

Review

Dyslipidemia in Patients with Chronic and End-Stage Kidney Disease

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Dyslipidemia · Oxidized low-density lipoprotein · Chronic kidney disease · End-stage renal disease

Abstract

In this review, we discuss the physiology, diagnosis and treatment of dyslipidemia in patients with chronic and end-stage renal disease. The recent important clinical trials in patients with chronic kidney disease and dyslipidemia are reviewed. Because of the lack of evidence in treating lipid abnormalities in this specific patient population, we propose that future studies should focus on the pathophysiological mechanisms and treatment of dyslipidemia in this special patient population.

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Introduction

The prevalence of chronic kidney disease (CKD) in the United States is increasing and affects about 19 million Americans [1]. Recently, data have demonstrated that the vast majority of patients with CKD would die from cardiovascular (CV) disease before dialysis is instituted. Over the last decade, it was established that CKD is associated with a very high mortality rate and accelerated CV disease [2]. Recent studies suggest that the risk for death is increased in individuals with less severe impairment of kidney function that does not require dialysis when compared to those who have preserved kidney function [3, 4]. Dyslipidemia contributes significantly to CV death in patients with normal renal function, and cholesterol lowering with statins is effective for primary or secondary prevention of CV disease [5]. However, the relationship between dyslipidemia and CV risk in patients with renal disease is less clear than in those with normal renal function, as is the efficacy of statins

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for preventing CV risk. A lack of evidence exists since patients with CKD were excluded from the major trials that target dyslipidemia treatment in primary and secondary prevention of CV disease. In this article, we discuss the abnormalities of lipid metabolism in CKD patients along with the most recent data on dyslipidemia treatment in this population.

Lipoprotein Physiology

A complete lipoprotein particle is usually formed by combining with apoproteins. There are multiple types of lipoproteins. Apoprotein B (ApoB)-containing lipoprotein is generally linked to the formation of the atherosclerotic plaque. These lipoproteins can be categorized into 3 subgroups: cholesterol-rich low-density lipoprotein (LDL) and lipoprotein (a), triglyceride (TG)-rich very low-density lipoprotein (VLDL), and intermediate-density lipoprotein. Among all lipoproteins, based on animal studies and epidemiology, LDL cholesterol (LDL-C) is the lipoprotein associated with the development of coronary artery disease (CAD), although direct evidence for the cause in humans is not present. LDL-C is found in various sizes and quantities, and its size and shape plays a major role in its ability to pass through the endothelium and bind to the subendothelial matrix [6]. Gardner et al. [7], studying the relationship between LDL size and atherosclerosis, found evidence to support the role of small, dense LDL particles in the etiology of atherosclerosis.

Oxidized LDL

Several potential mechanisms responsible for LDL-C contributing to the development of atherosclerosis have been investigated. The most studied is the contribution of oxidized LDL-C (oxLDL) to the development of atheromatous lesions. LDL particles, when exposed to reactive oxygen species, may become oxidized. Several authors observed that in vitro incubation of macrophages with oxLDL, but not with native LDL, led to the accumulation of cholesterol ester within the macrophage [8–12]. In addition, oxLDL has been shown to enhance the macrophage's motility and the chemotactic activity, suggesting that oxLDL, by converting macrophages to foam cells, can result in direct injury to endothelial cells. oxLDL may also induce apoptosis in different cell types including endothelial cells and therefore be a direct contributor to vascular injury [13]. Besides its direct toxicity, oxLDL impairs the anti-inflammatory properties of the endothelium by altering the bioavailability of nitric oxide that results in abnormalities in vasodilation, regulation of growth, and antithrombotic effects essential for vascular homeostasis [14].

Palinski et al. [15] showed that the oxidation of LDL creates some neoepitopes which are highly immunogenic and can elicit strong B and T cell responses. In animal models of atherosclerosis, elevated levels of autoantibodies are directed against oxLDL and correlate with the severity of atherosclerosis. In patients with overt atherosclerosis or individuals with risk factors for atherosclerosis, increased levels of anti-oxLDL antibodies have been observed. As seen with animal studies, in humans the titers of anti-oxLDL antibodies present in plasma of patients with atherosclerotic plaques correlated with the severity of atherosclerosis or the rate of lesion progression, suggesting that these autoantibodies may be a useful diagnostic and predictive tool for disease progression and outcome [14]. Many studies implying a cause-effect relationship between oxLDL and atherosclerosis are animal models. Recently, studies have evaluated the formation of cholesterol crystals and their role and presence in the early atherosclerotic lesions. Using a time course analysis, Duewell et al. [16] revealed that small crystals appeared as early as 1 h after incubation with oxLDL and larger crystals were visible after longer incubation times. This is a significant finding considering the work by Abela et al. [17], which showed the importance of statins in reducing crystal size.

