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Scientific Update™

Effect of Rosuvastatin on Cardiovascular Outcomes in Patients on Chronic Hemodialysis: The AURORA Study

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An educational report from a late-breaking clinical trials presentation at the 58th Annual Scientific Session of the American College of Cardiology (ACC 09)

March 29-31, 2009 Orlando, Florida

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Cardiovascular disease (CVD) is the single largest cause of premature mortality in patients with end-stage renal disease (ESRD). Although the beneficial effects of statins (hydroxy-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) in reducing CV morbidity and mortality in a variety of patient population is well-known, patients with ESRD have usually been excluded from outcome studies with statins because of their related comorbidities and issues over pharmacokinetics and safety. Observational studies suggest that in patients undergoing hemodialysis, statin therapy is also associated with improved survival, but benefits from statin therapy in these patients remained unproven. AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events) was the first large-scale international trial to assess the effects of a statin on CV morbidity and mortality in patients with ESRD on chronic hemodialysis, irrespective of baseline lipid levels. The results of AURORA and their clinical implications are the subject of this issue of *Cardiology Scientific Update*.

ESRD is the most advanced stage of chronic kidney disease (CKD). CVD is prevalent in patients with ESRD and is the single largest cause of premature mortality in this patient group.[1,2] Patients with ESRD undergoing maintenance hemodialysis (HD) have a particularly high risk for premature CVD.[3] Landmark trials have established the beneficial effect of statins in reducing CV morbidity and mortality.[4-10] Reductions in CV events have also been observed in patients receiving treatment with statins, but without elevated cholesterol levels.[5,6,9,11] A number of patients on HD do not have elevated total cholesterol or low-density lipoprotein cholesterol levels (LDL-C), but they have other atherogenic lipid abnormalities, including low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG), and a higher proportion of intermediate and small, dense LDL particles.[12] Furthermore, oxidative stress, endothelial dysfunction, and inflammation are all associated with reduced renal function and dialysis in patients with ESRD;[13,14] these conditions can promote atherosclerosis. Traditionally, patients with ESRD have been excluded from outcome studies of statins because of their related comorbidities and concerns over safety and uncertain pharmacokinetics. However, observational data, such as those from the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Wave-2 study, suggest that statin treatment may improve survival in patients with ESRD.[15] As a result, there was a need for randomized, controlled data from long-term studies of patients with ESRD to define the role of statins on CV outcomes in these patients. The AURORA study was designed to assess the effects of a statin on CV morbidity and mortality in patients with ESRD on chronic HD, irrespective of baseline lipid levels.

The study design and protocol of AURORA have been reported previously.[16] AURORA was a randomized, double-blind, multicentre, parallel-group, international, Phase IIIb trial (Figure 1). In brief, men and women 50 to 80 years of age who had ESRD and had been treated with regular HD or hemofiltration for at least 3 months were recruited from 280 centres in 25 countries. Major exclusion criteria included statin therapy within the previous 6 months, expected kidney transplantation within 1 year, and serious hematologic, neoplastic, gastrointestinal, infectious, or metabolic disease (excluding diabetes) predicted to limit life expectancy to <1 year. The primary endpoint was the time to a major adjudicated CV event, defined as a nonfatal myocardial infarction (MI), nonfatal stroke, or death from CV causes. Secondary endpoints

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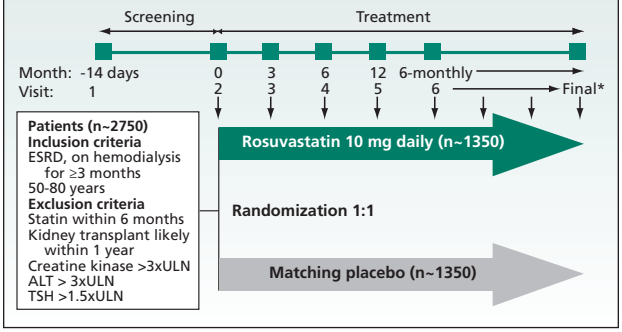
Figure 1: AURORA study design[16]



* Study medication was administered until ~620 patients had experienced a major cardiovascular (CV) event

ESRD = end-stage renal disease; ULN = upper limit of normal; ALT = alanine aminotransferase; TSH = thyroid-stimulating hormone

included all-cause mortality, CV event-free survival (freedom from nonfatal MI, nonfatal stroke, death from CV causes, and death from any other cause), procedures performed for stenosis or thrombosis of the vascular access for long-term hemodialysis (arteriovenous fistulas and grafts), and coronary or peripheral revascularization.

