Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: The Vytorin Versus Atorvastatin (VYVA) Study

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Background Low-density lipoprotein cholesterol (LDL-C) is the primary therapeutic target in the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines. This study tested the hypothesis that ezetimibe/simvastatin, a lipid-lowering agent that inhibits both intestinal cholesterol absorption and cholesterol synthesis, provides greater LDL-C reductions than atorvastatin across dose ranges.

Methods This multicenter, double-blind, 6-week parallel-group study randomized 1902 patients with LDL-C above ATP III goal to atorvastatin (10, 20, 40, or 80 mg) or to ezetimibe/simvastatin (10/10, 10/20, 10/40, or 10/80 mg). Patients were stratified by prerandomization LDL-C level.

Results At each milligram-equivalent statin dose comparison, and averaged across doses, ezetimibe/simvastatin provided greater LDL-C reductions (47%-59%) than atorvastatin (36%-53%). Ezetimibe/simvastatin 10/40 and 10/80 mg also provided significantly greater high-density lipoprotein cholesterol (HDL-C) increases than atorvastatin 40 and 80 mg. Triglyceride reductions were similar for all comparisons. More ezetimibe/simvastatin than atorvastatin patients with coronary heart disease (CHD) or CHD risk equivalents attained the ATP III LDL-C goal of <100 mg/dL and the optional LDL-C target of <70 mg/dL. C-reactive protein reductions were similar between treatment groups. Consecutive elevations in alanine aminotransferase and/or aspartate aminotransferase occurred in significantly more atorvastatin patients than ezetimibe/simvastatin patients. No myopathy or liver-related adverse events led to study discontinuation with either drug.

Conclusions Ezetimibe/simvastatin was more effective than atorvastatin in lowering LDL-C at each dose comparison and provided greater increases in HDL-C at the 40- and 80-mg statin dose. Ezetimibe/simvastatin is a highly efficacious, well-tolerated treatment option for hypercholesterolemic patients. (Am Heart J 2005;149:464-73.)

Guidelines emphasize low-density lipoprotein cholesterol (LDL-C) lowering as an essential strategy for cardiovascular risk reduction.[1] In addition, recent clinical trial experience has prompted a consideration for optional lower LDL-C targets as a reasonable clinical strategy in persons at very high risk for coronary heart disease (CHD) events.[2] Although large observational population studies in patients with CHD have shown that lipid-lowering treatment strategies and LDL-C goal attainment rates have improved over time, a large number of individuals remain above goal.[3] Logically, the proportion of very high risk patients who will achieve the optional goal of <70 mg/dL is expected to be even lower. The possibility of combining cholesterol-lowering medications to attain greater LDL-C lowering is therefore an important therapeutic option for more effective intervention on cardiovascular risk reduction for high– and very high–risk patients. One currently available approach is the simultaneous intervention by 2 complementary mechanisms regulating plasma cholesterol levels: intestinal cholesterol absorption and hepatic cholesterol synthesis.

Ezetimibe is the first entity in a new class of agents that lower cholesterol by blocking its intestinal absorption.[4,5] Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor that lowers cholesterol by

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inhibiting the rate-limiting enzyme in cholesterol synthesis. Single pill combining ezetimibe and simvastatin (Vytorin, Merck/Schering Plough Pharmaceuticals, West Point, Pa), recently approved by the US Food and Drug Administration, provides dual inhibition of the 2 pathways, thus, providing an opportunity for even greater reductions in LDL-C.[6,7]

This study examined the efficacy of reducing LDL-C with the combination tablet of ezetimibe/simvastatin compared with statin monotherapy with atorvastatin in patients with hypercholesterolemia. Also evaluated was the effectiveness of ezetimibe/simvastatin in achievement of LDL-C goals, including, in patients with CHD or CHD risk equivalent as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, a post hoc analysis of an optional LDL-C target of <70 mg/dL.

