

Rosuvastatin in Patients Undergoing Hemodialysis

TO THE EDITOR: In their article on A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), Fellström et al. (April 2 issue)¹ report little benefit for rosuvastatin in reducing the rates of cardiovascular events and death in patients undergoing hemodialysis. This distinction from the effect in the general population is primarily because the cause of cardiovascular disease in patients undergoing hemodialysis is multifactorial and goes beyond the traditional atherothrombotic mechanisms. Therefore, any study of the use of statins should elaborate on the extent of control of hyperphosphatemia² and hyperparathyroidism,² which affect vascular calcification, and the incidence of hyperhomocysteinemia³ in study patients. In AURORA, the baseline serum phosphorus level of 1.8 mmol per liter (5.6 mg per deciliter) corresponds to the third quintile in the United States Renal Data System study (waves 1, 3, and 4), which showed an already elevated baseline risk (1.13) for adverse cardiovascular events. Similarly, data on the incidence of left ventricular hypertrophy, a powerful predictor of cardiovascular events in patients undergoing hemodialysis,⁴ is missing from AURORA. Given the formidable task of adjusting for so many confounding factors, it is premature to write off the role of statins in protection against cardiovascular disease in patients undergoing hemodialysis.

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TO THE EDITOR: There are two factors that might explain why AURORA did not show a cardiovascular benefit for rosuvastatin in dialysis patients.

First, there was an almost statistically significant predominance of patients with diabetes ($P=0.06$) or diabetic nephropathy as the cause of end-stage renal disease ($P=0.08$) in the rosuvastatin group. Since diabetes is an independent cardiovascular risk factor and statins do not confer any cardiovascular benefit in dialysis patients with diabetes (as shown in the German Diabetes and Dialysis Study¹), this imbalance in AURORA may have masked a beneficial effect of statins in the overall dialysis population. Second, it is known that cardiovascular mortality increases progressively through the early stages of chronic kidney disease and becomes very high in dialysis patients (10 to 30 times as high as that in the general population).² Therefore, it might be too late for statins to provide any benefit in patients with such a high risk of death from cardiovascular causes. Conversely, given the evidence suggesting a benefit for statins in predialysis chronic kidney disease,^{3,4} the forthcoming results of Study of Heart and Renal Protection (SHARP) and the Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease Trial (PLANET) may provide good news about statins in patients with chronic kidney disease not requiring dialysis.

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TO THE EDITOR: AURORA showed no benefit of rosuvastatin in patients with end-stage renal dis-

ease undergoing hemodialysis. Conversely, in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER),¹ which evaluated the same statin in a much larger and healthier population, there was a significant benefit in all cardiovascular end points and total mortality.

It is possible that the devastating effects of hypertension, diabetes, dyslipidemia, and chronic inflammation long before and during end-stage renal disease may mitigate any benefit associated with statins. One other plausible explanation for this great discrepancy of statin effects in people with and without end-stage renal disease is the effect of inadequate dialysis. Large observational studies have shown that the vast majority of patients with end-stage renal disease were undertreated for many important cardiovascular risk factors, such as chronic hypervolemia and hypertension.^{2,3} Prospective, randomized clinical trials that compare not only the hemodialysis regimen but also treatment times and methods are urgently needed⁴ before statins are considered to be useless drugs in patients with end-stage renal disease who are undergoing hemodialysis.

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Dr. de Oliveira reports being an owner of and serving as a staff nephrologist for Clinica DERT, a private, for-profit dialysis unit. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: The pathogenesis of cardiovascular events in patients undergoing hemodialysis is multifactorial, involving calcification, inflammation, and dyslipidemia, although hyperlipidemia is not a risk factor. In our study, we could not demonstrate a beneficial effect of cholesterol reduction with statin therapy in patients undergoing hemodialysis. This may reflect the

lack of association between cholesterol levels and cardiovascular events, but as the correspondents suggest, there may be additional limitations of the study.

