A systematic review and meta-analysis of remote ischemic preconditioning for vascular surgery

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) is a method of preparing the body for a later prolonged ischemic episode to protect against subsequent detrimental effects. This study aimed to identify the effects of RIPC in vascular surgery.

Methods: A standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses search was conducted of randomized controlled trials of RIPC in patients undergoing open or endovascular aneurysm repair, carotid endarterectomy, or lower limb bypass reporting on mortality and renal or cardiac outcomes. Random-effects meta-analysis was performed using Review Manager 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark).

Results: A total of 13 randomized controlled trials in the meta-analysis included 548 patients in the RIPC cohort and 549 controls. There was no significant difference in mortality, renal dysfunction, myocardial infarction, myocardial injury, or length of stay between the groups, with subgroup and sensitivity analysis showing no significant difference.

Conclusions: Current evidence demonstrates no benefit of RIPC in vascular surgery. Further large multicenter trials of RIPC in major vascular surgery should be considered. (J Vasc Surg 2019;70:1353-63.)

Keywords: Remote ischemic preconditioning; Renal failure; Vascular

Remote ischemic preconditioning (RIPC) is a method of exposing the body to a stimulus in a controlled manner to initiate a cascade of effects to protect against the detrimental effects of a subsequent, perhaps more prolonged ischemic episode. This protection results from the RIPC generation of free radicals leading to the release of adenosine, bradykinin, and opioid receptor agonists, which leads to activation of matric metalloproteinases inducing the release of growth factors that are thought to be cytoprotective.[1] RIPC aims to induce the initial ischemia-reperfusion injury in a controlled manner, thus beginning activation of the cytoprotective effects that will then already be activated before a larger ischemia-reperfusion insult.

Previous studies and meta-analyses have investigated the effects of RIPC in both cardiac and noncardiac surgery, but the evidence remains inconclusive. Overall, there is no difference in all-cause mortality[2] and no difference in cardiac clinical outcomes[2,3] but significant reduction in cardiac troponin T[3] and inconclusive evidence regarding renal outcomes[2,4] and stroke rates.[2,3] Vascular surgery involves clamping of the main arterial supply to a particular territory; therefore, the ischemic insult is potentially significant in this cohort of patients, and hence the role of RIPC has the potential to be more pronounced. This study aimed to identify the effects of RIPC in vascular surgery.

METHODS

The systematic review followed quality reporting guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[5] MEDLINE, Embase, and Health and Psychosocial Instruments databases were searched using Ovid Online (version OvidSP_UI03.04.02.112; Ovid Technologies, Inc, Norwood, Mass) and PubMed in July 2018. There were no language restrictions or filters used to restrict study designs. In addition, reference lists were searched for further studies to be included.

Eligibility criteria and study selection. Potential studies were screened by two of the authors (P.S. and J.B.). For inclusion within the systematic review, the study had to be a randomized controlled trial, had to include RIPC, and had to have included participants undergoing surgery to the abdominal aorta, carotid artery, arteriovenous fistula, or arterial bypass. Each study must have reported data on mortality, renal dysfunction, myocardial infarction, or myocardial injury.

Data collection. Data were extracted independently by P.S. and J.B., with any discrepancies discussed. The following outcomes were recorded: mortality, renal impairment, myocardial infarction, myocardial injury, length of stay, and length of stay on the intensive care unit.

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Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2019.03.025

Statistical analysis. The data were analyzed using Review Manager 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark),[6] Stata version 15.1 (StataCorp LLC, College Station, Tex), and PASS version 14.0.8 (NCSS, LLC, Kaysville, Utah).

Separate analyses were performed for each individual outcome, with all possible papers included where they had published results on the outcome under analysis. Meta-analysis was performed using the Mantel-Haenszel method, with a standard continuity correction of 0.5. A random-effects model was used because of the variability of methods of RIPC between studies and the variability in types of procedures performed both between the studies and within individual studies. An α level of $\leq .05$ was used to determine statistical significance.

Sensitivity analyses. Separate analyses were performed for participants undergoing each individual vascular procedure where possible. In addition, sequential removal of each individual study from each analysis was performed, and subgroup analysis for those undergoing similar methods of RIPC was performed where possible.

Assessment of study quality. The quality of nonrandomized studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scale.[7] The study quality was assessed by examining patient randomization, blinding, and data completeness.

Assessment of heterogeneity. For each of the four outcomes, we assessed the homogeneity of the treatment effect across studies using Cochran *Q*. This test has low power when the number of studies included in the meta-analysis is low[8]; therefore, a higher statistical significance of $P < .1$ was assumed. In addition to test for heterogeneity, Higgins I^2 (95% uncertainty interval) was calculated.[9] I^2 provides a measure of the degree of inconsistency across the different study results—the percentage of total variation across studies that can be attributed to heterogeneity rather than to chance.[8] Values lie between 0% and 100%, 0% indicating no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity.[8,9]

Publication bias. Funnel plots with pseudo-95% confidence intervals were produced for all outcomes. Asymmetry in funnel plots was assessed to check for publication bias and to test for small-study effects. Small-study effects were tested using the model proposed by Harbord et al,[10-12] which tests the null hypothesis of no small-study effects where statistical significance of $P < .05$ is assumed.

Assessment of sample size and power calculation. Sample size and power calculations were based on the odds ratios (ORs) for each of the four outcomes—mortality, renal dysfunction, myocardial infarction, and myocardial injury. The proportion of events in the control group was calculated as the total number of events in the control group across all studies/total controls across all studies, assuming the same observation time across all studies. We test the null hypothesis (H_0) that the OR = 1 comparing RPIC with controls against the alternative hypothesis (H_1) that the OR $\neq$ 1. Power and sample size curves for ORs <1 were plotted to show the power for exposure to RIPC being associated with a lower odds of mortality, renal failure, myocardial infarction, and myocardial injury.

RESULTS

Identification of relevant studies. Search terms "vascular OR aneurysm OR carotid OR bypass OR fistula" AND "preconditioning OR pre-conditioning" and "randomized controlled trial OR RCT" were combined, resulting in 310 titles after removal of duplicates. All abstracts were reviewed, revealing 22 articles that were potentially relevant. A single article was identified through review of references. Of the 23 articles, 4 were removed because of being reviews,[1,4,13,14] 2 used anesthetic agents only,[15,16] 2 were protocols,[17,18] and 2 were not relevant,[19,20] leaving 13 articles for inclusion[21-33] (Fig 1).

