

Statins and acute kidney injury following cardiac surgery: has the last word been told?

Stefano Romagnoli^{1,2}, Zaccaria Ricci³

¹Department of Health Science, Section of Anesthesiology and Intensive Care, University of Florence, Florence, Italy; ²Department of Anesthesia and Intensive Care, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla, Florence, Italy; ³Department of Cardiology and Cardiac Surgery, Pediatric Cardiac Intensive Care Unit, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, Rome, Italy

Correspondence to: Zaccaria Ricci. Bambino Gesù Children's Hospital, IRCCS, Piazza S. Onofrio 4, 00165, Rome, Italy. Email: zaccaria.ricci@gmail.com.

Submitted Mar 23, 2016. Accepted for publication Mar 31, 2016.

doi: 10.21037/jtd.2016.04.34

View this article at: <http://dx.doi.org/10.21037/jtd.2016.04.34>

Cardiac surgery is the second most common cause of acute kidney injury (AKI) in intensive care and affects, depending on the definition, 8.9% to 39% of patients (1). Renal replacement therapy (RRT) is needed in 1–5 % (1,2) of post cardiac surgery cases. Importantly, AKI development, even when serum creatinine is restored to baseline values, is independently associated with short and long term morbidity and mortality and no specific therapy is available, so far (3,4). Progress has been made during the last years on the definition of the syndrome [i.e., Kidney Disease Improving Global Outcome (KDIGO) criteria, (5)], on better understanding of its pathophysiology, and on the identification of earlier severity stages (6). It is now clear that cardiac surgery associated AKI (CSA-AKI) has a multifactorial origin since different pathways simultaneously affect renal function: patients' pre-operative susceptibility, exogenous and endogenous toxins, metabolic factors, hemodynamic instability, ischemia/reperfusion injury, microembolization, neurohormonal activation, endothelial cells and renal epithelial cells activation, and release of inflammatory mediators and oxidative stress (7–9). Inflammation, deriving from several pathways, plays a key role in CSA-AKI: cardiopulmonary bypass and its contact activated response, aortic cross-clamp and circulatory arrest, tissue hypoxia, and transfusions co-act leading to a systemic inflammatory response syndrome (7,10–12). In light of these aspects, many strategical and therapeutic approaches have been attempted in order to limit the occurrence of AKI after cardiac surgery (13). Inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins) were

introduced in clinical practice in 1987 as lipid-lowering agents with the specific action to decrease plasma cholesterol concentrations (14). It is a matter of fact that statins have led to significant reductions in cardiovascular morbidity and mortality and, in addition to the cardiovascular benefits, they have been found to have anti-inflammatory effects, thus suggesting potential applications beyond cardiovascular diseases. Due to the potential properties of attenuation of inflammation and oxidative stress (15,16), statins have been administered as kidney protective agents for many years (17). Currently, experimental or retrospective studies have reached inconclusive and sometimes conflicting results (17–20). In a recent number of JAMA, Billings *et al.* published an interesting double blind randomized controlled trial entitled “High-Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery”, designed to test short-term high-dose perioperative atorvastatin, in both naive and previously treated patients, as a protective drug against CSA-AKI (21). Among the overall 615 recruited patients, AKI occurred in 20.8% in the atorvastatin group *vs.* 19.5% in the placebo group [P=0.75; relative risk (RR) 1.06 (95% CI, 0.78 to 1.46)]. Specifically, among the patients who were naive to statin treatment (n=199), AKI occurred in 21.6% in the atorvastatin group compared with 13.4% in the placebo group [RR, 1.61; (95% CI, 0.86 to 3.01); P=0.15] with a median serum creatinine increase by 0.11 mg/dL in the atorvastatin group and 0.05 mg/dL in the placebo group [mean difference, 0.08 mg/dL (95% CI, 0.01 to 0.15 mg/dL); P=0.007]. Importantly, in the subgroup of patients with

