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Systematic Review

Effect of remote ischaemic preconditioning on mortality and morbidity after non-cardiac surgery: meta-analysis

K. L. Wahlstrøm *, E. Bjerrum , I. Gögenur , J. Burcharth and S. Ekeloef

Department of Surgery, Centre for Surgical Science, Zealand University Hospital, Koege, Denmark

*Correspondence to: Department of Surgery, Centre for Surgical Science, Zealand University Hospital, Lykkebaekvej 1, 4600 Koege, Denmark (e-mail: kwah@regionsjaelland.dk)

Abstract

Background: Remote ischaemic preconditioning (RIPC) has been shown to have a protective role on vital organs exposed to reperfusion injury. The aim of this systematic review was to evaluate the effects of non-invasive RIPC on clinical and biochemical outcomes in patients undergoing non-cardiac surgery

Methods: A systematic literature search of PubMed, EMBASE, Scopus, and Cochrane databases was carried out in February 2020. RCTs investigating the effect of non-invasive RIPC in adults undergoing non-cardiac surgery were included. Meta-analyses and trial sequential analyses (TSAs) were performed on cardiovascular events, acute kidney injury, and short- and long-term mortality.

Results: Some 43 RCTs including 3660 patients were included. The surgical areas comprised orthopaedic, vascular, abdominal, pulmonary, neurological, and urological surgery. Meta-analysis showed RIPC to be associated with fewer cardiovascular events in non-cardiac surgery (13 trials, 1968 patients, 421 events; odds ratio (OR) 0.68, 95 per cent c.i. 0.47 to 0.96; $P = 0.03$). Meta-analyses of the effect of RIPC on acute kidney injury (12 trials, 1208 patients, 211 events; OR 1.14, 0.78 to 1.69; $P = 0.50$; $I^2 = 9$ per cent), short-term mortality (7 trials, 1239 patients, 65 events; OR 0.65, 0.37 to 1.12; $P = 0.12$; $I^2 = 0$ per cent), and long-term mortality (4 trials, 1167 patients, 9 events; OR 0.67, 0.18 to 2.55; $P = 0.56$; $I^2 = 0$ per cent) showed no significant differences for RIPC compared with standard perioperative care in non-cardiac surgery. However, TSAs showed that the required information sizes have not yet been reached.

Conclusion: Application of RIPC to non-cardiac surgery might reduce cardiovascular events, but not acute kidney injury or all-cause mortality, but currently available data are inadequate to confirm or reject an assumed intervention effect.

Introduction

Ischaemic preconditioning involves exposure of tissues or organs to brief episodes of ischaemia and reperfusion in order to initiate a systemic response that protects tissue and organs from reperfusion injury[1,2]. Remote ischaemic preconditioning (RIPC) most often refers to ischaemic preconditioning where a remote tissue or organ, such as the upper or lower extremity, is exposed to short cycles of ischaemia and reperfusion by repetitive inflation and deflation of a BP cuff[1,2].

Recent meta-analyses of the effect of RIPC have either included non-surgical studies[3], cardiovascular surgical studies[4,5], or all invasive procedures[6]. Considering that patients undergoing surgery are exposed to a great burden of surgical stress, which increases activity and oxygen demand[7], it is likely that both the mechanism and effect of RIPC differ considerably between a surgical and non-surgical setting. Moreover, cardiac surgery interferes with the natural pathophysiological response of the heart and vascular structures, for example when using extracorporeal circulation. This might affect the mechanisms and effects of RIPC in ways that non-cardiac surgery does not[8].

The surgical stress response can cause hypercoagulability, endothelial dysfunction, immunological dysfunction, and activation of the sympathetic nervous system[9–11]. All of these are possible contributors to the pathophysiology of a variety of postoperative complications[9–11]. Experimental and clinical studies[12–14] have suggested that the local tissue damage caused by RIPC leads to activation of systemic anti-inflammatory and antithrombotic mechanisms, and induces a cytoprotective state through activation of humoral mediators and neuronal signal transfer. Therefore, RIPC might have the potential to reduce the surgical stress response and the occurrence of postoperative complications.

The aim of the present study was to conduct a systematic review of RCTs of the effect of RIPC on biomarkers, clinical outcomes, and mortality in adult patients undergoing acute or elective non-cardiac surgery compared with standard preoperative and perioperative care.

Methods

Before initiation of the systematic review and meta-analysis, a written study protocol was registered with Prospero (CRD42019123171). The study is reported in accordance with the PRISMA statement[15].

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Study eligibility criteria

RCTs with a RIPC protocol were included. Both elective and acute surgery was included, and controls were defined as adult patients (aged at least 18 years of age) undergoing non-cardiac surgery without RIPC (standard preoperative and perioperative care or sham procedure) in hospital. Only original articles in English were included. Trials investigating exclusively intracorporal RIPC and trials including deceased or brain-dead donors were excluded.

Literature search strategy

A systematic literature search was conducted by one investigator under the guidance of an information specialist from the reference library at the University of Copenhagen in the MEDLINE, Embase, Cochrane, and SCOPUS databases. The full electronic search strategy is shown in *Appendix S1*. The searches were carried out from the inception date of each database to 3 February 2020.

Data collection and extraction

Duplicates were resolved in Mendeley before uploading references to Covidence (Covidence systematic review software; Veritas Health Innovation, Melbourne, Victoria, Australia). Records were screened by title and abstract by two assessors independently. Full reports were obtained for all titles that met the inclusion criteria and in cases of uncertainty. Any disagreement between the two assessors was settled by discussion with a third evaluator. To ensure literature saturation, the reference lists of included studies or relevant reviews identified through the search were examined.

Data assessment

The following data were extracted from the trials: title; design; inclusion and exclusion criteria; number of patients included and distribution into intervention groups, sham or control groups; surgical setting (acute, emergency or elective); surgical and anaesthetic details; sham or control specifications; timing of intervention in relation to anaesthesia and surgery; anatomical site of RIPC application; number of RIPC cycles; duration of ischaemia and reperfusion; inflation pressure of the tourniquet; clinical outcomes including mortality, biomarker outcomes, and duration of follow-up; and limitations. If there was any uncertainty regarding these data, the authors of the study in question were contacted.

The Cochrane risk-of-bias tool[16] was used to assess the risk of methodological bias in all included trials. Quantitative analyses were planned to examine the association between RIPC and clinical outcomes where more than three trials had homogeneous clinical outcomes. Statistical analyses were performed with Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark)[17]. Unadjusted odds ratios (ORs) with 95 per cent confidence intervals were reported for the meta-analyses. Heterogeneity was explored using the I^2 statistic; if I^2 exceeded 0 per cent, a random-effects model was used. Funnel plots were designed to evaluate the risk of publication bias. Planned sensitivity analyses were performed for each meta-analysis: excluding small trials (fewer than 40 patients in 1 arm); or excluding trials with a high risk of bias. Subgroup analyses for each surgical specialty were also undertaken.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of the evidence associated with each of the clinical outcomes using GRADEpro software[18]. The GRADE tool uses factors to upgrade or downgrade the quality assessment of an outcome, and then rates each variable as a very low-, low-, moderate-, or high-quality outcome.

Trial sequential analysis (TSA) was performed on all meta-analysis outcomes in order to adjust for the risk of drawing a conclusion on the basis of random error, type I errors or underestimations (type II errors)[19,20]. TSA provides a detailed imprecision assessment in the GRADE system as well as the means of calculating the heterogeneity-adjusted required information size (RIS), defined as the required number of participants or events necessary in a meta-analysis to detect or reject an assumed intervention effect[20,21]. The analysis applied the proportion of patients with each outcome in the standard-care group, the heterogeneity (I^2) estimate from each meta-analysis, the assumption of a relative risk reduction of the RIPC intervention effect of 20 per cent[22], and the assumptions of an overall type I error of 5 per cent and power of 80 per cent. Each trial was added sequentially in the TSA by publication year, which provided a timewise series of points that formed the basis of the cumulative analysis. TSA was performed using TSA software v0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark)[22].

