 = 24\%$								
Test for overall effect: $Z = 0.15$ ($P = 0.88$)								
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 [-25.77, -6.23]
Skyschally et al. 2010	25	6	4	35	6	4	1.7%	-10.00 [-18.32, -1.68]
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.1%	-7.60 [-11.16, -4.04]
Subtotal (95% CI)			**28**			**25**	**6.9%**	**-8.98 [-11.94, -6.02]**
Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 2.78$, df = 3 ($P = 0.43$); $I^2 = 0\%$								
Test for overall effect: $Z = 5.94$ ($P < 0.00001$)								
Total (95% CI)			**467**			**475**	**100.0%**	**-16.26 [-18.61, -13.91]**
Heterogeneity: $\text{Tau}^2 = 66.34$; $\text{Chi}^2 = 554.60$, df = 61 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: $Z = 13.56$ ($P < 0.00001$)								
Test for subgroup differences: $\text{Chi}^2 = 30.14$, df = 2 ($P < 0.00001$), $I^2 = 93.4\%$								

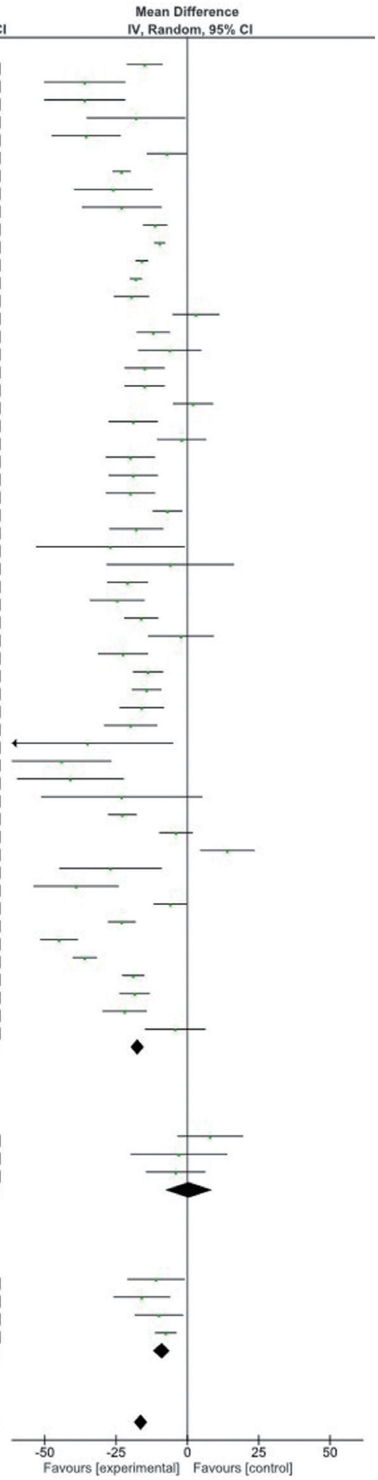

Figure S2 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by sex.

