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REVIEW ARTICLE

Renal Safety Assessment of Lipid-Lowering Drugs: Between Old Certainties and New Questions

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Abstract

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Quantitative and qualitative changes in plasma lipoprotein profiles are frequently associated with CKD and represent a significant risk factor for CVD in patients with CKD. Guidelines from the European Society of Cardiology and the European Atherosclerosis Society classify CKD as a condition with high or very high cardiovascular risk and set specific low-density lipoprotein cholesterol targets. Conventional lipid-lowering therapies (LLTs), such as statins, ezetimibe, and fibrates, can control CKD-associated dyslipidemia and, to some extent, prevent major atherosclerotic events in patients with CKD, but their use in clinical practice presents challenges because of the potential renal safety concerns. In recent years, novel therapies with the ability to lower both low-density lipoprotein cholesterol and triglycerides have been introduced to the market (e.g., proprotein convertase subtilisin/kexin type 9 inhibitors, bempedoic acid, lomitapide, volanesorsen) to improve our ability to control lipid abnormalities. However, their impact on kidney functionality has not been fully elucidated. The aim of this review was to examine the renal safety profiles of various LLTs, with special reference to novel medications, and to highlight important considerations and guidance for the use of these medications in overt CKD or in patients with some degree of renal function impairment. We underscore the lack of a comprehensive understanding of kidney safety, particularly for novel LLT therapies, and strongly emphasize the importance of future dedicated research to fully assess the safety and efficacy of these agents in patients with kidney abnormalities.

1 Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1, 2]. The current recommendation is to treat people with CKD with a holistic treatment strategy to reduce the risk of both progression of CKD and development of CVD complications [3]. Among the traditional risk factors, dyslipidemia is a key player in the pathogenesis of CVD in kidney disease [4]. Indeed, it is well known that progressive kidney damage leading to CKD and end-stage renal disease (ESRD) are associated with substantial alterations in the plasma lipoprotein profile, and this has been associated with a worse cardiovascular prognosis in patients with CKD [5, 6]. Guidelines from the European Society of Cardiology and the European Atherosclerosis Society indicate that the presence of CKD increases patients' cardiovascular risk to high (for those with an estimated glomerular filtration rate [eGFR] of 30–59 mL/min/m^2) and very high (for those with an eGFR <30 mL/min/m^2), and set recommended low-density lipoprotein cholesterol (LDL-C) targets at 70 mg/dL and 55 mg/dL, respectively [7]. A substantial body of literature has evaluated the efficacy of lipid-lowering therapies (LLTs) with various mechanisms of action (Fig. 1) in patients with CKD. Multiple studies have consistently demonstrated that LLTs are effective in reducing the risk of major atherosclerotic events in this patient population [8]. The 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients with CKD recommend that statin-based regimens should be used to maximize the absolute reduction in LDL-C to achieve the greatest treatment benefit [3]. Similarly, the prescription of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for people with CKD is suggested for patients who have an indication for their use [3]. Moreover, emerging therapies, such as inclisiran,

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Key Points

Conventional lipid-lowering therapies have been shown to improve lipid profiles in patients with chronic kidney disease (CKD); however, their use requires careful monitoring because of potential kidney safety concerns, particularly at higher doses and in advanced CKD stages.

The emergence of novel therapeutic interventions offers promising opportunities for managing dyslipidemia in CKD. However, their impact on renal function, especially in advanced disease stages, remains largely unexplored, necessitating further investigation.

Patients with CKD, particularly those in advanced stages, have often been excluded from clinical trials, and no studies have been specifically designed to assess the renal benefits of lipid-lowering therapies. Consequently, dyslipidemia management in CKD remains a significant unmet clinical need, underscoring the urgency for targeted research.

microsomal triglyceride transfer protein (MTP) inhibitors, angiopoietin-like 3 (ANGPTL3) inhibitors, and apolipoprotein C-III (apoC-III) inhibitors, offer novel approaches for treating more challenging or rare dyslipidemic phenotypes [9]. These innovative treatments provide additional approaches to managing dyslipidemia beyond conventional methods, enabling more personalized and effective interventions, even for patients with rarer lipid disorders. However, the pharmacological management of patients with CKD is often a challenge for clinicians because of potential safety concerns. Here, we review the evidence on the renal safety profile of the different LLTs, including established and new agents, focusing on their efficacy and renal safety profile in patients with CKD.

2 Literature Search Methodology

We conducted a comprehensive literature search of multiple electronic databases, including PubMed, Scopus, and Web of Science. We also queried ClinicalTrials.gov to identify relevant unpublished or ongoing studies. Search terms included a combination of "lipid-lowering therapies" AND "renal safety," "chronic kidney disease," OR "dyslipidemia," and additional terms specific to lipoprotein disorders and associated biomarkers, such as "hypercholesterolemia," "hypertriglyceridemia," "LDL-C," "HDL-C," "VLDL," and "apolipoproteins." To ensure coverage of individual pharmacological agents, the search included terms such as "statins," "atorvastatin," "rosuvastatin," "pravastatin," "simvastatin," "ezetimibe," "PCSK9 inhibitors," "evolocumab," "alirocumab," "inclisiran," "bempedoic acid," "lomitapide," "omega-3 fatty acids," "icosapent ethyl," "angiopoietin-like 3 inhibitors," "ApoC-III inhibitors," "volanesorsen," and "evinacumab." Terms related to renal function and outcomes, including "acute kidney injury," "proteinuria," "glomerular filtration rate," "renal impairment," and "kidney function," were included to ensure relevance. Search strategies were constructed using search combinations (such as "AND" and "OR") to maximize sensitivity and specificity. To ensure an exhaustive review of the available evidence, we did not set any language restrictions or limits on publication dates. We also searched the bibliographical references from the included studies for additional primary research that might have been missed during the electronic search. Randomized controlled trials (RCTs), cohort studies, and meta-analyses were prioritized, and we included observational studies, case series, review articles (both narrative and systematic), and post hoc analyses from larger trials when relevant data were presented. Data extracted from the selected studies included study design, patient characteristics (e.g., CKD stage, eGFR), therapeutic protocols (e.g., doses, durations), and renal outcomes (e.g., changes in eGFR, proteinuria, serum creatinine, or incidence of acute kidney injury [AKI]). We paid particular attention to differences in safety profiles between drug classes and individual agents, including newer therapies not yet fully evaluated in CKD populations. Findings were categorized by drug class and summarized in tables for clarity.

3 LDL-C-Lowering Medications in CKD

3.1 Conventional LDL-Lowering Therapies

3.1.1 Statins

Statins are commonly used to manage dyslipidemia and reduce the risk of atherosclerotic CVD (ASCVD) by inhibiting the rate-limiting enzyme in cholesterol synthesis, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [10]. After oral administration, most of the statin dose (>80%) undergoes hepatic and gastrointestinal clearance, with a minor fraction eliminated via renal pathways. Pravastatin (20%), pitavastatin (15%), and simvastatin (13%) exhibit higher renal excretion rates, whereas rosuvastatin (10%), atorvastatin (<2%), and fluvastatin (<3%) show lesser renal elimination by the kidney [11–18] (Table 1).

The efficacy of statin-based therapies in reducing LDL-C and the risk of ASCVD in individuals with and without

