Effects of Low-Dose Atorvastatin on Arterial Stiffness and Central Aortic Pressure Augmentation in Patients With Hypertension and Hypercholesterolemia

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BACKGROUND
Experimental and clinical data suggest that statins exert anti-inflammatory and antiproliferative actions on vasculature beyond their lipid-lowering properties. Whether these pleiotropic effects of statins translate into a beneficial effect on arterial stiffness is not clear. This study aimed to evaluate the potential effects of low-dose atorvastatin treatment on arterial stiffness and central arterial pressure waveforms in patients with mild hypertension and hypercholesterolemia.

METHODS
In a double-blind, randomized, placebo-controlled fashion, 50 hypertensive and hypercholesterolemic patients were allocated to receive 10 mg of atorvastatin or placebo for 26 weeks. Arterial stiffness was assessed by aortic pulse-wave velocity (PWV) using a Sphygmocor device. Central arterial pressure waveform parameters were estimated by radial artery applanation tonometry. Heart rate–adjusted augmentation index (AIx(75)) was used as measure of wave reflections.

RESULTS
At study end, aortic PWV (9.0 ± 1.5 vs. 10.9 ± 2.6 m/sec; P < 0.001) and AIx(75) (24.9% ± 9.7% vs 28.8% ± 11.8%; P < 0.001) were significantly lower in the atorvastatin group than that placebo group. Furthermore, decreases in central aortic systolic blood pressure and pulse pressure were evident at study-end with atorvastatin but not with placebo (130 ± 8 vs. 138 ± 6 mm Hg, P < 0.001; 48 ± 7 vs. 53 ± 6 mm Hg, P < 0.05, respectively). Atorvastatin-induced reductions in aortic PWV during follow-up showed significant associations with changes in AIx(75) and central aortic systolic blood pressure and pulse pressure.

CONCLUSIONS
This study shows that low-dose atorvastatin treatment improves arterial stiffness and exerts a reduction on central aortic pressures. These effects may represent a potential mechanism of cardiovascular risk reduction observed with statin use.© American Journal of Hypertension, Ltd 2013. All rights reserved.

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Effects of Low-Dose Atorvastatin on Arterial Stiffness

given contradictory results. In some of these, statins were shown to reduce pulse-wave velocity (PWV) in different segments of the arterial tree, whereas others suggested increase in arterial stiffness. Further, several studies failed to show any effect of statins, but this result could, in some cases, be because of methodological limitations (i.e., small sample sizes, short duration of follow-up, nonrandomized clinical design) instead of absence of a true treatment effect. The confusion surrounding this particular field may be also related to the fact that several studies evaluated PWV only in peripheral arterial segments and did not assess aortic PWV, which is considered the gold-standard method for arterial stiffness. The results of 2 substudies of a large-scale clinical trial could not resolve this controversy because they both assessed large artery elasticity with augmentation index (a rather indirect measure of arterial stiffness) and they also gave contradictory results.

The aim of this study was to investigate in detail the potential effects of low-dose atorvastatin treatment for 26 weeks (6 months) on aortic PWV, wave reflections, and central hemodynamic parameters in patients with mild hypertension and hypercholesterolemia.

METHODS

Study design

This article includes data on PWV, arterial waveforms, and related parameters of a double-blind, randomized, parallel-group, placebo-controlled study in 50 patients with mild hypertension and hypercholesterolemia. Data on PWV and related parameters were prespecified endpoints of a larger protocol that had changes in ambulatory systolic blood pressure (SBP) as primary endpoint; the later data have been published elsewhere. The study was registered in the ClinicalTrials.gov database (Identifier Number: NCT01126684), and the study protocol was approved by the ethics committee of Aristotle University Medical School and the Greek National Regulatory Drug Agency. All protocol procedures were conducted according to the Declaration of Helsinki (2000 amendment).

