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Statins in Chronic Kidney Disease: When and When Not to Use Them

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Statins in Chronic Kidney Disease: When and When Not to Use Them

Introduction

Chronic kidney disease (CKD) is recognized as a major global health burden,[1] the prevalence of which is increasing in the United States and is estimated to be around 10% or more than 20 million people.[2] Numerous studies have demonstrated higher cardiovascular mortality in patients with CKD compared with the general population.[3-8] Patients with even moderate renal impairment are more likely to die from cardiovascular causes than to progress to end-stage renal disease (ESRD), also known as end-stage kidney disease (ESKD),[9,10] and patients with CKD have an increased risk of atherosclerosis and its complications.[9]

Several large meta-analyses have shown that by effectively reducing low-density lipoprotein cholesterol (LDL-C), statins reduce atherosclerotic cardiovascular events in the general population,[11-15] and it has been widely assumed that statins will be equally effective in reducing atherosclerotic cardiovascular events in patients with CKD. However, to date, most large prospective, clinical trials specifically in patients with various stages of CKD have failed to show a benefit for statins in reducing cardiovascular outcomes,[16-18] calling this hypothesis into question. The purpose of this communication is to review the evidence from clinical trials for the appropriate use of statins in patients with CKD.

Stages of CKD

CKD is traditionally staged using serum creatinine levels or estimated glomerular filtration rate (eGFR). However, the latest kidney disease management guidelines recommend that CKD be staged using a combination of eGFR and urinary albumin levels, recognizing the important role that proteinuria plays in the diagnosis and prognosis of CKD and its complications[19] (Figure 1).

In this scheme, 5 stages of eGFR (G1–G5) and 3 stages of albuminuria (A1–A3) are identified[19] (Figure 1). Stage G5 is commonly referred to as ESRD, which may require renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation).

Figure 1. Stages and Prognosis of Chronic Kidney Disease by GFR and Albuminuria[19]

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk of CKD outcomes (if no other markers of kidney disease, no CKD).
Yellow: moderately increased risk of CKD outcomes.
Orange: high risk of CKD outcomes.
Red: very high risk of CKD outcomes.

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GFR is estimated with the CKD Epidemiology Collaboration equation and standardized serum creatinine. Albuminuria is determined by one measurement of albumin:creatinine ratio.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

Nephrotic syndrome is defined as the presence of nephrotic-range proteinuria (total urine protein ≥3500 mg/day in adult patients), and is commonly associated with hypoalbuminemia, edema, and hyperlipidemia (especially cholesterol and high triglycerides [TGs]). Patients undergoing peritoneal dialysis may develop features of nephrotic syndrome as a result of protein loss in the peritoneal dialysate drainage.[20]

Pathophysiology of Atherosclerosis and Cardiovascular Disease in CKD

The association between CKD and cardiovascular disease (CVD) is highly complex. Traditional risk factors that increase the likelihood of cardiovascular events in the general population are often highly prevalent in patients with CKD, eg, hypertension, diabetes, and obesity. In addition, nontraditional risk factors, including oxidative stress, systemic inflammation, anemia, albuminuria, and abnormalities in bone and mineral metabolism, contribute to accelerated CVD in patients with CKD.[21,22] There is increasing evidence that the pathology, manifestations, and complications of CVD in patients with CKD differ from those found in the general population.[23] In the general population, CVD most commonly manifests as obstructive coronary artery disease (CAD), whereas in CKD, it includes CAD, arteriosclerosis, cardiomyopathy, and sudden cardiac death from arrhythmia.[24]

Normal lipid metabolism is described in **Box 1**.[25,26] Oxidative stress contributes to CKD-associated dyslipidemia and plays a key role in the development of atherosclerosis and CVD in this population, as in the general population (**Figure 2**). Typical aberrations in lipid metabolism in CKD include accumulation of oxidation-prone and atherogenic intermediate-density lipoprotein (IDL), chylomicron remnants, and small, dense LDL (sdLDL), as well as hypertriglyceridemia and elevation of serum very-low-density lipoprotein (VLDL) levels.[25-27] Nephrotic syndrome is commonly associated with elevated LDL-C, including those undergoing peritoneal dialysis.[25] Oxidized IDL and sdLDL are avidly taken up by macrophages, involving a process that leads to the formation of foam cells and atherosclerotic plaques[25] (see **Box 1**). CKD simultaneously results in high-density lipoprotein (HDL) deficiency and dysfunction that is marked by the impairment of the HDL anti-oxidant, anti-inflammatory, and reverse cholesterol transport capacities.[25,26] These abnormalities produce a highly atherogenic profile, but this often occurs in the absence of elevated LDL-C.[25,26] In contrast, elevated LDL-C with high TGs can occur in nephrotic syndrome due to acquired hepatic LDL receptor deficiency, HDL docking receptor deficiency, and upregulation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase expression and activity.[28-30]

