Systematic Review and Meta-Analysis

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# Efficacy of short-term moderate or high-dose rosuvastatin in preventing contrast-induced nephropathy

## A meta-analysis of 15 randomized controlled trials

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**Abstract**

**Background:** The prophylactic efficacy of statin pretreatment for the prevention of contrast-induced nephropathy (CIN) in patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) remains controversial. The aim of the study was to perform a meta-analysis of randomized controlled trials (RCTs) to assess the effectiveness of short-term moderate or high-dose rosuvastatin pretreatment in preventing CIN.

**Methods:** We included RCTs comparing short-term moderate or high-dose rosuvastatin treatment versus low-dose rosuvastatin treatment or placebo for preventing CIN. The primary endpoint was the incidence of CIN within 2 to 5 days after contrast administration, and related-parameters including serum creatinine (SCr), cystatin C (CysC), hypersensitive C-reactive protein (hs-CRP), urine microalbumin (mALB) were also extracted.

**Results:** Fifteen RCTs with a total of 2673 patients were identified and analyzed. Patients who received moderate or high-dose rosuvastatin pretreatment had a 55% lower risk of CIN compared with low-dose rosuvastatin pretreatment or placebo group based on a fixed effect model (RR = 0.45, 95% CI 0.35–0.58, $P < .0001$). The benefit of moderate or high-dose rosuvastatin was consistent in both comparisons with low-dose rosuvastatin (RR = 0.40, 95% CI 0.27–0.59, $P < .0001$) or placebo (RR = 0.45, 95% CI 0.35–0.58, $P < .0001$). And moderate (20 mg) or high dose (≥40 mg) rosuvastatin significantly reduced the incidence of CIN compared with the control (RR = 0.39, 95% CI 0.29–0.54, $P < .0001$, RR = 0.56, 95% CI 0.37–0.85, $P = .006$, respectively). Subgroup analysis showed that moderate or high-dose rosuvastatin pretreatment could decrease the incidence of CIN in patients with chronic kidney disease (CKD) (RR = 0.53, 95% CI 0.30–0.93, $P = .03$) or diabetes mellitus (DM) (RR = 0.51, 95% CI 0.31–0.86, $P = .01$) or acute coronary syndrome (ACS) patients undergoing PCI (RR = 0.52, 95% CI 0.35–0.76, $P = .0009$) or in studies which received mean contrast volume ≥110 mL (RR = 0.43, 95% CI 0.32–0.58, $P < .0001$). The SCr, CysC, hs-CRP, and mALB after the operation in the moderate or high-dose rosuvastatin group were lower than those of low-dose rosuvastatin group.

**Conclusion:** This meta-analysis demonstrated that moderate or high-dose rosuvastatin treatment could reduce the incidence of CIN in patients undergoing CAG or PCI. Moreover, moderate or high-dose rosuvastatin would be beneficial in high-risk patients with CKD or DM or undergoing PCI.

**Abbreviations:** 95% CI = 95% confidence interval, ACS = acute coronary syndrome, CAG = coronary angiography, CIN = contrast-induced nephropathy, CKD = chronic kidney disease, CysC = cystatin C, DM = diabetes mellitus, hs-CRP = hypersensitive C-reactive protein, mALB = urine microalbumin, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, RR = risk ratio, SCr = serum creatinine, SMD = standardized mean difference.

**Keywords:** contrast-induced nephropathy, coronary angiography, percutaneous coronary intervention, rosuvastatin

## 1. Introduction

Contrast-induced nephropathy (CIN) is a common complication of diagnostic or interventional procedures caused by intravascular contrast median administration and is defined as an increase in baseline serum creatinine (SCr) level by ≥ 25% or an absolute increase ≥ 44.2 umol/L within 48 or 72 hours after administration of contrast media.[1] CIN has become the third leading cause of hospital-acquired acute kidney injury following surgical operation and nephrotoxic drug damage, accounting for 11%.[2] The reported incidence of CIN ranges from 5% in low-risk patients to 50% high-risk patients, especially in the patients with diabetes mellitus (DM) or pre-existing renal insufficiency.[3] It is closely associated with prolonged hospitalization, increased costs, and increased short and long-term morbidity and mortality.[1] Therefore, a number of strategies

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were conducted to prevent the incidence of CIN. However, none of strategies was proved effective in preventing CIN. Currently, European Society of Cardiology/European Association for Cardio-Thoracic Surgery or the ACCF/AHA/SCAI guideline merely recommend the intravenous hydration, use of iso- or low-osmolar contrast media, minimization of contrast volume to prevent the occurrence of CIN.[4,5]

Recently, increasing evidence has suggested that statins play a reno-protective role in the progression of CIN by its pleiotropic effect rather than lipid lowering effect. The pleiotropic effect includes antioxidant, anti-inflammatory, antithrombotic, and antiapoptotic properties with enhancement of endothelial nitric oxide production and reduction of endothelin secretion.[6] However, the pleiotropic effects of different statins were different. Previous randomized controlled trials (RCTs) and meta-analyses focused on classic lipophilic statin-atorvastatin for the prevention of CIN have been published with conflicting results. The hydrophilic statin-rosuvastatin may have a better tendency to prevent CIN than others, probably owing to a longer plasma half-life and stronger anti-inflammatory effect. Therefore, we performed a meta-analysis of RCTs to evaluate the efficacy of short-term moderate or high-dose rosuvastatin pretreatment for the prevention of CIN compared with low-dose rosuvastatin or placebo, especially in high-risk patients with DM or chronic kidney disease (CKD) undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI).

## 2. Methods

### 2.1. Ethics statement

As this study is a meta-analysis, ethical approval was not required.

### 2.2. Search strategy

We performed a literature search in PubMed, EMBACE, Web of science, CBM, CNKI, and Wanfang database from the date of inception to March 2017. The following search formula (rosuvastatin OR rosuvatatin calcium OR crestor) AND (contrast media OR contrast agent OR radiocontrast media) AND (acute kidney injury OR acute renal insufficiency OR acute renal failure) AND (coronary angiography OR percutaneous interventions OR cardiac catheterization) was used in English database. Rosuvastatin AND contrast-induced nephropathy was used in Chinese database. Language was restricted in English or Chinese.

### 2.3. Study selection

Two independent reviewers (ML and SY) screened the titles and abstracts of all selected articles. Only studies that were clearly irrelevant were excluded at this stage. Any disagreements between the investigators were resolved by a third reviewer (NF). Studies were included if they met the following criteria: RCTs investigating the efficacy of rosuvastatin in preventing CIN. The intervention was moderate or high-dose rosuvastatin (rosuvastatin 20 mg as moderate dose, rosuvastatin 40 mg as high dose) versus low-dose rosuvastatin treatment (defined as a daily dose of less than 10 mg) or placebo. Studies which applied concomitant prophylactic strategies (such as N-acetylcysteine) were only included if both arms received. Studies reported the definitions and incidences of CIN in both arms. Short-term treatment of rosuvastatin was defined as from preoperation to postoperation 7 days. Excluded criteria for studies were as follows: non-RCTs; duplicated publications; abstract that did not contain complete results. The primary endpoint was the incidence of CIN, defined as an increase in baseline SCr level of 25% or an absolute increase of 44.2 umol/L within 2 to 5 days after the administration of contrast media.