Lipid Profiles of Renal Patients

Patients with CKD have different particle size and composition than those without CKD. In general, TG levels are elevated in patients with CKD, which includes the TG-rich ApoB-containing VLDL and intermediate-density lipoprotein [18] particles due to reduction of lipoprotein lipase activity [19]. In addition, patients with CKD have abnormalities in LDL-C particle size and higher levels of oxLDL [14, 20, 21]. Similarly, most hemodialysis (HD) patients have high serum TG levels and low high-density lipoprotein (HDL) levels, although they have normal total cholesterol and LDL levels [22]. CKD patients and patients on HD share the same apoprotein abnormalities in that there are increases in ApoB, ApoE and ApoC-III as well as decreases in ApoA-I and ApoA-II levels [23]. Shoji et al. [24] suggested that HD patients have an atherogenic lipid profile even in the absence of dyslipidemia [25].

Among patients on dialysis, those receiving peritoneal dialysis (PD) have more lipid abnormalities than those treated with HD. It has been suggested that PD patients demonstrate more dyslipidemic risk factors including the elevation of LDL-C, TG, lipoprotein (a), or low HDL [19, 23, 25–27]. The low HDL cholesterol (HDL-C) and high ApoB-containing lipoproteins are attributed to the increased activity of cholesterol ester transfer protein found in this patient population [28, 29]. An alternative explanation for these findings is the increased loss of HDL through the peritoneal sieving compared to the loss of ApoB-containing lipoproteins, which is negligible [30]. Many potential etiologies for the increased atherogenicity of LDL in patients with CKD stage 5 have been suggested, such as a decreased affinity for the LDL receptor with increased uptake by the scavenger receptor, an increased susceptibility of LDL to oxidation, an increased filtration by the endothelium because of the smaller size of the LDL particles, and a greater affinity for binding to arterial wall proteoglycans [21].

oxLDL in Patients with Kidney Disease

Similar to individuals with normal kidney function, the accumulation of oxLDL in patients with kidney disease has been shown to occur primarily in sclerotic areas, whereas the amount of oxLDL correlated with more advanced renal disease [31]. This may be mediated through resident renal cells, i.e. mesangial cells, since Ruan et al. [32] showed expression of LDL receptors and an inducible scavenger receptor through which both LDL and oxLDL can interact. While mesangial cells have the capacity to oxidize LDL, high concentrations of oxLDL have been demonstrated to induce mesangial cell cytotoxicity [33]. Furthermore, expression of proinflammatory markers including cytokines (TNF- α and IL-6), chemokines (MCP-1), and growth factors (PDGF and MCSF) is increased with incubation of oxLDL [34, 35]. These findings suggest a role for oxLDL in the progression of glomerular injury, not only by its proinflammatory effects on vascular cells but also by activating mesangial cells [14].

In patients receiving HD and PD as part of renal replacement therapy, the presence of heme moieties promotes LDL oxidation. Levels of oxLDL are higher in those on HD compared to normal patients [36]. Furthermore, in HD and PD patients Lobo et al. [37] showed an increase in oxLDL and a decrease in anti-oxLDL IgG. The pro- or antiatherogenic role of antibodies to modified LDL particles is not completely elucidated. This specific immune humoral response may also be modulated differently when compared to other processes in atherogenesis [38–40]. These findings raise the possibility that anti-oxLDL IgG autoantibodies may have a protective effect, rather than being associated with the early stages of atherosclerosis in HD and PD patients.

