ORIGINAL RESEARCH

Meta-analysis of rosuvastatin efficacy in prevention of contrast-induced acute kidney injury

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Background: Contrast-induced nephropathy (CIN) is a complication after the intravascular administration of a contrast medium injection. Previous studies have investigated statins as therapy for CIN due to its positive results in the prevention of contrast-induced acute kidney injury (CI-AKI). Nevertheless, the beneficial effects of rosuvastatin pretreatment in preventing CIN in patients with acute coronary syndromes still remain controversial. In this study, we performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the beneficial impact of rosuvastatin in the prevention of CI-AKI in acute coronary syndrome patients.

Methods: PubMed, Embase, and Cochrane library were searched, for RCTs, updated on January 2018. The method was to evaluate rosuvastatin prior to angiography for the prevention of CI-AKI in patients undergoing coronary angiography, of which the main outcome was the incidence of CIN.

Results: A total of five RCTs were included in this analysis. Patients treated with rosuvastatin prior to invasive angiography had a significantly lower incidence of CI-AKI than controls (odds ratio [OR]: 0.53, 95% CI: 0.40–0.71, $P<0.0001$). Moreover, the subgroup analysis also showed that the benefit of rosuvastatin for patients with chronic kidney disease (OR: 0.49, 95% CI: 0.26–0.92, $P=0.03$) and diabetes mellitus (OR: 0.56, 95% CI: 0.38–0.83, $P=0.004$) which was consistent in compared with the respective control groups.

Conclusion: The findings of this meta-analysis suggest that the preoperative rosuvastatin treatment significantly reduces the risk of renal insufficiency of CIN in at-risk patients with chronic kidney disease or diabetes mellitus. Additional studies are needed to identify at-risk patients, provide optimum dose peri-procedural treatment, and reduce the incidence of CIN.

Keywords: contrast-induced nephropathy, coronary angiography, rosuvastatin, meta-analysis

Introduction

Contrast-induced nephropathy (CIN) is characterized by acute impairment of renal function after contrast exposure.[1] Patients with acute coronary syndrome (ACS) undergoing primary percutaneous intervention (p-PCI) are at a higher risk of developing contrast-induced acute kidney injury (CI-AKI).[2] Moreover, the incidence of contrast nephropathy was associated with patient characteristics that are risk factors for this disease.[3,4] As CI-AKI is associated with increased short- and long-term morbidity and mortality, nonfatal cardiovascular events, and a longer hospital stay,[5] the adoption of optimal therapeutic strategies is needed to prevent CIN, offering an opportunity to reduce patient morbidity and mortality.

In clinical practice, a number of studies have shown that the pleiotropic properties of statins exert a beneficial impact in the prevention of contrast nephropathy.[6] Apart from their cholesterol-lowering effects, statins have anti-inflammatory, antithrombotic, and antioxidative properties and may exercise nephron-protective action, thereby improving

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the endothelial function and reducing vascular inflammation and oxidative stress.[5] These favorable activities have a direct preventive effect against the development of CI-AKI.[7,8] However, the results concerning the efficacy of statin therapy in the prevention of CI-AKI are inconsistent.[6,9,10]

The hydrophilic form of the statin rosuvastatin may have better potential for prevention of CIN than other statin forms, probably owing to its longer plasma half-life and stronger anti-inflammatory effect. Previous randomized controlled trials (RCTs) focused mainly on the application of the lipophilic form of rosuvastatin for the prevention of CIN, but conflicting results have been reported.

Therefore, in this study, we performed a meta-analysis of RCTs to evaluate the efficacy of rosuvastatin pretreatment for the prevention of CIN as compared with placebo treatment.

Methods
Search strategy
To find all related articles, two investigators independently searched electronic databases (PubMed, Embase, and Cochrane Library) up to January 2018. The keywords "rosuvastatin" and "contrast-induced acute kidney injury," as well as relevant Medical Subject Heading terms were used in the search. We also checked the reference lists of all articles for additional eligible studies.

