ORIGINAL RESEARCH

Efficacy of atorvastatin on the prevention of contrast-induced acute kidney injury: a meta-analysis

Ling-Yun Liu[1]
Yang Liu[2]
Mei-Yan Wu[2]
Yan-Yan Sun[3]
Fu-Zhe Ma[2]

[1]Department of Andrology,
[2]Department of Nephrology, the
First Hospital of Jilin University,
[3]Department of Nephrology, the
Fourth Hospital of Jilin University,
Changchun, China

Background: Results of studies on the efficacy of atorvastatin pretreatment on reducing the prevalence of contrast-induced acute kidney injury (CIAKI) in patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) have been controversial.

Objective: We undertook a meta-analysis to evaluate the efficacy of atorvastatin on contrast-induced nephropathy (CIN) after CAG or PCI.

Materials and methods: We undertook a systematic search of electronic databases (PubMed, Embase, and the Cochrane Library) up to June 2017. A meta-analysis was carried out including randomized controlled trials (RCTs) that compared atorvastatin pretreatment with pretreatment with a low-dose statin or placebo for CIAKI prevention in patients undergoing CAG. The main endpoint was CIN prevalence.

Results: Nine RCTs were included in our meta-analysis. Atorvastatin pretreatment reduced the prevalence of CIN significantly (odds ratio [OR] 0.46; 95% confidence interval [95% CI] 0.27–0.79; $p=0.004$). The benefit of high-dose atorvastatin pretreatment was consistent when compared with the control group (OR 0.45; 95% CI 0.21–0.95; $p=0.04$).

Conclusion: At high doses, atorvastatin pretreatment was associated with a significant reduction in the prevalence of CIAKI in patients undergoing CAG. Pretreatment with high-dose atorvastatin could be employed to prevent CIAKI.

Keywords: atorvastatin, contrast-induced acute kidney injury, coronary angiography, percutaneous coronary intervention, contrast-induced nephropathy, meta-analysis

Introduction

Contrast-induced acute kidney injury (CIAKI) is a well-recognized vasoconstriction of renal arteries triggered by contrast media. CIAKI is a major contributor to hospital-acquired acute renal failure and is associated with mortality. Patients with acute coronary syndrome, baseline renal insufficiency, and those undergoing percutaneous coronary intervention (PCI) carry a higher risk for CIAKI, which may be a common cause of persistent worsening of renal function.[1,2]

Recently, interventional cardiologists have paid close attention to post-PCI CIAKI. Several studies have been carried out to explore the pathogenesis of contrast-induced nephropathy (CIN). Some studies have suggested that a potential interaction between oxidative stress, inflammation, reduction in renal blood flow, and direct damage to tubular cells by contrast media might be involved in CIN pathogenesis.[3] Other mechanisms of action include delayed intra-renal transit of the contrast agent caused by vasoconstriction resulting in damage by oxidative stress and direct damage to tubular cells due to receptor-mediated tubular reabsorption of filtered contrast.[4,5]

Correspondence: Fu-Zhe Ma
Department of Nephrology, the First
Hospital of Jilin University, No 71 Xinmin
Road, Changchun 130021, China
Tel +86 187 0430 8023
Email mfzkidney@163.com

Several approaches have examined how to prevent CIAKI. Among those approaches, pharmacologic prophylactic strategies based on antioxidant properties have garnered considerable interest. Studies using N-acetylcysteine have been debated widely.[6] Unfortunately, the development of treatments has shown little clinical efficacy for CIAKI prevention.[7]

Statins are prescribed frequently for the treatment of cardiovascular disease. However, they have recently been suggested to enhance endothelial function as well as reduce oxidative stress and inflammation.[8] It has been reported that short-term pretreatment with statins can achieve lipid-lowering pleiotropic effects such as a reduction in the prevalence of myocardial damage during PCI,[9–12] possibly via antioxidant, anti-inflammatory effects,[9] as well as their tendency to reduce endothelin secretion.[13] Inflammatory mechanisms and oxidative stress may also affect the pathogenesis of CIN.[14,15] Moreover, statins may reduce the reabsorption of contrast agents in renal tubules, thereby reducing toxicity within them.[5,16] Therefore, statins are considered to be promising candidate agents to prevent CIN. However, a consensus on the beneficial effects of statins on CIAKI prevention is lacking.