https://dx.doi.org/10.21037/atm-22-618

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference 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	7	59.4	7.4	7	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)	30	21	4	57	16	4	0.7%	-27.00 [-52.87, -1.13]
Laudi et al. 2007 (5mg/kg)	51	16	4	57	16	4	0.9%	-6.00 [-28.17, 16.17]
Leshnower et al. 2008	39	10	12	60	8	15	1.9%	-21.00 [-27.96, -14.04]
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	7	72	9	7	1.9%	-16.00 [-23.63, -8.37]
Niemann et al. 2002 (10mg/kg)	23	28	4	58	12	4	0.6%	-35.00 [-64.85, -5.15]
Niemann et al. 2002 (15mg/kg)	13.9	12.9	4	58	12	4	1.2%	-44.10 [-61.37, -26.83]
Niemann et al. 2002 (25mg/kg)	17	14.6	4	58	12	4	1.1%	-41.00 [-59.52, -22.48]
Niemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.7%	-23.00 [-51.06, 5.06]
Ranji et al. 2009	39.1	4.4	6	53.4	4.7	7	2.0%	-14.30 [-19.25, -9.35]
Shintani-Ishida et al. 2012 (before ischemia)	28	18	6	55	13	6	1.1%	-27.00 [-44.77, -9.23]
Subtotal (95% CI)			**94**			**96**	**20.0%**	**-22.86 [-27.98, -17.73]**
Heterogeneity: Tau² = 52.18; Chi² = 40.85, df = 14 (P = 0.0002); I² = 66%								
Test for overall effect: Z = 8.74 (P < 0.00001)								
During Ischemia								
Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	2.0%	-15.00 [-21.12, -8.88]
Choi et al. 2017	36.16	11.18	4	54.17	13.5	4	1.2%	-18.01 [-35.19, -0.83]
De Paulis et al. 2013 (during)	52.2	5.6	7	59.4	7.4	7	1.9%	-7.20 [-14.07, -0.33]
Fang et al. 2008	24.4	3.3	12	47.5	4.2	12	2.1%	-23.10 [-26.12, -20.08]
Gomez et al. 2008	35	14	8	58	15	9	1.4%	-23.00 [-36.79, -9.21]
Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.1%	-11.30 [-15.38, -7.22]
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	2.0%	-19.60 [-25.60, -13.60]
Huhn et al. 2010	61	9	7	58	6	7	1.8%	3.00 [-5.01, 11.01]
Hurt et al. 2016	49	5	6	61	5	6	2.0%	-12.00 [-17.66, -6.34]
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.6%	-6.20 [-17.11, 4.71]
Karlsson et al. 2010	49	14	12	41	16	15	1.6%	8.00 [-3.33, 19.33]
Karlsson et al. 2012	51	21	12	54	20	11	1.2%	-3.00 [-19.76, 13.76]
Kiss et al. 2016	45.9	6.3	7	63.8	11.6	8	1.7%	-17.90 [-27.19, -8.61]
Lie et al. 2010	47.3	15.7	19	51.4	16.5	19	1.7%	-4.10 [-14.34, 6.14]
Li et al. 2012	35.2	9.3	7	59.8	8.7	7	1.7%	-24.60 [-34.03, -15.17]
Li et al. 2014	26.1	6.1	6	42.3	3.9	6	2.0%	-16.20 [-21.99, -10.41]
Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.6%	-2.30 [-13.62, 9.02]
Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.8%	-22.60 [-31.17, -14.03]
Nazari et al. 2015	17.7	14.4	13	37.6	8.7	13	1.7%	-19.90 [-29.05, -10.75]
Nikolaou et al. 2019	25.17	2.6	7	48	6	7	2.0%	-22.83 [-27.67, -17.99]
Pagel & Krolikowski 2009	42	5	6	46	5	6	2.0%	-4.00 [-9.66, 1.66]
Skyschally et al. 2010	25	6	4	35	6	4	1.8%	-10.00 [-18.32, -1.68]
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	2.0%	-6.00 [-11.66, -0.34]
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	2.0%	-23.00 [-27.67, -18.33]
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.9%	-45.00 [-51.45, -38.55]
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.1%	-36.00 [-40.08, -31.92]
Wang et al. 2006	25	3	7	44	4	7	2.1%	-19.00 [-22.70, -15.30]
Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	2.0%	-18.50 [-23.62, -13.38]
Youcef et al. 2015	13	5	6	35	8	6	1.9%	-22.00 [-29.55, -14.45]
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.1%	-7.60 [-11.16, -4.04]
Zhu et al. 2013	51.1	10.4	8	55.4	10.9	8	1.6%	-4.30 [-14.74, 6.14]
Subtotal (95% CI)			**250**			**254**	**56.5%**	**-15.02 [-18.79, -11.25]**
Heterogeneity: Tau² = 97.78; Chi² = 342.59, df = 30 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 7.80 (P < 0.00001)								
After Ischemia								
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.4%	-36.00 [-50.03, -21.97]
Ikeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1.9%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.9%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.9%	2.00 [-4.86, 8.86]
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	7	8	1.8%	-19.00 [-27.46, -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: Tau² = 82.89; Chi² = 80.53, df = 12 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.45 (P < 0.00001)								
Total (95% CI)			**445**			**454**	**100.0%**	**-16.12 [-18.87, -13.37]**
Heterogeneity: Tau² = 91.35; Chi² = 492.88, df = 58 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 11.47 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.71, df = 2 (P = 0.01), I² = 77.0%								

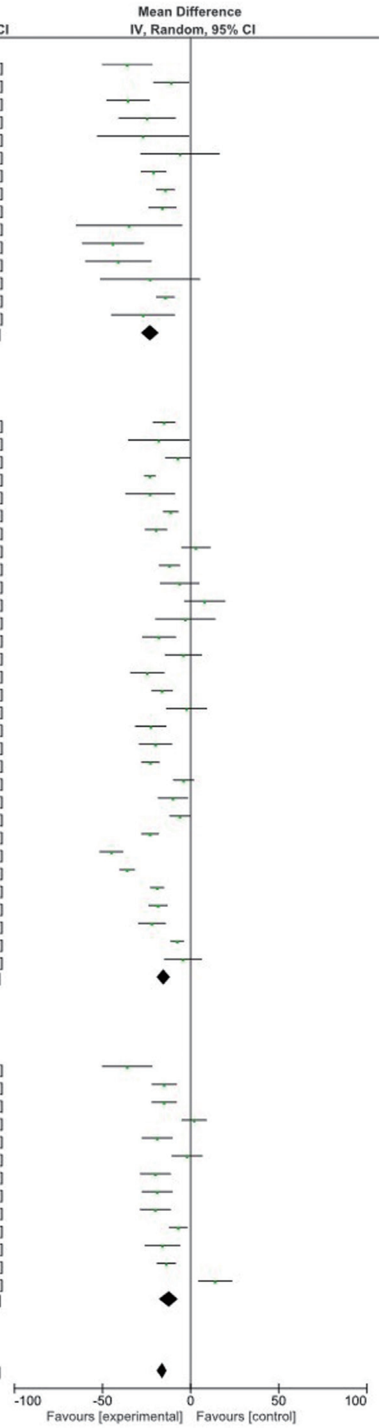

Figure S3 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by timing of treatment.

