Dyslipidemias in chronic kidney disease: Current guidelines and future perspectives

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Abstract

Introduction
Dyslipidemia is a major problem in chronic kidney disease (CKD) and haemodialysis patients. Although there has been much progress and reduction in the prevalence of dyslipidemia after the Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel), there were few specific recommendations for the evaluation and treatment of dyslipidemias in CKD patients in these reports. Besides, the NCEP guidelines are applicable to patients with stages 1–4 CKD and not specifically concerned with stage 5 CKD and kidney transplant recipients. It is also evident that when these guidelines were published, there were no large randomized controlled trials evaluating the effects of lipid-lowering therapy in this patient group. Given the fact that patients with CKD should be considered in the highest risk group for cardiovascular disease, it was decided that specific recommendations regarding dyslipidemia should be applied to patients with CKD. Thus from the outset of Kidney Disease Outcomes Quality Initiative (K/DOQI), it was strongly agreed that the management of dyslipidemias in patients with kidney disease would be one of the most important issues. However, recent randomized controlled trials showed that dyslipidemia treatment in these patients had shown modest benefit at best with regard to cardiovascular mortality. The specific recommendations about dyslipidemias in CKD patients are reviewed along with the new studies and future perspectives.

Conclusion
While preparing the dyslipidemia guidelines for CKD patients, the K/DOQI working group anticipated from the beginning that all the guidelines should be updated whenever new information becomes available. We do not know whether trial results from the general population are applicable to all patients with CKD. A new guideline incorporating the data of a recent research is necessary.

Introduction
The number of patients with chronic kidney disease (CKD) is increasing. Unfortunately, the survival of CKD patients remains poor. Among other factors, cardiovascular disease (CVD) is the leading cause of death in CKD patients. Both traditional and non-traditional factors play a role for increased cardiovascular mortality. Among traditional risk factors, diabetes, hypertension and dyslipidemia are the leading causes. Anaemia, inflammation, oxidative stress, disorders of calcium phosphorus metabolism, arterial stiffness and malnutrition can be stated as non-traditional risk factors. Thus, it is of no question that CKD patients can be considered as high-risk patients. In previous reports such as Adult Treatment Panel (ATP) III, there was no specific interest regarding the dyslipidemia in CKD patients. Thus in response to the recommendations of the National Kidney Foundation (NKF) Task Force on CVD, the NKF Kidney Disease Outcomes Quality Initiative (K/DOQI) convened a work group to develop guidelines for the management of dyslipidemias, one of the risk factors for CVD in CKD. This critical review gives brief information about these guidelines first and the interpretation of these guidelines based on the recently conducted randomized prospective studies thereafter.

Discussion
The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Adult Treatment Panel III guidelines
According to the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines, management of all lipid disorders begin with therapeutic lifestyle changes (TLCs). The fact that TLC has the potential to reduce cardiovascular risk through several mechanisms beyond low-density lipoprotein cholesterol (LDL-C) lowering. Along with TLC, diet (saturated fat <7% of calories, cholesterol <200 mg/day, increased viscous fibre...
Major risk factors other than LDL-C are atherosclerotic disease and diabetes. Non-coronary forms of clinical atherosclerotic disease include (1) established coronary heart disease (CHD) and CHD risk equivalents, (2) multiple (2+) risk factors and (3) zero to one (0–1) risk factor.

CHD risk equivalents include non-coronary forms of clinical atherosclerotic disease and diabetes. Major risk factors other than LDL-C include cigarette smoking, hyper-tension (BP >140/90 mmHg or on antihypertensive medication), low high-density lipoprotein cholesterol (HDL-C) (<40 mg/dl) and a family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years; age: men>45 years, women >55 years). Besides, HDL-C >60 mg/dl counts as a ‘negative’ risk factor, and its presence removes one risk factor from the total count. All people with CHD or CHD risk equivalents should be accepted as high risk.