### 2.4. Data extraction and quality assessment

Data was extracted by 2 independent reviewers (ML and SY). The extracted data included patient characteristics (number of patients, mean year, male proportion, proportion with DM, baseline SCr and estimated glomerular filtration rates (eGFR), postprocedural change in SCr, cystatin C (CysC), hypersensitive C-reactive protein (hs-CRP) and urine microalbumin (mALB)), inclusion and exclusion, type and dose of contrast media, protocols for treatment, hydration protocols, and definitions and incidences of CIN. Two reviewers independently assessed the methodological quality of identified studies. The quality assessment was judged on concealment of treatment allocation, similarity of the study groups at baseline, eligible criteria, use of any blinding procedure, completeness of follow-up, and intention-to-treat analysis. Disagreements were adjudicated by a third reviewer (NF).

### 2.5. Statistical analysis

All statistical analyses were conducted by using Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Dichotomous data (incidence of CIN) were shown as risk ratio (RR) with 95% confidence interval (CI). Continuous data (SCr, CysC, hs-CRP, and mALB) were given as standardized mean difference (SMD) with 95% CI. The Q statistic was calculated and heterogeneity was quantified using the $I^2$ statistic. When $I^2>50\%$, a random-effect model was used. Otherwise, a fixed-effect model was employed. A funnel plot was conducted to evaluate publication bias. To further identify potential differences in treatment across the trials, we also conducted several subgroup analyses based on experiment property (moderate or high dose rosuvastatin) and control property (low-dose rosuvastatin or placebo), patients with CKD or DM, ACS patients undergoing PCI and studies with mean contrast volume $\geq$110 mL. All the tests were 2 tailed and $P \leq .05$ was considered significant in this meta-analysis.

## 3. Results

### 3.1. Search results

The flow chart of search strategy is provided (Fig. 1). Three hundred seventy-eight potentially relevant articles were identified from initial search and 313 articles were remained after adjusting for duplication. Of these, 227 articles were excluded after independently screening the titles and abstracts, including 181 articles irrelevant to our aim, 44 narrative or systemic reviews, and 2 letters. Ultimately, 86 relevant articles were reviewed in full text. A further 70 articles were excluded after careful review of full text, including 3 articles for non-RCTs, 9 articles that did not report the definitions or incidences of CIN, 10 narrative or systemic reviews, 10 articles comparing rosuvastatin and other statins, 15 articles for repeated trial database, 2 articles for multiple treatment group according to rosuvastatin dose and 1

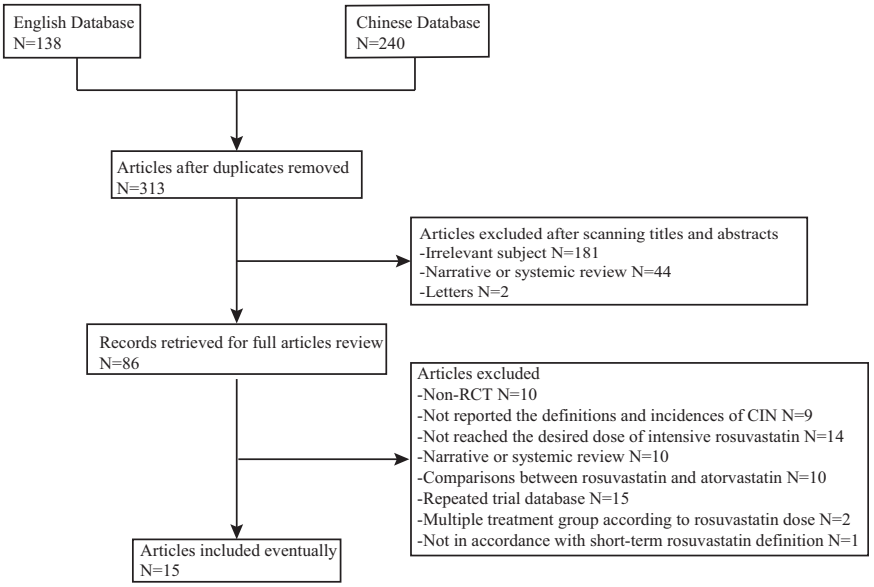


**Figure 1.** Flow diagram of study selection.

article was not in accordance with short-term rosuvastatin definition. Consequently, 15 RCTs[7–21] with a total of 2673 patients undergoing CAG or PCI met inclusion criteria and were included in the meta-analysis.

### 3.2. Characteristics of included studies

The main characteristics of the included studies are summarized in Table 1. Among the 15 trials, 11 trials[7–17] compared moderate or high-dose versus low-dose rosuvastatin pretreatment. Among all the patients, 1335 patients were assigned to moderate or high-dose rosuvastatin treatment group and 1338 patients were assigned to low-dose rosuvastatin or placebo treatment group. The mean patients' ages ranged from 50.7 ± 7.5 to 68.4 ± 9.5 years. The mean baseline SCr ranged from 64.90 ± 14.83 umol/L to 1.4 ± 0.5 mg/dL. All trials evaluated patients undergoing CAG or PCI, including 9 articles[7,9,10,13–17,21] which exclusively enrolled the patients undergoing PCI and 3 articles[12,18,20] which exclusively enrolled the patients undergoing CAG. The criteria used to define CIN were similar among the individual studies. Ten trials[7,8,10,11,14–19] used the definition of an increase ≥25% from baseline or an absolute increase in SCr ≥44.2 umol/L within 72 hours after contrast media exposure, and 4 trials[9,12,13,20] employed the same SCr change within 48 hours, and 1 trial[21] within 24 hours. Majority of trials used low-osmolar contrast media, whereas 3 trails[9,11,19] used iso-osmolar contrast media, and 1 trial[21] used high- and low-osmolar contrast media. The highest and lowest mean volumes of contrast media were 50.5 ± 15.0 and 222.19 ± 18.34 mL, respectively. The prevalence rates of DM varied from 20% to 54% in the moderate or high-dose rosuvastatin treatment group and 23% to 51% in the low-dose rosuvastatin or placebo treatment group. And 2 trials[11,15] only assessed patients with DM. One trial[18] exclusively evaluated patients with CKD which was defined eGFR <60 mL/min/1.73 $m^2$, and 2 trials[19,21] enrolled CKD patients defined as creatinine clearance rate <60 mL/min, and 1 trial[8] enrolled patients with eGFR>60 mL/min/1.73 $m^2$, and 1 trial[11] enrolled patients with 60 mLmin/1.73 $m^2$ ≤ eGFR ≤90 mL/min/1.73 $m^2$, and 6 trials[7,12–15,17] excluded patients with severe renal insufficiency, and 4 trials[9,10,16,20] did not record precise renal function.

### 3.3. Assessment of the study quality and publication bias

The quality characteristics of included studies are provided in Table 2. All of the studies included patients with similar baseline characteristics and provided detail about the eligible criteria and completeness of follow-up. Of the 15 studies, 7 studies described the detail methods of randomization and 1 study reported blinding of patients and providers to treatment assignment and 1 study provided the mention-to-treat analysis. The funnel plot was relatively symmetrical (Fig. 2).

