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Systematic Review

Hypertensive status is associated with renoprotection by remote ischemic conditioning for acute myocardial infarction—a meta-regression and trial sequential analysis of randomized clinical trials

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Abstract

The potential modifiable factors for remote ischemic conditioning (RIC) in reducing contrast-associated acute kidney injury (CA-AKI) in patients with acute myocardial infarction (AMI) have not been investigated. The aim of this meta-regression was to address these issues.We searched Pubmed, Embase and the Cochrane Library database for published randomized controlled trials (RCTs) with registration number CRD42020155532. Nine RCTs comprising of 1540 subjects were included in our meta-analysis. Compared with control group, RIC was associated with reduced incidence of CA-AKI [(9 studies, 1540 subjects, relative risk (RR) 0.51, 95% confidence intervals (CI) 0.35 to 0.76, $p = 0.000$, $I^2 = 52\%$, p for heterogeneity 0.04)] and major adverse cardiovascular events (MACE) (5 studies, 1078 subjects, RR 0.52, 95% CI 0.38 to 0.73, $p = 0.000$, $I^2 = 9\%$, p for heterogeneity 0.36) for AMI. In addition, both meta-regression and subgroup analyses have shown that RIC was more effective in the hypertensive patients in reducing CA-AKI for AMI (regression coefficient = –0.05, $p = 0.021$; for subgroup with more hypertensive patients: RR 0.36, 95% CI 0.25 to 0.52 vs the one with less hypertensive patients: RR 0.72, 95% CI (0.40 to 1.30, p for subgroup difference 0.008). Subsequent trial sequential analysis confirmed the effect of RIC in both CA-AKI and MACE. RIC is an effective strategy in reducing CA-AKI and MACE in patients with AMI, especially for patients with hypertension.

Keywords: RIC; AMI; CA-AKI; meta-analysis

1.Introduction

Acute myocardial infarction (AMI) is one of the leading causes of mortality and morbidity globally. Emergency percutaneous coronary intervention (PCI) was recommended as the standard therapy to perfuse the ischemic myocardium, especially for the ST-segment elevated myocardial infarction (STEMI) [1,2]. However, reperfusion seems like as a double-edged sword, acting the role of rescuing but causing injury for the myocardium. The latter is also known as ischemia-reperfusion injury (IRI) [3]. IRI during emergency PCI not only directly causes damage to heart, but also inducing systematic inflammatory response potentiating the impairment of vital organs such as kidney [4,5].

Contrast-associated acute kidney injury (CA-AKI), as defined by the increment of serum creatinine >44.2 mmoL/L or 25% above the baseline value within 48–72 h of contrast media exposure [6], is a common complication during cardiovascular intervention for reduced renal blood of renal medulla [7,8]. What's more, emergency PCI is more frequently associated with hemodynamic instability which could deteriorate the renal blood infusion. Moreover, patients breaking out with AMI are likely to possess other combined risk factors [9]. Many clinical studies have indicated that CA-AKI not only prolongs the hospitalization but also increases the mortality in long term [10]. Till now, many strategies such as use isotonic contrast agents, cysteine, statins have been tried but failed to show the effective results [11]. Remote ischemic conditioning (RIC), including pre-, per- and post-conditioning, a technique to apply the mild nonlethal ischemia and reperfusion in one organ and protect lethal IRI in other organs or tissues [12]. Accumulating experimental and clinical evidence have reported that RIC was effective in reducing infracted size, attenuating left ventricular remodeling and increasing myocardial salvage after AMI [13–16]. Many studies have reported that RIC is helpful to reduce CA-AKI in patient with stable coronary artery diseases undergoing either elective coronary artery bypass graft (CABG) surgery or PCI [17,18].

However, the effect of RIC on CA-AKI for AMI is still controversial. Some studies have indicated that RIC was helpful in reducing CA-AKI while others did not show the similar results [19–29]. Given the mixed background, we performed a meta-analysis of randomized controlled trials (RCTs) to explore the effect of RIC in reducing CA-AKI as well as to explore the potential factors affecting RIC in renoprotection for AMI.

