

## Review Article

# Effect of Chinese medicine injection for preventing contrast-induced nephropathy after coronary angiography/percutaneous coronary intervention: a systematic review and meta-analysis

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**Abstract:** *Background and aim:* With the increasing use of interventional therapy for coronary artery disease (CAD), contrast-induced nephropathy (CIN) has become the third leading cause of hospital-acquired acute renal injury. This meta-analysis aimed to evaluate the efficacy of Chinese medicine injection for preventing CIN. *Methods:* We retrieved relevant articles published up to August 30, 2017 from five databases: CNKI, Wanfang Data, VIP, PubMed, and Cochrane Controlled Trials Register. Only randomized controlled trials (RCTs) were eligible for inclusion. The fixed- and random-effects models were employed to calculate pooled risk ratios (RRs) and mean differences (MDs), respectively. *Results:* Thirteen RCTs with a total of 2022 patients were identified. Compared with conventional hydration therapy, Chinese medicine injection significantly reduced CIN incidence (RR: 0.36; 95% CI: 0.26-0.49;  $P < 0.0001$ ) and improved renal function by lowering serum creatinine at 24 h (MD: -7.03, 95% CI: -10.36, -3.69,  $P < 0.0001$ ), 48 h (MD: -9.32; 95% CI: -16.32, -2.32;  $P = 0.009$ ) and 72 h (MD: -8.15; 95% CI: -12.41, -3.89;  $P = 0.0002$ ) after operation. Furthermore, creatinine clearance at 48 h after operation (MD: 9.57; 95% CI: 3.11, 16.03;  $P = 0.004$ ) and cystatin C (Cys C) at 24 h after operation (MD: -0.12; 95% CI: -0.14, -0.10;  $P < 0.0001$ ) were decreased. *Conclusion:* This meta-analysis demonstrated that Chinese medicine injection lowers CIN incidence, marked by lower levels of Scr, Ccr, and Cys C, in patients undergoing PCI/CAG. However, more rigorously designed studies, with large sample sizes and long-term follow-up, are needed to reach more reliable conclusions.

**Keywords:** Chinese medicine injection, contrast-induced nephropathy

## Introduction

Coronary artery disease (CAD) occurs when atherosclerotic lesions develop in coronary arteries and cause stenosis or obstruction, leading to corresponding myocardial ischemia, hypoxia, or necrosis in varying degrees [1]. In recent years, percutaneous coronary intervention (PCI) and coronary angiography (CAG) have developed rapidly and become the optimal strategy for diagnosing and treating CAD [2]. However, cardiologists have raised concerns about the rising incidence of contrast-induced nephropathy (CIN), which may prolong patient stay, increase medical costs, and lower long-

term survival rate [3]. Currently, CIN is the third leading cause of acute renal injury [4].

CIN is generally described as an acute worsening of renal function within a narrow time interval after contrast agent exposure [5]. According to the Acute Kidney Injury Network [6], a diagnosis of CIN is based on the following conditions: (1) an absolute increase in serum creatinine (Scr) by  $\geq 0.3$  mg/dL from baseline, (2) a relative increase in Scr levels by  $\geq 50\%$  from baseline, or (3) a urine output reduced to  $\leq 0.5$  mL/kg/h for at least 6 h. A patient is diagnosed of CIN when at least one of these three conditions is met within 48 h after contrast agent application.