Data regarding the role of anti-oxLDL antibodies are rather inconsistent. Some authors suggest a proatherogenic action, whereas others support the hypothesis that immunity

against oxLDL plays an antiatherogenic role. Despite these controversies, the anti-oxLDL antibody titer is inversely associated with arterial wall thickness and an independent predictor of CV mortality in end-stage renal disease [37, 41–43]. In CKD patients on HD, unlike those without CKD, the relationship between plasma total cholesterol and mortality is U-shaped. Lowrie et al. [44], in a large administrative database, found that the patient group with total cholesterol levels between 200 and 250 mg/dl had the lowest risk for death, whereas those with levels above 350 mg/dl had a 1.3-fold relative risk and those with levels of 100 mg/dl had a 4.2-fold unadjusted relative risk. This risk was reduced with a statistical adjustment of the albumin level but remained elevated [45]. This apparent conflict was seen in the results of the CHOICE study showing a weak association between CV mortality and serum cholesterol in the presence of inflammation and malnutrition. In contrast, the relationship was positive in the absence of inflammation or malnutrition [46]. These observations support the hypothesis that a reduction of CV mortality by lipid-lowering medications is attributed to their effect on malnutrition and/or systemic inflammation and not only to their effects on high cholesterol [45].

Dyslipidemia Treatment

At the time of this review, the NIH Clinical Practice Guideline Managing Blood Cholesterol in Adults: Report of the Adult Treatment Panel (ATP-IV) was approaching the final stages of development [47]. The following recommendations are based upon the ATP-III recommendations, and comments regarding the potential impact of ATP-IV are so qualified. When starting dyslipidemia treatment, the risk for coronary heart disease (CHD) should always be evaluated first since it is directly related to the intensity of and need for pharmacological treatment. Individuals with existing CHD (or CHD risk equivalents such as peripheral vascular disease, diabetes mellitus, and, more recently, CKD stage 3 or higher) are at highest risk, thus they should receive the most intensive treatment with the lowest goal level for LDL in both short-term (10 years) and long-term risk. According to the ATP-III guidelines, risks for CHD were divided into lipid risk factors and nonlipid risk factors. LDL-C remained the primary target for cholesterol-lowering therapy in patients with hypercholesterolemia. We anticipate that treatment decisions in the newer ATP-IV guidelines may include the measurement of high-sensitivity C-reactive protein (hsCRP) to further subdivide the population into those with higher inflammatory potential as shown in the Jupiter trial [48]. Over the last several years, there has been a move to focusing on the impact of non-HDL-C levels especially in those patients with the metabolic syndrome. Lipid management starts with lifestyle modifications including weight reduction, exercise, and smoking cessation, and that will help modifying serum TG levels – a major component of non-HDL-C [49].

Prior epidemiology suggested that low serum HDL levels are also an independent risk factor for CHD, while high levels of HDL are associated with a reduced risk. However, recent trials are driving the field away from that thought process. The AIM-HIGH study [50] showed no incremental clinical benefit from adding niacin to statin therapy, which was targeting low HDL levels. Similarly, the Dal Outcomes study [51] showed no reduction in the risk of recurrent events after administration of dalcetrapib, an agent that increases HDL levels.

The ATP-III guidelines recommend identifying CHD risk factors and adjusting the LDL target level based upon the individual's absolute risk for CHD. In these guidelines, therapy is stratified based upon the 10-year risk. The first major risk category includes those patients with CAD equivalents (e.g. diabetes). The second risk category alters LDL goals based on risk factors that predict the 10-year risk of CAD. This segregation includes persons with multiple (≥ 2) risk factors. Based on the Framingham risk score, three 10-year risk categories have

Table 1. The relative potency of HMG CoA reductase inhibitors (statins) used in the management of dyslipidemia

Drug	Dose mg	Reduction in LDL %	Reference
Rosuvastatin	10–20	47–63	[89, 91]
Atorvastatin	10–80	15–61	[92]
Simvastatin	20–80	18–68	[90, 93]
Pravastatin	10–80	14–41	[94–96]
Lovastatin	40–80	36–41	[97]
Fluvastatin	20–80	32–36	[98]

been identified: >20%, 10–20%, and <10%. Thus, a person with a 10-year risk >20% is elevated to the category of CHD risk equivalent.