Eligibility criteria
To be included in the meta-analysis, the studies had to meet the following criteria: 1) RCTs comparing rosuvastatin pretreatment with placebo treatment in patients undergoing PCI; 2) they provided information about CI-AKI; 3) the outcome of interest was the incidence of CIN; 4) each paper had to be written in English.

Quality assessment
Two investigators independently rated the quality of the eligible RCTs. We choose the risk of bias items for RCTs recommended by The Cochrane Handbook for Systematic Reviews of Interventions.[32]

Data extraction
Two authors independently extracted the relevant data from each article. Any disagreement was resolved by consensus. The data extracted from the eligible studies included the following information: name of the first author, year of publication, characteristics of the trials, number of study

patients, mean age, mean baseline SCr, and definition of CIN in each trial.

Statistical analysis
All outcome comparisons were conducted and estimates calculated using the Review Manager version 5.3 software (Revman; The Cochrane Collaboration, Oxford, UK). Odds ratios (ORs) and their 95% CIs were calculated to assess the CIN events and make comparisons between the rosuvastatin and the control groups. The ORs and their 95% CIs were also mentioned in the summary statistics in the pooled subgroup analysis for patients with chronic kidney disease (CKD) or diabetes mellitus (DM).

A sensitivity analysis was also performed to examine the overall impact of heterogeneity on meta-analysis results. The I^2 test was employed to evaluate the heterogeneity of the results.[11] An I^2-value $\geq 50\%$ was considered to indicate moderate and high heterogeneity, whereas an I^2-value $< 50\%$ showed low heterogeneity.[12] A P-value < 0.05 was considered statistically significant.

Results
Overview of literature search and study characteristics
A total of 213 studies were identified and reviewed according to the criteria described in the methods, of which 10 publications were evaluated in more detail, but some did not provide information on the endpoint outcomes.

Thus, a total of five RCTs were finally included in the present analysis.[13–17] The search process is illustrated in Figure 1. All included studies in this meta-analysis were considered to be at least of moderate quality. Detailed information on the medication protocols of the eligible studies is presented in Table 1.

Effect of rosuvastatin on the incidence of CI-AKI
The data pooled from all five articles included in our research showed that the risk of CI-AKI (OR: 0.53, 95% CI: 0.40–0.71, $P < 0.0001$) in the atorvastatin treatment group was lower than that in the control group (Figure 2).

