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Treating Patients With Documented Atherosclerosis to National Cholesterol Education Program-Recommended Low-Density-Lipoprotein Cholesterol Goals With Atorvastatin, Fluvastatin, Lovastatin and Simvastatin

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Objectives. **This study compared the efficacy and safety of atorvastatin, fluvastatin, lovastatin, and simvastatin in patients with documented atherosclerosis treated to U.S. National Cholesterol Education Program (NCEP) recommended low-density-lipoprotein (LDL) cholesterol concentration (≤100 mg/dl [2.59 mmol/liter]).**

Background. **For patients with advanced atherosclerosis, NCEP recommends lipid-lowering drug therapy if LDL cholesterol remains ≥130 mg/dl (3.36 mmol/liter).**

Methods. **A total of 318 men or women with documented atherosclerosis and LDL cholesterol ≥130 mg/dl (3.36 mmol/liter) and ≤250 mg/dl (6.5 mmol/liter), and triglycerides ≤400 mg/dl (4.5 mmol/liter) participated in this 54-week, multicenter, open-label, randomized, parallel-group, active-controlled, treat-to-target study. Patients were titrated at 12-week intervals until the LDL cholesterol goal was reached. Number of patients reaching target LDL cholesterol levels and dose to reach target were evaluated.**

Results. **At the starting doses, atorvastatin 10 mg produced significantly greater decreases ($p < 0.05$) in plasma LDL cholesterol than the other treatments. Subsequently, the percentage of patients reaching goal at the starting dose was 32% for atorvastatin, 1% for fluvastatin, 10% for lovastatin and 22% for simvastatin. Atorvastatin-treated patients required a lower median dose than other treatments. Median doses at week 54 with the last available visit carried forward were atorvastatin 20 mg/day, fluvastatin 40 mg/day + colestipol 20 g/day, lovastatin 80 mg/day, simvastatin 40 mg/day.**

Conclusions. **A significantly greater number ($p < 0.05$) of patients with confirmed atherosclerosis treated with atorvastatin reached the target LDL cholesterol concentration at the starting dose than patients treated with fluvastatin or lovastatin, and significantly fewer ($p < 0.05$) patients treated with atorvastatin required combination therapy with colestipol to achieve target LDL cholesterol concentrations than all other statins tested.**

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As many as 13.5 million people in the United States are afflicted with coronary heart disease (CHD) (1). Subsequently, it remains the leading cause of death in Western society and results in a healthcare burden estimated by the American Heart Association at $66.4 billion in the United States in 1996 (1,2). The role of serum cholesterol in the development of atherosclerosis is well established (3). Clinical trials have demonstrated that elevated serum low-density-lipoprotein (LDL) cholesterol is associated with increased risk of CHD and that lowering LDL cholesterol reduces morbidity and mortality in patients with or without established cardiovascular disease (4–7). In 1993, the Adult Treatment Panel Report of the National Cholesterol Education Program (NCEP) outlined an updated systematic clinical approach to treating high blood cholesterol in adults (8). These NCEP guidelines are based on the patient's existing LDL cholesterol concentration and risk for CHD. For those patients with advanced disease and documented CHD or PVD, the expert panel recommends

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Abbreviations and Acronyms

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CHD = coronary heart disease
FRR = Food Record Rating
HDL = high-density-lipoprotein
LDL = low-density-lipoprotein
NCEP = National Cholesterol Education Program

lipid-lowering drug treatment if, after an attempt at dietary intervention, LDL cholesterol remains ≥130 mg/dl (3.36 mmol/liter) (8).

Atorvastatin is a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (reductase inhibitor) that has been shown to lower LDL cholesterol levels from 41% to 60% across the dose range in patients with primary hypercholesterolemia (9–11). In this study of patients with documented atherosclerosis, we prospectively evaluated the ability of atorvastatin to treat patients to their NCEP LDL cholesterol goal compared to three of the most frequently prescribed agents (fluvastatin, lovastatin and simvastatin), thereby providing the first direct comparison of marketed reductase inhibitors in this patient population.

