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CME CREDIT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should all patients with chronic kidney disease take a statin?

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Little evidence, but we would consider using statins to treat dyslipidemia in kidney patients not on dialysis

A: We think *some* patients with chronic kidney disease should take a statin, particularly those in stages 1 through 4 (ie, not yet on dialysis[1])* who have low-density lipoprotein cholesterol (LDL-C) levels higher than 100 mg/dL. However, few studies have addressed this question.

The answer is murkier in patients on dialysis. Only one study has been done in this population, and it found no benefit from statin therapy. However, we would prescribe a statin for a dialysis patient who had known coronary artery disease and an LDL-C level higher than 100 mg/dL.

RATIONALE FOR STATIN USE: KIDNEY PATIENTS ARE AT RISK

Cardiovascular disease is common among patients with chronic kidney disease. While the risks of cardiovascular disease and death are highest among those requiring dialysis, earlier stages of chronic kidney disease also are associated with cardiovascular disease.[2–4]

The prevalence of traditional risk factors, particularly diabetes and hypertension, is high in all stages of kidney disease, and dyslipidemia is extremely common. Patients with chronic kidney disease who are not on dialysis tend to have lower levels of high-density lipoprotein cholesterol and higher levels of triglycerides, lipoprotein remnants, lipoprotein(a), and LDL-C. The lipid profile of dialysis patients is more complex, as malnutrition and inflammation in this population may lead to low cholesterol levels.

Since statins are effective for primary and secondary prevention of cardiovascular events in those in the general population with high LDL-C,[5] we could expect that the same holds true for patients with chronic kidney disease. Furthermore, if kidney disease were considered a coronary heart disease equivalent, more than 85% of those with stage 3, 4, or 5 disease would qualify for lipid-lowering therapy by LDL-C criteria.[6]

However, compared with the large body of evidence in those without kidney disease, we have few data on the effect of statins on cardiovascular outcomes in those with kidney disease. Five of seven major trials of statins excluded patients with chronic kidney disease by using a creatinine cutoff or by excluding patients with known kidney disease.[7]

Renoprotective effects

Besides their cardiovascular effects, statins may slow the progression of kidney disease.

A subgroup analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) trial[8] showed a 12% increase in creatinine clearance in the group receiving atorvastatin (Lipitor) (P = .0001). In comparison, creatinine clearance decreased by 4% in the placebo group.

*Stages of chronic kidney disease[1]:
Stage 1--kidney damage with normal or high glomerular filtration rate (GFR ≥ 90 mL/min/1.73 m^2)
Stage 2--kidney damage with mildly decreased GFR (60–89 mL/min/1.73 m^2)
Stage 3--moderately decreased GFR (30–59 mL/min/1.73 m^2)
Stage 4--severely decreased GFR (15–29 mL/min/1.73 m^2)
Stage 5--kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis)

A subgroup analysis of the Cholesterol and Recurrent Events (CARE) trial, a secondary prevention trial of pravastatin (Pravachol) vs placebo, showed a similar effect for patients with a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 at baseline.[9]

A meta-analysis of 27 randomized trials (39,704 participants) concluded that, compared with no treatment, statins slowed the loss of GFR by a mean of 1.22 mL/min/year (95% confidence interval 0.44–2.0).[10]

Statins may confer this benefit independently of lipid-lowering. These drugs seem to decrease proteinuria, possibly by improving endothelial function or decreasing inflammation.[11] A meta-analysis (1,384 patients) noted that 13 of 15 published studies found an antiproteinuric effect, with a greater effect in those with greater baseline proteinuria.[12]

The Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease Trial (PLANET) will enroll 345 diabetic patients with proteinuria and hypercholesterolemia and examine the effects of rosuvastatin (Crestor) and atorvastatin on proteinuria and GFR.[13]

Cardioprotective effects in stages 1-4

Since patients with chronic kidney disease were excluded from most of the major statin trials, the best evidence in those with non-dialysis-dependent disease comes from post hoc analysis of data from the CARE study.[14] While this trial excluded patients with more than 2+ proteinuria on dipstick analysis and those with creatinine values greater than 1.5 times the upper limit of normal, 1,711 of the initial 4,159 patients had a creatinine clearance of less than 75 mL/min; the mean creatinine clearance in this subgroup was 61. In this subgroup, pravastatin therapy was associated with a significantly lower risk of cardiovascular death or recurrent nonfatal myocardial infarction (MI) (hazard ratio 0.72, $P < 0.05$).

Similarly, in the 4,491 patients with chronic kidney disease (mean GFR 55 mL/min/1.73 m^2) in the Pravastatin Pooling Project, the hazard of new MI, cardiovascular death, or cardiac intervention was nearly 25% lower in the pravastatin group.[15]

The ongoing Study of Heart and Renal Protection (SHARP),[16] a randomized trial of ezetimibe/simvastatin (Vytorin) that enrolled 6,000 people with stages 3 to 4 kidney disease and 3,000 dialysis patients, will help in determining whether statin therapy prevents new vascular events. The study was launched in 2003 and has now completed enrollment. The primary outcome measure will be the time to first vascular event; secondary analyses will address whether statins decrease proteinuria or slow the progression of kidney disease.

Cardioprotective effects in dialysis patients

The only major randomized trial of statins ever conducted in dialysis patients with diabetes, the German Diabetes and Dialysis Study (4D), did not find atorvastatin 20 mg to have any benefit compared with placebo in reducing a composite end point of death from cardiac causes, stroke, and nonfatal MI over a median of 4 years of follow-up, despite a decrease in LDL-C of over 40% in the treatment group.[17] Adverse events were similar in the two groups. The lack of a detectable benefit may be due to differences in the cardiovascular milieu in dialysis patients, who may have more advanced disease, with preexisting cardiac remodeling and congestive heart failure, which may not be modified to the same extent by statin therapy. Alternatively, the dose of atorvastatin may have been too low, or 4 years of treatment may not be sufficient to detect a benefit in these patients.

Statins may reduce proteinuria and slow the loss of GFR

An ongoing prospective, randomized, placebo-controlled trial in 3,000 hemodialysis patients, called A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: an Assessment of Survival and Cardiovascular Events (AURORA),[18] will help to clarify the role of statins in this population.

CONCLUSION

The National Kidney Foundation guidelines[1,19] note that people with chronic kidney disease are at high risk of cardiovascular disease and therefore should be treated according to guidelines for treating traditional risk factors in high-risk groups. We believe

that those with dyslipidemia who are in stages 1 through 4, particularly those with other risk factors for coronary heart disease, should receive a statin, with an LDL-C target of less than 100 mg/dL, even though we have few data from large trials focused on this population and even though LDL-C may not be the only reason to consider statin use. The pleiotropic effects of statins on proteinuria and progression of kidney function loss may be of benefit in this population as well, although we would not recommend starting a statin solely for these effects until more data are available.

Despite the negative results of the 4D trial, given the relative safety of statins and the lack of any trial data suggesting harm in patients with chronic kidney disease, in our practice we treat dialysis patients with known cardiovascular disease with a statin, with a target LDL-C level less than 100 mg/dL. In dialysis patients without known cardiovascular disease, the use of a statin is even more controversial, and decisions should be made on an individual basis.

Results from the SHARP, AURORA, and PLANET trials, each of which is focused on patients with chronic kidney disease, will help determine whether statins benefit patients at this stage of disease.

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