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Original Article

Statins for prevention of contrast induced nephropathy after coronary angiography: a network meta-analysis

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Abstract: Objective: A network meta-analysis to compare various statins for the prevention of contrast induced nephropathy (CIN) was performed in patients who underwent coronary angiography (CAG). Methods: Randomized controlled studies with a Modified Jadad score greater than 3 using statins as prevention for contrast induced nephropathy were utilized from the following databases: PubMed, Ovid EMBASE, Cochrane library and Web of Science. Results: Out of 456 articles, 19 studies were enrolled and 9000 patients were selected. The pooled analysis revealed that a high dose of atorvastatin and rosuvastatin reduced contrast induced nephropathy compared with a placebo/untreated group. No significance was found between various statins within the high and low dose groups. All treatments had similar effects on serious adverse events including death, myocardial infarction, revascularization, cerebral infarction, and dialysis after contrast administration. Conclusions: Fully hydrated, high perioperative statin use is an effective way to reduce the incidence of contrast induced nephropathy compared to a placebo/untreated group with a similar safety profile.

Keywords: Statins, contrast induced nephropathy, coronary angiography, network meta-analysis

Introduction

Contrast induced nephropathy (CIN) is a common complication after administration of contrast medium. As the third leading cause of hospital acquired acute kidney injury, CIN occurs in half of the patients undergoing coronary angiography (CAG) [1]. CIN has been validated to prolong the length of hospitalization, increase health care costs, induce chronic renal impairment, and increase risk of death [2, 3]. In the last few years, several protocols like N-acetylcysteine (NAC) have been utilized to reduce the incidence of CIN. However, there has been no consensusfor the optimal prevention strategy except prior to or after procedural hydration is reached [4]. Statins exert pleiotropic effects including lowering lipids, reducing inflammatory responses, oxidative stress, and endothelial function, etc. [5], which may protect the kidney. Several randomized controlled trials (RCTs) and observational studies evaluated the effectiveness of statins as a preventative measure for CIN having mixed results [6-10]. Similarly, meta-analyses have also been performed, but have not obtained significant conclusions [11-13]. Due to the limitation of head to head comparisons between statins, it is difficult to determine if differences exist amongst various statins including simvastatin, atorvastatin and rosuvastatin. Thus, we conducted a network meta-analysis aiming to compare all statins as prevention for contrast induced nephropathy in patients who underwent coronary angiography.

Methods

Search strategy

A comprehensive literature search of prospective controlled studies published prior to July 2015 was performed within various databases such as PubMed, Ovid EMBASE, Cochrane library, Web of Science and the Chinese Biomedical database. The search strings ("statin" OR "3-hydroxy-3-methylglutaryl coenzyme A" OR "HMG-CoA") AND ("contrast medium" OR "angiocardiography") AND ("contrast induced nephropathy" OR "acute kidney injury"

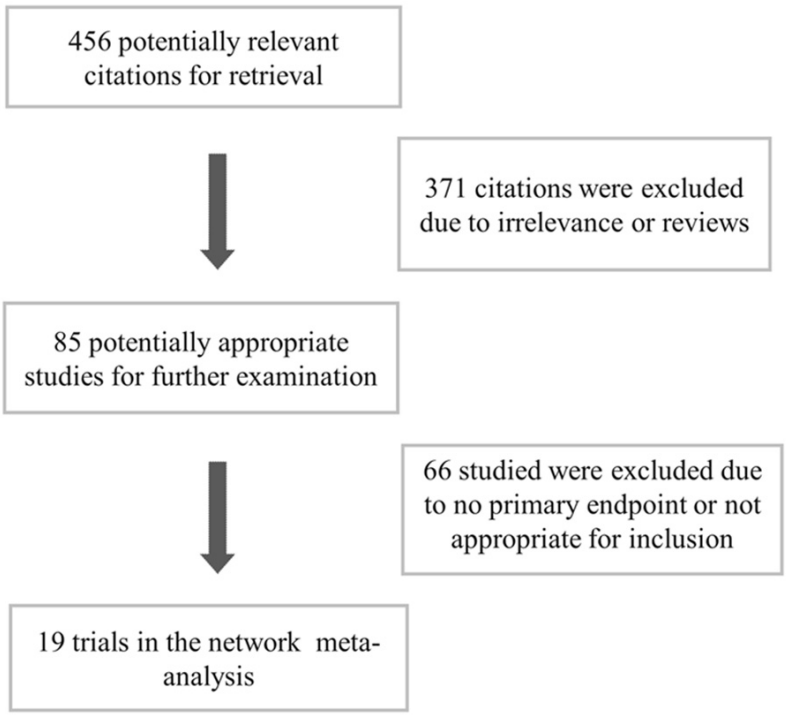

Figure 1. Flowchart describing literature search and study selection process.

