Atorvastatin Treatment Is Associated With Less Augmentation of the Carotid Pressure Waveform in Hypertension
A Substudy of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT)

Charlotte Manisty, Jamil Mayet, Robyn J. Tapp, Peter S. Sever, Neil Poulter, Simon A. McG. Thom, Alun D. Hughes; on behalf of the ASCOT Investigators

Abstract—Hydroxymethylglutaryl-CoA reductase inhibitors (statins) reduce cardiovascular events in hypertensive subjects, but their effect on carotid BP, pressure augmentation, and wave reflection is unknown. We compared the effect of atorvastatin with placebo in a substudy of the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA). Hypertensive patients (n=142; age=43 to 79 years; 127 male) with total cholesterol ≤6.5 mmol/L were randomized to atorvastatin 10 mg or placebo. Carotid BP and flow velocity were measured by tonometry and Doppler ultrasound. Augmentation index (carotid AIx) was calculated, and waveforms were separated into backward and forward components by wave intensity analysis. Brachial BP was similar in atorvastatin and placebo groups. Carotid AIx and augmentation pressure were significantly less in patients randomized to atorvastatin (mean [SD]: 21.7 [12.1] versus 25.9 [10.3] %; \( P = 0.027 \) and 10.2 [6.5] versus 13.1 [6.6] mm Hg; \( P = 0.016 \), respectively), and atorvastatin treatment was associated with significantly less wave reflection from the body. Carotid systolic BP was slightly lower in the atorvastatin group, but there was a statistically significant interaction between lipid-lowering and antihypertensive regimen with lower carotid systolic BP in patients randomized to amloidipine-based therapy and atorvastatin. Carotid wave velocity, timings of waves, and wave intensities did not differ significantly between atorvastatin and placebo groups. Atorvastatin treatment is associated with less augmentation of the carotid BP waveform and less wave reflection from the body. This could contribute to the reduction in risk of cardiovascular events by statins. (Hypertension. 2009; 54:1009-1013.)

Key Words: blood pressure ■ waves ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ cholesterol ■ tonometry ■ Doppler ultrasound

Inhibitors of hydroxymethylglutaryl CoA (statins) are widely prescribed, and there is extensive evidence showing that they prevent cardiovascular disease.\(^1\) Recently it has been suggested that statins, in addition to their ability to reduce low-density lipoprotein (LDL) cholesterol, may reduce blood pressure (BP).\(^2,3\) Further, evidence from a recent meta-analysis\(^4\) suggests that this effect is small, but could complement the primary effects of statins on serum cholesterol levels.

Measurement of brachial BP is a long-established technique, but it is recognized that brachial and central (aortic) systolic BP differ, sometimes markedly.\(^5\) These differences are proposed to arise from differences in augmentation of the systolic pressure waveform attributable to wave reflection.\(^6\) Importantly, a number of recent studies have shown that antihypertensive agents differentially affect central and brachial blood pressures,\(^7,8\) and it has been suggested that these differences could account for variations in cardiovascular outcomes between therapies. As yet, the possible effects of statins on carotid blood pressure have not been described.

The Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) examined the effect of 2 antihypertensive regimens (amlodipine- versus atenolol-based) and atorvastatin on cardiovascular events using a factorial design.\(^9\) This study therefore offered an opportunity to test whether atorvastatin affected the central blood pressure, pressure augmentation, and wave reflection in the context of a large prospective randomized hypertension treatment trial.

Methods

Participants

Individuals (n=142) who were eligible for the factorial lipid-lowering arm of ASCOT (ASCOT-LLA)\(^9,10\) participated in a carotid BP substudy based at St Mary’s Hospital, London, UK. Participants had a total blood cholesterol concentration ≤6.5 mmol/L and were not receiving lipid lowering agents at the time of randomization. All

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subjects recruited into ASCOT-LLA fulfilled the criteria for inclusion in the main ASCOT study and were randomized to receive atorvastatin 10 mg daily or matching placebo. In addition, all subjects were randomized to a regimen of amiodipine with perindopril added as required, or a regimen of atenolol with bendroflumethiazide-K added as required in a factorial design.13 Antihypertensive treatment was titrated to achieve target blood pressures (<140/90 mm Hg for people without diabetes and <130/80 mm Hg for people with diabetes). If necessary, additional antihypertensive agents were administered according to a prespecified algorithm.10

All measurements for the substudy were performed between 12 to 18 months after randomization, when on-treatment blood pressures were relatively stable. The study was approved by the St Mary's Hospital Research Ethics Committee and all subjects gave written informed consent.

