Calcium Antagonist Lacidipine Slows Down Progression of Asymptomatic Carotid Atherosclerosis

Principal Results of the European Lacidipine Study on Atherosclerosis (ELSA), a Randomized, Double-Blind, Long-Term Trial

Alberto Zanchetti, MD; M. Gene Bond, PhD; Michael Hennig, PhD; Albrecht Neiss, PhD; Giuseppe Mancia, MD; Cesare Dal Palù, MD; Lennart Hansson, MD; Bruno Magnani, MD; Karl-Heinz Rahn, MD; John L. Reid, MD; José Rodicio, MD; Michel Safar, MD; Lothar Eckes, MD, PhD; Paolo Rizzini, MD; on behalf of the ELSA investigators

Background—Most cardiovascular events associated with hypertension are complications of atherosclerosis. Some antihypertensive agents influence experimental models of atherosclerosis through mechanisms independent of blood pressure lowering.

Methods and Results—The European Lacidipine Study on Atherosclerosis (ELSA) was a randomized, double-blind trial in 2334 patients with hypertension that compared the effects of a 4-year treatment based on either lacidipine or atenolol on an index of carotid atherosclerosis, the mean of the maximum intima-media thicknesses (IMT) in far walls of common carotids and bifurcations (CBMmax). This index has been shown by epidemiological studies to be predictive of cardiovascular events. A significant (P<0.0001) effect of lacidipine was found compared with atenolol, with a treatment difference in 4-year CBMmax progression of −0.0227 mm (intention-to-treat population) and −0.0281 mm (completers). The yearly IMT progression rate was 0.0145 mm/y in atenolol-treated and 0.0087 mm/y in lacidipine-treated patients (completers, 40% reduction; P=0.0073). Patients with plaque progression were significantly less common, and patients with plaque regression were significantly more common in the lacidipine group. Clinic blood pressure reductions were identical with both treatments, but 24-hour ambulatory systolic/diastolic blood pressure changes were greater with atenolol (−10/−9 mm Hg) than with lacidipine (−7/−5 mm Hg). No significant difference between treatments was found in any cardiovascular events, although the relative risk for stroke, major cardiovascular events, and mortality showed a trend favoring lacidipine.

Conclusion—The greater efficacy of lacidipine on carotid IMT progression and number of plaques per patient, despite a smaller ambulatory blood pressure reduction, indicates an antiatherosclerotic action of lacidipine independent of its antihypertensive action. (Circulation. 2002;106:2422-2427.)

Key Words: atherosclerosis ■ carotid arteries ■ plaque ■ hypertension ■ drugs

The most cardiovascular events related to hypertension are complications of atherosclerosis. Experimental studies have shown that various antihypertensive agents may exert an antiatherosclerotic action that is partly independent of the blood pressure-lowering effect. Among calcium antagonists, highly lipophilic, antioxidant, long-acting dihydropyridines such as lacidipine were found to be particularly effective in experimental models of atherosclerosis. B-mode ultrasound examination of the carotid arteries with measurement of intima-media thickness (IMT) has been used...
as a measure of asymptomatic atherosclerosis progression. Three randomized trials of antihypertensive therapy showed smaller progression or greater regression of carotid lesions in patients treated with a calcium antagonist rather than a diuretic, but the changes were small and the trials had limited power to detect these differences. Whether different antihypertensive agents vary in their capacity to slow the progression of carotid atherosclerosis is clinically relevant, in view of the numerous epidemiological observations that differences in carotid IMT significantly predict cardiovascular events. Hence, the European Lacidipine Study on Atherosclerosis (ELSA) was planned with sufficient power to test whether long-term (4 years) antihypertensive therapy using the calcium antagonist lacidipine was equally effective as therapy with the β-blocker atenolol on carotid IMT changes.

Methods

Participants

Subjects aged 45 to 75 years with sitting systolic blood pressure (SBP) of 150 to 210 mm Hg and diastolic blood pressure (DBP) of 95 to 115 mm Hg were recruited by 410 clinical units in France, Germany, Greece, Italy, Spain, Sweden, and the United Kingdom. All patients gave written consent. The protocol was approved by Ethics Committees of all institutions involved.

Interventions

After a 4-week placebo wash-out period, patients were randomized to receive either lacidipine 4 mg once daily or atenolol 50 mg once daily. Randomization was computer-generated, using separate lists for each referral center with a block size of 4. If diastolic blood pressure was not <95 mm Hg with a fall of at least 5 mm Hg, the dose of lacidipine could be increased to 6 mg, and atenolol could be increased to 100 mg (month 1), with open-label hydrochlorothiazide added (12.5 mg daily month 3 and 25 mg daily month 6). Patients and study personnel, excluding the Safety Committee, were blinded to treatment assignment for the study duration.