OR "kidney failure") were used to search for relevant studies. Two authors worked independently to identify all the relevant studies.

Inclusion and exclusion criteria

Randomized, controlled trials of statins that reported clinically relevant outcomes including incidence of CIN and safety profile were selected. The study was eligible for inclusion if 1) the study was performed on patients who underwent coronary angiography; 2) patients were using statin as a preventative measure for CIN compared with other statins or placebo/untreated; 3) outcome measures included incidence of CIN and serious adverse events; and 4) the Modified Jaded Score was greater than 3. The study was excluded if it was 1) a single arm design; 2) the incidence of CIN was missing; and 3) if there were dual submissions. Two authors independently assessed the methodological quality of the included studies and extracted the relevant data.

Intervention

All statins including different doses were applied as treatments. Perioperative treatments were and taken daily and defined as follows: 1. placebo/untreated; 2. atorvastatin low dose (≤20 mg); 3. atorvastatin high dose (>20 mg); 4. rosuvastatin low dose (≤10 mg); 5. rosuvastatin high dose (>10 mg); 6. simvastatin low dose (≤20 mg); 7. simvastatin high dose (>20 mg).

Outcomes

An increase in serum creatinine >0.5 mg/dl or 25% above baseline 48-72 hours after contrast exposure is the most common definition of CIN. Occasionally, an increase in cystatin C >10% from baseline is also used to define CIN. The primary outcome of this study was the incidence of CIN. Serious adverse events (SAE) were assessed to compare safety between statins. We defined serious adverse events (SAE) as death, myocardial infarction, revascularization, cerebral infarction, dialysis or the proportion of alanine aminotransferase >3 * upper limit of the normal value after contrast administration.

Data extraction

Two investigators independently assessed the quality of trials, and disagreements were resolved through third party investigators. The Modified Jadad score was used to evaluate the quality of methodology (randomization, blinding and withdrawal from studies). The Modified Jadad scale ranges from 1 to 7, where 1-3 indicates poor quality and 4-7 indicates high quality.

Statistical analysis

Statistical analysis was performed using the software R (X64, 3.12, packages including gemtc and rjags). Data outputs were in the form of network plots and forest plots. The demographics (age, population, contrast types, concomitant diseases, etc.) of the patient varied in the different studies. Thus, we adopted a random effects model rather than a fixed effects

