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REVIEW ARTICLE

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The efficacy of remote ischemic conditioning in preventing contrast-induced nephropathy among patients undergoing coronary angiography or intervention: An updated systematic review and meta-analysis

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Abstract

Background: Numerous trials have investigated the effect of remote ischemic conditioning (RIC) in preventing contrast-induced nephropathy (CIN) in patients receiving contrast medium (CM). This meta analysis aims to validate the role of RIC in preventing CIN.

Methods: We searched the PubMed, EMBASE, and Web of Science databases for eligible randomized controlled trials (RCTs) published before April 27, 2019. Two investigators independently extracted basic characteristics from each study. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to examine the treatment effect.

Results: A total of 18 studies comprising 2,503 patients were included in our meta-analysis. Compared with conventional therapy, RIC significantly reduced the risk of CIN (OR = 0.43, 95% CI: 0.33, 0.56, $p < .05$). Subgroup analyses showed that the protective effect of RIC was stronger in the low-osmolar contrast media group (OR = 0.32; 95% CI: 0.23, 0.45, $p < .05$) and the nondiabetic group (OR = 0.39; 95% CI: 0.29, 0.53 $p < .05$). RIC also significantly reduced major adverse cardiovascular events within the first 6 months (OR = 0.39; $p < .05$), but the influence was not present after long-term follow-up.

Conclusions: Our meta-analysis showed that RIC could effectively reduce CIN risk and decrease the short-term incidence of relevant adverse events. Furthermore, the effects of CIN are more pronounced in nondiabetic patients and with the use of low-osmolar contrast medium. This meta-analysis of small trials suggests a possible protective effect of RIC on contrast-induced nephropathy and favors the performance of a large randomized trial to further investigate this strategy.

KEYWORDS
contrast medium, contrast-induced nephropathy, diabetes mellitus, remote ischemic conditioning

Biming Zhan and Bo Zhu are co-first authors.

1 | INTRODUCTION

With the increased use of contrast medium (CM) in hospitals, the incidence of contrast-induced nephropathy (CIN) has risen dramatically (Leoncini et al., 2014). CIN is the third leading cause of hospital-acquired acute renal failure (Gassanov, Nia, Caglayan, & Er, 2014; Quintavalle et al., 2012). Many risk factors, such as hypertension, diabetes mellitus, renal failure, older age, and different types of CM, have been found to accelerate the development of CIN (Han et al., 2014; Narula et al., 2014). However, there are no effective treatments or prophylactic measure for CIN because the mechanism is not fully understood, although conventional hydration has been routinely used (Sadat, Usman, Gillard, & Boyle, 2013).

Remote ischemic conditioning (RIC), including remote ischemic preconditioning (rIPC) and remote ischemic postconditioning (RIPostC), is a kind of measure that can effectively protect against ischemia/reperfusion injury (Bøtker et al., 2010). In 1993, Przyklenk et al first proposed the concept of RIC (Ferdinandy, Heusch, Baxter, & Schulz, 2014), describing a brief discontinuation of the blood supply to an organ followed by reperfusion; this technique is generally applied before the onset of prolonged ischemia to a distant organ or tissue (Hausenloy et al., 2015). RIC has been reported to provide protection to the heart, brain, and skeletal muscle (Giricz et al., 2014; Hausenloy & Yellon, 2016; White et al., 2015). However, the role of RIC in reducing the rate of CIN has remained controversial and contradictory. Zhou et al. (2017) conducted a meta-analysis examining the effect of RIC on CIN in patients undergoing intravascular contrast; however, the subanalysis did not separate diabetic patients from all patients. In particular, Moretti et al. (2018)) and Balbir Singh et al. (2016) recently showed that RIC exerted no benefit in diabetic patients. Moreover, an increasing number of studies have reported different results regarding the effectiveness of RIC in preventing CIN. Xie et al. (2018) analyzed 30 trials to investigate the effect of rIPC on kidney protection in cardiac surgery patients, but no significant benefit was found. Furthermore, Xu et al. (2015) and Menting et al. (2015) reported that RIC did not reduce the incidence of CIN after contrast administration. Therefore, with the aim of achieving a higher statistical power and identifying possible sources of disagreement among different studies, we combined the results from different studies and performed a stratified analysis to compare the efficacy of RIC in preventing CIN in patients who received a large quantity of CM during coronary angiography (CAG) or percutaneous coronary intervention (PCI).

2 | METHODS

2.1 | Study eligibility and search strategy

Two cardiologists, Z.B. and Bm.Z., systematically searched the MEDLINE, PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials databases through April 2019 for studies published in any language that reported the effect of RIC on the prevention of CIN after PCI or CAG. The Boolean operator "AND" was used to combine three groups of keywords: "remote ischemic postconditioning" OR "remote ischemic preconditioning" OR "remote ischemic conditioning" AND "coronary angiography" OR "CAG" OR "percutaneous coronary intervention" OR "percutaneous coronary angioplasty" OR "PCI", AND "contrast induced nephropathy" OR "CIN" OR "contrast associated nephropathy" OR "CAN" OR "contrast-induced acute kidney injury" OR "CI- AKI." We also reviewed the reference lists and conference abstracts of potential articles to identify other relevant studies.

