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META-ANALYSIS

Remote Ischemic Preconditioning Reduces Acute Kidney Injury After Cardiac Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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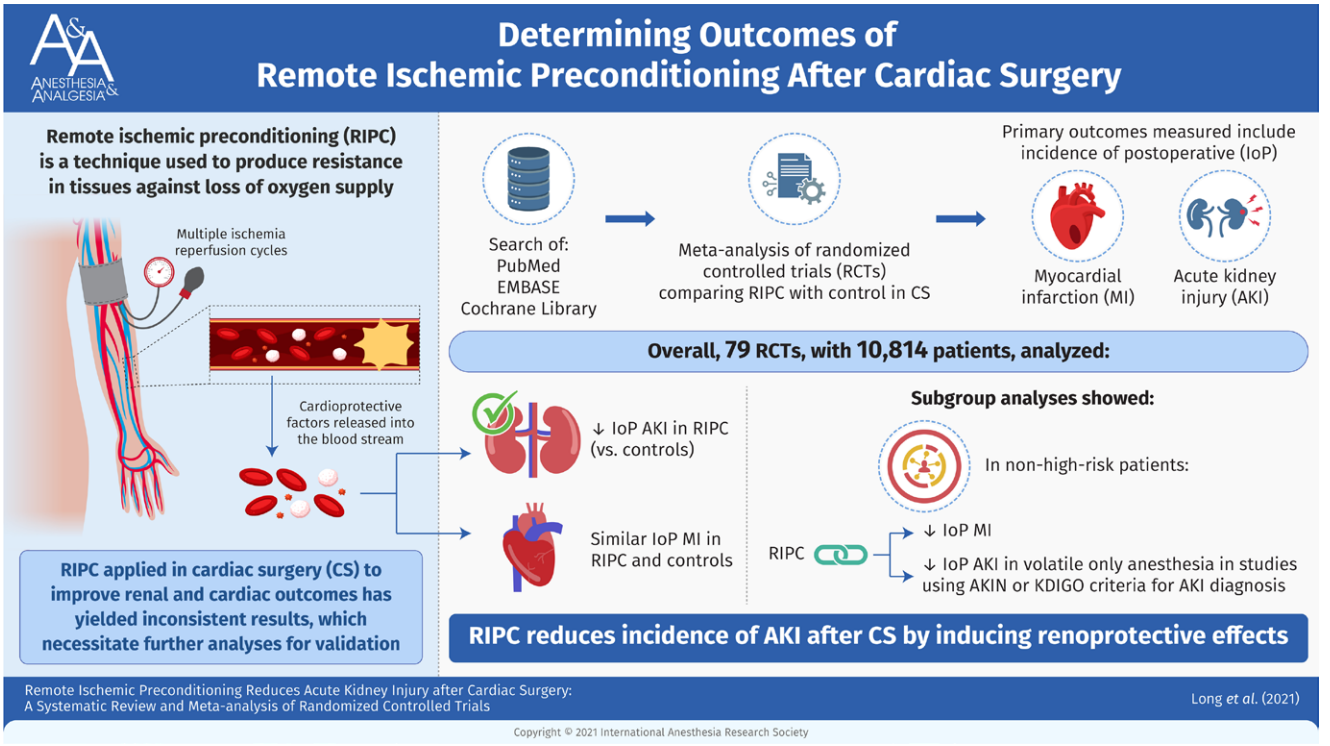

BACKGROUND: Results from previous studies evaluating the effects of remote ischemic preconditioning (RIPC) on morbidity and mortality after cardiac surgery are inconsistent. This meta-analysis of randomized controlled trials (RCTs) aims to determine whether RIPC improves cardiac and renal outcomes in adults undergoing cardiac surgery.

METHODS: PubMed, EMBASE, and Cochrane Library were comprehensively searched to identify RCTs comparing RIPC with control in cardiac surgery. The coprimary outcomes were the incidence of postoperative myocardial infarction (MI) and the incidence of postoperative acute kidney injury (AKI). Meta-analyses were performed using a random-effect model. Subgroup analyses were conducted according to volatile only anesthesia versus propofol anesthesia with or without volatiles, high-risk patients versus non–high-risk patients, and Acute Kidney Injury Network (AKIN) or Kidney Disease Improving Global Outcomes (KDIGO) criteria versus other criteria for AKI diagnosis.

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Reprints will not be available from the authors.

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RESULTS: A total of 79 RCTs with 10,814 patients were included. While the incidence of postoperative MI did not differ between the RIPC and control groups (8.2% vs 9.7%; risk ratio [RR] = 0.87, 95% confidence interval [CI], 0.76–1.01, $P = .07$, $I^2 = 0\%$), RIPC significantly reduced the incidence of postoperative AKI (22% vs 24.4%; RR = 0.86, 95% CI, 0.77–0.97, $P = .01$, $I^2 = 34\%$). The subgroup analyses showed that RIPC was associated with a reduced incidence of MI in non–high-risk patients, and that RIPC was associated with a reduced incidence of AKI in volatile only anesthesia, in non–high-risk patients, and in the studies using AKIN or KDIGO criteria for AKI diagnosis.

CONCLUSIONS: This meta-analysis demonstrates that RIPC reduces the incidence of AKI after cardiac surgery. This renoprotective effect of RIPC is mainly evident during volatile only anesthesia, in non–high-risk patients, and when AKIN or KDIGO criteria used for AKI diagnosis. (Anesth Analg 2022;134:592–605)

KEY POINTS

- **Question:** Does remote ischemic preconditioning (RIPC) reduce myocardial infarction (MI) and acute kidney injury (AKI) after cardiac surgery?
- **Findings:** While this meta-analysis did not show a significant decrease in the incidence of postoperative MI (8.2% vs 9.7%), RIPC significantly reduced the incidence of postoperative AKI (22% vs 24.4%), especially in volatile only anesthesia, in non–high-risk patients, and with the use of Acute Kidney Injury Network (AKIN) or Kidney Disease Improving Global Outcome (KDIGO) criteria for AKI diagnosis.
- **Meaning:** RIPC can be considered for the purpose of reducing AKI after cardiac surgery.

