Systematic Review/Meta-analysis

Preoperative Statin Therapy and Renal Outcomes After Cardiac Surgery: A Meta-analysis and Meta-regression of 59,771 Patients

Jiayang Wang, MD, Chengxiong Gu, MD, Mingxin Gao, MD, Wenyuan Yu, MD, and Yang Yu, MD, PhD

Department of Cardiac Surgery, Beijing An Zhen Hospital, Capital Medical University, Beijing 100029, China

ABSTRACT

Background: The purpose of this study was to investigate the effects of preoperative statin therapy (PST) on short- and long-term renal dysfunction after cardiac surgery.

Methods: We searched for reports that investigated the effects of PST on renal outcomes after cardiac surgery in the electronic literature databases PubMed, Ovid, and Elsevier.

Results: Twenty-six reports including 59,771 patients were selected for meta-analysis. The meta-analysis revealed that PST significantly reduced the incidence of postoperative renal dysfunction (odds ratio [OR], 0.44; 95% confidence interval [CI], 0.30-0.66; \( P < 0.0001 \)) without significant heterogeneity (\( I^2 = 28.1 \% \); \( P = 0.093 \)). PST also significantly reduced the need for postoperative renal replacement therapy (OR = 0.76; 95% CI, 0.62-0.92; \( z = 2.77 \); \( P = 0.006 \)); particularly in the subgroup of patients who underwent isolated coronary artery bypass grafting, the rate of renal replacement therapy was reduced by 56% (OR, 0.44; 95% CI, 0.30-0.66; \( z = 4.08 \); \( P < 0.0001 \)) with low heterogeneity (\( I^2 = 18.7 \% \); \( P = 0.297 \)). Meta-analysis for the incidence of renal replacement therapy (RRT) significantly reduced the need for postoperative RRT (OR, 0.76; 95% CI, 0.62-0.92; \( z = 2.77 \); \( P = 0.006 \)); particularly in the subgroup of patients who underwent isolated coronary artery bypass grafting, the rate of renal replacement therapy was reduced by 56% (OR, 0.44; 95% CI, 0.30-0.66; \( z = 4.08 \); \( P < 0.0001 \)).

RéSUMÉ

Introduction : Le but de la présente étude était d’examiner les effets du traitement préopératoire par statines (TPS) sur la dysfonction rénale à court et à long terme après la chirurgie du cœur.


Résultats : Pour la méta-analyse, nous avons sélectionné 26 rapports comprenant 59 771 patients. Cette méta-analyse a révélé que le TPS réduisait significativement l’incidence de la dysfonction rénale après la chirurgie (ratio d’incidence approché [RIA], 0.89; intervalle de confiance [IC] à 95%, 0.84-0.95; \( P < 0.0001 \)) sans hétérogénéité significative (\( I^2 = 28.1 \% \); \( P = 0.093 \)). Le TPS réduisait également de manière significative le besoin de thérapie de remplacement rénal après la chirurgie (RIA = 0.76; IC à 95%, 0.62-0.92; \( z = 2.77 \); \( P = 0.006 \)); particulièrement dans le sous-groupe de patients qui avaient subi le pontage aortocoronarien isolé, le taux de thérapie de remplacement delays the progression of coronary atherosclerosis and reduced the incidence of postoperative cardiovascular events in patients who underwent coronary artery bypass grafting (CABG).7 However, evidence to support the role of PST in preservation of renal function after cardiac surgery is still lacking. Results from studies that investigated the effects of PST on short- and long-term postoperative renal dysfunction are controversial. Singh et al. found that PST reduced the incidence of renal replacement therapy (RRT) significantly but exerted no effects on the incidence of acute kidney injury (AKI) after CABG.3 In a recent meta-analysis, Kuhn et al. also demonstrated that PST did not significantly affect the incidence of renal failure after cardiac surgery.2 Contrarily, Layton et al.10 and Brunelli et al.11 reported that PST was associated with a reduced risk of postoperative AKI in CABG patients. In the previous meta-analysis, studies using either the Acute Kidney Injury Network (AKIN) or the Risk, Injury, Failure, Loss, and End Stage (RIFLE) criteria for the diagnosis and classification of AKI were analyzed together. 