2. Methods

2.1 Literature search

We reported this meta-analysis following the guidance of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis)statement [30]. We searched Pubmed (Medline), Embase and the Cochrane Library database (http://www.cochrane.org) (up to June 2020) with registration number CRD42020155532. We also manually searched reference lists of the retrieved articles. The key words used in search were (ischemic post-conditioning or post-conditioning or ischemic pre-conditioning or pre-conditioning or remote ischemic conditioning) paired with (myocardial infarction or myocardial injury or percutaneous coronary intervention or acute kidney injury or contrast induced nephropathy).

2.2 Study outcomes and selection

The primary endpoint was CA-AKI, which was diagnosed by increment of serum creatinine >44.2 mmoL/L or above the base value of 25% with 48–72 h exposure of contrast without other obvious factors. The secondary outcome was long-term major adverse cardiovascular events (MACE). The definitions of MACE used by each study and included all cause death, cardiac death, heart failure, revascularization or myocardial infarction.The third outcome was the net change in creatinine or estimate glomerular filtration (eGFR) due to RIC.

Inclusion criteria for the retrieved studies were as follows: (1) prospective RCT design; (2) performed in the patients with AMI (including STEMI and non-STEMI (NSTEMI)); (3) inclusion of outcomes of CA-AKI; (4) inclusion of multivariable-adjusted or unadjusted relative risk (RR)/hazard ratio (HR) and their corresponding 95% confidence intervals (CI); or provided the number of events and total population in each group;

2.3 Quality assessment

Two authors (Yuehua Li and Ying Lou) assessed the quality of the RCTs by the Cochrane criteria including adequacy of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, intention-to-treat analysis and other bias [31]. Trials scored one point for each item addressed. If 3 quality criteria were not met, the study was classified as having high risk of bias; others were classified as having moderate (3–5 points) or low (≥5 points) risk of bias.

2.4 Data extraction

Data were extracted by two independent authors (Yuehua Li and Ying Lou). Discrepancies were resolved by group discussion. The extracted data included source of study (author, publication year, country), population characteristics [protocol, conditioning, patients number, mean age, male proportion, percentage of smoking, diabetes mellitus (DM), hypertension, hyperlipidemia, multi-vessel disease, left anterior descending (LAD)branch involving, use of angiotensin-converting enzyme inhibitor(ACEI)/angiotension receptor blocker (ARB), beta-blocker (BB) and statin, follow-up period], the clinical endpoints, RRs or HRs and their corresponding 95% CI.

2.5 Statistical analysis

We considered the HRs as RRs in the prospective studies. We calculated the RR by the number of events and total population in the RIC and control group. The random-effect model was also used in the pooled analysis for the potential clinical heterogeneity [32]. The heterogeneity was assessed by Q statistic, I^2 and p value ($I^2 > 50\%$, $p < 0.05$ was considered to be statistically significant). If there is no significant heterogeneity, we would use the fixed-effect model. Univariable meta-regression analyses (including age, percentage of male, smoking, DM, hypertension, hyperlipidemia, multi-vessel disease, LAD inclusion, use of ACEI/ARB, BB and statin, protocol time, study quality, area) were conducted to explore the potential sources of heterogeneity [33]. Subgroup analyses we real so conducted to explore the potential sources of heterogeneity by specified study characteristics including area (China or other countries), study quality [high risk (quality score <3 points) or moderate/low risk (quality score ≥3 points)], protocol (conditioning time ≥15 min or <15 min), conditioning (by pre-conditioning or post-conditioning), AMI type (STEMI or NSTEMI) and the mean of the mentioned factor such as age, proportion of smoking, DM, hypertension, hyperlipidemia, multi-vessel disease, LAD occlusion, use of ACEI/ARB, BB and statin [33].

