Dyslipidemias in Chronic Kidney Disease

Please characterize the typical lipid profile of patients with chronic kidney disease. Please describe its unique features compared with that of the general population.

As kidney function declines, there is a tendency for triglycerides to increase and HDL cholesterol to decline. Declining kidney function is not associated with increased levels of LDL cholesterol per se. However, patients can certainly have elevated levels of LDL cholesterol independently of the level of kidney function. In addition, many of the treatments we use for glomerulonephritis can also adversely affect lipid levels. In particular, corticosteroids and cyclosporine increase the levels of total and LDL cholesterol.

What about the patient receiving renal replacement therapy? Is there any difference based on their modality of dialysis, e.g., hemodialysis versus peritoneal dialysis?

Patients treated with maintenance hemodialysis (HD) tend to have lipid profiles that qualitatively resemble those of patients with stage III or IV chronic kidney disease (CKD). That is, they frequently have high triglycerides and low HDL cholesterol levels. Total and LDL cholesterol are often normal or even low in HD patients. Patients treated with maintenance peritoneal dialysis tend to have both increased triglycerides and low HDL cholesterol, but unlike HD patients, they often have elevated LDL cholesterol as well.

What about the posttransplant patient?

Kidney transplant patients typically take one or more immunosuppressive medications that can cause dyslipidemias. These include corticosteroids, cyclosporine, and mammalian target of rapamycin, also known as proliferation signal inhibitors. As a result, a typical kidney transplant recipient has high total and LDL cholesterol, and often increased triglycerides as well. Despite the fact that kidney function is often decreased, HDL cholesterol levels are usually normal. This may be due to the use of corticosteroids, which tend to raise HDL levels, although increased HDL cholesterol from corticosteroids may not reduce the risk of cardiovascular disease.

Please define reverse epidemiology in the context of dyslipidemias and CKD. What are your thoughts about this concept?

Reverse epidemiology has been associated with proteinuria and dyslipidemia—that is, total urine protein excretion greater than 3.0 g/24 h—often have increased total and LDL cholesterol as well as elevated triglycerides. The greater the amount of urine protein excretion, the more likely these lipoprotein abnormalities will be present.

Are there any guidelines regarding screening and monitoring for dyslipidemia in patients with various stages of CKD?

Kidney Disease Improving Quality Outcomes (KDOQI) published guidelines for the management of dyslipidemia in CKD in the American Journal of Kidney Disease in April 2003. However, these guidelines were written before the results of some major clinical trials were published, including the Assessment of Lescol in Renal Transplantation, Die Deutsche Diabetes Dialyse Studie (4D), the Study to Evaluate the Use of Rosuvastatin in Subjects with Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), and the SHARP study.

The KDOQI guidelines state that they would need updating in three years, especially because publication of these major trials was pending. The Kidney Disease Improving Global Outcomes organization is planning to develop updated guidelines when the results of the SHARP study are available. In the meantime, there are really no up-to-date evidence-based guidelines that address the screening and monitoring of dyslipidemia in patients with CKD.

Please summarize what we can conclude from the lipid landmark trials, namely 4D, AURORA, and SHARP?

Unlike the SHARP study, the 4D and AURORA studies failed to show a reduction in cardiac events. It is most likely that the 4D and AURORA studies did not have adequate statistical power to demonstrate that lowering LDL cholesterol reduced atherosclerotic coronary artery disease events.

In the 4D trial, 20 mg of atorvastatin daily in HD patients with type 2 diabetes resulted in a nonsignificant 8 percent reduction in cardiac death, nonfatal myocardial infarction, or stroke. In the AURORA trial, 10 mg of rosvastatin daily in HD patients resulted in a nonsignificant 4 percent reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Both the 4D and AURORA study endpoints likely included many cardiovascular deaths that were not caused by atherosclerotic coronary heart disease and thus could not be expected to be reduced by lowering LDL cholesterol.

