Chapter 11
Statins in Chronic Kidney Disease

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List of Abbreviations

4D	Die Deutsche Diabetes Dialyse Studie
ALERT	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
CKD	Chronic Kidney Disease
CPK	Creatine Phosphokinase
CUA	Calcific Uremic Arteriopathy
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
IDL	Intermediate Density Lipoprotein
KDIGO	Kidney Disease Improving Global Outcomes
LDL	Low Density Lipoprotein
Lp(a)	Lipoprotein a
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
PTH	Parathyroid Hormone
RR	Risk Ratio
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
SHARP	Study of Heart and Renal Protection
TG	Triglycerides
UK-Harp-II	Second United Kingdom Heart and Renal Protection
VLDL	Very Low Density Lipoprotein

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H. Yassine (ed.), *Lipid Management,* DOI 10.1007/978-3-319-11161-2_11

Introduction

Cardiovascular disease is the leading cause of death in the chronic kidney disease population which is by itself a heterogeneous population when it comes to cardiovascular risk. According to KDIGO guidelines [1], chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3months, with implications for health. It is classified into five stages based on glomerular Filtration rate (GFR) (Table 11.1).

CKD whether manifested by decreased GFR, proteinuria or both is an independent risk factor for CVD. Reduced GFR is associated with increased prevalence of left ventricular hypertrophy, coronary artery disease, diabetes mellitus, heart failure, more severe hypertension and dyslipidemia [2–5].It is an independent risk factor for CVD outcomes and all cause mortality in the high risk population (defined as those already having CVD, other vascular disease, or surrogates of CVD such as LVH or DM) [6, 7]; this risk is evident even with mild reduction in kidney function [8–10].

ESRD patients face a great risk of premature death. It is estimated that there is a 19–25% increased risk of death/year while on dialysis [11].The renal transplant population is a particular population with a unique set of risk factors. Mortality rates in kidney transplant recipients are higher than the general population but still less than age-matched patients on dialysis.

Most large studies that have assessed statins included people with mild stages of CKD (most had GFR >50 ml/min/1.73 m^2 or Creatinine <1.4 mg/dL) (Table 11.2). All of these studies have shown that statins reduce the risk of MI, stroke, cardiovascular mortality and all cause-mortality. It is not until 2005 when studies were conducted in the advanced stages of CKD and in the ESRD population (Table 11.3).

Epidemiology and Risk Factors of CVD in the CKD population

The CKD population shares the conventional risk factors for atherosclerotic disease including older age, hypertension, LVH, dyslipidemia, smoking, sedentary life style and Diabetes Mellitus. It also has its unique set of risk factors brought on by kidney failure itself; these are divided into uremia specific risk factors including anemia,

Table 11.1 Stages of chronic kidney disease

Stage 1	Normal or increased GFR with signs of kidney damage*		≥90 ml/min/1.73 m^2
Stage 2	Mildly decreased GFR		89–60 ml/min/1.73 m^2
Stage 3	3a	Mildly to moderately decreased GFR	59–45 ml/min/1.73 m^2
	3b	Moderately to severely decreased GFR	44–30 ml/min/1.73 m^2
Stage 4	Severely decreased GFR		29–15 ml/min/1.73 m^2
Stage 5	Kidney failure		<15 ml/min/1.73 m^2

*Kidney damage includes abnormalities in urine sediment (hematuria, proteinuria, pyuria, casts...), renal pathology or imaging studies.

Table 11.2 RCTs Evaluating statins in the general population with CKD subgroups

Study	Year	Region	Statin	CKD (%)	Mean baseline eGFR (ml/min/m^2) or SCr (mg/dl)	Primary end point
CARE, LIPID, WOSCOPS	2005	International	Pravastatin	23.7	eGFR 57	CV mortality, CV events, or need for revascularization
LIPS	2005	International	Lovastatin	19.9	SCr 1.3	No data
PREVENT IT	2005	Netherlands	Pravastatin	10	SCr 1	CV mortality or morbidity
4S	2007	Scandinavia	Simvastatin	60.2	eGFR 65.2	All-cause mortality
ALLHAT	2008	International	Pravastatin	15	eGFR 50.8	No data
TNT	2008	International	Atorvastatin	32.2	I: eGFR 53 C:eGFR 52.8	Major CV event
ALLIANCE	2009	United States	Atorvastatin	23.7	eGFR 51.3	MACE
CARDS	2009	UK and Ireland	Atorvastatin	34.2	I: eGFR 53.5 C:eGFR 54.1	Cardiac events, revascularization, or stroke
MEGA	2009	Japan	Pravastatin	41.4	I: eGFR 52.6 C:eGFR 52.5	MACE
AFCAPS TexCAPS	2010	United States	Lovastatin	4.6	SCr 1.4	First Major CV event
JUPITER	2010	International	Rosuvastatin	18.37	eGFR 56	CV Mortality, CV events, revascularization, and stroke

