



Dyslipidemias in Chronic Kidney Disease: Pathophysiology and Emerging Therapies

Abstract

Dyslipidemia plays a critical role in the pathogenesis of both cardiovascular (CVD) and chronic kidney diseases (CKD). Although modifiable, dyslipidemia remains undertreated, probably due to the differences in management across clinical guidelines and the lack of evidence supporting treatment benefits in patients with advanced CKD and those on dialysis. High levels of lipids or changes in their structure are involved in kidney damage due to oxidative stress, inflammation, and lipotoxicity. This review explores the pathophysiology of dyslipidemia in kidney injury and the current strategies for lipid management across different CKD populations, including non-dialysis, dialysis, and kidney transplant recipients. Statins remain the first-line therapy; however, their efficacy is reduced in advanced CKD and patients on dialysis. Emerging therapies, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bempedoic acid, inclisiran, and icosapent ethyl, offer promising options for patients with statin intolerance or persistent dyslipidemia and have been tested in patients with CKD with a glomerular filtration rate (GFR) > 30 mL/min/m². Newer targets, such as ANGPTL3, APOC3, CETP, and Lp(a), are currently being studied. Effective lipid management in patients with CKD requires a personalized, multidisciplinary approach involving nephrologists, cardiologists, endocrinologists, and primary care physicians to implement evidence-based interventions and improve long-term outcomes.

Keywords: Cholesterol, Chronic kidney disease, Dyslipidemia, Hyperlipidemia, Statins

Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide, with dyslipidemia being a major contributing factor, especially higher low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels, and lower high-density lipoprotein cholesterol (HDL-C).^{1,2} Dyslipidemia enhances chronic kidney disease (CKD) progression, and given that it is a modifiable risk factor, it has become one of the main treatment targets in this patient population by many professional societies, including the American Heart Association (AHA), the American College of Cardiology (ACC), the European Society of Cardiology (ESC), and the Kidney Disease: Improving Global Outcomes (KDIGO).¹⁻⁴

While cardiology societies suggest aggressive LDL-C lowering strategies,^{1,3} KDIGO guidelines⁴ offer a less aggressive approach. Residual cardiovascular risk (CVR) may persist despite treatment, prompting the development of new strategies. This review explores contemporary approaches

to lipid management across different CKD stages and discusses the current treatment guidelines and emerging therapies.

Pathophysiology of Dyslipidemia in Kidney Disease

The prevalence of dyslipidemia in CKD ranges between 23-30%, although the exact prevalence has not been established due to several factors.⁵ In patients with CKD, dyslipidemia does not follow a uniform pattern. It varies significantly depending on the stage, presence of proteinuria, type of kidney replacement therapy (KRT), and the pharmacological treatment received.⁶ In patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min/m²) and on hemodialysis, total cholesterol and LDL-C levels are usually normal or even low. In contrast, TG and very-low-density lipoprotein cholesterol (VLDL-C) levels are elevated due to reduced clearance of these particles. However, patients with nephrotic syndrome or those on peritoneal dialysis show more marked

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hyperlipidemia, with elevated LDL-C and total cholesterol. In kidney transplant recipients, immunosuppressants alter lipid metabolism, leading to increases in total cholesterol, LDL-C, and TG [Figure 1, Table 1]. In addition, the characteristics and activity of lipoproteins vary across all CKD stages.⁶

All these changes in the lipid levels and composition contribute to increasing CVD, an effect that may be higher in patients with additional diabetes and hypertension.⁷ The latter are associated with more albuminuria and CKD progression.⁸ In patients with advanced CKD, the azotemic environment enhances the oxidation of LDL-C and HDL-C particles, leading to higher oxidative stress and kidney toxicity.⁷ Lipid overload drives cellular lipid accumulation, where they form small droplets, disrupting normal cellular activity and increasing the expression of cytokines such as TNF- α , IL-6, and monocyte chemoattractant protein (MCP)-1, which recruit immune cells and sustain a chronic inflammatory microenvironment in the kidney

parenchyma. Moreover, lipid accumulation triggers the production of profibrotic mediators such as transforming growth factor-beta (TGF- β), which augments extracellular matrix expansion, glomerulosclerosis, and interstitial fibrosis [Figure 2], increasing the risk of CKD progression.⁹ Alternatively, podocytes are particularly vulnerable to lipid-induced injury. When lipid molecules deposit in podocytes, podocytes lose their cytoskeletal integrity, leading to apoptosis, proteinuria, and a reduction in the GFR.¹⁰

Vascular calcification is aggravated by elevated oxidized LDL-C, which can increase osteogenic transformation of vascular smooth muscle cells and promote calcium deposition within the vascular wall. Dysregulated mineral metabolism, including hyperphosphatemia and secondary hyperparathyroidism, may exacerbate lipid abnormalities by altering systemic inflammation. Moreover, some phosphate binders, especially calcium-based formulations, may affect lipid absorption in the gut, while others, such as sevelamer, have been shown to reduce LDL-C levels. Therefore, lipid-