Methods

Study design

This multicenter, double-blind, randomized, active-controlled, 8-arm parallel-group study (10 weeks, with 4-week placebo/diet run-in period followed by 6 weeks of active treatment) was designed to evaluate the efficacy and safety of ezetimibe/simvastatin versus atorvastatin monotherapy across their respective dose ranges in patients with hypercholesterolemia. The protocol was approved by appropriate institutional review boards, and all patients provided written informed consent before initiation of any study procedure. Patients discontinued fibrate therapy 9 weeks, and all other lipid-lowering therapy 7 weeks, before the start of the study. Patients with hypercholesterolemia not at their LDL-C goal as defined by NCEP ATP III guidelines,[1] after a 4-week placebo/diet run-in period, were randomized by an equal allocation to 8 treatment arms: ezetimibe/simvastatin (10/10, 10/20, 10/40, and 10/80 mg) and atorvastatin (10, 20, 40, and 80 mg). Patients were centrally randomized using an interactive voice response system and stratified according to visit 2 (week −1) LDL-C level (≥130 and <160, ≥160 and <190, and ≥190 mg/dL) to achieve balance among treatment groups.

With a sample size of approximately 205 patients per treatment arm (~1640 total patients), this study had >99% statistical power to detect a 5% treatment difference in LDL-C between ezetimibe/simvastatin and atorvastatin averaged across their dose ranges and 95% power to detect a 5% difference at milligram-equivalent statin doses, assuming an SD of 14% and a significance level of .05 (2-sided). The study had 90% power to detect a 2.0% treatment difference in high-density lipoprotein cholesterol (HDL-C) between ezetimibe/simvastatin and atorvastatin averaged across their dose ranges, assuming a 12.5% SD and a significance level of .05 (2-sided).

Study population

Men and women, 18 to 79 years, with an LDL-C level at or above drug treatment thresholds established by NCEP ATP III[1] were eligible for enrollment if they met the following criteria: established CHD or CHD risk equivalent with an LDL-C ≥130 mg/dL; no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD ≥10% and ≤20% with an LDL-C ≥130 mg/dL; no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD <10% with an LDL-C ≥160 mg/dL; and no established CHD or CHD risk equivalent, with <2 risk factors, and with LDL-C ≥190 mg/dL. Other criteria included fasting serum triglyceride (TG) level ≤350 mg/dL, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK) level ≤1.5 times the upper limit of normal, serum creatinine level ≤1.5 mg/dL, and hemoglobin A1C <9.0% in patients with diabetes.

Table I. Baseline patient characteristics for all randomized patients

	All atorvastatin (n = 951)	All ezetimibe/simvastatin (n = 951)
Age (y)	58.5 ± 10.2	59.0 ± 10.6
Sex		
Male	498 (52.4)	496 (52.2)
Race		
White	818 (86.0)	821 (86.3)
Black	71 (7.5)	72 (7.6)
Hispanic	45 (4.7)	42 (4.4)
Other	17 (1.8)	16 (1.7)
NCEP ATP III risk category		
CHD/CHD risk equivalent	438 (46.1)	441 (46.4)
2+ CHD risk factors	348 (36.6)	348 (36.6)
0-1 Risk factors	165 (17.4)	162 (17.0)
Visit 2 LDL-C strata		
≥130 to <160 mg/dL	303 (31.9)	302 (31.8)
≥160 to <190 mg/dL	325 (34.2)	325 (34.2)
≥190 mg/dL	323 (34.0)	324 (34.1)
Body mass index (kg/m^2)	30.1 ± 5.6	29.8 ± 5.5

Data are given as mean ± SD or n (%).

Efficacy and safety assessments

The primary efficacy end point was the percent change from baseline to the end of the 6-week treatment period in LDL-C for patients treated with ezetimibe/simvastatin or atorvastatin averaged across all doses. The secondary efficacy end points included the percent change from baseline in LDL-C at each milligram-equivalent statin dose comparison and at the ezetimibe/simvastatin 10/20 mg versus atorvastatin 10 mg dose comparison and the percent change from baseline in HDL-C at each milligram-equivalent statin dose comparison, averaged across all doses, and at the ezetimibe/simvastatin 10/20 mg versus atorvastatin 10 mg dose comparison after 6 weeks of treatment. Other efficacy measures included treatment comparisons (similar to those stated above) of the percentage of patients who achieved the NCEP ATP III goal for LDL-C per their risk category and treatment comparisons of percent change from baseline in total cholesterol (TC) and TG after 6 weeks of treatment.