Table 1. Characteristics of included studies

Study	Intervention	Country	Population	Contrast Type	CIN Definition	Follow-up Duration	Sample Size	Quality Score
Jo 2008	Simvastatin 80 mg for 2 d/placebo	Korea	chronic renal insufficiency	Iodixanol	a or b	6 months	247	5
Jia 2009	Simvastatin 20 mg/80 mg for 3 d	China	ACS	Iohexol	a or b	unclear	228	5
Zhou 2009	Atorvastatin 10 mg/90 mg for 1 d	China	undergoing CAG or PCI	Iopamidol	a or b	5 days	100	5
Acikel 2010	Atorvastatin 40 mg for 3 d/untreated	Turkey	eGFR >60 mL/min	Iohexol	a or b	unclear	160	5
Ozhan 2010	Atorvastatin 80 mg for 3 d/untreated	Turkey	SCr <1.5 mg/dl or eGFR >70 ml/min per m^3	Iopamidol	a or b	unclear	130	4
Toso 2010	Atorvastatin 80 mg for 4 d/placebo	Italy	Chronic Renal Disease	Iodixanol	a or b	1 month	304	5
Miao 2011	Atorvastatin 20 mg/80 mg	China	STEMI	unclear	a or b	unclear	268	4
Patti 2011	Atorvastatin 80 mg/placebo	Italy	ACS	Lobitridol	a or b	unclear	241	5
Oliveira 2012	Rosuvastatin 40 mg/placebo	Brazil	Elective PCI	High and low osmolarity	a or b	unclear	135	5
Li 2012	Atorvastatin 80 mg/placebo	China	STEMI	Iopromide	a or b	1 month	161	5
Quintavalle 2012	Atorvastatin 80 mg/placebo	Italy	CKD	Iodixanol	c	unclear	410	5
Jo 2013	Atorvastatin 80 mg/10 mg for 5 d	Korea	STEMI	unclear	a or b	unclear	218	5
Kaya 2013	Atorvastatin 80 mg/Rosuvastatin 40 mg	Turkey	STEMI	unclear	a or b	unclear	192	5
Han 2014	Rosuvastatin 10 mg for 5 d/untreated	China	Type 2 DM	Iodixanol	a or b	1 month	2998	6
Leoncini 2014	Rosuvastatin 40 mg admission, followed by 20 mg/day/untreated	Italy	ACS	Iodixanol	a or b	1 month	504	6
Liu 2014	Atorvastatin 20 mg/Rosuvastatin 10 mg	China	CKD	Iopamiron/Ultravist	a or b	2 years	1078	6
Liu 2014	Rosuvastatin 10 mg for 5 d/placebo	China	Diabetes combined CKD	iodixanol	a or b	1 month	1204	5
Bao 2014	Rosuvastatin 40 mg for 8 d/placebo	China	CAG	iopamidol	a or b	5 days	182	4
Deng 2013	Rosuvastatin 20/10 mg for 1 month	China	PCI	Iopamidol/Iopromide	a or b	1 month	240	4

CAG: coronary angiography; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; DM: diabetes mellitus; CKD: chronic kidney disease; ACS: acute coronary syndrome; a: an increase of serum creatinine >0.5 mg/dl; b: an increase of serum creatinine >25% above baseline; c: an increase in cystatin C >10% from baseline.