4S Scandinavian Simvastatin Survival Study; *AFCAPS/TexCAPS* Air Force Coronary Atherosclerosis Prevention study/Texas Coronary Atherosclerosis Prevention Study; *ALLHAT* Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; *ALLIANCE* Aggressive Lipid-Lowering to Alleviate New Cardiovascular Endpoints; *C* comparator group; *CARDS* Collaborative Atorvastatin Diabetes Study; *CARE* Cholesterol and Recurrent Events; *CHF* congestive heart failure; *CKD* chronic kidney disease; *CrCl* creatinine clearance; *CV* cardiovascular; *CVD* cardiovascular disease; *e GFR* estimated glomerular filtration rate; *ESRD* end stage renal disease; *I* intervention group; *JUPITER* Justification for the Use of Statins in Primary Prevention: An intervention Trial Evaluating Rosuvastatin; *LDL* low-density lipoprotein; *LIPID* Long-term Intervention with Pravastatin in Ischemic Disease; *LIPS* Lescol Intervention Prevention Study; *MACE* major adverse cardiac event; *MEGA* Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; *PREVEND IT* Prevention of Renal and Vascular End-Stage Disease Intervention Trial; *SCr* serum creatinine; *TNT* Treating to New Targets; *UK* United Kingdom; *US* United States; *WOSCOPS* West of Scotland Coronary Prevention Study

Table 11.3 Major RCTs of lipid-lowering therapy in patients with CKD

Study (Reference)	Year	Region	Population	Intervention	Size	Mean age (Yr)
ALERT [39]	2003	Europe and Canada	Kidney transplant recipients	Fluvastatin	I: 1050 C:1052	50
4D [40]	2005	Germany	HD recipients	Atorvastatin	I:619 C:636	66
UK-HARP-II [41]	2006	UK	Stage 3–5 CKD/HD and PD recipients	Simvastatin plus Ezetimibe	I:102 C:101	66
AURORA [42]	2009	Europe, Canada, Mexico, Brazil, Australia and South Korea	HD recipients	Rosuvastatin	I:1389 C:1384	64
SHARP [43]	2011	Europe, North America, Australia, New Zealand, China, Thailand and Malaysia	Stage 3–5 CKD/HD and PD recipients	Simvastatin plus Ezetimibe	I:4650 C:4620	62

ALERT Assessment of Lescol in Renal Transplantation; *4D* Die Deutsche Diabetes Dialyse Studie; *UK-Harp-II* Second United Kingdom Heart and Renal Protection; *AURORA* A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; *SHARP* Study of Heart and Renal Protection; *I* Intervention group; *C* Comparator group

phosphate retention, hyperparathyroidism, vascular calcification, hyperhomocysteinemia and volume overload and novel risk factors including: carbamylation of proteins, endothelial dysfunction, sympathetic activity, inflammation, oxidative stress and wasting.

Disordered Lipid Metabolism in Patients with Renal Failure

Based on animal studies, among the different lipoproteins, LDL is the one responsible for the pathogenesis of atherosclerotic plaques. LDL size seems to be an important factor with small dense LDL particles the most incriminated in the process.

Lipid Profile of the CKD Population

Patients with CKD tend to have increased Triglycerides (VLDL and IDL), apolipoprotein B and oxidized LDL, abnormalities in LDL particle size and decreased HDL

and apolipoprotein A1. People with CKD seem to have a more atherogenic lipid profile even in the absence of dyslipidemia.

People receiving renal replacement therapy in the form of hemodialysis are known to have high triglyceride, low HDL, and normal total Cholesterol and LDL levels [11]. This "normal" LDL level may not accurately represent the relative increase in the more atherogenic oxidized form. People receiving peritoneal dialysis seem to have a more dyslipidemic profile with increased LDL, TG and Lp(a) and decreased HDL. Lp(a) is clearly associated with coronary heart disease and in one meta-analysis, elevated Lp(a) increased the 10-year risk of a coronary event by 70% [12].

Role of Oxidized LDL

There are increased amounts of oxidized LDL in patients with kidney disease. The heme moieties in patients receiving hemodialysis and peritoneal dialysis increase the susceptibility to LDL oxidation [13]. Oxidized LDL enhances the expression of pro-inflammatory markers which may by themselves induce glomerular injury either to the vascular cells forming the capillary wall or to the mesangial cells forming the matrix.

