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Lipid disorders in patients with renal failure: Role in cardiovascular events and progression of chronic kidney disease

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ABSTRACT

The spectrum of lipid disorders in chronic kidney disease (CKD) is usually characterized by high triglycerides and reduced high dense lipoprotein (HDL), associated with normal or slightly reduced low dense lipoprotein (LDL)-cholesterol. This dyslipidemia is associated with an increased risk for atherosclerotic cardiovascular disease. Keys for the cardiovascular risk reduction in these patients are lowering the number and modifying the composition of the cholesterol-carrying atherogenic lipoprotein particles. Statins have an important role in primary prevention of cardiovascular events and mortality in non-hemodialyzed CKD patients. The benefits in terms of progression of renal failure are contradictory. Patient education regarding dietary regimen should be part of the CKD clinical management.

Introduction

Lipids are heterogeneous and fundamental biological molecules which, besides their energetic roles, are involved in cellular membrane function and synthesis of bile acids, steroid hormones and vitamin D. Circulating lipids are transported by lipoproteins, which are hydrosoluble particles constituted by a lipid nonpolar core of triglycerides and esterified cholesterol, enveloped by apolipoproteins, phospholipids and others polar lipids. In decreasing order of density, lipoprotein are divided in high density (HDL), low density (LDL), intermediate (IDL), very low density (VLDL) lipoproteins and chylomicrons [1].

It is well known that high levels of cholesterol-LDL represent an independent risk factor for atherosclerotic events and all-cause mortality, as shown for the first time in 1913 by Nikolay Anichkow [2]. He demonstrated a close direct relationship between aortic atherosclerosis and high cholesterol diet in rabbits. In the last decades, several larger epidemiological studies confirmed these finding in humans, as observed in Framingham Heart Study and Multiple Risk Factor Intervention Trial, where serum levels of cholesterol-LDL were related to coronary artery disease [3,4].

Statins modify profoundly the natural history of atherosclerosis and related complications, as they decrease cardiovascular mortality secondary to reduction of cholesterol-LDL by 20–55% in a dose-dependent manner after 30 days of therapy [5]. Beyond the effects on cholesterol levels exerted by the inhibition of hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, several pleiotropic effects have been linked to statins acting on inflammation, atheromatous plaques and endothelial dysfunction.

Here, we aim to review the lipid profile in patients with chronic kidney disease (CKD), patients on hemodialysis, and renal transplanted patients. We evaluate the influence of hyperlipemia on renal disease progression and cardiovascular outcomes, and the importance of diet. Finally, we mention future perspectives and potential new therapies that could improve survival and clinical outcomes in renal patients.

Chronic kidney disease and cardiovascular risk

The prevalence of CKD varies from 7 to 12.5% [6]. CKD is associated with an independent risk factor for cardiovascular disease

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(CVD), which is the main cause of morbidity and mortality in these patients [7]. Cardiovascular risk occurs early in CKD patients [8]. As shown in the PREVEND study, albuminuria represents an independent risk factor for cardiovascular and all-cause mortality [9], demonstrating that CKD influences CVD development and progression. However, the pathophysiological mechanisms of this correlation are not fully understood. In addition to arterial hypertension, diabetes mellitus or dyslipidemia, many other factors have been related to cardiovascular risk, such as chronic inflammation, uremic toxins, oxidative stress, reduced nitric oxide levels and an altered calcium-phosphorus imbalance [10].

CKD patients are usually characterized by high triglycerides and low HDL levels, normal or slightly reduced cholesterol-LDL [11]. Cholesterol-LDL is not a reliable predictive cardiovascular risk factor in patients with advanced CKD. Moreover, in ESRD, low cholesterol levels have been related to high mortality risk, probably reflecting chronic inflammation and malnutrition, leading to a seemingly paradoxical reversal of the well-established association of higher lipid levels with mortality in the general population [12]. The lipid and apo-lipoprotein profile characterizing pre-dialytic renal failure remains essentially unchanged during long-term dialysis, with qualitative and quantitative alterations.

In particular, disturbances in the density distribution of LDL subfractions have been assessed, showing a predominance of small, dense LDL particles, more atherogenic than the large ones, substantially contributing to the pathogenesis of atherosclerotic vascular disease. These structural modifications are related to the low triglycerides content within LDL, due to lipoprotein lipase and hepatic lipase actions [13,14].