### 3.4. Study outcomes

***3.4.1. Incidence of CIN.*** Patients who received moderate or high-dose rosuvastatin pretreatment had a 55% lower risk of CIN compared with low-dose rosuvastatin pretreatment or placebo group based on a fixed effect model (RR = 0.45, 95% CI 0.35–0.58, $P < .0001$). No significant heterogeneity was present across studies ($I^2 = 0\%$, $P = .93$) (Fig. 3).

***3.4.2. Parameters changes in SCr, CysC, hs-CRP, and mALB.*** The SCr values after operation 24 and 72 hours were both lower in the moderate or high-dose rosuvastatin group than that in the low-dose rosuvastatin group, with statistical significance only existing in postoperation 72 hours (SCr 24 hours: SMD = −0.30, 95% CI −0.62 to 0.01, $P = .06$; SCr 72 hours: SMD = −0.27, 95% CI −0.49 to −0.05, $P = .02$) (Fig. 4). The levels of CysC and hs-CRP after operation 24 and 72 hours were significantly lower in the moderate or high-dose rosuvastatin group than those in the low-dose rosuvastatin group (CysC 24 hours: SMD = −0.54, 95% CI −1.02 to −0.05, $P = .03$; CysC 72 hours: SMD = −0.66, 95% CI −1.11 to −0.21, $P = .004$; hs-CRP 24 hours: SMD = −0.54, 95% CI −0.96 to −0.12, $P = .01$; hs-CRP 72 hours: SMD = −1.01, 95% CI −1.45 to −0.56, $P < .0001$) (Figs. 5 and 6). The mALB values after operation 24

**Table 1**

**Characteristics of patients and interventions of included studies.**

| Author (y) | Patients number E/C | Inclusion criteria | Protocol | Definition of CIN | Contrast agent | Contrast volume, mL E/C | Mean age, year E/C | Mean baseline SCr, umol/L or mg/dL E/C | DM proportion, % E/C |
|---|---|---|---|---|---|---|---|---|---|
| Ahmed Eltahawy (2013) | 100/100 | Patients undergoing CAG | Rosuvastatin 20 mg/d from 3 d before to 7 d after procedure versus placebo | ≥25% SCr or ≥ 44.2 umol/L SCr within 48 h | Iopromide | 120.8±17.8/ 122.5±16.1 | 54.811.0/ 52.1±10.7 | 0.81±0.2 mg/dL 0.81±0.3 mg/dL | 49/37 |
| Dongwei Yang (2013) | 41/41 | ACS patients undergoing PCI | Rosuvastatin 20 mg/d versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 48 h | Iopromide | 128.0±10.6/ 120.0±11.1 | 59.21±7.00/ 62.54±6.10 | 74.1±17.22/ 73.3±17.41 | 54/51 |
| Jianchang Yang (2014) | 114/106 | Patients undergoing CAG | Rosuvastatin 20 mg/d 2–3 d before procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 48 h | Iohexol | 51.5±14.0/ 50.5±15.0 | 66.9±10.4/ 68.4±9.5 | 82.2±22.25/ 75.74±20.23 | 46/43 |
| Jun Fan (2016) | 60/60 | ACS patients undergoing PCI | Rosuvastatin 20 mg/d for 3 d before procedure, followed by 10 mg/d after procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 24–48 h | Iodixanol | 219.34±15.39/ 222.19±18.34 | 55.33±2.12/ 55.10±3.13 | 80.76±11.84/ 81.09±11.30 | 23/23 |
| Ling Zhang (2013) | 41/41 | Patients with DM undergoing PCI | Rosuvastatin 20 mg/d from 2 d before procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 48–72 h | Iohexol | 132.1 ± 52.9/ 131.3 ± 68.2 | 50.7±7.5/ 52.5±7.3 | NS NS | NS |
| Lingyu He (2014) | 30/30 | AMI patients undergoing urgent PCI | Rosuvastatin 40mg preload followed by 20 mg/d versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 72 h | Iohexol | 125±60/ 120±50 | 65.2±13/ 66.4±11 | 70.6±12.2/ 68.4±14.6 | NS |
| Mario Leoncini (2014) | 252/252 | NSTE-ACS patients undergoing CAG with or without PCI | Rosuvastatin 40mg followed by 20 mg/d versus placebo | ≥25% SCr or ≥ 44.2 umol/L SCr within 72 h | Iodixanol | 149.7±86.8/ 138.2±77.8 | 66.2±12.4/ 66.1±13.5 | 0.95±0.27 mg/dL/ 0.96±0.28 mg/dL | 20/23 |
| Min Liu (2015) | 38/38 | CKD patients with DM undergoing CAG with or without PCI | Rosuvastatin 20 mg/d from 3 days before procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 72 h | Iodixanol | 117.6±43.3/ 115.2±42.5 | 60.8±10.50/ 61.3±9.82 | 101.6±10.3/ 101.6±10.3 | 100/100 |
| Okay Abaci (2015) | 110/110 | Patients undergoing CAG | Rosuvastatin 40mg within 24 h before and 20 mg/d for 2 d versus placebo | ≥25% SCr or ≥ 44.2 umol/L SCr within 48–72 h | Ioversol | 139.2±77.4/ 117.7±56.8 | 67.5±8.9/ 67.7±8.9 | 1.3±0.4 mg/dL/ 1.4±0.5 mg/dL | 48/46 |
| Oliveira (2012) | 67/68 | ACS patients undergoing PCI | Rosuvastatin 40mg 2–6 h before procedure versus placebo | ≥25% SCr or ≥ 44.2 umol/L SCr within 24 h | High and low osmolarity | 72.2/78.2 | 59.4±8.6/ 62.2±9.8 | 0.89±0.24 mg/dL/ 0.98±0.21 mg/dL | 30/32 |
| Peng Guo (2016) | 100/102 | | | | Iopamidol | NS | 51.6±12.4 | 83.72±16.21/ | NS |

| Author (y) | Patients number E/C | Inclusion criteria | Protocol | Definition of CIN | Contrast agent | Contrast volume, mL E/C | Mean age, year E/C | Mean baseline SCr, umol/L or mg/dL E/C | DM proportion, % E/C |
|---|---|---|---|---|---|---|---|---|---|
| | | STEMI patients undergoing PCI | Rosuvastatin 20 mg/d from 1 d before to 3 d after procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 48–72 h | | | | | |
| Wei Tian (2015) | 46/46 | UA patients with DM undergoing CAG with or without PCI | Rosuvastatin 20 mg/d from 2 d before to 2 d after procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 24–72 h | Iohexol | 125.26±31.31/ | 64.28±4.93/ | 82.50±25.14<br>83.13±11.44/ | 100/100 |
| Yuming Lu (2016) | 180/188 | Patients undergoing PCI | Rosuvastatin 20 mg/d from 3 d before to 3 d after procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 72 h | NS | 119.33±32.86<br>162.5±71.8/ | 65.26±5.32<br>55.3±9.2/ | 82.54±14.17<br>72.3±16.1/ | 48/49 |
| Zhihong Zhou (2015) | 72/70 | ACS patients undergoing PCI | Rosuvastatin 20 mg/d from 1 day before to 7 d after procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 24–72 h | Iopromide | 161.2±70.3<br>NS | 59.1±7.6<br>62.1±10.8/ | 73.6±14.6<br>64.90±14.83/ | NS |
| Zhuowen Xu (2012) | 91/91 | Patients undergoing PCI | Rosuvastatin 20 mg/d 3 d before procedure versus rosuvastatin 10 mg/d | ≥25% SCr or ≥ 44.2 umol/L SCr within 48–72 h | Iohexol | NS | 61.6±11.3<br>52.3±11.2 | 65.97±15.81<br>83.45±18.27/<br>84.42±19.44 | NS |