Several randomized clinical trials (RCTs) have failed to show that statins exert beneficial effects on CIAKI prevention.[17–22] Conversely, some studies have reported that atorvastatin pretreatment can reduce the prevalence of CIN more effectively than other statins because it can reduce inflammation and oxidative stress to a greater extent.

Atorvastatin may work through different mechanisms to prevent activation of an intrinsic apoptotic pathway. Prospective studies have suggested that atorvastatin may have effects on CIN, but the results are conflicting. Hence, we undertook a meta-analysis to evaluate the role of atorvastatin in the prevention of CIAKI compared with control groups.

Materials and methods
Search strategy
A systematic search of PubMed, Embase, and the Cochrane Library databases up to June 2017 was carried out using the keywords "atorvastatin" and "contrast-induced acute kidney injury". Relevant medical subject heading terms were utilized. The reference lists of all articles were also checked for potential additional eligible studies.

Eligibility criteria
Studies were included in the meta-analysis 1) if they were original studies evaluating the effectiveness of atorvastatin pretreatment in reducing the prevalence of CIAKI in patients undergoing PCI; 2) if they offered information about CIAKI; 3) if the main endpoint was the prevalence of CIN; 4) if they contained reference groups composed of participants who were prescribed atorvastatin compared with a control group; and 5) if the articles were written in English.

Assessment of the quality of studies
Two investigators rated the quality of eligible RCTs independently. We chose the risk of bias items for RCTs as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*.

Data extraction
Two independent investigators extracted the data from included studies. Differing conclusions were resolved by consensus. For each of the eligible studies, the main categories were the name of the first author, characteristics of the RCT, study design, year of publication, number of study patients, patient age, eligibility criteria of each RCT, and definition of CIAKI in each RCT.

"High-dose atorvastatin" was defined as atorvastatin administered at a daily dose of ≥ 80 mg. "Low-dose atorvastatin" was defined as atorvastatin administered at a daily dose of <80 mg.

Statistical analyses
All endpoint comparisons were calculated using Review Manager v5.3 (Revman; the Cochrane Collaboration, Oxford, UK). Odds ratios (ORs) and their 95% confidence intervals (CIs), or relevant data for their calculation, were used to assess the prevalence of CIN events between the atorvastatin group and control group. The OR and its 95% CI were also mentioned in the summary statistics for the pooled analysis of the effect to assess the prevalence of CIN events between the high-dose atorvastatin group and control group. Statistical variables were pooled directly if they were described in the literature; otherwise, the variables were calculated based on the available numerical data in the articles according to the methods described by Parmar et al.[23]

The endpoint was considered as a weighted average of the individual estimate of the OR in each included study using the inverse variance method.

A sensitivity analysis was also carried out to examine the impact on the overall results depending on the heterogeneity across the included studies. The I^2 test was carried out to assess the heterogeneity of the results.[24] Studies with an I^2 of 25%–50%, 50%–75%, or >75% were considered to have

"low", "moderate", or "high" heterogeneity, respectively.[25] If there was low heterogeneity among the studies, the fixed-effects model was used. Otherwise, the random-effects model was used. $p < 0.05$ was considered significant.

Results
Overview of the literature search and study characteristics

A total of 326 studies were found based on the inclusion criteria stated earlier. Eighteen publications were evaluated in more detail, but some did not provide the endpoint of the study.

Finally, nine RCTs were included.[20,22,26–32] The literature search is described in Figure 1. All included studies were considered to be of moderate quality at least. Table 1 shows the detailed medication protocols of the eligible studies in more detail.

Effect of atorvastatin on CIAKI prevalence

Pooling the data from all nine RCTs showed that atorvastatin could reduce the risk of CIAKI (OR 0.46; 95% CI 0.27–0.79; $p=0.004$) compared with the control group (Figure 2).

