ORIGINAL RESEARCH

Role of statins in preventing cardiac surgery-associated acute kidney injury: an updated meta-analysis of randomized controlled trials

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Background: The prevention of cardiac surgery-associated acute kidney injury (CSA-AKI) by statins remains controversial. Therefore, the present meta-analysis including randomized controlled trials (RCTs) was performed to assess the effect of perioperative statin on CSA-AKI.
Methods: Two reviewers independently searched for RCTs about perioperative statin for prevention of CSA-AKI. The primary endpoint was CSA-AKI. Relative risk was calculated between statin and placebo for preventing CSA-AKI using the random-effect model or fixed-effect model according to different heterogeneity.
Results: Eight RCTs met inclusion criteria, including five studies with atorvastatin, two with rosuvastatin, and one with simvastatin. There were 1,603 patients receiving statin treatment and 1,601 with placebo. Perioperative statin therapy did not reduce the incidence of CSA-AKI (relative risk =1.17, 95% CI: 0.98–1.39, p=0.076). Furthermore, perioperative statin increased the risk of CSA-AKI in the subgroup analysis with clear definition of CSA-AKI and those with JADAD score >3. Perioperative rosuvastatin produced slightly significantly higher risk of AKI than atorvastatin therapy (p=0.070). Statin intervention both pre and post surgery slightly increased the risk of CSA-AKI versus preoperative statin therapy alone (p=0.040).
Conclusions: Perioperative statin therapy might increase the risk of CSA-AKI after cardiac surgery.
Keywords: statin, perioperative, acute kidney injury, cardiac surgery, meta-analysis

Introduction

Acute kidney injury (AKI) is an important and common complication of cardiac surgery and has reported rates of 8.9%–45.8%.[1–4] AKI independently increases the length and cost of hospitalization[5] and is also associated with higher in-hospital mortality and poor long-term survival.[6,7] Therefore, a number of studies have focused on preoperative therapies to prevent cardiac surgery-associated acute kidney injury (CSA-AKI).

Statins, with pleiotropic antiinflammatory and antioxidant effects, have been considered to reduce the risk of CSA-AKI, which is related to inflammation and oxidative stress.[8,9] Wang et al[10] systematically reviewed 21 observational studies and 5 randomized controlled trials (RCTs) and found that preoperative statin treatment reduced the incidence of short- and long-term renal dysfunction after surgery. However, they mainly included observational studies, in which the results could be influenced by confounding factors. A recent meta-analysis of 10 RCTs showed that perioperative statin therapy did not reduce CSA-AKI, and in contrast, appeared to produce unfavorable outcomes.[11] However, this study combined the effects of dialysis and CSA-AKI, which could influence the conclusions. In addition, whether different statins type

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(atorvastatin or rosuvastatin) or administration time (pre and post operation) had different effects on CSA-AKI was not elucidated. Therefore, the present updated meta-analysis included studies of the incidence of CSA-AKI only and performed subgroup analyses to better demonstrate the efficacy of perioperative statins for the prevention of CSA-AKI.

Methods
Literature search
A systematic search of PubMed, ClinicalTrials.gov, Web of Science, Embase, Medline, and the Cochrane Library was performed from inception to July 2016 using the following terms: (surgery or cardiac surgery or coronary artery bypass surgery or heart surgery or valve surgery) AND (statin or atorvastatin or rosuvastatin or simvastatin) AND (renal failure or acute renal failure or acute kidney failure or ARF or renal insufficiency or acute renal insufficiency or acute kidney insufficiency or renal dysfunction or acute kidney injury or AKI or acute tubular necrosis or ATN). RCTs comparing statin versus placebo for preventing AKI after cardiac surgery were selected. Potentially suitable studies were also obtained from references of the included papers and meta-analyses. Furthermore, related abstracts with complete results sections from the American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the American Society of Nephrology were included in this analysis. The language was restricted to English.

Study selection and quality assessment
Eligible articles were independently identified through their titles and abstracts by two reviewers. If unidentified, the full text of the paper was carefully reviewed for inclusion. Any controversies were discussed with a third reviewer. RCTs comparing perioperative statin versus placebo in preventing CSA-AKI were included. The following exclusion criteria were used: 1) duplicate papers, 2) non-RCTs, 3) preclinical (in vitro or animal) studies, and 4) studies lacking data about occurrence of CSA-AKI.