ACS = acute coronary syndrome, CAG = coronary angiography, CIN = contrast-induced nephropathy, CKD = chronic kidney disease, DM = diabetes mellitus, NS=not specified or available, PCI = percutaneous coronary intervention, SCr = serum creatinine,

**Table 2**

**Quality of included RCTs.**

| Study | Jadad score | Allocation concealment | Similarity of baseline characteristics | Eligible criteria | Blinding | | | Completeness of follow-up | Intention-to-treat analysis |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Outcome assessor | Care provider | Patients | | |
| Ahmed Eltahawy | 1 | NS | Yes | Yes | Yes | No | NS | Yes | No |
| Dongwei Yang | 1 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Jianchang Yang | 1 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Jun Fan | 2 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Ling Zhang | 2 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Lingyu He | 2 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Mario Leoncini | 5 | NS | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Min Liu | 1 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Okay Abaci | 3 | NS | Yes | Yes | Yes | No | No | Yes | Yes |
| Oliveira | 1 | No | Yes | Yes | Yes | No | No | Yes | No |
| Peng Guo | 2 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Wei Tian | 2 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Yuming Lu | 1 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Zhihong Zhou | 1 | NS | Yes | Yes | NS | NS | NS | Yes | No |
| Zhuowen Xu | 1 | NS | Yes | Yes | NS | NS | NS | Yes | No |

NS = not specified or available, RCT = randomized controlled trial.

and 72 hours were both lower in the moderate or high-dose rosuvastatin group than that in the low-dose rosuvastatin group, with only postoperation 24 hours arriving at statistical significance (mALB 24 hours: SMD = −0.73, 95% CI −1.32 to −0.15, $P = .01$; mALB 72 hours: SMD = −0.52, 95% CI −1.12 to 0.08, $P = .09$) (Fig. 7). Although all the parameters were based on random-effect model, the heterogeneity still existed ($I^2 > 50\%$).

### 3.5. Subgroup analysis

Classified according to low-dose rosuvastatin treatment or not in control group, studies that received moderate or high-dose rosuvastatin treatment had significantly reduced incidence of CIN than those that received low-dose rosuvastatin treatment (RR = 0.40, 95% CI 0.27–0.59, $P < .0001$; $I^2 = 0\%$) and the same effect was seen in other comparisons between moderate or high-dose rosuvastatin treatment group with placebo group (RR = 0.49, 95% CI 0.35–0.69, $P < .0001$; $I^2 = 17\%$) (Fig. 8). In

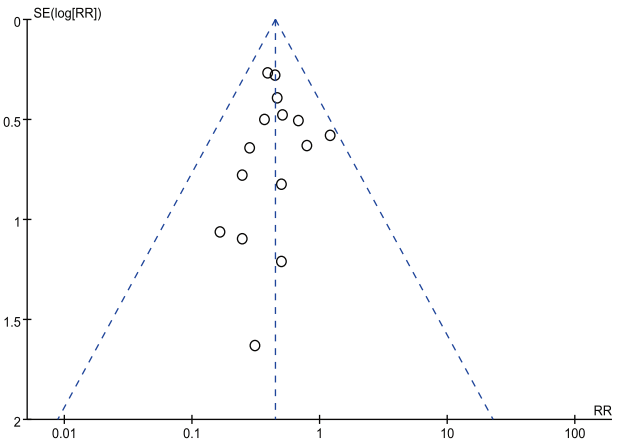


**Figure 2.** Funnel plot with 95% confidence interval (CI) for subjective assessment of bias among the included studies.

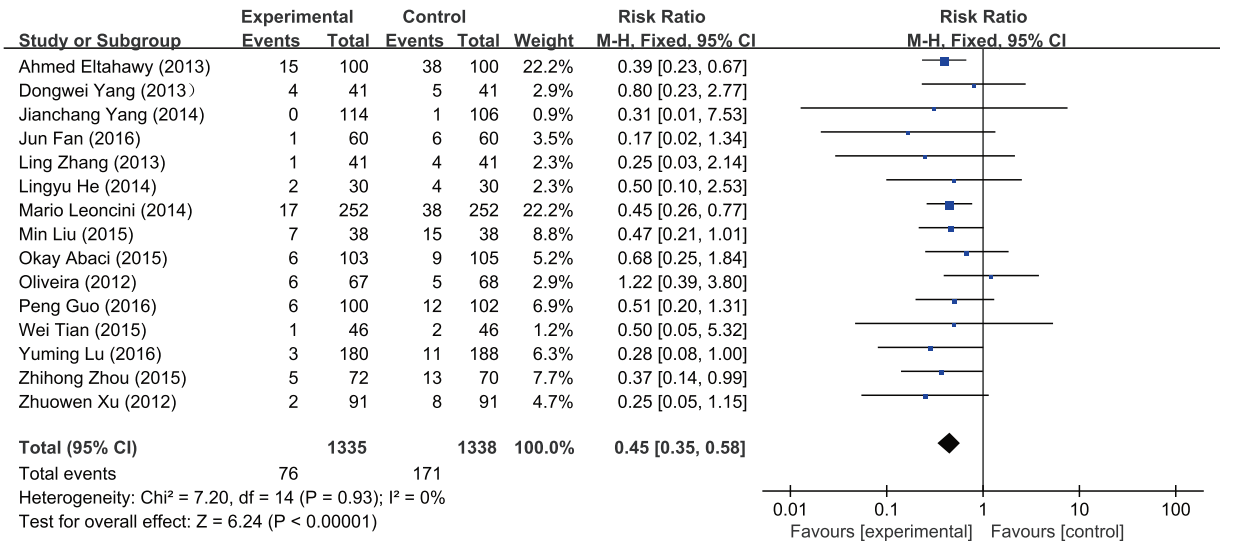


**Figure 3.** Forest plot of the risk ratio (RR) and 95% confidence interval (CI) for contrast-induced nephropathy (CIN) among patients assigned to moderate or high-dose rosuvastatin versus low-dose rosuvastatin or placebo therapy.

