AVALON-AWC: Arterial Wall Compliance in the Atorvastatin and Amlodipine in Patients With Elevated Lipids and Hypertension Trial

Disclosures

Linda Brookes, MSc

Presenter: Jay N. Cohn, MD (University of Minnesota, Minneapolis)

A substudy of the Atorvastatin and Amlodipine in Patients With Elevated Lipids and Hypertension (AVALON) trial suggests that greater early vascular benefit can be achieved by treating hypertension and dyslipidemia simultaneously with a combination of amlodipine and atorvastatin, respectively, than treatment with either atorvastatin or amlodipine alone. This combination may result in a synergistic effect that confers additional vascular protection and reduction of cardiovascular events, the trial investigators believe.

The AVALON Arterial Wall Compliance (AVALON-AWC) trial was based on a unique methodology for measuring the luminal elasticity of both the large and small arteries of patients before and after treatment. This allows early identification of loss of elasticity, which is important because premature arterial stiffening is an apparent marker for the early onset of cardiovascular disease.

AVALON

The main AVALON study, the results of which were reported last year at the 20th Scientific Meeting of the International Society of Hypertension in São Paulo, Brazil, showed that amlodipine 5 mg administered once daily in combination with atorvastatin 10 mg is an effective treatment for concomitant hypertension/dyslipidemia. The double-blind, randomized trial compared the amlodipine/atorvastatin fixed-dose combination with atorvastatin 10 mg alone, amlodipine 5 mg alone, or placebo each administered daily in adults with hypertension and dyslipidemia. After 8 weeks of treatment, significantly more patients on the combination treatment achieved either their blood pressure goals, as defined by the sixth report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC VI) or their LDL-cholesterol goals, as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, or both goals compared with patients on amlodipine or atorvastatin alone.

AVALON-AWC

The AVALON-AWC study was based on the hypothesis that because the lipid-lowering agent atorvastatin and the calcium-channel blocker amlodipine have each been shown to have beneficial effects on the endothelium in vitro, they may have a greater effect on endothelial function and arterial compliance when administered together.

To assess endothelial effects in vivo, a novel device (HDI/PulseWave CR-2000; Hypertension Diagnostics; Eagan, Minnesota) that uses a noninvasive system incorporating proprietary blood pressure waveform analysis methodology was used. Developed by Jay Cohn, MD (who has a proprietary interest in the device), the methodology is based on the decay of pressure in the radial artery with time. The device measures the pressure wave peak in systole, then as it decays in diastole. The resulting waveform has 2 peaks in the diastole portion of the decay wave, the first representing the restrictive compliance of the large arteries (C1), and the second smaller peak representing the compliance of the small arteries (C2). The 2 measures of arterial wall compliance (C1 and C2) were assessed at baseline and at 8 weeks, as part of the larger, longer-term AVALON trial.

Of the 847 patients randomized in the main AVALON trial, 667 (404 men and 263 women) at 103 centers agreed to participate in the AVALON-AWC trial. These patients were between 24 and 76 years of age and they all had concomitant hypertension, defined as systolic blood pressure (SBP) 130-179 mmHg and/or diastolic blood pressure (DBP) 85-109 mmHg, and dyslipidemia, defined as LDL-cholesterol 100-250 mg/dL.
**Blood Pressure and LDL-Cholesterol**

In the AVALON-AWC population, systolic blood pressure (SBP), diastolic blood pressure (DBP), and LDL-cholesterol were similar at baseline in all 4 treatment groups (Table 1).

**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Mean value</th>
<th>Amlodipine + Atorvastatin</th>
<th>Amlodipine</th>
<th>Atorvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55.6</td>
<td>56.3</td>
<td>55.3</td>
<td>55.8</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67</td>
<td>55</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>146.3</td>
<td>147.7</td>
<td>146.7</td>
<td>147.0</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>92.7</td>
<td>92.8</td>
<td>91.8</td>
<td>93.0</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>165.4</td>
<td>164.5</td>
<td>161.7</td>
<td>163.0</td>
</tr>
</tbody>
</table>

*DBP = diastolic blood pressure; LDL = low-density lipoprotein; SBP = systolic blood pressure*

After 8 weeks of treatment, SBP and DBP reductions with amlodipine or amlodipine plus atorvastatin were significantly greater than with placebo or atorvastatin alone (Table 2). Similar significant reductions in LDL-cholesterol were seen in the atorvastatin and amlodipine-plus-atorvastatin groups compared with placebo and amlodipine alone.

