

Statins for Slowing Kidney Disease Progression: An as yet Unproven Indication

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Statins are among the best-studied medications, with more than 100,000 patients enrolled in randomized trials comparing them with placebo, other lipid-modifying agents, or each other. The available data conclusively indicate that statin treatment reduces cardiovascular event rates in patients at higher than average vascular risk due to hypercholesterolemia, hypertension, prior symptomatic atherosclerosis, or other cardiovascular risk factors.¹

In 2002, the lipid-lowering trial component of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), or ALLHAT-LLT, reported that randomization to receive pravastatin 40 mg daily did not reduce mortality or cardiovascular events among 10,355 people aged 55 years or greater, all of whom had hypertension and dyslipidemia.² On first glance, this result would seem to cast doubt on the cardiovascular benefits of statins. However, closer scrutiny indicates that unique aspects of the design and conduct of ALLHAT-LLT (rather than lack of efficacy for statins generally or pravastatin specifically) may explain the negative result.

In this issue of the *American Journal of Kidney Diseases*, Rahman et al report a post hoc analysis of data from a subgroup of ALLHAT-LLT participants, and compare the risk of kidney disease progression in the pravastatin group with that among controls.³ Like the parent study, this analysis found no benefit of statin treatment, but many of the limitations of the original publication apply also to this post hoc analysis. Nonetheless, this report has implications for future studies of the putative effects of statins on kidney disease. Below, I discuss the interpretation of findings from ALLHAT-LLT generally (and those from Rahman et al specifically), review current evidence suggesting that statins may slow the progression of kidney disease, and briefly discuss 2 relevant ongoing studies.

ALLHAT-LLT was a substudy of ALLHAT, a 4-armed randomized study that compared thiazide diuretics with 3 other antihypertensive regi-

mens. Like the parent study, ALLHAT-LLT included only people who were at least 55 years old and had at least one additional cardiovascular risk factor in addition to stage 1 or 2 hypertension. ALLHAT participants who were already receiving lipid-modifying drugs at baseline or who had a contraindication to the use of statins were excluded from participating in ALLHAT-LLT.

The unique design of ALLHAT-LLT has been discussed in detail elsewhere.⁴ First, unlike many other landmark statin trials, ALLHAT-LLT was an open-label study that compared pravastatin 40 mg daily with “usual care” (which could include a statin). Shortly after ALLHAT-LLT began, results of the Scandinavian Simvastatin Survival Study (4S) were published, and showed for the first time that statin treatment reduced mortality in patients at risk. The resulting changes in clinical practice that followed publication of 4S would have been challenging even for a placebo-controlled trial, and were especially problematic for an open-label study like ALLHAT-LLT. Consequently, the recruitment target for the trial had to be reduced from 20,000 to approximately 10,000 participants (with a commensurate reduction in power). More importantly, by the sixth year of follow-up, fully 23.3% of usual care participants in Rahman et al’s analysis were receiving statin treatment. As with other statin trials, some participants who were randomized to the treatment group discontinued therapy; by the sixth year of follow-up, only 86.6% of these participants were still receiving treatment with any statin.

These drop-in and drop-out effects markedly reduced the power of the trial to show a benefit of statin therapy, as reflected by the modest 0.47 mmol/L difference in low-density lipoprotein (LDL) cholesterol levels between the 2 arms in

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the Rahman et al analysis. Multiple studies have shown a direct relation between cardiovascular risk reduction and the extent of LDL cholesterol reduction, either because LDL cholesterol reduction is itself an important determinant of atherosclerosis (as seems likely), or because LDL cholesterol reduction is a good proxy for exposure to statins.^{1,5} Either way, it is clear that the difference in LDL cholesterol between arms was much less pronounced in ALLHAT-LLT than in other landmark statin trials (typically 1 to 1.5 mmol/L). Finally, even the difference in LDL levels between arms may overestimate the true difference, because on-treatment cholesterol levels were measured only in a subset of participants (10% in the pravastatin group; 5% in the usual care group). Since those returning for testing may have adhered more than average to the study protocols, it is possible that the difference in the overall trial population was even smaller.

How do these caveats influence interpretation of the main findings from ALLHAT-LLT? Since other large trials studying hypertensive patients have shown a cardiovascular benefit of statin therapy,⁶ most observers have concluded that ALLHAT-LLT found no benefit of statin therapy because there was an insufficient difference in LDL cholesterol between the treatment and control groups.

