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EDITORIAL

Statins do not prevent cardiac surgery-associated AKI: is ubiquinone the missing link?

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Statins have become one of the most commonly prescribed drugs worldwide in the prevention of cardiovascular disease. Most benefits are secondary to inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase) which lowers low-density lipoprotein cholesterol levels. However, statins also have cholesterol-independent, pleiotropic effects that occur within hours of initiation and include improved endothelial function, anti-apoptotic, anti-inflammatiory, antioxidant, antithrombotic, and immunomodulatory effects [1].

Cardiac surgery-associated acute kidney injury (AKI) is the second most common cause of AKI in critically ill patients. It is associated with poor short- and long-term outcome [2]. Attempts at pharmacologic prevention have been disappointing. Its pathogenesis is complex, but inflammation, oxidative stress, and endothelial dysfunction are pathogenic factors [2] that could, potentially, be mitigated by the pleiotropic effects of statins. Animal models of ischemia–reperfusion indeed show a beneficial effect of statins on kidney function [3]. In patients receiving radiocontrast for coronary angiography and percutaneous coronary interventions, statins reduce the incidence of post-contrast AKI [4]. In the setting of cardiac surgery, observational trials found inconsistent results regarding the association between preoperative statin use and postoperative AKI [5, 6]. A Cochrane meta-analysis of small randomized controlled trials (RCTs), mostly with high risk of bias, could, however, not find a beneficial effect of statins on AKI after cardiac surgery [7]. This meta-analysis concludes that large high-quality trials are required.

In an article published in *Intensive Care Medicine*, Park et al. report an investigator-initiated double-blind randomized placebo-controlled trial evaluating the perioperative short-term use of high-dose atorvastatin in 200 statin-naïve patients scheduled for elective valvular heart surgery [8]. The choice for valvular surgery is motivated by the high prevalence of statin use in coronary artery bypass graft (CABG) patients and the possible rebound inflammatory response due to statin withdrawal [9]. Baseline characteristics and surgical procedures were well balanced. The primary endpoint, the incidence of AKI within the first 48 h according to the Acute Kidney Injury Network (AKIN) criteria, was not affected (21 % in the statin group and 26 % in the control group; $p = 0.404$). Only 6 % in both groups had AKI stage 2 or 3. In addition, more sensitive markers of kidney injury (creatinine, NGAL) and inflammation (IL-18, CRP), the secondary endpoints, were comparable between groups. Intraoperative vasopressor requirement was lower in the statin group, but this did not reflect in clinical benefit. There was no evidence for toxicity in terms of creatinine kinase (CK > 5000 U) [8].

Two other recent RCTs evaluated the renoprotective effect of statins in elective cardiac surgery [10, 11]. The first RCT randomized 199 statin-naïve patients and 416 patients already taking statins before surgery to a short course of high-dose atorvastatin or placebo. Statin treatment was resumed on day 2 in those taking statins before surgery. AKI occurred in 20.8 % in the atorvastatin group versus 19.5 % in the placebo group. The trial was stopped early because of futility. The statin-naïve arm was stopped even earlier by the safety monitoring board because of a higher incidence of AKI with statins (21.6

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versus 13.4 %), a difference that became significant in the statin-naïve group with chronic kidney disease (52.9 versus 15.8 %; $p = 0.03$). In addition, the statin-naïve subgroup showed a significantly higher postoperative increase of serum creatinine with atorvastatin ($p = 0.007$) [10]. In the second RCT the primary endpoint was the incidence of atrial fibrillation, with AKI being only a secondary endpoint. This trial included 1955 patients and found an increased incidence of AKI (24.7 versus 19.3 %) with rosuvastatin, despite a decrease of CRP as marker of inflammation [11].

The trial by Park et al. was well executed with trial registration, adequate randomization, allocation concealment, blinding, intention-to-treat analysis, complete follow-up, and use of objective endpoints. However, the sample size calculation assumed a higher baseline incidence resulting in the loss of power. Although the authors included AKIN urine output criteria, none of the patients reached these criteria because of an institutional protocol including the administration of diuretics in fluid-unresponsive oliguria. Other limitations include the single-center nature, the short follow-up (48 h for kidney function and 6 h for NGAL and IL-18), and the inclusion of elective surgery patients only.

The absence of an effect of statins on the incidence of postoperative AKI may have several explanations. First, the Park study may have lacked power. However, more sensitive markers of kidney injury were not affected and the results are confirmed by the other recent RCTs. Second, the absence of kidney protection could be related to the absence of an anti-inflammatory effect. However, the Zheng trial found a reduction of postoperative CRP while the incidence of AKI was increased [11]. Third, insufficient dosing is implausible because doses of atorvastatin of 20 mg or more are considered high. Alternatively, the dose may have caused too high serum levels because of interactions with cytochrome P450 3A4 inhibitors which delay statin breakdown [12]. However, hepatic or muscular toxicity was not found.