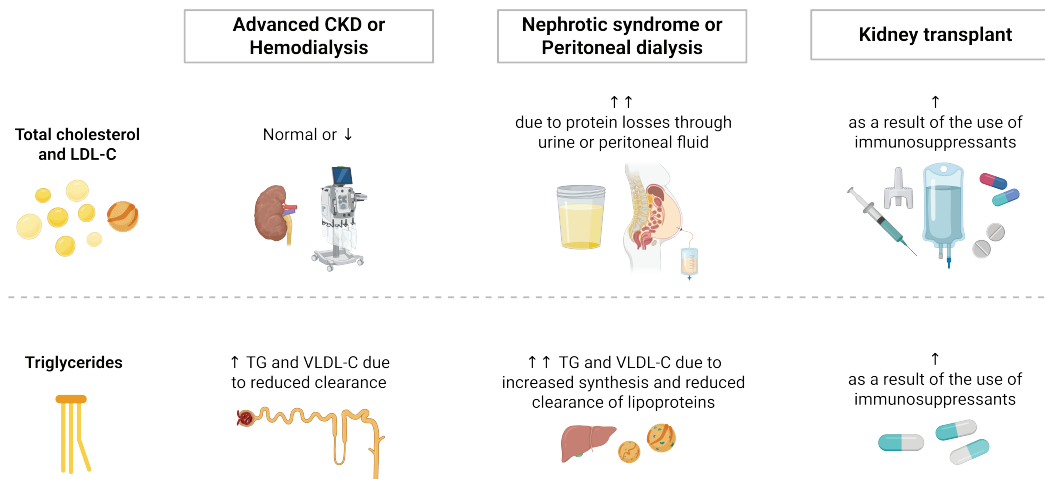


Figure 1: Lipid abnormalities in CKD, patients on dialysis, kidney transplant recipients, and nephrotic syndrome. “Created in BioRender. So, P. (2025) <https://BioRender.com/wizjph1>”. LDL-C: Low-density lipoprotein cholesterol, TG: Triglycerides, VLDL-C: Very low-density lipoprotein cholesterol.

Table 1: Lipid abnormalities in chronic kidney disease (CKD) and nephrotic syndrome

Condition/Stage CKD	Lipid profile alterations	Comments
Early CKD (eGFR \geq 30 mL/min/m ²)	<ul style="list-style-type: none"> Mild hypertriglyceridemia Normal or slightly increased LDL-C Decreased HDL-C 	Lipoprotein metabolism begins to change, with reduced activity of lipoprotein lipase and hepatic lipase.
Advanced CKD (eGFR < 30 mL/min/m ²) Hemodialysis	<ul style="list-style-type: none"> Moderate hypertriglyceridemia- Normal or low total cholesterol- Low HDL-C- Small dense LDL-C particles Elevated TGs- Decreased HDL-C- Normal or low LDL-C- Increased oxidized LDL-C 	Uremia alters lipoprotein clearance; increases VLDL-C production and impairs HDL-C maturation. Chronic inflammation and oxidative stress contribute to these changes.
Peritoneal dialysis	<ul style="list-style-type: none"> Elevated LDL-C and TGs- Reduced HDL-C 	Glucose absorbed from dialysis fluid promotes lipogenesis.
Kidney transplant	<ul style="list-style-type: none"> Increased total cholesterol, LDL-C, and TGs- Low HDL-C 	Immunosuppressants (e.g., corticosteroids, calcineurin inhibitors) contribute to dyslipidemia.
Nephrotic syndrome	<ul style="list-style-type: none"> Marked elevation of total cholesterol and LDL-C- Increased TGs- Elevated lipoprotein(a)- Low HDL-C 	Massive proteinuria leads to hepatic overproduction of lipoproteins and decreased catabolism.

CKD: Chronic kidney disease, eGFR: estimated Glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, VLDL-C: Very-low-density lipoprotein cholesterol, TGs: Triglycerides.

lowering strategies in CKD should consider the bone-vascular interplay to avoid interventions that might improve lipid profiles but worsen vascular calcification or bone fragility.¹¹

Management of Dyslipidemia in Chronic Kidney Disease

Given the significant impact of dyslipidemia on both kidney and cardiovascular outcomes in patients with CKD,

it is important to treat lipid abnormalities proactively and effectively.^{1,3,4} [Figure 3].