GLOSSARY

AKI = acute kidney injury; **AKIN** = Acute Kidney Injury Network; **CI** = confidence interval; **CKMB** = creatine kinase-MB; **cTnI/TnT** = cardiac troponin I/troponin T; **eGFR** = estimated glomerular filtration rate; **eNOS** = endothelial nitric oxide synthase; **ICU** = intensive care unit; **KDIGO** = Kidney Disease Improving Global Outcomes; **M-H** = Mantel-Haenszel; **MACCE** = major adverse cardiac and cerebrovascular events; **MI** = myocardial infarction; **NGAL** = neutrophil gelatinase–associated lipocalin; **POCD** = postoperative cognitive dysfunction; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PROSPERO** = International Prospective Register of Systematic Reviews; **RCT** = randomized controlled trial; **RIFLE** = Risk, Injury, Failure, Loss, End-stage renal failure; **RIPC** = remote ischemic preconditioning; **RR** = risk ratio; **s.e.** = standard error; **SMD** = standard mean difference; **STAT3** = signal transducer and activator of transcription 3; **STAT5** = signal transducer and activator of transcription 5; **WMD** = weighted mean difference

Myocardial and kidney injury are common in cardiac surgery, leading to increased postoperative morbidity and mortality.[1,2] Remote ischemic preconditioning (RIPC), a process of brief and repeated ischemia-reperfusion in the peripheral sites such as upper or lower extremities, has been shown to protect against subsequent organ injury.[3] Many studies have investigated the effects of RIPC on postoperative outcomes after cardiac surgery. Several studies reported that RIPC may provide myocardial and renal protection, whereas others argued that RIPC did not have significant impact on postoperative outcomes.[4–8]

The results from previous meta-analyses are also inconsistent. A meta-analysis of 21 randomized controlled trials (RCTs) showed that RIPC did not reduce postoperative morbidity or mortality after cardiac surgery; however, RIPC was associated with a reduced incidence of acute kidney injury (AKI) in the subgroup of volatile anesthesia.[9] In another meta-analysis, RIPC reduced cardiac troponin I/troponin T (cTnI/TnT) release after cardiac surgery, but not the incidence of myocardial infarction (MI), the incidence of AKI, or mortality.[10] Interestingly, subgroup analysis showed that RIPC reduced mortality in patients receiving volatile anesthesia. It is important to note that the previous meta-analyses did not include many recently published trials of RIPC in cardiac surgery.[11–19]

To date, whether RIPC reduces postoperative cardiac and renal complications after cardiac surgery remains inconclusive. Therefore, this systematic review and meta-analysis of RCTs was designed to determine the clinical benefits of RIPC in cardiac surgery, based on the most recent literature. We hypothesized that RIPC would reduce the incidence of postoperative MI and the incidence of postoperative AKI in adult patients undergoing cardiac surgery.

METHODS

Protocol and Registration

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The

PRISMA checklist is shown in Supplemental Digital Content, Table S1, http://links.lww.com/AA/D716. The review protocol was registered on PROSPERO International Prospective Register of Systematic Reviews (CRD42020178863).

Search Strategy

Three reviewers independently searched PubMed, EMBASE, and Cochrane Library from inception to October 12, 2020 using Medical Subject Headings combined with text words, without restrictions of language or publication date (Supplemental Digital Content, Table S2, http://links.lww.com/AA/D716). The same 3 reviewers also manually checked the reference lists of relevant articles for potentially eligible studies. The search results were collated using the EndNote software (version X7.8, Thomson Reuters).

Trial Selection

The inclusion criteria of this meta-analysis were as follows: (1) study design: RCT, (2) study population: adult patients undergoing cardiac surgery, (3) intervention: RIPC in upper and/or lower limbs versus control, and (4) outcomes: postoperative cardiac, renal, neurocognitive, pulmonary, gastrointestinal, and infectious outcomes, mechanical ventilation, length of intensive care unit (ICU) stay, length of hospital stay, and mortality. The exclusion criteria were as follows: (1) non-RCT, (2) duplicate datasets, (3) pediatric patients, or (4) lack of specific outcomes.

Three reviewers independently screened the titles and abstracts of all publications and reviewed full-text articles. Based on the inclusion and exclusion criteria, eligible RCTs were finally included into this meta-analysis. Any discrepancy over trial selection was resolved by a group consensus with another 2 reviewers.

Data Extraction

Three reviewers independently extracted the following data from each included RCT using a standardized form: first author name, publication year, region, comparative groups, number of patients, RIPC protocol, intervention in the control group, type of surgery, type of anesthesia, and outcomes reported. In case of incomplete data, the corresponding authors of the original studies would be contacted. Any disagreement over data extraction was resolved by a group consensus with another 2 authors.

Primary and Secondary Outcomes

The coprimary outcomes were the incidence of postoperative MI and the incidence of postoperative AKI. The secondary outcomes included cardiac outcomes (major adverse cardiac and cerebrovascular events [MACCE], cardiac death, postoperative atrial fibrillation, new onset of atrial fibrillation, ventricular tachycardia or fibrillation, low cardiac output, congestive heart failure, ejection fraction, total cTnI/TnT, and total creatine kinase-MB), renal outcomes (mild and severe AKI, renal failure, need for renal replacement therapy, oliguria, urine output at postoperative 24 hours, estimated glomerular filtration rate, and serum peak of creatinine and neutrophil gelatinase–associated lipocalin [NGAL]), neurocognitive outcomes (stroke, delirium, and postoperative cognitive dysfunction [POCD]), pulmonary outcomes (acute lung injury and respiratory failure), other postoperative outcomes (gastrointestinal complication, shock, wound infection, defibrillation, inotropic use, intra-aortic balloon pump use, reintubation, reoperation for bleeding, readmission, revascularization, and prolonged ventilation), mechanical ventilation time, length of ICU stay, length of hospital stay, and mortality (in-hospital, 30-day, 3–6 months, and ≥1 year after cardiac surgery).

The definitions of AKI included Risk, Injury, Failure, Loss, End-stage renal failure (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO),[21] as well as other criteria reported in the included studies. The mild AKI was defined as stage 1 kidney injury in the AKIN or KDIGO criteria, and "Risk" category in the RIFLE criteria. The severe AKI was defined as stage 2 or 3 kidney injury in the AKIN or KDIGO criteria, and "Injury" or "Failure" category in the RIFLE criteria.

Quality Assessment

Three reviewers independently assessed the methodological quality of each study using the Cochrane Collaboration tool.[22,23] This tool comprises 7 domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The overall risk of bias for each study was rated as high (high risk in one or more domains), low (low risk in all domains), or otherwise unclear. Any discrepancy over quality assessment was resolved by discussion and consensus with another 2 reviewers.