The ATP-III guidance targets primarily the treatment level for LDL-C. The patients with the highest risk receive the most intensive LDL-lowering therapy, and those with the lowest risk receive the least intensive therapy. For individuals whose LDL-C levels are above the goal for the category, the goal of therapy is achieved through the judicious use of therapeutic lifestyle changes and pharmacological therapies. Therapeutic lifestyle changes include (1) reduced intakes of saturated fats and cholesterol; (2) therapeutic dietary options to enhance LDL lowering (plant stanols/sterols and increased viscous fiber); (3) weight control, and (4) increased physical activity.

Early indications in ATP-IV suggest that not only the 10-year risk, but also the lifetime risk and the assessment of inflammatory burden using hsCRP may be added to the guidance to choose whether the addition of pharmacological therapy to nonpharmacological approaches to improve lipid levels is warranted. Dietary modifications may contribute to a program to manage dyslipidemia. For example, moderate fish consumption has been demonstrated to be associated with reduced sudden cardiac death or reduced CHD mortality in several prospective cohort studies [52] but not in all [53]. It is thought that, through ingestion of marine n-3 fatty acids, favorable effects on cardiac rhythm, platelet aggregation, inflammatory responses, and serum TG levels can be achieved.

After an appropriate trial of dietary therapy to reduce LDL-C (3 months or less for high-risk populations), two additional therapeutic decisions may be required. First, if the LDL-C goal has not been achieved, consideration is given to initiating drug therapy. Second, if the metabolic syndrome is present, additional lifestyle changes (i.e. weight reduction and increased physical activity) will be needed. Later, if lifestyle therapies do not alleviate the metabolic syndrome, drug therapy for the treatment of the metabolic risk factors may be required (ATP-III).

HMG CoA Reductase Inhibitors

The HMG CoA reductase inhibitor (statins) class of drugs consists of lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin. Statins remain the cornerstone in treating hypercholesterolemia, with evidence demonstrating reduced CHD events and all-cause mortality. The degree of the reduction is directly proportional to the reduction of LDL-C levels. Recent studies have reported the reduction in coronary artery events to be independent of their effects on plasma lipids but to be explained by effects on inflammation together with the reduced CRP levels [54, 55]. The antiatherogenic effect of statins is possibly related to the maintenance of the endothelial function and the permissive action on smooth muscle cell proliferation that allows for synthesis of extracellular matrix proteins involved in the reparative response. Table 1 shows the relative potency of the more commonly used HMG CoA reductase agents.

Statins are generally well tolerated by most patients. Dose-dependent elevations ($>3\times$ upper limit of normal) in hepatic transaminases can occur in 0.5–2.0% of cases [56]. Progression to hepatic failure is exceedingly rare, and reversal of transaminase elevation is frequently noted with a reduction in dose or even continued administration of the same dose. Individuals who develop increased transaminase levels should be monitored with a second evaluation of their liver function to confirm the finding and be followed thereafter with frequent liver function tests until the abnormalities return to normal. Recently, data have reported that the use of high-potency statins within the first 120 days of initiation was associated with an increased rate of acute kidney injury diagnoses during hospital admission when compared to low-potency statin use [57].

Contraindications to the use of statins include cholestasis and active liver disease. Additionally, under some circumstances statins may produce myopathy. Elevation of creatine kinase (CK) is the best indicator of statin-induced myopathy; however, overall, the incidence of myopathy with elevations in serum CK during statin therapy is low [58, 59]. Failure to recognize myopathy and to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal failure [60]. Myopathy is most likely to occur in patients with complex medical problems and/or in those taking multiple medications. Myopathy can occur more frequently when statins are used in combination with a variety of medications including cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs, and nicotinic acid [61, 62]. Unfortunately, statins have been discontinued for suspected myopathy due to nonspecific muscle aches or joint pains. These symptoms are usually not accompanied by an elevated CK level.

Bile Acid Sequestrants

The class of bile acid sequestrants includes cholestyramine, colestipol, and colesevelam. Through binding bile acids in the intestine, the major effect is to lower LDL-C [63–67]. The binding of bile acids reduces the enterohepatic recirculation releasing feedback regulation on conversion of cholesterol to bile acids in the liver. The resulting decrease in the hepatocyte cholesterol content enhances LDL receptor expression, which in turn lowers serum LDL-C concentrations. The first major clinical study to demonstrate that primary prevention reduced coronary events, the Lipid Research Clinics Coronary Primary Prevention Trial, used the bile acid sequestrant cholestyramine [68, 69]. Added to statins, sequestrants achieve a greater reduction in LDL levels than doubling the dose of a statin [68, 70, 71].

