Abstract—Whether angiotensin receptor blockers can dose-dependently remodel the arterial wall during long-term treatment has been largely debated. In this phase III, multicenter, randomized, double-blind, parallel-group study, 133 subjects with hypertension and metabolic syndrome were assigned to olmesartan, either 20 mg (n=44), 40 mg (n=42), or 80 mg (n=47) once a day, according to a force titration design during a 1-year period. Office blood pressure, 24-hour blood pressure, aortic stiffness (carotid-femoral pulse wave velocity), and carotid parameters were measured at baseline, 24 weeks, and 52 weeks. Pulse wave velocity significantly decreased (P<0.001) with time in each group, with no significant time–dose interaction, pulse velocity (P=0.0685) for a smaller effect of 20 mg, compared with 40 and 80 mg at week 52. When the 40 and 80 mg doses were combined (40/80 mg versus 20 mg), a significant blood pressure–independent reduction in pulse wave velocity (~0.61 m/s) was observed at week 52 (P=0.0066), whereas the nonadjusted reduction was ~1.31 m/s (P<0.0001). By contrast, after 20 mg, the blood pressure–independent reduction in pulse wave velocity was not significant. Patients receiving the highest dose of olmesartan (40 and 80 mg) had an inward carotid remodeling and were shifted toward a lower elastic modulus at a given circumferential wall stress, indicating an improvement in the intrinsic elastic properties of the carotid artery wall material. These data suggest that 40 and 80 mg olmesartan were able to significantly remodel and destiffen the arterial wall material during long-term treatment, partly independently of blood pressure, compared with 20 mg. (Hypertension. 2014;64:709-716.) • Online Data Supplement

Key Words: antihypertensive agents • aorta • arteries • blood pressure • compliance • hypertension • randomized controlled trial

Whether the reduction in arterial stiffness after antihypertensive treatment is only because of the blood pressure (BP) lowering, which unloads the stiff components of the arterial wall such as collagen, or whether additional BP-independent effects are involved, has been largely debated.1–4 An increasing body of evidence, including theoretical aspects of arterial mechanics,4 long-term observational studies in humans,5 and a recent meta-analysis of double-blind, randomized, controlled trials,6 suggests that only part of arterial stiffness could be reduced through the normalization of BP by pharmacological treatment, and further reduction of arterial stiffness would require long-term arterial remodeling, including reduction in collagen density and rearrangement of the wall materials.

Blockers of the renin–angiotensin–aldosterone system (RAAS) are privileged antihypertensive drugs for such a BP-independent effect on arterial stiffness, mainly through the reduction of arterial wall fibrosis and remodeling. In long-term controlled studies, the angiotensin-converting enzyme inhibitors (ACEIs) perindopril7 and trandolapril,8 the combined neutral endopeptidase/ACEI omapatrilat,9 the angiotensin receptor blocker (ARB) valsartan,10 and the aldosterone antagonist spironolactone11 had the capacity to reverse aortic stiffening independently of changes in BP. However, only 1 dose was tested in these studies.

A major argument in favor of a BP-independent reduction in aortic stiffness by a RAAS blocker would come from the demonstration of a dose-dependent reduction in aortic stiffness for a given mean BP (MBP) reduction. To our knowledge, no such pharmacodynamic data are yet available. We hypothesized that high doses of olmesartan medoxomil (OM), through various mechanisms common to RAAS blockers in general and ARBs in particular, and possible additional anti-inflammatory effects reported in subjects with hypertension and microinflammation12 would gradually lower aortic stiffness for a given MBP reduction. This is of particular interest in patients with metabolic syndrome. Impaired glucose metabolism13 and the clustering of risk factors known as the metabolic syndrome are associated with stiffening of the larger arteries.14–16 Metabolic syndrome is also associated with vascular inflammation,17 and...
olmesartan-based treatment has been shown to reduce vascular inflammatory markers such as C-reactive protein in patients with this condition,18 and so, hypertensive patients with metabolic syndrome were selected for the study.

The aim of the Vascular Mechanism study was to investigate the BP-independent effects of long-term (52 weeks) treatment with olmesartan on aortic and carotid stiffness in patients with hypertension and metabolic syndrome.

Methods

Study Design

This was an international, multicenter, randomized, double-blind, parallel-group, forced titration study (ClinicalTrials.gov; NCT00676845) conducted at 24 clinical centers and 10 echocardiographic measurement centers within Europe. The echocardiographic center measurements (pulse wave velocity [PWV], BP, and carotid parameters) were centralized and quality control assessments performed at a core echocardiographic center. This investigator-initiated/driven study was sponsored by Daiichi Sankyo Europe. The study was approved by institutional review committees in each country, and subjects gave informed consent.

Patients fulfilling inclusion criteria underwent a 2-week placebo run-in period, and then a 52-week double-blind treatment period. All eligible subjects were randomly allocated to 1 of the 3 treatment groups and received OM 20, 40, or 80 mg once daily for 1 year in a forced titration design. Each group received OM 20 mg at baseline. After 4 weeks, two third of subjects switched to OM 40 mg. After another 4 weeks, one third of subjects switched to OM 80 mg. Previous antihypertensive treatments were reduced and discontinued during a taper-off phase (1–3 weeks; depending on the judgment of physician) followed by a 2-week placebo run-in period. Patients who were already on statin maintained their medication.