Statistical Analysis

For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. For continuous outcomes, weighted mean differences (WMDs) or standard mean differences (SMDs) with 95% CIs were reported. SMD was chosen for pooling data when the specific parameter measurement varied among trials. A random-effect model was used to model the amount of between-study heterogeneity.[24] Heterogeneity was quantified using the I^2 statistic, with $I^2 > 30\%$ indicating evidence of significant heterogeneity.[23] Publication bias was assessed using Begg's and Egger's tests, and a funnel plot was generated for visual inspection. In

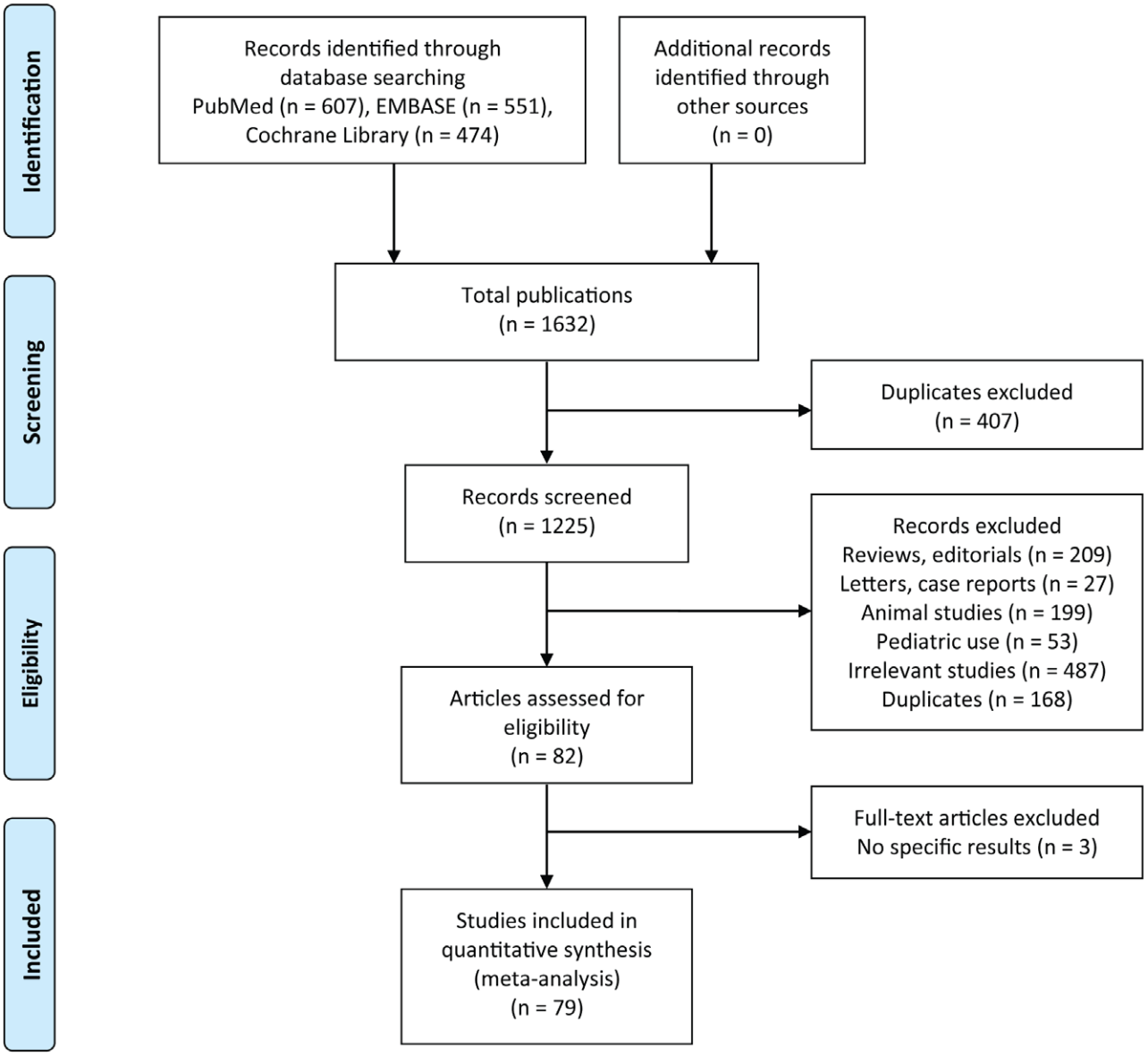

Figure 1. PRISMA flow diagram. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

addition, subgroup analyses were performed for the primary outcomes, according to volatile only anesthesia versus propofol anesthesia with or without a volatile agent, high-risk patients versus non–high-risk patients, and AKIN or KDIGO criteria versus RIFLE or other criteria used for AKI diagnosis.

One review author conducted the meta-analysis, assessed publication bias, and performed subgroup analyses using the RevMan software (version 5.3, Cochrane Collaboration), and all results were checked by another 2 review authors. Considering 2 coprimary outcomes, the significance level was set at 0.025 after adjustment using the Bonferroni method (ie, 0.05/2). For the secondary outcomes of this meta-analysis, no multiple testing adjustment was applied. In this context, the results of the secondary outcomes were reported as estimated effect size with unadjusted *P* value, and no firm clinical inferences could be made based on the secondary outcomes.[25]

RESULTS

Literature Search

The initial search identified 1632 potentially relevant publications. After removal of 407 duplicates in EndNote, 1225 studies were screened for eligibility. According to the inclusion and exclusion criteria, 1146 articles were removed through title and abstract screening. Thereafter, 3 full-text articles were removed due to lack of specific outcomes. Finally, a total of 79 RCTs involving 10,814 patients undergoing cardiac surgery were included in this meta-analysis (Figure 1).[4–8,11–19,26–90]

