Efficacy and Safety of Pravastatin in the Long-term Treatment of Elderly Patients With Hypercholesterolemia

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PURPOSE: Elevated cholesterol levels are a major risk factor for coronary heart disease, which remains a significant problem in patients beyond age 65 years. Because drug therapy for the control of hypercholesterolemia in elderly patients is frequently considered to be indicated, we investigated the efficacy and safety of pravastatin in the treatment of elderly subjects with primary hypercholesterolemia.

PATIENTS AND METHODS: In this 96-week, multicenter, double-blind, placebo-controlled study, 142 subjects (95 women, 47 men) 64 to 90 years of age with elevated cholesterol levels despite dietary intervention were randomized to receive pravastatin 20 mg at bedtime or matching placebo (2:1). Dosage could be doubled after 8 weeks, a bile acid-binding resin could be added after 16 weeks, and nicotinic acid or probucol could be added after 32 weeks, as needed, to adequately lower the low-density lipoprotein cholesterol (LDL-C) levels.

RESULTS: Significant reductions in the levels of LDL-C (-30.9%), total cholesterol (Total-C; -21.9%), and triglycerides (TG; -16.7%) and significant increases in the levels of high-density lipoprotein cholesterol (HDL-C; 11.3%) were noted in the group receiving pravastatin treatment at 16 weeks ($P \leq 0.001$ compared with baseline, $P \leq 0.01$ compared with placebo). The cholesterol-lowering effects of pravastatin were sustained throughout the 96 weeks of the trial. Pravastatin was well tolerated, with an overall incidence of adverse events nearly identical to that of placebo.

CONCLUSIONS: In this study, pravastatin was well tolerated and effective in lowering LDL-C, Total-C, and TG and in raising HDL-C during long-term treatment of elderly patients with primary hypercholesterolemia.

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The complications of atherosclerosis, including coronary heart disease (CHD), are the leading cause of death in most developed nations. Elevated low-density lipoprotein (LDL-C) and total cholesterol (Total-C) levels, as well as low levels of high-density lipoprotein cholesterol (HDL-C), are directly related to atherogenesis and are major risk factors for CHD.[1-4] The prevalence of hypercholesterolemia and frequency of CHD increase with age, and the correlation between elevated lipid levels and CHD appears to persist after age 65.[5,6] A clear relationship between lowering cholesterol levels and a reduction in cardiovascular morbidity and mortality in elderly patients with hypercholesterolemia has yet to be affirmed in controlled studies, and the overall benefit of lipid-lowering therapy in this population has not yet been determined. Maintaining a balanced, fat-restricted diet can be difficult in the elderly, and inconvenient dosage forms and unpleasant side effects have long hindered compliance with previously available lipid-lowering drugs in this population. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, with once-daily dosing and improved safety profiles, offer the potential for greater patient compliance and a more favorable balance of the risk of adverse effects versus the expected benefits of therapy.

Pravastatin, a hydrophilic HMG CoA reductase inhibitor, has been shown to be effective and well tolerated in extensive clinical trials involving more than 27,000 hypercholesterolemic subjects, including more than 15,000 taking the drug, some for up to 7 years or more.[7-9] By inhibiting cholesterol synthesis in the hepatocyte, increasing LDL receptor activity and number, and facilitating LDL uptake,[10-12] pravastatin produces dose-related reductions of up to 30% to 34% in levels of LDL-C, 22% to 27% in levels of Total-C, and 10% to 25% in levels of triglycerides (TG) and increases of 4% to 12% in the levels of HDL-C.[7,8,13,14] In comparative studies in primarily middle-aged subjects, pravastatin has proved an acceptable alternative to nicotinic acid,[15] probucol,[16] fibric acid derivatives,[17-19] and bile-acid sequestrants.[20] The goal of the present study was to evaluate the use of

pravastatin in the long-term treatment of elderly subjects with primary hypercholesterolemia.

PATIENTS AND METHODS

Subject Selection

Eligible subjects were men and women 65 years of age or older with primary (Type II) hypercholesterolemia. Potential subjects with elevated cholesterol levels were identified in medical clinics at the participating institutions and referred to a dietician for counseling. After at least 6 weeks on a low-fat, low-cholesterol diet, the mean of two consecutive determinations of fasting plasma LDL-C concentration was required to be greater than the 95th percentile for the corresponding age and gender group of the US population[21] (165 mg/dL for men or above 170 mg/dL for women), and the mean TG concentration in the same specimens was to be less than 250 mg/dL. Subjects with homozygous familial hypercholesterolemia, Type I, III, IV, or V hyperlipoproteinemia, or significant endocrine, renal, hepatic, metabolic, or cardiovascular disease were excluded, as were those taking medication (eg, corticosteroids, thiazide diuretics, beta-adrenergic blockers) that might affect lipid levels. Women receiving a stable dose of conjugated estrogens were eligible. Subjects were required to give informed written consent both at the beginning of the initial 48-week study and the 48-week extension phase. The protocol was approved by the institutional review boards of the three study centers.