Patients who undergo cardiac surgery often develop short- and long-term postoperative renal dysfunction,1,2 which sometimes leads to permanent renal damage. Multiple perioperative therapies to preserve renal function have been developed,3-6 among them preoperative statin therapy (PST) is emerging as the most promising one because statins inhibit inflammation and endothelial dysfunction, the 2 key contributors to cardiac surgery-induced renal complications.

The cardiovascular protective effects of PST have already been well recognized. Knatterud et al. have found that statins delayed the progression of coronary atherosclerosis and reduced the incidence of postoperative cardiovascular events in patients who underwent coronary artery bypass grafting (CABG).7 However, evidence to support the role of PST in preservation of renal function after cardiac surgery is still lacking. Results from studies that investigated the effects of PST on short- and long-term postoperative renal dysfunction are controversial. Singh et al. found that PST reduced the incidence of renal replacement therapy (RRT) significantly but exerted no effects on the incidence of acute kidney injury (AKI) after CABG.3 In a recent meta-analysis, Kuhn et al. also demonstrated that PST did not significantly affect the incidence of renal failure after cardiac surgery.2 Contrarily, Layton et al.10 and Brunelli et al.11 reported that PST was associated with a reduced risk of postoperative AKI in CABG patients. In the previous meta-analysis, studies using either the Acute Kidney Injury Network (AKIN) or the Risk, Injury, Failure, Loss, and End Stage (RIFLE) criteria for the diagnosis and classification of AKI were analyzed together. 

http://dx.doi.org/10.1016/j.cjca.2015.02.034
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outcome of acute kidney injury (AKI) revealed that PST reduced the incidence of postoperative AKI by 13% (OR, 0.87; 95% CI, 0.80-0.94; \( P = 0.001 \)) and 7% (OR, 0.93; 95% CI, 0.86-0.99; \( P = 0.031 \)), respectively, for subgroups of patients whose AKI was evaluated using the Acute Kidney Injury Network (AKIN) or the Risk, Injury, Failure, Loss, and End Stage (RIFLE) criteria, without significant heterogeneity for either.

Conclusions: PST might be a promising therapy to reduce renal complications after cardiac surgery although large-scaled randomized controlled trials are needed to further verify the conclusion.

Methods

Search strategy

The design for this meta-analysis and meta-regression stringently followed the guidelines for Quality of Reporting of Meta-Analysis (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA], Quality of Reporting of Meta-analyses [QUOROM], and Meta-analysis of Observational Studies in Epidemiology [MOOSE]).

We searched for reports (published between January 1996 and March 2014) that compared the risk of cardiac surgery-associated RRT, AKI, and renal failure in patients who received PST vs did not receive PST. Two investigators (M.G. and J.W.) independently searched the electronic literature databases, PubMed, Ovid, and Elsevier using the following predefined key words: ‘cardiac surgery,’ ‘coronary artery bypass surgery,’ ‘valve surgery,’ ‘statin,’ ‘renal replacement therapy,’ ‘acute renal failure,’ ‘acute kidney injury,’ ‘renal dysfunction,’ and ‘renal insufficiency.’ Citations were first screened by reviewing the title and abstract and only articles in English were selected. After potentially relevant reports were identified, the full text of the reports were evaluated.

Study inclusion and exclusion criteria

Studies that met the following criteria were included: (1) administration of any statin (any duration and dosage) before cardiac surgery; (2) comparison of end points in patients with vs without PST; and (3) assessment of postoperative adverse renal outcomes including postoperative RRT, AKI, and renal failure. Studies were excluded if they met any one of the following criteria: (1) duplicate publication; (2) ongoing or unpublished studies; (3) only published as abstracts or conference proceedings; and (4) less than 30 patients in the patient cohort.

Data extraction and quality assessment

Two coauthors (M.G. and J.W.) independently extracted data on interventions and end points. The outcome definitions in the original articles were adopted. The number of events was derived from tables and text in each original study. In addition, we used the Downs and Black score system to evaluate the quality of each study. The quality of studies with a score \( \geq 20 \) was considered good and a score \( < 20 \) was considered poor.