Measurements

Duplicate carotid scans were performed by certified sonographers at 23 referral centers between beginning of run-in and randomization, and subsequently at yearly intervals; scans were performed 4 years after randomization in patients who withdrew prematurely. B-mode scans were obtained in all referral centers by use of the same instrument (Biosound 2000 II SA, Biosound) with an 8 MHz annular array transducer. All scans were read at the Ultrasound Coordinating Center with quality assurance accomplished as reported.

Three measurements of sitting clinic blood pressure were taken by a mercury manometer at baseline, at each titration visit, and every 6 months thereafter. Ambulatory blood pressure monitoring was done at baseline and at yearly intervals thereafter. Diskettes were edited at the Ambulatory Blood Pressure Coordinating Center. All data were delivered to the Statistical Analysis Center.

Outcomes

The primary efficacy outcome was the change in mean maximum IMT of the 4 far walls in the distal common carotids and carotid bifurcations bilaterally (CBMₘₐₓ) during 4 years. All scans were read after study end within a 6-month period by 8 readers. Scans of any individual patient were assigned to the same reader, but the scan sequence was randomized so that the reader was blind to the time of recording. Four hundred duplicate scans were read for reproducibility assessment at study end.

Secondary efficacy variables were the proportion of patients with an increase or decrease in plaque number (focal IMT of ≥1.3 mm) at study-end, and incidence of fatal and nonfatal cardiovascular events and total mortality, adjudicated by an Event Monitoring Committee blinded to treatment assignment. Events were examined 3 times during the study by an Independent Safety Committee in an unblinded manner.

Statistics

Sample size calculation assumed a 4-year difference in CBMₘₐₓ changes between treatment groups of 0.04 mm, with a standard deviation of 0.1939 mm (including measurement error). With a two-sided 5% significance, a 95% power, and a 35% drop-out rate, a total sample size of 1884 patients was calculated and increased to at least 2000 patients to increase the precision of estimated treatment effect measurements. No interim analysis was performed during the study.

Data analyses were carried out according to an analysis plan established before the researchers were informed of the data. Two-sided significance tests were used. Treatment-related differences in CBMₘₐₓ changes were analyzed by repeated measurements ANOVA using all measurements by a 2-stage-mixed model and by ANOVA using the final measurement available minus baseline measurement, and yearly progression with time between baseline and actual measurement included.

Additional analyses were (1) treatment-related IMT changes separately for common carotids and bifurcations (repeated measurements analyses); (2) correlation of CBMₘₐₓ changes with common carotid diameter changes; (3) proportions of patients with increased or decreased plaque number at study end compared in lacidipine and atenolol groups by χ² test; (4) clinic and ambulatory blood pressures and heart rates (post-titration to end-study values) compared with baseline by paired t test, and treatment-related changes compared by unpaired t test; (5) treatment-related changes (end-of-study minus baseline) in laboratory parameters compared by Wilcoxon unpaired sample test; (6) cardiovascular events and death in the 2 treatment groups compared by Cox regression analyses and Kaplan-Meier curves; and (7) incidences of cardiovascular events in groups differing by baseline CBMₘₐₓ quintile or plaque number, compared by χ² test, Fisher’s exact test, or logistic regression analyses (exploratory post-hoc analyses).

Subgroups were prespecified in the analysis plan by the baseline variables of age, clinic SBP, DBP, pulse pressure, serum total cholesterol and creatinine concentrations (2 subgroups based on median values), smoking (smokers, exsmokers, nonsmokers), sex, and diabetes. Both subgroup-effects and subgroup-treatment interactions were investigated in the final model.

Results

Patients

A total of 3407 patients (Figure 1) were screened for possible randomization, 1073 of whom were excluded from participation. We randomly allocated 2334 patients to double-blind treatment (safety population, with 43 atenolol and 49 lacidipine patients lost to follow-up). The intention-to-treat (ITT) population consisted of all patients randomized to double-blind medication who had the baseline ultrasound scan and at least 1 follow-up scan, including scans performed after withdrawal (mean follow-up 3.75 years). The completer population was made up of patients who actually completed the 4-years of the study under randomized medication.

Baseline characteristics of randomized patients are listed in Table 1. There was no major difference between the 2 treatment groups.