Study characteristics. The publication dates of the eligible studies ranged from 2007 to 2018. All studies were prospective randomized controlled trials. The study size ranged from 40 to 201 participants, with a total of 582 patients in the RIPC cohort and 585 patients in the control cohort. Study characteristics are outlined in Table I, with a variety of methods of RIPC used and a range of vascular procedures. Study baseline characteristics are summarized in Table II and baseline medications in Table III. There was a standard representation of cardiovascular risk factors reported for a vascular cohort of patients, with significant differences within the studies as expected by the small sample sizes, and a large variation in uptake of standard cardiovascular medications.

Study quality was assessed using GRADE score (Supplementary Tables I and II, online only).

Combined outcomes. All extracted data are outlined in Table IV. Pooled analysis from all papers revealed no significant difference in mortality (5.3% RIPC vs 6.0% control; OR, 1.05 [0.48-2.29]; $P = .25$), renal impairment (17.4% RIPC vs 19.1% control; OR, 0.89 [0.56-1.39]; $P = .60$), myocardial infarction (10.5% RIPC vs 12.9% control; OR, 0.78 [0.50-1.20]; $P = .25$), or myocardial injury (22.4% RIPC vs 25.5% control; OR, 0.81 [0.44-1.51]; $P = .51$; Figs 2-5).

Length of stay on the intensive care unit was reported in three studies, showing no conclusive difference in median length of stay across the studies.[21,24,28] There was also no significant difference in overall length of stay in any study.[21,22,24,28,30,32,33]

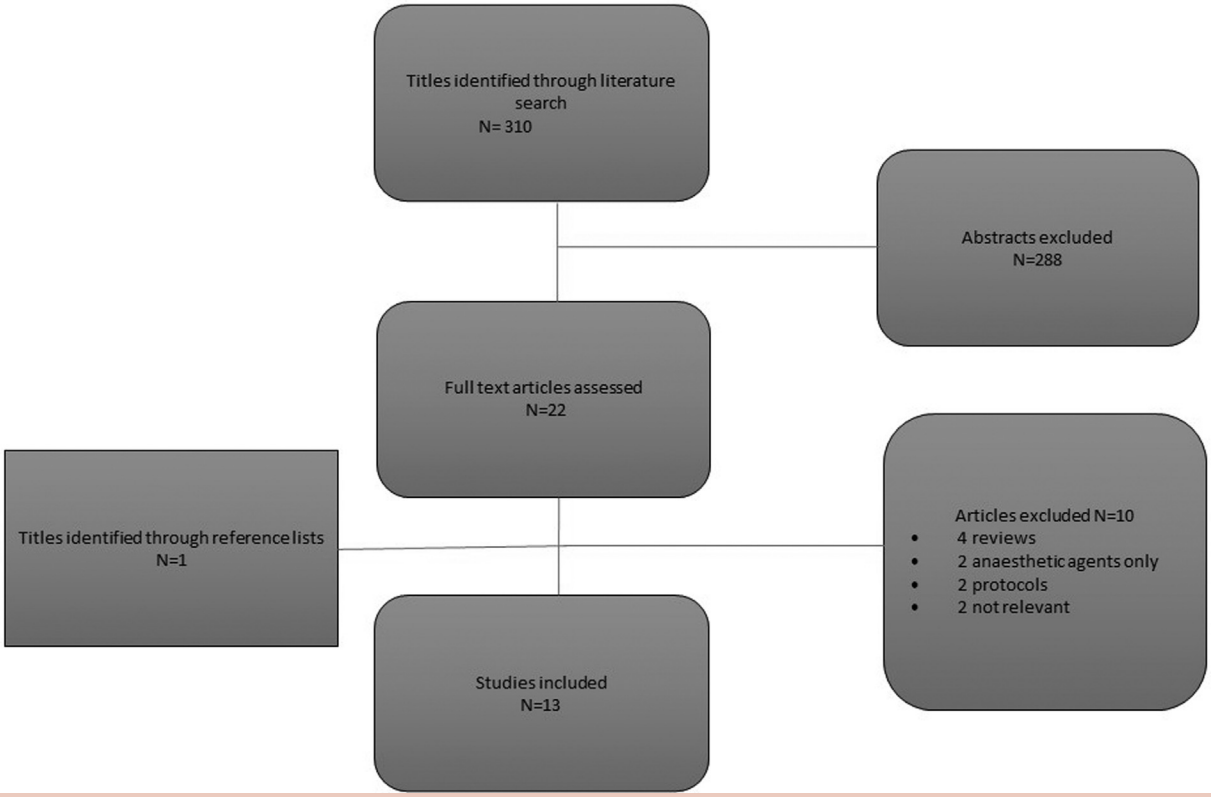

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Heterogeneity. Supplementary Table III (online only) shows heterogeneity statistics for the four outcomes considered. The test for heterogeneity at the 10% level is not significant for any of the four outcomes after vascular procedure in comparing RIPC with controls. Considering the values of I^2, all outcomes have low levels of inconsistency across studies—mortality (I^2 = 22%), renal impairment (I^2 = 30%), myocardial infarction (I^2 = 2%), and myocardial injury (I^2 = 41%)—and therefore variability across studies in each outcome cannot be attributed to heterogeneity.

Sensitivity analyses. Sensitivity analysis was possible for patients undergoing abdominal aortic aneurysm (AAA) repair only, showing no significant difference in any outcomes (Supplementary Table IV, online only). Further sensitivity analysis was performed by exclusion of individual studies and analyzing those studies using forearm ischemia only, both of which did not significantly alter results.

Publication bias. Testing for funnel plot asymmetry and small-study effects ideally should include at least 10 studies in a meta-analysis[10,12]; here, only renal impairment and myocardial infarction outcomes have 10 studies. The funnel plots in all four outcomes (Supplementary Fig 1, online only) suggest weak evidence of asymmetry; it is difficult to draw firm conclusions about funnel plot asymmetry because of the small number of studies in each of the four outcomes investigated. Supplementary Table V (online only) shows test results for small-study bias effects for each outcome. Only for the mortality outcome is there evidence of small-study effects (P = .037); however, this test has low power because of the small number of studies included in the meta-analysis.

Supplementary Fig 2 (online only) shows power curves for the four outcomes considered. Assuming a significance level of .05 in all cases, taking mortality as an outcome, group sample sizes of 550 in both the control and RIPC groups achieves 13.3% power to detect an OR of 0.8. For renal impairment as an outcome, group sample sizes of 525 in both the control and RIPC groups achieves 27.8% power to detect an OR of 0.8. Myocardial infarction with group sample sizes of 525 in both the control and RIPC groups achieves 21.4% power to detect an OR of 0.8; myocardial injury with group sample sizes of 300 in both the control and RIPC groups achieves 21.4% power to detect an OR of 0.8.

