



Managing dyslipidemia in chronic kidney disease: a comprehensive overview of evidence and recommendations

Ji Yoon Kim^{1,*}, Suk Min Chung^{2,3,*}, and Nam Hoon Kim⁴

¹Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; ²Division of Nephrology, Department of Internal Medicine, Gyeonggi Provincial Geriatric Siheung Hospital, Siheung; ³Division of Nephrology, Department of Internal Medicine, Korea University College of Medicine, Seoul; ⁴Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

*These authors contributed equally to this manuscript.

Patients with chronic kidney disease (CKD) have a significantly increased risk of developing cardiovascular disease (CVD), making dyslipidemia management a critical component of cardiovascular risk reduction in this population. However, as the estimated glomerular filtration rate declines, distinct pathophysiological mechanisms—unlike those observed in the general population—contribute to the development and progression of CVD. Consequently, dyslipidemia management in patients with CKD requires a tailored approach that considers altered lipid profiles, comorbid conditions, and potential safety concerns associated with pharmacological therapy. This review aimed to summarize key clinical trials evaluating lipid-lowering strategies in CKD and compare current international and regional clinical practice guidelines. We assessed cardiovascular outcomes associated with various lipid-lowering agents, including statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, fibrates, and omega-3 fatty acids. In addition, we discuss optimal therapeutic strategies across distinct patient subgroups, including those not treated with dialysis or kidney transplantation, those on dialysis, and kidney transplant recipients.

Keywords: Dyslipidemias; Renal insufficiency, chronic; Hydroxymethylglutaryl-CoA reductase inhibitors; Dialysis; Kidney transplantation

INTRODUCTION

Dyslipidemia, characterized by abnormal blood concentrations of cholesterol or triglycerides due to altered lipid metabolism, is a well-established risk factor for atherosclerotic cardiovascular disease (ASCVD). Elevated low-density lipoprotein cholesterol (LDL-C) levels are strongly associated with an increased risk of ASCVD, and LDL-C-lowering therapies, particularly statins, have consistently demonstrated cardiovascular benefits in individuals with or at high risk of

ASCVD [1-11]. Given the high prevalence of dyslipidemia in individuals with chronic kidney disease (CKD) [12] and the significantly increased risk of cardiovascular disease (CVD) in this population [13], effective lipid management in such patients is expected to reduce cardiovascular morbidity and mortality.

However, the relationship between dyslipidemia and CVD in CKD is complex, and growing evidence suggests that standard lipid management strategies may not be universally applicable across all stages of CKD. In patients with CKD, particularly those in advanced disease stages or those

on dialysis, the association between LDL-C and CVD risk is attenuated or even paradoxical [14]. Randomized controlled trials (RCTs) on statin therapy for advanced CKD often have failed to show significant reductions in primary cardiovascular outcomes [15,16]. These findings suggest the need for a tailored approach toward dyslipidemia management in patients with CKD, taking into account the CKD stage, comorbidities, and altered cardiovascular pathophysiology.

Over the past decade, several clinical practice guidelines have addressed lipid management in patients with CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) organization published lipid management recommendations in 2013 [17]. In 2024, they released guidelines addressing the overall evaluation and management of CKD, which include a lipid management section that largely retains the key principles of the 2013 guidelines but presents some updated recommendations [18]. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines [19] and the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines [20] also provide brief recommendations for lipid management in CKD. In South Korea, the Korean Society of Lipid and Atherosclerosis (KSoLA) released updated dyslipidemia guidelines in 2022 [21], and the Korean Society of Nephrology (KSN) issued guidelines for diabetic kidney disease in 2023, which included lipid management strategies [22].

In this review, we aimed to provide a comprehensive summary of the current evidence on dyslipidemia management in adults with CKD, with particular emphasis on cardiovascular outcomes and relevant clinical practice guidelines. Although various lipid-lowering agents are available, our discussion will primarily focus on statin therapy, given its central role and the abundance of RCT data in this context.

CHARACTERISTICS AND ASSESSMENTS OF DYSLIPIDEMIA IN CKD

Dyslipidemia in patients with CKD differs from that observed in the general population in terms of both lipid profile and pathophysiological mechanisms. From the early stages of CKD, triglyceride levels increase owing to enhanced hepatic production of triglyceride-rich lipoproteins (TRLs) and reduced clearance (Fig. 1), resulting from alterations in the activity of key enzymes and regulatory proteins involved in lipid metabolism [21]. Specifically, the activity of lipoprotein

