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Disease of the Month

Lipoprotein Metabolism and Lipid Management in Chronic Kidney Disease

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Dyslipidemia is an established cardiovascular (CV) risk factor in the general population. In chronic kidney disease (CKD), however, epidemiologic studies (1–3) and clinical trials (4–12) have raised uncertainties regarding the impact of dyslipidemia on clinical outcomes and, consequently, the optimal lipid profile. In this article, we review the pathophysiology of dyslipidemia in CKD and dialysis patients and its association with clinical outcome and the effects of therapy and compare them with those in the general population. Kidney transplant patients are excluded from the discussion. Dyslipidemia is empirically defined here as plasma lipid and lipoproteins that are associated with adverse outcomes such as CV disease (CVD) in the general population. Whether this definition is justified in patients with CKD requires further investigations.

Normal Structure and Function of Lipoproteins

Lipoproteins

Lipoproteins consist of lipids and proteins (known as apolipoproteins [apo]), with the main function of transporting water-insoluble lipids such as cholesterol or triglycerides in plasma from the sites of absorption (gut) and/or synthesis (liver) to the sites of utilization (peripheral tissues) or processing. Besides contributing to the structure and the stability of the macromolecule, apolipoproteins control the metabolism of the lipoproteins by activation or inhibition of enzymes and interaction with lipoprotein receptors. The major types of the plasma lipoproteins and their apolipoprotein components and physiologic functions are briefly presented in Table 1.

Lipoprotein Pathways

In the exogenous pathway (Figure 1), chylomicrons transport dietary lipids that are absorbed from the intestine *via* the systemic circulation. Chylomicrons are triglyceride-rich and normally catabolized within minutes by the endothelium-associated lipoprotein lipase (LPL), thereby generating free fatty acids (FFA), which are taken up by the liver, muscle, and adipose tissues. During this catabolic process, chylomicrons diminish in size and become chylomicron remnants, which are taken up by the liver *via* the low-density lipoprotein (LDL) receptor and the LDL receptor–related protein (LRP).

In the endogenous pathway (Figure 1), the liver assembles and secretes triglyceride-rich very low-density lipoprotein (VLDL) particles, which transport triglycerides from the liver to peripheral tissues. After hydrolysis of the triglycerides by LPL, the VLDL particles are reduced to intermediate-density lipoproteins (IDL), which can be taken up by the liver or can be further hydrolyzed to LDL particles. During this conversion, the particles become depleted of triglycerides but retain considerable amounts of cholesterol (13).

LDL transports cholesterol primarily to hepatocytes but also to peripheral tissues. ApoB-100 is responsible for the recognition and uptake of LDL by the LDL receptor, which clears approximately 60 to 80% of LDL in normal individuals. The remaining LDL is removed by other specific receptors, such as LRP, or by scavenger receptors (14). Oxidized LDL (ox-LDL) in particular can be taken up by scavenger receptors on macrophages and vascular smooth muscle cells. When these macrophages become overloaded with cholesteryl esters, they transform into foam cells, which is a major step in the development of atherosclerosis (14). When LDL becomes lipid depleted, small dense LDL (sdLDL) is generated, which has lower affinity for the LDL receptor but is more susceptible to oxidative modification. Thus, sdLDL are believed to be more atherogenic than larger LDL particles (15).

High-density lipoprotein (HDL) plays an important role in reverse cholesterol transport, which shuttles cholesterol from peripheral cells to the liver (16), an important step that relieves the peripheral cells from cholesterol burden (Figure 1). HDL precursor particles are secreted as disc-shaped structures by the liver and intestine and can absorb free cholesterol from cell membranes, a process that is mediated by ATP binding cassette transporter 1, apoA-I, and apoA-IV. ApoA-I is the major apolipoprotein of HDL and activates the enzyme lecithin:cholesterol acyltransferase (LCAT), which esterifies the accepted free cholesterol to allow more efficient packaging of the cholesterol for transport. By acquisition of additional apolipoproteins, cholesteryl esters, and triglycerides, HDL_3 particles are trans-

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Table 1. Types of lipoproteins in normal plasma[a]

Lipoprotein	Physiologic Function	Relative Content (%)[b]				Apolipoproteins[c]
		TG	Ch	Pl	Pr	
Chylomicron	Transport of dietary TG from gut to peripheral tissue and liver	90	5	3	2	B-48, C-II, C-III, A-IV, E
VLDL	Transport of endogenous TG from liver to peripheral tissues	60	20	14	6	B-100, C-II, C-III, E
IDL	Intermediary of VLDL metabolism; usually present in small concentrations in plasma but elevated in kidney failure	20	40	22	18	B-100, E
LDL	Transport of cholesterol from liver to peripheral tissues	7	50	22	21	B-100
HDL	Reverse transport of cholesterol from peripheral tissues to liver	5	25	26	44	A-I, A-II, A-IV
Lp(a)	Unknown	5	45	20	26	apo(a), B-100

[a]apo, apolipoproteins; Ch, cholesterol; CKD, chronic kidney disease; IDL, intermediate-density lipoprotein; LCAT, lecithin: cholesterol acyltransferase; Lp(a), Lipoprotein(a); Pl, phospholipids; Pr, proteins; TG, triglycerides.
[b]Relative content of TG, Ch, Pl, and Pr in the various plasma lipoproteins. Data are based on individuals without CKD. Lp(a) contains additionally 4% carbohydrates.
[c]Only the major (apolipoproteins) or the ones with particular pathogenetic importance in uremia are presented for each lipoprotein. ApoB is a ligand for cellular receptors for lipoprotein uptake. ApoC-II is an activator of lipoprotein lipase that hydrolyzes triglycerides, whereas apoC-III is an inhibitor of the lipases. ApoE is a ligand for hepatic receptors that mediate the uptake of VLDL and IDL. ApoA-I is an activator of LCAT, which catalyzes the esterification and hence the reverse transport of cholesterol from periphery to liver. ApoA-IV is another activator of LCAT and lipoprotein lipase. ApoA-II is an activator of another lipase, the hepatic lipase, which also hydrolyzes TG from lipoproteins. Increased apoC-III levels, decreased lipoprotein lipase activity, and low apoA-I and apoA-II levels are hallmarks of uremic dyslipidemia, resulting in the accumulation of apoB-containing lipoproteins (*e.g.*, IDL) and low levels of HDL cholesterol in plasma.

formed into larger HDL_2 particles (17). Reverse cholesterol transport can take three different routes. First, large HDL particles with multiple copies of apoE can be taken up by the liver *via* the LDL receptor (16). Second, the accumulated cholesteryl esters from HDL can be selectively taken up by the liver mediated by scavenger receptor B1 (18). This receptor is expressed primarily in liver and nonplacental steroidogenic tissues. Third, cholesteryl esters are transferred by the cholesteryl ester transfer protein from HDL to triglyceride-rich lipoproteins (16). Plasma HDL cholesterol levels are influenced by the complexity of these reverse cholesterol transport processes. Disturbances in the concentrations of apoproteins, function of enzymes, transport proteins, receptors, other lipoproteins, and the clearance from plasma can have a major impact on the antiatherogenic properties of HDL.