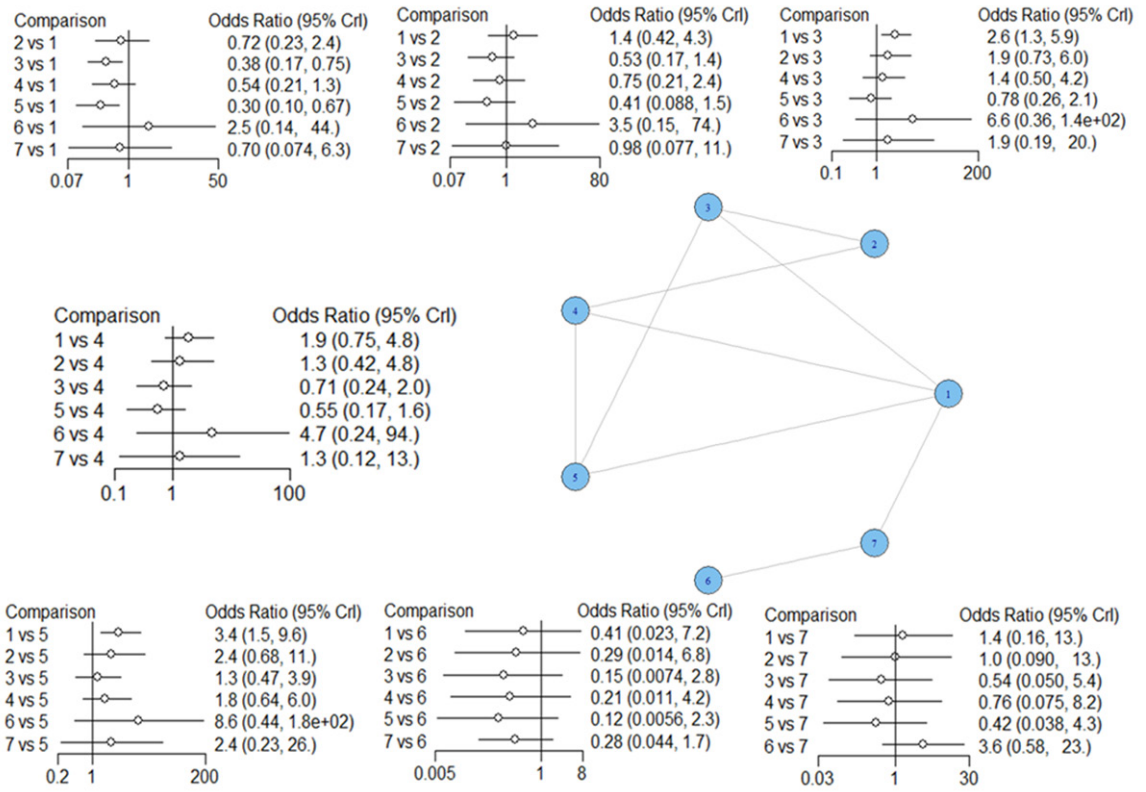

Figure 2. Network plot and forest plot with the random effects model in patients who underwent coronary angiography in reducing contrast induced nephropathy among all treatments. Odds ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at OR=1 indicates significance.

model. Comparisons of effects between groups were displayed as an odds ratio (OR) with its 95% confidence interval (95% CI). In order to avoid risk of bias, we included only the randomized, controlled trials and excluded observational, dual submissions and follow up studies.

Results

Descriptions of included studies

456 relevant studies were obtained by searching electronic databases. Of these, 371 were excluded on the basis of their title and abstract. The full texts of the remaining 85 articles were retrieved and read by two independent investigators. From these 85 articles, 66 were excluded because they did not match the inclusion criteria. The remaining 19 [6, 7, 9, 10, 14-28] articles met all entry criteria and were included in the network meta-analysis. The screening process is illustrated in **Figure 1**.

The characteristics of the included studies in this analysis were given in **Table 1**. In the seven treatment comparisons, a total of 9000 patients with coronary artery disease were included. All studies were published in high quality English journals (Modified Jadad score ≥4). These studies included two trials of simvastatin, nine trails of atorvastatin, six trials of rosuvastatin versus placebo and two trials of atorvastatin versus rosuvastatin. All patients of included in these studies were hydrated prior to treatment.

Incidence of CIN

Our analysis assessed the risk of developing contrast induced nephropathy. Overall results of comparisons between treatments, primary endpoints and network plots were showed in **Figure 2**. The results demonstrated that high dose atorvastatin and rosuvastatin may reduce the incidence of CIN compared to placebo or untreated groups, separately (OR 0.38, 95% CI: 0.17-0.75 and OR 0.30, 95% CI: 0.10-0.67). Due to minimal studies available concerning simvastatin in the network meta-analysis,