DISCUSSION

The study identified no significant difference in mortality, renal dysfunction, myocardial infarction, myocardial injury, or length of stay in patients undergoing RIPC for vascular surgery.

An early systematic review of RIPC in vascular surgery[13] was unable to identify any advantage of RIPC, and

Table I. Background of all studies comparing remote ischemic preconditioning (*RIPC*) and controls in vascular surgery

	Year	Country	Center	Funding	Blinding	No. of RIPC patients	No. of controls
Ali	2007	United Kingdom	Single	Public	Double	41	41
Fudickar	2014	Germany	Single	Unclear	Single	20	20
Garcia	2016	United States	Single	Public	Single	100	101
Healy	2015	Ireland	Multi	Nil	Nil	99	99
Li	2013	China	Single	Unclear	Double	31	31
Menting	2015	The Netherlands	Multi	Nil	Single	38	38
Mouton	2015	United Kingdom	Single	Public	Double	34	35
Murphy	2014	Ireland	Single	Unclear	Double	31	31
Pedersen	2018	Denmark	Single	Public	Nil	72	70
Thomas	2016	New Zealand	Single	Nil	Single	42	43
Walsh	2009	United Kingdom	Single	Public	Unclear	18	22
Walsh	2010	United Kingdom	Single	Public	Unclear	22	18
Walsh	2010	United Kingdom	Single	Public	Single	34	36

AAA, Abdominal aortic aneurysm; *CIN*, contrast-induced nephropathy; *EVAR*, endovascular aneurysm repair; *IR*, ischemia-reperfusion.
[a]CIN risk is defined as an estimated glomerular filtration rate <45 mL/min/1.73 m^2 or <60 mL/min/1.73 m^2 with diabetes or two additional risk factors, such as peripheral vascular disease, heart failure, age >75 years, anemia, dehydration, diuretics, and nonsteroidal anti-inflammatory drugs.

Table II. Baseline characteristics of all studies comparing remote ischemic preconditioning (*RIPC*) and controls in vascular surgery

	Age, years, mean		Ischemic heart disease		Hypertension		Diabetes		Current smoker	
	RIPC	Control	RIPC	Control	RIPC	Control	RIPC	Control	RIPC	Control
Ali	74	75	24	27	51	63	5	5	27	32
Fudickar	68	68	45	30			30	25	45	50
Garcia	69	69	45	42			16	11	37	31
Healy	69	69					18	13		
Li	62	67			77	58	45	29	23	19
Menting	71	73			78	67	22	28		
Moulton	72	72	38	26	77	71				
Murphy	75	69	13	16	64	52	23	16		
Pedersen	72	73	28	21	56	67	7	11	54	43
Thomas	74	75	29	25			10	19	21	14
Walsh	74	76	28	18	44	55	17	9	6	4
Walsh	75	72	5	17	54	88	5	0	36	17
Walsh	70	68	35	31	68	58	12	31	21	22

Percentages in each cohort are reported.

because of the paucity of data, it was unable to undertake a meta-analysis. A previous meta-analysis of 37 studies across all types of surgery[4] had identified a potential benefit for RIPC in renal protection; however, this was only in user-defined acute kidney injury and did not stand up to renal guidelines. A recent meta-analysis of patents undergoing percutaneous coronary intervention[34] revealed a significant reduction in myocardial infarction and acute kidney injury; however, these results are not reproduced in patients undergoing coronary artery bypass grafting.[3]

This study has several limitations. The majority of the studies included were small and of moderate quality, with a possibility of publication bias seen within the

Table I. Continued.

Surgery	Method	Cycles of ischemia-reperfusion	Phase of RIPC
Open elective AAA	Direct clamp	2 × 5/5 minutes	First
Lower limb bypass	Sevoflurane anesthesia and direct clamp	2 sevoflurane, 1 clamp, 6/6 minutes	First
Open AAA, EVAR, carotid, lower limb bypass	Forearm ischemia	3 × 5/5 minutes	Second
Open AAA, EVAR, carotid, lower limb bypass	Forearm ischemia	4 × 5/5 minutes	First
Open AAA	Forearm ischemia	3 × 5/5 minutes	First
IR procedure + CIN risk[a]	Forearm ischemia	4 × 5/5 minutes	First
Open AAA, EVAR	Forearm ischemia	3 × 5/5 minutes	First
Open AAA	Forearm ischemia	3 × 5/5 minutes	First
Open ruptured AAA	Forearm ischemia	4 × 5/5 minutes	First
Open AAA, EVAR, lower limb bypass	Forearm ischemia	3 × 5/5 minutes 24 hours preoperatively, 3 × 5/5 minutes immediately preoperatively	First and second
EVAR	Lower limb ischemia thigh tourniquet	2 × 10/10 minutes, one limb, then the other	First
Open AAA	Direct clamp	2 × 10/10 minutes, one limb, then the other	First
Carotid	Lower limb ischemia thigh tourniquet	2 × 10/10 minutes, one limb, then the other	First

Table II. Continued.

Hypercholesterolemia		Myocardial infarction		Cardiac failure		Renal impairment		Stroke	
RIPC	Control	RIPC	Control	RIPC	Control	RIPC	Control	RIPC	Control
39	46	20	32	5	2	5	2	20	5
70	60	45	30			20	5		
78	72	24	23	7	6	3	2	17	21
		16	19	8	7			23	16
		16	26						
		36	44	19	22			17	19
				15	3			18	20
61	55	22	13			19	7		
		21	19					11	13
		33	40			13	10		
		33	18						
		18	22						
				9	3			27	25

funnel plots. In addition, there is a significant degree of variability within the studies included in terms of types of procedure investigated; not all studies reported on every outcome, which could potentially be construed as reporting bias, and one study used second-phase RIPC.[23] The timing from RIPC to surgery was not consistent, ranging from daily RIPC episodes to anesthesia induction to intraoperative, which could affect the degree of RIPC protection at the time of cross-clamping.

Three studies[23,24,30] reported on vascular procedures combined; therefore, the decision was made to include all studies into vascular surgery as a whole, with separate subgroup analyses where possible. However, comparing the validity of RIPC outcomes in such a heterogeneous

Table III. Baseline medications of all studies comparing remote ischemic preconditioning (*RIPC*) and controls in vascular surgery

	Beta blocker		Calcium channel blocker	
	RIPC	Control	RIPC	Control
Ali	39	41	24	24
Fudickar	65	65	40	25
Garcia	71	61	19	21
Healy	36	39	18	27
Li	52	61	42	23
Menting	67	64	33	22
Moulton	35	31		
Murphy	32	36	41	16
Pedersen				
Thomas	67	51	38	28
Walsh			22	18
Walsh			36	28
Walsh				

ACE, Angiotensin-converting enzyme.
Percentages taking each medication are reported.