Patients

Adult male and female (≥18 and ≤75 years) outpatients were included in the study if at the screening visit they satisfied the criteria for hypertension and metabolic syndrome, which were modified from the definitions of the National Cholesterol Education Program Adult Treatment Panel III,19 the International Diabetes Federation,20 and the 2007 European Society of Hypertension/European Society of Cardiology Guidelines for the Treatment of Arterial Hypertension.21 Inclusion and exclusion criteria are detailed in the online-only Data Supplement.

BP Measurement

Brachial BP was measured using oscillometric devices, both at the general practitioner’s office and the echocardiographic centers for arterial measurements. Three measurements were performed and the average was retained. We performed 24-hour ambulatory BP monitoring (ABPM) and arterial measurements after the placebo wash-out period (baseline) and at week 24 (W24) and week 52 (W52). We collected demographic data with details of cardiovascular risk factors and treatments during the longitudinal follow-up. Mixed models were used to evaluate the influence of important covariates and treatments during the longitudinal follow-up.

Arterial Parameters Measurement

All measurements were performed by trained echocardiographic centers. Expanded materials and methods are available in online-only Data Supplement. In brief, central BP was determined at the carotid level, from common carotid artery pressure waveforms measured noninvasively with applanation tonometry (Sphygmocor system; Atcor, Sydney, Australia) as previously described and validated.1,22,23

Aortic stiffness was measured using the Sphygmocor device (Atcor) as carotid-to-femoral PWV according to international guidelines and previously published.1,6,23

The carotid internal diameter and wall thickness were measured on the right common carotid artery and 2 cm beneath the carotid bifurcation, using a 7.5-MHz high-resolution echotracking system (Wall Track System, Esaote Pie Medical, Maastricht, The Netherlands) as previously described and validated.1,22

Statistical Methods

Data are expressed as mean (standard deviation) or mean (95% confidence interval [CI]) as appropriate. The full analysis set was the primary analysis set for the tables (Figure 1). Because the difference between the full analysis set and the per protocol set was <20%, no additional analysis based on the per protocol set was performed. All tests were bilateral; P values <0.05 were considered significant. We used mixed models to evaluate the influence of important covariates and treatments during the longitudinal follow-up. Mixed models were constructed as follows: outcome variable=f(treatment, visit, treatment×visit, covariate 1, 2, 3, etc). Statistical analysis was performed using NCSS 2007 (Kaysville, UT).

Results

A total of 258 patients were screened, of which 125 were not eligible to participate (Figure 1). Two hundred two patients were treated for the run-in period, of which 133 patients were randomized and treated in the double-blind period. Among them, 44, 42, and 47 patients were randomized to OM 20, 40, and 80 mg treatment groups, respectively. Of the 133 randomized patients, 111 patients completed the study, and

![Flow chart](http://hyper.ahajournals.org/Downloaded from)
22 subjects prematurely discontinued the study (Figure 1). Reasons for discontinuation were withdrawal of consent (9 patients), adverse event (5 patients), sustained confirmed hypotension (2 patients), protocol violation (1 patient), death (1 patient), and others (6 patients).

The baseline characteristics of the untreated hypertensive subjects are presented in Table 1. There were no statistically significant differences in the demographic and clinical baseline characteristics between the treatment groups.

### Changes in Aortic Stiffness
At W52, mean±SD change of PWV from baseline was −1.08±1.88 m/s for all 3 treatment groups combined ($P<0.0001$). PWV significantly decreased ($P<0.001$) with time (W24 and W52) in each group (20, 40, 80 mg), with no significant time–dose interaction. Because PWV appeared to be reduced to a greater extent with OM 40 or 80 mg at W52, compared with OM 20 mg (Table 2), we combined 40 and 80 mg in 1 group and contrasted it with the 20 mg group. The reduction from baseline in PWV after OM 40/80 mg was −1.38±1.93 m/s at W24 and −1.31±1.87 m/s at W52, whereas it was only −0.85±1.81 m/s at W24 and −0.57±1.84 m/s at W52 after 20 mg, thus suggesting a higher effect of OM 40/80 mg than OM 20 mg in reducing PWV. Under these conditions, the time–dose interaction was almost significant ($P=0.0685$).

#### BP-Dependent Changes in PWV
At W52, MBP measured in the investigation room (ie, investigation MBP) decreased to a greater extent in the OM 40/80 mg group (change in MBP from baseline: −13.54 mm Hg; 95% CI, −11.31 to −15.77 mm Hg; $P<0.001$) than in the OM 20 mg group (change in MBP from baseline: −6.38 mm Hg; 95% CI, −4.26 to −8.53 mm Hg; $P<0.001$) with a significant ($P<0.001$) time–dose interaction. The fall in MBP was a major determinant of the reduction in PWV. For instance, a 10 mm Hg reduction in investigation MBP explained −0.53 m/s (95% CI, −0.34 to −0.72 m/s) reduction in PWV ($P<0.0001$), whatever the dose and the period.