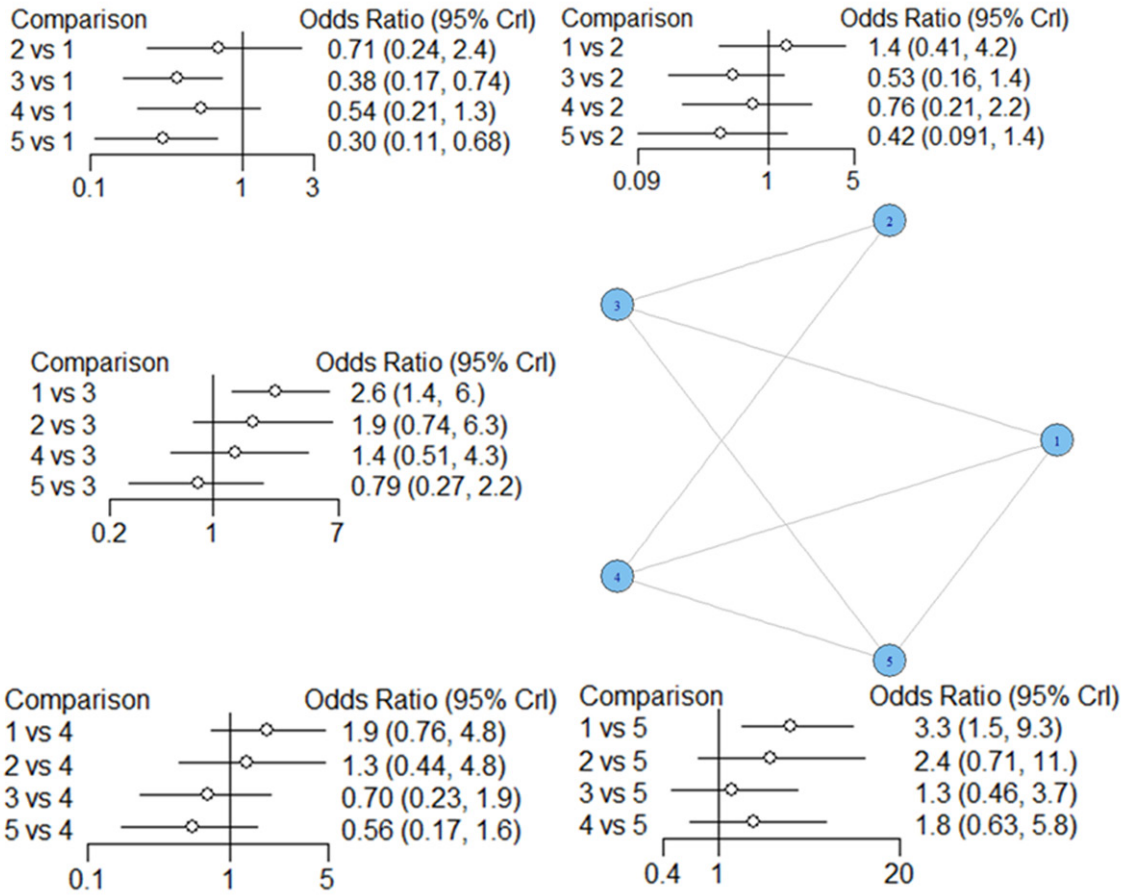

Figure 3. Network plot and forest plot with the random effects model in patients who underwent coronary angiography in reducing contrast induced nephropathy among all treatments excluded simvastatin. Odds ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at OR=1 indicates significance.

these were not included in the results. Hence, we compared all other treatments excluding the simvastatin treatment. The network plot and overall results of comparisons with treatment were displayed in **Figure 3**. Nevertheless, the results were consistent with previous analysis. High dose atorvastatin and rosuvastatin were still superior to placebo/untreated group, respectively (OR 0.38, 95% CI: 0.17-0.74 and OR 0.30, 95% CI: 0.11-0.68). No differences were found between other statin groups and placebo/untreated group in reducing the incidence of CIN.

Serious adverse events

10 trials recorded the safety of statins after procedures. The follow up duration varied from 5 days to 2 years. The pooled analysis of network plots and treatments were illustrated in **Figure 4**. In general, no significant differences were found between all treatment groups in the follow-up safety profile.

Discussion

The present network meta-analysis was conducted to compare various statins in the prevention of contrast induced nephropathy after coronary angiography. 19 clinical trials were identified and the data was pooled and analyzed. Overall, there were no significant difference between statins including simvastatin, atorvastatin and rosuvastatin in reducing the incidences of CIN or serious adverse events. However, high dose atorvastatin and rosuvastatin may reduce the incidence of CIN with a similar safety profile, providing an effective method to prevent this complication after contrast admission.