In light of recently published and updated NCEP ATP III treatment recommendations,[2] an additional analysis with respect to the proportion of patients who attained an optional target for LDL-C (<70 mg/dL) was further explored in the subgroup of patients with CHD or CHD risk equivalents per

Table II. Summary of efficacy results in the modified intention-to-treat population

Statistics	Atorva 10 mg (n = 235)	EZ/Simva 10 mg (n = 230)	Atorva 20 mg (n = 230)	EZ/Simva 20 mg (n = 233)	Atorva 40 mg (n = 232)	EZ/Simva 40 mg (n = 236)	Atorva 80 mg (n = 230)	EZ/Simva 80 mg (n = 224)	All Atorva (n = 927)	EZ/All Simva (n = 923)
LDL-C										
Baseline mean (SD)	175.3 (36.4)	176.7 (33.0)	178.2 (38.7)	178.5 (43.5)	179.7 (38.1)	177.9 (36.1)	182.7 (38.3)	177.7 (38.4)	178.9 (37.9)	177.7 (37.9)
% change from baseline*	−36.1	−47.1‡	−43.7	−50.6‡	−48.3	−57.4‡	−52.9	−58.6‡	−45.3	−53.4‡
HDL-C baseline mean (SD)	48.2 (12.5)	49.2 (12.1)	48.7 (11.7)	49.1 (13.2)	50.2 (13.1)	49.0 (12.2)	48.0 (10.2)	49.1 (12.8)	48.8 (11.9)	49.1 (12.6)
% change from baseline*	6.9	7.7	5.1	7.2	3.8	9.0‡	1.4	7.6‡	4.3	7.9‡
TC baseline mean (SD)	261.6 (39.9)	264.1 (37.5)	265.1 (44.5)	264.6 (47.6)	264.8 (43.0)	265.0 (41.6)	266.6 (40.6)	263.2 (40.6)	264.5 (42.0)	264.2 (42.0)
% change from baseline	−21.3	−25.5‡	−24.8	−25.4‡	−23.6	−27.3‡	−32.1	−30.8	−25.5	−27.4‡
TG† baseline median (Robust SD)	171.0 (95.8)	174.0 (93.0)	173.5 (100.5)	167.0 (98.6)	161.0 (95.3)	172.0 (97.7)	165.5 (80.0)	170.0 (87.0)	167.0 (94.0)	171.0 (94.9)
% change from baseline	−21.3	−25.5	−24.8	−25.4	−23.6	−27.3	−32.1	−30.8	−25.5	−27.4

EZ, Ezetimibe 10 mg; *All Atorva*, atorvastatin (10, 20, 40, and 80 mg) pooled across all doses; *EZ/All Simva*, ezetimibe/simvastatin (10/10, 10/20, 10/40, and 10/80 mg) pooled across all doses.
*Percent change from baseline is least square means based on ANOVA models with terms for treatment and week −1 LDL-C stratum (≥130 to <160, ≥160 to <190, and ≥190 mg/dL), and *P* values for the between-treatment differences were obtained from the same ANOVA models.
†Nonparametric results are presented. Robust SD = interquartile range/1.075.
‡*P* < .001 for between-treatment difference with same dose of atorvastatin.

NCEP ATP III definition. Data are also presented for CHD or CHD risk equivalent patients who achieved the currently recommended LDL-C target of <100 mg/dL. An additional post hoc analysis measured high-sensitivity C-reactive protein (hs-CRP) levels from archived baseline and postbaseline (after 6 weeks of treatment) plasma samples from 1832 patients.

Safety variables included the incidence of any clinical or laboratory adverse events. Investigators defined clinical adverse events based on signs, symptoms, and similar observations; laboratory adverse events were based on laboratory test results. Drug-related adverse events were categorized by blinded investigators as being possibly, probably, or definitely related to study treatment. Prespecified key laboratory safety variables included the incidence of consecutive elevations of ≥3 times the upper limit of normal for ALT or AST, and CK elevations ≥10 times the upper limit of normal, with or without muscle symptoms.