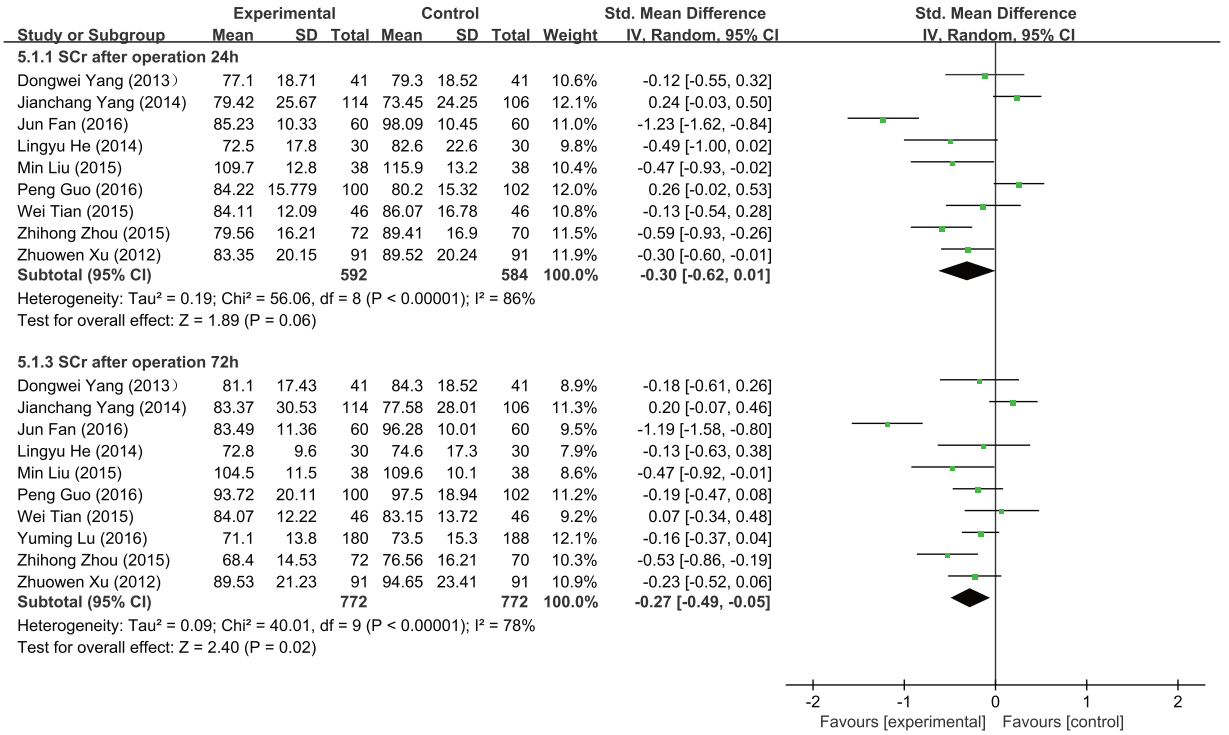


**Figure 4.** Comparison of 24 and 72 hours serum creatinine (SCr) between moderate or high-dose rosuvastatin group and low-dose rosuvastatin group.

addition, moderate (20 mg) or high dose (≥40 mg) rosuvastatin significantly reduced the incidence of CIN compared with the control (RR = 0.39, 95% CI 0.29–0.54, $P < .0001$, RR = 0.56, 95% CI 0.37–0.85, $P = .006$, respectively).

Three studies that included patients with CKD (eGFR <60 mL/min/1.73 $m^2$ or clearance rate <60 mL/min) indicated that moderate or high-dose rosuvastatin treatment also significantly reduced risk of CIN than control group (RR = 0.53, 95% CI 0.30–0.93, $P = .03$; $I^2 = 11\%$). The beneficial effect of moderate or high-dose rosuvastatin in the prevention of CIN was seen in patients with DM (RR = 0.51, 95% CI 0.31–0.86, $P = .01$; $I^2 = 0\%$) and in ACS patients undergoing PCI (RR = 0.52, 95% CI 0.35–0.76, $P = .0009$; $I^2 = 0\%$) and in studies that received contrast volume ≥110 mL (RR = 0.43, 95% CI 0.32–0.58, $P < .0001$; $I^2 = 0\%$) (Figs. 9 and 10)

## 4. Discussion

The present meta-analysis demonstrated that moderate or high-dose rosuvastatin pretreatment was strongly associated with a significantly lower incidence of CIN in patients undergoing CAG or PCI and the beneficial effect of moderate or high-dose rosuvastatin in preventing CIN was also observed in various subgroups of patients with CKD or DM and ACS patients

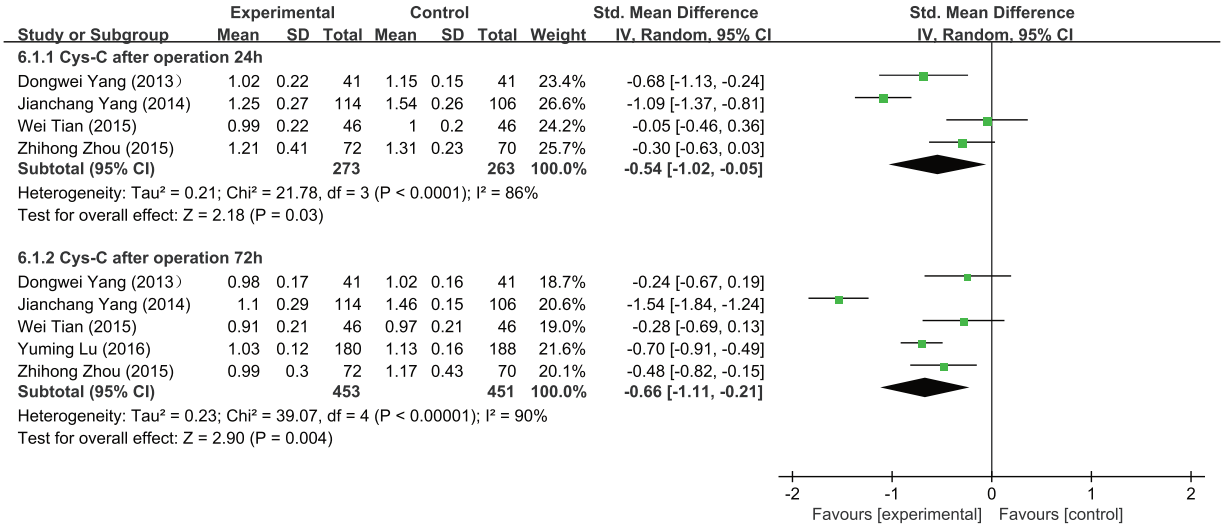


**Figure 5.** Comparison of 24 and 72 hours systatin C (CysC) between moderate or high-dose rosuvastatin group and low-dose rosuvastatin group.

