Clinical Investigation and Reports

Effects of Monotherapy With an HMG-CoA Reductase Inhibitor on the Progression of Coronary Atherosclerosis as Assessed by Serial Quantitative Arteriography

The Canadian Coronary Atherosclerosis Intervention Trial

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Background 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are widely prescribed for hyperlipidemia, yet their effect on the evolution of coronary atherosclerosis has not been defined.

Methods and Results To address this issue, 331 patients with diffuse but not necessarily severe coronary atherosclerosis documented on a recent arteriogram and with fasting serum cholesterol between 220 and 300 mg/dL were enrolled in a randomized, double-blind, placebo-controlled trial. All patients received intensive dietary counseling. Lovastatin or placebo was begun at 20 mg/d and was titrated to 40 and 80 mg during the first 16 weeks to attain a fasting low-density lipoprotein (LDL) cholesterol ≤130 mg/dL. The mean lovastatin dose was 36 mg/d. Coronary arteriography was repeated after 2 years. In 299 patients (92%), 3858 coronary segments containing 2309 stenoses were measured blindly on pairs of films with an automated computerized quantitative system. Total and LDL cholesterol decreased by 21±11% and 29±11%, respectively, in the lovastatin-treated group but changed by <2% in placebo patients. The primary end point, coronary change score, defined as the per-patient mean of the minimum lumen diameter changes (follow-up minus baseline angiogram) for all lesions measured, excluding those <25% on both films, worsened by 0.09±0.16 mm in the placebo group and by 0.05±0.13 mm in the lovastatin group (P=.01). Progression (a worsening in minimum diameter of one or more stenoses by ≥0.4 mm) with no regression at other sites occurred in 48 of 146 lovastatin and 76 of 153 placebo patients (33% versus 50%, P=.003). New coronary lesions developed in 23 lovastatin and 49 placebo patients (P=.001). The beneficial effect of treatment was most pronounced in the more numerous, milder lesions and in patients whose baseline total or LDL cholesterol levels were above the group median.

Conclusions Lovastatin slows the progression of coronary atherosclerosis and inhibits the development of new coronary lesions. (Circulation. 1994;89:959-968.)

Key Words • atherosclerosis • lovastatin • arteries • hydroxymethylglutaryl-CoA reductase

Several clinical trials have demonstrated that lipid-lowering therapy exerts a beneficial effect on the evolution of coronary atherosclerosis, as assessed by either visual estimation1-3 or computerized quantitative measurement4-6 of serial arteriograms. The methods used to lower cholesterol in these studies consisted of high doses of bile acid sequestrants,1,6 combined drug treatment with these agents plus niacin and/or lovastatin,2,4,5 and partial ileal bypass surgery.3 Bile acid sequestrants and niacin are poorly tolerated by many patients at the dose levels used in these trials, and partial ileal bypass surgery is rarely used to treat hypercholesterolemia. After diet, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are by far the most common form of treatment for hypercholesterolemia because of their efficacy and low incidence of adverse effects.7 The drugs in this class, when used without other lipid-lowering agents, are presumed to influence favorably the evolution of coronary atherosclerosis, based on extrapolations from the aforementioned studies. However, of the two trials of monotherapy with HMG-CoA reductase inhibitors reported to date, one yielded equivocal results, with no significant treatment benefit found for the primary end point,8 and the other is continuing to 4 years as planned, after assessment of the 2-year angiographic follow-up data.9

The purpose of this trial was to determine whether administration of the HMG-CoA reductase inhibitor lovastatin retards the progression or facilitates the regression of coronary atherosclerosis as assessed by serial quantitative coronary arteriography.

Methods

Patient Selection

The design features of this trial, including the criteria for patient selection, were described in detail in a previous report.10 Patients at higher risk for coronary progression were selected to reduce sample size requirements. In a retrospective

Received September 2, 1993; revision accepted December 4, 1993.

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analysis of 313 medically treated patients who had two coronary arteriograms, the only two variables available at the first arteriogram that independently predicted progression were younger age and higher extent score.\textsuperscript{11} Extent score was obtained by dividing the coronary tree into the 15 segments defined in the Coronary Artery Surgery Study.\textsuperscript{12} The score was calculated by counting the number of segments containing coronary lesions between 5% and 75% by visual assessment. Patients 21 to 50 years old with a score $\geq 4$, those 51 to 60 years old with a score $\geq 5$, and those 61 to 65 years old with a score $\geq 6$ had a high risk of coronary progression. In a previous prospective study using these criteria, 43% of patients developed progression of one or more stenoses over a period of 2 years.\textsuperscript{13} Thus, these criteria were used to select patients for the present study. The age limit was increased from 65 to 70 years after enrollment had begun.