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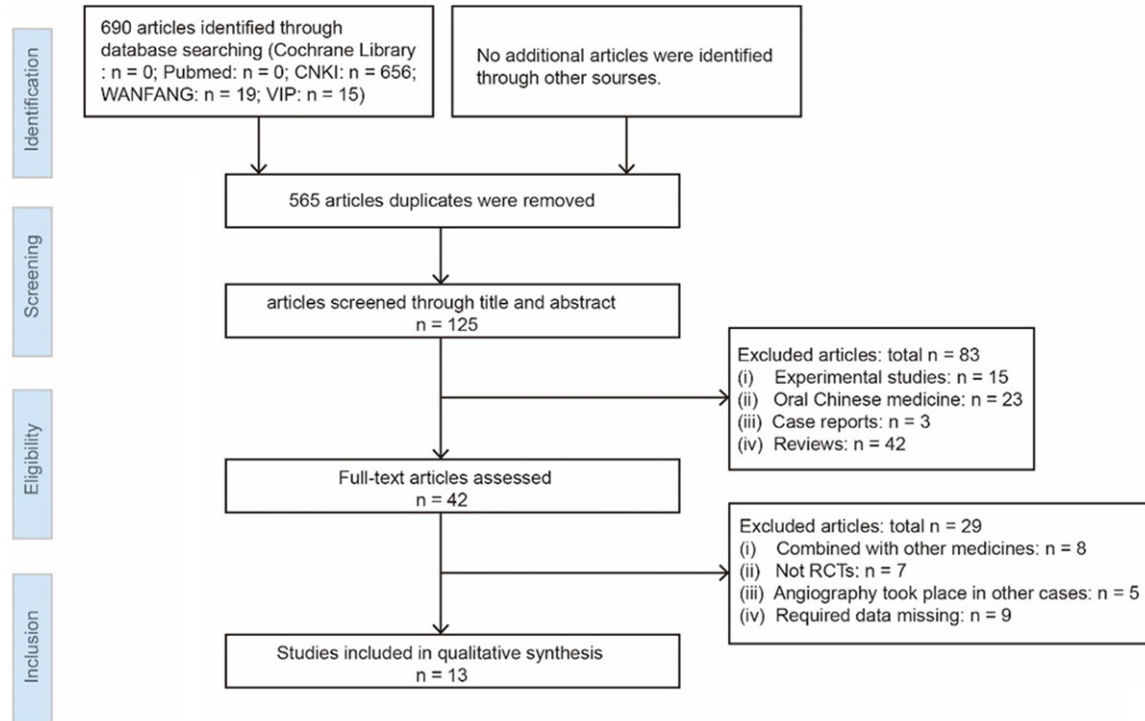


Figure 1. Flowchart of literature searching.

Several studies have indicated that Chinese medicine injection exerts a positive effect for preventing CIN. However, these randomized controlled trials (RCTs) had small sample sizes, making it difficult to draw a reliable conclusion. This study aimed to conduct a systematic review and meta-analysis studies on preventing CIN after PCI/CAG by Chinese medicine injection from the viewpoint of evidence-based medicine.

## Materials and methods

### Search strategy

Articles reporting RCTs on the administration of Chinese medicine injection in the prevention and treatment for CIN were located by searching the following electronic databases: China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Scientific Journal Database (VIP), PubMed, and the Cochrane Controlled Trials Register and assisted by manual retrieval from the date of inception to August 30, 2017. The search was limited to clinical research articles published in Chinese or English. The search terms of Chinese databases (CNKI, Wanfang Data, VIP) were as follows:

“zhong yi” OR “zhong yao” OR “zhong yi yao” OR “zhong xi yi jie he” OR “zhong yao zhu she ji” OR “zhong yao zhen ji” OR “zhong yao zhu she ye”) AND (“zao ying ji shen bing” OR “dui bi ji shen bing” OR “zao ying ji shen sun hai” OR “dui bi ji shen sun hai” OR “zao ying ji shen sun shang” OR “dui bi ji shen sun shang”). The search terms of English databases were as follows: (“Chinese medicine” OR “integrative medicine” OR “Chinese medicine injection”) AND (“contrast-induced nephropathy” OR “radiographic contrast nephropathy” OR “contrast associated nephropathy” OR “contrast media-induced nephropathy”).

### Inclusion criteria

Articles were included in the study when they met the following criteria: (1) RCT that aimed to evaluate the efficacy of Chinese medicine injection on the prevention and treatment of CIN; (2) study participants were patients receiving CAG or PCI; (3) at least one of the observation groups received Chinese medicine injection, of which the dose and duration time were not limited; (4) the indexes of all patients before operation were comparable; (5) the reported data included CIN incidence rate and levels of Scr,

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**Table 1.** Characteristics of studies included in meta-analysis

