Primary Prevention of Acute Coronary Events With Lovastatin in Men and Women With Average Cholesterol Levels

Results of AFCAPS/TexCAPS

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Context.—Although cholesterol-reducing treatment has been shown to reduce fatal and nonfatal coronary disease in patients with coronary heart disease (CHD), it is unknown whether benefit from the reduction of low-density lipoprotein cholesterol (LDL-C) in patients without CHD extends to individuals with average serum cholesterol levels, women, and older persons.

Objective.—To compare lovastatin with placebo for prevention of the first acute major coronary event in men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels.

Design.—A randomized, double-blind, placebo-controlled trial.

Setting.—Outpatient clinics in Texas.

Participants.—A total of 5608 men and 997 women with average TC and LDL-C and below-average HDL-C (as characterized by lipid percentiles for an age- and sex-matched cohort without cardiovascular disease from the National Health and Nutrition Examination Survey [NHANES] III). Mean (SD) TC level was 5.71 (0.54) mmol/L (221 [21] mg/dL) (51st percentile), mean (SD) LDL-C level was 3.89 (0.43) mmol/L (150 [17] mg/dL) (60th percentile), mean (SD) HDL-C level was 0.94 (0.14) mmol/L (36 [5] mg/dL) for men and 1.03 (0.14) mmol/L (40 [5] mg/dL) for women (25th and 16th percentiles, respectively), and median (SD) triglyceride levels were 1.78 (0.86) mmol/L (158 [76] mg/dL) (63rd percentile).

Intervention.—Lovastatin (20-40 mg daily) or placebo in addition to a low–saturated fat, low-cholesterol diet.

Main Outcome Measures.—First acute major coronary event defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death.

Results.—After an average follow-up of 5.2 years, lovastatin reduced the incidence of first acute major coronary events (183 vs 116 first events; relative risk [RR], 0.63; 95% confidence interval [CI], 0.50-0.79; $P<.001$), myocardial infarction (95 vs 57 myocardial infarctions; RR, 0.60; 95% CI, 0.43-0.83; $P=.002$), unstable angina (87 vs 60 first unstable angina events; RR, 0.68; 95% CI, 0.49-0.95; $P=.02$), coronary revascularization procedures (157 vs 106 procedures; RR, 0.67; 95% CI, 0.52-0.85; $P=.001$), coronary events (215 vs 163 coronary events; RR, 0.75; 95% CI, 0.61-0.92; $P=.006$), and cardiovascular events (255 vs 194 cardiovascular events; RR, 0.75; 95% CI, 0.62-0.91; $P=.003$). Lovastatin (20-40 mg daily) reduced LDL-C by 25% to 2.96 mmol/L (115 mg/dL) and increased HDL-C by 6% to 1.02 mmol/L (39 mg/dL). There were no clinically relevant differences in safety parameters between treatment groups.

Conclusions.—Lovastatin reduces the risk for the first acute major coronary event in men and women with average TC and LDL-C levels and below-average HDL-C levels. These findings support the inclusion of HDL-C in risk-factor assessment, confirm the benefit of LDL-C reduction to a target goal, and suggest the need for reassessment of the National Cholesterol Education Program guidelines regarding pharmacological intervention.

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EPIDEMIOLOGICAL observations have demonstrated consistently a strong positive, continuous, independent, graded relation between plasma total cholesterol (TC) and the incidence of coronary heart disease (CHD). This relation covers a wide range of cholesterol concentrations, including those considered normal or mildly elevated.[1-3] In the Multiple Risk Factor Intervention Trial follow-up of screened men, 69% of deaths from CHD in the first 6 years of follow-up occurred in subjects with TC values between 4.71 and 6.83 mmol/L (182-264 mg/dL).[4] In the first 16 years of the Framingham Heart Study, 40% of participants who developed a myocardial infarction had a TC level between 5.17 and 6.47 mmol/L (200-250 mg/dL).[5]

See also pp 1643 and 1659.

Large end point studies have demonstrated conclusively that effective cholesterol-lowering treatment can substantially reduce myocardial infarction and other coronary events. In the Scandinavian Simvastatin Survival Study

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the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin reduced total mortality in patients with CHD by 30% because of a 42% reduction in deaths from CHD.[6] Subsequently, pravastatin was shown to reduce fatal and nonfatal coronary events in patients with[7] and without[8] CHD. However, it is unknown whether benefit from reduction of low-density lipoprotein cholesterol (LDL-C) in patients without CHD (primary prevention) extends to individuals with average serum cholesterol levels, women, and older persons.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) targeted a cohort of generally healthy middle-aged and older men and women with average TC and LDL-C levels and with below-average high-density lipoprotein cholesterol (HDL-C) levels. The primary end point analysis was the incidence of first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The inclusion of unstable angina was a unique feature of this study, and its inclusion as a primary end point reflects the increasing frequency of unstable angina as the initial presentation of CHD in the United States.[9]

METHODS

The design of the study has been described in detail previously.[10] In summary, AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled primary prevention trial that included 6605 men and women and was conducted at 2 sites in Texas, Lackland Air Force Base in San Antonio (n = 3737) and University of North Texas Health Science Center in Fort Worth (n = 2868).

AFCAPS/TexCAPS was powered to investigate whether long-term lipid lowering with lovastatin would decrease the rate of first acute major coronary events compared with placebo during at least 5 years of follow-up in a cohort without clinical evidence of atherosclerotic cardiovascular disease and with average TC and LDL-C levels and below-average HDL-C levels. Unstable angina was prospectively defined and required new-onset exertional angina, accelerated or rest angina, or both, and at least 1 of the following: (1) electrocardiographic findings of at least 1-mm ST-segment changes and reversible defect on stress perfusion study, (2) angiographic findings of at least 90% epicardial vessel stenosis or at least 50% stenosis in the left main coronary artery (without exercise testing), or (3) at least 1-mm ST-segment changes with pain on electrocardiographic stress testing and/or rest electrocardiograph and evidence of at least 50% stenosis in a major epicardial vessel.