Effect of high-dose atorvastatin on CIAKI prevalence

High-dose atorvastatin reduced the risk of CIAKI (OR 0.45; 95% CI 0.21–0.95; $p=0.04$) when compared with the placebo group (Figure 3). Only two RCTs reported data on high-dose atorvastatin compared with low-dose atorvastatin, so a meta-analysis could not be carried out.

Discussion

Contrast media induce decreasing production of local prostaglandin-mediated vasodilatation and the damage caused by oxygen radicals, known as CIN.[15] CIN is reported to be a leading cause of in-hospital acute renal failure. The prevalence of CIN differs widely across RCTs depending on the risk profiles of different patients, such as advanced age, diabetes mellitus, cardiovascular disease, and preexisting renal dysfunction.[33–35] Development of CIN after PCI in patients with normal renal function or further deterioration in renal function in those with chronic renal failure might be followed by in-hospital adverse events and a higher risk of late cardiovascular events and mortality.[33–35] Thus, prevention of CIN may translate into improved clinical outcome during follow-up.
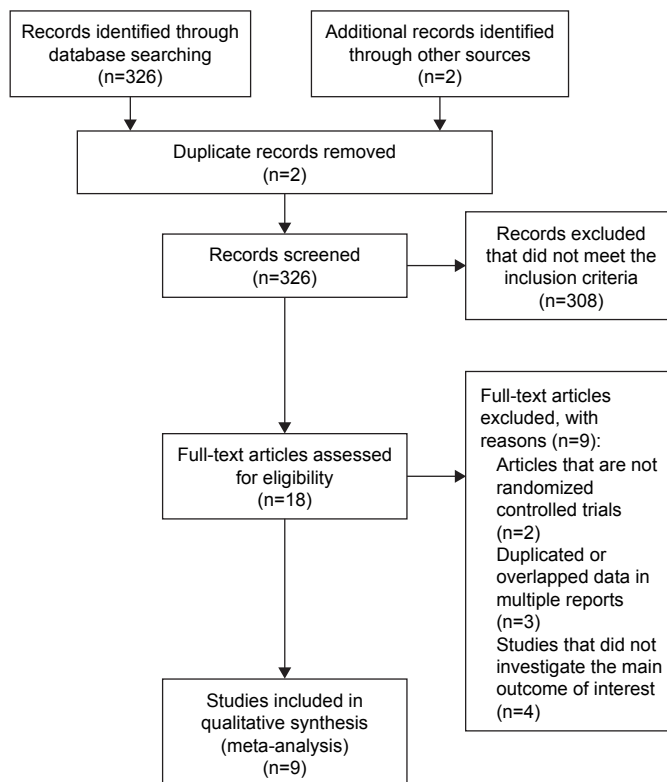

Figure 1 PRISMA flowchart of selection process to identify studies eligible for pooling.