Men or women without childbearing potential were recruited if their fasting total serum cholesterol was $\geq 220$ and $\leq 300$ mg/dL. Coronary arteriography had to have been performed within 12 weeks of study entry, and the treating physician had to have concurred with the study plan for medical treatment; ie, there was no coronary angioplasty or bypass surgery planned within the 24-month study period. The main exclusion criteria were (1) previous coronary bypass surgery; (2) coronary angioplasty in the 6 months preceding the qualifying coronary arteriogram; (3) ejection fraction $<40$%; (4) left main coronary artery stenosis $>50$%; (5) three-vessel disease with preexisting left anterior descending stenosis $>70$%; (6) any coexisting severe illness that would make repeat arteriography ethically unjustifiable; (7) myocardial infarction or unstable angina within 6 weeks before study entry or after the entry coronary arteriogram; (8) a technically suboptimal coronary arteriogram; (9) plasma triglycerides $>500$ mg/dL; (10) concurrent use of lipid-lowering drugs, cyclosporine, anticoagulants, corticosteroids, or cimetidine; (11) elevated hepatic enzymes or impaired renal function; and (12) patients living too far away from the clinic or having any potential condition or problem that might hinder follow-up or compliance or present an unacceptable risk to the patient. Written informed consent was obtained from each patient. The trial was approved by the ethics committees of each of the participating institutions.

**Enrollment Procedures**

All patients undergoing coronary arteriography in each of the clinical centers were tracked by the study nurses until they were either enrolled in the trial or declared ineligible. The reason for exclusion was noted in a log. The most common reasons for exclusion were failure to meet the age–extent score criteria, fasting total serum cholesterol outside the required range, previous coronary bypass surgery, ejection fraction $<40$%, and planned coronary revascularization. Between October 1988 and June 1990, 2139 consecutive arteriograms were screened to identify 488 patients who met the study entry criteria; 331 of them (68%) were enrolled. Patients were randomized and began treatment a mean of 31 $\pm$ 16 days (range, 0 to 79 days) after their baseline coronary arteriogram. Treatment allocation was stratified according to sex. Patients, study personnel, and other clinic staff were blinded as to treatment allocation and lipid levels throughout the trial.

**Drug Treatment**

Patients began double-blind treatment with either placebo or lovastatin 20 mg taken immediately after the evening meal. In each center, a physician otherwise uninvolved in the trial monitored serum lipid levels and recommended dose changes on the basis of the following rules. Patients whose low-density lipoprotein (LDL) cholesterol level at week 4 exceeded 130 mg/dL had their dosage doubled to one 40-mg lovastatin tablet or matching placebo when they returned at week 8 for their next visit. If the LDL cholesterol level still exceeded 130 mg/dL at week 12, the dose was increased to 40 mg twice per day at the next visit (week 16). Patients whose LDL cholesterol levels decreased below 80 mg/dL on one occasion or below 90 mg/dL on two successive visits had their dosage reduced by half. To preserve blinding, placebo patients had their doses modified in a similar pattern to patients receiving lovastatin.

All patients received counseling from a dietician at study entry with the goal of adhering to the American Heart Association phase I diet. Patients were also counseled with respect to caloric intake so that their body weight would not exceed 1.15 times the ideal. Compliance to diet was monitored throughout the trial by 3-day food records or 24-hour recalls at each of the six visits during the titration period of 16 weeks and at every other visit thereafter. If total cholesterol exceeded 340 mg/dL at any visit, the patient received special dietary counseling, and if no improvement occurred, cholestyramine was added. This drug was used for more than 1 month in seven patients in the placebo group; no patient in the lovastatin group received other therapy. With the exception of those who had contraindications or developed side effects, all patients were treated with enteric-coated aspirin 325 mg on alternate days to reduce the risk of thrombotic coronary events.

**Follow-up Procedures During the Study**

After the randomization visit when treatment was initiated, 20 visits were planned over the ensuing 24 months of the study. The interval between visits was 2 weeks for the first month, 4 weeks for the next 5 months, 6 weeks from months 6 through 15, and 8 weeks for the remainder of the trial. Blood lipids were measured at each of the first six visits and then at alternate visits. Plasma cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured on fasting blood samples by standard techniques: LDL cholesterol levels were calculated according to the modified Friedewald formula of Delong et al.\textsuperscript{14} Apolipoproteins A-1, A-2, and B were measured at baseline and at 4, 12, and 24 months. Blood chemistry, hematology, and urinalysis were performed at regular intervals to monitor safety. Compliance was verified by tablet counts at each visit and averaged $\geq 90$% for all participants. Compliance to diet was monitored by assessing 3-day food records; noncompliant patients received extra counseling from the study nurse and dietician. The use of concomitant medication to control angina was left to the discretion of the referring physician.

All cardiovascular intercurrent events were categorized according to predetermined standard definitions\textsuperscript{10} by one investigator who was blinded to treatment assignment. A Data and Safety Monitoring Board (see “Appendix”) reviewed intercurrent events, adverse effects, laboratory results, and other relevant data according to treatment group at 6-month intervals during the trial.

