Rosuvastatin Slows Carotid Atherosclerosis in Low-Risk Patients

**BY MARY ANN MOON**

**Los Angeles Bureau**

**NEW ORLEANS**—Rosuvastatin slowed the progression of carotid intima-media thickness in asymptomatic subjects at low risk of cardiovascular events but who nonetheless had subclinical atherosclerosis, Dr. John R. Crouse III reported at the American College of Cardiology meeting. DTI already has a role for assessing patients with hypertension to determine whether high blood pressure has begun to impair heart relaxation, which can lead to diastolic dysfunction and heart failure.

"If a patient has a DTI abnormality and even mild hypertension, it makes more aggressive [about reducing] blood pressure," he said in an interview.

Most Doppler echocardiography units made in recent years can assess DTI. The most robust measure of DTI to gauge heart relaxation is E' (E prime), the measure of the heart's early relaxation velocity. The study that Dr. Solomon reported at the meeting was designed to test whether blood pressure reduction using the angiotensin receptor blocker valsartan was especially effective for improving E', compared with other antihypertensive drugs associated with hypertensin and an impaired relaxation velocity.

The underlying hypothesis was that a drug that reduces activation of the renin-angiotensin aldosterone system (RAAS) would be more effective than other antihypertensive medications for reducing left ventricular hypertrophy and fibrosis and thereby improving diastolic function. The val- sartan in Diastolic Dysfunction study was sponsored by Novartis, which markets valsartan ( Diovan). Dr. Solomon is a consultant to and has received honoraria from Novartis. The study involved 384 patients aged 45 years or older with stage 1 or 2 hypertension, who also showed diastolic dysfunction based on their later- al E' measure. The average E' reading for all patients in the study was 7.5 cm/second, substantially below the normal level for age (see table). The group assigned to receive valsartan had an average E' level comparable with that of a 76-year-old person with no history of hypertension, Dr. Solomon said. Their average blood pressure at entry was about 144/86 mm Hg, and their average left ventricular ejection fraction was about 57%. About 4% of the patients had left ventricular hypertrophy.

The two groups were randomized to two different antihypertensive regimens. One group received as its primary drug 320 mg/day of val- sartan, followed by other, non- RAAS-affecting drugs as needed to reach a goal blood pressure of less than 135/80 mm Hg. The second group had the same goal blood pressure but did not receive any drugs that affect the RAAS.

Native agents were used in this order: a diuretic, β-blocker, calcium channel blocker, and α-blocker. The control pa- tients significantly more antihypertensive med- ications, especially diuretics and calcium channel blockers. After 9 months of treatment, the average blood pressure was 129/78 mm Hg in the patients treated with valsartan, and an average of 134/82 in the patients who did not get an RAAS-active drug. Follow-up DTI data were available for 341 patients. The study’s primary end point was an improvement in the E’ measure, which rose by an average of 0.60 cm/second in patients treated with valsartan and by an average of 0.44 cm/second in the control patients. The differ- ence between average improvements in the two groups was not statistically significant. But E’ was significantly improved over baseline levels in both groups, indicating that lowering blood pressure improves diastolic function.

The two groups did show a significant difference in two secondary efficacy measures made using DTI. Both the iso- tensional and systolic contraction velocity showed improvements that were significantly greater in the valsartan group, compared with the control patients.

**Normal Heart Relaxation Velocity**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>E'</th>
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</thead>
<tbody>
<tr>
<td>45-55</td>
<td>≥10 cm/sec</td>
</tr>
<tr>
<td>56-65</td>
<td>≥9 cm/sec</td>
</tr>
<tr>
<td>66-75</td>
<td>≥8 cm/sec</td>
</tr>
</tbody>
</table>

Note: Patients with an E' that is below these age-specific levels have diastolic dysfunction.

**Source:** Dr. Solomon

The significant difference in progres- sion between the placebo and rosuvastatin groups persisted across all clinical sub- groups, regardless of subject age, sex, geographical location, race, body mass index, risk factors, blood pressure levels, or lipid levels, Dr. Crouse said.

Rosuvastatin did not induce regression of carotid atherosclerosis, as it has been shown to do in previous studies involving patients with more advanced disease. This was focused on low-risk participants with- out advanced atherosclerosis, and this may have limited the opportunity to achieve disease regression," Dr. Crouse said.

LDL cholesterol declined by 49% and HDL cholesterol increased by 8% in patients taking rosuvastatin during the 2-year study. The frequency of adverse events was simi- lar between the two groups, and most were of mild or moderate severity. Myalgia was the most commonly reported adverse event.

In an editorial comment accompanying the published report, Dr. Michael S. Lauer of the Cleveland Clinic Heart Center said, "At first glance, the METEOR findings sug- gest there may be a role for routine arteri- al imaging in low-risk people, and that rosuvastatin therapy may be warrant- ed for those found to have increased carotid intima-media thickness. But this would be "a radically different approach to primary prevention than that recommended by current guidelines," and the results clearly do not justify such a change, he said (JAMA 2007;297:1376-8).

For one thing, carotid intima-media thickness is merely a surrogate end point for clinical events, and the medical literature is rife with "numerous bad experiences whereby agents that improved surrogate end points yielded no benefit or were even found to cause harm when tested for their ability to prevent clinical events. Classic ex- amples of this include vitamin E and post- menopausal hormone therapy," he wrote.

Moreover, there is only limited evidence that statin-induced changes in carotid intima-media thickness actually correlate with a decrease in atherosclerotic events.

The METEOR study had two addition- al weaknesses. "A fair number of enrolled patients failed to complete the protocol and were lost to follow-up. . . .[A] higher rate of follow-up clearly would have increased the credibility of the findings," he noted.

And the study was not powered to eval- uate the drug’s effect on clinical events. In nearly 1,000 subjects, only six ischemic events occurred—all of them, "curiously," in subjects taking the study drug. Ambi- tous event-based randomized trials involv- ing large numbers of patients and commu- nities must be done," Dr. Lauer said.