Endotext

Dyslipidemia in Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is associated with a dyslipidemia comprising high triglycerides, low HDL-C, and altered lipoprotein composition. Cardiovascular diseases are the leading cause of mortality in CKD, especially in end stage renal disease patients. Thus, therapies to reduce cardiovascular risk are urgently needed in CKD. Robust clinical trial evidence has found that the use of statins in pre-end stage CKD patients, as well as in renal transplant recipients, can decrease cardiovascular events; however, providers need to be aware of dose restrictions for statin therapy in CKD subjects. Furthermore, statin therapy does not reduce cardiovascular events in dialysis patients, nor does statin therapy confer any protection against the progression of renal disease. Niacin and fibrates are effective in lipid lowering in CKD and appear to have some cardiovascular benefit, but further study is needed to clearly define their role. Novel therapies with PCSK 9 inhibitors, bempedoic acid, and inclisiran have all been shown to improve LDL-C levels but there is currently limited data for reduction of cardiovascular events or mortality in patients with CKD/ESRD. This article reviews the epidemiology of CKD, association of CKD with cardiovascular events, and the effects of CKD on lipid levels and metabolism. The chapter discusses clinical trial evidence for and against statin and non-statin lipid lowering therapy in CKD patients.

CKD EPIDEMIOLOGY

Chronic kidney disease (CKD) is defined as renal impairment for greater than 3 months duration that results in an estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m^2. CKD is classified into 5 stages based on the eGFR (Table 1) and albuminuria category (Table 2). CKD is a worldwide health problem with a rising incidence and prevalence. CKD, especially in the early stages, is often asymptomatic; thus, the actual prevalence may be even higher than estimated. End stage renal disease (ESRD) is defined as needing dialysis or transplant, and the prevalence and incidence of ESRD have doubled over the past 10 years (1). The annual mortality rate of dialysis patients is greater than 20%. The burden of co-morbidities and the cost of caring for CKD patients is high, and thus a major focus is increased screening and early detection of CKD when interventions to delay or prevent progression to ESRD may be effective. There are multiple causes of CKD with the most common causes in Westernized nations being hypertension and diabetes; however, a wide range of etiologies including infectious, auto-immune, genetic, obstructive, and ischemic injury are all prevalent.

Table 1. Stages of CKD Based on eGFR		
GFR category	**GFR (ml/min/1.73 m^2)**	**Terms**
G1	≥ 90	Normal or High
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

In the absence of evidence of kidney damage, neither G1 nor G2 fulfills the criteria for CKD.

Table 2. Stages of CKD based on Albuminuria			
CKD stage	**AER (mg/24h)**	**ACR (mg/mmol)**	**ACR (mg/g)**
A1	<30	<3	<30
A2	30-300	3-30	30-300
A3	>300	>30	>300

AER: albumin excretion rate; ACR: albumin to creatinine ratio.

While the burden of CKD itself is significant, the leading causes of morbidity and mortality in CKD are cardiovascular diseases (CVD), primarily atherosclerotic coronary artery disease. Risk factors for CVD in CKD include the traditional risk factors – dyslipidemia, hypertension, sex, age, smoking, and family history and CKD patients appear to benefit similar to non-CKD patients from therapies targeting these risk factors. Regardless of the cause of CKD, patients with CKD are at increased risk for CVD, which has led to the National Kidney Foundation classifying all patients with CKD as “highest risk” for CVD regardless of their levels of traditional CVD risk factors. Per the 2022 ACC consensus for non-statin therapies, CKD is considered an ASCVD risk enhancer (2). The focus of this chapter is on the dyslipidemia of CKD and the risk of CVD in CKD.

Nephrotic Syndrome

Nephrotic syndrome differs from other types of CKD in its presentation and risks. Nephrotic syndrome is comprised of significant proteinuria (typically > 3g/24h), hypoalbuminemia, peripheral (+/- central) edema, and significant hyperlipidemia and lipiduria may also be seen. It is frequently seen in children, and the etiology includes minimal change disease (up to 85%), focal segmental glomerulosclerosis (up to 15%) and secondary causes (rare) including systemic lupus erythrematosis, Henoch Schonlein Purpura, or membrano-proliferative glomerulopathy. In adults, the etiology is more likely to involve a systemic disease such as diabetes, amyloidosis, or lupus. Nephrotic syndrome may be transient or persistent. Most (approximately 80% of children) cases of nephrotic syndrome are successfully treated with glucocorticoids with resolution of all features including hyperlipidemia; however, steroid-resistant nephrotic syndrome patients often have persistent dyslipidemia, which may place them at increased risk for CVD. For example, a small study found increased CVD markers including pulse wave velocity, carotid artery intima-media thickness, and left ventricular mass in patients with steroid-resistant nephrotic syndrome compared to controls (3), implying increased risk for CVD events. Treatment of nephrotic syndrome dyslipidemia includes therapies specifically targeting the renal disease (primarily glucocorticoids, but also renin-angiotensin system antagonists which can help decrease proteinuria) and lipid lowering agents.