The inclusion criteria were as follows: (a) randomized controlled trials (RCTs) investigating RIC for prevention of CIN in patients undergoing PCI or CAG, (b) availability of complete clinical data, and (c) a minimum of 20 participants enrolled in the study. Meanwhile, exclusion criteria included (a) duplicate reports without additional clinical outcomes, (b) no randomized and prospective design, (c) ongoing or unpublished studies, or (d) outcomes not clearly reported or unable to be extracted or calculated from the published results.

2.2 | Data extraction and management

Two reviewers, B.Z. and Bm.Z., independently extracted the data, with any disagreements resolved through discussion or consultation with a third researcher, X.H. or B.Z., if needed. For each study, the following data were recorded: first author; year of publication; sex, age, and sample size of participants; definition of CIN; serum creatinine (Scr); estimated glomerular filtration rate (eGFR) level at 24 hr, 48 hr, and 72 hr after PCI or CAG; diabetes mellitus status; and dosage and types of CM used.

The effective endpoint was the development of CIN and major cardiovascular events (MACEs) within 1 year of follow-up. No disagreements occurred between the two reviewers (Z.B. and Bm.Z). In addition, data management and entry into RevMan was mainly carried out by Z.B. The scoring parameters established by Jadad et al were used to assess the methodological quality of the RCTs. This process enabled evaluation of clinical trials based on the following criteria: concealment of treatment allocation, similarity of study groups at baseline, eligibility criteria, any blinding procedures used, reporting on those lost to follow-up, and intention-to-treat analysis. All studies were categorized as either low risk, unclear risk, or high risk of bias according to the Jadad score (Jadad et al., 1996).

Review Manager (RevMan) version 5.30 software (Nordic Cochrane Center) was used to perform all the statistical analyses. Based on the intention-to-treat strategy, Mantel–Haenszel odds ratios (MH-OR) with 95% CI were calculated, with the chi-square statistic calculated and a formal test of heterogeneity conducted. The I^2 index was used to evaluate between-study variation, with I^2 values ≤25%, 25%–50%, and ≥50% representing low, moderate, and high inconsistency, respectively. If the I^2 value was ≥50%, a random-effects model was used; otherwise, a fixed-effects model was used.

Subgroup and sensitivity analyses were performed to explore the causes of heterogeneity as necessary. A funnel plot was drawn to assess the degree of possible publication bias, with visually significant asymmetry in the funnel plots indicating major publication bias. All the tests were two-tailed, and a p value < .05 was regarded as statistically significant in this meta-analysis.

3 | RESULTS

3.1 | Study selection

From 872 initial relevant articles, we excluded 358 duplicates and 439 irrelevant articles, leaving 75 articles for in-depth assessment. Then, we excluded studies due to the lack of a trial protocol, no renal functional results, a retrospective observational design, or the inclusion of study subjects undergoing open surgery. Based on the inclusion and exclusion criteria, 18 relevant studies were included. The study selection process is shown in Figure 1 (Balbir Singh et al., 2016; Cao, Wang, Zhang, Xia, & Yang, 2018; Crimi et al., 2013; Deftereos et al., 2013; Elbadawi et al., 2017; Er et al., 2012; Gholoobi, Sajjadi, Shabestari, Eshraghi, & Shamloo, 2015; Hoole et al., 2009; Igarashi, Iino, Watanabe, & Ito, 2013; Lavi et al., 2014; Luo et al., 2013; Menting et al., 2015; Moretti et al., 2018; Savaj, Savoj, Jebraili, & Sezavar, 2014; Xu et al., 2015; Yamanaka et al., 2015; Zagidullin et al., 2017; Zhou et al., 2018).

Detailed characteristics of these studies are listed in Table 1 and Table S1. Our meta-analysis included 2,503 patients from 18 studies, of which 1,243 patients receiving RIC before or after surgery were assigned to the experimental group, and the remaining 1,260 patients were assigned to the control group. Two trials defined CIN as a relative increase of >25% from baseline (Crimi et al., 2013; Hoole et al., 2009); two trials used the definition of either an absolute increase in Scr > 0.5 mg/dl or 44.2 mmol/L or a relative increase of >25% from baseline within 16 hr after CM exposure (Luo et al., 2013; Xu et al., 2015), one trial used the same criteria as above within 24 hr after exposure (Lavi et al., 2014), three trials within 48 hr after exposure (Balbir Singh et al., 2016; Moretti et al., 2018; Zagidullin et al., 2017), three trials between 48 and 72 hr after exposure (Menting et al., 2015; Yamanaka et al., 2015; Zhou et al., 2018), one trial within 72 hr after exposure (Cao et al., 2018), and three trials within 96 hr after exposure (Deftereos et al., 2013; Elbadawi et al., 2017; Zagidullin et al., 2017); and two trials used the definition of an absolute increase in Scr of 0.3 mg/dl within 24 or 48 hr of exposure to the contrast agent (Gholoobi et al., 2015; Savaj et al., 2014). The mean CM dose ranged from 77.7 to 270 ml.

