

Effect of perioperative statin therapy on renal outcome in patients undergoing cardiac surgery

A meta-analysis of randomized controlled trials

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Abstract

Background: Acute renal injury (AKI) is a common renal complication after cardiac surgery. The aim of this study was to determine the effect of perioperative statin therapy (PST) on postoperative renal outcome in patients undergoing cardiac procedures.

Methods: We searched for the reports that evaluating the effect of PST on renal outcomes after cardiac surgery between March 1983 and June 2016 in the electronic database Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE/PubMed, and EMBASE/OVID.

Results: Nine randomized controlled trials (RCTs) enrolling 2832 patients, with 1419 in the PST group and 1413 in the control group, were included in this meta-analysis. Our results suggested that PST increased the incidence of postoperative renal complication (relative risk [RR] 1.18, 95% confidence interval [CI] 1.01–1.36, $P = .03$) with low heterogeneity ($I^2 = 30\%$, $P = .18$). Six studies with 3116 patients detected no significant difference in severe renal complication between PST and control groups (RR 1.23, 95%CI 0.84–1.79, $P = .28$). Postoperative serum creatinine (sCr) at 48 hours was shown to be higher in the PST group (mean difference [MD] 0.03, 95% CI 0.03–0.03; $P < .01$). The length of hospital stay was decreased slightly by 0.59 day in the PST group (95% CI –0.85 to –0.33; $P < .01$).

Conclusions: Perioperative statin therapy seems to jeopardize short-term renal outcome in patients undergoing cardiac surgery, but the occurrence of severe renal complication was not affected.

Abbreviations: AKI = acute renal injury, AKIN = Acute Kidney Injury Network, BUN = blood urea nitrogen, CABG = coronary artery bypass grafting, CI = confidence interval, CPB = cardiopulmonary bypass, MD = mean difference, PST = perioperative statin therapy, RCTs = randomized controlled trials, RIFLE = Risk, Injury, Failure, Loss and End-stage kidney disease, RR = relative risk, RRT = renal replacement therapy, sCr = serum creatinine.

Keywords: cardiac surgery, meta-analysis, perioperative statin therapy, renal outcome

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SW and HY contributed equally to the study.

Authorship: HY and BL provided the original idea of this meta-analysis, supervised the data analysis, and revised the article. HY, SW, HY, CC, RZ, and RW participated in the study selection, data collection. HY and SW participated in the statistical analysis and wrote the manuscript. All authors approved the final version of the manuscript.

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1. Introduction

Acute renal injury (AKI) is a common renal complication after cardiac surgery with cardiopulmonary bypass (CPB), its incidence remains 30% to 50%^[1–3] which leads to substantial increases in mortality, morbidity, and costs.^[4,5] Considering the adverse clinical impact of AKI, such as the accompanied higher incidence of postoperative arrhythmias, myocardial infarction, respiratory failure, and systemic infection,^[3,5–7] measures to prevent postoperative renal complications are in great need to improve postoperative outcome.

Perioperative statin therapy (PST) was reported to reduce the incidence of AKI after cardiac surgery through its anti-inflammatory and antioxidant activities^[8,9] in randomized controlled study,^[10] meta-analyses,^[11–13] and observational studies.^[14–17] However, some researchers had converse opinion that PST was not associated with decreased AKI after cardiac surgery.^[18–20] Thus, the preventive value of PST remains controversial. Recently, 3 large prospective randomized clinical trials (RCTs) revealed that PST did not prevent AKI following cardiac surgery^[21–23] and AKI was even more common with rosuvastatin^[23] and in patients with no statin use before study enrollment.^[21] Latest meta-analyses^[13,24] reported opposite viewpoints toward statin's effect on renal outcome. However, the researchers did not take severity of renal complication and

preoperative coexisting renal dysfunction into consideration, and sub-group analyses based on different statins, duration, dosage, and surgery type were not performed. In addition, Putzu et al^[24] seemed to regard renal dysfunction and renal failure as AKI, which may be not appropriate and lower the reliability of the results. To better specify the effect of PST, we conducted the present meta-analysis only focusing on high quality RCTs, discussing the impact of PST on postoperative renal outcome.