Methodological quality was evaluated using the JADAD scoring system[12] by two independent reviewers and disagreements were resolved by a third one.

Study outcomes
The primary outcome was CSA-AKI. We accepted the definition of CSA-AKI in each included study, including the risk, injury, failure, loss, end-stage renal disease (RIFLE),[13] acute kidney injury network (AKIN),[14] and other criteria. The secondary outcome was major adverse clinical events (MACEs) including death or stroke or myocardial infarction.

Data extraction
The period of enrollment, first author, number of patients, mean age, proportion of females, baseline creatinine, statin dosing regimen, definition of CSA-AKI, incidence of CSA-AKI, and mortality in each group were extracted from enrolled papers.

Statistical analysis
The pooled relative risks (RR) with 95% CIs were calculated to assess the effect of perioperative statin in preventing CSA-AKI or MACEs after cardiac surgery. Funnel plots were displayed to subjectively assess publication bias. In addition, Egger's and Begg's tests were used to quantify the bias of publication. Heterogeneity was assessed by I-squared statistics. I-squared values $<25\%$ were regarded as low heterogeneity, 25%–50% as moderate, and $>50\%$ as severe. A fixed-effect model was performed in the absence of significant heterogeneity, defined as a p-value >0.10 and $I^2 < 50\%$. On the contrary, random-effects model was used (p-value ≤ 0.10 or $I^2 \leq 50\%$). Several subgroup analyses were also conducted to identify potential differences in treatment across the trials. Subgroup analyses were performed according to different study protocols (definition of CSA-AKI, sample size, or population) and different types of statins (atorvastatin or rosuvastatin) or their administration time. A p-value <0.05 in a two-tailed test was considered statistically significant. Statistical analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX, USA).

Results
Characteristics of identified studies
There were 605 articles screened according to the search strategy, and 84 relevant papers addressed the incidence of CSA-AKI. Finally, eight RCTs were included according to the inclusion and exclusion criteria (Figure 1). The detailed characteristics are described in Table 1.

A total of 3,204 operative subjects were enrolled, of whom 1,603 were randomized to receive statin and 1,601 placebo. Five studies used therapy with atorvastatin,[15–19] two with rosuvastatin,[20,21] and one with simvastatin.[22] Four studies involved coronary-artery bypass grafting (CABG) alone,[18–20,22] one study focused on elective valvular heart surgery,[15] and the other three addressed complicated cardiac surgery including CABG, valvular heart disease, and ascending aortic lesions.[16,17,21] The interventions in four studies were performed before the operation,[18–20,22] and in the other four they were performed pre and post surgery.[15–17,21]

The definition of CSA-AKI varied in the included studies. In the study conducted by Christenson,[22] transient renal failure
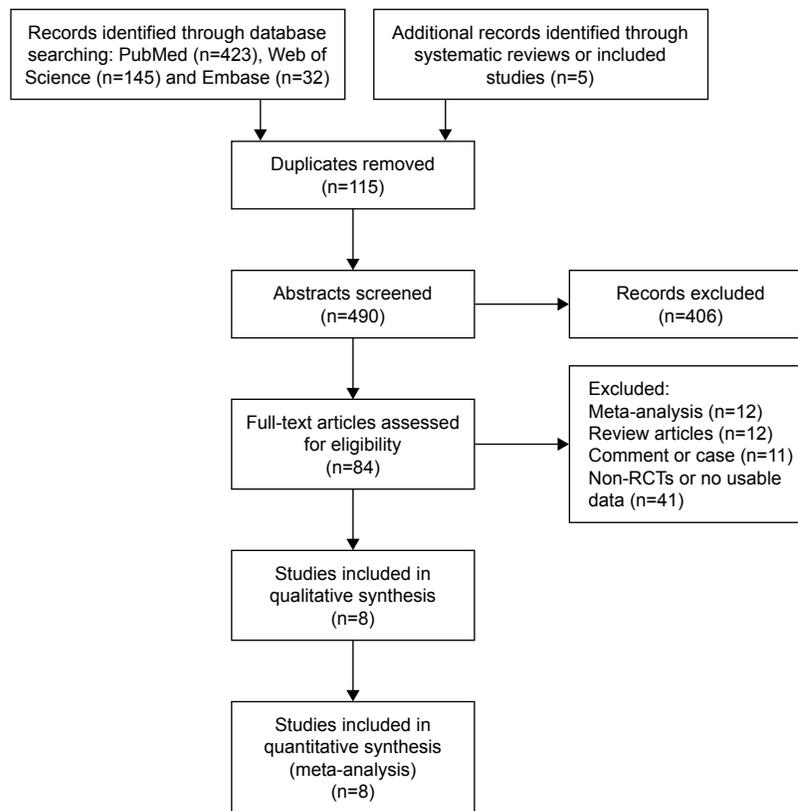
Figure 1 Flowchart of study selection.
Abbreviation: RCTs, randomized controlled trials.