Results

From 5881 citations, a total of 43 RCTs investigating the effect of RIPC on clinical or biomarker outcomes in non-cardiac surgery were included in the review (3660 patients) (*Fig. 1*). All studies were published in peer-reviewed journals between 2006 and 2020. Study characteristics are listed in *Table S1*. The overall risk of bias was low (*Fig. S1*).

The surgical areas investigated comprised vascular surgery (13 trials)[23–36], orthopaedic surgery (13 trials)[37–49], urological surgery (7 trials)[50–57], abdominal surgery (7 trials)[58–64], pulmonary surgery (2 trials)[65,66], and neurosurgery (1 trial)[67]. Across the trials, there were 104 different outcome measures, of which 58 were solely examined in one study. Outcomes investigated in only one study and as a secondary outcome were not further described in this review.

Cardiovascular events

Trials and outcomes

Thirteen trials[23–25,27,28,30–36,40] reported on cardiovascular events and were included in the meta-analysis. They reported on cardiovascular death, myocardial infarction, myocardial injury, new arrhythmia, cardiac arrest, cardiac failure, low cardiac output syndrome, ischaemic ECG changes, stroke, hypoperfusion syndrome, transient ischaemic attack and newly ischaemic brain lesions on MRI. One trial included emergent orthopaedic surgery on patients with known cardiovascular risk factors and twelve trials included patients undergoing vascular surgery.

RIPC was associated with reduced cardiovascular events in non-cardiac surgery (13 trials, 1968 patients, 421 events; OR 0.68, 95 per cent c.i. 0.47 to 0.96; $P = 0.03$) (*Fig. 2a*). Heterogeneity between trials was considerable ($I^2 = 41$ per cent) and the funnel plot was asymmetrical, showing risk of publication bias (missing small negative trials) (*Fig. S2a*). The risk-of-bias assessment showed little evidence of bias within any of the trials. Sensitivity analysis excluding small trials reduced the heterogeneity ($I^2 = 18$ per cent) and the analysis still favoured application of RIPC compared with control (9 trials, 1727 patients, 388 events; OR 0.56, 0.42 to 0.76; $P < 0.001$). Sensitivity analysis excluding the trial in emergency hip surgery in which the patients had known cardiovascular risk factors, leaving only trials in vascular surgery,

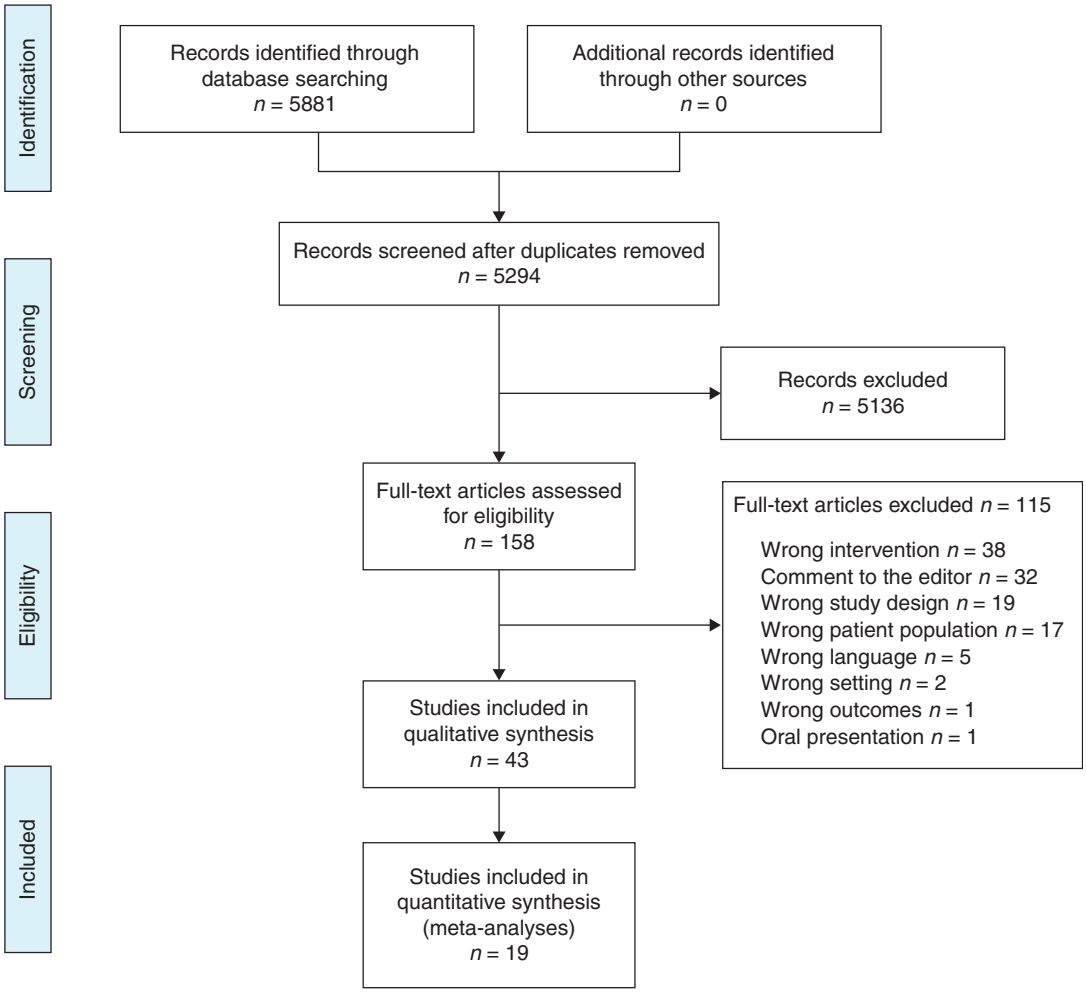


Fig. 1 PRISMA showing selection of articles for review

changed the result, showing no effect of RIPC (12 trials, 1395 patients, 358 events; OR 0.68, 0.45 to 1.03; $P = 0.07$). According to the GRADE assessment, the quality of evidence was low (*Table 1*) and TSA showed a RIS of 3150 participants (*Fig. 3*).

Biochemical markers

Twelve trials [23–25,30–35,40,46,61] measured troponin levels (TnI or TnT) as an individual outcome. Nine of these quantified troponin measurements in comparable units and were included in a meta-analysis This showed that RIPC was associated with a reduced occurrence of increased troponin level (9 trials, 1659 patients, 337 events; OR 0.63, 95 per cent c.i. 0.48 to 0.82; $P < 0.001$) (*Fig. 2b*). Trials were homogeneous ($I^2 = 0$ per cent) but the funnel plot were asymmetrical (*Fig. S2b*), indicating publication bias with small trials (both positive and negative) lacking. Sensitivity analyses excluding small trials or trials with a high risk of bias did not change the results, but subgroup analysis of patients undergoing vascular surgery showed no benefit of RIPC (6 trials, 933 patients, 117 events; OR 0.80, 0.53 to 1.22; $P = 0.30$).

Acute kidney injury

Twelve trials reported on acute kidney injury either in accordance with Acute Kidney Injury Network (AKIN) criteria[30,32,33,46,63], using measurements similar to AKIN criteria[23,25,31,35,50,62], or the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria[34]. Eight trials included patients undergoing major vascular surgery, one[46] was a trial in orthopaedic surgery, one[50] included patients having open partial nephrectomy, one[62] involved liver transplantation, and one[63] included patients undergoing liver resection.