2. Methods

Since this is a meta-analysis of previously published studies, ethical approval and patient consent are not required.

2.1. Search strategy

Study design of this meta-analysis followed the recommendations of the Cochrane Handbook for Systematic Review of Interventions statement and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE/PubMed and EMBASE/OVID and the System for information on Grey Literature between March 1983 and June 2016. No language restrictions were applied. Three search themes were used: (1) “cardiac surgery” or “coronary artery bypass surgery” or “valve surgery”; and (2) “statin” or “atorvastatin” or “simvastatin” or “pravastatin” or “rosuvastatin” or “HMG CoA reductase inhibitors”; and (3) “acute renal failure” or “acute kidney injury” or “renal dysfunction” or “renal insufficiency” or “renal replacement therapy” or “renal complication” or “kidney complication” or “creatinine” or “urea nitrogen” or “eGFR” or “estimated glomerular filtration rate” or “neutrophil gelatinase-associated lipocalin” or “NGAL” or “cystatin C” or “interleukin-18” or “IL-18.” A secondary search was performed by manually searching conferences and bibliographies to identify additional relevant studies. Title and abstract were reviewed to screen the citations first. Full texts of the researches were evaluated after identifying relevant reports.

2.2. Inclusion and exclusion criteria

Study inclusion criteria were as follows—(1) design: randomized controlled trials; (2) population: adult patients (>18 years) undergoing on-pump or off-pump cardiac procedures (i.e., coronary artery bypass graft, valvular surgery, or combined procedures including aortic surgery), regardless of redo or emergency operations; (3) intervention: any PST with any dose and duration; (4) control: no PST or placebo; (5) outcomes: the primary outcome was postoperative renal complication in any manner, including AKI, acute or chronic renal failure, renal dysfunction, renal insufficiency, and need for renal replacement therapy (RRT). AKI was defined in accordance with the AKIN or RIFLE staging systems. The Acute Kidney Injury Network (AKIN)^[25] defines 3 stages of injury (1, 2, and 3) based on increasingly severe reductions of kidney function (Stage 1 was defined as an increase of 0.3mg/dL or 50% within 48 hours of surgery; Stage 2, a 100% increase; and Stage 3, a 200% increase or initiation of dialysis). The RIFLE criteria, proposed by the Acute Dialysis Quality Initiative group,^[26] define 5 levels of AKI (risk, injury, failure, loss and end-stage kidney disease) based on incremental reductions in the kidney function. Secondary outcomes focused on severe renal complication including stage 2 or 3 AKI (diagnosed by the AKIN criteria), RIFLE stage I-E,

chronic or acute renal failure, RRT (if the stage or level of AKI was not clear, RRT was counted as severe renal complication), in-hospital mortality, duration of ICU stay, hospital stay, and postoperative sCr. Eligible studies must report at least 1 metric of primary outcome or renal function-related indicators. Studies were excluded when they met any following criteria: (1) duplicate publication; (2) animal research, reviews, comments, meta-analyses, and case; (3) patients undergoing heart transplantation or corrective surgery for congenital defects.

2.3. Data extraction

Two authors (SW and HY) independently assessed trials from titles and abstracts according to predefined criteria. Disagreements were resolved by consensus and after discussion with a third author. Full-text articles of potentially relevant studies that fit inclusion criteria were retrieved. Study data were extracted by 2 authors (HY and HY) with a standardized data collection form. Extracted information was as follows: authorship, article title, year of publication, study design, number of patients, applied statin regimen (statin type, dosage, and duration), preoperative renal disease, and outcomes mentioned above. We also contacted the corresponding author to request missing data and information we need if necessary.

2.4. Validity assessment

Cochrane Collaboration risk of bias tool was used to assess methodological quality that considered 7 different domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. And each study was labeled “low risk of bias,” “high risk of bias,” and “unclear risk of bias.”