Oxidized LDL enhances accumulation of LDL particles inside macrophages transforming them into foam cells. It was also shown to enhance macrophages motility and chemotactic activity. Foam cells can cause vascular injury through three mechanisms: direct toxic effect, inducing apoptosis and altering vascular homeostasis through interfering with Nitric Oxide pathway [13].

Oxidized LDL particles are strongly immunogenic. Antibody titers against oxidized LDL correlate with the severity of atherosclerosis and the rate of progression of the atherosclerotic plaques.

Disordered Mineral Metabolism in Patients with CKD Leading to Accelerated Atherosclerosis

Disordered mineral metabolism is a unique complication in patients with CKD. This complication accelerates with the progression of CKD and is especially manifested in end stage renal disease patients requiring renal replacement therapy.

As the GFR decreases, the ability of the kidney to excrete phosphorus decreases as well. This results in hyperphosphatemia which by itself exerts a positive feedback on the parathyroid gland to increase secretion of PTH which has a phosphaturic effect. Indeed, hyperparathyroidism is one of the earliest biomarkers of disturbed bone mineral metabolism in patients with CKD. It appears as early as stage 3 CKD.

The earlier rise in PTH is protective and aims to keep phosphorus within the normal range. Though PTH increases as early as stage 3 CKD, significant

hyperphosphatemia is not observed until stage 4 CKD. Hyperphosphatemia stimulates diffuse hyperplasia of the parathyroid gland (Secondary hyperparathyroidism). With worsening GFR and worsening hyperphosphatemia, the diffuse hyperplasia of the parathyroid gland transforms into monoclonal nodular hyperplasia which is responsible for autonomous unregulated increased PTH secretion (tertiary hyperparathyroidism).

As the renal failure continues to progress, the kidney loses its ability to activate 25-hydroxy vitamin D into its active form 1-25 di-hydroxy vitamin D. This usually becomes manifested at stage 4-5 CKD. Hyperparathyroidism in earlier stages of CKD helps to maintain calcium in the normal range as 1-25 di-hydroxy vitamin D level starts to decline.

Disordered mineral metabolism results in accelerated vascular calcification. This can be intimal and is usually seen in atherosclerosis or medial which is usually seen with diabetes mellitus and renal failure. These can only be differentiated based on biopsy.

Vascular calcification is an active process similar to bone resorption. Mesenchymal cells within the vessels acquire an osteoblastic phenotype and lay down hydroxy apatite matrix (similar to bone matrix) causing vascular calcifications. There is evidence that Phosphorus stimulates the change of mesenchymal cells into osteoblasts. This effect is concentration dependent and it has been shown in vitro studies with phosphorus concentration $\geq$6.2 mg/dl [14, 15]. In epidemiological studies, hyperphosphatemia even mild (4.5–5 mg/dl) has been associated with increased risk for non-fatal cardiovascular events, cardiovascular mortality and all cause mortality [16, 17]. The use of the phosphate binder sevelamer (Renagel©) has been shown to attenuate the progression of vascular calcification [18, 19]. It seems that calcium plays a synergistic effect inducing mineralization [15] while PTH is actually protective and inhibits vascular calcification. In ESRD population, vascular calcification leads to increased vascular stiffness and increased peripheral vascular resistance which subsequently leads to increased left ventricular mass index [20, 21].

Studies have also shown that ESRD population may have decreased levels of inhibitors of vascular calcifications namely Matrix G1a protein and Fetuin A [22, 23]. The data about vitamin D and vascular calcification is quite limited.

Disordered mineral metabolism leads to a unique complication known as calciphylaxis or calcific uremic arteriopathy (CUA). It is an ischemic vasculopathy that occurs primarily in the CKD and ESRD population. It mainly affects the skin leading to severe painful necrosis. The pathogenesis is not quite clear but has been attributed to high PTH levels, treatment with vitamin D analogues and calcium based phosphate binders, insufficient activation of inhibitors of calcification and hypercoagulable states [24].

Both coronary artery calcification and calcific uremic arteriopathy (CUA) are prototypes of arterial calcifications that are associated with disordered phosphate metabolism.

Proteinuria is a Risk Factor for Atherosclerosis in CKD

Microalbuminuria is an independent risk factor for CKD in diabetics [25, 26] and in non-diabetics [27–29]. Diabetics with proteinuria (>1 g/day) have increased coronary artery calcification scores as compared to age matched diabetics without proteinuria [30, 31]. People with nephrotic range proteinuria (>3.5 g/day) are at a particular risk for accelerated atherosclerosis [32]. This has been demonstrated in autopsies of children and young adults [33].