Publication bias was assessed by Begg's test and Egger's test [34]. We performed the trial sequential analyses (TSA) of CA-AKI or MACE following AMI based on the data from our pooled analysis (RR and incidence of CA-AKI and MACE) to calculate the required sample size for the statistical power (Two sided: Type-I error = 0.05; λ = 2.0; Power = 80%). Two sided p value < 0.05 was considered to be significant. All data analyses were performed by STATA software (10.0 version, StataCorporation, TX, USA), REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom) and Trail Sequential Analysis (Copenhagen Trial Unit, Copenhagen, Denmark).

Table 1. Characteristics of included randomized clinical trials.

Study	Country	MItype	Protocol Algorithm	Conditioning	Patients No. (RIC vs control)	Age	Male (%)	Diabetes (%)	Hypertension (%)	Smoking (%)
Deftereos *et al*. 2013 [19]	Greece	NSTEMI	4 × 1 min at lesion site	post-conditioning	113 vs 112	68	64	36	65	29
Crimi *et al*. 2014 [20]	Italy	STEMI	3 × 5 min/5 min at lower limb (200 mmHg)	post-conditioning	47 vs 48	58.5	87.5	12	53.5	53.5
Yamanaka *et al*. 2015 [21]	Japan	STEMI	3 × 5 min/5 min at upper limb (200 mmHg)	pre-conditioning	47 vs 47	67	74.5	33	63.8	55.3
Wang *et al*. 2016 [22]	China	STEMI	3 × 2 min at infarct-related artery	post-conditioning	123 vs 128	62.6	77.7	26.7	65.3	66.9
Cao *et al*. 2018 [24]	China	STEMI	4 × 5 min/5 min at upper limb (200 mmHg)	post-conditioning	36 vs 44	59	86.2	18.8	66.3	NA
Cao*et al*. 2018 [25]	China	STEMI	4 × 5 min/5 min at upper limb (200 mmHg)	post-conditioning	29 vs 35	59.2	87.5	18.8	65.6	71.9
Gaspar *et al*. 2018 [26]	Portugal	STEMI	3 × 5 min/5 min at upper limb (200 mmHg)	pre-conditioning	231 vs 217	60	80.1	27.9	50	58.9
Moretti *et al*. 2018 [27]	Italy	NSTEMI	4 × 5 min/5 min at upper limb (200 mmHg)	pre-conditioning	107 vs 116	72.3	67.2	38.4	89.2	16.7
Zhou *et al*. 2018 [28]	China	ACS	4 × 5 min/5 min at upper limb (200 mmHg)	pre-conditioning	50 vs 57	69.3	60.7	47.7	56.1	20.6
Elbadawi *et al*. 2018 [23]	USA	STEMI	3 × 5 min/5 min at upper limb (200 mmHg)	pre-conditioning	30 vs 30	51.5	83	41	32.4	70.4
Guo *et al*. 2019 [29]	China	NSTEMI	3 × 5 min/5 min at upper limb (200 mmHg)	pre-conditioning	110 vs 110	71.3	59.1	44	NA	NA

Table 2. Coronary involvement, risk factors, medication, and endpoints of included trials.

Study	Dyslipidemia (%)	Muti-vessel disease (%)	LAD occlusion (%)	ACEI/ARB (%)	β-blocker (%)	Statins (%)	CA-AKI (RIC vs control)	MACE
Deftereos *et al*. 2013 [19]	59	55.1	54.2	NA	17	36	14/113 vs 33/112	14/113 vs 25/112
Crimi *et al*. 2014 [20]	31.5	35	100	NA	100	100	7/47 vs 6/48	NA
Yamanaka *et al*. 2015 [21]	55.3	NA	42.6	95.7	5.32	16	5/47 vs 17/47	2/47 vs 7/47
Wang *et al*. 2016 [22]	NA	78.9	NA	NA	NA	NA	7/123 vs 18 /128	9/123 vs 20 /128
Cao *et al*. 2018 [24]	12.5	18.8	46.3	33.8	68.8	100	4/36 vs 18 /47	NA
Cao *et al*. 2018 [25]	20.3	12.5	48.4	42.2	85.9	100	3/29 vs 11/35	NA
Gaspar *et al*. 2018 [26]	50	11.6	44	35.9	15.2	29.2	45/231 vs 45/217	19/231 vs 28/217
Moretti *et al*. 2018 [27]	67.4	NA	NA	NA	NA	NA	10/57 vs 15/54	NA
Zhou *et al*. 2018 [28]	25.2	NA	NA	67.3	72.9	95.3	5/50 vs 15/57	2/50 vs 3/57
Elbadawi *et al*. 2018 [23]	76.7	10	NA	NA	NA	NA	1/30 vs 5/30	4/30 vs 2/30
Guo *et al*. 2019 [29]	NA	35	NA	86.4	75.9	94.5	12/110 vs 18/110	NA

