Baseline Values but Not Treatment-Induced Changes in Carotid Intima-Media Thickness Predict Incident Cardiovascular Events in Treated Hypertensive Patients

Findings in the European Lacidipine Study on Atherosclerosis (ELSA)

Alberto Zanchetti, MD; Michael Hennig, PhD; Regina Hollweck, MS; Gene Bond, PhD; Rong Tang, MD; Cesare Cuspidi, MD; Gianfranco Parati, MD; Rita Facchetti, MD; Giuseppe Mancia, MD

Background—Baseline carotid intima-media thickness (IMT) and plaques are considered predictors of cardiovascular events, but whether they maintain predictive value in treated hypertensive patients and whether time-related (or treatment-induced) IMT changes are additional predictors are unknown.

Methods and Results—Analyses were performed of the data from the European Lacidipine Study on Atherosclerosis (ELSA), a large, randomized, intervention trial in which 2334 hypertensive patients from 7 European countries were followed up under effective antihypertensive treatment for 3.75 years. Kaplan–Meier curves indicated progressively lower survival free of any type of outcome except stroke, with increasing baseline IMT quartiles or increasing IMT values, even after adjustment for major baseline risk factors. Incidence of any outcome except stroke also was related to baseline number of carotid plaques. However, when both baseline and on-treatment IMT values were entered in Cox proportional-hazards models, differences in IMT compared with baseline did not predict cardiovascular outcomes. Although on-treatment rather than baseline IMT values significantly entered some of the proportional-hazards models, baseline and on-treatment IMTs were highly correlated, and therefore these results are inconclusive.

Conclusions—ELSA shows that carotid intima-media thickening and plaques are important added risks of cardiovascular outcomes in a treated hypertensive population independently of blood pressure and traditional risk factors. However, the analysis failed to show a predictive role of treatment-dependent IMT changes. These negative conclusions should be tempered by the limitations inherent in the smallness of these changes compared with the large individual differences in baseline IMTs. (Circulation. 2009;120:1084-1090.)

Key Words: carotid arteries ■ cardiovascular outcomes ■ hypertension ■ prognosis ■ treatment

A number of prospective population or cohort studies, such as the Atherosclerosis Risk in Communities Study1,2 (ARIC), the Rotterdam Study,3,4 the Cardiovascular Health Study5 (CHS), and the Carotid Atherosclerosis Progression Study6 (CAPS), as well as several smaller studies,7–12 have shown that carotid intima-media thickness (IMT) is significantly related to incident cardiovascular events, both coronary events and stroke. There is also evidence that plaque presence4 and carotid plaque area13 measured by ultrasound are predictive of subsequent cardiovascular events. It also has been reported that plaque area may be a stronger predictor of myocardial infarction than IMT when measurements are restricted to the common carotid artery.14 Because of the predictive power of carotid ultrasound measurements, the European guidelines on the management of hypertension15 recommend the inclusion of carotid examination in hypertensive patients when a better stratification of total cardiovascular risk is required. However, several clinically relevant issues remain to be clarified.

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First, none of the large studies cited above was specifically carried out in hypertensive patients, and whether the relation between carotid IMT and cardiovascular events as described in populations also holds true in hypertensive cohorts, particularly in treated hypertensive patients, is at present unproven.
Therefore, it is not clear whether carotid intima-media thickening and plaques really are an added risk of cardiovascular outcomes in hypertensive individuals and maintain this added risk under prolonged treatment. Second, the relative predictive power of plaque or IMT measurements (either restricted to the common carotid or inclusive of bifurcation) is still debated. Most important, although several prospective interventional studies have shown that progression of IMT can be modified by antihypertensive and lipid-lowering agents,8,16-21 most of the prospective studies relating carotid IMT to cardiovascular outcomes have been observational,1-7,9-12 and little is known of the relative predictive value of IMT measurements when modified by long-term treatment. Only data from a prospective observational study of plaque area progression13 and from a very small interventional study, the Cholesterol Lowering Atherosclerosis Study22 (CLAS), are available at present. Both studies support the hypothesis that progression of asymptomatic atherosclerosis is accompanied by increased risk of cardiovascular events.