Table IV. All outcomes comparing remote ischemic preconditioning (*RIPC*) vs controls in vascular surgery

	ITU stay, days, median (IQR)			Length of stay, days, median (IQR)			Myocardial injury, No. (%)		
Author	RIPC	Control	*P* value	RIPC	Control	*P* value	RIPC	Control	*P* value
Ali	1 (1)	3 (3)	.03	9 (6)	11 (7)	.23	5 (12)	16 (39)	.01
Fudickar				5 (3-9)	5 (3-16)	NS	1	1	NS
Garcia							22 (22)	25 (24.7)	.74
Healy	1 (0-2)	0 (0-2)	.53	6 (3-10)	7 (3-12)	.17			
Li									
Menting									
Moulton									
Murphy	6 (4-7)	4 (3-7)	.07	15 (12-20)	14 (11-18)	.67	16 (51.6)	9 (29.0)	.11
Pedersen									
Thomas				5 (3-8)	6 (3-8)	.82	18 (42.9)	21 (48.8)	.58
Walsh				5 (4-8)	4 (3-7)	.51	1 (5.6)	2 (9.1)	.73
Walsh				11 (9-14)	10 (7-17)	.79			
Walsh							1 (2.9)	1 (2.8)	.97

IQR, Interquartile range; *ITU*, intensive therapy unit; *NS*, not significant.
[a]Renal failure.

group, such as carotid surgery vs open AAA repair, should be taken into account in interpreting the data. The systemic impact of open AAA repair is inherently much greater than that of endovascular aneurysm repair (EVAR) or even carotid endarterectomy, and including all of these procedures in a single analysis could mask an underlying significant finding in an individual procedure. In addition, one study included ruptured AAA, which has a much larger physiologic burden than elective repair. To minimize this effect, this study undertook a subgroup analysis of AAA repair (both open and EVAR) in addition as a sensitivity analysis; however, there were insufficient data to reproduce this for lower limb bypass, carotid endarterectomy, and EVAR or open AAA repair individually.

Although inconclusive, these data suggest that for procedures with a short ischemia time, such as carotid endarterectomy and EVAR, RIPC is unlikely to be of any significant physiologic benefit. The data regarding open AAA repair are less conclusive as the study by

Table III. Continued.

ACE inhibitor		Antiplatelet		Statin	
RIPC	Control	RIPC	Control	RIPC	Control
32	37	37	9	39	39
45	70	80	70	40	50
44	49	87	89	77	73
26	31	83	85	84	84
29	19			35	52
25	36	39	56		
59	49			77	71
54	60	80	80		
		40	33	40	40
60	60	16	12	79	77
44	45	67	46	72	23
32	55	45	44	41	61
		91	89	91	86

Table IV. Continued.

Myocardial infarction, No. (%)			Renal impairment, No. (%)			In-hospital or 6-week mortality, No. (%)			Composite		
RIPC	Control	*P* value	RIPC	Control	*P* value	RIPC	Control	*P* value	RIPC	Control	*P* value
2 (5)	11 (27)	<.01	3 (7)	12 (30)	.009	2 (5)	3 (7)	.77			
						0 (0)	0 (0)	NS			
4 (4)	5 (5)	.74	1 (1)	3 (3)	.15	0 (0)	0 (0)	NS			
8 (8)	13 (13)	.36	22 (22)	29 (29)	.33	3 (3)	2 (2)	1	14 (14)	19 (19)	.45
2 (6.4)	1 (3.2)	.50	0[a] (0)	0[a] (0)	NS	0 (0)	0 (0)	NS			
			2 (5.6)	2 (5.6)	1	2 (5.6)	0	.49			
5 (14.7)	2 (5.7)		16 (47.1)	12 (34.3)		0 (0)	3 (8.6)				
4 (12.9)	2 (6.5)	.67	17 (54.8)	11 (35.5)	.20	3 (9.7)	1 (3.2)	.61			
26 (36.1)	30 (42.9)	.502	14[a] (19.4)	17[a] (24.3)	.31	14 (19.4)	24 (34.3)	.04			
2 (4.8)	2 (4.7)	.44	2 (4.8)	3 (7.0)		1 (2.4)	0 (0)				
1 (5.6)	1 (4.5)	.99	4 (22.2)	2 (9.1)	.29	1 (5.6)	0 (0)	.45	3 (16.7)	4 (18.2)	.99
1 (4.5	1 (5.5)	.99	11 (50.0)	10 (55.6)	.73	3 (13.5)	0 (0)	.16	14 (63.6)	7 (38.9)	.12
0 (0)	0 (0)										

Pedersen et al[29] did highlight a reduced mortality in those with a ruptured AAA undergoing RIPC, and the study by Ali et al[17] identified a shorter intensive care unit stay, less myocardial injury and infarction, and lower renal impairment; however, the studies by Li et al,[26] Murphy et al,[28] and Walsh et al[32] showed no differences in these outcomes for elective open AAA repair. Last, each of the outcome measures remains underpowered to show a significant difference between RIPC and controls; therefore, an appropriately powered, multicenter trial of RIPC in those undergoing open AAA repair should be considered to truly evaluate the role of RIPC in this cohort specifically.

CONCLUSIONS

In this meta-analysis and systematic review of 13 studies in vascular surgery, RIPC did not significantly affect mortality, renal dysfunction, myocardial infarction, myocardial injury, or length of stay.