Secondary objectives were to investigate whether long-term treatment with lovastatin, compared with placebo, would decrease cardiovascular morbidity and mortality across the spectrum of clinical events by measuring the rates of 7 secondary end points, including 2 components of the primary end point. The secondary end points were (1) fatal or nonfatal coronary revascularization procedures, (2) unstable angina, (3) fatal or nonfatal myocardial infarction, (4) fatal or nonfatal cardiovascular events, (5) fatal or nonfatal coronary events, (6) cardiovascular mortality, and (7) CHD mortality.

The tertiary objectives were to investigate safety, that is, whether long-term treatment with lovastatin, compared with placebo, would result in similar rates of total mortality, noncardiovascular mortality (with subset analyses for unintentional or violent death and death from cancer), fatal and nonfatal cancer (excluding basal cell and squamous cell skin cancers), and discontinuation of medication because of adverse drug effects.

Participant Recruitment and Follow-up

Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years who met the lipid entrance criteria and had no prior history, signs, or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack were eligible for participation in the study. Lipid entry criteria (TC, 4.65-6.82 mmol/L [180-264 mg/dL]; LDL-C, 3.36-4.91 mmol/L [130-190 mg/dL]; HDL-C, ≤1.16 mmol/L [45 mg/dL] for men or ≤1.22 mmol/L [47 mg/dL] for women; and triglycerides, ≤4.52 mmol/L [400 mg/dL]) were to be met at both 4 and 2 weeks prior to randomization, with less than 15% difference in LDL-C values. In addition, participants with LDL-C values between 3.23 and 3.34 mmol/L (125-129 mg/dL) were included when the ratio of TC to HDL-C was more than 6.0. We excluded volunteers with uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with a glycohemoglobin level of at least 10% (20% above the upper limit of normal). Additionally, volunteers were excluded if, according to the 1983 Metropolitan Life Insurance tables, they had a body weight of more than 50% greater than the desirable limit for height. All participants provided written informed consent.

The Data and Safety Monitoring Board and the institutional review boards of the 2 participating centers approved the consent form and protocol. The study was conducted under the supervision of a steering committee. Administrative, clinical, and data management was performed by a contract research organization with staff at each site who were under the supervision of the clinical investigator. All personnel involved in participant care were blinded to treatment assignment and lipid levels.

Participants who met entrance criteria and completed a 12-week American Heart Association Step I diet run-in, including a 2-week placebo baseline run-in, were randomized to treatment with either lovastatin, 20 mg/d, or matching placebo. Participants in the lovastatin group were titrated to 40 mg/d if their LDL-C level was more than 2.84 mmol/L (110 mg/dL) at the 3-month study visit. The blind was maintained by titrating equal numbers of randomly selected placebo-group participants to 2 tablets daily. Throughout the trial, dietary reinforcement and other risk factor modification information was provided.

An extensive safety evaluation was performed prior to treatment, at 1 year, and at each subsequent year-end visit. Clinical visits were every 6 weeks for the first year. After 1 year, all randomized participants who continued the study drug were seen semiannually. Participants who discontinued use of the study drug were contacted on an annual basis for follow-up by questionnaire, which included an assessment of possible end point events and cancer occurrence. End point event information was compiled and adjudicated in the same manner for all participants, including those who had withdrawn from the study. An end point committee, blinded to treatment-group assignment and not involved in participant care, used prespecified criteria to adjudicate all end point events.

For analyses of changes in lipids, frozen serum samples obtained on the date of randomization before active treatment (day 1) and at the 1-year visit (post-treatment) were assayed at a specialized lipid laboratory at Johns Hopkins University, Baltimore, Md. This laboratory also analyzed lipids for the National Health and Nutrition Examination Survey (NHANES) III as noted by Sempos et al[11] (also P. S. Bachorik, PhD, unpublished data, 1997). The laboratory was standardized for lipid and lipoprotein measurements through the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Lipid Standardization Program.[12] All LDL-C values were calculated based on the Friedewald estimation.[13]

Statistical Analysis

The size of the sample was designed to provide 90% to 97% power to detect a 30% to 35% reduction in the number of participants with primary end point events by treatment with lovastatin. All analyses were performed on an inten-

tion-to-treat basis and all P values were 2-sided. A log-rank test, with study center and sex as stratification factors, was used to assess the effect of therapy on the rate of primary end point events. Analyses of relative reductions in risk resulting from lovastatin therapy were calculated using the Cox proportional hazards regression model that had study center and sex as stratification factors. The proportionality assumption was met for all Cox models. Cumulative incidence and interval estimates were calculated using the life-table method.

The effect of therapy on percent change in lipid parameters from baseline to 1 year was assessed using an analysis of variance model that included treatment, study center, and sex after first examining a model that also included the treatment-by-center and treatment-by-sex interaction effects. All participants with data at both baseline and 1 year were included.

The proportions of participants who discontinued therapy because of adverse events or had clinically important adverse events or laboratory abnormalities were compared between the 2 treatment groups using the Fisher exact test.

The trial was designed to continue until a total of 320 participants had experienced a first primary end point event or for a minimum of 5 years after the last participant was randomized, whichever occurred later. In addition to the final analysis, 2 interim analyses of the trial were planned for the points at which 120 and 240 participants, respectively, experienced the first primary end point event. A group sequential design was used with an early stopping rule, described previously,[10] which preserved the type I error probability of .05. The critical values for finding statistical significance for 120, 240, and 320 participants with primary end points were .003, .016, and .044, respectively.

RESULTS

Early Termination for Efficacy

Following a review of the second interim analysis (data from 267 participants who had experienced a primary end point event), the Data and Safety Monitoring Board recommended that the trial be stopped early for efficacy. The voting members of the steering committee agreed unanimously on July 3, 1997, to accept the recommendation for early termination. The steering committee required that the participants and personnel continue to be blinded throughout the final visit of the study to provide unbiased assessment of all additional end point and safety information in the final analysis. End point status was determined for all but 1 active participant within 3 months of the decision to stop the study (Figure 1).