End points

The primary end point of this meta-analysis was short- and long-term postoperative renal dysfunction in any manner, including AKI or acute renal failure, chronic kidney disease (an abnormality of kidney structure or function regardless of cause or specific clinical presentation\(^{17} \)), and chronic renal failure (a glomerular filtration rate persistently \( < 15 \text{ mL/min per 1.73 m}^2 \)).\(^{18} \) The secondary end points were incidence of AKI and RRT after cardiac surgery. AKI was defined according to the AKIN or RIFLE staging systems: (1) AKIN stage 1: increase in serum creatinine \( \geq 0.3 \text{ mg/dL} \) or \( \geq 50\% \) over any 48-hour period; (2) RIFLE-Risk [RIFLE-R]: increase in serum creatinine \( \geq 50\% \) or decrease in estimated glomerular filtration rate \( \geq 25\% \) over any 48-hour period; and (3) AKIN stages 2 and 3 (identical to RIFLE-Injury [RIFLE-I] and Failure [RIFLE-F]): doubling of serum creatinine or increase in serum creatinine \( \geq 0.5 \text{ mg/dL} \) to a level \( \geq 4 \text{ mg/dL} \) over any 48-hour period.
Statistical analysis

Data are presented as odds ratios (ORs) with 95% confidence interval (CI) for the predetermined end points. The $I^2$ index was calculated to estimate study heterogeneity. $I^2 = 25\%-49\%, 50\%-74\%, \text{and } \geq 75\%$ were considered low, moderate, and high heterogeneity, respectively. $I^2 \geq 50\%$ was considered significantly heterogeneous. For end points with $I^2 \geq 25\%$, meta-regression was performed to analyze the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Surgery type</th>
<th>Size, n</th>
<th>Statin/control, n</th>
<th>Statin type; dosage</th>
<th>Reported renal outcomes</th>
<th>Downs and Black score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christenson et al.</td>
<td>RCT</td>
<td>CABG</td>
<td>77</td>
<td>40/37</td>
<td>Simvastatin; 20 mg/d</td>
<td>Renal dysfunction</td>
<td>22</td>
</tr>
<tr>
<td>Pan et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>1663</td>
<td>943/720</td>
<td>Atorvastatin, simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin; NR</td>
<td>Renal dysfunction</td>
<td>20</td>
</tr>
<tr>
<td>Chello et al.</td>
<td>RCT</td>
<td>CABG</td>
<td>40</td>
<td>20/20</td>
<td>Atorvastatin; 20 mg/d; 54% atorvastatin, 39% simvastatin, 4% pravastatin, 1% lovastatin, 1% fluvastatin, 1% rosuvastatin; 5-80 mg/d</td>
<td>Renal dysfunction</td>
<td>25</td>
</tr>
<tr>
<td>Tabata et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>1802</td>
<td>1039/763</td>
<td>Atorvastatin, simvastatin, lovastatin; NR; rosuvastatin 20 mg/d</td>
<td>Renal dysfunction</td>
<td>19</td>
</tr>
<tr>
<td>Thielmann et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>3346</td>
<td>2592/754</td>
<td>Atorvastatin, simvastatin, lovastatin</td>
<td>RRT; renal dysfunction</td>
<td>22</td>
</tr>
<tr>
<td>Mannicio et al.</td>
<td>RCT</td>
<td>CABG</td>
<td>200</td>
<td>100/100</td>
<td>Pravastatin, fluvastatin, cerivastatin; NR; rosuvastatin 20 mg/d</td>
<td>Renal dysfunction</td>
<td>22</td>
</tr>
<tr>
<td>Fedorku et al.</td>
<td>Ob</td>
<td>Valve</td>
<td>447</td>
<td>203/244</td>
<td>Atorvastatin 40 mg/d</td>
<td>Renal dysfunction</td>
<td>20</td>
</tr>
<tr>
<td>Subramaniam et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>2460</td>
<td>1855/625</td>
<td>Atorvastatin; 20 mg/d</td>
<td>Renal dysfunction</td>
<td>20</td>
</tr>
<tr>
<td>Huffmyer et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>2760</td>
<td>1557/1203</td>
<td>NR; NR</td>
<td>Renal dysfunction; RRT; AKI (RIFLE)</td>
<td>18</td>
</tr>
<tr>
<td>Miceli et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>4304</td>
<td>2152/2152</td>
<td>NR</td>
<td>63.9% atorvastatin, 22.2% simvastatin, 12.5% pravastatin, 1.4% lovastatin; atorvastatin, simvastatin, lovastatin 20 mg/d, pravastatin 40 mg/d</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Martinez-Comendador et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>138</td>