How do these considerations influence interpretation of the analysis by Rahman et al? These authors carefully performed a series of analyses comparing the risk of progression to end-stage renal disease, a 50% loss of kidney function, or a composite of either outcome between treatment groups. Assignment to the pravastatin group did not influence the risk of any of these outcomes. This finding is consistent with findings from a recent meta-analysis⁷ whose authors make the point that these outcomes are relatively infrequent among participants in statin trials (the composite of end-stage renal disease or 50% reduction in glomerular filtration rate [GFR] occurred in 3.5% of ALLHAT-LLT participants).

Rahman et al report that the risk of a 25% decline in estimated GFR and the net change from baseline in GFR also did not significantly differ between treatment groups in ALLHAT-LLT. These findings differ from several previous analyses of placebo-controlled studies, including

a meta-analysis of 39,704 people, nearly 10,000 of whom received pravastatin.⁸ Collectively, this work suggests that statins may reduce proteinuria and the rate of kidney function loss, especially in people with more proteinuria at baseline.⁹ In addition, the apparent benefits on kidney disease were more pronounced with more intensive statin treatment, a finding which is similar to the relation between LDL reduction and cardiovascular benefit.¹⁰

What is the explanation for this discrepancy? It may simply be that drop-in, drop-out, and the low difference in LDL cholesterol between treatment groups in ALLHAT-LLT led to a null result for the kidney disease outcomes, just as it did for the cardiovascular outcomes. As Rahman et al mention, another possibility is that differences in study populations played a role and that ALLHAT-LLT participants had characteristics that made them less likely to benefit from statins (such as less proteinuria, better baseline kidney function, or slower intrinsic renal function loss). Although plausible, these suggestions are speculative.

Leaving ALLHAT-LLT aside for a moment, it may be worth considering the biological rationale for the putative ability of statins to slow kidney disease progression. First, the apparent benefits of statins could be due to their salutary effects on endothelial function,¹¹ potentially enhancing renal perfusion while reducing abnormal permeability to plasma proteins. Since proteinuria and transglomerular protein traffic may lead to kidney disease progression by causing inflammation and fibrosis,¹² reducing proteinuria may be beneficial. Statins may reduce protein traffic across proximal tubular cells by 2 mechanisms: by decreasing proteinuria directly as suggested above, but also by blocking receptor-mediated endocytosis of filtered protein through inhibition of G-protein prenylation.¹³ Second, statins could mitigate the damage due to residual protein traffic by inhibiting the ensuing inflammatory response through NF- κ B-dependent and independent pathways.¹⁴ These latter effects (the nonlipid-mediated or so-called pleiotropic actions) may be important for the beneficial cardiovascular effects of statins, although this is controversial.¹⁵

So, there are potential mechanistic explanations that could support a beneficial effect of

statins on the rate of kidney function loss and proteinuria. Unfortunately, the available clinical data and the experimental evidence are inconclusive to determine whether statins do or do not slow progression of kidney disease in addition to their proven cardiovascular benefits. It is possible that the reportedly lower risk of adverse kidney disease outcomes among statin recipients in previous studies was not driven by effects on the kidney at all, but rather by better renal perfusion due to improved endothelial or cardiac function and/or decreased exposure to events associated with acute renal failure (such as coronary revascularization).

Whether statin treatment reduces the risk of kidney function loss remains to be determined, and future studies are needed. The recently completed ESPLANADE (Statins in Proteinuric Nephropathies) study will soon report whether adding fluvastatin 80 mg daily to combination therapy with benazepril and valsartan reduces proteinuria in people with diabetic nephropathy.¹⁶ Although important, ESPLANADE is based on a surrogate primary outcome. An ideal trial would evaluate whether a statin (as an add-on to conventional therapy) reduces time to doubling of serum creatinine or end-stage renal disease, especially in a high risk population with heavy proteinuria. SHARP (Study of Heart and Renal Protection), which evaluates the benefit of combined simvastatin/ezetimibe therapy versus placebo in people and will include greater than 4,000 participants with non-dialysis-dependent kidney disease, will report in 2009 and offers the best opportunity so far to test this hypothesis.¹⁷

ESPLANADE, SHARP, and other ongoing studies will help to determine whether statins are renoprotective. In the meantime, current data do not support the prescription of statins solely to slow the progression of chronic kidney disease. Physicians should decide whether to prescribe these agents to people with impaired kidney function or proteinuria based on the patient's underlying risk of atherosclerosis.¹⁸

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