lipase (LPL), the primary enzyme responsible for hydrolyzing triglycerides in chylomicrons and very low-density lipoproteins (VLDL), is reduced in CKD [23-25]. This reduction is attributed to increased levels of apolipoprotein C-III, an endogenous inhibitor of LPL, as well as the accumulation of uremic toxins that impair LPL function [26]. Additionally, hepatic lipase activity may be diminished, further contributing to the delayed catabolism of TRLs [27,28]. Simultaneously, hepatic VLDL production is upregulated, partly due to insulin resistance and increased availability of free fatty acids, which serve as substrates for triglyceride synthesis [29]. These combined effects result in the accumulation of VLDL and intermediate-density lipoproteins in the circulation, leading to hypertriglyceridemia, a hallmark of dyslipidemia in CKD. Concurrently, the levels of high-density lipoprotein cholesterol (HDL-C) decrease owing to the reduced synthesis of apolipoprotein A-I and impaired HDL maturation. The activity of lecithin-cholesterol acyltransferase, which is involved in HDL maturation, is reduced [12,30,31]. Reduced catabolism of TRL particles leads to decreased LDL production; however, LDL clearance is also impaired owing to downregulation of the hepatic LDL receptor and its activity. Consequently, the total LDL-C levels generally remain unchanged [31]. Instead, qualitative alterations in LDL particles have been observed, with a shift toward a greater proportion of small dense LDL (sdLDL), which is more atherogenic [12,32]. Enhanced sdLDL production is attributed to both increased TRL levels and cholesteryl ester transfer protein activity. Thus, the dyslipidemia pattern in CKD is typically characterized by elevated triglycerides, reduced HDL-C, and increased sdLDL particles.

In the general population, numerous studies have shown that elevated LDL-C is a major contributor to cardiovascular risk [1,2] and that lowering LDL-C, especially with statins, reduces this risk [3-5]. Accordingly, measurement of LDL-C levels before and after initiating lipid-lowering therapy is recommended, with dose escalation considered if the target levels are not achieved [11,20,21]. However, in patients with CKD, LDL-C levels are less reliable as a marker of cardiovascular risk [17]. For example, patients on dialysis with very low LDL-C or total cholesterol levels have been found to have an increased risk of all-cause and cardiovascular mortality, likely reflecting underlying malnutrition and systemic inflammation [14,33]. Moreover, the effect of elevated LDL-C on cardiovascular risk appears to diminish as the estimated glomerular filtration rate (eGFR) declines [34].