Baseline Characteristics

Beginning May 30, 1990, and ending February 12, 1993, 6605 participants were randomized to treatment with lovastatin (2805 men and 499 women) or placebo (2803 men and 498 women). For comparison with the age- and sex-matched US population without clinical evidence of cardiovascular disease, the NHANES III percentile is presented for average baseline lipid levels.[14] Baseline lipid levels were similar in both treatment groups; combined averages were as follows: mean (SD) TC, 5.71 (0.54) mmol/L (221 [21] mg/dL) (51st percentile); mean (SD) LDL-C, 3.89 (0.43) mmol/L (150 [17] mg/dL) (60th percentile); mean (SD) HDL-C, 0.94 (0.14) mmol/L (36 [5] mg/dL) for men and 1.03 (0.14) mmol/L (40 [5] mg/dL) for women (25th and 16th percentiles, respectively); and median (SD) triglycerides, 1.78 (0.86) mmol/L (158 [76] mg/dL) (63rd percentile). The 2 treatment groups were also balanced with respect to baseline demographics, risk factors, and medications (Table 1). A more detailed description of the baseline characteristics of the study cohort in comparison with the US NHANES III reference population is provided elsewhere.[15]

Adherence and Dropouts

The mean (SD) duration of follow-up was 5.2 (0.9) years (range, 0.2-7.2 years) for those treated with lovastatin and 5.2 (0.9) years (range, 0.1-7.2 years) in the placebo group. As assessed by pill counts, 99% of participants adhered to their study regimen for at least 75% of the time that they were receiving active treatment. Study drug regimens were maintained until trial termination by 2335 (71%) of the 3304 participants randomized to lovastatin and by 2081 (63%) of the 3301 randomized to placebo (Figure 1). Participants treated with placebo were more likely to be withdrawn from the study as a result of developing CHD or starting cholesterol-reducing medication (generally at the request of their primary care physician). The frequency of discontinuation for other reasons was similar between treatment groups.

Lipid Parameters

Lovastatin had a significant effect on changes in lipid levels from baseline (day 1) to posttreatment as assessed at 1 year ($P<.001$). Low-density lipoprotein cholesterol levels were reduced by 25%, TC levels were reduced by 18%, triglyceride levels were reduced by 15%, HDL-C levels were increased by 6%, and the ratios of TC to HDL-C and LDL-C to HDL-C were decreased by

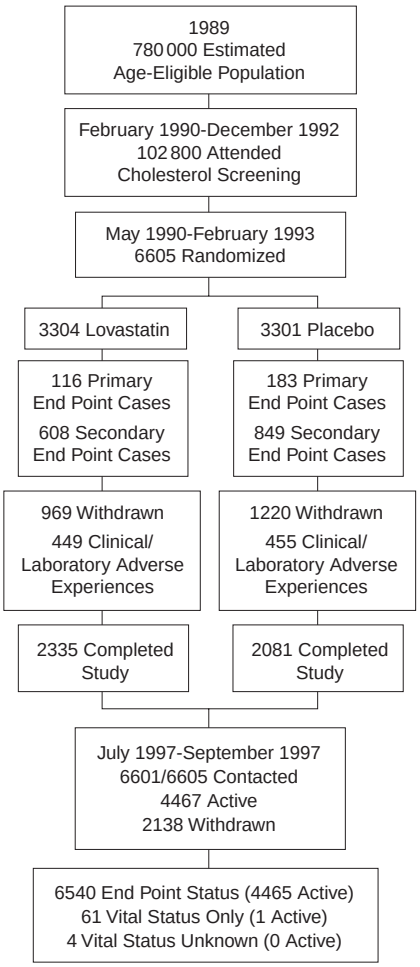

Figure 1.—Study chronology.

22% and 28%, respectively. By comparison, in the placebo group, there were small changes in lipid levels that were not clinically important (Figure 2). Treatment effects were similar in men and women (Table 2).

In the lovastatin group, 1657 participants (50%) were titrated from 20 mg/d to 40 mg/d, and of these, no participant was subsequently back-titrated. At 1 year, 1216 participants (42%) receiving lovastatin and 86 (3%) receiving placebo reached the study target for LDL-C values of no more than 2.84 mmol/L (110 mg/dL); 2334 participants (81%) receiving lovastatin and 350 (12%) receiving placebo reached an LDL-C level of 3.36 mmol/L (130 mg/dL) or less.

Efficacy End Points

Participants treated with lovastatin experienced a 37% lower incidence of the first acute major coronary event (primary end point defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) than did those treated with placebo (Cox model 95% confidence interval, 21%-50%; $P<.001$).

Table 1.—Baseline Characteristics and Medications for Study Cohort by Treatment Group*

