Statins and the Kidney: Friend or Foe?

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Abstract
Statins essentially are cholesterol-lowering drugs that are extensively prescribed for primary and secondary prevention of cardiovascular disease. Compelling evidence suggests that the beneficial effects of statins may not only be due to controlling cholesterol levels but also due to a pleiotropic cholesterol-independent anti-inflammatory, antioxidant, and plaque-stabilizing activity. Along this line, statins may also exert acute and long-term effects on renal function. We present a narrative literature review that summarizes arguments in favour or against the preventive and/or therapeutic use of statins in kidney-related diseases or complications. We also highlight the ongoing controversy regarding statin therapy in chronic and end-stage kidney disease.

Introduction
Statins are 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors and constitute the first-line drug treatment if exercise and a low-fat diet fail to correct hypercholesterolaemia. In this manner, statins substantially contribute to reduce morbidity and mortality in patients at the highest risk of cardiovascular events [1]. All available statins have similar pharmacology, established efficacy in terms of a dose-dependent beneficial effect on plasma cholesterol concentrations, and a comparable range and severity of adverse events. Atorvastatin and rosuvastatin are drugs with high cholesterol-lowering efficacy as compared with lovastatin, simvastatin, pravastatin, and fluvastatin, which have less cholesterol-lowering potency.

Apart from an intrinsic cholesterol-lowering effect, statins also exhibit anti-inflammatory, antioxidant, and plaque-stabilizing capacities that act in concert to prevent other than cardiovascular damage [1, 2]. In particular, statins may affect the kidneys via cholesterol-related and -unrelated mechanisms resulting in potential acute and long-term benefit on renal function [2, 3].

We reviewed the literature on statin use for the prevention and treatment of various acute or chronic kidney-related disorders. Statins are highlighted as a novel therapeutic approach with reference to potential beneficial or harmful effects.
As part of secondary outcome endpoints, an increased incidence of AKI at 48 h (24.7 vs. 19.3%; \( p = 0.005 \)) was observed in the statin group, most of the cases being Kidney Disease Improving Global Outcome stages 1 and 2 [13]. Billings et al. [14] randomly allocated 615 patients (199 statin-naive patients and 416 patients already on statin therapy) to receive high-dose atorvastatin or matching placebo. 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 CKD, developed more AKI [14]. Finally, Park et al. [15] compared high-dose atorvastatin with placebo treatment in 200 statin-naive patients undergoing elective valvular heart surgery. Despite better preoperative hemodynamics in the statin group, no statin-related difference in the incidence of AKI within 48 h after surgery and no effect on markers of kidney injury and inflammation could be demonstrated [15]. Studies that assessed the effect of statin treatment on post-cardiac surgery AKI are summarized in Table 1.

### Prevention of AKI after Major Non-Cardiac Surgery

A retrospective analysis of the electronic records of 57,246 patients who underwent elective non-cardiac surgery failed to show that preoperative statin therapy in doses routinely used to treat hypercholesterolemia changed the incidence of AKI, postoperative dialysis, or hospital mortality [16]. Pan et al. [17] systematically re-

### Table 1. Statin treatment and post-cardiac surgery AKI

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Patients included, ( n )</th>
<th>Effect on AKI</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huffmyer et al. [5], 2009</td>
<td>Observational</td>
<td>1,557</td>
<td>Less need for RRT</td>
<td>Decreased</td>
</tr>
<tr>
<td>Virani et al. [8], 2010</td>
<td>Observational</td>
<td>3,001</td>
<td>Reduced AKI incidence</td>
<td>No effect</td>
</tr>
<tr>
<td>Argalious et al. [9], 2010</td>
<td>Observational</td>
<td>10,648</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Nemati and Astaneh [10], 2015</td>
<td>Observational</td>
<td>1,064</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Mithani et al. [11], 2011</td>
<td>Observational</td>
<td>2,104</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Wang et al. [12], 2015</td>
<td>Meta-analysis and meta-regression</td>
<td>59,777</td>
<td>Reduced AKI incidence</td>
<td>No effect</td>
</tr>
<tr>
<td>Zheng et al. [13], 2016</td>
<td>Randomized, placebo-controlled</td>
<td>1,922</td>
<td>Higher incidence of AKI</td>
<td>No effect</td>
</tr>
<tr>
<td>Billings et al. [14], 2016</td>
<td>Randomized, placebo-controlled</td>
<td>199</td>
<td>No difference in AKI but more AKI in statin-naive patients and CKD</td>
<td>No effect</td>
</tr>
<tr>
<td>Park et al. [15], 2016</td>
<td>Randomized, placebo-controlled</td>
<td>200</td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; RRT, renal replacement therapy; CKD, chronic kidney disease.