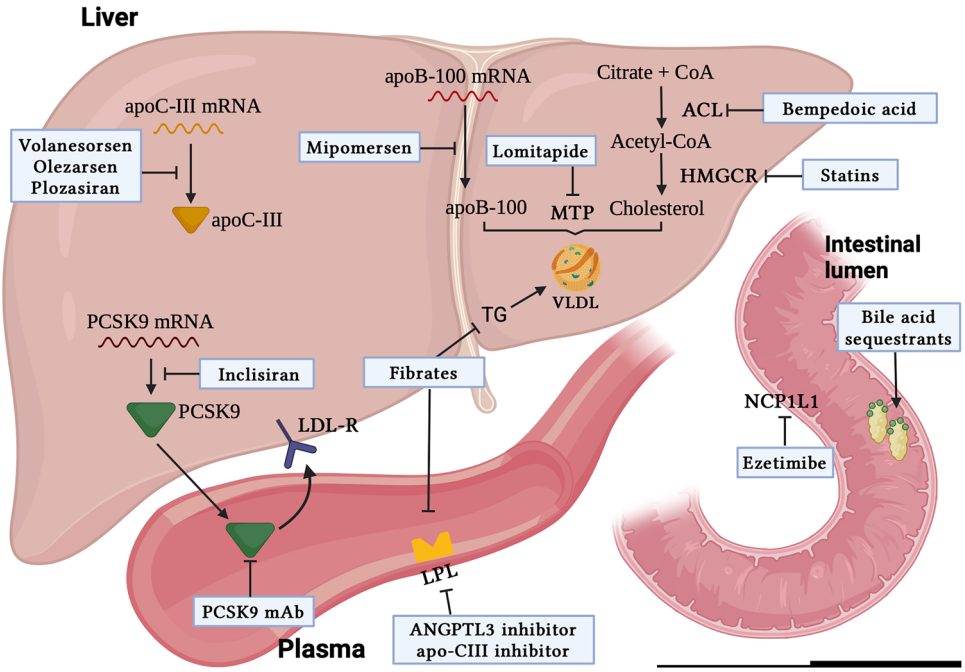

Fig. 1 Mechanisms of action of lipid-lowering therapies. Volanesorsen, olezarsen, and plozasiran target apolipoprotein C-III (apoC-III) messenger RNA (mRNA), reducing apoC-III levels. Mipomersen inhibits hepatic apolipoprotein B-100 (apoB-100) mRNA, decreasing the production of apoB-100. Lomitapide interferes with very-low-density lipoprotein (VLDL) and chylomicron assembly by inhibiting microsomal triglyceride transfer protein (MTP) in the liver. Bempedoic acid prevents cholesterol synthesis by inhibiting ATP citrate lyase (ACL). Statins block 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), reducing cholesterol synthesis. Inclisiran blocks the translation of proprotein convertase subtilisin/kexin type 9 (PCSK9) mRNA. PCSK9-inhibiting monoclonal antibodies (mAbs) block PCSK9 from binding to low-density lipoprotein receptors (LDL-R). Fibrates activate peroxisome proliferator-activated receptor alpha, increasing lipoprotein lipase (LPL) activity and reducing triglyceride (TG) levels. Angiopoietin-like 3 protein inhibitors (ANGPTL3i) enhance LPL function. Bile acid sequestrants bind bile acids in the small intestine, whereas ezetimibe inhibits Niemann–Pick C1-like protein 1 (NPC1L1), preventing sterol transport into enterocytes.

CKD is very well established. The KDIGO Clinical Practice Guideline for Lipid Management in CKD provides clear recommendations for the initiation of such therapies [19]. The KDIGO 2024 guideline strongly recommends statin or statin/ezetimibe combination therapy (grade 1A recommendation) for adults aged ≥50 years with an eGFR <60 mL/min/1.73 m^2 who are not on chronic dialysis or have not undergone kidney transplantation (GFR categories G3a–G5). For individuals in the same age group with CKD but an eGFR of ≥60 mL/min/1.73 m^2 (GFR categories G1–G2), statin therapy alone is recommended (grade 1B recommendation) [3]. Despite robust evidence supporting the efficacy of statins in reducing LDL-C and cardiovascular risk in individuals with and without CKD, the optimizing of statin therapy in patients with CKD presents several challenges in clinical practice. The results of studies evaluating the safety of statins in CKD populations are controversial. Some studies have suggested that certain statins may be associated with a potential risk of renal injury, and others have found no significant associations. These results are summarized in Table 2 [20–34].

The first large trial to evaluate kidney safety as a hard outcome, Study of Heart and Renal Protection (SHARP), found that the combination of simvastatin and ezetimibe had no significant effect on the composite outcome of doubling serum creatinine levels and progression to ESRD compared with placebo [20, 21]. Zhao et al. [22] conducted a meta-analysis to assess the efficacy of different statins in improving renal function in patients with CKD. The analysis included 33 RCTs with a total of 37,391 patients with CKD. It revealed that statin therapy was associated with a slowing of CKD progression, primarily by reducing urinary albumin (weighted mean difference [WMD] −2.04 [95% confidence interval {CI} −3.53 to −0.56]; p=0.007; I^2=99.2%) and protein excretion (WMD −0.58 [95% CI −0.95 to −0.21]; p=0.002; I^2=97.8%) and increasing creatinine clearance (WMD 0.86 [95% CI 0.32–1.41]; p=0.002; I^2=92.8%). However, no significant differences were observed between the statin and control groups regarding changes in eGFR (WMD 0.38 [95% CI −0.04–0.79]; p=0.075; I^2=98.3%) and serum creatinine levels (WMD −0.07 [95% CI −0.25–0.12]; p=0.475; I^2=94.1%) [22].

Table 1 Statin metabolism and recommended doses in adults with chronic kidney disease (CKD)

Agent	Metabolism	Kidney metabolism (%)	Dose adjustment in mild CKD (eGFR G1–G2)	Dose adjustment in eGFR G3a–G5 (mL/min)	References
Atorvastatin	Mainly hepatic (CYP3A4)	<2	General population	20	[11, 18]
Rosuvastatin	Hepatic (CYP2C9, 2C19 [minor]) and renal metabolism	10	General population	10	[12, 18]
Simvastatin	Mainly hepatic (CYP3A4)	13	General population	40	[13, 18]
Lovastatin	Mainly hepatic (CYP3A4)	<10	General population	Nd	[14, 18]
Fluvastatin	Mainly hepatic (CYP2C9)	<3	General population	80	[15, 18]
Pravastatin	Primarily renal	20	General population	40	[16, 18]
Pitavastatin	Hepatic (CYP2C9/2C8 [minor]) and renal	15	General population	2	[17, 18]

CYP, cytochrome P450; eGFR, estimated glomerular filtration rate

Further analyses of the effects of specific statins on renal function has focused on atorvastatin and rosuvastatin. Wu et al. [23] conducted a meta-analysis involving 24,278 participants from 16 trials and directly compared these two statins in terms of renal outcomes. Both atorvastatin and rosuvastatin improved eGFR, although atorvastatin demonstrated superior efficacy in reducing proteinuria (standardized mean difference −0.28 [95% CI −0.49 to −0.07]; p=0.009; I^2=83%) [23]. The PLANET studies provided additional evidence by comparing the renal effects of atorvastatin and rosuvastatin in patients with diabetes and proteinuria. In PLANET I, participants were randomized to receive atorvastatin 80 mg, rosuvastatin 10 mg, or rosuvastatin 40 mg. The primary endpoint was the change in mean urine protein-to-creatinine ratio (UPCR) from baseline to week 52. Results indicated that atorvastatin 80 mg significantly reduced UPCR (geometric mean ratio [GMR] 0.87 [95% CI 0.77–0.99]; p=0.033), whereas neither rosuvastatin 10 mg (GMR 1.02 [95% CI 0.88–1.18]; p=0.83) nor rosuvastatin 40 mg (GMR 0.96 [95% CI 0.83–1.11]; p=0.53) resulted in significant within-group changes. Additionally, adverse renal events, including proteinuria, elevated creatinine, and AKI, were less common in the atorvastatin group, with only 4.5% of patients in the atorvastatin 80 mg group experiencing such events, compared with 7.8% and 9.8% in the rosuvastatin 10 mg and 40 mg groups, respectively (p-value not reported) [24]. A post hoc analysis of PLANET I and PLANET II further confirmed the superior renoprotective action of atorvastatin, particularly when compared with high doses of rosuvastatin. Indeed, it was reported that atorvastatin 80 mg reduced UPCR significantly more than rosuvastatin 10 mg (15.6% [95% CI −28.3 to −0.5]; p=0.043) and rosuvastatin 40 mg (18.2% [95% CI −30.2 to −4.2]; p=0.013) [24]. Supporting these findings, Shin et al. [26] demonstrated that rosuvastatin was associated with a higher risk of hematuria and proteinuria than was atorvastatin. Notably, among patients with an eGFR <30 mL/min/1.73 m^2, 44% were prescribed daily doses of rosuvastatin exceeding the maximum of 10 mg recommended by the US Food and Drug Administration [26, 27]. Similarly, Han et al. [27] conducted a comparative study involving 484 patients with diabetes who had been on statin therapy for over 12 months. Both atorvastatin and rosuvastatin treatments led to reductions in eGFR (from 80.3 to 78.8 mL/min/1.73 m^2 for atorvastatin [p=0.012] and from 79.1 to 76.1 mL/min/1.73 m^2 for rosuvastatin [p=0.001]), with a more rapid decline in the rosuvastatin group [27]. Overall, these findings appear to suggest that atorvastatin may be safer than rosuvastatin, particularly at higher doses, in patients with renal impairment. However, the lack of a placebo group in the above-mentioned studies hinders our ability to determine whether the observed changes in eGFR reflect a true drug-related action or are related to the natural progression of the renal disease.

