The Role of Statins in Chronic Kidney Disease

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Key Words

Statins • Renal function • Proteinuria • Cardiovascular disease • Chronic kidney disease

Abstract

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality not only amongst the general population, but also in patients with chronic kidney disease (CKD). Persons with CKD are much more likely to die of CVD than to experience kidney failure. Clinical trials have demonstrated that statins are gaining widespread acceptance as a principal therapy for the primary and secondary prevention of atherosclerosis and CVD. In CKD patients the role of statins in primary prevention of CVD remains to be clarified. The absolute benefit of treatment with a statin seems to be greater among nondialysis-dependent-CKD patients. Studies in end-stage renal disease patients on dialysis did not confirm these results. Recently, however, the Study of Heart and Renal Protection (SHARP) has suggested that statins with ezetimibe may be beneficial even in dialysis patients. Clinical studies with statins on proteinuria reduction and renal disease progression have yielded conflicting results. Some studies have shown a prominent reduction in proteinuria, while other studies have shown that statins had no effect or may cause

proteinuria at high doses. This review examines the clinical evidence of the observed benefits of kidney function with the use of this drug category in CKD patients.

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Lipid Abnormalities in Chronic Kidney Disease Patients

In patients with chronic kidney disease (CKD), the abnormalities seen in lipoprotein metabolism typically result in high triglycerides and low high-density lipoprotein cholesterol [1]. More likely to be compared to people with normal kidney function, they also have higher levels of apolipoprotein B and lower levels of apolipoprotein A₁ [2]. In particular, patients with nephrotic syndrome have elevated low-density lipoprotein cholesterol (LDL-C) levels. However, in the absence of nephrotic syndrome, patients with mild CKD tend to have normal LDL-C levels, decreased high-density lipoprotein cholesterol levels and elevated triglycerides. It is still uncertain whether dyslipidemia itself causes kidney disease progression or whether kidney impairment and proteinuria are responsible for both renal disease progression and dyslipidemia [3, 4]. A small series has provided evidence that these lipoprotein

abnormalities can contribute to the progression of kidney failure in CKD patients and have demonstrated an association between progression of renal disease and hyperlipidemia [5].

Statin-Associated Cardiovascular Disease Risk Benefit across the Stages of CKD

Statins and Nondialysis-Dependent CKD

Clinical trials have demonstrated that inhibitors of hydroxymethylglutaryl CoA reductase (statins) are gaining widespread acceptance as a principal therapy for the primary and secondary prevention of atherosclerosis and CVD [6–8]. The role of statins in primary prevention of CVD in CKD patients remains to be clarified. No large randomized clinical trial has provided evidence that statins as a primary prevention strategy reduce CVD in these patients. It has been suggested that these agents are effective and appear safe for secondary prevention of cardiovascular events in individuals with mild chronic renal insufficiency. Meta-analysis and post-hoc analyses have reported benefits of statins on all-cause and cardiovascular mortality in CKD patients [9, 10]. In a recent post-hoc analysis of the Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, atorvastatin therapy compared with usual care, reduced the relative risk of the first cardiovascular event by 28% in patients with CKD and 11% in patients without CKD [11]. The absolute benefit of treatment with a statin seems to be greater among individuals with nondialysis-dependent (NDD)-CKD [12]. In a meta-analysis including 25,017 participants with CKD not requiring dialysis from 26 randomized controlled trials, statins decreased both the risk of all-cause mortality and cardiovascular events, [RR 0.81 (95% CI: 0.74–0.89) and RR 0.80 (95% CI: 0.70–0.90), respectively] [13]. The effect of statins seems to be dose-related. Indeed, a subanalysis of the Treating to New Targets (TNT) study showed that compared with atorvastatin 10 mg, atorvastatin 80 mg reduced the relative risk of major cardiovascular events by 32% in patients with CKD and 15% in patients with normal estimated glomerular filtration rate (eGFR) [14].

