Comparison of the Efficacy and Safety of *Rosuvastatin* Versus *Atorvastatin*, *Simvastatin*, and *Pravastatin* Across Doses (STELLAR* Trial)

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The primary objective of this 6-week, parallel-group, open-label, randomized, multicenter trial was to compare rosuvastatin with atorvastatin, pravastatin, and simvastatin across dose ranges for reduction of low-density lipoprotein (LDL) cholesterol. Secondary objectives included comparing rosuvastatin with comparators for other lipid modifications and achievement of National Cholesterol Education Program Adult Treatment Panel III and Joint European Task Force LDL cholesterol goals. After a dietary lead-in period, 2,431 adults with hypercholesterolemia (LDL cholesterol ≥160 and <250 mg/dl; triglycerides <400 mg/dl) were randomized to treatment with rosuvastatin 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; or pravastatin 10, 20, or 40 mg. At 6 weeks, across-dose analyses showed that rosuvastatin 10 to 80 mg reduced LDL cholesterol by a mean of 8.2% more than atorvastatin 10 to 80 mg, 26% more than pravastatin 10 to 40 mg, and 12% to 18% more than simvastatin 10 to 80 mg (all p <0.001). Mean percent changes in high-density lipoprotein cholesterol in the rosuvastatin groups were +7.7% to +9.6% compared with +2.1% to +6.8% in all other groups. Across dose ranges, rosuvastatin reduced total cholesterol significantly more (p <0.001) than all comparators and triglycerides significantly more (p <0.001) than simvastatin and pravastatin. Adult Treatment Panel III LDL cholesterol goals were achieved by 82% to 89% of patients treated with rosuvastatin 10 to 40 mg compared with 69% to 85% of patients treated with atorvastatin 10 to 80 mg; the European LDL cholesterol goal of <3.0 mmol/L was achieved by 79% to 92% in rosuvastatin groups compared with 52% to 81% in atorvastatin groups. Drug tolerability was similar across treatments. ©2003 by Excerpta Medica, Inc.

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At usual starting doses, rosuvastatin is more efficacious in reducing plasma low-density lipoprotein (LDL) cholesterol and achieving LDL cholesterol goals than atorvastatin, simvastatin, or pravastatin.[1–4] In a previous trial, atorvastatin was compared across its dose range with other statins (simvastatin, pravastatin, lovastatin, and fluvastatin), but patient numbers were small (10 to 73 per group) and pairwise comparisons were not prospectively planned.[5] Also, an across-the-dose range comparison of rosuvastatin with atorvastatin did not include enough patients per group (37 to 45) to allow for nonequivalent dose, pairwise comparisons.[6] The primary objective of this large, 6-week trial was to compare the LDL cholesterol reducing efficacy of the dose range of rosuvastatin with that of the Food and Drug Administration approved dose ranges of all 3 of the most widely prescribed statins: atorvastatin, simvastatin, and pravastatin. Secondary objectives included multiple, pairwise comparisons, safety assessments, and comparisons of efficacy for modifying other lipids and achieving National Cholesterol Education Program (NCEP) Adult Treatment Panel III[7] and European LDL cholesterol[8] goals.

METHODS

Trial design: This randomized, parallel-group, open-label, comparator-controlled trial (4522IL/0065) was conducted in 182 United States clinical centers between April 2001 and March 2002. After discontinuation of any lipid-lowering drugs and supplements, patients entered a 6-week, dietary lead-in period in which they were instructed to follow the NCEP Step I diet.[9] Patients who were compliant with the diet and met lipid criteria were randomized to 1 of 15 treatments taken orally once daily (before bedtime) for 6 weeks: rosuvastatin calcium (Crestor, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware; licensed from Shionogi & Co., Ltd., Osaka, Japan) 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40, or 80 mg (Lipitor, Pfizer,

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*STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin.

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New York, New York); simvastatin 10, 20, 40, or 80 mg (Zocor, Merck & Co, Whitehouse Station, New Jersey); and pravastatin 10, 20, or 40 mg (Pravachol, Bristol-Myers Squibb, Princeton, New Jersey). (At the time of trial initiation, the 80-mg dose of pravastatin was not approved by the Food and Drug Administration and therefore was not available for inclusion in this trial.) Sequential patient numbers were assigned at enrollment without assumptions about randomization eligibility. Site-specific randomization schedules were prespecified. Some patients were initially randomized to 3 cerivastatin groups, but the protocol and statistical analysis plan were amended and cerivastatin treatment was discontinued when cerivastatin was withdrawn from the market (August 2001). The incomplete data from these patients are not reported here.

Patients: Men and nonpregnant women with hypercholesterolemia who were ≥18 years of age were included in this trial. To be eligible for randomization, all patients were required to have stable LDL cholesterol concentrations of ≥160 and <250 mg/dl at the 2 most recent consecutive visits before randomization. Lipids were measured at up to 2 additional visits during the lead-in period if LDL cholesterol levels were not stable (measurements within 15% of each other). Triglyceride concentrations were required to be <400 mg/dl at all prerandomization visits.