RIPC did not reduce the occurrence of acute kidney injury (12 trials, 1208 patients, 211 events; OR 1.14, 95 per cent c.i. 0.78 to 1.69; $P = 0.50$) (*Fig. 4*). Heterogeneity between trials was acceptable ($I^2 = 9$ per cent) and the funnel plot was nearly symmetrical (*Fig. S3*). Sensitivity analysis showed that exclusion of one small trial[50] with only 16 patients reduced I^2 to 0 per cent for the remaining 11 trials (1192 patients, 205 events; OR 1.22, 0.85 to 1.74; $P = 0.28$). There was no gain in heterogeneity or significance in sensitivity analysis by excluding trials with a larger risk of bias; however, in a subgroup analysis investigating only patients having vascular surgery, heterogeneity was also reduced to $I^2 = 0$ per cent (8 trials, 936 patients, 114 events; OR 1.12, 0.72 to 1.75; $P = 0.61$). The quality of evidence according to GRADE assessment was high (*Table 1*), but TSA showed a required enrolment of 4263 patients (*Fig. 5*).

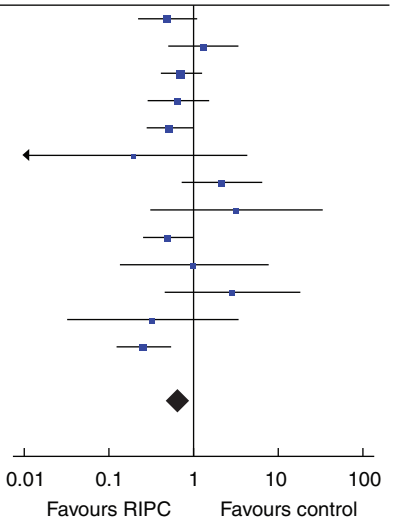
Short- and long-term all-cause mortality

Seven trials[23,25,30,31,34,35,40] reported short-term all-cause mortality (within 90 days of operation). All but one was in vascular surgery. The other trial[40] included patients with at least one

a Cardiovascular events

Reference	Cardiovascular events RIPC	Cardiovascular events Control/sham	Weight (%)	Odds ratio
Choi *et al.*[27]	27 of 54	36 of 54	10.7	0.50 (0.23, 1.09)
Coverdale *et al.*[35]	12 of 71	9 of 68	8.7	1.33 (0.52, 3.40)
Ekeloef *et al.*[40]	27 of 286	36 of 287	14.8	0.73 (0.43, 1.23)
Garcia *et al.*[33]	11 of 100	16 of 101	10.1	0.66 (0.29, 1.50)
Healy *et al.*[31]	23 of 99	36 of 99	13.1	0.53 (0.28, 0.99)
Kepler *et al.*[28]	0 of 45	2 of 47	1.3	0.20 (0.01, 4.28)
Mouton *et al.*[32]	12 of 34	7 of 35	7.2	2.18 (0.74, 6.47)
Murphy *et al.*[30]	3 of 31	1 of 31	2.1	3.21 (0.32, 32.74)
Pedersen *et al.*[25]	33 of 72	44 of 70	12.3	0.50 (0.26, 0.98)
Thomas *et al.*[34]	2 of 42	2 of 43	2.8	1.02 (0.14, 7.63)
Walsh *et al.*[23]	4 of 18	2 of 22	3.2	2.86 (0.46,17.80)
Walsh *et al.*[24]	1 of 34	3 of 36	2.1	0.33 (0.03, 3.37)
Zhao *et al.*[36]	12 of 63	60 of 126	11.6	0.26 (0.13, 0.53)
Total	167 of 949	254 of 1019	100.0	0.68 (0.47, 0.96)

Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 20.31$, 12 d.f., $P = 0.06$; $I^2 = 41\%$
Test for overall effect: $Z = 2.16$, $P = 0.03$



b Inesease in troponin level

Reference	Ineseared troponin RIPC	Ineseared troponin Control/sham	Weight (%)	Odds ratio
Antonowlcz *et al.*[61]	28 of 41	35 of 43	6.9	0.49 (0.18, 1.35)
Coverdale *et al.*[35]	3 of 68	2 of 71	2.1	1.59 (0.26, 9.84)
Ekeloef *et al.*[40]	57 of 287	90 of 286	48.5	0.54 (0.37, 0.79)
Garcia *et al.*[33]	22 of 200	25 of 201	19.1	0.87 (0.47, 1.60)
Healy *et al.*[31]	8 of 99	13 of 99	8.2	0.58 (0.23, 1.47)
Park *et al.*[46]	3 of 30	7 of 39	3.4	0.51 (0.12, 2.16)
Thomas *et al.*[34]	18 of 42	21 of 43	9.7	0.79 (0.33, 1.85)
Walsh *et al.*[23]	1 of 18	2 of 22	1.1	0.59 (0.05, 7.07)
Walsh *et al.*[24]	1 of 34	1 of 36	0.9	1.06 (0.06, 17.66)
Total	141 of 819	196 of 840	100.0	0.63 (0.48, 0.82)

Heterogeneity: $\chi^2 = 3.43$, 8 d.f., $P = 0.90$; $I^2 = 0\%$
Test for overall effect: $Z = 3.39$, $P < 0.001$

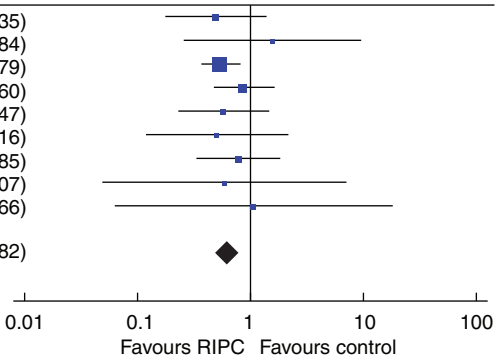


Fig. 2 Forest plot of RCTs comparing rates of cardiovascular events and increased postoperative troponin level in remote ischaemic preconditioning and control/sham groups

a Cardiovascular events and **b** increased postoperative troponin level. Inverse-variance random-effects (**a**) and inverse-variance fixed-effect (**b**) models were used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals.

cardiovascular risk factor having hip surgery. One trial[25] of patients undergoing open repair of a ruptured abdominal aortic aneurysm (AAA) had a distinctly higher mortality rate than the remaining trials. Three[32–34] of the four trials reporting on long-term all-cause mortality (after postoperative day 90) were in vascular surgery. The other trial[51] involved patients undergoing live-donor renal transplantation and reported 1-year mortality. This trial has also recently reported 5-year mortality[57], but these results are not included in the present meta-analysis.

A further five trials[29,53,59,64,65] registered short-term all-cause mortality and two[36,54] recorded long-term all-cause mortality, but there were no events in any of these trials and they were not included in the meta-analyses of mortality.

Neither short-term (7 trials, 1239 patients, 65 events; OR 0.65, 95 per cent c.i. 0.37 to 1.12; $P = 0.12$) (*Fig. 6a*) or long-term mortality (4 trials, 1167 patients, 9 events; OR 0.67, 0.18 to 2.55; $P = 0.56$) (*Fig. 6b*) were affected by RIPC in the meta-analyses. Heterogeneity between trials was minimal ($I^2 = 0$ per cent) in both meta-analyses. The funnel plot for long-term mortality was symmetrical, but that for short-term mortality indicated publication bias with a lack of negative trials (*Fig. S4*). Exclusion of small trials changed the results towards there being an effect of RIPC on short-term mortality (5 trials, 1137 patients, 60 events; OR 0.56, 0.31 to 0.99; $P = 0.04$; $I^2 = 0$ per cent). There was no change after exclusion of trials with a higher risk of bias. The body of evidence was of low quality according to GRADE assessment (*Table 1*). To confirm or reject whether RIPC has an effect on short- or long-term mortality, TSA indicated that a RIS of at least 7484 and 33 003 patients respectively would be necessary (*Fig. 7*).