High plasma triglyceride levels can also be explained by significant increases in plasma levels of apolipoprotein C-III, which is a potent inhibitor of LPL [15]. LPL, which is located in the capillary endothelium, is responsible for triglyceride and phospholipid hydrolysis of VLDL and chylomicrons, leading to their deposition in arterial vessels [16,17].

High levels of lipoprotein Lp (a) contribute to atherosclerosis and cardiovascular disease in CKD patients. Lp (a) is an LDL-like particle in which the specific apolipoprotein(a) is linked to apoB-100 by a single disulfide bond [18]. In kidney disease, plasma Lp(a) levels are significantly influenced by the glomerular filtration rate (GFR), and are increased in the earliest stages of renal impairment [19].

Furthermore, up-regulated HMG-CoA reductase and increased acetyl-coenzyme A acetyl-transferase (ACAT)-2 promote the accumulation of esterified cholesterol and the production of lipoproteins containing apo-B, namely LDL and VLDL [20].

CKD is associated with a reduced activity of lecithin-cholesterol acyl-transferase (LCAT), an enzyme linked to HDL and responsible for the conversion of cholesterol into its esterified forms, allowing hepatic removal of cholesterol. LCAT dysfunction causes morphological changes to HDL, which acquire a spherical rather than disc-shaped structure, with resulting alteration of their catabolism [21,22]. Furthermore, down-regulation of LP and LPL could be induced by a mechanistically poorly understood secondary hyperparathyroidism, a common complication observed in CKD leading to worsening dyslipidemia [23]. Indeed, hypotriglyceridemia was reported after parathyroidectomy [24] and high levels of phosphorus are notoriously associated with an increased risk of cardiovascular mortality, independent of calcium or parathyroid hormone levels [25].

Statins in patients with renal disease: role in cardiovascular outcomes

Whereas several studies have clearly demonstrated beneficial effects of statins on cardiovascular morbidity and mortality, contrasting data have been obtained when the CKD population has been evaluated [26]. Nevertheless, recent studies highlighted positive results also in CKD patients, independent of cholesterol levels. (Table 1) In particular, the Heart Protection Study [27] and the Anglo-Scandinavian Cardiac Outcomes (ASCOT) trial [31] demonstrated a reduction of cardiovascular morbidity and mortality in CKD patients treated with simvastatin. The Pravastatin Pooling Project data demonstrated that cardiovascular outcomes, including myocardial infarction, coronary revascularization and cardiac death, were reduced by this statin in CKD patients [29]. The Treating to New Targets (TNT) study compared the effects of two dosages of atorvastatin on cardiovascular events, revealing better outcomes with the higher statin dosage in patients with renal failure [33]. Similar conclusions were obtained by the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, in which atorvastatin reduced the relative risk of cardiovascular events by 28% in CKD patients and by 11% in patients without evidence of renal disease [36]. Positive results were also reported administering rosuvastatin. In the Justification for the Use of statins in

Table 1
Trials evaluating the reduction of cholesterol-LDL and cardiovascular risk in CKD populations

Trials	N° Patients, disease	Statin dosage	Follow-up (years)	LDL reduction %	CV event reduction %	P value
HPS (2002) [27]	1329 CKD	Simvastatin 40 mg	5	29%	28%	<0.001
SHARP (2011) [28]	9270 CKD and hemodialysis	Simvastatin 20 mg + Ezetimibe 10 mg	4.9	55%	17%	0.0021
PPP (2004) [29]	4491 CKD	Pravastatin 40 mg	5	31%	23%	<0.02
ALERT (2005) [30]	2102 Renal transplant	Fluvastatin 40 mg	5.1	32%	29%	<0.01
ASCOT (2003) [31]	6517 Arterial hypertension CKD	Atorvastatin 10 mg	3.3	29%	40%	0.0025
4D (2005) [32]	1255 Hemodialysis	Atorvastatin 20 mg	4	42%	–	0.35
TNT (2008) [33]	1602 CKD	Atorvastatin 80 mg	5	36%	32%	0.0003
AURORA (2009) [34]	2776 Hemodialysis	Rosuvastatin 10 mg	3.8	43%	–	0.59
JUPITER (2010) [35]	3267 CKD	Rosuvastatin 20 mg	4	40%	45%	0.002

Prevention – an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, CKD patients receiving rosuvastatin had a reduction in myocardial infarction, ischemic stroke and cardiovascular mortality by 45% compared to placebo [35].