NOTE: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CA-AKI, contrast-induced nephropathy; LAD, left anterior descending; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not available; RIC, remote ischemic conditioning.

Table 3. Univariable meta-regression of baseline characteristics for RIC in reducing CA-AKI for AMI.

Baseline characteristics	Number of trials	Risk of CA-AKI			
		Coefficient	95% CI	I^2 (%)	*p*
Age	10	–0.012	(–0.095 to 0.072)	47.54	0.75
Male proportion	10	0.004	(–0.037 to 0.045)	50.57	0.82
Diabetes proportion	10	–0.010	(–0.051 to 0.031)	50.94	0.59
Hypertension proportion	9	–0.050	(–0.090 to –0.010)	9.01	0.02
Smoking proportion	8	0.003	(–0.029 to 0.034)	55.61	0.83
Dyslipidemia proportion	8	0.002	(–0.030 to 0.034)	62.34	0.88
Multi-vessel disease proportion	8	–0.006	(–0.007 to 0.027)	39.23	0.49
LAD branch occlusion	6	0.016	(–0.023 to 0.056)	71.29	0.31
ACEI/ARB use proportion	6	–0.005	(–0.033 to 0.024)	56.72	0.68
Beta-blocker use proportion	8	0.002	(–0.014 to 0.017)	60.73	0.82
Statin use proportion	8	–0.0004	(–0.015 to 0.014)	59.22	0.95
Protocol	11	0.003	(–0.025 to 0.032)	45.91	0.79
Area	11	–0.366	(–1.082 to 0.349)	36.36	0.28
Conditioning time	11	0.358	(–0.322 to 1.038)	30.92	0.26
Qulity score	11	0.102	(–0.109 to 0.313)	42.71	0.30

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CI, confidence interval; CA-AKI, contrast-associated acute kidney injury; LAD, left anterior descending; RIC, remote ischemic conditioning.

3. Results

3.1 Search results

We initially identified 9223studies by database and manual searching. After exclusion of duplicates and non-relevant studies, 29 potential articles were selected for detailed evaluation. We further excluded 20 articles as shown in Fig. 1. Finally, nine studies were included. Among them, all have reported the impact of RIC on CA-AKI and five about the endpoint of long-term MACE [19,21–23,29].

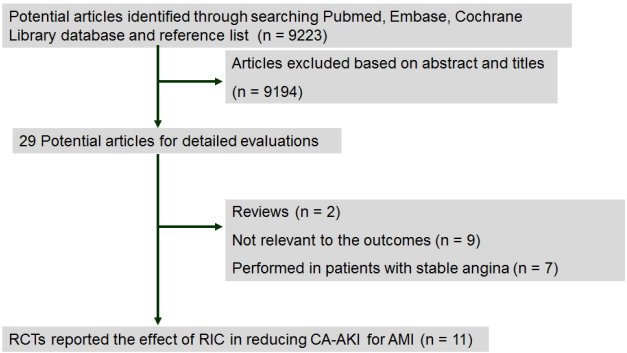

Fig. 1. Flow Chart of the Trial Selection Process. AMI, acute myocardial infarction; CA-AKI, contrast-associated acute kidney injury; RIC, remote ischemic conditioning.

