Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group

Context Studies have demonstrated that statins administered to individuals with risk factors for coronary heart disease (CHD) reduce CHD events. However, many of these studies were too small to assess all-cause mortality or outcomes in important subgroups.

Objective To determine whether pravastatin compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor.

Design and Setting Multicenter (513 primarily community-based North American clinical centers), randomized, nonblinded trial conducted from 1994 through March 2002 in a subset of participants from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

Participants Ambulatory persons (n=10355), aged 55 years or older, with low-density lipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL if known CHD) and triglycerides lower than 350 mg/dL, were randomized to pravastatin (n=5170) or to usual care (n=5185). Baseline mean total cholesterol was 224 mg/dL; LDL-C, 146 mg/dL; high-density lipoprotein cholesterol, 48 mg/dL; and triglycerides, 152 mg/dL. Mean age was 66 years, 49% were women, 38% black and 23% Hispanic, 14% had a history of CHD, and 35% had type 2 diabetes.

Intervention Pravastatin, 40 mg/d, vs usual care.

Main Outcome Measures The primary outcome was all-cause mortality, with follow-up for up to 8 years. Secondary outcomes included nonfatal myocardial infarction or fatal CHD (CHD events) combined, cause-specific mortality, and cancer.

Results Mean follow-up was 4.8 years. During the trial, 32% of usual care participants with and 29% without CHD started taking lipid-lowering drugs. At year 4, total cholesterol levels were reduced by 17% with pravastatin vs 8% with usual care; among the random sample who had LDL-C levels assessed, levels were reduced by 28% with pravastatin vs 11% with usual care. All-cause mortality was similar for the 2 groups (relative risk [RR], 0.99; 95% confidence interval [CI], 0.89-1.11; *P*=.88), with 6-year mortality rates of 14.9% for pravastatin vs 15.3% with usual care. CHD event rates were not significantly different between the groups (RR, 0.91; 95% CI, 0.79-1.04; *P*=.16), with 6-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care.

Conclusions Pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL-C. The results may be due to the modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between pravastatin and usual care compared with prior statin trials supporting cardiovascular disease prevention.

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THE IMPORTANT ETIOLOGIC ROLE of circulating levels of low-density lipoprotein cholesterol (LDL-C) in the development of atherosclerotic coronary heart disease (CHD) is well established. Numerous randomized trials in the 1970s and 1980s affirmed that lowering LDL-C levels with diet and/or drugs, such as bile acid sequestrant resins and fibrates, reduced CHD event rates.[1] However, the total cholesterol reductions attained in these trials were modest (approximately 10%), and the correspondingly modest reductions in CHD mortality were offset by small increases in noncardiovascular mortality, with no net effect on overall mortality.[1] In the mid-1980s, a new potent and well-tolerated class of drugs, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) provided the means to conduct randomized trials in which total cholesterol reductions of 20% and greater could be sustained long-term. These trials also allowed questions about the overall benefits and risks of cholesterol lowering to be effectively addressed.

The lipid-lowering trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[2] (ALLHAT-LLT) was originally envi-

See also pp 2981 and 3042.

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sioned as a free-standing double-blind trial to evaluate the effects of cholesterol lowering with a statin drug in a population that was older and more inclusive than those studied in prior trials. After successful completion of the Cholesterol Reduction In Seniors Program (CRISP),[3] a 2-year feasibility study, the concept was modified and incorporated into ALLHAT as a randomized, nonblinded trial comparing pravastatin treatment with a usual care control group in a moderately hypercholesterolemic subset of the planned 40 000 ALLHAT participants. The principal objectives of the ALLHAT-LLT were to evaluate the impact of large sustained cholesterol reductions on all-cause mortality in a hypertensive cohort with at least 1 other CHD risk factor and to assess CHD reduction and other benefits in populations that had been excluded or underrepresented in previous trials, particularly older persons, women, racial and ethnic minority groups, and persons with diabetes.[2] Emphasis on primary care settings was deemed important because of the study's substantial implications for these providers and their patients. Despite the publication of more than 20 long-term statin trials[4-13] since ALLHAT began in 1994 and the publication of the National Cholesterol Education Program (NCEP) Adult Treatment Panel Guidelines (ATP III)[14] in 2001, ALLHAT-LLT remains the second largest long-term statin trial and addresses a unique population.

This article presents results of the pravastatin vs usual care comparison for all-cause mortality and CHD end points in ALLHAT-LLT. Results of the ALLHAT antihypertensive trial appear in an accompanying article.[15]

METHODS

The design of ALLHAT, including the LLT, and its participant and clinical site recruitment and selection have been described previously.[2,16,17] Briefly, ALLHAT-LLT was a randomized, nonblinded, large simple trial conducted from February 1994 through March 2002 at 513 clinical centers in the United States, Puerto Rico, US Virgin Islands, and Canada. The intervention was open-label pravastatin (40 mg/d) vs usual care. Participants were drawn exclusively from ALLHAT, a 4-armed antihypertensive trial in which a calcium channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), and an α-adrenergic blocking agent (doxazosin) were each compared with a thiazide-like diuretic (chlorthalidone). The doxazosin arm of ALLHAT was discontinued in March 2000.[18] ALLHAT-LLT participants originally assigned to doxazosin continued in the LLT with their original visit schedule and were offered open-label chlorthalidone for antihypertensive treatment.

Eligibility for ALLHAT-LLT

The specific eligibility criteria for the ALLHAT-LLT included prior enrollment in ALLHAT (age ≥55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor); fasting LDL-C level of 120 to 189 mg/dL (3.1 to 4.9 mmol/L) for those with no known CHD, or 100 to 129 mg/dL (2.6 to 3.3 mmol/L) for those with known CHD (the upper limit was 159 mg/dL [4.1 mmol/L] prior to April 5, 1994, but was changed in light of 4S[4] findings); and fasting triglyceride levels lower than 350 mg/dL (3.9 mmol/L). Participants were excluded who were currently receiving lipid-lowering therapy, taking large doses of niacin, or taking probucol in the last year; were known to be intolerant of statins or to have significant liver or kidney disease (serum alanine aminotransferase [ALT] >100 IU/L or serum creatinine >2.0 mg/dL [176.8 µmol/L]) or other contraindications for statin therapy; or had a known secondary cause of hyperlipidemia. Enrollment was discouraged for participants whose personal physicians recommended cholesterol-lowering medications.