Abnormalities in lipid metabolism in CKD typically produce a highly atherogenic profile, but do not always result in elevated LDL-C.[25,26]

Box 1. Normal Lipid Metabolism

Lipoproteins consist of lipids and proteins (apolipoproteins) and have the function of transporting lipids in the plasma from sites of absorption or synthesis (gut and liver) to sites of utilization or processing.[25]

Lipoproteins are categorized based on their density: chylomicrons, VLDL, IDL, LDL, and HDL.[25]

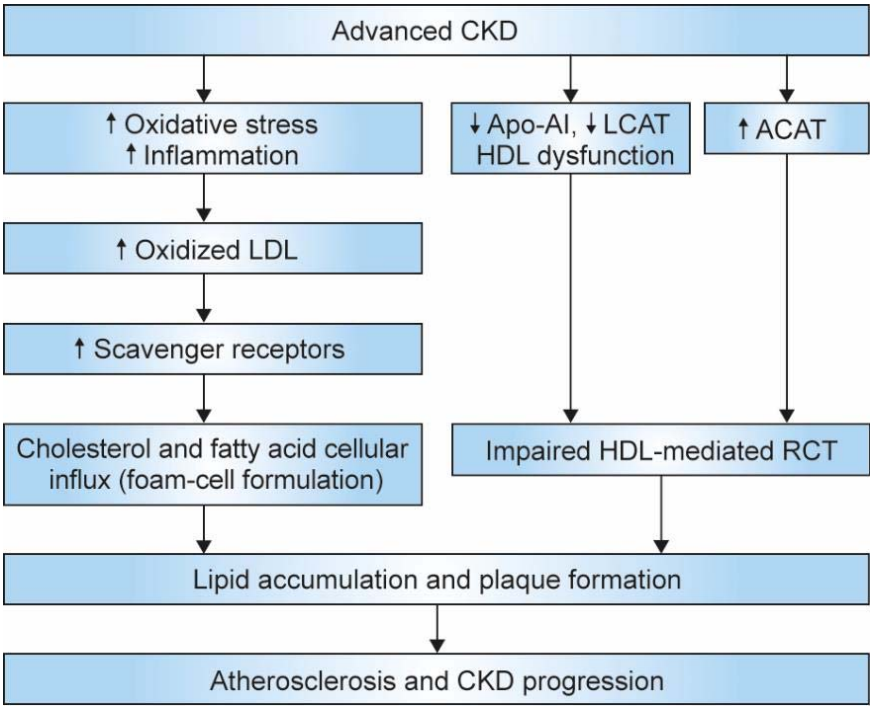
Chylomicrons are rich in TG and are metabolized by lipoprotein lipase to free fatty acids that are taken up by the tissues. The remaining chylomicron remnants are taken up by the liver via the LDL receptor and the LDL receptor–related protein.[25] Chylomicron remnants are highly prone to oxidization.[26]

VLDL is also TG-rich. After hydrolysis of TG by lipoprotein lipase, VLDL is reduced to IDL, which is taken up by the liver or further hydrolyzed into LDL. IDL is also prone to oxidization.[26]

LDL is the major transporter of cholesterol. In healthy individuals, approximately 60% to 80% of LDL is taken up by the LDL receptor, with the remainder removed by other receptors.[25] Oxidized LDL (which is highly inflammatory) is often taken up by scavenger receptors on macrophages and vascular smooth muscle cells. If macrophages become overloaded, for example, in hypercholesterolemia, they transform into foam cells, which contribute toward formation of atherosclerotic plaques.[25]

In healthy individuals, HDL mitigates foam cell formation by preventing or reversing lipid peroxidization via antioxidant enzymes (including paraoxonase 1 and glutathione peroxidase), preventing cholesterol influx into macrophages, and limiting monocyte adhesion and infiltration in the artery wall.[26] In addition, it is involved in reverse transport of cholesterol from the peripheral cells back to the liver, relieving the peripheral cells of cholesterol burden.[25,26]

Figure 2. Pathogenesis of Atherosclerosis in CKD[26]



Abbreviations: ACAT, acyl-coenzyme A acyltransferase; Apo-AI, apolipoprotein AI; CKD, chronic kidney disease; HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; RCT, reverse cholesterol transport.

It should also be noted that the pattern of dyslipidemia is not uniform across the different stages of CKD[25,27,30,31] (Table 1). Elevated TG levels are a feature common to all CKD stages.[25] During the earlier stages of CKD, which are commonly accompanied by proteinuria, LDL-C levels are typically elevated and HDL cholesterol (HDL-C) levels are low.[25] However, in the majority of patients who are maintained on hemodialysis, total cholesterol (TC), LDL-C, and non-HDL-C are within or below the normal limits (Table 1). In contrast, TC and LDL-C levels are generally elevated in most patients receiving peritoneal dialysis.[25] Therefore, different stages of CKD and renal replacement modalities are associated with different lipid profiles that can influence the suitability of statin treatment, as described in the following section.

