Commentary

No recommendation of routine perioperative statin use for prevention of acute kidney injury in patients undergoing cardiac surgery

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Acute kidney injury (AKI) develops up to approximately 30% of patients who undergo cardiac surgery (1), and independently associating with increased risk of morbidity and mortality (1,2). The prevention of AKI following cardiac surgery is predominantly important. Statin have been expected to reduce the development of AKI following cardiac surgery based on its anti-inflammatory effects. However, several observational cohort studies focusing on statin treatment as a preventive effect of AKI have been reported with conflicting results (3,4). Retrospective studies might have limitations of inevitable selection bias, and leading into the possibility of misleading and inconclusive results. To date, there is little evidence from randomized trials in populations receiving cardiac surgery to support the role of perioperative statin treatment to prevent AKI.

Recently, Billings and colleagues conducted the prospective double-blinded randomized controlled trial of a perioperative statin for prevention of AKI following cardiac surgery (5). Their hypothesis was that perioperative statin would reduce AKI following cardiac surgery by 30% as compared to placebo with an assumed AKI incidence of 27.6% in the placebo group, a type I error probability of 0.05, and 80% power. They enrolled a total of 615 patients (199 naïve to statin treatment and 416 already taking a statin). Enrolled patients were randomized to perioperative statin treatment (80 mg of atorvastatin the day prior surgery, 40 mg of atorvastatin the morning of surgery, and 40 mg of atorvastatin daily following surgery for the duration of hospitalization) or placebo. If patients already taking statin, their pre-enrollment statin was continued until the day of surgery and resumed taking their previously prescribed statin on postoperative day 2 because of ethical issue. The primary endpoint was the incidence of AKI, which was defined as an increase of 0.3 mg/dL in serum creatinine concentration or the initiation of renal replacement therapy within 48 hours of surgery.

The data and safety monitoring board recommended stopping the group naïve to statin treatment due to increased AKI among these participants with chronic kidney disease (CKD), defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2, receiving atorvastatin. Summary of study results are shown in *Table 1*. Among overall participants (n=615), AKI occurred in 64 of 308 (20.8%) in the atorvastatin group *vs.* 60 of 307 (19.5%) in the placebo group [relative risk (RR), 1.06 (95% confidence interval, 0.78 to 1.46); P=0.75]. Among patients naïve to statin treatment (n=199), AKI occurred in 22 of 102 (21.6%) in the atorvastatin group *vs.* 13 of 97 (13.4%) in the placebo group [RR, 1.61 (95% confidence interval: 0.86 to 3.01); P=0.15]. Among patients already taking a statin (n=416), AKI occurred in 42 of 206 (20.4%) in the atorvastatin group *vs.* 47 of 210 (22.4%) in the placebo group [RR, 0.91 (95% confidence interval: 0.63 to 1.32); P=0.63]. In the pre-specified subgroup of 36 statin-naïve patients with CKD, 9 of 17 (52.9%) in the atorvastatin group *vs.* 3 of 19 (15.8%) in the placebo group developed AKI ([RR, 3.35 (95% confidence interval: 1.12 to 10.05); P=0.03].

The study results from Billings and colleagues (5) showed high-dose perioperative atrovastatin treatment compared with placebo did not reduce the risk of AKI among patients undergoing cardiac surgery. Other important additional evidence is that continuing perioperative statin treatment is likely safe in patients who have already taking statin. In contrast, initiating perioperative statin treatment may be harmful to the kidney function in statin naïve patients with CKD.

Table 1 Efficacy of treatment to prevent AKI in all patients and pre-specified subgroups (5)

Subjects	No. with AKI/total No. (%)		RR (95% CI)	P value
	Atorvastatin	Placebo		
All patients	64/308 (20.8)	60/307 (19.5)	1.06 (0.78 to 1.46)	0.75
Naïve to statin treatment	22/102 (21.6)	13/97 (13.4)	1.61 (0.86 to 3.01)	0.15
Already taking statin	42/206 (20.4)	47/210 (22.4)	0.91 (0.63 to 1.32)	0.63
Patients with CKD	30/84 (35.7)	31/95 (32.6)	1.09 (0.73 to 1.65)	0.76
Naïve to statin treatment	9/17 (52.9)	3/19 (15.8)	3.35 (1.12 to 10.05)	0.03
Already taking statin	21/67 (31.3)	28/76 (36.8)	0.85 (0.54 to 1.35)	0.59

AKI, acute kidney injury; RR, relative risk; CI, confidence interval; CKD, chronic kidney disease.

The prevention of AKI following cardiac surgery is predominantly important because of significant association with increased risk of mortality and morbidity (1,2). The mechanisms of development of AKI following cardiac surgery are multifactorial, including preexisting CKD, diabetes, prior cardiac surgery, congestive heart failure, recent myocardial infarction, and use of intra-aortic balloon pumping (6). Statin have been expected to reduce the development of AKI or atrial fibrillation following cardiac surgery based on its antioxidant and anti-inflammatory effects. The results from several randomized trial demonstrated that perioperative statin treatment in patients with undergo cardiac surgery reduced the development of postoperative atrial fibrillation with decreasing the concentration of inflammatory cytokines (7,8). Several observational cohort studies focusing on statin treatment as a preventive effect of AKI have been reported with conflicting results (3,4). Nevertheless, the study results from Billings and colleagues (5) showed that perioperative statin treatment significantly increased the risk of development of AKI following cardiac surgery among statin naïve patients with CKD. The mechanism of harmful effects of *de novo* statin treatment on renal function is unclear. It should be noted that small patient subgroup with statin-naïve patients with CKD (n=36) might develop the possibility of type I error. However, in the absence of any other convincing evidence of benefit, the initiation of statin dose not be recommended to patients naïve to statin treatment with CKD who undergo cardiac surgery.

Preventive effects of statin treatment on AKI has been evaluating in other clinical setting. Among patients with coronary artery disease who undergo percutaneous coronary intervention, several recent studies showed that statin pretreatment reduced the risk of contrast-induced AKI (9-11). Contrast media induces production of reactive oxygen species and inflammation, leading into renal cytotoxicity, apoptosis of endothelial and tubular cells. The rational of statin use for the prevention of contrast-induced AKI relates to its pleiotropic effects, such as reduction of renal oxidative stress and enhancement of renal nitric oxide. On the other hand, in the recent randomized trial involving patients with sepsis-associated acute respiratory distress syndrome, rosuvastatin treatment was associated with fewer days free of renal failure (10.1±5.3 *vs.* 11.0±4.7 days for rosvastatin and placebo group, P=0.01) (12).

Statin treatment is widely expand in current clinical practice, therefore, study design might be difficult and challenging to evaluate the effect of perioperative statin among statin naïve patients. Even though the evidence of the statin use for the short-term prevention of AKI is negative, the long-term beneficial effects on cardiovascular risk reduction make statin use imperative in this patient population. Further studies on this topic may clarify the pathogenesis of development of AKI following cardiac surgery and the novel and promising intervention strategies for reducing AKI in this population.

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Footnote

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