Several large-scale clinical trials have demonstrated that intensive, once-daily statin regimens are safe for individuals undergoing dialysis [35, 36]. Similarly, a recently published meta-analysis of 27 studies (10 RCTs and 17 observational studies) involving 70,750 participants found that statin use among kidney transplant recipients is associated with a lower risk of cardiovascular events with an acceptable safety profile [37]. However, although statin use was linked to a higher risk of rhabdomyolysis (relative risk [RR] 1.37 [95% CI 1.10–1.70]; I^2=0%), no statistically significant differences were observed between the statin and non-statin groups regarding creatine kinase elevation (RR 0.97 [95% CI 0.50–1.89]; I^2=0%) [37]. Although guidelines recommend statins as the initial treatment in transplant recipients, they emphasize starting with low doses and monitoring closely because of potential interactions with immunosuppressive agents [7]. Therefore, careful consideration of the statin–immunosuppressant combination is essential for optimizing outcomes in patients after a transplant.

AKI is a frequent complication in critically ill patients, and the role of statins in its management remains under

Table 2 Association between statins and renal function: summary of studies

Agent	Population	Study design	Aim	Effects on renal function	References
Simvastatin	9270 CKD pts (3023 on dialysis, 6247 not)	Randomized double-blind trial (4650 pts assigned to simvastatin plus ezetimibe; 4620 to placebo)	Assess efficacy and safety of combined simvastatin plus ezetimibe in CKD pts	Reduction of LDL-C with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of pts with advanced CKD	[20]
Simvastatin, pravastatin, cerivastatin, fluvastatin, pitavastatin, atorvastatin, rosuvastatin	37,391 pts with CKD	Meta-analysis	Evaluate effects of statins on renal function in pts with CKD	Statin use in pts with CKD may slow CKD progression by lowering urinary albumin and protein excretions or increasing creatinine clearance	[22]
Atorvastatin, rosuvastatin	353 pts	Randomized, double-blind, parallel-group trial (118 pts assigned to rosuvastatin 10 mg, 124 to rosuvastatin 40 mg, 111 to atorvastatin 80 mg)	Evaluate renal effects of two statins (in pts with diabetes and proteinuria)	Atorvastatin seems to have more renoprotective effects for the studied CKD population	[24]
Rosuvastatin	1922 pts undergoing elective cardiac surgery	Randomized, double-blind, placebo-controlled trial (pts randomized to rosuvastatin 20 mg OD or placebo for ≤8 days before surgery and 5 days thereafter)	Investigated effects of perioperative rosuvastatin on postoperative AF and cardiac injury in pts undergoing cardiac surgery	Rosuvastatin vs. placebo increased absolute risk of postoperative AKI, however defined, by 4–5% in pts undergoing cardiac surgery	[25]
Atorvastatin, rosuvastatin	152,101 and 795,799 new users of rosuvastatin and atorvastatin, respectively	Post-marketing surveillance study	Assess associations of rosuvastatin use vs. atorvastatin use with risk of hematuria and proteinuria across a range of kidney function and rosuvastatin-dosing practice patterns in relation to kidney function	Compared with atorvastatin, rosuvastatin was associated with increased risk of hematuria, proteinuria, and kidney failure with replacement therapy	[26]
Atorvastatin, rosuvastatin	484 pts with diabetes who received statin treatment for >12 months	Observational study	Investigate whether, and which, statins affected renal function in Asian pts with diabetes	Both statin treatment groups: pts showed significantly reduced eGFR. More rapid eGFR decline in the rosuvastatin group than in the atorvastatin group	[27]
Simvastatin, pravastatin, cerivastatin, fluvastatin, lovastatin, atorvastatin, rosuvastatin	197,551 pts from the Department of Veterans Affairs VSIN16 database (USA)	Cross-sectional study	Evaluate effects of statins in pts without pre-existing renal disease	Statin use may slow development of renal dysfunction independently of their lipid-lowering effect	[28]
Simvastatin, pravastatin, atorvastatin, rosuvastatin	43,438 pts from the San Antonio area military healthcare system	Retrospective cohort study	Examine association of statin use and risk of kidney disease	In propensity score-matched overall cohort, statin users were 30% more likely to develop AKI and 36% more likely to develop CKD	[29]

Table 2 (continued)

Agent	Population	Study design	Aim	Effects on renal function	References
Simvastatin, pravastatin, cerivastatin, fluvastatin, lovastatin, atorvastatin, rosuvastatin	6452 CKD subjects	Meta-analysis	Investigate whether statins modulate renal function in pts with CKD	Statins might exert significant renoprotective effects in CKD pts, reducing urinary protein and serum creatinine, but only for long-term therapy	[30]
Atorvastatin, rosuvastatin	709 NSTE-ACS pts	Open-label, noninferiority study	Head-to-head comparison of acute nephroprotective effects of rosuvastatin and atorvastatin against AKI development in statin-naïve NSTE-ACS pts	AKI incidence was similar in the two groups (8.2% with rosuvastatin, 7.6% with atorvastatin; absolute risk difference 0.54; 90% CI –3.9–2.8), satisfying the noninferiority criteria	[31]
Atorvastatin, rosuvastatin	63 pts with T2DM	Interventional study (pts randomized to continue rosuvastatin therapy [control] or administered an equipotent dose of atorvastatin [intervention group])	Determine whether atorvastatin protects the podocytes and the proximal tubule in pts with T2DM	Atorvastatin exerts favorable effects on the kidney, reducing urinary podocytes and proximal tubule dysfunction biomarkers	[32]
Atorvastatin, rosuvastatin	1078 consecutive pts with CKD undergoing elective PCI	Interventional study	Compared preventive effects of rosuvastatin and atorvastatin on CIN in CKD pts undergoing PCI	Rosuvastatin and atorvastatin have similar efficacies for preventing CIN in pts with CKD undergoing PCI	[33]
Atorvastatin, rosuvastatin	29,147 pts	Meta-analysis	Compare effects of atorvastatin vs rosuvastatin on eGFR and new-onset proteinuria in pts at high cardiovascular risk	Atorvastatin and rosuvastatin show similar reno-protective effects in pts at high cardiovascular risk, with comparable rates of new-onset proteinuria	[34]

AF, atrial fibrillation; AKI, acute kidney injury; CI, confidence interval; CIN, contrast-induced nephropathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NSTE-ACS, non-ST-elevation acute coronary syndrome; OD, once daily; PCI, percutaneous coronary intervention; pt(s), patient(s); T2DM, type 2 diabetes mellitus

debate. Some studies suggest that statin therapy may reduce mortality and shorten hospital stays in patients with AKI, but the evidence is mixed [38]. A recent meta-analysis of three studies encompassing critically ill surgical patients diagnosed with AKI demonstrated that statin use was significantly associated with reduced mortality (odds ratio [OR] 0.73 [95% CI 0.69–0.77]; $p<0.001$) without affecting the development of AKI (OR 0.92 [95% CI 0.63–1.33]; $p=0.659$) [38]. In contrast, the STICS trial investigated the effects of rosuvastatin in patients undergoing cardiac surgery and found a higher incidence of AKI in the rosuvastatin group than in the placebo group (25% vs. 10%). This study also highlighted reductions in eGFR and increases in proteinuria and renal injury markers in the rosuvastatin group, suggesting a potential risk of renal impairment in this setting [29]. These contradictory findings likely reflect differences in clinical contexts and patient populations, underscoring the need for further research to better understand the impact of statins, particularly in high-risk settings such as cardiac surgery. Until more conclusive evidence emerges, statin therapy in patients at risk of AKI should be carefully selected.

The mechanisms proposed to explain such renal damage include immune-mediated acute interstitial nephritis, characterized by inflammatory cell infiltration in the renal interstitium, and the inhibition of HMG-CoA reductase in kidney cells, which reduces the synthesis of isoprenoids essential for preserving tubular cell integrity and function as well as protein reabsorption. Additionally, mitochondrial dysfunction, secondary to decreased coenzyme Q10 levels, has been implicated, particularly with high-potency statins at elevated doses [39–42].

3.1.2 Ezetimibe

Ezetimibe specifically targets and inhibits the Niemann–Pick C1-like 1 protein, located in the brush border of the jejunum, preventing cholesterol uptake from intestinal micelles into enterocytes [43]. Several studies have shown that combining ezetimibe, which is essential for cholesterol absorption, with statin therapy reduces atherosclerotic events, but few have investigated its efficacy and safety in patients with dyslipidemia and CKD.

