

Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients With Hypercholesterolemia (The CURVES Study)

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The objective of this multicenter, randomized, open-label, parallel-group, 8-week study was to evaluate the comparative dose efficacy of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor atorvastatin 10, 20, 40, and 80 mg compared with simvastatin 10, 20, and 40 mg, pravastatin 10, 20, and 40 mg, lovastatin 20, 40, and 80 mg, and fluvastatin 20 and 40 mg. Investigators enrolled 534 hypercholesterolemic patients (low-density lipoprotein [LDL] cholesterol ≥ 160 mg/dl [4.2 mmol/L] and triglycerides ≤ 400 mg/dl [4.5 mmol/L]). The efficacy end points were mean percent change in plasma LDL cholesterol (primary), total cholesterol, triglycerides, and high-density lipoprotein cholesterol concentrations from baseline to the end of treatment (week 8). Atorvastatin 10, 20, and 40 mg

produced greater ($p \leq 0.01$) reductions in LDL cholesterol, -38% , -46% , and -51% , respectively, than the milligram equivalent doses of simvastatin, pravastatin, lovastatin, and fluvastatin. Atorvastatin 10 mg produced LDL cholesterol reductions comparable to or greater than ($p \leq 0.02$) simvastatin 10, 20, and 40 mg, pravastatin 10, 20, and 40 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg. Atorvastatin 10, 20, and 40 mg produced greater ($p \leq 0.01$) reductions in total cholesterol than the milligram equivalent doses of simvastatin, pravastatin, lovastatin, and fluvastatin. All reductase inhibitors studied had similar tolerability. There were no incidences of persistent elevations in serum transaminases or myositis. ©1998 by Excerpta Medica, Inc. (Am J Cardiol 1998;81:582-587)

The Adult Treatment Panel of the National Cholesterol Education Program has established guidelines for the evaluation and treatment of elevated cholesterol concentrations based on an individual's risk factors for coronary artery disease.¹ The low-density lipoprotein (LDL) cholesterol treatment goals are (1) LDL cholesterol ≤ 100 mg/dl for patients with CAD; (2) LDL cholesterol < 130 mg/dl in patients with ≥ 2 risk factors for CAD; (3) LDL cholesterol < 160 mg/dl in patients with < 2 risk factors for CAD. The Adult Treatment Panel recommended bile acid resins, nicotinic acid, and the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors as first-line drug treatments to achieve these treatment goals. Simvastatin, pravastatin, lovastatin, and fluvastatin lower LDL cholesterol from 18% to 41% over the most commonly used recommended dose range of each agent.²⁻¹³ A recently approved synthetic HMG-CoA reductase inhibitor, atorvastatin, reduces LDL cholesterol from 35% to 61% over the dose range of

10 to 80 mg.¹⁴⁻¹⁸ The present multicenter study (CURVES) was designed to evaluate the comparative dose efficacy of the HMG-CoA reductase inhibitor, atorvastatin, with equivalent dose strengths of simvastatin, pravastatin, lovastatin, and fluvastatin, in hypercholesterolemic patients after 8 weeks of treatment.

METHODS

Study design: This study was a multicenter, open-label, randomized, parallel-group, 8-week comparative study evaluating the efficacy of once-daily doses of atorvastatin 10, 20, 40, and 80 mg compared with once-daily doses of simvastatin 10, 20, and 40 mg, pravastatin 10, 20, and 40 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg, and twice daily doses of lovastatin 40 mg (80 mg total daily dose). Male and female patients 18 to 80 years old with plasma LDL cholesterol concentrations ≥ 160 mg/dl (4.2 mmol/L) as calculated by the Friedewald formula, and triglyceride concentrations ≤ 400 mg/dl (4.5 mmol/L) at 2 consecutive visits (weeks -6 and -2) were eligible for inclusion.¹⁹ Patients with any of the following conditions were excluded: primary hypothyroidism; nephrotic syndrome; type 1 or uncontrolled type 2 diabetes mellitus; hepatic dysfunction; serum creatine phosphokinase levels > 3 times the upper limit of normal; body mass index > 32 kg/m²; uncontrolled hypertension; myocardial infarction, coronary angioplasty, coronary artery bypass graft, or severe or unstable angina pectoris within the 3 months

