Effect of Lovastatin on Early Carotid Atherosclerosis and Cardiovascular Events

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Background HMG CoA reductase inhibitors (or statins), a new class of lipid-lowering compounds, have raised expectations for more widespread use than that of the older lipid-lowering drugs. Not only are they more effective in lowering LDL cholesterol, but they are better tolerated as well. No data exist concerning the effect of statins on early carotid atherosclerosis and clinical events in men and women who have moderately elevated LDL cholesterol levels but are free of symptomatic cardiovascular disease.

Methods and Results Lovastatin (20 to 40 mg/d) or its placebo was evaluated in a double-blind, randomized clinical trial with factorial design along with warfarin (1 mg/d) or its placebo. This report is limited to the lovastatin component of the trial. Daily aspirin (81 mg/d) was recommended for everyone. Enrollment included 919 asymptomatic men and women, 40 to 79 years old, with early carotid atherosclerosis as defined by B-mode ultrasonography and LDL cholesterol between the 60th and 90th percentiles. The 3-year change in mean maximum intimal-medial thickness (IMT) in 12 walls of the carotid arteries was the primary outcome; change in single maximum IMT and incidence of major cardiovascular events were secondary outcomes. LDL cholesterol fell 28%, from 156.6 mg/dL at baseline to 113.1 mg/dL at 6 months (P .001), in the lovastatin groups and was largely unchanged in the lovastatin-placebo groups. Among participants not on warfarin, regression of the mean maximum IMT was seen after 12 months in the lovastatin group compared with the placebo group; the 3-year difference was statistically significant (P .001). A larger favorable effect of lovastatin was observed for the change in single maximum IMT but was not statistically significant (P .12). Five lovastatin-treated participants suffered major cardiovascular events—coronary heart disease mortality, nonfatal myocardial infarction, or stroke—versus 14 in the lovastatin-placebo groups (P .04). One lovastatin-treated participant died, compared with eight on lovastatin-placebo (P .02).

Conclusions In men and women with moderately elevated LDL cholesterol, lovastatin reverses progression of IMT in the carotid arteries and appears to reduce the risk of major cardiovascular events and mortality. Results from ongoing large-scale clinical trials may further establish the clinical benefit of statins. (Circulation. 1994;90:1679-1687.)

Key Words • lovastatin • clinical trial • atherosclerosis • cardiovascular diseases

In 1987, a new class of lipid-lowering compounds, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, or statins, was introduced in the United States and soon raised expectations for more widespread use than that of the older lipid-lowering drugs. Not only are these drugs much more effective in lowering LDL cholesterol, but they are better tolerated as well.1,2 The clinical benefit of the statins in the primary and secondary prevention of cardiovascular complications of advanced atherosclerosis, especially coronary artery disease, is being tested in several large ongoing multicenter clinical trials.3 Three other trials testing whether statins as monotherapy may reverse atherosclerosis have recently been completed.4-6 The Monitored Atherosclerosis Regression Study (MARS) and the Canadian Coronary Atherosclerosis Intervention Trial (CAAIT) both tested the effect of lovastatin on coronary atherosclerosis4,5 and demonstrated a significant slowing of progression. The trials had few major cardiovascular events. The Pravastatin, Lipids, and Atherosclerosis in the Carotids (PLAC-2) trial evaluated the effect of pravastatin in slowing early carotid atherosclerosis as measured by B-mode ultrasonography. This trial demonstrated a favorable effect on progression of intimal-medial thickness (IMT) in the common carotid artery and also showed a favorable trend for fewer coronary events.6

A large segment of the population typically not included in previous trials are asymptomatic subjects with LDL cholesterol below the levels recommended for drug therapy by the National Cholesterol Education Program (NCEP).7 The Asymptomatic Carotid Artery Progression Study (ACAPS) was designed to test, in a factorial design, whether either of two active agents, lovastatin or fixed minidose warfarin, retards the progression of early carotid atherosclerosis expressed as increased IMT in men and women with LDL cholesterol
levels between the 60th and 90th percentiles who were free of symptomatic cardiovascular disease. This report focuses on the effect of 33 to 36 months of treatment with lovastatin, a lipid-lowering agent, on both subclinical atherosclerosis and clinical cardiovascular outcome measures. Details concerning the warfarin component of the factorial design will be described in a separate publication.

Methods

Design

The ACAPS was a randomized, double-blind, placebo-controlled, multicenter clinical trial conducted in asymptomatic participants to determine the effects of lovastatin and warfarin on the progression of IMT in the carotid arteries and on the rate of cardiovascular events. The study population was men and women, 40 to 79 years old, with early carotid atherosclerosis and moderately elevated LDL cholesterol. Individuals with a history of myocardial infarction (MI), stroke, or angina were excluded. A factorial design was used, and participants were randomly assigned to one of four combination groups: active lovastatin/active warfarin, active lovastatin/warfarin placebo, lovastatin placebo/active warfarin, and lovastatin placebo/warfarin placebo. The rationale and design for ACAPS have been published previously.8