As mentioned, the SHARP study is one of the most significant trials evaluating the use of ezetimibe as an LLT in patients with CKD. This randomized trial involved 9438 patients with CKD, including 3056 on dialysis, and assessed the effects of simvastatin 20 mg combined with ezetimibe 10 mg over a median follow-up of 4.9 years. The study found a 17% reduction in major atherosclerotic events in patients with advanced CKD who received the combination therapy compared with placebo. Importantly, the treatment was well tolerated, with no significant increases in myopathy, liver toxicity, or biliary complications, confirming the safety of simvastatin–ezetimibe in this population [24]. Renal function was closely monitored in SHARP, with no significant differences in eGFR decline or serum creatinine levels between the treatment and control groups, reinforcing the renal safety of ezetimibe combined with statin therapy. These results are consistent with those from other studies, such as that by Morita et al. [43], who reported that ezetimibe positively affected renal function and arterial stiffness in patients with CKD [43]. Ezetimibe has also demonstrated benefits in reducing proteinuria and urinary liver-type fatty acid-binding protein in patients with CKD who cannot tolerate statins [44]. Additionally, a large-scale cohort study by Bae et al. [45] found that adding ezetimibe to a statin significantly lowered the incidence of adverse renal events compared with statin monotherapy. This combination also tended to better preserve renal function, as reflected by serum creatinine trends over time [45]. A meta-analysis by Lin et al. [46], encompassing seven studies and a total of 14,016 participants (7012 received statin–ezetimibe and 7004 received statin monotherapy or placebo), further corroborated these findings. The statin–ezetimibe combination significantly improved lipid profiles, with reductions in total cholesterol (WMD −20.31 mg/dL [95% CI −26.87 to −13.75]; $p<0.001$) and LDL-C (WMD −17.22 mg/dL [95% CI −18.93 to −15.51]; $p<0.001$), and reduced all-cause mortality and major adverse cardiovascular events (RR 0.86 [95% CI 0.77–0.97]; $p=0.01$) in patients with CKD [46]. Various studies have clearly shown that ezetimibe, alone or in combination with statins, is well tolerated in kidney transplant recipients and leads to a significant reduction in cholesterol, LDL-C, and triglyceride levels in the plasma. Additionally, this beneficial effect is not associated with any changes in renal or liver function, increased creatine kinase, electrolyte imbalances, or interactions with other medications [47].

3.2 Novel LDL-Lowering Therapies

3.2.1 Monoclonal Antibodies Against PCSK9

The use of monoclonal antibodies (mAbs) to inhibit PCSK9 has changed clinical practice for the treatment of dyslipidemia. PCSK9 is a protein that binds to LDL receptors and targets them for destruction. Reducing LDL-C decreases the risk of atherosclerotic vascular disease in a broad spectrum of patients with CKD, and the use of new PCSK9 inhibitors offers even greater reductions than statins [48]. Alirocumab and evolocumab are fully humanized mAbs of the immunoglobulin G (IgG) subclass that bind to PCSK9 in free plasma and remove it from circulation, reducing the destruction of LDL receptors and lowering LDL-C levels [48]. These antibodies are primarily metabolized by the reticuloendothelial system and, because of their large molecular size as IgG

antibodies, are not efficiently filtered by the kidneys. Consequently, renal impairment is assumed to have minimal impact on their pharmacokinetic and pharmacodynamic profiles, making them well suited for use in patients with CKD without increasing the risk of renal dysfunction [49–51]. Most studies on alirocumab and evolocumab have primarily focused on cardiovascular outcomes rather than directly improving renal function. Although some secondary analyses include patients with CKD, no large RCTs have specifically targeted the effect of these drugs on renal function. This notwithstanding, several sub-analyses of these cardiovascular outcomes trial studies have attempted to analyze the efficacy and safety of evolocumab and alirocumab in patients with various degrees of kidney function impairment.

The two major clinical trials that evaluated the safety and efficacy of PCSK9 mAbs were the FOURIER and ODYSSEY studies. The trials showed a significant 45–55% drop in LDL-C levels when PCSK9 mAbs were employed as add-ons to statin therapy, which translated into a marked reduction in major adverse cardiovascular events compared with placebo [52, 53]. The decrease in LDL-C levels was confirmed regardless of kidney function. Similarly, the RR reduction for the primary endpoint and key secondary cardiovascular outcomes was identical in patients across all stages of CKD.

However, evidence supporting the benefit of PCSK9 mAbs in patients with advanced CKD is limited (Table 3). Indeed, the FOURIER and ODYSSEY outcomes trials excluded patients with severely impaired kidney function (i.e. eGFR <20 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2). ODYSSEY OUTCOMES [54] included 7470 (39.5%) patients with eGFR ≥90 mL/min/1.73 m^2 (mean eGFR: 98.6 [94.3–103.5]), 9326 (49.3%) with eGFR 60 to <90 mL/min/1.73 m^2 (mean eGFR: 77.8 [70.6–84.2]), and 2122 (11.2%) with eGFR <60 mL/min/1.73 m^2 (mean eGFR: 51.4 [44.2–56.1]). Although eGFR <30 mL/min/1.73 m^2 was a screening exclusion criterion, 69 patients (0.4%) had eGFR <30 mL/min/1.73 m^2 at randomization. Primary outcome and annualized incidence rates of death increased progressively with decreasing eGFR; patients who received alirocumab had fewer major adverse cardiovascular events than those receiving placebo across all eGFR levels, and those with eGFR >60 mL/min/1.73 m^2 had greater RR reductions. Over the course of the study, alirocumab had no effect on eGFR and did not lead to more side effects than the placebo in various levels of kidney function, aside from the common injection site reactions. Therefore, both the efficacy and the safety of alirocumab appeared to be consistent across the eGFR categories included in ODYSSEY OUTCOMES. However, an important caveat is that the number of patients with advanced CKD in ODYSSEY OUTCOMES was too small to draw meaningful conclusions for patients with an eGFR <30 mL/min/1.73 m^2, and patients on dialysis were excluded from the study [54, 55]. Toth et al. [56] conducted a pooled analysis of eight randomized trials in which 4629 participants were classified as with or without impaired kidney function (i.e. eGFR <60 mL/min/1.73 m^2). The LDL-C-lowering efficacy of alirocumab was comparable in subjects with impaired kidney function and those without. Importantly, safety data were similar in both treatment subgroups, regardless of the degree of CKD [56]. Leiter et al. [57] investigated the safety and efficacy of alirocumab in preventing cardiovascular events in patients with type 1 or type 2 diabetes mellitus who were on insulin. Subgroup analyses showed that the efficacy and safety of alirocumab was similar regardless of moderate CKD [57]. Comparable results were observed with evolocumab. A sub-analysis of the FOURIER trial in patients with chronic ASCVD evaluated the efficacy and safety of evolocumab across different stages of CKD [58]. The study included 8077 patients with preserved kidney function: 15,034 with stage 2 CKD and 4443 with stage 3 or higher CKD. Evolocumab consistently reduced LDL-C levels by approximately 59% across all CKD groups, and the RR reduction for cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, was similar across these subgroups. Specifically, the hazard ratios (HRs) for the primary and secondary endpoints showed consistent benefits regardless of CKD severity, and no significant differences in renal function decline were observed during the follow-up. Additionally, adverse events, including those related to renal function, were infrequent and similar between the evolocumab and placebo groups across all CKD stages [58, 59]. Like in clinical trials, several real-world studies evaluating the safety of the use of PCSK9 mAbs have not shown worsening of renal function [60–63]. In summary, clinical trials evaluating PCSK9 mAbs have primarily focused on cardiovascular outcomes, and no studies have been specifically designed to assess renal outcomes. The data on patients with kidney disease come from secondary analyses rather than dedicated trials. Despite these limitations, both alirocumab and evolocumab have demonstrated cardiovascular benefits regardless of the presence of mild to moderate renal disease, with no safety concerns on kidney function.

Conversely, evidence for the use of PCSK9 mAbs in ESRD and kidney transplant recipients is very limited and not well defined. East et al. [64] conducted a phase III clinical trial to evaluate the efficacy and safety of alirocumab administered biweekly in 14 patients on a stable dialysis regimen for at least 3 months and with an LDL-C level >70 mg/dL treated for 12 weeks. Alirocumab resulted in a 45% reduction in the LDL-C level (p=0.005) and a 35% reduction in the level of apolipoprotein B (apoB; p=0.06). Responses to the PCSK9 inhibitor alirocumab were similar between patients who were on dialysis and those who were not [64]. Lee et al. [65] evaluated the impact of evolocumab

Table 3 Association between proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and renal function: summary of studies