<td>72/66</td>
<td>NR</td>
<td>Renal dysfunction</td>
<td>22</td>
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<tr>
<td>Song et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>144</td>
<td>72/72</td>
<td>35% atorvastatin, 25% rosuvastatin, 22% simvastatin, 18% pravastatin; 10-40 mg/d</td>
<td>RRT; renal dysfunction</td>
<td>17</td>
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<tr>
<td>Gan et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>534</td>
<td>267/267</td>
<td>Cerivastatin, fluvastatin, atorvastatin, simvastatin, lovastatin, pravastatin; simvastatin; NR</td>
<td>Renal dysfunction</td>
<td>21</td>
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<tr>
<td>Argalious et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>10,648</td>
<td>6157/4491</td>
<td>NR; NR</td>
<td>Renal dysfunction; RRT; AKI (RIFLE)</td>
<td>20</td>
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<tr>
<td>Spadaccio et al.</td>
<td>RCT</td>
<td>CABG</td>
<td>50</td>
<td>25/25</td>
<td>Atorvastatin; 20 mg/d</td>
<td>Renal dysfunction</td>
<td>23</td>
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<tr>
<td>Billings et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>324</td>
<td>174/150</td>
<td>NR; NR; AKI (AKIN); renal dysfunction</td>
<td>21</td>
<td></td>
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<tr>
<td>Virani et al.</td>
<td>Ob</td>
<td>CABG or valve; cardiac surgery</td>
<td>3001</td>
<td>1675/1326</td>
<td>Atorvastatin, simvastatin, fluvastatin, rosuvastatin, lovastatin, pravastatin; NR</td>
<td>RRT; renal dysfunction</td>
<td>18</td>
</tr>
<tr>
<td>Allou et al.</td>
<td>Ob</td>
<td>Valve</td>
<td>430</td>
<td>222/208</td>
<td>NR; NR</td>
<td>AKI (AKIN); renal dysfunction</td>
<td>19</td>
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<tr>
<td>Bolesta et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>563</td>
<td>356/207</td>
<td>NR; NR</td>
<td>AKI (AKIN); RRT; renal dysfunction</td>
<td>20</td>
</tr>
<tr>
<td>Mithani et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>2104</td>
<td>1434/670</td>
<td>Simvastatin; high-dose: &gt; 40 mg/d; low-dose: &lt; 40 mg/d</td>
<td>AKI (AKIN); renal dysfunction</td>
<td>21</td>
</tr>
<tr>
<td>Presta et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>69</td>
<td>39/30</td>
<td>74.4% atorvastatin, 25.6% simvastatin</td>
<td>AKI (AKIN); renal dysfunction</td>
<td>20</td>
</tr>
<tr>
<td>Prowle et al.</td>
<td>RCT</td>
<td>Cardiac surgery</td>
<td>100</td>
<td>50/50</td>
<td>Atorvastatin; 20 mg/d</td>
<td>Renal dysfunction</td>
<td>23</td>
</tr>
<tr>
<td>Brunelli et al.</td>
<td>Ob</td>
<td>Cardiac surgery</td>
<td>7490</td>
<td>3745/3745</td>
<td>Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin; NR</td>
<td>Renal dysfunction</td>
<td>22</td>
</tr>
<tr>
<td>Layton et al.</td>
<td>Ob</td>
<td>CABG</td>
<td>17,077</td>
<td>3085/13,992</td>
<td>NR/NR</td>
<td>Renal dysfunction</td>
<td>22</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CABG, coronary artery bypass grafting; NR, not reported; Ob, observational study; RCT, randomized controlled trial; RIFLE, Risk, Injury, Failure, Loss, and End Stage; RRT, renal replacement therapy.
source of heterogeneity. Q-statistics was performed to further examine study heterogeneity. \( P < 0.1 \) was considered significantly heterogeneous. Publication bias was estimated using a Funnel plot and Egger weighted regression. \( P < 0.05 \) was considered statistically significant. A fixed effects model was used for meta-analysis without heterogeneity. A random effect model was adopted when significant heterogeneity was found among studies. Analyses were performed using the STATA statistical analysis software (version 13.1; Stata Corp, College Station, TX). \( P \) value was 2-sided and \( P < 0.05 \) was considered statistically significant.