3.2 Study characteristics and data quality

Tables 1,2 (Ref. [19–29]) showed the main characteristics of the data extracted from the included studies. All included studies were randomized and prospective.Three study scored low risk of bias [19–21], three with moderate [23,26,29] and three with high risk of bias [22,24,25] (**Supplementary Fig. 1**).

3.3 Effect of RIC in reducing CA-AKI, MACE, serum creatinine and eGFRin AMI

All studies have reported the endpoint of CA-AKI and five reported the risk of MACE. Compared with the control group, the group with RIC was associated with reduced risk of CA-AKI (9 studies, 1540 subjects, RR 0.51, 95% CI 0.35 to 0.76, $p = 0.007$, $I^2 = 52\%$, p for heterogeneity 0.04) (Fig. 2A) and MACE (5 studies, 1078 subjects, RR 0.52, 95% CI 0.38 to 0.73, $p = 0.0001$, $I^2 = 9\%$, p for heterogeneity 0.36) (Fig. 2B) for patients with AMI. The net change in serum creatinine and eGFR were 0.52 (95% CI 0.38 to 0.53) and 17.96 (95% CI 14.92 to 21.00), respectively (**Supplementary Figs. 2,3**). Given the study by Crimi*et al.* [20] is a post-hoc analysis, we performed sensitivity analysis by excluding this study and found that the group with RIC was also associated with reduced risk of CA-AKI (8 studies, 1445 subjects, RR 0.47, 95% CI 0.32 to 0.71, $p = 0.0003$, $I^2 = 52\%$, p for heterogeneity 0.04).

3.4 Meta-regression and subgroup analysis

For the main endpoint of CA-AKI, we performed both meta-regression and subgroup analyses by specific study

