Arterial Destiffening With Atorvastatin in Overweight and Obese Middle-Aged and Older Adults

Jeb S. Orr, A. Laura Dengo, Jose M. Rivero, Kevin P. Davy

Abstract—We hypothesized that atorvastatin (ATOR) treatment would reduce arterial stiffness in overweight and obese middle-aged and older adults. Twenty-six (11 men and 15 women) overweight or obese (body mass index: 31.6±0.7 kg/m²) middle-aged and older adults (age: 54±2 years) were randomly assigned to receive either ATOR (80 mg/d) or placebo for 12 weeks. Arterial stiffness (β-stiffness and pulse wave velocity) was measured before and after the intervention. At baseline, the ATOR (n=16) and placebo (n=10) groups did not differ with respect to age, body mass index, blood pressure, serum lipid and lipoprotein concentrations, high-sensitivity C-reactive protein, indices of arterial stiffness, or compliance (all P>0.05). After the 12-week treatment period, the ATOR group experienced a 47% reduction in low-density lipoprotein cholesterol (149±6 to 80±8 mg/dL) and a 42% reduction in high-sensitivity C-reactive protein (3.6±0.8 to 2.1±0.5 mg/L; both P<0.05). In addition, β-stiffness (9.4±0.6 to 7.6±0.5 U) and aortic pulse wave velocity (1096±36 to 932±32 cm/s), but not brachial pulse wave velocity, decreased (both P<0.05) with ATOR. In contrast, there were no significant changes in β-stiffness (9.1±0.8 to 9.1±0.7 U) or aortic pulse wave velocity (1238±89 to 1191±90 cm/s; both P>0.05) in the placebo group. There were no relations between the reductions in arterial stiffness indices and any of the baseline cardiometabolic risk factors (all P>0.05). However, the reductions in arterial stiffness were correlated with the reduction in low-density lipoprotein cholesterol but not high-sensitivity C-reactive protein or any other cardiometabolic variables (all P<0.05). Taken together, these findings suggest that ATOR reduces arterial stiffness in overweight and obese middle-aged and older adults, and these favorable changes occur irrespective of baseline cardiometabolic risk factors. (Hypertension. 2009;54:763-768.)

Key Words: statins ■ arterial stiffness ■ arterial compliance ■ aging ■ obesity

Large artery stiffness in the cardiothoracic region increases with age in humans.1,2 Age-related arterial stiffening is amplified among individuals with visceral obesity3 and other characteristics of the metabolic syndrome.4 In this regard, arterial stiffness can viewed as a time-integrated index of an individual’s risk factor exposure. Indeed, arterial stiffness has long been regarded as an indicator of disease5 and is an independent predictor of cardiovascular events and mortality in both healthy and diseased populations.6 Numerous strategies have been used to reduce arterial stiffening. The major emphasis of pharmacological destiffening strategies has focused on reducing collagen cross-linking7 or smooth muscle tone by enhancing NO bioavailability or, for example, by blocking the activity of the renin-angiotensin system.8,9 There has been increasing interest in the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) as a destiffening therapy.8,9 The interest goes beyond the ability of statins to lower serum cholesterol and extends to the increasingly recognized anti-inflammatory, antiproliferative, and immunomodulatory actions10 (ie, the so-called vascular pleiotropic actions of statin drugs). In this regard, there is increasing evidence to suggest that intensive statin therapy is associated with a potent vascular pleiotropic effect.10

There is currently little information regarding the efficacy of statins as a destiffening therapy. The only randomized, placebo-controlled trials to have directly explored this issue have produced inconsistent results.11–16 Reasons for the disparate outcomes are unclear but may include differences in subject populations, duration of treatment, and/or the type of statin and doses used. The interpretation of these studies is also confounded by their use of blood pressure–dependent measures of arterial stiffness and methodologic flaws (eg, failure to measure central blood pressure). Accordingly, we tested the hypothesis that 12 weeks of intensive atorvastatin (ATOR) treatment would reduce large artery stiffness in overweight and obese middle-aged and older adults, a population with accelerated arterial stiffening and at increased risk for cardiovascular disease.