Adaptive immune response

One trial[43] investigated the effect of RIPC on the adaptive immune response in patients undergoing cruciate ligament reconstruction. It found that RIPC modulated T cell responses

Table 1 Assessment of the quality of evidence of RCTs included in the meta-analyses, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

Studies	Certainty assessment					Proportion with event*		Effect†		Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	RIPC	Control/sham	Relative	Absolute	
Cardiovascular events										
13 RCTs	Not serious	Serious‡	Not serious	Not serious	Publication bias strongly suspected§	167 of 949 (17.6)	254 of 1019 (24.9)	OR 0.68 (0.47, 0.96)	65 fewer (from 114 to 8 fewer) per 1000	Low
Acute kidney injury										
12 RCTs	Not serious	Not serious¶	Not serious	Not serious	None	110 of 603 (18.2)	101 of 605 (16.7)	OR 1.14 (0.78, 1.69)	19 more (from 32 fewer to 86 more) per 1000	High
Mortality ≤ 90 days										
7 RCTs	Not serious	Not serious	Not serious	Very serious#	None	27 of 619 (4.4)	38 of 620 (6.1)	OR 0.65 (0.37, 1.12)	21 fewer (from 38 fewer to 7 more) per 1000	Low
Mortality > 90 days										
4 RCTs	Not serious	Not serious	Not serious	Very serious#	None	3 of 585 (0.5)	6 of 582 (1.0)	OR 0.67 (0.18, 2.55)	3 fewer (from 8 fewer to 16 more) per 1000	Low

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡I^2 = 41 per cent. §Funnel plot asymmetrical. ¶I^2 = 9 per cent. #Small number of events, wide confidence interval. RIPC, remote ischaemic preconditioning; OR, odds ratio.

through reduced activation and proinflammatory cytokine production by CD4 cells, while preventing CD4/CD8 derangement.

Inflammatory markers

Ten trials[29,37,38,41–44,51,58,65] studied the effect of RIPC on circulating levels of inflammatory markers. Of these, five trials[29,43,44,58,65] showed a significant difference in favour of RIPC lowering the levels of inflammatory markers such as interleukin (IL) 6, IL-1β, interferon γ, and tumour necrosis factor (TNF) α, whereas the remaining five trials[37,38,41,42,51] did not. The trials that did not show significant results were studies of total knee arthroplasty[37,38,42], shoulder surgery in patients in the beach chair position[41], and RIPC in live-donor renal transplantation where patients were immunosuppressed[51]. However, among the RIPC-positive trials were also two studies[43,44] of RIPC in orthopaedic surgery, and one each in colonic surgery[58], pulmonary resection[65], major vascular surgery[29].

One orthopaedic trial[45] measured levels of inflammatory markers in the periarticular drainage fluid (IL-6 and TNF-α). No differences were seen between controls and the RIPC group.

Oxidative stress markers

Six trials[29,44,47,48,52,65] investigated the effect of RIPC on the levels of circulating oxidative stress markers. All measured malondialdehyde, three measured superoxide dismutase as well, and one trial also measured glutathione peroxidase, total antioxidant capacity, and total oxidant status. Five[29,44,47,48,65] of these six trials showed that RIPC reduced oxidative stress. These trials comprised both major[29,65] and minor surgery[44,47,48].

Neurological injury

Seven trials investigated whether RIPC had any neuroprotective effect on ischaemic lesions, markers of neurological injury, and cognitive assessment scales. The outcomes included levels of neurone-specific enolase (NSE)[36,39] and S100 calcium-binding protein B (S-100B)[36,39,58], regional cerebral oxygenation[38,41], the Montreal Cognitive Assessment (MoCA) score[58], median nerve somatosensory-evoked potentials (SEPS)[39], Japanese Orthopaedic Association criteria for the evaluation of operative results in patients with cervical myelopathy (JOA scale)[39] or saccadic latency[24]. One trial[36] in vascular surgery (carotid artery stenting) also investigated the incidence of new ischaemic lesions, and another trial[67] in brain surgery investigated both the incidence of new ischaemic lesions and infarct volumes. Trials investigating neurological injury comprised both minor[24,36,39] and moderate–major surgery[38,58,67].

Six of the seven trials showed significant neuroprotective effects of RIPC on NSE[36,39], S-100B[39,58], MoCA score[58], JOA scale[39], regional cerebral oxygenation[38,41], incidence of new ischaemic lesions[36,67], and infarct volumes[67]. Only median nerve SEPS and saccadic latency did not show any response to RIPC[24,39].

Pulmonary injury and function

Six trials studied the effect of RIPC on pulmonary injury and function. The outcomes investigated were: arterial–alveolar oxygen tension ratio and alveolar–arterial oxygen tension difference[29,44,65,66], ratio of arterial oxygen partial pressure and fraction of inspired oxygen and respiratory index[38,44,65,66], urinary desmosine level[37], static and dynamic lung compliance, as well as acute lung injury[65]. One trial[66] measured levels of 8-isoprostane, nitrite + nitrate, and hydrogen peroxide, and pH in both blood and exhaled breath condensate.

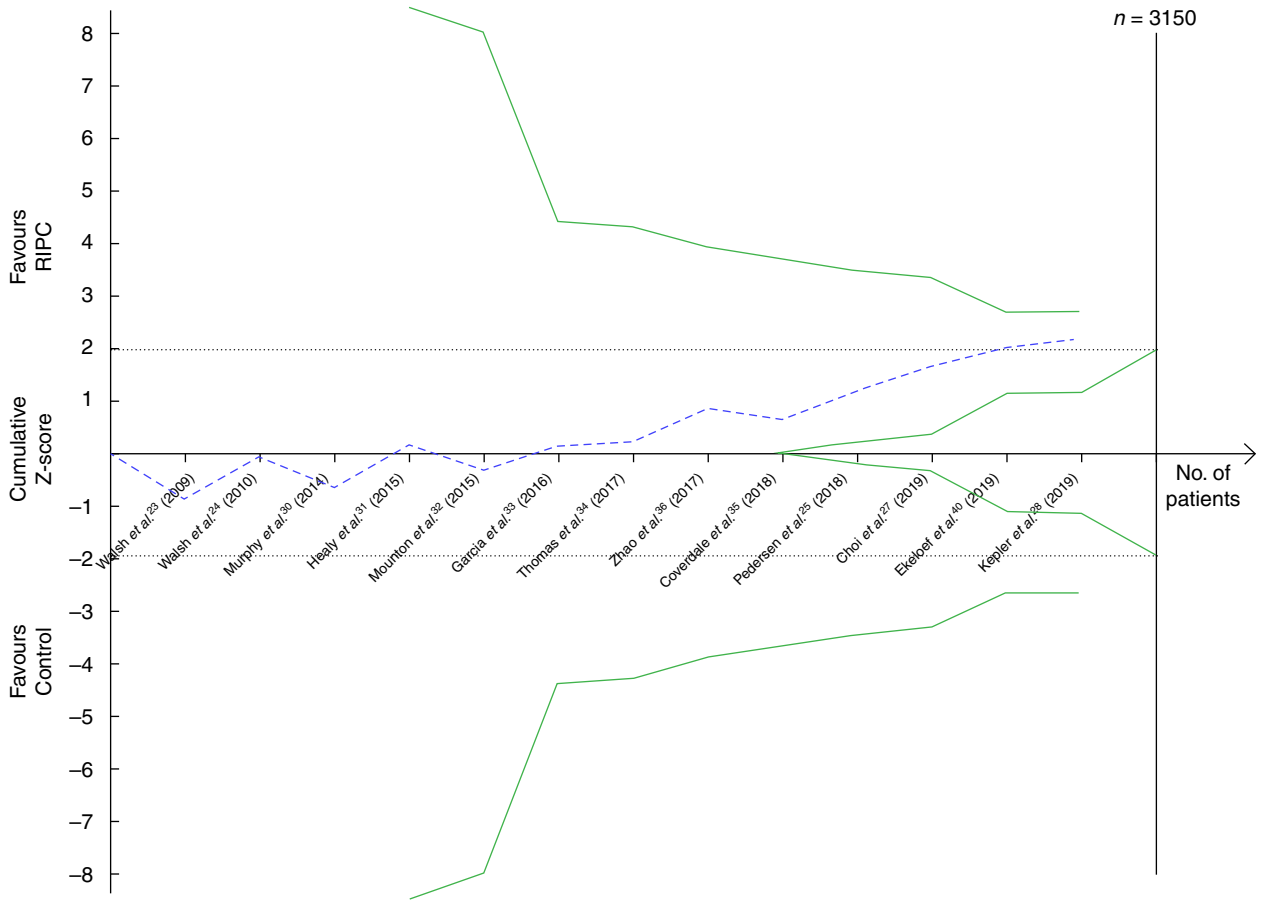


Fig. 3 Trial sequential analysis of the effect of remote ischaemic preconditioning on cardiovascular events