CVD IN CKD

CVD accounts for 40-50% of all deaths in ESRD patients, with CVD mortality rates approximately 15 times that seen in the general population (4). However, CVD is highly prevalent in patients who progress to ESRD implying that earlier stages of CKD increase the development of CVD. A number of factors have been proposed as risk factors for CVD in CKD including proteinuria, inflammation, anemia, malnutrition, oxidative stress, and uremic toxins (5). Ongoing research is investigating whether these (and other) markers may be therapeutic targets. Interestingly, proteinuria correlates with blood pressure, total cholesterol, TGs, and inversely correlates with HDL-C (6). Thus, it remains unclear if proteinuria itself is a risk factor (e.g. a *cause* of CVD) or a biomarker. Meta-analyses of the general population and high risk population cohorts found that both lower eGFR (<60 ml/min/1.73 m^2) and higher albuminuria (>10 mg/g creatinine) are predictors of total mortality and CVD mortality; furthermore, eGFR and albuminuria are independent of each other and of traditional CVD risk factors (7, 8). A meta-analysis that assessed individual participant data of over 22 million individuals from 64 global cohorts estimated the risk of myocardial infarction up to 6-fold higher for those with urine albumin/creatinine ratio over 300 mg/g and eGFR < 15 mL/min/1.73m^2; similar estimates were conducted for other CVD outcomes such as stroke, CVD mortality, heart failure and others (9). Estimated GFR > 60 ml/min/1.73 m^2 alone is not a risk factor for CVD or total mortality.

Dyslipidemia in CKD

EFFECT OF CKD ON LIPID LEVELS

CKD is associated with a dyslipidemia comprised of elevated TGs and low HDL-C. Levels of LDL-C (and thus, total cholesterol) are generally not elevated; however, proteinuria correlates with cholesterol and TGs. CKD leads to a down regulation of lipoprotein lipase and the LDL receptor, and increased TGs in CKD are due to delayed catabolism of TG rich lipoproteins, with no differences in production rate (10). CKD is associated with lower levels of apoA-I (due to decreased hepatic expression (11)) and higher apoB/apoA-I ratio. Decreased lecithin-cholesterol acyltransferase (LCAT) activity and increased cholesteryl ester transfer protein (CETP) activity contribute to decreased HDL-C levels. Beyond decreased HDL-C levels, the HDL in CKD is less effective in its anti-oxidative and anti-inflammatory functions [for review see (12)].

As CKD progresses the dyslipidemia often worsens. In an evaluation of 2001-2010 National Health and Nutrition Examination Survey (NHANES), the prevalence of dyslipidemia increased from 45.5% in CKD stage 1 (albuminuria with an eGFR ≥ 90 mL/min/1.73 m^2) to 67.8% in CKD stage 4 (eGFR 15-29 mL/min/1.73 m^2); similarly, the use of lipid lowering agents increased from 18.1% in CKD stage 1 to 44.7% in CKD stage 4 (13). Of more than 1000 hemodialysis patients studied only 20% had “normal” lipid levels (defined as LDL-C <130 mg/dl, HDL-C > 40 and TGs < 150); of 317 peritoneal dialysis patients only 15% had “normal” lipid levels (14). A larger study evaluating dyslipidemia in > 21,000 incident dialysis patients found 82% prevalence of dyslipidemia and suggested a threshold of non-HDL-C > 100 mg/dl (2.6mmol/L) to identify dyslipidemia in CKD stage 5 subjects (15). Peritoneal dialysis is associated with higher cholesterol levels than hemodialysis, although the reasons aren’t fully understood. In subjects who switched from peritoneal dialysis to hemodialysis there was a decrease in cholesterol levels of almost 20% following transition (16). The National Kidney Foundation recommends routine screening of all adults and adolescents with CKD using a standard fasting lipid profile (total cholesterol, LDL-C, HDL-C and TGs), and follows the classification of the National Cholesterol Education Panel for levels (desirable, borderline or high). Although some studies have found associations between Lp(a) and dialysis patients, this is not well defined and there is no current indication for routine screening of Lp(a).

EFFECT OF CKD ON LIPOPROTEIN COMPOSITION

Beyond simply measuring lipid levels, emerging evidence implies that lipoprotein particle size and composition is altered in CKD, with increased small dense LDL and decreased larger LDL particles in CKD subjects compared to controls (17). Small dense LDL is thought to be more atherogenic than larger LDL particles. An emerging theory is that beyond lipid levels or lipoprotein size, lipoprotein particle "cargo" can affect atherosclerosis development and progression. Lipoprotein particles transport numerous bioactive lipids, microRNAs, other small RNAs, proteins, hormones, etc. For example, a recent study compared LDL particle composition between subjects with stage 4/5 CKD and non-CKD controls, and found similar total lipid and cholesterol content, but altered content of various lipid subclasses, for example decreased phosphatidylcholines, sulfatides, and ceramides and increased N-acyltaurines (18). Many of these lipid species are known to have either pro- or anti-atherogenic properties and thus could directly affect atherogenesis.

EFFECT OF RENAL TRANSPLANTATION ON LIPID LEVELS

Dyslipidemia is frequently seen in renal transplant recipients, including increased total cholesterol, LDL-C, and TGs, and decreased HDL-C. The dyslipidemia may have existed pre-transplant or be related to transplantation associated factors. Cyclosporine increases LDL-C via both increased production and decreased clearance. Corticosteroids increase both cholesterol and TG levels in a dose-dependent manner. The adverse effects of cyclosporine and corticosteroids on lipid levels appear to be additive (19). Tacrolimus and azathioprine appear to have less induction of dyslipidemia than cyclosporine (20). Sirolimus increases both cholesterol and TGs, in part due to decreased LDL clearance (21).