Gastrointestinal intolerance, drug-drug interactions, and minimal impact on LDL-C levels limit the widespread use of bile acid sequestrants. This class is associated with significant gastrointestinal side effects such as constipation, abdominal pain, bloating, fullness, nausea, and flatulence [70]. In some patients, sequestrants increase hepatic VLDL production [71], thereby raising serum TG levels [72]. Since bile acid sequestrants can bind negatively charged drugs, absorption of drugs and/or fat-soluble vitamins is impaired.

Niacin (Nicotinic Acid)

Niacin favorably affects all lipids and lipoproteins when given in pharmacological dose. It acts by decreasing the hepatic production of VLDL and ApoB. Niacin lowers serum total cholesterol, LDL-C, and TG levels and raises HDL-C levels. Smaller doses often increase HDL-C levels, but doses of 2–3 g/day are generally required to produce LDL-C reductions of 15% or more [73–76]. The Coronary Drug Project showed that niacin reduced the risk of recurrent myocardial infarction (MI) [77]. During a 15-year follow-up, the total mortality was decreased in patients who had originally received niacin [78]. Recently, together with the more potent statin therapies, the AIM-HIGH study has shown no benefit from the combination therapy [50]. Additionally, in the HPS2-THRIVE trial, a large randomized placebo-controlled trial in high-risk Chinese patients, the use of extended-release niacin was associated with an increased

incidence of myopathy when used in combination with statin [79]. A significant and relatively common side effect of niacin therapy is skin flushing, which in some cases is intolerable and the major reason for drug discontinuation. Slow titration of the dose, taking the drug during meals, or pretreatment with aspirin can modulate the severity of flushing and allow for adequate dose titration. Other side effects include nausea, dyspepsia, flatulence, vomiting, and diarrhea, and the potential for activation of a peptic ulcer may also occur. Three other major adverse effects include hepatotoxicity, hyperuricemia, and hyperglycemia. The risk of these 3 side effects is increased with doses >2 g/day. Giving these multiple side effects, niacin is reserved for those patients with a high short-term risk of CHD.

Fibric Acid Derivatives (Fibrates)

Fibric acid derivatives include gemfibrozil, fenofibrate, and clofibrate. Fibrates, which are agonists of the nuclear transcription factor peroxisome proliferator-activated receptor- α (PPAR- α) [80], downregulate the ApoC-III gene and upregulate genes for ApoA-I, fatty acid transport protein, fatty acid oxidation, and lipoprotein lipase. The effects on lipoprotein lipase and ApoC-III enhance catabolism of TG and reduce formation of VLDL TG. Fenofibrate reduces LDL-C levels by 15–20% if TG levels are not elevated and by 25–50% if TG levels are severely increased [81]. Fibrates usually raise HDL-C by 10–15%, but greater increases can occur in individuals with very high TG levels and very low HDL-C levels. Primary prevention treatment with clofibrate or gemfibrozil reduced the risk of fatal and nonfatal MI in two large trials [82], and gemfibrozil reduced CHD death, nonfatal myocardial infarction, and stroke in a secondary prevention trial [83]. However, these beneficial effects were not observed in all large fibrate trials [77]. Gastrointestinal side effects are common. All drugs in this class appear to increase the lithogenicity of the bile, increasing the likelihood of cholesterol gallstones. Some drug-drug interactions, such as with warfarin, can occur given that fibrates bind to serum albumin. Fibrates are excreted primarily by the kidney; consequently, elevated serum levels occur in patients with renal failure and the risk for myopathy is greatly increased. The combination of a fibrate with a statin also increases the risk for myopathy, which can lead to rhabdomyolysis [60].

Fatty Acids

Fatty acids of the n-3 type such as linolenic acid, DHA, and EPA at high doses can lower serum TG levels by reducing hepatic secretion of TG-rich lipoproteins. Reductions in TG of 30–40% can be seen. LDL-C either remains the same or increases minimally with no appreciable effect on HDL-C. These agents represent alternatives to fibrates or nicotinic acid for the treatment of hypertriglyceridemia, particularly chylomicronemia. Recent clinical trials have also suggested that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils reduce the risk for major coronary events in patients with established CHD. The ATP-III panel recognized that n-3 fatty acids, whether derived from foods or supplements, can be a therapeutic option in secondary prevention.