Pathophysiology of Dyslipidemia in CKD and Dialysis

The spectrum of dyslipidemia in patients with CKD and dialysis patients is distinct from that of the general population. It involves all lipoprotein classes and shows considerable variations depending on the stage of CKD (Table 2). There seems to be a gradual shift to the uremic lipid profile as kidney function deteriorates (19,20), which is further modified by concurrent illnesses such as diabetes (21) and nephrotic syndrome (22). Apart from quantitative differences, major qualitative changes in lipoproteins can be observed, such as oxidization and modification to sdLDL, which render the particles more atherogenic.

Hypertriglyceridemia

Plasma triglycerides start to increase in early stages of CKD (Table 2) and show the highest concentrations in nephrotic syndrome and in dialysis patients, especially those who are treated with peritoneal dialysis (PD). Plasma triglycerides are predominantly found in two types of lipoproteins in normal individuals. These are chylomicrons, which are assembled in the intestine for the transport of dietary fatty acids, and VLDL, which are produced in the liver for the transport of endogenous fatty acids (23–25). The accumulation of triglycerides is the consequence of both a high production rate and a low fractional catabolic rate (24) (Figure 2). An increased production of triglyceride-rich lipoproteins is possibly a consequence of impaired carbohydrate tolerance and enhanced hepatic VLDL synthesis (26). The reduced fractional catabolic rate is likely due to the decreased activity of two endothelium-associated lipases, namely, LPL and hepatic triglyceride lipase, which have the primary physiologic function of cleaving triglycerides into FFA for energy production or storage. The cause of the decreased lipase activities in uremia is thought to be depletion of the enzyme pool induced by frequent heparinization in hemodialysis (HD) patients (27), an increase in the plasma apoC-III/apoC-II ratio, and the presence of other lipase inhibitors in plasma. ApoC-II is an activator of LPL, whereas apoC-III is an inhibitor of LPL. The increased apoC-III/apoC-II ratio is usually due to a disproportionate increase in plasma apoC-III (28). The impaired lipase activities in uremic plasma may also be caused by a decrease in LPL synthesis as a result of secondary hyperparathyroidism or suppressed insulin level (29).

Incomplete catabolism results in the accumulation of remnant particles (chylomicron remnants and IDL) that contribute to the heterogeneity of the plasma pool of triglyceride-rich lipoproteins, with different sites of origin, sizes, compositions (30), and degrees of atherogenicity (31). These remnants are rich in apoE, a ligand that is critical for the removal of the particles from the circulation by binding to LRP and perhaps other receptors on the vascular wall (32). The arterial wall therefore is exposed to high plasma levels of remnant lipoproteins for prolonged durations, which may predispose to atherogenesis.

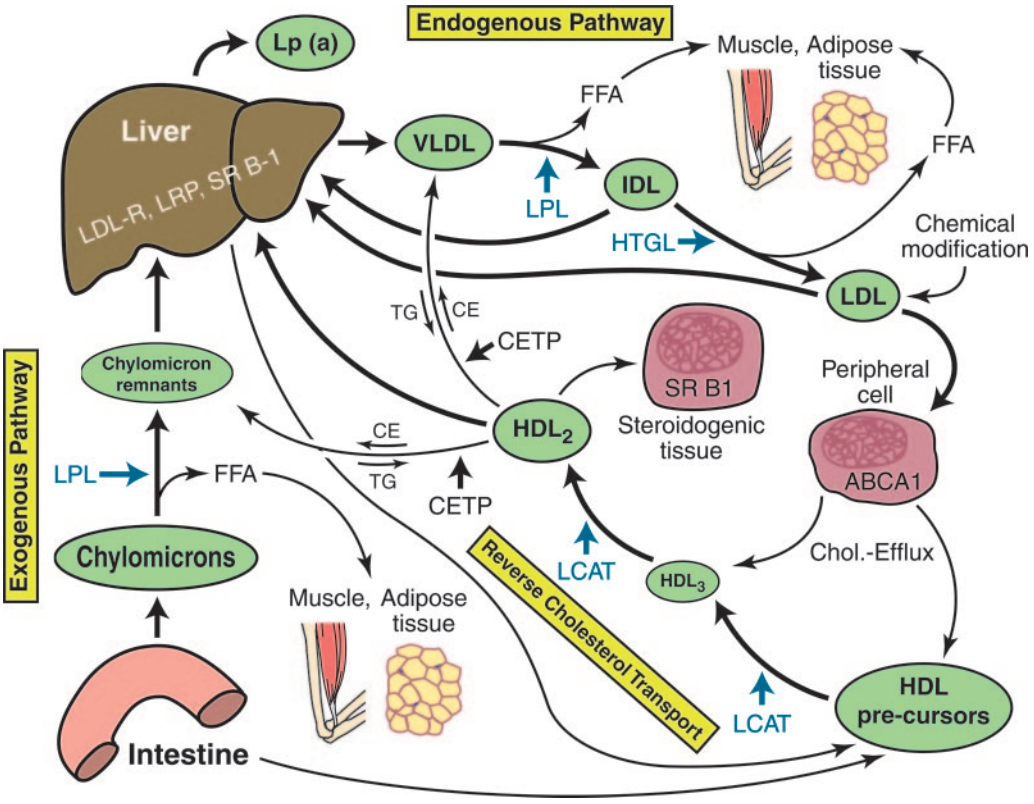

Figure 1. Major normal lipoprotein metabolic pathways. Refer to text for detailed explanation. Blue arrows refer to points of action of the respective enzymes in blue. ABCA1, ATP binding cassette transporter 1; CE, cholesterol ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HTGL, hepatic triglyceride lipase; IDL, intermediate-density lipoprotein; LCAT, lecithin: cholesterol acyltransferase; LDL-R, LDL receptor; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; LRP, LDL-R–related protein; SR B1, scavenger receptor B1; TG, triglyceride. Illustration by Josh Gramling—Gramling Medical Illustration.

High-Density Lipoprotein

Patients with CKD generally have reduced plasma HDL cholesterol concentrations compared with nonuremic individuals (Table 2). Furthermore, the distribution of HDL subfractions is different. Because of the low apo-AI level and decreased LCAT activity (see the Lipoprotein Pathways section), the esterification of free cholesterol and hence the conversion of HDL_3 to HDL_2 are diminished in uremia. This decreased ability of the HDL particles to carry cholesterol leads to an impairment in the reverse cholesterol transport from peripheral cells to the liver, thereby burdening the vasculature with cholesterol and promoting atherosclerosis (33–35).