https://dx.doi.org/10.21037/atm-22-618

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
≤1mg/kg								
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]
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.8%	2.00 [-4.86, 8.86]
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	7	8	1.6%	-19.00 [-27.46, -10.54]
Ikeda et al. 2021 (30min)	33	10	8	53	7	8	1.6%	-20.00 [-28.46, -11.54]
Ikeda et al. 2021 (60min)	65	6	8	72	4	8	1.9%	-7.00 [-12.00, -2.00]
Squadrito et al. 1999 (0.25mg/kg)	46	5	6	52	5	6	1.9%	-6.00 [-11.66, -0.34]
Squadrito et al. 1999 (0.5mg/kg)	29	3	6	52	5	6	1.9%	-23.00 [-27.67, -18.33]
Squadrito et al. 1999 (1mg/kg, 30min ischemia)	12	4	6	57	7	6	1.8%	-45.00 [-51.45, -38.55]
Squadrito et al. 1999 (1mg/kg)	16	1	6	52	5	6	2.0%	-36.00 [-40.08, -31.92]
Subtotal (95% CI)			**72**			**72**	**18.7%**	**-17.47 [-25.45, -9.49]**
Heterogeneity: Tau² = 156.83; Chi² = 277.72, df = 9 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 4.29 (P < 0.0001)								
2.5mg/kg								
Alexopoulos et al. 2017	22.7	9.8	18	37.7	8.9	18	1.8%	-15.00 [-21.12, -8.88]
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Huang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2.1%	-15.95 [-17.98, -13.92]
Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]
Ikeda et al. 2016 (2.5mg/kg)	49	10	8	51	7	8	1.6%	-2.00 [-10.46, 6.46]
Ikeda et al. 2016 (2.5mg/kg NP)	31	10	8	51	7	8	1.6%	-20.00 [-28.46, -11.54]
Karlsson et al. 2012	51	21	12	54	20	11	1.0%	-3.00 [-19.76, 13.76]
Subtotal (95% CI)			**76**			**75**	**12.4%**	**-16.35 [-21.70, -11.00]**
Heterogeneity: Tau² = 38.25; Chi² = 31.09, df = 7 (P < 0.0001); I² = 77%								
Test for overall effect: Z = 5.99 (P < 0.00001)								
: 5mg/kg								
Huang et al. 2014 (5mg/kg)	26.9	1.86	8	45	2.07	8	2.1%	-18.10 [-20.03, -16.17]
Huhn et al. 2008	31.8	7.7	9	51.4	5	9	1.8%	-19.60 [-25.60, -13.60]
Huhn et al. 2010	61	9	7	58	6	7	1.7%	3.00 [-5.01, 11.01]
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.4%	-6.20 [-17.11, 4.71]
Laudi et al. 2007 (5mg/kg)	51	16	4	57	16	4	0.7%	-6.00 [-28.17, 16.17]
Li et al. 2012	35.2	9.3	7	59.8	8.7	7	1.6%	-24.60 [-34.03, -15.17]
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 (5mg/kg)	35	26	4	58	12	4	0.5%	-23.00 [-51.06, 5.06]
Pagel & Krolikowski 2009	42	5	6	46	5	6	1.9%	-4.00 [-9.66, 1.66]
Skyschally et al. 2010	25	6	4	35	6	4	1.7%	-10.00 [-18.32, -1.68]
Subtotal (95% CI)			**67**			**67**	**14.9%**	**-12.57 [-18.29, -6.84]**
Heterogeneity: Tau² = 58.94; Chi² = 54.81, df = 9 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 4.30 (P < 0.0001)								
10mg/kg								
Boengler et al. 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	13.5	4	1.0%	-18.01 [-35.19, -0.83]
De Paulis et al. 2013 (before)	23.9	14.3	7	59.4	7.4	7	1.3%	-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]
Fancelli et al. 2014	32.6	14.1	8	57.3	18.1	8	1.0%	-24.70 [-40.60, -8.80]
Fang et al. 2008	24.4	3.3	12	47.5	4.2	12	2.0%	-23.10 [-26.12, -20.08]
Gomez et al. 2008	35	14	8	58	15	9	1.2%	-23.00 [-36.79, -9.21]
Ikeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Karlsson et al. 2010	49	14	12	41	16	15	1.4%	8.00 [-3.33, 19.33]
Kiss et al. 2016	45.9	6.3	7	63.8	11.6	8	1.6%	-17.90 [-27.19, -8.61]
Lie et al. 2010	47.3	15.7	19	51.4	16.5	19	1.5%	-4.10 [-14.34, 6.14]
Li et al. 2014	26.1	6.1	6	42.3	3.9	6	1.9%	-16.20 [-21.99, -10.41]
Lim et al. 2007	32	7	6	48	10	6	1.5%	-16.00 [-25.77, -6.23]
Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.4%	-2.30 [-13.62, 9.02]
Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.6%	-22.60 [-31.17, -14.03]
Nagaoka et al. 2015	56	5	7	72	9	7	1.7%	-16.00 [-23.63, -8.37]
Niemann et al. 2002 (10mg/kg)	23	28	4	58	12	4	0.5%	-35.00 [-64.85, -5.15]
Nikolaou et al. 2019	25.17	2.6	7	48	6	7	1.9%	-22.83 [-27.67, -17.99]
Rusinkevich et al. 2019	45	13	11	31	9	11	1.6%	14.00 [4.66, 23.34]
Wang et al. 2006	25	3	7	44	4	7	2.0%	-19.00 [-22.70, -15.30]
Xie & Yu 2007	30.3	2.7	6	48.8	5.8	6	1.9%	-18.50 [-23.62, -13.38]
Youcef et al. 2015	13	5	6	35	8	6	1.7%	-22.00 [-29.55, -14.45]
Zalewski et al. 2015	46.2	3.1	8	53.8	4.1	8	2.0%	-7.60 [-11.16, -4.04]
Zhu et al. 2013	51.1	10.4	8	55.4	10.9	8	1.5%	-4.30 [-14.74, 6.14]
Subtotal (95% CI)			**200**			**202**	**39.1%**	**-14.45 [-18.08, -10.82]**
Heterogeneity: Tau² = 63.10; Chi² = 152.44, df = 24 (P < 0.00001); I² = 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 [-52.87, -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 [-18.92, -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 [-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	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% CI)			**66**			**74**	**14.9%**	**-22.36 [-27.46, -17.26]**
Heterogeneity: Tau² = 41.49; Chi² = 32.87, df = 10 (P = 0.0003); I² = 70%								
Test for overall effect: Z = 8.59 (P < 0.00001)								
Total (95% CI)			**481**			**490**	**100.0%**	**-16.30 [-18.59, -14.01]**
Heterogeneity: Tau² = 64.71; Chi² = 556.12, df = 63 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 13.93 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.15, df = 4 (P = 0.09), I² = 50.9%								