EFFECT OF NEPHROTIC SYNDROME ON LIPID LEVELS

The dyslipidemia in nephrotic syndrome can be striking with significant elevations of cholesterol, LDL-C, TGs and lipoprotein(a); HDL-C is often low, especially HDL2. The cause of elevated lipid levels is multi-factorial, including reduction in oncotic pressure which stimulates hepatic apoB synthesis (although the exact mechanism by which this occurs is not known), decreased metabolism of lipoproteins, and decreased clearance. Patients with nephrotic syndrome have decreased LDL receptor activity and increased acyl-CoA cholesterol acytransferase (ACAT) and HMG-CoA reductase activity leading to increased LDL-C levels (22, 23). Low HDL-C is thought to be due at least in part to LCAT deficiency secondary to accelerated renal loss of LCAT (24). TGs are elevated due to impaired clearance of chylomicrons and TG-rich lipoproteins, as well as increased TG production (25).

EVIDENCE FOR/AGAINST LIPID LOWERING THERAPY IN CKD FOR CVD OUTCOMES

Given the high prevalence of CVD in CKD, and the robust clinical evidence in non-CKD subjects that lipid lowering reduces CVD outcomes, there is great interest in using lipid lowering therapy in CKD subjects. Statins are the most commonly used lipid-lowering medications and thus far have been shown to reduce CVD events and/or mortality in virtually every population studied. However, CKD patients seem to be a unique population in that at present there is no evidence of benefit for CVD outcomes in dialysis patients with statin therapy. The Canadian Journal of Cardiology lists CKD as a statin indicated condition in its newest guidelines published in 2021(26) while AHA/ACC lists CKD as a risk enhancer but not a high-risk condition based on 2018 guidelines (27). Despite growing evidence to support CKD as a CVD risk equivalent, the use of statin therapy in CKD does not appear to be rising more than in the non-CKD

population based on data from Mefford et al looking at trends in statin use amongst US adults with CKD from 1999-2014 (28). As discussed below it appears that statins can reduce CVD events in pre-end stage CKD subjects, and in post-renal transplant subjects, but not in dialysis patients (Table 3). The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 clinical practice guideline recommends using statin or statin/ezetimibe combination therapy for adults ≥ 50 years old with eGFR < 60 ml/min/1.73 m^2 (29). Additionally, they recommend that in adults aged18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, that statin treatment be used if the following risk factors are present; known coronary disease, diabetes, prior ischemic stroke, or estimated 10-year incidence of coronary death or nonfatal myocardial infarction >10%.

Use of Statins in Pre-ESRD CKD Patients

Although many of the initial statin CVD studies did not include many CKD patients, evidence from sub-group analyses of large statin studies suggested that CKD subjects had similar benefits to non-CKD individuals. For example, the Heart Protection Study (HPS) which assessed >20,000 subjects at high risk of CVD included a subgroup of 1,329 subjects with impaired kidney function. In this subgroup those that received simvastatin had a 28% proportional risk reduction and an 11% absolute risk reduction of a major cardiovascular event compared to those randomized to placebo, which was similar to the effect on the overall cohort (30). Further, in the Pravastatin Pooling Project, 4,991 subjects with CKD3 were examined and a 23% reduction in cardiovascular events was seen in the pravastatin group (31). In a retrospective study with 47,200 subjects followed through the Department of Veterans Affairs, starting statin therapy 12 months prior to transitioning to ESRD conferred a reduction in 12 month all-cause mortality (HR 0.79), cardiovascular events (HR 0.83) and hospitalization rate (HR 0.89) (32). Several other studies or meta-analyses similarly predicted that CKD subjects would have reduction in CVD with statin therapy. For example, a meta-analysis of 38 studies with >37,000 participants with CKD but not yet on dialysis found a consistent reduction in major cardiovascular events, all-cause mortality, cardiovascular death and myocardial infarction in statin users compared to placebo groups. There was no clear effect of statin on stroke, nor was there any effect of statin use on progression of the renal disease (33). Another meta-analysis similarly reported efficacy of statin therapy, but that the relative reductions in CVD evens with statin therapy declined with lower eGFR, to the point of no benefit in dialysis patients (34). Thus, CKD patients with pre-end stage renal disease statins effectively lower total cholesterol and LDL-C levels and decrease CVD risk. The different statins have different degrees of renal involvement in their metabolism, and providers should be aware of dose restrictions in CKD (Table 4).

Unclear Whether to Use Statins in Subjects with Nephrotic Syndrome

Several small clinical studies have investigated the use of lipid lowering therapies in nephrotic syndrome, but data is only available for statins and fibrates, and no CVD outcome data is available. Several small studies using statins have found efficacy in lowering LDL-C and that statins were safe and well tolerated (35, 36). Two recent small studies suggest that statin therapy in nephrotic syndrome may reduce CVD risk (37, 38). Thus, the use of statins in nephrotic syndrome appears to be safe and efficacious in terms of lipid lowering; however, it remains unclear if statins should be recommended for benefit on either CVD or renal outcomes.