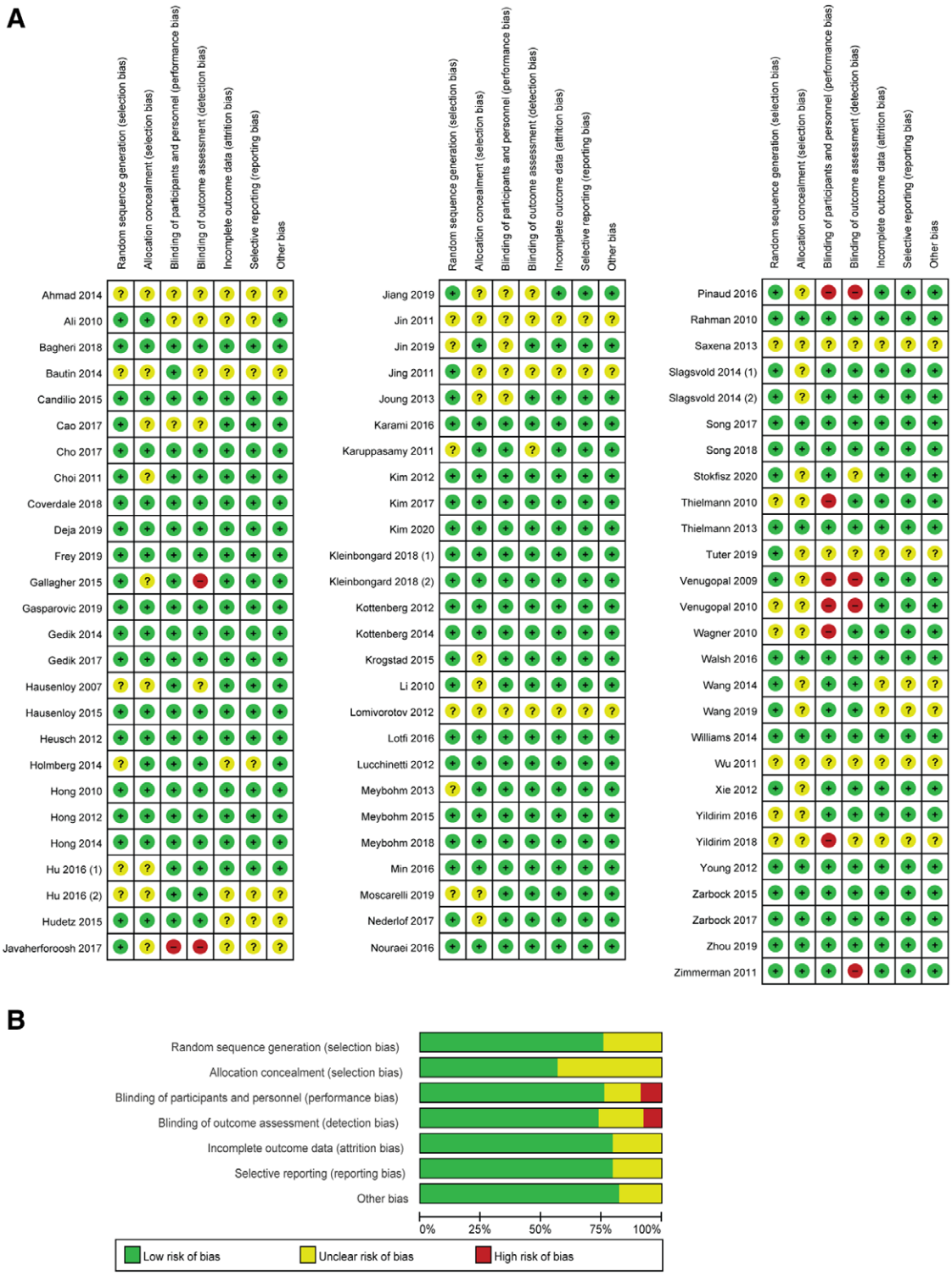

Figure 2. Risk of bias assessment. A, Risk of bias summary. B, Risk of bias graph.

Trial Characteristics

Supplemental Digital Content, Table S3, http://links.lww.com/AA/D716, shows the characteristics of the RCTs comparing RIPC with control in cardiac surgery for at least one of the outcomes designated in the inclusion criteria. These trials were conducted in 20 countries: 15 trials in Germany, 13 in China, 12 in Korea, 9 in United Kingdom, 4 in Iran, 3 in Norway, 3 in Russia, 3 in United States, 2 in Canada, 2 in New Zealand, 2 in Pakistan, 2 in Poland, 2 in Turkey, 1 in Australia, 1 in Croatia, 1 in Czech, 1 in Denmark, 1 in France, 1 in Netherland, and 1 in 4 countries (Canada, United States, India, and China).