3.2 | Literature quality evaluation

In 2 out of 18 articles, patients were identified and randomized 1:1 with computer-generated block randomization (Crimi et al., 2013; Yamanaka et al., 2015), while in the other studies, the randomization method was mentioned without a specific description. Eight studies reported completeness of follow-up (Crimi et al., 2013; Deftereos et al., 2013; Elbadawi et al., 2017; Er et al., 2012; Hoole et al., 2009; Menting et al., 2015; Moretti et al., 2018; Zhou et al., 2018), and almost all of the studies included patients with similar baseline characteristics and provided details about the inclusion

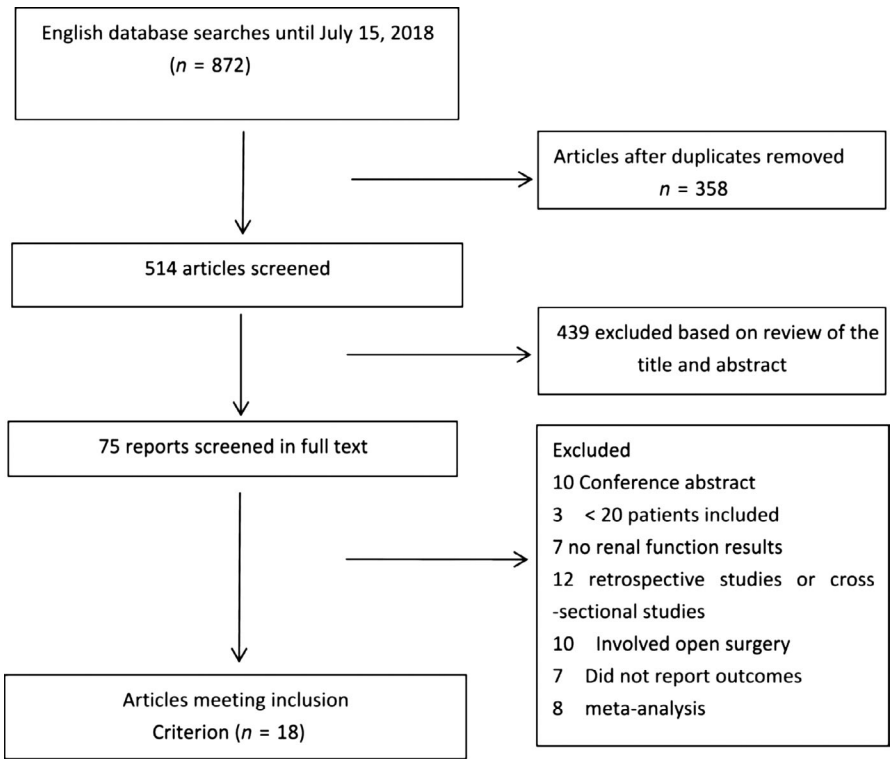

FIGURE 1 Study selection diagram

TABLE 1 Baseline characteristics of the included patients and interventions used in the included studies

	Age (years, mean ± *SD*)		Male gender (*n*, %)		DM (*n*, %)		Contrast medium (mls, mean ± *SD*)		
	RIC	Sham RIC	RIC	Sham RIC	RIC	Sham RIC	RIPC	Sham RIC	RIC intervention
Moretti et al.	71.8 ± 10.6	72.6 ± 9.6	74 (67.3%)	80 (67.2%)	43 (39.1%)	42 (37.1%)	174.4 ± 83.7	171.4 ± 78.6	5-min inflations of a blood pressure cuff to 200 mmHg around the upper nondominant arm for four times
Zhou et al.	69.42 ± 7.07	69.14 ± 7.80	30 (60.0%)	35 (61.4%)	24 (48.0%)	27 (47.3%)	114.76 ± 44.22	108.82 ± 43.25	5-min inflations of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-min intervals of reperfusion by four times
Shamilevich et al.	60.5 ± 1.95	62.96 ± 1.72	21 (80.7%)	22 (88.0%)	8 (30.8%)	8(32.0%)	155.8 ± 16.9	148.3 ± 16.7	A 5-min cycle cuff inflation on the upper arm with blood pressure cuff and with a 5-min rest between the cycles by 3 times
Igarashi et al.	71.3 ± 8.1	70.8 ± 7.6	20 (66.7%)	23 (76.7%)	11 (36.7%)	9 (30.0%)	92.9 ± 33.2	91.8 ± 39.4	Intermittent upper-arm ischemia 4 cycles of 5-min inflation of a blood pressure cuff to 200 mmHg and 5-min deflation
Er et al.	73.2 ± 9.1	72.7 ± 11.4	34 (68%)	37 (74%)	15 (30%)	18(36%)	103 ± 41	124 ± 44	Four cycles of alternating 5-min inflation and 5-min deflation of a standard upper-arm blood pressure cuff to individuals' systolic blood pressure plus 50 mmHg
Menting et al.	73 ± 8.5	71 ± 11	14 (39%)	21 (58%)	8 (22%)	10 (28%)	99 ± 29	98 ± 29	Four cycles of ischemia and reperfusion of the forearm by inflating a blood pressure cuff around the upper arm at 50 mmHg above the actual systolic pressure for 5 min, followed by 5 min of reperfusion.
Savaj et al.	63.0 ± 8.9	60.9 ± 9.6	17 (35.4%)	14 (29.1%)	48 (100.0%)	48 (100.0%)	126.6 ± 77.2	123.8 ± 66.6	Sphygmomanometer cuff was inflated on the right arm to the point of 200 mmHg pressure for 5 min and then it was deflated. Three cycles were repeated
Yamanaka et al.	67 ± 12	67 ± 15	34 (76%)	36 (76%)	14 (31%)	17 (37%)	177 ± 53	199 ± 87	Three cycles of ischemia/reperfusion of the upper arm achieved by 5-min cuff inflation at 200 mmHg followed by 5 min of complete cuff deflation
Balbir et al.	67.8 ± 7.6	69.0 ± 8.6	23 (45.1%)	25 (49.0%)	51 (100%)	51 (100%)	197.5 ± 114.3	196.3 ± 118.8	Manual inflation of the cuff to 200 mmHg for 5 min, followed by deflation of 5 min to allow reperfusion, and this cycle was performed 3 times
Crimi et al.	61 ± 11	56 ± 11	41 (85%)	43 (90%)	4 (9%)	7 (15%)	211 ± 55	229 ± 72	Lower limb was exposed to 3 cycles of ischemia/reperfusion, each obtained by 5-min cuff inflation at 200 mmHg, followed by 5-min complete deflation