Table 1 Study design of the included studies

Study	Population	Statin type and dose	AKI definition	MACEs included	JADAD
Christenson[22]	CABG	A 4-week preoperative treatment with simvastatin, 20 mg/day	Serum urea >9 mmol/L and serum creatinine >125 mmol/L in a patient with normal preoperative values	MI	1
Chello et al[19]	CABG	Atorvastatin 20 mg/day, 3 weeks before surgery	Renal insufficiency	Death, stroke, MI	4
Mannacio et al[20]	CABG	Rosuvastatin 20 mg/day, starting 7 days before the planned operation	An increase in serum creatinine value of >2.5 mg/dL	MI	5
Spadaccio et al[18]	CABG	Atorvastatin 20 mg/day 3 weeks before surgery	Renal insufficiency	Death, stroke, MI	4
Prowle et al[17]	Cardiac surgery with cardiopulmonary bypass	Atorvastatin 40 mg once daily for 4 days starting preoperatively; postoperative days 1, 2, and 3 for a total of 4×40 mg doses of atorvastatin	RIFLE consensus guidelines	Death	5
Billings et al[16]	Elective CABG, valvular heart surgery, or ascending aortic surgery	Atorvastatin, 80 mg the day prior to surgery, 40 mg on the morning of surgery (at least 3 hours prior to surgery), and 40 mg daily at 10 am following surgery for the duration of hospitalization	AKIN criteria	Death, stroke	5
Zheng et al[21]	Elective CABG, surgical aortic-valve replacement, or both	Rosuvastatin 20 mg once daily 8 days before surgery and for 5 days thereafter	AKIN criteria	Death, stroke, MI	6
Park et al[15]	Elective valvular heart	Atorvastatin 80 mg on the evening prior to surgery; 40 mg on the morning of surgery; and three further doses of 40 mg on the evenings of postoperative days 0, 1, and 2	AKIN criteria	Death, stroke	6

Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury network; CABG, coronary artery bypass grafting; MACEs, major adverse clinical events; MI, myocardial infarction; RIFLE, risk injury failure loss end-stage renal disease.

(serum urea >9 mmol/L and serum creatinine >125 mmol/L in a patient with normal preoperative values) was mentioned as a postoperative complication. Postoperative renal failure was defined as an increase in serum creatinine to >2.5 mg/dL in one study,[20] whereas Chello et al[19] and Spadaccio et al[18] just reported the incidence of renal insufficiency after CABG. Prowle et al[17] defined CSA-AKI according to the RIFLE consensus guidelines, whereas Park et al, Billings et al and Zheng et al all diagnosed CSA-AKI based on standards from the AKIN.[15,16,21]

Study endpoints

All the identified studies were evaluated by modified JADAD scores and had high technical quality. These studies were not symmetrically distributed in the funnel plots (Figure 2). There was significant publication bias according to Egger's test (bias =2.97, p=0.025). Moderate heterogeneity occurred in these studies (I-squared =28.3%; p=0.202). The fixed-effect model indicated that perioperative statin treatment did not significantly reduce incidence of CSA-AKI (RR =1.17, 95% CI: 0.98–1.39, p=0.076, Figure 3). In addition, statin therapy did not reduce the incidence of MACE (RR =1.01, 95% CI: 0.72–1.43, p=0.942, Figure 4), with low heterogeneity (I-squared =20.2%; p=0.281).