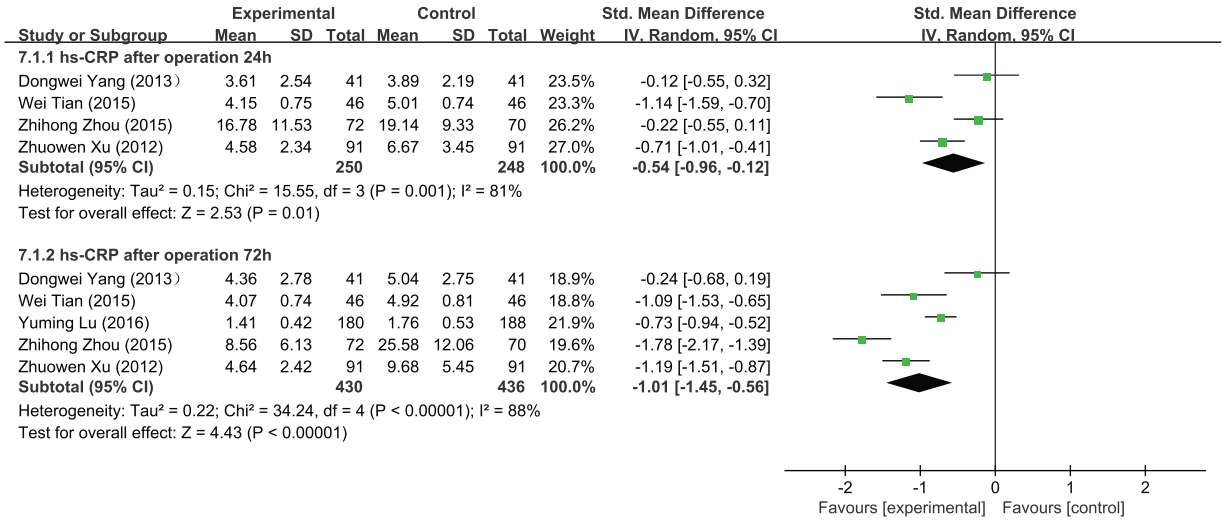


**Figure 6.** Comparison of 24 and 72 hours hypersensitive C-reactive protein (hs-CRP) between moderate or high-dose rosuvastatin group and low-dose rosuvastatin group.

undergoing PCI and studies that received mean contrast volume ≥110 mL. Furthermore, SCr, CysC, hs-CRP, and mALB in the moderate or high-dose rosuvastatin pretreatment group after operation were significantly lower than those in the low-dose rosuvastatin pretreatment group. To our knowledge, our meta-analysis might be the first to report that moderate or high-dose rosuvastatin pretreatment for prevention of CIN through various mechanisms.

Although the pathophysiological mechanisms of CIN are unclear, endothelin-mediated intensive vasoconstriction, nitric-mediated vasodilation inhibition, and oxidative stress caused by reactive oxygen species are responsible for the progression of CIN.[22] Recently, an increasing evidence has suggested that statins may play a reno-protective role in the prevention of CIN through its pleiotropic effect, including enhancement of endothelial nitric oxide production, anti-inflammatory and antioxidative effect, rather than its lipid lowering effect.[23,24] However, pleiotropic effects vary among different statins. Different from classic statin-atorvastatin, rosuvastatin, a hydrophilic statin, has a stronger anti-inflammatory property. An animal experiment has already confirmed that rosuvastatin and atorvastatin both exerted reno-protective effects in CIN rats, whereas rosuvastatin was more effective against inflammation.[25] A randomized controlled clinical study by Khurana et al[26] compared anti-inflammatory effect of atorvastatin and rosuvastatin in ACS patients who received atorvastatin 40 mg daily or rosuvastatin 20 mg daily for 4 weeks and found the level of CRP in rosuvastatin group after 4 weeks was significantly lower than that in the atorvastatin ($19.91 \pm 6.32$ vs $23.07 \pm 7.47$, $P < .05$). Another PRATO-ACS study[27] showed a close relationship between baseline hs-CRP levels and CIN occurrence in patients with ACS subjected to early invasive strategy and demonstrated that magnitude of CIN reduction attributable to rosuvastatin pretreatment was substantially greater in patients with higher baseline hs-CRP than in patients with lower levels. These findings were consistent with the results of present meta-analysis that hs-

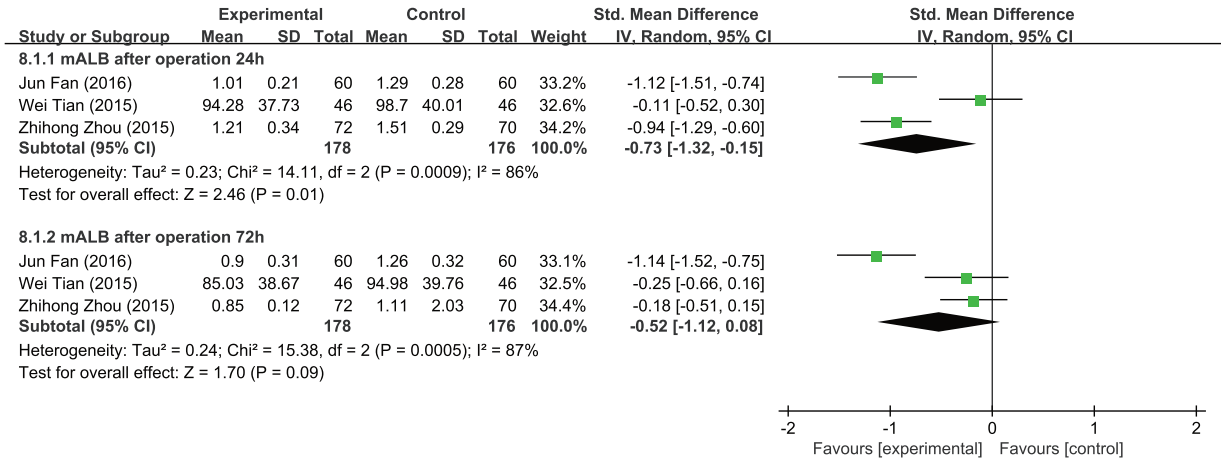


**Figure 7.** Comparison of 24 and 72 hours urine microalbumin (mALB) between moderate or high-dose rosuvastatin group and low-dose rosuvastatin group.