Convincing data were also obtained in renal transplanted patients. In particular, the ALERT study (Assessment of Lescol in Renal Transplant) evaluated the effects of fluvastatin, revealing better cardiovascular outcomes than those recorded in the placebo group. However, renal graft survival and all-cause mortality were not influenced by statin treatment in this study [30,37]. Overall these data demonstrate that statins exert positive effects in patients with CKD. However, these beneficial effects have not been demonstrated in ESRD patients. Several trials have been conducted in patients undergoing HD. The 4D Study (Die Deutsche Diabetes Dialyse Studie) demonstrated that there were no differences between the treated and untreated groups in the primary composite endpoint of cardiac death, stroke, or nonfatal myocardial infarction, whereas in the atorvastatin group, there was a two-fold increase in fatal strokes [32]. Similar conclusions emerged from the AURORA trial, a randomized placebo-controlled trial the enrolled over 2000 HD patients treated with rosuvastatin [34]. Different explanations could be proposed for these negative results. First, many cardiovascular events in dialysis patients were due to arrhythmia or non-ischemic cardiomyopathy, which might not be related to atherosclerosis. Second, the atherosclerosis was so advanced that these patients were unlikely to benefit from drug therapy [38].

The Study of Heart and Renal Protection (SHARP) was a prospective trial using statins in more than 3000 HD patients, randomized to simvastatin 20 mg/day or simvastatin 20 mg/day plus ezetimibe or placebo. During a follow-up period of 4.9 years, the greatest reduction of cholesterol-LDL and cardiovascular events was obtained in patients treated with simvastatin plus ezetimibe, without achieving statistical significance and without differences on mortality rate [28].

Lipids and statins: role in CKD

Several studies have demonstrated an association between abnormal lipid metabolism and progression of renal disease, but results are controversial. Whereas *in vitro* and animal studies suggest an important role of lipid alterations in initiation and progression of CKD, human studies did not provide uniform data.

Experimental studies

Animal studies have demonstrated that lipid alterations induce glomerular and tubular damage, with positive effects exerted by statin therapy [39]. The mechanisms are not fully understood, but the main hypothesized explanation is linked to the inhibition of mevalonate, a well known stimulant of cellular replication and glomerular proliferation.

Kasiske et al. evaluated the effects of lovastatin in obese and albuminuric rats with focal glomerulosclerosis [40]. They found a reduction of urine albumin excretion and an improvement of glomerular sclerosis in the treated group compared to placebo. Potential beneficial effects by statin treatment in glomerular disease were evaluated in a rat model of mesangial proliferative glomerulonephritis induced by anti-thymocyte antibodies. A suppression of 70% of glomerular cell proliferation was shown, together with a decreased glomerular alpha-smooth muscle actin expression, a marker for mesangial cell activation. Furthermore, an inhibition of monocyte/macrophage recruitment into glomeruli by simvastatin was also demonstrated [41].

Human studies

Several studies have been performed to assess the role of lipids in the development and progression of CKD. Mänttäri and colleagues reported an independent association between high LDL levels and decline of renal function in 2.702 dyslipidemic patients [42]. They also reported an elevated LDL/HDL ratio (>4.4) which was associated with a worse loss of renal function. However, the relatively short follow-up period of 5 years and the exclusive use of creatinine as marker of renal function are major limitations of this study. Similar conclusions were achieved by Muntner et al., evaluating over 2000 subjects [43]. In particular, high triglyceride and low HDL levels were independent risk factors for renal dysfunction. Conversely, cholesterol-LDL values were not predictive for increased risk of kidney injury, but the short follow-up period of 2.9 years could be an important limitation.

In a 14-year follow-up period, Schaeffner et al. demonstrated a significant association between abnormal cholesterol parameters, such as low HDL levels, and development of renal dysfunction [44].