Subgroup analysis of the effect of rosuvastatin on the incidence of CI-AKI
Rosuvastatin reduced also the risk of CI-AKI in patients with CKD (OR: 0.45, 95% CI: 0.21–0.95, $P=0.04$) (Figure 3) and DM (OR: 0.56, 95% CI: 0.38–0.83, $P=0.004$) (Figure 4), as compared with that in the placebo group.
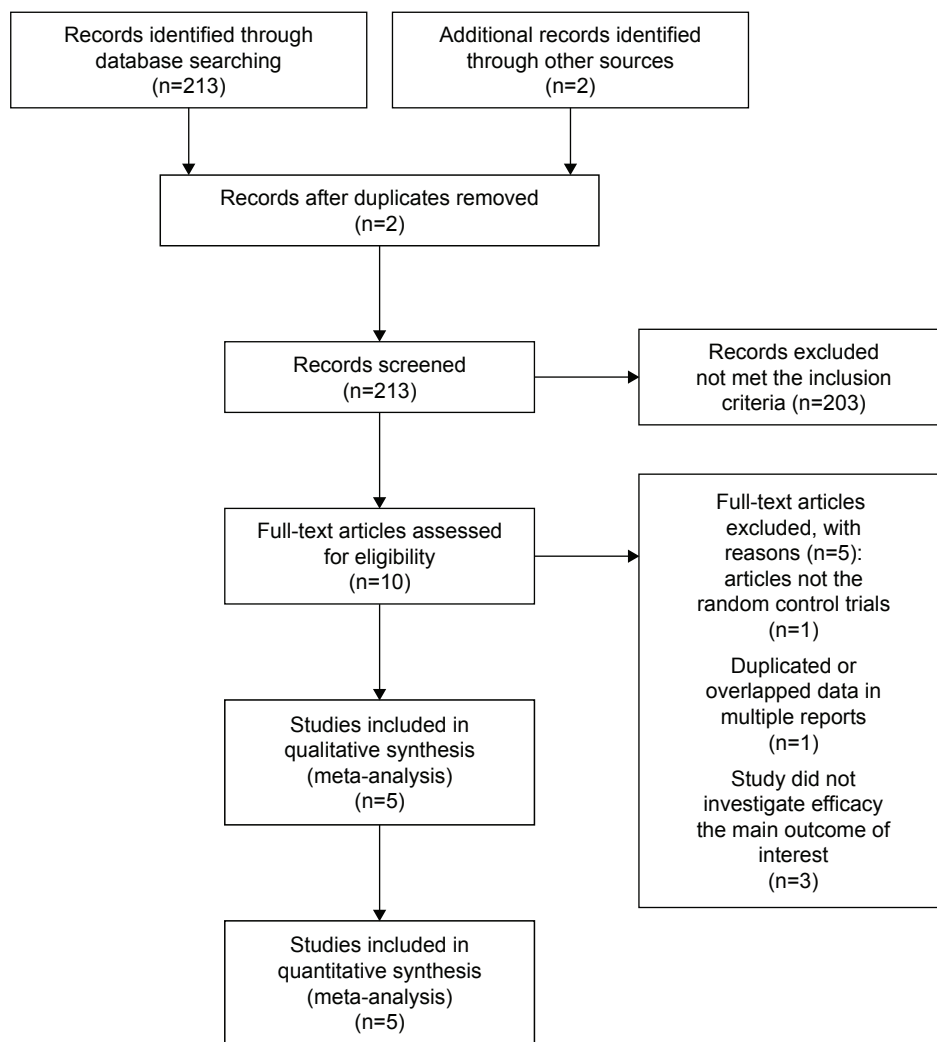
Figure 1 PRISMA flow chart of the selection process used to identify studies eligible for pooling.
Abbreviation: RCT, randomized controlled trial.

Discussion

The pathophysiological mechanism of CIN is still not entirely clear. Multiple mechanisms may be involved; in particular, adenosine, angiotensin, vasopressin, and endothelin secretion after contrast exposure is a logical cause for the reduction in the synthesis of nitric oxide and the induction of oxidative stress, causing hypoxia in the renal medulla. More recently, other renal damage mechanisms have been associated with the development of cellular lesions, necrosis, interstitial inflammation, and tubular injury.[5,7] It is noteworthy that the elevated preprocedural concentration of the high-sensitivity CRP was found to increase the risk of CIN in patients who had underwent PCI.[18]

In addition to their lipid-lowering activities, statins are also known to downregulate the angiotensin receptor, limit the production of endothelial nitric oxide synthase, and have antithrombotic and anti-inflammatory properties, which altogether constitutes their pleiotropic effects.[9] Due to these multidirectional activities, statins are considered to exert also a renoprotective effect and that the pretreatment with statin can affect the progression of the CI-AKI pathogenesis.

Basing on the beneficial clinical results observed in various subgroups of patients, we analyzed the additional functions of rosuvastatin which showed acute pleiotropic effects.[19] In one of the studies included in our research, healthy patients without hyperlipidemia (low-density lipoprotein cholesterol levels: <130 mg/dL) but with elevated high-sensitivity CRP levels (>2.0 mg/L)[20] and patients with estimated eGFR <60 mL/min/1.73 m^2 were found to be at the highest risk of CI-AKI.[21] Furthermore, the short-term treatment with rosuvastatin was indicated to play a protective role by improving eGFR independently of the lipid fraction changes,