To take into account the chronic unloading of the arterial wall exerted during the whole 24 hours, we also analyzed the dose-dependent effect of OM on 24-hour ABPM. At W52, the 24-hour MBP appeared to decrease to a greater extent in OM 40/80 mg group (change in 24-hour MBP from baseline: −8.84 mm Hg; 95% CI, −7.16 to −10.51 mm Hg; $P<0.001$) than in the 20 mg group (change in 24-hour MBP from baseline: −6.88 mm Hg; 95% CI, −5.57 to −8.26 mm Hg; $P<0.001$) group, but no significant time–dose interaction was observed. Similar results were observed for daytime MBP and night-time MBP. Thus, in the following analysis, we used either investigation MBP or 24-hour ABPM to analyze, in a covariate analysis, whether the fall in MBP could explain the reduction in PWV. We grouped OM 40 and 80 mg and compared it with 20 mg.

### BP-Independent Reduction in PWV
After OM 40/80 mg, the changes in PWV adjusted to investigation MBP were smaller than the unadjusted changes.

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**Table 1. Baseline Demographics and Hemodynamic Data (mean±SD)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>20 mg (n=37)</th>
<th>40 mg (n=39)</th>
<th>80 mg (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.7±10.3</td>
<td>54.1±9.0</td>
<td>52.3±10.6</td>
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<tr>
<td>BMI, kg/m²</td>
<td>31.9±3.2</td>
<td>30.9±3.5</td>
<td>31.9±4.1</td>
</tr>
<tr>
<td>Male/female sex</td>
<td>24/13 (65% vs 35%)</td>
<td>19/20 (49% vs 51%)</td>
<td>30/10 (75% vs 25%)</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>137.3±8.1</td>
<td>139.3±7.5</td>
<td>141.3±7.9</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>86.3±5.9</td>
<td>86.5±7.3</td>
<td>87.0±5.1</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>133.2±9.5</td>
<td>134.9±12.0</td>
<td>134.4±12.4</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>83.1±7.3</td>
<td>80.7±8.4</td>
<td>82.3±8.3</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>137.0±10.2</td>
<td>139.0±12.2</td>
<td>139.3±13.0</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>86.7±7.5</td>
<td>84.6±9.0</td>
<td>86.6±8.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation MBP, mm Hg</td>
<td>103.2±5.8</td>
<td>104.0±6.7</td>
<td>105.1±4.8</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>11.4±2.2</td>
<td>11.7±3.0</td>
<td>11.8±2.1</td>
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<tr>
<td>Carotid PP, mm Hg</td>
<td>47.5±11.9</td>
<td>50.1±14.2</td>
<td>50.5±12.9</td>
</tr>
<tr>
<td>Aortic PP, mm Hg</td>
<td>43.0±10.7</td>
<td>46.6±12.4</td>
<td>44.4±10.2</td>
</tr>
<tr>
<td>AIx, %</td>
<td>25.5±13.6</td>
<td>27.9±11.1</td>
<td>23.9±11.3</td>
</tr>
<tr>
<td>Carotid external diameter, mm</td>
<td>7.547±0.803</td>
<td>7.407±0.769</td>
<td>7.516±0.646</td>
</tr>
<tr>
<td>Carotid IMT, mm-10⁻³</td>
<td>627±160</td>
<td>643±134</td>
<td>639±153</td>
</tr>
<tr>
<td>WCSA, mm²</td>
<td>13.76±4.50</td>
<td>13.76±3.69</td>
<td>13.90±4.03</td>
</tr>
<tr>
<td>Carotid distensibility, kPa⁻¹-10⁻³</td>
<td>19.1±7.5</td>
<td>17.6±7.2</td>
<td>18.6±7.2</td>
</tr>
<tr>
<td>Carotid stiffness, kPa</td>
<td>7.66±1.58</td>
<td>7.99±1.59</td>
<td>7.72±1.51</td>
</tr>
<tr>
<td>Circumferential wall stress, kPa</td>
<td>72.7±20.1</td>
<td>68.5±18.0</td>
<td>72.3±18.4</td>
</tr>
</tbody>
</table>

For all parameters, no significant differences were seen between groups using ANOVA. AIx indicates augmentation index; BMI, body mass index; DBP, diastolic blood pressure; IMT, intima-media thickness; MBP, mean blood pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; and WCSA, wall cross-sectional area.
Hypertension

October 2014

in PWV, but remained significant. For instance, at W52, the MBP-adjusted reduction in PWV was $-0.61 \pm 1.74$ m/s ($P=0.0066$), whereas the unadjusted reduction in PWV was $-1.31 \pm 1.87$ m/s ($P<0.0001$), thus suggesting that the fall in MBP could explain ≤54% of the total (nonadjusted) reduction in PWV. By contrast, after OM 20 mg, the BP-independent reduction in PWV was not significant ($P=0.39$) at W52.