Baseline Characteristic	Placebo (N = 3301)	Lovastatin (N = 3304)
Men aged 45-73 y, No. (%)	2803 (85)	2805 (85)
Women aged 55-73 y, No. (%)	498 (15)	499 (15)
Age, mean (SD), y	58 (±7)	58 (±7)
Men	57 (±7)	58 (±7)
Women	63 (±5)	62 (±5)
≥65 y, No. (%)	701 (21)	715 (22)
Men	515 (18)	549 (20)
Women	186 (37)	166 (33)
Race, No. (%)		
White	2935 (89)	2925 (89)
Black	101 (3)	105 (3)
Hispanic	240 (7)	247 (7)
Weight, mean (SD), kg		
Men	86.4 (±11.36)	86.8 (±11.82)
Women	70.5 (±10.9)	70.9 (±10.9)
Body mass index, mean (SD), kg/m^2		
Men	27.0 (±3.0)	27.1 (±3.1)
Women	26.4 (±3.8)	26.4 (±3.5)
Blood pressure, mean (SD), mm Hg		
Systolic	138 (±17)	138 (±17)
Diastolic	78 (±10)	78 (±10)
Heart rate, mean (SD), beats/min	69 (±11)	69 (±11)
No. (%) who consume alcohol		
Men	1450 (52)	1366 (49)
Women	129 (26)	153 (31)
No. of drinks/wk, mean (SD)	5.9 (±6.3)	6.1 (±6.1)
Men	6.2 (±6.4)	6.3 (±6.2)
Women	3.0 (±3.5)	3.5 (±3.7)
NCEP CHD risk factors, No. (%)†		
Hypertension‡	729 (22)	719 (22)
Diabetes		
Non–insulin-treated diabetes	71 (2.0)	84 (3.0)
Non–insulin-treated diabetes or fasting blood glucose ≥6.99 mmol/L (126 mg/dL)	113 (3.4)	126 (3.8)
Current smoker	389 (12)	429 (13)
Family history of premature CHD	538 (16)	497 (15)
HDL-C <0.91 mmol/L (<35 mg/dL)	1146 (35)	1150 (35)
Medications, No. (%)		
Antihypertensives	695 (21.1)	661 (20.0)
ACE inhibitors	257 (7.8)	244 (7.4)
α-Blockers	67 (2.0)	68 (2.1)
β-Blockers	156 (4.7)	141 (4.3)
Calcium channel blockers	170 (5.1)	171 (5.2)
Diuretics	203 (6.1)	203 (6.1)
Estrogen with or without progestins§	137 (27.5)	155 (31.1)
Nonsteroidal anti-inflammatory drugs	445 (13.5)	494 (15.0)
Oral hypoglycemics	43 (1.3)	41 (1.2)
Thyroid replacement hormone	107 (3.2)	132 (4.0)
Aspirin	561 (17.0)	571 (17.3)

*NCEP indicates National Cholesterol Education Program; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; and ACE, angiotensin-converting enzyme.
†All Air Force/Texas Coronary Atherosclerosis Prevention Study participants met National Cholesterol Education Panel criteria for age-related risk (age ≥45 years for men and ≥55 years for women).
‡Hypertension includes those reporting history of hypertension and/or those treated with antihypertensive agents for hypertension.
§Data are for women only.

A total of 116 participants treated with lovastatin compared with 183 in the placebo group had at least 1 primary end point event. Results of primary and secondary end point analyses are summarized in Table 3. Participants are counted only once within a specific end point analysis; however, a participant may be included in more than 1 analysis in Table 3 if they experienced different types of end points, experienced an event that is comprised in more than 1 end point analysis (eg, the secondary end point, unstable angina, is also a component of the primary end point), or both.

Life-table plots (Figure 3) illustrate a difference between treatment groups beginning in the first year of treatment and continuing throughout the remainder of the study. These show the cumulative incidence and the number of participants at risk. By treatment year, the average risk reduction in the primary end point (acute major coronary events) with lovastatin was 43% in the first year and 12%, 30%, 41%, and 49% in the second, third, fourth, and fifth years, respectively. These yearly rates were not statistically different from each other.

For the primary end point, the event rate for subjects receiving lovastatin averaged 7 per 1000 patient-years and was 37% less than the 11 per 1000 patient-years observed for the placebo group. These rates correspond to cumulative incidences of 4.0% and 6.8% for the lovastatin and placebo groups, respectively, during the study period ($P<.001$).

For secondary end points, treatment with lovastatin resulted in significant, consistent benefit compared with placebo, including 33% reduction in revascularizations ($P=.001$), 32% reduction in unstable angina ($P=.02$), and 40% reduction in the incidence of fatal or nonfatal myocardial infarction ($P=.002$). For coronary and cardiovascular events (total fatal or nonfatal), treatment with lovastatin resulted in significant ($P=.006$ and $P=.003$, respectively) reductions of 25% compared with placebo. The category of cardiovascular events included all atherosclerotic cardiovascular events, as specified by the end point definitions, including stable angina, thrombotic cerebrovascular accidents, transient ischemic attacks, and peripheral arterial vascular disorders. For the secondary end points fatal cardiovascular events and fatal CHD events, there were too few events to perform survival analysis based on prespecified criteria (Table 3).

Figure 4 summarizes the effect of treatment on the rate of the first primary end point event for predefined factors: sex, age (*older* defined as above the median by sex: >57 years for men and >62 years for women), history of hypertension, active cigarette smoking, family history of CHD, baseline LDL-C, and baseline HDL-C. Treatment group, as well as each of these factors, demonstrated a significant association with risk (eg, smoking was positively associated with first acute major coronary events). Baseline triglyceride level ($P = .98$) and history of diabetes ($P = .34$, 155 participants with diabetes) were not significant predictors of outcome. Within a factor, the numerical rate of first acute major coronary events was similar among those treated with lovastatin in the CHD positive-risk subgroup and those treated with placebo who did *not* have the CHD risk factor (eg, lovastatin-treated smokers had rates similar to placebo-treated nonsmokers).