Methods

Study design. This 54-week, open-label, randomized, parallel-group, active-controlled, treat-to-target study in patients with documented atherosclerosis consisted of three phases: an optional 8-week screening/dietary assessment phase, a 4-week lead-in phase and a 54-week open-label treatment phase (Fig. 1). Ten primary lipid centers in the United States coordinated activities of 10 primary and 10 secondary care facilities (satellite centers) treating patients with established atherosclerosis. Identical protocols were submitted to each center and reviewed and approved by an appropriate institutional review board. Patients gave written informed consent prior to participation. Before the lead-in phase, men or women of nonchild-bearing potential with documented atherosclerosis, aged 18 to 80 years, with a body mass index not more than 32 kg/m^2, were screened for eligibility with a physical examination, medical history, clinical laboratory evaluation, urinalysis and a lipid profile. Patients taking a lipid-lowering drug could be considered for screening after a 4-week washout period with the exception of probucol, which must have been discontinued for at least 6 months. Eligible patients were required to adhere to the NCEP Step I or Step II diet or an equivalent lipid-restricted diet throughout the study and to complete and return a 3-day diet diary at the first visit of baseline (8,12). Lipid levels of patients beginning dietary modification were allowed to stabilize over an 8-week period before the patient entered the 4-week lead-in phase. The 4-week lead-in phase was used to further evaluate the patient's eligibility and to establish baseline values for a number of study parameters. Estimated mean LDL cholesterol values of ≥130 mg/dl (3.36 mmol/liter) and ≤250 mg/dl (6.5 mmol/liter) as calculated by the Friedewald formula were necessary for inclusion in the study (13). Patients were excluded if they had hypersensitivities to reductase inhibitors or bile acid sequestering resins; were taking any prohibited medications; were pregnant or breast-feeding; had secondary causes of hyperlipoproteinemia such as uncontrolled hypothyroidism, nephrotic syndrome, severe renal dysfunction or uncontrolled diabetes mellitus Type I or II; had active liver disease or hepatic dysfunction; had a myocardial infarction,

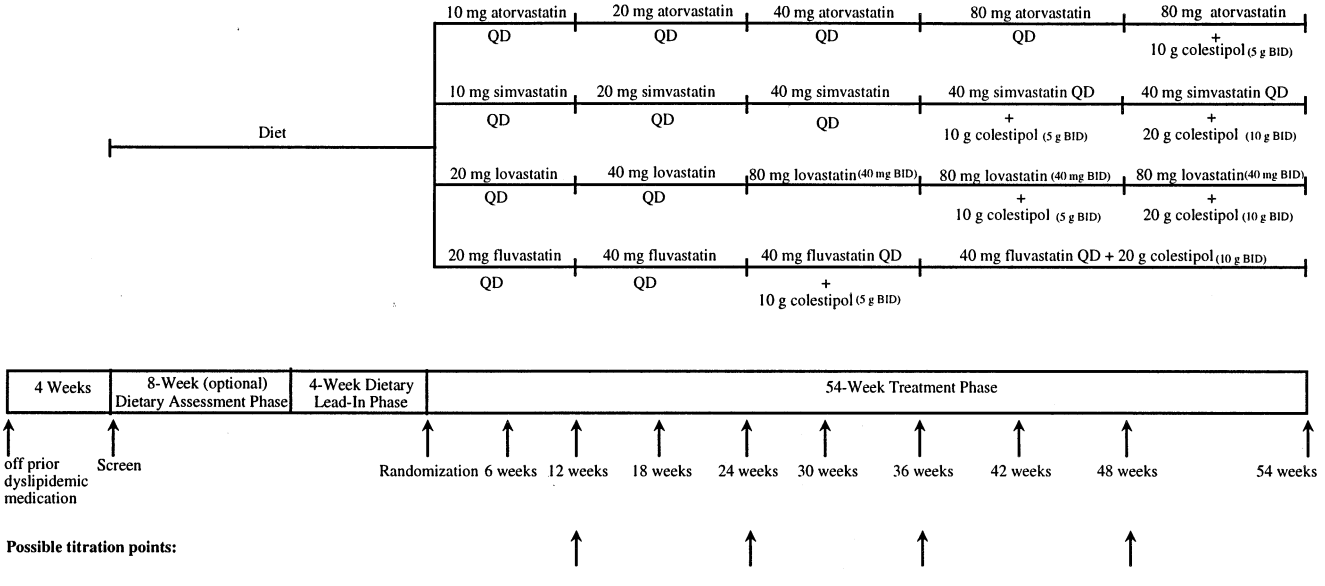

Figure 1. Study design. BID = administered twice daily; QD = administered once daily.

coronary angioplasty, coronary artery bypass graft surgery and/or severe or unstable angina pectoris within 1 month of screening; had participated in another clinical study in which study medication was received within 30 days of screening for this study; and/or had significant abnormalities that the investigator judged could compromise the patient's safety or successful participation in the study. Patients could not take lipid-regulating drugs not prescribed in the protocol, any immunosuppressive agent and/or drugs known to be associated with rhabdomyolysis in combination with reductase inhibitors.