Finally, the lack of renoprotective effect may be related to statin-induced depletion of ubiquinone (also known as coenzyme Q_{10}) and subsequent mitochondrial dysfunction [13]. Ubiquinone is an electron carrier in the mitochondrial respiratory chain which generates ATP. Low ubiquinone concentrations may limit energy production (see Fig. 1). The ubiquinone effect might explain the discrepant results of statins in different forms of AKI: protection in contrast-induced AKI [4], lack of effect or

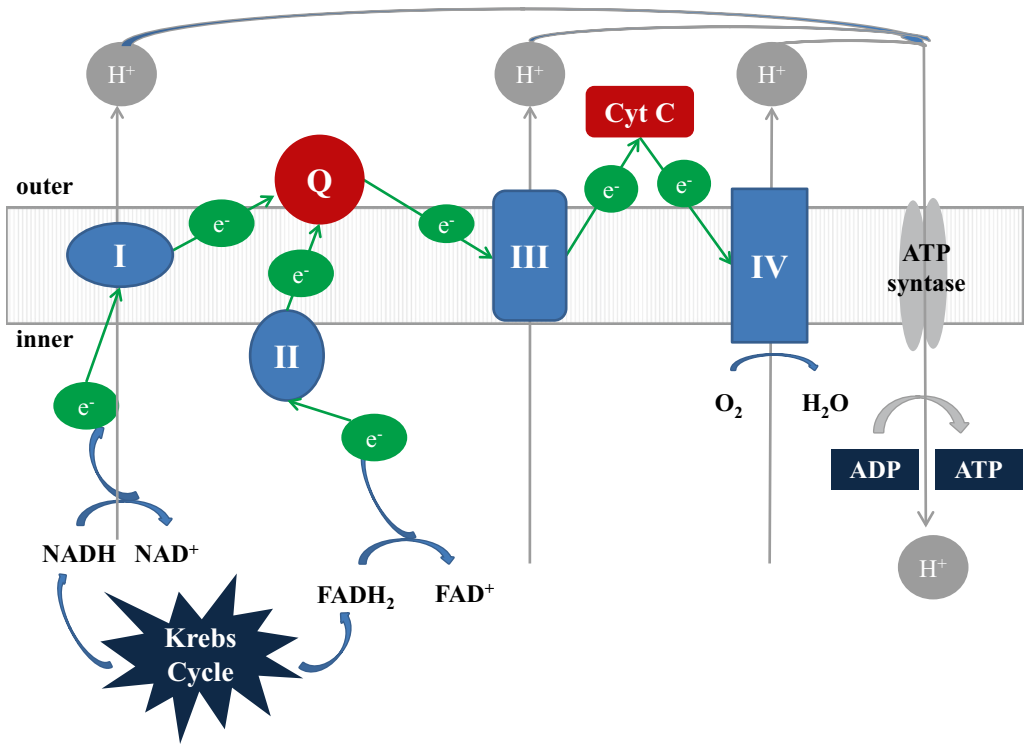

Fig. 1 The respiratory chain, which transfers electrons (e^-) via redox reactions coupled to the transfer of protons (H^+) across the mitochondrial membrane creating an electrochemical gradient that is finally used by ATP synthase to produce energy in the form of ATP. Complex I accepts electrons from the Krebs cycle and passes them to coenzyme Q (ubiquinone), which also receives electrons from complex II. Electrons are subsequently passed to complex III, cytochrome C (Cyt C), and complex IV, which uses the electrons and hydrogen ions to reduce molecular oxygen to water

possible harm in cardiac surgery-induced AKI [8, 10, 11], and possible toxicity as manifested by fewer days of renal and hepatic failure in patients with sepsis-induced ARDS [14]. Contrary to post-contrast AKI, cardiac surgery- and sepsis-induced AKI might be associated with more ischemia/reperfusion and associated mitochondrial damage, leading to bioenergetic failure, an emerging explanation for multiple organ dysfunction and AKI [15].

Statins may augment this bioenergetic failure [13]. This does not necessarily lead to high CK concentrations, the common signal for statin toxicity. The kidney may be more sensitive to bioenergetic failure after cardiac surgery than muscle. Furthermore, ubiquinone also has antioxidant properties and low concentrations diminish mitochondrial antioxidant protection. While the anti-inflammatory actions of statins may protect the kidney, their ubiquinone-lowering effects may decrease mitochondrial energy production and antioxidant protection, and may thereby be counterproductive [13]. High plasma concentrations due to critical illness- or medication-related inhibition of statin metabolism could enhance these effects.

In conclusion, contrary to protective effects on AKI after contrast administration, statins are not renoprotective after cardiac surgery. Signals of possible harm in studies after cardiac surgery and in sepsis-induced ARDS warrant further research on the ubiquinone-lowering effect of statins, which might aggravate an already compromised mitochondrial energy production.

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Compliance with ethical standards

Conflicts of interest
None.

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