2.5. Quality of evidence

We rated the evidence quality by GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system^[27] using the GRADE profiler 3.6.1 software. The GRADE system classifies the quality of evidence in 1 of 4 levels: high, moderate, low, and very low. Meta-analysis based on RCTs starts as high-quality evidence, but the confidence may decrease due to following reasons: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.6. Statistical analysis

Review Manager (Version 5.3) was used to perform statistical analysis. Relative risk (RR) and 95% confidence interval (CI) were estimated to describe the power of treatment effect for dichotomous outcome data, and for continuous variables (i.e., length of hospital stay and ICU stay), mean difference (MD) was calculated. If the reported data were medians and interquartile ranges, we contacted authors to retrieve mean values with standard deviations.

Q and I^2 statistics were tested for heterogeneity. It is calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic.^[28] The random-effects model ($\text{Chi}^2 P < .1$ or $I^2 > 50\%$) was used when substantial heterogeneity was detected; otherwise, a standard fixed-effect model ($\text{Chi}^2 P > .1$ or $I^2 < 50\%$) was applied.

We performed subgroup analyses in aspects of surgery type, different statin, PST duration, and drug dosage that were classified into high potency and low potency statins (high potency statin treatment was defined as daily dose at least 10 mg rosuvastatin, at least 20 mg atorvastatin, and at least 40 mg simvastatin; all other statin treatments were defined as having low potency).^[29]

3. Results

3.1. Literature identification and study characteristics

Our search yielded 348 potentially eligible articles (218 from MEDLINE/PubMed, 41 from EMBASE/OVID, 85 from CENTRAL, and 4 from other source). After removing 13 duplicated studies, 3 independent authors screened 335 articles according to the inclusion criteria. In total, 272 publications were eliminated based on titles or abstracts and 63 were screened based on full-texts. Eventually, 9 RCTs enrolling 2832 patients, with 1419 in the PST group and 1413 in the control group, were included in this meta-analysis (Fig. 1).^[18,21–23,30–34] Characteristics of the eligible trials were described in Table 1. Assessment of risk of bias was shown in Fig. 2. Among these 9 included studies, 8 studies reported postoperative renal complication, 5 evaluated atorvastatin,^[18,21,22,31,34] 2 evaluated simvastatin,^[30,33] and 2 evaluated rosuvastatin,^[23,32] 7 used high-potency statin, 5 administered statin less than 14 days, and 5 investigated patients undergoing coronary artery bypass grafting (CABG)^[18,31–34] (other studies included a variety of surgery type). All studies compared perioperative statin treatment with placebo.

3.2. Primary outcome

Our meta-analysis demonstrated that PST increased the occurrence of postoperative renal complication by 3.17% (8 studies, 2786 participants; 21.43% vs 18.26%; RR 1.18, 95% CI 1.01–1.36; $P < .05$; Fig. 3) with low heterogeneity ($P = .18$, $I^2 = 30\%$), which was analyzed by per protocol set. Besides, we did full analysis set that enrolled patients in the PST group who were lost to follow-up had the worst outcome, and those in the control group who were lost to follow-up had the best outcome, which indicated the same result as above-mentioned (RR 1.18, 95% CI 1.02–1.37; $P < .05$) and vice versa (RR 1.17, 95% CI 1.01–1.36; $P < .05$). The statistical power was 0.68 (Appendix 1, <http://links.lww.com/MD/B687>). Subgroup analysis of patients who received different statins showed no significant difference in the atorvastatin group or the simvastatin group. However, rosuvastatin was statistically related to more postoperative renal complication (RR 1.26, 95% CI 1.07–1.49; $P < .01$). In addition,