Statins and Dialysis Patients

Clinical studies in end-stage renal disease (ESRD) patients on dialysis did not confirm these results [15]. In Die Deutsche Diabetes Dialyse (4D), a multicenter, randomized, double-blind, prospective study of 1,255 subjects with type 2 diabetes mellitus receiving maintenance he-

modialysis randomly assigned to receive 20 mg of atorvastatin per day or matching placebo for a median follow-up period of 4 years, atorvastatin yielded a nonsignificant 8% reduction in the prespecified primary outcome of cardiovascular death, nonfatal myocardial infarction and stroke [15]. Similarly, the AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) has shown no benefits of statin therapy compared to placebo. AURORA was a randomized, double-blind, prospective trial involving 2,776 patients, 50–80 years of age, who were undergoing maintenance hemodialysis. Patients were randomly assigned to receive rosuvastatin, 10 mg daily or placebo. During a median follow-up period of 3.8 years, rosuvastatin lowered LDL-C by 39 mg/dl (1.0 mmol/l), but yielded a nonsignificant 4% reduction in the primary outcome of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. There was also no significant effect on all-cause mortality. These results suggested a different pathogenetic mechanism in ESRD patients for the primary outcomes compared with mild or moderate CKD or normal kidney function [16]. Lowering LDL-C with statin therapy in patients with ESRD did not produce significant reductions in the primary outcomes in these studies. The pathophysiologic implication of the disease has not been completely elucidated. It has been suggested that the advanced atherosclerotic state in chronic dialysis patients and the increased percentage of sudden death due to arrhythmia plays a significant role and that it is a condition not modifiable by statins.

Recently, The Study of Heart and Renal Protection (SHARP) enrolled 9,270 patients with CKD of whom 3,023 patients were receiving maintenance dialysis at randomization, [2,527 (27%) hemodialysis and 496 (5%) peritoneal dialysis], with creatinine ≥ 1.7 mg/dl (150 μ mol/l) for men and 1.5 mg/dl (130 μ mol/l) for women. Patients had no history of myocardial infarction or coronary revascularization. Mean age was 62 years, 5,800 (63%) were male, 2,094 (23%) had diabetes mellitus and 1,393 (15%) had a history of vascular disease (angina, stroke or peripheral vascular disease). Mean systolic/diastolic blood pressure was 139/79 mm Hg. There were 6,347 NDD-CKD patients, with a mean eGFR of 26.6 ml/min/1.73 m². Among 5,574 of the NDD-CKD patients (89%), 1,107 (20%) had an albumin-to-creatinine ratio lower than 30 mg/g, 2,108 (38%) had an albumin-to-creatinine ratio 30–300 mg/g and 2,359 (42%) had an albumin-to-creatinine ratio higher than 300 mg/g. Patients were randomized in a ratio of 4:4:1 to ezetimibe 10 mg plus simvastatin

20 mg daily versus matching placebo versus simvastatin 20 mg daily (with the latter arm re-randomized at 1 year to ezetimibe 10 mg plus simvastatin 20 mg daily vs. placebo).

The key outcome was the major atherosclerotic events, defined as the combination of myocardial infarction, coronary death, ischemic stroke or any revascularization procedure. Subsidiary outcomes were major vascular events (cardiac death, myocardial infarction, any stroke or any revascularization) and components of major atherosclerotic events. The main renal outcomes were ESRD, dialysis or transplantation. The final results of the study showed that after a median follow-up of 4.9 years, patients randomized to an ezetimibe/simvastatin (10/20 mg) combination experienced a 17% reduction in major atherosclerotic events compared with the placebo group [RR 0.83 (0.74–0.94); long rank $p = 0.0021$]. Mean LDL-C reductions were 32 mg/dl between treatment groups.

This study showed that a two thirds compliance with ezetimibe/simvastatin reduced the risk of major atherosclerotic events by 17%, which was consistent with a meta-analysis of previous statin trials, while full compliance would reduce the risk of major atherosclerotic events by one quarter, thus avoiding 30–40 events per 1,000 treated for 5 years. In subgroup analyses, the evidence that the proportional effects on major atherosclerotic events differed between patients on dialysis and NDD-CKD patients was not good ($\chi^2 = 1.3$, $p = 0.25$), and there were no trends towards smaller proportional reductions in NDD-CKD patients with lower eGFR (trend $\chi^2 = 0.38$, $p = 0.54$). One third of the patients in both arms progressed to dialysis or transplantation [17].

Such positive effects were not found in the aforementioned 4D and AURORA studies. This lack of benefit might be attributed to differences in the cause of cardiovascular death seen in the dialysis patients and smaller sample size, a matter which may be further explored. The lack of benefits in these two studies has been a matter of debate and should now be re-assessed. Overall, the results from SHARP study suggest that statins may be beneficial in a wide range of patients with CKD and even in dialysis patients.