Eligibility for ALLHAT-LLT was based on the average of 2 fasting (calculated) LDL-C measurements[19] taken at the ALLHAT baseline and 1-month follow-up visits. Enrollment in the LLT took place an average of 88 days after randomization into ALLHAT, from March 1994 through May 1998. By telephone, participants were randomly assigned to pravastatin or usual care in a ratio of 1:1. The concealed randomization scheme was generated by computer, implemented at the clinical trials center (CTC), stratified by center and antihypertensive treatment arm, and blocked in random block sizes of 4, 6, and 8 to maintain balance. All participants signed an informed consent form, and all centers received institutional review board approval.

Follow-up

Follow-up visits for the ALLHAT-LLT were scheduled to coincide with follow-up visits for the ALLHAT parent trial, ie, at 3, 6, 9, and 12 months following randomization into ALLHAT and every 4 months thereafter. At each visit, participants were questioned about intervening events since the previous visit and were provided refills of study medications. Baseline fasting lipid profiles and electrocardiograms (ECGs) were performed. Total cholesterol measurements and resting ECGs were also obtained at the 2-, 4-, and 6-year visits. At these same visits, a fasting lipid profile was obtained in random preselected samples of usual care (5%) and pravastatin (10%) participants. Levels of ALT were obtained for all ALLHAT-LLT participants at baseline and during follow-up in accordance with US Food and Drug Administration requirements. All blood samples were shipped with a frozen refrigerant pack to be analyzed at the ALLHAT Central Laboratory (Fairview-University Medical Center Clinical Laboratories, Minneapolis, Minn), a Centers for Disease Control and Prevention Standardized Laboratory.

Treatment

All ALLHAT-LLT participants were advised to follow the NCEP Step I diet.[20] Initially, pravastatin participants began with a dosage of 20 mg taken each evening. The dosage was increased to 40 mg/d as needed to achieve at least a 25% decrease in LDL-C. After the first 1000 participants had been enrolled, a uniform dosage of 40 mg/d was adopted for all participants in the pravastatin group.

Study practitioners retained the option to lower the dose of pravastatin, discontinue the drug if significant adverse effects occurred, or prescribe other lipid-lowering interventions, including cholesterol-lowering drugs not supplied by the study.[2]

The usual care group was treated for LDL-C lowering according to the discretion of their primary care physicians. However, vigorous cholesterol-lowering therapy in the usual care group was discouraged unless warranted by a change in clinical circumstances.

Sample Size

Originally, the sample size estimate of 20000 provided 80% power to detect a 12.5% reduction in mortality rate in the pravastatin vs usual care group with a 2-sided $\alpha = .05$.[2] With changing scientific and community standards of practice for persons with prevalent CHD,[4] evolving recruitment experience of the ALLHAT-LLT indicated that a sample size of approximately 10000 participants was the largest that could be realistically enrolled within the constraint of drawing exclusively from participants already enrolled in ALLHAT. Although 10000 participants would not provide adequate power for the originally assumed 12.5% reduction in mortality, this revised sample size was estimated to provide 84% power to detect a 20% reduction in mortality, a degree of reduction comparable to that observed in the 4S study.[4] This estimated power was considered sufficient to continue the study.

Outcomes

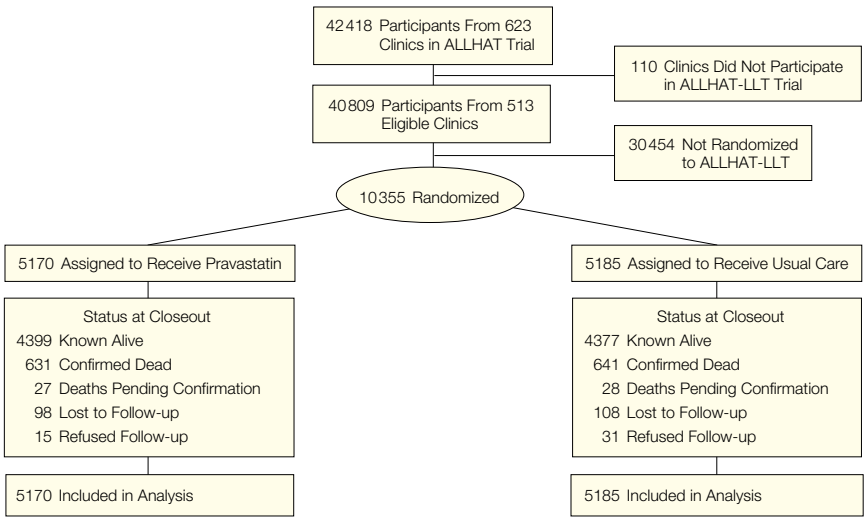
The primary outcome for the LLT was all-cause mortality. Secondary outcomes included (1) composite of fatal CHD or nonfatal myocardial infarction (MI) (CHD events), (2) cause-specific mortality, (3) total and site-specific cancers, (4) Q-wave MI identified in the biennial centrally and blindly coded ECGs (included in CHD events), (5) health-related quality of life, and (6) major costs of medical care. The last 2 outcomes are to be addressed in subsequent reports. Other end points of interest (though not specified a priori as secondary end points) were total incidence of stroke and heart failure.

Study end points, ascertained at follow-up visits, were reported to CTC by the site investigators, who submitted death certificates for each death and hospital discharge summaries for each hospitalized study event. Outcomes were primarily based on clinic investigator reports, and pathology reports were requested for cancer diagnoses. Each event report along with its documentation underwent medical review at the CTC to verify the investigator-assigned diagnosis or cause of death. In addition, searches for outcomes were conducted through the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, the National Death Index, and the Social Security Administration. A death was ascertained by clinic report or by match with the aforementioned databases plus a confirmatory death certificate. Death certificates with unspecified causes of death were submitted to a nosologist for *International Classification of Diseases, Ninth Revision (ICD-9)*[21] coding. In addition to the death certificates and hospital summaries, further documentation was requested for a random 10% sample of episodes of fatal CHD, hospitalized nonfatal MIs, and strokes (hospitalized and fatal) for quality control review.