(Continues)

TABLE 1 (Continued)

	Age (years, mean ± *SD*)		Male gender (*n*, %)		DM (*n*, %)		Contrast medium (mls, mean ± *SD*)		
	RIC	Sham RIC	RIC	Sham RIC	RIC	Sham RIC	RIPC	Sham RIC	RIC intervention
Gholoobi et al.	67.08 ± 12.49	70.31 ± 11.18	18 (49.0%)	12 (51.0%)	19 (76.0%)	18 (69.2%)	NG		A blood pressure cuff was fastened around the patient's arm an hour before coronary angiography, and it was inflated to 50 mmHg above systolic pressure for 5 min, and then, the cuff was deflated for 5 min; this cycle was repeated four times
Hoole et al.	63.2 ± 10.1	61.8 ± 10.3	84 (81%)	74 (76%)	24 (23%)	20 (20%)	196.7 ± 80.1	187.5 ± 74.2	The cuff was inflated to 200 mmHg pressure for 5 min, followed by 5 min of deflation, to allow reperfusion. This was repeated 2 more times
Lavi et al.	64.25 ± 9.95	63.7 ± 9.7	73 (72.0%)	90 (75%)	75 (31.3%)	37 (31%)	190 ± 90.5	185 ± 87	The cuff was inflated 3 times to ≥200 mmHg, and >50 mmHg above systolic blood pressure, for 5 min, followed by a 5-min deflation
Luo et al.	59.2 ± 10.3	59.3 ± 9.5	78 (77%)	78 (75%)	26 (26%)	31 (30%)	154 ± 46	145 ± 41	The pneumatic medical cuff was inflated to a pressure of 200 mmHg for 5 min, followed by 5 min of deflation to allow reperfusion. This procedure was repeated 3 times
Xu et al.	69.1 ± 3.8	68.9 ± 2.9	68 (66.7%)	68 (69.4%)	102 (100%)	98 (100%)	171.8 ± 37.9	163.3 ± 39.0	3 cycles of 5-min pneumatic medical cuff inflations to 200 mmHg, followed by 5 min of deflations to allow reperfusion
Deftereos et al.	68 ± 4	68 ± 5	74 (65.5%)	72 (62.5%)	45 (40%)	38 (34%)	270 ± 45	265 ± 25	Four 1-min cycles were performed, each consisting of 30 s of inflation of the stent balloon to the nominal pressure and 30 s of deflation
Elbadawi et al.	53 ± 7.5	50.1 ± 7.3	25 (83.3%)	25 (83.3%)	12 (40.0%)	13 (43.3%)	NG	NG	The lower limb was exposed to three cycles of ischemia through cuff inflation at 200 mmHg for 5 min, alternating with three cycles of reperfusion through complete cuff deflation for 5 min
Cao et al.	58.93 ± 12.82	59.24 ± 10.45	29 (80.5%)	40 (90.9%)	7 (19.4%)	8 (18.2%)	87.92 ± 21.05	92.50 ± 21.02	Four cycles of 5 min of occlusion and 5 min of reperfusion by cuff inflation and deflation of the upper arm

criteria and the intention-to-treat analysis. The literature quality scores are shown in Table 2.

3.3 | Outcomes

3.3.1 | Incidence of CIN

In a study by Lavi et al. (2014), the RIC group of patients was divided based on administration type: in the upper limb, in the lower limb, and the control group. Therefore, we divided this trial into two studies: Lavi and Lavi 2. When we combined the results of the 18 studies, our meta-analysis showed that RIC can significantly reduce the incidence of CIN (OR = 0.43; 95% CI: 0.33, 0.56; $p < .05$) with a fixed-effects model owing to the low heterogeneity ($I^2 = 28\%$), as shown in Figure 2.