Use of Statins in Subjects with only Microalbuminuria

The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) randomized 864 subjects with persistent microalbuminuria (urinary albumin of 15-300mg/24h x 2 samples) to fosinopril (an angiotensin converting enzyme inhibitor) or placebo and to pravastatin 20 mg or placebo. Inclusion

criteria for the study included blood pressure <160/100 mm Hg and no use of antihypertensive medications and total cholesterol < 300 mg/dl (8 mmol/L) or < 192 mg/dl (5 mmol/L) if patient had known CVD and no use of lipid lowering medications. Although diabetes was not an exclusion criteria, <3% of the subjects had diabetes (39). The use of statin did not affect either urinary albumin excretion or cardiovascular events; however, the use of fosinopril significantly decreased albuminuria and had a trend to reduce cardiovascular events. Thus, in the absence of other indications for statin therapy, this study suggests no benefit in subjects that solely have microalbuminuria; however the study was limited by small size and few CVD events. A subsequent analysis found that the subjects with isolated microalbuminuria had an increased risk for CVD events and mortality compared to those without risk factors (40); thus isolated microalbuminuria appears to indicate high risk and further study is needed to determine effective therapies to reduce risk.

No Benefit of Statins in Dialysis Patients

Studies specifically examining the role of statins in ESRD subjects have not found a benefit. The Deutsche Diabetes Dialyse Studie (4D) randomized 1255 type 2 diabetic subjects on maintenance hemodialysis to either 20 mg atorvastatin or placebo daily. The cholesterol and LDL-C reduction was similar to that seen in non-dialysis patients; however, unlike non-CKD subjects there was no significant reduction in cardiovascular death, nonfatal myocardial infarction, or stroke with atorvastatin compared to placebo (41). A long-term follow-up of the 4D study population found similar effects after 11.5 years as were found at the end of the original study: no CVD benefit, but also no evidence of harm (42). Similarly, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis (AURORA) randomized 2776 subjects on maintenance hemodialysis to rosuvastatin 10 mg or placebo. Again, the LDL-C lowering in dialysis patients was similar to that seen in other studies in non-dialysis patients, but there was no significant effect on the primary endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke (43). The Study of Heart and Renal Protection (SHARP) randomized 9270 CKD patients (3023 on dialysis) to simvastatin plus ezetimibe versus placebo. The SHARP study did report a significant reduction in major atherosclerotic events in the simvastatin plus ezetimibe group but was not powered to compare non-dialysis and dialysis patients (44). However, a meta-analysis of 25 studies involving 8289 dialysis patients found no benefit of statin therapy on major cardiovascular events, cardiovascular mortality, all-cause mortality, or myocardial infarction, despite efficacious lipid lowering (45). Nevertheless, a post-hoc analysis of the 4D study did demonstrate a benefit of statin therapy in the subgroup that had LDL-C > 145 mg/dl (3.76mmol/l) (46). Although the use of statins in dialysis patients does not clearly cause harm, at present there is no indication for use in dialysis patients, with the exception of a possible benefit in those with a significant elevation in LDL-C.

WHY IS STATIN THERAPY INEFFECTIVE IN DIALYSIS SUBJECTS?

Given the robust data demonstrating statin efficacy in CVD risk reduction in virtually all other populations studied, the lack of efficacy in ESRD subjects is perplexing. However, it may be due to different mechanisms of disease progression in ESRD populations compared to other populations. In ESRD subjects there is increased inflammation and oxidative stress as well as increased non-lipid-associated pro-atherogenic factors, which may be the major cause of atherosclerosis development or progression in CKD subjects [for review see (47)]. Therefore, the relative impact of dyslipidemia on CVD development and progression in ESRD subjects may be less than in other CKD and non-CKD subjects, and thus the potential benefit of lipid lowering therapy is reduced. In ESRD subjects with significant hyperlipidemia (such as genetic hyperlipidemias) there may still be a role for statins or other lipid lowering therapies. Furthermore, while no benefit has been found for statins in dialysis

subjects, there is no evidence of increased harm, and thus consideration of lipid lowering medications in particular individuals with ESRD is warranted.

Use of Statins in Renal Transplant Recipients

The Assessment of Lescol in Renal Transplant (ALERT) study randomized 2102 renal transplant recipients to fluvastatin or placebo. There was a non-significant 17% reduction in the combined primary endpoint (cardiac mortality, nonfatal myocardial infarction, or coronary intervention procedures) but a significant reduction in cardiac death or myocardial infarction (48, 49). Furthermore, a post hoc analysis suggested that earlier initiation of statins post-transplant was associated with greater benefit (50). A small study found no benefit of statin therapy on coronary calcification in renal transplant patients (51) albeit coronary calcium scores are not a good index of the benefits of statins (52). Furthermore, as with pre-end stage CKD patients there did not appear to be any benefit from statin therapy on progression of renal disease or graft loss in statin treated transplant recipients (53). Thus, renal transplant patients should be considered for statin therapy for CVD risk reduction, but not for graft preservation. Several of the statins have drug interactions, particularly with cyclosporine, thus providers must be aware of dose and drug restrictions (Table 4).