Agent	Population	Study design	Aim	Effects on renal function	References
Alirocumab	2122 pts (11.2%): eGFR <60 mL/min/1.73 m^2 7470 (39.5%): eGFR ≥90 mL/min/1.73 m^2 9326 (49.3%): eGFR 60 to <90 mL/min/1.73 m^2	Sub-analysis of ODISSEY RCT	Evaluate efficacy and safety of PCSK9 inhibitor alirocumab across prespecified subgroups	No effect on eGFR. Therefore, both efficacy and safety of alirocumab appeared consistent across eGFR categories	[54]
Alirocumab	4629 pts with or without impaired kidney function (eGFR <60 mL/min/1.73 m^2)	Pooled analysis of eight RCTs	Evaluate efficacy and safety of alirocumab	Safety and efficacy data were similar in both treatment subgroups, regardless of degree of CKD	[56]
Alirocumab	517 subjects with T2DM or T1DM	Randomized 2:1 to alirocumab : placebo	Investigate efficacy and safety of alirocumab in pts with T2DM or T1DM	Subgroup analyses showed that efficacy and safety of alirocumab was similar regardless of moderate CKD	[57]
Evolocumab	8077 pts with preserved kidney function, 15,034 with stage 2 CKD, 4443 with ≥stage 3 CKD	Sub-analysis of FOURIER RCT	Compare outcomes with evolocumab and placebo according to kidney function	LDL-C lowering, relative clinical efficacy, safety of evolocumab vs. placebo consistent across CKD groups	[58]
Alirocumab, evolocumab	80 pts: 51 evolocumab; 29 alirocumab	Real-world observational retrospective study	Assess real-world safety, adherence, and efficacy of PCSK9 inhibitors	No worsening of renal function	[60]
Alirocumab, evolocumab	141 pts: 90 alirocumab; 51 evolocumab	Real-world observational retrospective Study	Compare efficacy and safety of the two drugs	No worsening of renal function	[61]
Alirocumab, evolocumab	115 pts: 38 alirocumab; 77 evolocumab	Real-world ambispective study	Analyze effectiveness and safety of PCSK9 inhibitors in routine clinical practice	No worsening of renal function	[62]
Alirocumab, evolocumab	76 pts	Retrospective multicentric cohort study	Analyze evolution of renal function and proteinuria in a cohort of pts with CKD receiving PCSK9 inhibitors	During follow-up, proteinuria improved from 57 (9–481) to 30 (7–520) mg/g (p=0.021). eGFR remained stable; no AEs reported	[63]
Alirocumab	14 pts	Interventional study (pts receiving maintenance dialysis for ≥3 months and with LDL-C >70 mg/dL received alirocumab for 12 weeks)	Analyze effectiveness and safety of PCSK9 inhibitors in pts receiving hemodialysis	Individuals receiving maintenance dialysis had a similar response to the PCSK9 inhibitor alirocumab as pts not receiving dialysis. No unexpected AEs or laboratory abnormalities in this population receiving dialysis	[64]
Evolocumab	Pts with normal renal function (n=6), severe renal impairment (n=6), or ESRD receiving hemodialysis (n=6)	Open-label, parallel-design study	Evaluate impact of evolocumab on renal function in pts with normal renal function, severe renal impairment, or ESRD receiving hemodialysis	No meaningful differences in the use of evolocumab without dose adjustment in pts with severe renal impairment or ESRD	[65]

AEs, adverse events; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; LDL-C, low-density lipoprotein-cholesterol; pt(s), patient(s); RCT, randomized controlled trial; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

on renal function in participants with normal renal function, those with severe renal impairment, and those with ESRD receiving hemodialysis and found similar efficacy and safety profiles across all groups [65]. The use of PCSK9 mAbs in kidney transplant patients is limited. Some case reports on the use of PCSK9 mAbs in patients after kidney transplantation have been published, and no adverse events have been reported [66–68]. In a recent randomized double-blind study, the authors analyzed the outcomes of 197 kidney transplant recipients with a high cardiovascular risk score (>20) who received evolocumab 140 mg every 2 weeks ($n = 98$) or statin therapy ($n = 99$). Results showed that PCSK9 mAbs were safe and effective in the treatment of hypercholesterolemia after kidney transplantation for up to 24 months of treatment [69].

Another aspect worth discussing is the interaction between drugs, especially LLTs and immunosuppressants in kidney transplant recipients. However, PCSK9 inhibitors have no effect on the pathway by which statins and common immunosuppressive drugs are metabolized. Consequently, PCSK9 mAbs rarely interact with most immunosuppressants in transplant patients [70]. The combined use of immunosuppressants and PCSK9 mAbs has been reported in patients after heart transplantation, confirming its safety and good tolerability [71–73].

3.2.2 Inclisiran

Inclisiran is a subcutaneously administered, chemically synthesized, small-interfering RNA double-stranded oligonucleotide that inhibits the production of PCSK9 in the liver [74]. It has been proven effective in reducing LDL-C through a series of clinical studies, including initial findings from ORION-1 and subsequent phase III trials (ORION-9, ORION-10, ORION-11) [75–77]. These studies showed a sustained 50% reduction in LDL-C with biannual dosing, positioning inclisiran as a viable option for patients who either cannot tolerate statins or have suboptimal lipid levels despite statin therapy. Renal clearance is the main route of elimination of inclisiran, with approximately one-third of the total administered dose detected in urine within 24 h of dose.

Data on the safety and efficacy of inclisiran in patients with CKD are sparse. Like with PCSK9 mAbs, clinical trials have not specifically evaluated the efficacy of inclisiran on renal outcomes, and nor have they been designed to study the renal population in detail. Wright et al. [78] conducted an analysis using data from the phase I ORION-7 and the phase II ORION-1 studies, concluding that the pharmacodynamic effects and safety profile of inclisiran were similar in both individuals with normal renal function and those with renal impairment and that dose adjustments were not required [78]. In a post hoc analysis of seven studies, the authors found that, for the first 1.5 years, the incidence of kidney-related events with inclisiran was similar to that with placebo. Creatinine elevations were also rare in both placebo and treatment groups [79]. Recently published data from ORION-8 demonstrated no attenuation of LDL-C lowering over time, which was observed for a period of up to approximately 4 years of treatment. Furthermore, no new safety signals were identified in this analysis [80]. Inclisiran provided substantial and sustained LDL-C lowering across glycemic/body mass index strata, without significant kidney deterioration [81]. A patient-level pooled analysis of ORION-9, -10, and -11 included patients with heterozygous familial hypercholesterolemia, ASCVD, or ASCVD risk equivalent [82]. In the overall study population, 44.9% ($n = 1642$) had CKD, defined as an eGFR of ≥15 to <90 mL/min/1.73 m^2, at baseline. In this analysis, inclisiran reduced major adverse cardiovascular events (OR 0.74 [95% CI 0.58–0.94]) with no significant difference in the renal function tests compared with placebo. Ueberdiek et al. [83] recently published their real-world experience with inclisiran in a kidney transplant recipient. They demonstrated that inclisiran can be safely and conveniently administered and have a profound effect on LDL-C levels after renal transplantation without relevant side effects, increase in proteinuria or creatinine kinase, or change in everolimus level.

3.2.3 Bempedoic acid

Bempedoic acid (BA) is a prodrug that, upon activation in the liver, inhibits adenosine triphosphate citrate lyase, a key enzyme involved in cholesterol biosynthesis. By targeting the cholesterol synthesis pathway upstream of HMG-CoA reductase, BA is efficacious in lowering LDL-C with minimal muscle-related adverse effects, as its activation is primarily confined to the liver [84]. The predominant mechanism of excretion is through the kidneys as metabolites, with a smaller proportion being eliminated via the bile and feces. Renal excretion accounts for most of the drug clearance, with an elimination half-life of approximately 21 h [84]. At clinically relevant concentrations, BA and its glucuronide are weak inhibitors of organic anion transport polypeptides 1B1 and 1B3, which typically transport large hydrophobic organic anions, and weak inhibitors of OAT2 in vitro [85]. Weak inhibition of OAT2 is the mechanism likely to be responsible for the small increases in serum creatinine and uric acid levels observed in patients treated with BA. Although creatinine is primarily transported by OCT2 (an organic cation transporter), evidence suggests that OAT2 also plays a role in handling certain metabolites or alternative pathways affecting creatinine dynamics. Inhibition of OAT2 by BA may exert an indirect influence on renal hemodynamics, encompassing the processes involved in creatinine filtration and excretion. This mechanism is distinct from the direct OCT2-mediated transport and is consistent

with the modest and reversible increases in creatinine observed, which occur without impacting the markers of true renal function [86]. A phase I study evaluating the pharmacokinetics and safety of BA in 24 subjects with normal to severe renal impairment showed that BA exposure was up to approximately two times higher in subjects with renal impairment [87]. The CLEAR development program for BA was underpinned by a series of clinical trials, including studies that assessed the safety and efficacy of the drug in patients with varying degrees of renal function. The CLEAR Outcomes [88] study evaluated the efficacy and safety of BA in 13,970 patients who were unable or unwilling to take statins because of the occurrence of adverse effects that were deemed unacceptable ("statin-intolerant" patients) and who had or were at high risk of CVD. Overall, 20.6% of enrolled patients had an eGFR 30–60 mL/min/1.73 m^2. After 6 months, the reduction in LDL-C levels was more pronounced with BA than with the placebo, with a mean difference of 29.2 mg/dL (21.1% greater in the BA arm). The incidence of the four-component composite primary cardiovascular endpoint, comprising death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and coronary revascularization, was 13% lower with BA than with placebo. Analysis of the side effects revealed that renal events, including AKI, increases in serum creatinine, and reduced eGFR, were higher with BA than with placebo (11.5% in the BA group vs. 8.6% in the placebo group; p=0.03). Data pooled from four phase III studies indicated that BA was well tolerated in patients with stage 2 or stage 3a+b renal impairment and effectively lowered LDL-C across various renal function statuses [89]. A recent sub-analysis of the CLEAR Outcome study by Ray et al. [90] showed that BA compared with placebo reduced the risk of cardiovascular events in statin-intolerant patients with type 2 diabetes without previous ASCVD. However, they also reported a higher incidence of kidney impairment with BA than with placebo, particularly in patients with prediabetes or diabetes, which appeared to be largely attributable to elevations in creatinine concentrations from baseline [90, 91]. Because of the high prevalence of diabetic kidney disease, which affects approximately 40% of people with diabetes and often culminates in kidney failure, a careful evaluation of BA is crucial in this population [91].