The effect of treatment with lovastatin on the rate of first acute major coronary

Table 2.—Treatment Effects on Plasma Lipid Levels at 1 Year*

Lipid	Placebo, Mean or Median (SD)		Lovastatin, Mean or Median (SD)	
	mmol/L	mg/dL	mmol/L	mg/dL
Mean TC	5.90 (±0.72)	228 (±28)	4.75 (±0.62)	184 (±24)
Men	5.84 (±0.70)	226 (±27)	4.71 (±0.60)	182 (±23)
Women	6.20 (±0.75)	240 (±29)	4.97 (±0.65)	192 (±25)
Mean LDL-C	4.04 (±0.63)	156 (±25)	2.96 (±0.52)	115 (±20)
Men	4.02 (±0.63)	156 (±24)	2.96 (±0.51)	114 (±20)
Women	4.16 (±0.66)	161 (±26)	3.00 (±0.57)	116 (±22)
Median triglycerides	1.84 (±0.93)	163 (±82)	1.61 (±0.82)	143 (±73)
Men	1.82 (±0.90)	161 (±80)	1.59 (±0.79)	141 (±70)
Women	2.05 (±1.13)	181 (±100)	1.84 (±0.91)	163 (±81)
Mean HDL-C	0.97 (±0.20)	38 (±8)	1.02 (±0.21)	39 (±8)
Men	0.96 (±0.20)	37 (±8)	1.00 (±0.20)	39 (±8)
Women	1.05 (±0.21)	41 (±8)	1.11 (±0.21)	43 (±8)

*Data are for paired samples. Sample sizes are 2387-2495 for men and 420-439 for women. TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

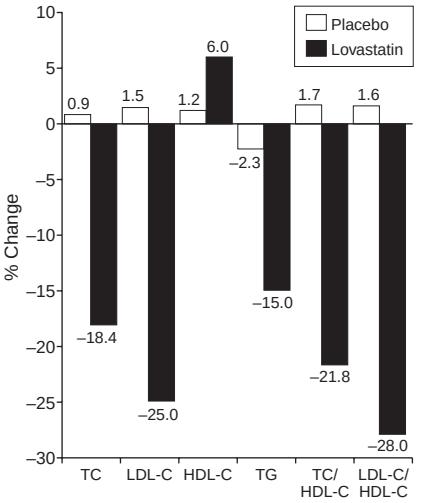

Figure 2.—Comparison of percent change in lipid parameters from baseline to 1 year by treatment group. All differences between treatment groups were significant ($P<.001$). TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides.

events was numerically greater in women than in men (46% vs 37% reduction in relative risk); however, the actual number of women who had a primary end point event was small (20 of 997), and there were no statistical differences in treatment effects between sexes. None of the subgroups differed significantly in treatment benefit (eg, treatment benefit was not different for participants with hypertension compared with participants without hypertension and benefit was not different for smokers compared with nonsmokers, since none of the treatment-by-subgroup interactions were significant). There were no significant interactions between treatment and either LDL-C ($P = .99$) or HDL-C ($P = .16$) when evaluated as continuous variables in a model with the other associated covariates. No threshold to benefit was observed in LDL-C and HDL-C ranges studied.

In addition to the protocol-specified rates that considered time to the first event for withdrawn and active participants, we also analyzed the total number of events experienced by active and withdrawn participants including multiple events of the same type (eg, multiple myocardial infarctions experienced by a participant). There were 142 and 209 acute major coronary events in participants treated with lovastatin and placebo, respectively, with rates of 8 and 12 per 1000 patient-years, respectively. There were 137 and 195 coronary revascularizations (8 and 11 per 1000 patient-years) in participants treated with lovastatin and placebo, respectively. Combining acute major coronary events and coronary revascularizations, there were 279 and 404 (16 and 23 per 1000 patient-years) in the lovastatin and placebo groups, respectively. If 1000 men and women were treated with lovastatin for 5 years, approximately 19 acute major coronary events (12 myocardial infarctions and 7 presentations of unstable angina) and 17 coronary revascularizations could be prevented.

Tolerability and Safety

Overall, treatment with lovastatin was well tolerated. Mortality and incidence of fatal and nonfatal cancer (tertiary end points to assess safety) did not demonstrate any difference between treatment groups. The overall mortality rate was similar in each group, with 80 deaths among participants treated with lovastatin and 77 deaths among participants treated with placebo (4.6 and 4.4 per 1000 patient-years in participants treated with lovastatin and placebo, respectively). The majority of deaths had noncardiovascular causes. There were 17 deaths from cardiovascular causes among participants treated with lovastatin and 25 in the placebo group (1.0 and 1.4 per 1000 patient-years in lovastatin and placebo groups, respectively) and 63 deaths from noncardiovascular causes among participants treated with lovastatin and 52 in the placebo group (3.6 and 3.0 per 1000 patient-years among participants treated with lovastatin and placebo, respectively). There were 4 deaths from trauma, 3 in the placebo group and 1 in the lovastatin group.

The overall incidence of fatal and nonfatal cancer, excluding nonmelanoma skin cancers, was 15.1 and 15.6 per 1000 patient-years (252 and 259 cases) among participants treated with lovastatin and placebo, respectively. The most frequently reported tertiary end point cancers are summarized in Table 4. The number of participants reporting nonmelanoma skin cancers, predominantly diagnoses of basal cell and squamous cell cancers, was 250 (7.6%) in the lovastatin group and 243 (7.4%) in the placebo group.

The number of participants with any adverse experience that led to discontinuation was 449 (13.6%) in the group treated with lovastatin and 445 (13.8%) in the placebo group. Both treatment groups had similar numbers of adverse experiences that were considered serious (ie, life-threatening, causing death or a permanent disability, resulting in or prolonging hospitalization, or diagnosis of any cancer), 1131 (34.2%) and 1126 (34.1%) in the groups treated with lovastatin and placebo, respectively. One participant from each treatment group was unblinded after discontinuation of the study drug and before the end of the study. A placebo-treated patient, who discontinued therapy because of idiopathic hepatitis, was unblinded because a primary care physician advised beginning lipid-reducing treatment. Another participant was unblinded when he developed study drug–related Stevens-Johnson syndrome after approximately 9 months of treatment with lovastatin. Following appropriate treatment and within 2 weeks of discontinuing lovastatin use, this participant recovered. No other lovastatin-related, life-threatening, serious, adverse experiences were reported.