Statin Therapy and Kidney Function

Statins and Proteinuria

The presence of proteinuria is an indicator of kidney disease with an increased probability of progressive kidney loss, and is associated with faster loss of GFR com-

pared with little or no proteinuria [18]. There is mounting evidence suggesting that proteinuria reduction slows CKD progression [18, 19].

The heightened recognition that statins may reduce proteinuria and may slow renal disease progression has been an area of growing interest and focus [20]. Clinical studies in this area have yielded conflicting results, and the role of the potential effects of statins in patients with kidney disease is less established. It is fairly well established that some studies have demonstrated a prominent reduction in proteinuria [21–23]. The reduction of proteinuria with statins is also evident in patients with normal blood pressure and microalbuminuria [24]. The most conclusive evidence of the beneficial effects of statins on proteinuria comes from post-hoc analyses and meta-analyses. In particular, a meta-analysis of 15 studies involving a total of 1,384 patients examined the proportional reduction in proteinuria with the use of statins. It was shown that statins reduced albuminuria and proteinuria in 13 of the 15 studies. In fact, the reduction of excretion was greater among studies with greater baseline albuminuria or proteinuria. More specifically, 440 patients with albuminuria ≥ 30 mg/day showed a 48% reduction of albuminuria relative to placebo [23]. Another meta-analysis of six randomized placebo control trials including 311 patients showed that compared to placebo, statins reduced proteinuria significantly (-0.73 g/24 h, CI: -0.95 to -0.52) [25].

In striking contrast, however, other studies have shown that statins had no effect on urinary albumin excretion [26] or (on the contrary) that high doses may cause proteinuria [27], suggesting that this may be due to reduced receptor-mediated endocytosis in proximal tubular cells [28]. A differential effect on proteinuria was also suggested, with different statins and a comparative postmarketing analysis showing differences in composite endpoints of proteinuria, nephropathy or renal failure with the use of various statins [29].

In concert with this, PLANET I (Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease) and PLANET II (Evaluation of Proteinuria and Renal Function in Non-Diabetic Patients with Progressive Renal Disease), two related randomized, double-blind, parallel-group, multinational, multicenter, phase IIb trials, evaluated the effects of atorvastatin 80 mg and rosuvastatin 10 and 40 mg on urinary protein excretion and kidney function from baseline to week 52 in hypercholesterolemic diabetic and nondiabetic patients, respectively. At baseline, patients had a urinary protein-to-creatinine ratio ≥ 500 and