Table 1. Lipid Profile at Various Stages of CKD[25]

Parameter	NDD CKD 1–5	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis
TC	↑↑↑	↑↑	↔↓	↑
LDL-C	↑↑↑	↑↑	↔↓	↑
HDL-C	↓	↓	↓	↓
Non-HDL-C	↑↑↑	↑↑	↔↓	↑
LDL-C	↑↑↑	↑↑	↑	↑

Explanation of arrows: Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with nonuremic individuals; increasing (↑↑↑) and decreasing (↓↓↓) plasma levels with decreasing GFR.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NDD, non-dialysis dependent; TC, total cholesterol; TG, triglyceride.

Dyslipidemia (elevated LDL-C, non-HDL-C, and TG, and low HDL-C) is not the only contributor to atherosclerosis and CVD in patients with CKD. In addition to affecting lipoprotein metabolism, oxidative stress and inflammation result in endothelial injury and dysfunction, leukocyte activation, adhesion, and infiltration in the artery wall, and development of myocardial dysfunction and fibrosis[26] (Figure 2).

Statins in CKD: Cardiovascular Outcomes

Nondialysis Dependent Patients

The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) randomized 864 nondialysis dependent (NDD) patients with microalbuminuria but no other indication for primary cardiovascular prevention to pravastatin 40 mg or placebo (another cohort received fosinopril)[32] (Table 2). The primary inclusion criteria were persistent microalbuminuria (urinary albumin concentration >10 mg/L in one early-morning spot urine sample and 15–300 mg/24 hours in two 24-hour urine samples at least once),

blood pressure <160/100 mm Hg and no use of antihypertensive medication, TC <309 mg/dL (or <193 mg/dL if previous myocardial infarction), and no use of lipid-lowering medication. Serum creatinine at baseline in the pravastatin group was 1.03 mg/dL and the mean age was 52 years. LDL-C in the pravastatin group was 159±39 mg/dL at baseline and 120±35 mg/dL at 4 years, compared with 155±39 mg/dL at baseline and 151±35 at 4 years in the placebo group (*P* <.05 for pravastatin vs placebo at 4 years). The incidence of the primary endpoint (cardiovascular mortality and hospitalization) was low in both the pravastatin (4.8%) and placebo (5.6%) groups, corresponding to a nonsignificant 13% reduction with pravastatin. Because the event rate was lower than expected, the study proved to be underpowered to demonstrate statistically significant differences in the primary endpoint.

The Study of Heart and Renal Protection (SHARP) was a randomized double-blind trial that investigated the effect of simvastatin 20 mg plus ezetimibe 10 mg versus matching placebo on atherosclerotic events in 9270 patients with CKD and no known history of myocardial infarction or coronary revascularization, including 6247 patients not on dialysis[18] (Table 2). The remaining 3023 patients received dialysis and these patients are discussed in the following section. The mean baseline LDL-C level was slightly higher in those patients not receiving dialysis vs the total population (112 mg/dL [SD 35 mg/dL] vs 101 mg/dL [SD 35 mg/dL], respectively), but the mean eGFR was the same in those not receiving dialysis as in the total population (26.6 mL/min/1.73 m^2 [SD 13 mL/min/1.73 m^2]). In the total population, treatment with simvastatin plus ezetimibe reduced LDL-C by 33 mg/dL and produced a 17% proportional reduction in major atherosclerotic events (the primary prespecified outcome) compared with placebo (*P* = .021).

Dialysis Dependent Patients

Three large, randomized studies (the Die Deutsche Diabetes Dialyse [4D] [4-year follow-up]; A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events [AURORA] [3.2-year follow-up]; and SHARP [5-year follow-up]), have evaluated cardiovascular outcomes in patients undergoing hemodialysis receiving statins (with or without ezetimibe) vs matching placebo[16-18] (Table 2). Each trial had a composite primary endpoint including outcomes such as cardiovascular death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, and arterial revascularization procedure. As expected in a population of patients undergoing hemodialysis, baseline cholesterol levels were not high (mean LDL-C levels at baseline in these three studies were 125 mg/dL, 100 mg/dL, and 107 mg/dL, respectively). Despite reductions in LDL-C ranging from 39% to 43%, none of the studies identified a significant difference between treatment groups in the primary endpoints (Table 2). These results suggest that CVD in patients undergoing hemodialysis may differ from CVD in other patients.