The a priori primary objective was to assess the effect of treatment on the average 3-year progression of a summary measure: the mean of the maximum IMT measurements from the 12 walls, near and far, of the common carotid, the bifurcation, and the internal carotid arteries on both sides of the neck. Methodological studies have shown that the use of a summary measure rather than individual IMTs markedly reduces variability and, thus, increases statistical power and that IMT measures in the near walls closely match those in the respective far walls.9 The secondary objectives of ACAPS were to determine the treatment effects on the incidence of major atherosclerotic events, to assess the safety of the two interventions individually and in combination, to quantify treatment effects on lipoproteins and prothrombin time, and to conduct natural history studies in the double-placebo group. Another B-mode measure, the progression of the single maximum IMT, was also assessed as a secondary outcome measure. All analyses were planned to be two-sided. The α-level for the main effects of lovastatin and warfarin was .05. A sample size of 900 was projected to provide adequate statistical power and to protect the trial from the influence of moderate levels of subadditivity in the combination group (active lovastatin/active warfarin) as described below.

Recruitment and Screening

Participants were recruited from clinical centers at four academic institutions (Bowman Gray School of Medicine and the universities of Iowa, Kentucky, and Tennessee). Randomization began in September 1989 and ended in October 1990. A fifth center was terminated after 6 months because of lagging recruitment. The 23 participants enrolled at that center had their medication stopped and were not followed beyond the closure of that center. No clinical events were reported among these individuals during the brief follow-up.

Due to the asymptomatic status of the participants, mass mailings and community screenings were organized in an effort to identify potential candidates. The first screening visit (SV1) included a questionnaire to identify major exclusions, a screening serum total cholesterol determination (Reflotron Analyzer), and an abbreviated B-mode ultrasound examination. Individuals who, on the basis of local reading of the B-mode images, appeared to have a qualifying ultrasonographic lesion were invited to the second screening visit (SV2). A fasting lipid profile and laboratory tests to ensure normal liver function (alanine aminotransferase [ALT]) were obtained at SV2. All trial lipids were analyzed at a central laboratory certified by the Centers for Disease Control-National Heart, Lung, and Blood Institute (NHLBI) Lipid Standardization Program. Subjects with serum triglycerides >400 mg/dL or ALT 20% greater than the upper limit of normal for the local laboratory were excluded. Those with LDL cholesterol in the 160 to 189 mg/dL range (4.13 to 4.89 mmol/L) with no or one coronary risk factor (as defined by NCEP) and those with LDL cholesterol 130 to 159 mg/dL (3.36 to 4.12 mmol/L) and any number of risk factors were immediately eligible for a third screening visit (SV3). Subjects who did not initially qualify—those with LDL cholesterol 190 to 210 mg/dL and no or one risk factor or those with 160 to 189 mg/dL and more than one risk factor—were invited to participate in an 8-week intensive dietary treatment program aimed at reducing their LDL cholesterol to qualifying levels.

Subjects attending SV3 underwent a complete ultrasound examination by an ACAPS-certified ultrasonographer to determine the presence of a qualifying carotid lesion. All scans were sent to the Ultrasonography Treatment Program Center for analysis. A second fasting lipid profile was also obtained at SV3.

Participants who were eligible at the completion of SV3 were enrolled in a 3- to 4-week run-in period during which they were given lovastatin placebo and open-labeled warfarin (1 mg/dL). At this time, the participants were also given open-labeled, low-dose aspirin (81 mg/dL). One purpose of the run-in phase was to identify and exclude participants who took <80% of their pills. Those intolerant of aspirin remained eligible.

Participants remaining eligible at the completion of the run-in phase returned for the baseline visit and underwent a series of tests that included a physical examination, a dietary assessment, a second B-mode scan, an ECG, a slit-lamp examination, and other blood tests.

Randomization and Treatment

After verification of eligibility, consenting participants were allocated to one of the four treatment groups by blocked randomization with stratification by clinical center.

The initial dose of lovastatin was 20 mg/d, while the warfarin dose was maintained at 1 mg/d. Throughout the study, all participants were encouraged to take one 81-mg aspirin tablet daily along with their study medication unless they could not tolerate it. Everyone was instructed to take all three ACAPS medications with the evening meal.

The goal of the lovastatin treatment was to reduce LDL cholesterol to the range of 90 to 110 mg/dL (2.31 to 2.85 mmol/L) over the first two postrandomization follow-up visits at 1.5 and 3 months. At the third follow-up visit (4.5 months), the lovastatin dose was either increased to 40 mg/d if LDL cholesterol exceeded this range or decreased to 10 mg/d if it was lower. A sample of the lovastatin-placebo participants also had an upward or downward dose adjustment to maintain the double-blind design. Thereafter, LDL cholesterol was regularly monitored in all participants to ensure maintenance of acceptable levels.

Follow-up

Regular clinic visits were scheduled every 6 weeks for the first 15 months and quarterly thereafter to permit safety monitoring. Fasting lipid profiles were obtained during follow-up at 1.5, 3, 6, and 12 months and then annually. B-mode ultrasonography was conducted semiannually. ALT and urine were examined at every visit. Drug adherence was assessed by pill count and participant report of usage. The annual visits involved a brief physical examination and dietary assessment.