3.3.2 | Incidence of adverse events

Eight studies (Crimi et al., 2013; Deftereos et al., 2013; Elbadawi et al., 2017; Er et al., 2012; Hoole et al., 2009; Menting et al., 2015; Moretti et al., 2018; Zhou et al., 2018) reported MACEs, including hospital admissions with unstable angina, acute coronary syndrome, myocardial infarction (MI), heart failure, and stroke/transient ischemic attack. During the 1-year follow-up, the incidence of MACEs was 7.2% of patients in the RIC group and 13.7% in the control group. RIC significantly reduced the rate of MACEs (OR = 0.39; 95% CI 0.23, 0.66; $p < .05$) within the first 6 months of follow-up, but over the next 6 months of follow-up, there was no significant difference (OR = 0.64; 95% CI 0.32, 1.29; $p = .21$; Figure 3).

3.4 | Subgroup analysis

3.4.1 | Volume and type of CM

We separated 18 studies into three groups according to the dose of CM administered: ≤100 ml group (low) 1 (Cao et al., 2018; Ferdinandy et al., 2014; Gholoobi et al., 2015; Igarashi et al., 2013), 100–200 ml group (medium) 1 (Balbir Singh et al., 2016; Bøtker et al., 2010; Er et al., 2012; Ferdinandy et al., 2014; Giricz et al., 2014; Han et al., 2014; Hausenloy et al., 2015; Hausenloy & Yellon, 2016; Hoole et al., 2009; Luo et al., 2013; Moretti et al., 2018; Narula et al., 2014; Sadat et al., 2013; Savaj et al., 2014; White et al., 2015; Xu et al., 2015; Yamanaka et al., 2015; Zagidullin et al., 2017; Zhou et al., 2017, 2018), and >200 ml group (high) 2 (Deftereos et al., 2013; Sadat et al., 2013). RIC significantly decreased the incidence of CIN in all three groups (low group: OR = 0.29, 95% CI 0.14, 0.60, $p < .05$; medium group: OR = 0.47, 95% CI 0.34, 0.64; $p < .05$; and high group: OR = 0.47, 95% CI 0.26, 0.56; $p < .05$; Table 3). Furthermore, we compared low-osmolar and iso-osmolar contrast agents focusing on renal safety and found that RIC decreased the rate of CIN in the low-osmolar contrast group (Cao et al., 2018; Deftereos et al., 2013; Er et al., 2012; Hoole et al., 2009; Igarashi et al., 2013; Luo et al., 2013; Menting et al., 2015; Moretti et al., 2018; Yamanaka et al., 2015; Zagidullin et al., 2017) (OR = 0.32; 95% CI 0.23, 0.45; $p < .05$); however, RIC was not effective in either the iso-osmolar contrast agent groups (Balbir Singh et al., 2016; Gholoobi et al., 2015) (OR = 0.75; 95% CI 0.31, 1.83; $p = .52$) or groups for which the contrast media type was not mentioned (OR = 0.66; 95% CI 0.41, 1.06; $p = .09$; Table 3).

3.4.2 | Diabetes

Diabetes is a risk factor for the development of CIN, and we found that the renoprotective effect of RIC was not conspicuous in diabetic patients (Balbir Singh et al., 2016; Er et al., 2012; Luo et al., 2013; Moretti et al., 2018) (OR = 0.39; 95% CI: 0.29, 0.52; $p < .00001$; Figure S1).

3.4.3 | Different areas of study

To determine whether the race of the participants would influence the RIC results, we divided the patients into two groups: Asian patients (OR = 0.40; 95% CI: 0.21, 0.76; $p = .005$) and Western patients (OR = 0.43; 95% CI 0.33, 0.58; $p < .00001$). The RIC results are shown in Figure S2.

3.4.4 | Publication bias

No significant heterogeneity was observed in the global analyses, including the subgroup analysis of CIN. Moreover, sensitivity analyses were performed for all outcomes to detect the potential role of each individual study on the pooled results. A funnel plot indicated no certain bias among all the articles included in our meta-analysis, as shown in Figure S3.

4 | DISCUSSION

Our meta-analysis included 18 RCTs, and the main findings were as follows: (a) patients treated with RIC may have a significantly lower risk of CIN than control participants among those treated for emergent PCI or elective CAG; (b) RIC significantly reduced the rate of MACEs within a follow-up period of <6 months, but this effect was not observed >6 months of follow-up; and (c) the renoprotective effect of RIC was not observed in patients with diabetes.

After the discovery of RIC induced by transient limb ischemia, this procedure became an attractive renoprotective method that has been further elucidated by several experimental studies and clinical trials. The meta-analyses conducted by Bei et al. (2016) and Zhou et al. (2017) both indicated that RIC had a protective effect against CIN and reduced the incidence of relevant adverse events. However, those two meta-analyses included participants who had undergone different interventions for their conditions, such as cardiac and vascular surgery, and new trials including patients with ST-elevation myocardial infarction had been published since those meta-analyses were conducted; thus, a new meta-analysis is needed.