Statistical Analyses

Data were analyzed according to participants' randomized treatment assignments regardless of their subsequent medication status (intention-to-treat). No imputation was used for missing data. Cumulative event rates were calculated using the Kaplan-Meier procedure.[22] An individual's duration in the study began at randomization to ALLHAT-LLT and ended at the date of last known follow-up. The log-rank test and the Cox proportional hazards model were used to evaluate differences between cumulative event curves and to obtain 2-sided *P* values. Only the proportional hazards results are presented because *P* values obtained by both methods were essentially identical. Hazard ratios, hereafter referred to as relative risks (RRs), and 95% confidence intervals (CIs) were obtained from the Cox proportional hazards model.[22] For fatal and nonfatal CHD, fatal and nonfatal cancer, cause-specific mortality, and stroke, the Cox model was also used. Hetero-

Figure 1. Randomization and Follow-up of Participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)



All participants in ALLHAT-LLT were enrolled in the ALLHAT antihypertensive trial. Eligibility data were not collected for nonrandomized screenees. All randomized participants were included in the analyses in the treatment group to which they were randomized. Closeout was October 1, 2001, to March 31, 2002.

geneity of effect in prespecified and other subgroups was examined by testing for treatment-covariate interaction with the proportional hazards model, using $P<.05$. For other outcomes, including cancer deaths and overall and site-specific cancers, comparison of proportions was used to evaluate differences between pravastatin and usual care. Analyses are presented for total follow-up unless specified otherwise.

A data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute met at least annually to review the accumulating data for safety and to monitor the trial for either superiority or inferiority of pravastatin compared with usual care. The Lan-DeMets version of the O'Brien-Fleming group sequential boundaries was used to assess treatment group differences, and conditional power was used to assess futility.[23,24] Data analyses were performed using SAS version 8 (SAS Institute, Cary, NC) and STATA version 7 (STATA Corp, College Station, Tex).

RESULTS

Numbers of individuals screened and enrolled, vital status, and losses to follow-up are depicted by treatment group in FIGURE 1. Ultimately, 10 355 participants were enrolled in ALLHAT-LLT after exclusion of 2 participants due to poor documentation of informed consent. The mean (SD) duration of follow-up was 4.8 (1.3) years (maximum, 7.8 years). At the end of the trial, 84.8% of participants were known to be alive, 12.3% were confirmed dead, 0.5% were reported dead with confirmation pending, and 2.4% had unknown vital status.

Baseline Characteristics

Baseline characteristics, including serum lipid levels, are shown in TABLE 1. Mean total cholesterol was 224 mg/dL (5.8 mmol/L); LDL-C, 146 mg/dL (3.8 mmol/L); high-density lipoprotein cholesterol, 48 mg/dL (1.2 mmol/L); and triglycerides, 152 mg/dL (1.7 mmol/L). Participants' mean age was 66 years; 49% were women, 38% were black, 23% were Hispanic, and 35% had diagnosed type 2 diabetes. A history of previous CHD diagnosis was reported by 13% of pravastatin participants and 15% of usual care participants. Higher mean total cholesterol and LDL-C values in LLT participants without a history of CHD reflect differences in eligibility criteria. Other baseline characteristics were similar in the 2 treatment groups.

Visit and Medication Adherence

Visit adherence is shown in TABLE 2. The percentage refusing to continue

Table 1. Baseline Characteristics of ALLHAT-LLT Participants by Treatment Group*

Characteristic	Pravastatin (n = 5170)	Usual Care (n = 5185)
Demographics		
Age		
Mean (SD), y	66.4 (7.6)	66.3 (7.5)
No. (%)		
55-64 y	2311 (44.7)	2337 (45.1)
≥65 y	2859 (55.3)	2848 (54.9)
Women, No. (%)	2511 (48.6)	2540 (49.0)
Race, No. (%)		
White, non-Hispanic	2107 (40.8)	2129 (41.1)
Black, non-Hispanic	1769 (34.2)	1722 (33.2)
White, Hispanic	759 (14.7)	803 (15.5)
Black, Hispanic	210 (4.1)	181 (3.5)
Other†	325 (6.3)	350 (6.8)
Years of education, mean (SD)	10.7 (4.1)	10.7 (4.1)
Medication use, No. (%)		
Women taking estrogen	390 (15.5)	399 (15.7)
Aspirin	1566 (30.3)	1637 (31.6)
Antihypertensive medication	4641 (89.8)	4663 (89.9)
Current cigarette smoking, No. (%)	1193 (23.1)	1208 (23.3)
History of CHD, No. (%)‡	695 (13.4)	780 (15.0)
Type 2 diabetes, No. (%)	1855 (35.9)	1783 (34.4)
Body mass index, mean (SD)	29.8 (5.9)	29.9 (6.1)
>30, No. (%)	2207 (42.8)	2199 (42.5)
Blood pressure, mean (SD), mm Hg	145 (13.8)/84 (9.8)	145 (14.0)/84 (9.8)
Fasting glucose, mean (SD), mg/dL	122.2 (55.6)	122.0 (56.2)
Lipid values, mean (SD)		
Participants with CHD at baseline		
Serum cholesterol, mg/dL	205.2 (27.7)	204.8 (26.8)
LDL cholesterol, mg/dL	129.3 (21.4)	128.6 (21.2)
LDL <130 mg/dL, No. (%)	418 (61.5)	484 (63.2)
HDL cholesterol, mg/dL	45.2 (13.8)	44.9 (12.7)
Fasting triglycerides, mg/dL	152.8 (74.9)	153.8 (71.2)
Participants without CHD at baseline		
Serum cholesterol, mg/dL	226.6 (25.6)	227.1 (25.2)
LDL cholesterol, mg/dL	148.1 (20.2)	148.4 (19.9)
LDL <130 mg/dL, No. (%)	884 (20.1)	827 (19.2)
HDL cholesterol, mg/dL	48.0 (13.3)	47.9 (13.7)
Fasting triglycerides, mg/dL	150.3 (69.6)	152.6 (73.3)
Antihypertensive randomization, No. (%)§		
Chlorthalidone	1872 (36.2)	1883 (36.3)
Amlodipine	1122 (21.7)	1118 (21.6)
Lisinopril	1094 (21.2)	1073 (20.7)
Doxazosin	1082 (20.9)	1111 (21.4)

*ALLHAT-LLT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CHD, coronary heart disease; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. To convert total cholesterol, LDL, and HDL to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.0113. To convert glucose to mmol/L, multiply values by 0.0555.
†The "other" race category includes 411 Hispanic participants (202 pravastatin and 209 usual care).
‡Pravastatin and usual care groups are significantly different ($\chi^2_1 = 5.43$; $P = .02$) only with respect to history of CHD at baseline. For all other comparisons the P value is >.11.
§ALLHAT randomization for chlorthalidone, amlodipine, lisinopril, and doxazosin was conducted in a ratio of 1.7:1:1:1.

participation during the trial was 0.3% (15/5170 pravastatin) and 0.6% (31/5185 usual care). At the close of the trial 2.2% (113) in the pravastatin and 2.7% (139) in the usual care groups had unknown vital status.