Studies		Sample Size	Intervention	Duration	Control	Type of contrast agent	Type of procedure	Outcome measure
Author	Year	T/C						
Dong et al.	2013	61/65	Sodium ferulate 300 mg + NS 250 mL, ivgtt, qd	2 days	Hydration therapy	Lohexol	PCI	Scr, Ccr, $\beta$ 2-MG
Li et al.	2017	40/40	Shenxiong glucose injection 200 mL, ivgtt, qd	3 days	Hydration therapy	Lopromide	CAG	CIN, Scr, Ccr
Yao et al.	2016	57/57	Ligustrazine 20 mg + NS 250 mL, ivgtt, qd	14 days	Hydration therapy	Lohexol	PCI	CIN, Scr, Cys C
Wang et al.	2011	40/40	Danhong injection 20 mL + NS 250 mL, ivgtt, qd	6 days	Hydration therapy	Lopromide	PCI	CIN, Scr, Cys C, $\beta$ 2-MG, mAlb
Niu et al.	2015	68/68	Danhong injection 20 mL + NS 250 mL, ivgtt, qd	3 days	Hydration therapy	Lohexol	PCI	CIN, Scr, Ccr
Zhang et al.	2015	41/41	Safflower yellow 150 mg + NS 250 mL, ivgtt, qd	6 days	Hydration therapy	Lohexol	PCI/CAG	CIN, Scr, Cys C
Qian et al.	2008	26/26	Astragalus injection 40 mL + 5% GS 250 mL	12 h before and after operation	Hydration therapy	Lopromide	CAG	CIN, Scr, Ccr
Zhou et al.	2017	100/100	Xuebijing injection 50 mL, ivgtt, qd	8 days	Hydration therapy	Unclear	PCI	CIN, Scr, Ccr, mAlb
Xu et al.	2013	120/120	Salvianolate injection 200 mg + 5% GS 250 mL, ivgtt, qd	14 days	Hydration therapy	Unclear	PCI/CAG	CIN, Scr, BUN
Huang et al.	2017	152/154	Salvianolate injection 400 mg + 5% GS 500 mL, ivgtt, qd	7 days	Hydration therapy	Lopromide	PCI	CIN, Scr, Cys C, eGFR
Xue et al.	2017	193/193	Rhodiola injection 250 mL, ivgtt, qd	3 days before and after operation	Hydration therapy	Lopamidol	PCI	BUN, Scr, Cys C, Ccr, eGFR
Li Xiao et al.	2017	78/80	Danshen chuanxiongqin injection 10 mg + 5% GS 250 mL, ivgtt, qd	14 days	Hydration therapy	Unclear	PCI	CIN, BUN, Scr, Ccr, CRP
Wang et al.	2013	31/31	Shenkang injection 100 mL + NS 250 mL, ivgtt, qd	12 h before and 24 h after operation	Hydration therapy	Lopromide	PCI/CAG	CIN, Scr, NGAL

**Table 2.** Methodological quality of included studies

Author	Year	Random allocation method	Allocation concealment	Blind method	Completion of the outcome data	Selective outcome reporting	Baseline data comparability	Follow-up
Dong et al.	2013	Unclear	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Li et al.	2017	Unclear	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Yao et al.	2016	Random number table	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Wang et al.	2011	Random number table	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Niu et al.	2015	Unclear	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Zhang et al.	2015	Random number table	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Qian et al.	2008	Unclear	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Zhou et al.	2017	Random number table	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Xu et al.	2013	Random number table	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Huang et al.	2017	Computer randomization method	Unclear	Single blind	Completed	Low risk	Comparable	1 month
Xue et al.	2017	Unclear	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Li Xiao et al.	2017	Unclear	Unclear	Unclear	Completed	Low risk	Comparable	N/A
Wang et al.	2013	Random number table	Unclear	Unclear	Completed	Low risk	Comparable	N/A

creatinine clearance (Ccr), and serum cystatin C (Cys C) after the operation; and (6) article was published in Chinese or English language.

### Exclusion criteria

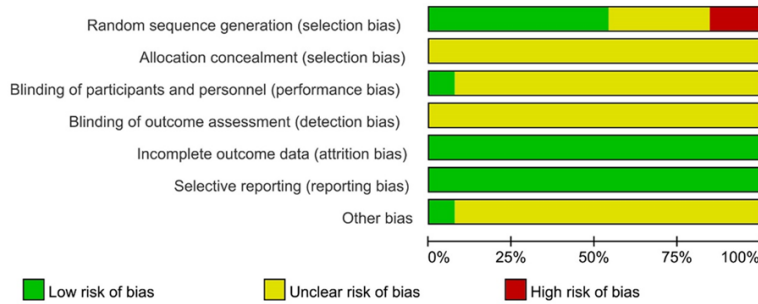
Articles were excluded from the study if they met any of the following criteria: (1) the trial applied a retrospective or nonrandomized design; (2) injection was used in combination

with other herbal medicines; (3) angiography was used for arteries other than coronary (renal artery angiography or cerebral artery angiography, etc.); or (4) data were incomplete or erroneous.