During the course of the study, participants with LDL cholesterol levels exceeding their age- and gender-specific 90th
percentile received dietary counseling. If the dietary intervention failed to reduce the LDL cholesterol below the 90th percentile, an open-label bile acid sequestrant, cholestyramine, was added to the study medication for the duration of the trial. Conversely, if LDL cholesterol fell below 90 mg/dL, the medication dose was reduced.

All participants were originally to be followed for 3 years. Because of delays in the initiation and completion of recruitment, the last cohort of 300 enrollees was followed for only 33 months. Follow-up ended on June 30, 1993.

B-Mode Ultrasoundography

The ultrasound methods and IMT measurement reproducibility have been described previously.8,10 Sonographers and B-mode image readers completed a 3-month central training and certification program before acquiring data on ACAPS participants. After a careful circumferential scan, sonographers used a high-resolution 10-MHz ultrasound system (Bio- sound Phase 2) to obtain longitudinal B-mode images of the arterial wall boundaries in each of the 12 defined carotid segments. The primary objective was to image and record on videotape the maximum IMT in each segment. All images were centrally analyzed by readers unaware of treatment assignment, and the maximum IMT of each segment was computed by use of locations of crosshairs placed on the wall boundaries to a precision of 0.05 mm. The mean absolute difference between 858 paired readings of the baseline mean maximum IMT performed 1 month apart before randomization was 0.11 mm. At the end of ACAPS, a sample of paired baseline and 36-month scans were reread to determine the possibility of reader drift.9 No such drift was observed.

Ultrasound Outcome Measures

The primary ultrasound outcome was the change over time of the mean maximum IMT across 12 preselected segments in the carotid arteries. A positive change over 3 years (ie, an increase in IMT) denoted progression; negative change (ie, a decrease in IMT) denoted regression. A secondary ultrasound outcome was the change over time of the single maximum IMT measurement among the same preselected carotid artery segments. There were two ultrasound examinations at baseline, one every 6 months for the next 30 months and two at the final clinic visit. Thus, participants had up to nine B-mode examinations during the trial.**

Major Clinical Events

At each follow-up visit, participants were asked about hospitalizations, including possible recent MIs and strokes. ECGs, enzyme data, symptom reports, and hospital records were obtained for each suspected MI. Computerized tomography scan reports, lumbar puncture results, and hospital records, including discharge summaries, were obtained for each possible stroke. Vital status was determined for all participants at trial termination. Copies of death certificates, autopsy reports (if available), hospital records, and interview reports were obtained for each death. All events were reviewed by the five clinicians of the ACAPS Morbidity and Mortality Committee, who were unaware of treatment group assignment. This committee determined whether any of the following major events had occurred: definite or probable fatal or nonfatal MI, definite or possible coronary death, and fatal or nonfatal hemorrhagic or ischemic stroke. Cause-specific mortality and nonfatal MIs were determined and coded according to the algorithm developed by the NHLBI-sponsored Cardiovascular Health Study.11 The diagnosis of silent or unrecognized MI was based on ECGs taken at the annual follow-up visits. ECGs identified as having a possible diagnostic Q wave were reviewed by a masked external electrocardiographer to determine whether major Q-wave changes had occurred since baseline.12 All strokes were coded according to the classification system developed for the Systolic Hypertension in the Elderly Program.13

Statistical Analyses

The factorial design used in ACAPS is optimal if the treatment effects are additive, ie, if the effect of the combined therapies is comparable to the sum of the effects of the monotherapies.14 In such cases, comparisons are most effectively made between marginal means, for example, comparing all persons assigned to receive lovastatin (regardless of warfarin assignment) with those assigned not to receive lovastatin. The analysis plan for ACAPS involved an initial test of the assumption of additivity using Tukey’s method.15 If the assumption of additivity appeared to be reasonable for a given outcome measure, marginal comparisons were to be performed. If the assumption did not appear to be reasonable, the analysis plan specified pairwise comparisons of each of the three active intervention groups with the double-placebo group. In such cases, a Bonferroni adjustment of P values was to be used to control the type I error across the three pairwise comparisons.

Comparisons of the annualized progression rates for the primary and secondary summary measures of IMT were performed among treatment arms according to the two-stage analysis plan described previously.8 The first stage consisted of computing these rates for each participant from the serial data collected across the study visits. Weighted linear regression16 was used to compute these rates (slopes), and the weights were proportional to the inverse of the variances of the summary measures for the different examinations. Since the number of quantifiable walls was expected to vary from examination to examination, a conditional maximum likelihood approach17 was used to adjust the outcome measure for missing data and to produce appropriate variance estimates for each outcome measure. Rather than focusing only on mean differences between baseline and trial termination, the regression model allowed data from intervening examinations to contribute to the analysis and increase the statistical power.

The second stage of the analysis process consisted of weighted ANCOVAs to compare the mean progression rates among treatment groups. In these analyses, the weight for each participant’s annualized progression rate was inversely proportional to the variance of that rate. Thus, participants with more follow-up examinations and more quantifiable walls across the examinations received greater emphasis in the comparisons. Two covariates were used in these analyses of the B-mode data: clinical site and the prerandomization value of the summary measure (averaged across the two baseline examinations). Separate comparisons of each of the active interventions with the placebo treatment were made with Bonferroni adjustments to control type I error for pairwise comparisons. All comparisons were by treatment allocation (intention to treat) and were two-sided.