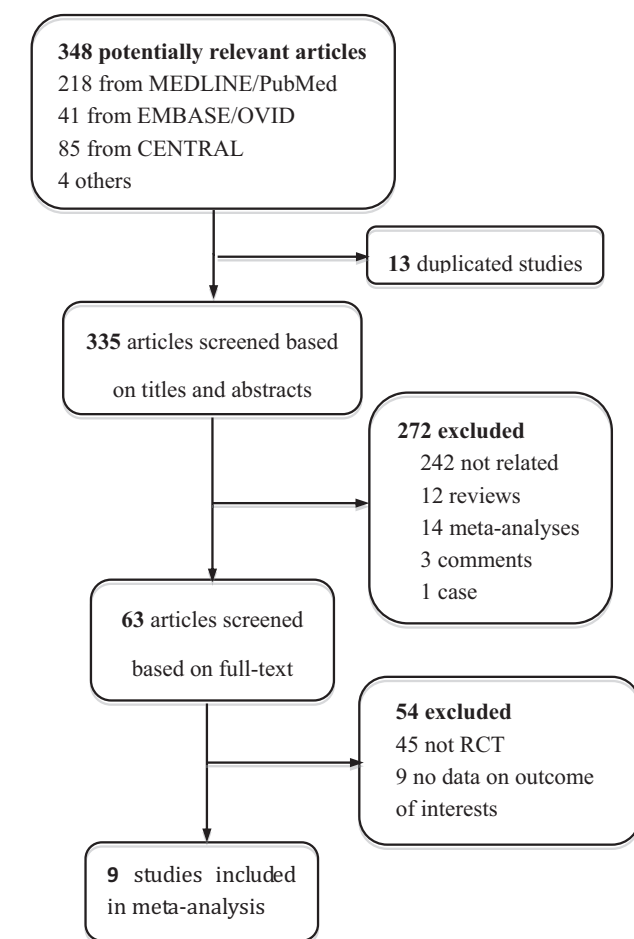


Figure 1. Study flow diagram.

daily statin dosage in 7 of the 9 included studies was categorized as high potency and subgroup analysis of these studies revealed that preoperative therapy with high potency statin was 20% more likely to result in postoperative AKI (RR 1.20, 95% CI 1.04–1.40; $P < .05$) (Appendix 2, <http://links.lww.com/MD/B687>). Analyses based on drug duration manifested statin treatment less than 14 days was statistically in association with more postoperative renal complication (RR 1.21, 95% CI 1.04–1.40; $P < .05$), but no difference in renal outcome was found between patients with PST over 14 days and placebo (RR 0.47, 95% CI 0.17–1.31; $P = .15$) (Appendix 3, <http://links.lww.com/MD/B687>).

Table 1

Characteristics of included randomized controlled trials.

Source	Study design	Country	Size, n	Statin/control, n	Surgery type	Statin type, dose	Reported renal outcomes
Christenson ^[33]	RCT	Switzerland	77	40/37	CABG	Simvastatin; 20 mg/d	Renal failure
Chello et al ^[34]	RCT	Italy	40	20/20	CABG	Atorvastatin; 20 mg/d	Renal dysfunction
Mannacio et al ^[32]	RCT	Italy	200	100/100	CABG	Rosuvastatin; 20 mg/d	Renal failure
Tamayo et al ^[30]	RCT	Spain	44	22/22	CABG	Simvastatin; 20 mg/d	sCr
Spadaccio et al ^[31]	RCT	Italy	50	25/25	CABG	Atorvastatin; 20 mg/d	Renal dysfunction
Prowle et al ^[18]	RCT	Australia	100	50/50	Cardiac surgery	Atorvastatin; 40 mg/d	AKI (RIFLE); RRT; sCr, BUN
Billings et al ^[21]	RCT	America	199	102/97	Cardiac surgery	Atorvastatin; 40–80 mg/d	AKI(AKIN), sCr
Park et al ^[22]	RCT	South Korea	200	100/100	Valvular heart surgery	Atorvastatin; 40–80 mg/d	AKI(AKIN), sCr
Zheng et al ^[23]	RCT	China, United Kingdom	1922	960/962	Cardiac surgery	Rosuvastatin; 20 mg/d	AKI(AKIN), sCr