The primary results of AURORA were recently presented at a late-breaking clinical trials session of ACC.09 and published the same day.[17] Between January 2003 and December 2004, 3021 patients were screened and 2776 patients were randomly assigned to double-blind treatment with rosuvastatin at a dose of 10 mg (n=1391) or placebo (n=1385 patients). A total of 245 patients did not undergo randomization, leaving a total of 2773 patients in the intention-to-treat population. The 2 groups were similar with respect to baseline characteristics including the duration of dialysis therapy (Table 1).[18] The mean length of follow-up was 3.2 years and no patients were lost to follow up. The changes in lipids and high sensitivity C-reactive protein (hs-CRP) are shown in Figure 2. Rosuvastatin therapy resulted in greater total cholesterol, LDL-C, TG, and hs-CRP protein reduction than placebo. At 3 months, the median hs-CRP level, which was elevated at baseline, had decreased by 12% in the rosuvastatin group.

The results for the primary endpoint, ie, time to a major CV event, are shown in Figure 3. There were no significant differences in the primary composite endpoint of time to CV death, nonfatal MI, or stroke (9.2 vs 9.5 events per 100 patient-years, $P = 0.59$). In addition, no significant differences were observed in the individual endpoints of CV death (7.2 vs 7.3 events/100 patient-years, $P = 0.97$), nonfatal MI (2.1 vs 2.5 events/100 patient-years, $P = 0.23$), or nonfatal stroke (1.2 vs 1.1 events/100 patient-years, $P = 0.42$), or in the secondary endpoints (Figure 4). Per-protocol analysis demonstrated no effect of rosuvastatin on the primary composite endpoint and the prespecified subgroup analysis was unable to identify any subgroup of patients who achieved significant benefit from rosuvastatin therapy with respect to the primary endpoint. No relationship was found between the primary CV endpoint and either baseline LDL-C (hazard ratio [HR] per 0.03 mmol/L, 1.00; 95% CI, 0.82 to 1.29; $P = 0.83$) or LDL-C levels at 3 months (HR 0.95; 95% confidence interval [CI], 0.83 to 1.09; $P = 0.48$). Adverse events were reported in 1338 patients who received rosuvastatin (96%) and in 1332 patients who received placebo (97%). Serious adverse events were reported in 82% of patients who received rosuvastatin and in 84% of patients who received placebo.

Table 1: Baseline characteristics[17]

Parameter*	Rosuvastatin (n=1389)	Placebo (n=1384)
Female gender, n (%)	538 (39)	512 (37)
Age, years	64 ± 8.6	64 ± 8.7
Caucasian, n (%)	1174 (85)	1180 (85)
Body-mass index, kg/m^2	25.4 ± 4.7	25.4 ± 5.1
Mean systolic/diastolic BP, mm Hg	137/76	137/76
Current smoker, n (%)	202 (15)	227 (16)
Time on hemodialysis, years	3.5 ± 3.9	3.5 ± 3.8
Dialysis, hours/week	11.9 ± 1.8	11.9 ± 1.8
Cause of ESRD, n (%)		
Nephrosclerosis	273 (20)	281 (20)
Glomerulonephritis/vasculitis	250 (18)	262 (19)
Diabetes	286 (21)	249 (18)
Tubulointerstitial disease	206 (15)	193 (14)
Hereditary	171 (12)	185 (13)
Other	203 (15)	214 (15)