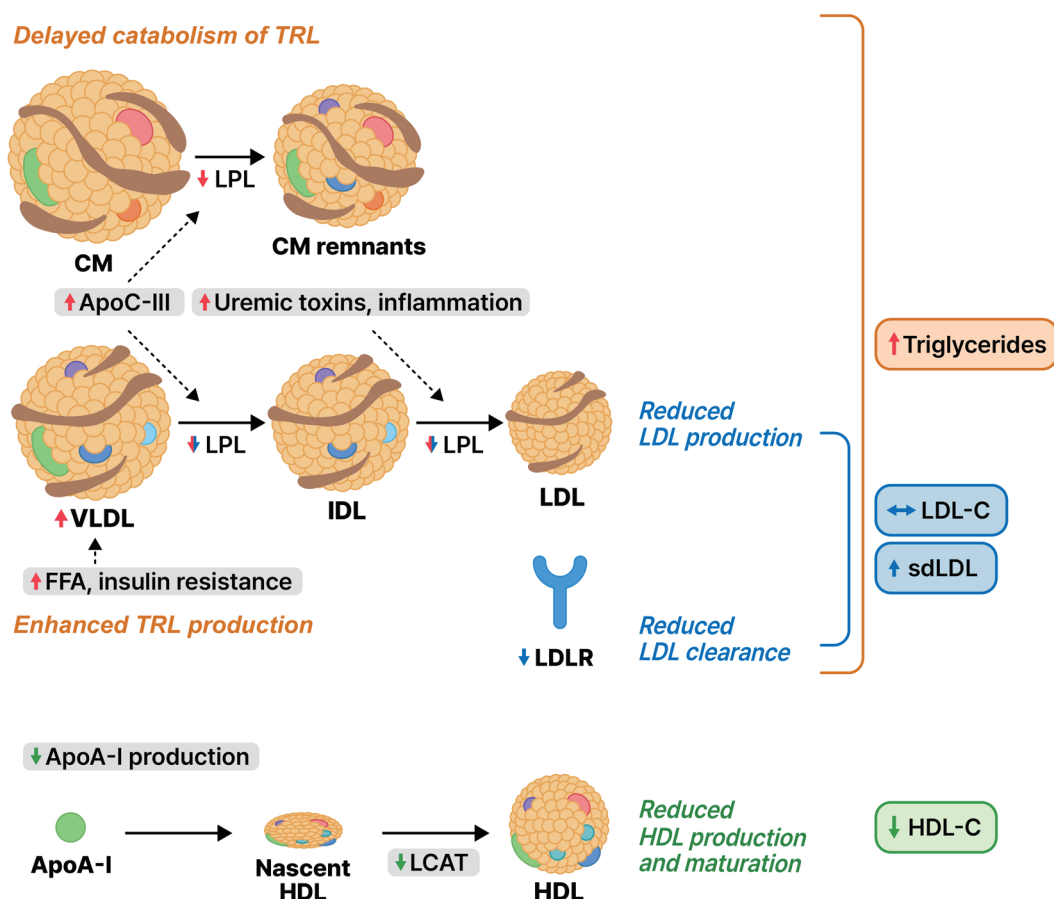


Figure 1. Altered lipid metabolism in chronic kidney disease (CKD). Lipid metabolism is markedly altered in CKD, contributing to accelerated atherosclerosis and increased cardiovascular risk. Triglyceride-rich lipoproteins (TRLs), including chylomicrons (CM) and very-low-density lipoproteins (VLDL), undergo delayed catabolism because of decreased lipoprotein lipase (LPL) activity and elevated levels of apolipoprotein C-III (ApoC-III), a known inhibitor of LPL. The accumulation of uremic toxins and systemic inflammation, which are both common in CKD, further exacerbate these disturbances. Hepatic lipase activity is also reduced, thereby impairing the conversion of intermediate-density lipoproteins (IDL) to low-density lipoproteins (LDL). Concurrently, TRL production increases, which is partly driven by insulin resistance and elevated free fatty acid (FFA) flux. LDL metabolism is disrupted by the downregulation of hepatic LDL receptor (LDLR) expression and activity, leading to reduced LDL clearance. However, impaired conversion of IDL to LDL may partially offset the reduction in LDL clearance, resulting in relatively unchanged plasma LDL cholesterol (LDL-C) levels. Nevertheless, the accumulation of small dense LDL (sdLDL), a more atherogenic LDL subclass, is promoted. The enhanced sdLDL production is attributed to increased TRL levels and cholesteryl ester transfer protein activity. High-density lipoprotein (HDL) metabolism is also adversely affected, and apolipoprotein A-I (ApoA-I) synthesis is reduced, leading to diminished formation of nascent HDL particles. Furthermore, lecithin-cholesterol acyltransferase (LCAT) activity is impaired, limiting HDL maturation. Collectively, these abnormalities characterize the proatherogenic lipid profile of CKD, featuring hypertriglyceridemia, reduced HDL cholesterol (HDL-C) levels, elevated sdLDL concentrations, and impaired lipoprotein remodeling and clearance.

Data from major statin trials show that the relative risk (RR) reduction per 1.0 mmol/L (38.7 mg/dL) decrease in LDL-C progressively declines with worsening kidney function, and is minimal among individuals on dialysis [35].

Given these considerations, the use of LDL-C as a treatment target, as well as the need for routine follow-up measurements in patients with CKD, varies among clinical guidelines. Table 1 summarizes the treatment indications

and LDL-C targets according to the major guidelines.

The KDIGO guidelines do not recommend using LDL-C levels as an indicator for initiating lipid-lowering therapy in CKD [17,18,36]. Instead, they advocate for treatment based on the estimated 10-year risk of coronary artery disease. Moreover, they do not support setting specific LDL-C target levels or performing routine follow-up measurements of LDL-C levels after initiating therapy. This approach is sup-

Table 1. Cholesterol-lowering treatment indications and target LDL-C levels for adults with CKD recommended by selected guidelines

	2013 (2024) ^{a)} KDIGO [17,18]	2018 AHA/ACC [19]	2019 ESC/EAS [20]	2022 KSoLA [21]
Treatment indications				
Non-dialysis/Non-transplant CKD	• Age ≥ 50 years • Age 18–49 years and high-risk for ASCVD^{b)}	• LDL-C 70–189 mg/dL & estimated 10-year ASCVD risk ≥ 7.5% • LDL-C ≥ 190 mg/dL^{c)} • ASCVD^{c)} • Diabetes^{c)}	• eGFR < 60 mL/min/1.73 m² • ASCVD^{c)} • Diabetes^{c)} • FH^{c)}	• CKD stage 3–5 • For CKD stage 1–2, consider age and risk factors for ASCVD^{b)}
Dialysis	• Patients already receiving statin ± ezetimibe (Initiation of a statin is not recommended)	• Patients already receiving a statin (Initiation of a statin is not recommended)	• Patients already receiving statin ± ezetimibe (Initiation of a statin is not recommended for those who are free of ASCVD)	• Patients already receiving statin ± ezetimibe (Initiation of a statin is not recommended)
KT	KT recipients	Not mentioned	KT recipients	(KT recipients ^{e)})
Target LDL-C	Not recommended	≥ 30% reduction from baseline for intermediate risk or ≥ 50% reduction for high risk ^{c)}	≥ 50% reduction from baseline & < 70 mg/dL (for high risk) or < 55 mg/dL (for very high risk) ^{d)}	• No specific target LDL-C levels are recommended for CKD; (however, LDL-C goals may be determined based on comorbidities and risk factors)

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; KDIGO, Kidney Disease: Improving Global Outcomes; KSoLA, The Korean Society of Lipid and Atherosclerosis; KT, kidney transplant; LDL-C, low-density lipoprotein cholesterol.

^{a)}2024 guideline is not exclusively for dyslipidemia management but for the overall evaluation and management of CKD, which includes a lipid management section that largely accepts the 2013 guidelines.

^{b)}With one or more of the following: known coronary disease, diabetes mellitus, prior ischemic stroke, or estimated 10-year incidence of coronary death or non-fatal myocardial infarction > 10%.

^{c)}These conditions are mentioned in the general discussion, not specifically in the CKD part.

^{d)}eGFR categories for risk stratification are as follows: high risk (eGFR 30–59 mL/min/1.73 m²) and very high risk (eGFR < 30 mL/min/1.73 m²).

^{e)}The recommendation does not include information related to KT recipients, but the description below provides an explanation.

ported by several considerations: LDL-C levels do not reliably predict cardiovascular risk in CKD patients [37]; there is considerable variability in LDL-C levels and potential measurement error across different assay methods [38–40]; and the safety of dose escalation to achieve specific LDL-C targets has not been established in the CKD population.