Laboratory methods

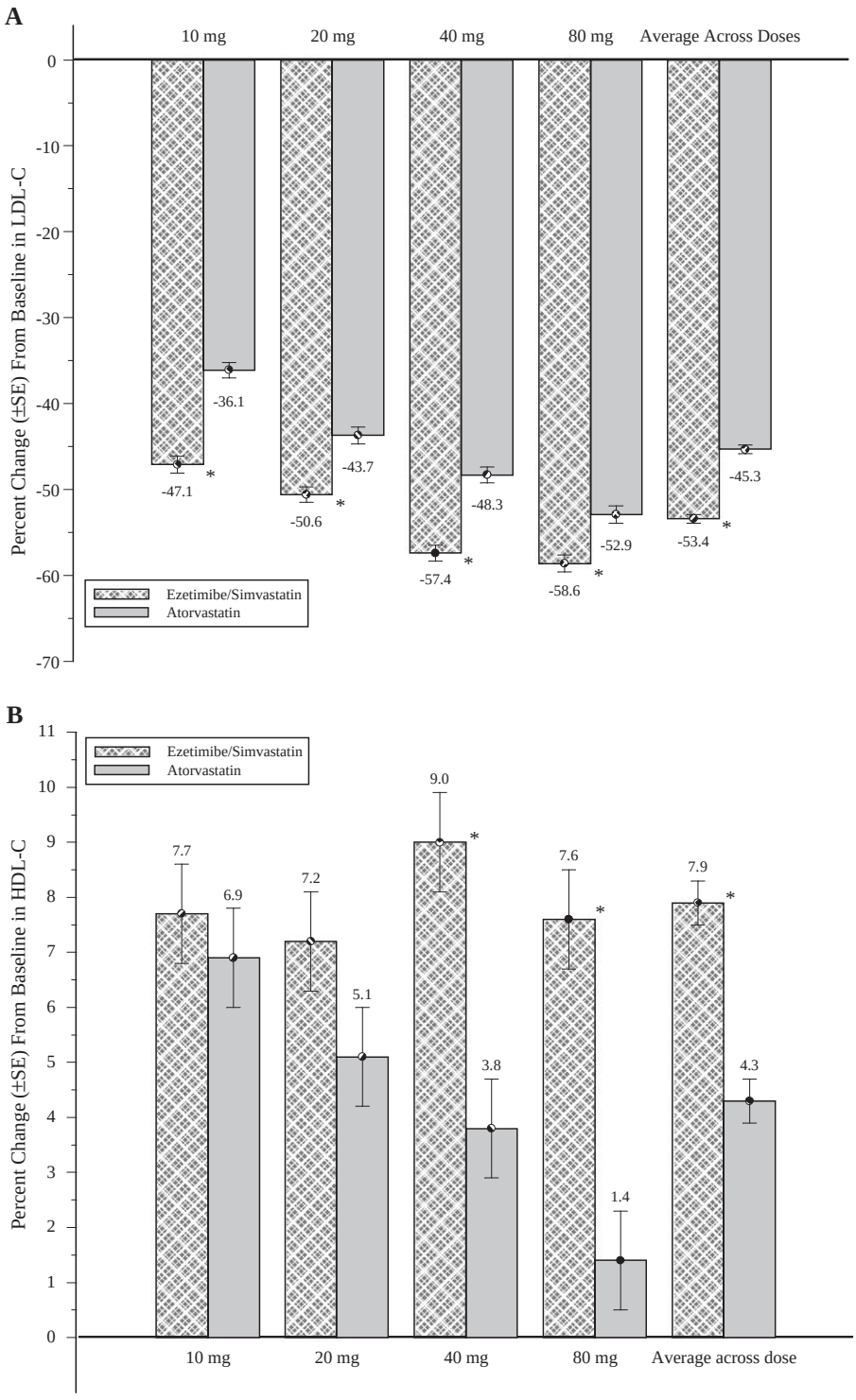
Analyses of samples for clinical laboratory measurements were performed at a certified central laboratory (Medical Research Laboratories International, Highland Heights, Ky). Lipid measurements were performed according to standards specified by the National Heart, Lung, and Blood Institute and Centers for Disease Control and Prevention.[8] LDL-C values were calculated by the method of Friedewald et al[9]: LDL-C = TC − (HDL-C + TG/5). When TG >400 mg/dL, direct LDL-C measurements were obtained using the beta-quantitative method. hs-CRP measurements were performed on archived samples obtained at baseline and at 6 weeks after treatment, stored at −70 °C, and analyzed at the same time by high-sensitivity immunonephelometry (Dade Behring, Inc., Deerfield, Ill), as previously described.[10]

Data and statistical analyses

For the efficacy analyses, a modified intent-to-treat (MITT) population was used, which included all randomized patients who had a valid baseline and at least one valid postbaseline measurement. The treatment comparison was carried out using an analysis of variance (ANOVA) model with terms for treatment (8 levels: atorvastatin 10, 20, 40, and 80 mg; ezetimibe/simvastatin: 10/10, 10/20, 10/40, and 10/80 mg) and week −1 LDL-C stratum (≥130 to <160, ≥160 to <190, and ≥190 mg/dL). With the appropriate contrast, this model compared the treatment efficacy and provided an estimate of the between-treatment difference, as well as 95% confidence intervals (CIs) for the difference.