### Data extraction and assessment of risk of bias

Data were independently extracted by two reviewers (Jiandong Chen and Peng Yu) using a

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**Figure 2.** Risk of bias graph of the included trials.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dong et al. 2013	?	?	?	?	+	+	?
Huang et al. 2017	+	?	+	?	+	+	+
Li et al. 2017	●	?	?	?	+	+	?
Li Xiao et al. 2017	?	?	?	?	+	+	?
Niu et al. 2015	●	?	?	?	+	+	?
Qian et al. 2008	?	?	?	?	+	+	?
Wang et al. 2011	+	?	?	?	+	+	?
Wang et al. 2013	+	?	?	?	+	+	?
Xue et al. 2017	?	?	?	?	+	+	?
Xu et al. 2013	+	?	?	?	+	+	?
Yao et al. 2016	+	?	?	?	+	+	?
Zhang et al. 2015	+	?	?	?	+	+	?
Zhou et al. 2017	+	?	?	?	+	+	?

**Figure 3.** Summary of risk of bias of all included studies.

data collection table. The collection of information included the author(s), publication year,

research design, size of the sample, patient characteristics, CIN diagnosis criteria, type of Chinese medicine injections, treatment duration, and withdrawal. Bias risk and quality assessments were conducted by other two reviewers (Le Shen and Li Yang) using the Cochrane Handbook, Version 5.1.0. The bias risk assessment tool involved seven aspects: random

sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias. Three levels were used to evaluate the trials: low risk of bias (all the items were in low risk of bias), high risk of bias (at least one item was in high risk of bias), and unclear risk of bias (at least one item was in unclear risk of bias). Disagreements were resolved through arbitration with a third person (Haibo Shi).

## Data analysis

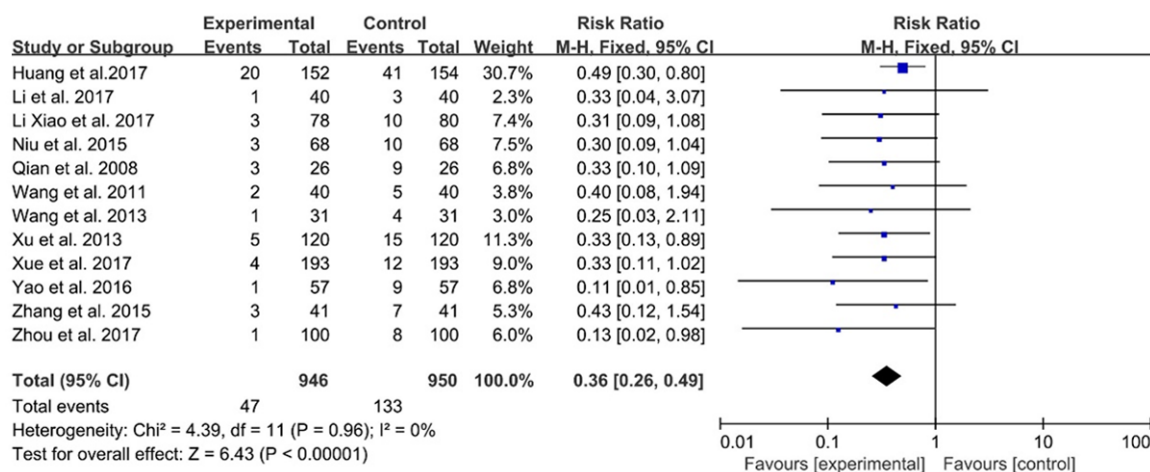
Review Manager Software (Version 5.3, Copenhagen, Nordic Cochrane Center, Cochrane Collaboration, 2014) was used for statistical analysis. Heterogeneity between similar studies was evaluated by the chi-square test and  $I^2$  statistic. Moderate heterogeneity was assumed to exist between studies when  $P < 0.05$  and  $I^2 > 50\%$ , requiring the need for sensitivity analysis. The enumeration data were evaluated as dichotomous data and expressed as risk ratios (RRs) with 95% confidence intervals (CIs). The measurement data were evaluated as continuous data and expressed as mean differences (MDs) with 95% CIs. A  $P$  value greater than 0.05 was considered statistically significant.