Eligible patients were randomized to the starting dose of atorvastatin 10 mg/day, fluvastatin 20 mg/day, lovastatin 20 mg/day or simvastatin 10 mg/day. During the 54-week treatment phase, lipids were measured at 6- to 12-week intervals, and dose titration occurred at 12-week intervals (weeks 12, 24, 36 and/or 48). Dose titration was based on the mean LDL cholesterol value of the two most recent measurements. Investigators had the option of increasing the study medication dose for patients whose mean LDL cholesterol was either ≥100 mg/dl (2.59 mmol/liter) (NCEP guideline) or ≥105 mg/dl (2.71 mmol/liter) (less stringent criterion). The less stringent criterion allowed for common clinical practice where an investigator may not wish to increase the dose of medication to lower an LDL cholesterol value from 105 mg/dl to 100 mg/dl. The doses of reductase inhibitors could be increased to a maximum of 80 mg/day for atorvastatin, 40 mg/day for fluvastatin, 80 mg/day for lovastatin and 40 mg/day for simvastatin. If the target LDL cholesterol concentration was not achieved at the maximum dose of reductase inhibitor, colestipol was added to the patient's regimen, initially at 10 g (5 g twice daily). Based on the patient's response, colestipol dose could be increased after another 12-week interval up to a maximum of 20 g/day. If the patient could not tolerate colestipol, the dose could be decreased or totally withheld. Once the target LDL cholesterol concentration was reached, the patient's dose of mono- or combination-therapy was maintained until the end of the study with no further titrations allowed regardless of subsequent LDL cholesterol values. At weeks 0 and 54, patients completed a 24-hour dietary diary. Contents of the diary were reviewed by the investigator for completeness and sent to the Chicago Center for Clinical Research where a Food Record Rating (FRR) score was calculated (14). Every effort within the bounds of safety, patient choice and the provisions of informed consent was made to enable patients to complete the study.

Patients received either atorvastatin, fluvastatin, lovastatin or simvastatin based on a randomization code. With the exception of atorvastatin, all study medications were supplied in marketed medication containers. Compliance was assessed at each clinic visit by inquiry and tablet count. The investigator reported patients who took less than 80% of their prescribed medication at each visit as noncompliant. Noncompliant patients were counseled regarding the importance of following dosing instructions but were not dropped from the study. Patients who were noncompliant because of intolerance to colestipol were instructed to continue in the study at the highest tolerated colestipol dose.

Efficacy and safety measurements. Clinical and safety evaluations and lipid profiles were managed through a central laboratory (Pacific Biometrics Research Foundation, Seattle, Washington) accredited by the College of American Pathologists and standardized by the Centers for Disease Control. Serum samples for lipid profiles were collected after a minimum 12-h fast (water allowed). If the patient had not fasted, the visit was rescheduled within 3 days. Study medication was taken at approximately the same time of day and blood samples for lipid profiles were drawn between 6 and 18 h postdose. Patients were not to miss any study medication doses within 48 h of a clinic visit; otherwise the visit was rescheduled.

LDL cholesterol, triglycerides, total cholesterol and high-density-lipoprotein (HDL) cholesterol were evaluated at 6- and 12-week intervals until patients reached NCEP goals, then at 12-week intervals through the remainder of the study. Total plasma cholesterol and triglyceride levels were determined enzymatically with the Hitachi 737 analyzer (15). Plasma HDL cholesterol was determined enzymatically after LDL- and very-low-density-lipoprotein cholesterol were selectively removed from the plasma sample by heparin and magnesium chloride precipitation (16). LDL cholesterol was estimated by the Friedewald formula (LDL cholesterol = total cholesterol − [HDL cholesterol + (triglyceride × 0.2)] for triglyceride levels <400 mg/dl (4.52 mmol/liter) (13). For triglycerides ≥400 mg/dl, LDL cholesterol was determined by ultracentrifugation (17). Apolipoprotein B was evaluated at 24 and 54 weeks and was determined by fixed-rate nephelometry (18).

A full clinical laboratory evaluation was determined at screening, at randomization and at the end of the study, while evaluations for safety (alanine aminotransferase, aspartate aminotransferase and creatine phosphokinase) were done at all intervening visits. Adverse events were recorded at each clinic visit and up to 15 days after treatment stopped. Associated adverse events were those the investigator judged definitely, probably or possibly related to treatment as well as those for which the investigator indicated an unknown relationship to treatment or insufficient available information for evaluation.