Similar results were obtained at W24 and W52 when 24-hour MBP (Figure 2), day MBP (data not shown), or night MBP (data not shown) were taken into account. The favourable BP-independent effect of the high-dose group was driven neither by 40 mg nor by 80 mg. Both dosages had similar effects (Table S1 in the online-only Data Supplement).

Altogether, these results support the conclusion that (1) the MBP-adjusted reduction in PWV consistently represented a large part (≤52%) of the total (nonadjusted) reduction in PWV, and (2) the BP-independent reduction in PWV was relatively more important and sustained with OM 40 or 80 mg than with OM 20 mg.

### Reduction in Central BP After Olmesartan

When all OM doses were analyzed globally, we observed a significant ($P<0.001$) reduction from baseline in carotid pulse pressure (PP; $-7.4 \pm 10.7$ mm Hg at W24 and $-7.5 \pm 11.6$ mm Hg at W52), aortic PP ($-6.0 \pm 9.1$ mm Hg at W24 and $-6.9 \pm 9.5$ mm Hg at W52), and augmentation index ($-3.2 \pm 7.9\%$ at W24 and $-3.1 \pm 7.9\%$ at W52). However, no significant time–dose interaction was observed. Because any reduction in PWV, by delaying the return of wave reflection, can reduce central SBP, PP, and augmentation index, we analyzed the influence of PWV changes on the reduction in central BP, through a covariate analysis. Indeed, there was a tendency ($P=0.054$) for the time changes in PWV to explain a significant amount of time changes in carotid PP.

### Table 2. Hemodynamic Changes (mean±SD) from Baseline at Week 24 (W24) and Week 52 (W52) After Olmesartan, According to the Dose Administered

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At W24</th>
<th>At W52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>$-10.8 \pm 8.4^*$</td>
<td>$-15.3 \pm 9.1^*$</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>$-6.2 \pm 6.3^*$</td>
<td>$-8.6 \pm 6.5^*$</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>$-8.5 \pm 9.7^*$</td>
<td>$-13.1 \pm 10.9^*$</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>$-5.3 \pm 6.4^*$</td>
<td>$-6.3 \pm 7.3^*$</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>$-8.6 \pm 9.5^*$</td>
<td>$-12.3 \pm 12.0^*$</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>$-5.7 \pm 6.1^*$</td>
<td>$-7.5 \pm 6.4^*$</td>
</tr>
</tbody>
</table>

Ax indicates augmentation index; DBP, diastolic blood pressure; IMT, intima-media thickness; MBP, mean blood pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; and WCSA, wall cross-sectional area.

* $P<0.01$; † $P<0.05$.

**Figure 2.** Reduction in pulse wave velocity (PWV; m/s) at week 24 (W24), and week 52 (W52) from baseline, presented either as nonadjusted to mean blood pressure (MBP) reduction, or adjusted to MBP reduction. MBP values were those measured either during PWV measurement (investigation MBP) or during ABPM 24h (ABPM24). * $P<0.05$ vs baseline values; † $P<0.01$ vs baseline values.
changes in investigation MBP were included in a covariate analysis, the time changes in PWV no more had significant influence on the time changes in carotid PP. By contrast, the time changes in MBP were significantly associated with the time changes in PWV ($P<0.0001$). We observed similar results when we studied aortic PP instead of carotid PP. In none of these analyses was there a significant difference between doses.

**Changes in Carotid Stiffness After Olmesartan**

When all OM doses were analyzed globally, we observed a significant reduction from baseline in carotid external diameter ($−0.165±0.459$ mm at W24 and $−0.177±0.578$ mm at W52; $P=0.0014$) and carotid internal diameter ($−0.171±0.462$ mm at W24 and $−0.217±0.483$ mm at W52; $P=0.0002$), with no change in wall cross-sectional area. These changes indicate a chronic inward eutrophic arterial remodeling. The time changes in external diameter were significantly ($P<0.001$) associated with the time changes in investigation MBP. There was a tendency ($P=0.0647$) for an association between internal diameter and MBP. We did not observe any significant time–dose interaction. By contrast to diameters, the time changes in carotid intima-media thickness and wall cross-sectional area were not significant.

With OM 20, 40 or 80 mg, we also observed a significant ($P<0.001$) reduction from baseline in carotid stiffness, circumferential wall stress, and elastic modulus, without time–dose interaction (Table 2). In covariate analysis, the time changes in investigation MBP explained most ($P<0.0001$) of the time changes in carotid stiffness. In univariate analysis, elastic modulus was significantly dependent on circumferential wall stress, according to the law of physics (Figure 3). Moreover, in covariate analysis, the time changes in circumferential wall stress explained ($P<0.0001$) most of the time changes in elastic modulus. We thus used a covariate analysis to determine the influence of OM dose (either 40/80 mg or 20 mg) on the relationship between elastic modulus and circumferential wall stress. At W52, carotid elastic modulus, calculated for a given circumferential wall stress (63.7 kPa), was significantly reduced after OM 40/80 mg ($−77.1$ kPa; 95% CI, $−123.5$ to $−30.7$ kPa; $P<0.01$) but not after 20 mg ($−17.9$ kPa; 95% CI, $−102.1$ to $50.8$ kPa; Figure 4). These results indicate that only the higher doses of OM were able to significantly improve the elastic properties of the arterial wall material. Similar results were observed at W24.