Treatment

In the ITT population, 49.7% of the patients randomized to atenolol and 46.6% of those randomized to lacidipine were maintained at the low dose. A total of 12.2% and 11%...
respectively, received the higher dose, and 35.9% and 31.8%, respectively, received add-on hydrochlorothiazide. Among completers, low-dose monotherapy was maintained in 53.7% and 47.6%, high-dose monotherapy in 10.9% and 17.9%, and hydrochlorothiazide was added in 35.5% and 34.4% of atenolol and lacidipine patients, respectively.

Nonrandomized cardiovascular therapies were given for variable times during the treatment period to limited numbers of patients; antihypertensive agents other than protocol drugs were given to 1.0% and 1.1% of atenolol and lacidipine patients, lipid-lowering agents to 6.3% and 5.6%, and antiplatelet agents to 4.3% and 3.1% (ITT).

Treatment-Related Changes in Carotid Wall
The primary efficacy variable CBM max changed to a significantly smaller extent in lacidipine-treated patients than in atenolol-treated patients. The estimated treatment effect (lacidipine minus atenolol) was \(-0.0227\) (ITT) and \(-0.0281\) mm (completers) (Figure 2). The effects were significant \((P<0.0001)\) in all populations for treatment, time points, and baseline CBM max (the greater the effect the greater was baseline CBM max). The estimated treatment effect in favor of lacidipine was significant \((P<0.01)\) in both common carotids and bifurcations, with a greater treatment effect at the bifurcation (Figure 2).

CBM max progressed in both treatment groups, but it progressed more slowly in lacidipine-treated patients (Table 2). Yearly progression rate was 15% (ITT) and 40% (completers) lower in the lacidipine group than in the atenolol group.

Carotid internal diameter decreased very slightly with atenolol and increased very slightly with lacidipine, with a mean treatment-related difference of 0.1079 mm (ITT); however, Pearson correlation coefficients with CBM max changes were extremely small \((r=-0.100)\) for all patients together, \(r=-0.096\) for atenolol, and \(r=-0.098\) for lacidipine patients), indicating that only 1% of CBM max variation could be explained by carotid diameter.

Table 3 shows that fewer lacidipine-treated than atenolol-treated patients had more plaques at end than beginning of treatment and more lacidipine-treated than atenolol-treated patients ended the study with fewer plaques than at baseline. In the ITT population, the proportion of patients with progression was 25.9% (lacidipine) versus 29.0% (atenolol) and the proportion with regression was 19.8% (lacidipine) versus 15.7% (atenolol) \((\chi^2\ test, P=0.0404)\). Among completers, numbers of patients with progression were 25.3% (lacidipine) versus 31.3% (atenolol), and those with regression were

### Table 1. Baseline Characteristics of Patients Randomly Allocated to Either Atenolol or Lacidipine

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Atenolol</th>
<th>Lacidipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % male</td>
<td>55.4</td>
<td>54.2</td>
</tr>
<tr>
<td>Race, % white</td>
<td>98.5</td>
<td>97.9</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>18.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Age, years</td>
<td>55.9 (7.5)</td>
<td>56.1 (7.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 (2.6)</td>
<td>27.2 (3.9)</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.85 (1.01)</td>
<td>5.81 (0.98)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.34 (0.46)</td>
<td>1.35 (0.43)</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.75 (0.98)</td>
<td>3.70 (0.94)</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.53 (0.78)</td>
<td>1.53 (0.72)</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>5.37 (1.05)</td>
<td>5.31 (1.04)</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>84.9 (15.9)</td>
<td>84.0 (16.8)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment, %</td>
<td>62.8</td>
<td>63.8</td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>11.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Calcium antagonists, %</td>
<td>13.2</td>
<td>13.6</td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>15.5</td>
<td>16.1</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Other drugs, %</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Multiple drugs, %</td>
<td>18.8</td>
<td>19.6</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>163.1 (12.5)</td>
<td>163.9 (12.2)</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>101.3 (4.9)</td>
<td>101.4 (5.3)</td>
</tr>
<tr>
<td>Clinic HR, beats/min</td>
<td>76.0 (9.4)</td>
<td>76.3 (9.1)</td>
</tr>
<tr>
<td>24-Hour ambulatory SBP, mm Hg</td>
<td>140.4 (14.2)</td>
<td>141.4 (14.0)</td>
</tr>
<tr>
<td>24-Hour ambulatory DBP, mm Hg</td>
<td>87.6 (9.3)</td>
<td>88.2 (9.3)</td>
</tr>
<tr>
<td>24-Hour ambulatory HR, beats/min</td>
<td>74.1 (9.0)</td>
<td>74.3 (8.9)</td>
</tr>
<tr>
<td>CBM max, mm</td>
<td>1.1619 (0.2480)</td>
<td>1.1589 (0.2399)</td>
</tr>
<tr>
<td>IMT-CC, mm</td>
<td>1.0173 (0.2152)</td>
<td>1.0090 (0.1980)</td>
</tr>
<tr>
<td>IMT-CB, mm</td>
<td>1.3115 (0.3782)</td>
<td>1.3131 (0.3594)</td>
</tr>
<tr>
<td>Patients with no plaques, n</td>
<td>423</td>
<td>409</td>
</tr>
<tr>
<td>Patients with 1 plaque, n</td>
<td>318</td>
<td>347</td>
</tr>
<tr>
<td>Patients with 2 plaques, n</td>
<td>186</td>
<td>188</td>
</tr>
<tr>
<td>Patients with 3 or more plaques, n</td>
<td>85</td>
<td>79</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD) unless otherwise indicated. Intention-to-treat population (atenolol, 1012 patients and lacidipine, 1023 patients, except for ambulatory blood pressures, with 763 and 760 patients, respectively) is shown.