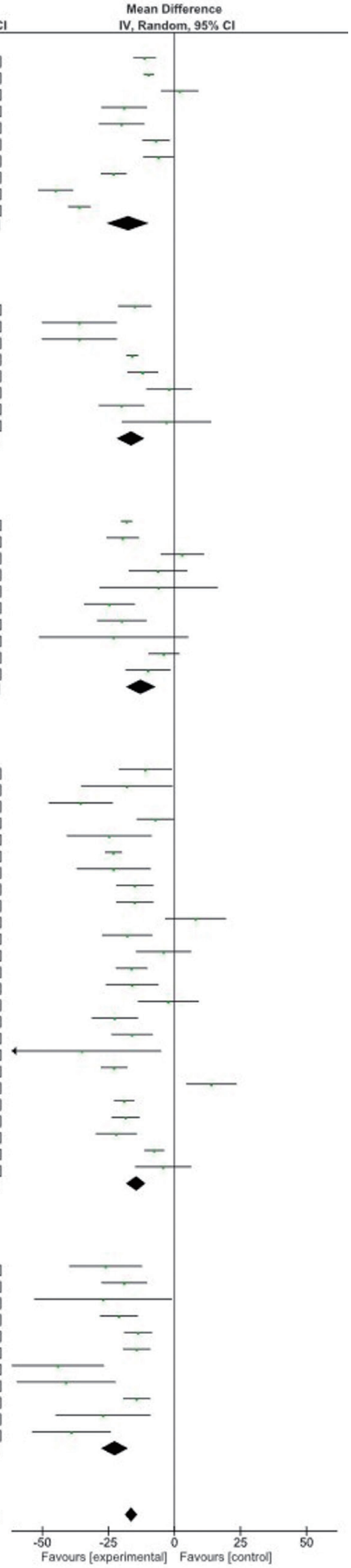

Figure S4 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by dose.