Exclusion criteria included a history of sensitivity to statins; serious or unstable medical or psychological conditions that could compromise the patient's safety or successful trial participation; a history of heterozygous or homozygous familial hypercholesterolemia or familial dysbetalipoproteinemia; use of concomitant medications known to affect the lipid profile or present a potential safety concern; a history of drug or alcohol abuse; unexplained increases in creatine kinase to >3 times the upper limit of normal during the dietary lead-in period; alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin values ≥1.5 times the upper limit of normal during the dietary lead-in period; and participation in another investigational drug trial within 4 weeks of trial enrollment.

All participants gave informed consent before any trial procedure was initiated. The relevant institutional review boards approved the trial protocol and any amendments, and the trial was performed in accordance with the ethical principles consistent with good clinical practice.

Measurements and statistical analyses: Blood samples were collected before randomization (≥3 times), at randomization, and after 4 and 6 weeks of treatment. Patients were instructed to fast and avoid alcohol consumption and cigarette smoking for ≥12 hours before blood collection. All lipid and lipoprotein analyses were performed on plasma samples at a central laboratory (Medical Research Laboratories International, Highland Heights, Kentucky), which remained Part III certified by the Centers for Disease Control (Atlanta, Georgia)/National Heart, Lung, and Blood Institute (Bethesda, Maryland) throughout the trial.[10] High-density lipoprotein (HDL) cholesterol was isolated with heparin-2 manganese chloride.[11] LDL cholesterol was calculated by the Friedewald formula,[12] if triglyceride levels were <400 mg/dl, and measured using preparative ultracentrifugation at d = 1.006 if triglycerides were >400 mg/dl.[13]

The primary end point was percent change in LDL cholesterol from baseline to 6 weeks. Baseline was the mean of 3 values (the 2 values obtained at the 2 consecutive visits before randomization and the value obtained at randomization). All results shown are from the intention-to-treat population, which included patients randomized to the relevant treatment groups who received ≥1 dose of drug and had ≥1 postbaseline value. The last observation was carried forward if the patient did not complete 6 weeks of treatment. Per-protocol analyses that excluded patients who did not meet entrance criteria, were misrandomized, or had other major protocol violations or deviations were done as a robustness check of the primary intention-to-treat analysis.

A 6% difference between treatments in LDL cholesterol reduction was predefined as clinically meaningful.[14] Assuming a SD of 12%, and to show this 6% difference in each of 25 potential comparisons of interest with a power of 85%, it was estimated that approximately 150 patients needed to be randomized to each group to provide data on 141 patients.

To obtain the overall across-dose-range treatment effects, the average differences between log-dose slopes for percent changes from baseline in lipids were obtained for rosuvastatin versus each comparator in separate analyses. These analyses used an analysis of covariance model that included terms for treatment-by-log-dose interaction (indicator of dose response across the dose range), baseline, treatment, log dose, center, and treatment-by-center interaction. (Log dose was the log [base 10] of the drug dose in milligrams.) Then, if the treatment-by-log-dose interaction was not significant, it was concluded that the log-dose response percent reduction slopes for rosuvastatin and the comparator were parallel, the treatment-by-log-dose term was dropped from the model, and the remaining terms were reestimated. If the treatment effect was significant, it was used to estimate the distance between the dose-response slopes, which is reported as least-squares mean differences. However, if the treatment-by-log-dose interaction was significant (i.e., the log-dose slopes of rosuvastatin and the comparator were not parallel), the difference between each equivalent dose was analyzed separately with no adjustments for multiple testing.

In addition to the log-dose comparisons across dose ranges, selected specific, pairwise comparisons of interest between rosuvastatin doses and equivalent or higher doses of comparators were prospectively planned and performed using analysis of variance. To present clinically relevant results that would be consistent with proposed labeling at initial drug approval, 22 pairwise comparisons with only rosuvastatin 10, 20, and 40 mg were prospectively planned (before data availability). These comparisons were as follows: rosuvastatin 10 mg versus atorvastatin 10, 20, and 40

TABLE 1 Patient Characteristics at Randomization

	Rosuvastatin 10–40 mg (n = 480)	Rosuvastatin 10–80 mg (n = 643)	Atorvastatin 10–80 mg (n = 641)	Simvastatin 10–80 mg (n = 655)	Pravastatin 10–40 mg (n = 492)
Women	249 (52%)	333 (52%)	320 (50%)	333 (51%)	244 (50%)
Men	231 (48%)	310 (48%)	321 (50%)	322 (49%)	248 (50%)
Age (mean ± SD) (yrs)	58 ± 12	57 ± 12	58 ± 12	58 ± 12	57 ± 11
Age (range; yrs)	21–92	21–92	21–86	22–87	24–85
≥65 yrs	138 (29%)	182 (28%)	197 (31%)	191 (29%)	134 (27%)
White	412 (86%)	553 (86%)	548 (85%)	566 (86%)	420 (85%)
Black	37 (8%)	51 (8%)	54 (8%)	51 (8%)	48 (10%)
Hispanic	23 (5%)	29 (4%)	22 (3%)	26 (4%)	14 (3%)
Other	8 (2%)	10 (2%)	17 (3%)	12 (2%)	10 (2%)
BMI (mean ± SD)* (kg/m^2)	29 ± 6	29 ± 6	29 ± 6	29 ± 5	30 ± 5
BMI >30 (kg/m^2)	169 (35%)	225 (35%)	228 (36%)	225 (34%)	185 (38%)
Atherosclerosis†	84 (18%)	114 (18%)	129 (20%)	128 (20%)	88 (18%)
Diabetes mellitus	38 (8%)	47 (7%)	47 (7%)	47 (7%)	38 (8%)

*Body mass index (BMI) (killograms per square meter) was not calculated for the following numbers of patients: 4 in the rosuvastatin 10- to 40-mg group, 9 in the rosuvastatin 10- to 80-mg group, 6 in the atorvastatin 10- to 80-mg group, 3 in the simvastatin 10- to 80-mg group, and 2 in the pravastatin 10- to 40-mg group.
†History of angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, or intermittent claudication, or any documented carotid artery, peripheral vascular, or coronary artery disease.