Repeat coronary arteriography was scheduled for 24 months after study entry but was performed earlier in 21 patients. The interval from study entry to repeat arteriography was 9.6 $\pm$ 6.1 months in the 8 lovastatin patients and 11.4 $\pm$ 5.9 months in the 13 placebo patients who had early arteriography ($P$=NS). The reason for early arteriography was myocardial infarction in 5 patients, documented or suspected unstable angina in 10 patients, and a persistent, unacceptable level of stable angina in 6 patients. At the visit 1 week before coronary arteriography, antianginal medication was adjusted to be identical to that taken at the time of the first arteriogram, especially with respect to coronary vasodilators. The angiographic procedures followed in the trial have been described previously.\textsuperscript{10} No patient suffered a serious complication related to the follow-up angiogram.

**Quantitative Coronary Arteriography**

The pair of arteriograms for each patient were interpreted together in the core quantitative angiographic laboratory by a radiologist and technicians blinded to treatment allocation, the
order of the films, and the identity of the patient. For each lesion and segment, an end-diastolic frame from each arteriogram with identical angulation that best showed the stenosis at its most severe was chosen. The Cardiovascular Measurement System developed by Reiber et al.\(^\text{15}\) was used in this trial to measure coronary segments and lesions, as previously described in detail.\(^\text{10,16}\) In summary, the cineframe is digitized and displayed on a video monitor. The cardiac catheter image is measured for calibration. The coronary artery tree is divided into segments using branch points as boundaries, according to the nomenclature of the Bypass Angioplasty Revascularization (BARI).\(^\text{17}\) Segments <1.0 to 1.5 mm in diameter by visual inspection, segments distal to total occlusions, and segments poorly visualized because of TIMI grade 1 or 2 antegrade flow or competitive flow from collaterals were not measured. Because of unacceptable differences in coronary tone between the two films, 51 other segments were also excluded. Two nondominant right coronary arteries and one left anterior descending artery, a total of 9 segments, were not injected at repeat angiography and were also excluded. After selection of the boundaries of a segment, the arterial borders were defined by an automated edge detection algorithm, and dimensions were calculated and displayed automatically. The interpolated reference diameter was used to calculate percent diameter stenosis, except in rare cases, such as a stenosis situated at a branch point, when the interpolated diameter was inaccurate and the user-defined reference diameter was selected.

We have assessed the reproducibility of the Cardiovascular Measurement System as used in this trial in a series of 54 lesions from patients who had serial arteriograms from 3 to 189 days apart.\(^\text{16}\) The SD for repeat measurements of minimum lumen diameter increased from 0.087 mm when the same frames from the same film were remeasured to 0.240 mm for films recorded from 1 to 6 months apart. The comparable SDs for diameter stenosis were 3.7% and 8.6%. A change in minimum diameter ≥0.4 mm or a change in diameter stenosis ≥15% (eg, 30% to ≥45%) is more than 4 SD of the variability of same frame measurements and almost 2 SD of the 1- to 6-month variability and was therefore taken to represent a true change, either progression or regression. Our minimum diameter cutoff point of 0.4 mm has been used in previous angiographic studies,\(^\text{13,18}\) although both 10%\(^\text{,4,13}\) and 20%\(^\text{,18}\) have been used as criteria for diameter stenosis change.

**End Points of the Trial**

The angiographic definitions and end points of this trial were established before the study was unblinded and any of the arteriograms were interpreted; they are described in detail elsewhere.\(^\text{14}\) The primary end point of the trial is a comparison between the lovastatin and placebo groups for coronary change score, defined as the per-patient mean of the minimum lumen diameter changes (follow-up minus baseline angiogram) for all lesions measured, excluding those <25% on both films. The treatment groups were compared for five secondary end points: (1) proportion of patients classified as progressors, (2) proportion of patients classified as regressors, (3) proportion of patients with one or more new lesions, (4) proportion of patients with one or more new total occlusions, and (5) coronary change score, including only lesions ≥50% in diameter stenosis at baseline.

Progressors and regressors were defined as patients with one or more lesions narrowing or widening, respectively, by ≥0.4 mm. A new lesion was defined as a stenosis that was not apparent on the first film or was <25% in diameter stenosis but that narrowed by ≥0.4 mm in minimum lumen diameter at the second angiogram. An all-patients-treated approach was used for the analyses reported here.