https://dx.doi.org/10.21037/atm-22-618

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
20-30min								
Gomez et al. 2005	51	12	6	77	12	6	1.2%	-26.00 [-39.58, -12.42]
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	7	58	6	7	1.7%	3.00 [-5.01, 11.01]
Ikeda 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)			**54**			**54**	**14.5%**	**-21.62 [-32.08, -11.15]**
Heterogeneity: Tau² = 213.52; Chi² = 159.61, df = 7 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 4.05 (P < 0.0001)								
30-40min								
Argaud et al. 2005 (after)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Argaud et al. 2005 (before)	24	11	8	60	17	8	1.2%	-36.00 [-50.03, -21.97]
Boengler et al. 2010	50	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]
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]
Fancelli et al. 2014	32.6	14.1	8	57.3	18.1	8	1.1%	-24.70 [-40.60, -8.80]
Fang et al. 2008	24.4	3.3	12	47.5	4.2	12	2.1%	-23.10 [-26.12, -20.08]
Gross et al. 2013	51.5	3.4	8	62.8	4.8	8	2.1%	-11.30 [-15.38, -7.22]
Huang et al. 2014 (1mg/kg)	35.29	1.52	8	45	2.07	8	2.2%	-9.71 [-11.49, -7.93]
Huang et al. 2014 (2.5mg/kg)	29.05	2.08	8	45	2.07	8	2.2%	-15.95 [-17.98, -13.92]
Huang et al. 2014 (5mg/kg)	26.9	1.86	8	45	2.07	8	2.2%	-18.10 [-20.03, -16.17]
Hurt et al. 2016	49	5	6	61	5	6	1.9%	-12.00 [-17.66, -6.34]
Ikeda et al. 2016 (10mg/kg)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (10mg/kg NP)	36	7	8	51	7	8	1.8%	-15.00 [-21.86, -8.14]
Ikeda et al. 2016 (1mg/kg)	53	7	8	51	7	8	1.8%	2.00 [-4.86, 8.86]
Ikeda et al. 2016 (1mg/kg NP)	32	10	8	51	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]
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]
Lim et al. 2007	32	7	6	48	10	6	1.6%	-16.00 [-25.77, -6.23]
Liu et al. 2011 (old)	49.6	10.9	7	51.9	10.7	7	1.4%	-2.30 [-13.62, 9.02]
Liu et al. 2011 (young)	31.9	8.9	7	54.5	7.4	7	1.7%	-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]
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]
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]
Niemann et al. 2002 (5mg/kg)	35	26	4	58	12	4	0.5%	-23.00 [-51.06, 5.06]
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	1.9%	-4.00 [-9.66, 1.66]
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	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]
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)			**315**			**321**	**71.1%**	**-17.12 [-19.27, -14.97]**
Heterogeneity: Tau² = 32.92; Chi² = 235.08, df = 44 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 15.62 (P < 0.00001)								
>40min								
Alexopoulos 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]
Hwang et al. 2018	11.5	8.9	5	17.7	8.7	5	1.5%	-6.20 [-17.11, 4.71]
Ikeda et al. 2021 (60min)	65	6	8	72	4	8	2.0%	-7.00 [-12.00, -2.00]
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]
Nagaoka 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
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)			**97**			**100**	**14.4%**	**-8.63 [-13.01, -4.25]**
Heterogeneity: Tau² = 24.62; Chi² = 22.31, df = 8 (P = 0.004); I² = 64%								
Test for overall effect: Z = 3.86 (P = 0.0001)								
Total (95% CI)			**466**			**475**	**100.0%**	**-16.87 [-19.14, -14.60]**
Heterogeneity: Tau² = 60.48; Chi² = 515.51, df = 61 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 14.57 (P < 0.00001)								
Test for subgroup differences: Chi² = 12.92, df = 2 (P = 0.002), I² = 84.5%								

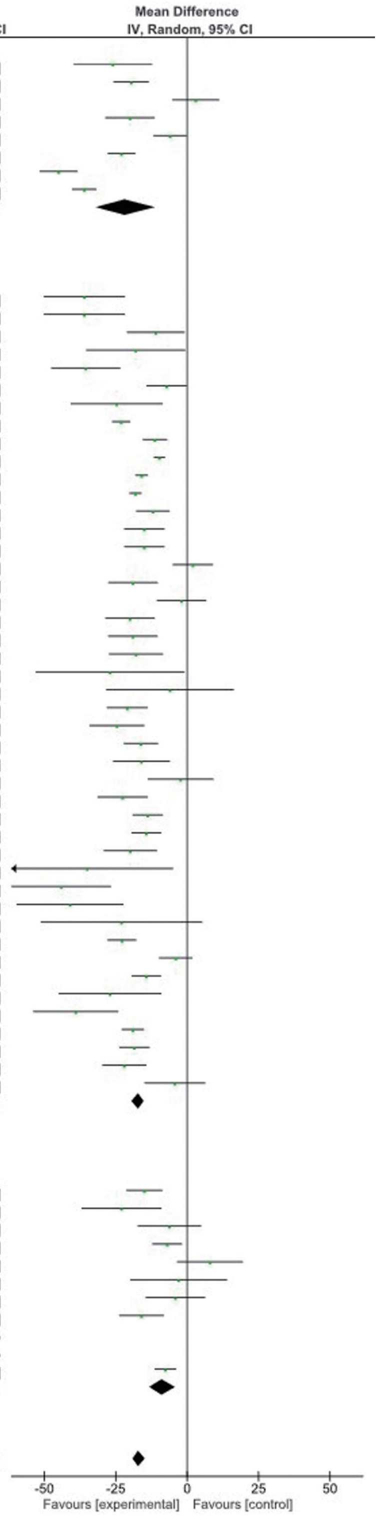

Figure S5 Subgroup meta-analysis of coronary occlusion models of myocardial ischemia-reperfusion injury treated with cyclosporine a, stratified by duration of ischemia.