Study Design

This clinical trial was a randomized, double-blind, parallel, placebo-controlled examination of the efficacy and safety of pravastatin in elderly subjects with primary hypercholesterolemia inadequately responsive to dietary intervention. With counseling by dietitians, a low-fat, low-cholesterol, eucaloric diet, equivalent to the American Heart Association Phase I, was started 6 weeks or more before blood was drawn for the qualifying lipid evaluations. This diet was continued throughout the trial and periodically evaluated at clinic visits by means of a 3-day food record. Subjects were instructed not to otherwise change their lifestyles (eg, start an exercise program) during the study. Any lipid-lowering medications were discontinued at least 9 weeks before randomization. After a dietary stabilization period of 7 to 14 weeks, subjects who qualified were randomly assigned to one of two treatment groups, pravastatin 20 mg at bedtime or placebo, in a 2:1 ratio. The short-term treatment phase was 16 weeks in duration. After completing the initial 8 weeks, a treatment decision was made for all subjects dependent upon their week 8 LDL-C results, with blinded therapy increased from 20 mg at bedtime to 40 mg at bedtime if the subject's LDL-C concentration was still above the 95th percentile. After 16 weeks of double-blind therapy in the short-term phase, if the LDL-C concentration remained above the 75th percentile, a bile acid-binding resin could be added to the regimen of subjects in either treatment group at the beginning of the long-term phase of the study. Later, in the long-term phase, nicotinic acid or probucol could be added as needed to attempt to reduce LDL-C levels below the 75th percentile. The initial 48-week study was followed by a 48-week extension period, with the treatment regimen to remain as it was in the final 16 weeks of the first year.

Clinical Safety and Laboratory Evaluation

Subjects returned to the clinic at 2- to 6-week intervals throughout the trial. Health status, interim illnesses, and the use of non-study drugs were evaluated and recorded at each clinic visit. Comprehensive physical examinations, clinical tests, and dietary compliance evaluations were performed at specified intervals. Clinical adverse events, defined as any new or worsening illnesses, signs, or symptoms, and compliance with study drug, as determined by counting the remaining supply of tablets, were assessed at each clinic visit.

Lipid analyses were performed by the Lipid Research Laboratory, Sinai Hospital of Detroit, which is certified by the Centers for Disease Control/ National Heart, Lung and Blood Institute Standardization Program. Concentrations of Total-C and TG were determined using standard enzymatic procedures. Levels of HDL-C were determined after precipitation of apolipoprotein B containing lipoproteins with dextran sulfate-$MgCl_2$. The LDL-C values were calculated using a variation of the Friedewald formula described by Delong: LDL-C = Total-C - (0.16TG + HDL-C).[22]

Baseline clinical safety assessments, including a complete medical history, a physical examination, a 12-lead electrocardiogram, a complete ophthalmologic examination (including slit-lamp examination and lens opacity grading), and a chest roentgenogram (if a film taken in the previous 3 months was not on file), were completed within the dietary stabilization/lead-in period. Laboratory safety tests included hematology (complete blood count, including differential), clinical chemistry, and urinalysis on a freshly voided morning specimen (with microscopic examination of the sediment if the dipstick results were positive for blood or white blood cells) at each clinic visit; serum thyroxine (T_4) determination at baseline and at weeks 16 and 48; and a stool test for occult blood at baseline and at weeks 8, 16, and 48. The laboratory tests were performed by SmithKline Beecham Clinical Laboratories (Van Nuys, CA) employing quality assurance procedures in accordance with standards required by the US government agencies licensing clinical laboratories.

