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Dyslipidemia in patients with chronic kidney disease

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Abstract Chronic kidney disease (CKD) is associated with high risk for cardiovascular disease (CVD). This association is multifactorial, but CKD is often associated with dyslipidemia, which likely contributes. Patients with CKD have dyslipidemia even at early stages of renal dysfunction and dyslipidemia tends to progress with deterioration of kidney function. The dyslipidemia in CKD is largely due to increased triglyceride levels, decreased HDL-C and varying levels of LDL-C. Current management of CKD may also affect lipid levels. Robust clinical trials demonstrate that statins are safe and efficacious in both lipid lowering and prevention of CVD events in pre-end stage CKD and post-transplant. However, there is no evidence of improved CVD outcomes with statin use in dialysis patients. This review will focus on mechanisms underlying dyslipidemia in CKD and clinical trial evidence for lipid lowering therapy in patients with CKD.

Keywords Cholesterol · Chronic kidney disease · Lipids · Renal · Statins · Cardiovascular disease

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1 Introduction

Chronic Kidney Disease (CKD) is defined by the National Institute of Diabetes and Digestive and Kidney Diseases as a sustained reduction in kidney function where the glomerular filtration rate (GFR) remains below 60 mL per minute or when the urine albumin-to-creatinine ratio is over 30 mg of albumin for each gram of creatinine for more than 3 months [1]. There are 5 stages of CKD which are determined by the estimated glomerular filtration rate (eGFR); see Table 1. End-stage renal disease (ESRD) is defined as total and permanent kidney failure typically requiring either dialysis or transplantation. CKD affects 10–13% of the general population [2] (approximately 20 million Americans) and the prevalence in the U. S. population has been increasing by up to 5% per year [3]. The incidence of CKD is increasing most rapidly in patients over age 65 years; however, the incidence of ESRD has leveled off after increasing steadily from 1980 to 2001 [1]. The incidence of ESRD is three times higher for African Americans than for Caucasians but since 2000 the incidence rates have been stable across all races [1].

Cardiovascular disease (CVD) is the leading cause of death in the United States and in particular the leading cause of death in patients with CKD and ESRD [4, 5]. The Cardiovascular Health Study was a prospective study of people greater than or equal to 65 years that showed that people with renal insufficiency (defined as a creatinine >1.5 mg/dL in men and >1.3 mg/dL in women) were more likely to develop CVD, heart failure and peripheral vascular disease [6]. More specifically, up to 50% of patients with CKD pass away from CVD even prior to being labeled as ESRD [7]. Dyslipidemia is a major risk factor for CVD. Approximately 100 million or 1/3rd of Americans have total cholesterol levels greater than 200 mg/dL and more than 34 million have levels above 240 mg/dL according to the American Heart Association. Robust clinic trial evidence demonstrates that lipid lowering

Table 1 Chronic kidney disease stages

CKD Stage	GFR
Stage 1	>90 mL/min
Stage 2	60–90 mL/min
Stage 3A	45-59 mL/min
Stage 3B	30-44 mL/min
Stage 4	15-29 mL/min
Stage 5	<15 mL/min

via medications such as statins, leads to decreased CVD events and mortality.

2 Lipid levels in CKD

Lipoproteins are organic assemblies of lipids, cholesterols and proteins that function to transport insoluble lipids and cholesterol through blood and lymph. The major lipoproteins include chylomicrons, very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). Lipoproteins vary in the type of apolipoprotein as well as the composition of proteins and lipids. Apolipoproteins bind the lipids to make the assembly soluble; in addition, different apoproteins have specific functions. Apolipoprotein (apo)B is the main structural protein on VLDL and LDL and as there is one apoB per particle, apoB is a measure of particle numbers. ApoA-I is the major structural protein on HDL. The other apoproteins have various roles in regulating lipoprotein particle size, structure and catabolism. The dyslipidemia in CKD is largely due to increased triglyceride levels, decreased HDL-C, varying levels of LDL-C, and an increase in apoB to apoA-I ratio. Further delineation is stated as per below.

2.1 Triglyceride rich lipoproteins (VLDL, chylomicrons, chylomicron remnants)

Hypertriglyceridemia starts to increase at early stages of CKD and is one of the most common quantitative lipid abnormalities. Hypertriglyceridemia is multifactorial with a likely component of delayed catabolism due to depressed lipoprotein lipase (LPL) mediated hydrolysis in VLDL and chylomicrons. This reduction in LPL activity has been attributed to parathyroid hormone (PTH)-induced insulin resistance [8] and an excess of lipase inhibitors such as apoC-III and pre-beta-HDL in uremic plasma [9]. Another study investigated apoC-I and C-III levels in both diabetic and nondiabetic nephropathy. Diabetic nephropathy was associated with an increased apoC-I, whereas apoC-III was elevated in both subgroups of chronic renal failure [10].

2.2 Low density lipoprotein

Low density lipoprotein levels are generally not elevated in patients with CKD although the literature is unclear if the onset of CKD induces changes in LDL cholesterol. One study suggested that patients on hemodialysis had decreased hepatic triglyceride lipase, used for conversion of IDL to LDL, with evidence of increased IDL-C and decreased LDL-C [11]. Another study suggested increased levels of both LDL and IDL due to severely impaired catabolism of these particles. They also suggested that increased particle time in circulation leads to further modifications of apoB that will reduce recognition by LDL receptors causing rising level of LDLs. The reduced catabolism is also masked by decreased production [12]. Patients with nephrotic range proteinuria have an acquired LDL receptor deficiency as well as excess small dense LDL and lipoprotein remnants that also relate to increased plasma triglyceride [13, 14].

2.3 High density lipoprotein

Low HDL levels are established as a significant risk factor for CHD and were shown to be an independent predictor of first ischemic heart disease by a study of over 2000 men being followed for 5 years [15]. Patients with advanced kidney disease have decreased lecithin cholesterol ester transfer protein making HDL fail to mature. This results in increased pre-beta HDL and triglyceride-rich HDL with decreased effective antioxidation activity [16]. Chronic renal failure downregulates hepatic apoA-I gene expression and hepatic LCAT mRNA expression, which result in lower plasma apoA-I and plasma LCAT activity respectively. This accounts for the reduced HDL and leads to impaired HDL-mediated cholesterol uptake from vascular tissue (reverse cholesterol transport) [17, 18].

2.4 Lipoprotein (a) [Lp(a)]

Elevated Lp(a) (defined as serum levels over 10–30 mg/dL) is seen more commonly in patients with CKD than those without, and has been noted that these levels increase inversely with eGFR. Compared to age- and sex-matched healthy controls with average Lp(a) concentration of 22 mg/dL, those with Stage 4 and 5 CKD have levels of 34 mg/dL and 49 mg/dL respectively [19]. The reasons for increased Lp(a) in CKD are unclear. However, increasing data indicates that high levels of Lp(a) in patients with CKD are due to decreased renal clearance as opposed to increased production. Some studies suggest renal clearance is key based on data showing a drop in Lp(a) levels in the renal vein compared to the ascending aorta [20]. In another study rats were injected with Lp(a) and immunostaining revealed accumulation in the kidney tubules as well as urinary excretion of apo(a) fragments [21]. Moreover, a turnover study comparing Lp(a) levels in patients on hemodialysis showed markedly increased

residence time without a significant difference in production rate of apo(a) compared to control [22]. On the other hand, there are studies that suggest the liver is the major organ for clearance such as a study with mice when injected with radiolabeled Lp(a) [23]. Further research is needed to clarify the reasons for elevated Lp(a) in CKD, but current guidelines do not recommend measuring Lp(a) unless there are specific indications.

