Editorial

Ameliorating acute kidney injury following cardiac surgery: do high dose perioperative statins play a role?

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Acute kidney injury (AKI) is relatively common in the patients undergoing cardiac surgery. Over the past decade, several consensus definitions (namely the RIFLE, AKIN and KIDGO) have been developed to provide uniform criteria for the diagnosis of AKI, in order to facilitate comparisons between studies and the development of quantitative research (1-3). The incidence of AKI after cardiac surgery differs slightly depending on the classification criteria, ranging from 31–46% (3-5). It is well known that patients who developed AKI after cardiac surgery are at an increased risk of short-term and long-term morbidity and mortality. These patients tend to have higher mortality rates, prolonged ICU and hospital stay (5-7). These patients also have an increased risk of subsequent developing chronic kidney disease (CKD), which is associated with a higher long-term mortality (8).

The pathogenesis of AKI after cardiac surgery is complex and still not fully understood. Numerous factors have been suggested to play a role in the development of AKI in the post-operative period, which include exposure to both exogenous [i.e., NSAIDs (9), certain antibiotics (10,11), IV contrast agents (12)] and endogenous [i.e., iron or heme pigments (13)] nephrotoxins, regional hypoxia due to neurohormonal activation (14), atherosclerotic embolism (15), mechanical blood trauma associated with cardiopulmonary bypass use (16), and systemic inflammatory response syndrome thought to be triggered by the contact between blood and artificial surface of the cardiopulmonary bypass circuit (17).

Besides its major role as a lipid-lowering agent, statins has been associated with some pleotropic effects that favor kidney protection. These effects include reduction in systemic inflammatory markers such as interleukin-6, interleukin-8, and neutrophil-endothelial adhesion (18). Statins may stabilize the endothelium and recover vascular responsiveness in a shock setting by decreasing nitrate plasma concentration (19). Several large retrospective cohort studies have demonstrated possible protective effect of statins against AKI in patients undergoing cardiac surgery. Huffmyer *et al.* showed that preoperative use of statins is associated with decreased in-hospital mortality and a reduction in the need for renal replacement therapy (20). Another observational study of 17,077 patients reported that statin initiation immediately before CABG reduced the incidence of AKI with a risk ratio of 0.78 (95% CI, 0.63 to 0.96) after propensity score adjustment (21). However, another vigorous propensity matched analysis failed to reveal the same beneficial effect of statins in renal protection (22).

Data from observational studies can often be misleading due to confounding and bias. Therefore, randomized clinical trials (RCT) are critical to confirm or reject these findings. Billings IV *et al.* (23) recently published in *JAMA* a well-designed, double blinded, placebo-controlled, randomized trial to investigate the role of high dose perioperative atorvastatin in reducing AKI following cardiac surgery. A total of 199 patients naive to statin treatment and 416 patients already taking a statin were enrolled into this trial, who were subsequently randomized to either high-dose perioperative atorvastatin or matching placebo. The primary end point was the diagnosis of AKI based on AKIN Criteria (2), 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.

Overall, the incidence of AKI in the atorvastatin group and the placebo group was similar [20.8% *vs.* 19.5%;

relative risk (RR): 1.06; 95% CI, 0.78 to 1.46; P=0.75]. Among patients naïve to statin treatment, AKI occurred in 21.6% in the atorvastatin group *vs.* 13.4% in the placebo group (RR: 1.61; 95% CI, 0.86 to 3.01; P=0.15). The risk of AKI was further increased in this group of patients with preexisting CKD: 52.9% in the atorvastatin group compared with 15.8% in the placebo group (RR: 3.35; 95% CI, 1.12 to 10.05; P=0.03). As a result, following the second interim analysis, the recruitment of patients naïve to statins was discontinued under the recommendation of the data and safety monitoring board (DSMB) due to increased risk of AKI. In contrast, the incidence of AKI was not increased in the patients already taking a statin (RR: 0.91; 95% CI, 0.63 to 1.32; P=0.63), even in those with preexisting CKD (RR: 1.09; 95% CI, 0.73 to 1.65; P=0.76). Following a conditional power analysis, the DSMB subsequently recommended discontinuation of the recruitment of patients already taking a statin due to futility on the primary end point.

The findings from this study have several clinical implications. Initiating statins perioperatively with a nephroprotective intent in cardiac surgery patients naïve to statins might have deleterious effects instead, and therefore should be avoided. Patients already on statin therapy are safe to continue their usual statin dose throughout the entire period of cardiac surgery. High dose perioperative statins do not seem to exert a protective effect against AKI after cardiac surgery.

In summary, AKI is a common complication among cardiac surgery patients and is independently associated with worse clinical outcomes. Interventions capable of ameliorating AKI following cardiac surgery are expected to yield substantial clinical benefit. However, no intervention or pharmacologic strategies have been proven to be effective so far. Therefore, further effort to delineate the exact pathogenesis of post-cardiac surgery AKI and ongoing exploration of promising preventive and therapeutic strategies continue to be warranted.

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Footnote

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