The European Lacidipine Study on Atherosclerosis19 (ELSA) lends itself to further analyses to answer the questions mentioned above. ELSA was a large prospective study including 2334 subjects, all of whom were hypertensive at baseline (inclusion criteria were diastolic blood pressure of 95 to 115 mm Hg and systolic blood pressure of 150 to 210 mm Hg after at least 4 weeks off treatment). The major exclusion criterion was IMT >4.0 mm. Carotid IMT and plaque number were measured through a detailed protocol by certified sonographers; all measurements were read at a single center; and longitudinal controls were instituted to avoid reading bias and drifts.23 Measurements were made at baseline and repeated yearly for up to 4 years (average, 3.75 years), during which time patients double-blindly received either lacidipine-based or atenolol-based antihypertensive treatment by stepwise strategies (with proportional-hazards models selected with variables to enter and stay time-varying (on-treatment) covariates via time-dependent assessment). ELSA was a large prospective study (ELSA) lends itself to further analyses to answer the questions mentioned above. ELSA was a large prospective study including 2334 subjects, all of whom were hypertensive at baseline (inclusion criteria were diastolic blood pressure of 95 to 115 mm Hg and systolic blood pressure of 150 to 210 mm Hg after at least 4 weeks off treatment). The major exclusion criterion was IMT >4.0 mm. Carotid IMT and plaque number were measured through a detailed protocol by certified sonographers; all measurements were read at a single center; and longitudinal controls were instituted to avoid reading bias and drifts.23 Measurements were made at baseline and repeated yearly for up to 4 years (average, 3.75 years), during which time patients double-blindly received either lacidipine-based or atenolol-based antihypertensive treatment by random assignment. Antihypertensive treatment markedly reduced blood pressure (−21.7/−15.5 mm Hg) and mildly influenced high-density lipoprotein cholesterol and triglycerides.19 Although the principal results of ELSA have shown that lacidipine-based treatment significantly reduced the progression of carotid IMT compared with atenolol-based treatment,19 for the analyses presented here, all data have been pooled independently of treatment, but treatment has been entered as a covariate in multivariate analyses.

**Methods**

**Measurement**

Acquisition of carotid artery intima-media images, evaluation/measurements of IMTs, sonographer- and reader-quality assessment, and quality control have been previously reported.19,23,24 The primary efficacy ultrasound end point was CBM_{max} which was defined as the average of the thickest IMT recorded from far walls of the distal 1.0 cm of the common carotid artery and carotid bifurcation bilaterally.

Secondary end points were the mean maximum values of bifurcation (CBM_{max}) and common carotid (CC_{max}) scans computed separately and plaque number (ie, the number of far walls in all 4 segments in which the IMT was ≥1.3 mm). All patient scans were performed by certified sonographers, and measurements were made by certified readers who were assessed quantitatively for quality (proficiency) annually. All ultrasound tracings were read in batches after all final ultrasound exams were submitted on the last patient evaluation. Every scan on every patient was coded with a random number. Readers did not have any patient identification information (name, initials, birth date, date of examination, referral center information, sonographer identification, etc), and all patient scan sets were randomly shuffled, relative to scan date, by the Institute for Medical Statistics and Epidemiology (Technical University of Munich).

Reproducibility of baseline and on-treatment IMT measurements in ELSA has previously been reported to be very good.23,24 In particular, the within-reader and between-reader coefficients of variation were 4.8±4.7% and 5.4±4.4%, respectively.

**Cardiovascular Outcomes**

Incidence of the following events was monitored throughout the study and adjudicated by an Event Monitoring Committee according to predetermined criteria: (1) fatal and nonfatal myocardial infarction, (2) fatal and nonfatal stroke, (3) major cardiovascular events (including fatal and nonfatal myocardial infarction and stroke and cardiovascular death), (4) all death (death resulting from any cause), (5) minor cardiovascular events (hospitalized heart failure, angina, atrial fibrillation, and claudication), (6) all major and minor cardiovascular events, and (7) all cardiac events (all cardiovascular events except stroke and claudication).