Potential participants were recruited from the Outpatient Hypertension Clinic of our department. Consecutive patients were informed about the study, and those interested were later screened for eligibility by study investigators. Screening evaluation was performed at our outpatient clinic and included medical history recording, physical examination, and routine laboratory tests. Inclusion criteria consisted of (i) mild hypertension with inadequate control (office blood pressure (BP) levels > 140/90 and < 160/100 mm Hg) under antihypertensive treatment with 1 agent or stage 1 hypertension of recent onset without treatment; (ii) recently diagnosed hypercholesterolemia (LDL > 150 mg/dl for patients at low cardiovascular risk and LDL > 130 mg/dl for patients with 1–2 additional risk factors); and (iii) absence of hypolipidemic treatment before study enrollment. Patients were excluded from the study in the following cases: (i) current pregnancy; (ii) history of myocardial infarction, unstable angina, or transient ischemic attack in the previous 6 months; (iii) stage 3–4 congestive heart failure, according to New York Heart Association classification; (iv) chronic kidney disease, defined as estimated glomerular filtration rate (<60 ml/min/1.73m²); (v) active liver disease; (vi) history of malignancy; (vii) history of drug and alcohol abuse; (viii) current corticosteroid treatment; and (ix) any other clinical condition associated with poor prognosis. All study subjects provided informed written consent before study enrollment.

Study protocol

Eligible participants visited our Clinical Research Laboratory at 7:00 AM after a 12-hour fast to undertake the protocol procedures. Anthropometric measurements were performed, blood was sampled for lipid profile and routine laboratory parameters, and an ambulatory BP monitor was fitted for 24 hours. Subjects with a valid ambulatory BP measurement had office BP recordings and determination of central aortic BP and parameters of arterial stiffness by applanation tonometry of peripheral arteries the following morning, as described below. All the later measurements were performed in a quiet room with controlled air temperature (approximately 22 °C).

After the baseline evaluation, study participants were randomized to either atorvastatin 10 mg once daily (n = 25) or masked placebo (n = 25) in a double-blind fashion for 26 weeks. Background treatment, if any, remained unchanged throughout follow-up, and subjects were advised to keep their regular habits in terms of physical activity and dietary patterns. Follow-up visits for BP measurements, physical examination, standard laboratory tests, and study medication dispensation were performed every 2 months. Adherence of study participants to the administered therapy was assessed in the follow-up visits by tablet counts. At study end (6 months), all baseline measurements were repeated.

Assessments

Peripheral BP. Peripheral BP at the level of brachial artery was measured in the sitting posture after a 10-minute rest with a mercury sphygmomanometer and cuffs with bladder size encircling at least 80% of arm circumference and covering two-thirds of arm length. Brachial BP was measured in both arms, and if there was a difference in BP levels between the two arms, measurements in the arm with the highest BP were taken into account. Three BP measurements with at least a 1-minute interval between them were obtained, and the mean of the 3 measurements was recorded. Phase 1 and V Korotkoff sounds were recorded for SBP and diastolic BP (DBP) respectively.

Pulse-wave velocity. We assessed arterial pulse waveforms and aortic PWV with the SphygmoCor device (PWV and BP analysis system; ArtCor, Sydney, Australia). To obtain pulse waveforms, the investigator performed applanation tonometry at the carotid and femoral arteries. This technique uses a high-fidelity strain-gauge transducer with a small pressure-sensitive ceramic sensor area at the tip (SPT-301; Millar Instruments, Houston, Texas, USA).
Pressure waves at carotid and femoral sites were recorded sequentially to determine aortic PWV. For each measurement, wave transit time was calculated by the device software, using as reference frame the R-wave of a simultaneously recorded electrocardiogram. The distance traveled by the pulse wave was measured over the body surface as the distance between the recording site at the femoral artery to the suprasternal notch minus the distance from the recording site at the carotid artery to the suprasternal notch (D), as previously described elsewhere.26,27 Pulse wave velocity was calculated as PWV = D/t, where t is the transit time of pulse wave between the recording sites. For each subject, PWV was measured over 10 consecutive heartbeats to cover a complete respiratory cycle, from which the average of 3 valid measurements was used in the analysis. Normalized PWV values (PWV-n) for mean blood pressure (MBP) and heart rate (HR) were calculated with the use of the equation PWV-n = PWV-n × (MBP-n/MBP-o) × (HR-n/HR-o), where MBP-n represents the normalized MBP (reference value = 90 mm Hg), MBP-o is the observed MBP, HR-n represents the normalized HR (reference value = 75 beats per minute), and HR-o is the observed HR, as elsewhere described.28