**Statistical Analyses**

The sample size calculation for the trial was described in a previous report.\(^\text{10}\) Baseline characteristics of the treatment groups were compared by χ² test, Fisher’s Exact Test, or a two-sample t test as appropriate. All randomized patients with interpretable follow-up arteriograms are included in the endpoint analyses regardless of their response status or the timing of the follow-up arteriogram. Coronary change score was compared between treatment groups with an ANOVA model. The model included terms for center and “center by treatment” interaction; no significant interaction was found. ANCOVA was also done with the number of lesions and baseline minimum lumen diameter as covariants; again, no significant interaction was found. The categorical secondary end points were analyzed by the Mantel-Haenszel test with center as a blocking factor. A general linear model with intraclass correlation, as developed by Gibson et al,\(^\text{19}\) was used for all lesion-based analyses. Pearson and Spearman correlation coefficients were used to assess the relation between coronary change score and plasma lipid values (baseline, on treatment, and percent change). Coronary change score was also compared between treatments for subgroups of patients with different baseline plasma lipid levels. Multivariable regression analyses that included clinical and angiographic descriptors, concomitant medication, and baseline lipid values were done to determine which factors correlated with mean minimum lumen diameter at baseline, coronary change score, and progression. A probability value of .05 was considered significant, and tests were two-sided.

**Results**

**Baseline Characteristics of the Study Population**

The clinical features of the study patients at baseline, according to treatment allocation, are listed in Table 1. Overall, there were 269 men (81%) and 62 women; the mean age was 52±8 years (range, 27 to 70 years) for men and 58±8 years (range, 31 to 69 years) for women. Approximately half had a history of previous myocardial infarction, one third were hypertensive, and one quarter were current smokers. By the standard criterion of a stenosis ≥50% being considered significant, approximately one third of the patients had multivessel coronary disease. The treatment groups were well balanced with respect to baseline characteristics.

**Effect of Treatment on Plasma Cholesterol Levels**

The plasma lipid levels for the two treatment groups at baseline and during the trial are listed in Table 2. Titration of lovastatin according to the study protocol resulted in 91 patients receiving 20 mg/d, 41 patients receiving 40 mg/d, and 33 patients receiving 80 mg/d as their maximal dose during the study. The mean lovastatin dose in the active treatment group was 36 mg/d. The target LDL cholesterol level of ≤130 mg/dL was attained by 114 (69%) of the 165 lovastatin patients and 17 (10%) of the 166 placebo patients. Averaged over the 24 months of the study, the reductions in total and LDL cholesterol were 21±11% (<.001) and 29±11% (<.001), respectively, in the patients randomized to lovastatin, including 9 who withdrew from treatment. Over the same period, the mean HDL cholesterol level increased by 7.3±19% (<.001), and apolipoprotein B decreased by 21±12% (<.001). In the placebo group, the mean change over the duration of the study was <4% for total cholesterol, LDL and HDL cholesterol, and apolipoproteins A-1, A-2, and B.

**Coronary Events and Angina Class During the Trial**

Coronary events and Canadian Cardiovascular Society angina class during the trial were classified accord-
TABLE 1. Clinical and Angiographic Features of the Treatment Groups at Baseline

<table>
<thead>
<tr>
<th>Feature</th>
<th>Lovastatin (n=165)</th>
<th>Placebo (n=166)</th>
<th>Total (n=331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±9</td>
<td>53±8</td>
<td>53±8</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>135 (82)</td>
<td>134 (81)</td>
<td>269 (81)</td>
</tr>
<tr>
<td>Hypertension by history, n (%)</td>
<td>70 (42)</td>
<td>54 (32)</td>
<td>124 (37)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>25 (15)</td>
<td>21 (13)</td>
<td>46 (14)</td>
</tr>
<tr>
<td>Smoking (current), n (%)</td>
<td>44 (27)</td>
<td>46 (28)</td>
<td>90 (27)</td>
</tr>
<tr>
<td>Previous infarction, n (%)</td>
<td>95 (58)</td>
<td>85 (51)</td>
<td>180 (54)</td>
</tr>
<tr>
<td>Previous angioplasty, n (%)</td>
<td>29 (18)</td>
<td>29 (17)</td>
<td>60 (18)</td>
</tr>
<tr>
<td>Angina duration, y</td>
<td>3.6±4.6</td>
<td>3.2±3.5</td>
<td>3.4±4.0</td>
</tr>
<tr>
<td>Angina class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48 (29)</td>
<td>52 (31)</td>
<td>100 (30)</td>
</tr>
<tr>
<td>2</td>
<td>44 (27)</td>
<td>58 (35)</td>
<td>102 (31)</td>
</tr>
<tr>
<td>3</td>
<td>10 (6)</td>
<td>6 (4)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>No angina</td>
<td>63 (38)</td>
<td>50 (30)</td>
<td>113 (34)</td>
</tr>
<tr>
<td>Concomitant medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>85 (52)</td>
<td>79 (48)</td>
<td>164 (50)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>8 (5)</td>
<td>9 (5)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>21 (13)</td>
<td>21 (13)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>93 (56)</td>
<td>92 (55)</td>
<td>185 (56)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>6 (4)</td>
<td>6 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Coronary arteries with ≥50% stenosis per patient, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>48 (29)</td>
<td>59 (36)</td>
<td>107 (32)</td>
</tr>
<tr>
<td>1</td>
<td>64 (39)</td>
<td>53 (32)</td>
<td>117 (35)</td>
</tr>
<tr>
<td>2</td>
<td>43 (26)</td>
<td>35 (21)</td>
<td>78 (24)</td>
</tr>
<tr>
<td>3</td>
<td>10 (6)</td>
<td>19 (11)</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>0.63±0.10</td>
<td>0.63±0.10</td>
<td>0.63±0.10</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

*P* > .05 indicates statistically significant differences between groups.