In support of this explanation, a post-hoc analysis of all 1255 patients in the 4D trial found that treatment with atorvastatin resulted in a 31% reduction in the risk of cardiovascular events in the subgroup of patients (n=314) with elevated LDL-C (≥145 mg/dL)[33] (Table 2). This suggests that a subgroup of patients receiving hemodialysis who do have elevated LDL-C may benefit from statin therapy, and that the presence of elevated LDL-C, as opposed to the different stages of CKD or renal replacement modalities, determines the efficacy of statins in patients with CKD/ESRD.

To date, no studies have investigated cardiovascular outcomes in patients undergoing peritoneal dialysis. As mentioned previously, in contrast to patients receiving hemodialysis, elevated LDL-C, non-HDL-C, and TG levels, and low HDL-C levels are common in patients receiving peritoneal dialysis (Table 1). A retrospective study has demonstrated that statin therapy was associated with lower C-reactive protein levels, indicating an anti-inflammatory activity of statins in patients undergoing peritoneal dialysis.[34]

Patients with a Kidney Transplant

Elevated LDL-C (>100 mg/dL) is reported to occur in approximately 45% of post-transplant patients,[35] and is generally due to certain commonly used immunosuppressive medications, including calcineurin inhibitors such as cyclosporine-A and rapamycin (which can increase serum TG and cholesterol), and steroids (which raise TG levels). Therefore, transplant recipients who have elevated LDL-C may potentially benefit from statin therapy, although the potential for drug–drug interactions with immunosuppressive agents needs to be considered before use.

The Assessment of LEscol in Renal Transplantation (ALERT) study evaluated the effect of fluvastatin in renal transplant recipients. At the first analysis of the study (5-year follow-up), fluvastatin treatment was not associated with a significant reduction in cardiovascular outcomes compared with placebo.[36] However, in a 2-year extension study, fluvastatin produced a 21% reduction in the incidence of the primary endpoint of first occurrence of a major coronary event (cardiac death, nonfatal myocardial infarction, and cardiac intervention procedure)[37] (Table 2).

Subgroup Analyses of Cardiovascular Outcomes in Patients with CKD

Subgroup analyses of several cardiovascular outcome studies have also evaluated statin therapy in patients with CKD.[38-40] When considering these subgroup analyses, it is important to remember that the primary studies were not designed to specifically look at patients with CKD and that the definitions of CKD varied between the identified subgroups. Nevertheless, these studies demonstrated a reduction in cardiovascular event risk in patients with NDD early-stage CKD receiving statins (Table 2). This is not surprising, as most, but not all, patients with mild to moderate CKD have significant proteinuria, which typically leads to elevated cholesterol, TG, LDL, VLDL, and apolipoprotein (Apo) B levels, and low HDL-C and Apo A levels.[41]

Statins may reduce the risk of cardiovascular events in a subset of patients with NDD (mild to moderate) CKD and kidney transplant recipients who have elevated LDL-C.

Table 2. Statins in CKD: Cardiovascular Outcomes

Trial	Treatment	Baseline patient characteristics	Occurrence of cardiovascular event (primary endpoint)		
			Statin	Placebo	

					Difference (95% CI)
NDD Patients					
PREVEND IT[32]	Pravastatin 40 mg 4-year follow-up	n=864 Members of the general population of Groningen, the Netherlands with microalbuminuria; 2%–3% had diabetes and 2% –4% had prior cardiovascular event Serum creatinine: 1.02 mg/dL LDL-C: 159 mg/dL	4.8% of patients	5.6% of patients	Hazard ratio: 0.87 (0.49 –1.57), *P* = .649
Heart Protection Study subgroup analysis[38]	Simvastatin 40 mg 5-year follow-up	n=1329 of 20,536 Coronary disease, other occlusive arterial disease or diabetes Creatinine: ≥1.24 mg/dL for women and ≥1.47 mg/dL for men, but <2.26 mg/dL for both LDL-C: 131 mg/dL	28.2% of patients	39.2% of patients	*P* = not reported
CARE subgroup analysis[39]	Pravastatin 40 mg 5-year follow-up	n=1711 of 4159 Acute MI 3–20 months before randomization and TC <240 mg/dL Creatinine clearance: <75 mL/min LDL-C: 140 mg/dL	10.5% of patients	14.5% of patients	Hazard ratio: 0.72 (0.55 –0.95), ***P* = .02**
SHARP subgroup analysis[18]	Simvastatin 20 mg plus ezetimibe 10 mg 5-year follow-up	n=6247 of 9270 No known history of myocardial infarction or coronary revascularization Serum or plasma creatinine of at least 1.7 mg/dL in men or 1.5 mg/dL in women eGFR: 26.6 mL/min/1.73 m^2 LDL-C: 108 mg/dL	9.5% of patients	11.9% of patients	Risk ratio: 0.78 (0.67 –0.91); *P* = not reported