**Pulse-wave analysis.** Applanation tonometry was used to record radial artery pressure waveforms. A validated radial-to-aortic transfer function from the radial artery pressure waveform was used to construct central aortic pressure waveforms (Sphygmocor; ArtCor, Sydney Australia), assuming a similar MBP throughout the arterial tree, as previously described elsewhere.26,27 We used brachial artery pressures for the calibration of central aortic pressures, assuming radial SBP and DBP to be equal to brachial SBP and DBP.26-27 The average of 3 valid recordings was used in the analysis. We calculated augmentation index (Alx) as the difference between the second and the first systolic peaks, expressed as percentage of the central aortic PP. HR-adjusted augmentation index (Alx(75)) was calculated by adjusting Alx at an inverse rate of 4.8% for each 10-beats-per-minute increment in heart rate.26,27

Furthermore, we estimated subendocardial viability index as a measure of the balance between the cardiac oxygen supply and demand, and it was calculated as the ratio of diastolic pressure time index to systolic tension time index.28

**Statistical analysis**

All analyses were performed using the Statistical Package for Social Sciences version 17.0 for Windows XP (SPSS, Chicago, IL). Categorical variables are presented as absolute and relevant frequencies. Continuous variables are presented as mean ± SD, or median (range). Paired t tests and χ² or Fisher exact tests were used to assess baseline differences between the 2 study groups. The normality of the distribution of variables under study was assessed with Kolmogorov–Smirnov test. For comparisons between the baseline and the end of the study in each study group, paired Student t tests or Wilcoxon signed rank tests were used depending on the normality of the distribution. Similarly, independent t tests or Mann–Whitney U tests, where appropriate, were used for between-group comparisons. All analyses were done by intention to treat. We also calculated bivariable correlation coefficients (r) using the Pearson product formula or the Spearman product formula, according to the normality of the distribution, to explore possible relationships between changes in the parameters under study.

Sample size calculation was carried out with nQuery advisor version 5.0. software (Statistical Solutions, Boston, MA). The study had 90% power to detect a difference of 1.7 m/sec in aortic PWV between atorvastatin and placebo groups, with α = 0.01 (2-sided) and assuming a mean of 10 m/sec and SD of 1.5 m/sec.

**RESULTS**

A total of 131 patients from our outpatient hypertension clinic that were interested in entering the study were initially screened for eligibility; among these, 77 did not satisfy the inclusion/exclusion criteria, and 4 withdrew consent before randomization (Figure 1). A total of 50 patients were randomized to receive either 10 mg of atorvastatin or placebo for 6 months. Table 1 displays demographic and routine biochemical characteristics, SBP and DBP levels at the level of brachial artery, and background antihypertensive medication at baseline for the atorvastatin and placebo groups respectively. Age, sex distribution, duration of hypertension, BMI, smoking status, fasting plasma glucose, serum lipids, and other biochemical parameters did not differ between groups at baseline evaluation. No difference was also noted between study groups in baseline brachial SBP and DBP levels and background antihypertensive agents.