Consecutive elevations of more than 3 times the upper limit of normal in either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were rare, and the incidence was similar in both treatment groups (18 [0.6%] of 3242 participants and 11 [0.3%] of 3248 receiving lovastatin and placebo, respectively). (Not all participants had postrandomization tests.) Examining these elevations by final dose for those who were titrated also revealed no significant trends. Consecutive elevations of more than 3 times the upper limit of the normal range in

Table 3.—Efficacy End Points*

End Points	Placebo (N = 3301) n	Placebo (N = 3301) Rate§	Lovastatin (N = 3304) n	Lovastatin (N = 3304) Rate§	Relative Risk (95% CI)†	*P* Value‡
Primary end point: acute major coronary events defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death	183	10.9	116	6.8	0.63 (0.50-0.79)	<.001
Secondary end points						
Revascularizations	157	9.3	106	6.2	0.67 (0.52-0.85)	.001
Unstable angina	87	5.1	60	3.5	0.68 (0.49-0.95)	.02
Fatal and nonfatal myocardial infarction	95	5.6	57	3.3	0.60 (0.43-0.83)	.002
Fatal and nonfatal cardiovascular events	255	15.3	194	11.5	0.75 (0.62-0.91)	.003
Fatal and nonfatal coronary events	215	12.8	163	9.6	0.75 (0.61-0.92)	.006
Fatal cardiovascular events	25	1.4	17	1.0	. . .	. . .
Fatal CHD events	15	0.9	11	0.6	. . .	. . .

*CI indicates confidence interval; CHD, coronary heart disease; and ellipses, too few for survival analysis.
†To calculate risk reduction, subtract relative risk from 1. Relative risk and confidence interval calculated with Cox proportional hazards model.
‡*P* value calculated with log-rank test and adjusted for the interim analysis for the primary end point only. *P* values for secondary end points are unadjusted.
§Rate per 1000 patient-years.

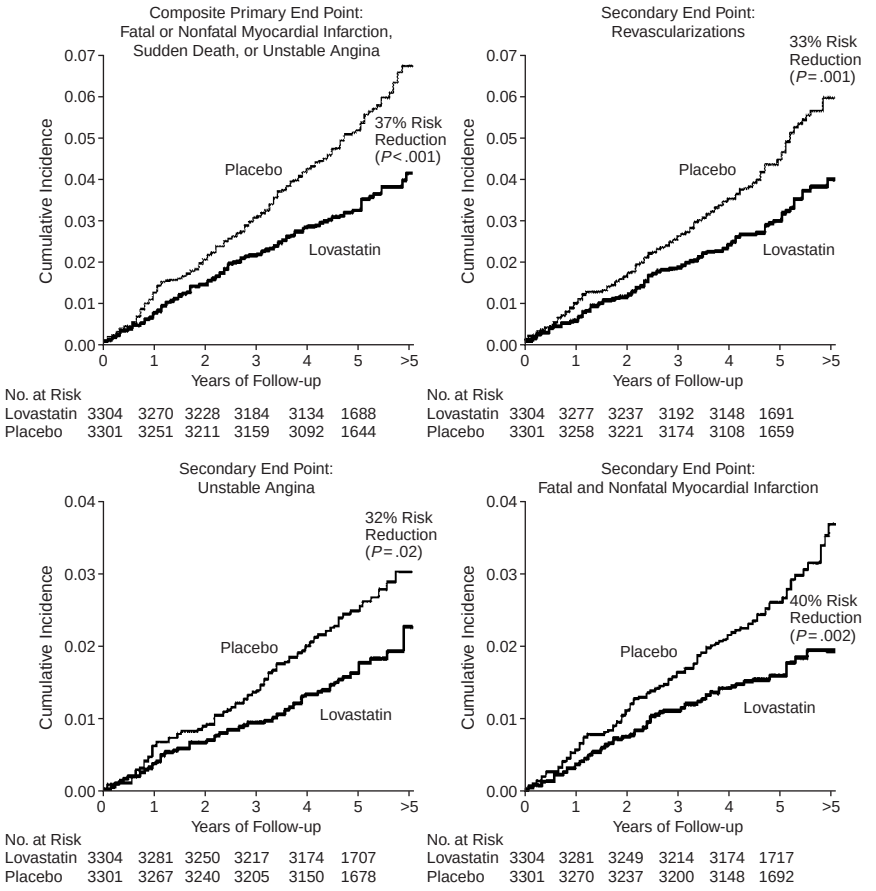

Figure 3.—Cumulative incidence of primary end points (composite of fatal and nonfatal myocardial infarction, sudden death, and unstable angina) and secondary end points (fatal and nonfatal myocardial infarction, unstable angina, and coronary revascularizations) by treatment group.

either AST or ALT were reported in 11 (0.7%) of 1585 participants and 7 (0.4%) of 1657 receiving lovastatin, 20 mg/d, and lovastatin, 40 mg/d, respectively. (Unlike the other comparisons of randomized treatment groups, the dose comparisons are of nonrandomized groups.) The number of participants with any drug-attributable AST elevation above the upper limit of normal was similar between treatment groups (33 [1.0%] and 34 [1.0%] in the groups treated with lovastatin and placebo, respectively); however, the number with any ALT drug-related elevations was significantly ($P = .003$) higher in the group treated with lovastatin (110 [3.3%] and 70 [2.1%] for lovastatin and placebo, respectively). The percentage of participants reporting myalgia leading to discontinuation was 0.3% for both treatment groups.

Creatine kinase (CK) elevations greater than 10 times the upper limit of normal were rare, and the incidence was similar in both treatment groups (11 [0.7%] of 1586, 10 [0.6%] of 1657, and 21 [0.6%] of 3248 receiving lovastatin, 20 mg/d, lovastatin, 40 mg/d, and placebo, respectively). (Denominators are participants having postrandomization tests; unlike the other comparisons of randomized treatment groups, the dose comparisons are of nonrandomized groups.) There were no cases of myopathy (defined as muscle symptoms accompanied with CK elevations >10 times the upper limit of normal). There were 3 cases of rhabdomyolysis; 2 cases occurred in placebo-treated participants, and 1 case occurred in a participant treated with lovastatin following surgery for prostate cancer.