Adherence to assigned treatment declined over time (Table 2). For those assigned to pravastatin, adherence dropped from 87% at year 2 to 80% at year 4 (and 77% at year 6, though the participant number was small). Approximately 70% to 75% of the participants reported taking 80% or more of their assigned pravastatin. About half of those discontinuing pravastatin did so without citing a specific reason, while the remainder cited adverse effects and other medical and nonmedical reasons. Specific adverse effects data were not collected. Elevation of ALT to levels greater than 3 times the upper limit of normal (>150 IU/L) occurred in 0.4% (21/5170) of the pravastatin group.

In the usual care group, crossovers to statin treatment increased from 8% at year 2 to 17% by year 4 (Table 2). This increase continued in year 6, but the number of participants was small.

Among usual care participants with CHD at baseline, 32% (251/780) started lipid-lowering drugs at some time during the trial. For those without CHD at baseline, 29% (1279/4405) started lipid-lowering drugs; of these, less than 5% (61/1279) had a preceding CHD event (data not shown).

Table 2. Visit Compliance and Use of Lipid-Lowering Medications in the Pravastatin and Usual Care Groups*

	Year 2	Year 4	Year 6
Pravastatin			
Expected visits, No.	4990	3464	927
Actual visits, No.	4353	3063	848
Actual/expected, %	87.2	88.4	91.5
Receiving study drug, No. (%)	3785 (87.0)	2456 (80.2)	656 (77.4)
40 mg	3346 (76.9)	2254 (73.6)	596 (70.3)
20 mg	372 (8.5)	172 (5.6)	53 (6.3)
10 mg	66 (1.5)	23 (0.8)	5 (0.6)
Other	1 (0.0)	7 (0.2)	2 (0.2)
Not receiving study drug, No. (%)	568 (13.0)	607 (19.8)	192 (22.6)
Nonstudy statin	67 (1.5)	118 (3.9)	50 (5.9)
Other lipid-lowering drug	17 (0.4)	11 (0.4)	5 (0.6)
No lipid-lowering drug	484 (11.1)	478 (15.6)	137 (16.2)
Usual Care			
Expected visits, No.	5015	3444	904
Actual visits, No.	4295	2996	824
Actual/expected, %	85.6	87.0	91.2
Receiving medication, No. (%)			
Statin	353 (8.2)	513 (17.1)	215 (26.1)
Other lipid-lowering drug	68 (1.6)	58 (1.9)	20 (2.4)
No lipid-lowering drug	3874 (90.2)	2425 (80.9)	589 (71.5)

*Participants were allocated to the "receiving study drug" and "not receiving study drug" categories for pravastatin as follows: any participant who fit in multiple categories was assigned to only 1 category in the order that the categories appear in the table. The same assignment rule was used for the 3 drug categories under usual care.

Lipid Levels

Lipid and lipoprotein changes during the trial are shown in TABLE 3 and FIGURE 2. After 4 years of follow-up, total cholesterol levels decreased by 17.2% in the pravastatin group and by 7.6% in usual care (Figure 2A). The resultant total cholesterol differential was 9.6%. At 4 years calculated LDL-C levels decreased by 27.7% in the pravastatin group and by 11.0% in usual care (Figure 2B). The re-

Table 3. Lipid Values at Baseline and Years 2, 4, and 6 of Follow-up*

	Pravastatin				Usual Care			
	Baseline	Year 2†	Year 4†	Year 6†	Baseline	Year 2†	Year 4†	Year 6†
Total cholesterol								
No.	5134‡	4102	2998	912	5139‡	3763	2781	854
Mean (SD), mg/dL	223.7 (26.9)	188.4 (35.9)	184.3 (35.3)	177.6 (33.8)	223.7 (26.7)	213.7 (34.4)	205.9 (36.6)	196.5 (37.3)
LDL cholesterol								
No.	5129	850	572	157	5131	508	330	75
Mean (SD), mg/dL	145.6 (21.4)	111.0 (32.2)	104.5 (28.1)	104.0 (29.1)	145.5 (21.3)	134.9 (29.7)	128.7 (32.6)	121.2 (34.6)
HDL cholesterol								
No.	5134	880	593	161	5137	533	348	77
Mean (SD), mg/dL	47.6 (13.4)	48.7 (14.3)	48.9 (14.2)	48.5 (14.9)	47.4 (13.6)	47.0 (14.8)	45.9 (13.0)	44.9 (14.3)
Fasting triglycerides								
No.	4457	664	442	106	4473	396	236	53
Mean (SD), mg/dL	150.6 (70.4)	149.5 (89.7)	145.4 (81.0)	141.0 (77.4)	152.8 (73.0)	159.6 (92.0)	166.1 (84.3)	143.0 (55.8)

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. LDL has been calculated using the Friedewald formula[19] [LDL = Total Cholesterol – HDL – (Triglycerides/5)]. To convert total cholesterol, LDL, and HDL to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.0113. The number of participants expected at visits (see Table 2) includes those who had sufficient follow-up time for inclusion. Participants were recruited to ALLHAT-LLT over a period of 4 years, giving 25% of participants a maximum follow-up period of fewer than 4 years and 77% a maximum of fewer than 6 years.

†At 2, 4, and 6 years following antihypertensive randomization, the fasting lipid profile was obtained from 10% of participants randomized to pravastatin and 5% of participants randomized to usual care. To obtain numbers based on 2, 4, and 6 years following ALLHAT-LLT randomization, windows of ± 6 months for the time from LLT randomization were used to capture as many of the lipid measurements as possible.

‡Thirty-six participants in the pravastatin group and 46 in the usual care group qualified for ALLHAT-LLT based on local lipid laboratory measurements but did not have central laboratory measurements.

sultant LDL-C differential was 16.7%. Mean total cholesterol differences (usual care – pravastatin) were 25.3 mg/dL at 2 years, 21.6 mg/dL at 4 years, and 18.9 mg/dL at 6 years. Mean LDL differences (usual care – pravastatin) were 23.8 mg/dL at 2 years, 24.2 mg/dL at 4 years, and 17.2 mg/dL at 6 years. (To convert values to mmol/L, multiply by 0.0259.) High-density lipoprotein cholesterol increased by 3.3% in the pravastatin group and 2.4% in the usual care group (data not shown). Body weight data were not gathered following randomization.