Another important component of HDL is paraoxonase, an enzyme that inhibits the oxidation of LDL. Plasma paraoxonase activity is reduced in patients with CKD (36), thereby predisposing the LDL and possibly also HDL particles to oxidation. Furthermore, infection-associated or uremia-associated inflam-

Table 2. Trend of changes in lipids, lipoproteins, and apoA-IV in various stages of CKD[a]

Parameter	CKD 1 to 5	Nephrotic Syndrome	Hemodialysis	Peritoneal Dialysis
Total cholesterol	↗	↑ ↑	↔ ↓	↑
LDL cholesterol	↗	↑ ↑	↔ ↓	↑
HDL cholesterol	↓	↓	↓	↓
Non–HDL cholesterol	↗	↑ ↑	↔ ↓	↑
TG	↗	↑ ↑	↑	↑
Lp(a)	↗	↑ ↑	↑	↑ ↑
ApoA-I	↘	↗	↓	↓
ApoA-IV	↗	↑ ↘	↑	↑
ApoB	↗	↑ ↑	↔ ↓	↑

[a]These trends are derived from the composite of the literature. Non–HDL cholesterol includes cholesterol in LDL, VLDL, IDL, and chylomicron and its remnant. Explanation of arrows: Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with nonuremic indviduals; increasing (↗) and decreasing (↘) plasma levels with decreasing GFR.

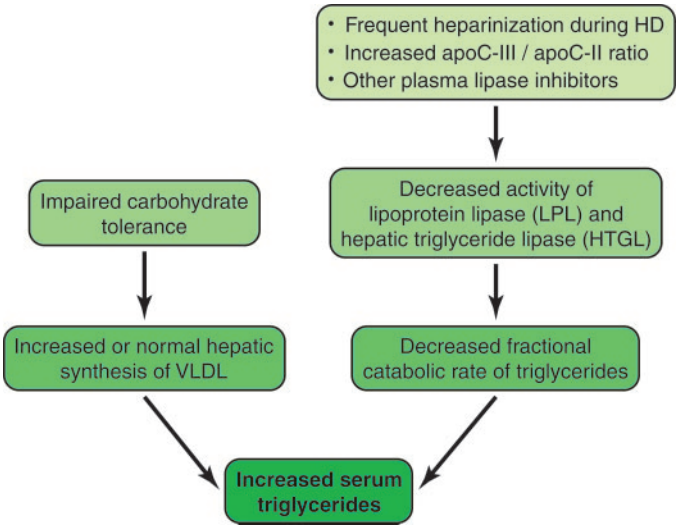

Figure 2. Pathophysiology of hypertriglyceridemia in uremia. Illustration by Josh Gramling—Gramling Medical Illustration.

mation might convert HDL from an antioxidant into a pro-oxidant particle (37,38). All of these may contribute to atherogenesis in CKD.

Apolipoprotein A-IV

ApoA-IV is a 46-kDa glycoprotein that is synthesized primarily in enterocytes of the small intestine. *In vitro* studies suggest that apoA-IV might protect against atherosclerosis by promoting several steps in the reverse cholesterol transport pathway, which removes cholesterol from peripheral cells and directs the cholesterol to liver and steroidogenic organs for metabolism (39–41). Specifically, apoA-IV activates LCAT (42,43) and modulates the activation of LPL (44) as well as the protein-mediated transfer of cholesteryl esters from HDL to LDL (45). Cross-sectional studies have shown an inverse relationship between plasma apoA-IV levels and presence of coronary artery disease in the general population (46,47) as well as in patients with CKD (20).

ApoA-IV has also been identified as a marker of primary CKD, and its plasma levels are already increased when glomerular filtration rate (GFR) is still normal (Table 2) (20). Furthermore, high plasma apoA-IV concentrations predicted, independent of baseline GFR, the progression of primary nondiabetic kidney disease, defined as doubling of serum creatinine or necessity of renal replacement therapy, during a prospective 7-yr follow-up study (48). These findings were unexpected, given the physiologic functions in reverse cholesterol transport and the antioxidative properties of apoA-IV. The high apoA-IV levels that were caused by the impairment of GFR are further modulated by nephrotic syndrome. Specifically, a tubular type of proteinuria and severe proteinuria cause a decrease in plasma apoA-IV levels (49). These observations suggest that the human kidney is involved in apoA-IV metabolism, a hypothesis that is further supported by the presence of apoA-IV in kidney tubular cells (50). In dialysis patients, apoA-IV levels are twice as high as in the general population (51–54).

Low-Density Lipoprotein

Elevated plasma LDL cholesterol concentration is common in nephrotic syndrome but is not a typical feature of patients with advanced CKD, especially those who are on HD (Table 2). There are, however, qualitative changes in LDL in patients with CKD and dialysis patients. The proportions of sdLDL and IDL, which are considered to be highly atherogenic, are increased. sdLDL is a subtype of LDL that has high propensity to penetrate the vessel wall, becomes oxidized, and triggers the atherosclerotic process. IDL is an intermediate metabolite of VLDL that is normally further degraded to LDL with the cleavage of triglycerides by lipases (see the Hypertriglyceridemia section). Because of decreased hepatic triglyceride lipase activities in HD patients, the conversion of IDL to LDL is impaired and IDL accumulates in plasma (55). IDL and sdLDL have high affinity for macrophages, which theoretically promote their entry into the vascular wall to participate in the formation of foam cells and atherosclerotic plaques (56–59). The plasma levels of apoB, which is the major apolipoprotein of LDL and IDL, are strongly correlated with levels of these lipoproteins.

A vicious cycle has been suggested in uremia in which the decreased catabolism of IDL and LDL leads to their increased plasma residence time and further modification of the apoB contained in these lipoproteins by oxidation, carbamylation, and glycation (60). These modifications lead to the reduced recognition and binding of these lipoproteins to LDL receptors and LRP in the liver and hence further reduction in plasma clearance by this physiologic pathway. Using stable isotope techniques, it was shown recently that the plasma residence time of LDL and IDL is more than twice as long in HD patients as in nonuremic individuals (Figure 3). This reduced catabolism, however, is masked by the decreased production of LDL, resulting in near-normal plasma levels of LDL (60). In contrast to the decreased clearance by the liver, there is an increased clearance of these altered lipoproteins *via* the scavenger pathway. Modified LDL particles, such as ox-LDL and malondialdehyde-modified LDL, are taken up by macrophages *via* binding to several cell surface scavenger receptors. The accumulation of cholesterol leads to the transformation of macrophages into foam cells in the vascular wall and contributes to atherogenesis (56–59,61).