The symptom level of most patients did not change during the study. Angina class improved by at least one grade in 50 lovastatin and 43 placebo patients and worsened by at least one grade in 23 lovastatin and 27 placebo patients. The difference between groups for change in angina class from baseline to end of study is statistically significant (*P* = .007).

Of the 331 patients enrolled in the trial, a second arteriogram suitable for analysis was obtained in 299 (90%). In addition to the 4 patients who died, 17 lovastatin and 11 placebo patients either dropped out of the trial or did not undergo repeat arteriography at 24 months (n=27) or had a second film of poor quality unfit for quantitative analysis (n=1). All lovastatin and all but 1 placebo patient with nonfatal coronary events had a second arteriogram. Among the 299 patients with paired angiograms suitable for analysis, treatment was permanently discontinued during the trial (because of patient noncompliance or possible adverse effects) in 4Lovastatin and 9 placebo patients.

**Coronary Change Score**

The difference between lovastatin and placebo groups for coronary change score, the primary end point of the trial, is shown in Table 3. Coronary change score was defined as the per-patient mean of the minimum lumen diameter changes (follow-up minus baseline angiogram) for all lesions measured, excluding those <25% on both films. In the 146Lovastatin patients with follow-up arteriograms (1095 qualifying lesions), the mean minimum lumen diameter was 1.54±0.25 mm on the first film and 1.49±0.27 mm on the second film. Among the 153 placebo patients (1214 qualifying lesions), the change in mean minimum lumen diameter was from 1.49±0.31 to 1.40±0.30 mm. The mean change per patient in the lovastatin group, −0.05±0.13 mm, was less than in the placebo group, −0.09±0.16 mm.
(P=.01). Expressed as mean percent diameter stenosis, the worsening in lovastatin-treated lesions, 1.66±4.5%, was less than in placebo-treated lesions, 2.89±5.59% (P=.039).

A secondary end point of the trial was the difference between treatment groups for coronary change score for stenoses ≥50% at baseline. As shown in Table 3, comparatively few lesions fell into this category, 230 in lovastatin and 249 in placebo patients, and little change occurred: coronary change score improved by 0.02±0.28 mm in the lovastatin and by 0.01±0.20 mm in the placebo group (P=.73). The difference between treatment groups for qualifying lesions <50% at baseline was more impressive: coronary change score worsened by −0.11±0.18 mm in placebo patients and by only −0.06±0.14 mm in lovastatin patients (P=.014).

Categorical Analyses

Progression

Progression, defined as a worsening of minimum lumen diameter by ≥0.4 mm of one or more lesions, occurred in 62 of the 146 lovastatin patients and 86 of the 153 placebo patients (42% versus 56%, P=.018). Some of these patients also had regression at other coronary sites, ie, mixed changes. However, 48 lovastatin patients (33%) and 76 placebo patients (50%) had progression only (P=.003), with no regression at other sites, as shown in Fig 1. On a per-lesion basis, 75 of the 1095 lovastatin lesions and 114 of the 1214 placebo lesions progressed (6.8% versus 9.4%, P=.017). Using a worsening of diameter stenosis by ≥15% as the criterion for progression would yield similar rates, 5.9% among lovastatin lesions and 9.6% among placebo lesions (P=.008). Progression to a new total occlusion was seen in 17 stenoses (1.6%) in the lovastatin group and 23 stenoses (1.9%) in the placebo group.

Most lesions were <50% in diameter stenosis severity at baseline, and thus most stenoses that progressed began as mild lesions. Among qualifying stenoses <50% in diameter stenosis at baseline, 59 of 865 lovastatin lesions (6.8%) and 108 of 965 placebo lesions (11.2%) progressed by ≥15% (P=.005). There were 166 lovastatin and 173 placebo lesions ≥50% but not total occlusions on the baseline arteriogram; using the diameter stenosis criterion of ≥15%, only 6 lovastatin and 8 placebo lesions in this range progressed.

The cutoff points used to define progression and regression can exert a major influence on the assessment of results. As illustrated in Fig 2, the cumulative distribution curve for change in minimum lumen diameter for lovastatin lesions is shifted along its entire length in the direction of less progression compared with the curve for placebo lesions. Choosing a different cutoff point to define progression and regression would yield a roughly similar difference between treatment groups. The cumulative distribution curves for coronary change score, a patient-based analysis, are also separate and roughly parallel, with a better outcome in lovastatin patients (P=.01).