Table 1 The primary characteristics of the eligible studies in more detail

First author	Year	Intervention dose	Patients (n)		Mean baseline SCr (mg/dL)		Events (n)		Mean age		Diabetics (%)		Country	Procedure	Definition of CIN
			Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control			
Bidram et al[57]	2015	Patients in the intervention group received 80 mg oral atorvastatin; the placebo group was treated as the intervention group with placebo similar to the atorvastatin	100	100	1.18	1.14	1	2	59	60	0	0	Iran	CAG	CIN was defined as an increase in post-procedural SCr of >0.5 mg/dL or >25% from baseline in the absence of any other causes
Li et al[26]	2012	80 mg PO pre-procedure, then 40 mg daily	78	83	1.48	1.49	2	13	70	70	27	29	China	PCI	Increase in SCr >0.5 mg/dL or >25% within 72 h
Patti et al[27]	2011	80 mg for 12 h and 40 mg for 2 h pre-procedure, then 40 mg daily for 2 days post-procedure	120	121	1.04	1.04	6	16	65	66	30	25	Italy	CAG/PCI	Increase in SCr >0.5 mg/dL or >25% within 48 h
Özhan et al[20]	2010	80 mg for 1 day pre-procedure and 2 days post-procedure	60	70	1.5	1.5	2	7	54	55	15	17	Turkey	CAG/PCI	Increase in SCr >0.5 mg/dL or >25% within 48 h
Park et al[28]	2016	Group I (atorvastatin 40 mg orally before PCI and 40 mg orally daily for 48 h after PCI) Group II (atorvastatin 80 mg orally before PCI and 40 mg orally twice daily for 48 h after PCI)	84	83	0.85	0.79	15	28	63.8	60.6	25.6	21.4	Korean	PCI	CIN was defined as an increase of ≥25% or ≥0.5 mg/dL compared to pre-procedure SCr after primary PCI[23]
Quintavalle et al[29]	2012	80 mg within 24 h of the procedure	202	208	1.23	1.25	9	37	70	70	44	39	Italy	CAG/PCI	Increase in SCr ≥0.5 mg/dL or ≥25% over base
Toso et al[30]	2010	80 mg daily for 2 days pre-procedure and 2 days post-procedure	152	152	1.2	1.18	15	16	75	76	20	22	Italy	CAG/PCI	Increase in SCr >0.5 mg/dL within 5 days
Ha et al[31]	2011	80 mg PO 6 hours pre-procedure	165	274	NA	NA	10	10	NA	NA	NA	NA	South Korea	PCI	SCr ≥0.5 mg/dL or >25%
Jo et al[32]	2012	Atorvastatin 80 mg before angiography followed by atorvastatin 80 mg/day for 5 days and then 10 mg/day vs atorvastatin 10 mg/day	110	108	1.09	1.02	6	11	57.6	61	33	25	South Korea	PCI	–

Abbreviations: CAG, coronary angiography; CIN, contrast-induced nephropathy; NA, not applicable; PCI, percutaneous coronary intervention; PO, per oral; SCr, serum creatinine.
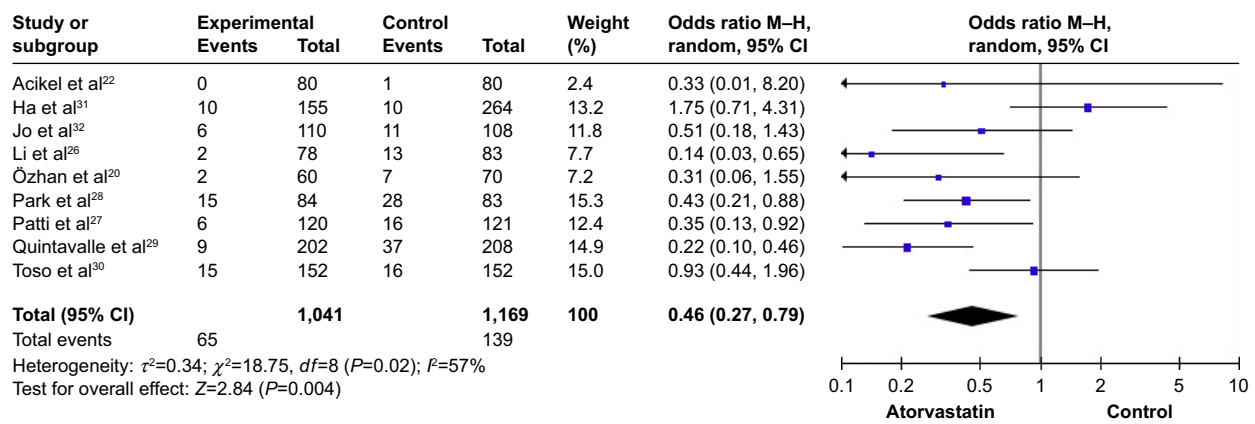
Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI	Odds ratio M–H, random, 95% CI
Acikel et al[22]	0	80	1	80	2.4	0.33 (0.01, 8.20)	
Ha et al[31]	10	155	10	264	13.2	1.75 (0.71, 4.31)	
Jo et al[32]	6	110	11	108	11.8	0.51 (0.18, 1.43)	
Li et al[26]	2	78	13	83	7.7	0.14 (0.03, 0.65)	
Özhan et al[20]	2	60	7	70	7.2	0.31 (0.06, 1.55)	
Park et al[28]	15	84	28	83	15.3	0.43 (0.21, 0.88)	
Patti et al[27]	6	120	16	121	12.4	0.35 (0.13, 0.92)	
Quintavalle et al[29]	9	202	37	208	14.9	0.22 (0.10, 0.46)	
Toso et al[30]	15	152	16	152	15.0	0.93 (0.44, 1.96)	
Total (95% CI)		**1,041**		**1,169**	**100**	**0.46 (0.27, 0.79)**	
Total events	65		139				
Heterogeneity: $\tau^2=0.34$; $\chi^2=18.75$, $df=8$ ($P=0.02$); $I^2=57\%$							
Test for overall effect: $Z=2.84$ ($P=0.004$)							