Table 3. Use of Statins in Various CKD Subgroups

Patient population	Statin indicated? Yes/no
Microalbuminuria*	Unclear
CKD 1-4	Yes
Nephrotic syndrome	Unclear
Dialysis patients	No
Renal transplant recipients	Yes

* in the absence of any other indication

EVIDENCE FOR/AGAINST LIPID LOWERING THERAPY IN CKD FOR RENAL OUTCOMES

Given the evidence that renal lipid deposition is associated with progression of renal disease itself, there has been an ongoing interest in whether targeting dyslipidemia in CKD can help delay the progression of the renal disease. The dyslipidemia in CKD is associated not only with increased CVD but also with adverse renal prognosis (54, 55). Biopsy studies have found that the amount of renal apoB/apoE is correlated with increased progression of the renal disease itself (56). Animal studies have supported this concept. A meta-analysis of several small, older studies suggested that the rate of decline in GFR was decreased in subjects receiving a lipid-lowering agent (the included studies mainly used statins but the meta-analysis also included a study using gemfibrozil and another using probucol) (57). However, the relationship between lipid levels and renal disease is unclear, as prospective cohort studies have not found any relationship of lipid levels to progression of kidney disease (58). Furthermore, the SHARP study, which included subjects with earlier stages of CKD (stages 3-5 were included) found no benefit of lipid lowering therapy on the progression of renal disease. A meta-analysis of statins in pre-end stage CKD patients found no overall effect of statins on renal disease progression (33) and the ALERT study found no benefit of statin use on renal graft or renal disease parameters (53). Thus, there does not appear to be any use for statins to improve renal function or CKD itself.

SAFETY OF STATINS IN CKD

Statin Safety– Renal Outcomes

An observational study using administrative databases containing information on > 2 million patients suggested that the use of high potency statins was associated with acute kidney injury, especially within the first 120 days of statin use (59). However, a subsequent analysis of 24 placebo-controlled statin studies and 2 high versus low-dose statin studies found no evidence of renal injury from statin use (60). These discrepant results can be explained by the quality of the data: in randomized controlled trials, albeit not designed or powered to look at renal injury, data quality tends to be higher than that in administrative data sets, which often contain bias for selection, ascertainment, and classification. Furthermore, statins appear to have a nephron-protective role in the prevention of contrast induced acute kidney injury. A meta-analysis of 15 trials examining the effect of statin pre-treatment before coronary angiography found a significant reduction in acute kidney injury in those treated with high dose statin compared to controls treated with either placebo or low dose statin (61). One study specifically examined the use of statins in subjects with diabetes and existing CKD undergoing angiography and found a benefit to statin pre-treatment in reducing the risk of contrast induced acute renal injury (62). As discussed above, the use of statins in pre-end stage CKD or post-renal transplant patients demonstrates neither benefit nor harm on renal outcomes. Thus, based on available evidence there does not seem to be any renal harm from statin use, and the presence of CKD should not be a contra-indication to statin use, although some statins require dose restrictions in CKD (Table 4).

Statin Safety – Diabetes Outcomes

As a class, emerging evidence demonstrates that statins increase new diagnoses of diabetes (63). As diabetes can lead to or exacerbate renal injury, this is another potential harm of statins. However, there is no evidence that statin therapy acutely raises normal fasting glucose into the diabetic range and rather the evidence from clinical trials suggests that statin therapy instead leads individuals at high risk of diabetes to progress to diabetes diagnosis sooner than may have happened without statin therapy. A subsequent meta-analysis of 5 statin trials with >32,000 patients without diabetes at baseline found that high dose statin was associated with increased risk for new diabetes diagnosis compared to low or moderate dose statin therapy (64). However, the number needed to harm (induce diabetes) is 498 whereas the number needed to treat (prevent cardiovascular events) is 155 for intensive statin therapy; implying that despite the increased risk of new onset diabetes, statin therapy's benefits outweigh the risks.

Which Statins to use in CKD?

The various statins have different degrees of renal clearance; thus, with CKD patients it is important to be aware of the metabolism of the agent of interest and understand if/when dose adjustments are needed. Most statins are primarily metabolized through hepatic pathways, and dose adjustment in early CKD is typically not needed (eGFR> 30 ml/min). However, with more advanced CKD, eGFR< 30 ml/min (or ESRD, although statins are not indicated in this population) most agents have maximum dose restrictions (Table 4).

Table 4. Statin Dosing in CKD					
Statin	**Usual dose range (mg/d)**	**Clearance route**	**Dose range for CKD stages1-3**	**Dose range for CKD stages4-5**	**Use with cyclosporine**
Atorvastatin	10-80	Liver	10-80	10-80	Avoid use with cyclosporine
Fluvastatin	20-80	Liver	20-80	20-40	Max dose 20 mg/d with cyclosporine
Lovastatin	10-80	Liver	10-80	10-20	Avoid use with cyclosporine
Pitavastatin	1-4	Liver/Kidney	1-2	1-2	Avoid use with cyclosporine
Pravastatin	10-80	Liver/Kidney	10-80	10-20	Max dose 20 mg/d when used with cyclosporine
Rosuvastatin	10-40	Liver/Kidney	5-40	5-10	Max dose 5 mg/d with cyclosporine
Simvastatin	5-40	Liver	5-40	5-40	Avoid use with cyclosporine

BEYOND STATINS

There has been relatively little research into the use of non-statin lipid lowering agents in CKD. There is an emerging interest in niacin in CKD patients for its phosphorus-lowering effects, and niacin has similar lipid-altering efficacy in CKD as compared to non-CKD subjects. Fibrates are metabolized via the kidney and thus are generally contraindicated in CKD. Ezetimibe has been shown to be safe and effective in reducing LDL-C in patients with CKD; however, studies have typically compared treatment with ezetimibe added to statin therapy vs. control and few studies compare ezetimibe monotherapy vs. control. PCSK9-inhibitors have been shown to be safe in CKD and efficacious in lowering LDL-C but there remains limited data regarding morbidity and mortality outcomes with this therapy. Newer therapies include bempedoic acid and inclisiran both remain relatively unstudied in CKD/ESRD. The following sections summarize the available data on the use of other lipid lowering agents in CKD (Table 5).