Lipid-Lowering Trials in Patients with CKD

Over the past two decades, most major clinical trials using statins in evaluating either primary or secondary prevention of CHD excluded those patients with the most severe forms of CKD. The use of statins to treat dyslipidemia in patients with severe CKD was largely based on expert opinion and retrospective analyses of treatment regimens. Recently, 5 large randomized controlled trials of lipid-lowering therapy have been conducted in patients with CKD (table 2). As part of all of these trials, dietary guidance and lifestyle modifications were recommended, but neither was specifically studied in a rigorous manner.

Table 2. Major clinical trials using lipid-lowering therapy to assess outcomes in patients with kidney disease

Study	Drug/dose	Population (number of patients)	Control group (number of participants)	Outcome
ALERT (2003) [98]	Fluvastatin 40 mg	Renal transplant (n = 1,050)	Placebo (n = 1,052)	Fluvastatin reduced cardiac deaths and nonfatal MI, but did not reduce rates of coronary intervention procedures or mortality versus placebo
4D (2005) [86]	Atorvastatin 20 mg	HD (n = 619)	Placebo (n = 636)	Atorvastatin did not lower incidence of cardiovascular death, nonfatal MI, and stroke versus placebo
UK-HARP II (2006) [85]	Simvastatin 20 mg plus ezetimibe 10 mg	CKD (stages 3–5), HD and PD (n = 102)	Simvastatin 20 mg (n = 101)	Combination therapy produced improved LDL-lowering effect
AURORA (2009) [89]	Rosuvastatin 10 mg	HD (n = 1,389)	Placebo (n = 1,384)	Rosuvastatin did not improve death from CV causes, nonfatal MI, or nonfatal stroke versus placebo
SHARP (2011) [90]	Simvastatin 20 mg plus ezetimibe 10 mg	CKD (stages 3–5), HD and PD (n = 4,650)	Placebo (n = 4,620)	Combination therapy lowered major atherosclerotic events

ALERT Trial

The ALERT trial (Assessment of Lescol in Renal Transplantation) evaluated long-term cardiac outcomes in patients receiving fluvastatin. This trial was the first to evaluate statin treatment in patients with kidney disease. Those with kidney transplantation (n = 2,102 patients) were randomized to receive fluvastatin (40 mg/day) or placebo and were followed for 5–6 years. The primary end points were major adverse cardiac events, which included cardiac death, nonfatal MI, or coronary intervention. Patients receiving fluvastatin had a 26% reduction in cardiac death along with a 28% reduction in nonfatal MI. There was no difference in the all-cause mortality between the two groups. When compared to studies in patients without renal transplantation, the lipid-lowering and CV benefits from fluvastatin were comparable, thus supporting the use of fluvastatin in renal transplant recipients [84].

UK-HARP-II Study

The UK-HARP-II study (Second United Kingdom Heart and Renal Protection Study) randomized 203 patients with CKD or on HD/PD to receive simvastatin 20 mg plus ezetimibe 10 mg daily versus simvastatin 20 mg daily and ezetimibe placebo. The trial evaluated the tolerability and efficacy of the lipid-lowering therapy in this patient population. Due to the short-term nature of the study, clinical outcomes were not assessed. After 6 months of therapy, the combination of simvastatin and ezetimibe reduced non-HDL-C by 23%, which was 19% greater than with simvastatin alone. While not powered for subgroup assessment (CKD, HD, and PD), there was no meaningful difference in the effects observed. Ezetimibe was tolerated with similar adverse events and drug discontinuation in both groups [85].

4D Study

The 4D study (Die Deutsche Diabetes Dialyse Studie) randomized 1,255 patients with type 2 diabetes mellitus receiving HD to atorvastatin 20 mg/day versus placebo with major adverse cardiac events as the primary end points (death from cardiac causes, nonfatal MI, and stroke). After 4 weeks of treatment, atorvastatin decreased LDL-C by 42% compared to 1.3%

in placebo patients. The median follow-up was similar and about 4 years in both groups. The relative risk reduction for the primary end point in those receiving atorvastatin was 8% when compared to placebo ($p = 0.37$). Based on these findings, the authors concluded that, in patients with type 2 diabetes receiving HD, routine treatment with a statin to reduce the primary composite end point of death from cardiac causes, MI, and stroke is not warranted [86].