Table 1. Summary of Outcomes

Outcomes	RIPC (n)	Control (n)	Effect size (95% confidence interval)	*P* value	I^2 (%)
Coprimary outcomes[a]					
MI	280/3397	332/3413	RR = 0.87 (0.76–1.01)	.07	0
AKI	790/3587	881/3613	RR = 0.86 (0.77–0.97)	.01	34
Secondary outcomes[b]					
Cardiac outcomes					
MI ≥1 y	231/2137	279/2140	RR = 0.76 (0.55–1.05)	.10	57
MACCE	210/1640	249/1647	RR = 0.71 (0.44–1.13)	.15	48
MACCE ≥1 y	310/1607	349/1614	RR = 0.82 (0.60–1.11)	.20	67
Cardiac death	42/1815	43/1824	RR = 0.94 (0.53–1.67)	.83	27
Cardiac death ≥1 y	61/1607	64/1614	RR = 0.66 (0.23–1.91)	.45	81
Total atrial fibrillation	791/2926	833/2941	RR = 0.96 (0.86–1.06)	.41	12
New onset of atrial fibrillation	201/1060	249/1064	RR = 0.77 (0.62–0.96)	.02	14
Ventricular tachycardia/fibrillation	25/827	29/817	RR = 0.91 (0.56–1.45)	.68	0
Low cardiac output	51/347	53/348	RR = 1.01 (0.63–1.61)	.97	26
Congestive heart failure	1/92	2/92	RR = 0.73 (0.05–10.45)	.82	32
Ejection fraction	116	113	WMD = 0.06 (−2.31 to 2.43)%	.96	0
Total cTnI/TnT	2079	2100	SMD = −0.63 (−0.99 to −0.28)	.0004	96
Total CKMB	176	179	SMD = −0.08 (−0.29 to 0.13)	.44	0
Renal outcomes					
Mild AKI	468/2501	528/2536	RR = 0.83 (0.69–1.00)	.06	44
Severe AKI	184/2501	217/2536	RR = 0.83 (0.62–1.13)	.24	40
Renal failure	102/1535	92/1534	RR = 1.11 (0.81–1.51)	.51	15
Renal replacement therapy	32/1225	43/1233	RR = 0.79 (0.43–1.45)	.45	22
Oliguria	6/179	5/183	RR = 1.28 (0.17–9.46)	.81	54
Urine output 24 h	154	154	WMD = 0.32 (−345.69 to 346.33) mL	.99	68
eGFR	129	127	WMD = 12.29 (−5.52 to 30.10) mL/min/1.73 m2	.18	86
Serum creatinine peak	565	576	SMD = −0.27 (−0.53 to −0.01)	.04	76
Serum NGAL peak	250	253	WMD = −46.62 (−93.20 to −0.05) ng/mL	.05	94
Other outcomes					
Stroke	55/3629	57/3648	RR = 0.97 (0.67–1.40)	.86	0
Stroke ≥1 y	59/2241	65/2242	RR = 0.91 (0.64–1.30)	.61	0
Delirium	227/835	236/835	RR = 0.97 (0.83–1.13)	.65	0
POCD	94/240	95/234	RR = 0.93 (0.75–1.15)	.51	0
Acute lung injury	97/249	124/247	RR = 0.77 (0.63–0.94)	.01	0
Respiratory failure	47/866	60/863	RR = 0.78 (0.54–1.13)	.20	0
Shock	110/1480	105/1441	RR = 1.02 (0.79–1.31)	.87	0
Gastrointestinal complication	7/724	11/716	RR = 0.63 (0.25–1.62)	.34	0
Wound infection	8/879	20/885	RR = 0.41 (0.18–0.94)	.03	0
Defibrillation	25/89	20/86	RR = 1.22 (0.75–2.00)	.42	0
Inotropic use	895/1925	839/1888	RR = 1.04 (0.98–1.10)	.22	0
Intra-aortic balloon pump	29/1101	26/1068	RR = 1.06 (0.64–1.78)	.81	0
Reintubation	15/297	12/294	RR = 1.17 (0.55–2.49)	.68	0
Reoperation for bleeding	76/1922	84/1918	RR = 0.93 (0.69–1.27)	.65	0
Readmission	11/78	9/79	RR = 1.24 (0.54–2.82)	.61	0
Revascularization	9/1080	12/1095	RR = 0.77 (0.33–1.80)	.55	0
Prolonged ventilation	21/316	42/318	RR = 0.52 (0.28–0.97)	.04	13
Ventilation time	2300	2291	WMD = −0.57 (−0.96 to −0.18) h	.004	58
Length of ICU stay	3692	3689	WMD = −0.12 (−0.23 to −0.01) d	.03	92
Length of hospital stay	3711	3714	WMD = −0.12 (−0.33 to 0.09) d	.26	57
Mortality					
In-hospital	36/2632	41/2636	RR = 0.88 (0.56–1.39)	.59	0
30 d postoperatively	36/2490	44/2494	RR = 0.89 (0.57–1.39)	.61	0
3–6 mo postoperatively	40/1088	36/1091	RR = 1.13 (0.73–1.75)	.59	0
1 y and longer postoperatively	149/2638	155/2643	RR = 0.90 (0.63–1.30)	.58	48

Abbreviations: AKI, acute kidney injury; CKMB, creatine kinase-MB; cTnI/TnT, cardiac troponin I/T; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NGAL, neutrophil gelatinase–associated lipocalin; POCD, postoperative cognitive dysfunction; RIPC, remote ischemic preconditioning; RR, risk ratio; SMD, standard mean difference; WMD, weighted mean difference.

[a]For the 2 primary outcomes, the significance level is $P < .025$ after adjustment with Bonferroni correction.

[b]For the secondary outcomes, estimated effect size with unadjusted *P* value is reported, without multiple testing adjustment.

Among the 79 included RCTs, 69 trials used 3 or 4 cycles of 5-minute ischemia (an inflation pressure of 200–300 mm Hg, or 20–40 mm Hg above the systolic blood pressure) and 5-minute reperfusion in the upper or lower limb,[4–8,11,13–18,26–29,31,33–44,46–50,52,54–59,61–77,79–81,83–90] 4 trials applied 3 cycles of 5-minute ischemia (600 mm Hg) and 5-minute reperfusion in the lower limb,[19,45,60,82] 3 trials used 3 cycles of 10-minute ischemia (200–250 mm Hg) and 10-minute reperfusion in the lower limb,[32,53,78] 2 trials utilized 2 cycles of 5-minute ischemia (200 mm Hg) and 5-minute reperfusion in both arm and thigh,[12,30] and 1 trial used 3 cycles of 5-minute ischemia (100 mm

