DIALYSIS

AURORA confirms lack of statin benefit in dialysis patients

A second, randomized, placebo-controlled trial has failed to demonstrate any beneficial effect of statins on cardiovascular outcomes in patients receiving hemodialysis. Consistent with the findings of the 4D study (Die Deutsche Diabetes Dialyse Studie), AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) shows that rosuvastatin does not reduce the risk of cardiovascular events in these individuals. “These results ... raise the questions of whether statin therapy becomes ineffective with worsening renal disease and, if so, at which stage?” say the AURORA study team.

Lipid lowering has proven benefit in early stages of kidney disease and in renal transplant recipients, and observational data suggest that statin use is cardioprotective in patients receiving dialysis. “Dialysis patients have 20 times greater cardiovascular risk than the general population, but their lipid and LDL cholesterol levels tend to be low,” notes AURORA researcher Alan Jardine, from the British Heart Foundation Glasgow Cardiovascular Research Centre. When AURORA was initiated, therefore, the role of statins in the dialysis population was an “unanswered question”.

AURORA enrolled 2,776 patients aged 50–80 years who had begun maintenance hemodialysis or hemofiltration at least 3 months earlier at one of 280 centers in 25 countries. Use of statins within the preceding 6 months and expectation of kidney transplantation within 1 year were among the exclusion criteria. The investigators randomly assigned participants in a double-blind, 1:1 fashion to receive rosuvastatin 10 mg daily ($n = 1,391$) or placebo ($n = 1,385$).

Despite markedly reducing lipid levels, rosuvastatin had no significant effect on the composite primary end point of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke

or death from a cardiovascular cause): the 804 individuals who experienced an event during follow-up (mean duration 3.2 years) were evenly distributed between the two groups. Similarly, individual major cardiovascular events and the secondary outcome measures of all-cause mortality and death from a noncardiovascular cause were unaffected by rosuvastatin treatment. The drug was not associated with any increase in the risk of hepatotoxic effects or rhabdomyolysis.

In an editorial accompanying the publication of the AURORA results in the *New England Journal of Medicine*, Giovanni Strippoli and Jonathan Craig from the Cochrane Renal Group caution that the trial might have been underpowered to detect a beneficial effect of rosuvastatin. In addition, the high rate of discontinuation (approximately 50%) and the exclusion of patients who were receiving statins (and therefore probably stood to benefit most from treatment) might have contributed to the null result. Of note, the conclusions cannot be applied to young patients (who have particularly elevated cardiovascular risk) or those with low cholesterol levels.

Strippoli and Craig concede, however, that the most likely explanation for the lack of benefit of statins in AURORA is that patients on dialysis have a different type of cardiovascular disease than

individuals with earlier stages of kidney disease. Dialysis patients tend to die of sudden cardiac death or progressive heart failure rather than myocardial infarction. Therefore, uremic cardiomyopathy is likely to be a better target for intervention than lipid lowering. This notion is underscored by the results of the above-mentioned 4D study, in which atorvastatin reduced median LDL cholesterol level by 42%, but failed to significantly improve cardiovascular outcomes in patients with type 2 diabetes on hemodialysis.

Stopping evidence-based statin treatment in a patient who progresses to dialysis would be illogical, says Jardine, but the AURORA findings do suggest that statins should not be initiated automatically in the dialysis setting. Statins “should probably not be used for all dialysis patients just because they are very high-risk for cardiovascular disease,” agrees Alfred Cheung, Executive Director of the Dialysis Program at the University of Utah School of Medicine.

Other ways of reducing cardiovascular risk in the dialysis population—such as optimizing fluid management, blood pressure control and phosphate balance—need to be investigated, according to Jardine. To this end, the AURORA researchers plan to exploit the large bank of serum samples collected during the study as the basis for hypothesis-generating post hoc analyses. Whether the ongoing Study of Heart and Renal Protection (SHARP)—which is evaluating the utility of cholesterol lowering with simvastatin and ezetimibe in a larger and broader population of patients with kidney disease than AURORA—will be stopped as a result of AURORA’s findings remains to be seen.

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