 https://dx.doi.org/10.21037/atm-22-618

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

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 *et al.* (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 *et al.* (2002)	rat (Sprague-Dawley, ♂, 6 mo, 4/4/4/4/4)	5 ×3 (PO)	30 (LCA)	58±6% *vs.* 35±13% (P>0.03)	NR
		10 ×3 (PO)		*vs.* 23±14% (P<0.03)	
		15 ×3 (PO)		*vs.* 13.9±6.5% (P<0.03)	
		25 ×3 (PO)		*vs.* 17.0±7.3% (P>0.03)	
Laudi *et al.* (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)		*vs.* 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 *et al.* (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 *et al.* (2015)	rat (Sprague-Dawley, ♂, NR, 7/7)	10 (IV)	45 (LAD)	72±4% *vs.* 56±2% (P<0.05)	NR
Argaud *et al.* (2005)	rabbit (New Zealand white, ♂, NR, 8/8)	2.5 (IV)	30 (left marginal)	60±6% *vs.* 24±4% (P<0.0001)	NR
Ranji *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (2004)[‡]	mouse (NR, NR, NR, 6/6)	40 ×3 (IP)	25 (NR)	72±4% *vs.* 56±4% (P<0.05)	NR
Gomez *et al.* (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 *et al.* (2010)	rat (Sprague-Dawley, ♂, NR, 10/10	2 x2 (IP)	30 (LAD)	NR	• TnI 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 *et al.* (2007)[‡]	mouse (NR, NR, NR, 9/9)	10 (IV)	60 (NR)	56±5% *vs.* 36%* (P<0.05)	NR
Gomez *et al.* (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 (C57Bl/6, ♂, 22 mo, 5–7/5–7)	10 (IV)	30 (LAD)	35±3% *vs.* 13±2% (P<0.05)	NR
Nikolaou *et al.* (2019)	mouse (C57Bl/6, ♂, 8–12 wk, 7/7)	10 (IV)	30 (LAD)	48±2% *vs.* 25.17±1.0% (P<0.0001)	NR
Squadrito *et al.* (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)		*vs.* 29±1% (P<0.05)	
		1 (IV)		*vs.* 16±0% (P<0.005)	
		1 (IV)	30 (LCA)	57±3% *vs.* 12±2% (P<0.01)	

Table S1 (*continued*)

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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 *et al.* (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 *et al.* (2010)	rat (Zucker obese, ♂, 10 wk, 7/7)	5 (IV)	25 (LCA branch)	58±2% *vs.* 61±3% (P>0.05)	NR
Liu *et al.* (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 *et al.* (2012)	rat (Sprague-Dawley, ♂, NR, 7/7)	5 (IV)	30 (LAD)	59.8±3.3% *vs.* 35.2±3.5% (P<0.001)	• dP/dt_{max} 686 mmHg/s* *vs.* 1286±147 mmHg/s (P<0.001)
De Paulis *et al.* (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 *et al.* (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 *et al.* (2013)	rat (Fischer 344, ♂, 22–24 mo, 8/8)	10 (IV)	30 (LAD)	54±4% *vs.* 51±4% (P>0.05)	NR
Li *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (2016)	rat (Sprague-Dawley, ♂, 8–10 wk, 6/6)	2.5 (NR)	30 (LAD)	61±2% *vs.* 49±2% (P<0.01)	NR
Kiss *et al.* (2016)	rat (Wistar, ♂, NR, 8/7)	10 (IV)	30 (LAD)	63.8±4.1% *vs.* 45.9±2.4% (P<0.05)	NR
Choi *et al.* (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 *et al.* (2018)	rat (Sprague-Dawley, ♂, 8 wk, 5/5)	5 (IP)	45 (LAD)	17.7±3.9% *vs.* 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 *et al.* (2019)[§]	rat (Sprague-Dawley, ♂, NR, NR)	2.5 (IV)	30 (LAD)	46±5% *vs.* 36±4% (P>0.01)	• TnI 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)		*vs.* 19±4% (P<0.01)	• TnI 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 *et al.* (2005)[§]	rabbit (New Zealand white, ♂, NR, NR)	5 (IV)	30 (left marginal)	42±7% *vs.* 43±6% (P>0.05)	NR
		10 (IV)		*vs.* 21±4% (P<0.05)	
Wang *et al.* (2006)	rabbit (New Zealand white, ♂, NR, 7–8/7–8)	10 (IV)	30 (LAD)	44±1% *vs.* 25±1% (P<0.05)	NR
Pagel & Krolikowski (2009)	rabbit (New Zealand white, ♂, NR, 6/6)	5 (IV)	30 (LAD)	46±2% *vs.* 42±2% (P>0.05)	NR
Paillard *et al.* (2009)	rabbit (New Zealand white, ♂, NR, 8/8)	5 (IV)	30 (left marginal)	NR	• Preservation of myofibril organization & mitochondrial structure in CsA group on EM

Table S1 (*continued*)