Lifestyle interventions

Lifestyle interventions are the universally recommended, first-line treatment, although evidence in patients with CKD is limited.¹⁻⁴ Some recommendations include: following a healthy diet, regular exercise, smoking cessation, and weight loss.¹² Importantly, dietary interventions must

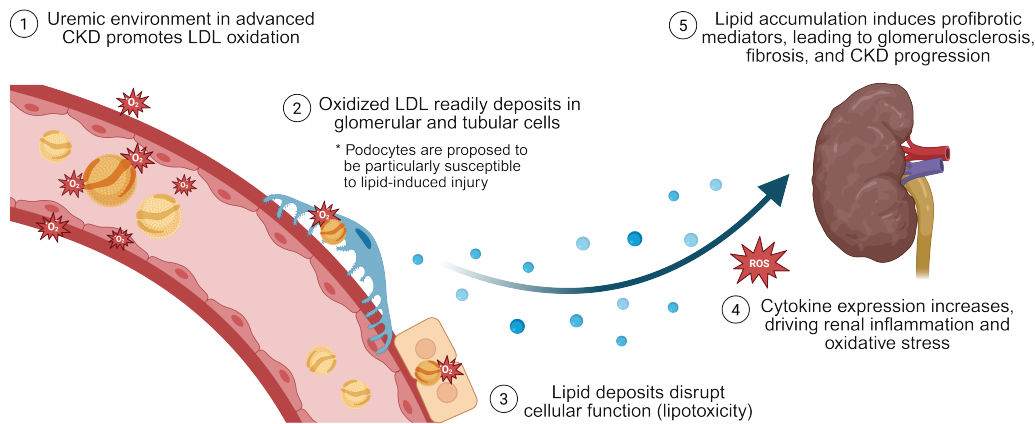


Figure 2: Pathophysiology of Dyslipidemia-Induced Kidney Injury. "Created in BioRender. So, P. (2025) <https://BioRender.com/zkr7653>". CKD: Chronic kidney disease, LDL: Low-density lipoprotein, ROS: Reactive oxygen species.

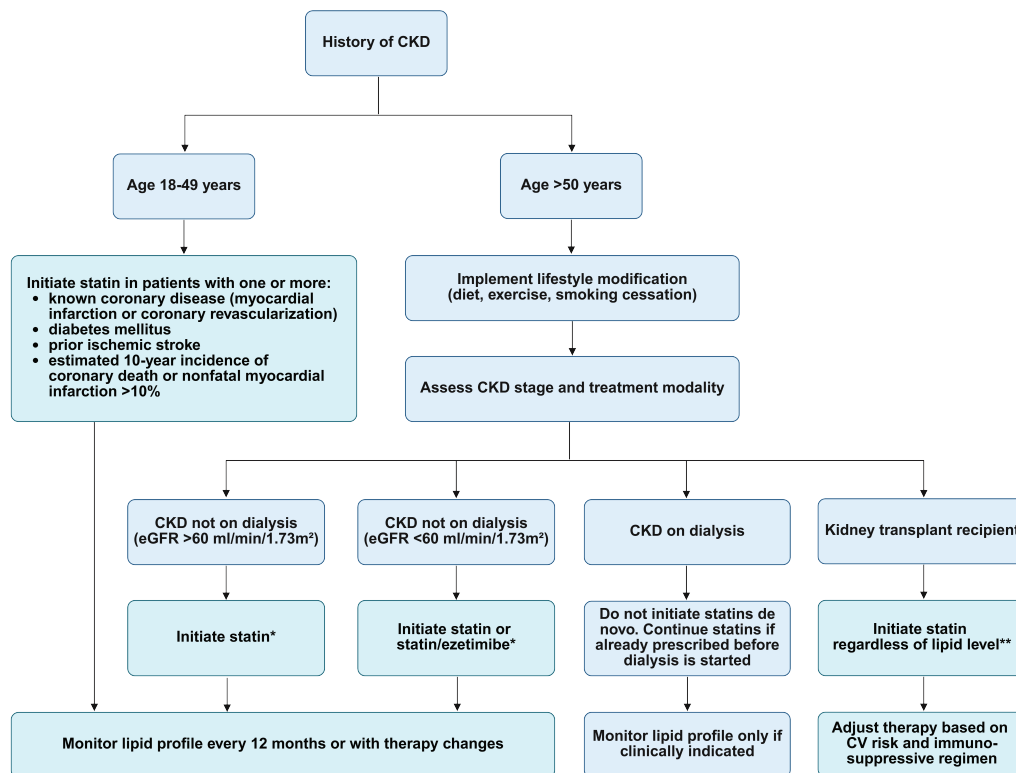


Figure 3: Proposed algorithm for the monitoring and management of dyslipidemia in patients with CKD according to KDIGO guidelines. "Created in BioRender. So, P. (2026) <https://BioRender.com/tq4fkqx>". CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, HD: Hemodialysis, CV: Cardiovascular. * Avoid initiating statins if the patient is frail or has limited life expectancy. ** Watch for drug interactions (e.g., cyclosporine + statins ↑ risk of myopathy)

be tailored to the special needs of patients with CKD, particularly concerning potassium and protein intake.