Nevertheless, baseline LDL-C measurement is recommended to differentiate secondary dyslipidemia and identify potentially correctable factors, such as hypothyroidism, excessive alcohol intake, nephrotic syndrome, diabetes, liver disease, and certain medications [17,41]. Baseline testing is also important for identifying individuals who may require specialist referral, such as those with severe hypertriglycer-

idemia (triglyceride level > 1,000 mg/dL) or marked hypercholesterolemia (LDL-C level > 190 mg/dL). Follow-up LDL-C testing may be warranted in specific clinical contexts, including assessing medication adherence, evaluating changes in dialysis modality, investigating newly developed secondary dyslipidemia, and reassessing cardiovascular risk when a change in therapeutic strategy is considered.

On the other hand, the 2018 AHA/ACC guidelines recognize CKD (eGFR of 15–59 mL/min/1.73 m², not treated with dialysis or kidney transplantation [KT]) as a risk-enhancing factor when evaluating individuals for primary prevention. The guidelines recommend statin therapy for patients with LDL-C levels of 70–189 mg/dL and a 10-year ASCVD risk

of $\geq 7.5\%$ when CKD is present [19]. Statin therapy is also indicated regardless of an estimated 10-year ASCVD risk in cases of secondary prevention, in individuals with LDL-C levels of ≥ 190 mg/dL, or in those aged 40–75 years having diabetes.

The 2019 ESC/EAS guidelines stratify cardiovascular risk based on eGFR and provide the corresponding LDL-C targets [20]. Patients with an eGFR of 30–59 mL/min/1.73 m² are classified as high risk, with a recommended LDL-C reduction of $\geq 50\%$ from baseline and a target of < 70 mg/dL. Those with an eGFR of < 30 mL/min/1.73 m² are considered to be at very high risk, with a recommended target of < 55 mg/dL.

The KSoLA does not specify a fixed LDL-C target, but recommends an LDL-C goal of < 70 mg/dL in patients with diabetes and coexisting CKD. A more stringent target of < 55 mg/dL may also be considered [21]. The KSN guidelines for diabetic kidney disease generally align with the KDIGO principles but allow for reference to both domestic and international guideline targets to guide clinical decision-making [22].

Collectively, the current guidelines reflect different approaches to LDL-C monitoring and treatment goals in patients with CKD, shaped by varying interpretations of the available evidence. The KDIGO guidelines [17,18] prioritize a risk-based strategy rather than LDL-C levels, emphasizing simplicity and safety in a population with complex comorbidities. In contrast, the AHA/ACC [19] and ESC/EAS [20] guidelines incorporate LDL-C thresholds and reduction targets, particularly in the earlier stages of CKD, aligning more closely with the traditional lipid management frameworks used in the general population. Korean guidelines, including those from the KSoLA [21] and KSN [22], generally follow the KDIGO principles while allowing for flexibility by referencing international targets. These variations highlight the need for individualized treatment strategies based on the CKD stage, comorbid conditions, and overall cardiovascular risk, while underscoring the importance of further research to establish optimal lipid management approaches in this high-risk population.

PHARMACOLOGICAL CHOLESTEROL-LOWERING THERAPY IN CKD

Although statin therapy does not appear to significantly de-

lay progression to kidney failure in patients with CKD [42–44], several studies have demonstrated the cardiovascular benefits of lipid-lowering therapy in this population. In particular, combination therapy with statins and ezetimibe has shown favorable outcomes in patients not on dialysis [45]; however, its benefit in patients on dialysis remains uncertain [15,16]. This section focuses on the cardiovascular effects of pharmacological lipid-lowering interventions in patients with CKD.

Non-dialysis/non-transplant CKD

The Study of Heart and Renal Protection (SHARP) trial is the only large RCT specifically designed to evaluate the efficacy and safety of lipid-lowering therapy in patients with CKD including those not on dialysis [45] (Table 2). This study enrolled 9,270 patients with stage 3–5 CKD and no history of myocardial infarction (MI) or coronary revascularization. Among them, 6,247 were not on dialysis (mean eGFR, 27 mL/min/1.73 m²), while 3,023 were on dialysis. Participants were randomized to receive simvastatin (20 mg) with ezetimibe (10 mg) or a placebo. The primary composite outcomes included non-fatal MI, coronary death, non-hemorrhagic stroke, or arterial revascularization. Over a median follow-up of 4.9 years, the treatment group showed a significant 17% reduction in the primary outcome compared to the placebo group. No major safety concerns were observed, which supports the tolerability of this regimen in patients with CKD.

Multiple clinical studies support the use of statin monotherapy in patients with CKD. Post hoc analyses and meta-analyses of statin RCTs have shown that statins reduce cardiovascular risk in patients with CKD not requiring dialysis [42,46,47]. A recent meta-analysis including 43 studies and 41,273 patients with eGFR ranging from 15 to 90 mL/min/1.73 m² demonstrated a 28% RR reduction in major cardiovascular events with statin therapy [42]. Although no significant reduction in stroke risk was observed, statins significantly decreased the risk of all-cause mortality, cardiovascular death, and MI.