AKI = acute kidney injury, AKIN = acute kidney injury network, BUN = blood urea nitrogen, CABG = coronary artery bypass grafting, RCT = randomized controlled trial, RIFLE = risk, injury, failure, loss, and end stage, RRT = renal replacement therapy, sCr = serum creatinine.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Billings 2016	+	+	+	+	+	+	+
Chello 2006	?	?	+	+	+	?	+
Christenson 1999	?	?	+	+	+	?	-
Mannacio 2008	+	+	+	+	+	-	?
Park 2016	+	+	+	?	?	+	+
Prowle 2012	+	+	+	+	+	+	+
Spadaccio 2010	?	?	+	+	+	+	?
Tamayo 2009	?	?	+	+	+	-	?
Zheng 2016	+	+	+	+	+	+	+

Figure 2. Risk of bias summary.

com/MD/B687). Subgroup analysis of the population undergoing CABG indicated that the incidence of renal complication in the PST group (8.09%) was lower than that in the control group (12.5%), but the difference did not reach statistical significance (5 studies, 467 participants. RR 0.64; 95% CI 0.39–1.08, $P = .09$; P for heterogeneity = .73, $I^2 = 0\%$) (Appendix 4, <http://links.lww.com/MD/B687>).

3.3. Secondary outcome

Six included studies with 3116 patients reported severe renal complication and no statistical difference was found between PST and control groups (RR 1.23, 95% CI 0.84–1.79; $P = .28$) (Appendix 5, <http://links.lww.com/MD/B687>). Three studies with 2164 participants focused on postoperative sCr at 48 hours and we figured out higher sCr in the PST group with no heterogeneity (MD 0.03, 95% CI 0.03–0.03; $P < .01$) (Appendix 6, <http://links.lww.com/MD/B687>). The length of hospital stay was decreased statistically by 0.59 day in the PST group (4 trials, 367 patients; 95% CI -0.85 to -0.33; $P < .01$; P for heterogeneity

= .10, $I^2 = 51\%$) (Appendix 7, <http://links.lww.com/MD/B687>), but there were no significant differences between the 2 groups neither in the length of ICU stay (MD -0.12; 95% CI -0.33 to 0.09; $P = .26$) (Appendix 8, <http://links.lww.com/MD/B687>) nor in-hospital mortality (RR 3.38; 95% CI 0.83–13.78; $P = .09$) (Appendix 9, <http://links.lww.com/MD/B687>). All outcomes and GRADE system grades of evidence were listed in Appendix 10, <http://links.lww.com/MD/B687>.

3.4. Sensitivity analysis

We performed sensitivity analyses for each outcome in order to assess the influence of risk of bias. After excluding the study of Zheng et al, the results changed to no significant differences both in postoperative renal complication and sCr between the PST group and the control group.

3.5. Trial sequential analysis

Trial sequential analysis is a cumulative meta-analysis to avoid random errors (false positive). We assumed the incidence of postoperative renal complication was 18.26% in the control arm and 21.43% in the PST arm according to our meta-analysis with 80% power and a 0.05 two-side α (Fig. 4). The cumulative Z value had not been crossed with Lan-DeMets sequential monitoring boundary, and the Z value did not reach the required information size (RIS), indicating that more trials are needed to reliably detect a plausible effect of PST.

4. Discussion

This study determined the effect of PST on postoperative renal complication in patients undergoing cardiac surgery. Our primary analysis showed that PST may increase the incidence of postoperative renal complication and elevated the level of sCr in patients undergoing cardiac surgery. Nevertheless, we found neutral effects of PST on severe renal complication, similar in-hospital mortality, and length of ICU stay. Interestingly, a possible positive effect of statins on decreasing length of hospital stay was detected. Hence, we hypothesized that PST may potentially affect postoperative renal outcome, but its deleterious effect may be reflected in the increased sCr, which seemed to be a transient or short-term elevation during in-hospital days. It remains unclear about statin's effect on long-term renal outcome, as it was not reported in the included studies. For several years, PST is considered as a promising therapy for decreasing the occurrence of postoperative AKI. It is recommended for all patients who undergo CABG without contraindication by the 2014 European Society of Cardiology/European Association of Cardio-Thoracic Surgery Guidelines.^[35] This may be based on the results in favor of PST from various small-size studies with relatively low-quality and publication bias. However, our meta-analysis pooled data from rigorously included RCTs, and highlighted that PST seems to have an impact on short-term renal function in patients undergoing cardiac surgery, but the patients may not be affected in regarding to severe postoperative renal complication and can get discharged after even shorter in-hospital days as patients in the control group.