Furthermore, in a prospective controlled open-label trial the effects of one-year treatment with atorvastatin on proteinuria and progression of kidney disease were evaluated in 56 CKD patients [45]. After one year, urine protein excretion and rate of progression of kidney disease decreased in patients treated with atorvastatin in association with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin AT1 receptor antagonists (ARBs).

However the SHARP trial, which evaluated the effects of simvastatin plus ezetimibe on cardiovascular outcomes in CKD patients, failed to confirm a benefit on renal disease progression [46]. Recently, the CRIC study failed to demonstrate the predictive role of measured plasma lipids and lipoproteins on the progression of kidney disease in over 2000 patients with CKD [47]. Moreover, numerous meta-analyses led to similar results. In particular, Sanguankeo et al. concluded that only high-intensity therapy with statins can improve GFR decline, whereas moderate- and low-intensity statins did not achieve the same positive results. Furthermore, this analysis demonstrated that statin therapy did not reduce proteinuria in CKD patients [48].

Another recent meta-analysis, including 57 studies with a total of 143,888 participants, revealed that statins do not reduce the risk of kidney failure, but improved proteinuria [49]. Finally, recent studies showed that the pleiotropic actions of statins may induce beneficial effects in the formation and expansion of kidney cysts in autosomal dominant polycystic kidney disease (ADPKD) [50,51].

In conclusion, whereas hypolipidemic drugs should be recommended to prevent and reduce atherosclerotic disease incidence in CKD patients, convincing evidence does not exist to consider their use for slowing the progression of renal disease. Moreover, most of these studies are post-hoc analyses that were not specifically designed to evaluate the efficacy of statin therapy in preserving kidney function.

Nutritional aspects of lipid disorders in CKD

CKD management often includes nutritional recommendations to reduce protein intake and to regulate electrolyte disorders. However, little attention is dedicated to lipid consumption, probably due to contrasting data emerging from trials about their role in CKD progression. Nevertheless, considering that dyslipidemia represents an independent risk factor for cardiovascular disease, dietary fat intake should be monitored from a quantitative and quality points of view [52].

The long-term effect of low-fat, Mediterranean, or low-carbohydrate diets has been examined in CKD patients with or without diabetes mellitus, evaluating urinary albumin excretion and

GFR. Significant improvements in renal function were achieved in all dietary regimens, independently of confounding factors, such as use of ACEIs or weight loss. However, a decrease in fasting insulin and systolic blood pressure remained associated with GFR after multivariate analysis, contributing to the observed improvements [53].

Furthermore, the association between CKD and macronutrient intake, including total, animal, and plant proteins, carbohydrate, simple sugar, fructose, total fat, saturated fatty acids, poly- and monounsaturated-fatty acids (PUFA and MUFA), and n-3 and n-6 fatty acids, was assessed.

After adjustment for serum triglycerides and cholesterol, body mass index, and hypertension, the risk of CKD decreased in the highest quartile compared to the lowest quartile of plant proteins, PUFA and n-6 fatty acids, while animal proteins may be a risk factor for CKD in adults [54].

In patients with renal transplantation, low-lipid and low-caloric diet allowed the avoidance of hyperfiltration, reduction of hyperlipidemia and obesity, lowering the prevalence of metabolic syndrome [55]. These data demonstrated the importance of dietary prescription, including quantity and quality of fats in CKD patients.

New therapeutical approach

Whereas high cholesterol-LDL levels are closely related to increased cardiovascular morbidity and mortality risk in general population, their utility as a marker in CKD patients remains unclear. Indeed, in patients with impaired GFR values the association between higher LDL-C and risk of myocardial infarction was weak [56]. Moreover, hemodialysis patients are characterized by low LDL values associated with high cardiovascular risk, reflecting the complex puzzle constituted by several, independent and prognostic factors, such as chronic inflammation, malnutrition or vascular calcification [57,58].

Initially, in the general population, the purpose of hypolipidemic treatments was to achieve a correct cholesterol-LDL level and reduce cardiovascular risk (treat to target method) [59]. This was obtained with the highest tolerated dose to obtain the most benefits, despite an increased risk of side effects. In 2013 new guideline changed this therapeutical approach [60]. This was especially true in CKD patients, with several comorbidities, and for these reasons subjected to multiple therapies. In particular, lower dosage of statins is suggested in patients with GFR lower than 60 ml/min/1.73 m^2 or in ESRD, without the need to achieve a specific target of cholesterol-LDL. This strategy, defined as “fire and forget”, is based on exclusive initial evaluation of lipid profile, to exclude severe hypercholesterolemia, hypertriglyceridemia or secondary causes of dyslipidemia, since there are no evidences of benefits for frequent lipid measurements [61].