Based on these findings, clinical guidelines generally recommend the use of statins or statin plus ezetimibe therapy in patients with CKD who are not treated with dialysis or KT (Table 1). However, the 2013 KDIGO guidelines do not recommend universal treatment for all patients with CKD. Instead, lipid-lowering therapy is recommended for individuals with an estimated 10-year coronary artery disease risk

Table 2. Major randomized controlled trials evaluating cardiovascular outcomes in patients with CKD

	SHARP (2011) [45]	4D (2005) [15]	AURORA (2009) [16]	ALERT (2003) [55]
Study population	9,270 patients (age $\geq$ 40 yr) with CKD (3,023 on dialysis and 6,247 not) with no known history of MI or coronary revascularization	1,255 patients (age 18–80 yr) with T2D receiving maintenance HD & LDL-C 80–190 mg/dL	2,766 patients (age 50–80 yr) receiving maintenance HD	2,102 KT recipients (age 30–75 yr) with TC 155–348 mg/dL
Intervention	Simvastatin 20 mg + ezetimibe vs. placebo	Atorvastatin 20 mg vs. placebo	Rosuvastatin 10 mg vs. placebo	Fluvastatin 40–80 mg vs. placebo
Median follow-up	4.9 years	4 years	3.8 years	5.4 years
Primary outcome (placebo as a reference group)	Rate ratio (95% CI) for a composite of non-fatal MI, coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure: 0.83 (0.74–0.94)	Relative risk (95% CI) for a composite of death from cardiac causes, non-fatal MI, and stroke: 0.92 (0.77–1.10)	Hazard ratio (95% CI) for a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke: 0.96 (0.84–1.11)	Risk ratio (95% CI) for a composite of cardiac death, non-fatal MI, or coronary intervention procedure: 0.83 (95% CI, 0.64–1.06)
Adverse events	No evidence of excess risks of hepatitis, gallstones, or cancer	No cases of rhabdomyolysis or severe liver disease were detected in either group	No significant difference between treatment groups, including muscle-related adverse events, rhabdomyolysis, or liver disease	No significant difference between treatment groups
Change in LDL-C in treatment group	–39 mg/dL at 26–31 months (from baseline 107 mg/dL)	–42% after four weeks (from 121 mg/dL at baseline to 72 mg/dL)	–43% after three months (from 100 mg/dL)	–~25% after 6 weeks (from 159 mg/dL at baseline)

ALERT, The Assessment of LEScol in Renal Transplantation; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CI, confidence interval; CKD, chronic kidney disease; HD, hemodialysis; KT, kidney transplant; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SHARP, Study of Heart and Renal Protection; TC, total cholesterol; T2D, type 2 diabetes; 4D, The Die Deutsche Diabetes Dialyse Studie.

exceeding 10% [48]. This threshold was based on findings from the Alberta Kidney Disease Cohort, which included 1,268,028 individuals [49] and showed that most patients aged < 50 years without diabetes or prior CVD had a 10-year coronary artery disease risk below 10%.

According to KDIGO, individuals with an estimated 10-year coronary artery disease risk > 10%—who are, therefore, candidates for statin or statin/ezetimibe therapy—include patients with CKD aged $\geq$ 50 years, and those aged < 50 years with any of the following: established coronary disease (MI or revascularization), type 1 or type 2 diabetes, prior ischemic stroke, or other conditions with an estimated 10-year coronary artery disease risk of > 10%. The updated 2024 KDIGO guidelines [18] further note that initiating treatment at a lower risk threshold, such as 7.5% (in alignment with the AHA/ACC guideline [19]), may be appropri-

ate in clinical practice.

The 2018 AHA/ACC guideline recommends initiating moderate-intensity statin therapy, or moderate-intensity statin combined with ezetimibe, in individuals with LDL-C levels of 70–189 mg/dL and a 10-year ASCVD risk of $\geq$ 7.5% when CKD is present [19]. Meanwhile, the 2019 ESC/EAS guidelines classify non-dialysis-dependent stage 3–5 CKD as a high- or very high-risk condition and recommend statin or statin with ezetimibe therapy regardless of other risk factors [20]. The KSoLA recommends statin with or without ezetimibe for patients with stage 3–5 CKD not on dialysis. For patients with stage 1–2 CKD, treatment decisions should consider age, presence of diabetes, history of coronary artery disease or ischemic stroke, and the overall cardiovascular risk profile [21].

Maximizing absolute LDL-C reduction is a key therapeu-

tic goal when selecting pharmacological agents [18]. For patients with an eGFR of ≥ 60 mL/min/1.73 m² (i.e., CKD with albuminuria only), lipid-lowering agents and dosages used in the general population can typically be employed. In contrast, for those with an eGFR of < 60 mL/min/1.73 m², increased susceptibility to adverse effects warrants more cautious dosing. Where possible, the same dosages as those used in large-scale RCTs should be applied. Pharmacological agents proven safe and effective in CKD trials include atorvastatin (20 mg) [15], rosuvastatin (10 mg) [16], and simvastatin (20 mg) in combination with ezetimibe (10 mg) [45]. A summary of the dosages recommended by KDIGO is provided in Table 3. These dosages can be considered reasonably safe, and statin therapy may be used accordingly based on the clinical context. Notably, lower statin doses reportedly achieve meaningful LDL-C reduction and favorable clinical outcomes in some Asian populations [50,51], suggesting that lower initial doses may be appropriate in selected individuals.

Dialysis-dependent CKD

Approximately one-third of the participants in the SHARP study were on dialysis [45]. Although the primary outcome—a composite of major atherosclerotic events—was significantly reduced in the overall cohort, the benefit was not statistically significant when the dialysis-dependent subgroup was analyzed separately [45]. However, the trial lacked adequate statistical power to detect different treatment effects within subgroups.