**Figure 4.** Reduction in elastic modulus (Einc, kPa) after olmesartan (OLM) 20 mg or 40/80 mg (combined groups) observed at week 24 (W24) and week 52 (W52), after adjustment to circumferential wall stress (multivariate analysis). Independently of circumferential wall stress, the higher doses of olmesartan are more effective ($P<0.05$) than the 20 mg dose for reducing elastic modulus, either at W24 or W52.

**Discussion**

Whether the reduction in arterial stiffness after antihypertensive treatment is only because of the BP lowering, or whether additional BP-independent effects are involved, has been largely debated. The present study is the first randomized clinical trial that addresses this issue with a dose–response experimental design. Our major finding is that long-term administration (1 year) of higher doses of olmesartan (40/80 mg) decreased PWV to a greater extent than the 20 mg dose of olmesartan in hypertensive patients with metabolic syndrome, independently of BP reduction. A second important finding is that the 40 and 80 mg doses of
olmesartan induced a destiffening of the carotid artery wall material along with an inward remodeling, by contrast to the 20 mg dose. The aim of this randomized, double-blind, parallel-group, forced titration study was to show a significantly higher effect of OM 80 mg compared with OM 20 mg on PWV after 1 year of treatment. However, no significant difference in time change PWV was observed between 80 mg and 20 mg. When OM 20, 40, and 80 mg were compared, no time–dose interaction was observed, although the reduction in PWV with time was significant in each group and larger in the 40 and 80 mg groups. Because PWV appeared to be reduced to a greater extent after OM 40 or 80 mg than after OM 20 mg, we combined 40 and 80 mg in 1 group and contrasted it with the 20 mg group in all subsequent analyses. Under these conditions, the time–dose interaction was almost significant ($P=0.0685$).

With OM 40/80 mg, the MBP-adjusted time changes in PWV remained significant, by contrast to the effects of OM 20 mg (Figure 2). These findings were observed whether MBP was measured during PWV measurement (investigation MBP: acute loading of the arterial wall) or during the 24-hour, day or night period (ABPM: chronic load and remodeling). Altogether, these results support the conclusion that (1) the MBP-adjusted reduction in PWV consistently represented a large part ($\geq62\%$) of the total reduction in PWV, and (2) the BP-independent reduction in PWV was relatively more important and sustained with OM 40 or 80 mg than with OM 20 mg.

A second important finding is that the 40 and 80 mg doses of olmesartan induced a destiffening of the carotid artery wall material, by contrast to the 20 mg dose. These changes occurred along with an inward eutrophic remodeling. Indeed, patients receiving higher doses of OM (40 and 80 mg) had lower external and internal carotid diameters at the end of the study, with no change in wall cross-sectional area, had lower carotid stiffness, and were shifted toward a lower elastic modulus at a given lower circumferential wall stress (Table 2; Figure 4). These data suggest that higher doses of OM were able to significantly remodel the carotid artery and thus to improve the intrinsic elastic properties of the wall material during long-term treatment.

The consequences of arterial destiffening on central BP are important to consider. Indeed, any reduction in PWV, by delaying the return of wave reflection, can reduce central SBP, PP, and augmentation index. A covariate analysis showed a tendency ($P=0.054$) for the time changes in PWV to explain a significant amount of the time changes in central PP. When investigation MBP was included in the covariate analysis, PWV no longer had significant influence on carotid PP, whereas MBP was significantly associated with PWV. These results suggest that the part of the changes in PWV that is BP-independent is not sufficient to explain the changes in central BP. Thus, it is likely that both BP-dependent and BP-independent changes in PWV contribute to the reduction in central BP.

The present findings are consistent with previous studies suggesting that the reduction in aortic stiffness, which occurs during antihypertensive treatment, may be in part because of BP-independent structural mechanisms, that is, long-term changes in the structure of the arterial wall (less amount of stiff component, higher relative amount of elastic components, 3-dimensional reorganization of the connections between stiff and elastic components). This has been well exemplified by an observational study under conditions of routine clinical practice, comprising 97 hypertensive patients with normalized BP, during which we showed a significant reduction in PWV >5.4 years of follow-up contrasting with a much smaller change in brachial SBP. In a multivariate analysis, the reduction in PWV was only partially explained by the reduction in MBP. In addition, in a recent meta-analysis of double-blind, randomized, controlled trials comparing different antihypertensive drugs or placebo both in short term and long term, we showed that active treatment was associated with a significant reduction in arterial stiffness compared with placebo for a given MBP reduction.