Lipoprotein(a)

There is strong evidence that lipoprotein(a) [Lp(a)] is a risk factor for CVD in the general population (62,63). Lp(a) is an LDL-like lipoprotein that consists of apo(a) that is covalently bound to an LDL particle. Apo(a) shows a high homology with plasminogen and competes with this protein for binding to plasminogen receptors, fibrinogen, and fibrin (64). Plasma Lp(a) concentrations are strongly genetically determined by the apo(a) gene, which contains a heritable number of kringle-IV (K-IV) repeats. The number of K-IV repeats is the basis for the apo(a) K-IV repeat polymorphism (65). The molecular weight of apo(a) increases with the number of K-IV repeats, ranging from 300 to >800 kDa, and is inversely related to the plasma Lp(a) concentration. Thus, individuals with high molecular weight or large apo(a) isoforms have on average low plasma Lp(a) concentrations, whereas those with low molecular weight or small isoforms usu-

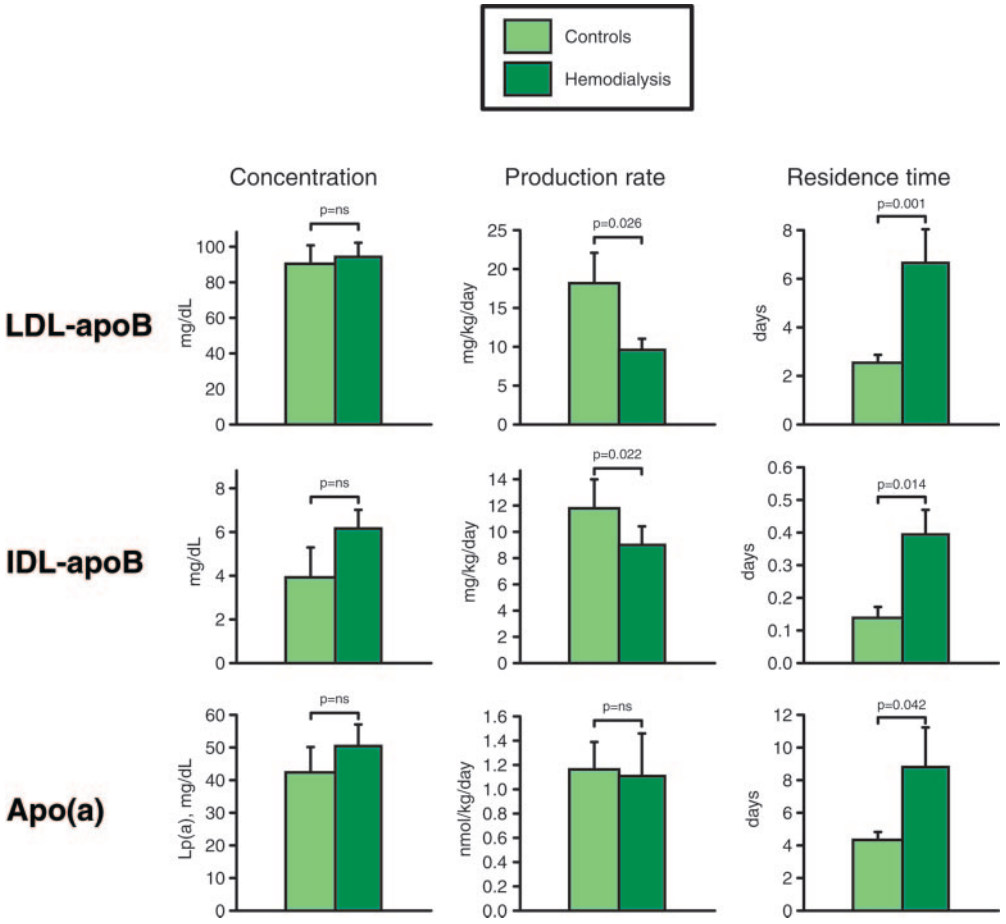

Figure 3. Kinetic parameters of apolipoprotein B (apoB) in LDL, apoB in IDL, and apolipoprotein(a) [apo(a)] in Lp(a). The concentration, production rate, and residence time in plasma are presented for control subjects (light green) and HD patients (dark green). Each bar represents mean ± SEM. Data for LDL and IDL are derived from reference (60); data for Lp(a) are derived from reference (76). Despite differences in the production rate and residence time, there were no statistically significant differences in plasma concentration of the three lipoprotein particles between HD patients and nonuremic control subjects. Illustration by Josh Gramling—Gramling Medical Illustration.

ally exhibit high plasma Lp(a) concentrations. Depending on the population under investigation, this association explains between 30 and 70% of the variability in plasma Lp(a) levels.

In kidney disease, plasma Lp(a) levels are also influenced by GFR. In patients with large apo(a) isoforms but not those with small apo(a) isoforms, plasma Lp(a) levels begin to increase in stage 1 CKD before GFR starts to decrease (19). This isoform-specific increase in plasma Lp(a) levels was observed in several but not all studies in non-nephrotic patients with CKD and HD patients (19,54,66–69). In contrast, in patients with nephrotic syndrome (70,71) and PD patients (54), increases in plasma Lp(a) levels occur in all apo(a) isoform groups, probably as a consequence of the pronounced protein loss and a subsequently increased production in the liver (72). After successful kidney transplantation, a decrease in plasma Lp(a) can be regularly observed in HD patients with large apo(a) isoforms (73,74) and in PD patients with all apo(a) isoform groups (75). Thus, the elevation of Lp(a) in CKD is an acquired abnormality, mostly influenced by the degree of proteinuria (19,71) and less by the cause of kidney disease (54).

In vivo turnover studies using stable-isotope techniques recently elucidated the mechanism for the increased plasma Lp(a) levels in HD patients (76). The production rates of apo(a) and apoB, the two apolipoproteins that are contained in Lp(a), were normal when compared with control subjects with similar plasma Lp(a) concentrations (Figure 3). The fractional catabolic rate of these apolipoproteins, however, was significantly reduced compared with control subjects. This resulted in a much longer residence time in plasma of almost 9 days for apo(a), compared with only 4.4 days in control subjects. This decreased clearance is likely the result of loss in kidney function in HD patients (76).

Malnutrition and inflammation have also been associated with high plasma Lp(a) levels in HD patients (68,69,77,78). The elevation of plasma Lp(a), however, can even be observed in patients with normal plasma C-reactive protein and/or normal plasma amyloid A levels (69). It therefore seems that inflammation only modifies Lp(a) concentrations but fails to explain the apo(a) phenotype-specific elevation of plasma Lp(a).

In summary, the hallmarks of uremic dyslipidemia are hypertriglyceridemia; increased remnant lipoproteins (chylomicron remnants and IDL); reduced HDL cholesterol; and in-

creased sdLDL, Lp(a), and apoA-IV. Elevated plasma LDL cholesterol level is not typical but can mostly be observed in patients with nephrotic syndrome and PD patients.