Investigations

Brachial blood pressure was measured in the seated position after at least 5 minutes rest using a validated semiautomated device (Omron HEM 705CP, Omron). All other measurements were performed in a temperature-controlled darkened room, with subjects having rested supine for at least 10 minutes. Applanation tonometry was performed on the right common carotid using a Millar tonometer (SPT-301, Millar Instruments Inc) and calibrated to brachial artery pressure as previously described.11 Carotid tonometry was successful in all individuals. Carotid artery flow velocity measurements were made approximately 2 cm from the right carotid bulb by pulsed wave Doppler with an HDI 5000 ultrasound machine (Philips Medical Systems) equipped with a 7.5 to 10 MHz linear array transducer at a Doppler angle of 60°. Carotid pressure and flow velocity were sampled at a frequency of 200 Hz, and waveforms were ensemble averaged for each of six cardiac cycles to reduce random error. Both pressure and flow data from at least 6 cardiac cycles were acquired, digitized, and analyzed off-line using a custom-designed software package in Matlab 5.3 (Mathworks).

Echocardiography was performed on all patients using an HDI 5000 ultrasound machine. Measurements were made in accordance with the American Society of Echocardiography guidelines.12 Arterial compliance was estimated as stroke volume (SV)/carotid pulse pressure (cPP). Blood was taken for analysis of plasma glucose and serum lipids, creatinine C-reactive protein (CRP), and serum amyloid A (SAA). Details of the analytic assays for CRP and SAA have been reported previously.13 Diabetes was diagnosed on the basis of a fasting plasma glucose of >7.0 mmol/l or a previous diagnosis of diabetes mellitus.14

Wave Intensity and Pressure Waveform Analysis

Wave intensity analysis was performed and waves were separated into forward and backward components as previously described.15,16 Local wave velocity was calculated using the pressure-velocity loop method, a validated method for measuring local wave velocity.17 Waves were identified by measuring the integral under the wave (cumulative wave intensity) which corresponds to the total energy density carried by the wave (for further details please see http://hyper.ahajournals.org). Two principal waves originating from the heart were measured: S, the forward traveling compression wave attributable to ventricular ejection and D, the forward traveling decompression wave attributable to deceleration of ventricular contraction in prostodiastole.18 Reflections returning down the carotid (ie, from the head) and up the carotid (ie, from the body) were quantified separately using the wave reflection index (WRI): the cumulative reflected wave intensity expressed as a proportion of the cumulative wave intensity of the incident wave. S. An early forward decompression wave, a re-reflection of the reflected wave from the head,16 was not taken into account when calculating WRI. Augmentation index in the carotid artery (carotid AIx), the pressure difference between the first shoulder of the pressure waveform and the systolic peak expressed as a percentage of the pulse pressure was calculated from the carotid pressure waveform as described by Kelly et al.19 This has been shown to correlate highly with directly measured aortic AIx.20 Waveforms were also classified into Type A, B, and C as described by Murgu et al,21 and when the peak systolic pressure preceded a well-defined inflection point (type C) AIx was calculated as a negative value. Although AIx is an indirect measure of wave reflection and is also influenced by other factors such as heart rate, height, and arterial stiffness,22 carotid AIx and WRI showed a reasonably close correlation (r=0.40; P<0.001) suggesting that carotid AIx provides some insight into wave reflection in the absence of wave separation.