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*See Appendix for list of CURVES investigators.

before the study; known hypersensitivities to HMG-CoA reductase inhibitors; or significant abnormalities that the investigator believed could compromise the patient's safety or successful participation in the study. Medications known to effect lipid levels, interact with study medications, or effect clinical laboratory parameters (erythromycin, anticoagulants, isotretinoin, immunosuppressive agents, lipid-regulating drugs, systemic steroids) were not allowed during the study.

Eligible patients were instructed to follow the step 1 diet for 6 weeks before randomization and throughout the duration of the study. After dietary stabilization, patients who qualified were randomized to 1 of 15 treatment groups, as described above, and were treated for 8 weeks. All study medication was taken according to recommended dosing. The study was performed using a common protocol at 34 sites. An appropriate institutional review board at all sites approved the protocol and all patients signed written informed consent.

Laboratory methods: Using standardized procedures, Medical Research Laboratories, Highland Heights, Kentucky, performed lipid and clinical laboratory measurements for all sites. The laboratory was certified for standardization of lipid analyses as specified by the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute.²⁰ After patients fasted overnight (minimum of 12 hours), blood was drawn in evacuated tubes containing ethylenediaminetetraacetic acid (1 mg/ml). Total plasma cholesterol and triglycerides were determined enzymatically with the Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Indiana).²¹ Plasma high-density lipoprotein (HDL) cholesterol was determined enzymatically after LDL and very low density lipoprotein cholesterol were selectively removed from the plasma by heparin and manganese chloride precipitation.²² LDL cholesterol concentration was estimated by the Friedewald formula.¹⁹ Fibrinogen was measured by immunonephelometry using an antiserum to human fibrinogen (BNA-100 Behring Diagnostics, Westwood, Massachusetts) in EDTA plasma stored at 70°C before analysis.

Safety: To monitor safety, complete clinical laboratory determinations were obtained at screening, randomization, and the end of the active treatment period. Physical examinations were performed at the beginning and end of the study. Adverse events were recorded at each clinic visit. Serum transaminases and creatinine phosphokinase concentrations were determined at every study visit and as deemed necessary by the investigator.

Statistical methods: Sample sizes were calculated based on the 2-sided Dunnett's test with a significance level of 5% and a standard deviation of 13% to detect differences in LDL cholesterol reductions of 8% (e.g., simvastatin 10 mg vs atorvastatin 10 mg) to 24% (e.g., fluvastatin 40 mg vs atorvastatin 40 mg) between atorvastatin and other reductase inhibitors at each dose level with at least 80% power.²³ The sample size in

each treatment arm varied greatly due to the large range of differences in lipid-lowering efficacy between atorvastatin and the other reductase inhibitors. Sample sizes were inflated by 5% for enrollment targets to allow for potential dropouts.

The intent-to-treat analysis performed for all efficacy end points included all randomized patients with post-treatment efficacy data for the primary efficacy end point of percent change in LDL cholesterol from baseline to week 8, and the secondary efficacy end points of percent change from baseline to week 8 in total cholesterol, triglycerides, and HDL cholesterol. Baseline was defined as the mean of measurements at week -2 and week 0 (randomization).

For each lipid parameter, the percent change was analyzed using an analysis of covariance model to test the treatment effect while controlling for baseline lipids. The least-squares means and mean square error from this model were used to compare atorvastatin with other reductase inhibitors at each dose level using Dunnett's procedure to fix the dose-wise type I error rate at 5%.²³ An analysis of variance model was used to test the assumption of no treatment-by-baseline lipid interaction.

Comparison between the least-squares means from the analysis of covariance model were used to evaluate (post hoc) the effect of each reductase inhibitor at all dose levels compared with atorvastatin 10 mg and atorvastatin 20 mg.

