
Sunset for Statins after AURORA?

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Reducing mortality from cardiovascular disease among patients undergoing dialysis is a global public health challenge. The past 10 years have seen trials of many interventions designed to improve survival and cardiovascular outcomes in these patients.¹⁻⁴ Unfortunately, none of these interventions have been shown to be effective, despite beneficial effects in surrogate markers.^{5,6} It appears that statins have now joined this group of “promising but ineffective” interventions.

In this issue of the *Journal*, Fellström et al.⁷ report on the results of A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA). There were no significant effects of rosuvastatin, at a dose of 10 mg per day, in 2776 patients undergoing hemodialysis, either on a composite end point (hazard ratio for the combined end point in the rosuvastatin group, 0.96; 95% confidence interval [CI], 0.84 to 1.11) or on its single components. Yet rosuvastatin low-

ered low-density lipoprotein (LDL) cholesterol levels significantly and with a magnitude that the researchers had predicted. Given the consistent benefits of statins shown in many large trials involving other patients,⁸ the obvious question is why the same benefit was not shown in AURORA.

First, the study may not have had sufficient statistical power. Event rates in the placebo group in AURORA were lower than expected (9.5%, vs. 11.0% anticipated). The basis of the calculation of the sample size was a postulated 25% reduction in event rates, which is consistent with the observed linear relationship between the magnitude of LDL cholesterol lowering with statin therapy as compared with placebo observed in AURORA and the proportional reduction in cardiovascular events in other trials.⁸ The lower bound of the 95% confidence interval for the primary end point was 0.84; hence, the results of AURORA are consistent with a relative reduction in major cardiovascular events of up to 16%, which (with absolute

annual event rates of 10 to 15%) would correspond to about 2 patients with major cardiovascular events avoided per 100 patients treated per year. However, such an interpretation is probably too optimistic, since the point estimates for all the event rates reported in AURORA were close to 1.0 (a null effect). In addition, a previous large trial of statins in patients undergoing hemodialysis, Die Deutsche Diabetes Dialyse Studie (the 4D study), which enrolled only patients with type 2 diabetes, also showed no significant reduction in the same composite end point (relative risk, 0.92; 95% CI, 0.77 to 1.10).

Second, approximately 50% of subjects in AURORA discontinued treatment; this tended to bias the estimated effect toward a null result. The reported differences in lipid levels between the two study groups may be misleading, because not all subjects contributed data at each time point. The real magnitude of these differences across the entire trial may have been substantially lower and may have had an effect on cardiovascular end points that was smaller than expected.

Third, the trial may have excluded patients who were most likely to benefit from statin treatment. Enrollment was limited to patients who had not been treated with statins during the previous 6 months. This group probably included patients with previous cardiovascular events or other evidence of increased risk.

A fourth interpretation is that there really is no cardiovascular benefit of statins in patients undergoing hemodialysis. This lack of benefit may be a function of low baseline LDL cholesterol levels below which statins are ineffective. However, this seems to be an unlikely explanation, given that trials of lipid-lowering agents involving subjects with a wide range of baseline LDL cholesterol levels have been conducted, and the number of cardiovascular events has been consistently reduced.⁸

The most likely explanation is that, as compared with other populations, differences may exist in the causal pathway for early cardiovascular events and death in patients undergoing dialysis. In the general population, cardiac disease is usually caused by atheromatous coronary lesions, whereas about 75% of patients undergoing dialysis have left ventricular hypertrophy and aortic calcification.⁹ In the United States, only about one quarter of deaths from cardiovascular causes among patients undergoing dialysis are attributed

to myocardial infarction, with the remainder attributed to causes for which statins are not indicated: sudden death or death due to arrhythmia.⁹ Lipid lowering with statins has also been shown to be ineffective in improving cardiovascular outcomes in patients with heart failure; in these patients, coronary events such as myocardial infarction are not responsible for most deaths.^{10,11}

Is there a broader message for policymakers, trial investigators, and clinicians? AURORA showed that there is no such thing as a universally valid surrogate, and even the validity of well-established surrogates like LDL cholesterol may vary unexpectedly according to the clinical setting. The benefits of LDL cholesterol reduction are not transferable directly from the general population to patients undergoing hemodialysis, in whom the causal pathway and disease spectrum are very different.

What are the implications for the ongoing Study of Heart and Renal Protection (SHARP), which is also investigating the effect of lipid-lowering therapy in patients with renal disease?¹² One would expect that the data and safety monitoring board and the steering committee will consider the findings of AURORA in detail and will form a view on the science and ethics of continuing the study. SHARP, which involves about 9000 patients, is substantially larger than AURORA. It includes patients who have not undergone dialysis yet, patients who are undergoing peritoneal dialysis, and patients who are undergoing hemodialysis. The patients in SHARP may have received previous statin treatment. Since SHARP is evaluating the effect of combined simvastatin-ezetimibe therapy, it is concerned with an overlapping but different research question.

Does lipid lowering with statins do more good than harm in patients undergoing hemodialysis? The findings of AURORA suggest that it probably does not, although rosuvastatin was not associated with an increased risk of rhabdomyolysis or hepatotoxicity. AURORA also showed no excess risk of stroke, contrary to the findings of the 4D study.¹³ Thus, statins appear to be safe, but their benefits are probably very small at best.

AURORA has shown that the hope of effective interventions to lower cardiovascular risk among patients undergoing hemodialysis remains unrealized. The search is on for more promising interventions for a desperately needy group of people with very poor outcomes. Such interventions need

to be based on a more complete understanding of the causal pathway of cardiac disease in patients undergoing hemodialysis.

Dr. Craig reports being a member of the international steering committee of the Study of Heart and Renal Protection (SHARP). No other potential conflict of interest relevant to this article was reported.

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