Clinical Outcomes

The effect of pravastatin treatment on clinical outcomes is shown in TABLE 4; Kaplan-Meier plots and subgroup analyses for mortality and CHD events are shown in FIGURES 3 and 4. All-cause mortality, the primary end point, did not differ significantly between the pravastatin and usual care treatment groups (Table 4 and Figure 3A). There were 631 deaths in the pravastatin group and 641 deaths in the usual care group (RR, 0.99; 95% CI, 0.89-1.11; $P=.88$). The 6-year mortality rate for pravastatin was 14.9%, and for usual care, 15.3%. The results were similar when the unconfirmed deaths (27 pravastatin vs 28 usual care) were included (data not shown). Numbers of cardiovascular deaths were similar in the 2 groups. There were more cancer deaths and slightly fewer other medical deaths with pravastatin than usual care. None of the differences in cause-specific mortality was statistically significant (Table 4).

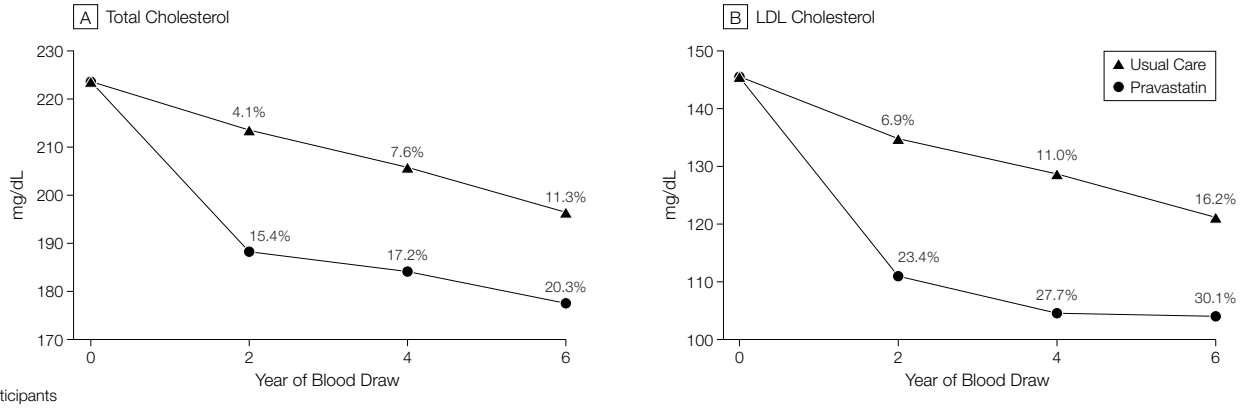
Rates of CHD (fatal CHD plus nonfatal MI; Table 4 and Figure 3B) and stroke (Table 4) were somewhat lower in the pravastatin than in the usual care group. There were 380 CHD events in the pravastatin group and 421 in the usual care group (RR, 0.91; 95% CI, 0.79-1.04; $P=.16$). The 6-year incidence rate was 9.3% for the pravastatin group and 10.4% for usual care. There were 209 total strokes in the pravastatin group and 231 in usual care (RR, 0.91; 95% CI, 0.75-1.09; $P=.31$). Heart failure rates were similar in the 2 groups (Table 4).

The 6-year incident cancer rates (Table 4) were similar in the 2 groups. The largest differences for cancers at specific sites were for lung cancer (63 pravastatin vs 78 usual care) and colon cancer (46 pravastatin vs 38 usual care). The number of participants who developed breast cancer was similar in the 2 groups (34 pravastatin vs 37 usual care). All comparisons were nonsignificant

An important secondary objective of the ALLHAT-LLT was to address the generalizability of the effects of cholesterol lowering to population groups that had been underrepresented in prior trials. Thus, the homogeneity of the results for mortality and for CHD events was assessed in prespecified subgroups by age (≥65 vs <65 years), sex, race (black vs nonblack), and presence or absence of diabetes (Figure 4). There was no significant heterogeneity for any of these outcomes with regard to age, sex, or history of type 2 diabetes. However, pravastatin showed a significantly more favorable effect on CHD events (RR, 0.73 vs 1.02) in blacks than in nonblacks ($P=.03$). Parallel analyses for stroke showed a significantly less favorable effect (RR, 1.12 vs 0.74) in blacks than in nonblacks ($P=.03$). No difference in effect was observed in a parallel analysis of combined cardiovascular disease outcomes (data not shown).

No statistically significant heterogeneity of the pravastatin treatment effect was observed across the 4 ALLHAT hypertensive treatment groups. For mortality, the RR in the chlorthalidone group was 1.03; amlodipine, 1.06; lisinopril, 0.95; and doxazosin, 0.91; for the interaction $P=.77$. For CHD the RR in the chlorthalidone group was 1.05; amlodipine, 0.79; lisinopril, 0.90; and doxazosin, 0.83; for the interaction $P=.43$. Similarly, no statistically significant heterogeneity was observed for subgroups defined by CHD status and LDL-C levels (with CHD, without CHD plus LDL-C ≥130 mg/dL [3.4 mmol/

Figure 2. Total and LDL Cholesterol Levels by Treatment Group and Year of Follow-up



LDL indicates low-density lipoprotein. The percentage decrease from baseline is shown above each time point. To convert values to mmol/L, multiply by 0.0259.

L], and without CHD plus LDL-C <130 mg/dL [3.4 mmol/L]) (Figure 4).

COMMENT

ALLHAT provided a diverse population base for ALLHAT-LLT. This study, comparing pravastatin with usual care, assessed the value of cholesterol lowering in a population underrepresented in prior cholesterol trials—individuals with well-controlled hypertension, almost half women, 38% black, 35% with a history of diabetes, 55% at least 65 years of age, and 25% with LDL-C lower than 130 mg/dL (3.4 mmol/L). Adherence to pravastatin in ALLHAT-LLT, 80% at 4 years of follow-up, was comparable to adherence in other large statin trials[4-11,18] and decreased levels of total cholesterol by 17% and LDL-C by 28% from baseline. However, unlike other statin trials, our study found no significant reductions in total mortality, CHD, or stroke with pravastatin vs usual care.

There are several possible explanations for the findings of ALLHAT-LLT, including the smaller than expected differential in total cholesterol between the 2 treatment groups; the trial's unique participant population; and the study's nonblinded design.