Subgroup analysis

Four studies had a clear definition of CSA-AKI based on RIFLE or AKIN. The pooled estimate demonstrated that perioperative statin therapy significantly increased the risk of CSA-AKI (I-squared =36.1%, RR =1.21, 95% CI: 1.02–1.45, p=0.032). The analysis based on different sample size showed that statin therapy was associated with a higher incidence

of CSA-AKI in studies with a sample size >500[15,16,21] (I-squared =5.6%, RR =1.29, 95% CI: 1.07–1.57, p=0.008), but no statistical difference in studies with a sample size <500 (I-squared =0%, RR =0.66, 95% CI: 0.41–1.04, p=0.074). Studies with a JADAD score >3 showed that perioperative statin was related to a higher risk of CSA-AKI (I-squared =0%, RR =1.20, 95% CI: 1.01–1.43, p=0.042).[15–21] In addition, statin treatment did not significantly reduce the incidence of CSA-AKI in patients undergoing isolated CABG (I-squared =0%, RR =0.41, 95% CI: 0.15–1.12, p=0.081). Furthermore, perioperative rosuvastatin therapy produced slightly significantly higher risks of AKI than atorvastatin therapy (p=0.070, Figure 5). The effects of different intervention times were also evaluated, and the results showed that statin treatment both pre and post operation was associated with higher risk of CSA-AKI than preoperative statin therapy alone (p=0.040, Figure 6). Due to the greater statistical weight of the study performed by Zheng et al,[21] we also performed a subgroup analysis without this study, and the results showed that statin treatment did not significantly reduce the incidence of CSA-AKI (I-squared =0%, RR =0.74, 95% CI: 0.49–1.12, p=0.161).

Discussion

This meta-analysis demonstrated that perioperative statin therapy might in fact increase the risk of CSA-AKI, which was in accordance with the recent research by Putzu et al.[11] However, we also demonstrated that rosuvastatin showed a tendency to increase the risk of CSA-AKI more than atorvastatin. In addition, compared with preoperative statin therapy, statin therapy both pre- and postoperatively seemed to have a higher risk of CSA-AKI.

The relationship between statin therapy and CSA-AKI was first shown in an RCT conducted by Christenson[22] and no significant differences in the occurrence of transient renal failure were found. However, in a later meta-analysis, preoperative statin treatment was reported to reduce both short-term and long-term postoperative renal dysfunction.[10] In addition, the incidence of CSA-AKI varied based on the different diagnostic criteria. The development of the RIFLE[13] and AKIN[14] criteria has standardized the definition of CSA-AKI. In a subgroup analysis of previous meta-analysis, statin therapy was associated with a lower incidence of CSA-AKI diagnosed using the AKIN or RIFLE criteria.[10] However, three new RCTs did not find a favorable effect of statins.[15,16,21]

Recently, Li et al[23] included these three RCTs and reported that patients undergoing cardiac surgery might benefit from
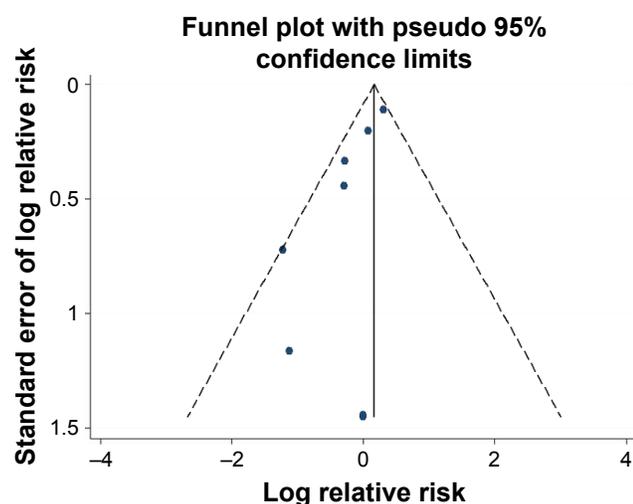