To check the assumption of linearity implicit in basing analyses on annualized rates, Laird-Ware models18 using restricted maximum-likelihood methods19 were employed to compare the fit of linear and nonlinear progression models. Polynomial and higher-order models for time were used to characterize nonlinear progression in these analyses, as specified in the protocol.8 Secondary analyses included the weighted ANCOVAs to assess the impact of additional covariates. Fisher’s exact tests were used to contrast differences in event frequencies between marginals, and Kaplan-Meier life tables20 were constructed to describe and test the distribution times of these events.

Differences in the baseline characteristics among the four randomized cohorts were assessed by a general linear model for the ANOVA, χ² tests, and Fisher’s exact tests.
Results

Recruitment

A total of 15,415 subjects were examined at SV1. Twenty-one percent (n = 3,247) qualified for SV2. The most common exclusion criteria were the absence of a carotid lesion (n = 5,590) and having a normal Reflotron cholesterol value (n = 2,722). SV2 was attended by 3,237 subjects. Approximately 60%, or 1,953 subjects, met the eligibility criteria for SV3. At SV2, 82 participants with LDL cholesterol values slightly greater than the ACAPS eligibility levels agreed to participate in an 8-week intensive dietary treatment program; 38 of them eventually qualified for SV3, and 23 were subsequently randomized.

SV3 included 1,075 subjects, and those still eligible for the randomization entered the run-in phase. Of the 960 persons returning for the baseline visit, only 4% (n = 41) failed to qualify for randomization. The majority (33 of the 41) failed the run-in because of adherence problems. Thus, 919 men and women were randomized. Twelve individuals were inappropriately randomized (2 inappropriate combinations of coronary risk factors and LDL cholesterol level, 8 ineligible ultrasound examinations, and 2 participants with overlooked exclusion criteria). These people remained in the trial and are included in all analyses.

Baseline Characteristics and Group Comparability

The mean age of the ACAPS participants was 62 years; 52% were men, and 92% were white (Table 1). Average systolic and diastolic blood pressures were 131 and 77 mm Hg, respectively. Only 12% were current smokers, and 45% reported being former smokers. Twenty-nine percent had a history of hypertension, and 23% had non-insulin-dependent diabetes mellitus. Thirteen percent were using diuretics for the treatment of hypertension, and 26% of the women were taking noncontraceptive estrogen medication. Baseline serum total cholesterol and LDL cholesterol means were 235.3 and 155.6 mg/dL (6.1 and 4.0 mmol/L), respectively. The HDL cholesterol means were 45.8 and 58.3 mg/dL (1.2 and 1.5 mmol/L) for men and women, respectively. Serum triglycerides were 139.7 mg/dL (3.6 mmol/L). Mean maximum IMT was 1.32 mm, and single maximum IMT was 2.29 mm. The average IMT was 1.14 mm in the common carotid artery, 1.58 mm in the bifurcation, and 1.23 mm in the internal carotid artery. Randomization produced four comparable study groups at baseline (Table 1).

Follow-up

Nine participants died during the follow-up period. The remaining 910 subjects were followed for at least 33 months. The mean follow-up time was 34.1 months. Vital status was confirmed for all participants at the completion of ACAPS. The completion rate for follow-up visits was very high, averaging 95% (93% to 97% for the four clinical centers). Twenty-four participants (2.6%) missed two or more consecutive visits. Fifteen percent of the participants were not taking study medication at the last visit. Seventy-seven percent of the participants took at least 80% of their prescribed lovastatin or its placebo based on pill count. Fifty-five participants (12%) in the lovastatin-treated groups received additional nonstudy lipid-lowering medication by their private physicians compared with 92 persons (20%) assigned to the lovastatin-placebo groups.

Forty-four percent of the participants continued on their initial dose of 20 mg lovastatin, 50% had an increase to 40 mg/d, and 5% a decrease to 10 mg/d. Thirty-six high-LDL alerts occurred during the follow-up; 27 led to an LDL action such as dietary intervention, and 12 of these received additional open-label therapy. One participant with a low-LDL alert had the medication dose lowered to 10 mg.

Drug-Treatment Changes

LDL cholesterol fell by 28%, from 156.6 mg/dL (4.0 mmol/L) at baseline to 113.1 mg/dL (2.9 mmol/L) at 6 months in the lovastatin-treated subjects (P < .0001), and was largely unchanged in the lovastatin-placebo groups (Fig 1). This difference decreased slightly during the 3-year follow-up. HDL cholesterol rose by 5% in the lovastatin-treated group, from 51.7 mg/dL (1.3 mmol/L) at baseline to 54.3 (1.4 mmol/L) at 6 months (P < .0001). The lovastatin effects on LDL and HDL cholesterol did not appear to be influenced by the use of 1 mg warfarin. Regular users of aspirin had an approximately 25% greater lovastatin effect on LDL cholesterol than the nonregular users. Placebo participants regularly using aspirin had a slightly greater LDL reduction than the nonregular users.