Statins open to speculation [4, 5]. Statins probably act by inhibiting postoperative inflammatory processes [3]. Compared with statin-naive subjects, patients taking statins indeed had reduced levels of circulating C-reactive protein, tumour necrosis factor alpha, myeloperoxidase, and pro-inflammatory interleukin (IL)-1, IL-6, and IL-8 and higher concentrations of the anti-inflammatory IL-10 [6]. In addition, many other factors such as concomitant disease (e.g. presence of sepsis), perioperative complications (e.g. shock), concomitant potential nephrotoxic medication, type of surgical intervention, and preexisting chronic kidney disease (CKD) must be considered. Cardiac surgery patients may react differently to the type and dose of the statin. For example, statins of high potency have been shown to increase the risk of AKI in a general patient population, whereas corresponding doses of these statins in cardiac surgery patients exhibited renal protective effects [7]. Observational studies on renal protection of preoperative statin use in cardiac surgery patients either demonstrated a decreased incidence of postoperative renal insufficiency [8] or reported no benefit [9–11]. A meta-analysis and meta-regression of almost 60,000 patients showed a 13% reduction of postoperative AKI in patients who received preoperative statin treatment [12]. Three randomized controlled trials (RCTs) recently reported the effects of statin treatment on kidney function in cardiac surgery patients. Zheng et al. [13] studied rosuvastatin vs. placebo in 1,922 patients.
viewed and analyzed all studies on the association between preoperative statin treatment and postoperative AKI in patients undergoing major surgery. When all studies are considered together, preoperative statin therapy was associated with a significant risk reduction for cumulative AKI and for AKI requiring renal replacement therapy. However, this protective effect was lost when restricting the analysis to RCTs only [13–15].

Prevention of Contrast-Induced Nephropathy
Exposure to iodinated contrast during coronary angiography and associated coronary interventions may cause acute and persistent worsening of kidney function and is associated with increased mortality. Advanced age, diabetes, congestive heart failure, CKD, hemodynamic instability, and type and volume of contrast may all precipitate the development of contrast-induced nephropathy (CIN) [18]. Previous research accentuated that initiating adequate intravenous hydration with iso-osmolar crystalloids and limiting the amount of low-osmolar and iso-osmolar contrast are crucial actions for preventing CIN. Several trials in various clinical conditions, including acute coronary syndromes, examined the effect of different types of statins, high- versus low-dose statins and loading versus chronic dosing of statins. In general, pre-treatment with statins decreased the occurrence of CIN as compared with placebo. Statin efficacy at preventing CIN was dose- but not product-dependent and higher in patients with acute coronary syndromes and underlying chronic heart or kidney disease. High doses of high-efficacy statins (40–60 mg atorvastatin) may be more effective [19]. Due to a paucity of controlled data, recommendations on duration or type of chronic statin pre-treatment cannot be made. A recent meta-analysis confirmed that short-term, pre-procedural, intensive statin treatment significantly reduced the incidence of CIN in patients with acute coronary syndromes undergoing coronary angiography and percutaneous coronary intervention [20].

Attenuation of the Cardiorenal Syndrome
Important bidirectional interactions exist between heart and kidney disease. Acute or chronic dysfunction of the heart or kidneys can induce acute or chronic dysfunction in the other organ [21]. For instance, patients with heart failure with a deteriorating glomerular filtration rate have higher mortality. Inversely, patients with CKD have an increased risk of heart failure, which is responsible for up to 50% mortality. This "vicious liaison" is known as the cardiorenal syndrome (CRS). Oxidative stress, endothelial dysfunction, and vascular inflammation are pathophysiological factors that are strongly related to the CRS. The pleiotropic effects of statins on cardiovascular processes, in particular their anti-inflammatory/antioxidant potential and capacity to improve nitric oxide bioavailability, support a benefit on the progression of chronic kidney and heart failure [22].

Reduction of Major Cardiovascular Events and Mortality in CKD
Cardiovascular disease is the most frequent cause of premature death in early stage CKD. A recent Cochrane review found that statin therapy consistently prevented major cardiovascular events and lowered mortality in patients with CKD not requiring dialysis and without cardiovascular disease at baseline [23]. Statin-related effects on stroke and progression of CKD were less evident [23]. However, high-efficacy statin therapy (atorvastatin 80 mg or rosuvastatin 20/40 mg) was associated with a significant decrease of the risk of stroke in patients with CKD [24]. Few trials reported data on individual adverse events leaving doubt on the safety of chronic statin treatment in CKD [25].

Preventing Aminoglycoside Toxicity
The pleiotropic properties of statins, though theoretically promising for preventing aminoglycoside toxicity, have only been explored in experimental settings. Ozek et al. [26] studied the effect of atorvastatin on gentamicin-induced nephrotoxicity in rats. Gentamycin infusion markedly reduced kidney function, increased oxidative stress, and was associated with tubular necrosis especially in the renal cortex. Renal function and tissue oxidative stress parameters normalized and tubular necrosis was attenuated in atorvastatin-treated animals. Atorvastatin reduced expressions of mitogen-activated protein kinase, nuclear factor kappa B, and inducible nitric oxide synthase confirming a statin-mediated anti-inflammatory and anti-oxidant activity. In a similar rodent model, simvastatin was found to improve gentamicin-induced changes in renal histopathology and function in a dose-dependent fashion [27].