Statistical analysis. *Power.* The sample size calculation was based on a two-sided *t*-test at the 5% level of significance. The percent of patients reaching target at each visit and the mean number of visits needed to achieve target LDL cholesterol levels were estimated. Based on these estimates, the difference in the mean number of visits to reach target between atorvastatin and simvastatin was 1.80. The estimated standard deviation was 3.0. Using these parameters, a sample of 45 patients per group would detect a difference of 1.8 visits with 80% power. Estimating a 20% dropout rate yielded a treatment group requirement of approximately 60 patients.

Efficacy. Descriptive statistics were prepared for all baseline demographic and lipid variables. Statistical tests were performed on all data from weeks 12 (starting doses), 24 (prior to any colestipol combination therapy) and 54 (end of study).

Table 1. Baseline Patient Characteristics

Characteristic	Atorvastatin (n = 80)	Fluvastatin (n = 80)	Lovastatin (n = 81)	Simvastatin (n = 77)	All Patients (n = 318)
Sex (n, %)					
Men	50 (63)	62 (78)	51 (63)	53 (69)	216 (68)
Women	30 (38)	18 (23)	30 (37)	24 (31)	102 (32)
Race (n, %)					
White	75 (94)	74 (93)	74 (91)	73 (95)	296 (93)
Other	5 (6)	6 (7)	7 (8)	4 (5)	22 (7)
Age (yr)					
Median	64	64	65	63	64
Range	34–79	44–77	35–80	34–79	34–80
Mean (SE)	62 (1.1)	62 (1.0)	64 (1.1)	63 (1.1)	63 (0.5)
Lipid values (mg/dl) (Mean [SE])					
LDL-C	173 (4.0)	170 (3.1)	175 (3.3)	172 (3.4)	173 (1.7)
TC	254 (4.4)	250 (4.0)	258 (3.7)	252 (4.2)	254 (2.0)
Total TG	203 (8.7)	191 (7.0)	214 (9.3)	193 (7.8)	201 (4.1)
HDL-C	41 (1.2)	41 (1.2)	40 (1.2)	41 (1.4)	41 (0.6)
Total apoB	127 (2.1)	125 (1.9)	131 (2.0)	128 (2.2)	128 (1.0)

apoB = apolipoprotein B; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; SE = standard error; TC = total cholesterol; TG = triglyceride.

Efficacy analyses were performed on data from an intent-to-treat population, defined as all patients randomized to treatment and received at least 1 dose of study medication and who had at least 1 lipid measurement taken after randomization. For this population, the last available postrandomization lipid measurement was carried forward to impute missing observations. All statistical tests were two-sided and conducted at the 5% level of significance. A comparison between treatment groups of the percent change from baseline at weeks 12, 24 and 54 was carried out using analysis of covariance. The primary model included treatment and center effects and the baseline lipid value as a covariate. Treatment-by-center and treatment-by-covariate interactions were evaluated. Dunnett's test was used to perform pairwise comparisons between atorvastatin and each of the other three treatments.

For determining the number of patients reaching LDL cholesterol goal, patients whose mean LDL cholesterol was <105 mg/dl (2.7 mmol/liter) and whose study medication had not been increased were considered responders. Patients were counted as responders at week 54 if they had achieved responder status at that visit or at any prior titration visit, regardless of titration. All patients who withdrew before week 54 without having met responder criteria were counted as nonresponders. To validate the use of 105 mg/dl as an alternative and reliable NCEP LDL cholesterol goal, a comparative sensitivity analysis was performed on the number of patients reaching LDL cholesterol goal using the accepted NCEP criteria of 100 mg/dl (2.58 mmol/liter).

A comparison between treatment groups in responders by week 54 of the study was carried out using a Cochran–Mantel–Haenszel (CMH) analysis stratified by center. The colestipol required by each treatment group to reach LDL-cholesterol goal was compared by analysis of variance. A between-treatment comparison of the time to reach target LDL cholesterol values was carried out using the generalized Wilcoxon test without stratification by center.

Safety. All patients who received study medication were evaluated for safety. Adverse events and laboratory deviations outside the normal range were recorded at clinic visits throughout the study. Adverse events were summarized to assess the adverse event rate for the treatment groups. An increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal and an increase in creatine kinase greater than 10 times upper limit of normal with muscle pain, tenderness or weakness were considered clinically important laboratory deviations due to the increased incidence of these laboratory events with reductase inhibitors.

Results

Demographics. A total of 318 patients with documented atherosclerosis were randomized into the study with baseline characteristics similar for all treatment groups (Table 1). Overall, the majority of participants were men (68%), primarily white (93%), with a mean age of 63 years (range 34 to 80 years). Mean baseline lipid values appeared similar across treatment groups.