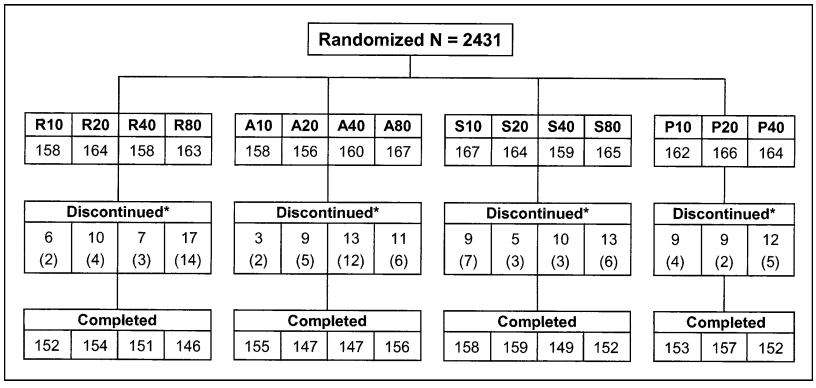

FIGURE 1. Patient disposition. *Numbers in parentheses are the number of patients who discontinued the study because of adverse events. Other reasons for withdrawal in the total patient population were: inclusion criteria not met (4); investigator's discretion (10); lost to follow-up (1); protocol noncompliance (16); withdrawal of consent (30); and randomized in error (2). A = atorvastatin; P = pravastatin; R = rosuvastatin; S = simvastatin. Numbers listed with the drugs represent the drug doses (in milligrams).

mg, simvastatin 10, 20, and 40 mg, and pravastatin 10, 20, and 40 mg; rosuvastatin 20 mg versus atorvastatin 20, 40, and 80 mg, simvastatin 20, 40, and 80 mg, and pravastatin 20 and 40 mg; and rosuvastatin 40 mg versus atorvastatin 40 and 80 mg, simvastatin 40 and 80 mg, and pravastatin 40 mg. Differences were significant if the p value was <0.002 (using Bonferroni's adjustment for multiple comparisons).[15] These pairwise comparisons were repeated for each lipid measurement.

To determine patients' NCEP LDL cholesterol goals, patients were classified into risk categories as defined by the NCEP Adult Treatment Panel III guidelines.[7] LDL cholesterol goals were <100 mg/dl for patients with coronary heart disease, coronary heart disease risk equivalents, or multiple risk factors that conferred a 10-year coronary heart disease risk of >20%; LDL cholesterol goals were <130 and <160 mg/dl for patients at lower risk. The European goal was <116 mg/dl (<3 mmol/L) according to the guidelines of the European Joint Task Force.[8] Pairwise comparisons (with the significance level adjusted for multiple comparisons) of the proportions of patients who achieved NCEP or European LDL cholesterol goals were performed with a logistic regression model that included terms for treatment, baseline, LDL cholesterol, and risk group.

Safety assessments included recording of treatment-emergent adverse events (adverse events that started or worsened during randomized treatment), hematologic and clinical chemistry measurements (performed in the same central laboratory), and physical examinations. Additional monitoring was performed for patients who had creatine kinase values >10 times the upper limit of normal or elevated ALT, AST, alkaline phosphatase, or bilirubin values. All patients who received any study drug were included in the safety analysis, and safety data were summarized descriptively without statistical analysis.

RESULTS

Patient characteristics: Baseline patient characteristics were very similar among groups. Table 1 shows characteristics by drug assignment. Of the 2,431 patients randomized to treatment, 94% completed the 6-week trial (Figure 1). Drug compliance as assessed by tablet counts was similar among treatments, and means of tablets taken ranged from 90.5% to 95.3%.

Efficacy: According to the dose-response analyses, mean differences between the LDL cholesterol dose-response slopes of rosuvastatin 10 to 80 mg versus