Safety was assessed among all patients receiving study medication using adverse events (coded using a modified COSTART dictionary) and clinical laboratory assessments. Particular attention focused on the presence of myopathy or elevated serum transaminase levels because these conditions have been associated with the use of reductase inhibitors.²⁴

RESULTS

Patient characteristics: Of the 534 patients randomized to treatment, 518 patients completed the study. Sixteen patients (3%) withdrew before the end of the study: 8 because of adverse events, 4 for personal reasons, and 4 who were lost to follow-up. The intent-to-treat analysis included 522 patients who provided post-treatment efficacy data. Fifty-nine percent of patients (307) were men and 41% (215) were women; 90% (469) were white. Mean age was 55 years (range 20 to 80), and 17% of patients had established CAD.

Effects on serum lipids: Mean baseline LDL cholesterol concentrations ranged from 192 to 244 mg/dl (5.0 to 6.3 mmol/L) and were similar across treatment groups (Table I). When given once daily in equivalent (mg) doses, atorvastatin 10, 20, and 40 mg produced greater ($p \leq 0.01$) reductions in LDL cholesterol than simvastatin, pravastatin, lovastatin, and fluvastatin (Figure 1). Atorvastatin administered once daily at 80 mg reduced LDL cholesterol by 54%, whereas lovastatin administered as 40 mg twice daily reduced LDL cholesterol by 48%. This difference was not statistically significant ($p = 0.17$) (Table II).

Atorvastatin 10 mg produced greater ($p \leq 0.02$) reductions in LDL cholesterol than simvastatin 10 mg,

TABLE I Baseline Lipid and Lipoprotein Cholesterol Concentrations

Treatment	Dose (mg)	Number of Patients	Total Cholesterol	Triglycerides	HDL Cholesterol	LDL Cholesterol
Atorvastatin	10	73	298 (7.72)	169 (1.91)	51 (1.33)	213 (5.52)
Pravastatin	10	14	309 (8.00)	176 (1.98)	49 (1.26)	226 (5.83)
Simvastatin	10	70	289 (7.48)	157 (1.78)	51 (1.31)	207 (5.36)
Atorvastatin	20	51	297 (7.68)	172 (1.94)	49 (1.28)	213 (5.51)
Pravastatin	20	41	315 (8.14)	147 (1.66)	48 (1.25)	237 (6.14)
Simvastatin	20	49	313 (8.09)	159 (1.79)	51 (1.32)	230 (5.95)
Fluvastatin	20	12	322 (8.34)	188 (2.12)	49 (1.26)	236 (6.10)
Lovastatin	20	16	334 (8.63)	192 (2.17)	51 (1.32)	244 (6.32)
Atorvastatin	40	61	286 (7.40)	153 (1.73)	50 (1.29)	206 (5.32)
Pravastatin	40	25	299 (7.73)	172 (1.94)	49 (1.28)	215 (5.57)
Simvastatin	40	61	300 (7.77)	173 (1.95)	47 (1.20)	219 (5.66)
Fluvastatin	40	12	275 (7.12)	173 (1.95)	49 (1.26)	192 (4.97)
Lovastatin	40	16	301 (7.79)	172 (1.94)	49 (1.26)	219 (5.65)
Atorvastatin	80	10	296 (7.65)	150 (1.69)	53 (1.37)	213 (5.51)
Lovastatin	80	11	306 (7.90)	200 (2.26)	47 (1.21)	219 (5.66)

Values are expressed as mean mg/dl (mmol/L).