**Statistics**

The relation of various types of cardiovascular outcome with IMT measurements was analyzed by use of the measurements chosen as efficacy variables in the principal analysis of ELSA,19 ie, measurements recorded within a 6-month period at study end (CBM_{max} of 4 sites, CB_{max} of 2 sites, CC_{max} of 2 sites, plaques found at 4 sites). CB_{max} and CC_{max} are the 2 components of CBM_{max} but were analyzed separately in addition to CBM_{max} as 1 measurement (CB_{max} is thought to be more closely related to atherosclerosis and CC_{max} to vascular hypertrophy).16,17,21

Initial IMT measurements were first subdivided into quartiles, and outcome frequencies and times to events were compared between the various quartiles by Cox regression analyses. Kaplan–Meier curves for cumulative annual event-free time also were calculated by quartiles, with significance evaluated by log-rank tests. The relative risk of various outcomes by initial IMT measurements, taken as continuous variables rather than quartiles, also was assessed by Cox regression analyses both before and after adjustment for age, sex, systolic blood pressure, and treatment. Outcome incidences were compared between 3 groups of patients: those with no plaque, patients with 1 segment with plaque, those with >1 segment with plaques.

Finally, to test the hypothesis that treatment-dependent IMT changes detected by yearly ultrasound examinations may add predictive value about the incidence of cardiovascular outcomes, we assessed the relation of both baseline IMT values and IMT values as time-varying (on-treatment) covariates via time-dependent proportional-hazards models selected with variables to enter and stay by stepwise strategies (with P=0.05). Time-varying covariates in Cox regression models used the baseline IMT value until the first on-treatment evaluation, used the first on-treatment observation until the next IMT evaluation, and repeated this process until the occurrence of an event for patients with incident events or the end of the study for patients without incident events. Thus, for any cardiovascular event occurring at a given time, that event was associated with the most recent IMT value at that time. The same procedure was followed for relating IMT differences from baseline to cardiovascular events. Cox models were adjusted by use of the following baseline variables as covariates: age, sex, smoking status, systolic blood pressure, diastolic blood pressure, body mass index, serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and randomized treatment. Correlations between IMT values at baseline and on-treatment were expressed as Pearson coefficients. All statistical analyses were carried out with the SAS (version 9.1) package (SAS Institute Inc, Cary, NC).

**Results**

**Patients’ Baseline Characteristics**

Patients’ baseline characteristics are reported in detail in a previous publication.19 In brief, of the 2334 subjects, mean...
age was 56 years, 55% were men, average baseline blood pressure was 163.5/101.3 mm Hg, mean total serum cholesterol was 5.83 mmol/L, mean high-density lipoprotein cholesterol was 1.34 mmol/L, mean serum creatinine was 84.5 μmol/L, and 20.5% were current smokers. Baseline CBM\textsubscript{max} averaged 1.16 mm; CB\textsubscript{max}, 1.31 mm; and CC\textsubscript{max}, 1.01 mm.

### Baseline Carotid IMT and Cardiovascular Events

Values of the primary efficacy measurement of ELSA, CBM\textsubscript{max}, measured at 4 sites, were subdivided into quartiles (quartile 1: \(n = 563\); range, 0.57 to 0.97 mm; quartile 2: \(n = 565\); range, 0.98 to 1.15 mm; quartile 3: \(n = 564\); range, 1.16 to 1.32 mm; and quartile 4: \(n = 563\); range, 1.33 to 2.9 mm). The Figure illustrates Kaplan–Meier curves for event-free survival and shows progressively lower survival free of myocardial infarction, all cardiac events, major cardiovascular events, all cardiovascular events, and all deaths, but not stroke, with increasing CBM\textsubscript{max} quartiles. Although some overlap between the curves occurred occasionally, differences between quartiles for all types of outcome except stroke were significant at least with \(P<0.001\) (log-rank test). Table 1 shows that rates of all outcomes except stroke were significantly different between different quartiles. For most outcomes, rates increased progressively from the lowest to the highest quartile, but the increase was particularly steep from the third to the fourth quartile.

The relation of various outcomes to initial IMT also was explored by using CBM\textsubscript{max} (4 sites), CB\textsubscript{max} (2 sites), and CC\textsubscript{max} (2 sites), reread at study end, as continuous variables. Results are shown in Table 2 as hazard ratios (HRs) for a 1-mm IMT increase with 95% confidence intervals (CIs). Stroke was significantly correlated with CBM\textsubscript{max} only before adjustments; myocardial infarction was significantly correlated with CBM\textsubscript{max} and CC\textsubscript{max} before and after adjustment for other risk factors but was no longer correlated with CB\textsubscript{max} after adjustments. All cardiac and all cardiovascular events were highly correlated with all IMT measurements both before and after adjustment. The size of the adjusted HRs indicates that all cardiac and cardiovascular events increased by \(\approx 25\%\) to \(35\%\) for each 0.1-mm increase in CBM\textsubscript{max} independently of age, sex, systolic blood pressure, and treatment, although the precision of these calculations is limited by the width of the CIs. Adjustment using 24-hour ambulatory systolic blood pressure was 163.5/101.3 mm Hg, mean total serum cholesterol was 5.83 mmol/L, mean high-density lipoprotein cholesterol was 1.34 mmol/L, mean serum creatinine was 84.5 μmol/L, and 20.5% were current smokers. Baseline CBM\textsubscript{max} averaged 1.16 mm; CB\textsubscript{max}, 1.31 mm; and CC\textsubscript{max}, 1.01 mm.