3 Guidelines for dyslipidemia

Several different sets of guidelines exist to guide health care providers in both screening and treatment of dyslipidemia, but many guidelines have not provided specific recommendations for the CKD population. The following sections summarize the current major guidelines with a focus on the CKD population where applicable.

3.1 The United States Preventive Services Task Force (USPSTF) guidelines

The USPSTF recommends checking total cholesterol and HDL-C as a screening test for atherosclerotic cardiovascular disease (ASCVD) risk assessment in men and women over 35 and 45 years old respectively as well as those over 20 years old with increased risk for coronary heart disease (CHD). Although LDL-C and triglycerides are commonly combined with the lipid profile, the USPSTF believes there is insufficient evidence to include triglycerides as part of the initial screen for dyslipidemia. The USPSTF recommends low to moderate dose statins for primary prevention of CVD in those aged 40–75 years, with 1 or more CVD risk factors and 10 year risk ≥10%. These guidelines do not specifically address the CKD population.

3.2 The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines

The ACC/AHA released guidelines titled "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risks in Adults". This guideline focuses on ASCVD, and a major change from prior guidelines was to move away from lipid target levels and instead advise based on statin treatment intensity. Statin intensity is defined by percent lowering of LDL-C from baseline: low intensity <30%; moderate intensity 20–50%, and high intensity >50%. These guidelines recommend statin therapy for four patient groups; see Table 2. The first group is those with clinical ASCVD (defined as acute coronary syndrome, prior myocardial infarction, stable/unstable angina, prior coronary or arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin). High-intensity statin treatment is recommended for all patients in this group aged less than 75 years old (moderate-intensity statin recommended for those 75 years or older). A high-intensity statin is also recommended for the second group which includes those with a LDL-C > 190 mg/dL but no evidence of ASCVD. The third group comprises patients with diabetes ages 40–75 years old. The Framingham risk calculation is used to calculate each individual's 10-year ASCVD risk. For those with an estimated risk of >7.5% the recommendation is to receive a high-intensity statin; all others in this group should receive a moderate-intensity statin. The fourth group includes patients between 40 and 75 years old not meeting the above qualifications. A moderate or high intensity statin is recommended for any individual with a 10 year ASCVD risk ≥7.5%. This guideline does not advise statin therapy for individuals who do not fall into one of these risk categories. Statins are the cornerstone of lipid management; when a particular statin intensity is not tolerated, the next lower intensity should be tried. These guidelines do not specifically comment on individuals with CKD, and CKD is not included in the risk calculator.

3.3 The kidney disease improving global outcomes (KDIGO) work group guidelines

KDIGO provides recommendations for patients with CKD. KDIGO recommends all patients newly diagnosed with CKD should have a lipid profile measured including total cholesterol, LDL-C, HDL-C, and triglycerides. A statin or statin/ezetimibe combination is recommended for adults over 50 years not on dialysis but with an eGFR <60 mL/min/1.73m^2. If the patient is between 18 and 49 years old, statin therapy is recommended based on comorbid conditions such as CVD, diabetes, stroke, or 10 year risk over 10%. KDIGO does not recommend initiating statin therapy for patients on dialysis, although a statin can be continued if a patient was on one prior to initiating dialysis. These guidelines also recommend statins for all adult patients with a transplant [24]. Somewhat similar to the ACC/AHA guidelines, KDIGO has moved away from lipid targets, and instead recommends a "fire-and-forget" strategy for patients who have indications to start hyperlipidemia medications. "Fire and forget" means follow up lipid measurements are only indicated if the results would influence adherence or treatment adjustments. Treatment adjustments are similar to the AHA/ACC guidelines such as if a new disease (ie diabetes, hypertension, ASCVD) is diagnosed or if the patient moves into a new age group.

3.4 National lipid association (NLA) guidelines

The NLA published guidelines regarding the management of dyslipidemia in 2014. It recommends that every 5 years a fasting or non-fasting lipid panel be obtained in all adults >20 years of age. Treatment goals are determined by an adult's risk assessment for ASCVD. Adults with CKD stage 3B or 4

Table 2 Abbreviated ACC/AHA guideline on the treatment of blood cholesterol

Treatment group		Treatment
Clinical ASCVD	Age ≤ 75 y	High-intensity statin
	Age > 75 y	Moderate-intensity statin
LDL-C > 190 mg/dL		High-intensity statin
Diabetes Mellitus, age 40-75y, LDL 70–189 mg/dL	10 y ASCVD risk ≥7.5%	High-intensity statin
	10 y ASCVD risk <7.5%	Moderate-intensity statin
No Diabetes Mellitus, age 40-75y, LDL 70–189 mg/dL	10 y ASCVD risk ≥7.5%	Moderate or high-intensity statin
	10 y ASCVD risk <7.5%	Individualized treatment

are considered "high" risk while adults with diabetes and evidence of end-organ damage (defined as an albumin/creatinine ratio > 30 mg/g, eGFR < 60 mL/min/1.73m^2, or retinopathy) are classified as "very high" risk. The treatment goal for "high" risk adults is LDL < 100 mg/dL and the treatment goal for "very high" risk adults is LDL < 70 mg/dL (non-HDL cholesterol goals are 30 mg/dL above the LDL goals, for each risk category). Pharmacotherapy with moderate or high intensity statin is recommended for those with LDL levels above target, and should be considered even for those with pretreatment LDL below targets unless contraindicated. The NLA guidelines note that while stage 5 CKD (or hemodialysis) is a very high-risk condition, results from trials have not provided convincing evidence of benefit, thus the NLA does not provide treatment goals defined for lipid therapy in stage 5 CKD [25].

3.5 Canadian cardiovascular society lipid guidelines

The Canadian Cardiovascular Society released updated guidelines in 2016 that specifically addressed adults with CKD. Per these guidelines, it is recommended that screening for dyslipidemia be considered for any person older than 40 years of age or at any age for patients with certain conditions that are associated with high CVD risk, which includes CKD. More specifically, the guidelines list five conditions for which risk assessment is not needed because statin therapy is indicated regardless of their individual risk. These high-risk conditions include clinical atherosclerosis (known ASCVD), abdominal aortic aneurysm (AAA) with aortic diameter > 3.0 cm or previous AAA surgery, diabetes mellitus (age > 40y, or age > 30y with 15 years diabetes duration, or presence of microvascular complications), LDL > 5.0 mmol/L (approx. 190 mg/dL), or CKD (eGFR <60 mL/min/1.73m^2 or albumin/creatinine ratio > 3 mg/mmol [approx. 30 mg/g]). The guidelines recommend treatment with either a statin or a statin/ezetimibe combination to reduce cardiovascular disease risk in adults over the age of 50 with CKD who are not treated with dialysis or a kidney transplant. Lipid-lowering therapy should not be started in adults who are dialysis –dependent; however, therapy can be continued in adults already receiving therapy at the time of dialysis initiation. Finally, the guidelines recommend the use of a statin in adults who have received a kidney transplant [26].