Two major RCTs have specifically addressed lipid-lowering therapy in patients on dialysis: the Die Deutsche Diabetes

Dialysis Study (4D study) [15] and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA Study) [16] (Table 2).

The 4D study [15] enrolled 1,255 adults aged 18–80 years with type 2 diabetes undergoing maintenance hemodialysis, who were randomized to receive atorvastatin (20 mg) or placebo. In the atorvastatin group, the baseline LDL-C level was 121 mg/dL and decreased by 42% to 72 mg/dL. Over a median follow-up of 4 years, the primary composite outcome—cardiac death, non-fatal MI, or stroke—was not significantly reduced (RR, 0.92; 95% confidence interval [CI], 0.77–1.10). However, one of the secondary outcomes—all cardiac events including cardiac death, non-fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and other coronary interventions—was significantly reduced in the atorvastatin group (RR, 0.82; 95% CI, 0.68–0.99), although a higher incidence of fatal stroke was observed in the statin group. No cases of rhabdomyolysis or severe hepatotoxicity were reported, indicating an acceptable safety profile.

The AURORA study [16] was a multicenter international RCT that evaluated the efficacy and safety of rosuvastatin (10 mg) versus placebo in 2,776 adults aged 50–80 years undergoing chronic hemodialysis. The baseline LDL-C level was approximately 100 mg/dL and rosuvastatin therapy achieved a 43% reduction. Despite this substantial lipid-lowering effect, there was no significant difference in the primary composite outcome—cardiovascular death, non-fatal MI, or non-fatal stroke—between the two groups over a median follow-up of 3.8 years (hazard ratio [HR], 0.96; 95% CI, 0.84–1.11). Rosuvastatin was well tolerated, with no increase in serious adverse events, including myopathy, rhabdomyolysis, or hepatic dysfunction.

The lack of significant cardiovascular benefits of statin therapy in patients on dialysis may be attributable to the predominance of non-atherosclerotic mechanisms in this population. While ASCVD is the major cause of cardiovascular events in individuals with preserved renal function, patients with advanced CKD (eGFR < 30 mL/min/1.73 m²) exhibit a distinct pathophysiological profile characterized by arterial stiffness, vascular calcification, structural cardiac abnormalities, and increased sympathetic activity, which collectively increase the risk of arrhythmias and heart failure [45,52]. Such conditions are likely to be less modified by statin therapy than is ASCVD [53]. Furthermore, a sin-

Table 3. Recommended doses of statin for adults with chronic kidney disease stage 3–5, including patients on dialysis or kidney transplant recipients, according to KDIGO guidelines

Statin	Recommended dose
Lovastatin	Not studied
Pravastatin	40 mg/day
Simvastatin	40 mg/day or 20 mg/day with 10 mg ezetimibe
Atorvastatin	20 mg/day
Fluvastatin	80 mg/day
Rosuvastatin	10 mg/day
Pitavastatin	2 mg/day

KDIGO, Kidney Disease: Improving Global Outcomes.

gle intervention with statin therapy may be insufficient to meaningfully reduce the cardiovascular risk in individuals with an exceptionally high risk of death. In addition, the low baseline LDL-C levels of the study participants may have influenced the results [15].

Given the absence of demonstrated cardiovascular benefits in multiple large-scale RCTs and meta-analyses, the KDIGO guidelines do not recommend initiating statin or statin/ezetimibe therapy in dialysis [18,48]. However, statin therapy should be considered in selected patients who strongly prefer treatment. Initiation may be especially reasonable in patients with markedly elevated LDL-C levels, as a post hoc analysis of the 4D study showed a significant reduction in cardiac events and mortality among those with baseline LDL-C levels of > 145 mg/dL [54]. Statin therapy may also be appropriate in patients with a recent history of MI or ischemic stroke, or those with a long life expectancy. Conversely, initiation may be less favorable in patients with multiple comorbidities or polypharmacy.

In contrast to the recommendations against initiating statin therapy de novo in individuals on dialysis, current guidelines support continuing statin with or without ezetimibe therapy in those who are already receiving treatment prior to dialysis initiation. Although no RCTs have specifically evaluated the continuation versus discontinuation of statins at the onset of dialysis, the SHARP study included 2,141 participants (34% of the non-dialysis group) who commenced dialysis during the trial period [45]. These individuals were included in the non-dialysis cohort for analysis and contributed to the observed cardiovascular benefits. On this basis, existing guidelines recommend the continuation of statin with or without ezetimibe therapy in patients who initiated treatment before transitioning to dialysis.

Guidelines from the 2018 AHA/ACC [19], 2019 ESC/EAS [20], 2022 KSoLA [21], and 2023 KSN [22] are generally aligned with the KDIGO recommendations in this context (Table 1).

KT recipients

KT recipients are at a significantly increased risk of future coronary events [48]. This elevated cardiovascular risk is partly attributable to the adverse effects of immunosuppressive therapies on lipid metabolism, making dyslipidemia highly prevalent in this population.