Pharmacological management

Statins

Statin therapy has been well-established for reducing cardiovascular events (CVE) in the general population and is the cornerstone of pharmacological management of dyslipidemias. In patients with CKD, the strongest evidence came from the SHARP trial, which compared major CVE rates in 4,650 patients with CKD stages III-V who received the combination of simvastatin (20 mg) and ezetimibe (10 mg) with those of 4,620 patients who received placebo. A 17% relative reduction in atherosclerotic events with simvastatin plus ezetimibe was demonstrated >5 years. However, the study did not detect a significant reduction in overall or cardiovascular mortality.¹³ These results are supported by several meta-analyses that evaluated subgroups with CKD.¹³⁻¹⁵ The largest meta-analysis is the one conducted by Tunncliffe *et al.*,^[16] including 63 studies with 50,725 randomized patients. It concluded that compared to placebo or standard care, statins prevent major CVE, cardiovascular death, myocardial infarction, and overall mortality.¹⁶ A meta-analysis by Liao *et al.*^[17] evaluated different antilipidemic therapies in patients with CKD (eGFR \leq 60 mL/min/1.73 m²), including high and low-intensity statins, and several combination therapies, including statins and ezetimibe, statins and PCSK9 inhibitors, and statins and fibrates. PCSK9 inhibitor therapy was the most effective treatment (OR 0.62), and high and low-intensity statins also reduced mortality (OR 0.76 and 0.89, respectively).¹⁷ Regarding side effects, statins had little effect on liver enzymes, and very few studies reported rhabdomyolysis or elevated creatinine.¹⁶ Although proteinuria has been associated with certain statins, such as rosuvastatin, the association of this side effect has not been well established in clinical trials.¹⁸

The KDIGO guidelines recommend that patients aged \geq 50 years with an eGFR $<$ 60 mL/min/1.73 m² be treated with a statin or a statin/ezetimibe combination, regardless of baseline LDL levels,⁴ although clinical guidelines do not specify the exact statin to initiate.^{1,3,4} Younger patients with diabetes, established CVD, or high calculated CVR also benefit from lipid-lowering therapy.⁴ Although the KDIGO guidelines have not updated the lipid guidelines in CKD since 2013, the 2024 CKD guidelines highlight a section dedicated to lipid management, maintaining the same recommendations and emphasizing that statin-based regimens should be selected to achieve the greatest possible absolute reduction in LDL-C.¹⁹ Some authors have referred to this treatment strategy as "fire and forget", because treatment is initiated without aiming for specific LDL-C targets and without recommending routine follow-up of lipid levels.²⁰ On the other hand, the AHA/ACC 2018 guidelines recommend initiating moderate-intensity statins, alone or in combination with ezetimibe, for adults

aged 40-75 years with LDL-C concentrations between 70 and 189 mg/dL who have a 10-year atherosclerotic CVD risk of 7.5% or higher.¹ [Table 2]. In contrast, the ESC/EAS categorizes patients as high risk (G3a-3b CKD category) and very high risk (G4-5 not on dialysis). For both groups, the recommended LDL-C reduction is at least 50% from baseline, with targets of $<$ 70 mg/dL for high-risk patients and $<$ 55 mg/dL for those at very high risk.³ Similarly, the UK Renal Association outlines specific treatment thresholds: total cholesterol \leq 4 mmol/L, LDL-C \leq 2 mmol/L, and non-HDL-C \leq 2.5 mmol/L, further emphasizing a quantitative approach to dyslipidemia management in CKD.²¹

However, evidence for initiating statins in patients on dialysis is limited. The 4D and AURORA trials did not demonstrate a significant CVE reduction with statin use in this population, but showed an increase in hemorrhagic stroke in the intervention group.^{22,23} On the other hand, although the SHARP trial observed a reduction in CVR in the overall treatment group receiving statins, this effect was not replicated in the subgroup on dialysis.¹³ Furthermore, observational data suggest a U-shaped relationship between cholesterol levels and mortality in dialysis populations, a phenomenon known as reverse epidemiology.²⁴ This phenomenon could be explained by the fact that in patients with CKD, low cholesterol levels are often associated with malnutrition or a syndrome known as malnutrition-inflammation complex syndrome (MICS), which is associated with higher mortality.¹² Although patients on peritoneal dialysis may benefit from more aggressive lipid management due to their higher LDL-C levels from glucose absorption from the dialysate, current KDIGO guidelines recommend against initiating statin therapy in patients on dialysis, though patients who were already receiving treatment before dialysis initiation can continue therapy.⁴

In kidney transplant recipients, statins are considered safe and are recommended by KDIGO for all patients to reduce CVR.⁴ The largest meta-analysis in transplant recipients did not show an overall reduction in major CVE in patients treated with statins.²⁵ Nevertheless, given the high CVR in this group, statin therapy remains an important treatment for long-term management of dyslipidemia in this patient population.⁴ It is important to consider various potential drug interactions in transplant recipients, especially with cyclosporine, which is metabolized by the CYP3A4 enzyme system and can increase blood concentrations of statins, potentially elevating the risk of myopathy.³ Fluvastatin, pravastatin, pitavastatin, and rosuvastatin are metabolized by enzymes other than CYP3A4, which reduces their potential for interaction with cyclosporine.²⁶ On the other hand, tacrolimus appears to have a lower risk of interaction with statins compared to cyclosporine.