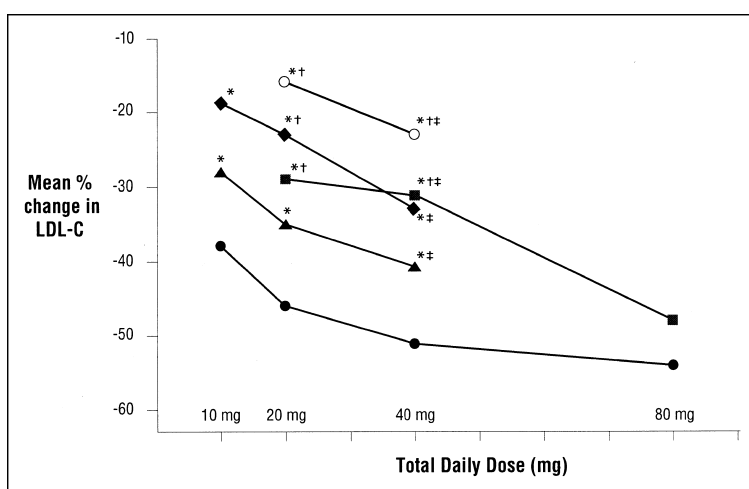


FIGURE 1. Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with atorvastatin (●), simvastatin (▲), pravastatin (◆), lovastatin (■), and fluvastatin (○). * $p \leq 0.01$ versus atorvastatin at mg equivalent doses; † $p \leq 0.02$ versus atorvastatin 10 mg; ‡ $p \leq$ versus atorvastatin 20 mg.

pravastatin 10 and 20 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg (Table III). Atorvastatin 20 mg produced greater ($p \leq 0.01$) reductions in LDL cholesterol than simvastatin 10, 20, and 40 mg, pravastatin 10, 20, and 40 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg (Table III).

As with LDL cholesterol, atorvastatin 10, 20, and 40 mg produced greater ($p \leq 0.01$) reductions in total cholesterol than simvastatin, pravastatin, lovastatin, and fluvastatin at milligram-equivalent doses (Table II). The effects on triglycerides were not different between atorvastatin and the other reductase inhibitors except at the 40-mg dose when atorvastatin produced greater ($p \leq 0.05$) reductions in triglycerides than the 40-mg doses of simvastatin, pravastatin, lovastatin, and fluvastatin (Table II). Effects on HDL cholesterol, ranging from 3.0% to 9.9%, were not different between atorvastatin and the other reductase inhibitors except at the 40-mg

dose when simvastatin produced greater ($p \leq 0.05$) elevations in HDL cholesterol than atorvastatin (Table II).

Safety: The overall frequency of adverse events was similar between treatment groups. Fifty-two patients (10%) reported adverse events that were judged by the investigator to be possibly, probably, or definitely associated with treatment, most of which were mild to moderate in intensity. Of these, the most commonly reported events were myalgia (1.5%), abdominal pain (1.3%), diarrhea (1.1%), flatulence (1%), and nausea (1%). Eight patients withdrew from the study due to adverse events: 2 in the atorvastatin group (1%), 4 in the simvastatin group (2%), and 1 each in the pravastatin (1%) and fluvastatin groups (4%) (Table IV). The adverse

events leading to withdrawal included gastrointestinal complaints, dizziness, depression, myalgia, hypertonionia, angina, and back pain.

There were no incidences of persistent (2 measurements within 1 week) elevations in serum transaminases >3 times the upper limit of normal. There were no incidences of elevations in creatine phosphokinase >3 times the upper limit of normal or reports of myopathy in any treatment group. There were no significant changes from baseline in mean fibrinogen levels for any of the reductase inhibitors.

DISCUSSION

The CURVES study is the first trial to compare the lipid-lowering efficacy of all marketed HMG-CoA reductase inhibitors, including the recently approved synthetic HMG-CoA reductase, atorvastatin, across their dose ranges. An open-label design was chosen