Relative risk reduction of cardiovascular events is 20 per cent, acceptable risk of type I error is 5 per cent, and power is 20 per cent on a two-sided graph. The Z-curve did not reach the diversity-adjusted required information size for a 20 per cent relative risk reduction of a cardiovascular event, of 3150 patients. Neither did the Z-curve cross the monitoring efficacy boundary (upper curve) or the futility boundary (lower curve). RIPC, remote ischaemic preconditioning.

The black dotted lines are the conventional efficacy boundaries (nominal statistical significance). The uppermost green line and the lowermost green line are both the monitoring efficacy boundaries on a two-sided test. The two shorter green line (within the dotted lines representing the conventional efficacy boundaries) are the futility boundaries on a two-sided test.

	Acute kidney injury			
Reference	**RIPC**	**Control/sham**	**Weight (%)**	**Odds ratio**
Coverdale *et al.*[35]	4 of 71	5 of 68	7.5	0.75 (0.19, 2.93)
Garcia *et al.*[33]	1 of 100	3 of 101	2.8	0.33 (0.03, 3.23)
Healy *et al.*[31]	1 of 99	2 of 99	2.5	0.49 (0.04, 5.55)
Jung *et al.*[62]	44 of 74	38 of 72	25.2	1.31 (0.68, 2.53)
Kil *et al.*[50]	1 of 8	5 of 8	2.3	0.09 (0.01, 1.08)
Mouton *et al.*[32]	16 of 34	12 of 35	13.6	1.70 (0.65, 4.49)
Murphy *et al.*[30]	17 of 31	11 of 31	12.5	2.21 (0.80, 6.13)
Park *et al.*[46]	4 of 30	1 of 30	2.9	4.46 (0.47, 42.51)
Pedersen *et al.*[25]	14 of 72	17 of 70	18.7	0.75 (0.34, 1.67)
Teo *et al.*[63]	2 of 24	2 of 26	3.5	1.09 (0.14, 8.42)
Thomas *et al.*[34]	2 of 42	3 of 43	4.2	0.67 (0.11, 4.21)
Walsh *et al.*[23]	4 of 18	2 of 22	4.3	2.86 (0.46, 17.80)
Total	110 of 603	101 of 605	100.0	1.14 (0.78, 1.69)

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 12.13$, 11 d.f., $P = 0.35$; $I^2 = 9\%$

Test for overall effect: $Z = 0.68$, $P = 0.50$

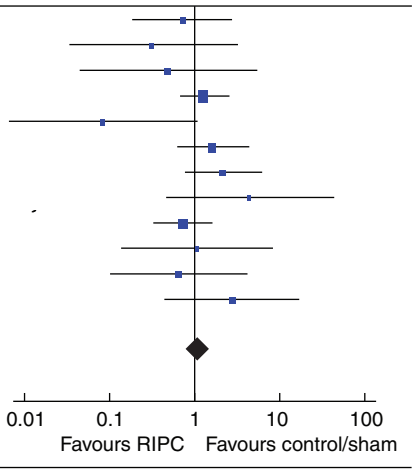


Fig. 4 Forest plot of RCTs comparing rates of acute kidney injury in remote ischaemic preconditioning and control/sham groups

An inverse-variance random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals.

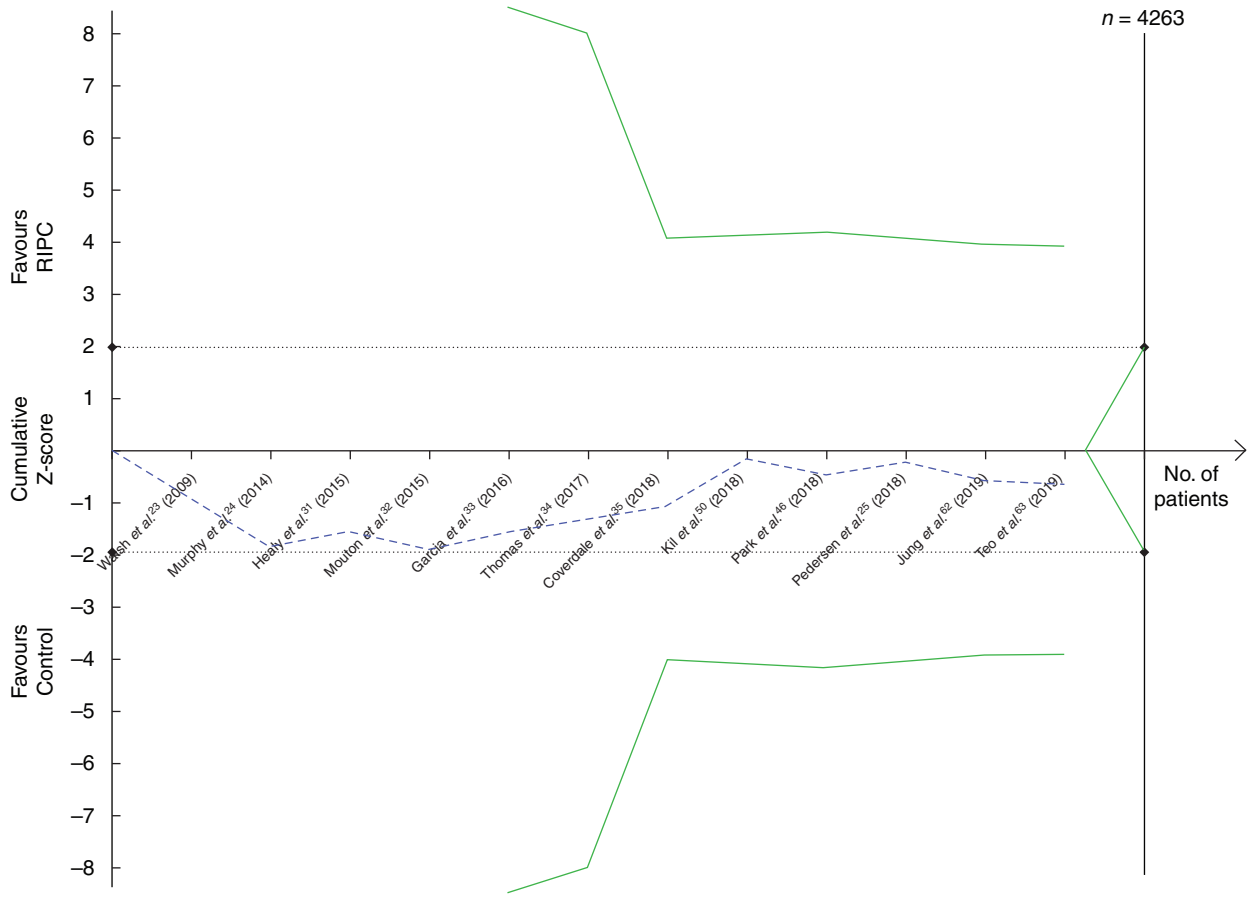


Fig. 5 Trial sequential analysis of the effect of remote ischaemic preconditioning on acute kidney injury

Relative risk reduction of acute kidney injury is 20 per cent, acceptable risk of type I error is 5 per cent, and power is 20 per cent on a two-sided graph. The Z-curve did not reach the diversity-adjusted required information size of 4263 patients. Neither did the Z-curve cross the monitoring efficacy boundary (upper curve) or the futility boundary (lower curve). RIPC, remote ischaemic preconditioning.