According to these considerations, Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended an initial monotherapy with statins or statins plus ezetimibe in patients older than 50 years and GFR lower than <60 ml/min/1.73 m^2. In patients younger than 50 years of age, hypolipidemic therapy is recommended for those with high cardiovascular risk (diabetes mellitus, existence of cardiovascular disease or 10-year risks >10%).

In hemodialysis patients statins should not be initiated *de novo*, given the lack of beneficial effects on cardiovascular risk, whereas it should be continued for those already receiving treatment. In renal transplant patients, statins are suggested, due to their high coronary heart disease risk. Hypertriglyceridemia should be initially corrected with lifestyle modification, adding fibrates only for triglyceride levels >1000 mg/dl due to the high acute pancreatitis risk [62].

Future perspectives

Although statins improve cardiovascular morbidity and mortality, there is still a percentage of patients not at target for LDL and, therefore, at high risk for cardiovascular disease. In the last years, several hypolipidemic drugs, with different mechanisms, have been studied (Table 2).

Antisense oligonucleotides (ASO)

This group of drugs is characterized by nucleotide sequences that are complementary to RNA sense. These single-stranded DNA or RNA molecules bind specific regions of mRNA, inhibiting the synthesis of the corresponding protein, as obtained for apolipoprotein B100. The consequent impaired synthesis of apoB-100 induces a decrease in serum levels of LDL and Lp(a), since apoB-100 is the essential apolipoprotein of these atherogenic lipoproteins [70].

Mipomersen, considered the precursor of the ASO hypolipidemic drugs, has been approved by the Food and Drug Administration for patients with homozygous familial hypercholesterolemia in association with classic hypolipidemic drugs and specific lifestyle and dietary prescriptions. When compared to placebo, mipomersen showed better results in terms of LDL reduction, despite a greater number of side effects, such as skin reactions, flu-like symptoms and reversible hepatic enzyme increment [63]. These adverse reactions led the European Medicines Agency (EMA) to deny approval for mipomersen.

Microsomal triglyceride transfer protein (MTP) inhibitors

MTP is an intracellular protein responsible for the binding and movement of lipids through the cellular membrane and plays a pivotal role in the synthesis of apo-B, leading to lower levels of cho-

Table 2
New hypolipidemic drugs

Molecule	Pharmacological class	Patients	Dosage	Follow-up (years)	LDL reduction	Trial phase
Mipomersen [63] (not approved by EMA)	ASO	158 Patients with hypercholesterolemia and high cardiovascular risk	200 mg/week	2	37%	3
Lomitapide [64]	MTP inhibitor	29 Patients with homozygous familial hypercholesterolemia	60 mg/day	4.3	50%	3
Alirocumab [65]	PCSK9 inhibitor	2341 Patients with high cardiovascular risk and LDL > 70 mg/dl	150 mg/2 weeks	2	62%	3
Evolocumab [66]	PCSK9 inhibitor	4465 Patients with high cardiovascular risk	140 mg/2 weeks	0.93	62%	3
Bococizumab [67]	PCSK9 inhibitor	354 Patients with hypercholesterolemia	50, 100, and 150 mg/2 weeks	2	33.4–53.4%	2
Anacetrapib [68]	CEPT inhibitor	1623 Patients with high cardiovascular risk	100 mg/day	2–6	39.8%	3 On going
Evacetrapib [69]	CEPT inhibitor	398 Patients with hypercholesterolemia	30, 100, and 500 mg/day	1	13.6–35.9%	2

lesterol and triglycerides. Clinical applications of MTP inhibitors have been focused particularly in patients with homozygous familial hypercholesterolemia.