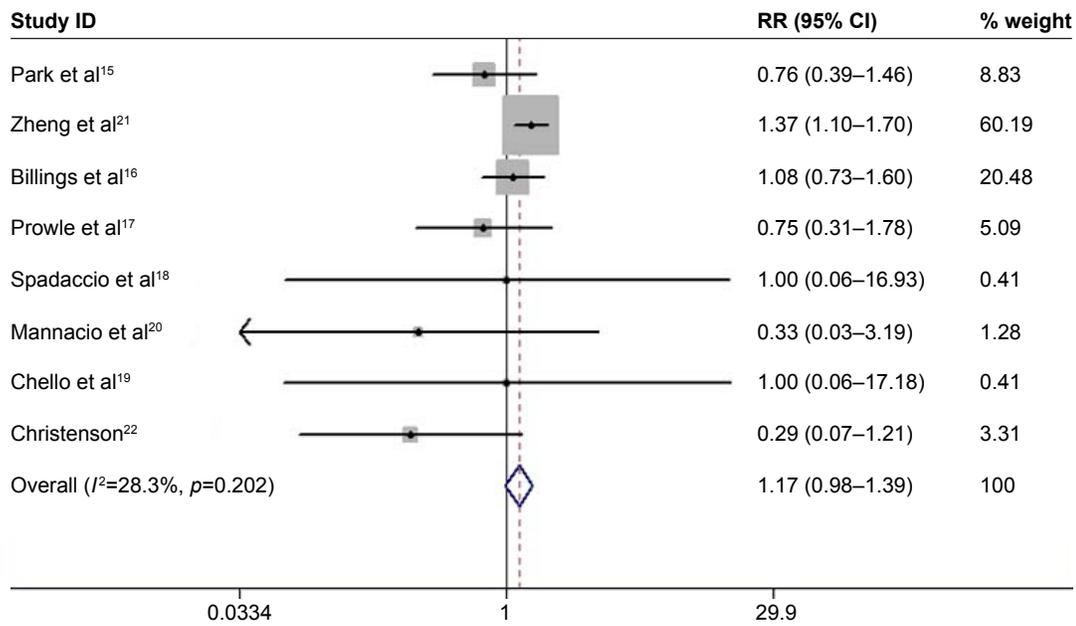**Figure 2** Funnel plot of included studies in the meta-analysis.

Study ID		RR (95% CI)	% weight
Park et al[15]		0.76 (0.39–1.46)	8.83
Zheng et al[21]		1.37 (1.10–1.70)	60.19
Billings et al[16]		1.08 (0.73–1.60)	20.48
Prowle et al[17]		0.75 (0.31–1.78)	5.09
Spadaccio et al[18]		1.00 (0.06–16.93)	0.41
Mannacio et al[20]		0.33 (0.03–3.19)	1.28
Chello et al[19]		1.00 (0.06–17.18)	0.41
Christenson[22]		0.29 (0.07–1.21)	3.31
Overall (I^2=28.3%, p=0.202)		1.17 (0.98–1.39)	100

0.0334   1   29.9

Figure 3 Forest plot of RR and 95% CI for postoperative AKI.
Abbreviations: AKI, acute kidney injury; RR, relative risk.

statins by reducing CSA-AKI and the mortality of the patients suffering from CSA-AKI. However, our results showed that perioperative statin therapy did not reduce CSA-AKI, and in contrast, appeared to produce an unfavorable influence. This finding was not in accordance with previous meta-analyses.[10,23] Some differences could account for this phenomenon. In the meta-analysis conducted by Wang et al,[10] most of the included research was observational studies, in which confounding factors could impact the reported effects

of statins on CSA-AKI. Also, the meta-analysis of Li et al[23] combined observational and randomized studies, which could increase heterogeneity. Although a recent meta-analysis[11] reported results similar to ours, they also included two studies with incident dialysis but not CSA-AKI[24,25] which were excluded in our analysis.