The black dotted lines are the conventional efficacy boundaries (nominal statistical significance). The uppermost green line and the lowermost green line are both the monitoring efficacy boundaries on a two-sided test. The two shorter green line (within the dotted lines representing the conventional efficacy boundaries) are the futility boundaries on a two-sided test.

Five[29,38,44,65,66] of the six trials investigating the effects of RIPC on pulmonary injury showed a beneficial effect of RIPC on the broad variety of markers of lung injury described above. Only one study[37], which measuring urinary desmosine levels, did not find a significant difference between the control and RIPC groups. Trials investigating lung injury comprised primarily major procedures[29,37,38,65,66] in orthopaedic, vascular, and pulmonary surgery, and only one trial[44] in minor surgery (orthopaedic).

Renal transplantation and renal injury

Renal transplantation

Live-donor renal transplantation and the effects of RIPC were investigated in four trials[51–53,56] that measured estimated glomerular filtration rate (eGFR), creatinine concentration, urinary volume, levels of serum cystatin C, plasma neutrophil gelatinase-associated lipocalin (NGAL), urinary neutrophil gelatinase-associated lipocalin, urinary retinol-binding protein (RBP), urinary *N*-acetyl-D-glucosaminidase, and urinary liver-type fatty acid-binding protein, and outcomes in relation to graft function and rejection. One trial[56] also investigated the incidence of chronic kidney disease 1 year after surgery in donors, according to the Kidney Disease Improving Global Outcomes criteria. Another trial[51] assessed changes in tissue pathology. Overall, the results were negative, with the exception of two trials. In one multicentre, international trial[51], RIPC decreased the incidence of delayed graft function (secondary outcome), and at 5-year follow-up there was a sustained improvement in eGFR after RIPC immediately before surgery compared with that in controls ($P = 0.004$) (primary outcome)[57]. Another trial[56] reported that creatinine levels were increased significantly in the donor control group at discharge ($P = 0.003$), and donors with high creatinine levels at discharge had a higher prevalence of chronic kidney disease after 1 year ($P = 0.003$) (both secondary outcomes).

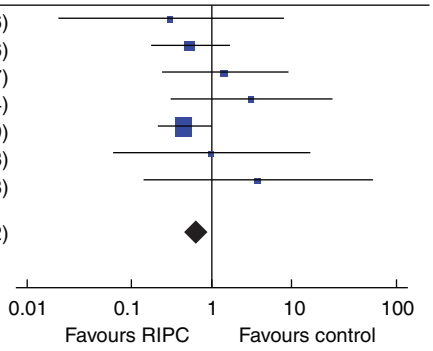
Renal injury in nephrectomy

Three trials in partial nephrectomy, both open[50] and laparoscopic[54,55], showed a significant advantageous effect of RIPC. One trial[54] assessed absolute change in GFR of the affected kidney by renal scintigraphy and urinary RBP measurement, and another[50] assessed eGFR, serum creatinine, fraction of excreted sodium, and acute kidney injury in accordance with AKIN criteria. The final trial[55] exposed one group of patients to RIPC 24 h before surgery and another group immediately before surgery. Plasma NGAL and serum cystatin C levels were decreased significantly in intervention groups compared with controls, and late-phase protection was

a Short-term mortality

Reference	Death within 90 days: RIPC	Death within 90 days: Control/sham	Weight (%)	Odds ratio
Coverdale *et al.*[35]	0 of 71	1 of 68	2.9	0.31 (0.01, 7.86)
Ekeloe *et al.*[40]	5 of 286	9 of 287	0.55	0.55 (0.18, 1.66)
Healy *et al.*[31]	3 of 99	2 of 99	1.52	1.52 (0.25, 9.27)
Murphy *et al.*[30]	3 of 31	1 of 31	3.21	3.21 (0.32, 32.74)
Pedersen *et al.*[25]	14 of 72	24 of 70	0.46	0.46 (0.22, 0.99)
Thomas *et al.*[34]	1 of 42	1 of 43	1.02	1.02 (0.06, 16.93)
Walsh *et al.*[23]	1 of 18	0 of 22	3.86	3.86 (0.15, 100.58)
Total	27 of 619	38 of 620	100.0	0.65 (0.37, 1.12)

Heterogeneity: $\chi^2 = 4.95$, 6 d.f., $P = 0.55$; $I^2 = 0\%$
Test for overall effect: $Z = 1.55$, $P = 0.12$



b Long-term mortality

Reference	Death after 90 days: RIPC	Death after 90 days: Control/sham	Weight (%)	Odds ratio
Garcia *et al.*[35]	0 of 100	1 of 101	17.2	0.33 (0.01, 8.28)
Macallister *et al.*[40]	2 of 409	2 of 403	46.0	0.99 (0.14, 7.03)
Mouton *et al.*[31]	0 of 34	3 of 35	19.7	0.13 (0.01, 2.71)
Thomas *et al.*[30]	1 of 42	0 of 43	17.0	3.14 (0.12, 79.39)
Total	3 of 585	6 of 582	100.0	0.67 (0.18, 2.55)

Heterogeneity: $\chi^2 = 2.31$, 3 d.f., $P = 0.51$; $I^2 = 0\%$
Test for overall effect: $Z = 0.58$, $P = 0.56$

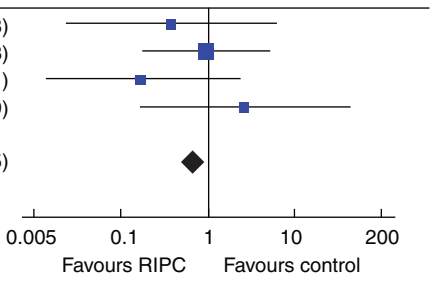


Fig. 6 Forest plot of RCTs comparing rates of death within 90 days or more than 90 days after surgery in remote ischaemic preconditioning and control/sham groups

a Short-term and **b** long-term mortality. An inverse-variance fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals.

more prominent. Furthermore, GFR assessed by renal scintigraphy was lower in both intervention groups at 3-month follow-up.

Renal injury in vascular surgery

Four trials in vascular surgery investigated the renoprotective effect of RIPC. Three[30,33,34] reported no effect of RIPC. One trial[23], which included patients undergoing elective endovascular aneurysm repair, found that RIPC was associated with improved tubular function indicated by a significantly higher urine albumin/creatinine ratio and lower urinary RBP levels, implying less distal tubule damage.

Liver injury

Five trials[59,60,62–64] investigated the hepatoprotective effect of RIPC. All trials included liver surgery only. Four trials investigated RIPC in patients undergoing major hepatectomy[59,63,64] or liver resections[60] for hepatocellular carcinoma or colorectal liver metastasis. The trial on liver resections compared the hepatoprotective effects of RIPC *versus* local ischaemic preconditioning. The four trials had different results. One[59] showed a reduction in postoperative serum aminotransferase levels and increased indocyanine green (ICG) clearance, but no effect on serum bilirubin or histological examination of the resected liver specimen for signs of ischaemia–reperfusion injury, steatosis, and fibrosis. Another trial[60], however, found ischaemic preconditioning to be beneficial in terms of postoperative serum cholinesterase and serum bilirubin levels, as well as a higher Doppler ultrasound flow through the hepatic artery; there were significant differences between groups in histopathological evaluation of hepatocyte necrosis. Prothrombin time (PT), activated partial thromboplastin time, and alkaline phosphatase, albumin, total protein, and carbamide levels did not differ between the groups. The third trial[63] assessed postoperative liver function by measurement of alanine (ALT) and aspartate (AST) aminotransferase, and ICG levels; and the fourth trial[64] by total bilirubin, ALT and AST levels, PT, international normalized ratio, and serum albumin level. Neither trial found differences between the RIPC and control groups.