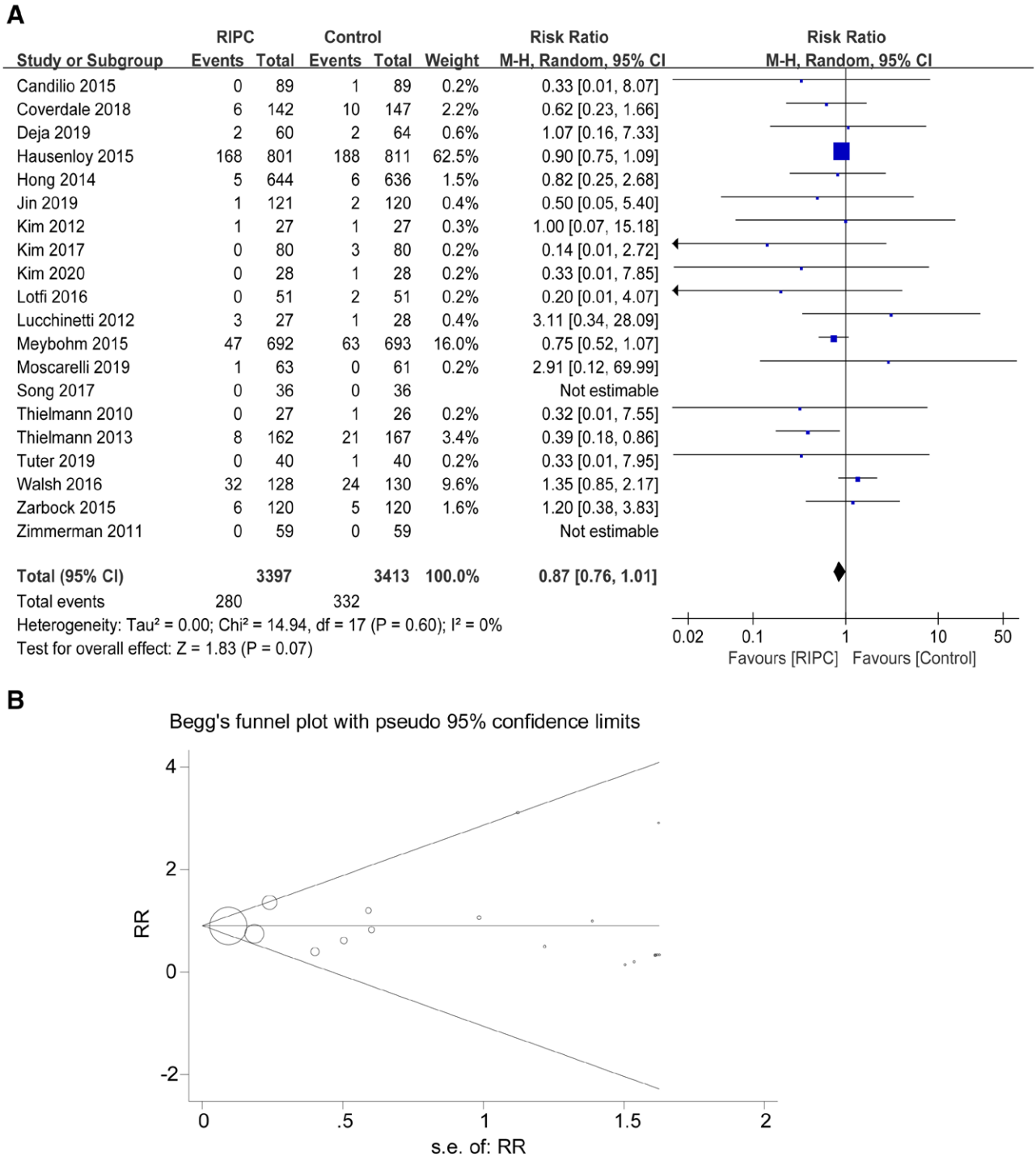

Figure 3. Effect of RIPC versus control on myocardial infarction after cardiac surgery. A, Forest plot. B, Begg's funnel plot. CI indicates confidence interval; M-H, Mantel-Haenszel; RIPC, remote ischemic preconditioning; RR, risk ratio; s.e., standard error.

Hg above the systolic blood pressure) and 5-minute reperfusion in both arm and thigh.[51] All studies compared RIPC with a sham procedure (a deflated cuff or inflation pressure ≤20 mm Hg), except that 2 studies did not report on details of interventions in the control group.[42,78] In 37 trials, anesthesia was maintained with a volatile agent only (sevoflurane or isoflurane),[8,14,15,26,30–32,35–39,41–43,46,47,49,51–53,55,56,60–63,68,70,72–75,83,84,86,90] while the other trials used propofol anesthesia with or without a volatile. The risk of bias was low for 38 trials,[4–8,11,14–18,28,30,33–35,37–39,41,43,44,51,53–58,62,63,65,66,69,71,75,84,89] unclear for 32 trials,[12,13,19,26,27,29,31,32,40,42,45,46,48–50,52,59–61,64,67,68,72–74,76,78,82,83,85–87] and high for 9 trials (Figure 2).[36,47,70,77,79–81,88,90]

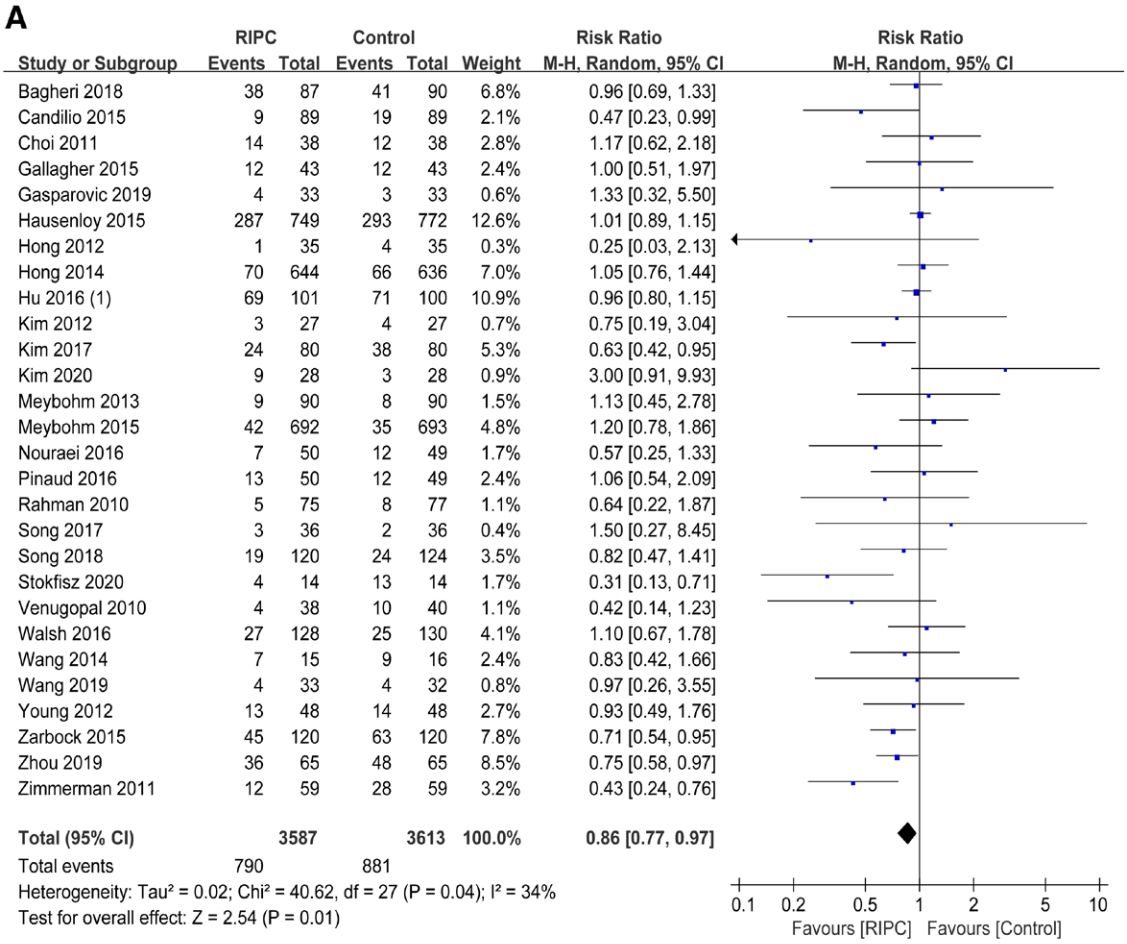

Figure 4. Effect of RIPC versus control on acute kidney injury after cardiac surgery. A, Forest plot. B, Begg's funnel plot. CI indicates confidence interval; M-H, Mantel-Haenszel; RIPC, remote ischemic preconditioning; RR, risk ratio; s.e.,standard error.