There are several possible explanations for our finding that statins had no protective effect against CAS-AKI. First, cardiac surgery was commonly accompanied by ischemic
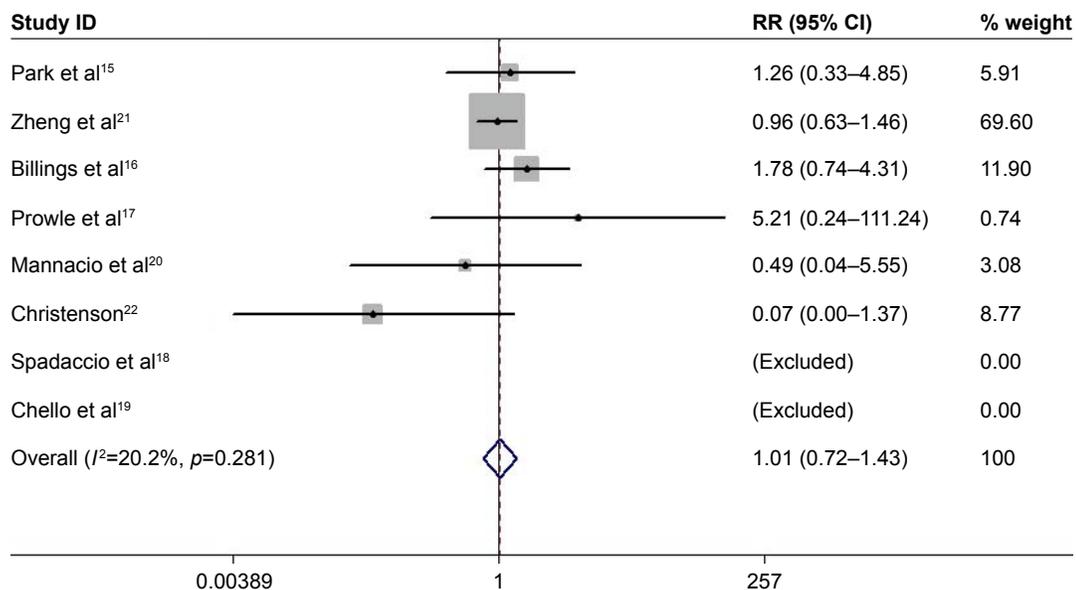
Study ID		RR (95% CI)	% weight
Park et al[15]		1.26 (0.33–4.85)	5.91
Zheng et al[21]		0.96 (0.63–1.46)	69.60
Billings et al[16]		1.78 (0.74–4.31)	11.90
Prowle et al[17]		5.21 (0.24–111.24)	0.74
Mannacio et al[20]		0.49 (0.04–5.55)	3.08
Christenson[22]		0.07 (0.00–1.37)	8.77
Spadaccio et al[18]		(Excluded)	0.00
Chello et al[19]		(Excluded)	0.00
Overall (I^2=20.2%, p=0.281)		1.01 (0.72–1.43)	100

0.00389   1   257

Figure 4 Forest plot of RR and 95% CI for MACEs.
Abbreviations: MACEs, major adverse clinical events; RR, relative risk.

Study ID	(Atorvastatin vs rosuvastatin)	RR (95% CI)	% weight
A			
Park et al[15]		0.76 (0.39–1.46)	9.14
Billings et al[16]		1.08 (0.73–1.60)	21.18
Prowle et al[17]		0.75 (0.31–1.78)	5.27
Spadaccio et al[18]		1.00 (0.06–16.93)	0.43
Chello et al[19]		1.00 (0.06–17.18)	0.42
Subtotal (I^2=0.0%, p=0.884)		0.95 (0.70–1.29)	36.43
B			
Zheng et al[21]		1.37 (1.10–1.70)	62.25
Mannacio et al[20]		0.33 (0.03–3.19)	1.32
Subtotal (I^2=33.4%, p=0.220)		1.35 (1.08–1.67)	63.57
Overall (I^2=0.0%, p=0.424)		1.20 (1.01–1.43)	100