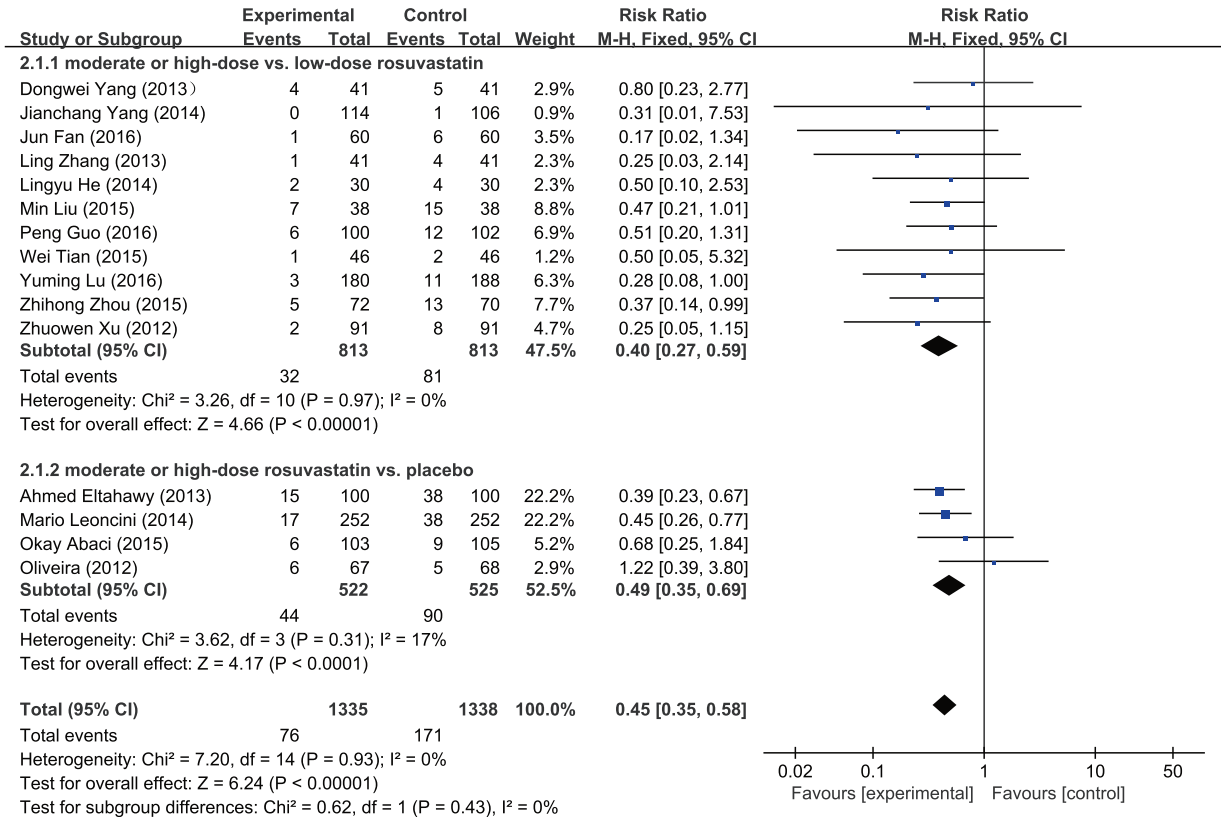


**Figure 8.** Subgroup analysis of forest plot of risk ratio (RR) and 95% confidence interval (CI) for contrast-induced nephropathy (CIN) among patients assigned to moderate or high-dose rosuvastatin treatment versus low-dose rosuvastatin or placebo.

CRP after operation 24 and 72 hours in the moderate or high-dose rosuvastatin treatment group was significantly decreased compared with low-dose rosuvastatin treatment group.

Based on existed evidence, the role of rosuvastatin for the prevention of CIN has already been assessed in several clinical trials and meta-analyses. The TRACK-D[28] trial was the first large randomized, multicenter, prospective study to evaluate the safety and efficacy of rosuvastatin therapy in preventing CIN in diabetic patients with mild-to-moderate CKD (1498 patients in the rosuvastatin group, 1500 patients in the control group). This trial revealed that rosuvastatin significantly lowered the incidence of CIN (2.3% vs 3.9%, $P=.01$) and the rate of worsening heart failure during 30 days' follow-up (2.6% vs 4.3%, $P=.02$) than the control in high-risk patients. These results were in line with our meta-analysis subgroup findings that a significant reduction of incidence of CIN in patients with CKD or DM who received moderate or high-dose rosuvastatin pretreatment. Rosuvastatin may be more effective in CKD patients, because such patients had a significant higher mean CRP concentration.[29] A meta-analysis by Yang et al[30] compared rosuvastatin treatment with no-statin treatment in preventing CIN and found that patients with rosuvastatin had 51% lower risk of CIN compared with the control group (OR = 0.49, 95% CI = 0.37–0.66, $P<.001$). However, this meta-analysis showed that rosuvastatin treatment had no effect for preventing CIN in patients with CKD undergoing elective cardiac catheterization (OR = 0.81, 95% CI = 0.41–1.61, $P=.55$). The difference may be from the different dose of rosuvastatin in the experiment or small size sample.

In addition, in the subgroup analysis of patients with ACS undergoing PCI (541 patients in the moderate or high-dose rosuvastatin group, 533 in the control group), we also found that moderate or high-dose rosuvastatin treatment could effectively prevent the occurrence of CIN in such high-risk population (OR = 0.52, 95% CI 0.35–0.76, $P=.0009$). These findings were similar to another meta-analysis[31], which enrolled 7 RCTs with a total 5174 patients and demonstrated moderate or high-dose statins (rosuvastatin 40 mg/d, atorvastatin 80 mg/d, or simvastatin 80 mg/d) were effectively in preventing the development of CIN in patients with ACS undergoing PCI. Moreover, to demonstrate the efficacy of moderate or high-dose rosuvastatin in patients receiving more contrast volume, the subgroup analyzed the effect of moderate or high-dose rosuvastatin in studies with contrast volume≥110 mL. According to the existing evidence, the administration of contrast volume≥140 mL was defined as high-dose [32], but only one of the included studies reported the incidence of CIN in such patients. It was reported that the average amount of contrast agent used for CAG and coronary angioplasty was 55 and 110 mL respectively[33], hence we chose the studies with contrast volume=110 mL as the cut-off value. And our study showed that moderate or high-dose rosuvastatin was also effectively in preventing the occurrence of CIN in subgroup analysis of studies with contrast volume≥110 mL (OR = 0.43, 95% CI 0.32–0.58, $P<.0001$).

Whether rosuvastatin is superior to atorvastatin for the prevention of CIN remains controversial. A large prospective, observational study by Liu et al[34] compared the effective effects of rosuvastatin and atorvastatin on CIN in patients with CKD undergoing PCI (273 patients received rosuvastatin 10 mg and 805 patients received atorvastatin 20 mg) and demonstrated that pretreatment with either rosuvastatin or atorvastatin had similar