Table I Detailed medication protocols of the eligible studies

Study	Patients number E/C	Inclusion criteria	Protocol	Definition of CIN	Mean age, years E/C	Mean baseline SCr, µmol/L or mg/dL E/C
Fahmy et al,[13] 2013	100/100	Patients undergoing CAG	Rosuvastatin 20 mg/d from 3 days before to 7 days after procedure vs placebo	≥25% SCr or ≥44.2 µmol/L SCr within 48 hours	54.8±11.0/52.1±10.7	0.81±0.2/0.81±0.3 mg/dL
Leoncini et al,[14] 2014	252/252	NSTE-ACS patients undergoing CAG with or without PCI	Rosuvastatin 40 mg followed by 20 mg/d vs placebo	≥25% SCr or ≥44.2 µmol/L SCr within 72 hours	66.2±12.4/66.1±13.5	0.95±0.27/0.96±0.28 mg/dL
Abaci et al,[15] 2015	110/110	Patients undergoing CAG	Rosuvastatin 40 mg within 24 hours before and 20 mg/d for 2 days vs placebo	≥25% SCr or≥ 44.2 µmol/L SCr within 48–72 hours	67.5±8.9/67.7±8.9	1.3±0.4/1.4±0.5 mg/dL
Msd et al,[16] 2012	67/68	ACS patients undergoing PCI	Rosuvastatin 40 mg 2–6 hours before procedure vs placebo	≥25% SCr or ≥44.2 µmol/L SCr within 24 hours	59.4±8.6/62.2±9.8	0.89±0.24/0.98±0.21 mg/dL
Han et al,[17] 2014	1,498/1,500	Patients with DM and CKD undergoing coronary/peripheral arterial diagnostic angiography, left ventriculography, or PCI were eligible	rosuvastatin,10 mg every evening, from 2 days before to 3 days after contrast medium administration (total dose of 50 mg of rosuvastatin over 5 days) or to a control group	≥0.5 mg/dL (44.2 mmol/L) or ≥25% above baseline at 72 hours after exposure to the contrast medium	61.45±8.64/61.44±8.64	95.08±22.92/94.95±20.84 mg/dL

Abbreviations: CAG, coronary angiography; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; DM, diabetes mellitus; PCI, percutaneous coronary intervention.

suggesting that the pleiotropic effect of rosuvastatin included also renoprotective functions.[22] The preventive impact of rosuvastatin on the magnitude of CIN reduction could be due to of its inhibitory influence on the synthesis of inflammatory mediators, a phenomenon observed in the JUPITER trial.[20]

Previous studies have shown the beneficial, preventive effects of statins against CI-AKI. For example, Leoncini et al[14] established that rosuvastatin significantly reduced CI-AKI. However, Abaci et al[15] found that the high-dose rosuvastatin treatment had no beneficial effects in decreasing the occurrence of CI-AKI in patients with suspected coronary artery disease.

Preexisting kidney disease is known to be the greatest risk for CI-AKI development, especially in patients with acute coronary syndrome because of their diminished renal reserve.[23] Nevertheless, whether the short-term high-dose statin pretreatment in patients with stable coronary artery disease lowers the risk of CI-AKI and reduces the renal function still remains debatable, and thus additional research is needed to further elucidate this issue.[24–26] Moreover, patients with DM are at the highest risk of CI-AKI due to the pathophysiologic changes caused by contrast materials, including increased production of reactive oxygen species, vascular endothelial injury, and dysregulated microcirculation. Thus, patients with CKD and DM are at increased risk of CI-AKI.[27]

In the current study, we found that the beneficial effects of rosuvastatin were consistent in patients with renal dysfunction and diabetes with a significant reduction of CI-AKI rate. The pathophysiology contributing to kidney injury in CIN is not completely understood. Given their multiple pleiotropic effects, statins are likely to exert a renoprotective effect and limit the injury of renal function over time.[5] Preclinical studies have demonstrated that statins inhibit receptor-mediated endocytosis, which is responsible for the protein uptake in proximal tubular cells, in a dose-dependent manner.[28,29]

