Editorial

Does high-dose perioperative use of statins ameliorate acute kidney injury following cardiac surgery?

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Acute kidney injury (AKI) is a well-known, frequent complication in patients after cardiac surgery, occurring in 7% to 40%, depending on its definition (1). Subsequently, it is independently associated with substantial morbidity [such as need for renal replacement therapy, longer length of hospital stay and progression of chronic kidney disease (CKD)] and mortality (2). Even a minimal increase in post-operative serum creatinine is associated with an increased mortality in cardiac surgery patients (3).

Due to the complex pathophysiology of AKI with multiple contributing factors, exact mechanisms are not yet fully understood and challenges remain concerning early recognition, prevention and treatment. Currently, therapy consist of supportive measures, while numerous studies and attempts on (pharmaceutical) treatment have failed to show beneficial effects in (cardiac surgery induced) AKI (4).

Lipid lowering therapy with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) is a widely used therapy to lower cholesterol levels and prevent cardiovascular events. Its use among patients who undergo cardiac surgery is associated with a reduced incidence of perioperative mortality after coronary artery bypass graft surgery (5). Besides the lipid lowering effects of statins, established pleiotropic anti-inflammatory and endothelial stabilizing effects of statins are believed to (indirectly) contribute to this protective effect after cardiac surgery (6).

As inflammatory pathways and endothelial dysfunction are also believed to play a major role in the development of AKI (7), it has been proposed that short-term use of statins could possibly improve renal outcome. Given this rationale, multiple, mostly observational, studies regarding the effect of statin use on renal outcome after cardiac surgery have been conducted and reported contradictory results. A recent meta-analysis by Wang *et al.*, including 11 studies, showed that preoperative statin treatment reduced the incidence of post-operative AKI by 13% (8). However, the results of this meta-analysis should be interpreted with caution as the presence of supporting evidence of attenuation of AKI after cardiac surgery with preoperative statin treatment has been challenged (9). Prior studies examining specifically short-term initiation of statins have also showed contradictory results. In a pilot randomized controlled trial (RCT) (n=100) short-term use of statins did not affect AKI incidence (10), while in a recent observational study of 17,000 patients who underwent cardiac surgery, a 22% lower relative risk for the development of AKI was observed in patients on statins in adjusted analyses (11).

In this respect, Billings *et al.* recently tested the hypothesis that short-term high-dose perioperative use of statins would reduce AKI following cardiac surgery for both patients naïve to statin treatment and for patients already on chronic statin therapy. The primary endpoint was diagnosis of AKI according to the criteria form the acute kidney injury network (AKIN), defined by an increase of at least 0.3 mg/dL in serum creatinine concentration or the initiation of renal replacement therapy within the first 48 hours following cardiac surgery. Secondary endpoints included the maximum increase in serum creatinine concentration, the incidence and duration of delirium during ICU admission, the degree of myocardial injury, the incidence of postoperative atrial fibrillation, pneumonia and stroke.

In this monocenter double-blind, placebo-controlled,

RCT, a total of 615 patients were enrolled. Patients naïve to statin treatment received 80 mg the day before surgery, 40 mg atorvastatin on the day of surgery and 40 mg the day following surgery (n=102) or matching placebo (n=97). Patients already on statin treatment continued their prescribed statin dosing regimen and were randomized to receive either 80 mg atorvastatin on the morning of surgery and 40 mg the morning after surgery (n=206), or matching placebo (n=210). Patients scheduled for elective coronary artery bypass grafting (CABG), valve, and/or ascending aortic surgery were included. Main exclusion criteria were presence of acute coronary syndrome (ACS), statin intolerance, and liver dysfunction. Randomisation was stratified to presence of diabetes mellitus (DM) and the class of pre-existent CKD. Interim analyses by a DSMB were planned twice during the study at the first third and the second third of planned enrollment. The DSMB recommended stopping the group naïve to atorvastatin treatment, as patients with a baseline estimated GFR <60 mL/min showed increased AKI, and following enrollment of 615 patients the DSMB recommended stopping of the trial for futility.