**Results**

**Characteristics and quality of the included studies**

As illustrated in Figure 1, 1724 studies were excluded from the initially identified 1771 citations after review of the titles and abstracts, and 47 were selected to obtain full-text reports for a comprehensive review. A total of 24 articles including 5 randomized controlled trials and 19 observational studies were selected for meta-analysis (Table 1).

The meta-analysis was performed on a total of 59,771 patients including 27,854 who received PST and 31,917 who did not receive PST. Among the 24 included studies, 13 investigated patients who underwent isolated CABG and 2 focused on patients who underwent isolated valve surgery. In one study patients were examined who underwent isolated CABG, isolated valve surgery, and both procedures separately. We treated this particular study as 3 independent studies and extracted data from the 3 categories separately.36 Thus, the total number of studies included in the analysis was 26. Downs and Black Score analysis revealed that the score was between 17 and 25; 18 articles had good quality (score \( \geq 20 \)) and 6 studies had poor quality (score \( < 20 \)).

**PST significantly reduced short- and long-term postoperative renal dysfunction**

Our meta-analysis revealed that PST reduced the incidence of short- and long-term postoperative renal dysfunction by 11% (OR, 0.89; 95% CI, 0.84-0.95; \( Z = 3.76; P < 0.0001 \); Fig. 2) with low heterogeneity (\( I^2 = 28.1\% \); \( P = 0.093 \)). Thus, a fixed effect model was used. Sensitivity analysis did not reveal significant effects of each individual study on the overall results. The results from a meta-regression demonstrate that the type of cardiac surgery, year of publication, and study design were not the sources of heterogeneity (Table 2). Neither visual examination of the funnel plot nor Egger weighted regression analysis \( (P = 0.294) \) revealed significant publication bias.
Table 2. Meta-regression analysis of the source of heterogeneity for the meta-analysis on renal dysfunction

<table>
<thead>
<tr>
<th>Meta-regression</th>
<th>Number of observations = 26</th>
<th>tau2 = 0.01192</th>
<th>$I^2_{\text{res}} = 30.91%$</th>
<th>Adjusted $R^2 = -674.24%$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-regression analysis of the covariant 'CABG'</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Meta-regression</td>
<td>Number of observations = 26</td>
<td>tau2 = 0.001646</td>
<td>$I^2_{\text{res}} = 27.67%$</td>
<td>Adjusted $R^2 = -6.91%$</td>
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<tr>
<td><strong>Meta-regression analysis of the covariant 'RCT'</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-regression</td>
<td>Number of observations = 26</td>
<td>tau2 = 0</td>
<td>$I^2_{\text{res}} = 25.93%$</td>
<td>Adjusted $R^2 = 100.00%$</td>
</tr>
<tr>
<td><strong>Meta-regression analysis of the covariant 'year'</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Logor | Exp (b) | SE | $t$ | $P > |t|$ | 95% CI |
|-------|---------|----|-----|--------|------|
| CABG  | 0.9445922 | 0.102014 | −0.53 | 0.602 | 0.7558603-1.180449 |
| _Cons | 0.9095013 | 0.0659248 | −1.31 | 0.203 | 0.7831276-1.056268 |
| RCT   | 0.6511636 | 0.2562504 | −1.09 | 0.286 | 0.2890389-1.466979 |
| _Cons | 0.8980607 | 0.0366174 | −2.64 | 0.014 | 0.8255787-0.9769063 |
| Year  | 0.9741977 | 0.0193015 | −1.32 | 0.199 | 0.9351649-1.01486 |
| _Cons | 5.99e+22 | 2.39e+24 | 1.32 | 0.200 | 1.18e-13 to 3.06e+58 |

_Cons, regression constants; CABG, coronary artery bypass grafting; CI, confidence interval; RCT, randomized controlled trial; REML, Restricted Estimation Maximum Likelihood; res, residual; SE, standard error.