chronic kidney disease (CKD) and naive to statin treatment, although limited in number (36 patients), atorvastatin was associated with worsening of renal outcome: acute on chronic kidney injury occurred in 52.9% in the atorvastatin group *vs.* 15.8% in the placebo group [RR, 3.35 (95% CI, 1.12 to 10.05); $P=0.03$]. On the contrary, no significant differences in renal function were observed in those patients with CKD who were already taking a statin ($P=0.59$). Importantly, the study board recommended ending enrolment of patients naive to statins because of the increased incidence of AKI among those with CKD. The trial was hence interrupted for futility. Billings *et al.*'s study has important clinical implications related to statin therapy as clearly underlined in a related editorial (22): for patients not preoperatively taking statins, the treatment should not be initiated for "renal protection" purpose. On the other hand, patients chronically taking statins should not withdraw the therapy due to its well-established "cardiovascular" benefits (23). In addition, the absence of kidney benefits demonstrated by Billings *et al.*'s trial is in line with many large observational studies (17-20) and a recent Cochrane meta-analysis (14) that do not suggest preoperative statin for kidney protection in adults after surgery under CPB. In order to better understand the potential role of statins and many other drugs and strategies, in CSA-AKI, it could be useful to increase the sensitivity of the investigations moving back from the acute kidney "injury" (a late clinical condition) to the acute kidney "stress" (AKS). AKS has recently been suggested as a sub-clinical phase of AKI pathophysiology (9). In light of this, a number of renal biomarkers have been evaluated and tested to enhance the understanding and diagnosis of AKI and cardiorenal syndrome (24,25). Molnar *et al.* conducted a post-cardiac surgery multi-center prospective cohort study of 625 adult patients (18). The primary study's outcome was the need of acute dialysis or a doubling in serum creatinine from the baseline; the secondary outcome was "kidney injury" as identified by elevation of kidney injury biomarkers [urine interleukin-18 (IL-18), urine neutrophil gelatinase-associated lipocalin (uNGAL), urine kidney injury molecule-1 (uKIM-1), and plasma neutrophil gelatinase-associated lipocalin, (uNGAL)]. Patients were divided into statin held group (in the 24 hours prior to surgery) and statin continued group. The authors showed that continuing (*vs.* holding) a statin prior to surgery was not associated with a lower risk of AKI defined by a doubling of serum creatinine or dialysis, {RR 1.09 [95% confidence interval (CI) 0.44-2.70]}, similarly to Billing *et al.*'s observations (18,21). Nevertheless, the continuing statin

group showed a lower elevation of AKI biomarkers when compared to patients who interrupted statin assumption: IL-18 [RR 0.34 (95% CI, 0.18-0.62)], uNGAL [RR 0.41 (95% CI, 0.22-0.76)], uKIM-1 [RR 0.37 (95% CI, 0.20-0.76)], and pNGAL [RR 0.62 (95% CI, 0.39-0.98)]. Molnar *et al.*'s study poses the basis for a pre-AKI syndrome, and could finally suggest that: (I) statins should not be interrupted in patients chronically assuming them; (II) they may actually perform as anti-inflammatory and endothelial sparing agents in CSA-AKI; (III) AKI criteria, due to their intrinsic inability to accurately diagnose AKI in its early stages, could be inadequate to select patients that may benefit from specific therapeutic approaches or procedures; (IV) biomarkers could provide new means with higher sensitivity to identify these patients. Similarly to Molnar *et al.*'s study, Kruger *et al.* evaluated in a Phase II, multicenter, prospective, randomized, double-blind, placebo-controlled trial plasma IL-6 concentration in a cohort of 250 critically ill patients with severe sepsis (123 receiving atorvastatin 20 mg daily *vs.* 127 placebo). Statin therapy did not affect IL-6 levels (survival, length of stay, SOFA score, or C-reactive protein concentration), but prior statin users had a lower baseline IL-6 concentration in comparison with *de novo* statin therapy; importantly, the continuation of atorvastatin in such patients was associated with improved 28-day survival (26). Probably, multi-centre randomized controlled trials combining "classic" AKI criteria with new, more sensitive, markers are needed to better select patients, investigate drugs, and deliver future recommendations. In particular it is possible that a different selection of enrolled patients may be encouraged: novel diagnostic tools should be applied to improve stratification of candidate subjects and allow administration of nephro-protective drugs (and procedures) to those patients who actually have a chance to be "protected". Furthermore the increased granularity of renal follow up in AKS or, more generically, "high risk" patients, potentially achieved through systematic biomarkers dosing, may also lead to a better understanding of renal pathophysiology, disease processes and treatment effects. As a final comment, it should be remarked that CSA-AKI is a multifactorial syndrome that needs a multi-modal strategy to limit its occurrence and severity: even if single procedural strategies [e.g., off-pump technique (10) or remote ischemic preconditioning (27)] and isolated pharmacological approaches [e.g., statins (21) or fenoldopam (28)] have nowadays failed to prove definitive benefit, a combined approach, applying multiple therapies to specifically selected patients, has yet to be attempted.