TABLE 2 Quality of the included randomized controlled trials

	Jadad score	Randomization	Allocation concealment	Similarity of baseline characteristics	Eligibility criteria	Blinding	Completeness of follow-up	ITT analysis
Moretti et al.	5	Yes	Yes	Yes	Yes	Double blind	Yes	Yes
Zhou et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Shamilevich et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Igarashi et al.	3	Yes	Yes	Yes	Yes	None	Yes	Yes
Er et al.	5	Yes	Yes	Yes	Yes	Double blind	Yes	Yes
Menting et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Savaj et al.	1	Yes	No	Yes	Yes	None	No	Yes
Yamanaka et al.	4	Yes	No	Yes	Yes	Single blind	Yes	Yes
Balbir et al.	5	Yes	Yes	Yes	Yes	Double blind	Yes	Yes
Crimi et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Gholoobi	5	Yes	Yes	Yes	Yes	Double blind	Yes	Yes
Hoole et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	No
Lavi et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Luo et al.	3	Yes	No	Yes	Yes	Single blind	Yes	Yes
Xu et al.	3	Yes	No	Yes	Yes	Single blind	No	Yes
Deftereos et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Elbadawi et al.	4	Yes	Yes	Yes	Yes	Single blind	Yes	Yes
Cao et al.	3	Yes	No	Yes	Yes	Single blind	No	Yes

We analyzed 2,503 patients who were administered contrast agents and found that RIC could reduce the CIN rate; furthermore, the subanalyses, which included the patients' race, diabetes status, and the volume and type of CM, revealed that RIC was ineffective in the diabetes group. The possible reasons are as follows. First, patients with diabetes mellitus (DM) had a much higher increase in Scr and eGFR than patients without DM after contrast exposure. Second, experiments using mouse models of DM revealed that DM

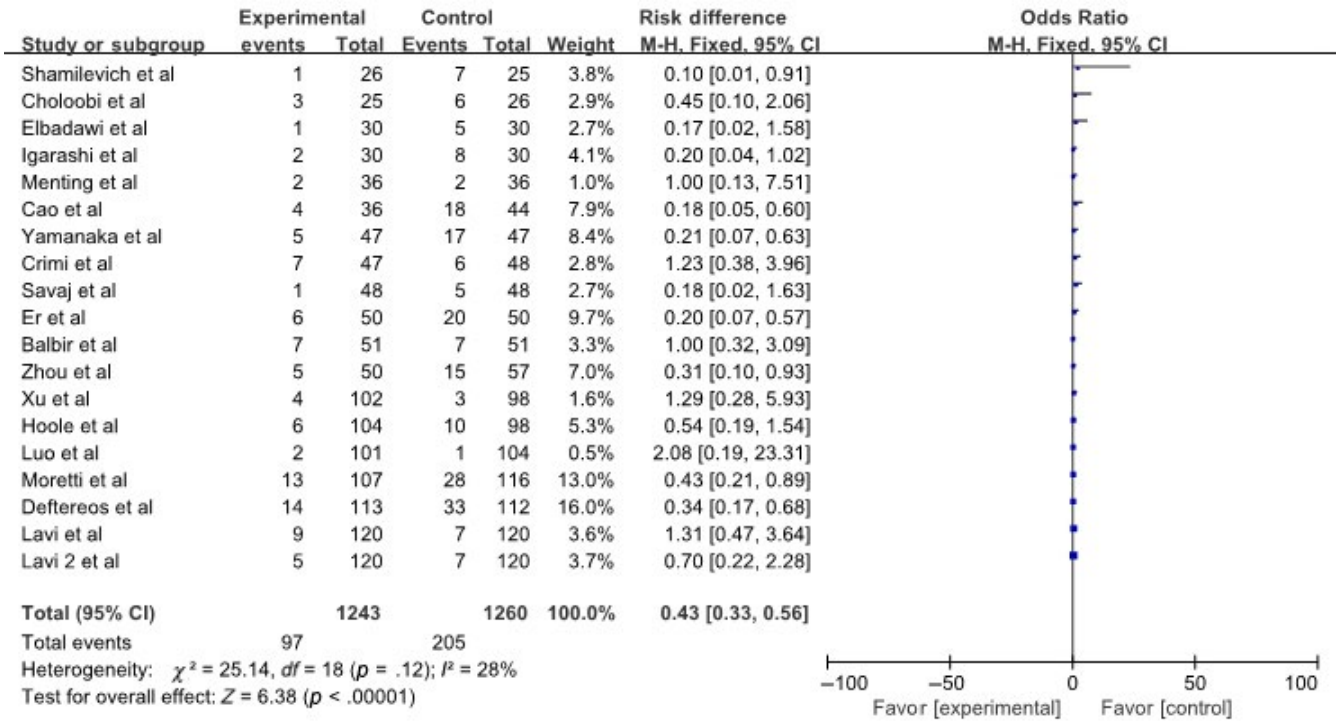

FIGURE 2 Forest plot of the odds ratio (OR) and 95% confidence interval (CI) for contrast-induced nephropathy among patients assigned to the remote ischemic conditioning compared with those in the control group