Cholesterol Differential Between Pravastatin and Usual Care

The usual care group had reductions of 8% in total cholesterol and 11% in LDL-C at 4 years, in contrast to other placebo-controlled statin trials, which observed little or no cholesterol reduction in the placebo groups.[4-9,11] The resulting 9.6% total cholesterol differential was less than half the average for the 8 other long-term statin trials with at least 1000 participants[4-11] (TABLE 5) and comparable to the cholesterol differential attained in prestatin trials using resins, niacin, diet, or fibrates.[1] Under the assumption of no change from baseline total cholesterol levels among participants in whom follow-up extended to 4 years but whose cholesterol was not measured at their fourth annual visit, the true total cholesterol differential might have been as low as 8.8% (14.9% in pravastatin vs 6.1% in usual care), and the true LDL-C differential might have been as low as 15.1% (24.0% in pravastatin vs 8.9% in usual care).

The effect of attaining only a modest total cholesterol differential is best appreciated by plotting the natural log of the odds ratio (ln OR) and the 95% CI for mortality (FIGURE 5A) and CHD events (Figure 5B) in each of the trials in Table 5 vs the mean cholesterol differential between the treatment and control groups in that trial. In addition, regression lines based on a prior meta-analysis of 45 cholesterol-lowering trials of 2 or more years' duration published before the end of 2000[25] are plotted for comparison. While the observed 95% CI of ln OR for all-cause mortality and CHD in ALLHAT-LLT do not exclude the null value, they are also consistent with the predicted OR for a 10% cholesterol reduction. However, because of the modest cholesterol differential between pravastatin and usual care, ALLHAT-LLT lacked the power to discriminate between the expected reductions in mortality and CHD events and the null hypothesis.

The reduction in study power was not due to low mortality rates; the number of deaths in the ALLHAT-LLT usual care group (641) differed only slightly from the estimate (625) used in the revised power calculation for a sample size of 10000. Moreover, the numbers of participants and deaths in ALLHAT-LLT were larger than in any other statin trial except the Heart Protection Study (HPS).[9] The lack of study power likely was due to a failure to achieve a total cho-

Table 4. Six-Year Incidence Rates for Primary and Secondary Outcomes in ALLHAT-LLT; Cumulative Events, and Relative Risks for Both Groups Based on Entire Follow-up*

Outcome	Cumulative Events		6-Year Rate per 100 Participants (SE)		Pravastatin vs Usual Care		
	Pravastatin	Usual Care	Pravastatin (n = 5170)	Usual Care (n = 5185)	Relative Risk (95% CI)	*z* Score	*P* Value
All-cause mortality	631	641	14.9 (0.6)	15.3 (0.6)	0.99 (0.89-1.11)	–0.15	.88
CVD deaths	295	300	6.9 (0.4)	7.1 (0.5)	0.99 (0.84-1.16)	–0.12	.91
CHD†	160	162	3.7 (0.3)	3.9 (0.4)	0.99 (0.80-1.24)	–0.05	.96
Stroke	53	56	1.2 (0.2)	1.4 (0.2)	0.95 (0.66-1.39)	–0.25	.81
Other CVD	82	82	2.1 (0.3)	2.0 (0.3)	1.01 (0.74-1.37)	0.04	.96
Non-CVD deaths	302	302	7.7 (0.5)	7.8 (0.5)	1.01 (0.86-1.18)	0.10	.92
Cancer	163	148	4.1 (0.4)	3.7 (0.4)	1.11 (0.89-1.39)	0.91	.36
Other medical	122	138	3.4 (0.3)	3.8 (0.4)	0.89 (0.70-1.14)	–0.92	.36
Unintentional injury/suicide/homicide	17	16	0.3 (0.1)	0.4 (0.1)	1.07 (0.54-2.12)	0.20	.84
Cause unknown	34	39	1.0 (0.2)	1.1 (0.2)	0.88 (0.55-1.39)	–0.56	.58
Fatal CHD and nonfatal MI†	380	421	9.3 (0.5)	10.4 (0.5)	0.91 (0.79-1.04)	–1.40	.16
Stroke (fatal and nonfatal)	209	231	5.3 (0.4)	5.8 (0.4)	0.91 (0.75-1.09)	–1.01	.31
Heart failure (hospitalized or fatal)	243	248	6.0 (0.4)	6.2 (0.4)	0.99 (0.83-1.18)	–0.13	.89
Cancer	378	369	9.6 (0.5)	9.3 (0.5)	1.03 (0.89-1.19)	0.44	.66

*CI indicates confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; and MI, myocardial infarction.
†Fatal CHD events were ascertained by clinic report or by match with national databases (see the "Methods" section) plus a confirmatory death certificate. Hospitalized outcomes, such as nonfatal MIs, were primarily based on clinic investigator reports for which supporting copies of death certificates and hospital discharge summaries were requested. Clinical trials center medical reviewers verified the clinician-assigned diagnoses of outcomes. More detailed information was collected on a random 10% subset of CHD events to validate the procedure of using clinician diagnoses.

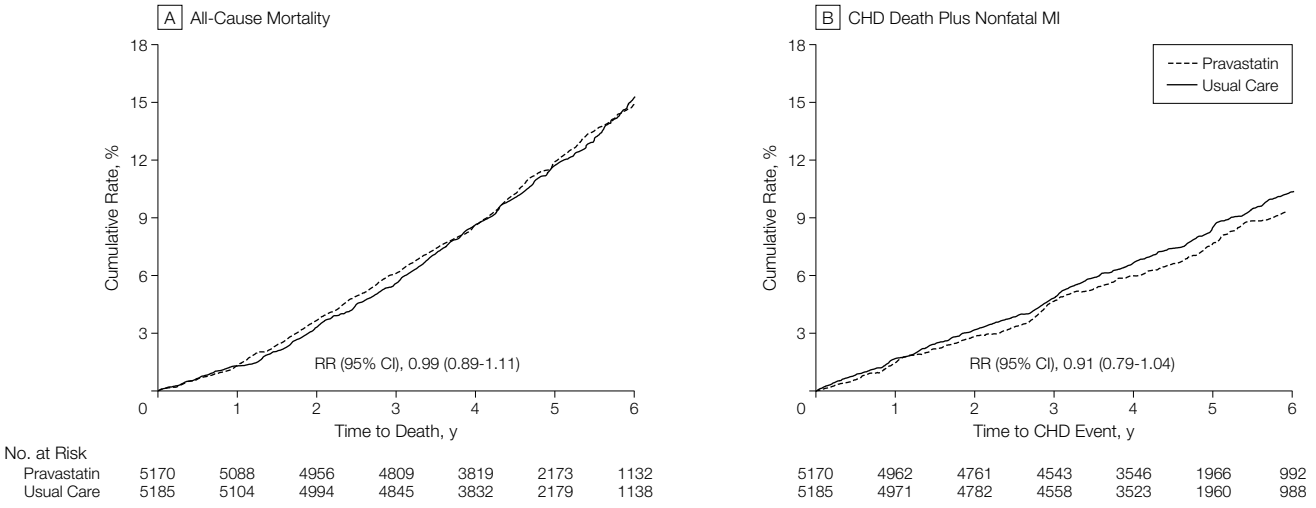
lesterol differential sufficient to yield the anticipated 20% reduction in mortality, which would be about 20% according to the regression model (Figure 5A).