Statistical Analysis

The two treatment groups were compared for homogeneity of baseline measures. Efficacy parameters were analyzed after logarithmic transformations resulting in normality and homogeneity of variance. Model assumptions were assessed by Shapiro-Wilk-W-test and Levene's test. Analyses of covariance were performed on the natural logarithms of the follow-up visit value and the baseline value with treatment and investigator as model effects and logarithmic value of baseline measure as a covariate. The statistical significance tests were performed for between- and within-group comparisons, and *P*-values were determined for short-term visits only. For the long-term period, only within-group comparisons were made, and 95% confidence limits without *P*-values were reported. Within-group changes from baseline were assessed through a paired t-statistic using the least squares means and mean squared error from the linear model above. The 95% confidence limits for the mean percent changes, adjusted for baseline differences and numerical imbalances among investigators, were obtained by exponentiating their upper and lower confidence limits in the logarithmic scale. The results of the analyses were summarized by arithmetic means, standard deviations, and adjusted percent changes from baseline with 95% confidence limits.

TABLE I

Baseline Demographic Characteristics of the Intent-to-Treat Population

Variable	Treatment Group: Pravastatin (n = 93)	Placebo (n = 48)	Total (n = 141)
Sex			
Male	33 (35%)	14 (29%)	47 (33%)
Female	60 (65%)	34 (71%)	94 (67%)
Age (years)			
Mean	70.3	70.8	70.5
SD	4.8	5.7	5.1
Range	64-86	65-90	64-90
Race			
White	73 (78%)	33 (69%)	106 (75%)
Black	20 (22%)	14 (29%)	34 (24%)
Oriental	0 (0.0%)	1 (2.1%)	1 (0.7%)
Lipids (mg/dL)			
LDL-C	199.0	207.9	202.0
Total-C	272.2	278.7	274.4
HDL-C*	50.4	45.9	48.9
TG	142.6	155.5	147.0

* Significant difference between treatment groups at baseline ($P \leq 0.05$).
LDL-C = low-density lipoprotein cholesterol; Total-C = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

RESULTS

A total of 142 patients were randomized. All 142 patients received study medication and were included in the safety database; however, 1 patient discontinued prior to any efficacy data being obtained in the active-treatment phase, leaving 141 subjects in the intent-to-treat population (all randomized subjects who had at least one follow-up visit with efficacy determination). Of the 141 patients, 136 completed the first 16 weeks of the study, 114 completed the next 32 weeks, and 96 completed 96 weeks.

As shown in **Table I**, the intent-to-treat population included more women (94, or 67%) than men (47, or 33%), had an overall mean age of 70.5 years, and was

TABLE II

Effect of Treatment on Lipid Values at Week 16

Lipid/ Treatment*	Baseline (mg/dL) Mean (SD)	Week 16 (mg/dL) Mean (SD)	% Change† Mean (95% CL)
LDL-C			
Pravastatin	198.4 (23.6)	138.7 (24.4)	-30.9‡ (-33.1, -28.7)
Placebo	208.4 (40.8)	209.8 (49.0)	0.6 (-3.7, 5.17)
Total-C			
Pravastatin	271.6 (28.2)	213.6 (31.1)	-21.9‡ (-23.7, -20.0)
Placebo	279.2 (42.8)	281.9 (49.3)	0.9 (-2.3, 4.25)
HDL-C			
Pravastatin	50.2 (12.6)	55.4 (14.2)	11.3§ (8.5, 14.2)
Placebo	46.0 (10.6)	47.7 (9.1)	3.6¶ (0.1, 7.2)
TG			
Pravastatin	144.1 (41.5)	121.8 (39.1)	-16.7§ (-21.1, -12.1)
Placebo	154.5 (46.1)	152.2 (70.0)	-4.2 (-11.1, 3.2)

* N=90 for the pravastatin-treatment group; N = 47 for the placebo-treatment group.
† Adjusted for pretreatment differences and numerical imbalances among investigators.
‡ $P \leq 0.001$ versus baseline and placebo.
§ $P \leq 0.001$ versus baseline and $P \leq 0.01$ versus placebo.
¶ $P \leq 0.05$ versus baseline.
SD = standard deviation; CL = confidence limits; LDL-C = low-density lipoprotein cholesterol; Total-C = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