Methods

Subjects

Twenty-six men (n=11) and women (n=15) 40 to 65 years of age participated in the study. All of the subjects were overweight or

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obese (body mass index: $\geq 25$ kg/m$^2$), with a brachial arterial blood pressure $\leq 159/99$ mm Hg. Individuals with blood pressure $\geq 160/100$ mm Hg, total cholesterol $\geq 200$ mg/dL, fasting plasma glucose $\geq 126$ mg/dL, triglyceride concentration $\geq 450$ mg/dL, or elevated transaminase levels were excluded from the study. All of the subjects were otherwise free from chronic disease, as assessed by medical history, physical examination, negative screening blood cell count, blood chemistry, and urinalysis. All of the subjects were weight stable ($\pm 2.0$ kg for the previous 6 months), nonsmokers, and not taking medications or dietary supplements that may influence the dependent variables or interact with statin drugs. Female participants were not receiving hormone replacement therapy. The Virginia Tech Institutional Review Board approved all of the experimental protocols. The nature, purpose, risks, and benefits of the study were explained to all of the subjects before obtaining informed consent.

Experimental Design and Protocol

After baseline measurements, subjects were randomized in a double-blind manner to receive either 80 mg of ATOR (n = 16) or placebo (n = 10) once daily for 12 weeks. Subjects were provided with a predetermined excess number of tablets at the onset and every 2 weeks throughout the treatment period. Subject compliance was assessed by counting the number of tablets returned at each refill. Because of the blinded nature of the study, all of the subjects were continuously screened for adverse events throughout the treatment period. In addition, subjects were instructed to maintain their current dietary intake, daily physical activity level, and body weight for the duration of the study. After the 12-week treatment period, baseline measurements were repeated over 2 weeks, during which subjects continued to receive either ATOR or placebo. Measurements were performed in all of the subjects between 8:00 and 11:00 AM after a 12-hour fast and having performed no vigorous physical activity for 48 hours before each testing session. All of the subjects reported being free of acute illnesses (eg, influenza) for the week before testing.

Measurements

Body mass and height were measured with a digital scale and stadiometer (Scale-Tronix model 50022, respectively). Waist circumference was measured at the level of the iliac crest, according to established guidelines. Body composition was determined via dual-energy x-ray absorptiometry (GE Lunar Prodigy Advance, software version 8.10e). Casual blood pressure was measured over a brachial artery via automated sphygmomanometry (Pilot 9200, Colin Medical Instruments). Blood pressure measurements were obtained after 15 minutes of seated rest in a quiet room and were repeated until within-session stability was achieved ($\pm 5$ mm Hg on 3 sequential measurements). Resting heart rate was determined from lead II of an ECG. Habitual dietary intake and physical activity were assessed via self-reported 4-day food intake records and accelerometer (GT1M, Actigraph Inc), respectively. Energy and macronutrient intake were assessed using nutritional analysis software (NDS-R 6.0, University of Minnesota). Plasma lipid and lipoprotein concentrations were measured in a Clinical Laboratory Improvement Amendments-certified laboratory using conventional enzymatic techniques. High-sensitivity C-reactive protein (hs-CRP) concentrations were determined via immunometric assay (IMMULITE 2000, Diagnostic Products Corp). Standard enzymatic methods and a commercially available ELISA (Diagnostic Systems Laboratory) were used to measure fasting serum glucose and insulin concentrations, respectively. The homeostasis model assessment score $\left[ \text{glucose} \times \text{insulin} \times \text{micro-International Units} \right]^{-2/3}$ was used to provide an estimate of insulin resistance.

Pulse wave velocity (PWV) measurements were performed after 15 to 20 minutes of quiet rest in a supine position and the subsequent achievement of blood pressure stability, as measured over a brachial artery, by automated sphygmomanometry ($\pm 5$ mm Hg on 3 sequential measurements). Once blood pressure stability had been established, noninvasive pulse tonometers (PIT-301, Millar Instruments) were used to simultaneously obtain arterial pressure waveforms at the carotid and femoral arteries throughout 10 cardiac cycles. Surface distance between the 2 recording sites was then measured to the nearest 0.5 cm. Subsequently, this process was repeated to measure arterial pressure waveforms at the carotid and radial arteries. All of the arterial pressure waveforms were digitized at 500 Hz and analyzed using signal processing software (Windaq, Data Instruments). PWV for the carotid-femoral (aortic PWV; aPWV) and carotid-radial (brachial PWV) recordings were determined by normalizing the waveform foot-to-foot time delay to the distance between recording sites (ie, PWV = distance in centimeters/Δt in seconds).