Epidemiologic Association between Dyslipidemia and CV Outcome in CKD

In the general population, high plasma concentrations of LDL cholesterol, low concentrations of HDL cholesterol, and to some extent high total triglyceride concentrations are associated with increased atherosclerotic CV risk (79). In the dialysis populations, the preponderance of the literature, including cross-sectional (35,80–82) and longitudinal (2,3,34,69,83–90) studies, does not support a strong association between dyslipidemia and CVD (Table 3). This seemingly aberrant relationship may be due, in part, to the approaches of dyslipidemia assessment. The precise contributions of lipids to atherogenicity should probably be evaluated longitudinally using multiple measurements over time, because the plasma lipid patterns change substantially as kidney disease progresses, as illustrated by the decline of plasma LDL levels from the nephrotic stage to the HD stage. Furthermore, the atherogenic potential of dyslipidemia in CKD may depend more on the apolipoprotein than on lipid abnormalities and may not always be recognized by measurement of plasma lipids alone, as suggested by Attman and Alaupovic (91). An additional caveat is that, in many dialysis patients, CVD is caused or accentuated by other risk factors, such as volume overload, medial calcification, and arrhythmogenicity, and may not necessarily be related to atherosclerosis.

Total Cholesterol

In large administrative databases, the relationship between plasma total cholesterol and mortality in HD patients has been found to be U-shaped (92,93). The group with total cholesterol between 200 and 250 mg/dl had the lowest risk for death, whereas those with levels >350 mg/dl had a relative risk of 1.3-fold and those with levels <100 mg/dl had a relative risk of 4.2-fold. The association between low total cholesterol and increased mortality, however, was reduced after statistical adjustment for plasma albumin levels. Subgroup analysis provides further insights into the potential effects of plasma total cholesterol on clinical outcomes. A recent study of 1167 HD patients found that among those with low plasma albumin levels (3.5 to 3.9 g/dl), low plasma total cholesterol levels were also associated with increased all-cause mortality. Among those with plasma albumin >4.5 g/dl, however, high plasma total cholesterol levels were associated with increased mortality (1), as observed in the general population. This dichotomous relationship was confirmed in the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study (84,94), which showed a nonsignificant negative association of cardiovascular mortality with plasma total as well as non–HDL cholesterol levels in the presence of inflammation and/or malnutrition (Figure 4); in contrast, there was a positive association between total and non–HDL cholesterol and mortality in the absence of inflammation or malnutrition. These observations are compatible with the hypothesis that the inverse association of total cholesterol levels with mortality in dialysis patients is mediated by the cholesterol-lowering effect of malnutrition and/or systemic inflammation and not due to a protective effect of high cholesterol concentrations.

IDL Cholesterol

In observational studies, high plasma IDL cholesterol levels have been shown to be a risk factor independent of LDL cholesterol for coronary artery disease in the general population (95) and may also be a predictor for aortic atherosclerosis in HD patients (96). As discussed, IDL cholesterol is often elevated in uremia. Unfortunately, the current clinical assays do not differentiate between LDL cholesterol and IDL cholesterol. Therefore, current clinical assays may not accurately assess the atherosclerotic burden of plasma cholesterol in uremia.

Lp(a) Concentrations and Apo(a) Polymorphism

The association of Lp(a) with atherosclerotic complications has been investigated in numerous studies in dialysis patients. The results were inconsistent in prospective as well as in retrospective studies (Table 3) (3,85,97). This inconsistency might have been due, at least in part, to the nonstandardized assay method for Lp(a) in the past. When apo(a) phenotyping was performed in conjunction with plasma Lp(a) concentrations, however, an association between the apo(a) K-IV repeat polymorphism and CV complications was consistently observed (3,35,85,97–104) (Table 3). A cross-sectional study in 607 HD patients showed an association between low molecular weight apo(a) phenotype with history of coronary events (35). Two large prospective studies also found a clear association of the apo(a) polymorphism with coronary events and total mortality, respectively (3,85,97). Kronenberg *et al.* (3) followed 440 HD patients for 5 yr and found a strong association between the low molecular weight apo(a) phenotype and severe coronary events. In contrast, plasma Lp(a) in those with clinical events showed only a trend toward elevated levels and did not reach statistical significance. Similarly, the CHOICE Study recently reported small apo(a) isoforms to be associated with total mortality in an inception cohort of >800 incident dialysis patients who were followed for a median of 33.7 mo (85,97). In that study, Lp(a) concentrations were associated with CV events (85) but not with total mortality (97).

Apolipoproteins

In the general population, plasma apoA-IV was reported to be lower in patients with CVD compared with control subjects, and this association was independent of HDL cholesterol and triglyceride concentrations (46,47). Similarly, participants in the Mild to Moderate Kidney Disease Study with CVD complications also had lower apoA-IV levels than those without (20). More data in various stages of CKD are required to confirm these findings.

Lipid Management in CKD

Limitations of Clinical Lipid Assays in Uremia

In the general population, plasma levels of total, HDL, and LDL cholesterol as well as triglycerides are the parameters that usually are measured clinically. As discussed, the total and LDL cholesterol levels are often normal in the CKD and HD

Table 3. Association of dyslipidemia and clinical outcomes in dialysis patients[a]

Study[b]	*N*	Outcome	High TC	High LDL Cholesterol	Low HDL Cholesterol	High TG	High Lp(a)	LMW Apo(a) Isoforms
Longitudinal studies								
Iseki *et al.*, 1996 (83)	1491	Incident stroke	↔			↔		
Degoulet *et al.*, 1982 (2)	1453	Cardiovascular and all-cause mortality	↓			↔		
CHOICE Study (84,85)	833	Cardiovascular and all-cause mortality	↓ in presence of inflammation/ malnutrition; ↑ in absence of inflammation/malnutrition					
CHOICE Study (84,85)		Incident fatal or nonfatal atherosclerotic cardiovascular events					↑	↑
Kronenberg *et al.*, 1999 (3)	440	Incident coronary events	↔	↔	↓	↔	↔	↑
Koda 1999 *et al.*, (86)	390	Cardiovascular mortality					↑	
Zimmermann *et al.*, 1999 (69)	280	Cardiovascular and all-cause mortality	↔	↔	↔	↔	↔	
Ohashi *et al.*, 1999 (87)	268	Cardiovascular mortality	↔		↔		↑	
Shoji *et al.*, 2001 (88)	265	Cardiovascular and all-cause mortality			↔			
Hocher *et al.*, 2003 (89)	245	Cardiovascular and all-cause mortality	↔		↓		↔	
Schwaiger *et al.*, 2006 (90)	165	Cardiovascular events	↔	↔	↔	↔	↔	↑
Cressmann *et al.*, 1992 (34)	129	Incident atherosclerotic cardiovascular events	↔	↔	↔	↔	↑	
Cross-sectional studies								
Stack *et al.*, 2001 (80)	4025	History of coronary artery disease	↔	↔	↔	↔		
Koch *et al.*, 1997 (35)	607	History of MI or ≥50% coronary artery stenosis	↔	↔	↓	↔	↔	↑
Cheung *et al.*, 2000 (81)	936	Presence or history of cardiovascular events	↔					
Güz *et al.*, 2000 (82)	269	Carotid artery intima media thickness	↔	↔	↔	↔	↔	
Overall			↔	↔	↔↓	↔	↔↑	↑

[a]MI, myocardial infarction.