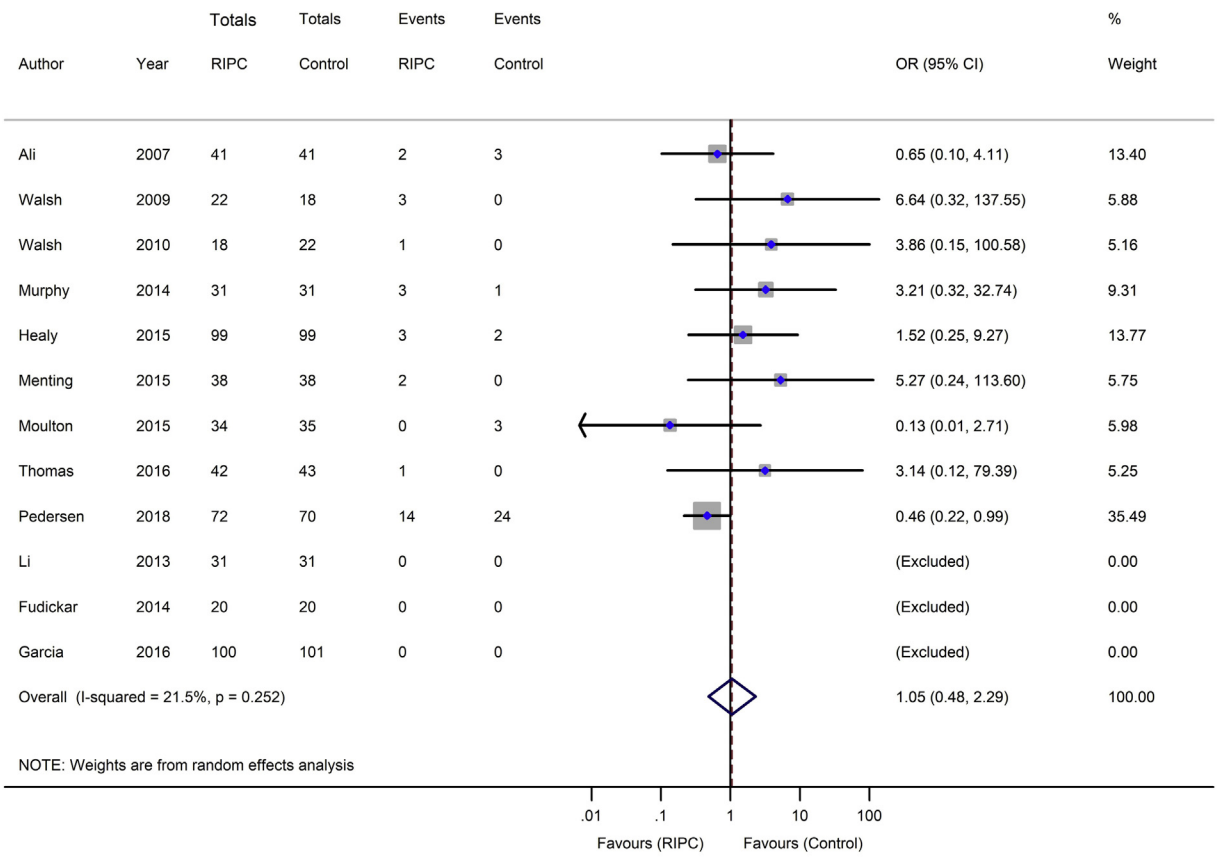

Fig 2. Meta-analysis of studies reporting mortality after vascular procedure, comparing remote ischemic preconditioning (*RIPC*) with controls. *CI,* Confidence interval; *OR,* odds ratio.

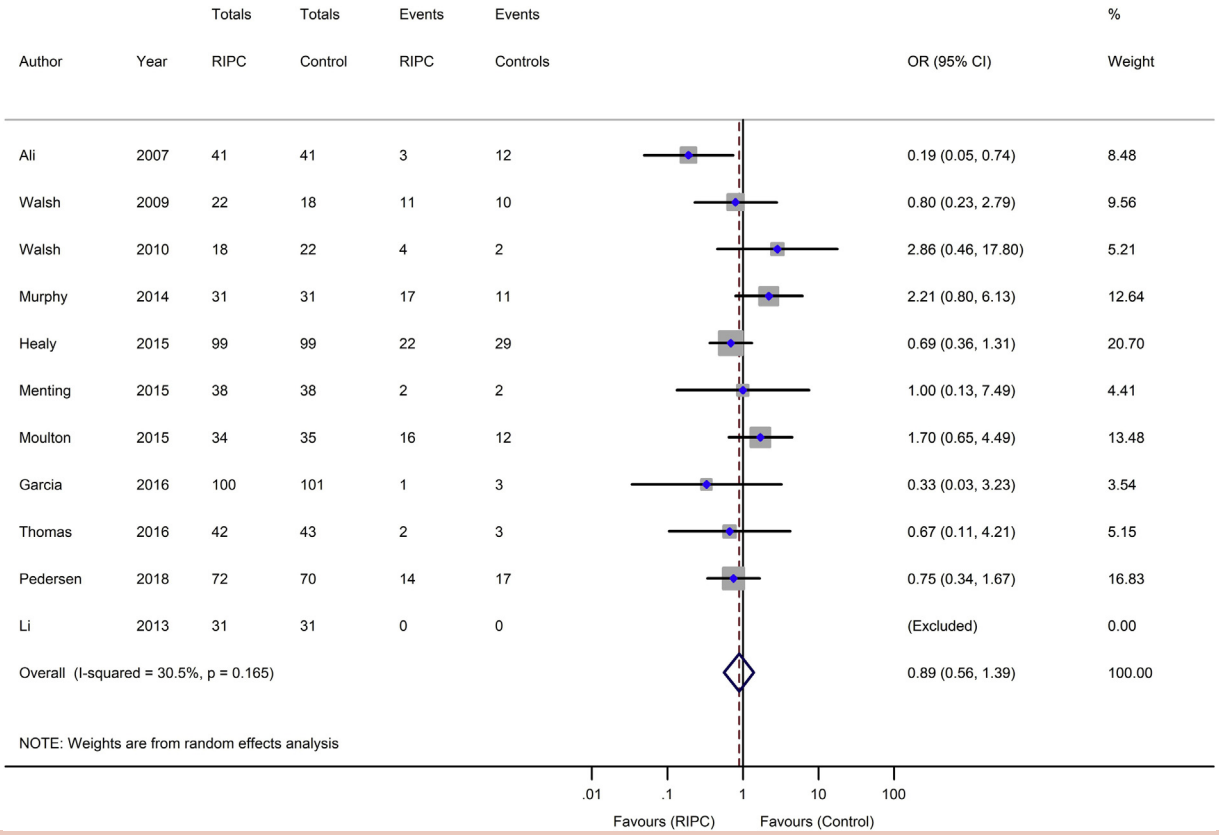

Fig 3. Meta-analysis of studies reporting renal impairment after vascular procedure, comparing remote ischemic preconditioning (*RIPC*) with controls. *CI,* Confidence interval; *OR,* odds ratio.