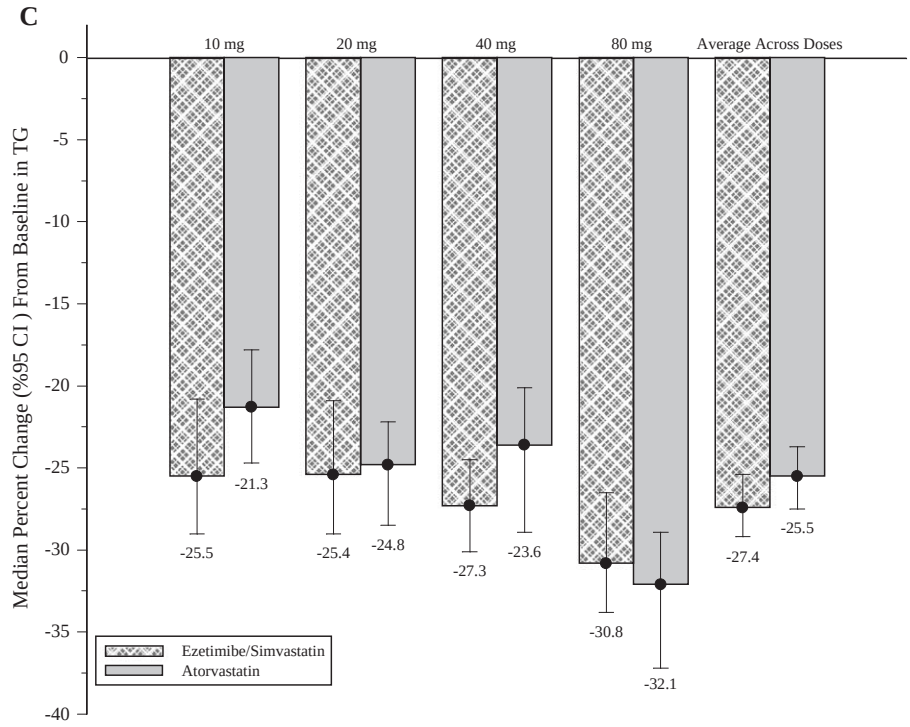
As prespecified in the data analysis plan, if the primary hypothesis was significant at the .05 level, then, in a closed testing approach, the LDL-C secondary hypotheses with respect to the percent change from baseline in LDL-C after 6 weeks of treatment were tested using the Hochberg procedure.[11] If any of the secondary LDL-C hypotheses were significant, then, in a closed testing approach, the secondary HDL-C hypotheses were tested using an ordered approach (order: averaged across doses, 10/80 vs 80, 10/40 vs 40, 10/20 vs 10, 10/20 vs 20, 10/10 vs 10). Testing stopped when a *P* value was >.05 in any one of the ordered comparisons. All

Figure 1



Percent change from baseline in LDL-C (**A**), HDL-C (**B**), and TGs (**C**). *$P < .001$ versus atorvastatin, $P > .05$ for all pairwise comparisons of TG versus atorvastatin. Statin doses are listed on the x-axis; ezetimibe is a fixed 10-mg dose.

Figure 1 continued



treatment comparisons on the secondary efficacy end points and other efficacy parameters (including TC and hs-CRP) were carried out using the ANOVA model described above. Because of the skewed distribution of TG, the above ANOVA model was analyzed using Tukey normal scores rank transformations of percent change from baseline. Statistical inferences were based on nonparametric ANOVA results, and medians and 95% CIs for the medians were presented. Because hs-CRP levels follow a log-normal distribution, logarithms of the ratios of postbaseline to baseline values (log-ratio) were used in the ANOVA model. The geometric mean percent changes from baseline in hs-CRP levels were calculated based on back-transformation via exponentiation of the model-based least squares means, and expressed as (geometric mean − 1) multiplied by 100. The treatment differences in geometric mean percent changes from baseline were calculated based on the difference in the back-transformed model-based least squares means, and 95% CIs for the differences were calculated using the delta method.