The fifth trial[62] investigated the effect of RIPC on donors and recipients after liver transplantation. The donors underwent RIPC before surgery. The postoperative AST concentration was lower in recipients who received a preconditioned graft ($P = 0.029$), but there were no differences in postoperative AST or ALT levels in donors. RIPC did not reduce the incidence of delayed graft hepatic function, early allograft dysfunction or graft failure.

Intestinal injury

Three trials[25,29,31], all in vascular surgery, assessed the effect of RIPC on intestinal injury. One trial[29] investigated the impact of RIPC in patients undergoing elective open infrarenal AAA repair. Intestinal injury was assessed by measuring the serum concentrations of intestinal fatty acid-binding protein and endotoxin, and the activity of diamine oxidase. To evaluate intestinal function, a modified intestinal dysfunction score was recorded from

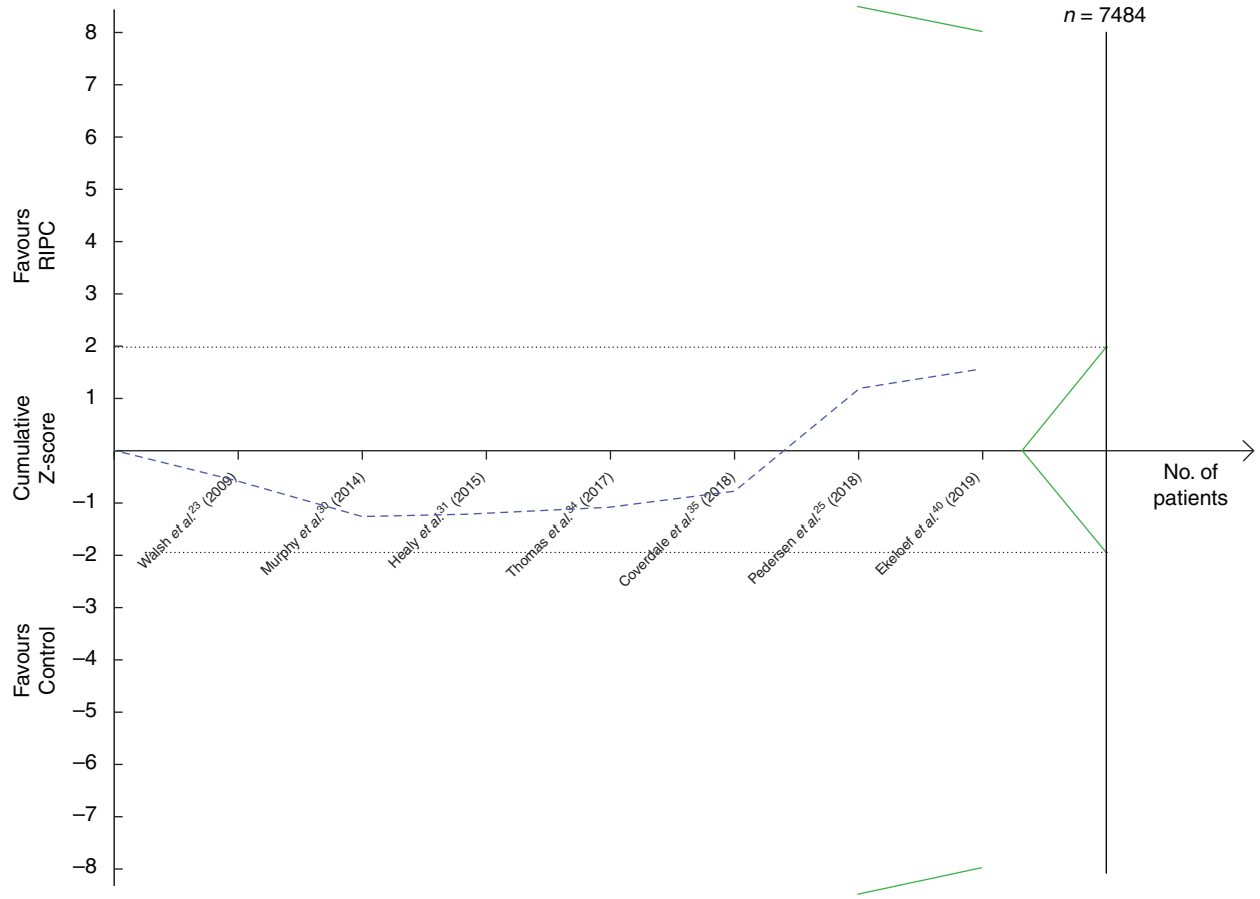


Fig. 7 Trial sequential analysis of the effect of remote ischaemic preconditioning on short-term mortality

Relative risk reduction of short-term mortality is 20 per cent, acceptable risk of type I error is 5 per cent, and power is 20 per cent on a two-sided graph. The Z-curve did not reach the diversity-adjusted required information size of 7484 patients. Neither did the Z-curve cross the monitoring efficacy boundary (upper curve) or the futility boundary (lower curve). Too few trials and numbers of patients were available for a trial sequential analysis graph to be produced for the effect of remote ischaemic preconditioning (RIPC) on long-term mortality.

The black dotted lines are the conventional efficacy boundaries (nominal statistical significance). The uppermost green line and the lowermost green line are both the monitoring efficacy boundaries on a two-sided test. The two shorter green line (within the dotted lines representing the conventional efficacy boundaries) are the futility boundaries on a two-sided test.

72 h after operation. All biomarkers reflecting intestinal injury were reduced in favour of RIPC ($P < 0.001$).

Two trials[25,31] investigated the effect of RIPC on intestinal injury as a clinical outcome of intestinal ischaemia. One trial[25], in open surgery for ruptured AAA, defined intestinal ischaemia in terms of surgical removal of ischaemic bowel. Ischaemic bowel developed in five patients in the RIPC group and 12 in the control group ($P = 0.052$). The other trial[31], comprising a composite of elective major vascular surgery, defined intestinal ischaemia as small or large bowel ischaemia requiring laparotomy, found at autopsy or proven on colonic biopsy; no significant difference between the control and RIPC groups was found.

Muscular injury and pain

Four trials in orthopaedic surgery (total knee replacement and knee ligamentoplasty) examined the effects of RIPC on postoperative pain[37,45,49], analgesic consumption[45,49], muscle oxygenation[45], muscular injury[49], and gene expression profile of muscle biopsies[42].

The three trials investigating pain scores and analgesic consumption showed heterogenous results. One[49] reported no difference in pain scores, but a reduction in analgesic consumption in the RIPC group. The other two[37,45] reported less pain at rest and during exercise, but found no differences in analgesic consumption. All three trials performed RIPC on the operative limb just before surgery.

RIPC did not have any effect on muscular oxygenation[45] or injury measured as the level of myoglobin and creatinine phosphokinase in plasma[49]. However, muscle gene expression profiles showed a statistically significant increase in the expression of oxidative stress defence genes, immediate early response genes, and mitochondrial genes. Upregulation of prosurvival genes was also observed and correlated with a downregulation of proapoptotic gene expression[42].

Arterial stiffness

One trial[26] investigated the effect of RIPC on arterial stiffness parameters (augmentation index and pulse wave velocity) as a primary outcome in patients undergoing vascular surgery. There were no significant differences between the RIPC and control groups.