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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)	• TnI 159.2±10.4 ng/mL *vs.* 101.7±10 ng/mL (P<0.05)
Karlsson *et al.* (2010)	pig (Swedish Landrace, ♀, NR, 15/12)	10 (IV)	45 (LAD)	41±4% *vs.* 49±4% (P>0.05)	NR
Lie *et al.* (2010)	pig (mixed Danish Landrace/Yorkshire, ♀, NR, 19/19)	10 (IV)	40 (LAD)	51.4±3.8% *vs.* 47.3±3.6% (P>0.05)	• TnT 6.4±0.7 ng/mL *vs.* 9.7±1.1 ng/mL (P>0.05) • CO at 180 min after reperfusion 3.8±0.2 L/min *vs.* 3.8±0.2 L/min (P>0.05)
Skyschally *et al.* (2010)	pig (Göttinger minipigs, ♂/♀, NR, 4/4)	5 (IV)	90 (LAD hypoperfusion)	35±3 % *vs.* 25±3% (P<0.05)	• dP/dt_{max} at 120 min after reperfusion 1222±174 mmHg/s *vs.* 946±111 mmHg/s (P>0.05)
Karlsson *et al.* (2012)	pig (mixed Swedish/Pigham/Yorkshire, ♀, NR, 11/12)	2.5 (IV)	40 (left marginal)	54±6% *vs.* 51±6% (P=0.75)	NR
Zalewski *et al.* (2014)[‡]	pig (NR, NR, NR, 8/8)	NR	60 (NR)	54±1% *vs.* 44±2% (P=0.017)	• LVEF (%Δ) −15.6±3.7% *vs.* −7.9±2.2% (P=0.015)
Zalewski *et al.* (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 *et al.* (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 *et al.* (2007)	mouse (B6Sv129F1, ♂/♀, 8–10 wk, 6/6)	10 (NR)	30 (LAD)	48±4% *vs.* 32±3% (P<0.05)	NR
Horstkotte *et al.* (2011)	mouse (dtTomato, NR, NR, 6/6)	10 (IV)	90 (LAD)	NR	• dP/dt_{max} 19,000±3,000 mmHg/s *vs.* 18,000±4,000 mmHg/s (P>0.05)
Ikeda *et al.* (2016)	mouse (C57Bl/6, ♂, 10–12 wk, 8/8/8/8/8/8/8/8)	1 (IV)	NR (left marginal)	51±3% *vs.* 53±3% (P>0.05)	• LVEF 33.0±2.0% *vs.* 32.0±2.6% (P>0.05)
		1 (nanoparticle)		51±3% *vs.* 32±3% (P<0.001)	• LVEF 33.0±2.0% *vs.* 49.0±2.0% (<0.05)
		2.5 (IV)		51±3% *vs.* 49±3% (P>0.05)	
		2.5 (nanoparticle)		51±3% *vs.* 31±3% (P<0.001)	
		10 (IV)		51±3% *vs.* 36±3% (P<0.05)	• LVEF 33.0±2.0% *vs.* 43.2±2.0% (P<0.05)
		10 (nanoparticle)		51±3% *vs.* 36±3% (P<0.01)	
		25 (IV)		51±3% *vs.* 32±3% (P<0.01)	
Rusinkevich *et al.* (2019)	mouse (C57Bl/6, ♂, 12–14 wk, 11/11)	10 x5 (IP)	90 (LAD)	31±3% *vs.* 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 *et al.* (2021)	mouse (C57Bl/6, ♂, 10–12 wk, 8–9/8–9/8–9/8–9	1 (nanoparticle)	30 (LAD) 60 (LAD)	53±2% *vs.* 33±3% (P<0.0001) 72±1% *vs.* 65±2% (P<0.001)	NR
Argaud *et al.* (2005)	rabbit (New Zealand white, ♂, NR, 8/8)	2.5 (IV)	30 (left marginal)	60±6% *vs.* 24±4% (P<0.0001)	NR
Matsubara *et al.* (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					
Ikeda *et al.* (2014)[‡]	mouse (NR, NR, NR, 8/8)	(nanoparticle)	NR	52±4% *vs.* 32±9% (P<0.05)	NR
Ikeda *et al.* (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
Ikeda *et al.* (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, 8/8/8/8)	1 (NR)	30 (LAD)	45.00±0.73% *vs.* 35.29±0.54% (P<0.05)	• TnI 12.98±0.46 ng/mL *vs.* 9.38±0.38 ng/mL (P<0.05) • CK-MB 125.38±2.07 U/mL *vs.* 109.79±1.51 U/mL (P<0.05)
		2.5 (NR)		*vs.* 29.05±0.74% (P<0.05)	• TnI 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)	• TnI 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 *et al.* (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.