Table 1. Statins and CKD progression

Study		Subjects in the study, n	Follow-up	Treatment	Outcome	Results
HPS [36]	retrospective analysis	5,963 patients with DM2	4–6 years	simvastatin 40 mg/day of placebo	rate of kidney function decline	GFR decline (5.9 vs. 6.9 ml/min; $p = 0.003$) in the simvastatin group vs. placebo
GREACE [32]	post-hoc subgroup analysis	1,600 patients with dyslipidemia and CHD	3 years	atorvastatin 10–80 mg/day or usual medical care	rate of kidney function decline	CrCl had a 12% increase in atorvastatin group ($p < 0.0001$); CrCl had a 5.2% decrease in patients not treated with statins ($p < 0.0001$); CrCl had a 4.9% increase in the usual care group on various statins; HR 0.84 (CI: 0.73–0.95; $p = 0.003$) with every 5% increase in CrCl
ALLIANCE [54]	post-hoc subgroup analysis	2,442 patients with dyslipidemia	4 years	atorvastatin 10–80 mg/day or usual medical care	rate of kidney function decline	CrCl did not change in the atorvastatin group ($p < 0.0001$) vs. baseline; CrCl declined by 4.4% in the usual care group ($p = 0.0001$ vs. baseline)
CARE [33]	post-hoc subgroup analysis	3,402 CKD patients with or at risk for CVD	5 years	pravastatin 40 mg/day vs. placebo	change in eGFR	in patients with GFR of 30–59.9 ml/min per 1.73 m ² , pravastatin reduced the adjusted rate of kidney function loss by approximately 34%; the absolute reduction in the rate of loss was small (0.22 ml/min per 1.73 m ² /year; 95% CI: 0.07–0.37)
CARE [35]	post-hoc subgroup analysis	3,384 individuals, of whom 690 (20.4%) had eGFR <60 ml/min per 1.73 m ²	4 years	pravastatin 40 mg/day vs. placebo	change in eGFR	the decline in the pravastatin group vs. placebo group was NS (0.1 ml/min per 1.73 m ² /year slower; 95% CI: –0.2 to 0.4; $p = 0.49$); in patients with eGFR <40 ml/min per 1.73 m ² /year, the rate of change in the pravastatin vs. placebo group was 2.5 ml/min per 1.73 m ² /year slower (95% CI: 1.4–3.6; $p = 0.0001$)
TNT [55]	post-hoc subgroup analysis	9,656 participants with CHD	59.5 months	atorvastatin 10 vs. 80 mg	change in eGFR	mean change in eGFR showed an increase of 3.5 ± 0.14 ml/min per 1.73 m ² with atorvastatin 10 mg and 5.2 ± 0.14 ml/min per 1.73 m ² with atorvastatin 80 mg, respectively ($p < 0.0001$)
PREVEND-IT [26]	randomized controlled trial	of the 3,440 patients 469 used statins	4 years	pravastatin 40 mg/day or placebo or fosinopril or placebo (2 × 2 factorial)	change in eGFR	GFR fell in both statin users and nonusers (4.6 ± 13.5 and 2.4 ± 11.2 , respectively); statin treatment was not associated with a significant change in GFR with only modestly impaired GFR ($p = 0.11$)
ALLHAT-LLT [37]	post-hoc analyses	10,060 participants	4.8 years	pravastatin, 40 mg/day, or usual care	ESRD, change in eGFR	no significant differences were seen between: (1) groups for rates of ESRD (1.36 vs. 1.45/100 patient-years; $p = 0.9$) (2) composite endpoints of ESRD and 50 or 25% decrease in eGFR (3) rate of change in eGFR
SHARP [17]	randomized double blind trial	9,270 participants	4.9 years	ezetimibe 10 mg/day plus simvastatin 20 mg/day vs. matching placebo vs. simvastatin 20 mg/day	ESRD, major atherosclerotic events	17% reduction in major atherosclerotic events; no difference of progression to ESRD
Stripolli et al. [25]		11 studies, 548 patients		different statins	change in eGFR	statins did not improve eGFR [1.48 ml/min (0.02 ml/s), –2.32 to 5.28]

Table 1 (continued)

Study	Subjects in the study, n	Follow-up	Treatment	Outcome	Results
Sandhu et al. [34]	27 studies with 39,704 participants (21 with data for eGFR)		different statins	change in eGFR	in statin recipients the change in the weighted mean differences for eGFR was statistically significant (1.22 ml/min/year slower; 95% CI: 0.44–2.00); the benefit in studies with CVD patients was slower than control subjects (0.93 ml/min/year; 95% CI: 0.10–1.76) and statistically significant, but was NS for studies of participants with DM or HKD or GLN

HPS = Heart Protection Study; GREACE = Greek Atorvastatin and Coronary Heart Disease Evaluation; CARE = Cholesterol And Recurrent Events; PREVENT-IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; DM2 = diabetes mellitus; CHD = coronary heart disease; CrCl = creatinine clearance; HKD = hypertensive kidney disease; GLN = glomerulonephritis.

$\leq 5,000$ mg/g, fasting LDL-C ≥ 90 mg/dl (2.33 mmol/l) and were receiving current treatment with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers for a period ≥ 3 months prior to screening. PLANET I involved 353 patients with type 1 or 2 diabetes with a mean eGFR of 71.2 ml/min/1.73 m², and PLANET II involved 237 patients with a mean eGFR of 74.9 ml/min/1.73 m² at baseline [30]. For PLANET I, atorvastatin significantly reduced proteinuria by about 15%, whereas rosuvastatin had no significant effect on proteinuria. In PLANET II, atorvastatin reduced proteinuria by 23.8% ($p = 0.0056$). These results suggest that these two drugs may exert different effects in favor of atorvastatin and dispelled the idea of a statin class effect; however, this information remains to be clarified [31].

Statins and CKD Progression

A lot has been written about the effect of statins on kidney function decline. There are conflicting data concerning this effect on kidney disease progression in patients with mild-to-moderate kidney failure. The majority of these data also come from post-hoc analyses or from patients randomized for cardiovascular primary endpoint trials. These data suggest that statins slow the rate of renal function decline [24, 32–36]. However, other studies have shown no benefits [25, 26, 37] (table 1).