3.6 Summary of guidelines for CKD patients

While only a few of the guidelines mentioned here address CKD patients as a specific population, there is apparent consensus that patients with CKD are recognized as being at high risk for CVD, and those with stages CKD3-CKD4 should be treated with statin or statin plus ezetimibe to reduce risk. For patients on dialysis there is consensus that lipid lowering therapy should not be started, but if already present at the time of initiation of dialysis, should not be discontinued. Patients post renal transplant are considered appropriate for statin treatment.

4 CKD management and its effect on lipoproteins

4.1 Peritoneal and hemodialysis

The effect of peritoneal dialysis and hemodialysis on lipoprotein composition is generally similar. According to one study, both hemodialysis and peritoneal dialysis patients have enrichment of apoC-III in VLDL, IDL, and LDL compared to healthy controls. However, there was a difference with elevated apoB for patients with peritoneal dialysis compared to hemodialysis [27]. Serum levels of lipoproteins and phospholipids were compared in 140 patients on hemodialysis and 122 non-CKD healthy controls. Patients with hemodialysis had a significant decrease in HDL and increase in triglycerides. This study also showed significant alterations in phospholipid concentrations with increased levels of sphingomyelin and diphosphatidylglycerol and decreased levels of phosphatidylcholine and phosphatidylinositol in patients undergoing maintenance hemodialysis [28]. A comparative observational study

of 120 patients compared lipid profiles between subjects with stage 5 CKD on conservative management with subjects on maintenance hemodialysis. Results showed significantly lower total cholesterol and HDL-C with increased levels of triglycerides in those undergoing maintenance hemodialysis [29]. The type of hemodialysis can vary lipoprotein levels according to some studies. For example, using high flux has been shown to lead to an increase in apoA-I and HDL cholesterol levels [30]. The type of dialysate has also shown to effect plasma HDL levels. Patients with acetate as buffer had lower HDL levels compared to bicarbonate, but the author concluded that other contributory factors would need to be excluded [31]. Although there are many studies comparing lipid profiles of those undergoing hemodialysis to conservative management, the clinical significance of the profiles is complex but tend to have a paradoxical association with survival. In an analysis of over 15,000 patients on maintenance hemodialysis, decreased total cholesterol, LDL-C and those with lower serum triglyceride levels (<200 mg/dL) have been associated with decreased survival. However, high serum LDL (>100 mg/mL) was associated with increased cardiovascular death in black patients [32]. This study brings up the point that certain patients on hemodialysis are severely malnourished and have low lipid profiles (which are normally favorable in the general population) but in this case low lipid profiles are due to malnutrition and these patients have worse outcomes. However, there are also some hemodialysis subgroups who have normal nutrition with highly elevated cholesterol; these patients also do poorly and are the ones we might need to target with lipid lowering therapy if not already on it. Further studies of subgroups of patients undergoing hemodialysis might help determine specific populations that would benefit from cholesterol lowering therapy, especially those not malnourished with elevated LDL-C.

4.2 Renal transplantation

Renal transplantation improves quality of life and increases long-term survival [33]. However, patients undergoing renal transplantation require immunosuppressive medications such as corticosteroids and calcineurin inhibitors such as cyclosporine and tacrolimus that frequently cause secondary dyslipidemias. Corticosteroids elevate cholesterol via several pathways including increased hepatic VLDL synthesis due to hyperinsulinemia-mediated stimulation and downregulation of LDL receptors thought to be due to adrenocorticotropic suppression. In patients post renal transplant steroid withdrawal tends to lead to a reduction in total LDL and HDL- C [34]. Cyclosporine is associated with a dose dependent elevation in total and LDL-C with reductions in HDL-C to a greater extent than tacrolimus [35, 36]. After renal replacement Lp(a) levels are generally decreased [37]. In general, a dyslipidemia characterized by increased total cholesterol, LDL-C, and triglycerides and decreased HDL-C is common in post renal transplant patients. Although balancing risks of rejection and ASCVD development with immunosuppressive therapy is complex, many physicians replace cyclosporine with tacrolimus and discontinue sirolimus if dyslipidemia occurs. The guidelines for discontinuation or dose adjustment of corticosteroids are not definite, but in general recommend keeping corticosteroids at lower doses.

4.3 Metabolic acidosis treatment

Small studies have shown that alkali supplementation can reduce progression of CKD and therefore KDIGO has recommended oral bicarbonate supplementation to keep serum bicarbonate concentration over 21 mmol/L [24]. A small study followed 9 patients on hemodialysis with metabolic acidosis and hyperlipidemia for about a month. These patients had high triglycerides, low HDL and normal total cholesterol at baseline compared to non-CKD patients. After 2 weeks of sodium bicarbonate treatment there was a significant decrease in triglyceride levels; however, total cholesterol and HDL did not change [38]. Another study in young non-CKD patients with moderate hypercholesterolemia compared lipid levels after consuming one liter of mineral water daily for four weeks followed by one liter of bicarbonate mineral water daily for four weeks. Results showed a reduction in total cholesterol (6.3%, $p = 0.012$), LDL cholesterol (10%; $p = 0.001$), total/HDL-C, LDL-C/HDL-C, and apoB concentrations without a significant change in triacylglycerol or apoA-I levels [39].

4.4 Anemia treatment

Anemia is common in patients with CKD and there are multiple treatment options including transfusions, erythropoietin, and iron supplementation. The presence of anemia adds to the complexity of CVD and has been associated with increased CHD risk and mortality. However, it is unclear if treatment of anemia affects lipid levels. In a study on 33 patients on hemodialysis who received erythropoietin, long term erythropoietin was inferred to positively affect the lipid profile compared to age matched controls also on hemodialysis without erythropoietin [40]. Over one hundred patients on dialysis were followed during the initiation of erythropoietin therapy for about ten months. Overall, their lipid profile had significant drops of total cholesterol, serum triglycerides and apoB, but LDL, HDL and apoA-I did not have significant changes [41]. However, a group of 10 subjects on hemodialysis with elevated serum ferritin were given deferoxamine therapy and no statistically significant effects on the lipid profile were seen [42]. Importantly, anemia treatment helps overall CVD risk independent of effects on lipids.