[b]Included are only reports with at least 125 patients in prospective studies and at least 200 patients in cross-sectional studies. Presented are outcome measures that were increased (↑), unchanged (↔) or decreased (↓) associated with the indicated dyslipidemia. LMW, low molecular weight; TC, total cholesterol.

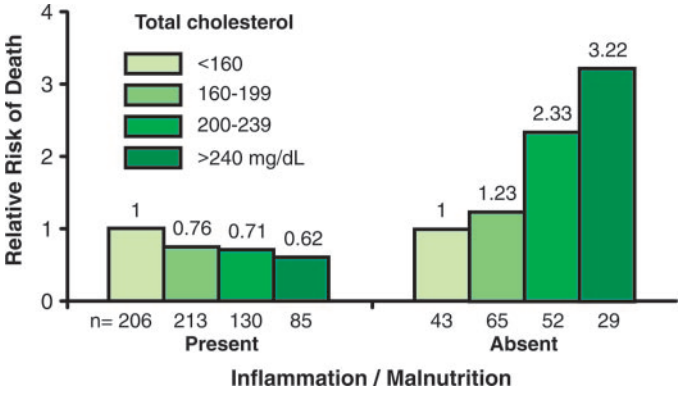

Figure 4. Relative risk for all-cause mortality associated with plasma total cholesterol stratified by the presence or absence of inflammation and/or malnutrition in the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study (84). Inflammation and/or malnutrition was defined as the composite of plasma albumin <3.6 mg/dl, CRP ≥10 mg/L or IL-6 ≥3.09 pg/ml (n = 634). The remaining 189 patients were free of inflammation and malnutrition. Illustration by Josh Gramling—Gramling Medical Illustration.

populations, but there are increased levels of sdLDL, IDL, and modified (oxidized, glycated, or carbamylated) LDL that are presumably more atherogenic. Similarly, the clinical assays do not differentiate among LDL and Lp(a) and its low molecular weight isoform, which are independent risk factors for atherosclerotic disease and are often elevated in CKD. Clinical assays for HDL cholesterol also cannot capture the alterations in the distribution of cholesterol subclasses with different antiatherogenic properties that are observed in CKD.

Recently, the use of non–HDL cholesterol, calculated as total cholesterol minus HDL cholesterol, was suggested as an alternative (105). Non–HDL cholesterol includes and does not distinguish among LDL cholesterol and subfractions that are considered to be highly atherogenic, such as Lp(a) and lipoprotein remnant particles. To date, there are insufficient data to establish the role of non–HDL cholesterol for atherosclerosis risk assessment.

Drug Therapies for Dyslipidemia in CKD

Statins. As in the general population, statins are very effective in lowering total and LDL cholesterol in uremic patients (12,106). The efficacy of statins in reducing CV events, however, may differ depending on the stage of CKD. In several randomized, placebo-controlled trials of statins, *post hoc* analyses of subgroups with impaired kidney function have been performed (Table 4). In the Pravastatin Pooling Project (10), which combined data from three randomized trials, a total of 4991 patients with stage 3 CKD were examined. These analyses showed that 40 mg/d pravastatin was associated with a 23% reduction in the composite outcome of nonfatal myocardial infarction, coronary mortality, and coronary revascularization in stage 3 CKD over 5 yr. In a prespecified subgroup analysis of 6517 patients with kidney dysfunction in the Anglo-Scandinavian Cardiac Outcomes Trial (6),10 mg/d atorvastatin significantly reduced the risk for the primary composite end point of nonfatal myocardial infarction and cardiac death by 39% over a median of 3.3 yr. It should be noted that in both studies, individuals with known CVD or high CV risk were recruited; therefore, it is unclear whether these positive results are generalizable to all patients with moderate CKD.

In a retrospective analysis of a registry of 3716 incident dialysis patients, the use of statins at baseline was associated with a significant 36% reduction in CV and 32% reduction in all-cause mortality (107). This study, however, was limited by the small number of patients who were on statins (n = 362) and possible selection bias. These findings were in general not confirmed by the Die Deutsche Diabetes-Dialyse (4D) study, a randomized, controlled trial of 1255 HD patients with diabetes (12). In the 4D study, randomization to 20 mg/d atorvastatin resulted in the reduction in plasma LDL cholesterol levels by 40%, compared with placebo (12). Despite this difference in cholesterol, there were no statistically significant differences (8% reduction) between the groups in the primary composite end point of cardiac death, stroke, or nonfatal myocardial infarction. In the atorvastatin group, there was also an 18% decrease in cardiac events (205 *versus* 246; P = 0.03) but a two-fold increase in fatal strokes (27 *versus* 13; P = 0.04).

These results, along with the seemingly paradoxic epidemiologic relationship between plasma cholesterol levels and mortality (12), have been interpreted by some to be rationales for abstaining from the use of statins in dialysis patients. Proponents of the use of statins in dialysis patients, however, point out that the 4D Study was powered only to detect a 27% difference in the primary end point and not a more modest effect size of, for example, even 15%. Despite the two-fold increase in fatal stroke in the 4D Study, the absolute number of events was small, compared with the number of cardiac events, which seemed to respond favorably to atorvastatin. Moreover, approximately 15% of the patients in the placebo arm received a nonstudy statin, and 15% of the patients who received atorvastatin required a dosage reduction to 10 mg/d. These drop-ins and dropouts might have resulted in the convergent trend in plasma LDL cholesterol levels between the two treatment arms over time. Nonetheless, the time-averaged difference in plasma LDL cholesterol was approximately 0.9 mmol/L, which was similar in magnitude to that observed in many statin trials with more positive clinical outcomes. Many CV events in dialysis patients were due to arrhythmia or nonischemic cardiomyopathy, which might not be related to atherosclerosis and could have diluted the potentially beneficial effects of statins. Finally, even though statins were effective in lowering plasma LDL cholesterol, they have minimal effects on plasma triglycerides and HDL cholesterol and no effects on Lp(a). Because uremic dyslipidemia is characterized by these three components and not elevated LDL cholesterol, lowering of plasma LDL cholesterol levels in uremic patients might not produce substantial clinical benefits. Controversies notwithstanding, a reasonable conclusion from the 4D Study is that, in dialysis patients without very high plasma LDL cholesterol levels, the effect of statins on clinical outcome is probably not large, but a modest effect cannot be ruled out.