Changes in Ultrasonographically Determined Early Carotid Atherosclerosis

A statistically significant interaction (P = .04) was detected for the primary outcome measure, the progression rate of mean maximum IMT: the observed effect of the lovastatin and warfarin combination on progression was less than the effect of lovastatin alone (Table 2). For this reason, progression data from the four individual treatment groups, rather than marginals of the factorial design, were compared.

No statistically significant nonlinearity was found for IMT progression across the cohorts. Thus, a linear model for analyzing the 3-year progression rates was appropriate for the primary comparison of treatment effects as described in the protocol. Graphical examinations of residuals from the regressions justified the assumption of an underlying normal distribution for random error. Supplemental analyses also assessed the impact of using weighted versus nonweighted regression, using two-stage versus one-stage approaches, and using conditional maximum likelihood versus ignoring nonquantifiable walls. Each of these supported the analytic choices specified in the design of the study, but none affected the overall interpretation of study results.

Fig 2 portrays the serial mean maximum IMTs for the lovastatin and placebo groups, excluding those assigned to active warfarin. These curves have been aligned so that the baseline values coincide. The mean maximum IMT for the lovastatin group appears to parallel the progression in the placebo group for 6 to 12 months. Beyond this time point, there was a marked decrease in mean maximum IMT. The overall annualized progression rates for the lovastatin group and the placebo group, −0.009 and 0.006 mm/y, respectively, were significantly different (P = .001, Bonferroni-adjusted; Table 2). The effects of lovastatin were similar in men and
TABLE 1. Selected Baseline Characteristics of Randomized ACAPS Participants by Treatment Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Mean (SD)</th>
<th>L Placebo+ W Placebo (N=230)</th>
<th>L Active+ W Placebo (N=231)</th>
<th>L Placebo+ W Active (N=229)</th>
<th>L Active+ W Active (N=229)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.7 (8.3)</td>
<td>61.3</td>
<td>61.9</td>
<td>62.0</td>
<td>61.7</td>
<td>.81</td>
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<tr>
<td>Sex, % male</td>
<td>51.5 (50.7)</td>
<td>50.7</td>
<td>50.0</td>
<td>50.4</td>
<td>55.0</td>
<td>.68</td>
</tr>
<tr>
<td>Race, % white</td>
<td>92.1 (93.5)</td>
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<td>91.3</td>
<td>92.1</td>
<td>91.3</td>
<td>.80</td>
</tr>
<tr>
<td>Education, % ≤ high school</td>
<td>40.6 (37.0)</td>
<td>45.2</td>
<td>42.8</td>
<td>37.6</td>
<td>37.6</td>
<td>.20</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>130.6 (17.1)</td>
<td>130.8</td>
<td>130.3</td>
<td>131.4</td>
<td>130.1</td>
<td>.86</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.6 (8.9)</td>
<td>77.0</td>
<td>76.2</td>
<td>77.3</td>
<td>75.9</td>
<td>.27</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26.3 (9.6)</td>
<td>25.8</td>
<td>26.0</td>
<td>27.8</td>
<td>25.6</td>
<td>.29</td>
</tr>
<tr>
<td>Female</td>
<td>25.4 (4.6)</td>
<td>25.2</td>
<td>26.2</td>
<td>25.0</td>
<td>24.9</td>
<td>.12</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>11.9 (14.8)</td>
<td>8.3</td>
<td>14.0</td>
<td>10.5</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>44.6 (37.0)</td>
<td>49.1</td>
<td>43.7</td>
<td>48.5</td>
<td>.45</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>43.6 (48.3)</td>
<td>42.6</td>
<td>42.4</td>
<td>41.1</td>
<td>.30</td>
<td></td>
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<tr>
<td>History of hypertension, %</td>
<td>28.8 (32.3)</td>
<td>30.0</td>
<td>28.0</td>
<td>24.9</td>
<td>.34</td>
<td></td>
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<tr>
<td>History of NIDDM, %</td>
<td>2.3 (2.2)</td>
<td>1.8</td>
<td>4.4</td>
<td>0.9</td>
<td>.08</td>
<td></td>
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<tr>
<td>Current medications, %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Diuretics</td>
<td>13.1 (13.5)</td>
<td>13.0</td>
<td>14.0</td>
<td>11.9</td>
<td>.91</td>
<td></td>
</tr>
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<td>Noncontraceptive estrogen</td>
<td>26.3 (23.7)</td>
<td>27.0</td>
<td>27.4</td>
<td>27.2</td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>235.3 (23.2)</td>
<td>236.2</td>
<td>236.1</td>
<td>234.3</td>
<td>234.3</td>
<td>.71</td>
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<td>LDL</td>
<td>155.6 (15.5)</td>
<td>155.6</td>
<td>157.1</td>
<td>153.6</td>
<td>156.0</td>
<td>.15</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>45.8 (45.7)</td>
<td>45.4</td>
<td>45.3</td>
<td>46.9</td>
<td>.62</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>58.3 (58.1)</td>
<td>59.0</td>
<td>59.7</td>
<td>56.5</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>3.6 (3.7)</td>
<td>3.5</td>
<td>3.7</td>
<td>3.7</td>
<td>3.5</td>
<td>.30</td>
</tr>
<tr>
<td>Mean pre-run-in PT time, s</td>
<td>11.6 (11.9)</td>
<td>11.9</td>
<td>11.9</td>
<td>12.1</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Mean ALT ratio</td>
<td>0.50 (0.51)</td>
<td>0.48</td>
<td>0.49</td>
<td>0.50</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>B-mode IMT, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean maximum</td>
<td>1.32 (1.32)</td>
<td>1.33</td>
<td>1.31</td>
<td>1.31</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Single maximum</td>
<td>2.29 (2.31)</td>
<td>2.32</td>
<td>2.28</td>
<td>2.25</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>Common carotid</td>
<td>1.14 (1.14)</td>
<td>1.15</td>
<td>1.14</td>
<td>1.14</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Bifurcation</td>
<td>1.58 (1.58)</td>
<td>1.60</td>
<td>1.57</td>
<td>1.57</td>
<td>.56</td>
<td></td>
</tr>
<tr>
<td>Internal carotid</td>
<td>1.23 (1.25)</td>
<td>1.25</td>
<td>1.25</td>
<td>1.21</td>
<td>.11</td>
<td></td>
</tr>
</tbody>
</table>