0.0334   1   29.9
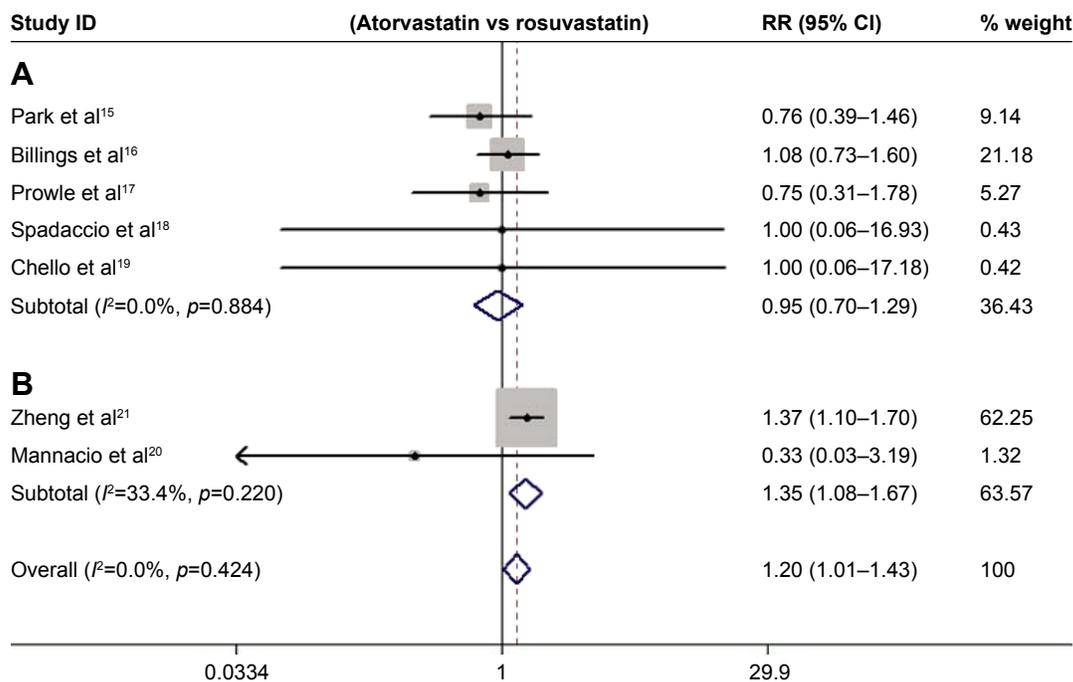
Figure 5 Subgroup analysis for postoperative AKI based on different interventions (**A**: atorvastatin; **B**: rosuvastatin).
Abbreviations: AKI, acute kidney injury; RR, relative risk.

injury, and resultant liver and renal dysfunction.[26,27] Statins, which are mainly metabolized by the liver and kidney, might aggravate the stress on these organs and increase the incidence of CSA-AKI. Second, although statins may exert

favorable effects on contrast-induced AKI via antiinflammatory and antioxidant actions,[28,29] this was not shown to have benefits on CSA-AKI. Different degrees of antiinflammatory actions could account for this discrepancy. Notable systemic
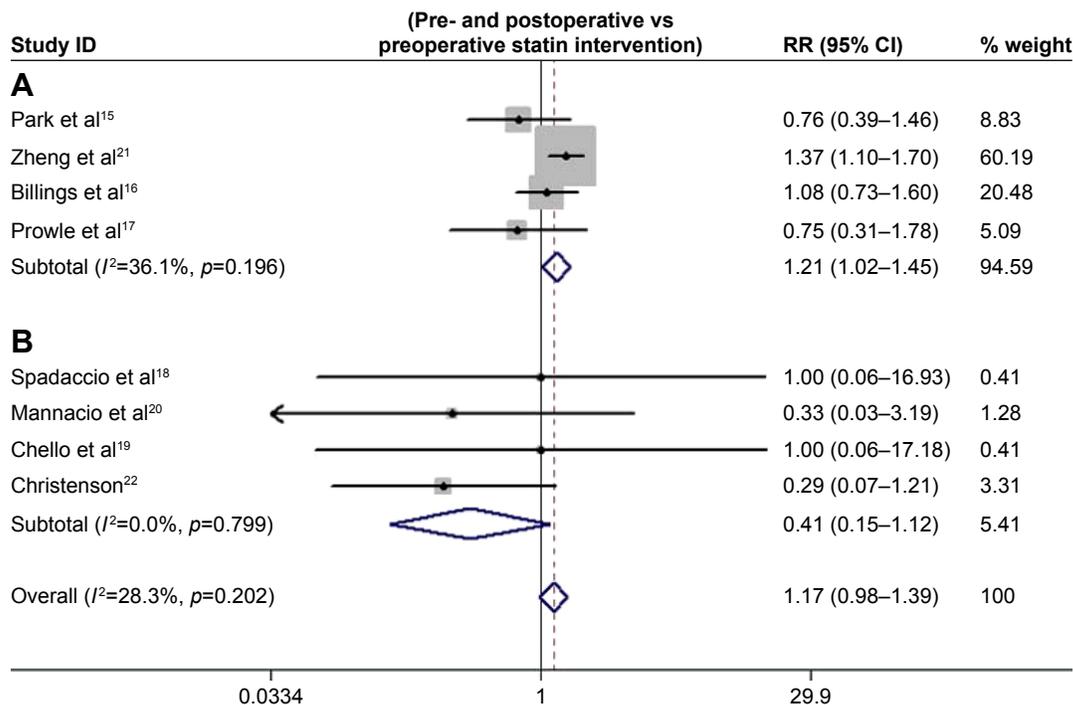
Study ID	(Pre- and postoperative vs preoperative statin intervention)	RR (95% CI)	% weight
A			
Park et al[15]		0.76 (0.39–1.46)	8.83
Zheng et al[21]		1.37 (1.10–1.70)	60.19
Billings et al[16]		1.08 (0.73–1.60)	20.48
Prowle et al[17]		0.75 (0.31–1.78)	5.09
Subtotal (I^2=36.1%, p=0.196)		1.21 (1.02–1.45)	94.59
B			
Spadaccio et al[18]		1.00 (0.06–16.93)	0.41
Mannacio et al[20]		0.33 (0.03–3.19)	1.28
Chello et al[19]		1.00 (0.06–17.18)	0.41
Christenson[22]		0.29 (0.07–1.21)	3.31
Subtotal (I^2=0.0%, p=0.799)		0.41 (0.15–1.12)	5.41
Overall (I^2=28.3%, p=0.202)		1.17 (0.98–1.39)	100