The Assessment of LEscol in Renal Transplantation (ALERT) trial is a multicenter RCT that investigated the efficacy and

safety of fluvastatin in KT recipients aged 30–75 years [55] (Table 2). A total of 2,102 KT recipients were randomized to receive fluvastatin (40–80 mg) or a placebo. The primary outcome was a composite of cardiac death, non-fatal MI, and coronary revascularization procedures. After a median follow-up of 5.4 years, the fluvastatin group showed a 17% RR reduction in the primary outcome compared to the placebo group; however, this did not reach statistical significance. In contrast, a prespecified secondary outcome—comprising cardiac death or non-fatal MI—was significantly reduced by 35% in the fluvastatin group. The incidence of adverse events was similar between groups, suggesting that fluvastatin was well tolerated. In the subsequent ALERT Extension Study, which extended the follow-up to a median of 6.7 years, fluvastatin therapy was associated with a statistically significant reduction in the primary composite outcome (HR, 0.79; 95% CI, 0.55–0.93) [56].

Although the overall level of evidence remains relatively limited, current guidelines generally recommend the initiation of statin therapy in adult KT recipients to reduce cardiovascular risk. It is advisable to begin with a low-dose statin and titrate it upward as tolerated [20,21]. Importantly, clinicians must be vigilant regarding potential drug-drug interactions, particularly with immunosuppressants such as cyclosporine, which is metabolized via cytochrome P450 (CYP) 3A4. Cyclosporine can increase systemic exposure to statins, thereby increasing the risk of statin-associated myopathy. Among the available statins, fluvastatin, pravastatin, pitavastatin, and rosuvastatin are metabolized via alternative CYP pathways and are associated with lower interaction potentials [57]. While tacrolimus is also metabolized by CYP3A4, it appears to have a lower risk of significant interactions with statins than cyclosporine.

To further minimize adverse effects, the concomitant use of other agents known to inhibit or induce CYP3A4 should be avoided or used with caution in patients receiving both calcineurin inhibitor and statin therapy. The 2022 KSoLA guidelines specifically recommend the use of fluvastatin or pravastatin in patients receiving cyclosporine to reduce the risk of clinically significant drug–drug interactions [21].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in non-dialysis/non-transplant CKD

PCSK9 inhibitors, such as evolocumab and alirocumab, are monoclonal antibodies that have been shown to significant-

ly reduce cardiovascular events in patients with established ASCVD [58,59]. Their role in patients with CKD, particularly those who are not undergoing dialysis or have not undergone KT, is of growing clinical interest.

The effects of evolocumab on cardiovascular outcomes across a spectrum of kidney function—stratified into preserved kidney function, stage 2 CKD, and stage ≥ 3 CKD—were evaluated among participants in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial [60]. This study demonstrated consistent RR reductions in cardiovascular events across all eGFR categories with no significant interaction with renal function status. However, it is important to note that the trial excluded individuals with an eGFR of < 20 mL/min/1.73 m² and those with a history of KT.

In a pooled analysis of eight phase 3 ODYSSEY trials investigating the efficacy and safety of alirocumab, adverse event rates were comparable between the alirocumab group and the control groups (placebo or ezetimibe) in patients with an eGFR of 30–59 mL/min/1.73 m² and those with an eGFR of ≥ 60 mL/min/1.73 m². Moreover, alirocumab effectively reduced LDL-C levels irrespective of baseline renal function, indicating consistent lipid-lowering efficacy across different stages of CKD [61].

Based on these findings, the 2024 KDIGO guidelines suggest that PCSK9 inhibitors may be considered in appropriate clinical contexts, such as in individuals with ASCVD or adults with heterozygous familial hypercholesterolemia who require additional LDL-C lowering despite maximally tolerated statin therapy [18]. Although data on patients with advanced CKD or KT are limited, available evidence supports the safety and efficacy of PCSK9 inhibitors in individuals with mild-to-moderate renal impairment.

PHARMACOLOGICAL TRIGLYCERIDE-LOWERING THERAPY IN CKD

Hypertriglyceridemia, often accompanied by low HDL-C levels, is a characteristic feature of dyslipidemia in patients with CKD. This lipid abnormality has prompted interest in triglyceride-lowering therapies to reduce cardiovascular risk in this population. However, in contrast to statins, the cardiovascular benefits of agents such as fibrates and omega-3 fatty acids remain controversial in the general population, and supporting evidence in patients with CKD is even more

limited. Consequently, current clinical guidelines offer minimal or cautious recommendations regarding their use in this setting.

Fenofibrates

Two large-scale RCTs assessed the efficacy and safety of fenofibrate: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [62] and the Action to Control Cardiovascular Risk in Diabetes-Lipid (ACCORD-Lipid) trial [63]. However, both trials enrolled very few participants with an eGFR of < 60 mL/min/1.73 m², limiting the applicability of their findings to people with CKD.

In addition to the lack of direct trial evidence, observational studies have raised safety concerns regarding fenofibrate use, particularly in older adults, linking its use to increases in serum creatinine levels, a higher rate of hospitalization, and more frequent referrals to the nephrology department [64]. These concerns, combined with limited efficacy data, have led the KDIGO and KSoLA guidelines to advise against the routine use of fibrates for cardiovascular prevention in patients with CKD [17,21,65].