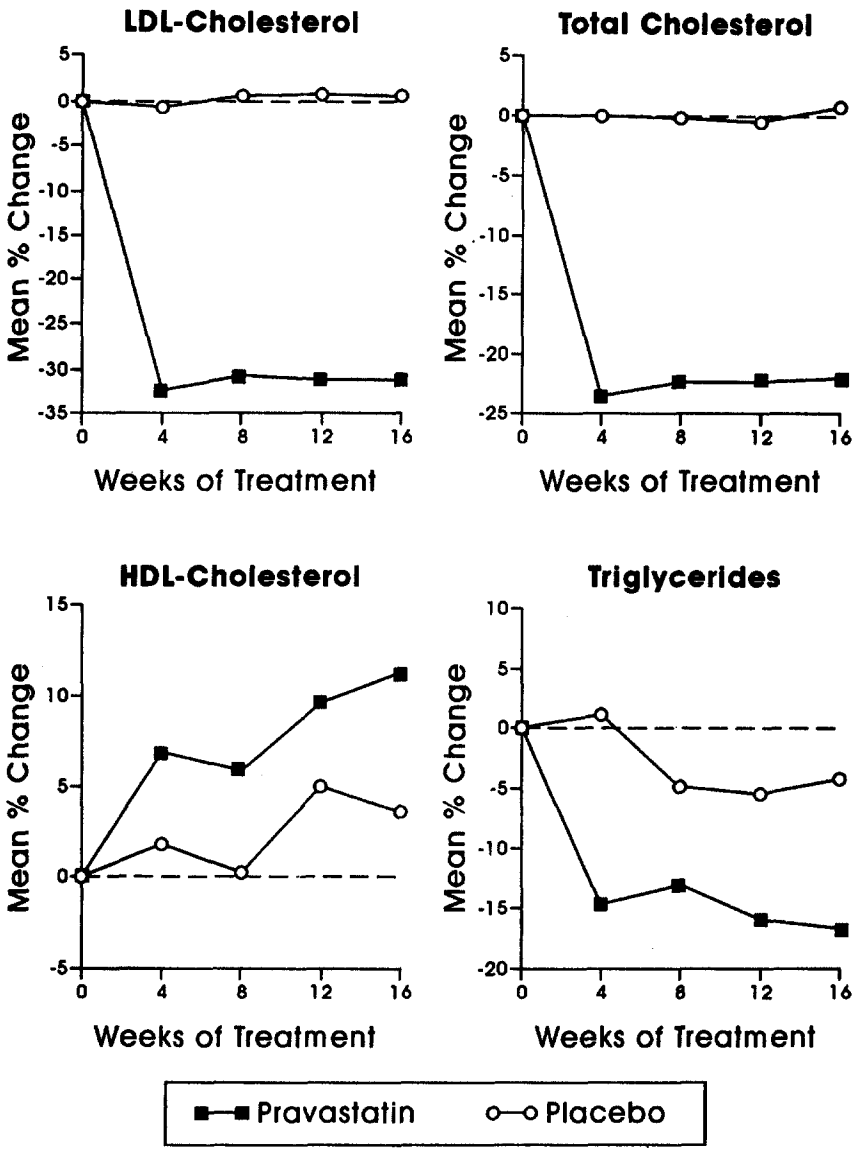

Figure. Adjusted mean percentage changes in lipid and lipoprotein values through the first 16-week phase of the study. LDL-cholesterol = low-density lipoprotein cholesterol; HDL-cholesterol = high-density lipoprotein cholesterol.

predominantly white (75%). The median age of the study population was determined to be 69 years. With the exception of baseline HDL-C values, no significant differences in the demographic characteristics between the two treatment groups were detected by a chi-square test of association or a linear model adjusted for numerical differences among investigators.

Efficacy Analyses

The primary efficacy criterion was the reduction at week 16 in fasting plasma LDL-C levels from the baseline value. Changes in levels of Total-C, HDL-C, and TG were secondary efficacy criteria. After week 16, all subjects were eligible to be treated with additional lipid-lowering therapy. The average daily dose of pravastatin in the active-treatment group at week 16 was 20.4 mg, with only 1 of 88 patients in the pravastatin treatment group having the dose increased after the measurement of LDL-C at week 8.

Lipid and Lipoprotein Response

The mean percentage changes in adjusted mean lipid values from baseline at week 16 are presented in **Table II.** The **Figure** plots the percentage changes in these parameters throughout the short-term phase.