The development program data clearly demonstrated that BA exposure increased in patients with renal impairment, especially in those with severe impairment. The area under the plasma concentration–time curve (AUC) exposure to BA in patients with normal renal function is approximately 348 µgh/mL. In patients with renal impairment, the AUC increased by approximately 1.4-fold in mild impairment, 1.9-fold in moderate impairment, and 2.4-fold in severe impairment compared with in those with normal renal function [92]. Based on the current evidence, no dose adjustment is required for patients with mild to moderate CKD [92], but those with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or ESRD were generally excluded from most clinical trials. Consequently, the use of BA in this population is not recommended. Further studies are needed to establish its safety profile in patients with severe kidney disease and to better understand its long-term effects in this setting.

A recent review of the literature on the efficacy and safety of BA was published in the Position Paper 2023 from the International Lipid Expert Panel [93]. The authors concluded that BA is safe and well tolerated and that the adverse effects are mild and reversible. These include an increase in creatinine level (estimated to be 0.05 ± 0.2 mg/dL) and uricemia (estimated to be 0.76 ± 1.2 mg/dL), both of which are considered clinically insignificant.

3.2.4 Lomitapide

MTP is an intracellular protein responsible for the binding and transport of lipids across the cellular membrane and has a pivotal role in the synthesis of apoB [94, 95]. By blocking the coupling of triglycerides with apoB-100 in the liver and apoB-48 in the intestine, MTP inhibitors such as lomitapide reduce the secretion of very low-density lipoproteins (VLDLs) and chylomicrons [96]. This process reduces the production of VLDLs and chylomicrons, thereby decreasing LDL-C levels in plasma in an LDL-receptor-independent manner. Lomitapide is mainly metabolized by cytochrome P450 (CYP)-3A4 to its inactive metabolites, M1 and M3. CYP enzymes that metabolize lomitapide to a minor extent include CYP1A2, -2B6, -2C8, and -2C19. Approximately 52.9–59.5% is then eliminated in the urine and 33.4–35.1% is eliminated in the feces [97].

Lomitapide has demonstrated significant efficacy in reducing LDL-C, particularly in patients with homozygous familial hypercholesterolemia (HoFH), and showed a sustained 40–50% reduction in LDL-C with ongoing therapy [96]. Although a formal study is yet to be conducted, real-world data indicate that the use of lomitapide in HoFH may also be associated with a clinical benefit in terms of reduced CVD [96]. However, these data are still preliminary, and no definitive conclusions can yet be drawn. At present, lomitapide is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of HoFH based on the results from a pivotal phase III clinical trial [98, 99]. In addition to its use in HoFH, lomitapide has been investigated for its efficacy in treating severe hypertriglyceridemia, including familial chylomicronemia syndrome (FCS). The LOCHNES study, which included 18 adult patients with FCS, demonstrated a significant median reduction of 70.5% in triglyceride levels after 26 weeks of treatment with lomitapide. The study reported that 66.7% of

patients experienced a triglyceride reduction of over 50%, with 55.6% achieving triglyceride levels <500 mg/dL [100].

Common side effects associated with lomitapide include gastrointestinal disturbances and elevations in liver enzymes, which require careful monitoring. Lomitapide has also been associated with hepatic steatosis, as it can lead to significant increases in liver fat content, necessitating ongoing evaluation of hepatic function during treatment [101]. Data on the safety of lomitapide in patients with impaired kidney function are limited. Compared with the values observed in healthy volunteers with a creatinine clearance of 80 mL/min (4.8 L/h), the lomitapide AUC and maximum plasma drug concentration values were 40% and 50% higher, respectively, in patients with ESRD undergoing hemodialysis after a single dose of lomitapide 60 mg. The pharmacokinetics of lomitapide have not yet been evaluated in patients with ESRD not receiving dialysis or in patients with mild, moderate, or severe renal impairment [102]. However, current evidence suggests that lomitapide does not require dose adjustments in patients with mild to moderate renal impairment. In patients with ESRD on dialysis, the daily dosage should be limited to 40 mg [97, 103]. Further research is needed to assess its safety in patients with CKD or renal function impairment.

3.2.5 Evinacumab

ANGPTL3 inhibitors represent a promising new class of LLTs, targeting a key regulator of lipid metabolism [104]. ANGPTL3 is primarily expressed in the liver and plays a crucial role in inhibiting lipoprotein lipase (LPL) and endothelial lipase, which are enzymes involved in the metabolism of triglycerides and high-density lipoprotein cholesterol (HDL-C) [105, 106]. By inhibiting ANGPTL3, these drugs significantly reduce levels of triglycerides, LDL-C, and HDL-C, offering a comprehensive approach to managing dyslipidemia [107, 108].

Evinacumab is a fully human mAb against ANGPTL3 that has shown substantial efficacy in clinical trials, reducing LDL-C by up to 50% in patients with HoFH and refractory hypercholesterolemia [109–115]. A recently published post hoc analysis of three phase III trials reported a significant reduction in plasma levels of triglyceride-rich lipoproteins (e.g. very-low-density lipoprotein and remnants), reaching >50% reduction from baseline at the highest doses of evinacumab (15 mg/kg intravenously every 4 weeks or 450 mg subcutaneously every week) [116]. Although formal trials are lacking, real-world data have shown that the use of evinacumab in HoFH is associated with regression of carotid and coronary atheroma, suggesting a clinical benefit on CVD risk [117–119]. These results suggest that evinacumab could be particularly beneficial in high-risk populations where managing dyslipidemia is crucial to reducing cardiovascular risk.

Patients with mild to moderate renal impairment in phase II and III studies had steady-state concentrations similar to those observed in people with normal renal function [120, 121]. However, it is important to note that these patients represented a minority of the study population and that individuals with more severe renal impairment, such as those with advanced renal failure, were excluded.

The metabolic pathway of evinacumab remains uncharacterized, but it is thought to be degraded via catabolic pathways to small peptides and amino acids, such as endogenous IgG [120]. Although the exact metabolic pathway of evinacumab is unknown, it is not believed to be renally cleared. This assumption is based on data from mAbs in general, rather than direct studies of evinacumab itself. Therefore, no dose adjustment is planned for patients with mild or moderate renal insufficiency; conversely, as no data exist for patients with severe renal insufficiency, use in these patients is not recommended [122]. In the future, real-world evidence and post-marketing data may provide additional insight into the efficacy and safety of evinacumab in more diverse populations, including those with renal impairment.

4 Triglyceride-Lowering Medications in CKD

4.1 Conventional Triglyceride-Lowering Therapies

The safety of triglyceride-lowering therapies in kidney disease remains under debate.