β-Stiffness index and arterial compliance were assessed by combining simultaneous measurements of carotid artery diameter and blood pressure, as described previously. Briefly, longitudinal B-mode images of the left common carotid artery (1 to 2 cm proximal to the carotid bulb) were obtained with an ultrasound unit (HP Sonos 7500, Philips Healthcare) equipped with a high-resolution linear array transducer (3 to 11 MHz). Concomitant measurement of arterial blood pressure was obtained via applanation tonometry of the contralateral common carotid artery. Carotid diameters were then quantified offline using commercially available software (Vascular Research Tools 5, Medical Imaging Applications, LLC). and tonometric pressure waveforms were calibrated to brachial diastolic and mean arterial pressures. The reproducibility of measurements of β-stiffness index in our laboratory is excellent ($r=0.90$; $P<0.05$).

Statistical Analysis

Independent-sample t tests were used to assess baseline differences in subject characteristics and dependent variables between ATOR and placebo groups. Variables displaying a nonnormal distribution (as assessed by the Shapiro-Wilk test) were log transformed before statistical analyses. Variables for which log-transformation was performed are indicated in the appropriate table, but the untransformed data are reported for clarity. Repeated-measures ANOVA was used to assess changes in subject characteristics and dependent variables in the ATOR and placebo groups, and independent-sample $t$ tests were used to test for differences in the magnitude of change in these variables between groups. Simple correlation analyses were used to assess relations among variables of interest. All of the data are expressed as mean±SE. The significance level was set a priori at $P<0.05$.

Results

Subject characteristics at baseline and after the intervention are shown in Table 1. At baseline, the ATOR and placebo groups did not differ with respect to any of the subject characteristics (all $P>0.05$). There were no changes in body weight or composition during the study in either group ($P>0.05$). As expected, ATOR treatment resulted in significantly greater reductions in total cholesterol ($-71\pm8$ versus $-14\pm10$ mg/dL), low-density lipoprotein (LDL) cholesterol ($-69\pm8$ versus $-27\pm7$ mg/dL), very LDL cholesterol ($-7\pm2$ versus $+6\pm3$ mg/dL), and triglycerides ($-37\pm8$ versus $+31\pm15$ mg/dL) compared with placebo (all $P<0.001$). There was a small, but significant, decrease in high-density lipoprotein cholesterol over time in both groups ($-3\pm1$ versus $-2\pm1$ mg/dL for ATOR and placebo, respectively). There was a tendency ($P=0.09$) for hs-CRP to decline after ATOR but not after placebo; the magnitude of change in hs-CRP was greater in the ATOR group compared with placebo ($-1.5\pm0.6$ versus $+0.2\pm1.1$ mg/L; $P<0.05$). Systolic blood pressure decreased similarly over time in both groups ($-4\pm2$ versus $-3\pm2$ mm Hg for ATOR and placebo, respectively; $P<0.05$), whereas diastolic blood pressure and heart rate remained unchanged (both $P>0.05$).
There were no adverse events reported during the study. ATOR treatment significantly increased aspartate aminotransferase (24.5±1.6 to 28.2±1.8 U/L) and alanine aminotransaminase (75.7±5.9 to 85.3±6.7 U/L; both P<0.05), but both remained well within the normal reference ranges throughout the intervention period. There were no significant changes in serum creatine kinase concentrations during the intervention in either group (data not shown).

Physical activity and dietary intake before and after treatment are shown in Table 2. There were no significant changes in habitual physical activity during the study. Dietary energy intake and macronutrient composition remained unchanged.