Compliance. In this study compliance, based on tablet counts at each visit, was similar and high for all treatment groups, ranging across visits from 92% to 100% in the atorvastatin group, 83% to 97% in the fluvastatin group, 91% to 96% in the lovastatin group and 88% to 99% in the simvastatin group. FRR scores at baseline and the end of the study were similar across treatments, suggesting that consistent dietary practices were maintained throughout the study.

Disposition. Five patients lacked a postrandomization lipid measurement and five patients were off study medication >3

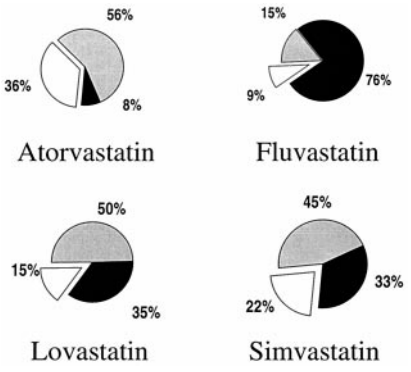

Figure 2. Dose distribution by percentages of patients in each treatment group at week 54 (with the last available observation carried forward). Starting dose: 10 mg atorvastatin and simvastatin; 20 mg fluvastatin and lovastatin. All other monotherapy doses: 20 to 80 mg atorvastatin; 40 mg fluvastatin; 40 to 80 mg lovastatin; 20 to 40 mg simvastatin. Highest dose plus colestipol (up to 20 g/day): 80 mg atorvastatin and lovastatin; 40 mg fluvastatin and simvastatin. **White portion** = starting dose; **gray portion** = all other monotherapy doses; **black portion** = highest dose of reductase inhibitors plus colestipol.

days before their only lipid measurement. Data for these patients were not included in efficacy evaluations. Baseline lipid values of patients with efficacy data were similar among treatment groups and similar to those of the entire population. For all treatment groups, the majority of nonresponders completed the study.

Exposure. The greatest exposure to atorvastatin was at the initial dose of 10 mg/day. In comparison, the greatest exposure to the other reductase inhibitors occurred at the maximum doses of 40 mg/day for fluvastatin, 80 mg/day for lovastatin, and 40 mg/day for simvastatin. The greatest exposure to reductase inhibitor plus colestipol combination therapy was among patients randomized to fluvastatin. Median dose of each treatment group at week 54 (with the last available observation carried forward) was: atorvastatin, 20 mg/day; fluvastatin, 40 mg/day plus colestipol 20 g/day; lovastatin, 80 mg/day; and simvastatin, 40 mg/day. The percentage of each treatment group at initial dose, monotherapy with all other doses and highest dose combined with colestipol for each reductase inhibitor is shown in Figure 2. At the end of the study, 36% of the atorvastatin patients were being treated at the starting dose and only 8% required colestipol combination therapy. In contrast, only 9% of fluvastatin patients were still at the starting dose and 76% required combination therapy, 15% of lovastatin patients were at the starting dose and 35% required combination therapy and 22% of simvastatin patients were still at the starting dose and 33% required combination therapy.

Efficacy. At weeks 12 and 24 the mean percent decrease in LDL cholesterol from baseline was greater among atorvastatin-treated patients than among patients in other treatment groups (Table 2). Statistical evaluation at week 12 data indicated that, at the starting dose, atorvastatin decreased LDL cholesterol to a significantly greater degree than fluvastatin, lovastatin or simvastatin ($p < 0.05$). At week 24, with patients allowed one increase in dose, atorvastatin decreased LDL cholesterol to a significantly greater degree than fluvastatin or lovastatin ($p < 0.05$). Statistical evaluation of week 54 data, where patients may have received the full dosage range plus colestipol combination therapy, indicated that atorvastatin decreased LDL cholesterol from baseline to a significantly greater degree than fluvastatin ($p < 0.05$).