Fibrates are lipid-lowering drugs that work by binding to peroxisome proliferator activated receptor alpha, which leads to the activation or inhibition of multiple genes involved in lipid metabolism [123]. This mechanism not only reduces plasma triglyceride levels by altering fatty acid metabolism but also increases HDL-C by increasing apolipoprotein synthesis and reduces inflammation by modulating nuclear factor-kappa B activity, a crucial intracellular signal transduction system involved in several inflammatory diseases, including atherosclerosis [123, 124]. Several studies have shown that fibrates, including gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate, may increase serum creatinine levels [125, 126]. However, this increase is most often transient and reversible. Several hypotheses for the mechanism of fenofibrate-associated nephrotoxicity have been described [127]. Although the proposed mechanisms are biologically plausible, none have been rigorously tested in clinical trials. One prevailing hypothesis is that fenofibrate may interfere with the production of vasodilatory prostaglandins, resulting in reduced afferent arteriolar dilation, thereby affecting glomerular capillary pressure and renal perfusion. Another hypothesis is that fenofibrate may

competitively inhibit creatinine secretion in the proximal tubular lumen. It has also been suggested that fenofibrate may contribute to increased production of endogenous creatinine [127]. Regardless of the mechanism underlying this effect, data from clinical trials on the use of fibrates, such as fenofibrate, show a significant association between their use and increased serum creatinine levels. Nevertheless, results from RCTs also confirmed that this effect is generally reversible and does not indicate structural kidney damage. Indeed, in the placebo-controlled FIELD trial [128] in 9795 people with type 2 diabetes mellitus treated with fenofibrate, the creatinine elevation was fully reversible after 8 weeks of treatment discontinuation. It is important to note that, in this trial, although the between-group difference in the primary cardiovascular outcomes did not reach statistical significance, a significant benefit was apparent for some components of the primary outcome such as non-fatal myocardial infarctions (HR 0.76 [95% CI 0.62–0.94]; p=0.010) and coronary revascularizations (HR 0.79 [95% CI 0.68–0.93]; p=0.003). Similarly, in the ACCORD trial [129], the eGFR returned to baseline values after stopping fenofibrate. It is worth mentioning that the FIELD [128], ACCORD [129], and DAIS [130] trials showed a beneficial effect of fibrates on albuminuria in the diabetic subgroup. Furthermore, in a subgroup of participants in the ACCORD trial, Chauhan et al. [131] demonstrated that elevated serum creatinine was not associated with increased urine biomarkers of tubular injury, inflammation, or fibrosis. A recent meta-analysis that included 29 studies with a total of 20,176 patients, confirmed that treatment with fibrates resulted in increased creatinine (standardized mean difference 1.05 [95% CI 0.63–1.46]; p<0.001) compared with the comparator, and this was similar in all other subgroups. However, treatment with fibrates appeared to not only reduce the progression of albuminuria (RR 0.86 [95% CI 0.76–0.98]; p=0.065; I^2=63.5%) but also to increase the regression of albuminuria (RR 1.19 [95% CI 1.08–1.31]; I^2=0%; p=0.501) in patients with and without diabetes when used to treat hyperlipidemia [132]. Although the use of fibrates has been associated with increased serum creatinine, the observed decrease in the progression of albuminuria and the increase in regression may provide a rationale for their continued use. It is noteworthy that some results from this meta-analysis did not meet conventional thresholds for statistical significance, and no data were presented on the impact of fibrates on the emergence of ESRD. Therefore, no definitive conclusion can be drawn in this population. Moreover, it is crucial to highlight that the follow-up period of all the trials was relatively brief. In conclusion, the current evidence suggests that a modest increase in creatinine should not be a limiting factor for starting fibrates in people with preserved renal function or mild CKD and that increased serum creatinine should be expected when treating patients with these drugs.

Omega-3 ($n-3$) fatty acids lower plasma triglycerides by increasing fatty acid oxidation, which suppresses hepatic lipogenesis and subsequent VLDL production [133]. $n-3$ has been shown to be effective in reducing proteinuria in a dose-dependent manner in patients with chronic glomerular disease [134, 135]. The current hypothetical mechanisms of action in certain forms of CKD also include the effect of $n-3$ polyunsaturated fatty acids ($n-3$ PUFAs) on renal inflammatory pathways and glomerular proteinuria [136, 137]. Ong et al. [138] conducted a pooled analysis of 19 studies from 12 countries that measured $n-3$ PUFA biomarker data and incident CKD; the primary outcome analysis included 25,570 participants without prevalent CKD. Results showed that higher seafood-derived $n-3$ PUFA levels were associated with a 13% lower risk of incident CKD (RR 0.87 [95% CI 0.80–0.96]; p=0.005), although this association was not found for plant-derived $n-3$ PUFAs. These results support a potential beneficial role for $n-3$ PUFAs in the prevention of CKD [138]. Similarly, a recently published prospective observational cohort study on the UK Biobank population reported that, among individuals without CKD, higher plasma $n-3$ PUFA levels were associated with a lower risk of incident CKD. In individuals with CKD, only the $n-3$ component of PUFAs, docosahexaenoic acid, was associated with a lower risk of kidney failure [139]. Despite these positive results, there is a potential concern about increased bleeding risk in patients receiving $n-3$ PUFAs. This might be particularly relevant in patients with CKD who are prone to developing alterations in hemostasis. Nevertheless, the results of a recent meta-analysis [140] including a total of 120,643 patients from 11 RCTs showed no difference in the pooled events of bleeding among patients receiving n-3 PUFAs and those in the control group (RR 1.09 [95% CI 0.91–1.31]; p=0.34). Likewise, the incidence of hemorrhagic stroke, intracranial bleeding, and gastrointestinal bleeding were similar. A prespecified analysis in those receiving high-dose purified eicosapentaenoic acid (EPA) demonstrated a 50% increase in the RR of bleeding but only a modest increase in the absolute risk of bleeding (0.6%) when compared with placebo. Although these findings appear reassuring, careful monitoring of patients with CKD taking these drugs is highly recommended.

4.2 Novel Triglyceride-Lowering Therapies

4.2.1 Icosapent Ethyl

Icosapent ethyl (IPE) is a stable, highly purified ethyl ester of EPA that safely and significantly reduced cardiovascular risks in statin-treated patients with established CVD or diabetes [141].

In the REDUCE-IT trial, IPE achieved a 25% RR reduction in major cardiovascular events over 4.9 years (p<0.001)

and a 26% reduction in the risk of cardiovascular death, myocardial infarction, or stroke ($p<0.001$) compared with the placebo group [141]. The REDUCE-IT RENAL [142] study was conducted to evaluate the cardiovascular benefits of IPE across different levels of kidney function. Among the 8179 patients in REDUCE-IT, median baseline eGFR was 75 mL/min/1.73 m^2 (range 17–123), and there were no meaningful changes in median eGFR in IPE versus placebo groups. It is noteworthy that treatment with IPE consistently reduced both the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina, and the key secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke across all baseline eGFR categories. Although patients with eGFR <60 mL/min/1.73 m^2 exhibited numerically higher absolute rates of atrial fibrillation/flutter and serious bleeding, the HR for these safety endpoints did not differ significantly across eGFR categories [142]. Further studies are needed to definitively establish the benefits and long-term safety of using IPE in kidney disease

4.2.2 apoC-III Inhibitors

apoC-III is a glycoprotein that plays a key role in lipid metabolism, specifically in the regulation of triglyceride levels in the blood [139]. It is primarily produced in the liver and to a lesser extent in the intestines. apoC-III inhibits the activity of LPL, an enzyme crucial for the hydrolysis of triglycerides in lipoproteins. By inhibiting LPL, apoC-III slows the clearance of triglyceride-rich lipoproteins from the bloodstream, contributing to elevated triglyceride levels, which are associated with an increased risk of CVD [143].

Volanesorsen is a 20-nucleotide partially 2′-*O*-(2-methoxyethyl)-modified antisense oligonucleotide gapmer that selectively binds within the 3′ untranslated region of apoC-III messenger RNA and prevents the translation of apoC-III messenger RNA in a dose-dependent manner [144]. Consequently, a decrease in apoC-III protein promotes triglyceride clearance and reduces plasma triglyceride levels. The phase III trials showed that treatment with volanesorsen leads to a robust decrease in both apoC-III production and triglyceride concentrations up to 70% even in the more severe genetic form of hypertriglyceridemia such as FCS [145]. The pharmacokinetic and metabolic properties of volanesorsen have been comprehensively delineated across species, from mice to humans. The pharmacokinetic properties of volanesorsen are comparable among patients with FCS, healthy volunteers, and patients with hypertriglyceridemia [146]. Volanesorsen exhibits a high degree of binding to plasma proteins, exceeding 98% in a concentration-independent manner; after injection, the drug rapidly distributes from plasma to tissues, especially the liver and kidneys. The primary clearance pathway is through urinary excretion of metabolites, although <3% of a dose was recovered within 24 h [147]. No specific data have been analyzed to determine the tolerability of volanesorsen in patients with renal impairment. In the recently published extension of the APPROACH study, common adverse events were injection site reactions and decreased platelet counts, but no renal impairment was described [148]. However, renal toxicity has been observed after administration of volanesorsen and other subcutaneously and intravenously administered antisense oligonucleotides. The study on partial lipodystrophy revealed that the arm treated with volanesorsen experienced several serious adverse events, including pancreatitis, acute respiratory distress syndrome, and AKI associated with hypertriglyceridemia-induced pancreatitis and peri-rectal abscess [148]. Therefore, the current European Medicines Agency recommendation is to monitor for evidence of nephrotoxicity via routine quarterly urine dipstick [149]. If results are positive, a broader assessment of renal function, including serum creatinine and a 24-h collection to quantify the proteinuria and assess creatinine clearance, should be performed. To date, dose adjustment is considered necessary in patients with mild to moderate renal impairment, but no recommendation is provided for patients with severe disease, in whom close monitoring is required [149]

5 Discussion

This narrative review has explored the current landscape of LLTs in patients with CKD, with particular attention to the balance between cardiorenal protection and renal safety. As well established in the literature, dyslipidemia is a major contributing factor to cardiovascular morbidity and mortality in patients with CKD [4]. Therefore, clinicians must consider the well-established cardiovascular benefits of LLTs alongside the potential impact of these medications on renal function. Given the high global prevalence of CKD and that cardiovascular events are the leading cause of death in these patients [1], there is a clear clinical need to understand how different LLTs affect kidney function.