4.5 Albuminuria treatment with ACE-I/ARB

Moderately increased albuminuria (formerly called "microalbuminuria") is elevation of albumin excretion (30 to 300 mg/day) for over 3–6 months. Severely increased albuminuria (formerly called "macroalbuminuria") is elevation of albumin excretion over 300 mg/day. KDIGO has four main recommendations for treatment of increased albuminuria in patients with CKD. For moderately and severely increased albuminuria, KDIGO suggests that angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACE-I) be used in all non-diabetic patients with hypertension and used in all patients with diabetes as tolerated. Studies are limited to the effect of lipid profiles in patients with CKD being treated with an ARB or ACE-I. Some evidence suggests an interaction between hyperlipidemia and the activation of the renin-angiotensin system (RAS). A study that compared RAS activation and renal injuries on apolipoprotein knockout mice with a high fat diet suggested progression of CKD due to synergistic effects of hyperlipidemia and RAS activation [43]. Being an oxidant, angiotensin II alters the binding of LDL to its receptors and increases uptake of LDL into the endothelial cell. In theory, the combination of lipid lowering strategies and ACE inhibitors may have an additive effect in preventing coronary atherosclerosis progression, but further testing needs to be done [44].

4.6 Renal osteodystrophy treatment

Patients with CKD often have elevated phosphorus due to decreased excretion as well as low calcium leading to an increase in serum PTH. Common strategies to decrease serum phosphorus include dietary restriction and oral phosphorus binders. Sevelamer hydrochloride is a nonabsorbable calcium- and aluminum- free phosphorus binder that is frequently used especially in the setting of increased calcium. Sevelamer has been shown to significantly reduce the concentration of total cholesterol and apolipoprotein B in hemodialysis patients [45]. A study of about 700 patients on hemodialysis compared lipid profiles on patients either on sevelamer or a calcium based phosphorus binder. Using a logistic regression model, the authors suggest that patients on sevelamer have both lower serum C-reactive protein and lower LDL-C as compared to a calcium based phosphorus binder. This analysis suggests sevelamer may be a new promising therapy in patients with high risk of cardiovascular disease [46]. A crossover study of 30 stable patients comparing lipid profiles on sevelamer compared to aluminum hydroxide showed similar findings. Results show that sevelamer was well tolerated and had similar phosphorus reductions with improved lipid profiles of both total cholesterol and LDL-C of about 10% and 20% respectively [47]. Calcitriol has also been studied and appears to have modest effects to decrease triglycerides and apoA-1 concentrations [48, 49].

5 Current dyslipidemia treatment options in CKD

5.1 HMG CoA reductase inhibitors (statins)

Statins are the most commonly used and best studied lipid lowering agents in CKD (evidence reviewed in Section 6). Statins work by inhibiting HMG CoA reductase, which is involved in cholesterol synthesis. As a result, cells up-regulate their expression of the LDL receptor, and there is increased clearance of LDL-C from the circulation. Atorvastatin and rosuvastatin are classified as high intensity statins, all others are moderate or low intensity statins based on their percent LDL reduction. Robust clinical trial evidence demonstrates that statin therapy effectively lowers LDL cholesterol and reduces CVD events; thus, statins are the first-line treatment for most dyslipidemias. Clinical trials demonstrate that overall side effects are rare, but include muscle aches, elevated transaminase levels, or of greatest concern, rhabdomyolysis. Contraindications for statin use include cholestasis and active liver disease or history of rhabdomyolysis. In patients presenting with intolerance of statins (generally non-specific muscle aches) measurement of creatine kinase (CK), aminotransferase levels, and thyroid stimulating hormone (TSH) are recommended, although not required. Elevations in hepatic transaminases can occur in 0.5–2.0% of cases. Muscle aches without CK elevations are the most commonly reported side effect but in clinical trials occurred at <5%, usually <1%, and were not significantly different to placebo. Table 3 summarizes the expected LDL lowering, route of clearance and dose adjustment needed in CKD for currently available statins. Although dose adjustments for patients on hemodialysis are typically not defined, it is suggested that only atorvastatin or fluvastatin should be used in severe renal impairment.

5.2 Cholesterol absorption inhibitor (ezetimibe)

Ezetimibe is a compound of the 2-azetidinone class that inhibits intestinal cholesterol absorption by preventing the uptake of dietary and biliary cholesterol into the enterocytes of the brush border by binding to the Niemann-Pick C1-like-1 receptor thus lowering LDL levels [50, 51]. However, ezetimibe does not have much effect on the absorption of triglycerides or fat-soluble vitamins. Given that ezetimibe is only circulated in the enterohepatic circulation and does not directly act on the kidneys it may be an ideal candidate for use in patients with CKD [52]. However, as

Table 3 Statin doses with intensity in various CKD subgroups

Statin	Dose (mg/d)	Intensity	LDL Reduction (%)	Clearance	Dose adjustment in CKD (mg/d)	Use with Cyclosporine
Simvastatin	5–10 20–40	Low Moderate	18–68	Liver	CKD 4–5, start dose: 5	Avoid use
Pravastatin	10–20 40–80	Low Moderate	14–41	Liver/ Kidney	CKD 4–5, max dose: 10–20	Max dose: 20 mg/d
Lovastatin	10–20 40–80	Low Moderate	36–41	Liver	CKD 4–5, max dose: 10–20	Avoid use
Fluvastatin	20–40 80	Low Moderate	32–36	Liver	None	Max dose: 20 mg/d
Pitavastatin	1 2–4	Low Moderate	32–43	Liver/ Kidney	CKD 3–5, max dose: 1–2	Avoid use
Atorvastatin	10–20 40–80	Moderate High	15–61	Liver	None	Avoid use
Rosuvastatin	5–10 20–40	Moderate High	47–63	Liver/Kidney	CKD 3–4, max dose: 5–10	Max dose: 5 mg/d

monotherapy ezetimibe has relatively modest lipid lowering effects (lowers LDL-cholesterol up to 20%). As described in the SHARP study (see section 6), ezetimibe may be effectively used in combination with a statin to induce greater LDL lowering than statin alone, or to allow use of lower doses of statins if side effects are a concern.

5.3 Nicotinic acid derivatives (niacin)

Niacin is a water-soluble vitamin that is converted to nicotinamide which is a component of nicotinamide adenine dinucleotide (NAD) or NAD Phosphate (NADP) which act as coenzymes for many different oxidation-reduction reactions [53]. Nicotinic acid is used in the treatment of dyslipidemias as it inhibits the production of VLDL by inhibiting the mobilization of free fatty acids from adipose tissue to the liver [54], which in turn decreases LDL production. Nicotinic acid has also been shown to increase HDL by 30–35% by delaying HDL clearance and reducing the transfer of cholesterol from HDL to VLDL [54]. It has a theoretical benefit of being used in patients with CKD because it is not renally excreted. Despite this niacin has limited use in treatment of dyslipidemia due to a common side effect of "facial flushing" even at standard doses and overall limited data suggesting benefit in clinical trials. Furthermore, recent evidence has not found any benefit to statin + niacin combinations [55, 56]. According to prescribing information for Niaspan (a commonly prescribed drug in the US), the product is metabolized in the liver but excreted through the kidneys. Thus, caution should be used in patients who have renal impairment; however, no studies have been performed in this population [57].