Possible reasons contributed to our results include disparate preoperative coexisting disease, interruption time of previous statin therapy, statin type and dosage, patients' ethnics. Higher preoperative sCr was considered as an independent risk factor for postoperative AKI.^[36] The studies of Christenson,^[33] Prowle

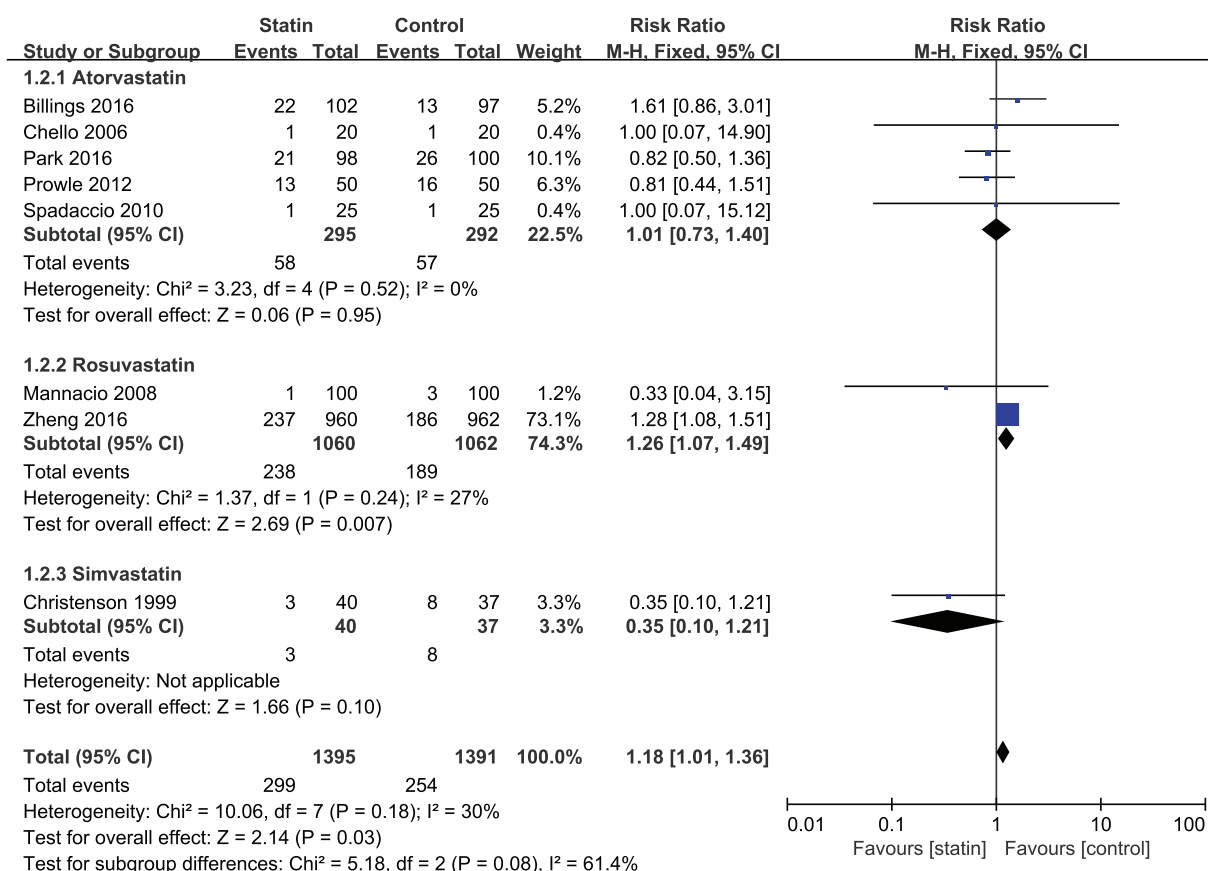


Figure 3. Forest plot for the incidence of postoperative renal complication and subgroup analysis based on different statin. A pooled RR was calculated using the fixed-effect model according to the Mantel-Haenszel (M-H) method. Preoperative statin therapy increased the incidence of postoperative renal dysfunction statistically, especially with the use of rosuvastatin. RR = relative risk.