Figure 2 Effect of atorvastatin on the incidence of contrast-induced acute kidney injury.
Abbreviation: M–H, Mantel–Haenszel.

A large number of drugs have been used to prevent kidney injury following PCI,[36–38] including statins, but the optimal regimen for preventing CIN is not known. Various mechanisms are involved in CIN pathogenesis, and several studies have reported that statins may be effective in preventing CIN.[39,40] Inflammation and reactive oxygen species (ROS) production may contribute to CIAKI pathogenesis. Clinical and experimental results have clearly shown that hypoxia and increased production of ROS within the kidney following administration of contrast media affect CIN development.[41]

Previously, the possible role of statins in the prevention of renal deterioration in patients undergoing diagnostic or therapeutic angiographic procedures has been investigated. Statins have been used widely for primary and secondary prevention of coronary artery disease. Studies have reported the cholesterol-independent or pleiotropic effects of statins, including amelioration of endothelial function, stabilization of atherosclerotic plaques, as well as reduction of systemic inflammation and oxidative stress.[42]

Several RCTs have reported that statins have beneficial effects on reducing CIAKI prevalence.[43,44] The underlying pathophysiologic mechanisms are complex. In addition to their impact on cholesterol, statins may help to prevent CIAKI causing direct toxicity to renal tubules, oxidative stress, and ischemic injury,[45] but some conflicting results have been obtained.[46,47]

Among the statins available, atorvastatin has multiple beneficial pleiotropic effects of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors. Atorvastatin can improve endothelial function, stabilize coronary plaques, suppress the proliferation of smooth muscle cells in vessels and platelet aggregation, and reduce inflammation and oxidative stress.[42]

Recently, the possible role of atorvastatin in preventing renal deterioration in patients undergoing diagnostic or therapeutic angiographic procedures has been investigated. Atorvastatin may modulate kidney hypoperfusion after radio-contrast exposure by downregulating expression of angiotensin receptors and reducing synthesis of endothelin-1.[48] Also, the anti-inflammatory effect of atorvastatin may prevent damage to renal cells by reducing the expression of

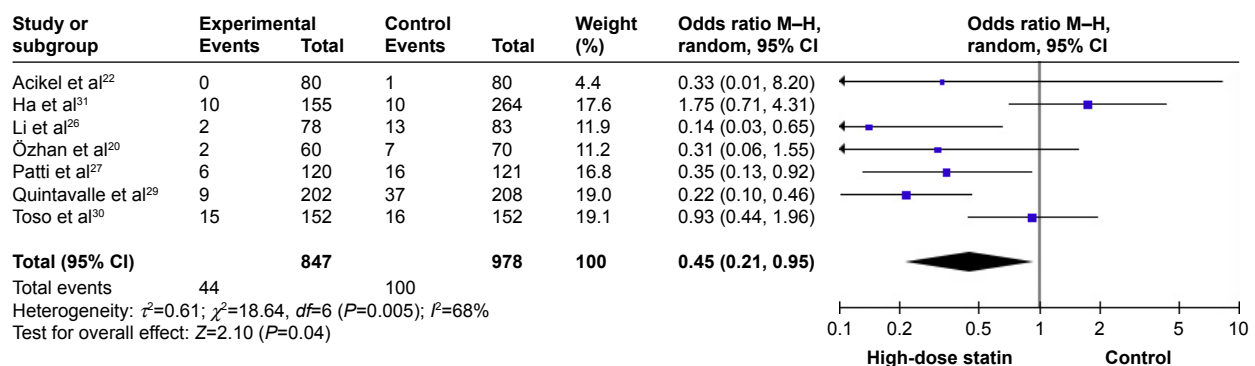| Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI	Odds ratio M–H, random, 95% CI
Acikel et al[22]	0	80	1	80	4.4	0.33 (0.01, 8.20)	
Ha et al[31]	10	155	10	264	17.6	1.75 (0.71, 4.31)	
Li et al[26]	2	78	13	83	11.9	0.14 (0.03, 0.65)	
Özhan et al[20]	2	60	7	70	11.2	0.31 (0.06, 1.55)	
Patti et al[27]	6	120	16	121	16.8	0.35 (0.13, 0.92)	
Quintavalle et al[29]	9	202	37	208	19.0	0.22 (0.10, 0.46)	
Toso et al[30]	15	152	16	152	19.1	0.93 (0.44, 1.96)	
Total (95% CI)		**847**		**978**	**100**	**0.45 (0.21, 0.95)**	
Total events	44		100				
Heterogeneity: $\tau^2=0.61$; $\chi^2=18.64$, $df=6$ ($P=0.005$); $I^2=68\%$							
Test for overall effect: $Z=2.10$ ($P=0.04$)							