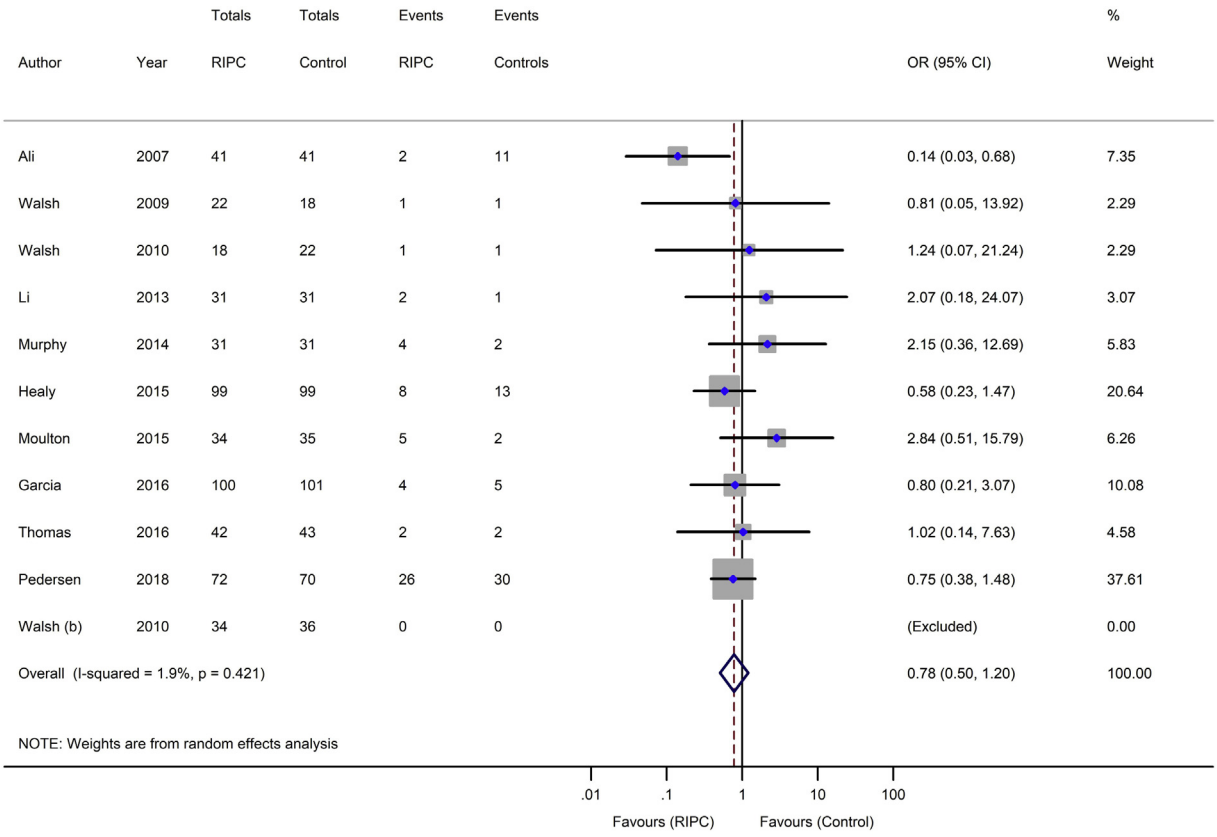

Fig 4. Meta-analysis of studies reporting myocardial infarction after vascular procedure, comparing remote ischemic preconditioning (*RIPC*) with controls. *CI,* Confidence interval; *OR,* odds ratio.

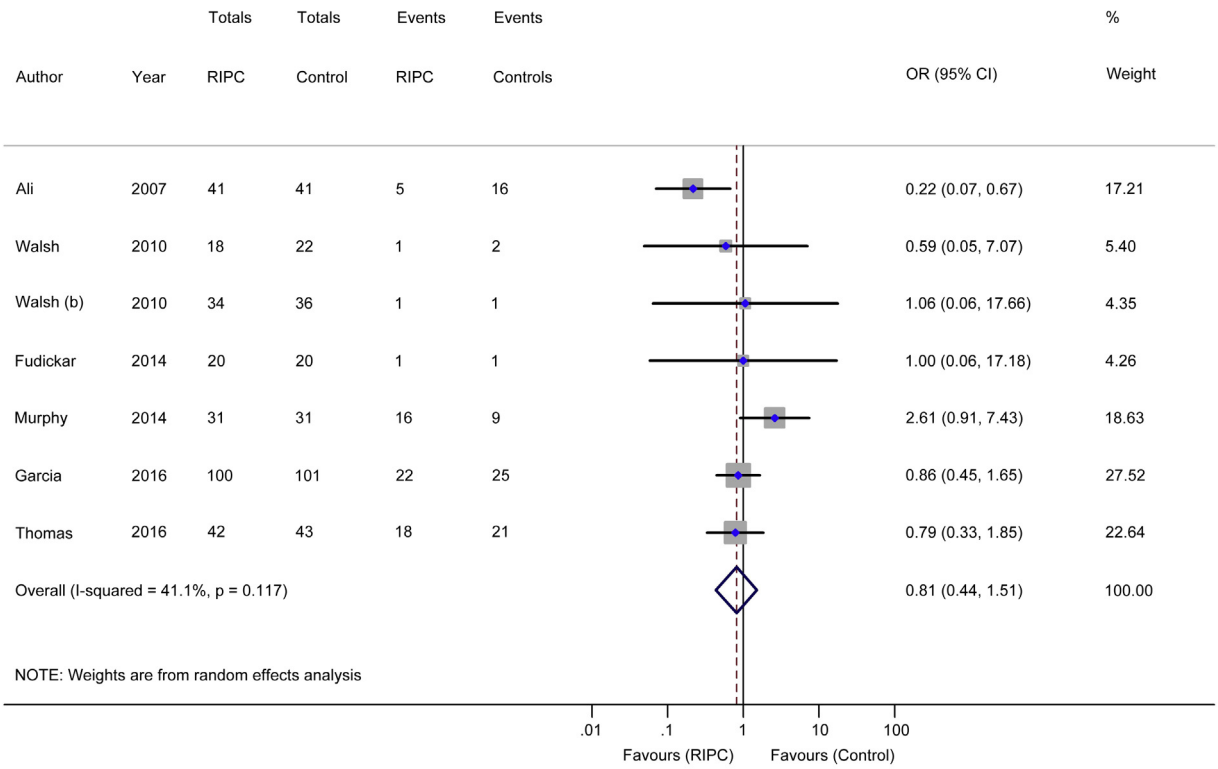

Fig 5. Meta-analysis of studies reporting myocardial injury after vascular procedure, comparing remote ischemic preconditioning (*RIPC*) with controls. *CI,* Confidence interval; *OR,* odds ratio.

AUTHOR CONTRIBUTIONS

Conception and design: PS
Analysis and interpretation: PS, JW
Data collection: PS, JB
Writing the article: PS, JB
Critical revision of the article: PS, JW, JB
Final approval of the article: PS, JW, JB
Statistical analysis: PS, JB
Obtained funding: Not applicable
Overall responsibility: PS

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Submitted Oct 5, 2018; accepted Mar 19, 2019.