Lomitapide, an orally administered MTP inhibitor, was tested in 29 patients affected by homozygous familial hypercholesterolemia, at escalating daily doses of 5 to 60 mg, and demonstrated safety and tolerability with a reduction of serum LDL cholesterol by 50% from baseline. Gastrointestinal symptoms were the most common adverse events, whereas four patients had reversible increase in amino-transaminase levels that did not lead to drug discontinuation [64]. Moreover, in the following 5 years no additional side effects or metabolic complications were observed [71]. Based on these promising data, FDA and EMA approved this drug for treating patients with homozygous familial hypercholesterolemia, in addition to low-fat diet and other hypolipidemic drugs.

Pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

PCSK9, which belongs to the family of proprotein convertases, binds LDL receptors (LDLr) thus preventing the removal of LDL particles from the blood. Inhibiting PCSK9 results in improved LDLr recycling, increased LDLr availability on hepatocyte cell surfaces, and reduced blood LDL-C levels.

In the last years, several molecules have been tested to block PCSK9, but only specific monoclonal antibodies were approved for clinical use. In particular, alirocumab, evolocumab and bococizumab, administered subcutaneously every two to four weeks, lead to a reduction of cholesterol-LDL by 50%.

Alirocumab demonstrated a significant reduction of LDL cholesterol levels in a recent randomized trial, involving more than two thousands patients at high risk for cardiovascular events. The post-hoc analysis showed also a reduction in the rate of cardiovascular events.

Injection site reactions, myalgia, neuro-cognitive disorders and visual dysfunctions were the major side effects recorded [65].

Similarly, the Osler-1 and Osler-2 trials revealed positive effects of evolocumab, in addition to other hypolipidemic drugs, on cholesterol-LDL levels. Exploratory analysis demonstrated beneficial effect on cardiovascular events. Neuro-cognitive alterations represented the most common side effects [66].

Data from a phase 3 trial evaluating bococizumab will be available in 2018. Nevertheless, phase 2 studies showed a significant reduction of LDL cholesterol compared to placebo, without differences in side effects between the two groups [67].

Cholesteryl ester transfer protein (CETP) inhibitors

Cholesteryl ester transfer protein (CETP) promotes the transfer of esterified cholesterol and triglycerides from HDL to lipoproteins expressing apo B, such as VLDL and LDL.

The inhibition of this protein induces increased levels of HDL and decreased levels of LDL.

The phase 3 trial with torcetrapib, the first CEPT inhibitor, was interrupted due to the high mortality rate in the treated group [72]. The same complication was observed with Dalcetrapib, which, despite positive effects on HDL levels, did not show a reduction of cardiovascular events [73].

A recent trial showed that evacetrapib, a new CEPT inhibitor, as monotherapy or in association with statin, reduced the concentrations of atherogenic apoB-containing lipoproteins, including Lp(a), LDL-P, and sLDL [69]. Another molecule, anacetrapib, is being evaluated in a phase 3 trial, that is expected to give definitive answers on safety and effectiveness of this class of hypolipidemic drugs [68].

To date, no data are available about the effects of these novel drugs on renal outcomes, such as the progression of chronic renal failure. Homozygous familial hypercholesterolemia is the main indication for these novel agents, although patients at high cardiovascular risk may represent, in our opinion, an emerging target population.

Ongoing trials are evaluating the effects of these drugs on cardiovascular disease. In particular, a multi-center long-term open-label non-comparative study will evaluate carotid and aortic atherosclerosis, in patients treated with lomitapide [74]. Moreover, a randomized, double-blind, placebo-controlled trial will evaluate the effect of Alirocumab on the occurrence of cardiovascular events in patients with recent episodes of acute coronary syndrome [75]. However, whether these new therapeutic options will be effective and safe, alone or in combination with statins, and lead to beneficial effects on cardiovascular disease morbidity and mortality and renal disease progression in CKD will require further evaluation.

Conclusion

CKD patients are characterized by high cardiovascular risk, which begins in the early stages of the disease. Comorbidities, such as arterial hypertension, diabetes mellitus and dyslipidemia, contribute to this risk.

Statins exert positive effects in CKD and in renal transplanted patients, whereas no advantages have been revealed in ESRD, in terms of survival or cardiovascular morbidities.

New hypolipidemic therapies lead to an additional lowering of cholesterol levels, but further studies are necessary to evaluate their potential application to CKD patients in order to improve clinical outcomes.

Conflict of Interest

The authors declare they have no conflicts of interest.

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