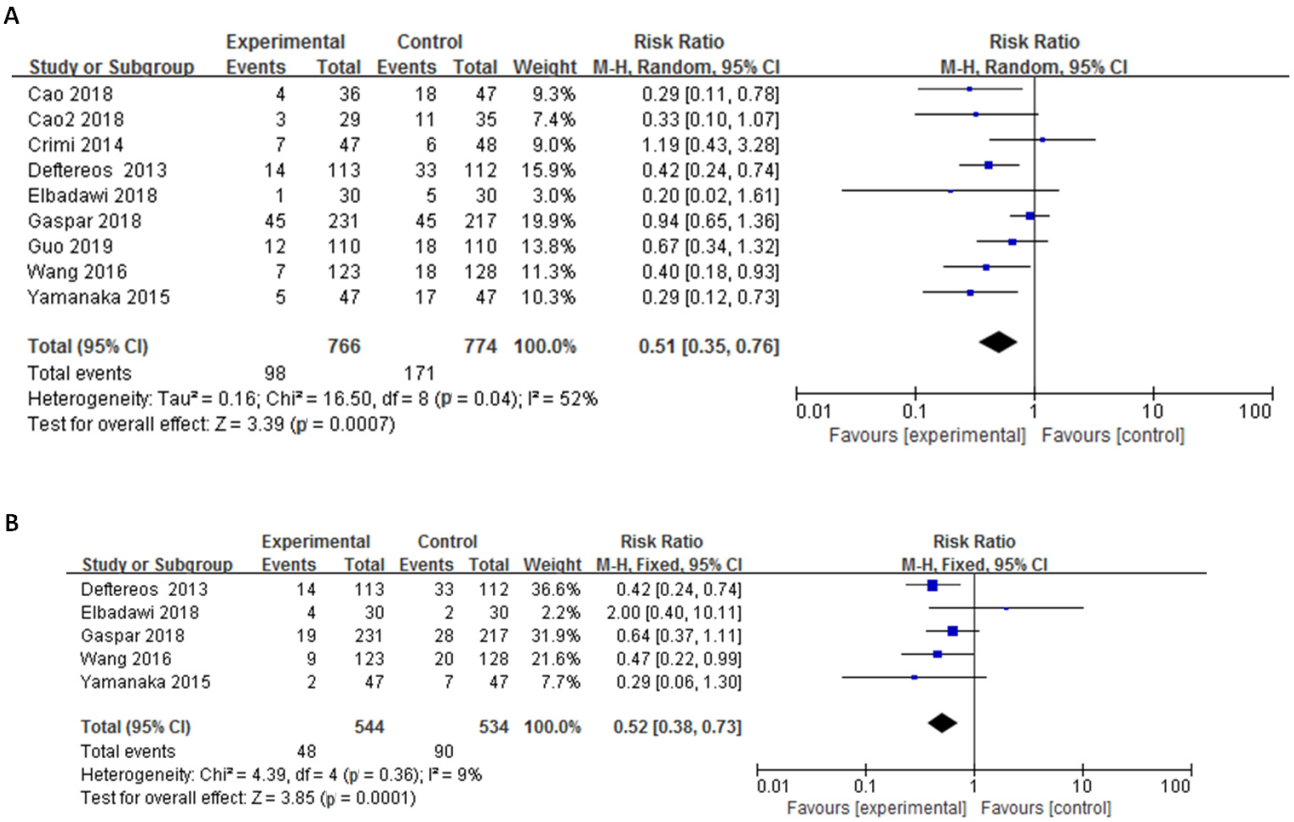

Fig. 2. Funnel plot of RIC in Reducing CA-AKI (2A) and MACE (2B) in AMI. Meta-analysis of the effect of RIC in reducing CA-AKI (A) and risk of MACE (B) in the condition of AMI. AMI, acute myocardial infarction; CI, confidence intervals; CA-AKI, contrast-associated acute kidney injury; MACE, major adverse cardiovascular events; RIC, remote ischemic conditioning.

characteristics which was mentioned above. In univariable meta-regression, the percentage of hypertension at baseline was negatively related to risk of CA-AKI (regression coefficient = –0.05, $p = 0.021$) (Table 2, Fig. 3). This factor was further confirmed by subgroup analysis [for subgroup with hypertensive patients over 58% (mean): RR 0.36, 95% CI 0.25 to 0.52 vsless than 58% (mean): RR 0.72, 95% CI 0.40 to 1.30, p for subgroup difference 0.008] (Table 3). The subgroup analysis also has indicated that the proportion of age, male, DM, conditioning, quality score might be possible modifiable factors, however these factors were not verified by meta-regression analyses (Tables 3,4).

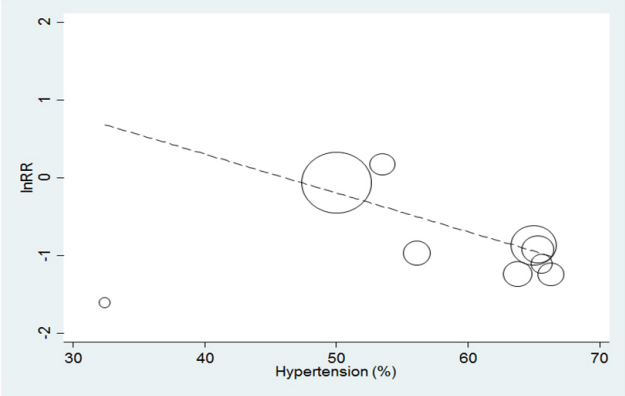

Fig. 3. Meta-regression plot on the incidence of CA-AKI against proportion of hypertension. Meta-regression analysis of the percentage of hypertension as a modifiable factor for CA-AKI. CA-AKI, contrast-associated acute kidney injury; RR, risk ratio.

3.5 Trial sequential analysis

To confirmed the pooled effect sizes of CA-AKI or MACE as true estimated effect, the required sample sizes for the CA-AKI is 959 (RR reduction = 50.0%, incidence of Control arm = 22.0%), and MACE (RR reduction = 50.0%, incidence of Control arm = 17.0%) is 561. However, the same size of CA-AKI (1540 vs 959) or MACE (1078 vs 561) is enough for the estimated effect (**Supplementary Figs. 4,5**).