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

Model type	Species (strain, sex, age, n = control/ experimental group)	Dose (mg/kg; route)	Duration of Ischemia (min; method)	Cardiac Function (SEM)	Additional Clinically Relevant Outcomes
Cardiac arrest					
Before/during ischemia					
Ayoub *et al.* (2017)	rat (Sprague-Dawley, ♂, NR, 6/12)	10 (NR)	10 (electricity)	CI 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)	• TnI 130±76 ng/mL *vs.* 210±61 ng/mL (ns)
During ischemia					
Huang *et al.* (2011)*	rat (Wistar, ♂, 8 wk, NR)	10 (IV)	8.5 (asphyxia)	CO 80.7±20.0 mL/min *vs.* 87.6±22.6 mL/min (P=0.58)	• 72 hr survival 16.7% *vs.* 58.3% (P=0.016)
Huang *et al.* (2012)	rat (Wistar, ♂, 8 wk, 10/10)	10 (IV)	8.5 (asphyxia)	CO 22±3 mL/min *vs.* 71±10 mL/min at 1 hr, 22±1 mL/min *vs.* 76±11 mL/min at 2 hr, 31±3 mL/min *vs.* 49±3 mL/min at 3 hr, 36±3 mL/min *vs.* 53±3 mL/min at 4 hr (P<0.01)	• Mitochondrial injury score 1.5±0.2 *vs.* 0.6±0.2 on EM (P<0.01) • 72 hr survival 18.2% *vs.* 53.8% (P=0.046)
Cour *et al.* (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)	• TnI 34±10 ng/mL *vs.* 10±2 ng/mL (P<0.05) • Survival 67% *vs.* 89%‡
After ischemia					
Huang *et al.* (2012)	rat (Wistar, ♂, 8 wk, 10/10)	10 (IV)	8.5 (asphyxia)	CO 18±1 mL/min *vs.* 22±3 mL/min at 1 hr, 27±1 mL/min *vs.* 36±4 mL/min at 2 hr, 49±8 mL/min *vs.* 44±6 mL/min at 3 hr, 58±7 mL/min *vs.* 49±3 mL/min at 4 hr (P=0.690)	• Mitochondrial injury score 1.5±0.2 *vs.* 1.3±0.2 on EM (P>0.01) • 72 hr survival 20% *vs.* 30% (P=0.829)
Cardiopulmonary bypass					
Oka *et al.* (2008)	pig (NR, NR, 2 wk, 5/5)	10 (IV)	60 (cardioplegia)	NR	• Preservation of cristae architecture & intermembrane space in CsA-treated group compared to controls on EM
Hoyer *et al.* (2016)*	pig (Landrace, NR, NR, 6/6)	1.2mg/L (cardioplegia)	90 (cardioplegia)	NR	• No difference in cross striation (P=0.917), eosinophil infiltration (P=0.661), loss of cell boundaries (P=0.362) or myocardial edema (P=0.998) on histology
Hoyer *et al.* (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 *et al.* (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 striation (P=0.845), eosinophilia (P=0.510), myocardial edema (P=0.596), cellular infiltration (P=0.279), visible bleeding (P=0.876) or loss of cell boundaries (P=0.510) on histology
Hypoxia					
Gill *et al.* (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.* 4.9±0.4 mM at 2 hr (P>0.05), 4.4±0.8 mM *vs.* 2.8±0.2 mM 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.* 7.0±0.7 mM at 2 hr (P>0.05), 4.4±0.8 mM *vs.* 4.2±0.9 mM at 6 hr (P>0.05)
Gill *et al.* (2012)b	pig (mixed, NR, 1–4 d, 8/8/8/8)	2.5 (IV)	120 (ventilation with FiO_2 0.10–0.15)	CI 57±8% *vs.* 88±8% of baseline (P<0.05)	• TnI 1.2±0.2 ng/mL *vs.* 0.6±0.1 ng/mL (P<0.05) • Lactate 11.3±2.9 mM *vs.* 11.3±3.3 mM at 30 min (P>0.05), 5.5±3.3 mM *vs.* 3.2±2.2 mM at 4 hr (P>0.05)
		10 (IV)		*vs.* 100±7% of baseline (P<0.05)	• TnI 1.2±0.2 ng/mL *vs.* 0.7±0.2 ng/mL (P<0.05) • Lactate 11.3±2.9 mM *vs.* 11.7±4.3 mM at 30 min (P>0.05), 5.5±3.3 mM *vs.* 3.1±1.0 mM at 4 hr (P>0.05)
		25 (IV)		*vs.* 85±11% of baseline (P<0.05)	• TnI 1.2±0.2 ng/mL *vs.* 1.2±0.2 ng/mL (P>0.05) • Lactate 11.3±2.9 mM *vs.* 11.8±1.8 mM at 30 min (P>0.05), 5.5±3.3 mM *vs.* 2.6±0.6 mM at 4 hr (P>0.05)
Gill *et al.* (2013)	pig (mixed, NR, 1–4 d, 8/8)	10 (IV)	120 (ventilation with FiO_2 0.10–0.15)	NR	• TnI 1.2±0.2 ng/mL *vs.* 0.6±0.2 ng/mL (P<0.05)
Cardiac transplantation					
Laudi *et al.* (2006)*	rat (Lewis, ♂, NR, 7/7/7/7)	12.5 x3 (PO)	NR	NR	• 28 d survival 75% *vs.* 100% if administered 3 d prior *vs.* 33% if administer day of transplant *vs.* 78% if administered 3 d post-transplant (P=0.041)

*, conference abstract; †, results presented with standard deviation; ‡, P value not reported. CI, cardiac index; CO, cardiac output; CsA, cyclosporine A; EM, electron microscopy; FiO_2, 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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