## Results

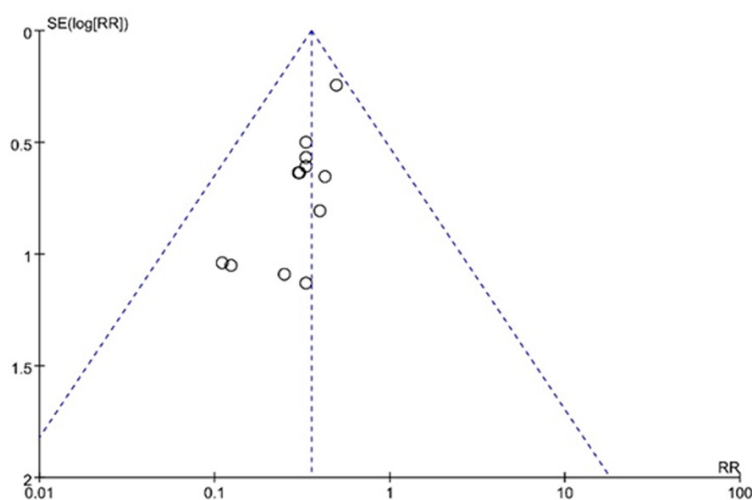
### Database search

After conducting a primary search in the selected databases, we identified 690 relevant articles: 656 from CNKI, 15 from VIP, and 19 from Wanfang Data. No relevant articles were found in PubMed or the Cochrane Controlled Trials

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**Figure 4.** Incidence rate of CIN comparing Chinese medicine injection to control.



**Figure 5.** Funnel plot of incidence rate of CIN.

Register. With careful selection, a total of 565 studies were excluded due to duplication. By reading the titles and abstracts, we excluded 83 studies due to lack of relevance. The full text of the remaining 42 articles was read and assessed in detail. In total, 13 articles were included for systematic review and meta-analysis. The article selection process is summarized in **Figure 1**.

All included articles reported RCTs that were conducted in China and were published in Chinese. An overview of the 13 included studies is shown in **Table 1**. Together, these studies represented 2022 patients undergoing PCI/CAG who were treated with Chinese medicine injection or a control injection to prevent CIN. All studies exhibited comparable baseline

patient characteristics, and there were no significant differences among them.

### Study characteristics

Of the included studies, 8 enrolled patients who underwent PCI only [7, 9-11, 14, 16-18], 2 enrolled patients who underwent CAG only [8, 13], and 3 enrolled patients who underwent PCI or CAG [12, 15, 19]. For clinical outcomes, 12 studies evaluated the CIN incidence rate [8-19], 7 evaluated 24-h Scr levels [7, 9, 10, 12-14, 19], 9 articles evaluated 48-h Scr levels [7-14, 19], and 7 evaluated 72-h Scr levels [9, 10, 12, 14, 15, 17, 18]. In addition, 5 studies observed Ccr levels at 48 h after operation [7, 8, 11, 13, 14], and 3 detected Cys C levels at 24 h after the operation [9, 10, 12]. The characteristics of these included studies are summarized in **Table 1**.

### Quality evaluation of included studies

The majority of the included studies were found to be of poor methodological quality, according to the predefined quality assessment criteria (**Table 2**). The randomized allocation of participants was mentioned in all studies. However, only 7 studies reported the methods for sequence generation: 6 by random number table [9, 10, 12, 14, 15, 19] and 1 by computer



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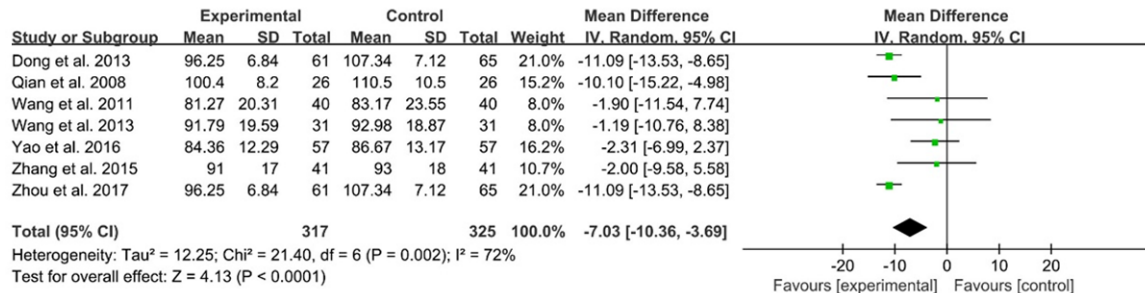


Figure 6. Scr level 24 hours after operation between two groups.