Statistics and Reproducibility

Reproducibility data have been published in detail elsewhere.18 On the basis of this and additional unpublished data in untreated hypertensive subjects we calculated that a total of 140 subjects would be required to detect a difference of 5 mm Hg in carotid SBP or 3% in carotid AIx with 90% power at the 5% significance level. As this was a factorial design, possible interactions were tested and the main effect (ie, all lipid lowering treatment versus all placebo) only analyzed if the interaction term was not significant.23 P values for interactions have not been reported if they were not statistically significant. Statistical analysis was performed using Stata 10.0 (StataCorp LP). Population characteristics are reported as mean (SD), median (interquartile range) for skewed data, categorical data are presented as n (%). Comparisons between groups were made by a Student t test, Mann–Whitney rank sum test, or χ² test as appropriate.

Results

The characteristics of participants at the time of the study are shown in Table 1. The 2 groups were very similar with the exception of the expected differences in total cholesterol, LDL cholesterol, and triglycerides. In particular brachial blood pressures did not differ significantly between groups. Overall the data in this substudy were similar to those seen in the lipid-lowering limb of the main ASCOT study.9

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>Atorvastatin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64 (7)</td>
<td>64 (8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>57 (92)</td>
<td>59 (90)</td>
<td>0.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.2 (4.3)</td>
<td>28.5 (4.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>164 (20)</td>
<td>158 (20)</td>
<td>0.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>94 (10)</td>
<td>93 (10)</td>
<td>0.6</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>67 (12)</td>
<td>68 (12)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.4 (0.8)</td>
<td>5.4 (0.8)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>3.4 (0.8)</td>
<td>3.4 (0.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1.3 (1.0, 1.6)</td>
<td>1.2 (1.0, 1.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/l</td>
<td>1.3 (0.9, 1.8)</td>
<td>1.3 (1.1, 1.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.5 (5.1, 6.4)</td>
<td>5.4 (5.1, 6.1)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Creatinine, mmol/l</td>
<td>102 (16)</td>
<td>100 (14)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>12 (19)</td>
<td>12 (25)</td>
<td>0.4</td>
</tr>
<tr>
<td>Randomized to atenolol, n (%)</td>
<td>36 (48)</td>
<td>39 (52)</td>
<td>0.4</td>
</tr>
<tr>
<td>Antihypertensive agents, n</td>
<td>2.3 (1.1)</td>
<td>2.1 (0.9)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; LVMi, left ventricular mass index; SBP, systolic blood pressure. Continuous data are presented as means (SD) or median (interquartile range) for skewed data. Categorical data are presented as n (%). Comparisons between groups were made by a Student t test, Mann–Whitney rank sum test, or χ² test as appropriate.
There was evidence of an interaction between lipid-lowering therapy and antihypertensive therapy with lower carotid systolic BP (cSBP) in individuals randomized to the combination of atorvastatin and amlodipine-based therapy (Figure). No other instances of a significant interaction between regimens were observed for any other parameters reported in Table 2, including carotid AIx, PAug and measures of wave reflection.

Pressure augmentation, measured either as carotid AIx or PAug, was significantly less in people randomized to atorvastatin (Table 2). The magnitude of the pressure at the shoulder did not differ significantly between groups and the timings of the foot and shoulder of the pressure waveform were not altered by atorvastatin treatment. Both markers of inflammation, CRP and SAA, were significantly lower in individuals randomized to atorvastatin and showed reduced values with the combination of atorvastatin and amlodipine-based therapy. Both markers of inflammation, CRP and SAA, were significantly lower in individuals randomized to atorvastatin treatment. Both markers of inflammation, CRP and SAA, were lower in individuals randomized to atorvastatin and showed reduced values with the combination of atorvastatin and amlodipine-based therapy. Both markers of inflammation, CRP and SAA, were lower in individuals randomized to atorvastatin and showed reduced values with the combination of atorvastatin and amlodipine-based therapy.

Analysis of wave reflection showed that atorvastatin was associated with significantly less wave reflection from the body (Table 2) and less wave reflection from the head, although this latter effect was not statistically significant.