Statistically significant decreases in LDL-C and Total-C were noted in the pravastatin-treatment group after 4 weeks of therapy ($P \leq 0.001$ compared with baseline and placebo). These effects were sustained and remained significant at all timepoints for the duration of the 16-week pravastatin-placebo comparison period ($P \leq 0.001$ compared with baseline and placebo). Mean percent elevations of HDL-C levels and mean percent reductions in TG values with pravastatin therapy were significantly different from baseline and placebo at all timepoints in the first 16 weeks ($P \leq 0.05$ to 0.001). At week 96, the group originally assigned pravastatin had reductions in levels of LDL-C of 29.9%, Total-C 20.2%, and TG 9.0% and ele-

TABLE III
Most Common Adverse Events, Weeks 1 Through 16*

Adverse Event	Number (%) of Subjects: Pravastatin (n=94)	Placebo (n=48)
Musculoskeletal pain	13 (13.8)	6 (12.5)
Upper respiratory infection	11 (11.7)	7 (14.6)
Headache	7 (7.4)	5 (10.4)
Dizziness	9 (9.6)	2 (4.2)
Cough	7 (7.4)	3 (6.3)
Flatulence	6 (6.4)	4 (8.3)
Influenza	7 (7.4)	3 (6.3)
Abnormal urination	6 (6.4)	3 (6.3)
Fatigue	4 (4.3)	5 (10.4)
Insomnia	3 (3.2)	5 (10.4)

*The events listed are the 10 most common events for both treatment groups, in decreasing order of frequency.

TABLE IV
Most Common Adverse Events, Weeks 17 Through 102*

Adverse Event	Number (%) of Subjects: Pravastatin (n=89)	Placebo (n=47)
Musculoskeletal pain	29 (32.6)	13 (27.7)
Upper respiratory infection	25 (28.1)	6 (12.3)
Constipation	4 (4.5)	14 (29.8)
Dizziness	8 (9.0)	8 (17.0)
Abdominal pain	7 (7.9)	8 (17.0)
Diarrhea	8 (9.0)	7 (14.9)
Influenza	13 (4.6)	2 (4.3)
Nausea/vomiting	6 (6.7)	9 (19.1)
Vision disturbance	12 (13.5)	3 (6.4)
Pharyngitis	11 (12.4)	2 (4.3)

*The events listed are the 10 most common events for both treatment groups, in decreasing order of frequency.

vations of levels of HDL-C by 11.6%. The corresponding 96-week results for the group originally assigned placebo, but at this time receiving alternative therapy, were 18.8%, 13.7%, 0.1%, and 3.5%, respectively.

Safety Results

The evaluation of drug safety was conducted for the two distinct phases of the trial, the short-term (weeks 1 through 16) phase and the long-term (weeks 17 through 102) phase. Safety analyses were performed on the total randomized population. Although the study was 96 weeks in duration, some patients were evaluated up to 102 weeks after randomization.

Pravastatin was well tolerated in this study. Four of 142 subjects (2.8%) discontinued treatment because of clinical adverse events during the first 16 weeks of the study, 3 of 94 (3.2%) in the pravastatin group (generalized weakness, epigastric pain, and dizziness), and 1 of 48 (2.1%) in the placebo group (skin rash). The frequencies of adverse events during the short-term phase were 26.6% and 33.3% for the pravastatin- and placebo-treatment groups, respectively. The 10 most common adverse events in the short-term phase are shown in **Table III**. There were no statistically significant differences between treatment groups in the frequency of these 10 events. There was one serious cardiovascular adverse event reported in the short-term, a case of angina leading to hospitalization in a subject receiving placebo. Four subjects (2.8%) were withdrawn from the study during the first 16 weeks because of laboratory abnormalities, two (2.1%) in the pravastatin group and two (4.2%) in the placebo group. Of the two pravastatin-treated subjects withdrawn, one had elevated Y-glutamyl transferase (GGT) and alkaline phosphatase values, and the second had proteinuria, as evidenced by dipstick reading. Of the two placebo-treated subjects withdrawn, one experienced elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values, and the other had an asymptomatic decrease in white cells.

Eighteen of 136 subjects (13.2%), 9 of 89 (10.1%) pravastatin-treated subjects, and 9 of 47 (19.1%) placebo-treated subjects, discontinued due to an adverse event or a marked laboratory abnormality (predefined by the protocol) during the 80-week long-term phase. There was a high frequency of adverse events in this elderly study population in both the pravastatin-treated group (96.6%) and the placebo-treated group (95.7%). The increases in discontinuates and the frequency of adverse events in the long-term phase are to be expected in light of the six-fold increase in length of exposure. The 10 most common events in the long-term phase are shown in **Table IV**. The syndrome of drug-induced myopathy (myalgia associated with increase in creatine kinase more than 10 times the upper limit of normal) was not observed in any pravastatin-treated subject at any time during the trial. There were three serious cardiovascular adverse events involving cardiac ischemia reported in each treatment group during the long-term (3.4% in the pravastatin group and 6.4% in the placebo group).