et al^[18] and Billings et al.^[21] did not exclude patients with preoperative renal dysfunction which was diagnosed by elevated sCr and these 3 studies showed no protective effect of PST on renal outcome. Billings et al^[21] even found that PST was associated with increased sCr on postoperative day 2 and AKI occurred in more patients with preoperative chronic kidney disease (CKD) randomized to atorvastatin than placebo. This enlightened us that patients with preoperative renal dysfunction may not benefit from PST. After excluding above-mentioned 3 trials, sensitivity analysis confirmed that our meta-analysis had low sensitivity and desirable stability, indicating that PST may potentially worsen postoperative kidney function in patients without preoperative renal dysfunction. It is demonstrated that many short-term pleiotropic effects of statin therapy occur within 2 weeks after drug intake,^[37] whereas the interruption time of pre-study statins in Mannacio et al,^[32] Prowle et al,^[18] and Zheng et al^[23] was less than 2 weeks and was much shorter than that of other studies. The residual effect of pre-study statins together with PST could probably influence postoperative renal outcome. It is noteworthy that the patient population recruited in Zheng et al^[37] were Chinese, and patients were administered with high-potency rosuvastatin (20 mg per day). Research showed that plasma exposure to rosuvastatin and its metabolites is significantly higher for a given dose in Asian persons (especially in Chinese) than in whites,^[38] which may be related to higher incidence of renal complication in this study. Considering the high potency statin, Zheng et al^[23] used and large population of different ethnic they enrolled, which accounted for about 68.0%

of the patients population in this meta-analysis, we did sensitivity analysis excluding this study and detected a different result: PST exerted a neutral effect on postoperative renal outcome. However, the same result cannot be found after excluding any one of the rest studies, indicating the high weight of Zheng et al research, and current results should be prudently interpreted. However, the same dosage in the study of Mannacio et al^[32]

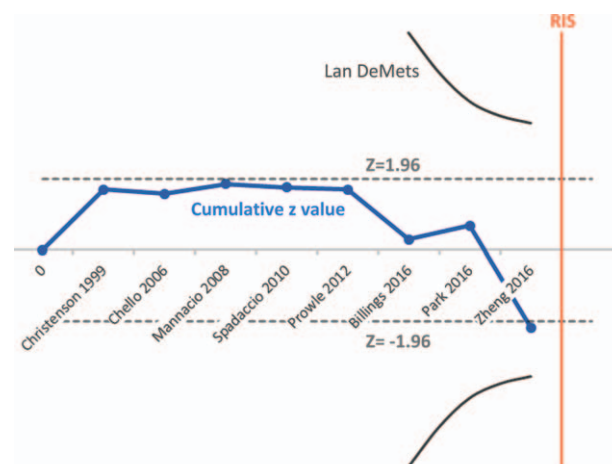


Figure 4. Trials sequential analysis assessing the effect of preoperative statin therapy on renal outcomes in patients undergoing cardiac surgery.

enrolling European patients did not detect kidney-detrimental effect of rosuvastatin. Consequently, it is debatable about patients' ethnics, dosage, and effect on kidney of rosuvastatin.