JUPITER subgroup analysis[40]	Rosuvastatin 20 mg 5-year follow-up	n=3267 of 17,802 No CVD; hsCRP ≥2 mg/L eGFR: 56 mL/min/1.73 m^2 LDL-C: 109 mg/dL	1.08 per 100 PY	1.95 per 100 PY	Hazard ratio: 0.55 (0.38 –0.82), ***P* = .002**
Dialysis Dependent Patients (ie, hemodialysis)					
4D[16]	Atorvastatin 20 mg 4-year follow-up	n=1255 LDL-C: 125 mg/dL Type 2 diabetes	37% of patients	38% of patients	Relative risk: 0.92 (0.77 –1.10), *P* = .37
AURORA[17]	Rosuvastatin 10 mg Mean follow-up: 3.2 years	n=2776 ESRD, hemodialysis or hemofiltration for ≥3 months LDL-C:100 mg/dL	9.2 events per 100 PY	9.5 events per 100 PY	Hazard ratio: 0.96 (0.84 –1.11), *P* = .59
SHARP[18]	Simvastatin 20 mg plus ezetimibe 10 mg 5-year follow-up	n=3023 of 9270 No known history of myocardial infarction or coronary revascularization Serum or plasma creatinine ≥1.7 mg/dL in men or 1.5 mg/dL in women, receiving dialysis or not eGFR: 26.6 mL/min/1.73 m^2 LDL-C: 108 mg/dL	15.2% of patients	15.9% of patients	Risk ratio: 0.95 (0.78 –1.15); *P* = not reported
Dialysis Dependent Patients with Elevated LDL-C					
4D post hoc analysis[33]	Atorvastatin 20 mg Mean follow-up: 4 years	n=1255 of 1255 LDL-C: 125 mg/dL Type 2 diabetes	–	–	Hazard ratio: 0.69 (0.48 –1.00) if LDL-C ≥145 mg/dL; ***P* = significant** (value not reported)
Patients with a Kidney Transplant					
ALERT[36]	Fluvastatin 40 –80 mg 5.1-year follow-up	n=2102 Stable graft function, TC 154–347 mg/dL; not receiving statin therapy Creatinine: 1.63 mg/dL	10.7% of patients	12.7% of patients	Risk ratio 0.83 (0.64–1.06); *P* = .139

		LDL-C: 160 mg/dL			
ALERT extension[37]	Fluvastatin 40 –80 mg 6.7-year follow-up	n=2102 Stable graft function, TC 154–347 mg/dL; not receiving statin therapy Creatinine: 1.63 mg/dL LDL-C: 160 mg/dL	13.0% of patients	16.5% of patients	Risk ratio: 0.79 (0.63 –0.99), ***P* = .036**

Abbreviations: 4D, Die Deutsche Diabetes Dialyse; ALERT, The Assessment of LEscol in Renal Transplantation; AURORA, A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events; CARE, Cardiac Angiography in Renally Impaired Patients; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; NDD, non-dialysis dependent; PREVEND IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PY, patient-years; SHARP, Study of Heart and Renal Protection; TC, total cholesterol.

To convert serum creatinine values from mg/dL to µmol/L, multiply by 88.4.

Statins in CKD: Renal Parameters

Data on the effect of statin therapy on renal parameters in patients with CKD also vary (Table 3).

Table 3. Statins in CKD: Renal Parameters

Trial	Treatment	Baseline patient characteristics	Outcome
Meta-Analyses – Mixed Renal Disease			
Fried (2001)[43]	Gemfibrozil Fluvastatin Lovastatin Pravastatin Probucol Simvastatin +/- pravastatin	n=362 12 studies GFR: 64–119 mL/min LDL-C: NR	Change from baseline in eGFR: 0.156 mL/min (***P* = .008**)
Sandhu (2006)[44]	Atorvastatin Cerivastatin Fluvastatin Lovastatin Pravastatin Simvastatin	n=39,704 27 studies GFR: 50–99 mL/min Proteinuria: 0.98–6.70 g/day Albuminuria: 0.01–0.75 g/day TC: 198–397 mg/dL	Change from baseline in eGFR: 1.22 mL/min/year (***P* = .002**) Change from baseline in proteinuria: -0.37 g/24h (*P* = NS) Change from baseline in albuminuria: -0.02 g/24h (*P* = NS)
Douglas (2006)[45]	Atorvastatin Cerivastatin Fluvastatin Lovastatin Pravastatin Simvastatin	n=1384 15 studies LDL-C: 121–228 mg/dL Albuminuria/proteinuria: 0.22–5.92 g/day	Change from baseline in proteinuria: <30 mg/dL: 2% (*P* = .27) 30–300 mg/dL: -48% (*P* = .64) >300 mg/dL: -47% (***P* = .02**)
Strippoli (2008)[46]	Atorvastatin	n=30,144	Change from baseline in protein excretion (pre-dialysis): -0.73

	Cerivastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	50 trials GFR: 30–99 mL/min/1.73 m^2 TC: 143–315 mg/dL	g/day (***P* = significant, value not reported)** Change from baseline in creatinine clearance: 1.48 mL/min (*P* = NS)
Randomized Studies – NDD Patients			
SHARP[18]	Simvastatin 20 mg plus ezetimibe 10 mg 5-year follow-up	n=6247 of 9270 Serum or plasma creatinine ≥1.7 mg/dL in men or 1.5 mg/dL in women, receiving dialysis or not eGFR: 26.6 mL/min/1.73 m^2 LDL-C: 108 mg/dL	ESRD: RR 0.97 (*P* = .41) ESRD or death: RR 0.97 (*P* = .34) ESRD or doubling of baseline creatinine: RR 0.93 (***P* = .09**)
PLANET I[47]	Atorvastatin 80 mg Rosuvastatin 10 mg Rosuvastatin 40 mg 1-year follow-up	n=325 eGFR:68.8–72.6 mL/min/1.73 m^2 LDL-C: 150–156 mg/dL Diabetics with proteinuria	Change from baseline in U_{PCR} Atorvastatin 80 mg: 0.87 (***P* = .033**) Rosuvastatin 10 mg: 1.02 (*P* = .83) Rosuvastatin 40 mg: 0.96 (*P* = .53) Change from baseline in eGFR Atorvastatin 80 mg: -1.61 mL/min/1.73 m^2 (*P* = .21) Rosuvastatin 10 mg: -3.7 mL/min/1.73 m^2 (***P* = .0002**) Rosuvastatin 40 mg: -7.29 mL/min/1.73 m^2 (***P* = .0098**)
PLANET II[47]	Atorvastatin 80 mg Rosuvastatin 10 mg Rosuvastatin 40 mg 1-year follow-up	n=220 eGFR: 71.5–78.3 mL/min/1.73 m^2 LDL-C: 162–167 mg/dL Nondiabetics with proteinuria	Change from baseline in U_{PCR} Atorvastatin 80 mg: 0.76 (***P* = .0030**) Rosuvastatin 10 mg: 1.08 (*P* = .31) Rosuvastatin 40 mg: 0.94 (*P* = .62) Change from baseline in eGFR Atorvastatin 80 mg: -1.74 mL/min/1.73 m^2 (*P* = .28) Rosuvastatin 10 mg: -2.71 mL/min/1.73 m^2 (*P* = .10) Rosuvastatin 40 mg: -3.30 mL/min/1.73 m^2 (***P* = .019**)
Post-Hoc Analyses – Mixed Subjects			
ALLHAT-LLT[48]	Pravastatin 40mg 4.8-year follow-	n=10,060 of 10,355 eGFR: 78.6	ESRD or 25% decrease in eGFR: RR 0.95 (*P* = .3)

	up Hypertensive patients	mL/min/1.73 m^2 LDL-C: 146 mg/dL	
JUPITER[49]	Rosuvastatin 20 mg 2.3-year follow-up Apparently healthy adults	n=16,279 of 17,802 Creatinine: 1.01 mg/dL LDL-C: <130 mg/dL	Change from baseline at 1 year, rosuvastatin vs placebo Serum creatinine: 0.08 vs 0.09 (***P* = .001**) MDRD eGFR: -7.1 vs -7.7 (***P* = .0003**) CKD-EPI eGFR: -6.3 vs -6.9 (***P* = .0035**)
TNT[50]	Atorvastatin 10 or 80 mg 5-year follow-up CHD patients	n=9656 of 10,001 eGFR: 65–66 mL/min/1.73 m^2 LDL-C: 97–98 mg/dL	Change in eGFR: 10 mg: 3.5 mL/min/1.73 m^2 80 mg: 5.2 mL/min/1.73 m^2 ***P* < .0001** for between treatment groups

Abbreviations: ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid-Lowering Therapy; CHD, coronary heart disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; NDD, non-dialysis dependent; NR, not reported; NS, non-significant; PLANET, Prospective Evaluation of Proteinuria and Renal Function in Diabetic and Non-Diabetic Patients with Progressive Renal Disease; RR, relative risk; SHARP, Study of Heart and Renal Protection; TC, total cholesterol; TNT, Treating to New Targets; UPCR, urine protein:urine creatinine ratio

Meta-Analyses

Several meta-analyses have evaluated the effect of statins (predominantly low-intensity statins[42] such as fluvastatin, pravastatin, and simvastatin) on renal parameters. While some of the analyses showed that statins can reduce proteinuria, particularly in those with baseline proteinuria >30 mg/dL, others did not. The analyses also showed that statins may improve eGFR[43-46] (Table 3).

Prospective, Randomized Studies

Three studies published after the meta-analyses described above have also investigated the effect of statin therapy on renal disease (Table 3).