COMMENT

In AFCAPS/TexCAPS, treatment with lovastatin resulted in a 37% reduction ($P<.001$) in the risk for first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The study was originally powered to detect a 30% difference between the treatment groups after 320 participants had experienced a primary event; however, the benefit after the second interim analysis (with 267 participants experiencing an event) was of such magnitude that the predefined conditions for stopping the study were met. The differences between the 2 treatment groups appeared as early as 1 year (40 participants with events in the placebo group vs 23 treated with lovastatin).

Analysis of secondary end points confirmed that the composite primary end point was representative of its components: lovastatin therapy significantly reduced the risk for fatal or nonfatal myocardial infarction by 40% and unstable angina by 32%. Risk reduction with lovastatin across the spectrum of cardiovascular events was further confirmed by a 33% risk reduction in the need for revascularizations ($P = .001$) and 25% risk reductions in both total cardiovascular and total coronary events ($P \leq .006$). The number of deaths in AFCAPS/TexCAPS was low (157 total deaths; 42 cardiovascular deaths, of which 26 were CHD deaths), and as predicted,[10] the study was not adequately powered to detect treatment differences in the low frequency end points of cardiovascular mortality and CHD mortality.

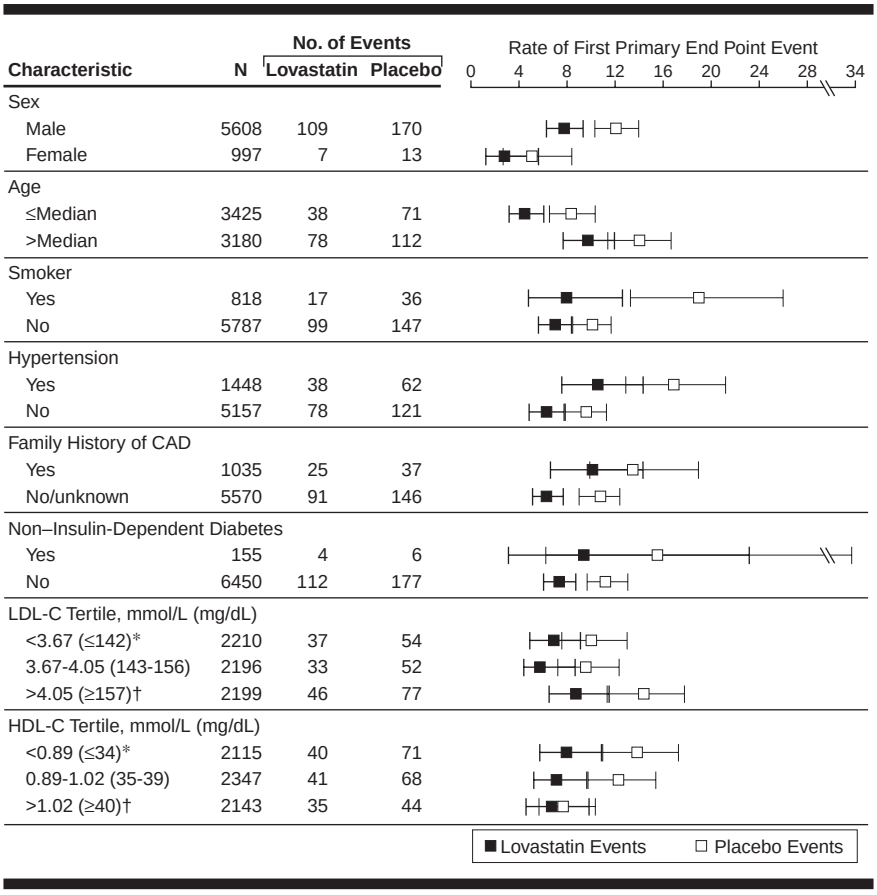

Figure 4.—Comparison of primary end point event rates (per 1000 patient-years at risk) and 95% confidence intervals by treatment within demographic and risk factor subgroups at baseline. CAD indicates coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; asterisks, bottom tertile; and daggers, top tertile.

Table 4.—Treatment Group Comparison of Participants With Cancer

Cancer	Placebo (N = 3301)	Lovastatin (N = 3304)	*P* Value*
All fatal and nonfatal most frequently reported	259	252	.75
Prostate	108	109	>.99
Melanoma	27	14	.04
Colon	20	25	.55
Lung	17	22	.52
Lymphoma	11	12	>.99
Bladder	11	12	>.99
Breast	9	13	.52

**P* values are for between-treatment-group differences.

Primary end point risk reduction with lovastatin was apparent across all baseline LDL-C tertiles with no threshold to benefit observed across baseline LDL-C levels (range, 2.33-6.08 mmol/L [90-235 mg/dL]). Benefit was also apparent within subgroups, including women, men older than the median age (>57 years), women older than the median age (>62 years), and for participants with additional CHD risk factors. As observed in secondary prevention trials,[6,7] female AFCAPS/TexCAPS participants responded to treatment as well as, if not better than, male participants. Lovastatin appeared to attenuate (Figure 4) the risk conferred by sex, age, family history, hypertension, smoking, LDL-C levels, and below-average HDL-C levels.