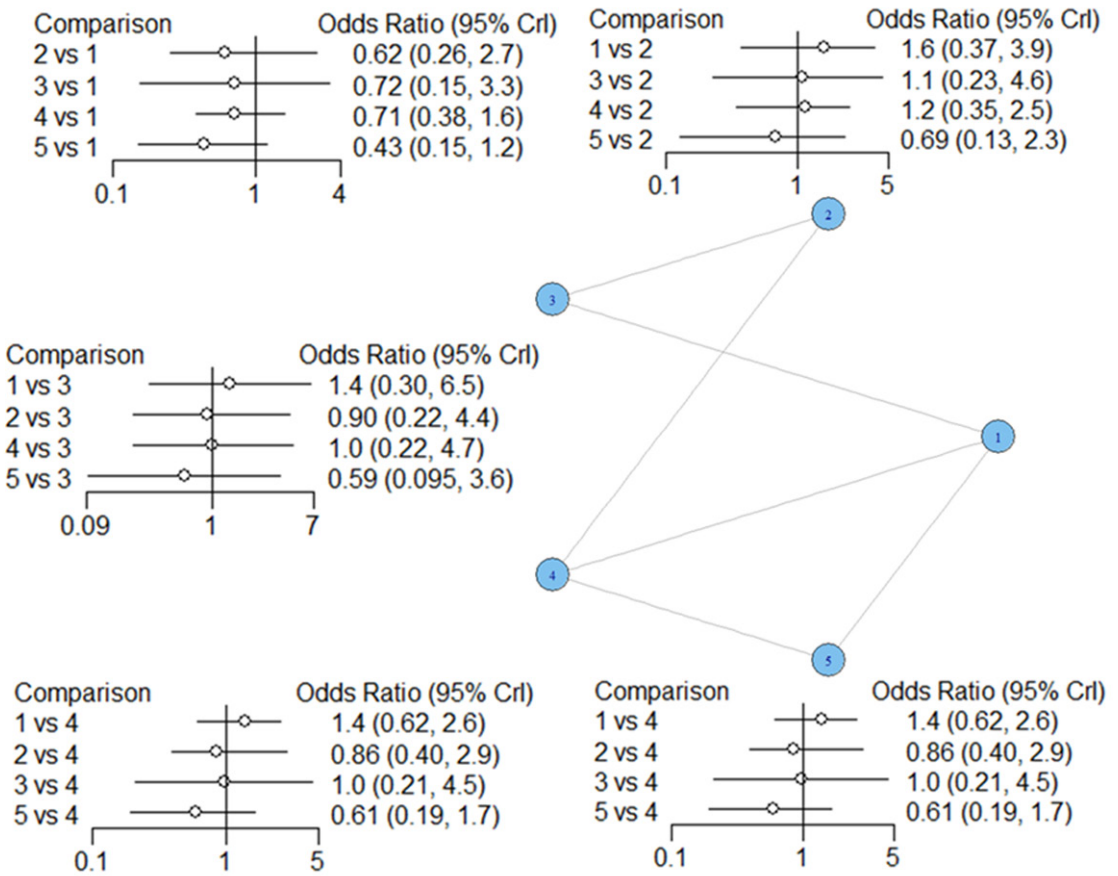

Figure 4. Network plot and forest plot with the random effects model in patients who underwent coronary angiography in serious adverse events among all treatments excluded simvastatin. Odds ratio (circle) and 95% CI (horizontal line) for each study are plotted on the graph. A comparison that does not cross the vertical line at OR=1 indicates significance.

Statins, which are mainly used for their cholesterol-lowering effects, also have anti-inflammatory and anti-oxidant activity and improve endothelial function [29]. The mechanism of statins for CIN protection may reduce tubular reabsorption of contrast medium and mitigate their deleterious effects on the renal tubules [30]. It is unclear if statins exert these benefits as a class or whether it depends on statin potency, dose, or molecular structure (lipophilic or hydrophilic) [31]. Hence, the purpose of this network meta-analysis was to compare every statin and dosagesbefore procedures that may influence the incidences of CIN. According to the results, simvastatin, atorvastatin and rosuvastatin were the most commonly used as pre-procedural protection drugs among all statins. Kaya [9] et al. and Liu [25] et al. conducted a clinical trial in chronic kidney disease or ST-segment elevation of myocardial infarction patients to compare atorvastatin and rosuvastatin for reducing the incidence of CIN separately and reached the same conclusion that no difference exists between these two drugs. Some previous meta-analyses [11-13, 32-36] have been performed to compare the high-dose statins to low-dose statins and placebo or just statin groups with control groups. In accordance with the conclusion of existing meta-analyses, we found that daily high doses of statins could reduce the incidence of CIN compared with placebo controls. However, statins including atorvastatin, rosuvastatin and simvastatin did not significantly differ between each other.

In conclusion, based on our results of pooled analysis, multiple types of statins taken with various daily doses were all similar in reducing CIN when patients were fully hydrated. High

doses of statins may exert a positive impact compared with placebo/untreated group. In view of the risk of mortality and morbidity CIN could add, other effective measures are still needed to cut down the adverse impact.

Disclosure of conflict of interest

None.

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