However, in ATP III guidelines, no specific comments were made on patients with CKD, and CKD patients were not managed differently from other patients. The ATP III only notes that nephrotic syndrome is a cause of secondary dyslipidemia and suggests consideration be given to the use of cholesterol-lowering drugs if hyperlipidemia persists despite specific treatment for kidney disease. The ATP III also notes that various dyslipidemias have been reported in patients with kidney failure. However, the ATP III suggests that a cautious approach be taken, since these patients are prone to drug side effects, for example, they are at increased risk of myopathy from both fibrates and statins. Indeed, fibrates are contraindicated in stage 5 CKD patients in ATP III reports.

K/DOQI guidelines for dyslipidemia

As suggested above, no specific recommendation was mentioned in the major guidelines regarding dyslipidemia and CKD. Thus by the recommendations of the NKF Task Force on CVD, the NKF K/DOQI convened a work group to develop guidelines for the management of dyslipidemias. The K/DOQI working group suggests that:

- All adults and adolescents with CKD should be evaluated for dyslipidemias (moderate evidence).
- For adults and adolescents with CKD, the assessment of dyslipidemias should include a complete fasting lipid profile with total cholesterol, LDL-C, HDL-C and triglycerides (moderate evidence).
- For adults and adolescents with stage 5 CKD, dyslipidemias should be evaluated upon presentation (when the patient is stable), at 2–3 months after a change in treatment or other conditions known to cause dyslipidemias, and at least annually thereafter (moderate evidence).
- For adults and adolescents with stage 5 CKD, a complete lipid profile should be measured after an overnight fast whenever possible (moderate evidence).
- Haemodialysis patients should have lipid profiles measured either before dialysis, or on days they are not receiving dialysis (moderate evidence).
- Stage 5 CKD patients with dyslipidemias should be evaluated for remediable, secondary causes (moderate evidence).

Treating dyslipidemias according to K/DOQI

The K/DOQI suggests that:

- For adults with stage 5 CKD and fasting triglycerides ≥ 500 mg/dl, which cannot be corrected by removing an underlying cause, treatment with TLCs and a triglyceride-lowering agent should be considered (weak evidence).
- For adults with stage 5 CKD and LDL >100 mg/dl (≥2.59 mmol/l), treatment should be considered to reduce LDL to <100 mg/dl (<2.59 mmol/l) (moderate evidence).
- For adults with stage 5 CKD and LDL <100 mg/dl, fasting triglycerides ≥200 mg/dl and non-HDL cholesterol (total cholesterol minus HDL) ≥130 mg/dl, treatment should be considered to reduce non-HDL cholesterol to <130 mg/dl (weak evidence).
- For adolescents with stage 5 CKD and LDL ≥130 mg/dl, treatment should be considered to reduce LDL to <130 mg/dl (weak evidence).
- For adolescents with stage 5 CKD and LDL <130 mg/dl, fasting triglycerides ≥200 mg/dl and non-HDL cholesterol (total cholesterol minus HDL) ≥160 mg/dl, treatment should be considered to reduce non-HDL cholesterol to <160 mg/dl (weak evidence).

Until the guidelines published by the K/DOQI working group, there were very scarce randomized controlled studies examining the effect of lipid-lowering therapy in CKD patients. However, after the report of K/DOQI working group, prospective studies were performed regarding the use of lipid-lowering agents and cardiovascular outcomes in CKD patients including peritoneal and haemodialysis patients. Since these studies are very important in the field of treatment of dyslipidemias in CKD patients, they should be mentioned briefly.

Studies of dyslipidemia treatment in CKD patients not on dialysis

Few studies have been designed primarily to investigate the effects of statins (HMG-CoA [3-hydroxy-3-methylglutaryl coenzyme A] inhibitors). Critical review