With regard to subgroup-analyses, first, higher incidence of postoperative renal complication was found in patients with perioperative rosuvastatin administration, whereas atorvastatin showed no effect. Second, it was suggested that statins exert their full pleiotropic effect in 14 days.^[39] Subgroup analysis of studies with PST less than 14 days manifested that PST increased the risk of postoperative complication, but no impact was detected when analyzing studies with statin treatment over 14 days, enlightening us that PST may be initiated within a sufficient duration or would probably related to negative renal outcome. Moreover, perioperative therapy with high potency statin was 20% more likely to result in postoperative renal complication. Thus, we assumed that high potency statin therapy, especially rosuvastatin before surgery may potentially increase the risk of postoperative renal complication in patients following cardiac procedures. Supportively, a large study conducted by Hippisley-Cox et al^[40] revealed that statin was related to elevated risk of AKI and this effectiveness was dose-dependent. Furthermore, as CABG was the most common type of surgery among included researches and most patients undergoing CABG may have hyperlipemia and were on chronic statin therapy, subgroup analysis was conducted, manifesting that there was no beneficial or detrimental effect of PST on renal outcome in these patients.

It remains unclear concerning the possible mechanisms of the negative effects of PST on renal function. Present clues include mitochondrial dysfunction and muscle toxicity. Statins predispose to mitochondrial defects reducing coenzyme Q10 (CoQ10, ubiquinone), which is a key mitochondrial antioxidant and electron transport carrier, resulting in decreased cellular energy. Reduction in CoQ10 in skeletal muscle may contribute to statin-induced muscle injury.^[41] Additionally, atrogen-1, a muscle-specific ubiquitin protein ligase, may play an important role in statin toxicity.^[42] Myoglobinuria associated with rhabdomyolysis, increased level of creatinine kinase, and proteinuria caused by tubular inhibition of active transport of small molecular weight proteins^[43,44] may give us more information about the potential mechanisms.

The statistical power was tested, indicating more high-quality randomized RCTs are necessary to further demonstrate the effect of PST, which was also supported by the result of our trials sequential analysis. In addition, we should not ignore the systemic effect of PST considering statin's pharmacological characteristics, such as attenuating lymphocyte activation,^[45] limiting vascular superoxide generation,^[46,47] reducing endothelial dysfunction by restoring endothelial derived nitric oxide synthase activity during hypoxia.^[47] Patients may have better outcomes in other organs except kidney, which could possibly shorten in-hospital days.

Previous meta-analyses hold inconsistent conclusions with ours. Wang et al^[48] and Li et al.^[13] included a great number of observational or retrospective studies and limited number of RCTs, carrying the limitations consisted of high heterogeneity, significant publication bias and nature weaknesses of non-prospective randomized trials. Kuhn et al^[49] investigated a large population but had the same deficiencies, besides, renal complication was not their primary outcome and was only reported in limited number of studies they enrolled. In addition, the above-mentioned 3 studies did not describe or analyze severe renal complication, dose effect, type of statins, population ethnics, and preoperative coexisting diseases. In meta-analysis of Putzu et al,^[24] however, the results suggested that statins were

associated with increased risk of AKI. But they seemed to mix the definition of different renal outcomes among included studies and analyzed renal dysfunction as AKI, which was not appropriate and could possibly lower the reliability of their results. Moreover, they did not analyze severity of renal outcome and did not elaborate the potential impact of Zheng et al's study on results. The current meta-analysis made up for the above-mentioned shortcomings.

Our meta-analysis has the following strengths. In the first, we rigorously included high-quality RCTs with low risk of bias providing relatively strong evidence. In addition, statin's effect on postoperative stage or level of AKI was analyzed for the first time so far as we know. Moreover, our sensitivity and sub-group analyses were more comprehensive than other meta-analyses, which made our conclusion more prudent and convincing. Despite all these, the number of included studies was relatively small due to the strict inclusion criteria and several potential confounders (e.g., age, gender, medicine-taking compliance, as well as CPB time) that may affect the incidence of renal complication were not taken into account in the current study. Therefore, we cautiously drew a conclusion that though the effect of PST on long-term postoperative renal outcome is not clear until now, the possibility of statin's potential risk on short-term renal outcome still remains and should not be overlooked, especially the risk of high-potency statins in patients without preoperative renal dysfunction. Further well-designed large, multi-centered, blinded and randomized studies are in great need.

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