Commentary



# Statins barely touch the heart but bite the kidneys after cardiac surgery. Coenzyme Q10 deficiency in the dock?

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Submitted Sep 13, 2016. Accepted for publication Sep 18, 2016.
doi: 10.21037/atm.2016.10.14
**View this article at:** http://dx.doi.org/10.21037/atm.2016.10.14

Many patients undergoing coronary artery bypass grafting or surgery for valvular disease either have pre-existent acute kidney injury (AKI) or are at risk for developing AKI. In addition, cardiac surgery exposes patients to various peri-operative renal "insults" such as the cardiopulmonary bypass (CPB) procedure itself ("post pump syndrome"), aortic cross-clamping time, excess transfusion, and high or prolonged catecholamine support. Major pathophysiological mechanisms that determine cardiac surgery-related AKI (CS-AKI) are systemic inflammation, ischemia-reperfusion injury, oxidative stress, metabolic distress, thrombo-embolic events, and neurohormonal activation (1). CS-AKI is a serious postoperative complication and affects more than 30% of patients. Preventive measures are limited and strive to maintain adequate renal perfusion, to limit duration of CPB exposure, and to avoid overloading the patient with high-chloride containing solutions (2). To date, no pharmacologic strategy has demonstrated clear efficacy in the prevention of CS-AKI.

Statins are amongst the most commonly prescribed drugs in cardiovascular disease prevention. Statins are of undisputed efficacy for treatment of hypercholesterolemia by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. However, statins also exert pleiotropic anti-inflammatory, antioxidant, and immunomodulatory effects which act in concert to improve endothelial function and to avert or attenuate systemic immune-inflammatory aggression (3). Moreover, statins are easy-to-use, inexpensive and relatively non-toxic. The largest meta-analysis to date, including 17 studies comparing 18,684 statin with 24,033 non-statin users suggested that statins reduced the occurrence and related mortality of CS-AKI (4). However, many of the included studies were prone to selection, publication, or ascertainment bias stressing the need for large-size randomized clinical trials (RCTs) to better define the role of statins in CS-AKI prevention.

Zheng *et al*. recently studied perioperative use of rosuvastatin versus placebo in 1922 cardiac surgery patients (5). Primary endpoint of the study was the incidence of atrial fibrillation (AF) and myocardial injury. Occurrence of CS-AKI was part of a panel of secondary study outcome endpoints. They found that statin therapy, despite significantly lowering low-density lipoprotein cholesterol and C-reactive protein, did not prevent postoperative AF or peri-operative myocardial injury but was associated with an increased incidence of AKI at 48 hours (24.7% *vs*. 19.3%; P=0.005), most of the cases being Kidney Disease Improving Global Outcome stage 1 and 2. Two other recent RCTs evaluated the renoprotective effect of high-dose atorvastatin versus placebo. Billings *et al*. randomly allocated 615 patients (199 statin-naive patients and 416 patients already on statin therapy) to receive 80 mg atorvastatin or matching placebo (6). Among all participants, AKI occurred in 20.8% in the atorvastatin and in 19.5% in the placebo group. However, statin-naive subjects, and particularly those with underlying chronic kidney disease, developed more AKI. Park *et al*. studied the effect of atorvastatin versus placebo on the incidence of AKI in 200 statin-naive patients undergoing elective valvular heart surgery (7). Despite better peroperative hemodynamics in the statin group, the incidence of AKI within 48 hours after surgery was similar between the statin and placebo group. (21% *vs*. 16%; P=0.40). Also, markers of kidney injury and inflammation were not influenced by statin treatment.

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Taken together, any renoprotective effect of statin therapy suggested by retrospective or observational studies could not be confirmed by these large prospective RCTs that were adequately powered (5,6), evaluated high statin doses (6,7), or clearly demonstrated an anti-inflammatory statin effect (5). The observed statin-related adverse effect on renal function, however, was unexpected and not explained. This fueled a hypothesis, recently put forward by Schetz and Oudemans-van Straaten, linking the lack of renoprotection to a statin-induced depletion of coenzyme Q10 (CoQ10, aka ubiquinone) (8). CoQ10 is a naturally occurring, lipid-soluble electron carrier which is essential for mitochondrial oxidative phosphorylation and production of adenosine triphosphate (9). Reduced CoQ10 may also protect cell membranes and circulating lipoproteins from oxidation. Blocking of CoQ10 synthesis by statins causes mitochondrial respiratory chain dysfunction and may limit energy production (10). This may lure the organism into a state of generalized bio-energetic failure which is increasingly thought to play a key role in the development of organ (11), including kidney (12), failure.

Rosenfeldt *et al*. studied the effect of a daily 300 mg dose of CoQ10 *vs*. placebo before cardiac surgery (13). CoQ10 supplementation improved mitochondrial function and enhanced myocardial tolerance to *in vitro* hypoxia-reoxygenation stress. A recent systematic review and meta-analysis showed that prophylactic CoQ10 therapy in patients undergoing cardiac surgery with CPB was safe and associated with less need for inotropic support and a lower incidence of ventricular but not atrial arrhythmias (14). Interestingly, patients with heart failure developed less AF when given continuous CoQ10 treatment (15).

In conclusion, despite being armed with an impressive "back catalogue" of pleiotropic beneficial effects beyond cholesterol lowering, statins are actually not advocated and probably should be discouraged for prevention of CS-AKI. The main culprit behind this failure might be statin-induced depletion of CoQ10 stores perturbing bio-energetic kidney homeostasis. High-quality RCTs are needed to clarify whether CoQ10 has a place in the prophylaxis of CS-AKI.

## Acknowledgements

None.

## Footnote

*Provenance:* This is a Guest Commentary commissioned by Section Editor Busheng Zhang, MD, PhD (Department of Cardiac Surgery, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China).
*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Comment on:* Zheng Z, Jayaram R, Jiang L, *et al*. Perioperative Rosuvastatin in Cardiac Surgery. N Engl J Med 2016;374:1744-53.

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**Cite this article as:** Honore PM, Jacobs R, Hendrckx I, Spapen HD. Statins barely touch the heart but bite the kidneys after cardiac surgery. Coenzyme Q10 deficiency in the dock? Ann Transl Med 2016;4(Suppl 1):S48. doi: 10.21037/atm.2016.10.14

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