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reductase inhibitor) on cardiovascular outcomes in patients with CKD who are not undergoing dialysis therapy. The pravastatin pooling project showed that the relative risk reduction in major cardiovascular events observed among patients with an estimated glomerular filtration rate (GFR) of ≥30 ml/min/1.73 m² and <60 ml/min/1.73 m² was similar to that observed in patients with a GFR ≥60 ml/min/1.73 m² (23% and 22%, respectively)⁶. A meta-analysis of randomized, placebo-controlled trials that included >6,500 patients with CKD demonstrated that statins significantly reduced both serum lipids concentrations and the incidence of cardiovascular end points, without evidence of increased adverse effects⁷. However, since the studies were primarily designed to assess cardiovascular outcomes in patients with cardiac disease or at high risk of developing cardiac disease and lacked predefined kidney function outcomes, consequently, the renal findings derived from post hoc analyses might be misleading⁸. Thus to diminish these drawbacks, various trials randomly assigned participants to statin therapy versus control⁹–¹¹. As a cumulative result of these studies, it was concluded that statins did not decrease all-cause mortality or stroke in participants with diabetes and CKD¹². However, statin therapy increased regression of microalbuminuria to normoalbuminuria, but did not attenuate the decrease in estimated GFR (eGFR) in patients with baseline albuminuria⁹. However, the aforementioned studies were conducted on diabetic CKD patients. To be more comprehensive, Navaneethan et al. evaluated the benefits of statins in patients with non-dialysis-dependent CKD with or without cardiovascular comorbidities, including randomized controlled trials and comparing statins with placebo. The meta-analysis involved more than 18,500 patients, and showed that statins reduced the relative risk of all-cause mortality by 19%, the relative risk of cardiovascular mortality by 20% and the relative risk of non-fatal cardiovascular events by 25%¹³. Thus it was concluded that statin therapy is effective in reducing CVD especially in the early stages of CKD¹⁴–¹⁷. Based on the data, a recent review suggested more specifically that it is better for CKD patients with stage 1–3 to use statins, whereas the beneficial role of statins beyond stage 3 CKD is less clear⁹. Apart from statins, there are also studies investigating the effects of fibrates in CKD patients. In a randomized study, Tonelli et al. investigated the effects of gemfibrozil in secondary prevention of cardiovascular events. After a median follow-up of 5.3 years, gemfibrozil treatment significantly reduced the risk of the composite outcome of fatal CHD, non-fatal myocardial infarction and stroke compared with placebo¹⁸. In another study, Davis et al. investigated the effect of fenofibrate therapy on renal functions in 9,795 type 2 diabetic patients. Estimated GFR had fallen less from baseline on fenofibrate than on placebo (P < 0.001). Fenofibrate reduced urine albumin concentrations and hence albumin/creatinine ratio by 24% versus 11% (P < 0.001; mean difference 14% [95% CI 9–18]; P < 0.001), with 14% less progression and 18% more albuminuria regression (P < 0.001) than in participants on placebo. End-stage renal event frequency was similar (n = 21 vs. 26, P = 0.48). The authors concluded that fenofibrate reduced albuminuria and slowed eGFR loss over 5 years, and fenofibrate may delay albuminuria and GFR impairment in type 2 diabetes patients¹⁹.

**Studies of dyslipidemia treatment in CKD patients on dialysis**

In a 4D study, Wanner et al. recruited 1,255 diabetic patients with end-stage renal disease (ESRD). About 619 patients were in the intervention group (atorvastatin 20mg/dl) and 636 served as a control. The primary end point was a composite of death from cardiac causes, non-fatal myocardial infarction and stroke. Secondary end points included death from all causes and all cardiac and cerebrovascular events combined. After a median of a 4-year follow-up, 469 patients (37%) reached the primary end point, of whom 226 were assigned to atorvastatin and 243 to placebo (relative risk 0.92; 95% CI 0.77–1.10; P = 0.37). Atorvastatin had no significant effect on the individual components of the primary end point, except that the relative risk of fatal stroke among those receiving the drug was 2.03 (95% Cl 1.05–3.93; P = 0.04). The authors concluded that atorvastatin had no statistical significance effect on the composite primary end point of cardiovascular death, non-fatal myocardial infarction and stroke in patients with diabetes receiving haemodialysis²⁰. However, post hoc analysis of the 4D study demonstrated that atorvastatin significantly reduced the rate of adverse outcomes in patients with a baseline LDL-C level in the highest quartile but not in any of the other three quartiles²¹.