In a subanalysis of the LIVALO Effectiveness and Safety (LIVES) study, increased eGFR (+5.4 ml/min/1.73 m², $p < 0.001$) was also noted after 104 weeks of treatment with pitavastatin in 958 hypercholesterolemic patients with a baseline eGFR of < 60 ml/min/1.73 m² [38]. However, in a retrospective analysis of diabetic patients with moderate CKD, even though statins were associated

with a significant decrease in the rate of eGFR decline (-6.0 vs. -9.8 ml/min/1.73 m²/year, $p = 0.01$), only LDL-C, but no statins, were associated with ESRD progression after adjustment for the propensity score [39]. Concerning the secondary endpoint of progression to ESRD in SHARP, no difference was seen between groups. In fact, one third of the patients in both arms progressed to dialysis or transplantation [17].

Potential Mechanisms for Observed Benefits

There are potential explanations for the putative effects of statins on the rate of kidney disease progression and proteinuria. Statins may exert their protection on kidney disease through a variety of immunomodulatory effects. Statin therapy attenuates endothelial dysfunction [40], enhances renal perfusion and reduces abnormal permeability to plasma proteins [40]. It has been suggested that statins may reduce blood pressure [41]. A meta-analysis showed that this effect is small [42], but also exists. In general, the higher the baseline blood pressure, the greater the effect of statins on blood pressure [42]. Although small, blood pressure reductions following statin treatment are possibly clinically relevant [43–45]. Many investigators wondered if all these are the results of better kidney perfusion as a response to an improved endothelial and cardiac function and/or decreased exposure to the risk of acute renal failure from all the coronary revascularization procedures [46].

Safety and Tolerability Considerations for Statins in CKD

It has become increasingly clear that the side effect profile of statins is similar to that of placebo [25]. The use of high doses of statins has been largely demonstrated to be safe and well tolerated [47]. Statins can cause an elevation of liver function enzymes in a dose-related manner. The totality of the data supports a 0.5–3% occurrence of persistent elevations in aminotransferases in patients receiving statins. The question debated is whether this increase reflects true hepatotoxicity, and has been a source of concern. However, the actual risk appears to be very small. In a recent post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study, it was shown that the frequency of liver-related adverse effects during statin treatment is low (1.1%) in CVD patients and does not differ from rates reported in patients not treated with statins [48]. Another important side effect, although relatively uncommon, is myopathy. It happens especially when statins are used in high doses [49]. SHARP recently showed that there was no increase in the risk of myopathy, liver and biliary disorders, cancer, or nonvascular mortality. Pravastatin and fluvastatin appear to have much less intrinsic muscle toxicity. The risk is substantially increased for most statins extensively metabolized by cytochrome P-450 3A4, such as lovastatin and simvastatin, and to a lesser extent to atorvastatin with concurrent therapy with drugs that interfere with CYP3A4. Predisposing factors include hypothyroidism and inflammatory myopathies, such as polymyositis and dermatomyositis [50, 51].

Statins are safe drugs in CKD patients. Statins with minimal kidney elimination should be preferred as GFR declines substantially. Atorvastatin seems to be the statin of choice in patients with CKD stages 4–5. Fluvastatin as well as other statins may also be used at more advanced stages of CKD after appropriate dose adjustments. In addition, statins also have a good side effect profile with respect to adverse events in dialysis and renal transplant recipients [52, 53]. Patients with diabetes mellitus and renal impairment should be monitored carefully because of increased risk of myopathy [49]. It is important to bear in mind that the liver function enzymes and creatinine kinase levels must be monitored and guidelines should be strictly followed.

Conclusions

The role of statins in primary prevention of CVD in CKD patients remains to be clarified. Meta-analysis and post-hoc analyses have reported benefits of statins on all-cause and cardiovascular mortality in CKD patients. It has been suggested that the absolute benefit of treatment with statins seems to be greater among individuals with NDD-CKD. Studies in ESRD patients on dialysis yielded conflicting results and such positive effects were not found in the 4D and AURORA studies. Results from SHARP suggest that statins may be beneficial even in dialysis patients. The available data and the evidence are inconclusive to answer the question if statins slow the kidney disease progression. It is premature to recommend statin therapy for renal protection alone. The use of high doses of statins in CKD patients has largely been demonstrated to be safe and well tolerated.

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