### Table 1. Outcome Incidence According to Quartiles of Initial IMT (CBM\textsubscript{max})

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>35</td>
<td>1.60</td>
<td>2.72</td>
<td>4.02</td>
<td>11.30</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>23</td>
<td>2.67</td>
<td>1.09</td>
<td>3.44</td>
<td>5.65</td>
<td>0.12</td>
</tr>
<tr>
<td>All death</td>
<td>30</td>
<td>1.07</td>
<td>3.81</td>
<td>2.87</td>
<td>8.47</td>
<td>0.0047</td>
</tr>
<tr>
<td>Major CV events</td>
<td>60</td>
<td>4.27</td>
<td>4.35</td>
<td>8.03</td>
<td>16.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All cardiac events</td>
<td>126</td>
<td>6.95</td>
<td>12.50</td>
<td>18.93</td>
<td>31.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All CV events</td>
<td>142</td>
<td>9.62</td>
<td>13.59</td>
<td>21.80</td>
<td>34.46</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(Q\) indicates quartile; MI, myocardial infarction; and CV, cardiovascular.
pressure rather than clinic systolic blood pressure did not substantially change either the HRs or the significance.

**Baseline Plaques and Cardiovascular Events**

Outcome incidence also was compared between groups of patients classified according to number of carotid segments with plaques as measured at baseline. As shown in Table 3, the incidence of most outcomes increased moderately from the group of patients with no plaques to the group of patients with 1 carotid segment with at least a plaque and more markedly to the group of patients with >1 segment with plaques. Outcome progression with increasing number of plaques was significant for all outcomes listed in Table 3, with stroke being the only exception.

**Baseline and On-Treatment IMT and Cardiovascular Events**

The relative roles of baseline and on-treatment IMT values and other baseline variables in cardiovascular outcomes were explored by proportional-hazards models with variables selected by stepwise strategies as detailed in Methods. The results are summarized in Table 4. No IMT change from baseline ever achieved the significance limits ($P<0.05$) required to enter and stay. On-treatment CBM$_{max}$, but not baseline CBM$_{max}$, significantly stayed in the proportional-hazards model for all cardiovascular events, but for all cardiac and major cardiovascular events, baseline IMT values rather than on-treatment values significantly stayed in the models. Baseline and on-treatment IMT values were always highly correlated (CBM$_{max}$, 0.82; CB$_{max}$, 0.75; CC$_{max}$, 0.74; $P<0.0001$ for all), which explains that either baseline or on-treatment values could variably stay in the proportional-hazards models.

Of the other baseline variables, only age, sex, and systolic blood pressure remained significantly in the proportional-hazard models, but total cholesterol and low-density lipoprotein cholesterol remained significantly correlated with all cardiovascular and all cardiac events.

**Discussion**

The detailed analyses of ELSA provided here help to clarify 3 major issues: They clearly confirm the relationship between carotid wall lesions (both IMT and plaque number) and
subsequent cardiovascular outcomes; they show for the first time that this relationship also exists in hypertensive patients and therefore that carotid wall lesions really represent an added risk of cardiovascular outcomes over that represented by high blood pressure; and they provide large-scale, long-term information on the relative role of baseline and treatment-related carotid wall changes and of traditional risk factors with cardiovascular events in hypertensive patients under long-term treatment.