Regression and Recanalization

Regression, defined as an improvement in minimum lumen diameter ≥0.4 mm of one or more lesions, excluding recanalization of total occlusions, was observed in 28 lovastatin and 20 placebo patients (19% versus 13%, P=NS), as shown in Fig 1. Some of these patients had mixed changes; that is, progression of one or more stenoses in addition to regression. Regression with no progression elsewhere occurred in 14 lovastatin patients (10%) and 10 placebo patients (7%), a difference that was not statistically significant. Recanalization of a total occlusion was uncommon, occurring in only 9 patients, 7 of whom were in the lovastatin group (P=.077 for intergroup difference).
TABLE 3. Quantitative Coronary Arteriographic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Lovastatin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All qualifying lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>146</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>1095</td>
<td>1214</td>
<td></td>
</tr>
<tr>
<td>MLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>1.54±0.25</td>
<td>1.49±0.31</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mm</td>
<td>1.49±0.27</td>
<td>1.40±0.30</td>
<td></td>
</tr>
<tr>
<td>Coronary change score, mm</td>
<td>-0.05±0.13</td>
<td>-0.09±0.16</td>
<td>.010</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>40.15±6.93</td>
<td>39.83±9.90</td>
<td></td>
</tr>
<tr>
<td>Follow-up, %</td>
<td>41.80±7.96</td>
<td>42.72±10.35</td>
<td></td>
</tr>
<tr>
<td>Change, %</td>
<td>1.66±4.50</td>
<td>2.89±5.59</td>
<td>.039</td>
</tr>
<tr>
<td>Stenoses ≥50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>117</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>230</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td>MLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>0.76±0.51</td>
<td>0.67±0.45</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mm</td>
<td>0.78±0.54</td>
<td>0.68±0.51</td>
<td></td>
</tr>
<tr>
<td>Coronary change score, mm</td>
<td>+0.02±0.28</td>
<td>+0.01±0.20</td>
<td>.730</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>71.67±16.51</td>
<td>73.82±16.31</td>
<td></td>
</tr>
<tr>
<td>Follow-up, %</td>
<td>70.65±17.8</td>
<td>73.47±18.94</td>
<td></td>
</tr>
<tr>
<td>Change, %</td>
<td>-1.02±11.13</td>
<td>-0.35±7.93</td>
<td>.646</td>
</tr>
<tr>
<td>Stenoses &lt;50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>146</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Number of lesions</td>
<td>865</td>
<td>965</td>
<td></td>
</tr>
<tr>
<td>MLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>1.74±0.29</td>
<td>1.69±0.30</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mm</td>
<td>1.68±0.29</td>
<td>1.59±0.31</td>
<td></td>
</tr>
<tr>
<td>Coronary change score, mm</td>
<td>-0.06±0.14</td>
<td>-0.11±0.18</td>
<td>.014</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>32.4±3.8</td>
<td>31.9±4.2</td>
<td></td>
</tr>
<tr>
<td>Follow-up, %</td>
<td>34.6±5.3</td>
<td>35.3±6.7</td>
<td></td>
</tr>
<tr>
<td>Change, %</td>
<td>2.2±4.9</td>
<td>3.5±6.0</td>
<td>.045</td>
</tr>
</tbody>
</table>

MLD indicates minimum lumen diameter.

New Lesions

One or more new coronary lesions developed during the trial in 23 (16%) of the 146 lovastatin patients and in 49 (32%) of the 153 placebo patients (P=.001), as shown in Fig 1.

Clinical Subgroups

The difference between treatment groups was observed consistently across various patient subgroups, as shown in Table 4. The 62 women who enrolled in the trial were older (mean age, 58 versus 52 years, P<.001) and were more likely than the men to have a history of angina (95% versus 83%, P=.016), hypertension (58% versus 33%, P<.001), and diabetes (23% versus 12%, P=.04) and less likely to have had a previous myocardial infarction (39% versus 58%, P=.007). The mean coronary change score for the 54 with repeat angiography, −0.05 mm in 25 lovastatin and −0.09 mm in 29 placebo women, was the same as for the entire study population but did not attain statistical significance because of the smaller numbers. However, women were less likely to have had progression in the lovastatin compared with the placebo group: 7 of 25 compared with 17 of 29 (28% versus 59%, P=.026). New lesions developed in only one (4%) of the women in the lovastatin group but in 13 (45%) in the placebo group (P=.001).

Although only 34 lovastatin and 38 placebo patients with follow-up angiography were smokers at baseline, the mean coronary change scores for the two groups were significantly different: −0.07±0.15 versus −0.16±0.16 mm, respectively (P=.024).
Angiographic Outcomes Related to Lipid Measurements

In patients with a baseline plasma LDL cholesterol ≤176 mg/dL, the median for patients with repeat angiography, coronary change score in the lovastatin group was −0.05±0.13 mm, compared with −0.07±0.14 mm in the placebo group (P=.56). In patients with a baseline LDL cholesterol above the median, coronary change score was better in lovastatin patients, −0.04±0.12 mm versus −0.11±0.14 mm in placebo patients (P=.004).