0.0334   1   29.9

Figure 6 Subgroup analysis for postoperative AKI based on different intervention time (**A**: pre and post operation; **B**: pre-operation).
Abbreviations: AKI, acute kidney injury; RR, relative risk.

oxidative stress and inflammation would be expected in patients undergoing cardiac surgery,[30] and this may not be inhibited significantly by statin therapy.[15] Lastly, Allou et al[31] reported that the positive effect of statin on CSA-AKI was seen only in patients with high cardiovascular risk. The four initial studies[18–20,22] that included only patients undergoing CABG showed that statin therapy seemed to protect against CSA-AKI (RR =0.41, p=0.081). The later studies[15–17,21] with relatively larger sample sizes did not focus on these population, so protective effects were not documented. Therefore, whether the effects of statins on CSA-AKI are influenced by operative types was unclear.

Rosuvastatin has more potent antiinflammatory effects than atorvastatin, which is thought to play an important role in AKI development.[32,33] However, we found that rosuvastatin increased the risk of CSA-AKI more than atorvastatin. This was driven primarily by the results of Zheng et al[21] who reported AKI was more common with rosuvastatin. Previous research found that rosuvastatin might increase the risk of proteinuria due to its sulfur structure,[34] but not creatinine level or the incidence of kidney injury.[35] The way of excretion was another reason for our finding. Less than 1% of atorvastatin was excreted by kidney, so the renal toxic effect was not common.[36]

Subgroup analysis of the different administration times indicated that statin intervention during the entire perioperative period slightly increased the risk of CSA-AKI relative to preoperative statin therapy alone. However, preoperative statin therapy was performed only in the initial studies,[18–20,22] which included patients with high cardiovascular risk. The inconsistent definitions of CSA-AKI and small sample sizes may affect the result. Unfortunately, the later studies did not continue this research design. Therefore, the value of statin administration times on the risk of CSA-AKI was not confirmed.

Limitations

Some limitations should be considered when applying the findings of this study. First, the inherent weakness of meta-analysis, in which publication bias and data from different or variable protocols are combined, might impact the results. Second, CSA-AKI might be considered a secondary endpoint in the included research studies, which could lead to miss some potentially relevant studies. However, we also included studies from previously published reviews. Third, the dose-dependent effects of statins on CSA-AKI are not fully understood because of the restrictions of the meta-analysis. Finally, although we performed subgroup analyses

of different definitions of CSA-AKI, non-standardized definitions might influence the results. Therefore, the roles of statins (different types or administration times) in preventing CSA-AKI in patients with or without high cardiovascular risk remain to be clarified by further high-quality RCTs.

Conclusions

Perioperative statin therapy did not reduce the incidence of CSA-AKI, and in contrast, may exert unfavorable effects on renal function. Rosuvastatin showed a tendency of increasing risk of CSA-AKI compared with atorvastatin. In addition, compared with preoperative statin therapy, statin therapy throughout the perioperative period seemed to confer a higher risk of CSA-AKI.

Disclosure

The authors report no conflicts of interest in this work.

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