Finally, ALLHAT-LLT did not test the widely advanced hypothesis that statin treatment reduces CHD risk and mortality by mechanisms independent of cholesterol lowering (eg, anti-inflammatory effects).[26] Furthermore, the observed differences in both CHD events and all-cause mortality in ALLHAT-LLT were consistent with those predicted for a 10% total cholesterol differential in a model based on trials using a wide array of cholesterol-lowering interventions.

Unique Participant Population

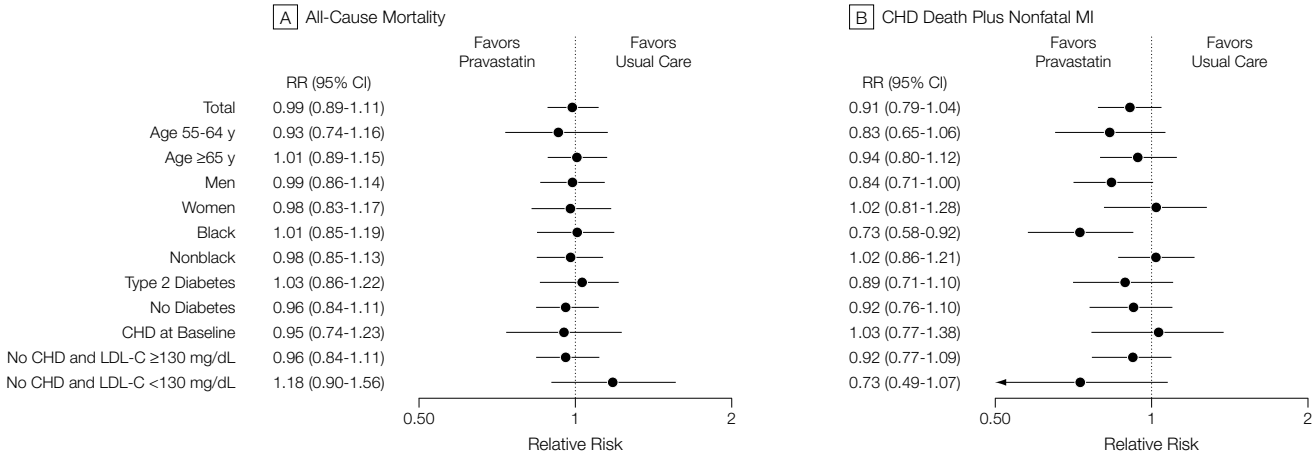
ALLHAT-LLT is the only published statin trial, to our knowledge, conducted exclusively in treated hypertensive participants. In a meta-analysis of 3 published pravastatin trials,[26] treatment was associated with only a 14% CHD event rate reduction ($P=.03$) in 6568 hypertensive participants vs 33% ($P<.001$) in 13 200 nonhypertensive participants. The difference in CHD event rate reduction between hypertensive and nonhypertensive participants was statistically significant and might help explain the modest 10% CHD event rate reduction in ALLHAT-LLT. However, in the hypertensive subgroup of the HPS,[9] simvastatin treatment was associated with the same 24%

Figure 3. Kaplan-Meier Curves for All-Cause Mortality and Cumulative CHD Death Plus Nonfatal MI



CHD indicates coronary heart disease; MI, myocardial infarction; RR, relative risk; and CI, confidence interval.

Figure 4. Cox Proportional Hazards for All-Cause Mortality and Cumulative CHD Death Plus Nonfatal MI



CHD indicates coronary heart disease; MI, myocardial infarction; RR, relative risk; CI, confidence interval; and LDL-C, low-density lipoprotein cholesterol. To convert LDL-C to mmol/L, multiply values by 0.0259. The axes are plotted on a natural logarithmic scale. Subgroups of CHD at baseline and LDL levels in both plots were not selected a priori. In plot B, there is a black/nonblack treatment interaction ($P=.03$).

reduction in CHD event rates ($P<.001$) as in nonhypertensive participants.

ALLHAT-LLT included larger proportions of older participants, women, blacks, and Hispanics than any other statin trial completed. However, subgroup analyses of ALLHAT-LLT, like those of prior statin trials,[9,27] do not show age- or sex-related differences in RRs for CHD event rates. The RR for pravastatin vs usual care was significantly lower in blacks than nonblacks for CHD events (Figure 4B) but was higher for strokes, with no overall difference for combined cardiovascular events (data not shown). In the absence of racial differences for the efficacy of pravastatin regarding all-cause mortality or other end points, the biological significance of the racial differences for CHD and stroke is unclear.

Although only a small proportion of ALLHAT-LLT participants had overt CHD at entry, they were predominantly a cohort with multiple CHD risk factors, considered "CHD equivalents" by the 2001 NCEP-ATP III.[14] Other than the HPS,[9] which contained a different mixture of participants with CHD, atherosclerotic cardiovascular disease, diabetes, and treated hypertension, this category of participants—not purely primary or secondary prevention—has not been explicitly addressed by prior statin trials. While the 14% of LLT participants with overt CHD at entry had higher event rates than those with comparable LDL-C levels (<130 mg/dL [3.4 mmol/L]) but without CHD, the pravastatin/usual care RRs for mortality and CHD were similar in both groups. These RRs were also unaffected by LDL-C level at baseline. By contrast, HPS[9] reported similar estimates of benefits with simvastatin at all levels of LDL-C, while a pooled analysis of 3 large pravastatin trials[27] suggested benefit only in participants with LDL-C levels higher than 125 mg/dL (3.2 mmol/L). None of these unique subgroups, including blacks, seems a likely explanation for the results of ALLHAT-LLT.