Local wave velocity, c, a measure of carotid artery stiffness, was slightly, but not significantly, lower in people randomized to atorvastatin (Table 2) and estimated arterial compliance (SV/PP) was not significantly different (Table 2). There were no significant differences between the 2 groups for either the cumulative wave energy associated with ejection, or the cumulative wave energy of the decompression wave occurring in protodiastole (Table 2).

Discussion

This study has shown in a prospective randomized clinical trial that atorvastatin is associated with less pressure augmentation and wave reflection in the carotid artery in patients with well controlled hypertension. Atorvastatin also caused a small average reduction in cSBP, but this effect differed by antihypertensive regimen with a more marked reduction in cSBP in well controlled hypertension. Atorvastatin also caused a small average reduction in cSBP, but this effect differed by antihypertensive regimen with a more marked reduction in cSBP in well controlled hypertension. Atorvastatin also caused a small average reduction in cSBP, but this effect differed by antihypertensive regimen with a more marked reduction in cSBP in well controlled hypertension. Atorvastatin also caused a small average reduction in cSBP, but this effect differed by antihypertensive regimen with a more marked reduction in cSBP in well controlled hypertension. Atorvastatin also caused a small average reduction in cSBP, but this effect differed by antihypertensive regimen with a more marked reduction in cSBP in well controlled hypertension.
after randomization (approximately the time of investigations in the current study). This is comparable to the \( \approx 1 \) mm Hg lower brachial blood pressure in individuals randomized to atorvastatin in our study, albeit not statistically significant.

Atorvastatin had significant effects on pressure augmentation measured in the carotid artery and reduced wave reflection from the body. Direct measurement of carotid AI\(_x\) has been shown to correlate highly with invasive measurements of AI\(_x\) in the aorta\(^2\) and, as we show, correlates with a more specific measurement of wave reflection (WRI) in the carotid artery. Carotid artery tonometry, although more technically demanding, is superior to measurements derived from application of a generalized transfer function to radial waveforms because the latter technique results in a systematic underestimation of the aortic AI\(_x\).\(^{25}\) and central AI\(_x\) derived from radial tonometry is not closely correlated with invasively measured aortic AI\(_x\).\(^{26}\) The effect of atorvastatin on augmentation and wave reflection may be important because there is extensive evidence that altered wave reflections have adverse effects on cardiac function through increased afterload and impaired arterio-ventricular coupling.\(^{27,28}\) The effect of atorvastatin on augmentation and wave reflection may be attributable to beneficial effects of statin treatment on endothelial function,\(^{29}\) because release of nitric oxide is an important factor in determining wave reflection arising from sites of potential impedance mismatching, such as arterial bifurcations.\(^{30}\) The relationship between carotid AI\(_x\) and the inflammatory markers CRP and SAA suggests a possible role for inflammation in increased augmentation and wave reflection, possibly related to endothelial dysfunction. Whether the antiinflammatory effect of statins could account for the lower augmentation in the individuals treated with atorvastatin merits further study. A previous small study\(^{31}\) has reported that atorvastatin reduced arterial stiffness in individuals with isolated systolic hypertension, although in this case there was also a significant reduction in brachial blood pressure. Interpreting the effect of atorvastatin on cSBP is less straightforward because the existence of a significant interaction between atorvastatin and antihypertensive regimen is indicative of a positive interaction between atorvastatin and amlodipine-based regimen or a negative (inhibitory) interaction between atenolol-based therapy and atorvastatin. Our data suggest a nonsignificant lower carotid blood pressure after randomization to atorvastatin, but the factorial design of the study precludes a definitive interpretation. Recently, another substudy of ASCOT (CAFE-LLA)\(^{32}\) also reported that atorvastatin had no significant effect on central blood pressure estimated using radial artery tonometry, however, the possibility of interaction between lipid lowering and antihypertensive therapy was not examined.