**BMI** indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin-converting-enzyme; HR, heart rate; CC, common carotids; and CB, carotid bifurcations.
Concerned high-density lipoprotein-cholesterol, which slightly
in metabolic changes between atenolol and lacidipine con-

Clinic SBP and DBP decreased markedly and equally in both
treatment groups (atenolol 21.6/15.6 mm Hg and lacidip-
one 21.8/15.5 mm Hg), whereas treatment-induced reductions
in 24-hour ambulatory SBP and DBP were significantly
(P<0.0001) larger in the atenolol group (210.3/
8.7 mm Hg) than in the lacidipine group (26.8/
4.9 mm Hg). Clinic and 24-hour heart rates decreased by 10
beats/min with atenolol and did not change with lacidipine.

No significant treatment-subgroup interactions were found
for any subgroup considered. Although significant subgroup
effects were found for sex, age, baseline DBP, pulse pressure,
and baseline cholesterol, adjustments for these interactions
were negligible.

**Treatment-Related Changes in Blood Pressure,
Heart Rate, and Laboratory Variables**

Clinic SBP and DBP decreased markedly and equally in both
treatment groups (atenolol −21.6/−15.6 mm Hg and lacidip-

TABLE 2. Treatment-Related Changes in CBMmax

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Mean</th>
<th>SE</th>
<th>Absolute Difference</th>
<th>P</th>
<th>Relative Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final scan minus baseline scan, mm</td>
<td>Atenolol</td>
<td>0.0469</td>
<td>0.0053</td>
<td></td>
<td>0.2647</td>
<td>0.80 (0.56–1.13)</td>
</tr>
<tr>
<td></td>
<td>Lacidipine</td>
<td>0.0377</td>
<td>0.0051</td>
<td>−0.0092</td>
<td>0.60 (0.39–0.87)</td>
<td>0.80 (0.56–1.13)</td>
</tr>
<tr>
<td>Completers</td>
<td>Atenolol</td>
<td>0.0579</td>
<td>0.0059</td>
<td>−0.0220</td>
<td>0.0099</td>
<td>0.62 (0.41–0.89)</td>
</tr>
<tr>
<td></td>
<td>Lacidipine</td>
<td>0.0359</td>
<td>0.0059</td>
<td></td>
<td>0.62 (0.41–0.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yearly progression, mm/y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>0.0153</td>
<td>0.0027</td>
<td></td>
<td>0.6134</td>
<td>0.85 (0.45–1.48)</td>
</tr>
<tr>
<td></td>
<td>Lacidipine</td>
<td>0.0130</td>
<td>0.0028</td>
<td>−0.0023</td>
<td>0.85 (0.45–1.48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Completers</td>
<td>0.0145</td>
<td>0.0015</td>
<td></td>
<td>0.85 (0.45–1.48)</td>
<td></td>
</tr>
</tbody>
</table>

Differences are of lacidipine vs atenolol. CI indicates confidence interval.
number of plaques. A relevant effect of carotid diameter changes on IMT is unlikely because of the very low correlation coefficients between diameter and IMT changes in both treatment groups.