Figure 3 Effect of high-dose atorvastatin on the incidence of contrast-induced acute kidney injury.
Abbreviation: M–H, Mantel–Haenszel.

pro-inflammatory cytokines. This phenomenon can induce the expression of tissue factors by macrophages and activate the nuclear factor-kappa B pathway,[49] and renal protection by atorvastatin after PCI is probably due to such attenuation of expression (though other pleiotropic effects may be responsible). However, observational reports on this topic have produced conflicting results. In our meta-analysis, atorvastatin treatment was shown to reduce the prevalence of CIN significantly.

The effective dose of high-dose atorvastatin for CIAKI prevention is not known. Results from studies focusing on the efficacy of high-dose statin pretreatment to prevent CIAKI are inconsistent.[50,51] Recently, three RCTs with relatively large cohorts (NAPLES II, PRATO-ACS, TRACK-D) reported promising results, suggesting that high-dose statins can reduce the prevalence of CIAKI.[29,52,53] Considering the beneficial effects of pretreatment with high-dose statins, we evaluated the efficacy of pretreatment with high-dose atorvastatin in reducing the prevalence of CIAKI. The pooled analysis showed that high-dose atorvastatin reduced the risk of CIN in patients undergoing coronary angiography with iodinated contrast media compared with control (placebo or low-dose statin).

Although administration of a high-dose statin clearly showed a beneficial effect in preventing CIAKI, the adverse effects of high-dose statins may result in lasting damage. In the TRACK-D trial,[52] the authors reported that the prevalence of adverse effects such as muscle pain, gastrointestinal disorders, liver-function abnormalities, edema, or rash was not significantly different between high-dose statin and control groups. Data on adverse events in the RCTs included in our meta-analysis were limited, so we could not calculate the hazard ratios of pretreatment with high-dose atorvastatin. Also, there are insufficient RCT data to ascertain reliably if higher doses of statin therapy are more efficacious than lower doses. Data from two RCTs have reported conflicting results.[28,32]

Our meta-analysis is the first study to compare the effect of atorvastatin for CIAKI prevention in patients undergoing coronary angiography. Previous meta-analyses on similar topics have shown inconsistent results about the efficacy of statin pretreatment mainly because of the limited sample sizes of included trials.[54–56] However, two inherent flaws of our meta-analysis must be mentioned because they could have led to biases. First, all RCTs included in our meta-analysis used different definitions of CIAKI. Second, due to a lack of patient-level data, we could not adjust for patient-level confounders. Hence, clinical heterogeneity among trials should be taken into consideration when interpreting our findings.

Conclusion

At high doses, atorvastatin pretreatment was associated with a significant reduction in the prevalence of CIAKI in patients undergoing coronary angiography. Pretreatment with high-dose atorvastatin could be employed to prevent CIAKI.

Disclosure

The authors report no conflicts of interest in this work.

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