Arguments Against Statin Use

Uncertain or Undesirable Effects on Kidney Function
A large retrospective cohort study comparing long-term statin users with a matched group of nonusers found an association between statin treatment and an increased
incidence of acute and chronic renal disease [28]. A recently published systematic review and meta-analysis including 143,888 adult patients showed that statins did not prevent AKI, modestly decreased proteinuria, and attenuated the decline in glomerular filtration rate only in adult patients not receiving dialysis [29]. Compared with low-efficacy drugs, treatment with high-efficacy statins has been associated with a 13% increased hazard for developing severe renal failure, which remained consistent across specific populations at risk (ischaemic heart disease, diabetes, and CKD) [30].

Increased Risk for Rhabdomyolysis in CKD
Statins are associated with skeletal muscle complaints, ranging from mild serum creatine kinase elevations and myalgia to severe muscle weakness, muscle cramps, myositis and rhabdomyolysis [31]. Among others, CKD is a common risk factor for the development of statin-induced myopathy. Patients with CKD may become more prone to this invalidating and potential life-threatening complication when other significant risk factors (e.g., advanced age, female gender, liver dysfunction, and diabetes mellitus) are accumulating.

One case report described acute rhabdomyolysis and purpura fulminans in a patient who had used pravastatin for 3 years and developed CKD [32]. However, the patient was highly aged and had received several hemodialysis sessions prior to presentation.

Induction of Tubulo-Interstitial Nephritis
Some case studies reported a link between statins and (sub)acute tubulo-interstitial nephritis [33, 34]. Nephritis was biopsy-proven, resolved after discontinuing statin treatment, responded to steroids, and relapsed after re-challenging the patient with a statin. A dose-dependent class effect was suggested but not proven. Statin-induced tubulo-interstitial nephritis is probably underreported because it evolves insidiously in patients who are prone to develop AKI for other reasons (e.g., comorbid conditions such as diabetes and arterial hypertension, concomitant nephrotoxic drug treatment, and so on).

Controversy Regarding Statin Use in CKD
The effects of statins in patients with CKD remain uncertain. In 2003, the Kidney Disease Outcomes Quality Initiative (KDOQI) dyslipidemia guidelines recommended statin therapy in all patients with CKD, irrespective of dialysis need, targeting low-density lipoprotein cholesterol (LDL-C) concentration below 100 mg/dL [35]. A sharp reduction in LDL-C with daily simvastatin plus ezetimibe safely reduced the incidence of major atherosclerotic events but did not slow 5-year kidney disease progression in a wide range of patients with advanced CKD [36]. Moreover, the high-efficacy statins atorvastatin [37] and rosuvastatin [38] substantially lowered LDL-C levels but had no statistically significant effect on cardiovascular death, non-fatal myocardial infarction, and stroke in patients with end-stage renal disease (ESRD; i.e., undergoing permanent hemodialysis). Several studies even observed an unexpected and counterintuitive inverse relationship between cholesterol levels and mortality in ESRD patients [39, 40]. Cardiovascular disease processes in ESRD patients may evolve differently from those in CKD subjects [41]. In fact, they may be primarily driven by oxidative stress, inflammation, and discrepancies between noxious and protective lipoprotein levels and additionally enhanced by hypertension and arrhythmias. Cholesterol lowering by statins in ESRD not only fails to show a benefit but also potentially exposes patients to statin-related side-effects [42, 43]. In a 2012 update of the KDOQI guidelines, recommendations were revised to lowering LDL-C in all patients with CKD except when dialysis was initiated [42]. Clinicians should decide on an individual patient basis whether or not to initiate statins in ESRD. A statin may be justified for secondary prevention of cardiovascular events, in patients with longer life expectancies, and in non-diabetics [42].

Conclusions
Large well-conducted RCTs did not demonstrate any benefit of pre- or perioperative statin treatment in patients undergoing various types of cardiac surgery. For unknown reasons, statins may even harm the kidneys in this particular patient population. A potential renal protective effect of preoperative statin therapy after major non-cardiac surgery is suggested by observational studies but not confirmed by RCTs. Statins arguably exert protective effects on the kidney in a general adult population and on the cardiovascular system in patients with CKD who do not require dialysis. Adjunctive therapy with statins can dose-dependently prevent CIN and attenuate the CRS. Whether statins affect stroke risk and progression of CKD is less evident. Statin-related rhabdomyolysis remains a matter of concern. High-efficacy agents may
harm the kidney in patients with vascular compromise and CKD. Also, statins are relatively contra-indicated in patients with ESRD.

Overall, statins are of undisputed efficacy for treatment of hypercholesterolemia and play a prominent role in primary and secondary prevention of cardiovascular disease. However, there is currently insufficient evidence to recommend the routine use of these agents for kidney protection.

References


Disclosure Statement

The authors declare to have no competing interests.

Authors’ Contributions

P.M.H. and H.D.S. designed the paper. All authors participated in drafting the manuscript. All authors have read and approved of the final version.