AFCAPS/TexCAPS is, to our knowledge, the first primary prevention trial to demonstrate risk reduction from lipid modification in generally healthy men and women without clinical evidence of cardiovascular disease and with average TC and LDL-C levels and below-average HDL-C levels. The baseline means for TC and LDL-C (5.71 mmol/L [221 mg/dL] and 3.89 mmol/L [150 mg/dL], respectively) are similar to the average levels for age- and sex-matched individuals without cardiovascular disease in NHANES III.[14] Mean baseline HDL-C values (0.94 mmol/L [36 mg/dL] for men and 1.03 mmol/L [40 mg/dL] for women) were below the average for the NHANES III reference population; however, the HDL-C range for the cohort is 0.47 to 1.58 mmol/L (18-61 mg/dL). Only 17% of AFCAPS/TexCAPS participants would have met current National Cholesterol Education Program (NCEP) guidelines for drug therapy (TC, ≥6.21 mmol/L [240 mg/dL]; LDL-C, ≥4.14 mmol/L [160 mg/dL]; and 2 or more risk factors) and 32% would not have a fasting lipid profile measurement by current NCEP guidelines (TC, <6.21 mmol/L [240 mg/dL] without 2 or more risk factors).[16]

Earlier primary CHD prevention studies included only middle-aged men with very high TC and LDL-C concentrations.[8,17,18] In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),[17] the upper age limit was 59 years (mean age, 47.8 years), and the mean TC, LDL-C, and HDL-C concentrations at baseline (prior to diet therapy) were 7.55 mmol/L (292 mg/dL), 5.59 mmol/L (216 mg/dL), and 1.16 mmol/L (45 mg/dL), respectively. In the Helsinki Heart Study,[18] the upper age limit was 55 years (mean age, 47.3 years), and the mean baseline lipid values for TC, LDL-C, and HDL-C were 6.98 mmol/L (270 mg/dL), 4.86 mmol/L (188 mg/dL), and 1.22 mmol/L (47 mg/dL), respectively. Likewise, the West of Scotland Coronary Prevention Study (WOSCOPS)[8] was limited to middle-aged men; the upper age limit was 64 years (mean age, 55.2 years) and the mean baseline lipid values for TC, LDL-C, and HDL-C were 7.03 mmol/L (272 mg/dL), 4.97 mmol/L (192 mg/dL), and 1.14 mmol/L (44 mg/dL), respectively. All of these trials reported statistically significant reductions in the primary end point of the combined incidence of nonfatal myocardial infarction and CHD death; the risk reductions were 19% in LRC-CPPT,[17] 34% in the Helsinki Heart Study,[18] and 31% in WOSCOPS.[8] Extrapolation of the results of these 3 trials of middle-aged men with moderate-to-severe hypercholesterolemia to the general population with lower TC and LDL-C levels, to women, and to older individuals has remained a matter of debate.[19]

Results from AFCAPS/TexCAPS are consistent with findings from previous primary prevention trials with high-risk cohorts[8,17,18]; however, treatment with lovastatin in AFCAPS/TexCAPS extends the benefit to a lower-risk segment of the general population. In contrast with earlier studies, the AFCAPS/TexCAPS cohort included Hispanics, African Americans, and older persons (baseline mean age, 58.2 years; upper limit, 73 years; 21% older than 65 years).[15] The AFCAPS/TexCAPS trial is also the first large-scale primary prevention trial of LDL-C reduction to include a substantial number of women (997 of the 6605 participants randomized). The cohort was also generally healthy, with only 12% active smokers, 22% with hypertension, and 2% with diabetes.

Inclusion of unstable angina in the primary end point analysis resulted from the observations that hospital admissions for diagnostic and surgical intervention fol-

lowing unstable angina were increasing while myocardial infarction, as the cause for initial presentation, was decreasing.[9] AFCAPS/TexCAPS data indicate that approximately equal numbers of patients initially present with unstable angina and nonfatal myocardial infarction.

The issue of safety and drug tolerance is particularly important in primary prevention, where the risks of long-term drug therapy must be considered in the context of achievable benefit. AFCAPS/TexCAPS provides long-term safety data on a cohort treated up to 7 years with lovastatin. The withdrawal rate was comparable to that seen in other primary prevention trials,[8,18] and frequency of withdrawal for adverse experiences was similar in the treatment groups.

The results confirm and, by longer treatment duration, extend those from the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial,[20] in which 8245 participants were studied for 1 year using regimens representative of the entire lovastatin dosage range. Both EXCEL and AFCAPS/TexCAPS demonstrated no cases of lovastatin-induced myopathy, no significant differences between treatment with lovastatin, 20 mg/d, and placebo in the number of participants experiencing clinically important elevations in transaminase concentrations (>3 times the upper limit of normal) and CK elevations (10 times the upper limit of normal). Furthermore, AFCAPS/TexCAPS provides reassuring data about long-term treatment with lovastatin, cancer rates, and traumatic deaths, and confirms the safety shown in other large long-term studies with simvastatin and pravastatin.[6-8]

The AFCAPS/TexCAPS results indicate that cholesterol reduction with lovastatin for men and women with average TC and LDL-C levels could potentially improve quality of life by extending CHD event-free survival and conserving invasive treatments. The economic impact of treatment requires resource utilization analyses that consider the cost of long-term treatment, hospitalization, and the cost of diagnostic and therapeutic intervention.

These findings support and extend the recommendations of the NCEP to include HDL-C in addition to TC in initial risk-factor assessment, target LDL-C reduction as the primary goal of therapy, and, if necessary, titrate treatment to achieve an LDL-C goal level. The benefit seen in all subgroups and across all tertiles of LDL-C in AFCAPS/TexCAPS occurred with 25% LDL-C reduction and suggests that treatment with lovastatin could be considered in asymptomatic participants at relatively low risk for CHD and with average TC and LDL-C levels (>3.36 mmol/L [130 mg/dL]) and below-average HDL-C levels (<1.29 mmol/L [50 mg/dL]).

AFCAPS/TexCAPS demonstrates that lovastatin, 20 to 40 mg/d, can reduce the risk for first acute major coronary events in men and women with average or mildly elevated TC and LDL-C levels and below-average HDL-C levels. Using NHANES III survey data,[14,15] approximately 8 million Americans without documented cardiovascular disease meet the age and lipid criteria of AFCAPS/TexCAPS. Assuming that only 17% of the reference population would qualify for drug treatment by current NCEP guidelines, we estimate that 6 million Americans currently not recommended for drug treatment may benefit from LDL-C reduction with lovastatin. These results support the inclusion of HDL-C measurement in initial risk-factor assessment and suggest reassessment of NCEP guidelines regarding pharmacological intervention.

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