Another randomized, double-blind prospective trial with rosuvastatin in ESRD was recently published. The AURORA trial (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) involved 2,776 patients, 50–80 years of age, who were undergoing maintenance haemodialysis. Patients were randomly assigned patients to receive rosuvastatin, 10 mg daily, or placebo. The combined primary end point was death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. Secondary end points included death from all causes and individual cardiac and vascular events. During a median follow-up period of 3.8 years, rosuvastatin had no effect on the individual components of the primary end point. There was also no significant

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effect on all-cause mortality. Interestingly, an increased incidence of fatal haemorrhagic stroke was noted in patients with diabetes mellitus in the rosuvastatin group, compared with patients with diabetes mellitus in the placebo group. The authors concluded that the initiation of treatment with rosuvastatin lowered the LDL-C level in patients undergoing haemodialysis but had no significant effect on the composite primary end point of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.

Last, it is worth mentioning the study of Heart and Renal Protection (SHARP) trial. This randomized double-blind trial included 9,270 patients with both CKD and ESRD on haemodialysis and peritoneal dialysis (3,023 on dialysis and 6,247 not on dialysis) with no known history of myocardial infarction or coronary revascularization. Patients were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg daily (4,650 patients) versus matching placebo (4,620 patients). The key prespecified outcome was the first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke or any arterial revascularization procedure). All analyses were by intention to treat. After a 4.9-year follow-up, there was a 17% proportional reduction in major atherosclerotic events in simvastatin plus ezetimibe vs. placebo (rate ratio [RR] 0.83, 95% CI 0.74–0.94; log-rank P = 0.021), and there were significant reductions in non-haemorrhagic stroke (131 [2.8%] vs. 174 [3.8%]; RR 0.75, 95% CI 0.60–0.94; P = 0.01) and arterial revascularization procedures (284 [6.1%] vs. 352 [7.6%]; RR 0.79, 95% CI 0.68–0.93; P = 0.0036) in simvastatin plus ezetimibe group. On subgroup analysis, however, the investigators did not observe a clinically or statistically significant reduction in either mortality or the cardiovascular event rate in the dialysis population given active treatment compared with those on placebo (15% vs. 16.5%, respectively). Consequently, the results of the SHARP study for patients on dialysis were similar to those from the AURORA and 4D studies.

Thus it is obvious that by the light of aforementioned studies, more studies are needed to determine whether statins are useful in CKD and ESRD. Table 1 summarizes the possible factors related with inefficiency of statin treatments in randomized controlled trials.

**Conclusion**

While preparing the dyslipidemia guidelines for CKD patients, the K/DOQI working group anticipated from the beginning that all guidelines should be updated whenever new, pertinent information becomes available. To anticipate when these guidelines may need to be updated, the Work Group discussed ongoing clinical trials in the general population and in patients with CKD, as those results may be pertinent to some recommendations. They also have reasonable doubt as to whether trial results from the general population are applicable to all patients with CKD. The major trials (4D, AURORA, SHARP) were not completed when these guidelines were prepared. Thus from these findings, a new guideline incorporating the data of a recent research is necessary. It is of no question that a new research is strongly warranted regarding the pathophysiology of dyslipidemias in CKD and ESRD patients, with newer treatment options, more patient and extended follow-up.

**Abbreviations list**

ATP, Adult Treatment Panel; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated GFR; ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; K/DOQI, Kidney Disease Outcomes Quality Initiative; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; NKF, National Kidney Foundation; RR, rate ratio; TLC, therapeutic lifestyle change

**References**


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**Table 1 Possible factors related with inefficiency of statin treatments in randomized controlled trials**

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<tr>
<td>Lack of statistical power</td>
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<td>High dropout rate</td>
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<td>Low dose of drugs</td>
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<td>Advanced stage of disease</td>
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<td>Different pathophysiologic mechanisms of dyslipidemia in CKD patients compared with normal population</td>
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<td>Predominance of non-traditional cardiovascular risk factors</td>
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<td>Ignorance of causes of renal failure and the age of the subjects</td>
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<td>Reverse epidemiology</td>
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