Effects of blood pressure lowering with amlodipine or lisinopril on vascular structure of the common carotid artery

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ABSTRACT

Increased intima-media thickness of the common carotid artery predicts increased risk of myocardial infarction and stroke. Preliminary evidence suggests that a decrease in blood pressure (BP) is associated with diminished wall thickness. It is not known if all classes of anti-hypertensive agents have similar protective effects. In this double-blind parallel-group clinical trial, 69 previously untreated patients with hypertension were allocated randomly to 1 year of treatment with either amlodipine (5–10 mg daily) or lisinopril (5–20 mg daily). Doxazosin and bendrofluazide were added if required to achieve BP control. After 12 months of treatment, clinic BP, ambulatory BP and cardiac mass were reduced similarly by the two treatment regimens. Common carotid artery intima-media thickness decreased by 0.048 mm (95% confidence intervals 0.066, 0.031 mm) in the amlodipine-treated group, but decreased by only 0.027 mm (0.046, 0.007 mm) in the lisinopril-treated group (P < 0.05 for difference between treatments). Common carotid artery lumen diameter declined significantly only in patients treated with lisinopril [amlodipine, 0.02 mm (0.14, 0.10 mm); lisinopril, 0.21 mm (0.32, 0.11 mm); P < 0.02], while intima-media area declined similarly in the two treatment groups [amlodipine, 1.32 mm2 (1.91, 0.74 mm2); lisinopril, 1.26 mm2 (1.80, 0.72 mm2); not significant]. The results confirm that a decrease in BP causes regression of structural changes in the carotid artery in hypertensive patients. The nature of the structural regression differed markedly between the two treatment regimens, in spite of similar decreases in BP. The calcium channel blocker induced greater regression of common carotid artery intima-media thickness than the angiotensin-converting enzyme inhibitor. However, carotid artery wall mass, as indicated by intima-media area, was reduced to a similar extent by the two treatments. It remains to be established whether such differences confer a prognostic advantage.

INTRODUCTION

Studies of the impact of anti-hypertensive therapy on cardiovascular structure have focused mainly on the heart and resistance arteries. In both settings there is evidence that different drugs promote regression or remodelling of the structural changes associated with hypertension with varying efficacy [1–3]. Interest in these parameters as intermediate end-points in the assessment of therapeutic response is enhanced by the recognition that regression...

Key words: anti-hypertensive agents, atherosclerosis, carotid artery, hypertension, intima-media thickness, remodelling, ultrasound.

Abbreviations: ACE, angiotensin-converting enzyme; ANCOVA, analysis of co-variance; BP, blood pressure; CI, confidence intervals; CTS, circumferential tensile stress; HDL, high-density lipoprotein; IMA, intima-media area; IMT, intima-media thickness; LD, lumen diameter; LVMI, left ventricular mass index; SL index, Sokolow–Lyon index; W/L ratio, wall/lumen ratio.

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of left ventricular mass confers a survival advantage, and that remodelling of the resistance arteries impacts on a fundamental mechanism that sustains hypertension. There have been few studies of the structural regression of large arteries, despite this being an important target of hypertensive disease.

High-resolution B-mode ultrasonography allows non-invasive visualization of the walls of large superficial arteries, and intima-media thickness (IMT) measured from B-mode carotid ultrasound correlates closely with histological measurements [4,5]. Studies in the carotid artery have demonstrated an increase in IMT in association with hypertension [6,7]. In addition, increased carotid IMT is associated with a wide spectrum of other cardiovascular risk factors, including age, male sex, race, hyperlipidaemia, smoking, diabetes mellitus, left ventricular hypertrophy, plasma homocysteine, uric acid and fibrinogen [8,9]. Importantly, five prospective studies have now shown that increased carotid IMT is associated with greater risk of both myocardial infarction and stroke [10–14]. These data support the view that carotid arterial wall thickening reflects early atherosclerosis.

A number of previous studies have suggested that lowering of blood pressure (BP) is associated with a decrease in carotid wall thickness [15–19]. It is not known if all classes of anti-hypertensive agents have similar anti-atherosclerosis effects. The primary aim of this present study was to compare the effects of two anti-hypertensive regimens (an amlodipine-based regimen and a lisinopril-based regimen) on common carotid artery IMT in previously untreated hypertensive patients.