At study end, levels of total cholesterol (183.5 ± 24.5 vs. 247.4 ± 21.2; P < 0.001) and LDL-C (100.7 ± 19.7 vs. 166.7 ± 19.6; P < 0.001) were significantly lower and those of high-density lipoprotein cholesterol were slightly higher (55.6 ± 16.0 vs. 53.8 ± 12.0; P = 0.09) in the atorvastatin group compared with the placebo group. Treatment with low-dose atorvastatin for 26 weeks resulted in significantly lower levels of aortic PWV and PWV-n compared with treatment with placebo (P < 0.001), as shown in Figure 2 and Table 2. In addition to improvement of aortic stiffness, atorvastatin treatment was associated with decrease of wave reflections from peripheral sites compared with placebo treatment, as Alx, HR-adjusted Alx, and augmentation pressure were significantly lower in the atorvastatin group than in the placebo group (P < 0.001 for between-groups comparison) (Figure 3 and Table 2).

Peripheral SBP, DBP, and PP at the level of brachial artery were not significantly changed during follow-up in both the active treatment group and the placebo group, as shown in Table 3. In contrast with peripheral BP, values of central aortic SBP (P < 0.001), aortic DBP (P < 0.001), and aortic PP levels (P < 0.05) were significantly lower in the atorvastatin group compared with the placebo group (Table 3). This beneficial effect of atorvastatin on central hemodynamic parameters was accompanied by a statistically significant increase in subendocardial viability index levels and decrease in ejection duration between baseline and study end in the atorvastatin group but not in the placebo group (Table 3). During the study period, no major adverse events or clinically
Table 1. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Atorvastatin group (n = 25)</th>
<th>Placebo group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.7 ± 8.9</td>
<td>58.8 ± 10.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>12 (48)</td>
<td>12 (48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension duration, years</td>
<td>7 (1–25)</td>
<td>6 (1–20)</td>
<td>0.89</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4 ± 4.3</td>
<td>29.6 ± 3.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Current smokers, No. (%)</td>
<td>7 (28)</td>
<td>8 (32)</td>
<td>0.76</td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>148 ± 7</td>
<td>150 ± 6</td>
<td>0.24</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>83 ± 6</td>
<td>85 ± 8</td>
<td>0.47</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>94.8 ± 8.6</td>
<td>94.9 ± 12.1</td>
<td>0.96</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.12 ± 0.3</td>
<td>5.08 ± 0.4</td>
<td>0.72</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>256.1 ± 29.0</td>
<td>244.1 ± 28.0</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>174.6 ± 26.9</td>
<td>164.0 ± 24.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>157.7 ± 67.8</td>
<td>137.7 ± 55.2</td>
<td>0.26</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>50.0 ± 13.1</td>
<td>52.7 ± 13.0</td>
<td>0.47</td>
</tr>
<tr>
<td>ACEI or ARB treatment, No. (%)</td>
<td>8 (32)</td>
<td>12 (48)</td>
<td>0.25</td>
</tr>
<tr>
<td>CCB treatment, No. (%)</td>
<td>14 (56)</td>
<td>12 (48)</td>
<td>0.57</td>
</tr>
<tr>
<td>β-blocker treatment, No. (%)</td>
<td>5 (20)</td>
<td>3 (12)</td>
<td>0.44</td>
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<tr>
<td>Diuretic treatment, No. (%)</td>
<td>7 (28)</td>
<td>6 (20)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Categorical variables are presented as absolute and relevant frequencies. Continuous variables are presented as mean ± SD, with the exception of hypertension duration, which is presented as median (range).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; CCB, calcium channel blocker; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
important changes in routine safety parameters (including liver and renal function tests) were noted in the atorvastatin or placebo group. No patient withdrew consent because of side effects.

We also performed exploratory correlation analyses to identify possible determinants of the observed atorvastatin-induced reduction in aortic PWV levels. As shown in Figure 4, changes in aortic PWV levels during follow-up showed significant associations with changes in HR-adjusted AIX (r = 0.438; P < 0.05), as well as with changes in central aortic SBP (r = 0.407; P < 0.05) and PP (r = 0.234; P < 0.05), but not with aortic DBP (r = 0.149; P = 0.48). In contrast, changes in aortic PWV in the atorvastatin group during follow-up were not associated with changes in total cholesterol (r = 0.072; P = 0.73) and LDL-C levels (r = 0.007; P = 0.97).