### Table 1. Subject Characteristics Before and After Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (5 Women and 5 Men)</th>
<th>Atorvastatin (10 Women and 6 Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±3</td>
<td>NA</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>94.0±4.0</td>
<td>94.2±4.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.1±0.9</td>
<td>31.1±1.1</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>38.8±1.8</td>
<td>38.9±1.9</td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>34.4±0.9</td>
<td>34.5±1.0</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>55.7±3.8</td>
<td>55.8±4.0</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>107±2</td>
<td>107±3</td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>127±4</td>
<td>124±4</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>75±2</td>
<td>75±3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>59±2</td>
<td>59±2</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>125±17</td>
<td>156±23</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>227±11</td>
<td>213±12</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>43±5</td>
<td>41±5</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>162±8</td>
<td>135±10</td>
</tr>
<tr>
<td>Very LDL cholesterol, mg/dL</td>
<td>25±3</td>
<td>31±5</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>2.8±0.6</td>
<td>3.0±0.9</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>101±4</td>
<td>102±3</td>
</tr>
<tr>
<td>Insulin, μU/ml</td>
<td>13±3</td>
<td>12±2</td>
</tr>
<tr>
<td>HOMA score</td>
<td>3.27±0.73</td>
<td>3.04±0.60</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SE. FFM indicates fat-free mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; NA, not applicable.

Effects of time (*), group (†), and time×group interaction (‡) are shown at P<0.05.

### Table 2. Physical Activity and Dietary Intake Before and After Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>Physical activity, counts per day×10³</td>
<td>252±35</td>
<td>212±29</td>
</tr>
<tr>
<td>kcal</td>
<td>2293±78</td>
<td>2137±176</td>
</tr>
<tr>
<td>Fat, %</td>
<td>38±2</td>
<td>38±2</td>
</tr>
<tr>
<td>Carbohydrates, %</td>
<td>45±2</td>
<td>46±3</td>
</tr>
<tr>
<td>Protein, %</td>
<td>17±1</td>
<td>16±1</td>
</tr>
<tr>
<td>Alcohol, %</td>
<td>2±1</td>
<td>1±1</td>
</tr>
<tr>
<td>Cholesterol, mg</td>
<td>368±45</td>
<td>380±67</td>
</tr>
<tr>
<td>SFA, g</td>
<td>32±3</td>
<td>29±3</td>
</tr>
<tr>
<td>MUFA, g</td>
<td>37±2</td>
<td>37±5</td>
</tr>
<tr>
<td>PUFA, g</td>
<td>19±2</td>
<td>20±2</td>
</tr>
<tr>
<td>Trans-fatty acids, g</td>
<td>6±1</td>
<td>8±1</td>
</tr>
<tr>
<td>Sodium, mg</td>
<td>4336±328</td>
<td>3567±463</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SE. SFA indicates saturated fatty-acids; MUFA, monounsaturated fatty-acids; PUFA, polyunsaturated fatty-acids.

Effects of time (*), group (†), and time×group interaction (‡) are shown at P<0.05.
(P>0.05), although sodium intake and the percentage of total energy intake from alcohol decreased in both groups similarly over time (both P<0.05). There was no significant difference in the percentage of extra tablets returned by the 2 groups (97.8±0.5% versus 98.3±0.4% in ATOR and placebo, respectively).

Indices of arterial stiffness before and after treatment are shown in Table 3. There were no differences at baseline between the ATOR and placebo groups with respect to β-stiffness index, arterial compliance, aPWV, or brachial PWV (all P>0.05). As hypothesized, β-stiffness index and aPWV decreased and arterial compliance increased in the ATOR group but not in the placebo group (P<0.05). In addition, the magnitude of reductions in β-stiffness index (−1.8±0.4 versus +0.1±0.1 U; P<0.001; Figure 1, top) and aPWV (−163±21 versus −48±34 cm/s; P<0.001; Figure 2, top) and increases in arterial compliance (+0.26±0.07 versus 0.00±0.03 mm²/mm Hg×10⁻¹; P<0.001; Figure 1, bottom) were greater in the ATOR compared with the placebo group. However, brachial PWV did not change in either group (P>0.05; Figure 2, bottom).