5.4 Fibric acid derivatives (fibrates)

Fibric acid derivatives such as gemfibrozil and fenofibrate are agonists for peroxisome proliferator alpha receptors which decrease triglyceride levels and increase HDL levels [58]. Their mechanism of action is multifaceted and includes the induction of lipoprotein lipolysis, induction of hepatic fatty acid uptake, increased LDL removal and increased production of apoA-I and apoA-II in the liver [59]. According to a systematic review and meta-analysis on the effects of fibrates in kidney disease, in patients with mild-to-moderate kidney disease, fibrates significantly lowered total cholesterol and triglyceride levels but had no significant effect on LDL levels [60]. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) are two double-blind, randomized placebo-controlled trials that showed an increase in serum creatinine with fenofibrate. A follow-up to the FIELD study showed a statistically significant increase in creatinine level in patients receiving fenofibrate compared to patients receiving placebo, and a greater fall in estimated GFR however the GFR loss over time was slower as compared to the placebo group. [61] As fenofibrate is renally excreted and studies demonstrated an increase in creatinine, there is some concern regarding their use in patients with CKD; however, an analysis of two studies with over 12,326 participants showed that there was a reduction in the risk of major CV events in patients on fibrate therapy. Given the robust data in support of statin therapy, statins should be first line. However, fibrates should be considered in patients who cannot tolerate statins. Fibric acid derivatives come as gemfibrozil or several different formulations of fenofibrate. Dose reductions are needed if GFR is <60 mL/min/1.73m^2, and all fibrates are contraindicated with a GFR <30 mL/min/1.73m^2.

5.5 Fatty acid derivatives (fish oil)

Fish oil and/or consumption of oily fish have been shown in some studies to have cardioprotective effects [62]. Their greatest effect is to reduce triglycerides and this appears to be dose related [63]. It remains controversial as to whether the addition of fish oil reduces major ASCVD events and the AHA/ACC guidelines do not explicitly recommend use of fish oil. There is conflicting data regarding the use and effect of fish oil in patients with CKD in the literature. For example a meta-analysis found that fish oil was not associated with a lower risk of cardiac death, MI, or stroke [64] but another study found that fatty acid derivatives may be protective against progression to CKD [65]. Overall more research is needed to clarify a role for fish oil in hyperlipidemia and CVD prevention.

5.6 Bile acid sequestrants

Bile acid resins such as cholestyramine and colestipol bind bile acids in the intestine via anion exchange which results in decreased enterohepatic reuptake of the bile acids thus leading to fecal loss of LDL [66]. These agents are contraindicated in patients with baseline fasting triglycerides >300 mg/dL or type III hyperlipoproteinemia as they can exacerbate hypertriglyceridemia. The use of bile acid sequestrants is limited by gastrointestinal side effects and interactions with multiple other medications [67]. Since bile acid sequestrants are metabolized in the intestine as opposed to the renal system there is no specific dosage adjustment provided in manufacturer's labeling; however, there are limited studies and data from which to guide treatment decisions. Studies in the general population suggest that bile acid sequestrants are effective and safe for lowering LDL in the general population; however, there are few studies regarding their safety and efficacy in patients who have CKD. In addition, bile acid sequestrants many interfere with the absorption of immunosuppressive medications limiting their use in patients with renal transplants [68].

5.7 PCSK9 inhibitors

Proprotein convertase subtilisin kexin 9 (PCSK9) has a role in the recycling of LDL receptors: in the presence of PCSK9 LDL receptors that have bound LDL are internalized and directed to the lysosome for degradation. This reduces cell surface expression of LDL receptors, which decreases cell uptake of LDL-C and leads to a rise in circulating LDL-C. PCSK9 inhibitors are monoclonal antibodies directed against PCSK9. When PCSK9 is inhibited LDL receptors take up LDL-C from the circulation, are internalized, but then recycled to the cell surface where they can again take up LDL-C. Thus, PCSK9 inhibitors lead to significant lowering of LDL-cholesterol, and in a manner that is additive to statins [69]. PCSK9 inhibitors are delivered by subcutaneous injections ranging from weekly to monthly depending on the agent. At present, they are only indicated for adults with homozygous or heterozygous familial hypercholesterolemia or those with ASCVD who require additional lowering of LDL-C. As PCSK9 inhibitors are not cleared renally there is theoretically little concern regarding their use in CKD; however, there is little clinical data available in severe CKD. The prescribing information indicates no dose adjustment is needed for patients with mild to moderate CKD.

6 Evidence/outcomes for lipid-lowering therapy in CKD

6.1 Pre-ESRD patients

6.1.1 UK-HARP I study

UK HARP-I study (First United Kingdom Heart and Renal Protection) focused on efficacy and safety of simvastatin and low dose aspirin in patients with CKD. The study analyzed 448 patients with CKD (242 pre-dialysis, 73 on dialysis, and 133 with a functional transplant) and used a 2 × 2 factorial design for the administration of simvastatin 20 mg versus placebo and aspirin 100 mg versus placebo. After 12 months of follow up, simvastatin significantly reduced non fasting total cholesterol by 18%, LDL-C by 24%, and triglyceride level by 13%. There was no significant change in HDL-C levels. Simvastatin was not associated with elevated creatine kinase or abnormal liver function. Aspirin use caused a 3-fold increase in minor bleeds although no significant risk of major bleeds [70].

6.1.2 UK-HARP II study

The UK-HARP-II study (Second United Kingdom Heart and Renal Protection) examined the efficacy, safety, and tolerability of adding ezetimibe, 10 mg/d, to simvastatin, 20 mg/d, in patients with chronic kidney disease. This study randomized 203 patients over 18 years old with CKD (51 were on dialysis). The patients were followed up to 6 months with good show rates (>98%). At 6 months, results of total cholesterol in simvastatin monotherapy showed a 19% decrease from baseline compared to a 30% decrease in simvastatin plus ezetimibe, $p < 0.0001$. The study assessed tolerability by evaluating for muscle pain, weakness, gastrointestinal symptoms and safety by evaluating ALT, AST, alkaline phosphatase, gamma glutamyl transferase, CK, and deterioration in renal function. The only significant difference was an increase in complaint of diarrhea in simvastatin monotherapy group. [71].

6.1.3 SHARP trial

The UK-HARP I and II studies examined the efficacy and safety of simvastatin and ezetimibe in patients with CKD. The SHARP trial (Study of Heart and Renal Protection) examined the effects of lowering LDL cholesterol on CVD outcomes in patients with moderate to severe kidney disease. The chief aim of SHARP was to determine whether the lowering of LDL-C in patients with CKD could reduce the risk of CVD, non-hemorrhagic stroke, and the need for revascularization procedures. This was a randomized, double blinded trial consisting of 9270 patients over 40 years old without a history of myocardial infarction or coronary revascularization with known CKD (3023 on dialysis and 6247 not on dialysis). The pre-specified outcome was the first major atherosclerotic event as described by non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or arterial revascularization procedure.