Similarly, coronary change score for patients with a baseline total cholesterol ≤246 mg/dL, the median, was not different between lovastatin and placebo groups (−0.06±0.14 and −0.07±0.14 mm, respectively, P=.63) but was better above the median for lovastatin patients (−0.04±0.12 versus −0.11±0.18 mm, P=.003). Because the trial was designed to titrate LDL cholesterol to a target of ≤130 mg/dL, the mean dose of lovastatin in patients below the median was less than in those above, 28 versus 43 mg. Also, the difference in the benefit of treatment above versus below the median LDL cholesterol value was not significant (P=.37).

In lovastatin-treated patients, coronary change score did not correlate with plasma LDL cholesterol levels before or during treatment or with the percent change in LDL cholesterol (Pearson correlation coefficients, .015, .076, and 0.52, respectively, each P>.1). Coronary change score did correlate with HDL cholesterol levels before (r=.29, P=.0003) and during treatment (r=.25, P=.0023). Coronary change score in placebo patients correlated with LDL (r=−.17, P=.045) and HDL-cholesterol levels (r=.16, P=.047) during the trial.

Multivariable Analysis

A multiple regression analysis was performed on coronary change score using the following factors: treat-

![Graph showing cumulative distribution curves for change in minimum lumen diameter for lovastatin lesions and placebo lesions](image)

![Graph showing cumulative distribution curves for coronary change score for lovastatin and placebo patients](image)
ment group; sex; history of hypertension, diabetes, or angina; treatment with β-blockers, calcium channel blockers, or ACE inhibitors; history of smoking; current smoking; number of coronary lesions; baseline minimum lumen diameter; and baseline lipid values. Better coronary change scores were associated with higher baseline HDL cholesterol levels (P=.001), wider baseline minimum lumen diameters (P=.002), the lovastatin treatment group (P=.002), the presence of hypertension (P=.02), and more lesions ≥25% at baseline (P=.028). Current smoking was associated with a greater decrease in coronary change score (P=.006). None of the other factors were significant at the P<.10 level.

Discussion
The results of this study indicate that monotherapy with the HMG-CoA reductase inhibitor lovastatin in a diverse population of coronary disease patients slows the progression of coronary atherosclerosis and reduces the development of new coronary lesions. Regression and recanalization were uncommon. Stenoses ≥50% (excluding occlusions) composed <15% of lesions and changed only infrequently, with no differences between groups. The beneficial effect of treatment was most pronounced in the more numerous, milder lesions and in patients whose baseline total or LDL cholesterol levels were above the median for the entire group.

Previous Studies
The mean decrease in plasma LDL cholesterol in this study, 29%, is less than the decreases of 32%,4 37.7%,5 38%,6 43%,7 and 46%8 reported in other angiographic trials in which the intervention was multiple drug therapy or iliac bypass surgery. HDL cholesterol levels were raised by 15% to 43% in the groups with multiple drug treatment in those studies,2,4,5 but the 4% difference in HDL cholesterol levels between the treatment and control groups in the Program on the Surgical Control of Hyperlipidemias (POSCH)9 is similar to the difference in our trial. Regression was a common finding in the multidrug intervention groups but was uncommon in POSCH and in this trial. A treatment that favorably influences both HDL and LDL cholesterol levels might produce greater angiographic benefit than would a treatment that reduces only LDL cholesterol levels.

In the Familial Atherosclerosis Treatment Study (FATS),4 percent diameter stenoses of lesions ≥50%, including occlusions, worsened in the control group but improved in the multidrug treatment groups. In contrast, the mean change in severe lesions in our trial was slight, in the direction of regression, in both the lovastatin and control groups, with very few individual lesions showing significant change. Coronary thrombosis may play a major role in the progression of stenoses ≥50%, and the antithrombotic effect of aspirin, which was prescribed to both of our treatment groups, may account for the lack of progression of severe lesions in this study. In both FATS and our trial, stenoses <50% progressed on average in the control group, with progression being significantly reduced with lipid-lowering therapy. New coronary lesions appeared in 32% of our placebo patients during the 2 years of the trial and in only 16% of lovastatin patients.