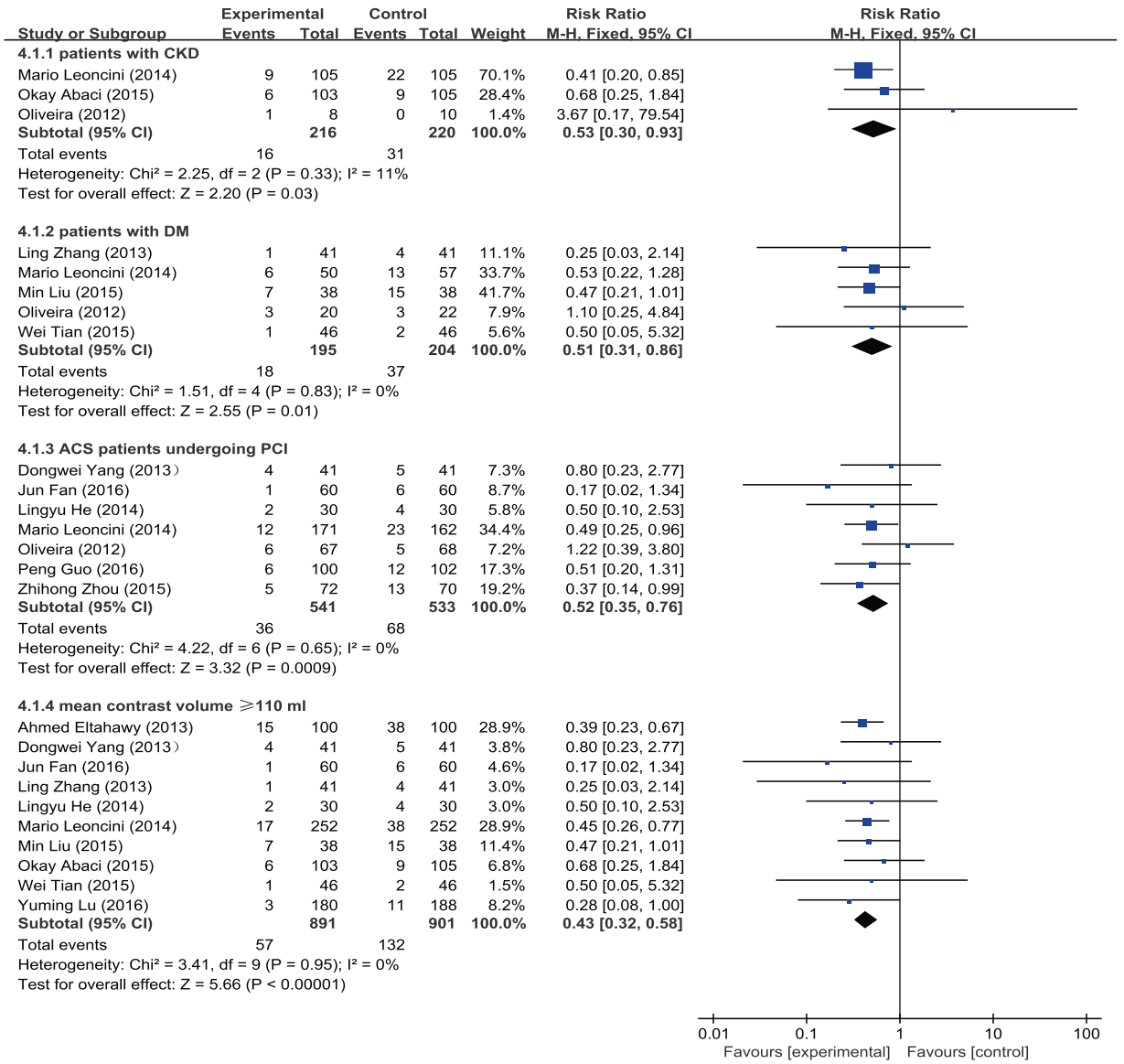


**Figure 9.** Subgroup analysis of forest plot of risk ratio (RR) and 95% confidence interval (CI) among patients assigned to moderate or high-dose rosuvastatin versus control therapy.

efficacies for preventing CIN. ROSA-CIN trial[35] also showed similar results in patients with STEMI undergoing primary PCI. Taking multiple pathophysiological mechanisms of CIN into consideration, rosuvastatin, and atorvastatin have their own characteristics in prevention of CIN. An animal study demonstrated that atorvastatin was more effective against NO system dysfunction and cell apoptosis and rosuvastatin was more effective against inflammation.[25] Therefore, a large number of well-designed randomized controlled clinical trials are needed to demonstrate advantages of rosuvastatin in various situation.

This meta-analysis had several limitations. First, most of the included studies did not separately report the incidence of CIN in patients with high-risk factors such as CKD or DM, which could influence the effect of short-term rosuvastatin pretreatment on the risk of CIN. Second, studies investigated the effect of rosuvastatin on hard clinical outcomes such as acute renal injury needing dialysis and in-hospital mortality. Third, when analyzing continuous variables (SCr, CysC, hs-CRP, and mALB), I2 was found to be far over 50%, which may reduce the efficacy of moderate or high-dose rosuvastatin. Fourth, publication bias is always a potential limitation. Namely, neutral or negative studies may not be published in a peer-reviewed journal, whereas positive studies are more likely to be published. Finally, the majority of included studies samples are small, which may influence the credibility of findings of the present meta-analysis.

## 5. Conclusion

In conclusion, our meta-analysis demonstrated that preprocedural moderate or high-dose rosuvastatin treatment could significantly reduce the incidence of CIN in patients undergoing CAG or PCI than low-dose rosuvastatin or no-statin treatment. Furthermore, the preventive effect of rosuvastatin on CIN was also shown advantages in patients with CKD or DM or ACS patients undergoing PCI or in studies that received mean contrast volume ≥110 mL. In addition, the present meta-analysis also

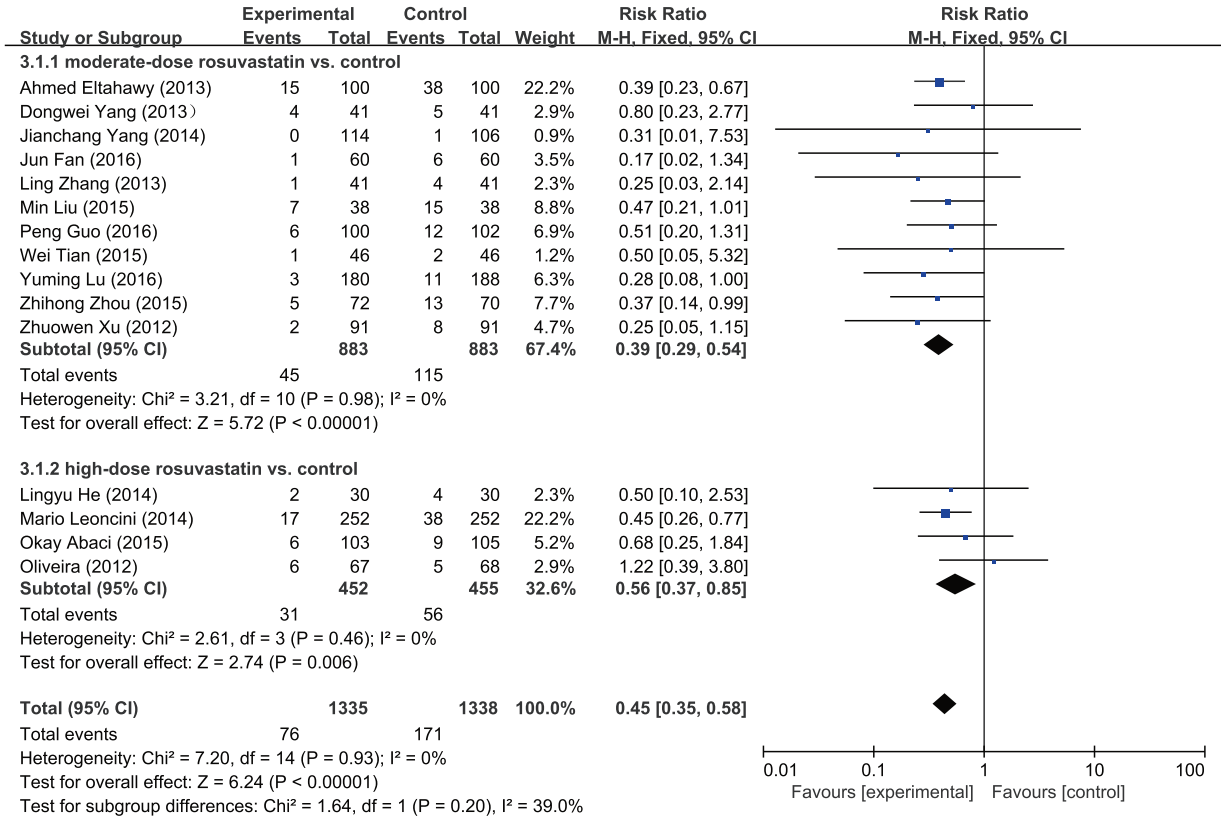


**Figure 10.** Subgroup analysis of forest plot of risk ratio (RR) and 95% confidence interval (CI) for contrast-induced nephropathy (CIN) among patients assigned to moderate or high-dose rosuvastatin treatment compared with control.

showed that moderate or high-dose rosuvastatin pretreatment significantly decreased SCr, CysC, hs-CRP, and mALB after contrast administration.

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