The latest meta-analysis published suggested that the moderate- or high-dose rosuvastatin treatment may have preventive effects against CIN in patients undergoing coronary angiography or PCI. As the data available on this dose-dependent influence are limited, in this meta-analysis, we did not assess the impact of the potentially hazardous high-dose rosuvastatin pretreatment.[30]

The main relative strength of our analysis as compared with previous meta-analyses on the same topic is the inclusion and analysis of the results of randomized controlled trials published in English. Nonetheless, several inherent flaws of the study should not be ignored as that might have led to potential bias. First, data were pooled from a number
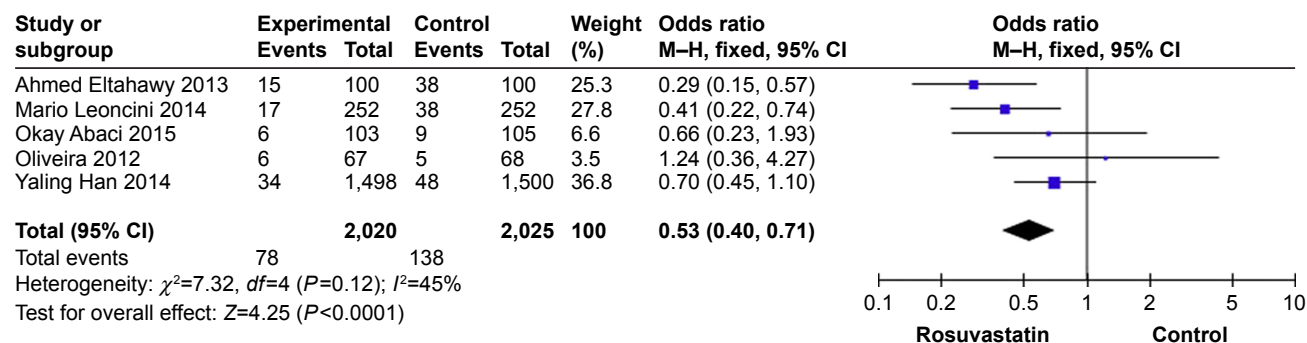
Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Ahmed Eltahawy 2013	15	100	38	100	25.3	0.29 (0.15, 0.57)	
Mario Leoncini 2014	17	252	38	252	27.8	0.41 (0.22, 0.74)	
Okay Abaci 2015	6	103	9	105	6.6	0.66 (0.23, 1.93)	
Oliveira 2012	6	67	5	68	3.5	1.24 (0.36, 4.27)	
Yaling Han 2014	34	1,498	48	1,500	36.8	0.70 (0.45, 1.10)	
Total (95% CI)		**2,020**		**2,025**	**100**	**0.53 (0.40, 0.71)**	
Total events	78		138				

Heterogeneity: χ^2=7.32, df=4 (P=0.12); I^2=45%
Test for overall effect: Z=4.25 (P<0.0001)

Figure 2 Effect of rosuvastatin on the incidence of CI-AKI.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; OR, odds ratio.

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Mario Leoncini 2014	9	105	22	105	69.6	0.35 (0.15, 0.81)	
Okay Abaci 2015	6	103	9	105	29.1	0.66 (0.23, 1.93)	
Oliveira 2012	1	8	0	10	1.3	4.20 (0.15, 117.92)	
Total (95% CI)		**216**		**220**	**100**	**0.49 (0.26, 0.92)**	
Total events	16		31				