**METHODS**

**Patients and study design**

Both male and female patients (age range 20–80 years) with untreated hypertension (previously untreated or anti-hypertensive treatment discontinued for at least 1 year) (sitting systolic BP 140–220 mmHg and/or sitting diastolic BP 90–120 mmHg) were included in the study population. Individuals were not eligible if they had malignant or accelerated hypertension, diabetes mellitus, familial hypercholesterolaemia, or significant concomitant systemic disease. A total of 60 patients were required to complete the study. All participants were recruited from a single clinical centre, the Peart–Rose Hypertension and Cardiovascular Disease Prevention Clinic at St. Mary’s Hospital, Paddington, London, U.K. All subjects gave written informed consent, the local research ethics committee approved the study protocol, and the research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

This was a prospective randomized parallel-group clinical trial. After a 4-week run-in period (2 weeks on single-blinded placebo tablets), eligible patients were randomized, double-blind, with minimization for age, ethnic origin, sex and mean sitting systolic BP, to receive either amlodipine (5 mg daily) or lisinopril (5 mg daily). Follow-up visits were at 2-week intervals until BP was controlled and every 3 months thereafter. Amlodipine dosages (5–10 mg daily) and lisinopril dosages (5–20 mg daily) were titrated upwards until satisfactory control of BP was achieved (sitting BP ≤140/90 mmHg). Doxazosin (1–8 mg daily) and bendrofluazide (2.5–5 mg daily) were added as second-line and third-line therapies as required.

Ultrasonography of the common carotid and femoral arteries, echocardiography and 12-lead ECG were carried out at baseline, after 14 and 26 weeks of active treatment and at the end of the study. Baseline examination included complete medical history, physical examination, clinic and ambulatory BP measurement, laboratory tests, and chest X-ray. During each follow-up visit, clinic BP adverse events, concurrent medication and compliance with study medication were recorded. Laboratory tests were repeated after 2 weeks of active treatment and at the end of the study. A 24-h ambulatory BP measurement was repeated at the end of the study.

**BP and heart rate measurement**

Clinic BP and heart rate were measured from the right arm using a regularly calibrated semi-automated sphygmomanometer (Sentron). Systolic BP was taken as the appearance of the Korotkoff sound (phase I) and diastolic BP as the disappearance of the Korotkoff sound (phase V) to the nearest 2 mmHg. Clinic BP and heart rate were calculated as the means of three consecutive sitting measurements, taken after 5 min of rest and with 5-min intervals between readings. The 24-h ambulatory BP measurement was performed using Spacelabs 90207 monitors. Measurements were made every 30 min throughout the 24-h period, and monitoring was deemed acceptable if more than 90% of readings were recorded. Mean 24-h BP was calculated as the mean of the hourly means over the whole 24 h.

**Ultrasound of carotid and femoral arteries**

High-resolution ultrasound imaging was performed by a single ultrasonographer using an Ultramark 4 scanner (Advanced Technologies Laboratories, Washington, DC, U.S.A.) with a high-resolution 7.5 MHz linear-array scan head. All images were coded and stored in original digital quality for off-line analysis. Bilateral common carotid scanning was performed with the subject in the supine position, with the neck extended and rotated 45° to the contra-lateral side. Carotid bulb dilation served as a landmark indicating the border between the distal common carotid artery and the bifurcation area. For the determination of common carotid IMT and lumen
diameter (LD), longitudinal images of the distal common carotid artery focused on the far wall were utilized. Using ECG gating, images from each of three projections (posterior oblique, lateral and anterior oblique) were frozen at end-diastole. In analogous fashion, both femoral arterial systems were scanned with the subject in the supine position, hips extended and externally rotated by approx. 30°. Images of right and left distal common femoral arteries from each of two projections (anterolateral and anteromedial) were frozen at end-diastole.