Figure 3. Forest plot of subgroup analysis of the effects of preoperative statin therapy on the incidence of acute kidney injury diagnosed using the AKIN criteria. AKIN, Acute Kidney Injury Network; CI, confidence interval; OR, odds ratio.
PST significantly reduced the incidence of postoperative AKI

Ten studies that included 41,565 patients investigated the correlation between PST and the incidence of postoperative AKI. We performed analyses on subgroups of patients whose AKI was diagnosed using the AKIN and patients whose AKI was evaluated according to the RIFLE criteria. For studies using the AKIN criteria, PST reduced the incidence of postoperative AKI by 13% (OR, 0.87; 95% CI, 0.80-0.94; \( z = 3.33; P = 0.001 \); Fig. 3) without heterogeneity (\( I^2 = 0.0\% ; P = 0.496 \)). For studies using the RIFLE criteria, PST reduced the incidence of postoperative AKI by

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**Figure 4.** Forest plot of subgroup analysis of the effects of preoperative statin therapy on the incidence of postoperative acute kidney injury diagnosed using the RIFLE criteria. CI, confidence interval; OR, odds ratio; RIFLE, Risk, Injury, Failure, Loss, and End Stage.

**Figure 5.** Forest plot of analysis on the effects of preoperative statin therapy on the incidence of postoperative renal replacement therapy. CI, confidence interval; OR, odds ratio.
7% (OR, 0.93; 95% CI, 0.86-0.99; \( z = 2.16; P = 0.031\); Fig. 4) with very low heterogeneity (\( I^2 = 1.0\%; P = 0.401\)).

**PST significantly reduced the postoperative requirement for RRT**

Eleven studies investigated the effects of PST on the requirement for postoperative RRT:\(^{11,27,28,31,33,36,38,39,41}\) PST reduced the incidence of postoperative RRT by 24% (OR, 0.76; 95% CI, 0.62-0.92; \( z = 2.77; P = 0.006\); Fig. 5) with low heterogeneity (\( I^2 = 41.1\%; P = 0.075\)). The type of cardiac surgery was a significant source of study heterogeneity (\( P < 0.1\); Table 3); studies on patients who underwent isolated valve surgery or any cardiac surgery contributed significantly to the study heterogeneity. The heterogeneity of studies on patients with isolated CABG was lower than that of studies with other types of cardiac surgery (Fig. 6). Thus, we performed subgroup analysis on patients who underwent isolated CABG and found that PST markedly reduced the requirement for RRT by 56% (OR, 0.44; 95% CI, 0.30-0.66; \( z = 4.08; P < 0.0001\); Fig. 7) without significant study heterogeneity (\( I^2 = 18.7\%; P = 0.297\)) and publication bias (\( P = 0.450\)).

**Discussion**

In this study, we performed a meta-analysis on 59,771 patients pooled from 26 studies and found that PST significantly reduced the incidence of short- and long-term postoperative renal dysfunction, the need for RRT, and the incidence of postoperative AKI in patients who underwent cardiac surgery. Similarly, in an observational study, Layton et al. found that PST reduced the incidence of postoperative AKI and renal failure.\(^{10}\) In contrast, Liakopoulos et al. found that PST reduced the incidence of postoperative atrial fibrillation.
fibrillation and stroke but exerted no beneficial effects on renal failure.43 Pan et al. also suggested that PST might reduce the risk of early mortality after on-pump CABG surgery, but it might not reduce the risk of postoperative renal dysfunction.21 The inconsistent results from the previous meta-analyses might be associated with the fact that a combined definition of renal dysfunction was used. Here, we found that PST significantly reduced the incidence of postoperative AKI in subgroups of patients evaluated using the AKIN criteria and patients assessed using the RIFLE criteria. Our study provides evidence to support the role of PST in preservation of renal function after cardiac surgery.

RRT after cardiac surgery sometimes is required to save the patient’s life; however, some disadvantages are associated with RRT. Conventional intermittent hemodialysis frequently leads to hemodynamic instability. Although ultrafiltration with continuous RRT is better tolerated than intermittent hemodialysis, the procedure is expensive, inconvenient, and requires intensive nursing care and continuous anticoagulation.43,44 In addition, after cardiac surgery, RRT increases medical expense and mortality.45 Thus, protection of renal function to avoid postoperative RRT might reduce morbidity and mortality after cardiac surgery. In this meta-analysis, we found that PST significantly reduced the requirement for postoperative RRT in patients who undergo isolated CABG, the reduction reached 56%. Thus, PST appears to be an effective therapy to avoid RRT, improve renal outcomes for patients who undergo isolated CABG, and reduce financial burden.