Table 5. Comparison of the ALLHAT-LLT to Other Large, Long-term Statin Trials*

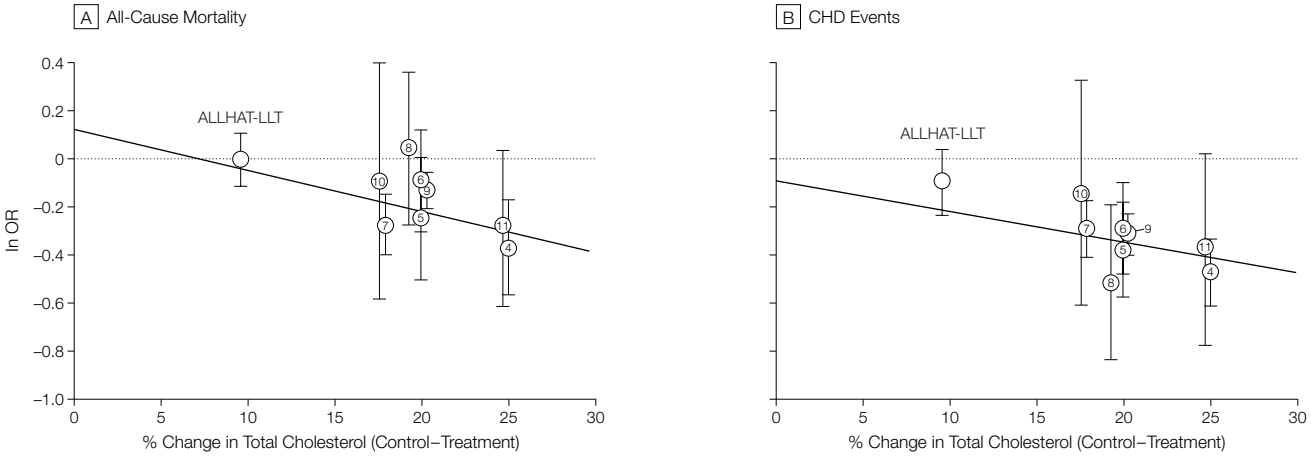
Trial	Sample Size	% Change in Total Cholesterol†	Odds Ratio (95% CI)†	
			All-Cause Mortality	CHD Events
Prior trials‡	54 381	20.2	0.83 (0.78-0.88)	0.70 (0.67-0.74)
4S[4]	4444	25.0	0.69 (0.56-0.84)	0.62 (0.54-0.72)
LIPS[11]	1677	24.7	0.72 (0.46-1.11)	0.68 (0.45-1.01)
HPS[9]	20 536	20.3	0.86 (0.80-0.94)	0.72 (0.66-0.78)
WOSCOPS[5]	6595	20.0	0.78 (0.60-1.01)	0.69 (0.56-0.84)
CARE[6]	4159	20.0	0.91 (0.74-1.12)	0.75 (0.62-0.90)
AFCAPS[8]	6605	19.3	1.04 (0.76-1.43)	0.60 (0.43-0.83)
LIPID[7]	9014	17.9	0.76 (0.67-0.86)	0.75 (0.66-0.84)
PostCABG[10]	1351	17.6	0.91 (0.57-1.48)	0.87 (0.54-1.38)
ALLHAT-LLT	10 355	9.6	0.99 (0.89-1.11)	0.91 (0.79-1.04)
All Trials‡	**64 736**	18.5	0.86 (0.82-0.90)	0.73 (0.69-0.77)

*ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; LLT, Lipid-Lowering Trial; and CHD, coronary heart disease. Other trial names are listed in their corresponding references (superscript numbers). Statin trials of at least 2 years' duration and with at least 1000 participants were eligible for inclusion.

†The percentage change in total cholesterol is the approximate differential in total cholesterol during the trial in the statin group relative to the control group. The odds ratios (statin/control) and corresponding 95% confidence intervals (CIs) summarize the relative differences in all-cause mortality and CHD events across trials, which had varying lengths of follow-up.

‡Meta-analysis was performed using the method of Peto R et al (*Br J Cancer*. 1977;35:1-39), which sums the difference between observed and expected events in the active treatment groups and variances for the component trials and computes the overall odds ratio as the ratio of the sum of observed minus expected events to the sum of variances. Note that odds ratios are based on simple proportions of events and often differ slightly from published hazard ratios for these trials.

Figure 5. Reductions in Mortality and Coronary Heart Disease (CHD) Event Rates vs Total Cholesterol Differential



Log odds ratios (ln OR) and 95% confidence intervals for active treatment vs control for 9 large statin trials (Table 5) are compared with regression lines (solid) from meta-analyses of 45 long-term trials using statins and other cholesterol-lowering interventions published before December 31, 2000.[25] Numbers inside data markers are references.

Nonblinded Study Design

ALLHAT-LLT was a nonblinded trial, designed and carried out during a period in which a series of landmark trials[4-11] and guidelines[14,20] stimulated the prescription of statins and progressively broadened the indications for their use in individuals targeted by ALLHAT-LLT. This may have contributed to the use of open-label statins in the usual care group. Because the study was not blinded, there may also have been greater use of nonpharmacologic cholesterol-lowering interventions in usual care than in pravastatin, although changes in participants' diets, exercise habits, and weight were not examined in ALLHAT.

Overview of Statin Trials

Do the results of ALLHAT-LLT indicate a need to draw back from the widespread use of statins? When viewed in context, the overall experience with statins remains highly favorable (Table 5, Figure 5). In the 8 prior large long-term statin trials,[4-11] a mean 20% cholesterol reduction was associated with a 30% reduction in CHD events (95% CI, 26%-33%) and a 17% reduction in all-cause mortality (95% CI, 12%-22%). After including ALLHAT-LLT, the 9 large long-term statin trials now show a 27% reduction in CHD events (95% CI, 23%-31%) and a 14% reduction in all-cause mortality (95% CI, 10%-18%) associated with an 18% reduction in mean total cholesterol level. Both results remain highly significant statistically. There remains little evidence in ALLHAT-LLT or elsewhere that statins specifically increase any category of noncardiovascular mortality.

CONCLUSION

ALLHAT-LLT demonstrated no significant difference between pravastatin and usual care groups in all-cause mortality or combined fatal and nonfatal CHD. However, in the context of the modest cholesterol differential, the results are consistent with the evidence from other large trials. Indeed, the overall findings from the 9 large long-term statin trials (including ALLHAT-LLT) leave little doubt regarding the broad efficacy and safety of this treatment in the prevention and treatment of atherosclerotic cardiovascular disease. In the absence of evidence for increases in any category of noncardiovascular mortality, the ALLHAT-LLT results should be interpreted as consistent with current recommendations for cholesterol control in the prevention and treatment of cardiovascular disease. These results emphasize the need for obtaining an adequate reduction in LDL-C in clinical practice when lipid-lowering therapy is implemented.

Authors, Author Contributions, and Acknowledgment appear in the accompanying article that begins on page 2981.

Dr Davis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis in this article and its companion article on page 2981.

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