Heterogeneity: χ^2=2.49, df=2 (P=0.29); I^2=20%
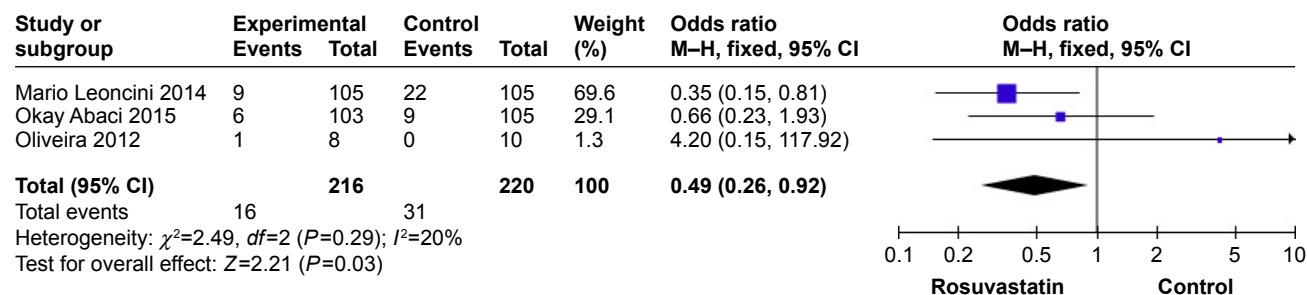Test for overall effect: Z=2.21 (P=0.03)

Figure 3 Influence of rosuvastatin treatment on the incidence of CI-AKI in patients with CKD.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; CKD, chronic kidney disease; OR, odds ratio.
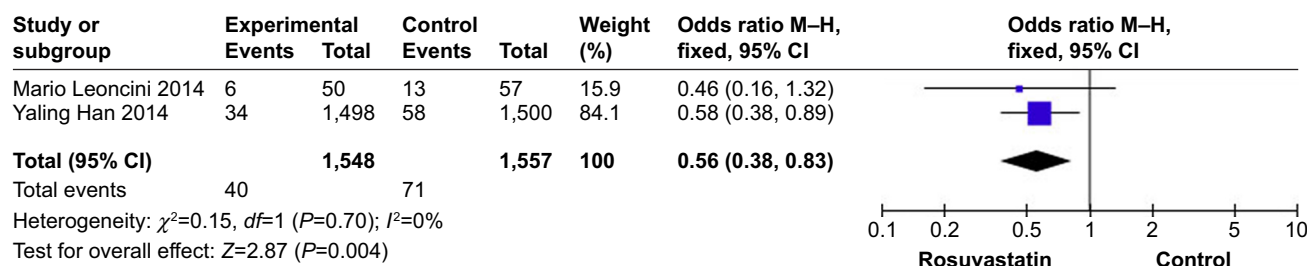
Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Mario Leoncini 2014	6	50	13	57	15.9	0.46 (0.16, 1.32)	
Yaling Han 2014	34	1,498	58	1,500	84.1	0.58 (0.38, 0.89)	
Total (95% CI)		**1,548**		**1,557**	**100**	**0.56 (0.38, 0.83)**	
Total events	40		71				

Heterogeneity: χ^2=0.15, df=1 (P=0.70); I^2=0%
Test for overall effect: Z=2.87 (P=0.004)

Figure 4 Impact of rosuvastatin administration on the incidence of CI-AKI in patients with DM.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; DM, diabetes mellitus; OR, odds ratio.

of RCTs with different inclusion criteria with insignificant heterogeneity among the included studies. Second, patients might have had differential responses to treatment with different doses of rosuvastatin. Third, the entire meta-analysis is based upon 5 RCTs, of which only three related to CKD and two related to DM, which limits the ability to statistically analyze the effect of rosuvastatin on the incidence of interested outcomes, so future research should be conducted to identify these subgroups.

Contrast administration is well-established in the literature as a risk factor for CI-AKI. The incidence of CI-AKI varies widely depending on the patient cohorts evaluated, definition criteria used, and preventive strategies adopted.[31]

In conclusion, the current evidence indicates that rosuvastatin prevents the occurrence of CIN in patients after an episode of CI-AKI, especially in high-risk patients with DM or CKD.

The best approaches established so far to prevent CIN are to identify at-risk patients, provide adequate therapeutic doses, and minimize the amount of contrast administered. However, the actual mechanism by which statins may lower the risk of contrast nephropathy remains uncertain. Therefore, further research is needed to better understand their underlying mechanisms of action.

Disclosure

The authors report no conflicts of interest in this work.

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