There are two more large, ongoing, randomized trials using statins in patients with CKD. The Study of Heart and Renal Protection (SHARP) examines the effect of lowering plasma

Table 4. Completed large studies on lipid modification in patients with CKD[a]

Study	Drug	Design	Patient Characteristics	No. of Patients	Follow-Up	HR (95% CI) of Outcomes
Randomized trials						
4D (12)	Atorvastatin 20 mg/d	Randomized, double-blind, placebo-controlled, investigator-initiated	Type 2 diabetes on HD <2 yr with LDL cholesterol 80 to 190 mg/dl and TG <1000 mg/dl	1255	4 yr	0.92 (0.77 to 1.10) for primary end point (cardiac death, stroke, or nonfatal MI); 0.82 (0.68 to 0.99) for secondary end point (total death, all cardiac or cerebrovascular events)
CARE (11)	Pravastatin 40 mg/d	*Post hoc* subgroup analysis of investigator-initiated, randomized, double-blind, placebo-controlled trial	Previous MI with TC <240 mg/dl; subgroup analysis of patients with CrCl ≤75 ml/min but plasma creatinine <1.5 times upper limit of normal	1711	59 mo	0.72 (0.55 to 0.95) for primary end point (coronary death or nonfatal MI); 0.72 (0.59 to 0.88) for major coronary events; 0.81 (0.61 to 1.08) for total death; 0.62 (0.39 to 1.00) for stroke
PPP (10)	Pravastatin 40 mg/d	*Post hoc* subgroup analysis of pooled data from three randomized, double-blind, placebo-controlled trials (WOSCOPS, CARE, and LIPID)	CKD stage 3; WOSCOPS studied primary prevention of high-risk patients with high TC; CARE and LIPID studied secondary prevention with average TC	4491	5 yr	0.77 (0.68 to 0.86) for primary end point (MI, coronary death, or coronary revascularization); 0.79 (0.71 to 0.88) for extended end point (primary end point or stroke); 0.86 (0.74 to 1.00) for total death
VA-HIT (9)	Gemfibrozil 1200 mg/d	*Post hoc* subgroup analysis of randomized, double-blind, placebo-controlled trial	Established coronary disease with HDL cholesterol ≤40 mg/dl, LDL cholesterol ≤140 mg/dl, and TG ≤300 mg/dl; subgroup analysis of patients with CrCl ≤75 ml/min but plasma creatinine <2.0 mg/dl	1046	5.3 yr	0.73 (0.56 to 0.96) for primary end point (coronary death or nonfatal MI); 0.74 (0.58 to 0.95) for coronary death, nonfatal MI, or stroke; 0.85 (0.66 to 1.10) for coronary revascularization; 1.03 (0.78 to 1.35) for total death
HPS (7)	Simvastatin 40 mg/d	Prespecified subgroup analysis of randomized, double-blind, placebo-controlled trial	Coronary or other occlusive arterial disease or diabetes; plasma creatinine 110 to 200 μmol/L for women and 130 to 200 μmol/L for men	1329	5 yr	0.78 (significantly different) for first major vascular event (including coronary events, stroke, and revascularization)
LIPS (8)	Fluvastatin 40 mg twice daily	*Post hoc* subgroup analysis of randomized, placebo-controlled trial	After first successful percutaneous coronary intervention; CrCl <56 ml/min but plasma creatinine <1.8 mg/dl	310	3.8 yr	15% experienced cardiac death, MI, or re-intervention unrelated to restenosis *versus* 29% in placebo group ($P = 0.004$)
ASCOT-LLA (6)	Atorvastatin 10 mg/d	Prespecified subgroup analysis of randomized, double-blind, placebo-controlled trial	Hypertension with three additional CVD risk factors, TC <250 mg/dl and plasma creatinine <200 μmol/L	6517	3.3 yr	0.61 (0.44 to 0.84) for primary end point (nonfatal MI or fatal CHD)

(Table continues)

Table 4. Continued

Holdaas *et al.* (5)	Fluvastatin	*Post hoc* subgroup analysis of pooled data from 30 randomized, double-blind trials	CrCl <50 ml/min	1563	6 wk to 6 yr	0.83 (0.63 to 1.09) for cardiac death, nonfatal MI, or coronary interventions; 0.59 (0.40 to 0.87) for cardiac death or MI; 0.78 (0.57 to 1.06) for total death; 0.87 (0.60 to 1.26) for noncardiac death
Ferramosca *et al.* (4)	Sevelamer	Randomized trial comparing sevelamer or calcium acetate	Prevalent HD	108	1 yr	Coronary artery score progressed significantly in calcium-treated patients but not in sevelamer-treated patients
Observational studies						
USRDS (107)	Statins, fibrates	Retrospective analysis of existing database	All PD patients and 20% random sample of all HD patients in United States	3716 (statin = 362; fibrate = 78)	1996 to mid-1998	Statin: 0.68 (0.53 to 0.86) for total death; 0.63 (0.44 to 0.91) for CVD death fibrate: 1.29 (0.85 to 1.95) for total death; 1.41 (0.79 to 2.51) for CVD death
DOPPS (140)	Statins	Retrospective analysis of existing database	Prevalent HD	7365 (statins = 11.8%)	Through mid-2001	0.69 (0.60 to 0.79) for total death; 0.78 (0.62 to 0.98) for cardiac events; 0.77 (0.61 to 0.97) for cardiac death; 0.56 (0.46 to 0.69) for noncardiac death
Winkelmayer *et al.* (141)	Statins	Retrospective analysis of existing database	Post-MI dialysis patients aged ≥65 yr	494 (statin = 96)	1 yr	0.97 (0.65 to 1.45) for total death
GENDIAN (142)	Statins	Prospective	Prevalent HD with type 2 diabetes irrespective of lipid levels	445 (statin = 122)	4 yr	0.58 (0.34 to 0.99) for total death

[a]CHD, coronary heart disease; CI, confidence interval; CrCl, creatinine clearance; CVD, cardiovascular disease; HD, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis; 4D, Die Deutsche Diabetes-Dialyse Study; CARE, Cholesterol and Recurrent Events Trial; PPP, Pravastatin Pooling Project; VA-HIT, Veterans Affairs HDL Intervention Trial; HPS, Heart Projection Study; LIPS, Lescol Intervention Prevention Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial: Lipid-Lowering; USRDS, United States Renal Data System; DOPPS, Dialysis Outcomes and Practice Patterns Study; GENDIAN, Genetic and Clinical Predictors of Morbidity, Mortality, and Diabetic Nephropathy with ESRD Renal Disease in Diabetes Mellitus Type 2.

cholesterol using the combination of simvastatin and ezetimibe on the primary prevention of heart disease and stroke. It aims to recruit 6000 patients with CKD and plasma creatinine ≥1.7 mg/dl (150 μmol/L) in men and ≥1.5 mg/dl (130 μmol/L) in women as well as 3000 patients who are on dialysis (108). There are no lipid inclusion criteria in this trial. The Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) Study examines the effect of rosuvastatin on the incidence of heart attacks, strokes, and CV deaths in HD patients both with and without diabetes, irrespective of baseline lipid levels (109,110).