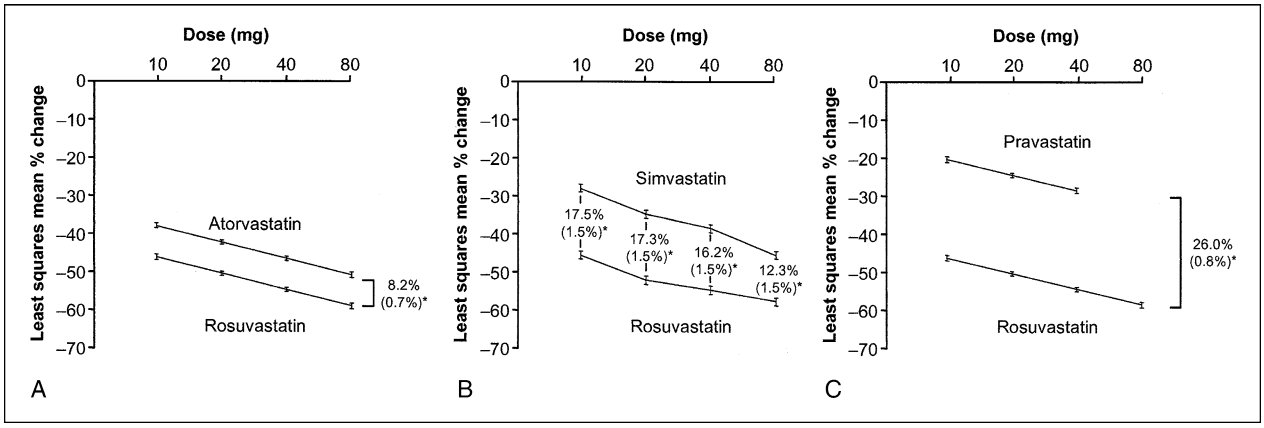

FIGURE 2. Least-squares mean (SE) percentage changes from baseline in LDL cholesterol at week 6, and mean differences (SE) across the dose ranges from the analysis of covariance (versus atorvastatin and pravastatin) and analysis of variance (versus simvastatin) for *(A)* rosuvastatin versus atorvastatin (95% confidence interval 6.8% to 9.7%), *(B)* rosuvastatin versus simvastatin, and *(C)* rosuvastatin versus pravastatin (95% confidence interval 24.4% to 27.5%). *p <0.001. (The difference across the dose ranges for the rosuvastatin vs simvastatin comparison could not be calculated, because the slopes were nonparallel.)

TABLE 2 Mean (SD) Baseline (BL) and Least-squares Mean Percentage Change from Baseline in LDL Cholesterol

	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin
10 mg				
n	156	158	165	160
BL (mean ± SD) (mg/dl)	188 ± 19	189 ± 18	189 ± 19	189 ± 18
% Change	−45.8	−36.8	−28.3	−20.1
p Value (CI)* vs rosuvastatin 10 mg		<0.001 (−13.5, −4.7)	<0.001 (−22.0, −13.2)	<0.001 (−30.1, −21.3)
20 mg				
n	160	155	162	164
BL (mean ± SD) (mg/dl)	187 ± 18	190 ± 20	189 ± 19	187 ± 17
% Change	−52.4	−42.6	−35.0	−24.4
p Value (CI)* vs rosuvastatin 10 mg		0.026 (−7.7, 1.3)	<0.001 (−15.2, −6.4)	<0.001 (−25.9, −17.1)
p Value (CI)* vs rosuvastatin 20 mg		<0.001 (−14.2, −5.3)	<0.001 (−21.7, −13.0)	<0.001 (−32.4, −23.7)
40 mg				
n	157	156	158	161
BL (mean ± SD) (mg/dl)	194 ± 19	189 ± 20	187 ± 16	190 ± 19
% Change	−55.0	−47.8	−38.8	−29.7
p Value (CI)* vs rosuvastatin 10 mg		0.164 (−2.4, 6.5)	<0.001 (−11.4, −2.6)	<0.001 (−20.6, −11.7)
p Value (CI)* vs rosuvastatin 20 mg		<0.002 (−9.0, −0.1)	<0.001 (−18.0, −9.1)	<0.001 (−27.1, −18.3)
p Value (CI)* vs rosuvastatin 40 mg		<0.001 (−11.6, −2.7)	<0.001 (−20.6, −11.7)	<0.001 (−29.7, −20.9)
80 mg				
n	NA	165	163	NA
BL (mean ± SD) (mg/dl)	NA	190 ± 20	190 ± 19	NA
% Change	NA	−51.1	−45.8	NA
p Value (CI)* vs rosuvastatin 20 mg		0.363 (−5.6, 3.1)	<0.001 (−11.0, −2.2)	
p Value (CI)* vs rosuvastatin 40 mg		0.006 (−8.3, 0.5)	<0.001 (−13.6, −4.8)	

Results of statistical analyses of 22 comparisons of percentage changes versus rosuvastatin 10, 20, and 40 mg are also shown.

*p Value and 99.8% confidence intervals (CI) for the difference between rosuvastatin and the comparator from an analysis of variance. p values <0.002 are statistically significant.

atorvastatin 10 to 80 mg and pravastatin 10 to 40 mg were significant (both p <0.001) (Figure 2). The log-dose slopes of rosuvastatin and simvastatin were not parallel, but equivalent doses were significantly different (Figure 2). All differences that were >6% were considered clinically significant.

In the pairwise, dose-to-dose comparisons with atorvastatin, rosuvastatin 10 mg reduced LDL cholesterol significantly more than atorvastatin 10 mg, rosuvastatin 20 mg reduced LDL cholesterol significantly more than atorvastatin 20 and 40 mg, and rosuvastatin 40 mg reduced LDL cholesterol significantly more than atorvastatin 40 mg (Table 2). In all but 1 of the other pairwise comparisons with atorvastatin (rosuvastatin 10 vs atorvastatin 40 mg), rosuvastatin produced numerically greater LDL cholesterol reductions, but these differences were not significantly different (Table 2). Rosuvastatin reduced LDL cholesterol significantly more than simvastatin and pravastatin in all 14 pairwise comparisons analyzed (Table 2). The best LDL cholesterol reduction (55%) was achieved in the rosuvastatin 40-mg group and was not significantly different (p = 0.006) from the next highest LDL cholesterol reduction (51%) observed in the atorvastatin 80-mg group.