L indicates lovastatin; W, warfarin; NIDDM, non-insulin-dependent diabetes mellitus; PT, prothrombin; ALT, alanine aminotransferase; and IMT, intimal-medial thickness.

women, in participants with higher and lower LDL cholesterol at baseline (>160 versus <160 mg/dL), in older and younger participants (>60 versus <60 years old), and in those with greater and smaller baseline mean maximum IMT (>2.5 versus <2.5 mm). The results were also similar if the IMT analyses were restricted to measurements in the far walls. Finally, adjusting for baseline histories of smoking and non-insulin-dependent diabetes mellitus (two characteristics that were possibly distributed differentially among the treatment groups at baseline) produced P values that were nearly identical to those from unadjusted analyses.

Mean progression rates for the single maximum IMT are listed in Table 2. The difference for this outcome between the lovastatin and the placebo groups was greater than that observed for mean maximum IMT, although it did not reach statistical significance (P=.12). It should be noted that the variability of this outcome measure is three to four times greater than that for the mean maximum IMT.
Incidence of Major Cardiovascular Events and Mortality

Fourteen of the 459 ACAPS participants in the lovastatin-placebo groups had a major cardiovascular event (4 coronary heart disease deaths, 5 strokes, and 5 nonfatal MIs) compared with 5 of the 460 participants in the lovastatin groups (all nonfatal MIs). Cumulative event curves differed significantly, with a value of \( P = .04 \) (Fig 3).

Among the nine deaths in ACAPS, one was in a participant treated with lovastatin and eight in participants receiving lovastatin-placebo (Fig 4, \( P = .02 \)). All six cardiovascular deaths were in the lovastatin-placebo group; the remaining three deaths were cancer deaths. There were no violent deaths.

Adverse Events

The occurrences of 19 potential adverse events were monitored during the trial. One reached nominal statistical significance for the comparison lovastatin versus lovastatin-placebo. Skin tissue deterioration was reported more often in the placebo group, 43 versus 27 (\( P = .05 \)).

For the warfarin versus warfarin-placebo comparisons, the combined occurrence of muscle weakness, soreness, or cramping was more common in the placebo group, 297 versus 264 (\( P = .04 \)). Unusual bleeding was slightly more common in the warfarin group: 142 versus 120 (\( P = .10 \)). There was no evidence that the lovastatin-warfarin combination increased the risk of any of the 19 prespecified potential adverse events.

Monitoring of ALT showed no difference between lovastatin and lovastatin-placebo. Six participants in each group had an ALT at least 200% greater than the upper limit of normal for the local laboratory. Three of the lovastatin and two of the placebo participants went off their study medication permanently.

Discussion

Given the population studied, this trial adds new information to the ever-growing pool of data regarding lipid-lowering regimens. ACAPS is the first trial to demonstrate the benefit of lipid-lowering treatment in asymptomatic subjects with LDL cholesterol below recommended NCEP treatment levels. These findings apply to both men and women. It is also the first trial to demonstrate the effects of statins on both cardiovascular disease incidence (exclusive of cardiovascular procedures) and all-cause mortality. Finally, ACAPS is the first trial to demonstrate the validity and statistical efficiency of B-mode ultrasonography as an outcome measure of the progression of early carotid atherosclerosis in a multicenter clinical trial setting.