At completion of the study, all images were measured by a single observer using a purpose-designed user-directed edge-detection image analysis program. The observer was blinded to patient identity, treatment allocation and date of examination. IMT was determined as the median distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far wall, over a 5–15 mm length in the distal vessel, from each of the images. Where the image analysis program failed to delineate the relevant interfaces clearly, five estimates of IMT were made using a mouse-controlled on-screen cross-hair, and the median was calculated. LD for each image was taken as the median of five mouse-controlled measures of the distance from the leading edge of the intima–lumen interface of the near wall to the leading edge of the lumen–intima interface of the far wall. The mean values of all six measurements were taken as the IMT and LD for the common carotid artery for each subject. The mean values of four measurements were taken as the IMT and LD for the common femoral for each subject.

The wall/lumen (W/L) ratio and the intima-media area (IMA) for the common carotid artery and the common femoral artery were calculated according to the following formulae:

\[ W/L \text{ ratio} = \frac{\text{IMT}}{\text{LD}} \]

\[ \text{IMA} (\text{mm}^2) = \pi \left( \text{LD} \cdot \text{IMT} + \text{IMT}^2 \right) \]

Circumferential tensile stress (CTS) was calculated from mean arterial pressure (MAP), LD and IMT according to the formula:

\[ \text{CTS} (\text{mmHg}) = \frac{\text{MAP} \cdot \text{LD}}{\text{IMT}} \]

Prior to commencement of anti-hypertensive treatment, six subjects underwent a second carotid and femoral artery ultrasonography. This repeat occurred within 1–4 weeks of the first procedure. These scans were performed by the same ultrasonographer, and the same observer directed off-line measurements of IMT and LD in the common carotid and common femoral arteries.

Echocardiography

Echocardiography was performed with the patient in the left lateral position using a phased-array sector scanner (General Electric Pass II, 3.5 MHz transducer; General Electric, Milwaukee, WI, U.S.A.). Interventricular septal wall thickness (IVST), posterior wall thickness (PWT) and left ventricular internal diameter (LVID) were measured from the left ventricular short-axis view using two-dimensional guided M-mode echocardiography. Measurements were made at end-diastole in accordance with the Penn convention. Three consecutive cardiac cycles were measured and average values were obtained. Left ventricular mass (LVM) was calculated using the cubed formula:

\[ \text{LVM} = 1.04 \times \left( (\text{IVST} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3 \right) - 14 \text{ g} \]

This was then divided by body surface area to give a value for left ventricular mass index (LVMI).

Electrocardiography

Twelve-lead electrocardiograms were evaluated for evidence of left ventricular hypertrophy according to the Sokolow–Lyon voltage criteria: the larger of the sum of the S wave in lead 1 plus the R wave in lead 5 (S1 + R5; mm) or the sum of the S wave in lead 1 plus the R wave in lead 6 (S1 + R6; mm) [Sokolow–Lyon index (SL index)].

Statistical methods

All statistical analyses were performed with SAS software. All outcome analyses were conducted according to the intention-to-treat principle. Statistical comparisons were based on two-tailed tests.

The primary study outcome was the change from baseline in common carotid artery IMT after 1 year of active treatment. Between-scan reproducibility for common carotid artery IMT in patients with uncomplicated hypertension was estimated to be 0.01 ± 0.05 mm (mean difference ± S.D. of difference) [7,15]. Hence the study sample size of 30 patients in each treatment group was chosen so as to provide 80% power to detect a 0.02 mm difference between groups in mean change from baseline in common carotid artery IMT, with a significance level of 5%. Adjustments for multiple comparisons were made in all analyses concerning secondary end-points (common carotid artery LD, W/L ratio and IMA; common femoral artery IMT, LD, W/L ratio and IMA; SL index; LVMI) using Bonferroni’s correction.