TABLE II Mean Percent Change (\pm SD) in Lipoprotein Concentrations

Treatment	Dose (mg)	Number of Patients	Total Cholesterol	Triglycerides	HDL Cholesterol	LDL Cholesterol
Atorvastatin	10	73	-28 (9)	-13 (25)	5.5 (12)	-38 (10)
Pravastatin	10	14	-13 (12) [†]	3 (46)	9.9 (13)	-19 (14) [†]
Simvastatin	10	70	-21 (9) [†]	-12 (30)	6.8 (9)	-28 (12) [†]
Atorvastatin	20	51	-35 (6)	-20 (25)	5.1 (11)	-46 (8)
Pravastatin	20	41	-18 (7) [†]	-15 (17)	3.0 (8)	-24 (9) ^{***,†}
Simvastatin	20	49	-26 (8) [†]	-17 (22)	5.2 (10)	-35 (11) ^{**}
Fluvastatin	20	12	-13 (6) [†]	-5 (32)	0.9 (8)	-17 (8) ^{***,†}
Lovastatin	20	16	-21 (9) [†]	-12 (23)	7.3 (12)	-29 (13) ^{***,†}
Atorvastatin	40	61	-40 (8)	-32 (19)	4.8 (12)	-51 (10)
Pravastatin	40	25	-24 (7) [†]	-10 (22) [†]	6.2 (11)	-34 (9) ^{***,‡}
Simvastatin	40	61	-30 (10) [†]	-15 (29) [†]	9.6 (13) [*]	-41 (13) ^{***,‡}
Fluvastatin	40	12	-19 (9) [†]	-13 (34) [*]	-3.0 (10)	-23 (10) ^{***,†,‡}
Lovastatin	40	16	-23 (6) [†]	-2 (27) [†]	4.6 (13)	-31 (7) ^{***,†,‡}
Atorvastatin	80	10	-42 (7)	-25 (22)	-0.1 (9)	-54 (9)
Lovastatin	80	11	-36 (6)	-13 (28)	8.0 (13)	-48 (8)

* $p \leq 0.05$; [†] $p \leq 0.01$, Dunnett's test of significance compared with atorvastatin at milligram-equivalent doses.

[†]Atorvastatin 10 mg statistically significantly better ($p \leq 0.02$).

[‡]Atorvastatin 20 mg statistically significantly better ($p \leq 0.01$).

Values are expressed as mean percent change from baseline.

TABLE III Comparison of Percent Change in Low-Density Lipoprotein (LDL) Cholesterol: Atorvastatin 10 and 20 mg Versus All Treatments

Treatment Group	Dose (mg)	Number of Patients	Mean* Percent Change from Baseline LDL Cholesterol	p Value vs Atorvastatin 10 mg	p Value vs Atorvastatin 20 mg
Atorvastatin	10	73	-38	Referent	—
Atorvastatin	20	51	-46	—	Referent
Fluvastatin	20	12	-17	0.0001	0.0001
Fluvastatin	40	12	-23	0.0001	0.0001
Lovastatin	20	16	-29	0.0019	0.0001
Lovastatin	40	16	-31	0.0197	0.0001
Lovastatin	80	11	-48	NS	NS
Pravastatin	10	14	-19	0.0001	0.0001
Pravastatin	20	41	-24	0.0001	0.0001
Pravastatin	40	25	-34	NS	0.0001
Simvastatin	10	70	-28	0.0001	0.0001
Simvastatin	20	49	-35	NS	0.0001
Simvastatin	40	61	-41	NS	0.0083

*Least-squares mean.

NS = atorvastatin not statistically significantly better.

for this study because of the impracticality of blinding 15 treatment arms. Efficacy end points were based on objective laboratory measurements.

Atorvastatin 10, 20, and 40 mg produced greater ($p \leq 0.01$) reductions in total and LDL cholesterol than the other reductase inhibitors studied at milligram-equivalent doses. Atorvastatin 10 mg produced greater ($p \leq 0.02$) reductions in LDL cholesterol than to simvastatin 10 mg, pravastatin 10 and 20 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg. The reduction in LDL cholesterol with atorvastatin 80 mg once daily (-54%) was numerically, but not statistically, greater than lovastatin administered as 40 mg twice daily (-48%) in a small sample of 10 and 11 patients, respectively.