No statistically significant differences between treatment groups in the frequency of marked laboratory test abnormalities were noted in either the short-term or the long-term analyses. No significant changes from baseline or differences between groups were observed for mean creatine kinase values during the short-term phase. The pravastatin group showed statistically significant ($P \leq 0.05$) increases in mean AST and ALT levels in the short-term phase relative to both baseline and the placebo group, but these had no apparent clinical importance as they were small (0.7 to 2.4 u/L) and did not result in mean values outside the normal range. During the long-term phase, the values for creatine kinase, AST, and ALT were similar to those observed in the short-term period.

There was no difference between treatment groups in the overall incidence of lens opacity progression or in any of the individual lens parameters, except for cortical opacity, in which the control group experienced an unexplained improvement.

COMMENTS

Hypercholesterolemia remains a substantial problem in the elderly (patients more than 65 years of age), with one third of older men and one half of older women having serum cholesterol levels greater than 240 mg/dL.[21] Age is an additional risk factor for CHD, with the prevalence, incidence, morbidity, and mortality of CHD increasing with advancing age.[23] There are distinct sex-related differences. For men, CHD increases rapidly after middle age, whereas for women the largest increase is beyond age 65.[23] Pharmacologic management of cholesterol abnormalities in the elderly using HMG CoA reductase inhibitors is becoming the preferred choice of treatment owing to the dependable efficacy and excellent tolerability of these drugs, the undesirable side effects of other therapeutic agents, and the difficulties in maintaining a balanced low-cholesterol, low-fat diet in this population.[24]

Controversy remains regarding the use of pharmacologic agents in the management of hypercholesterolemia in the elderly, despite increasing evidence of the association of serum cholesterol and CHD in this population. Although early data from Framingham demonstrated no association of Total-C with coronary events in subjects over age 65 years,[25] subsequent analyses have shown a direct relationship of LDL-C values and an inverse relationship of HDL-C levels to the occurrence of coronary events in the elderly.[26] The most recent review of the Framingham data on the elderly population suggested that elevated Total-C remains a significant risk factor in older patients and that this relationship is stronger for women than for men.[27] The Honolulu Heart Program, which studied a cohort of men of Japanese ancestry, has reported an association of coronary events with elevated serum cholesterol values in men 65 to 75 years of age.[5] The Coronary Heart Disease in the Elderly Study by the Kaiser Permanente Medical Care Program concluded that increased serum cholesterol is directly associated with CHD mortality in elderly men.[28] Finally, the trend toward decreased mortality from coronary disease from 1961 to 1983 has been shown in the elderly as well as in the younger populations.[29] Thus, although differences of opinion still exist, the majority of the clinical evidence at this time supports the premise that elevated serum cholesterol is an important risk factor for CHD in the elderly.

Although the relative risk of CHD morbidity and mortality from hypercholesterolemia may be somewhat lower in the elderly than in the younger population, the prevalence, and therefore the attributable risk, is high. Denke and Grundy suggest an assessment of the relative risks and benefits as well as consideration of the individual's overall health status and competing risks prior to administering cholesterol-lowering therapy to elderly patients.[24] As concluded by Bilheimer, the elderly are likely to benefit from risk factor reduction, and decisions on treatment for elevated cholesterol levels should not be made simply on the basis of age but should also consider the presence and severity of other diseases, the patient's mental status, and his or her expectations from medical care.[30] In clinical practice, the elderly patient with vascular disease is often very aware of the importance of cardiovascular risk factor control and will be greatly concerned about elevated cholesterol levels. If patients over the age of 65 years have a demonstrated vascular abnormality, such as coronary, carotid, or peripheral vascular disease, and also have elevated lipid levels, then strong consideration of pharmacologic treatment is indicated, especially if they are otherwise in good health.

In this study, pravastatin was effective in significantly reducing the levels of LDL-C, Total-C, and TG in elderly subjects with hypercholesterolemia. Pravastatin was also effective in raising HDL-C levels from baseline. These lipid effects observed with pravastatin treatment at an average daily dose of approximately 20 mg are comparable to those reported in several other clinical trials involving primarily younger subjects.[7,8] Advancing age does not appear to have an impact on the efficacy of pravastatin. In addition, pravastatin exhibited a high degree of safety and was well tolerated during extended treatment in these older patients, as has previously been reported to be the long-term experience of the drug in younger patients.[9] In conclusion, long-term pravastatin therapy was successful in improving the lipid profile of this elderly population without appreciable adverse effects.

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