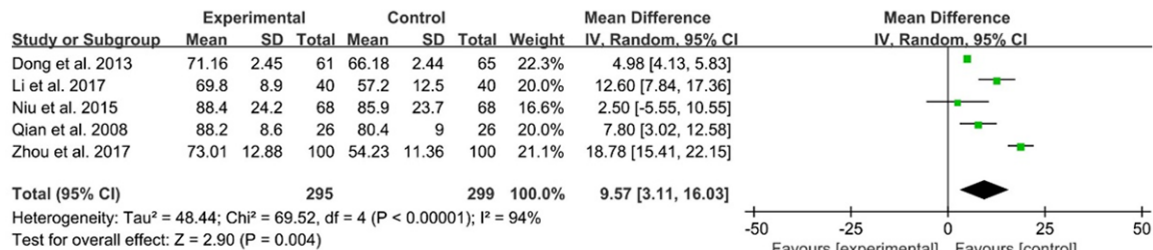


Figure 7. Scr level 48 hours after operation between two groups.

randomization [16]. The remaining 6 studies [7, 8, 11, 13, 17, 18] were assessed with a high risk of bias because the reported randomization was not detailed enough to make a judgment. No studies reported adequate allocation concealment. In addition, no double-blinding was applied in these studies; however, one study [16] used single-blind methods.

None of the studies reported dropout or withdrawal. None of the studies had a pretrial estimation of sample size. Although one study [16] mentioned follow-up, none reported whether they had used intention-to-treat analysis. All studies provided baseline data for comparability among groups. The results of the risk of bias assessment are summarized in **Figures 2** and **3**, as produced by RevMan 5.3.

### Incidence rate of CIN

**Figure 4** presents the findings of the included studies for meta-analysis. A total of 12 articles [8-19] reported the incidence rate of CIN, including 946 patients in a Chinese medicine injection group and 950 patients in a control group. Because the results of the meta-analysis demonstrated that the heterogeneity of each study was low (I<sup>2</sup> = 0%; P = 0.98; **Figure 5**), the fixed-effects model was chosen. The inci-

dence of CIN was 4.97% (47/946) in the Chinese medicine injection group and 14% (133/950) in the control group. This difference in CIN incidence between the two groups was statistically significant (RR: 0.36; 95% CI: 0.26-0.49; P < 0.0001), suggesting that Chinese medicine injection was superior to standard hydration therapy in preventing CIN.

### Scr level 24 h after operation

For analysis of Scr levels at 24 h after operation, the random-effects model was applied due to the high heterogeneity (I<sup>2</sup> = 72%, P = 0.002). Among the 7 studies [7, 9, 10, 12-14, 19] reporting Scr levels at 24 hours after operation (injection group: 317 patients; control group: 325 patients), patients receiving Chinese medicine injection had significantly lower levels of Scr than those who received standard hydration therapy (MD: -7.03; 95% CI: -10.36, -3.69; P < 0.0001; **Figure 6**).

### Scr level 48 h after operation

For analysis of Scr levels at 48 h after operation, the random-effects model was used (I<sup>2</sup> = 94%, P < 0.0001). Among the 9 articles [7-14, 19] reporting Scr levels at 48 h after operation, meta-analysis showed a significant amelioration in the Chinese medicine injection group.

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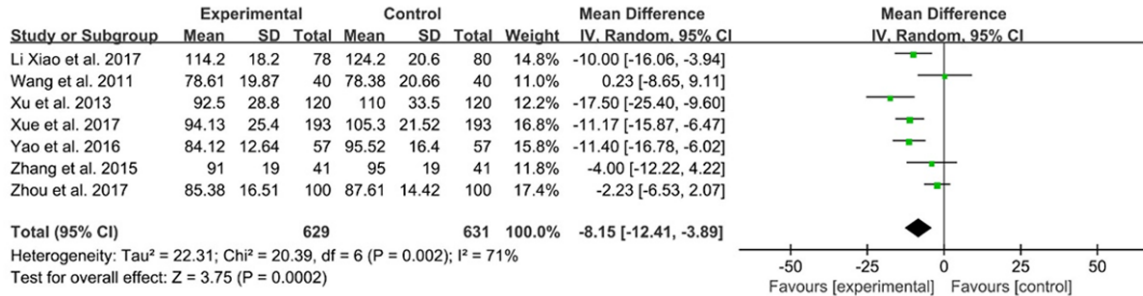


Figure 8. Scr level 72 hours after operation between two groups.