There are several explanations as to why albuminuria is a risk factor for atherosclerosis in CKD. It might denote a more damaged endothelium. It is sometimes preceded by nocturnal non-dipping pattern in blood pressure and it is associated with more inflammatory and hypercoagulable states [34, 35].

CVD in the Transplant Population

CVD is responsible for 35–50% of all-cause mortality in kidney transplant recipients [36, 37]. The transplant population shares the traditional risk factors for CVD and the non-traditional risk factors associated with low GFR. It also has its unique risk factors that are attributed to immunosuppression medications and episodes of rejection. Medications used for maintenance Immunosuppression are known to cause post-transplant DM (tacrolimus, cyclosporine, sirolimus, prednisone) and post -transplant dyslipidemia(sirolimus, cyclosporine, prednisone) [38].

Treatment of Dyslipidemia in CKD and ESRD

Lipid management starts with life style modifications including weight loss, smoking cessation and exercise. Few randomized controlled trials have evaluated the use of statins in CKD and ESRD patients (Table 11.3).

The SHARP Trial (Study of Heart and Renal Protection) was an international randomized double blinded trial conducted in 2011 and compared simvastatin 20 mg plus ezitimibe 10 mg daily versus a matching placebo [43]. It included CKD patients stage 3–5 and ESRD receiving renal replacement therapy. Two thirds of the study group was not receiving renal replacement therapy. One third was receiving either hemodialysis or peritoneal dialysis (Table 11.4). The mean GFR in both the treatment and the placebo groups was 26.6 ml/min/m^2 (Table 11.5).

The SHARP trial showed a 17% reduction in major atherosclerotic events in the treatment study groups (95% CI 16–26%; p value = 0.0021). The major reduction in LDL with Simvastatin and ezetimibe occurred in the 1st year.

Table 11.4 Subgroups of the CKD population in the SHARP study

	Study drug	Placebo
On dialysis	1533 (33%)	1490 (32%)
HD	1275 (27%)	1252 (27%)
PD	258 (6%)	238 (5%)
Not on dialysis	3117 (67%)	3130 (68%)

CKD Chronic Kidney Disease; *SHARP* Study of heart and renal protection; *HD* Hemodialysis; *PD* Peritoneal dialysis

Table 11.5 Subgroups of the CKD population not on dialysis in the SHARP study

GFR (ml/min/m^2)	Study drug	Placebo
Mean (SD)	26.6(12.9)	26.6(13.1)
>=60	1%	1%
30–60	37%	35%
15–29	41%	44%
<15	20%	20%

CKD Chronic Kidney Disease; *SHARP* Study of heart and renal protection

Upon subgroup analysis, the beneficial effect on major atherosclerotic events was statistically significant in the CKD group not receiving dialysis (RR 0.78 with a 95% CI of 0.67–0.91) but it was not statistically significant in the dialysis population (RR 0.9 with a 95%CI of 0.75–1.08). The SHARP trial did not show any beneficial effect on cause-specific and overall mortality. It also did not show any difference in cancer incidence, cancer mortality or side effects profile.

The AURORA Trial (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) was an international RCT done on patients with ESRD on hemodialysis [42]. The study included patients aged 50–80 years and examined the effect of rosuvastatin 10 mg versus placebo on major cardiovascular events (non-fatal MI, non-fatal stroke, death from cardiovascular events). In spite of showing a statistically significant 42.9% reduction in LDL level at 3 months, the AURORA trial failed to show a beneficial effect on dialysis patients receiving statins (RR 0.96 with a 95% CI of 0.84–1.11; *p* value 0.59).The study excluded people already receiving a statin.

The results of the AURORA study was consistent with the 4D study (Die Deutsche Diabetes Dialyse Studie) which also failed to show a significant reduction in composite primary cardiovascular endpoints in the Hemodialysis population with type 2 diabetes Mellitus in spite of 42% reduction in LDL levels [40].

In 2012, a group lead by Palmer conducted a meta-analysis to assess the benefits and harms of statin therapy in the CKD population including those receiving dialysis [44]. This meta-analysis concluded that there is a clear and significant beneficial effect for statins on the CKD population not receiving dialysis. This beneficial effect was in terms of all cause mortality, CV mortality, major cardiovascular events, fatal

and nonfatal MI and fatal and non-fatal stroke. It did not show any significant beneficial effect on the dialysis population [44]. Of note, subgroup analysis of the group receiving dialysis had an increased number of fatal or non-fatal strokes. The level of evidence was high for the CKD population not receiving dialysis, moderate for the dialysis population and low for Kidney transplant recipients. The lack of beneficial effect on the dialysis population might reflect the different epidemiology of cardiovascular death in that population with arrhythmia, sudden cardiac death and cardiomyopathy being more frequent causes of death than atherosclerotic heart disease. Statins were safe with no increase in side effects between the statin and the placebo groups.