Rosuvastatin 40 mg had the most effect and ator-

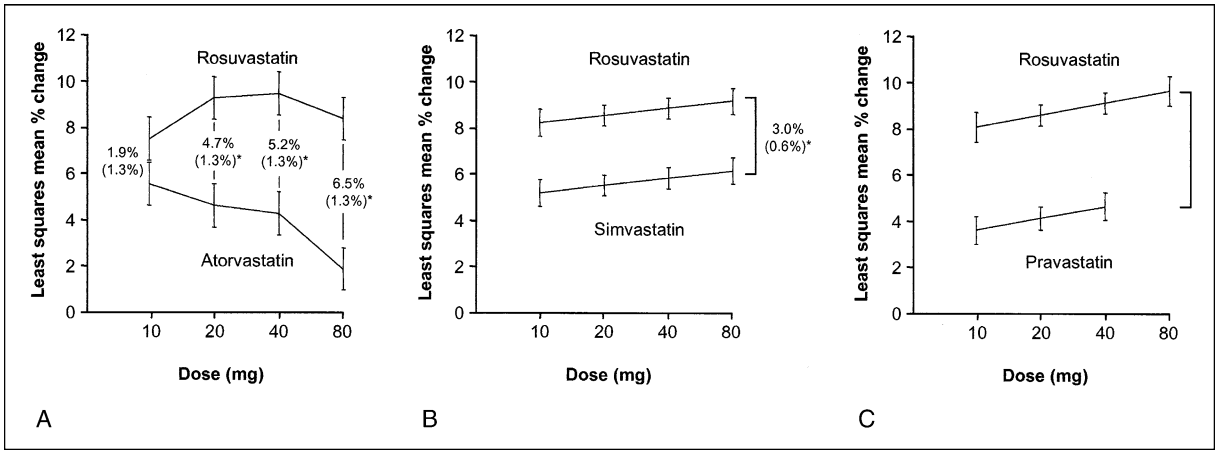

FIGURE 3. Least-squares mean (SE) percentage changes from baseline in HDL cholesterol at week 6 across dose ranges, and mean differences (SE) from analysis of variance (versus atorvastatin) or covariance (versus simvastatin and pravastatin) for *(A)* rosuvastatin versus atorvastatin for equivalent doses (the difference across the dose range for the rosuvastatin vs atorvastatin comparison could not be calculated, because the slopes were nonparallel), *(B)* rosuvastatin versus simvastatin, and *(C)* rosuvastatin versus pravastatin. *p <0.001.

vastatin 80 mg had the least effect on HDL cholesterol (Figure 3). Across dose ranges, the HDL cholesterol increasing effect of rosuvastatin was consistent across the dose range in contrast to atorvastatin and was significantly higher ($p < 0.001$) compared with simvastatin and pravastatin (Figure 3). The log-dose analysis across dose ranges showed that rosuvastatin 10 to 80 mg reduced total cholesterol 4.7% more than atorvastatin 10 to 80 mg and 18.7% more than pravastatin 10 to 40 mg (both $p < 0.001$) (data not shown). The log-dose slopes of rosuvastatin 10 to 80 mg and simvastatin 10 to 80 mg were not parallel, and differences ranged from 9.0% (80-mg doses) to 12.5% (10-mg doses). Across the dose ranges, rosuvastatin 10 to 80 mg reduced triglycerides 7.5% more than simvastatin and 13.1% more than pravastatin (both $p < 0.001$), but the log-dose slopes for triglyceride reductions were not different between rosuvastatin and atorvastatin (data not shown). Pairwise comparisons among groups for HDL cholesterol, total cholesterol, and triglycerides are shown in Table 3.

The per-protocol analyses included 122 to 138 patients per group. The results from these analyses were consistent with those obtained in the intention-to-treat analyses and supported the conclusions based on the primary analyses.

In this analysis, the highest proportions of patients (89%) who met NCEP LDL cholesterol goals were in the rosuvastatin 20- and 40-mg groups (Figure 4). The percentage of patients who reached NCEP LDL cholesterol goals in the rosuvastatin 10-mg group (82%) was similar to the highest percentages in the atorvastatin and simvastatin groups (85% and 82%, respectively). Overall, 29% of these patients had goals of <100 mg/dl. Also, the highest percentages of patients reaching the European goal of <116 mg/dl (<3.0 mmol/L) were in the rosuvastatin 20- and 40-mg groups (92% and 91%, respectively) (Figure 5). The percentage of patients (79%) who reached this goal with rosuvastatin 10 mg was similar to the percentage who reached this goal with the highest doses of atorvastatin and simvastatin (81% and 77%, respectively).

Safety: Overall, trial treatments were well tolerated. The percentages of patients who reported adverse events during randomized treatment were similar among groups and ranged from 40% to 56% per group and were 46% in the total study population. The percentages of patients who withdrew from treatment because of adverse events were also similar among groups (Figure 1). Twenty-nine patients had serious adverse events; the number per group ranged from 0 (rosuvastatin 40-mg group) to 5 (simvastatin 40-mg group). Two of these patients with serious adverse events died (1 who received simvastatin 10 mg and 1 who received atorvastatin 40 mg) from causes unrelated to treatment (cardiovascular disease). Two patients in the rosuvastatin 80-mg group developed acute renal failure of uncertain etiology. One of them required a short interval of dialysis, and both patients recovered after discontinuation of medications.