Baseline data are expressed as mean ± S.D. or as median (range), and study outcomes are expressed as mean change from baseline [95% confidence intervals (CI)]. The homogeneity of the randomized groups at baseline was determined by means of the unpaired Student’s t test for continuous variables, and by means of χ² tests or continuity-adjusted χ² tests for categorical variables. Baseline associations between cardiovascular structure and systolic BP were explored using regression analysis. Within-treatment changes from baseline were analysed using paired t-tests. Between-treatment comparisons of
changes from baseline were made using analysis of covariance (ANCOVA), with the change in sitting systolic BP as the co-variate. Other terms included in the ANCOVA model were treatment group, age, sex, race and baseline sitting systolic BP. Assumptions of normality and homogeneity of variance were tested using the Shapiro–Wilks statistic, stem-and-leaf plots and normal probability plots. Where logarithmic or square-root transformations did not result in data satisfying the assumptions of normality, ANCOVA was applied to ranked data.

RESULTS

Characteristics of study participants at baseline

A total of 69 patients were randomly allocated to treatment groups, representing 86% of the 80 potentially eligible patients who entered the pre-randomization run-in period. The 35 patients randomly allocated to receive amlodipine and the 34 patients allocated to receive lisinopril had similar sex and ethnic group distributions, and were well matched for age, alcohol intake, weight, height, serum creatinine and triacylglycerols (Table 1). The number of patients who smoked or were ex-smokers was higher in the amlodipine group (22 compared with 14), and median time since first diagnosis of hypertension was longer in the lisinopril group. No patient was taking lipid-lowering therapy at baseline. There was a trend for total cholesterol to be greater in those in the lisinopril group at baseline, and high-density lipoprotein (HDL)-cholesterol was significantly higher in this group than in the amlodipine group. Clinic and mean 24-h ambulatory BP levels were similar in the two treatment groups at baseline (Table 1), as were measures of carotid vessel dimensions and cardiac hypertrophy (Table 2). Common femoral artery IMT was similar in the two groups, but femoral LD was significantly greater among those patients allocated to lisinopril therapy. At baseline, common carotid and femoral artery IMTs, as well as

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amlodipine group</th>
<th>Lisinopril group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common carotid artery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.763 ± 0.130</td>
<td>0.792 ± 0.170</td>
<td>0.41</td>
</tr>
<tr>
<td>LD (mm)</td>
<td>6.56 ± 0.74</td>
<td>6.57 ± 0.71</td>
<td>0.95</td>
</tr>
<tr>
<td>W/L ratio</td>
<td>0.094 ± 0.012</td>
<td>0.097 ± 0.016</td>
<td>0.40</td>
</tr>
<tr>
<td>IMA (mm²)</td>
<td>17.74 ± 4.51</td>
<td>18.65 ± 5.63</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Common femoral artery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.672 ± 0.174</td>
<td>0.708 ± 0.169</td>
<td>0.40</td>
</tr>
<tr>
<td>LD (mm)</td>
<td>7.77 ± 1.02</td>
<td>8.79 ± 1.05</td>
<td>0.00</td>
</tr>
<tr>
<td>W/L ratio</td>
<td>0.074 ± 0.016</td>
<td>0.070 ± 0.015</td>
<td>0.30</td>
</tr>
<tr>
<td>IMA (mm²)</td>
<td>18.00 ± 5.91</td>
<td>21.41 ± 6.33</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Cardiac hypertrophy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL index (mm)</td>
<td>28.1 ± 8.2</td>
<td>31.7 ± 9.5</td>
<td>0.09</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>119 ± 29</td>
<td>130 ± 30</td>
<td>0.17</td>
</tr>
</tbody>
</table>
LVMi and SL index, were all positively associated with baseline systolic BP ($P < 0.02$ in all cases).

**Treatment**

Of the 69 patients randomly allocated to treatment groups, 60 completed 26 weeks of active treatment (31 amlodipine; 29 lisinopril), and 55 completed 50 weeks of active treatment (28 amlodipine; 27 lisinopril). A total of 34 of the 35 patients on amlodipine therapy and 34 of the 34 patients on lisinopril therapy reported at least one adverse event during the treatment period ($P = 1.00$ for difference between treatments). The most commonly reported adverse event was headache (14 of 35 patients in the amlodipine group and 18 of 34 patients in the lisinopril group). Nine patients withdrew from the study due to adverse events: three on amlodipine (complete heart-block and ischaemic stroke, renal carcinoma, impotence) and six on lisinopril [rise in serum creatinine, chest pain, coughing (three cases), headaches].