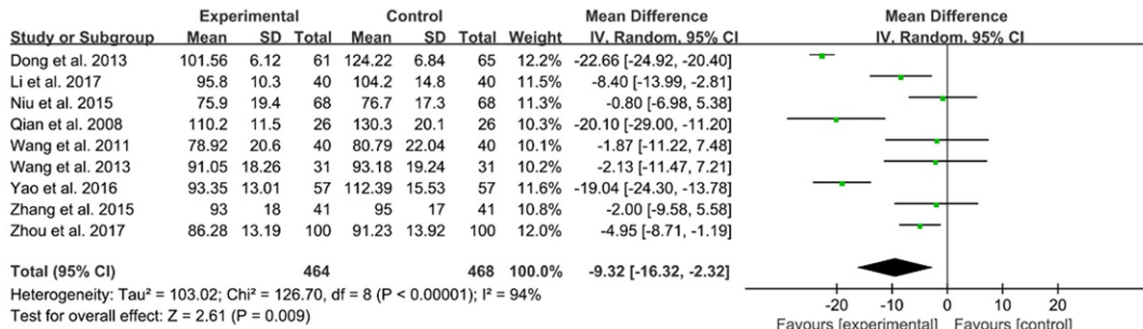


Figure 9. Ccr level 48 hours after operation between two groups.

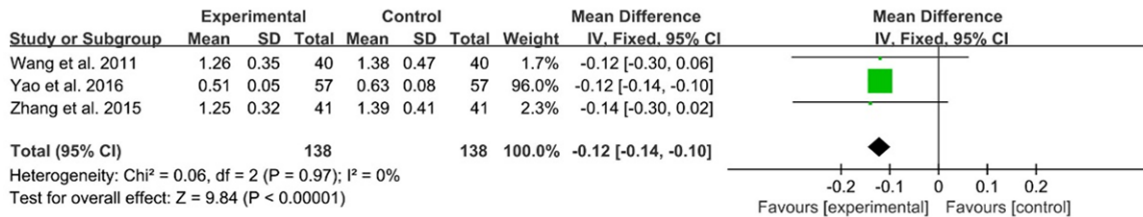


Figure 10. Cys C level 24 hours after operation between two groups.

The results showed lower Scr levels in the Chinese medicine injection group than in the control group at 48 h after operation; this difference was statistically significant (MD: -9.32; 95% CI: -16.32; -2.32; P = 0.009; **Figure 7**).

### Scr level 72 h after operation

For analysis of Scr levels at 72 h after operation, 7 studies included 629 patients in the Chinese medicine injection group and 631 patients in the control group [9, 10, 12, 14, 15, 17, 18]. Meta-analysis showed lower Scr levels in the Chinese medicine injection group than in the control group at 72 h after operation (MD: -8.15; 95% CI: -12.41, -3.89; P = 0.0002; **Figure 8**).

### Ccr level 48 h after operation

Of the 5 studies reporting Ccr levels at 48 h after operation [7, 8, 11, 13, 14], there were 295 patients in the Chinese medicine injection group and 299 patients in the control group. Meta-analysis demonstrated higher Ccr levels in the Chinese medicine injection group than in the control group at 48 h after operation; this difference was statistically significant (MD: 9.57; 95% CI: 3.11, 16.03; P = 0.004; **Figure 9**).

### Cys C level 24 h after operation

Of the three studies [9, 10, 12] reporting Cys C levels at 24 h after operation, meta-analysis found that the Chinese medicine injection

group achieved a greater improvement in these levels than the control group (MD: -0.12; 95% CI: -0.14, -0.10;  $P < 0.0001$ ; **Figure 10**). This result indicated that Chinese medicine injection is significantly better than conventional hydration therapy for reducing Cys C levels in patients who underwent PCI/CAG. Heterogeneity was low among these three studies ( $I^2 = 0\%$ ,  $P = 0.97$ ).

### Discussion

CIN is a type of acute renal function damage caused by intravenous administration of a contrast agent. However, the mechanisms of action that results in CIN are still unclear. Several potential mechanisms have been proposed, including renal medulla ischemia due to changes in hemodynamics [20, 21], toxic injury of renal tubules epithelial cells and vascular endothelium [22, 23], and renal tubular injury caused by an increase in oxygen free radicals [24, 25]. There are several widely accepted risk factors for CIN: preexisting renal dysfunction, diabetes mellitus, congestive heart failure, hypovolemia, combined use of nephrotoxic drugs, and hypercalcemia [26]. The morbidity of CIN may be also associated with the type and dosage of the contrast agent; most studies suggest that hyperosmolar contrast agents and high dosage use are more likely to cause CIN [27]. In the field of coronary artery intervention, CIN has become another major challenge for cardiologists, following restenosis and stent thrombosis.