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Supplementary Table I (online only). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) risk of bias table for all studies included in meta-analysis

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Completeness of data
Ali	+	+	+	+
Fudickar	+	+	−	−
Garcia	+	−	+	−
Healy	+	+	−	+
Li	+	+	+	+
Menting	?	?	+	+
Moulton	+	+	+	+
Murphy	+	+	+	+
Pedersen	+	−	−	+
Thomas	+	+	−	?
Walsh	+	−	?	+
Walsh	+	−	?	+
Walsh	+	−	−	+

Supplementary Table II (online only). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile: remote ischemic preconditioning (*RIPC*) vs controls in vascular surgery

	Quality assessment					Summary of findings		
						Study event rates		
No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	RIPC	Control	OR
Mortality								
1097 (12)	Serious	Not serious	Not serious	Very serious	Not serious	29/548	33/549	1.05 (0.48-2.29)
Renal impairment								
1057 (11)	Serious	Not serious	Not serious	Serious	Serious	92/528	101/529	0.89 (0.56-1.39)
Myocardial infarction								
1051 (11)	Serious	Not serious	Not serious	Very serious	Serious	55/524	68/527	0.78 (0.50-1.20)
Myocardial injury								
580 (7)	Serious	Not serious	Serious	Very serious	Serious	64/286	75/294	0.81 (0.44-1.51)

OR, Odds ratio.

Supplementary Table III (online only). Heterogeneity statistics from the meta-analysis of the four outcome measures of mortality, renal impairment, myocardial infarction, and myocardial injury after vascular procedure, comparing remote ischemic preconditioning (RIPC) with controls

		Heterogeneity test			
Outcome	No. of studies	*Q*	*df*	*P* value	I^2, % (95% uncertainty level)
Mortality	9	10.19	8	.25	22 (0-63)
Renal impairment	10	12.94	9	.17	30 (0-67)
Myocardial infarction	10	9.18	9	.42	2 (0-63)
Myocardial injury	7	10.19	6	.12	41 (0-75)

df, Degrees of freedom; I^2, Higgins I^2 statistic; *Q*, Cochran *Q* statistic.

Supplementary Table IV (online only). Sensitivity analysis comparing all studies reporting on open or endovascular abdominal aortic aneurysm (AAA) repair

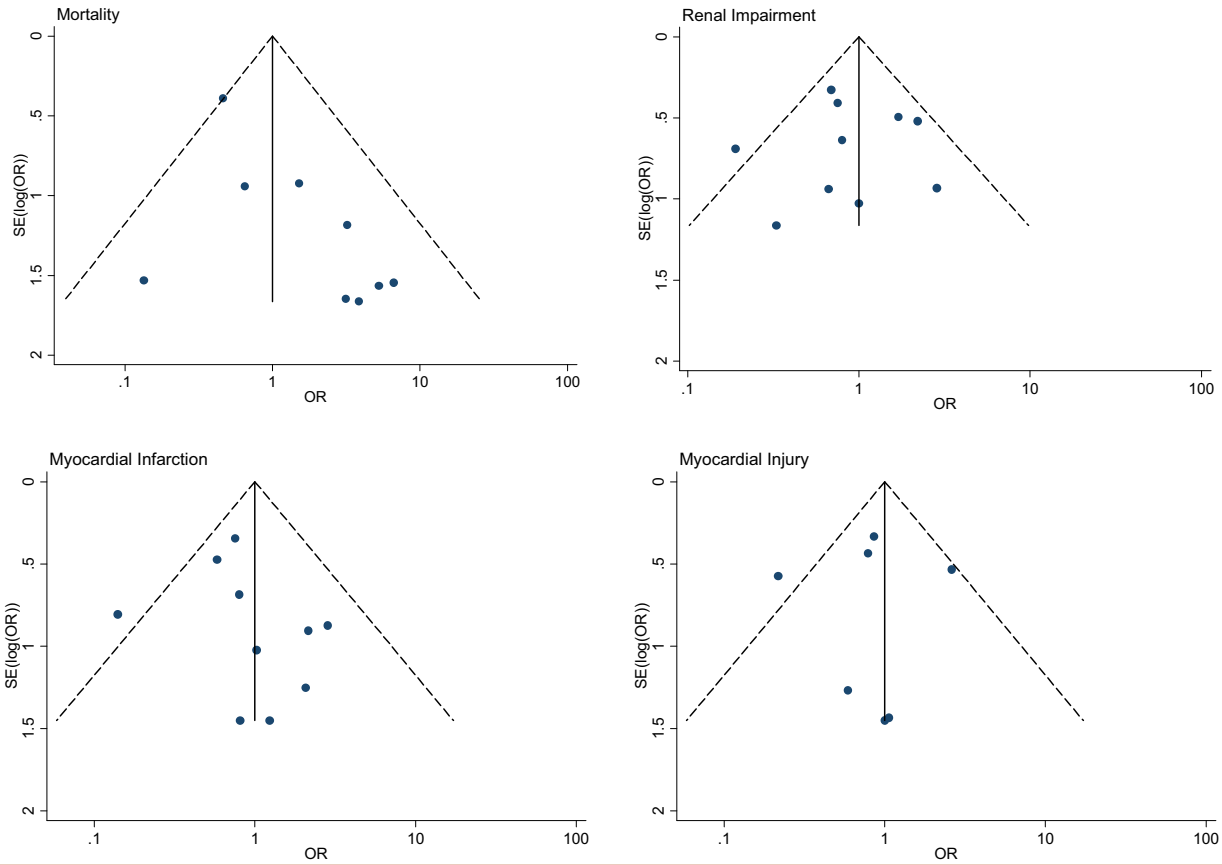
Outcome	No. of studies	RIPC	Control	OR	*P* value
Mortality	7	23/249	31/248	0.69 (0.38-1.23)	.20
Renal dysfunction	7	65/249	64/248	0.99 (0.65-1.51)	.95
Myocardial infarction	7	41/249	48/248	0.79 (0.48-1.28)	.34
Myocardial injury	3	22/90	27/94	0.77 (0.39-1.49)	.43

OR, Odds ratio; *RIPC*, remote ischemic preconditioning.