In conclusion, based on recent high level evidence, statins should not be started before cardiac surgery in patients not chronically taking them for AKI prevention being useless or potentially harmful. Possibly, patients already receiving them in chronic therapy should not discontinue this therapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Provenance: This is an invited Commentary commissioned by Ming Zhong (Associate Professor, Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

References

- Romagnoli S, Ricci Z. Postoperative acute kidney injury. *Minerva Anestesiol* 2015;81:684-96.
- Parolari A, Pesce LL, Pacini D, et al. Risk factors for perioperative acute kidney injury after adult cardiac surgery: role of perioperative management. *Ann Thorac Surg* 2012;93:584-91.
- Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005;294:813-8.
- Bihorac A, Yavas S, Subbiah S, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg* 2009;249:851-8.
- Kasiske BL, Wheeler DC. Kidney Disease: Improving Global Outcomes—an update. *Nephrol Dial Transplant* 2013;28:1-138.
- Garrido JM, Candela-Toha AM, Parise-Roux D, et al. Impact of a new definition of acute kidney injury based on creatinine kinetics in cardiac surgery patients: a comparison with the RIFLE classification. *Interact Cardiovasc Thorac Surg* 2015;20:338-44.
- Gaffney AM, Sladen RN. Acute kidney injury in cardiac surgery. *Curr Opin Anaesthesiol* 2015;28:50-9.
- Boyle EM Jr, Pohlman TH, Johnson MC, et al. Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. *Ann Thorac Surg* 1997;63:277-84.
- Katz N, Ronco C. Acute kidney stress—a useful term based on evolution in the understanding of acute kidney injury. *Crit Care* 2016;20:23.
- Seabra VF, Alobaidi S, Balk EM, et al. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized controlled trials. *Clin J Am Soc Nephrol* 2010;5:1734-44.
- Ranucci M, Ballotta A, Agnelli B, et al. Acute kidney injury in patients undergoing cardiac surgery and coronary angiography on the same day. *Ann Thorac Surg* 2013;95:513-9.
- Mariscalco G, Lorusso R, Dominici C, et al. Acute kidney injury: a relevant complication after cardiac surgery. *Ann Thorac Surg* 2011;92:1539-47.
- Coleman MD, Shaefi S, Sladen RN. Preventing acute kidney injury after cardiac surgery. *Curr Opin Anaesthesiol* 2011;24:70-6.
- Lewicki M, Ng I, Schneider AG. HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. *Cochrane Database Syst Rev* 2015;3:CD010480.
- Antonopoulos AS, Margaritis M, Lee R, et al. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. *Curr Pharm Des* 2012;18:1519-30.
- Yokota N, O'Donnell M, Daniels F, et al. Protective effect of HMG-CoA reductase inhibitor on experimental renal ischemia-reperfusion injury. *Am J Nephrol* 2003;23:13-7.
- Liakopoulos OJ, Choi YH, Haldenwang PL, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. *Eur Heart J* 2008;29:1548-59.
- Molnar AO, Parikh CR, Coca SG, et al. Association between preoperative statin use and acute kidney injury biomarkers in cardiac surgical procedures. *Ann Thorac Surg* 2014;97:2081-7.
- Layton JB, Kshirsagar AV, Simpson RJ Jr, et al. Effect of statin use on acute kidney injury risk following coronary artery bypass grafting. *Am J Cardiol* 2013;111:823-8.
- Argalious M, Xu M, Sun Z, Smedira N, Koch CG. Preoperative statin therapy is not associated with a reduced incidence of postoperative acute kidney injury after cardiac surgery. *Anesth Analg* 2010;111:324-30.
- Billings FT 4th, Hendricks PA, Schildcrout JS, et al. High-Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery: A Randomized Clinical Trial. *JAMA* 2016;315:877-88.
- Bellomo R. Perioperative Statins in Cardiac Surgery and

- Acute Kidney Injury. *JAMA* 2016;315:873-4.
23. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.
 24. Murray PT, Mehta RL, Shaw A, et al. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int* 2014;85:513-21.
 25. Cruz DN, Soni S, Slavin L, et al. Biomarkers of cardiac and kidney dysfunction in cardiorenal syndromes. *Contrib Nephrol* 2010;165:83-92.
 26. Kruger P, Bailey M, Bellomo R, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. *Am J Respir Crit Care Med* 2013;187:743-50.
 27. Hausenloy DJ, Candilio L, Evans R, et al. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *N Engl J Med* 2015;373:1408-17.
 28. Bove T, Zangrillo A, Guarracino F, et al. Effect of fenoldopam on use of renal replacement therapy among patients with acute kidney injury after cardiac surgery: a randomized clinical trial. *JAMA* 2014;312:2244-53.

Cite this article as: Romagnoli S, Ricci Z. Statins and acute kidney injury following cardiac surgery: has the last word been told? *J Thorac Dis* 2016. doi: 10.21037/jtd.2016.04.34