Several studies showed that RAAS blockers were privileged antihypertensive drugs for such a BP-independent effect on arterial stiffness. Indeed, they inhibit the action of tissue and circulating angiotensin II, thus reducing arterial wall fibrosis, collagen synthesis, proliferation of smooth muscle cells, accumulation and activation of inflammatory cells, and endothelial dysfunction. We previously showed7 a dose-dependent (8 versus 4 mg) and BP-independent effect of an ACEI (perindopril) on carotid artery stiffness in hypertensive patients with type II diabetes mellitus after 6 months’ treatment. In long-term controlled studies, the ACEI trandolapril,4 the combined neutral endopeptidase/A ACEI omapatrilat,7 the ARB valsartan,12 and the aldosterone antagonist spironolactone11 reduced arterial stiffness to a greater extent than the reference drug or placebo for a given MBP reduction.

We selected OM because its pharmacodynamic profile is suitable for investigating the effects of ARB treatment on arterial stiffness. Olmesartan has beneficial effects on various aspects of endothelial function. In the European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis, olmesartan significantly reduced several markers of vascular inflammation, including tumor necrosis factor-α and C-reactive protein in patients with essential hypertension and vascular microinflammation. The C-reactive protein–lowering effect of olmesartan has been confirmed in patients with essential hypertension, in patients with stable angina, and in patients with type II diabetes mellitus. In the present study, we selected patients with hypertension and metabolic syndrome. Indeed, impaired glucose metabolism and the clustering of risk factors known as the metabolic syndrome are associated with stiffening of the larger arteries. Metabolic syndrome is also associated with vascular inflammation, and, as seen above, olmesartan-based treatment has been shown to reduce vascular inflammatory markers such as C-reactive protein in patients with this condition.

In the present study, we used 2 marketed doses of olmesartan (20 and 40 mg) and an experimental high dose (80 mg), which has never been used for such a long duration. Several observations supported this choice. First, it is well accepted that high doses of ARBs, such as olmesartan, are not related to higher incidence of side effects, that is, there is...
no dose-dependency of side effects with ARBs. For instance, an additional antiproteinuric effect beyond the maximum dose approved for control of BP has been observed with irbesartan 900 mg per day (3x the maximum approved dose), valsartan 640 mg per day (twice the maximum dose), and candesartan 128 mg (4x the maximum dose). In all these studies, the significantly greater reduction in proteinuria was related to non-BP-lowering effects. In none of these studies was there an increase in side effects, adverse events, or serious adverse events. In addition, the dose–response curve for BP lowering is rather flat for blockers of the RAAS (ACEIs and ARBs) by contrast to calcium channel blockers. This is advantageous for such a study, where we wanted to uncouple the BP-lowering effect from the direct arterial effect. In the present study, the higher OM dose was not associated with more adverse events.

Several limitations of the study should be noted. First, the number of patients included in the study was smaller than initially planned. Although 92 subjects per group were required to demonstrate a difference of 0.5 m/s PWV between OM 80 mg and 20 mg at W52 (see the online-only Data Supplement), we included a lower number of patients (44, 42, and 47 patients in the 20, 40, and 80 mg groups, respectively). Thus, our study may not have reached the statistical power to conclude a true lack of difference in the reduction in PWV between OM 80 mg and 20 mg at W52. Second, it would have been interesting to measure inflammatory biomarkers and relate changes in mechanics to changes in biomarkers. However, for technical reasons, those measurements were not available. Third, patients who were already on statin maintained their medication, which may have influenced the findings. However, only a small number of patients were concerned (see Table S2). It is thus unlikely that this could have influenced our results.

Perspectives
This study indicates that, after long-term administration of higher doses of olmesartan (40 and 80 mg), aortic destiffening was partly independent of the reduction in BP, was associated with a carotid destiffening secondary to an inward eutrophic remodeling, and likely contributed to the reduction in central PP. Higher doses of OM were thus able to significantly remodel the arterial artery wall during long-term treatment, and consequently to improve the intrinsic elastic properties of the wall material and the central hemodynamics.

Acknowledgments
We thank all the investigators who contributed to this study, and our patients who agreed to participate.

1. Author contributions—Drs Laurent and Boutouyrie were principal investigator and coordinator of echocardiographic centers, respectively. They had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They were involved in the study concept and design, statistical analysis and interpretation of data, and writing the article.


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This study was supported by Daiichi Sankyo Europe. The sponsor participated in discussions regarding the design and conduct of the study and provided logistical support during the trial. Monitoring of the study and maintenance of the trial was performed by a contract research organization (CRO; SGS Life Science) under contract with the sponsor. Collection management and analysis of the data were performed by the sponsor and the CRO under contract with the sponsor. The article was prepared by the authors. The sponsor was permitted to review the article and suggest changes, but the final approval of content was exclusively retained by the authors.

Disclosures
Drs Laurent and Boutouyrie have all received honoraria, research grants, or both from Daiichi-Sankyo Europe.