The goal of using combination of simvastatin and ezetimibe versus monotherapy was to reduce the risk of myopathy due to high dose statin while still achieving an average reduction in LDL of 1 mmol/l (38 mg/dL). After a median 4.9 year follow-up, the active treatment yielded a 33 mg/dL lower LDL. This resulted in a 17% (RR 0.83, 95% Cl 0.74–0.94; $p = 0.002$) proportional reduction in major atherosclerotic events. The analysis is likely an underestimate since one-third of the treatment arm had noncompliance in addition to 15% of the patients in the placebo group who started a statin. The study showed clinical significance with a 23% reduction of coronary revascularization procedures (RR 0.73, 95% Cl 0.59–0.90; $p = 0.003$). This suggests a real benefit in coronary events; however, it did not show significance in major coronary events including non-fatal MI or CHD death. The study also showed clinical significance with 25% reduction in any non-hemorrhagic stroke (RR 0.75, 95% CI 0.60–0.94; $p = 0.01$). A subset analysis found a trend to larger reductions of atherosclerotic events in patients with a baseline total cholesterol >212 mg/dl, non-smokers, and patients with body-mass index >28 kg/m^2. The study also compared patients not on dialysis to those on dialysis. Those patients with CKD not on dialysis had a 22% reduction in atherosclerotic events (RR 0.78, 96% CI 0.67–0.91; $p > 0.5$) while those on dialysis had a 10% reduction (RR 0.90, 95% CI 0.75–1.08; $p = 0.2$). Simvastatin and ezetimibe were well tolerated as found in HARP I and II and no evidence of excess risks of hepatitis, gallstones, or cancer was found [72].

6.2 Dialysis patients

6.2.1 4D study

The 4D study was a placebo-controlled, double-blind randomized trial designed to determine the effects of atorvastatin in patients with type 2 diabetes on hemodialysis. The trial enrolled 1255 people with type 2 diabetes aged 18–80 years old who were on hemodialysis for less than 2 years. Patients received a four-week placebo run in phase and were then randomized to receive either placebo or atorvastatin 20 mg daily. The primary endpoints of the study were death from cardiac causes, nonfatal MI and fatal and nonfatal stroke. Patients were followed for a median of four years over which time 37% reached the primary end point. The study showed that while 20 mg Atorvastatin daily lowered LDL cholesterol levels by approximately 42% there was no significant reduction in the primary outcomes. Of note, there was an increase in relative risk of fatal stroke in those patients taking atorvastatin at 2.03 (95% CI 1.05 to 3.93; $p = 0.04$). Based on the results of this trial it was suggested that the benefits of statin therapy are likely limited once patients have already developed ESRD [73].

6.2.2 AURORA trial

The Assessment of Survival and Cardiovascular Events (AURORA) trial was a randomized, double-blind placebo controlled multicenter trial that enrolled men and women age 50 to 80 years with ESRD who had been on treatment for at least 3 months. Patients were then randomly assigned to receive either placebo or rosuvastatin 10 mg daily. The primary end point of the study was the time to major cardiovascular events which were defined as a nonfatal MI, nonfatal stroke or death from cardiovascular causes. Secondary endpoints included all-cause mortality, cardiovascular event-free survival, procedures for stenosis or thrombosis of long-term hemodialysis access, death from CV causes, coronary or peripheral revascularization and death from non-cardiovascular causes. Follow-up data was obtained 3 months after randomization and then every 6 months. 2773 patients were included in the intention to treat analysis with an average follow-up of 3.2 years. The primary end point occurred in 396 patients who received rosuvastatin and in 408 patients who received placebo with no significant effect of treatment; hazard ratio of 0.96, 95% CI of 0.84 to 1.11 and $p = 0.59$. Death from any cause occurred in 660 patients in the placebo group and 636 patients in the rosuvastatin group. Hazard ratio was 0.96, 95% CI 0.86–1.07 and $p = 0.51$ suggesting no significant effect of rosuvastatin on all-cause mortality or on death from non-cardiovascular causes based on a hazard ratio of 0.92, 95% CI 0.77 to 1.09 and $p = 0.34$ [74].

Together, the results of the 4D study and AURORA trial demonstrate that statin therapy offers no significant benefit to patients already undergoing dialysis. Despite this the KDIGO Clinical Practice Guidelines recommends continuing statins or statin/ezetimibe combination therapy for patients already taking the medication at the time of dialysis initiation [24].

6.3 Renal transplant patients

6.3.1 ALERT trial

The Assessment of Lescol in Renal Transplantation (ALERT) trial determined the effects of fluvastatin therapy on cardiac and renal endpoint in patients with renal transplants. The randomized double-blind placebo-controlled trial followed 2102 renal transplant patients aged 30–75 years over 5–6 years who either received fluvastatin 40 mg daily or placebo. The primary endpoint was defined as cardiac death, non-fatal MI, and coronary revascularization procedure. Fluvastatin significantly lowered average LDL cholesterol levels by 32% compared to placebo; however, the reduction in the primary endpoint of major adverse cardiac events was 17% and not statistically significant ($p = 0.139$). Treatment with fluvastatin did reduce the risk of cardiac death by 38% and definite non-fatal MI by 32% for a 35% risk reduction in the combined endpoint. Based on the results of this trial while statin therapy did not show a reduction in the primary endpoint, the reduction in secondary endpoints of cardiac death and nonfatal MI were consistent with other beneficial effects of statins seen in other populations [75]. A follow-up study called ALERT extension study completed in 2005 followed the patients in the original study for an additional 2 years on open-label fluvastatin XL 80 mg/day. 1652 patients of the 1787 who completed the ALERT trial were included. This follow-up study showed that patients on fluvastatin therapy had lower LDL cholesterol levels with a significant reduction in the risk of cardiac death, non-fatal MI, and cardiac interventional procedures of 21% ($p = 0.036$) as compared to patients taking placebo. Treatment with fluvastatin XL also showed no significant difference in adverse events compared to patients in the original ALERT trial including infection, malignancy, increased CK or increased alanine transferase making it a good treatment option for patient with renal transplants [76].

7 Conclusion

ASCVD is the leading cause of death in developed countries and there are many strategies for both primary prevention and secondary prevention. Dyslipidemia is defined by an unfavorable lipid profile and is a major risk factor for developing ASCVD. Patients with CKD have dyslipidemia even at early stages of renal disease and dyslipidemia tends to progress with deterioration of kidney function. The dyslipidemia in CKD is largely due to increased triglyceride levels, decreased HDL-C and varying levels of LDL-C. There are many national guidelines for treatment of dyslipidemia in the general population as well as those with CKD and collectively the guidelines advocate for the use of statins as first line therapy in patients with ASCVD or at high risk for ASCVD. The guidelines that included CKD as a specific at risk population support the use of statins to reduce ASCVD risk in those with pre-end stage CKD and in those post renal transplant. However, there is little evidence to support use of statins in patients on dialysis, although continuing statin therapy upon dialysis initiation in patients already on statin therapy is reasonable. Most guidelines focus on using statins based on their LDL lowering intensity rather than focusing on particular treatment targets. It is important to be aware of dose adjustments needed in patients with CKD or use of immunosuppressive agents. Patients who cannot tolerate statin therapy at high doses can benefit from lower dose statin combined with ezetimibe. Those with contraindications or intolerant to statin might have some benefit with fibrates or niacin but further studies need to be performed to establish improved CVD outcomes in CKD patients.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