Fibrates

Fibrates (fenofibrate, bezafibrate, and gemfibrozil) may have cardiovascular benefit in patients with GFR between 30–60

Table 2: Treatment recommendations for dyslipidemia in patients with non-dialysis CKD, patients on dialysis, and kidney transplant recipients

Society/Guideline	CKD (non-dialysis)	Dialysis	Kidney transplant recipients
ACC 2010 ²	No specific recommendations, provides data from TNT study: patients with diabetes and mild to moderate CKD demonstrated a marked reduction in cardiovascular events with intensive lipid-lowering	No specific recommendations.	No specific recommendations.
KDIGO 2024 ⁴	<ul style="list-style-type: none"> • ≥ 50 years with eGFR ≥ 60 mL/min/1.73 m²: Recommend statin (1B) • ≥ 50 years with eGFR < 60 mL/min/1.73 m²: Recommend statin or statin/ezetimibe combination therapy (1A). • 18-49 years: Consider statin if diabetes, CV disease, prior ischemic stroke, or >10 % CV risk over 10 years. (2A) 	<ul style="list-style-type: none"> • Do not initiate statins (2A). • Continue if already on treatment before dialysis start (2C). 	Suggest statins for all adult recipients (2B).
AHA/ACC 2018 ¹	<ul style="list-style-type: none"> • 40-75 years with LDL-C 70-189 mg/dL who are at 10-year ASCVD risk of 7.5% or higher: initiate a moderate-intensity statin or moderate-intensity statins combined with ezetimibe (2A) • No specific LDL-C target 	<ul style="list-style-type: none"> • Do not initiate statins (3). • Continue if already on treatment before dialysis start (2B). • No specific LDL-C target 	<ul style="list-style-type: none"> • No specific recommendations; reasonable if CV risk exists. • No specific LDL-C target
ESC/EAS 2019 ³	<ul style="list-style-type: none"> • Patients with stage 3-5 CKD: recommended statin/ezetimibe combination (IA) • LDL-C reduction goal: ≥50% from baseline or target <70 mg/dL (high risk G3a-G3b), <55 mg/dL (very high risk G4-G5). 	<ul style="list-style-type: none"> • Do not initiate statins (3). • Continue if already on treatment before dialysis start (2B). 	<ul style="list-style-type: none"> • Initiate statins as first-line agents. Initiation should be at low doses. • Same LDL-C targets as other high-CV-risk groups. • Drug interactions with immunosuppressant must be considered.

CKD: Chronic kidney disease, ACC: American college of cardiology, AHA/ACC: American heart association/American college of cardiology, ESC/EAS: European society of cardiology/atherosclerosis society, LDL-C: Low-density lipoprotein cholesterol, eGFR: Estimated glomerular filtration rate, CV: Cardiovascular

mL/min/1.73 m².²⁷ The meta-analysis conducted by Liao *et al.*¹⁷ did not show a clear mortality benefit in patients with CKD (eGFR ≤ 60 mL/min/1.73 m²) treated with a combination of statins and fibrates, and a slight worsening of kidney function was observed when a combination of rosuvastatin and fenofibrate was administered, though this effect was reversible upon discontinuation of treatment.¹⁷ Furthermore, several studies have associated an increased risk of rhabdomyolysis with the combination of statins and fibrates.²⁸ Thus, the KDIGO guidelines recommend against the combined use of statins and fibrates in patients with CKD.

Bile acid sequestrants

Bile acid sequestrants (cholestyramine, colestipol, colesevelam) are resins that bind to bile acids, preventing their absorption from the intestinal lumen. This forces the liver to produce more bile acids from hepatic cholesterol, thereby increasing LDL-C receptor expression and reducing circulating LDL-C. These drugs are currently used as second-line therapy in patients with CVD who do not have kidney disease,³ and have been associated with a 25% LDL-C reduction, with a decrease in CVR proportional to LDL-C.²⁹ However, the evidence in patients with CKD, on dialysis, or kidney transplant recipients is limited. There are no specific recommendations in any guideline regarding the use of bile acid sequestrants in patients with CKD.^{1,3,4}

Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor indicated for treating obesity that decreases the absorption of dietary fats in the gastrointestinal tract. There is limited data on Orlistat use in kidney disease. MacLaughlin *et al.* conducted a prospective, non-randomized study evaluating weight loss in 44 patients with CKD (eGFR 15–60 mL/min/1.73 m²) following a program that included a low-calorie diet, exercise, nutritional education, and orlistat. A significant decrease in total cholesterol, LDL-C, and TG levels, and weight loss was observed at 24 months. Side effects were mild and primarily gastrointestinal.³⁰

Niacin

Niacin is a lipid-modulating agent that decreases the release of free fatty acids from adipose tissue by blocking lipase. This reduces hepatic TG synthesis and the production of LDL-C and VLDL-C. Furthermore, by inhibiting hepatic uptake of apoA-I, it increases the half-life of HDL-C. Despite some data supporting the use of niacin for CVR prevention, a meta-analysis of 11 clinical trials with 35,031 patients showed no statistically significant reduction in all-cause mortality or mortality from coronary artery disease.³¹ Adverse effects included flushing, increased risk of diabetes, and major bleeding.^{31,32} Data in patients with CKD is limited, with no current specific clinical guidelines guiding their use in patients with kidney disease.^{1,3,4}

Protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
 PCSK9 inhibitors (evolocumab and alirocumab) are monoclonal antibodies against PCSK9, both approved by the Food and Drug Administration (FDA) in 2015 for the treatment of heterozygous familial hypercholesterolemia and atherosclerotic CVD. They inhibit the degradation of LDL-C receptors and increase the clearance of LDL-C molecules. The FOURIER trial³³ assessed the safety and efficacy of evolocumab compared with placebo in patients with atherosclerotic disease on statin therapy. A significant reduction in the primary composite outcome (cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina or coronary revascularization) was observed with evolocumab compared to placebo. In a sub-analysis of patients with CKD (GFR > 30 mL/min/m²), evolocumab maintained a relative risk reduction of the primary outcome and reductions in LDL-C. Similarly, the ODYSSEY OUTCOMES trial evaluated the efficacy of alirocumab compared with ezetimibe in patients with high CVR and elevated LDL-C despite maximal statin

doses.³⁴ This trial showed a greater reduction in LDL-C in patients who were treated with alirocumab, with a similar rate of CVE in both groups. This effect was maintained even in patients with CKD, although it diminished as GFR decreased.³⁴ As monoclonal antibodies are not cleared through the kidneys, no dose adjustments are necessary, making them safe for use even in CKD. However, clinical trials in patients on dialysis are still limited.

Emerging Therapies

While statins remain the cornerstone of lipid management, residual CVR may persist, especially in advanced CKD, where conventional therapies may show less efficacy.¹³ In recent years, new agents have been developed to target lipid metabolism through alternative pathways, to increase the efficacy of currently available drugs [Table 3].

Bempedoic acid

Bempedoic acids (nexletol and nexlizet) are FDA-approved prodrugs that inhibit adenosine triphosphate citrate lyase

Table 3: Lipid-lowering agents in CKD: Mechanisms and renal considerations

Therapy	Mechanism of action	Primary metabolism	Administration	Main adverse effects	Studies in CKD
Statins ^{14,15,17}	Inhibit HMG-CoA reductase, reducing hepatic cholesterol synthesis	Liver(CYP450)	Oral, daily	Muscle pain, elevated liver enzymes	SHARP, metanalysis eGFR ≥ 30 mL/min/m ²
Ezetimibe ¹³	Inhibits intestinal absorption of cholesterol	Liver and Intestine	Oral, daily	GI upset, rare liver enzyme elevations	SHARP eGFR ≥ 30 mL/min/m ²
Fibrates ^{17,27}	Activate PPARα, reducing TG and increasing HDL	Kidney and Liver	Oral, daily	Increased creatinine, possible nephrotoxicity	30-60 mL/min in limited studies, avoid in ESKD
PCSK9 inhibitors (evolocumab) ^{33,34}	Block PCSK9 to increase LDL receptor recycling and LDL clearance	Liver	Subcutaneous, every 2-4 weeks	Injection site reactions, nasopharyngitis	FOURIER/ODYSSEY eGFR ≥ 30 mL/min/m ²
Bempedoic acid ³⁵	Inhibits ATP citrate lyase upstream of HMG-CoA reductase	Liver (minimal kidney excretion)	Oral, daily	Elevated uric acid and creatinine	CLEAR eGFR ≥ 30 mL/min/m ²
Inclisiran ³⁷	siRNA that inhibits PCSK9 synthesis in hepatocytes	Liver	Subcutaneous, every 6 months	Injection site reactions, mild flu-like symptoms	ORION eGFR ≥ 30 mL/min/m ² Not studied in dialysis
Icosapent ethyl ³⁹	Purified EPA with anti-inflammatory and lipid-lowering effects	Liver	Oral, daily	Arthralgia, bleeding risk	REDUCE-IT RENAL eGFR ≥ 30 mL/min/m ² Not in ESKD
CETP inhibitors (Anacetrapib, obicetrapib) ⁴³	Inhibit CETP, raising HDL and lowering LDL	Under investigation	Oral	Hypertension, no proven benefit	No CKD-specific data
ANGPTL3 inhibitors (Evinacumab) ^{44,46}	Inhibit ANGPTL3 to reduce LDL and TG levels	Liver	Intravenous	Possible liver enzyme elevation	No CKD-specific data
APOC3 inhibitors (volanesorsen, olezarsen) ^{47,48}	Inhibit APOC3 to reduce plasma triglycerides	Liver	Subcutaneous	Injection site reactions, thrombocytopenia	No CKD-specific data
Lipoprotein A inhibitors (Pelacarsen) ⁴⁹	Antisense oligonucleotide targeting Lp(a) mRNA to lower Lp(a)	Liver	Subcutaneous	Uncertain; studies ongoing	No CKD-specific data

LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, PCSK9: Proprotein convertase subtilisin/kexin type 9, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A, ATP: Adenosine triphosphate, EPA: Eicosapentaenoic acid, PPARα: Peroxisome proliferator-activated receptor alpha, CETP: Cholesteryl ester transfer protein, ANGPTL3: Angiotensin-like protein 3, APOC3: Apolipoprotein C-III, Lp(a): Lipoprotein(a), siRNA: Small interfering RNA, CKD: Chronic kidney disease, ESKD: End-stage kidney disease, eGFR: Estimated glomerular filtration rate, GI: Gastrointestinal, IV: Intravenous, mRNA: Messenger RNA.

(ACLY), a key enzyme upstream of HMG-CoA reductase in the cholesterol synthesis pathway. Activated only in the liver, it avoids muscle tissue, making it potentially beneficial for statin-intolerant patients. The CLEAR Outcomes trial showed that bempedoic acid reduced LDL-C by 21.1% and the risk of major CVE by 13% (HR 0.87; 95% CI, 0.79–0.96). Among patients with CKD, the drug also showed a significant reduction in CVR with a hazard ratio of 0.77 (95% CI, 0.66–0.91).³⁵ Bempedoic acid has been associated with higher levels of creatinine and uric acid, probably due to tubular secretion inhibition.³⁶ As there are no data in patients with eGFR < 30 mL/min/1.73 m², it is currently not recommended for use in these patients.

Inclisiran

Inclisiran is a small interfering RNA molecule that inhibits hepatic PCSK9 synthesis. It was approved by the FDA in 2021 for the treatment of heterozygous familial hypercholesterolemia and atherosclerotic CVD. In the ORION trial, patients who received the treatment reduced LDL-C levels up to 50%.³⁷ This trial included patients with GFR > 30 mL/min/1.73 m², and did not show less efficacy or an increase in secondary effects in this group of patients. However, it has not been tested in patients with eGFR < 30 mL/min/m² or patients on dialysis.³⁷ Its administration is a biannual dose, and the liver metabolizes it; hence, there is no need for dose adjustment in patients with CKD. Future studies will provide more data about Inclisiran use in CKD populations [ClinicalTrials.gov Identifier: NCT03705234].

Icosapent ethyl

Icosapent ethyl is an omega-3 fatty acid that inhibits hepatic production of TG and VLDL and has an anti-inflammatory effect that stabilizes atheroma plaques. In the REDUCE-IT trial,³⁸ it was associated with a 25% reduction in major CVE in statin-treated (HR 0.75; 95% CI, 0.68–0.83). In a sub-analysis (REDUCE-IT RENAL trial), patients with CKD > 30 mL/min/1.73 m² maintained their kidney function during the treatment.³⁹ Icosapent ethyl has a hepatic metabolism, therefore it may have a favorable safety profile in the CKD population. It was initially approved by the FDA in 2012 as a treatment for hypercholesterolemia, although in 2019 the FDA expanded the indication to reduce the risk of major CVE (heart attack, stroke, revascularization, CV death) in patients with established CVD or diabetes and other risk factors, and elevated TG levels (≥150 mg/dL) despite statin treatment.

Cholesterol ester transfer protein (CETP) inhibitors

CETP inhibitors aim to raise HDL-C and lower LDL-C by modifying lipid exchange between lipoproteins. Despite promising lipid effects, most CETP inhibitors have failed to demonstrate clinical benefits or have been associated with adverse outcomes. Torcetrapib was associated with increased mortality and higher hypertension, and was withdrawn from clinical development before reaching the market.⁴⁰ Dalcetrapib and evacetrapib were discontinued after showing no cardiovascular benefit.^{41,42} On the other

hand, Anacetrapib, studied in the REVEAL trial, showed modest efficacy in major coronary events (HR 0.91; 95% CI 0.85–0.97; $p = 0.004$), although it was not evaluated in patients with advanced CKD or macroalbuminuria.⁴³ The latest CETP inhibitor, obicetrapib, is still under investigation. Therefore, none of these treatments has been approved by the FDA.