Of the 69 patients, 24 received only first-line therapy, and, of these, 15 (eight in the amlodipine group and seven in the lisinopril group) completed 50 weeks of active treatment. Titration to higher doses was required for 60% of the patients treated with amlodipine and 71% of those who received lisinopril. Second-line therapy with doxazosin was required by 51% of the amlodipine group and 62% of the lisinopril group, with a median dosage of 4 mg daily in both groups. Third-line therapy with bendrofluazide was required by 29% of the amlodipine-treated patients and 18% of the lisinopril-treated patients. Median bendrofluazide dosage was 5 mg and 2.5 mg daily for the amlodipine and lisinopril groups respectively.

**BP, heart rate and lipids**

Over the 12 months of the follow-up clinic, systolic and diastolic BPs were similar in the two treatment groups (Figure 1). Furthermore, the decreases in ambulatory BP from baseline to the end of the study were similar; mean (95% CI) changes were as follows: amlodipine, systolic $-21 (-26, -15)$ mmHg, diastolic $-14(-17, -11)$ mmHg; lisinopril, systolic $-20 (-27, -13)$ mmHg, diastolic $-15(-19, -11)$ mmHg. There were no significant changes in clinic heart rate with treatment. Ambulatory heart rate remained unchanged in amlodipine-treated patients [$+1 (-2, +3)$ beats/min], but rose in lisinopril-treated patients [$+4 (+1, +7)$ beats/min]. However, there was no statistically significant difference between treatments.

No patient received lipid-lowering therapy during the treatment phase of the study. However, total cholesterol fell significantly in those treated with lisinopril over the 1-year study period: amlodipine, $-0.13$ (95% CI $-0.20$ to $-0.06$, $P < 0.001$).
Changes in IMT

For the six subjects who underwent repeated ultrasonography prior to commencement of therapy, between-scan reproducibility, expressed as mean difference ± S.D. of the difference, was 0.01 ± 0.03 mm for common carotid IMT, −0.02 ± 0.17 mm for common carotid LD, 0.01 ± 0.03 mm for common femoral IMT and 0.05 ± 0.23 mm for common femoral LD.

The IMT of the common carotid artery declined during the 1 year of treatment in both treatment groups (Figure 2). At 14 weeks a significant reduction in common carotid artery IMT was seen in those patients treated with amlodipine, but the wall thickness was virtually unchanged in the lisinopril group. Statistically significant decreases from baseline were seen in both treatment groups at week 26 and at the end of the study. The decrease in common carotid IMT, from baseline to the end of the study, was significantly greater in the amlodipine group than in the patients who received lisinopril (P = 0.044; ANCOVA on ranked data).

Regression of common carotid artery IMT in those patients who only received first-line therapy (eight in the amlodipine group and seven in the lisinopril group) paralleled the regression seen with the whole study population. In these patients, statistically significant decreases from baseline were seen in the amlodipine group only at week 26 and at the end of the study.

In order to explore whether the disparities between the two treatment groups (detailed in Table 1) contributed to the between-treatment difference in the regression of IMT, a further between-treatment comparison of the change in common carotid artery IMT from baseline to the end of the study was performed using ANCOVA, fitting smoking, duration of hypertension, total cholesterol and HDL-cholesterol as additional co-variates. The difference in IMT regression between amlodipine and lisinopril remained significant (mean difference −0.030 mm; 95% CI −0.036 to −0.024).

Femoral artery IMT did not decrease significantly in either treatment group over the 50 weeks of the study (Table 3).

LD, W/L ratio and IMA

At the end of the study, the LD of both the common carotid artery and the common femoral artery had declined significantly in patients treated with lisinopril, but not in those treated with amlodipine (Figure 2; Table 3). The decrease in common carotid artery LD in the lisinopril-treated patients was apparent at 14 weeks and persisted throughout the study period. The decline in femoral artery LD in the lisinopril-treated patients was only apparent at the 50th week of observation.