The other adverse events reported were generally mild and similar across groups. The most common adverse events were pain, pharyngitis, myalgia, and headache, which were reported by 6%, 5%, 4%, and 3%, respectively, of overall patients. The highest number (>5%) of patients reporting myalgia were in the groups receiving rosuvastatin 80 mg (7.3%), atorvastatin 20 mg (6.4%), atorvastatin 80 mg (5.4%), or pravastatin 20 mg (5.4%). The lowest numbers (<2%) of patients reporting myalgia were in the rosuvastatin 40-mg and simvastatin 40-mg groups.

Changes in clinical laboratory results were generally small. Five patients (atorvastatin 80 mg, 2 patients; atorvastatin 20 mg, 1 patient; simvastatin 40 mg, 1 patient; and simvastatin 80 mg, 1 patient) had clinically important ALT elevations (>3 times the upper limit of normal at 2 consecutive visits). No cases of myopathy (creatine kinase >10 times the upper limit of normal with associated muscle symptoms) were observed. Three patients (rosuvastatin 80

TABLE 3 Mean ± SD Baseline (BL) and Least-squares Mean Percentage Changes from BL in HDL Cholesterol, Triglycerides, and Total Cholesterol

	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin
HDL				
10 mg				
BL (mean ± SD) (mg/dl)	51 ± 11	50 ± 12	51 ± 12	50 ± 13
% Change	+7.7	+5.7	+5.3	+3.2*
20 mg				
BL (mean ± SD) (mg/dl)	51 ± 11	50 ± 12	50 ± 12	49 ± 11
% Change	+9.5	+4.8†	+6.0	+4.4†
40 mg				
BL (mean ± SD) (mg/dl)	50 ± 12	50 ± 11	51 ± 11	50 ± 10
% change	+9.6	+4.4†‡	+5.2†‡	+5.6†‡
80 mg				
BL (mean ± SD) (mg/dl)	NA	51 ± 13	51 ± 12	NA
% Change	NA	+2.1†‡	+6.8	NA
Triglycerides				
10 mg				
BL (mean ± SD) (mg/dl)	179 ± 62	174 ± 59	174 ± 59	187 ± 63
% Change	−19.8	−20.0	−11.9	−8.2*
20 mg				
BL (mean ± SD) (mg/dl)	180 ± 72	176 ± 64	182 ± 65	179 ± 67
% Change	−23.7	−22.6	−17.6	−7.7*†
40 mg				
BL (mean ± SD) (mg/dl)	183 ± 59	178 ± 64	172 ± 61	181 ± 63
% Change	−26.1	−26.8	−14.8†‡	−13.2†‡
80 mg				
BL (mean ± SD) (mg/dl)	NA	181 ± 66	178 ± 64	NA
% Change	NA	−28.2	−18.2	NA
Total cholesterol				
10 mg				
BL (mean ± SD) (mg/dl)	275 ± 23	274 ± 24	275 ± 24	276 ± 24
% Change	−32.9	−27.1*	−20.3*	−14.7*
20 mg				
BL (mean ± SD) (mg/dl)	274 ± 24	275 ± 27	276 ± 24	271 ± 21
% Change	−37.6	−31.8†	−25.7*†	−17.2*†
40 mg				
BL (mean ± SD) (mg/dl)	280 ± 22	275 ± 25	272 ± 23	276 ± 24
% Change	−40.2	−35.8‡	−27.9*†‡	−21.5*†‡
80 mg				
BL (mean ± SD), mg/dl	NA	279 ± 26	277 ± 24	NA
% Change	NA	−38.9	−32.9†‡	NA

Pairwise comparisons were performed between rosuvastatin 10 mg and atorvastatin 10, 20, and 40 mg, simvastatin 10, 20, and 40 mg, and pravastatin 10, 20, and 40 mg; between rosuvastatin 20 mg and atorvastatin 20, 40, and 80 mg, simvastatin 20, 40, and 80 mg, and pravastatin 20 and 40 mg; and between rosuvastatin 40 mg and atorvastatin 40 and 80 mg, simvastatin 40 and 80 mg, and pravastatin 40 mg.

*Significantly different versus rosuvastatin 10 mg; †significantly different versus rosuvastatin 20 mg; ‡significantly different versus rosuvastatin 40 mg (p values <0.002 are statistically significant).

mg, 1 patient; and simvastatin 10 mg, 2 patients) had a clinically important elevation (>10 times the upper limit of normal) of creatine kinase, without associated muscle-related symptoms.

DISCUSSION

This multicenter trial, which is the largest trial of its kind to date comparing the lipid-modifying efficacy of statins, showed the greater efficacy of rosuvastatin in reducing LDL cholesterol, compared with atorvastatin, simvastatin, and pravastatin across dose ranges. The significantly greater LDL cholesterol reduction achieved with rosuvastatin 10 to 80 mg, compared with atorvastatin 10 to 80 mg, which was an average difference of 8.2% across the dose-range slopes, exceeded the predefined clinically meaningful difference of 6% and was similar to the 8.4% greater reduction observed by Schneck et al.[6] Also, the greater LDL cholesterol reductions achieved across dose ranges with rosuvastatin than with simvastatin and pravastatin confirmed the relative differences in the LDL cholesterol reducing efficacy of these statins, which has been previously shown.[3–5] Pairwise comparisons in this trial showed that a dose of the comparators that was 2 or 4 times higher than rosuvastatin 10 and 20 mg did not result in significantly greater LDL cholesterol reductions. These greater LDL cholesterol reductions with rosuvastatin than with the comparators resulted in a higher percentage of patients who achieved their NCEP and European LDL cholesterol goals. Importantly, rosuvastatin can achieve most of these lipid-modifying benefits at a dose of 10 mg/day.