At present, there is no consensus on the prevention and treatment of CIN. The European Society of Urogenital Radiology (ESUR) recommended that prophylactic intravenous hydration in patients at risk for CIN before and after contrast agent application may be beneficial [28]. Some researchers believe that oxygen free radical injury and inflammation reaction play a major role in the pathogenesis of CIN [29]. Many Chinese medicines have been reported to contain the ability to inhibit oxidative stress injury and reduce cell inflammatory response, thereby protecting cell function. Modern pharmacological studies have confirmed that salvianolic acid A, a major active component of Danshen (*Salvia miltiorrhiza*), has a potent effect on reducing myocardial cell apoptosis and damage induced by oxidative

stress ( $H_2O_2$ ) [30]. Ligustrazine, one of the primary effective components of Chuanxiong (*Ligusticum wallichii*), could provide renal protection against ischemia/reperfusion injury by downregulating oxidative stress and inhibiting the overexpression of inflammatory factors (ICAM-1 and TNF- $\alpha$ ) [31]. Ferulic acid, another primary effective component of Chuanxiong, has been found to have a cardioprotective effect by increasing superoxide dismutase activity and NO levels and inhibiting oxidative stress in the plasma and myocardium of diabetes rats [32]. Astragalosie IV, the effective component of Huangqi (*Radix Astragali*) demonstrated the abilities of attenuating oxidative stress [33] and suppressing inflammation [34]. Safflower yellow A, extracted from Chinese medicine safflower (*carthamus tinctorius*), was reported to protect neonatal rat cardiomyocytes against hypoxia/reoxygenation damage in vitro [35]. In addition, according to a recent study, *Rhodiola crenulata* root extract significantly ameliorates oxidative stress of human umbilical vein endothelial cells in high glucose conditions by regulation of the AMPK-Akt-eNOS-NO pathway [36]. As a complementary and alternative therapy, Chinese medicine injection has sparked a wide interest among CIN researchers for its potential ability to enhance the preventive effect of conventional hydration therapy. Moreover, Chinese medicine injection with pharmacological effects of anti-oxidative stress and anti-inflammation may be beneficial for primary diseases involving CAD, heart failure, and diabetes mellitus.

This is the first meta-analysis evaluating the efficacy of Chinese medicine injection for preventing CIN after PCI/CAG. A total of 13 RCTs representing 2022 patients were included in this review. We considered the levels of Scr, Ccr, and Cys C at various time points post-operation to evaluate the efficacy of this therapy. Scr and Ccr are sensitive indicators for renal function assessment in CIN diagnosis and evaluation, and measuring their levels at different time points can reflect changes in renal function. Furthermore, serum Cys C is another important indicator for CIN. The advantage of this indicator is that its levels are rarely influenced by external factors such as age and gender. Our results suggest that Chinese medicine injection is associated with a significant reduction in the postoperative incidence rate of CIN.



This finding was bolstered by corresponding reductions in the levels of Scr, Ccr, and Cys C. From these results, a preliminary conclusion could be that Chinese medicine injection is able to prevent the occurrence of CIN and protect renal function in patients undergoing PCI/CAG. However, these results are based on studies with small sample sizes, and therefore, we recommend further investigation on this topic.

There are several limitations in our meta-analysis. First, high heterogeneity was found in our meta-analysis of postoperative Scr and Ccr levels. This heterogeneity may be attributed to several potential confounding factors. The dose of solvents and the duration of intervention were inconsistent among the included studies. The dose of solvents ranged from 100 mL to 500 mL, and the duration of intervention ranged from 24 h to 14 days, both of which could influence the experimental results. In addition, the dose of contrast agent used in different studies were unclear. Larger doses of contrast agent may cause more serious renal injury. Second, although all included studies were RCTs, six studies simply mentioned "randomization" without a detailed description. Only one study mentioned blinding and follow-up, and none of the studies mentioned the use of allocation concealment. Third, all included studies were conducted in China, demonstrating a lack of RCTs on this topic from Europe and North America.

In conclusion, this meta-analysis indicates that Chinese medicine injection can decrease the incidence of CIN and reduce the levels of Scr, Ccr, and Cys C in patients undergoing PCI/CAG. Nevertheless, an appropriate administration strategy for Chinese medicine injection, including dose and duration, is required. Thus, researchers need to design large-scale and multi-center RCTs with long-term follow-up in the future to obtain more powerful evidence and clinical guidance for this therapy.

## Acknowledgements

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## Disclosure of conflict of interest

None.

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