Currently, effective therapies for AKI are still limited.46,47 Evidence-based studies to investigate the beneficial role of PST in reduction of postoperative AKI are also sparse. Available reports on the association between PST and the incidence of AKI after cardiac surgery show conflicting results. In an observational study, Billings et al. found that PST did not reduce the incidence of postoperative AKI.35 Pan et al. demonstrated a 15.5% increase in the incidence of postoperative AKI using PST although the difference was not statistically significant.21 In this study, to accurately evaluate the effects of PST on the incidence of AKI after cardiac surgery, we performed meta-analysis on subgroups of patients whose AKI was diagnosed and staged using the AKIN definition and patients whose AKI was evaluated according to the RIFLE definition. The results from the 2 subgroup analyses consistently demonstrated that PST reduced the incidence of AKI after cardiac surgery. Molnar et al. recently reported that PST appeared to be associated with reduced levels of AKI biomarkers, such as urine interleukin-18, urine neutrophil gelatinase-associated lipocalin, urine kidney injury molecule-1, and plasma neutrophil gelatinase-associated lipocalin.46 Thus, our findings indicate that continuous PST might protect the kidney from cardiac surgery-induced injury, although randomized controlled trials are required to verify this conclusion. The 2014 European Society of Cardiology/European Association of Cardio-Thoracic Surgery Guidelines on myocardial revascularization recommend that all of the patients who undergo CABG without contraindication should receive statins preoperatively and continuously until surgery.48 Our study provides evidence that shows the protective role of PST in postoperative renal outcomes to further support this recommendation.

The mechanism underlying the beneficial effects of PST on renal outcomes might be associated with the non-lipid-lowering activities of statins, such as anti-inflammation, antithrombosis, and improvement in endothelial function.49 Cardiopulmonary bypass (CPB)-induced inflammation is thought to contribute to cardiac surgery-associated renal dysfunction.50 Statins have been shown to reduce the levels of acute-phase proteins and inflammatory cytokines including interleukin-1, -6, and -8 and increase the release of anti-inflammation cytokines, such as

Figure 7. Forest plot of subgroup analysis of the effects of preoperative statin therapy on the incidence of postoperative renal replacement therapy in patients undergoing isolated coronary artery bypass grafting. CI, confidence interval; OR, odds ratio.
interleukin-10. Chello et al. found that patients who received statin therapy before CPB showed an increased level of apoptotic neutrophils after CPB, suggesting that statins play a role in anti-inflammation during CPB. Patti et al. conducted a randomized controlled trial and found that high-dose atorvastatin reduced ischemia-reperfusion injury, alleviated endothelial damage, and consequently protected myocardium in patients who underwent percutaneous coronary intervention. Thus, we believe that the non- lipid-lowering activities of statins contribute to the PST-mediated reduction of postoperative renal complications.

Some limitations in this study should not be overlooked. The number of reports included in this meta-analysis is small. Only 11 reports were included for the meta-analysis of the requirement of postoperative RRT and 10 for the incidence of AKI. In addition, our study unavoidably carries the limitations associated with meta-analyses, such as variation in study design, publication bias, and use of observational data. Moreover, the dose effects of statins and the effects of individual statins were not evaluated in the included studies.

In conclusion, PST significantly reduced the incidence of short- and long-term postoperative renal dysfunction and the need for RRT after cardiac surgery, particularly for patients who underwent isolated CABG. PST also significantly reduced the incidence of postoperative AKI regardless of the types of diagnosis and staging criteria (AKIN or RIFLE) used in the included studies. These findings suggest that PST might protect renal function and improve renal outcomes in patients who undergo cardiac surgery, although large-scale randomized controlled trials are needed to further verify the findings.

Funding Sources
This study was supported by the National Natural Science Foundation of China (No. 81470529).

Disclosures
The authors have no conflicts of interest to disclose.

References