The lipid-lowering effects observed in the present study are consistent with those seen in previous comparisons between HMG-CoA reductase inhibitors. Simvastatin 10 to 40 mg produced reductions in LDL cholesterol of 28% to 41%, pravastatin 10 to 40 mg

produced reductions in LDL cholesterol of 18% to 34%, lovastatin 20 to 40 mg produced reductions in LDL cholesterol of 25% to 38%, and fluvastatin 20 to 40 mg produced reductions in LDL cholesterol of 18% to 27%.²⁻¹³ Only the lovastatin 40 mg twice-a-day treatment group had a greater reduction in LDL cholesterol in this study (48%) than anticipated based on the results from a large clinical trial—Expanded Clinical Evaluation of Lovastatin (EXCEL)—in which reductions were reported as 40%.²⁵ The greater than expected LDL cholesterol reductions in this group may be partially explained by the small sample size.

An HMG-CoA reductase inhibitor's efficacy is measured by its ability to lower LDL cholesterol regardless of the amount of drug substance needed to accomplish this result (potency). Atorvastatin, administered in doses of 10 to 80 mg to patients with primary hypercholesterolemia, lowers LDL cholesterol by 35% to 61%.¹⁴⁻¹⁸ The present study, in conjunction with previous comparative studies that have

TABLE IV Withdrawals Due to Adverse Events

Treatment	Dose (mg)	No. of Patients	No. of Patients Withdrawn Due to Adverse Events	Event(s)	Relation to Therapy*
Atorvastatin	10	74	1	Abdominal pain/diarrhea	Possibly
Pravastatin	10	14	0		
Simvastatin	10	70	1	Depression/dizziness	Possibly
Atorvastatin	20	51	1	Myalgia	Definitely not
Pravastatin	20	42	1	Dizziness	Probably
Simvastatin	20	51	2	Hypertonia/nausea Abdominal pain/flatulence	Possibly Probably
Fluvastatin	20	12	0		
Lovastatin	20	16	0		
Atorvastatin	40	61	0		
Pravastatin	40	25	0		
Simvastatin	40	61	1	Angina	Unlikely
Fluvastatin	40	12	1	Back pain	Probably
Lovastatin	40	16	0		
Atorvastatin	80	10	0		
Lovastatin	80	11	0		

*Relation to therapy was judged by the investigator.

included atorvastatin, have clearly established atorvastatin as the most efficacious HMG-CoA reductase inhibitor for lowering LDL cholesterol.¹⁶⁻¹⁸

This study was not powered to detect differences in effects on triglycerides. The patient population studied consisted mostly (74%) of patients with elevated cholesterol without elevated triglycerides (mean baseline triglycerides ranged from 147 to 200 mg/dl [1.66 to 2.26 mmol/L]). Atorvastatin 10, 20, and 80 mg produced numerically, but not statistically, greater reductions in triglycerides than the other reductase inhibitors at milligram-equivalent doses, and statistically greater reductions in triglycerides at the 40 mg dose. As with LDL cholesterol, the reductions in triglycerides seen in all of the treatment groups in the present study are consistent with those reported in previous studies.²⁻¹⁸

Reductase inhibitors are generally well tolerated.²⁴ Clinically important adverse effects of the drugs include increases in serum transaminase concentrations and myositis, with or without complicating rhabdomyolysis. In the present study, no patient in any treatment arm experienced persistent clinically significant increases in serum transaminases. Most cases of significant elevations in serum transaminases have been reported to occur within the first 2 to 5 months of treatment, and the duration of this study (8 weeks) may not have been long enough to detect such cases.²⁶ In rare instances, severe creatine phosphokinase elevations (>10 times the upper limit of normal) and myositis have been associated with the use of reductase inhibitors.²⁷ In the present study, no subject experienced creatine phosphokinase concentrations >3 times the upper limit of normal, or myopathy.

Acknowledgment: We acknowledge and thank Boston Biostatistics Inc., Framingham, Massachusetts, for

their support and efforts related to the conduct of the study and the data analysis.

APPENDIX

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