In the pooled sample, baseline β-stiffness index and aPWV were correlated with homeostasis model assessment score (r=0.502 and 0.578, respectively; both P<0.05). In addition, baseline arterial compliance was correlated with percentage of body fat (r=−0.447; P<0.05); there was a trend for a similar relation between β-stiffness index and percentage of body fat (r=0.368; P=0.07). The magnitudes of reduction in β-stiffness index, aPWV, and compliance were not correlated with any baseline subject characteristics (all P>0.05). However, the magnitudes of change in β-stiffness index, aPWV, and arterial compliance after ATOR treatment were significantly correlated with the magnitude of change in LDL cholesterol (r=−0.598, 0.515, and −0.539, respectively; all P<0.05) but not with the magnitude of change in hs-CRP (P>0.05). The magnitude of reduction in β-stiffness index was correlated with the reduction in aPWV (r=0.643; P<0.05) and, as expected, with the magnitude of increase in arterial compliance (r=−0.682; P<0.05).

Table 3. Indices of Arterial Stiffness at Before and After Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th></th>
<th>Atorvastatin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Pretreatment</td>
<td>Posttreatment</td>
<td>n</td>
</tr>
<tr>
<td>β-Stiffness index, U</td>
<td>10</td>
<td>9.1±0.8</td>
<td>9.1±0.7</td>
<td>15</td>
</tr>
<tr>
<td>Arterial compliance, mm²/mm Hg×10⁻¹</td>
<td>10</td>
<td>0.96±0.14</td>
<td>0.96±0.12</td>
<td>15</td>
</tr>
<tr>
<td>aPWV, cm/s</td>
<td>9</td>
<td>1238±89</td>
<td>1191±90</td>
<td>13</td>
</tr>
<tr>
<td>Brachial PWV, cm/s</td>
<td>9</td>
<td>981±42</td>
<td>982±36</td>
<td>11</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SE.
Effects of time (*), group (†), and time×group interaction (‡) are shown at P<0.05.

Figure 1. Top, Change in β-stiffness index after placebo and ATOR treatment. Bottom, Change in arterial compliance after placebo and ATOR treatment. Values are mean±SE (*P<0.05 vs placebo).

Figure 2. Top, Change in aPWV after placebo and ATOR treatment. Bottom, Change in brachial PWV after placebo and ATOR treatment. Values are mean±SE (*P<0.05 vs placebo).
Discussion

The major finding of the present study is that 12 weeks of ATOR treatment reduced large artery stiffness in overweight and obese middle-aged and older adults. Our findings are consistent with the results of some12,13 but not all11,14–16 of the previous randomized placebo controlled trials. Importantly, our study extends previous reports in at least 2 important aspects. First, our study overcame limitations of several previous studies in that we obtained direct measurements of elastic artery stiffness using high-resolution ultrasound and applanation tonometry in the same central location. However, we also estimated aortic stiffness using PWV measurements. Importantly, ATOR treatment reduced arterial stiffness in the present study regardless of how it was measured.

Second, our subjects were heterogeneous with respect to a number of cardiometabolic risk factors. In this regard, we observed no significant relation between the reduction in arterial stiffness with ATOR treatment and baseline body mass index, waist circumference, LDL cholesterol, homocysteine model assessment, brachial systolic or diastolic blood pressure, or hs-CRP. Taken together, our findings suggest that ATOR reduces arterial stiffness independent of baseline cardiometabolic risk factors. As such, these observations suggest that there could be many healthy middle-aged and older adults who might benefit from the arterial destiffening effects of ATOR treatment.

The mechanisms mediating the large artery destiffening effects of ATOR treatment remain unclear. The current prevailing view of arterial stiffness, as it relates to central elastic arteries, is predominantly focused on structural alterations of the arterial wall as a consequence of exposure to distending stress cycles over time.5 In keeping with the progressive decrease in arterial compliance with age, these structural changes represent, at some level, an immutable consequence of the aging process. In this context, it is unlikely that any short-term intervention, such as in the present study, would result in favorable structural modifications to the arterial wall. Thus, a more plausible explanation for our findings is that statin therapy reduces arterial stiffness by reducing smooth muscle tone by either improving endothelial function (ie, enhancing NO bioavailability) or by modifying neurohumoral influences. Numerous experimental and clinical studies suggest that statin therapy improves endothelial function by reducing oxidative stress and improving NO bioavailability.21 In addition, systemic NO synthase inhibition (during α-adrenergic blockade) acutely increases β-stiffness index of the common carotid artery,22 suggesting a direct contribution of the endothelium to large artery stiffness in humans. As such, it is possible that the reductions in large artery stiffness observed in the present study were the result of statin-mediated improvements in endothelial function. That the magnitude of reduction in arterial stiffness with statin therapy was correlated with the degree of LDL cholesterol lowering in the present study suggests that lipid lowering may be contributing, at least in part, to this effect.