* All values are means ± standard deviation unless stated otherwise
BP = blood pressure
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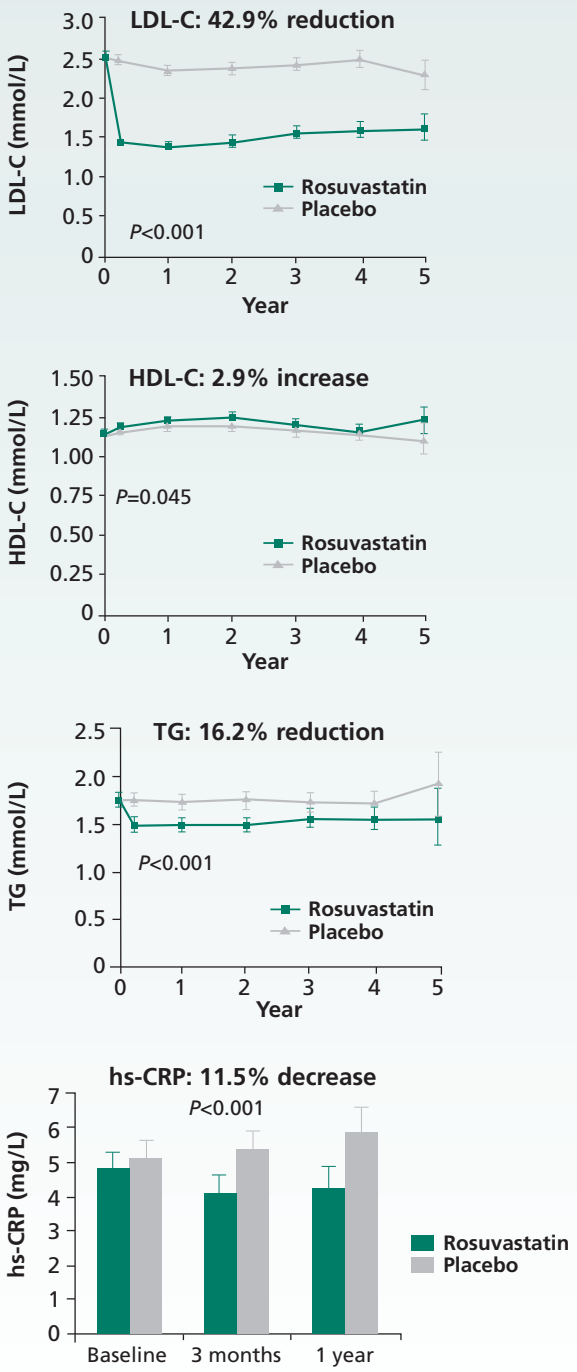
Discussion and clinical implications

The AURORA trial is the largest study to date examining CV outcomes in patients with ESRD on maintenance HD. In AURORA, initiation of rosuvastatin did not cause a reduction in the combined endpoint of CV death, MI or stroke, even though LDL-C was significantly reduced. The Deutsche Diabetes Dialysis Study (4D),[19] conducted in 1255 patients with diabetes mellitus receiving maintenance HD, demonstrated no reduction in primary endpoint of death from cardiac causes, nonfatal MI, and stroke compared with placebo. However, rates of fatal stroke were higher in the atorvastatin group despite finding no difference in nonfatal stroke. The results from AURORA, a larger trial of rosuvastatin therapy, complement the findings of the 4D trial and suggest that patients with ESRD receiving HD may not benefit from the initiation of statin therapy. Other trials, examining CV outcomes in patients with CKD, have involved predominantly *post hoc* assessments of a subgroup of CKD patients from larger clinical trials,[20,21] or renal transplantation patients[22] and, in some of these studies, statin therapy was shown to reduce the incidence of CV events.[9,23,24] These seemingly contradictory findings raise intriguing questions:

Figure 2: Changes in lipids and hs-CRP[17]