The W/L ratio of the common carotid artery was reduced by approx. 4% in those patients who received

### Table 3  Changes in common carotid artery, common femoral artery and cardiac structure in amlodipine- and lisinopril-treated groups at the end of the study (50 weeks of active treatment)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>Between-treatment P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>−0.048 (−0.066, −0.031)**</td>
<td>−0.027 (−0.046, −0.007)*</td>
<td>0.044</td>
</tr>
<tr>
<td>LD (mm)</td>
<td>−0.02 (−0.14, +0.10)</td>
<td>−0.21 (−0.32, −0.11)**</td>
<td>0.017</td>
</tr>
<tr>
<td>W/L ratio</td>
<td>−0.004 (−0.006, −0.002)**</td>
<td>0.000 (−0.002, +0.003)</td>
<td>0.004</td>
</tr>
<tr>
<td>IMA (mm²)</td>
<td>−1.32 (−1.91, −0.74)**</td>
<td>−1.26 (−1.80, −0.72)**</td>
<td>0.866</td>
</tr>
<tr>
<td>Common femoral artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>−0.015 (−0.055, +0.024)</td>
<td>−0.015 (−0.053, +0.022)</td>
<td>0.998</td>
</tr>
<tr>
<td>LD (mm)</td>
<td>+0.12 (−0.07, +0.30)</td>
<td>−0.19 (−0.36, −0.03)*</td>
<td>0.015</td>
</tr>
<tr>
<td>W/L ratio</td>
<td>−0.003 (−0.006, +0.001)</td>
<td>+0.000 (−0.003, +0.004)</td>
<td>0.321</td>
</tr>
<tr>
<td>IMA (mm²)</td>
<td>−0.25 (−1.48, +0.99)</td>
<td>−0.99 (−2.24, +0.26)</td>
<td>0.410</td>
</tr>
<tr>
<td>Cardiac hypertrophy</td>
<td></td>
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</tr>
<tr>
<td>SL index (mm)</td>
<td>−2.4 (−4.0, −0.8)*</td>
<td>−5.0 (−7.0, −2.9)**</td>
<td>0.165</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>−5 (−14, +5)</td>
<td>−15 (−26, −5)*</td>
<td>0.356</td>
</tr>
</tbody>
</table>

−0.32, +0.06 mmol/l; lisinopril, −0.26 (−0.44, −0.08) mmol/l. Triacylglycerols remained essentially unchanged throughout the study period in both treatment groups: amlodipine, −0.08 (−0.39, +0.23) mmol/l; lisinopril, −0.07 (−0.27, +0.13) mmol/l. HDL-cholesterol rose in patients treated with amlodipine: amlodipine, 0.09 (+0.01, +0.16) mmol/l; lisinopril, −0.02 (−0.10, +0.06) mmol/l. However, no statistically significant differences occurred between treatments for any of the changes in lipid levels.
amlodipine for 1 year (Table 3). In contrast, proportionate decreases in common carotid artery IMT and LD resulted in an unchanged W/L ratio in patients treated with lisinopril.

The common carotid artery IMA, calculated from measures of IMT and LD, declined during the 1 year of treatment in both treatment groups (Figure 2). Significant reductions were seen as early as 14 weeks in both groups, and IMA continued to decrease over the entire observation period. At no time point during the year of treatment was there a difference in the regression of IMA between the two treatment groups.

The W/L ratio and the IMA in the common femoral artery did not change significantly in either treatment group throughout the study (Table 3).

**Changes in CTS**

CTS levels in the common carotid artery and the common femoral artery were similar in the two treatment groups at baseline (common carotid CTS: amlodipine group, 1303 ± 210 mmHg; lisinopril group, 1282 ± 226 mmHg; femoral CTS: amlodipine group, 1702 ± 370 mmHg; lisinopril group, 1809 ± 376 mmHg; means ± S.D.). Due to the greater decreases in LD with lisinopril, calculated wall stress tended to be reduced more in lisinopril-treated patients than in patients receiving amlodipine [mean (95% CI) change in common carotid CTS: amlodipine, -144 (-210, -80) mmHg; lisinopril, -212 (-275, -150) mmHg; change in femoral CTS: amlodipine, -195 (-308, -83) mmHg; lisinopril, -274 (-362, -186) mmHg].