ELSA was designed as the largest study of this kind, and particular care was taken to maximize the accuracy of ultrasound measurements. In each reference center, ultrasound scans were performed in duplicate by sonographers initially trained and annually re-certified by the Ultrasound Coordinating Center. Each patient was scanned twice annually, and 310 duplicate readings were used to calculate intra- and inter-reader reliability, which was very high (0.915 and 0.872 at baseline, respectively16). Procedures intended to minimize reading variability and bias have been described in Methods.

Three of 4 placebo-controlled studies18–21 conducted not in patients with hypertension but in vascular disease patients showed a beneficial effect of the antihypertensive agent used (amlodipine in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial [PREVENT],18 ramipril in the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E [SECURE],20 and metoprolol in the Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study [BCAPS]21). The result of BCAPS,21 which tested a β-blocker, suggests that the slowing of CBMax seen in ELSA with lacidipine may be over and above the slowing possibly exerted by atenolol.

Three intervention studies with carotid IMT as an end point7–9,18–21 found a beneficial effect of calcium antagonists over that of diuretics that was about the same magnitude as the effect we found in ELSA for lacidipine versus atenolol. The results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS),7 however, are difficult to interpret because of a reading drift. The Verapamil in Hypertension and Atherosclerosis Study (VHAS)8 and the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment-Intima Media Thickness substudy (INSIGHT- IMT)9 were relatively small studies (498 and 324 patients). Furthermore, the direction of the changes is difficult to evaluate in studies that did not avoid possible reading bias by keeping the operator blind to the scan time sequence. On the whole, however, the results of previous studies7–9,18–21 support the conclusions of the large and accurate ELSA trial.

The greater antiatherosclerotic action of lacidipine with respect to atenolol seems to be independent of the blood-pressure-lowering effect, as 24-hour ambulatory SBP and DBP reductions were slightly lower in lacidipine-treated subjects than in atenolol-treated subjects. Concomitant use of antiplatelet and lipid-lowering agents was quite low in ELSA and was slightly more prevalent among atenolol- than lacidipine-treated subjects. High-density lipoprotein-cholesterol changes differed significantly in the 2 treatment groups, with a decrease in the atenolol group and an increase in the lacidipine group, and serum triglycerides increased significantly in atenolol patients. Other mechanisms, however, are likely to be more important. Lacidipine has been shown to inhibit fatty-streak formation in hypercholesterolemic rabbits,4 to inhibit aortic plaque formation in apolipoprotein-E knockout mice,5 to inhibit production of reactive oxygen species in endothelial cells,2 and to reduce adhesion molecule expression in endothelial cells.3 Particularly relevant to an interpretation of ELSA results are the recent findings of Taddei et al.,22 which show that in essential hypertensive

---

**Table 3. Changes in Number of Plaques per Patient, End-Study Minus Baseline in Atenolol- and Lacidipine-Treated Patients**

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Atenolol</th>
<th>Lacidipine</th>
<th>Relative Risk and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>(n/1000)</td>
<td>(n/1000)</td>
<td></td>
</tr>
<tr>
<td>MI (fatal and nonfatal)</td>
<td>4</td>
<td>2</td>
<td>2.00</td>
</tr>
<tr>
<td>Stroke (fatal and nonfatal)</td>
<td>14</td>
<td>3.95</td>
<td>2.49</td>
</tr>
<tr>
<td>Major CV events</td>
<td>34</td>
<td>9.89</td>
<td>7.46</td>
</tr>
<tr>
<td>CV death</td>
<td>8</td>
<td>2.20</td>
<td>4.10</td>
</tr>
<tr>
<td>All death</td>
<td>17</td>
<td>4.40</td>
<td>3.29</td>
</tr>
<tr>
<td>Minor CV events</td>
<td>42</td>
<td>11.29</td>
<td>12.41</td>
</tr>
<tr>
<td>All (major and minor) CV events</td>
<td>73</td>
<td>19.05</td>
<td>19.64</td>
</tr>
<tr>
<td>All serious AE</td>
<td>201</td>
<td>45.37</td>
<td>51.38</td>
</tr>
</tbody>
</table>

---

**Figure 3. Cardiovascular (CV) end points and serious adverse events (AE) in atenolol and lacidipine-treated patients. Number (n) of patients with an event, event rates (n/1000 patient-years) and relative risk of lacidipine versus atenolol with 95% confidence intervals (CI). Cox-regression analysis uses treatment and reference center as covariates. Major CV events include nonfatal myocardial infarction (MI) and stroke plus CV death; minor CV events include hospitalized heart failure, angina, atrial fibrillation, and claudication. All serious AE include any event defined as fatal, life-threatening, involving or prolonging hospitalization, disabling or incapacitating, any laboratory abnormality causing major clinical concern, or relevant signs or symptoms.**

---

**Note:**

χ² tests P = 0.0404 for ITT and 0.0036 for completers.
patients, lacidipine, but not atenolol, restores endothelium-dependent vasodilatation and reduces circulating markers of oxidative stress.