Values are means (95% CI) for LDL-C, TG and HDL-C and medians (95% CI) for Hs-CRP; % change from baseline at 3 months is quoted and *p* values are for change at 3 months versus placebo. LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; hs-CRP = high sensitivity C-reactive protein; CI = confidence interval.
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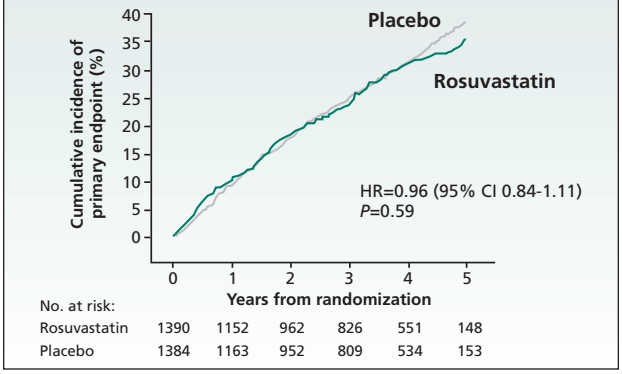
Figure 3: Kaplan-Meier curves for the primary endpoint (first major CV event)[17]



HR = hazard risk
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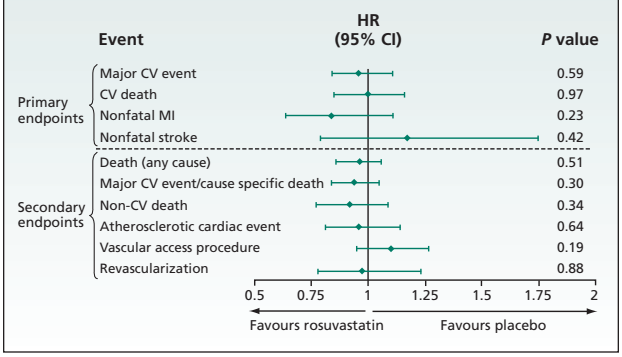
- Does statin therapy become ineffective with renal disease progression, and if so, at what stage of the disease does it become ineffective?
- Does maintenance HD itself have an impact on the response to statins?
- Do increased oxidative stress, endothelial dysfunction, vascular calcification, and increased inflammation associated with reduced renal function and dialysis reduce the response to statins in patients with ESRD?[13,14]

These questions may hopefully be answered by the ongoing Study of Heart and Renal Protection (SHARP);[25] this trial is evaluating the benefit of simvastatin plus ezetimibe in patients exhibiting a broad spectrum of renal dysfunction.

Several other practical considerations in AURORA may be relevant to physicians' interpretation of the trial results, and warrant further discussion. First, the dose of rosuvastatin, namely 10 mg daily, was relatively low, probably due to safety considerations for an HD population. A higher dose, ie, 20 mg daily, was used in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[11] Therefore, a positive effect cannot be ruled out if a higher

Figure 4: Primary and secondary endpoints[17]



MI = myocardial infarction

dose of rosuvastatin was used. Second, by study design, patients were excluded if they were already on statin treatment, were considered by the investigator to have an indication for open statin treatment, or if they were <50 years old. The first 2 exclusion criteria may have created a selection bias by excluding patients who already had, or were deemed a high risk for CV events. It is known that increased CV risks affect all age groups of patients undergoing HD therapy and is disproportionately higher among younger patients.[1] Thus, the possible benefits of rosuvastatin in younger HD patients who were represented in AURORA could not be ruled out. Third, approximately 50% of subjects discontinued treatment, which may bias the estimated effect towards a null result. Fourth, the mechanisms for adverse CV events differ between HD patients and those in the general population with heart disease. For example, in the US only one-quarter of the CV deaths in patients undergoing HD are attributable to MI, with the remainder attributable to causes such as sudden death or heart failure, and statins may not be useful in those cases.[26,27] Finally, the use of statins appears to be relatively safe in the ESRD patient population. There was no increase in rhabdomyolysis, liver disease, cancer, stroke, or new onset diabetes, as had been suspected in previous trials.[11,19,28]

Summary

Rosuvastatin (10 mg daily) does not reduce adverse CV events in patients with ESRD undergoing maintenance HD; therefore, the benefits of LDL-C lowering are not directly transferable from the traditional high-risk patients to patients with ESRD undergoing HD. On the other hand, these observations should not change the practice of physicians in prescribing statins to patients who are deemed high risk for CV events.

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Dr. Moe states that he has no disclosures to announce in association with the contents of this issue.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from AstraZeneca to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.

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