**Left ventricular hypertrophy**

The SL index decreased from baseline to the end of the study in both treatment groups. The reduction in the index appeared to be more marked in the lisinopril group (Table 3). However, there was no statistically significant difference between the two treatment groups. Similarly, the decrease in LVM tended to be greater in patients treated with lisinopril than in those treated with amlodipine, but this difference did not reach standard statistical significance. Regression of echocardiographically measured cardiac mass with both lisinopril and amlodipine appeared to be due primarily to reductions in wall thickness, whereas chamber dimensions remained unchanged (results not shown).

**DISCUSSION**

This double-blind comparative study confirms that structural changes of the carotid wall due to hypertension can be reversed by effective anti-hypertensive therapy. It extends previous evidence that lowering of BP is associated with a reduction in both wall thickness and mass of larger arteries [15–19]. The most interesting aspect of these data is that the character of the structural regression differed markedly between the amlodipine and lisinopril groups, despite similar decreases in brachial BP. Common carotid IMT was reduced to a greater extent by amlodipine treatment, but the decrease in LD in the lisinopril group alone resulted in equivalent decreases in wall mass.

Which of the two measures – carotid wall thickness (IMT) or carotid wall mass (IMA) – is likely to hold stronger prognostic value? The present study provides no opportunity to address this issue. Carotid IMT has been strongly associated with cardiovascular risk factors [6–9] and events in large observational and prospective studies [10–14]. Few data regarding IMA and prognosis have been presented. However, due to the incompressibility of arterial wall tissue [20], IMA, unlike wall thickness, is independent of variations in distending pressure, and hence may be the better measure of vascular hypertrophy.

The use of both angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists has been reported to be associated with structural remodelling of small arteries in human hypertension [3, 21–23]. Both drug classes evidently confer very striking survival benefits in clinical trials – calcium antagonists more specifically in the context of hypertension [24], while in a recent trial in high-risk patients ACE inhibitor use was associated with reduced cardiovascular events despite only modest reduction in BP [25]. It remains to be seen whether structural regression of large-artery walls induced by treatment relates in any way to these benefits. Comparison with lipid-lowering treatment in the Asymptomatic Carotid Artery Progression Study (ACAPS) offers an interesting perspective on the magnitude of the decrease in IMT seen in the present study. After 3 years in ACAPS there was 0.04 mm difference in mean carotid IMT between patients treated with lovastatin and those receiving placebo. This difference was associated with a halving of cardiovascular events, and an 8-fold reduction in mortality [26]. In this present study, IMT regressions of 0.05 and 0.03 mm were achieved in the amlodipine- and lisinopril-treated patients respectively. From population studies, a difference of 0.04 mm in common carotid IMT has been associated with a 10% difference in risk of stroke or myocardial infarct [14].

A number of studies have reported that anti-hypertensive treatment induces changes in the wall structure of large arteries. We previously performed a small uncontrolled study that suggested that a reduction of carotid IMT was achievable by means of ACE inhibition, with or without the addition of calcium channel blockade [15]. In that study we also observed an early decrease in carotid artery LD associated with lowering of BP. Schartl et al. [16] noted an 11% reduction in the ratio of iliac artery IMA to lumen area after 6 months of treatment.

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with quinapril. In the present study, however, we found no statistically significant decreases in femoral artery IMT, IMA or W/L ratio following BP lowering in either treatment group. One explanation for this discrepancy may be a difference in the sensitivity and precision of intra-arterial and percutaneous ultrasonography for the detection of early arterial disease. Another possible explanation is that different BP-lowering drugs may have disparate effects on the walls of iliac, femoral and carotid arteries. In a recent double-blind comparison of 9 months of treatment with either celeriprol or enalapril in 98 hypertensive patients, IMT in both the common carotid and radial arteries declined significantly, with no difference between the two groups [17].