As rosuvastatin doses increased to 40 mg, HDL

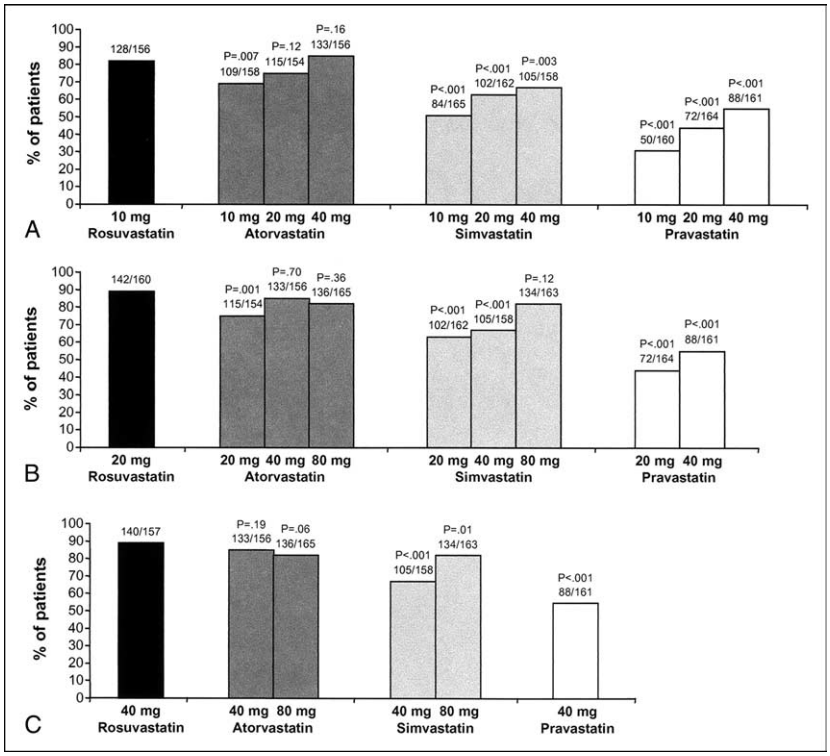

FIGURE 4. Percentages of patients who met LDL cholesterol NCEP's Adult Treatment Panel III goals at the end of treatment, and results of logistic regression analyses for 22 comparisons versus *(A)* rosuvastatin 10 mg, *(B)* rosuvastatin 20 mg, and *(C)* rosuvastatin 40 mg. (p values <0.002 are statistically significant.)

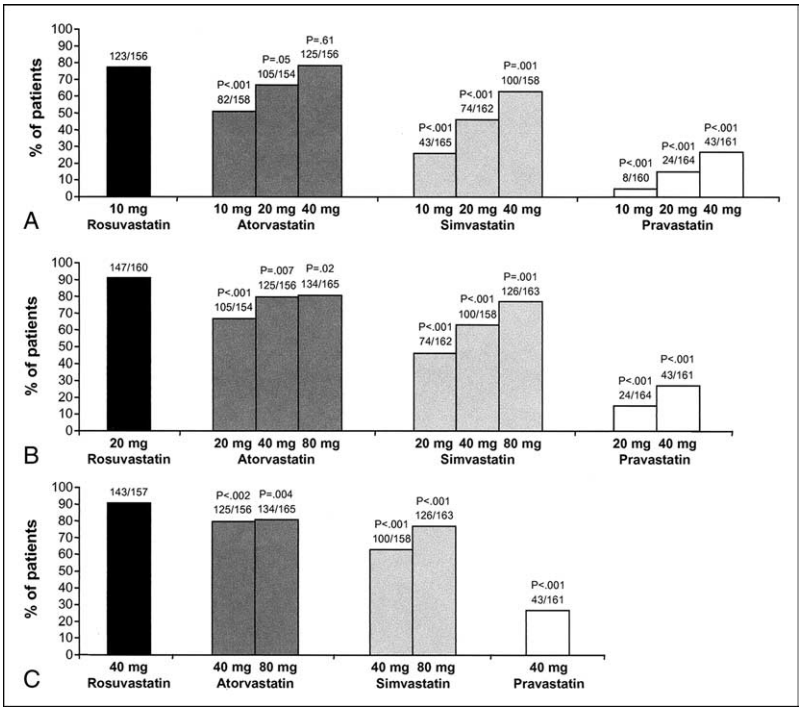

FIGURE 5. Percentages of patients who had LDL cholesterol values below the European goal of 116 mg/dl (3.0 mmol/L) at the end of treatment, and results of logistic regression analyses for 22 comparisons versus *(A)* rosuvastatin 10 mg, *(B)* rosuvastatin 20 mg, and *(C)* rosuvastatin 40 mg. (p values <0.002 are statistically significant.).

cholesterol changes from baseline were increased, in contrast with atorvastatin, which produced lesser percentage increases in HDL cholesterol levels with increased doses. This attenuation of the increase in HDL cholesterol levels with higher doses of atorvastatin has been shown previously in other well-controlled, randomized, double-blind trials.[5,6,16] When rosuvastatin was compared across the dose ranges with simvastatin or pravastatin, the log-dose slopes were parallel, and HDL cholesterol was increased significantly more with rosuvastatin. Rosuvastatin also produced significantly better reductions in total cholesterol and similar or significantly better reductions in triglycerides, compared with atorvastatin, simvastatin, and pravastatin.