NCEP goals. After 12 weeks of treatment, when all patients were at the starting dose of treatment, a significantly greater percentage of the atorvastatin-treated patients (32%) achieved the target LDL cholesterol goal compared to 1% for fluvastatin- and 10% for lovastatin-treated patients, respectively ($p < 0.05$), but not compared to 22% for simvastatin-treated patients. A significantly greater percentage of atorvastatin- (53%) than fluvastatin- (10%) or lovastatin-treated patients (31%) reached target LDL cholesterol levels by week 24 ($p < 0.05$), but not compared to 39% for simvastatin-treated patients. A total of 223 patients met their target LDL cholesterol goal by week 54. Response by week 54 was significantly better among atorvastatin-treated patients (83%) compared to fluvastatin-treated patients (50%) ($p < 0.05$). This response was not significantly better than in

Table 2. Mean Percent Change† From Baseline in Lipid Parameters

Lipid Parameter	Atorvastatin (n = 78)	Fluvastatin (n = 76)	Lovastatin (n = 78)	Simvastatin (n = 76)
LDL-C				
Week 12‡	−33 (1.3)	−17* (1.3)	−26* (1.3)	−28* (1.3)
Week 24§	−36 (1.3)	−21* (1.4)	−30* (1.3)	−33 (1.4)
Week 54‖	−41 (1.6)	−30* (1.6)	−41 (1.6)	−37 (1.6)
Total cholesterol				
Week 12‡	−23 (1.0)	−12* (1.0)	−19* (1.0)	−20 (1.0)
Week 24§	−26 (1.1)	−15* (1.1)	−23* (1.1)	−24 (1.1)
Week 54‖	−30 (1.2)	−20* (1.3)	−29 (1.2)	−26 (1.2)
Triglycerides				
Week 12‡	−11 (3.1)	−6 (3.1)	−6 (3.1)	−11 (3.1)
Week 24§	−16 (2.9)	−9 (2.9)	−14 (2.9)	−20 (2.9)
Week 54‖	−19 (2.9)	−2* (3.0)	−14 (2.9)	−15 (3.0)
HDL-C				
Week 12‡	9 (1.3)	5 (1.4)	6 (1.3)	9 (1.3)
Week 24§	8 (1.5)	8 (1.5)	9 (1.5)	10 (1.5)
Week 54‖	7 (1.7)	7 (1.7)	12 (1.7)	11 (1.7)
apoB				
Week 12‡	ND	ND	ND	ND
Week 24§	−27 (1.2)	−16* (1.3)	−23* (1.2)	−24* (1.2)
Week 54‖	−29 (1.4)	−21* (1.4)	−27 (1.3)	−25* (1.4)
NonHDL-C/HDL-C				
Week 12‡	−34 (1.5)	−19* (1.5)	−26* (1.5)	−31 (1.5)
Week 24§	−36 (1.6)	−24 (1.6)	−33 (1.6)	−36 (1.6)
Week 54‖	−40 (1.7)	−29 (1.8)	−41 (1.7)	−39 (1.8)

apoB = apolipoprotein B; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; ND = not determined. *Significantly different from atorvastatin ($p < 0.05$). †Adjusted mean provided for percent change based on analysis of covariance models. ‡These data represent the use of drugs at the starting dose: atorvastatin 10 mg, fluvastatin 20 mg, lovastatin 20 mg and simvastatin 10 mg. §These data represent the use of drugs across dosage ranges: atorvastatin 10 to 20 mg, fluvastatin 20 to 40 mg, lovastatin 20 to 40 mg and simvastatin 10 to 20 mg. ‖These data represent the use of drugs across the full dosage range and in combination with colestipol.

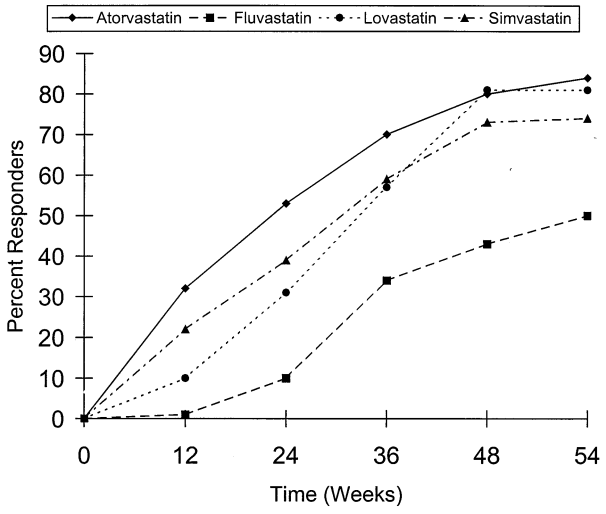

Figure 3. Cumulative percentage of patients reaching the NCEP-recommended LDL cholesterol goal (≤100 mg/dl). The median dose for each treatment group at week 54 (with the last available observation carried forward) was atorvastatin 20 mg/day, fluvastatin 40 mg/day plus colestipol 20 g/day, lovastatin 80 mg/day and simvastatin 40 mg/day.

lovastatin- (81%) or simvastatin-patients (75%) treated; however, the amount of colestipol needed to achieve LDL cholesterol goals was significantly greater in the lovastatin and simvastatin groups than in the atorvastatin group ($p < 0.05$). A post hoc analysis looked at the percentage of patients who attained their NCEP target LDL cholesterol concentration on reductase inhibitor alone (monotherapy). Seventy-nine percent of atorvastatin patients met goal compared to 11% on fluvastatin, 56% on lovastatin and 59% on simvastatin ($p < 0.05$).