References

1. National Institution of Diabetes and Digestive and Kidney Diseases. Kidney disease statistic for the US. https://www.niddk.nih.gov/. Accessed 08 Aug 2016.
2. Reiss AB, Voloshyna I, De Leon J, Miyawaki N, Mattana J. Cholesterol metabolism in CKD. Am J Kidney Dis. 2015;66(6):1071–82.
3. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, et al. Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med. 2016;165(7):473–81.
4. Tannock L. Dyslipidemia in Chronic Kidney Disease. In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K, Grossman A, Hershman JM et al., editors. Endotext. South Dartmouth (MA): 2000.
5. Vaziri ND, Norris K. Lipid disorders and their relevance to outcomes in chronic kidney disease. Blood Purif. 2011;31(1–3):189–96.
6. Mittalhenkle A, Stehman-Breen CO, Shlipak MG, Fried LF, Katz R, Young BA, et al. Cardiovascular risk factors and incident acute renal failure in older adults: the cardiovascular health study. Clin J Am Soc Nephrol. 2008;3(2):450–6.
7. Matsushita K, Ballew SH, Coresh J. Cardiovascular risk prediction in people with chronic kidney disease. Curr Opin Nephrol Hypertens. 2016;25(6):518–23.
8. Vaziri ND, Wang XQ, Liang K. Secondary hyperparathyroidism downregulates lipoprotein lipase expression in chronic renal failure. Am J Phys. 1997;273(6 Pt 2):F925–30.
9. Vaziri ND, Liang K. Down-regulation of tissue lipoprotein lipase expression in experimental chronic renal failure. Kidney Int. 1996;50(6):1928–35.
10. Hirano T, Sakaue T, Misaki A, Murayama S, Takahashi T, Okada K, et al. Very low-density lipoprotein-apoprotein CI is increased in

diabetic nephropathy: comparison with apoprotein CIII. Kidney Int. 2003;63(6):2171–7.
11. Oi K, Hirano T, Sakai S, Kawaguchi Y, Hosoya T. Role of hepatic lipase in intermediate-density lipoprotein and small, dense low-density lipoprotein formation in hemodialysis patients. Kidney Int Suppl. 1999;71:S227–8.
12. Ikewaki K, Schaefer JR, Frischmann ME, Okubo K, Hosoya T, Mochizuki S, et al. Delayed *in vivo* catabolism of intermediate-density lipoprotein and low-density lipoprotein in hemodialysis patients as potential cause of premature atherosclerosis. Arterioscler Thromb Vasc Biol. 2005;25(12):2615–22.
13. Deighan CJ, Caslake MJ, McConnell M, Boulton-Jones JM, Packard CJ. The atherogenic lipoprotein phenotype: small dense LDL and lipoprotein remnants in nephrotic range proteinuria. Atherosclerosis. 2001;157(1):211–20.
14. Vaziri ND, Sato T, Liang K. Molecular mechanisms of altered cholesterol metabolism in rats with spontaneous focal glomerulosclerosis. Kidney Int. 2003;63(5):1756–63.
15. Despres JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B. HDL-cholesterol as a marker of coronary heart disease risk: the Quebec cardiovascular study. Atherosclerosis. 2000;153(2):263–72.
16. Kaysen GA. Lipid and lipoprotein metabolism in chronic kidney disease. J Ren Nutr. 2009;19(1):73–7.
17. Vaziri ND, Deng G, Liang K, Hepatic HDL. Receptor, SR-B1 and Apo A-I expression in chronic renal failure. Nephrol Dial Transplant. 1999;14(6):1462–6.
18. Vaziri ND, Liang K, Parks JS. Down-regulation of hepatic lecithin: cholesterol acyltransferase gene expression in chronic renal failure. Kidney Int. 2001;59(6):2192–6.
19. Kalra OP, Khaira A, Gambhir JK, Agarwal S, Bhargava SK. Lipoprotein (a) in chronic renal failure: effect of maintenance hemodialysis. Hemodial Int. 2003;7(4):326–31.
20. Kronenberg F, Trenkwalder E, Lingenhel A, Friedrich G, Lhotta K, Schober M, et al. Renovascular arteriovenous differences in Lp[a] plasma concentrations suggest removal of Lp[a] from the renal circulation. J Lipid Res. 1997;38(9):1755–63.
21. Reblin T, Donarski N, Fineder L, Brasen JH, Dieplinger H, Thaiss F, et al. Renal handling of human apolipoprotein(a) and its fragments in the rat. Am J Kidney Dis. 2001;38(3):619–30.
22. Frischmann ME, Kronenberg F, Trenkwalder E, Schaefer JR, Schweer H, Dieplinger B, et al. *Vivo* turnover study demonstrates diminished clearance of lipoprotein(a) in hemodialysis patients. Kidney Int. 2007;71(10):1036–43.
23. Cain WJ, Millar JS, Himebauch AS, Tietge UJ, Maugeais C, Usher D, et al. Lipoprotein [a] is cleared from the plasma primarily by the liver in a process mediated by apolipoprotein [a]. J Lipid Res. 2005;46(12):2681–91.
24. Kidney Disease Improving Global Outcomes. http://kdigo.org/home/. Accessed 08 Aug 2016.
25. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. J Clin Lipidol. 2015;9(2):129–69.
26. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M, et al. 2016 Canadian cardiovascular society guidelines for the Management of Dyslipidemia for the prevention of cardiovascular disease in the adult. The Canadian journal of cardiology. 2016;32(11):1263–82.
27. Moberly JB, Attman PO, Samuelsson O, Johansson AC, Knight-Gibson C, Alaupovic P. Alterations in lipoprotein composition in peritoneal dialysis patients. Perit Dial Int. 2002;22(2):220–8.
28. Piperi C, Kalofoutis C, Tzivras M, Troupis T, Skenderis A, Kalofoutis A. Effects of hemodialysis on serum lipids and phospholipids of end-stage renal failure patients. Mol Cell Biochem. 2004;265(1–2):57–61.
29. Rathi TK, Dhrolia MF, Imtiaz S. More hostile dyslipidaemia in chronic kidney disease patients on maintenance haemodialysis than on conservative management. J Pak Med Assoc. 2016;66(8):928–31.
30. Blankestijn PJ, Vos PF, Rabelink TJ, van Rijn HJ, Jansen H, Koomans HA. High-flux dialysis membranes improve lipid profile in chronic hemodialysis patients. J Am Soc Nephrol. 1995;5(9):1703–8.
31. Jung K, Scheifler A, Schulze BD, Scholz M. Lower serum high-density lipoprotein-cholesterol concentration in patients undergoing maintenance hemodialysis with acetate than with bicarbonate. Am J Kidney Dis. 1995;25(4):584–8.
32. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol. 2007;18(1):293–303.
33. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725–30.
34. Hricik DE, Bartucci MR, Mayes JT, Schulak JA. The effects of steroid withdrawal on the lipoprotein profiles of cyclosporine-treated kidney and kidney-pancreas transplant recipients. Transplantation. 1992;54(5):868–71.
35. Hricik DE, Mayes JT, Schulak JA. Independent effects of cyclosporine and prednisone on posttransplant hypercholesterolemia. Am J Kidney Dis. 1991;18(3):353–8.
36. Kuster GM, Drexel H, Bleisch JA, Rentsch K, Pei P, Binswanger U, et al. Relation of cyclosporine blood levels to adverse effects on lipoproteins. Transplantation. 1994;57(10):1479–83.
37. Kronenberg F, Konig P, Lhotta K, Ofner D, Sandholzer C, Margreiter R, et al. Apolipoprotein(a) phenotype-associated decrease in lipoprotein(a) plasma concentrations after renal transplantation. Arterioscler Thromb. 1994;14(9):1399–404.
38. Mak RH. Effect of metabolic acidosis on hyperlipidemia in uremia. Pediatr Nephrol. 1999;13(9):891–3.
39. Perez-Granados AM, Navas-Carretero S, Schoppen S, Vaquero MP. Reduction in cardiovascular risk by sodium-bicarbonated mineral water in moderately hypercholesterolemic young adults. J Nutr Biochem. 2010;21(10):948–53.
40. Allegra V, Martimbianco L, Vasile A. Lipid and apolipoprotein patterns during erythropoietin therapy: roles of erythropoietin, route of administration, and diet. Nephrol Dial Transplant. 1997;12(5):924–32.
41. Pollock CA, Wyndham R, Collett PV, Elder G, Field MJ, Kalowski S, et al. Effects of erythropoietin therapy on the lipid profile in end-stage renal failure. Kidney Int. 1994;45(3):897–902.
42. Alnahal AA, Tahan M, Fathy A, Fathy T. Effect of deferoxamine therapy on insulin resistance in end-stage renal disease patients with iron overload. Saudi J Kidney Dis Transpl. 2014;25(4):808–13.
43. Wang Y, Lu H, Huang Z, Lin H, Lei Z, Chen X, et al. Apolipoprotein E-knockout mice on high-fat diet show autoimmune injury on kidney and aorta. Biochem Biophys Res Commun. 2014;450(1):788–93.
44. Pitt B. The potential use of angiotensin-converting enzyme inhibitors in patients with hyperlipidemia. Am J Cardiol. 1997;79(5A):24–8.
45. Chertow GM, Burke SK, Raggi P. Treat to goal working G. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62(1):245–52.
46. Shantouf R, Budoff MJ, Ahmadi N, Tiano J, Flores F, Kalantar-Zadeh K. Effects of sevelamer and calcium-based phosphate binders on lipid and inflammatory markers in hemodialysis patients. Am J Nephrol. 2008;28(2):275–9.
47. Katopodis KP, Andrikos EK, Gouva CD, Bairaktari ET, Nikolopoulos PM, Takouli LK, et al. Sevelamer hydrochloride