Lipid Lowering

The LDL cholesterol-lowering effect of lovastatin has been well established.\(^1\),\(^2\),\(^1\),\(^2\) In the largest clinical trial reported to date, the mean reduction in LDL cholesterol was 24% with a single 20-mg evening dose and 30% with a single 40-mg evening dose.\(^3\) The average daily dose in ACAPS was 26 mg. Thus, the observed reductions in LDL cholesterol of 28% at 6 months and 25% at 3 years were as expected. Mean increases in HDL cholesterol ranging from 5% to 10% have gener-

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**TABLE 2. Progression Rates for Primary and Secondary Outcome Measures of Intimal-Medial Thickness by Randomization Assignment**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>L placebo +W placebo</th>
<th>L active +W placebo</th>
<th>L active +W active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maximum</td>
<td>0.006±0.003</td>
<td>-0.009±0.003</td>
<td>-0.003±0.003</td>
</tr>
<tr>
<td></td>
<td>((P=.001)^*)</td>
<td>((P=.06)^*)</td>
<td></td>
</tr>
<tr>
<td>Single maximum</td>
<td>0.000±0.011</td>
<td>-0.036±0.011</td>
<td>-0.023±0.011</td>
</tr>
<tr>
<td></td>
<td>((P=.12)^*)</td>
<td>((P=.34)^*)</td>
<td></td>
</tr>
</tbody>
</table>

*Indicates lovastatin; W, warfarin. Values are in mm/y, mean±SEM.

*Difference from double placebo based on Bonferroni-adjusted ANCOVA with clinical center and baseline value as covariates. Significant differences \((P<.05)\) in boldface type.

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**FIG 1.** Graph showing lipoprotein levels by lovastatin use.

**FIG 2.** Graph showing cross-sectional intimal-medial thicknesses for the lovastatin and placebo groups, excluding participants assigned to warfarin.

**FIG 3.** Graph showing incidence of fatal/nonfatal cardiovascular disease by treatment group.
ally been observed. The increase in HDL cholesterol is mildly dose dependent, although larger increases have been observed in patients with low baseline HDL cholesterol and high triglyceride values. Thus, the 5% increase in HDL cholesterol in this study was consistent with other reports. The LDL cholesterol reduction was the same in participants on warfarin and warfarin-placebo, respectively. The observation that regular aspirin users had a 25% greater relative LDL cholesterol reduction than the irregular aspirin users may suggest less than optimal adherence to lovastatin in the latter group.

B-Mode Ultrasonography

With proper standardization, B-mode imaging represents a valuable research tool for the noninvasive assessment of carotid atherosclerosis. Rigorous training and standardization are essential to any project, particularly multicenter studies. Variability in the scanning and the reading of images contributes to the imprecision of the technique. The use of duplicate examinations at baseline and at the completion of the trial, together with the semianual interim examinations and the use of a summary outcome measure, reduced the intraperson variability and allowed estimation of changes over time. Although it is not known whether mean maximum IMT progresses linearly or episodically in individuals, statistical analyses of the double-placebo group suggest that population means may increase uniformly across time. Because of variability, it is difficult to comment on progression patterns in individuals. The changes in group mean data are smaller than the resolution of the methodology in individual participants. Two large-scale population-based cohort studies, the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study, are gathering B-mode data and will eventually be able to better describe the change over time and to define the predictors of progression.

Carotid intimal-medial arterial wall thickening, as measured by B-mode ultrasonography, has been used to define atherosclerosis in a number of recent clinical trials. The theoretical bases for this include the positive cross-sectional and longitudinal relations of IMT with the traditional risk factors for coronary heart disease and with prevalent and incident coronary disease and stroke.

The observed 6- to 12-month delay from initiation of lipid-lowering treatment in the lovastatin group to the apparent slowing of the typical progression of early carotid atherosclerosis has not been reported previously. The Lipid Research Clinic Coronary Primary Prevention Trial and the Helsinki trial reported a 1-to 2-year lag time between initiation of cholestyramine and gemfibrozil treatment, respectively, and the first sign of a reduction in coronary events. It is unknown whether treatment beyond 3 years in ACAPS would have led to further regression in the lovastatin group. Since the typical IMT for a healthy middle-aged person is 0.60 mm, a return to this value at a regression rate of 0.01 to 0.02 mm/y would require extended treatment for people with subclinical disease. If the issue of regression remains unresolved, however, one can conclude with greater certainty that lovastatin is capable of halting progression in the population. The IMT changes in ACAPS are similar to the changes in lumen diameter reported in several coronary angiographic trials of lipid-lowering. Furthermore, Waters et al observed that patients with a fast progression had a higher risk of a clinical event than patients with no or a slow progression, a finding that has been noted in other studies. Questions have been raised regarding the clinical significance of the small changes in lumen diameter and IMT reported from these so-called regression studies. One must keep in mind that the observed rate of change within an individual in ACAPS represents a mean of measurements at 12 sites, and many of these sites showed no or little change during the 3-year follow-up. Brown et al speculated that lipid-lowering agents exert a stabilizing effect on existing atherosclerotic lesions, thereby preventing fissures and their associated clinical events. The failure of ACAPS to demonstrate a statistically significant effect of lovastatin on the progression of the single maximum IMT is probably a result of the large variability associated with single wall measurements.

Cardiovascular Events

The observed reduction in cardiovascular events, 14 versus 5, is substantially greater than the reductions reported for the older and less effective lipid-lowering agents. A similar 60% treatment benefit was seen in two trials of pravastatin in coronary patients, PLAC-1 (B. Pitt, MD, oral communication, March 1994) and PLAC-2. Thus, three small but independent trials have suggested a substantial clinical benefit from the statins. Until there are direct comparative trials between statins, one would have to assume that the benefit is a class effect of the HMG CoA reductase inhibitors.