Overall, risk of post-operative AKI was not affected by short-term high-dose administration of atorvastatin. Among patients in the atorvastatin group 64 of 308 (20.8%) patients developed AKI, in the placebo group 60 of 307 (19.5%) patients (RR 1.06; 95% CI: 0.78–1.46; P=0.75). However, contrary to the hypothesis , among patients naïve to statin treatment AKI tended to occur more often in the treatment group: 22 of 102 (21.6%) patients developed AKI *vs.* 13 of 97 (13.4%) patients in the placebo group (RR 1.61; 95% CI: 0.86–3.01; P=0.15). Also, the increase in post-operative serum creatinine concentration was significantly more distinct in the treatment group: median 0.11 mg/dL in the atorvastatine group *vs.* 0.05 mg/dL in the placebo group (mean difference 0.08 mg/dL; 95% CI: 0.01–0.015 mg/dL; P=0.007). This adverse outcome on renal function was even more pronounced among patients in the subgroup of pre-existent CKD and naïve to statin treatment: AKI occurred in 9 of 17 (52.9%) in the atorvastatin group *vs.* 3 of 19 (15.8%) in the placebo group (RR 3.35; 95% CI: 1.12–10.05; P=0.03) and in this subgroup a median postoperative increase in serum creatinine levels of 0.26 mg/dL was observed in the atorvastatin group *vs.* a median decrease of 0.06 mg/dL in the placebo group (mean difference 0.28 mg/dL; 95% CI: 0.02–0.54; P=0.04). In the patients that were already on statin therapy, no effects of atorvastatine were observed, as AKI occurred in 20.4% of the active group and 22.4% of the placebo treated patients (RR 0.91; 95% CI: 0.63–1.32; P=0.63). Apart from a higher incidence and longer duration of delirium, and a higher incidence of atrial fibrillation in the atorvastatine group compared to the placebo-group, no statistically significant effects on the other secondary end-points were found.

As conducted research in this field mainly included observational retrospective studies, the authors appreciated the essential need for prospective research in this field. In this well-conducted double-blind RCT it has been clearly demonstrated that there is no additional benefit for the initiation of high-dose short-term statin therapy. In contrast, short-term initiation of statin therapy in patients naive to the statin treatment may even be detrimental and enhance the development of AKI after cardiac surgery, as overall creatinine concentrations significantly increased to a greater extent in the atorvastatine group and further deterioration of renal function was more likely in patients with CKD.

The evidence of this trial is of high quality in this double-blind, placebo-controlled set-up, however there are some limitations. The authors already addressed some of these limitations, for example the fact that the trial was conducted in a single center, possibly limiting its generalizability. Furthermore, the definition of the primary outcome may pose some limitations and/or bias. First, the authors chose to use the AKIN criteria to define development of AKI, whereas for comparability the more frequently used RIFLE or KDIGO criteria would have possibly been a better option. Nevertheless, the observed increase in creatinine concentrations confirms the proof of principle effect on renal function. Second, by using AKIN criteria the authors committed to the corresponding post-operative window of 48 hours, hereby not accounting for late-onset AKI. And last, only the creatinine criterium, not the urinary output criterium, to detect AKI was used.

Further, the investigators also enrolled patients undergoing cardiac surgery without the use of extra corporeal circulation (ECC). As the use of ECC causes extensive activation of the innate immune system and exposes kidneys to ischaemia-reperfusion damage, it is therefore regarded as a main contributor to the development of post-operative AKI (12). The risk of developing AKI among patients without the use of ECC may therefore be lower. In the present cohort, surgery with the use of ECC was performed only in 71% of patients (n=218 atorvastatin, n=217 placebo), this could substantially limit the statistical power of the study, in particular in the smaller subgroup of patients naïve to statin treatment.

Finally, the timing of the very short treatment window (one day before surgery until one day after surgery) is remarkable and inconsistent with the multi-day treatment windows previously used by Prowle *et al.* (10) and Layton *et al.* (11). Although no other current literature describes adverse outcomes in patients naïve to statin treatment following a very short peri-operative statin dosing regimen, the detrimental effect as observed in this trial appears valid.

Billings *et al.* have demonstrated that short-term statin treatment in cardiac surgery patients yields no renal benefits and therefore do no support initiation of statin therapy to prevent AKI following cardiac surgery.

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Footnote

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