versus aluminum hydroxide: effect on serum phosphorus and lipids in CAPD patients. Perit Dial Int. 2006;26(3):320–7.
48. Khajehdehi P, Taheri S. Effect of oral calcitriol pulse therapy on the lipid, calcium, and glucose homeostasis of hemodialysis-patients: its safety in a combination with oral calcium carbonate. J Ren Nutr. 2003;13(2):78–83.
49. Wehmeier K, Beers A, Haas MJ, Wong NC, Steinmeyer A, Zugel U, et al. Inhibition of apolipoprotein AI gene expression by 1, 25-dihydroxyvitamin D3. Biochim Biophys Acta. 2005;1737(1):16–26.
50. Shapiro MD, Fazio S. From lipids to inflammation: new approaches to reducing atherosclerotic risk. Circ Res. 2016;118(4):732–49.
51. Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 2002;106(15):1943–8.
52. Morita T, Morimoto S, Nakano C, Kubo R, Okuno Y, Seo M, et al. Renal and vascular protective effects of ezetimibe in chronic kidney disease. Intern Med. 2014;53(4):307–14.
53. He YM, Feng L, Huo DM, Yang ZH, Liao YH. Benefits and harm of niacin and its analog for renal dialysis patients: a systematic review and meta-analysis. Int Urol Nephrol. 2014;46(2):433–42.
54. Knopp RH, Ginsberg J, Albers JJ, Hoff C, Ogilvie JT, Warnick GR, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism. 1985;34(7):642–50.
55. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–67.
56. Group HTC, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371(3):203–12.
57. Highlights of Prescribing Information (database on the Internet). Available from http://www.rxabbvie.com/pdf/niaspan.pdf. Accessed 18 Aug 2016.
58. Tenenbaum A, Fisman EZ. Balanced pan-PPAR activator bezafibrate in combination with statin: comprehensive lipids control and diabetes prevention? Cardiovasc Diabetol. 2012;11:140.
59. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation. 1998;98(19):2088–93.
60. Jun M, Zhu B, Tonelli M, Jardine MJ, Patel A, Neal B, et al. Effects of fibrates in kidney disease: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;60(20):2061–71.
61. Davis TM, Ting R. Best JD, Donoghoe MW, Drury PL, Sullivan DR et al. effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the fenofibrate intervention and event lowering in diabetes (FIELD) study. Diabetologia. 2011;54(2):280–90.
62. Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. Int J Cardiol. 2009;136(1):4–16.
63. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006;189(1):19–30.
64. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012;308(10):1024–33.
65. Lauretani F, Maggio M, Pizzarelli F, Michelassi S, Ruggiero C, Ceda GP, et al. Omega-3 and renal function in older adults. Curr Pharm Des. 2009;15(36):4149–56.
66. Sando KR, Knight M. Nonstatin therapies for management of dyslipidemia: a review. Clin Ther. 2015;37(10):2153–79.
67. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation. 2014;129(25 Suppl 2):S1–45.
68. KDOQI. KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. http://www2.kidney.org/professional/kdoqi/guidelines_lipids/iii.htm. Accessed 30 Aug 2016.
69. Page MM. Watts GF. PCSK9 inhibitors - mechanisms of action. Aust Prescr. 2016;39(5):164–7.
70. Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, et al. First United Kingdom heart and renal protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis. 2005;45(3):473–84.
71. Landray M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J, et al. The second United Kingdom heart and renal protection (UK-HARP-II) study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis. 2006;47(3):385–95.
72. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.
73. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–48.
74. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407.
75. Holdaas H, Fellstrom B, Holme I, Nyberg G, Fauchald P, Jardine A, et al. Effects of fluvastatin on cardiac events in renal transplant patients: ALERT (assessment of Lescol in renal transplantation) study design and baseline data. J Cardiovasc Risk. 2001;8(2):63–71.
76. Holdaas H, Fellstrom B, Cole E, Nyberg G, Olsson AG, Pedersen TR, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant. 2005;5(12):2929–36.