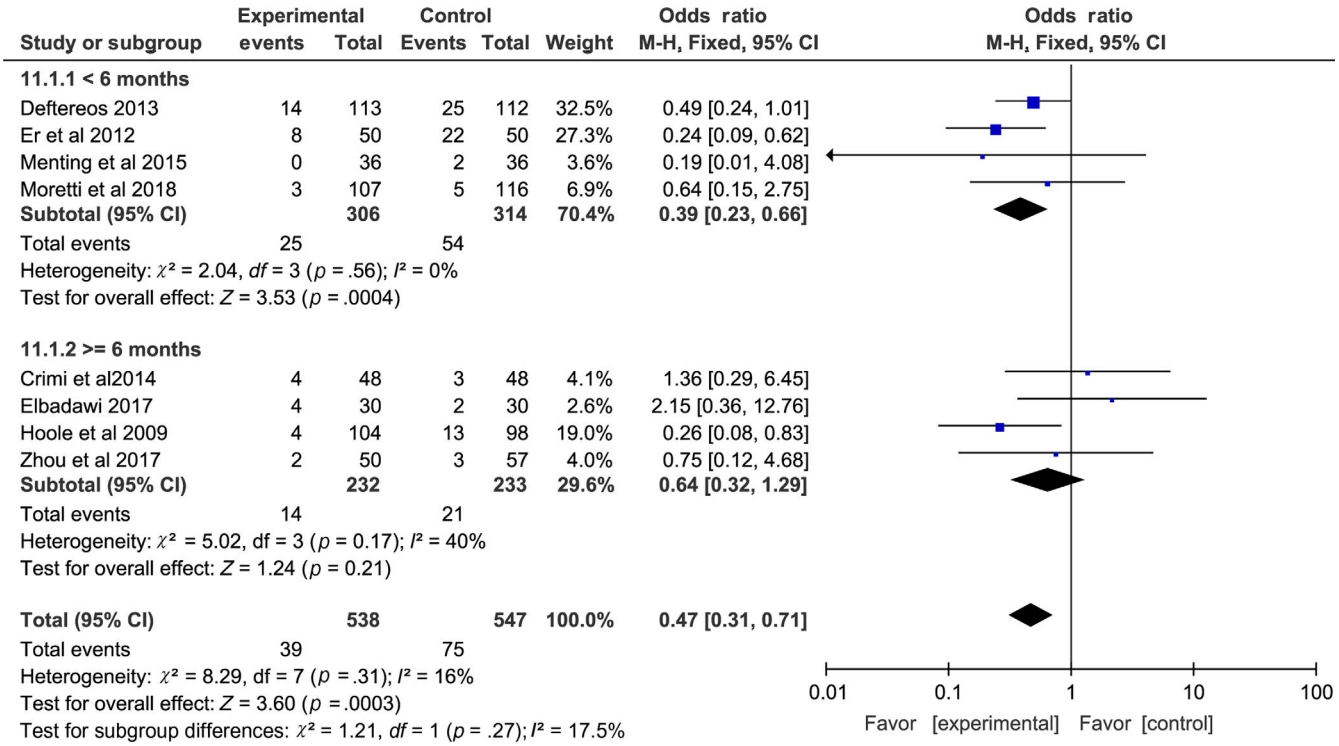

FIGURE 3 Forest plot of the odds ratio (OR) and 95% confidence interval (CI) for major adverse cardiovascular events within 6 months and longer than 6 months after contrast agent administration between the remote ischemic conditioning group and the control group

might reduce the cardioprotective effect of ischemic postconditioning (Heinzel et al., 2018). Using a diabetic rat model, Whittington et al also found that DM impaired Akt signaling, which plays a central role in the prosurvival intracellular pathway, and the cardioprotective effect of RIC may be weakened in the hearts of diabetic rats (Whittington et al., 2013). Third, antihyperglycemic agents, pathophysiology relating to endothelial function, micro-angioplasty, and neuropathy could perhaps abolish the protective effect of RIC in subjects with diabetes (Oosterlinck et al., 2013).

Another novelty of our work was that RIC was observed to reduce the short-term incidence of MACEs, but this protection was lost during long-term follow-up. In accordance with Zhou et al. (2017), RIC was found to reduce the CIN rate without aggravating the incidence of adverse events, but the significance was diminished after 6 months of follow-up. This finding may be due to the inclusion of longer-term follow-up studies, which comprised patients with a history of CKD (Er et al., 2012; Zhou et al., 2018), and the elevated severity of postoperative blood flow thrombolysis in MI patients (Crimi et al., 2013). Another explanation is that medication and stent implantation played a stronger role in controlling MACEs. However, in our meta-analysis, only Crimi et al. (2013) reported a mean follow-up of over 1 year; thus, the benefit of RIC to prevent or minimize CIN over a longer follow-up period should be assessed in future RCTs.