Cardiovascular outcomes from SHARP have already been discussed; however, this randomized, double-blind study also prospectively investigated the effect of simvastatin 20 mg plus ezetimibe treatment on renal disease progression.[18] The study found that in the group of patients with CKD but not on dialysis (baseline mean eGFR of 26.6 mL/min/1.73 m^2) (n=6247 of 9270), statin-ezetimibe combination treatment did not produce significant reductions in any of the prespecified measures of renal disease progression.

The effect of moderate- and high-intensity statins[42] on renal parameters has also been investigated. The Prospective Evaluation of Proteinuria and Renal Function in Diabetic and Non-Diabetic Patients with Progressive Renal Disease (PLANET I and PLANET II) double-blind, randomized, parallel-group studies were designed to assess change in proteinuria as a primary endpoint in patients with CKD and proteinuria receiving rosuvastatin 10 mg or 40 mg, or atorvastatin 80 mg.[47]

In PLANET I (n=325; 85.5% type 2 diabetes), atorvastatin 80 mg significantly lowered the urine protein:creatinine ratio at 52 weeks compared with baseline (*P* = .033). However, there were no differences in the changes from baseline in the urine protein:creatinine ratios in the rosuvastatin groups.[47] Results were similar for the 220 nondiabetic, proteinuric patients in PLANET II. Atorvastatin 80 mg significantly lowered the urine protein:creatinine ratio at 52 weeks (*P* =.030), whereas rosuvastatin 10 mg or 40 mg did not. For the secondary endpoint of change in eGFR at week 52 compared with baseline, eGFR levels in these diabetic patients with proteinuria (PLANET I) receiving atorvastatin remained stable, whereas those receiving rosuvastatin 10 mg and 40 mg had significant reductions in eGFR levels (*P* =.0098 and *P* =.0002, respectively). In the nondiabetic, proteinuric patients (PLANET II), eGFR levels remained stable with rosuvastatin 10 mg and atorvastatin 80 mg, but were significantly reduced with rosuvastatin 40 mg (*P* =.019).[47]

These 2 small trials highlight possible differences in the effects of different statins on proteinuria and eGFR.

Post-Hoc Analyses

Several post-hoc analyses of kidney disease outcomes in large cardiovascular outcomes trials have also been published (Table 3).

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid-Lowering Trial (ALLHAT-LLT) post-hoc analysis, 10,060 of 10,355 patients randomized to receive either pravastatin 40 mg or usual care were stratified by baseline eGFR (mean 78.6±19.0 mL/min/1.73 m^2) and the effect on kidney disease outcomes measured. The study found no significant differences in ESRD rates, regardless of baseline eGFR and despite significant reductions in cardiovascular outcomes.[48]

The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and the Treating to New Targets (TNT) trial post-hoc analyses both looked at the effect of moderate-to-high intensity statins[42] (rosuvastatin 20 mg and atorvastatin 10 mg or 80 mg, respectively) on renal parameters. In the JUPITER post-hoc analysis, 16,279 of 17,802 apparently healthy adults with high-

sensitivity C-reactive protein ≥2.0 mg/L and serum creatinine ≤2.0 mg/dL (baseline mean [SD] 1.01 [0.19]) received rosuvastatin
20 mg or placebo daily.[49] While reductions in eGFR levels were greater in those with higher baseline eGFR levels, the change in eGFR versus baseline was similar for rosuvastatin and placebo (Table 3).

However, in a post-hoc analysis of the Treating to New Targets (TNT) trial, 9656 of 10,001 patients with coronary heart disease, a baseline mean eGFR of approximately 65.0 mL/min/1.73 m^2, and treated with atorvastatin 10 mg or 80 mg showed significant increases in eGFR over 5 years.[50] It was also found that LDL-C was a predictor of eGFR response, with greater increases in eGFR with lower on-treatment LDL-C.

Finally, a retrospective analysis of 36 long-term studies from the rosuvastatin clinical trial program reviewed the effects of rosuvastatin on the risk of developing renal impairment and/or failure in 40,600 patients from diverse populations. No differences were seen between study participants receiving rosuvastatin 10 to 40 mg, compared with placebo.[51]

Mechanism of Action and Adverse Effects of Statins

Cholesterol biosynthesis takes place via the mevalonate pathway, which can be blocked by statins through inhibition of the pathway's key enzyme, HMG-CoA reductase. By limiting biosynthesis of essential products of the mevalonate pathway, such as arnesyl pyrophosphate and geranylgeranyl pyrophosphate which are essential for regulation of cell growth and gene transcription as well as transport of newly synthesized proteins between endoplasmic reticulum and Golgi apparatus, indiscriminate use of statins can cause mitochondrial dysfunction, disruptions of intra-cellular traffic, signal transduction, gene transcription, and production of structural proteins.[52] These unintended actions may be responsible for the recognized adverse effects of statins, such as myopathy and liver injury, which have been attributed to statin-induced mitochondrial dysfunction.[53]

Many patients with CKD already have mitochondrial dysfunction (there is a close association between mitochondrial dysfunction and CKD progression),[54] as well as neuropathy, myopathy, type 2 diabetes, and insulin resistance, and so may be more vulnerable to the adverse effects of statins. Therefore, it is most important to assess the appropriate use of statins in these patients.