References


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Stephane Laurent and Pierre Boutouyrie
on behalf of the Vascular Mechanism Collaboration

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EXPANDED MATERIALS AND METHODS

DOSE-DEPENDENT ARTERIAL DESTIFFENING AND INWARD REMODELLING AFTER OLMESARTAN IN HYPERTENSIVES WITH METABOLIC SYNDROME

Stephane LAURENT, M.D, Ph.D a,b,c

Pierre BOUTOUYRIE, M.D, Ph.D a,b,c

On behalf of the Vascular Mechanism Collaboration
Patients

Patients who were not receiving antihypertensive or lipid-lowering therapy were included if their levels of systolic and diastolic BP (SBP/DBP) were in the range ≥130/85 to <150/95 mmHg and if they fulfilled at least one of the following criteria: abdominal obesity (waist circumference >102 cm for men, >88 cm for women); elevated triglyceride concentrations (≥150 mg/dL [≥1.7 mmol/L]); low concentrations of high-density lipoprotein cholesterol ([HDL] <40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women); elevated fasting blood glucose without type 2 diabetes (≥110–<126 mg/dL [≥6.1–<7.0 mmol/L]).

Patients who were taking antihypertensive medication (no more than 1 agent) were included if their SBP/DBP was in the range ≥120/80 to <130/85 mmHg and if they fulfilled ≥1 of the above criteria for abdominal obesity, dyslipidaemia or elevated fasting blood glucose. Patients who were taking a lipid-lowering agent at screening were included if their SBP/DBP was in the range ≥130/85 to <150/95 mmHg and if they fulfilled the criterion for abdominal obesity or for elevated fasting blood glucose listed above.

Patients were not included if they had diabetes (type 1 or 2), resistant hypertension, or a BP level in the upper mild (SBP and/or DBP 150-159 and/or 95-99 mmHg), or moderate (SBP and/or DBP 160-179 and/or 100-109 mmHg), or severe (SBP and/or DBP ≥180 and/or ≥110 mmHg) hypertensive categories. Particularly, patients in the higher moiety of BP interval for grade I hypertension (140-159 or 90-99 mmHg), i.e. SBP/DBP above 150/95 mmHg, were not included. The main reason was ethical, since treatment duration was one year for patients with metabolic syndrome, who are usually considered as at high CV risk, and one third of them received 20 mg olmesartan only, without any other antihypertensive drug.

Methods

The investigation at the ECHO centers was carried out in a controlled environment at 22 ± 1° C after being recumbent for 15 minutes.

Central BP was determined at the carotid level, from common carotid artery (CCA) pressure waveforms measured non-invasively with applanation tonometry (SphygmoCor® system, Atcor, Sydney Australia), as previously described and validated (11,23,27). In brief, MBP was calculated from the AUC of the radial pressure-time curve, itself calibrated with brachial SBP and DBP. Carotid MBP was calculated from the AUC of the carotid pressure-time curve, and set equal to radial MBP. Carotid DBP was set equal to brachial DBP. Carotid SBP was then calibrated from the carotid pressure-time curve, MBP and DBP. Thus, the form factor was taken into account. Augmentation index (AIx) was calculated as the ratio of augmented pressure (AP) over pulse pressure (PP).

Aortic stiffness was measured using carotid-to-femoral pulse wave velocity (PWV), using the SphygmoCor® system (Atcor, Sydney Australia) according to international Guidelines (1) and was recorded along the descending thoraco-abdominal aorta. Briefly, wave forms were obtained transcutaneously over the right common carotid artery and femoral artery, and the time delay (t) was measured between the feet of two waveforms according to ECG signals at both sites. The distance (D) covered by the waves was established as the direct distance between the two recording sites. PWV was calculated as PWV=Dx0.8/t (m/s), according to International recommendations (1,28).
The carotid internal diameter and wall thickness were measured on the right common carotid artery (CCA) and 2 cm beneath the carotid bifurcation, using a 7.5 MHz high resolution echotracking system (Wall Track System, Esaote Pie Medical, Maastricht, The Netherlands). The short-term within-observer within-patient repeatability between two determinations, taken at 15 min intervals by a senior technician and physician, has been previously published (29,30). The absolute difference between measurement 1 and measurement 2 did not exceed 6 % of the mean value for each parameter (29,30). This system has been validated and described in detail and has been used in various clinical studies (11,23,27,29,30).

Arterial wall cross-sectional area (WCSA) was calculated in diastole as \( \text{WCSA} = \pi R_e^2 - \pi R_i^2 \) where \( R_e \) and \( R_i \) are the values of diastolic external and internal radii, respectively, as previously described and validated (29,30). Wall to lumen ratio was calculated in diastole as \( \frac{2h_d}{D_d} \), where \( h_d \) and \( D_d \) are the values of wall thickness and internal diameter during end-diastole. Circumferential wall stress (\( \sigma \theta \), kPa) was calculated according to Lamé's equation as \( \sigma \theta = \frac{(\text{MBP} \cdot \text{D}_m)}{2h_m} \), where MBP is mean blood pressure, and \( \text{D}_m \) and \( h_m \) are the mean values of internal diameter and wall thickness during the cardiac cycle (29).