Supplementary Table V (online only). Results using Harbord modified test for small-study effects[11,12] from the meta-analysis of the four outcome measures of mortality, renal impairment, myocardial infarction, and myocardial injury after vascular procedure, comparing remote ischemic preconditioning (RIPC) with controls

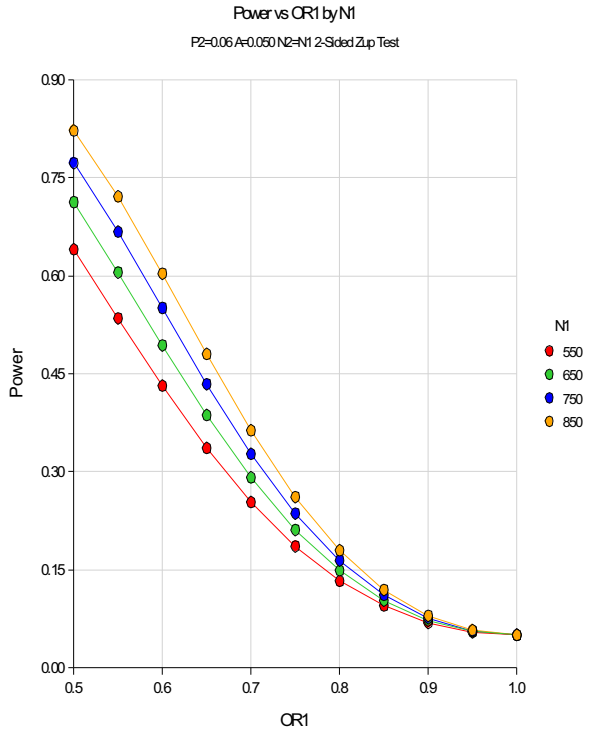
Outcome	No. of studies	Bias	SE	*P* value
Mortality	9	1.74	0.68	.037
Renal impairment	10	0.17	1.14	.884
Myocardial infarction	10	0.87	0.75	.282
Myocardial injury	7	0.03	1.20	.980

SE, Standard error.

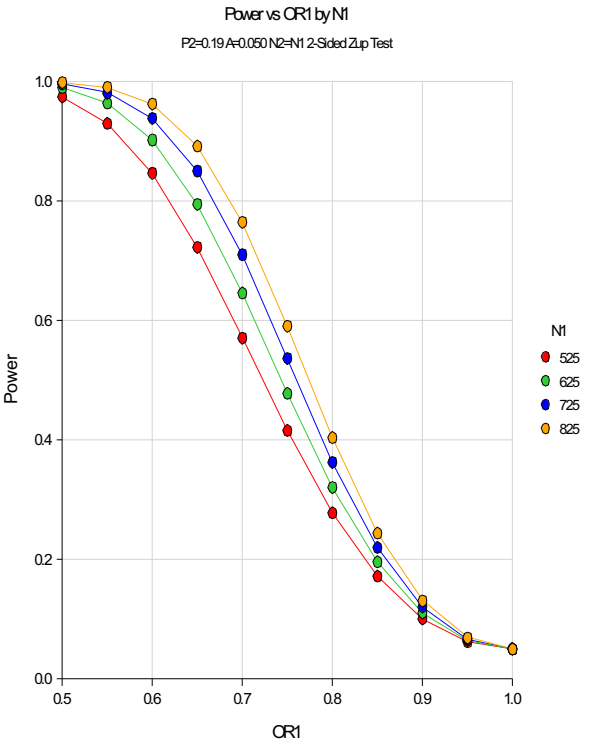


Supplementary Fig 1 (online only). Funnel plots with pseudo-95% confidence intervals for all studies reporting mortality, renal impairment, myocardial infarction, and myocardial injury comparing remote ischemic preconditioning (RIPC) and controls. *OR*, Odds ratio; *SE*, standard error.

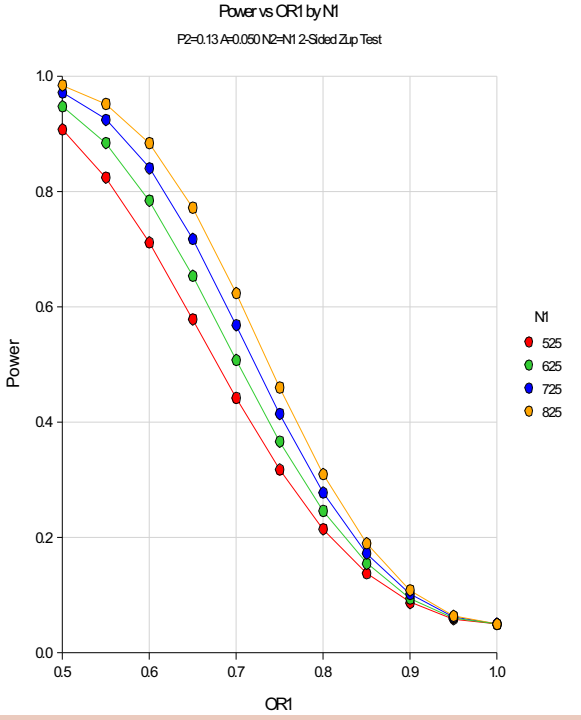
Mortality



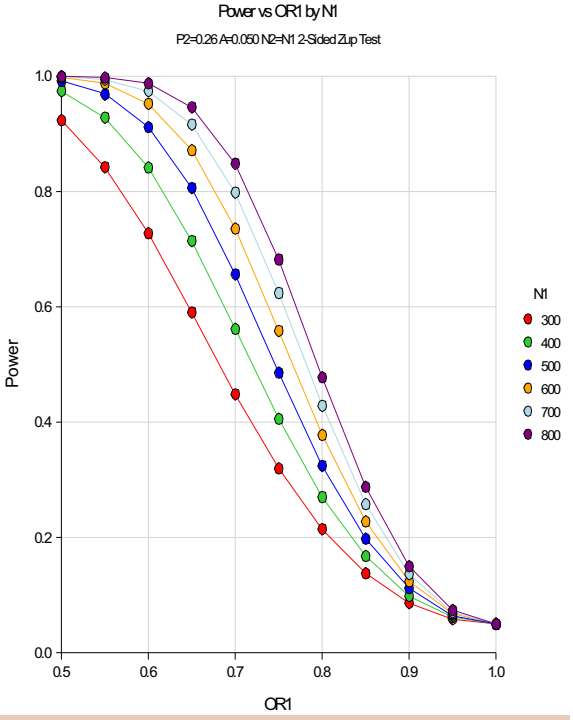
Renal Impairment



Myocardial Infarction



Myocardial Injury



Supplementary Fig 2 (online only). Power and sample size curves for studies reporting mortality, renal impairment, myocardial infarction, and myocardial injury comparing remote ischemic preconditioning (RIPC) and controls. *OR*, Odds ratio.