Effects of RIPC on Postoperative MI and AKI

The effects of RIPC on postoperative outcomes are summarized in Table 1. Postoperative MI occurred in 280 of 3397 (8.2%) patients in the RIPC group, as compared to 332 of 3413 (9.7%) in the control group (RR = 0.87, 95% CI, 0.76–1.01, P = .07, I^2 = 0%; Figure 3A). There was no publication bias based on Begg's funnel plot (P = .82; Figure 3B) or Egger's test (P = .96) for this outcome. Supplemental Digital Content, Table S4, http://links.lww.com/AA/D716, shows the definition criteria for postoperative MI in the included studies.

Table 2. Subgroup Analyses for Postoperative MI and AKI

Outcomes	RIPC (n)	Control (n)	Risk ratio (95% CI)	*P* value	I^2 (%)	*P* interaction
MI						
Volatile only	10/409	10/410	1.07 (0.44–2.57)	.88	0	.65
Propofol with or without volatile	270/2988	322/3003	0.87 (0.74–1.01)	.06	1	
High-risk patients	212/1191	227/1208	0.97 (0.78–1.20)	.77	10	.05
Non–high-risk patients	68/2206	105/2205	0.68 (0.50–0.91)	.009	0	
AKI						
Volatile only	138/648	183/650	0.76 (0.63–0.92)	.006	4	.18
Propofol with or without volatile	652/2939	698/2963	0.90 (0.78–1.02)	.11	39	
High-risk patients	420/1153	455/1178	0.89 (0.75–1.04)	.15	38	.63
Non–high-risk patients	370/2434	426/2435	0.84 (0.71–0.99)	.03	35	
AKIN or KDIGO criteria	651/2027	747/2059	0.83 (0.72–0.95)	.006	44	.09
RIFLE or other criteria	139/1560	134/1554	1.03 (0.83–1.30)	.76	0	

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes; MI, myocardial infarction; RIFLE, Risk, Injury, Failure, Loss, End-stage renal failure; RIPC, remote ischemic preconditioning.

Compared with controls, RIPC led to a significantly reduced incidence of postoperative AKI (790 of 3587, 22.0% vs 881 of 3613, 24.4%; RR = 0.86, 95% CI, 0.77–0.97, $P = .01$, $I^2 = 34\%$; Figure 4A). No evidence of publication bias was detected with the Begg's funnel plot ($P = .92$; Figure 4B) or Egger's test ($P = .62$). Supplemental Digital Content, Table S5, http://links.lww.com/AA/D716, shows the definition criteria for postoperative AKI in the included studies. Among the 28 included RCTs, 21 studies used the AKIN or KDIGO criteria for AKI diagnosis, and 24 studies assessed AKI during the early postoperative days (ie, a timeframe for AKI diagnosis of 48–72 hours in 17 studies and 4–7 days in 7 studies).

Effects of RIPC on the Secondary Outcomes

For the cardiac outcomes, RIPC was associated with a reduced incidence of new onset of atrial fibrillation (RR = 0.77, 95% CI, 0.62–0.96; Supplemental Digital Content, Figure S1, http://links.lww.com/AA/D716) and a decrease in total cTnI/TnT level (SMD = −0.63, 95% CI, −0.99 to −0.28; Table 1). For the renal outcomes, RIPC was associated with reduced serum peak creatinine (SMD = −0.27, 95% CI, −0.53 to −0.01) and peak NGAL (WMD = −46.62 ng/mL, 95% CI, −93.20 to −0.05 ng/mL) after cardiac surgery (Supplemental Digital Content, Figure S2, http://links.lww.com/AA/D716). In addition, RIPC was associated with reduced incidences of acute lung injury (RR = 0.77, 95% CI, 0.63–0.94) and wound infection (RR = 0.41, 95% CI, 0.18–0.94), less patients with prolonged ventilation (RR = 0.52, 95% CI, 0.28–0.97), and reduced ventilation time (WMD = −0.57 hours, 95% CI, −0.96 to −0.18; Supplemental Digital Content, Figure S3, http://links.lww.com/AA/D716) and length of ICU stay (WMD = −0.12 days, 95% CI, −0.23 to −0.01; Supplemental Digital Content, Figure S4, http://links.lww.com/AA/D716). The results of postoperative mortality were comparable between groups, including in-hospital mortality (1.4% vs 1.6%) and postoperative mortality at 30 days (1.4% vs 1.8%), during 3 to 6 months, and after 1 year (5.6% vs 5.9%).

Subgroup Analyses

Table 2 shows the subgroup analyses for the primary outcomes of postoperative MI and AKI. The incidence of MI did not differ between the RIPC and control groups in either anesthesia type subgroup (Supplemental Digital Content, Figure S5, http://links.lww.com/AA/D716). RIPC led to a significantly reduced incidence of MI in non–high-risk patients (RR = 0.68, 95% CI, 0.50–0.91, $P = .009$, $I^2 = 0\%$), other than in high-risk patients (Supplemental Digital Content, Figure S6, http://links.lww.com/AA/D716). The patients' risk profile is shown in Supplemental Digital Content, Table S6, http://links.lww.com/AA/D716.

For the incidence of AKI, RIPC was associated with a lower AKI incidence in the subgroup of volatile only anesthesia (RR = 0.76, 95% CI, 0.63–0.92, $P = .006$, $I^2 = 4\%$) (Supplemental Digital Content, Figure S7, http://links.lww.com/AA/D716), in the subgroup of non–high-risk patients (RR = 0.84, 95% CI, 0.71–0.99, $P = .03$, $I^2 = 35\%$) (Supplemental Digital Content, Figure S8, http://links.lww.com/AA/D716), and in the subgroup of AKIN or KDIGO criteria used for AKI diagnosis (RR = 0.83, 95% CI, 0.72–0.95, $P = .006$, $I^2 = 44\%$; Supplemental Digital Content, Figure S9, http://links.lww.com/AA/D716).