The KDIGO guidelines recommend measuring a lipid profile in each patient with newly diagnosed CKD. Each Patient with stage 1–5 CKD aged above 50 years should be started on a statin regardless of his/her LDL level. Patients aged < 50 years of age should be addressed according to their cardiovascular risk rather than their absolute LDL value since the association between LDL and adverse outcomes is weak in the CKD population. LDL level per se is not enough to identify CKD patients with high risk for CVD. Some studies have shown that LDL level and the risk of MI decrease with reduction in GFR but these results are rather misleading. The lower LDL level with advanced CKD rather reflects the poor nutritional status imposed with worsening kidney function and doesn't correlate with cardiovascular risk. Besides, increased amounts of LDL in the CKD population occur in the oxidized more atherogenic form. The cardiovascular risk in the CKD population is worse with age and MI fatality is higher in the CKD population as compared to an age matched control.

In contrary to the general practice, there is no set target for LDL cholesterol in the CKD population and thus a follow up LDL cholesterol level is not indicated expect in instances where it will change treatment plans. These instances include change in RRT modality, concern about secondary causes of dyslipidemia or change in cardiovascular risk. A lipid profile might be helpful to determine compliance with treatment. Cardiovascular risk should be assessed yearly in the CKD population.

The CKD population is at a higher risk of medication-induced side effects; this is likely related to poly-pharmacy, decreased drug clearance and frequent co-morbidities. Therefore, lower doses are recommended for the CKD population. The recommended doses are those used in the major trials (Table 11.6). These doses are well tolerated and there is no statistically significant difference in adverse events including myalgias, elevation in CPK or increase in liver enzymes [45].

Table 11.6 Statins used in major trials

Trial	Statin	Dose
SHARP	Simvastatin + Ezitimibe	20 + 10 mg/day
4D	Atorvastatin	20 mg/day
AURORA	Rosuvastatin	10 mg/day
ALERT	Fluvastatin	10 mg/day

ALERT Assessment of Lescol in Renal Transplantation; *4D* Die Deutsche Diabetes Dialyse Studie; *AURORA* A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; *SHARP* Study of Heart and Renal Protection

There was a concern that rosuvastatin in doses >80 mg daily increases the risk of proteinuria. This dose is twice the dose approved by FDA for rosuvastatin and 8 times the dose used in the AURORA trial (10 mg/day). The proposed mechanism is by inhibition of tubular reabsorption of protein [46]. Whether statins decrease the rate of progression of CKD as well as proteinuria is still controversial.

Baseline transaminases levels should be obtained before commencing therapy. Baseline CPK level is not recommended in the CKD population. It should be checked if patients develop symptoms of myopathy. Concomitant fibrates carry higher risk of transaminitis and rhabdomyolysis in the CKD population and should be avoided. Statins are considered category X in Pregnancy and are not safe with breast feeding as well. They should not be given to patients with active liver disease or baseline transaminase level 3 times above normal limits.

Summary of KDIGO Clinical Practice Guidelines 2013 for Lipid Management in CKD[1]

Assessment of Lipid Status in Adults with CKD

1. In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) is recommended. (1C)
2. In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow up measurement of lipid profile is not required for the majority of patients. (Not Graded)

Pharmacological Cholesterol-Lowering Therapy in Adults

1. In adults aged ≥50 years with an eGFR <60 ml/min/1.73 m^2 but not treated with dialysis or kidney transplantation, treatment with a statin or a statin/ezetimibe combination is recommended. (1A)
2. In adults aged ≥50 years with an eGFR ≥60 ml/min/1.73 m^2, treatment with a statin is recommended. (1B)
3. In adults aged 18–49 years with CKD but not treated with chronic dialysis or Kidney transplantation, statin treatment is recommended in people with one or more of the following: (2A)
   - known coronary artery disease (myocardial infarction or coronary revascularization)
   - diabetes mellitus
   - Prior ischemic stroke
   - estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%

4. In adults with dialysis-dependent CKD, statins or statin/ezetimibe combination should not be initiated. (2A)
5. In adults already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, these agents can be continued. (2C)
6. In adult kidney transplant recipients, treatment with a statin is suggested. (2B)

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