Nonetheless, fibrates may be considered in patients with severe hypertriglyceridemia (triglyceride level $> 1,000$ mg/dL), where reducing the risk of pancreatitis is a clinical priority. In such cases, careful dose adjustments based on renal function are essential. The concomitant use of fibrates with statins is generally discouraged owing to the increased risk of adverse effects, particularly rhabdomyolysis. Additional caution is warranted in KT recipients because fibrates may lower cyclosporine levels and increase the risk of myopathy.

Despite these concerns, emerging evidence suggests a potential benefit in selected populations with CKD. A meta-analysis reported that fibrates significantly reduced major cardiovascular events and cardiovascular mortality in patients with an eGFR of 30–59.9 mL/min/1.73 m² [66]. Additionally, among patients with diabetes, fibrates were associated with a reduced progression of albuminuria. More recently, a post hoc analysis of the FIELD study suggested that fenofibrate may slow the decline in eGFR compared with placebo, although the number of participants with CKD was limited, and the results should be interpreted cautiously [67].

Taken together, although the current evidence does not support the routine use of fenofibrates for cardiovascular risk reduction in CKD, they may play a role in selecting clinical scenarios. Large-scale prospective trials specifically targeting patients with CKD are required to clarify their safety

and efficacy.

Omega-3 fatty acids

RCTs evaluating the cardiovascular effects of omega-3 fatty acids in the general population have yielded inconsistent results. In particular, studies using low-dose formulations have largely failed to demonstrate significant cardiovascular benefit [68].

The Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT) [69] assessed high-dose icosapent ethyl (IPE), a purified eicosapentaenoic acid (EPA) formulation, at 4 g/day. Compared to a placebo (mineral oil), IPE significantly reduced the primary composite outcome of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina (HR, 0.72; 95% CI, 0.68–0.83). The median baseline eGFR of participants was 75 mL/min/1.73 m² (range, 17–123 mL/min/1.73 m²). In a prespecified subgroup analysis (REDUCE-IT RENAL), IPE was associated with a significant reduction in the primary endpoint among individuals with an eGFR of < 60 mL/min/1.73 m² (HR, 0.71; 95% CI, 0.59–0.85) [70]. The risks of atrial fibrillation/flutter and serious bleeding were consistent across renal function strata, with no significant interaction observed.

In contrast, the STatin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial investigated a 4 g/day combination of EPA and docosahexaenoic acid and found no significant difference in cardiovascular outcomes compared to corn oil placebo [71]. Subgroup analyses stratified by renal function (eGFR of < 60 vs. ≥ 60 mL/min/1.73 m²) also showed no treatment benefit. A possible explanation for the divergence in findings is the use of mineral oil as a placebo in the REDUCE-IT trial, which may have had adverse effects on lipid parameters, including increased LDL-C, apolipoprotein B, and high-sensitivity C-reactive protein levels.

Considering these conflicting results, the role of omega-3 fatty acids in CKD remains unclear. Among the current clinical guidelines—including the KDIGO, 2018 AHA/ACC, 2019 ESC/EAS, 2022 KSoLA, and 2023 KSN guidelines—only the 2022 KDIGO *Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* specifically addresses omega-3 therapy [72]. This guideline states that IPE may be considered in patients having diabetes with CKD when clinically indicated, based on ASCVD risk and lipid profiles.

CONCLUSIONS

Patients with CKD have a markedly increased risk of CVD, making dyslipidemia management a critical component of risk reduction among this population. However, the association between LDL-C levels and cardiovascular risk is attenuated as kidney function declines, and the complex relationship between CKD and CVD underscores the need for a nuanced approach to lipid management in CKD.

In patients with CKD (stages 1–5) who are not on dialysis, robust evidence from RCTs and meta-analyses supports the use of statins with or without ezetimibe for cardiovascular risk reduction [42,45]. Clinical guidelines generally endorse statin-based therapy in these patients, particularly for those aged ≥ 50 years or with diabetes, ASCVD, or elevated 10-year coronary artery disease risk scores. PCSK9 inhibitors may be considered in selected individuals. However, in patients on dialysis, guidelines do not recommend initiating statins because multiple large RCTs have failed to demonstrate a significant reduction in major cardiovascular outcomes with statin therapy [15,16]. Nevertheless, the continuation of statin therapy is supported in patients who were already receiving statins before dialysis initiation. KT recipients represent another high-risk population for whom statin therapy is generally recommended, with careful attention paid to potential drug–drug interactions. The role of triglyceride-lowering agents, including fibrates and omega-3 fatty acids, remains uncertain in CKD.

Overall, lipid management in CKD should be individualized according to the patient's kidney disease stage, comorbid conditions, cardiovascular risk profile, and treatment tolerability. Further large-scale CKD-specific trials are needed to define the optimal use of lipid-lowering therapies and to refine guideline recommendations for this high-risk population.

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Correspondence to

Nam Hoon Kim, M.D., Ph.D.

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, 73, Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea

Tel: +82-2-920-5421, Fax: +82-2-953-9355

E-mail: pourlife@korea.ac.kr

<https://orcid.org/0000-0002-9926-1344>

Credit authorship contributions

Ji Yoon Kim: conceptualization, investigation, writing - original draft, writing - review & editing, funding acquisition; Suk Min Chung: conceptualization, investigation, writing - review & editing, funding acquisition; Nam Hoon Kim: conceptualization, investigation, writing - re-

view & editing, supervision, project administration, funding acquisition

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