Niacin

As niacin is not cleared via the kidney it is theoretically safe in CKD; however, its use is limited due to side effects (predominantly flushing) and a lack of data. Several short-term studies have evaluated niacin in CKD patients, and it is efficacious in lipid lowering. There is an emerging interest in the use of niacin or its analog niacinamide in CKD and ESRD patients for their effects to decrease phosphate levels. A meta-analysis of randomized controlled trials of niacin and niacinamide in dialysis patients found that niacin reduced serum phosphorus but did not change serum calcium levels; furthermore niacin increased HDL-C levels but had no significant effect on LDL-C, TGs, or total cholesterol levels; no CVD outcomes data were provided (65). Animal studies have suggested a beneficial effect of niacin on renal outcomes (66), and clinical literature is suggestive that this may occur in humans (67). Kang et al treated patients with CKD stages 2-4 with niacin 500mg/d x 6 months; niacin led to increased HDL-C and decreased TG levels, and improved GFR compared to baseline levels (68).

Laropiprant has been developed as an inhibitor of prostaglandin-medicated niacin-induced flushing. In a sub-study examining the use of niacin with laropiprant in dyslipidemic subjects with impaired renal function, the use of niacin resulted in a mean decrease in serum phosphorus of 11% with similar effects between those with eGFR above or below 60 ml/min/1.73 m^2(69); the parent study reported a significant reduction in lipid parameters including a decrease in LDL-C of 18%, decrease in TGs of 25%, and an increase in HDL-C of 20% (70). Thus, there may be an indication for the use of niacin in CKD subjects beyond lipid lowering considerations. However, cardiovascular outcome studies evaluating the combination of statin plus niacin in patient without kidney disease have not found any additional benefit compared to statin alone (71, 72); thus, at this time further research is needed in CKD subjects to determine if niacin may be more beneficial than statins, or if the addition of niacin to statin may confer non-CVD benefit, for example, phosphorus lowering.

Fibrates

Fibric acid derivatives are used primarily to raise HDL-C and lower TGs; thus, they target two major components of CKD associated dyslipidemia. However, fibrates are known to decrease renal blood flow and glomerular filtration and they are cleared renally (73); therefore, there is significant concern regarding their use in CKD. Furthermore, fibric acid derivatives raise serum creatinine levels and thus trigger medical investigations into renal disease progression. Thus, there is concern regarding their use in CKD. However, there is a potential for fibric acid derivatives to improve both CVD and CKD outcomes. The acute changes in serum creatinine do not necessarily indicate adverse renal effects. A meta-analysis (74) examined the use of fibrates in CKD subjects and reported beneficial effects to reduce total cholesterol and TG levels and raise HDL-C levels with no effect on LDL-C levels. In addition, 3 trials reporting on > 14,000 patients reported that fibrates reduced risk of albuminuria progression in diabetic subjects, with 2 trials (>2,000 patients) reporting albuminuria regression (75-77). This was associated with a reduction in major cardiovascular events, CVD death, stroke and all-cause mortality in subjects with moderate renal dysfunction, but not in those with eGFR > 60 ml/min/1.73m^2. Thus, despite the elevations in serum creatinine seen with fibrates, there is the potential for both cardiac and renal benefit, and further studies specifically designed to evaluate these outcomes in CKD subjects are needed. At this point, providers are encouraged to consider fibrate therapy for appropriate subjects, especially if statins are not tolerated or are contra-indicated.

Ezetimibe

Ezetimibe is presently the only member of the class of cholesterol absorption inhibitors. As monotherapy it can lower LDL-C approximately 15-20%; however, the majority of research has examined ezetimibe in combination with a statin (primarily simvastatin) where the addition of ezetimibe can induce a further 20-25% lowering of LDL-C. Ezetimibe is metabolized through intestinal and hepatic metabolism and does not require any dose adjustment in CKD or ESRD, making it a potentially attractive therapy in CKD. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) study demonstrated that the combination of a statin + ezetimibe led to further LDL-C lowering and improved CVD outcomes compared to statin alone in high-risk patients (78). A secondary analysis of this study evaluating outcomes based on eGFR showed that compared to statin alone, the combination of statin + ezetimibe was more effective in reducing risk of CVD outcomes in those with eGFR < 60/ml/min/1.73m^2 (79). The Study of Heart and Renal Protection (SHARP) compared CVD and renal effects in CKD patients treated with statin + ezetimibe versus placebo. There was a reduction in CVD events (44); however, there was no effect on renal disease progression (80). Note, neither of these studies included an ezetimibe only arm; thus, the effects of ezetimibe monotherapy on outcomes are unknown, although it can be expected to reduce CVD events in

proportion to its degree of LDL-C lowering. A small study evaluating ezetimibe monotherapy in CKD patients found it safe and effective (81). Thus, the use of ezetimibe with or without statin is likely to benefit pre-end stage CKD patients in terms of CVD outcomes. Given that the impact of ezetimibe is on lowering LDL-C we can anticipate lack of CVD benefit in ESRD subjects based on the statin studies and SHARP.