The results of the PLANET I study, in which eGFR declined in diabetic, proteinuric patients receiving rosuvastatin, raise the question about whether to use this drug in diabetic, proteinuric patients with CKD,[47] and it has been suggested that the high concentration of rosuvastatin and its metabolites in the kidney may increase proteinuria and worsen renal function, especially at high doses.[30] Caution is needed when interpreting the results from PLANET I as the trial lacked a placebo control arm. Statin treatment has been shown to decrease insulin sensitivity and reduce insulin secretion, thereby significantly increasing the risk of type 2 diabetes.[55] Caution should be used in prescribing these drugs in patients with CKD, the majority of whom have either type 2 diabetes or elevated plasma glucose (prediabetes) that can be exacerbated by statin use.[2] Therefore, it is important that statins be used only in those patients with elevated cholesterol, and then at the appropriate dose for the individual patient[56-59] (Table 4).

Table 4. Dose Adjustments of Statins for Patients with Renal Disease

Statin	Recommended daily dose in adults with normal kidney function	Recommended dose adjustments in patients with renal disease
Atorvastatin[56]	Starting dose: 10 mg Maximum dose: 80 mg	No modification required
Pravastatin[57]	10–40 mg	**Moderate or severe**: recommended starting dose is 10 mg daily. The dosage should be adjusted according to the response of lipid parameters and under medical supervision
Rosuvastatin[58]	Starting dose: 5 or 10 mg Maximum dose: 40 mg	***Mild to moderate***: no dose adjustment is necessary ***Moderate***: recommended start dose is 5 mg. A 40 mg dose is contraindicated ***Severe***: contraindicated
Simvastatin[59]	5–80 mg	***Moderate***: no modification required ***Severe***: doses >10 mg should be carefully considered, and implemented cautiously

Statins should only be used in those patients with elevated cholesterol, and then at the appropriate dose for the individual patient.

Conclusions and Recommendations

Patients with even moderate CKD are at an increased risk of CVD mortality, with an increased risk of atherosclerosis and its complications. Statins have consistently been shown to reduce LDL-C in patients with CKD. However, their effect on cardiovascular outcomes is not as clear. In NDD patients across various stages of CKD, several subgroup and post hoc studies suggest a reduction in cardiovascular event risk with statin therapy, especially in those with elevated LDL-C. Patients undergoing hemodialysis generally do not have elevated LDL-C, and although statins reduce LDL-C levels in this group, they do not appear to improve cardiovascular outcomes. However, in those patients on hemodialysis who do have elevated LDL-C levels, statin therapy has been shown to reduce both LDL-C levels and cardiovascular events. Nevertheless, statins should be used with caution in this group.

The ability of statins to improve renal parameters in individuals with CKD is still under debate. NDD, early-stage CKD patients, kidney transplant patients, and patients receiving peritoneal dialysis treated with statins have all reported reductions in proteinuria and kidney function preservation. Therefore, statin use can be considered in the subset of these patient groups with elevated LDL-C, particularly in those with nephrotic proteinuria. However, statin use should be very cautiously considered in individuals with CKD and normal LDL-C levels regardless of the stage of CKD, and particular attention should be given to the unique risk factors of the particular individual.[42,60]

Many patients with CKD have mitochondrial dysfunction, neuropathy, myopathy, type 2 diabetes, and insulin resistance, which may increase the risk of adverse effects with statins.[54] It should also be noted that statin treatment has been shown to decrease insulin sensitivity and reduce insulin secretion, thereby significantly increasing the risk of type 2 diabetes.[55] It is, therefore, particularly important to avoid indiscriminate use of statins in patients with CKD and to use statins with caution in patients with pre-existing type 2 diabetes or prediabetes.

Taken together, the presence of elevated LDL-C, as opposed to the different stages of CKD or renal replacement modalities, should dictate the use of statins in patients with CKD and ESRD. Statins that are minimally metabolized by the kidneys may be preferable (see **Table 4**), and dose modification starting with the recommended licensed dose and titrating based on an individual's response and adverse events should be considered.

In general, statins should be given only to patients with hypercholesterolemia, in whom they have been proven to reduce LDL-C and cardiovascular outcomes. An individualized approach should be taken toward statin therapy in patients with CKD, with the benefits and risks carefully weighed.

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