Additional parameters were measured. They are linked together and with circumferential stress, but give separate useful information. Indeed, the elastic properties of the artery as a hollow structure were assessed through arterial distensibility, determined from the systolic-diastolic variations in arterial cross-sectional area (\( \Delta A \)) and local pulse pressure (\( \Delta P \)), as previously described (29,30) assuming the lumen to be circular. Cross-sectional distensibility coefficient was calculated as \( \text{DC} = \Delta A / A \cdot \Delta P \), where \( A \) is the diastolic lumen area, \( \Delta A \) is the stroke change in lumen area and \( \Delta P \) is local pulse pressure (PP). Local carotid artery PP, directly measured with applanation tonometry (SphygmoCor®, Atcor, Sydney Australia) was used in these calculations. We converted carotid distensibility into carotid stiffness, by using the Moens-Korteweg equation - \( \text{PWV} = (\text{PP} \cdot A / \Delta A)^{\frac{1}{2}} \) - which gives carotid stiffness=\((\text{DC})^{\frac{1}{5}}\).

The elastic properties of the arterial wall, as wall material, were estimated by the incremental Young's elastic modulus (\( E_{inc} \)), calculated, as previously described (30) as \( E_{inc} = \frac{[3(1 + A/WCSA)]/\text{DC}}{\text{DC}} \), where \( A \) is the diastolic lumen area, WCSA is the mean wall cross-sectional area and DC is the cross-sectional distensibility.

Certification of centers and quality control

All ECHO centres involved in arterial measurements were already experienced with arterial stiffness and central BP measurements. All centers used the Sphygmocor system. They all underwent training both at the CORE-ECHO centre of Pompidou Hospital, Paris, France, and on site. Centres were certified on the basis of five consecutive measurements fulfilling pre-established quality features. All measurements were centrally reviewed by the CORE-ECHO centre immediately after having being performed. A trained technician, blinded as to the center, period and treatment, checked for quality of tracings and inconsistencies in BP values. In the event of a mismatch, BP values could either be corrected or measured again within one week. Investigators performing arterial measurements were unaware of patient’s drug treatment. Tracings were blinded before electronic transfer as to the center, the period and the identity of the patient.
Statistical analysis

Sample size and statistical power

The sample size was estimated for the primary objective: the difference between OM 20 mg and OM 80 mg for the change from baseline in aortic PWV. The expected difference in PWV between OM 80 mg and OM 20 mg was estimated as ≥ 0.5 m/s, from a meta-analysis of individual data in 185 subjects participating to various long-term studies performed with similar methodology (10). In these patients receiving either placebo or an anti-hypertensive treatment for a mean duration of 2.4 months, the change (mean ± SD) in PWV under active treatment in this meta-analysis was -1.30 ± 1.27 m/s and the change in PWV under placebo was -0.44 ± 1.13 m/s. We considered that 92 subjects per group were required to demonstrate a difference of 0.5 m/s PWV between OM 80 mg and OM 20 mg at W52, at an alpha risk = 0.05 and a beta-risk = 0.20 in a 2-sided t-test, assuming a SD of 1.2 m/s. To end up with 92 evaluable subjects per group, we planned to enrol 350 subjects into the placebo period overall and to randomize 106 subjects per group.

Models

Models were allowed up to 3 ways initially, then pruned by eliminating the higher levels interaction terms with least significance. Patient number was used as a random variable. Random coefficients were set to diagonals, and the Newton Raphson solution method was used. Multiple comparisons were limited to the visit*treatment interaction. Bonferroni correction was applied to P values. We report raw and adjusted differences versus baseline, together with meaningful beta coefficients, either raw or standardized (data transformation (value-mean)/SD). Statistical analysis was performed using NCSS 2007 (Hintze J. (2009), Kaysville, Utah, USA).
### Tables and supporting information

**BP-independent effect of olmesartan on PWV**

The favourable BP-independent effect of the high dose group was driven neither by 40 mg nor by 80 mg. Both dosages had similar effects, as shown by the additional table below, displaying the 24hMBP-adjusted reduction in PWV.

#### Table S1

<table>
<thead>
<tr>
<th>Period</th>
<th>Dosage</th>
<th>24hMBP-adjusted decrease in PWV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to W24</td>
<td>20 mg</td>
<td>-0.40 ± 1.69 m/s</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>-0.84 ± 1.71 m/s</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>80 mg</td>
<td>-0.56 ± 1.67 m/s</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline to W52</td>
<td>20 mg</td>
<td>-0.12 ± 1.78 m/s</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>-0.77 ± 1.81 m/s</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>80 mg</td>
<td>-0.67 ± 1.85 m/s</td>
<td>0.01</td>
</tr>
</tbody>
</table>

#### Table S2

**Concomitant lipid lowering drugs**

<table>
<thead>
<tr>
<th>ATC class 2/ Generic term, n (%)</th>
<th>OM 20 mg N = 44</th>
<th>OM 40 mg N = 42</th>
<th>OM 80 mg N = 47</th>
<th>Total N = 133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Modifying Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>2 (4.5)</td>
<td>3 (7.1)</td>
<td>0</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1 (2.3)</td>
<td>3 (7.1)</td>
<td>8 (17.0)</td>
<td>12 (9.0)</td>
</tr>
</tbody>
</table>