### Influence of Baseline Carotid Wall Alterations on Cardiovascular Outcomes

The ELSA data confirm that carotid IMT, wherever measured (bifurcation, common carotid, combination of bifurcation, and common carotid), has a strong continuous relationship with a number of outcomes (myocardial infarction, major cardiovascular events, all cardiac events, all cardiovascular events, all death), risk of at least myocardial infarction than IMT, as indicated in the Figure and Table 1) indicate that, although the risk increases progressively from 1 quartile to the next, for a number of outcomes (myocardial infarction, all death), risk appears to increase more steeply from the third to the fourth quartile. At variance with the studies mentioned above, the relation between any IMT measurement and stroke did not attain statistical significance either when IMT was considered in quartiles or when it was used as a continuous variable. This might be due to the small number of strokes that occurred in ELSA (only 25 strokes), possibly resulting from the fact that patients with very thick carotid walls (IMT >4.0 mm), ie, those most likely to develop ischemic cerebrovascular events,25 were excluded according to the ELSA protocol because these lesions are unlikely to be significantly modified by treatment.

The analyses reported here on the relation of the number of carotid plaques with incident outcomes also provide important information about an aspect that has scarcely been explored so far. Indeed, to the best of our knowledge, this analysis was performed in the Rotterdam study4 only for stroke and in a much smaller Dutch study9 for all-cause mortality. In ELSA, the incidence of most outcomes increased from subjects with no plaque to subjects with 1 plaque and particularly those with >1 plaque. Differences were significant for all outcomes except stroke, although a positive trend was detectable for this outcome.

As to the relative predictive value of the various types of carotid wall alterations that we measured, it should be underlined that CBmax and CCmax are components of CBMmax and hence related to CBMmax. Therefore, the most relevant observations are those related to CBMmax, which was the primary end point of ELSA. No major overt difference was seen between the relative risk of the various IMT measurements and number of segments with plaque (an ~4-fold increase in all major cardiovascular events in the highest versus the lowest CMBmax quartile, an ~3-fold increase in the group of patients with >1 plaque versus those with no plaque). In the continuous analysis of IMT measurements, CCmax appeared slightly more predictive than CBmax, but this is likely due to less variability in CC than in CB measurements. The design of ELSA did not include measurement of total plaque area,13 and we cannot exclude that it is better predictive of at least myocardial infarction than IMT, as recently suggested in the Tromsø Study.14 However, the risk increase we calculated in ELSA between the lowest and highest quartiles of IMT is similar to that calculated by Spence et al13 between the lowest and highest quartiles of plaque area.

The finding in ELSA that incident outcomes were related to the number of plaques and to an IMT measurement such as CBMmax that included the bifurcations substantiates the conclusion that cardiovascular outcomes can be predicted by indexes of carotid atherosclerosis, a conclusion that cannot be drawn from studies measuring only common carotid IMT because the common carotid is an infrequent location of atherosclerosis.19 Because common carotid IMT also has been found to be related to subsequent outcomes, this may indicate that not only atherosclerosis but also hypertension-associated vascular hypertrophy is predictive of cardiovascular events.

A new important piece of information provided by the present analyses of ELSA is that asymptomatic carotid atherosclerosis also is predictive of subsequent outcomes in hypertensive patients. Indeed, none of the previous large studies describing this relationship was done specifically in hypertensive patients, whereas ELSA exclusively involved a large cohort (n=2334) of subjects specifically recruited as
being hypertensive. The finding that the predictive power of all indexes of carotid atherosclerosis also remained significant after adjustment for baseline risk factors, including blood pressure, clearly indicates that asymptomatic carotid atherosclerosis adds to the risk of hypertension and therefore supports the statement of the European Society of Hypertension–European Society of Cardiology guidelines that ultrasound examination of the carotid arteries can help to better stratify cardiovascular risk of hypertensive patients. Nonetheless, the wide overlapping of risk between quartiles of IMT suggests that this measurement may be more useful for identifying or stratifying groups of subjects than predicting individual risk of cardiovascular events.

Influence of Baseline and On-Treatment Measurements on Cardiovascular Outcomes

An important aspect of the present analyses of ELSA is that they have explored an issue that has rarely been approached so far, ie, whether in patients under long-term treatment time-dependent or treatment-dependent measurements of carotid wall are also predictive of cardiovascular outcomes. This type of information has obvious bearing on the clinical significance of the changes in carotid wall that can be induced by antihypertensive or lipid-lowering treatments. D’Agostino has recently commented that the use of time-varying covariates beyond baseline data may provide a statistical basis for the clinical practice approach, in which the physician uses the most recent measurements to adjust the patient’s prognosis.