In contrast to the 4D and AURORA studies, the primary endpoint in the SHARP study was nonfatal myocardial infarction, coronary death, nonhemorrhagic stroke, or any revascularization procedure. This endpoint was designed to exclude noncoronary heart disease deaths. In addition, the SHARP study, which included about two thirds CKD patients not receiving dialysis, was much larger than both the 4D and AURORA trials put together. Thus, the reduction in the primary endpoint with ezetimibe plus simvastatin in SHARP was likely the result of adequate statistical power. A meta-analysis of the results of 4D, AURORA, and dialysis patients in SHARP is planned and will help us better understand the differences in these important trials.

On the basis of the above trials, should we use statin therapy in CKD patients? Does the stage of CKD have any bearing on the initiation of statin therapy?

Reducing LDL cholesterol is beneficial in patients at any stage of CKD, and statins are the safest and most effective for reduc-
There are no comparison trials showing that any statin is better than any other for preventing coronary heart disease events beyond the differences in their ability to lower LDL cholesterol. The lower the reduction of LDL cholesterol, the lower the risk of coronary heart disease has been. Of course, any statin should be used only at doses proved to be safe.

How about fibrates? Please comment on the use of combination statin and fibrate therapy in CKD patients.

Studies in the general population have shown that fibrates are not as effective as statins in lowering LDL cholesterol and reducing coronary heart disease events. Therefore, statins should be considered to be first-line agents for the reduction of LDL cholesterol. Combining simvastatin with ezetimibe was shown to be safe and effective in the SHARP trial. Otherwise, combining a statin with a lipid-lowering agent other than ezetimibe should probably be used only if additional trial evidence showing safety and efficacy becomes available in the future.

There are no trials of fibrates, either alone or in combination with other lipid-lowering drugs in patients with CKD, showing that fibrates are safe and effective for reducing coronary heart disease events. The safety of fibrates is a major concern, given that blood levels of most fibrates increase in patients with low levels of kidney function and especially in patients receiving dialysis. Therefore, if fibrates are used in patients with CKD, the dose of the fibrate should be adjusted according to the level of kidney function. Blood levels of gemfibrozil appear to be less affected by reduced kidney function than are blood levels of other fibrates, but all fibrates should be used cautiously if at all in patients with advanced CKD. Given the lack of data on efficacy and concerns about safety, I would generally avoid combining statins with fibrates in patients with CKD.

If a CKD patient is intolerant of statin/fibrate therapy, what alternative choices are available, and how effective are they in this population?

The only large randomized controlled trial examining the safety and efficacy of LDL cholesterol reduction in CKD with an agent other than a statin is the SHARP trial. In the SHARP trial, the combination of ezetimibe 10 mg with simvastatin 20 mg was compared with simvastatin 20 mg alone and placebo for 1 year. During this first year, the incidence of adverse events was similar in patients receiving ezetimibe plus simvastatin compared with simvastatin alone and compared with placebo. The levels of LDL cholesterol at 1 year were (mean ± SE) 1 ± 1 mg/dL in the placebo group, −29 ± 3 mg/dL with simvastatin alone, and −42 ± 2 mg/dL in the ezetimibe plus simvastatin group. Thus, as expected, the combination of ezetimibe with simvastatin appeared to result in a greater reduction in LDL cholesterol than did simvastatin alone. Therefore, if fibrates are used in patients with CKD, the dose of the fibrate should be adjusted according to the level of kidney function. Blood levels of gemfibrozil appear to be less affected by reduced kidney function than are blood levels of other fibrates, but all fibrates should be used cautiously if at all in patients with advanced CKD. Given the lack of data on efficacy and concerns about safety, I would generally avoid combining statins with fibrates in patients with CKD.

What practice pointers would you like to give our readers?

Many, if not most, patients with CKD are at increased risk for coronary heart disease and should be taking a statin. Although some patients may develop myopathies, the incidence of this and other adverse effects attributed to statins in CKD patients has not been different in comparison with placebo.

The greatest barrier to reducing coronary heart disease events with a statin is not an adverse effect of a statin, but patient nonadherence to statin therapy. Therefore, strongly encourage patients to adhere to statin therapy, perhaps try a different statin if they think they are having adverse effects from a particular statin, or consider using the “statin-sparing” combination of ezetimibe 10 mg with simvastatin 20 mg.

Patients generally need considerable education and encouragement to take medication to prevent complications that they may have not yet experienced.