Two clinical trials of monotherapy with an HMG-CoA reductase inhibitor have been reported. In the Monitored Atherosclerosis Regression Study (MARS),8 an 80-mg daily dose of lovastatin was used, resulting in a 32% decrease in total cholesterol and a 38% decrease in LDL cholesterol level in the drug treatment group. By visual interpretation by a consensus panel, the angiographic outcome was significantly better in the lovastatin group. However, for the primary end point of the study, mean per-patient change in percent diameter stenosis measured by quantitative coronary arteriography, the difference between treatment groups was not significant (P=.48). In the Multicenter Anti-Atheroma Study (MAAS),9 383 patients were randomized to either simvastatin 20 mg/d or placebo. Coronary arteriography was repeated after 2 years of treatment and will be done again at the end of the study after a further 2 years. The 2-year angiograms have been analyzed but not reported, and the trial is continuing.9

Clinical Relevance
The difference in coronary change score between the treatment groups, 0.04 mm, is small, and its clinical relevance might be questioned. However, on a per-patient basis, active treatment reduced the progression rate (without regression elsewhere) from one half to one third. Although this was not associated with a significant reduction in coronary events during the trial, evidence from other studies indicates that coronary progression exerts a major impact on subsequent coronary events and that preventing progression will prevent future events. In the POSCH study,3 no difference in coronary event rates between the treatment groups was seen during the first 3 years, even though progression was seen in 41% of control subjects and 28% of surgery patients; however, patients in either group who progressed during this interval were more than twice as likely to experience cardiac death or myocardial infarction as nonprogressors were over the next 7 years.20

In a previous angiographic trial,13 we found that 41 (42%) of 335 patients who underwent repeat coronary arteriography after 2 years had progression. During a subsequent mean follow-up of 44±10 months, 19 of these patients experienced cardiac death and 21 had nonfatal myocardial infarction.21 The relative risk of cardiac death for progressors was 7.3 (95% confidence interval, 2.2 to 24.7; P<.001) and for either event was 2.3 (1.3 to 4.2, P=.009). Progression was as strong a predictor of future coronary events in these patients as ejection fraction or number of diseased vessels, the predictors used routinely in clinical practice. These data indicate that coronary progression is a clinically relevant and meaningful end point.

The ability of lovastatin to prevent the formation of new coronary lesions may be more important than its effect on established lesions. Coronary atherosclerosis is a diffuse process that is present even in coronary segments that appear normal angiographically in patients with coronary disease.22 However, the risk of a coronary event increases with the number of coronary lesions seen at angiography,23,24 and the lesion responsible for a coronary event is usually mild until it undergoes plaque rupture.25 An early coronary lesion with a high lipid content and a thin fibrous cap is most likely to lead to an acute coronary event.26

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The level of total or LDL cholesterol at which treatment should be initiated for patients both with and without coronary disease has been the subject of much debate. The treatment goal in this study, an LDL cholesterol level \( \leq 130 \text{ mg/dL} \), was consistent with the 1988 recommendations of the National Cholesterol Education Program Expert Panel.\(^7\) However, the panel has recently published revised recommendations that include an LDL cholesterol goal of \( \leq 100 \text{ mg/dL} \) for patients with coronary disease.\(^8\) The position that all patients with coronary disease should be treated, irrespective of their cholesterol levels, has also been advocated.\(^9\)

In this study, for patients whose baseline total cholesterol was above the group median of 246 mg/dL or whose baseline LDL cholesterol was above the group median of 176 mg/dL, the angiographic benefit of treatment was indisputable (\( P = .002 \) to .004). Lovastatin-treated patients with baseline lipid levels below these cutoff points did not have a significantly better angiographic outcome than did placebo patients. However, because the study was designed to titrate LDL cholesterol to a target level, the mean dose of lovastatin in patients with baseline lipid levels below the median was less than in patients with baseline levels above the median (28 versus 43 mg). Furthermore, the difference in the benefit of treatment above versus below the median LDL cholesterol value was not significant. To conclude, the results of this trial do not define baseline cholesterol levels below which treatment has no effect; patients with baseline values above the group median, however, demonstrated unequivocal benefit.

Although lovastatin significantly slows the progression of coronary atherosclerosis, neither this drug nor other forms of lipid-lowering therapy halt the process entirely: 42% of the patients in the lovastatin group in our study experienced progression, including those with mixed changes. In the niacin plus colestipol treatment group of the FATS trial,\(^4\) progression developed over 2.5 years in one quarter of the patients, even though LDL cholesterol was lowered by 32% and HDL cholesterol raised by 43%. Therefore, other approaches to stabilize coronary atherosclerosis should be investigated. Nevertheless, this trial clearly demonstrates that lovastatin slows coronary disease progression and prevents the development of new coronary lesions.

**Appendix**

**Study Personnel**

**Clinical Centers**

Montreal Heart Institute: David Waters, MD; Marilyn Francetic, RN.

University of Ottawa Heart Institute: Lyall Higgins, MD; Michel Le May, MD; Hetty Martin, RN.

The Toronto Hospital Corp: Peter Gladstone, MD; Brian Kimball, MD; Virginia Flintoft, RN.

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**Data Analysis**

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**References**


Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial.

D Waters, L Higginson, P Gladstone, B Kimball, M Le May, S J Boccuzzi and J Lespérance

_Circulation._ 1994;89:959-968
doi: 10.1161/01.CIR.89.3.959

_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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