A re-analysis of the REGRESS trial [27] suggested that the addition of calcium channel blockers to pravastatin provided further benefit in retarding the progression of coronary atherosclerosis. However, in both the Multi-centre Irudine Diuretic Atherosclerosis Study (MIDAS) [28] and the Verapamil Hypertension Atherosclerosis Study (VHAS) [29] there was progression of carotid IMT. This was despite BP lowering with calcium channel blockers or diuretics of similar magnitude to that observed in the present study. In contrast with the present study, the majority of participants in both VHAS and MIDAS were already on anti-hypertensive medication; in addition, intima-media thickening was more advanced, and many subjects displayed focal wall thickening and early plaque. It is possible that the more advanced disease seen in these previous studies is less susceptible to regression.

Alternatively, amlodipine, a member of the new generation of long-acting highly lipophilic dihydropyridines, may provide greater protection against atherosclerosis than older calcium channel blockers. Amlodipine has a marked inhibitory influence on the oxygen free radicals involved in lipid peroxidation [30], and has been shown to prevent experimental atherosclerosis [31]. Two recently published studies, both of which showed regression of carotid IMT with amlodipine treatment, lend support to this proposal. Koshiyama et al. [18], in a very small open study, found a significant decrease in common carotid IMT in 11 hypertensive patients with Type II diabetes treated with amlodipine, while those treated with ACE inhibitors showed no change [18]. The results of PREVENT, a multicentre, placebo-controlled clinical trial involving 377 patients with previously documented coronary artery disease, included a significant effect in slowing the 36-month progression of carotid artery atherosclerosis by amlodipine in comparison with placebo [19].

The LD of large vessels is enlarged in patients at cardiovascular risk, and has been proposed as an additional valuable prognostic indicator [32,33]. The difference in common carotid artery LD between subjects undergoing calcium antagonist- and ACE inhibitor-based treatments found in our present study was not expected. However, in keeping with our observations, calcium antagonists have been reported to increase carotid arterial compliance, with no change in carotid artery LD occurring despite a reduction in BP [34]. Lowering of BP by ACE inhibitor treatment in humans has been associated with increased arterial compliance and either no significant change or a decrease in the LD of the common carotid artery, despite concurrent increases in brachial artery LD [17,35].

The changes in common carotid artery IMT, W/L ratio, IMA and LD observed in the present study, and the disparate vascular remodelling seen in the two treatment groups, may not be attributable to direct actions of the drugs on the arterial wall, but to differences in local haemodynamics, shear and tensile stresses within the carotid artery [32,36,37]. Blood flow was not measured in the present study, and hence any changes in shear stress with treatment cannot be estimated. Wall CTS fell with both treatments in both the common carotid and femoral arteries over the course of the study. Due principally to reorganization or remodelling of the arterial wall around a narrower lumen, there was a non-significant trend for the reduction in wall stress in the lisinopril group to be greater. Wall CTS was calculated using brachial BP, which may differ from arterial pressure in the carotid artery [38,39]. A previous study comparing perindopril with nitrendipine in hypertensive patients with end-stage renal disease did not show a difference between these agents with regard to carotid BP [40]. Interestingly, in the recent clinical trial comparing enalapril and celiprolol, regression of carotid artery wall thickness was reported to be dependent on the reduction in carotid pulse pressure rather than on changes in mean brachial BP or brachial pulse pressure [17].

In the present study, regression of left ventricular hypertrophy tended to be greater in patients given lisinopril-based therapy than in those given amlodipine. This is in agreement with previous reports showing that nearly all classes of anti-hypertensive drugs may reduce cardiac hypertrophy [1], but that ACE inhibitors may be the most efficacious agents [2].

In summary, our study confirms that a decrease in BP can induce regression of common carotid artery IMT in previously untreated hypertensive patients. Furthermore, this is the first double-blind comparative study to show that different anti-hypertensive agents modify large arterial wall structure to different extents. This extends observations that have shown a differential effect of anti-hypertensive therapies on cardiac structure [1,2], and adds to existing evidence regarding the heterogeneity of the response of different blood vessels [3,21–23]. The significance of these different patterns of regression in terms of their implication for risk remains uncertain. Future studies exploring whether such differences reflect direct actions of the drug on the arterial wall or
differences in local haemodynamics within a specific artery will be of interest.

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REFERENCES