Fish Oil

Omega-3 polyunsaturated fatty acids can lower TG levels, making them a potential therapy in CKD. The role of fish oil/ omega-3 supplements in the general population for prevention of CVD events remains unclear, with some studies suggesting benefit but others finding no CVD protection. A recent meta-analysis found no evidence for CVD protection (82) while a meta-analysis of thirteen randomized control trials involving 127,477 patients demonstrated marine omega-3 supplementation was associated with small but significantly lower risk of MI, CHD death, total CHD, CVD death, and total CVD with linear relationship to dose (83). In CKD patients there is little data to support the use of fish oil and much of the data is conflicting. A small, randomized study evaluated omega-3 fish oil supplements, coenzyme Q10, or both in subjects with CKD stage 3 for 8 weeks. The group that received the omega-3 supplements had decreased heart rate and blood pressure and TGs, but there was no effect on renal function (eGFR, or albuminuria) (84). Conversely, a study evaluating dietary omega-3 intake found that higher consumption was associated with reduced likelihood of CKD (85). A randomized controlled trial in patients with CKD and microalbuminuria showed that omega-3 fatty acid supplementation had no effect on urine albumin excretion; however, there was a beneficial effect on serum TG levels and pulse wave velocity (86). Fish oil supplementation has not been found to have any clear benefit on hemodialysis arteriovenous graft function (87, 88) or on cardiovascular events or mortality in hemodialysis patients (89). Thus, there is no clear benefit for the use of fish oil supplements in CKD, but further research is needed.

Bile Acid Resins

The bile acid resins tend to be used less commonly than other classes of lipid lowering agents overall, and their use in CKD is limited by a lack of data. Bile acid resins as a class can lower LDL-C by 10-20% so they are less effective than statins; furthermore, they can raise TG levels and their use is contraindicated with elevated TG levels, for example > 400-500 mg/dl (>4.5 – 5.6 mmol/L). Thus, overall bile acid resins are rarely used in CKD patients. However, their metabolism is intestinal and thus there are no required modifications for their use in mild-moderate CKD. Although there are no theoretical concerns regarding their use in ESRD there is no data to address safety or efficacy.

PCSK9 Inhibitors

Monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) have been developed and approved for patients with clinical atherosclerotic CVD not meeting lipid goals despite maximally tolerated statin therapy. Statins can cause higher PCSK9 levels through activation of sterol regulatory element-binding protein-2 with co-expression of LDL receptors & PCSK9 (90). PCSK9 inhibitors lower LDL-C in addition to statin-mediated lowering and have been shown to decrease CVD events in outcome studies in secondary prevention populations (91). Two PCSK9 monoclonal antibodies are presently available in the US – evolucumab and alirocumab. PCSK9 plasma levels are not influenced by eGFR in CKD patients (92) but are increased in nephrotic syndrome (93). The German Chronic Kidney Disease study (GCKD) investigated the association between PCSK9 and cardiovascular disease in patients with moderate CKD (eGFR >30 ml/min/1.73 m^2 or eGFR >60 ml/min/1.73 m^2 with UACR >300 mg/g). GCKD showed no association of PCSK9 concentrations with eGFR or UACR (except for those with nephrotic-range albuminuria) but did show that higher baseline PCSK9

concentrations increased the odds of baseline cardiovascular disease (90). As monoclonal antibodies are not cleared by the kidney and thus are approved for use in CKD and ESRD with no dose adjustment. The ODYSSEY OUTCOME trial randomized post-acute coronary syndrome patients with LDL-C > 70mg/dL on maximally tolerated statin to placebo vs alirocumab; the intervention arm with alirocumab had nearly twice the absolute reduction in cardiovascular events (94). Of note patients with eGFR < 30 ml/min/m^2 were excluded from the ODYSSEY OUTCOME trial. However, a later sub analysis looked at the effect of alirocumab on major adverse cardiovascular events based on renal function. The sub analysis showed that irrespective of eGFR alirocumab was efficacious in reducing LDL-C. Further, annualized incidence rates of major adverse cardiovascular events and death increased with decreasing eGFR but rates were lower in the alirocumab group compared to placebo and there were no significant difference in incidence of major adverse events between treatment groups with eGFR < 60 ml/min/m^2 (95). Further, data from a pooled analysis of nine trials comparing alirocumab vs control showed that among patients with ASCVD and LDL-C > 100 mg/dL those with additional risk factors including CKD had the greatest absolute cardiovascular benefit from alirocumab therapy in addition to maximally tolerated statin compared to placebo (96). A recent systematic review of 7 studies including 5 RCTs and 2 review studies showed safety of PCSK-9 inhibitors in mild-moderate CKD. However, this conclusion is somewhat limited as patients with an eGFR <20 ml/min/m^2 were not included in the trials (97). Furthermore, the relationship between PCSK-9 inhibitors' lipid lowering and lower cardiovascular risks resulting in improved morbidity and mortality is altered with severe CKD due to non-thrombotic causes of morbidity and mortality. Studies remain ongoing to further look at mortality and morbidity outcome in PCSK-9 inhibitors specifically in patients with CKD 3 or higher. The ALIDIAL study examined the safety and efficacy of alirocumab in patients receiving dialysis and the dialysis patients had a similar response at the same alirocumab dose with reduced cholesterol levels and no unexpected adverse events when compared to the patients not receiving dialysis (98). There remains very limited data in patients with ESRD and PCSK-9 inhibitor use as monotherapy for dyslipidemia.