DISCUSSION

This meta-analysis included 79 RCTs with 10,814 patients to investigate the cardiac and renal benefits of RIPC in cardiac surgery. While there was no significant difference in the incidence of postoperative MI between the RIPC and control groups, RIPC led to a significantly lower incidence of postoperative AKI after cardiac surgery. In addition, RIPC may reduce the incidence of new onset of atrial fibrillation, total cTnI/TnT levels, peak levels of serum creatinine and NGAL, acute lung injury, wound infection, mechanical ventilation time, and length of ICU stay. Furthermore, the subgroup analyses showed that RIPC was associated with a reduced incidence of MI in non–high-risk patients, and a reduced incidence of AKI in volatile only anesthesia,

in non–high-risk patients, and in the studies using AKIN or KDIGO criteria for AKI diagnosis.

RIPC is a simple and promising strategy that can be used to protect major organs and improve outcomes after cardiac surgery. The application of RIPC is safe, without significant local adverse events. Because most cardiac surgical patients have preoperative existing comorbidities which are associated with increased risks for postoperative morbidity and mortality, the additional benefits provided by RIPC are particularly welcome. Although the precise mechanism of RIPC is not fully understood, it is likely that the protective signal is activated at the remote site and thereafter transfers to the target organs through both neuronal and humoral pathways. Jones et al[91] showed that an abdominal incision induced peripheral nociception and produced remote nonischemic myocardial protection by neurogenic activation of protein kinase C signaling. In addition, humoral pathways have been observed. Adenosine, bradykinin, cytokines, and chemokines which are induced locally by ischemic preconditioning activate specific receptors during signal transduction.[92,93] A recent study reported that RIPC improved heart function after tetralogy of Fallot repair surgery, suggesting that the protective mechanism of RIPC is the improved mitochondrial function and increased expression of hypoxia inducible factor-1α and phosphorylated protein kinase B, signal transducer and activator of transcription 3 (STAT3), signal transducer and activator of transcription 5 (STAT5) and endothelial nitric oxide synthase (eNOS).[94]

AKI is a major complication after cardiac surgery, which occurs in 20% to 70% of patients undergoing cardiac surgical procedures and accounts for up to 60% of all-cause mortality.[95] This meta-analysis revealed that patients receiving RIPC had improved postoperative renal outcomes, as reflected by the reduced incidence of AKI and the decreased peak levels of serum creatinine and NGAL. However, there was a significant heterogeneity (I^2 = 34%) among the included studies for the AKI result, possibly due to different AKI definitions, different RIPC protocols, varied surgical procedures, and different anesthetic agents. Regarding the types of AKI, we found a similar therapeutic effect of RIPC versus control on mild AKI (RR [95% CI] = 0.83 [0.69–1.00]) and severe AKI (RR [95% CI] = 0.83 [0.62–1.13]). However, the significant level was not reached in either mild or severe AKI result, and that is possibly due to an insufficient power for each of these AKI types.

While our results showed that RIPC significantly reduced the incidence of AKI (22% vs 24.4%; an absolute difference of 2.4%) with a combined sample size of approximately 7200, the between-group difference in MI is nonsignificant. The risk of MI was 8.2% in the RIPC group versus 9.7% in the control group (an absolute difference of 1.5%), which is close in magnitude to the AKI result. It is possible that the current sample size for MI is still not enough to achieve a statistically significant level. Regarding the possible mechanism, there may be an important difference between the effects of RIPC on MI and its effects on AKI. While the heart undergoes a process of cardiopulmonary bypass with consecutive ischemia-reperfusion injury, the kidney does not. That said, our meta-analysis showed that the incidence of AKI (22%–24.4%) was much higher than MI (8.2%–9.7%), suggesting that the renal tissues are susceptible to hypoperfusion during cardiopulmonary bypass. Taken together, our results support the use of RIPC in cardiac surgical patients to protect the kidneys and help to protect the hearts.

Volatile anesthetic agents mimic the early phase of ischemic preconditioning and produce a synergistic effect with RIPC, contributing to the protection of major organ function.[96] A previous meta-analysis showed that RIPC reduced the incidence of AKI after cardiac surgery when propofol was not used, which was based on 3 trials only.[9] A later meta-analysis of 4 trials showed that RIPC reduced mortality after cardiac surgical patients receiving volatile anesthesia.[10] Our meta-analysis found that RIPC was associated with a significantly reduced incidence of postoperative AKI, other than MI, in the subgroup of volatile only anesthesia. Regarding the patients' risk profile, some studies showed that high-risk patients undergoing cardiac surgery may especially benefit from RIPC.[8,11,15] However, our subgroup analysis revealed that RIPC was associated with reduced incidences of MI and AKI in non–high-risk patients, other than in high-risk patients. It is possibly because the presence of severe preexisting comorbidities in high-risk patients hampers RIPC-induced activation of protective signaling. Regarding different AKI definition criteria, the use of AKIN or KDIGO considering a small increase in serum creatinine (>0.3 mg/dL) over time (>48 hours) contributed to the detection of AKI. Hence, the present meta-analysis suggests that the benefits of RIPC in cardiac surgery may depend on the choice of anesthetic agent and patients' risk profile, and we support further studies to investigate the exact mechanisms underlying these phenomena.

There are several limitations. First, the definitions of postoperative complications were not uniform among the included trials, which may have confounded the current results. Second, while RIPC led to a significantly reduced AKI incidence after cardiac surgery, this meta-analysis may be underpowered to detect any between-group differences in other outcomes including the incidence of postoperative MI. Third, regarding the reduced incidence of AKI associated with RIPC, the significant heterogeneity among the included studies suggests that considerations are still needed when interpreting this result. Fourth, our study did not obtain the individual patient data to evaluate the effects of RIPC on the outcomes after cardiac surgery. Therefore, further large clinical trials of RIPC in cardiac surgery are desirable to corroborate our findings.

CONCLUSIONS

This comprehensive systematic review and meta-analysis demonstrates that RIPC reduced the incidence of AKI in patients undergoing cardiac surgery. This renoprotective effect of RIPC is mainly evident during volatile only anesthesia, in non–high-risk patients, and when AKIN or KDIGO criteria used for AKI diagnosis.

DISCLOSURES

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