Discussion

In this systematic review of the effect of RIPC on clinical or biomarker outcomes in non-cardiac surgery, meta-analysis showed

a positive association between RIPC and improved cardiovascular outcomes. There was, however, substantial heterogeneity, possibly as a consequence of several different cardiovascular outcomes being included. The majority of included patients were undergoing vascular surgery, but the timing of RIPC in relation to anaesthesia and surgery differed between studies, as did the number and duration of cycles, and the anatomical site of RIPC. The positive effects of RPIC remained in a sensitivity analysis excluding small trials.

The meta-analysis of acute kidney injury did not show an effect of RIPC. The quality of evidence according to GRADE assessment was high, but the TSA showed that the required information size had not yet been reached. Finally, RIPC had no effect on all-cause short- or long-term postoperative mortality. The body of evidence was of low quality according to GRADE assessment, and the TSA indicated that the RIS had not been reached.

The finding of a reduction in cardiovascular events with use of RIPC in non-cardiac surgery contradicts the findings of a meta-analysis[6] that included both ischaemic preconditioning and post-conditioning, central and remote conditioning, in both children and adults undergoing invasive procedures, including cardiac surgery. It showed no effect of ischaemic conditioning (both central and remote) on the overall risk of death or cardiovascular events. Furthermore, effects on stroke and acute kidney injury were uncertain given methodological concerns and low event rates. Furthermore, meta-analyses investigating the clinical effect of RIPC in only one surgical area, such as AAA repair[4,68] and cardiac surgery[5,69], did not consistently show cardiac or renal protection, and there was no effect on mortality. Some of the meta-analyses did, however, show a reduced incidence of acute kidney injury[5,69] and mortality[5] in subgroup analyses of patients receiving volatile anaesthetics in cardiac surgery.

Despite investigation of the use of RIPC in a number of clinical settings over several decades[70], the underlying mechanism is still not fully understood. Several experimental and clinical studies[71–75] have suggested that the stimulus is transmitted from the preconditioned tissue to other organs by humoral, neural, and systemic anti-inflammatory mediators. Considering the complex interaction of pathways in which RIPC might exert its effect, it is tempting to establish the hypothesis that the effect of RIPC also depends on the level of surgical stress the patients are exposed to. This hypothesis remains untested. Interestingly, there seems to be a pattern in the organs protected by RIPC. Focusing on the target organ, twice as many trials showed significant results in the form of protection of the operated organ[28,36,39,50,51,54,55,59,60,65–67], than in trials investigating a protective effect on target organs other than the operated organ[18,21,28,30,44]. This gives further reason to believe that the amount of surgical stress is crucial for demonstrating an important effect of RIPC. Trials that did not show significant protective results in the operated organ either referred to renal protection in renal transplantation[52,53], liver protection in hepatectomy[63,64], or cardiovascular protection in vascular surgery[24,31–34].

Many trials have shown a significant effect of RIPC on inflammatory markers[29,43,44,58,65] and oxidative stress markers[29,44,47,48,65], supporting the hypothesis that RIPC has an opposing effect on surgical stress. Cardiovascular complications account for a substantial proportion of both postoperative complications and mortality in non-cardiac surgery[76–78]. The pathophysiology of perioperative cardiac events has not been fully clarified, even though efforts to identify the underlying pathophysiology have been made[79–85]. The systemic stress response leads to a myocardial oxygen supply–demand mismatch, which, in the presence of endothelial dysfunction, stress-induced rupture of arteriosclerotic plaques, and hypercoagulability, may cause myocardial injury[77]. A reduction in the surgical stress response resulting from RIPC could partially explain the reduced risk of cardiovascular events after non-cardiac surgery using such preconditioning.

Methods of performing RIPC, timing, anaesthesia, surgical procedures, and patient populations differed, and this was of concern when comparing the trials in this meta-analysis. Furthermore, low event rates for clinical outcomes, especially death, prevented meaningful comparison between trials and statistical power was generally low (only 5 RCTs in this review included more than 200 patients). RIS values determined by TSA were 3150, 4263, 7484, and 33 003 to confirm or reject any effect of RIPC on serious cardiovascular events, acute kidney injury, short-term and long-term mortality respectively. These numbers are similar to those of TSA in another meta-analysis[6].

Small proof-of-concept studies reported an effect of RIPC on several biomarkers, although not enough to demonstrate a clinical effect. Trials measuring oxidative stress markers (5 of 6 trials[29,44,47,48,65]), markers of neurological injury (6 of 7 trials[36,38,39,41,58,67]), markers of lung injury (5 of 6 trials[29,38,44,65,66]), and markers of renal injury in nephrectomy (3 of 3 trials[50,54,55]) reported positive results of RIPC. Only one trial[29] investigated markers of intestinal injury, with positive results.

Several trials lacked detailed information on the choice of anaesthesia, which is believed to have an impact on the effect on RIPC. Propofol may inhibit, whereas sevoflurane might preserve, myocardial protection afforded by RIPC[86,87]. However, a recent study[88] investigated the effect of RIPC on humans in settings of anaesthesia with propofol, sevoflurane or carvedilol before RIPC (no anaesthesia) and a control group. Plasma was perfused through an isolated rat heart subjected to 30 min of ischaemia and 60 min of reperfusion; thereafter, myocardial infarct size was determined. Controls not exposed to either propofol, sevoflurane or carvedilol had significantly reduced myocardial infarct sizes after RIPC, suggesting that all three agents blocked the effect of RIPC[88].

RIPC is believed to exert both early and late protection; the early phase of protection lasts only a few hours after the RIPC stimulus, and is followed 24 h later by a second window lasting for up to 48 h[89]. Most trials in this review applied RIPC after induction of anaesthesia; nevertheless one trial[55] also applied RIPC to investigate the late-phase protection, and reported significant results and a more prominent protection than that seen in the early phase. One trial[36] exposed subjects to RIPC twice daily for 2 weeks before carotid artery stenting, with positive results in terms of the incidence and volume of new ischaemic lesions in the brain after stenting. Another trial[60] also reported a significant effect of RIPC applied after the laparotomy incision. This trial involved patients undergoing liver resections, and in all patients the Pringle manoeuvre was used to avoid blood loss, which itself might work as a preconditioning stimulus. This consideration is also relevant in vascular surgery, where the cross-clamping techniques might exert a preconditioning stimulus, leading to underestimation of the effect in the intervention groups compared with controls[31,33–35].

Heterogeneity in RIPC procedures across trials (timing, duration, and number of cycles) was notable, ranging from one cycle of 5 min to two cycles of 10 min on one leg after another, to four cycles of 5 min of ischaemia and reperfusion[24,37,51]. An experimental study[90] has shown that the effects of RIPC differ depending on the number and duration of cycles. It even seems that prolonged cycles lasting 10 min can abrogate the protective

effect[90]. Furthermore, differences in eligibility criteria are of concern when comparing trials. For instance, co-morbidities such as hypercholesterolaemia and diabetes have been shown to interfere with the efficacy of RIPC[91–94], as has advanced age[95].

In general, the trials in this review had a low overall risk of bias, but most had small sample sizes and funnel plots revealed signs of publication bias, particularly among trials reporting on cardiovascular events. Furthermore, many of the trials were underpowered in terms of exploring any impact RIPC might have on postoperative clinical outcomes, and several studies did not report anaesthetic regimens in detail.

The evidence remains insufficient to reach a firm conclusion on the effects of RIPC in non-cardiac surgery. Further understanding of the mechanisms underlying RIPC is required to design a trial with sufficient statistical power, using an optimal RIPC process, with relevant eligibility criteria and using optimal anaesthesia.

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Supplementary material

Supplementary material is available at *BJS Open* online

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