**Table 2. Mean Changes in Blood Pressure and LDL From Baseline to Week 8**

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine + Atorvastatin</th>
<th>Amlodipine</th>
<th>Atorvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>-12.9*</td>
<td>-15.0*</td>
<td>-6.7</td>
<td>-5.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-8.4*</td>
<td>-8.7*</td>
<td>-4.3</td>
<td>-3.4</td>
</tr>
<tr>
<td>LDL-cholesterol (%)</td>
<td>-37.5†</td>
<td>-3.1†</td>
<td>-34.5†</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

*P < .0001 vs atorvastatin; P < .0001 vs placebo*  
†P < .0001 vs amlodipine; P < .0001 vs placebo*  
‡P = .02 vs placebo*

**Arterial Wall Compliance**

C1 (large artery elasticity) and C2 (small artery elasticity) values were similar at baseline in all 4 treatment groups. Mean C1 was about 12.5 mL/mmHg x 100, a low normal value for a typical population with a mean age of about 55 years. C2 was significantly lower than normal for men and women, consistent with values in individuals with vascular disease (hypertension and dyslipidemia).

After 8 weeks of treatment, both C1 and C2 were significantly increased with amlodipine plus atorvastatin and amlodipine alone compared with baseline and with placebo, but these effects were greater in the amlodipine-plus-atorvastatin group. C1 increased by 10% in both the combination and amlodipine groups. The increase in C2 with amlodipine plus atorvastatin at 8 weeks (about 19.6%) was highly significant compared with baseline, and was also significant when compared with amlodipine alone (Table 3).

**Table 3. Changes in Small Artery Compliance (C2) Between Baseline and 8 Weeks**

Over the following 8 weeks of the trial, when all patients were given amlodipine 5 mg plus atorvastatin 10 mg, C2 showed a continued dramatic improvement in all patients.

**Implications**

The increase in C1 was largely due to the reduction in SBP, Dr. Cohn believes. In contrast, amlodipine produces an early improvement in C2, suggesting improved endothelial function. This effect is greater, and sustained, when atorvastatin is coadministered with amlodipine.

The results of the AVALON-AWC study are consistent with preliminary data reported from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[6] which suggested that there was a greater reduction in vascular events with amlodipine-based antihypertensive therapy and an additive benefit with atorvastatin vs placebo.

**Amlodipine/Atorvastatin**

Tablets containing a combination of amlodipine and atorvastatin are available in the United States, Mexico, and a number of countries in Latin America and Asia. Caduet (Pfizer; New York, NY) is indicated in patients for whom both amlodipine besylate and atorvastatin calcium are appropriate and is available in multiple dosage strengths. Caduet was submitted for marketing approval in Europe in 2003. In September 2004, a change to US prescribing information for Caduet was approved to include prevention of cardiovascular disease.

Supported by an independent educational grant from Pfizer.

**References**


<table>
<thead>
<tr>
<th>C2 (mL/mmHg × 100)</th>
<th>Amlodipine + Atorvastatin</th>
<th>Amlodipine</th>
<th>Atorvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.61</td>
<td>4.26</td>
<td>4.52</td>
<td>4.72</td>
</tr>
<tr>
<td>8 weeks</td>
<td>5.50</td>
<td>4.76</td>
<td>4.66</td>
<td>4.66</td>
</tr>
<tr>
<td>Change</td>
<td>0.91*</td>
<td>0.45†</td>
<td>0.13</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

*P < .001 vs placebo, P < .0298 vs amlodipine
†P < .05 vs placebo