Bempedoic Acid

Currently approved for use in combination with maximally tolerated statin, bempedoic acid facilitates further LDL-C reduction by inhibiting cholesterol synthesis in the liver through blocking adenosine triphosphate-citrate lyase (ACL). Currently, use in CKD is approved without dosage adjustment for eGFR > 30ml/minute/1.73$m^{2;}$ however, below this eGFR threshold there is insufficient data to guide its use. As bempedoic acid has hepatic metabolism it is presumably safe in CKD. Bempedoic acid increases serum creatinine and uric acid levels through interference with tubular secretion (99). A 52-week study in very high-risk CVD patients demonstrated that bempedoic acid added to maximally tolerated statin therapy was safe and led to a significant reduction in LDL-C levels (100). Further, combination with ezetimibe is safe and can increase the cholesterol-lowering effect more than either agent alone when added to standard therapy (101). The Cholesterol Lowering via bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial, a cardiovascular outcome study that was published March 2023, demonstrated a decrease in cardiovascular events but excluded patients with eGFR <30 ml/minute/1.73 m2 as well as nephritic or nephrotic syndrome (102). At this time, the data remains limited regarding the benefit and use of bempedoic acid in ESRD.

Inclisiran

Newest to the market, inclisiran is a small interfering RNA (siRNA) that acts in hepatocytes to break down mRNA for PCSK-9 which increases LDL receptor recycling thus increasing LDL cholesterol uptake. It is FDA approved for use in heterozygous familial hypercholesterolemia and in secondary prevention of

cardiovascular events as an adjunct to lifestyle and maximally tolerated statin. It is administered by subcutaneous injections at 3 and then 6-month intervals. There are no cardiovascular outcomes studies yet available. There is no recommended dosage adjustment in CKD, but there have been no studies done in patients with ESRD. An analysis of the ORION-1 and ORION-7 studies compared inclisiran in patients with renal impairment and those with normal renal function found similar safety and efficacy, suggesting no dose adjustment is needed in CKD (103). However, no patients on dialysis were studied in these trials. ORION-8 is a 3-year extension of the preceding ORION-3, ORION-9, ORION-10 and ORION-11 studies that examined long-term efficacy and safety in regard to treatment-emergent adverse events (TEAEs) and treatment-emergent severe adverse events (TESAEs). More than 70% of patients at each visit in ORION-8 achieved the preset LDL-C goals. Almost 78% of patients had TEAEs and 30% had TESAEs. It is unclear if patients with CKD were included as there is no clear renal exclusion criteria (many subjective criteria) or stratification of patients by renal function (104). A post-hoc analysis of 7 clinical trials of inclisiran from 2023 showed no detection of safety signals related to kidney TEAEs and found inclisiran to be well-tolerated for up to 6 years (105). The ORION-4 trial is investigating the impact of inclisiran on MACE but results will not be available until 2026. Further studies will be required to assess the safety of inclisiran use in CKD and ESRD.

Table 5. Non-Statin Treatments

Agent	Usual dose range (mg/d)	Clearance route	Dose range for CKD stages1-3	Dose range for CKD stages 4-5	Use with cyclosporine
Niaspan	500-2000	Hepatic/renal	No data	No data	No data
Gemfibrozil	1200	Renal	Avoid if creatinine > 2.0 mg/dl	Avoid if creatinine > 2.0 mg/dl	Cautious use
Fenofibrate	40-200	renal	40-60	avoid	Cautious use
Ezetimibe	10	Intestinal/hepatic	10	10	Cautious use
Colsevelam	3750 (6 x 625 mg tablets daily)	Intestinal	No change	unknown	May reduce levels of cyclosporine
Fish oil	4000		No change	Caution	No data
PCSK9 inhibitors	Alirocumab 75-150mg SC q 2 weeks Evolocumab 140mg weekly SC - 420mg monthly SC	Unknown	No change	Potentially safe and effective in dialysis	No data

Bempedoic acid	180 mg daily	Hepatic	No change	Not defined	No data
Inclisiran	284 mg SC at 0 and 3 months then every 6 months	Nucleases	No change	Not defined	No data

SUMMARY

CVD is the leading cause of mortality in CKD, and as with the non-CKD population dyslipidemia is a significant contributor. The dyslipidemia of CKD comprises primarily high TG levels and low HDL-C levels; however, emerging data suggests that the composition of the lipoprotein particles is altered by CKD, and that altered composition and/or lipoprotein cargo may be a cause of the increased CVD in CKD. The use of statins has been shown to be safe and efficacious in lipid lowering in CKD, and of benefit in reducing CVD events in individuals with pre-end stage CKD, or post renal transplant, but not in dialysis patients. The various available agents have different clearance routes, and some statins need dose adjustment in CKD. In patients that cannot tolerate or who have contra-indications to statin therapy, there may be some benefit from use of PCSK9 inhibitors, ezetimibe, fibrates, niacin, or newer therapies such as bempedoic acid and inclisiran, but further studies are needed to better investigate their use.

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