The mortality data in ACAPS were not expected, but since the results are based on a simple count and there was complete participant follow-up, it is difficult to downplay the findings. However, the 8-to-1 split (P = .02) may be extreme. The mortality data in the PLAC trials also tended to show fewer events in the statin group. The pattern in ACAPS is biologically consistent: lovastatin causes regression in evidence of atherosclerosis and reduces cardiovascular events and mortality. Several ongoing large-scale trials of statins with adequate power to determine reasonable morbidity and mortality benefits may further establish the clinical benefit of these compounds.

ACAPS provided neither adequate power nor the duration of treatment needed to determine the link
between IMT progression and cardiovascular events. Reliability analyses indicate that several years of additional follow-up would be required to characterize individual participants as fast, average, or slow progressors. Additional population follow-up is needed to link progression to subsequent clinical events. The clinical data in ACAPS thus should be viewed as complementary to the B-mode data.

**Clinical Implications**

The reversal or slowing of the typical progression of IMT in the carotid arteries is consistent with reported effects of statins on coronary atherosclerosis. These findings are consistent with the concept that atherosclerosis is a generalized condition and that one vascular bed can serve as an appropriate marker for others. ACAPS adds to the overwhelming scientific and clinical evidence that the statins have much greater lipid-lowering potential than the older lipid-lowering agents. In addition, they are safe and well tolerated by asymptomatic subjects.

The primary evidence of a clinical benefit of lipid-lowering in ACAPS comes from a reduction in the count of clinical events. The strength of the evidence for a reduction in cardiovascular events in ACAPS, however, should not be exaggerated. Because of the small sample size, a clinical benefit was not expected. Nonetheless, the very large relative reduction in events did yield an observed value of $P = 0.04$. This observation takes on additional meaning because two small, recent trials of pravastatin have shown similar benefits. The consistency of the findings across these trials conveys a strong message that the statins may have substantial clinical benefits to coronary patients and to those with significant subclinical atherosclerotic disease as measured by B-mode ultrasonography of the carotid arteries. Ongoing large-scale trials will determine whether the clinical benefits extend to primary prevention and to the most important outcome, all-cause mortality.

Although the standardization of B-mode ultrasonography in the typical clinical setting is less stringent than that in research projects such as ACAPS, clinical B-mode data would be adequate for the diagnosis of subclinical carotid atherosclerosis in individuals and treatment decisions. However, the use of the technique for monitoring individual treatment effects in individuals is still investigational. Furthermore, it does seem reasonable to extrapolate the ACAPS findings in subjects with subclinical atherosclerosis to patients with clinically manifest atherosclerosis. If so, the results lend support to the new NCEP guidelines for more aggressive use of lipid-lowering therapy in patients with coronary disease.40 These guidelines recommend lowering the cutoff point for initiation of treatment to 130 mg/dL (3.36 mmol/L), which was the low eligibility limit for LDL cholesterol in ACAPS.

**Appendix**

**Members of the Asymptomatic Carotid Artery Progression Study Research Group**

ACAPS Clinics: Bowman Gray School of Medicine (Winston-Salem, NC): David S. Lefkowitz, MD; Philip R. Aronson, MD; Catherine Nunn, RN, RVT; Kimberly S. Darmworth; Steve Meads; Mitzie H. Spainhour, LPN; Dianne Combs, RN. University of Iowa College of Medicine (Iowa City): Harold P. Adams, Jr, MD; John Corson, MD; José Biller, MD; Marta Heffner, RN, MA; Alicia Romont. University of Kentucky Medical Center (Lexington): Byron Young, MD; Robert Dempsey, MD; Louise Diana, PhD; Linda Rice, RN; Vicki Gatz, RVT. University of Tennessee (Memphis): William B. Applegate, MD, MPH; William C. Cushman, MD; Nancy L. Miles, MSN, FNP; Kathleen P. Nash, RN, FNP; Pamela Rickman; Evelyn Clark; Lisa Anderson. Administrative Center (Bowman Gray School of Medicine): Curt D. Furberg, MD, PhD; Robert P. Byington, PhD; Mark A. Espeland, PhD; Therese A. Dolecek, PhD, RD; James Toole, MD; Susan Margitíć, MS; Helena Hoen, MS. Data Coordinating Center (Research Triangle Institute, Research Triangle Park, NC): Tyler Hartwell, PhD; Vicki Davis, PhD; Betty Hastings; Renee Karlsen; Supatra Campbell; David Myers. Ultrasound Center (AUTREC, Inc, Winston-Salem, NC): Ward A. Riley, PhD; Ralph W. Barnes, PhD; Lois W. Hoots; Cynthia S. Garrison; Betsy D. Vestal. Central Laboratory (Bowman Gray School of Medicine): Richard W. St. Clair, PhD; Nina Ann Stokes; Tricia Seitz-Wood; Marcia L. Burris; Catherine S. Butler; Patricia A. Shaw. NHLBI Project Officers: Jeffrey Probstfield, MD; Debra Egan. Steering Committee Chairman: Donald B. Hunninghake, MD (University of Minnesota, Minneapolis).

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Hunninghake, D S Leffkowitz, J Probstfield and W A Riley

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