3.6 Publication bias

The publication bias of CA-AKI was not observed by Begg's adjusted rank correlation test ($p = 0.35$) and Egger's test ($p = 0.06$) (**Supplementary Fig. 6**).

Table 4. Subgroup analysis by specific study characteristics for RIC in reducing CA-AKI for AMI.

Characteristic	Risk of CA-AKI			
	Data points, No	Pooled RR (95% CI)	p^a	p^b
All studies	11	0.52 (0.38 to 0.72)	0.07	
age				
<63	6	0.55 (0.31 to 0.95)	0.491	0.049
≥63	4	0.45 (0.31to 0.64)	0.048	
Male proportion				
<76%	4	0.45 (0.31to 0.64)	0. 048	0.049
≥76%	6	0.55 (0.31 to 0.95)	0.491	
Percentage of hypertension				
<58%	4	0.72 (0.40 to 1.30)	0.156	0.000
≥58%	5	0.36 (0.25 to 0.52)	0.942	
Percentage of diabetes				
<31%	4	0.58 (0.33 to 1.02)	0.042	0.031
≥31%	5	0.44 (0.311 to 0.62)	0.573	
Percentage of multi-vessel diseases				
<32%	4	0.46 (0.20 to 1.05)	0.041	0.215
≥32%	4	0.55 (0.36 to 0.85)	0.262	
Percentage of LAD occlusion				0.205
<56%	5	0.45 (0.25 to 0.89)	0.012	
≥56%	1	1.19 (0.43to 3.29)	0	
Percentage of dyslipidemia				
<41%	4	0.46 (0.24 to 0.87)	0.197	0.230
≥41%	4	0.49 (0.25 to 0.96)	0.016	
Percentage of smoking				
<53%	2	0.41 (0.25 to 0.66)	0.857	0.062
≥53	6	0.54 (0.31 to 0.94)	0.039	
Percentage of ACEI/ARB use				
<60%	3	0.50 (0.21 to 1.22)	0.032	0.094
≥60%	3	0.46 (0.27 to 0.76)	0.310	
Percentage of beta-blocker use				
<55%	3	0.52 (0.26 to 1.07)	0.01	0.343
≥55%	5	0.52 (0.32 to 0.84)	0.244	
Percentage of statin use				
<71%	3	0.52 (0.26 to 1.07)	0.010	0.343
≥71%	5	0.52 (0.32 to 0.84)	0.244	
Study quality				
High risk	6	0.42 (0.29 to 0.63)	0.697	0.044
Moderate/low risk	5	0.62 (0.39 to 1.00)	0.034	
By protocol time				
<15 min	2	0.41 (0.26 to 0.66)	0.923	0.086
≥15 min	9	0.55 (0.38 to 0.80)	0.069	
By conditioning				
Pre-conditioning	5	0.61 (0.40 to 0.92)	0.395	0.035
Post-conditioning	6	0.43 (0.30 to 0.63)	0.097	
By type of myocardial infarction				0.348
STEMI	7	0.49 (0.29 to 0.83)		
NSTEMI	2	0.51 (0.33 to 0.80)		
By area				0.067
China	5	0.44 (0.30 to 0.65)		
others	6	0.59 (0.37 to 0.95)		

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotension receptor blocker; CI, confidence interval; CA-AKI, contrast-associated acute kidney injury; LAD, left anterior descending; NSTEMI, non-STEMI; RIC, remote ischemic conditioning; STEMI, ST-segment elevated myocardial infarction. [a]: p for heterogeneity; [b]: p for subgroup analysis analysis.

4.Discussion

In this meta-analysis of nine RCTs including 1540 subjects, we found that RIC was an effective strategy in reducing the incidence of CA-AKI in patients with AMI, with a profound protection associated with a 0.51-fold lower risk. What's more, our meta-regression showed that the effect of RIC seemed to be more beneficial for the hypertensive patients. In addition, RIC was also showed long-term protective effect with a reduce risk of MACE for long term (RR 0.52). To our knowledge, this is the first meta-regression analysis focusing on the modifiable factors for renoprotection of RIC in AMI patient.