AURORA Trial

In the AURORA trial (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), 2,776 maintenance HD patients between the ages of 50 and 80 years were randomized to receive rosuvastatin 10 mg/day versus placebo. The combined primary end points were major adverse cardiac events including CV death, nonfatal MI, or nonfatal stroke. LDL-C was reduced by 43% in patients receiving rosuvastatin after 3 months, while the reduction in placebo patients was only 2%. In addition, hsCRP was decreased by 11.5% in the rosuvastatin-treated group compared with an increase in the placebo group ($p < 0.001$). Despite these findings at 3 months, the primary end point after a mean follow-up of 3.2 years occurred in 396 patients receiving rosuvastatin and in 408 patients receiving placebo. Compared to placebo, active treatment reduced the combined primary end point by 4% ($p = 0.59$) [87]. In addition, a high proportion of cardiac deaths in these trials (4D study and AURORA trial) were not attributable to CHD but not reduced by active treatment [88, 89]. Although lowering LDL-C with statin therapy among patients with end-stage renal failure did not produce statistically significant reductions in the primary outcomes in these trials, there were promising proportional reductions of 18% in major cardiac events in the 4D study [86, 90] and of 16% in nonfatal MI in the AURORA trial [87, 90]. These findings raised the possibility of small, but worthwhile, proportional benefits on atherosclerotic outcomes among dialysis patients and of larger proportional benefits among those with less severe renal impairment [90].

SHARP Trial

Most recently, the SHARP trial (Study of Heart and Renal Protection) randomized 9,270 patients with CKD (3,023 were on dialysis) to receive simvastatin 20 mg/day plus ezetimibe 10 mg/day versus placebo. The key prespecified outcome was first major atherosclerotic event (nonfatal MI or coronary death, nonhemorrhagic stroke, or any arterial revascularization procedure). Most patients not on dialysis were in CKD stages 3 and 4. Active treatment compared to placebo reduced LDL-C by 1.09 mmol/l between 8 and 13 months of treatment (baseline level: 2.77 mmol/l). Patients were followed for a median of 4.9 years. With active treatment, the primary end point was decreased by 17% ($p = 0.0021$). Despite the overall impact, the effect of treatment on coronary events (CHD death and nonfatal MI) was not different ($p = 0.37$). A unique component of this trial is the non-study statin use in the active arm and the 14% use of statins in the placebo arm by 4 years of follow-up, which can complicate its interpretation. Further, analysis of the subgroups suggests to us that those with the highest levels of pretreatment cholesterol and BMI as well as smokers seem to benefit the most from the treatment. Compared to previous studies (ALERT trial, 4D study, and AURORA trial), the SHARP trial results achieved statistical significance in the primary outcome. While the outcome measures were slightly different, when comparing those that were consistent, the degree of effect was similar among the trials. The authors of the SHARP trial propose that these effects were significant due to the increased number of events and the larger trial size [90].

Overall Perspective in Patients with CKD or on Dialysis

Based upon these trials, it is our practice to aggressively manage lipids in patients with CKD or on dialysis. However, when taken together, it is surprising that the overall results are not more impressive in this high-risk group of patients. With high CHD morbidity and mortality in those with CKD, extrapolation of results from major clinical trials using statins in those without CKD would suggest a profound impact. Given the findings from these trials, it is likely that factors other than LDL-C lowering are contributing to the morbidity and mortality in this population. Further work is needed to identify and address the underlying pathophysiological causes for this apparent gap, optimal goals for treatment, and other approaches that may improve outcomes as well as identify selected individuals that may benefit from these therapies.

In summary, diagnosis and management of lipid abnormalities are important in patients with CKD or on dialysis. The impact of treatment in this patient population appears less significant than in those without CKD at the present time. Further work is necessary to identify the root cause for the increases in CHD morbidity and mortality as well as optimal treatment approaches.

Disclosure Statement

The authors have no conflict of interest to disclose.

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