Our study has a number of limitations. Participants were predominantly male, and it is questionable whether these data can be extrapolated to women. Because of its factorial design, use of atorvastatin was combined with use of antihypertensive treatment, and antihypertensive drug use was up-titrated during the study to achieve similar BP targets based on measurements of brachial blood pressure. There was slightly more use of third line antihypertensive agents in the group receiving placebo, and this will have tended to obscure blood pressure differences between the groups. Measurements of blood pressure were made in the carotid artery, not the aorta. Although pressures in the aorta and carotid artery are very similar,\(^{20}\) wave reflection patterns differ somewhat,\(^{20}\) with a more prominent reflected component from the head, and a slightly lower carotid AI\(_x\).\(^{20}\) Because reflection from the body was more affected by atorvastatin than reflection from the head, this may also have tended to lead to an underestimation of the overall effect of atorvastatin on wave reflection. The strengths of this study are its randomized design and the comprehensive range of measurements made, including direct measurement of carotid pressure as an estimate of aortic pressure without the use of mathematical transformation using a transfer function.

**Clinical Perspective**

Atorvastatin treatment is associated with less augmentation of the carotid artery pressure waveform in well-controlled hypertensive individuals. This effect appears to be primarily attributable to less wave reflection. There may also be a potential beneficial interaction between atorvastatin- and amlodipine-based antihypertensive treatment on central systolic blood pressure. The beneficial effects of atorvastatin on wave reflection may contribute to its action in preventing cardiovascular disease.

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**References**


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Calculation of wave reflection index (WRI) from the carotid artery wave intensity profile

A wave is a transmitted disturbance that propagates in time and space and the propagation of a wave invariably involves exchange of energy. In our usage, the term wave is distinct from the term waveform (by which we mean a measured trace of pressure or velocity over time). Waves in arteries can be classified by their direction of travel (forward or backward) and their relationship to pressure changes (waves occurring during positive changes in pressure are termed compression waves, and waves occurring during negative pressure changes are termed decompression wave). Wave intensity is a measure of the energy flux density (or power) of the wave, while the integral of the wave intensity is a measure of the energy of the wave. This latter quantity is used to calculate the wave reflection index (WRI) as a measure of wave reflection.

Wave intensity analysis at the carotid artery reveals a characteristic pattern of waves that are similar to those seen elsewhere in the systemic circulation, including the aorta (Figure 1). By convention forward travelling waves are assigned positive wave intensity.

Left ventricular contraction results in a forward travelling compression wave (S wave) that propagates into the carotid artery in early systole causing an acceleration of flow velocity. Subsequently there is a backward-travelling compression wave (c_1^-) which is due to reflection of the systolic wave from presumed sites of admittance mismatching in territory supplied by the carotid artery (the head). This wave decelerates blood flow velocity in the carotid artery. Subsequently there is a small forward travelling decompression wave (d_1^+) that causes a deceleration of flow. The d_1^+ wave is thought to result from re-reflection of c_1^- reflected wave at the junction between the carotid and brachiocephalic artery and was not included in the calculation of the wave reflection index. The d_1^+ wave is followed by another forward compression wave (c_1^+) that is attributed to reflection of the initial systolic S wave from sites of admittance mismatching in the rest of the body. Although c_1^- is a reflected wave (i.e. it travels retrogradely in the aorta (see Figure 1A), it appears as a forward travelling wave in the carotid artery as a result of the anatomical relationship of the carotid artery to the aorta. A forward travelling decompression wave (D wave) arising from the heart appears towards the end of systole (protodiastole). This wave is due to the decline in the rate of myocardial contraction and is not included in the calculation of wave reflection. This wave contributes to aortic valve closure.

Wave reflection index (WRI) is calculated as:

\[
\frac{\Sigma c_1^- + \Sigma c_1^+}{\Sigma S}
\]

where \(\Sigma c_1^-\) and \(\Sigma c_1^+\) are the cumulative wave intensities (i.e. the integral under the curve) of the reflected waves, c_1^- and c_1^+ respectively (shown in magenta in figure 1) and \(\Sigma S\) is the cumulative wave intensity of the incident wave, S, generated by the ventricle during ejection (shown in green in figure S1).
References


Figure S1. A) Right common carotid artery and its relation to other arteries, indicating routes followed by waves arising from the head and body and their direction in the common carotid artery. B) Schematic representation of a typical wave intensity profile in the right common carotid artery.