Because of the open-label design, patients' reporting of adverse events could have been affected by their awareness of their drug treatment or expectations from previous experiences with statin drugs. However, the numbers and nature of adverse events were generally consistent with those observed in previous double-blind trials[2,3,17] and not different among drug treatments. The number of reported adverse events tended to be highest with higher doses. Likewise, although a few patients had elevated transaminase and creatine kinase levels, laboratory value results were generally similar among the groups, and no cases of myopathy were observed.

Although the trial treatments were administered in an open-label manner, the laboratory analyses and data analyses were blinded to patients and investigators, thereby removing analysis bias. Furthermore, the potential for randomization bias was minimized by the assignment of sequential numbers to patients at enrollment before trial eligibility was determined and the use of a prespecified randomization schedule that took the choice of treatment away from the investigator.

The 6-week study period was shorter than in most previous studies of statin efficacy[2,3,5,18]; however, it is well established that sta-

tins exhibit most of their LDL cholesterol reducing effects within 2 weeks and produce full effects by 4 to 6 weeks.[2,3] Therefore, 6 weeks was considered an adequate time to show the relative LDL cholesterol reducing efficacy of the statins studied.

A strength of this trial was the absence of an upper age limit for participants, which resulted in the inclusion of many patients in older age categories. The most important strength of this trial was the study design, which included many patients per treatment group and the prospectively determined ability to make multiple comparisons across doses in a statistically valid manner. Because a greater number of analyses increase the chances that a significant difference will be found among groups, the number of pairwise comparisons was limited to those comparisons of most interest. The use of the Bonferroni adjustment of the significance level resulted in a conservative interpretation and increased the confidence in the results.

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APPENDIX

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1. Davidson M, Ma P, Stein EA, Gotto AM Jr, Raza A, Chitra R, Hutchinson H. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol* 2002;89:268–275.

2. Olsson AG, Istad H, Luurila O, Ose L, Stender S, Tuomilehto J, Wiklund O, Southworth H, Pears J, Wilpshaar JW, on behalf of the Rosuvastatin Investigators Group. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J* 2002;144:1044–1051.

3. Brown WV, Bays HE, Hassman DR, McKenney J, Chitra R, Hutchinson H, Miller E, for the Rosuvastatin Study Group. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J* 2002;144:1036–1043.

4. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H. Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. *J Cardiovasc Risk* 2001;8:383–390.

5. Jones P, Kafonek S, Laurora I, Hunninghake D, for the CURVES Investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;81:582–587.

6. Schneck DW, Knopp RH, Ballantyne CM, McPherson R, Chitra RR, Simonson SG. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. *Am J Cardiol* 2003;91:33–41.

7. NCEP Expert Panel. Third Report of National Cholesterol Education Program (NCER) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. *Circulation* 2002;106:3143–3421.

8. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorola K. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J* 1998;19:1434–1503.

9. Remmell PS, Gorder DD, Hall Y, Tillotson JL. Assessing dietary adherence in the Multiple Risk Factor Intervention Trial (MRFIT). I. Use of a dietary monitoring tool. *J Am Diet Assoc* 1980;76:351–356.

10. Myers GL, Cooper GR, Winn CL, Smith SJ. The Centers for Disease Control–National Heart, Lung, and Blood Institute Lipid Standardization Program: an approach to accurate and precise lipid measurements. *Clin Lab Med* 1989;9:105–135.
11. Warnick G, Albers J. A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high-density lipoprotein cholesterol. *J Lipid Res* 1978;19:65–76.
12. Friedewald WT, Levy RI, Frederickson DS. Estimation of concentration of low density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
13. Lipid Research Clinics Program. Manual of Operations: Lipid and Lipoprotein Analysis. Washington, DC: US Department of Health, Education, and Welfare. Publication no. NIH 75-628, 1982.
14. Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341:498–511.
15. Miller RG Jr. Simultaneous Statistical Inference. 2nd Ed. New York, NY: Springer-Verlag, 1981.
16. Illingworth DR, Crouse JR III, Hunninghake DB, Davidson MH, Escobar ID, Stalenhoef AF, Paragh G, Ma PT, Liu M, et al, for the Simvastatin Atorvastatin HDL Study Group. A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr Med Res Opin* 2001;17:43–50.
17. Olsson AG, Pears J, McKellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol* 2001;88:504–508.
18. Hunninghake D, Bakker-Arkema RG, Wigand JP, Drehobl M, Schrott H, Early JL, Abdallah P, McBride S, Black DM. Treating to meet NCEP-recommended LDL cholesterol concentrations with atorvastatin, fluvastatin, lovastatin, or simvastatin in patients with risk factors for coronary heart disease. *J Fam Pract* 1998;47:349–356.