tabase, GFR levels were measured longitudinally using creatinine- and cystatin-C-based methods. If cystatin-C is truly a more accurate marker of GFR than serum creatinine,[6] then this design is very attractive because it should give a truer measure of GFR trajectories.

The Peralta *et al.* study had all of the inherently attractive features of all prospective studies that incorporate regularly scheduled assessments of analytes such as kidney function. This being said, some of the design features demand reflection. Despite careful follow-up, the available follow-up time is comparatively small, and the average number of GFR assessments per study subject is modest at approximately 2.8. The study excluded 11% of subjects because creatinine-based estimated GFR ($eGFR_{creatinine}$) was <60 ml/min per 1.73 m^2, and GFR trajectories in the excluded population might be very informative. A unique feature of this study was the diversity of race and ethnicity in the study population. On a cautionary note, GFR estimating equations probably need to be validated in each separate ethnic group. Death also has potential to be a competing event, and comparative death rates were not reported in the study. If, as seems plausible, GFR loss was accelerating between the last available GFR test and death, GFR declines might be underestimated in the subgroup with the highest mortality rate. Incident cases are classically defined with a denominator consisting of the population without the condition of interest. Because subjects with a cystatin-C-based estimated GFR ($eGFR_{cystatin\ C}$) < 60 at baseline were not formally excluded, the proportion of subjects with $eGFR_{creatinine} \geq 60$ and $eGFR_{cystatin\ C} < 60$ may not have been trivial. In addition, the modest numbers of incident cases available probably prevent definitive quantification of racial disparities at this point.

Regarding cystatin-C-based GFR ($GFR_{cystatin\ C}$), an important finding of this study was a more rapid rate of decline in kidney function in African American participants, a disparity that could not be explained by participant characteristics at study inception. Returning to the previously mentioned hypothesis of linear convergence at ESRD from different starting GFRs, it is noteworthy that baseline $GFR_{cystatin\ C}$ levels are identical in African American and Caucasian subgroups at 94 ml/min per 1.73 m^2. The situation for $eGFR_{creatinine}$ could be described as "the same but different": Although GFR loss patterns appear similar when based on serum creatinine, baseline GFR values are clearly lower in Caucasian participants.

Although this paper provides important insights, it appears that we still have a pattern of observations that amounts to "a riddle wrapped in a mystery inside an enigma, but perhaps there is a key."[7] Regarding racial disparities in CKD and trajectories of GFR, this study suggests that models other than linear convergence should be considered.

DISCLOSURES

None.

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Sunrise of Statins after AURORA and 4D?

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Ten years ago, a placebo-controlled trial of statin treatment for hemodialysis patients was considered unethical by many nephrologists. In 2005, to the surprise of many, the results of the 4D study (the German Diabetes and Dialysis Study)[1] demonstrated that lowering LDL cholesterol with atorvastatin (20 mg/d) in 1255 hemodialysis patients with type 2 diabetes did not produce statistically significant reductions in the primary outcome measure. Four years later, AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[2] was hoped to provide clarification of whether LDL

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lowering with rosuvastatin (10 mg/d) would offer any benefit to 2776 hemodialysis patients. Like 4D, the main results of AURORA were negative.

Analyses now are being conducted to find the reasons for these unexpected findings. A different cardiovascular pathology with vascular stiffness, calcification, structural heart disease, and sympathetic overactivity contributing to an increasing risk for cardiac arrhythmia and heart failure was deemed responsible.[3] The results of the Study of Heart and Renal Protection (SHARP)[4] might change this view again, showing a 17% decrease in major atherosclerotic events (coronary event, nonhemorrhagic stroke, any revascularization procedure) with simvastatin and ezetimibe compared with placebo in dialysis-dependent and non–dialysis-dependent patients.

Against this background, Holdaas *et al.*[5] in this issue of *JASN* focus on a subgroup of 731 hemodialysis patients who had diabetes and took part in AURORA. In this *post hoc* analysis (which we refer to as AURORA-diabetes), rosuvastatin significantly reduced the rates of cardiac events combined (cardiac death and nonfatal myocardial infarction [MI]) by 32% (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.51 to 0.90). Analyzing the original AURORA primary end point (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) in AURORA-diabetes, patients showed a larger, albeit NS, 16% relative risk (RR) reduction (HR 0.84; 95% CI 0.65 to 1.07). For comparison, an 8% NS RR reduction for the primary end point (HR 0.92; 95% CI 0.77 to 1.1) was observed in the 4D study. Holdaas *et al.*[5] built the rationale of their analysis on the results of a secondary end point of the 4D study (all cardiac events combined) with a nominal significant reduction by 18% (RR 0.82; 95% CI 0.68 to 0.99). This is similar to the 22% relative reduction in MI or coronary death (HR 0.78; 95% CI 0.69 to 0.87) obtained in the Cholesterol Treatment Trialists (CTT) meta-analysis[6] of 18,686 people with diabetes from 14 randomized statin trials.

We agree that in assessing an anti-atherosclerotic therapy, it would be most logical to examine an end point including nonfatal events such as coronary revascularization and/or ischemic stroke, which are clearly affected by LDL lowering. It would even be more logical in a population such as dialysis patients, in whom there remains uncertainty about the relative contributions of structural heart disease and coronary disease to cardiac death. Thus, it seems reasonable to have chosen both cardiac and cerebrovascular events to be represented within the primary end point. One might vote for picking out hemorrhagic strokes from the primary end point and also nonatherosclerotic cardiac events.