The results of many,23–26 but not all,22 studies suggest that large artery compliance is modulated by sympathetically mediated adrenergic smooth muscle tone. In this regard, statin therapy has been demonstrated to reduce sympathetic neural activity in experimental animals.27,28 As such, it is possible that the reduction in large artery stiffness with statin therapy observed in the present study was the result of a reduction in sympathetic neural activity. Future studies will be necessary to address this possibility.

There are some limitations of our study that warrant discussion. First, our sample size was relatively small, and the age range was limited to 40 to 65 years. Thus, larger studies are needed in older individuals to extend the generalizability of our findings.

Second, our treatment period was only 12 weeks in duration. Therefore, we cannot be certain that observed reductions in arterial stiffness would persist with long-term treatment.

Third, our study was not designed to address the dose-response effect of statin on arterial stiffness. However, Karter et al39 demonstrated similar improvements in arterial stiffness after 12 weeks of ATOR treatment using a low-dose (20 mg/d) and high-dose (80 mg/d) regimen. In contrast, the results of previous studies suggest that lower doses of ATOR (ie, 10 mg/d) may not reduce arterial stiffness.15,30 Collectively, these findings suggest that there may be a threshold effect; however, additional studies will be needed to determine the dose-response effects of ATOR therapy on large artery stiffness.

Fourth, our study was not designed to determine the autonomic-cardiovascular consequences of arterial destiffening with ATOR. Future studies will be necessary to address this important issue.

Finally, we observed a significant reduction in LDL cholesterol in our control group. The reason(s) for this is (are) unclear. However, there is considerable variability in LDL cholesterol measured under fasted conditions, and at least 2 and as many as 5 serial blood samples may have to be analyzed and averaged to detect most LDL cholesterol responses to intervention.31,32 We should emphasize that LDL cholesterol was not a primary outcome variable, but the anticipated reduction in LDL cholesterol after ATOR treatment was expected to be ≥40%. Thus, we obtained only a single sample at baseline and follow-up. The large variability resulting from the reliance on a single measurement at baseline and follow-up and our small sample size may account for the observed reduction in LDL cholesterol in our control group.

In summary, these findings suggest that ATOR reduces arterial stiffness in overweight and obese middle-aged and older adults irrespective of baseline cardiometabolic risk factors. However, reductions in LDL cholesterol may be important in mediating, at least in part, the reduction in arterial stiffness with ATOR therapy. In light of the present findings, futures studies on the mechanisms and consequences of arterial destiffening with statin treatment are needed.

Perspectives

Advancing age is associated with stiffening of the elastic arteries of the cardiothoracic region. Arterial stiffness can be viewed as a time-integrated index of an individual’s risk factor exposure, has long been regarded as an indicator of disease,5 and is an independent predictor of cardiovascular events and mortality in both healthy and diseased popula-
tions. The findings of our present study indicate that ATOR treatment reduces arterial stiffness in overweight and obese middle-aged and older adults. The large reductions in aPWV (ie, ~150 cm/s) would equate to reversing ~15 to 20 years of age-related arterial stiffening. Importantly, the reductions in arterial stiffness with ATOR treatment in the present study were independent of baseline cardiometabolic risk factors. Taken together, these observations suggest that there could be many healthy middle-aged and older adults who might benefit from the arterial destiffening effects of ATOR treatment.

Acknowledgments
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Disclosures
None.

References
2. Vaitkevicius PV, Fleg JL, Engel JH, O’Connor FC, Wright JG, Lakatta E, Spurgeon H, Vaitkevicius P. Aortic stiffness is associated with age-related arterial stiffening.1,2 Importantly, the reductions in aPWV and body composition.
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