**DISCUSSION**

This study investigated in detail the potential effects of low-dose atorvastatin on aortic stiffness, wave reflections, and central hemodynamic parameters in patients with mild hypertension and hypercholesterolemia. Treatment with 10 mg of atorvastatin daily for 26 weeks significantly reduced aortic PWV and wave reflections from peripheral sites as compared with treatment with placebo. This atorvastatin-induced improvement of arterial stiffness was associated with a parallel significant reduction in central aortic SBP and PP levels, whereas peripheral BP at the level of brachial remained unchanged during follow-up.

Previous studies exploring the potential effects of statin therapy on arterial stiffness gave variable results. Observational and single-arm studies in the field examined populations of 10–73 subjects with various primary diseases, extended 1–12 months of follow-up, and investigated different indices of arterial stiffness and/or segments of arterial tree. However, they could not provide a definite answer, as some suggested improvement of arterial stiffness, but others did not. Studies with crossover design comparing a statin to placebo or other agents had rather small sample sizes (<30 individuals) and short follow-up (<3 months) and gave conflicting results, reporting increase, decrease, or no change in the stiffness indices studied.

The potential effects of statins on large artery elasticity were also explored in randomized studies with parallel-group design, yet again with contradictory results. In some of these, statins produced significant reductions in PWV levels in different segments of the arterial tree, but others showed no change or even an increase in arterial stiffness. An important problem of relevant studies is that many used suboptimal indices of arterial stiffness or included measurements of PWV only in peripheral muscle-type arterial segments and not in the elastic aorta, which is the gold-standard method for estimation of arterial stiffness.

Another issue is the distinct characteristics of the studied populations (i.e., patients with chronic kidney disease or end-stage renal disease, patients with rheumatoid arthritis, or even healthy individuals). There are only 2 previous randomized controlled trials including hypercholesterolemic subjects and measuring aortic PWV; one of them included 23 subjects for 3 months and showed increase of arterial stiffness, whereas the other included 71 subjects for 1 month and showed decrease of arterial stiffness. The inconsistency of previous findings in randomized controlled trials could also be related to methodological issues, such as small sample sizes and short (<1 month) duration in negative studies, as well as other points, such as the dose of statin, the baseline LDL-C levels, and the methodology used for arterial stiffness assessment.

Statin effects on wave reflections and central hemodynamic parameters were evaluated in the Conduit Artery Function Evaluation-Lipid Lowering Arm (CAFE-LLA)
study, which included 891 participants of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial, which randomized subjects to a regimen of amlodipine with perindopril or atenolol with bendroflumethiazide with or without the addition of atorvastatin 10 mg daily in a 2 × 2 factorial design. After 3.5 years, atorvastatin in CAFE-LLA lowered LDL-C by 32.4 mg/dl relative to placebo but had no impact on AIx and central aortic BP. The effects of atorvastatin on central arterial waveform parameters were evaluated in another ASCOT substudy with 142 hypertensive patients. In contrast with the findings of CAFE-LLA, atorvastatin treatment for about 18 months in the ASCOT-LLA study was associated with less augmentation of carotid pressure waveform, as carotid AIx and carotid SBP levels were significantly lower at study end in the atorvastatin group than in the placebo group. However, both these substudies are limited by the absence of simultaneous determination of aortic PWV and potentially by their complex factorial design and the concomitant administration of BP-lowering therapy. Given these contrasting results, it remained unclear what the actual effect of atorvastatin on arterial stiffness was and whether the beneficial effect of atorvastatin in ASCOT-LLA was because of improvement of large artery elastic properties or because of changes in other parameters affecting carotid AIx.