Atorvastatin-treated patients had a median response time of 170 days compared to 344 days for fluvastatin-, 253 for lovastatin- and 253 for simvastatin-treated patients, from life-table analyses ($p < 0.05$). Cumulative response over time is shown in Figure 3. Of the 223 patients who met an LDL cholesterol goal of 105 mg/dl (2.71 mmol/liter), 204 also met the stricter criteria of 100 mg/dl (2.58 mmol/liter). Those patients whom the investigators chose not to titrate up in dose were evenly distributed across treatment groups. The sensitivity analysis which considered the strict goal of 100 mg/dl (2.58 mmol/liter) showed similar results to the data at 105 mg/dl (2.71 mmol/liter), where 78% of atorvastatin-treated patients at week 54 reached goal versus 42% fluvastatin-, 74% lovastatin- and 70% simvastatin-treated patients.

Safety. *Adverse events.* At week 54, atorvastatin showed a safety profile similar to that of the other reductase inhibitors. Adverse events occurring on combination therapy at week 54 were summarized as treatment-related when judged related to either reductase inhibitor or colestipol treatment or both. Patients in the fluvastatin treatment group had about a twofold higher overall incidence of treatment-related adverse events than patients in the other treatment groups. This higher percentage in the fluvastatin group was due primarily to a higher incidence of digestive system symptoms, particularly constipation and flatulence, which are often associated with colestipol treatment (Table 3). Approximately 76% of patients in the fluvastatin group were receiving add-on colestipol therapy. With this exception, no notable treatment differences were observed when adverse events were stratified by age, gender or race. Related adverse events that occurred in at least two atorvastatin-treated patients were constipation, headache, dizziness, arthralgia and rash. Within a body system other than digestive, the number (1 to 4) and percentage (1% to 5%) of patients with a specific type of event were too low to make clinically meaningful comparisons between treatment groups.

Serious adverse events were most often related to the cardiovascular system, with angina pectoris and myocardial infarction the most frequent events. With the exception of one lovastatin-treated patient (pancreatitis), none of these events was considered related to treatment.

Eleven patients withdrew because of treatment-related adverse events, with the overall incidence of events similar between treatment groups (three patients withdrew in the atorvastatin group, four in the fluvastatin group, two in the lovastatin group and two in the simvastatin group). One atorvastatin-, one fluvastatin- and two simvastatin-treated patients died. None of these deaths was considered related to treatment.

Laboratory parameters. Minor and sporadic elevations in ALT and AST were noted in all treatment groups. One fluvastatin patient had persistent alanine transaminase levels >3 times the upper limit of normal, and another fluvastatin patient had persistent aspartate transaminase elevations >3 times the upper limit of normal. There were no clinically

Table 3. Week 54: Related† Adverse Events Experienced by at Least 3% of Patients in Any Randomized Treatment Group‡ (Number [%] of Patients)

Body System Adverse Event	Atorvastatin (n = 80)	Fluvastatin (n = 80)	Lovastatin (n = 81)	Simvastatin (n = 77)
Digestive	5 (6)	23 (29)	12 (15)	9 (12)
Constipation	2 (3)	7 (9)	6 (7)	5 (6)
Flatulence	0 (0)	8 (10)	3 (4)	2 (3)
Nausea	1 (1)	4 (5)	0 (0)	0 (0)
Diarrhea	1 (1)	3 (4)	0 (0)	0 (0)
Dyspepsia	0 (0)	2 (3)	2 (2)	2 (3)
Body as a whole	5 (6)	6 (8)	2 (2)	2 (3)
Headache	2 (3)	0 (0)	0 (0)	4 (5)
Asthenia	1 (1)	3 (4)	0 (0)	2 (3)
Abdominal Pain	0 (0)	2 (3)	2 (2)	2 (3)
Pain	0 (0)	2 (3)	0 (0)	0 (0)
Nervous system	3 (4)	1 (1)	1 (1)	1 (1)
Dizziness	2 (3)	0 (0)	0 (0)	1 (1)
Musculoskeletal	2 (3)	3 (4)	1 (1)	3 (4)
Arthralgia	2 (3)	0 (0)	1 (1)	1 (1)
Skin and appendages	2 (3)	3 (4)	2 (2)	2 (3)
Rash	2 (3)	2 (3)	1 (1)	2 (3)
Any Event	15 (19)	33 (41)	16 (20)	18 (23)