A few questions remain: Why did Holdaas *et al.*[5] embark on this type of *post hoc* research? Was it not to lose an important therapeutic principle for patients in whom cardiovascular protection is highly desired and in whom a small but worthwhile therapeutic proportional benefit of statins would be accepted? In AURORA, the risk for nonfatal stroke was nonsignificantly higher in the active arm, and the effect of treatment, although not significantly different by subgroup of baseline diabetic status, was shifted toward benefit in patients with diabetes (12.6 *versus* 15.1%). So, in hindsight, if one wanted to go in search of a significant benefit, it would be interesting to investigate cardiac events in patients with diabetes. Is this what Holdaas *et al.* have done? They suggest in this exploratory analysis that those who have diabetes and are on dialysis may have reduced risk for cardiac events if taking rosuvastatin. However, interpretation of any *post hoc* analysis should be treated with caution and is at best hypothesis generating rather than hypothesis testing.

Two specific questions arise. First, are the authors suggesting that statins do not work in dialysis patients without diabetes or even cause harm? Diabetes was a prespecified subgroup, but no comparison was made with patients who did not have diabetes at randomization. Because the group without diabetes is substantially larger, the assessment for any treatment effect would be more reliable. By not including this group for comparison, the authors run a risk of misinterpreting the possible effects of treatment. Second, the implication of heterogeneity in treatment effect between dialysis patients with and without diabetes is at odds with the results from SHARP, which did not show significant heterogeneity in their key outcome of major atherosclerotic events by the subgroup of baseline diabetes status. This result, although not solely in dialysis patients, included nearly three times as many participants followed for substantially longer (median 4.9 years; for comparison 2.8 years in AURORA-diabetes, 3.2 years in AURORA, 4 years in 4D) and so is likely to be more reliable. One might also question the statistical power of the secondary analysis when looking at the reduced sample size (26% of the initial trial population) and the lower-than-expected event rate.

Another possible implication is that rosuvastatin affects cardiac events but not stroke. The evidence from the general population (CTT meta-analysis) is that lipid lowering significantly reduces the risk for development of several different manifestations of atherosclerosis (coronary disease, ischemic stroke, coronary revascularizations) and that the significant effects on a combination of these vascular end points are consistent in patients with mildly to moderately reduced GFR and in those with normal GFR (CTT webfigure 10). Therefore, one would expect that ischemic stroke would be reduced by LDL cholesterol lowering, but Holdaas *et al.*[5] do not include this in their *post hoc* analysis. It is possible that as for 4D, the increased rate of stroke observed in the main results is the play of chance, but its lack of inclusion here is surprising. Holdaas *et al.* suggest that end point choice is arbitrary. Rather, it has been defined as follows: "The primary variable . . . should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial."[7] We admit that choosing the appropriate outcome measures in clinical trials is difficult, and even more difficult and with certain variability is the outcome adjudication.

Meta-analysis data from 170,000 participants in large-scale statin trials found statins to reduce the risk for ischemic strokes by 16% (HR 0.84; 95% CI 5 to 26).[8] In SHARP, LDL cholesterol was

lowered by an average of 33 mg/dl, which produced a reduction of 19% in total stroke (HR 0.81; 95% CI 0.66 to 0.99), driven by a 28% reduction in ischemic stroke. There was a NS excess of hemorrhagic stroke (HR 1.21; 95% CI 0.78 to 1.86). AURORA-diabetes showed an excess of hemorrhagic stroke as well (HR 5.21; 95% CI 1.17 to 23.3), but the result is not in keeping with the 4D study (eight *versus* five hemorrhagic strokes in placebo *versus* active), which included more patients with diabetes and followed them for longer. Is this a concern, and should this discourage the use of statins in dialysis patients? A recent meta-analysis suggested that statins might increase the risk for hemorrhagic stroke, but this increase is of the order of 20%, and because the risk for ischemic stroke in most populations is substantially higher, the absolute effect on all stroke is beneficial.[8] Nevertheless, the small number of events (two *versus* 12) in this analysis means that this result should be interpreted with caution.

How does one resolve these issues? The evidence would be stronger if all of the available evidence were included in a meta-analysis of the individual data from AURORA, 4D, and the dialysis patients in SHARP. This might have enough events to assess reliably the effects of statin therapy in patients both with and without diabetes on coronary events as well as stroke. Such an analysis should resolve the questions raised by this study. If there is going to be a sunrise for statins in dialysis patients, this study so far is just the beginning of more to come.

DISCLOSURES

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See related article, "Rosuvastatin in Diabetic Hemodialysis Patients," on pages 1335–1341.

The Fourth Dimension: Associations of Change in Albuminuria over Time

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Albuminuria is a powerful predictor of cardiovascular disease and death in health and a variety of disease states.[1,2] However, once albuminuria has been detected, the value of monitoring changes in excretion rates over time is unclear and has not been tested rigorously. Furthermore, because no studies have directly assessed whether targeted reduction of albuminuria reduces future cardiovascular risk, controversy exists as to whether it may be considered a *modifiable* risk factor, suitable for clinical monitoring and specific intervention.

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