Most previous studies investigating the relationship between carotid walls and outcomes measured IMT initially and followed up cardiovascular outcomes only prospectively and therefore did not provide any information on the relation between incident changes in carotid wall and incident outcomes. At variance with these studies, ELSA was the largest controlled treatment study in which carotid IMT was carefully monitored yearly for 4 years, ie, the entire period during which outcomes also were monitored. During this period, all patients randomly received 2 different antihypertensive regimens, one of which (the calcium antagonist lacidipine) delayed IMT progression compared with the other regimen (the β-blocker atenolol) despite an equally marked blood pressure reduction. Hence, the ELSA data lend themselves to an analysis of the role of on-treatment IMT values on cardiovascular outcomes.

The proportional-hazards model analyses in which baseline and on-treatment data were entered failed to prove a significant predictive role of time-dependent (or treatment-dependent) IMT changes for any type of cardiovascular outcome. The finding that stepwise analyses sometimes retained on-treatment rather than baseline IMT values (and sometimes baseline rather than on-treatment values) is likely explained by the high collinearity of these measurements. The conclusion that treatment-induced IMT changes have no significant predictive values on outcomes appears clinically important in that it may weaken the relevance of IMT changes as an intermediate end point in intervention trials. This negative conclusion must be tempered, however, by the limitations inherent in the use of IMT changes. Indeed, these changes are much smaller (0.03 to 0.06 mm during 4 years) than the differences between individual baseline values (range, 0.575 to 2.910 mm; SD, 0.2460 mm), and their contribution to total variability can be only minor with respect to the contribution of baseline values. Thus, the use of plaque area changes, which are larger than IMT changes, may have some advantages, as suggested by the study of Spence et al.

The major limitation of the present analyses of ELSA is that patients included were, on the whole, at relatively low risk and had their hypertension very well controlled by treatment; consequently, the incidence of cardiovascular outcomes during the 4-year study was rather low. Thus, the power of detecting correlation with organ-specific events (such as stroke) was rather low, and the most valuable information was derived from pooling major and minor cardiovascular outcomes, including clinically relevant events such as hospitalized heart failure, angina, atrial fibrillation, and claudication, in addition to stroke, myocardial infarction, and cardiovascular death.

The strength of these analyses resides in the large number of patients included in ELSA; in the homogeneity of the cohort (because all subjects were hypertensive, the study is particularly meaningful for hypertension); in the accurateness and yearly monitoring of the IMT measurements, all made by certified sonographers and read centrally on the basis of a precise protocol with incorporated control procedures; and in the adjudication of all outcomes by an Event Monitoring Committee. Finally, ELSA is the first and only trial in which IMT was measured repeatedly during long-term antihypertensive treatment in a cohort large enough to allow significant correlation with cardiovascular outcomes. Therefore, the conclusion that carotid IMT is a significantly important added risk throughout long-term antihypertensive treatment appears to be particularly solid.

Sources of Funding

ELSA was an investigator-generated trial sponsored by Glaxo Smith Kline Italy, Verona and Boehringer Ingelheim International GmbH, Ingelheim am Rhein. The analyses on which this article is based have been done independently by the authors, who were supported by a European Commission contract (6th Framework Programme, InGenious HyperCare, LSHM–CT–2006–37093).

Disclosures

During the ELSA trial, Drs Zanchetti, Henning, Bond, and Mancia and their institutions received research grants from the sponsoring companies. The analyses on which this article is based have been done independently by the authors without financial support from the sponsors. Dr Parati declares recent research grants from Boehringer Ingelheim International. Dr Mancia reports being a consultant to Boehringer Ingelheim International and on the speakers’ bureaus for Bayer, Merck, Menarini, Novartis, Recordati, Sanofi, Sankyo, and Servier. The other authors report no conflicts.

References

Carotid intima-media thickness (IMT) is recommended for stratifying cardiovascular risk because a number of observational studies have shown its value in predicting cardiovascular events. Whether this predictive value is independent of high blood pressure and is preserved when hypertension is treated effectively is unknown but has now been shown to be true. In the hypertensive patients of the European Lacidipine Study on Atherosclerosis (ELSA), baseline IMT strongly predicts the occurrence of new strokes and subtypes of cerebral infarction: the Rotterdam Study. Circulation. 2000;103:919–925.


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_Circulation_. 2009;120:1084-1090; originally published online September 8, 2009;
doi: 10.1161/CIRCULATIONAHA.108.773119

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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