Epidemiological evidence indicates that an effect on carotid IMT of the magnitude shown for lacidipine in ELSA is clinically relevant. In agreement with these previous prospective studies, we found that the risk of cardiovascular events progressively increased in ELSA with increasing baseline carotid CBMmax and with baseline plaque number, suggesting that a statistically greater effect of lacidipine on both carotid parameters may also be significant clinically. Obviously, ELSA, which compares 2 active treatments in relatively low-risk patients, was not expected to find statistically significant treatment differences in cardiovascular events, but the trend toward a lower incidence of strokes and cardiovascular death observed with lacidipine is consistent with the ultrasound findings and their interpretation.

Appendix

Steering Committee
Alberto Zanchetti, MD; M. Gene Bond, PhD; Michael Hennig, PhD; Albrecht Neiss, PhD; Giuseppe Mancia, MD; Cesare Dal Palù, MD; Lennart Hansson, MD; Bruno Magnani, MD; Karl-Heinz Rahn, MD; John L. Reid, MD; José Rodicio, MD; Michel Safar, MD; Lothar Eckes, MD, PhD; and Paolo Rizzini, MD.

Ultrasound Coordinating Center
M.G. Bond; R. Tong; D. Angel; J. Cai; J. Graig; L. Du; P. Miller; R. Phillips; D. Pozo; B. Xiao; Winston Salem, NC.

Statistical Analysis Center
A. Neiss; M. Hennig; B. Flatau; C. Klaus; R. Hollweck; B. Thomasson; A. Houzer; A. Helms; J. Geiger; I. Bstech; Munich, Germany.

Ambulatory Blood Pressure Reading Center
G. Mancia, Monza, Italy; G. Parati, A. Groppelli, S. Omboni, A. Villani, Milan, Italy.

Referral Centers
A. Rappelli, Ancona, Italy; P. Toutouzas, C. Pitsavos, I. Kalliakazaros, Athens, Greece; A. Roca Cusachs, Barcelona, Spain; J. Scholze, Berlin, Germany; E. Ambrosioni, E. Strocchi, Bologna, Italy; E. Agabiti Rosei, Brescia, Italy; H.-J. Gilfrich, A. Romer, Frankfurt, Germany; J. Reid, H. Elliott, Glasgow, UK; J.M. Mallion, Grenoble, France; C. Hamm, Hamburg, Germany; T. Thulin, Land, Sweden; J. Rodicio, L. Ruijope, Madrid, Spain; C. Cuspidi, L. Leonetti, Milan, Italy; H. Holzgreve, Munich, Germany; M. Barenbrock, Munster, Germany; F. Zannad, Nancy, France; B. Trimarco, Naples, Italy; A. Pessina, P. Pauletto, Padua, Italy; S. Laurent, Paris, France; A. Salvetti, F. Arzilli, Pisa, Italy; A. Bucci, Rome, Italy; L. Ramsey, Sheffield, UK; U. de Faire, Stockholm, Sweden.

Independent Clinical Event Committee
G. Just; C. Fieschi; T. Hedner.

Independent Safety Committee
P. Sleight; M.E. Bertrand; P.A. van Zwieten.

Acknowledgments
We thank all participating investigators for their dedicated work.

References
Calcium Antagonist Lacidipine Slows Down Progression of Asymptomatic Carotid Atherosclerosis: Principal Results of the European Lacidipine Study on Atherosclerosis (ELSA), a Randomized, Double-Blind, Long-Term Trial
Alberto Zanchetti, M. Gene Bond, Michael Hennig, Albrecht Neiss, Giuseppe Mancia, Cesare Dal Palù, Lennart Hansson, Bruno Magnani, Karl-Heinz Rahn, John L. Reid, José Rodicio, Michel Safar, Lothar Eckes and Paolo Rizzini
on behalf of the ELSA investigators

Circulation. 2002;106:2422-2427
doi: 10.1161/01.CIR.0000039288.86470.DD
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/19/2422

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/