This study was designed to carefully capture any potential beneficial effects of atorvastatin on arterial cushioning function. The findings are strengthened by the parallel-group, double-blind, randomized, placebo-controlled design, the simultaneous determination of both arterial stiffness and central arterial pressure waveform parameters, and the fact that any background antihypertensive medication was constant throughout follow-up. Further, we studied patients with mild hypertension and hypercholesterolemia, a population in whom statins are commonly used but relevant well-conducted studies are missing. Thus, this work adds to previous observations by showing the net impact of low-dose atorvastatin on several factors of arterial stiffness, including central aortic segments, in a common population and avoids confounding effects of background antihypertensive treatment. To this end, our study clarifies that these statin effects on central pressure waveform come predominantly from reduction in aortic PWV, which was shown to be significantly associated with changes in AIx and central aortic SBP and PP levels during follow-up.

With regards to mechanistic background of these statin effects, atorvastatin-induced reduction in aortic PWV levels throughout this study was independent from changes in serum lipids. Thus, lipid lowering does not seem a very plausible mechanistic explanation for the statin effects in this study. However, background data bring to light several other potential pathways through which these drugs may influence large artery elasticity. Statins were shown to increase endothelial nitric oxide synthase expression and to reduce reactive oxygen species production. The statin-mediated improvement in endothelial function may translate into decrease in vascular tone and could contribute to arterial stiffness amelioration. Statins may also affect vascular tone by interfering with the vasoconstricting...
action of endothelin 1, as well as by reducing intracellular calcium concentration in vascular smooth muscle cells. Moreover, animal studies have reported that statins down-regulate the expression of angiotensin II type 1 receptor in vascular smooth muscle cells and reverse the angiotensin II–mediated structural alterations in arterial walls; thus, interference with the renin–angiotensin system could represent another mechanistic explanation for their action on arterial stiffness.

This study has some limitations that must be acknowledged. Although the follow-up period of our study is one of the longest in duration among statin studies that included aortic PWV measurements, it was restricted to 26 weeks; thus, the beneficial effects of atorvastatin on arterial stiffness have to be confirmed in studies with longer follow-up periods. Determination of arterial stiffness and wave reflection parameters with the use of the indirect method of applanation tonometry of peripheral arteries could be considered another possible limitation of this study (together with all other studies investigating the statin effects on arterial stiffness). However, this method is widely accepted in both clinical practice and research and has been shown to be highly reproducible in patients with hypertension. In addition, dietary habits and physical activity of participants were not recorded during follow-up; thus, although they were advised to keep these patterns constant throughout the study, it is unknown whether any changes occurred during follow-up.

This study shows that low-dose atorvastatin treatment for 6 months reduces arterial stiffness and the intensity of arterial wave reflected at peripheral sites in patients with mild hypertension and hypercholesterolemia. This improvement of large artery elasticity was associated with a mild preferential reduction of central aortic pressures, in contrast with BP at the level of brachial artery. These positive effects of atorvastatin on arterial stiffness and central hemodynamic parameters can yet be an additional

Figure 4. Correlations between changes during the follow-up in the atorvastatin group in aortic pulse wave velocity (PWV) and changes in (a) heart rate–adjusted augmentation index (AIx) \( r = 0.438; P < 0.05 \), (b) aortic systolic blood pressure (SBP) \( r = 0.407; P < 0.05 \), (c) aortic diastolic blood pressure (DBP) \( r = 0.149; P = 0.48 \), and (d) aortic pulse pressure (PP) \( r = 0.234; P < 0.05 \), respectively.
mechanism through which this drug class provides cardiovascular risk reduction in patients with hypertension and hypercholesterolemia.

DISCLOSURE

A.N. Lasaridis received an independent research grant from Pfizer Hellas S.A. as the primary investigator for this investigator-initiated study. All other authors declared no conflict of interest.

REFERENCES