The mainstay of treatment for dyslipidemia in CKD involves a strategy based on the use of statins, frequently supplemented by ezetimibe, to reduce LDL-C levels [7]. A substantial body of evidence, including data from large trials such as SHARP [20], has confirmed that conventional LDL-C-lowering therapy reduces cardiovascular risk in both early- and mid-stage CKD. However, the benefits of these treatments in advanced CKD stages are less clear, as many clinical trials have systematically excluded patients with severely reduced eGFR. Questions also remain about the long-term renal effects, particularly with higher-potency statins, in these patients. Episodes of transient proteinuria or

creatinine elevations, although frequently benign and reversible, underscore the importance of vigilance in such vulnerable populations [24, 25].

Recent advancements in the field of lipid therapeutics have led to the identification of novel targets, such as PCSK9 [48]. Therapeutic inhibition of PCSK9 with mAbs has resulted in a paradigm shift in the management of LDL-C in high-risk patients. Alirocumab and evolocumab have demonstrated robust LDL-C reductions and improved cardiovascular outcomes in large-scale trials [52, 53], with post hoc sub-analyses indicating similar RR reductions across varying CKD stages, although these studies largely excluded individuals with advanced CKD [55, 58]. Early real-world evidence from dialysis or post-transplant populations also suggests no major nephrotoxicity signals [64–69]. However, large, dedicated clinical trials are needed to confirm these preliminary observations, clarify the optimal dosing, and establish monitoring protocols in advanced CKD. Therefore, considering the limited evidence on the use of PCSK9 mAbs for eGFR <30 mL/min, these drugs are not recommended in patients with ESRD or with kidney transplant; if they are prescribed, eGFR should be closely monitored [150, 151].

Inclisiran, a next-generation therapy employing small interfering RNA technology, is administered biannually to inhibit hepatic PCSK9 synthesis and achieve durable LDL-C reductions [74]. Post hoc analyses from the ORION-9, -10, and -11 trials suggest similar safety profiles among individuals with mild-to-moderate renal impairment, and recent data have shown no new safety signals over extended follow-up periods of up to 4 years [80]. Nevertheless, patients with advanced CKD remain underrepresented, and definitive conclusions on renal safety in later-stage disease cannot be drawn. Nonetheless, current regulatory guidelines do not require inclisiran dosages to be adjusted for patients exhibiting renal impairment of any severity, including mild, moderate, or severe categories, in instances of ESRD during its administration [152].

More recently, oral therapies such as BA, an adenosine triphosphate citrate lyase inhibitor acid, have demonstrated notable efficacy in improving lipid profiles and reducing cardiovascular events [88], although data in advanced CKD remain limited. It must be noted that the use of BA in patients with hypercholesterolemia has been associated with mild and often reversible elevations in serum creatinine due to the potential pharmacological inhibition of OAT2 [85, 86]. The safety of BA for patients with mild to moderate CKD is well established [89, 90], but evidence to support its use in more advanced cases of kidney disease or in the long term are scarce.

Fibrates are widely used in the treatment of hypertriglyceridemia but are known to be associated with increased serum creatinine [125, 126]. However, current evidence suggests that this effect is often hemodynamic and reversible rather than indicative of intrinsic nephrotoxicity [127]. Moreover, some data suggest possible benefits in reducing albuminuria, although these findings remain controversial [128–130]. To date, no dose adjustment is necessary for patients with renal impairment if serum creatinine is >80 mL/min. In patients with moderate renal impairment, dose adjustment is required; however, fibrates are contraindicated if the serum creatinine clearance is <30 mL/min or in cases of ESRD because of reduced drug clearance and an increased risk of myositis [153]. The direct impact of standard EPA/docosahexaenoic acid-based formulations on kidney outcomes is not fully defined, yet most data suggest they can be used safely in CKD [134, 135]. The summary of available evidence supports the potential of $n-3$ PUFA as a safe and effective adjunctive therapy in managing patients with CKD. IPE provides a significant reduction in cardiovascular events in patients with elevated triglycerides and either established CVD or diabetes [141], and this benefit is consistent across different eGFR categories. Whether $n-3$ PUFA are useful in kidney protection remains unclear because specifically designed clinical trials are lacking. In any case, the possible increased risk of bleeding and cardiac rhythm disturbances associated with the use of $n-3$ PUFA requires rigorous monitoring in patients with CKD using these drugs. Current evidence and the limitations associated with hypolipidemic therapies clearly highlight the management of hypertriglyceridemia as an important unmet clinical need. Hypertriglyceridemia is frequently observed in patients with CKD. Greater efforts are required to evaluate the efficacy and safety of these therapies in this patient population and to expand the therapeutic armamentarium available for addressing this critical issue.

New agents addressing different molecular pathways are broadening the scope of LLT. Agents such as evinacumab, lomitapide, and apoC-III inhibitors offer key options for managing refractory and rare genetic dyslipidemias [104]. However, evidence in moderate-to-severe CKD is often limited. Although pivotal trials have not highlighted major renal safety signals, these studies typically enrolled small cohorts with relatively preserved renal function, limiting generalizability to advanced CKD. Real-world evidence similarly remains sparse, and further dedicated research is needed to confirm kidney safety in patients with significantly reduced eGFR or those on dialysis.

Despite the identified gaps in the evidence, the overall trajectory remains encouraging. Although some LLTs have been associated with transient increases in serum creatinine or proteinuria, most data suggest that these changes are often reversible and not associated with meaningful declines in long-term renal function. These findings emphasize the importance of personalizing treatment to the individual patient's baseline renal status and comorbidity profile and

the risk of adverse effects. The multifactorial nature of CKD signifies that patients may follow divergent trajectories of disease progression, including complications related to dyslipidemia. This emphasizes the need for tailored therapeutic strategies. A key goal should be to include patients with advanced CKD, including those on dialysis, in large-scale clinical trials of both existing and emerging LLTs. Furthermore, clinical trials that recognize CKD outcomes as primary aims should be developed. This will help define optimal dosing strategies, clarify monitoring protocols, and refine safety thresholds in individuals at the highest cardiovascular risk. Incorporating more sensitive biomarkers, such as cystatin C, may also provide a clearer picture of kidney integrity. Addressing these knowledge gaps is crucial to ensure that patients with CKD can fully benefit from contemporary dyslipidemia management without incurring undue renal risk. By adopting patient-centered approaches and integrating emerging evidence, clinicians can continue to refine the balance between cardiovascular protection and kidney preservation in this complex population.

Declarations

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Conflict of Interest M.A. has received research grant support from Amryt Pharmaceutical, Amgen, IONIS, Akcea Therapeutics, Daiichi-Sankyo, Novartis, Pfizer, and Regeneron; served as a consultant for Amgen, Akcea Therapeutics, Daiichi-Sankyo, and Ultragenyx; and received fees for lecturing, congress participation, and advisory board participation from Amgen, Amryt Pharmaceutical, Daiichi-Sankyo, Regeneron, Sanofi, Amarin, and Ultragenyx. L.D. has received personal fees for public speaking or consultancy or grant support from Amryt Pharmaceutical, Akcea Therapeutics, SOBI, AuroraBiopharma, Novartis, Amarin, Daiichi-Sankyo, Bayer, and Sandoz. S.B. has received personal fees for public speaking from SOBI; retains stock options in Eli Lilly, UnitedHealth, Novo Nordisk, Merck, and Thermo Fisher Scientific; and received grants for meeting participation from Novartis. D.T. has received personal fees for public speaking from SOBI. C.M., A.D.C., D.C., I.M., M.C., J.C., I.A., S.C., and G.S. have no competing interests.

Author Contributions D.T. and L.D. were primarily responsible for the conceptualization, methodology, revision of selected articles, and writing of the original draft. L.D. supervised the project. S.B., A.D.C., and I.M. critically revised the manuscript and contributed to the analysis of pharmacokinetic and pharmacodynamic aspects. D.C., as a pharmacist, reviewed the technical aspects related to the medications and critically revised the manuscript. C.M., M.C., J.C., I.A., S.C., and G.S. extensively researched the literature, assisted in reviewing the studies and the selection process, and critically revised the manuscript. M.A. reviewed the selected literature and contributed to the final organization of the manuscript. All authors reviewed and approved the final version of the manuscript

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