Biondi-Zoccai et al. (2014) focused on the influence of different types of contrast media on the risk of CIN, and the authors found that the risk of CIN was lower in the low-osmolar group than in the iso-osmolar group. However, Han, Zhang, Liu, Tan, and Zhang (2018) reported a significantly reduced risk of CIN in the iso-osmolar group compared with the low-osmolar group. The two previous meta-analyses reached different conclusions, perhaps due to differences in the included patients. In our study, we found that RIC could improve the CIN rate with different volumes of contrast medium and discovered that the protective effect of RIC was superior in the low-osmolar group. This finding could not be explained by osmolality alone and thus warrants further exploration of other possible mechanisms.

The existence of racial differences in healthcare outcomes has been documented. Chen, Nallamothu, Spertus, Tang, and Chan (2018) found that black patients who survive in-hospital cardiac arrest have a lower long-term survival rate than do white patients. Batchelor et al. (2013) assessed the influence of race on long-term outcomes following PCI by comparing 5-year outcomes among 2,301 white patients, 127 black patients, and 169 Asian patients, and they found that compared with white patients, black but not Asian patients had

TABLE 3 Subgroup analysis of CIN incidence

	OR	95% CI	*p*
Mean contrast dose			
Low (<100)	0.29	0.14, 0.60	*p* = .0009
Medium (100–200)	0.47	0.34, 0.64	*p* < .0001
High (>200)	0.47	0.26, 0.84	*p* = .01
Contrast type			
Low-osmolar	0.32	0.23, 0.45	*p* < .0001
Iso-osmolar	0.75	0.31, 1.83	*p* = .52
NG	0.66	0.41, 1.06	*p* = .09

a higher incidence of major thrombotic events after PCI. Khambatta et al. (2013) first examined the association between race and the risk of CIN after PCI and found that compared with white patients, black patients undergoing PCI have a higher likelihood of developing CIN. One possible explanation for these results was that black patients are more likely to receive care at low-quality hospitals and have fewer resources (Li, Cai, & Glance, 2015), and black patients have a higher severity of comorbid conditions at baseline. However, in our meta-analysis, we first demonstrated that RIC is available in both Asian and Western populations. Due to its low cost and lack of known adverse risks, RIC could even be administered in the emergency room to black patients with suspected acute coronary syndrome.

Although the mechanism of CIN in patients exposed to contrast medium has yet to be elucidated, renal ischemic injury and direct tubule toxicity in renal tubular cells have already been proposed (Igarashi et al., 2013; Zagidullin et al., 2017; Zhou et al., 2018). Another possible mechanism of injury is that CM elicits hypoxia of the renal medulla and leads to free radical production via postischemic oxidative stress in the renal tissue (Er et al., 2012; Savaj et al., 2014). The possible mechanisms by which RIC protects against CIN are as follows. Shimizu et al. (2009) reported that plasma from humans or rabbits after RIC could protect isolated perfused rabbit hearts and isolated rabbit cardiomyocytes by reducing the production of inflammatory molecules in the myocardium and activating adenosine triphosphate-sensitive potassium channels. Cao et al. (2018) demonstrated that RIC could regulate stromal cell-derived factor-1a, apoptosis, and nitric oxide in the myocardium of patients who underwent PCI. Moreover, the protective effect of RIC on reperfusion injury was associated with activation of the phosphatidylinositol 3-kinase/Akt (PI3K-Akt) pathway, which can reduce oxidative stress and induce the expression of superoxide dismutase (Dai et al., 2007).

Our present study, which included 18 RCTs, is the largest study to date to evaluate the effect of RIC on CIN. However, there might be several limitations in our meta-analysis: (a) although we conducted subanalyses (which included the doses of contrast administered and race of the participants) to assess the stability of the results, the sample size of some of the studies included in this analysis was relatively small, especially the subgroups of diabetic patients. (b) Among the different studies, there were no standardized methods of RIC, which needs future investigation. (c) The concomitant use of other medications such as statins, angiotensin-converting enzyme inhibitors, and nicorandil was frequently reported in patients with coronary heart disease, which might have biased our outcome because these medications might potentially affect renal function in an unknown manner. However, since these different medications were randomly used by patients in both the control and experimental groups, their effect on renal function might be offset; nonetheless, this aspect needs further investigation. (d) Some RCTs did not report specific details of randomization. (e) Several studies have used renal function indicators, such as eGFR and Scr, as the observation index in the trials. However, the small number of studies and different data reporting in the trials resulted in an inability to assess changes in renal function before and after CM between the two groups.

5 | CONCLUSION

Our meta-analysis of RCTs showed that RIC could effectively reduce the risk of CIN and decrease the short-term incidence of relevant adverse events after PCI or CAG. Furthermore, the effect is more pronounced in nondiabetic patients. Due to the limitations of the included articles, future trials with long-term follow-up and use of a standard method are needed to draw a more credible conclusion.

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CONFLICT OF INTEREST

All authors take responsibility for all aspects of the research, and there are no conflicts of interest.

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SUPPORTING INFORMATION

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