Diabetes was the cause of renal failure in 19% of the patients in our study. Diabetes is one of the strongest risk factors for cardiovascular disease in patients with chronic kidney disease; this was also the case in our study. There was a trend toward a treatment benefit for rosuvastatin among patients with diabetes, although the difference in the primary outcome of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction was not statistically significant.

Hyperphosphatemia is an important risk factor contributing to vascular calcification and is not treatable with statins. In our study, a high phosphate level was one of the strongest risk factors for the occurrence of cardiovascular end points. (These results were presented at the World Congress of Nephrology in Milan on May 23, 2009.)

Another important risk factor is inflammation. Levels of high-sensitivity C-reactive protein (hsCRP) were elevated (5 mg per liter) in both study groups, and there was a reduction of 11% from baseline in the group receiving 10 mg of rosuvastatin, whereas the level remained increased in the placebo group. However, the reduction in the rosuvastatin group was less than that in JUPITER (ClinicalTrials.gov number, NCT00239681), and the achieved median levels were higher. Increased baseline hsCRP levels were associated with a risk of major cardiovascular events in our study. It is possible that the lack of a reduction in the rate of cardiovascular events may have been at least partially a consequence of the limited reduction in hsCRP, which in turn may have been a consequence of the causes of elevated hsCRP in this population, including the hemodialysis procedure used rather than inflammation within the atherosclerotic plaque.

The time point for starting treatment may also be important. In our study, only patients over 50 years of age were included. It is possible that younger patients who start statin treatment at an earlier point (e.g., during stages 2 to 4 of chronic kidney disease) might benefit from statin treatment. However, starting treatment with a statin in patients who are over the age of 50 years and who have been undergoing dialysis for 3 to 4 years is not beneficial, probably because the deleterious

vascular consequences of dialysis are irreversible by this stage.

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Cetuximab for Metastatic Colorectal Cancer

TO THE EDITOR: As a gastroenterologist who claims to have been the first physician in Connecticut to give fluorouracil to a patient with colon cancer, I was delighted to read in the Conclusions of the Abstract of the article by Van Cutsem et al. (April 2 issue)¹ that “First-line treatment with cetuximab plus FOLFIRI [irinotecan, fluorouracil, and leucovorin], as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer.” My enthusiasm was tempered when I then read in the Results of the Abstract — and in the body of the article — that “There was no significant difference in the overall survival between the two treatment groups.”

That caveat might well have been required to appear in the Conclusions of the Abstract, lest the wrong overly sanguine impression appear in other publications.

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1. Van Cutsem E, Köhne C-H, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408-17.

TO THE EDITOR: In the study by Van Cutsem et al., the addition of cetuximab to FOLFIRI increased the median progression-free survival from 8.0 months to 8.9 months. This difference, even if it is statistically significant ($P < 0.05$), seems to us to be clinically irrelevant because the 95% confidence intervals of the separate estimations are overlapping. Furthermore, the emphasis given to the results of a retrospective subgroup analysis to investigate the influence of the tumor *KRAS* mutation status on outcome appears to be unjustified, not only because it was performed in 540 of 1198 patients who were not randomly selected (45%), but also because the interaction was not significant ($P = 0.07$); thus, the difference could have

been due to chance. Instead of considering this result as a hypothesis for a prospective randomized trial, the authors, as well as the National Cancer Comprehensive Network guidelines for colorectal cancer, a provisional clinical opinion of the American Society of Clinical Oncology,¹ and, even worse, the European Medicines Agency, which all have approved the use of cetuximab only in patients with *KRAS* wild-type tumors, seem to accept these results without criticism. We are afraid that this lack of criticism could contribute to acceleration of the process that is leading clinical studies away from the standards of scientific research.

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TO THE EDITOR: The trial exploring the effect of first-line treatment with cetuximab plus chemotherapy and the association between the *KRAS* gene mutation and the clinical response to cetuximab provides the opportunity to speculate about the predictive and prognostic role of the *KRAS* mutation status of tumors. The results are consistent with those of studies showing that the benefit of cetuximab is limited to patients with *KRAS* wild-type tumors.^{1,2} *KRAS* mutation status seems not to be prognostic in patients receiving