The effect of RIC from previous studies in reducing CA-AKI in patients with AMI was inconsistent. We combined all available RCTs and found that RIC was an effective strategy in preventing RIC. Our study was in line with previous two meta-analyses which have showed that RIC was beneficial for prevention of acute kidney injury in patients with PCI, coronary artery bypass grafting and other cardiac surgeries [35,36]. However, these two meta-analyses did not discriminate the effect of RIC in different conditions separately. Our study has found that RIC was not only effective in reducing the incidence of CA-AKI in AMI, but also associated with an improved long-term prognosis. The current meta-analysis has extended previous finding that that RIC was effective in reducing CA-AKI in elective PCI [37,38]. In addition, our meta-analysis has indicated that RIC also showed a long-term cardiac protection in reducing MACE. This result was consistent with recent studies which have reported that RIC was an benefit for AMI patents in reducing MACE, heart failure as well as myocardial edema levels, myocardial salvage index [26]. Moreover, the TSA results showed that, assuming future trials record the same event rates as the published trials, they did not need additional participants to provide future meta-analysis with the power to confirm the benefit for CA-AKI and MACE. This meaningful and intriguing finding indicates that RIC is probably an effective renoprotection strategy in the condition of AMI.

The effect of RIC in reducing CA-AKI for AMI may be influenced by some modifiable factors. Our meta-regression has showed that hypertension status was negatively associated with the reduced risk of CA-AKI. What's more, our subgroup analyses have showed that the group with more percentage of hypertensive patients was benefit more (RR 0.36 vs 0.72) from RIC treatment under the condition of AMI. Our results were in lined with previous studies which have reported that RIC was effective in reducing systolic blood pressure about 5 mmHg [39,40]. In addition, hypertension is a well-known risk factor for AMI and our results have also suggested that RIC might be more effective for some high-risk patients. Our study was consistent with previous trials which have also suggested that RIC was more effective in kidney protection for high-risk patients undergoing PCI or cardiac surgery [41,42]. Nevertheless, the influential effect of hypertension in RIC-induced renoprotection needs more large sample-size and high-quality clinical trials to verify in future.

Results from our meta-analysis indicated that RIC was an effective strategy in reducing CA-AKI and MACE for AMI. This meaningful and intriguing finding indicates that RIC is probably an effective renoprotection strategy in AMI. Hence, routine performance of RIC would be helpful for renal protection under the condition of acute ischemic events. Future experimental studies are needed to explore the mechanism about the RIC for kidney protection. In addition, large randomized controlled trials are necessary to extend the investigation of the effect of RIC for renal protection in both cardiac and non-cardiac conditions.

5. Limitation

Our meta-analysis has some limitations. First, we did not use the multivariable adjusted RR for the effect size, resulting inpotential residual confounders. Second, the excluded studies which performed in patients with acute coronary syndrome might influence on the effect size. Third, five included studies were from China. Although our subgroup analyses have indicated that area was not a modifiable factor, it needs further investigation for RIC in reducing CA-AKI for AMI. Finally, our meta-analysis used pooled data, rather than individual data, which restricted detailed analysis for the potential confounding factors.

6. Conclusions

Our meta-analysis of nine RCTs comprising 1540 patients has demonstrated that RIC remains an effective strategy in reducing CA-AKI for AMI, especially for the hypertensive group. Routine RIC in AMI should be recommended for renal protection.

Author contributions

Conceptualization, CZ and HP; methodology, YLi; software, YLi; validation, YLi, YLo, HP, and CZ; formal analysis, YLi; investigation, YLo; resources, YLo; data curation, YLo; writing—original draft preparation, YLi; writing—review and editing, YLo, HP, and CZ; visualization, CZ; supervision, CZ; project administration, HP; funding acquisition, HP, and CZ. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/RCM/23/3/10.31083/j.rcm2303102.

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