Angiopoietin-like protein 3 (ANGPTL3) and apolipoprotein C-III (APOC3) inhibitors

ANGPTL3 and APOC3 were first described in patients with loss-of-function mutations of genes *ANGPTL3* and *APOC3*, who had less CVR.^{44,45} Evinacumab, an ANGPTL3 monoclonal antibody, was tested in patients with familial hypercholesterolemia and mixed dyslipidemia showing significant reduction in LDL-C and TG levels, and was approved by FDA in 2021.⁴⁶ Although it has not been studied in the CKD population, its hepatic metabolism may make it a safe option for patients with CKD.⁴⁶ Similarly, volanesorsen and olezarsen, antisense oligonucleotides targeting APOC3, have been associated with a reduction in TG levels in patients with familial chylomicronemia syndrome.^{47,48} In the same way, their impact on patients with CKD remains unknown. Of these, olezarsen was approved by the FDA in December 2024. ANGPTL3 is administered intravenously and APOC3 subcutaneously.^{44,45}

Lipoprotein(a) targeted therapies

Elevated lipoprotein(a) [Lp(a)] is a strong independent risk factor for cardiovascular and CKD progression. Pelacarsen is an antisense oligonucleotide designed to lower Lp(a) by targeting its mRNA.⁴⁹ It has been studied in the HORIZON trial and was associated with up to 80% reduction in Lp(a) levels⁵⁰ (NCT04023552), although its cardiovascular profile is still under investigation. Given the high prevalence of elevated levels of Lp(a) in patients with CKD, especially when it is associated with nephrotic syndrome, targeting Lp(a) may be a promising strategy for the management of dyslipidemia in these patients.

Limitations Of Emerging Therapies

Despite promising lipid-lowering efficacy, emerging therapies such as PCSK9 inhibitors, bempedoic acid, inclisiran, and ANGPTL3 or APOC3 inhibitors face important barriers to widespread implementation in CKD. Most clinical trials have limited representation of patients with advanced CKD, particularly kidney transplant recipients or patients on dialysis, which limits the generalizability of results. Additionally, the high cost and limited availability in low-resource settings limit access to treatment. The safety of these drugs in patients with CKD has not been fully established yet, limiting their current use in patients with kidney disease.

Lipid Management in Resource-Limited Settings

In low-resource areas, implementing lipid-lowering strategies in CKD faces multiple challenges, including

limited access to medications, laboratory services, lack of health insurance, and increased cost burden of lab tests and medications. In such settings, the KDIGO guidelines offer specific recommendations, prioritizing statin prescription based on clinical risk factors rather than biochemical parameters, adopting a “fire-and-forget” strategy to avoid unnecessary follow-up testing.⁴ Additionally, the high cost of medications, particularly the latest therapies, complicate access to medications. Generic statins, which are inexpensive and widely available, remain the most practical option and are supported by strong evidence even in CKD population. Governmental insurance programs are required to cover generic therapies and improve access of patients with CKD to lipid-lowering therapy.

Summary and Future Directions

Dyslipidemia is a key contributor to both cardiovascular morbidity and kidney disease progression in patients with CKD. Although KDIGO guidelines recommend statin or statin-ezetimibe therapy without defined LDL-C targets, this conservative approach contrasts with cardiology guidelines, which support more aggressive, goal-directed lipid-lowering strategies tailored to CVR levels. Given the heterogeneity in CKD presentation, lipid management should be individualized, taking into account kidney function, CVR, and therapy’s tolerability. Novel agents, including PCSK9 inhibitors, inclisiran, bempedoic acid, and icosapent ethyl, are promising alternatives, although cost-minimization strategies and specific clinical trials in the CKD population are necessary. Multidisciplinary approaches involving nephrologists, cardiologists, endocrinologists, and primary care providers are key to optimizing dyslipidemia management. In the future, health systems should prioritize developing cost-effective models, generating real-world evidence, and implementing quality improvement initiatives to bridge the gap between innovation and access. While emerging therapies offer potential to reduce residual CV risk, their impact will ultimately depend on affordability, accessibility, and thoughtful integration into current care pathways.

Conflicts of interest: Edgar V. Lerma: - Speaker/Advisory Board: Amgen, AstraZeneca, Bayer, Calliditas, Novartis, Novo Nordisk, Otsuka, scPharmaceuticals, Traverso, Vera, Vertex, Vifor - Royalty: Elsevier, McGraw-Hill, Springer, Wolters Kluwer. All other authors report no conflicts of interest.

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