†Definitely, probably or possibly related to study medication. ‡Includes patients on monotherapy and those on reductase inhibitor plus colestipol therapy.

important changes in liver transaminase levels in any other group. The proportion of patients with glucose elevations was similar across treatment groups. For all patients this abnormality was transient and not clinically meaningful. There were no clinically important creatine kinase levels in any treatment group. Changes in remaining parameters were not clinically meaningful and showed no treatment-associated trends.

Discussion

This treat-to-target study provides a first-time, prospective, direct comparison of lipid lowering in patients with established atherosclerosis treated to their NCEP-recommended plasma LDL cholesterol goal among four marketed reductase inhibitors: atorvastatin, fluvastatin, lovastatin and simvastatin.

Efficacy. At week 12, the time point at which all patients were receiving a starting dose of reductase inhibitor, atorvastatin decreased LDL cholesterol significantly more than the other compounds tested ($p < 0.05$). The week 54 time point provided a 1-year look at treatment with patients on a variety of doses and combination treatments. Baseline characteristics between treatment groups were similar and all patients were treated to the same LDL cholesterol goal. Median doses at week 54 with the last available visit carried forward were atorvastatin 20 mg/day, fluvastatin 40 mg/day + colestipol 20 g/day, lovastatin 80 mg/day and simvastatin 40 mg/day. At week 54, atorvastatin decreased LDL cholesterol to a greater extent than the other reductase inhibitors with statistical significance ($p < 0.05$) compared to fluvastatin.

NCEP goals. In this study atorvastatin's significant lipid-lowering activity enabled more patients with established atherosclerosis to reach the NCEP-recommended LDL cholesterol concentration at the starting dose than patients treated with fluvastatin or lovastatin ($p < 0.05$). Thirty-two percent of the atorvastatin-treated patients achieved their target LDL cholesterol concentration compared to 1% for fluvastatin-, 10% for lovastatin- and 22% for simvastatin-treated patients. Only 8% of atorvastatin patients required colestipol combination therapy to achieve goal, compared to 76% of fluvastatin-, 35% of lovastatin- and 33% of simvastatin patients. In fact, the slightly higher compliance rate for patients treated with atorvastatin may be a reflection of these patients reaching their LDL cholesterol goal quickly and with a low rate of colestipol combination therapy. The largest obstacle to adjuvant therapy may be reduced compliance due to the occurrence of adverse effects. A retrospective cohort study in patients with cardiovascular disease has reported that in patients treated with niacin and/or colestipol, the cumulative drug discontinuance rate for these agents was over 50% (19).

It can be argued that the type of patients recruited for this study favored atorvastatin in respect to their starting LDL cholesterol levels (170 to 175 mg/dl) and the level of reduction required by most patients to reach their NCEP goal (approximately 40%). It is important to note, however, that patients had to have a starting LDL cholesterol level of ≥130 mg/dl to enter the study. The patient population recruited for this study is representative of the general patient population for which lipid-lowering therapy would be prescribed.

Although the majority of analyses were performed on patients achieving a slightly less stringent goal (105 mg/dl [2.71 mmol/liter]) than that outlined in NCEP guidelines (100 mg/dl [2.58 mmol/liter]), the results of the analyses were unaffected by this variation. We believe that the results at 105 mg/dl provide a realistic interpretation of the data whereby most physicians would not increase a patient's dose of medication to lower their LDL cholesterol from 105 to below 100 mg/dl (2.71 to 2.58 mmol/liter).

Conclusions. Medical practice guidelines are expanding in use as the economic and clinical demands on medical practice increase. Considering the well-established relationship between LDL cholesterol and atherosclerotic disease, the use of NCEP guidelines is a logical and reasonable approach for the treatment of hypercholesterolemia and ultimately CHD. Several studies are currently ongoing to examine the effect of atorvastatin on cardiovascular events. This study demonstrates that more patients with established atherosclerosis reached NCEP-recommended target LDL cholesterol concentration at the starting dose ($p < 0.05$) with atorvastatin than with fluvastatin or lovastatin and with less colestipol combination therapy ($p < 0.05$) than fluvastatin, lovastatin or simvastatin. Atorvastatin is a highly effective treatment for lowering LDL cholesterol to NCEP guidelines.

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