Some investigators have raised the possibility of increased incidence of adverse effects that are associated with the use of statins (*e.g.*, liver damage and rhabdomyolysis in those with CKD or on dialysis [111,112]). This concern was not substantiated by the 4D study (12) and most other large studies (7,10,11). In contrast, the risk for myopathy in patients with CKD seems to be increased when statins are used in combination with fibrates (113,114).

Fibrates. These agents are effective in reducing plasma triglyceride concentrations and modestly increasing HDL cholesterol concentrations in the general population (115,116). The use of gemfibrozil was associated with a 20% reduction in CV events in those with creatinine clearances of 30 to 75 ml/min (9). There are no data on the effects of fibrates on clinical outcomes in patients with CKD or HD patients. Evidence is strong in support of an increased risk for myopathy that is associated with this class of drug in patients with advanced GFR impairment (117,118).

Nicotinic Acids and Derivatives. Nicotinic acids may be the most suitable drug that is available to produce a positive impact on uremic dyslipidemia. It is very effective in raising plasma HDL cholesterol level and is the only drug available to lower plasma Lp(a) substantially (119). It reduces total triglyceride levels by 20 to 50% (120); lowers VLDL cholesterol and FFA; and shifts the sdLDL fraction to larger, more buoyant particles (121). It also lowers plasma LDL cholesterol levels. The immediate-release formulations that were marketed earlier, however, were plagued by cutaneous flushing, pruritus, rashes, nausea, and gastrointestinal adverse effects. These adverse effects are less often observed with the newer, extended-release formulations and are in many cases transient when they occur. The compliance of patients can be increased by the co-administration of aspirin and gradual dosage escalation that decrease the adverse effects (for details, see review [122]). In the general population, nicotinic acid has been shown to improve cardiac and cerebrovascular outcomes (123–126). Studies that used nicotinic acid in patients with CKD were mostly small with short durations of follow-up but showed the expected changes in lipid and lipoprotein profiles (122). No studies have examined the impact of nicotinic acid on CVD outcomes in patients with CKD or HD patients.

Sevelamer. This metal-free phosphate binder has also been shown to reduce plasma total and LDL cholesterol concentrations by 18 to 22% and 30 to 37%, respectively, by acting as a bile acid sequestrant (127). Whether this reduction in cholesterol contributes to the decreased progression of coronary calcification (128) is unclear.

Antioxidants. Dialysis patients are generally in a state of high oxidative stress. A beneficial effect of vitamin E on the oxidative susceptibility of LDL cholesterol in dialysis patients has been shown (129–131). Treatment with α-tocopherol also resulted in partial normalization of malondialdehyde modifications of LDL cholesterol in dialysis patients (132). Vitamin E may also exert an additive or synergistic effect with statins. In a 2 × 2 study in dialysis patients, treatment with atorvastatin was found to be effective in lowering plasma total cholesterol, triglycerides, LDL cholesterol, apoB, and ox-LDL levels by 30 to 40%, and the addition of α-tocopherol to atorvastatin further reduced *in vitro* LDL oxidation (130). The Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial suggested that vitamin E supplementation lowered the incidence of major CV events in HD patients without significantly affecting total mortality (133). To date, the impact of antioxidants on the clinical outcomes of patients with CKD and dialysis patients is not definitive and needs further clinical trials (134).

Other Therapies. When compared with high-flux modified cellulosic membrane, HD using high-flux polysulfone membranes was associated with a decrease in plasma total triglycerides by 10%, cholesterol in remnant particles by 21%, and ox-LDL by 15% (135). The underlying mechanisms of these differences are unclear but might be related to potential differences in dialysis membrane biocompatibility that affect inflammatory responses and/or differences in the removal of plasma lipase inhibitory molecules.

Antioxidant effects can also be achieved in HD using a vitamin E–coated membrane dialyzer, which results in a significant reduction in ox-LDL or malondialdehyde-rich LDL and an attenuation of the increase in aortic calcification index after 24 months (131). Lipid apheresis is very effective in lowering plasma LDL cholesterol and, depending on the technique, can also lower plasma Lp(a), triglycerides, and fibrinogen (136). The effects of these extracorporeal therapies on clinical outcomes are uncertain.

Experimental Therapies. A number of novel therapeutic strategies are in various stages of development for modulating lipids and lipoproteins, including lipase gene transfer (137), apoA-I(Milano) infusion (138), and short interfering RNA for apoB (139). Although they are not ready for clinical use, the potency and the specificities of these techniques for abnormalities that are characteristics of uremic dyslipidemia represent intriguing promises.

Conclusions

The optimal targets for plasma lipids in patients with CKD and dialysis patients are unknown. The commonly used clinical assays to measure triglycerides and total, LDL, and HDL cholesterol may not capture the clinically relevant lipid abnormalities of uremia, such as elevated Lp(a), IDL cholesterol, modified LDL cholesterol, and alterations in HDL cholesterol subfractions. *Post hoc* analyses of large clinical trials support the beneficial effects of statins in early stages of CKD, whereas

there is a lack of data on the use of statins in stages 4 and 5 CKD. Data in patients who are treated by PD as well as in nondiabetic HD patients are too sparse to draw any conclusion on these subpopulations. Statins are generally ineffective in correcting the elevated plasma concentrations of triglycerides and Lp(a) as well as decreased plasma concentrations of HDL cholesterol, which are the major lipid abnormalities seen in uremia. Although there is a trend toward benefits, the 4D Study did not provide definitive evidence for statins to improve CV outcomes in HD patients with diabetes. Nicotinic acid derivatives and, to a lesser extent, fibrates may be more suitable to treat uremic dyslipidemia, but there are no studies on the efficacy of these agents to improve CV outcomes in CKD.

Nephrologists and primary care physicians should detect and treat dyslipidemia at early stages of CKD using the guidelines developed for the general population. A great deal of research is urgently needed to elucidate the relationship between putatively atherogenic lipoproteins and clinical outcomes in advanced CKD. Targeting these lipoproteins may be important to decrease CVD in this population.

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Disclosures

None.

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