Percentages of patients reaching their NCEP ATP III LDL-C goal by risk category, and the additional analysis for LDL-C <70 mg/dL in the CHD or CHD risk-equivalent population, were compared between treatments using a logistic regression model with terms for treatment, week −1 LDL-C stratum, and the percent difference between the LDL-C baseline and NCEP ATP III goal (or treatment target of <100 or <70 mg/dL, respectively). Results are presented as means ± SE.

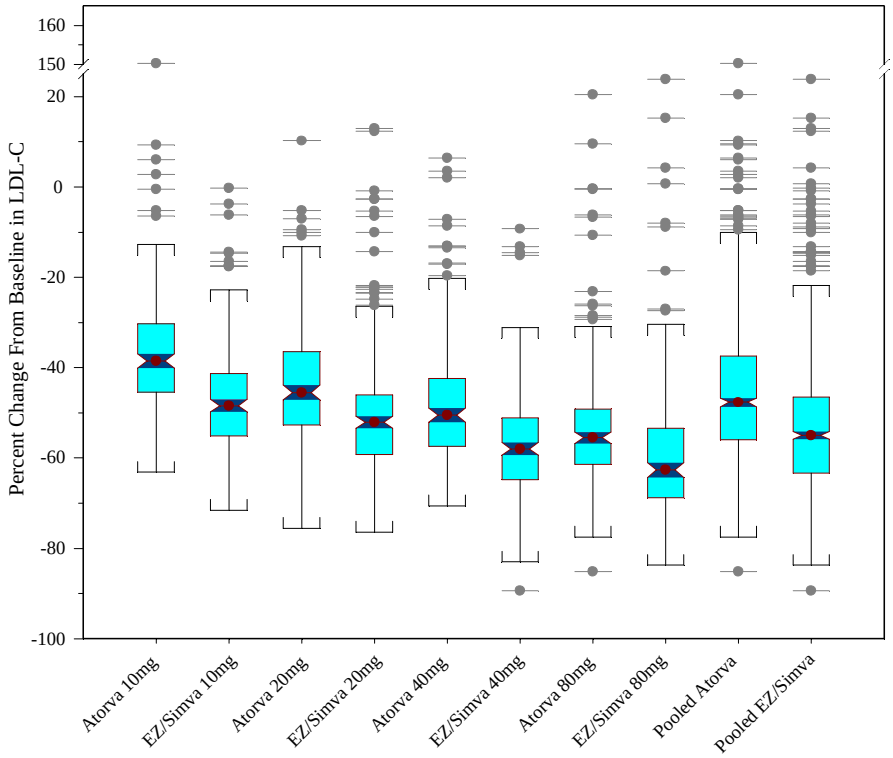
All patients who received at least one dose of double-blind study medication were included in the safety analyses. Fisher exact tests were used for comparisons between the pooled treatment groups on the incidence of adverse events (including percentages of patients with ≥1 adverse events, drug-related adverse events, serious adverse events, and discontinuations due to an adverse event) and on the incidences of the following predefined elevations: consecutive elevations of ALT and/or AST ≥3 times the upper limit of normal (this category includes those patients with 2 consecutive measurements for ALT and/or AST ≥3 times the upper limit of normal; a single, last measurement ≥3 times the upper limit of normal; or a measurement ≥3 times the upper limit of normal that had no follow-up measurements within 2 days of the last dose of study medication), CK elevations ≥10 times the upper limit of normal, and CK elevations ≥10 times the upper limit of normal with muscle symptoms.

Results

Patients

Of 4343 patients screened, a total of 1902 patients (951 each to ezetimibe/simvastatin and to atorvastatin) from 216 sites in the United States were randomized in a 1:1:1:1:1:1:1:1 ratio to each of the 8 treatment arms. Patients were primarily excluded from randomization for failure to meet eligibility criteria (1953), withdrawal of consent (282), and loss to follow-up during the placebo/diet run-in phase (75). Of the 1902

Figure 2



Distribution of percent change from baseline in LDL-C for treatment groups. *Atorva*, atorvastatin; *EZ/Simva*, ezetimibe/simvastatin.

patients randomized, 1847 (97.1%) completed the study; 55 (2.9%) discontinued for the following reasons: 32 (1.7%) for an adverse event, 11 (0.6%) withdrew consent, 5 (0.3%) were lost to follow-up, 3 (0.2%) because of protocol deviation, and 4 (0.2%) for other reasons.

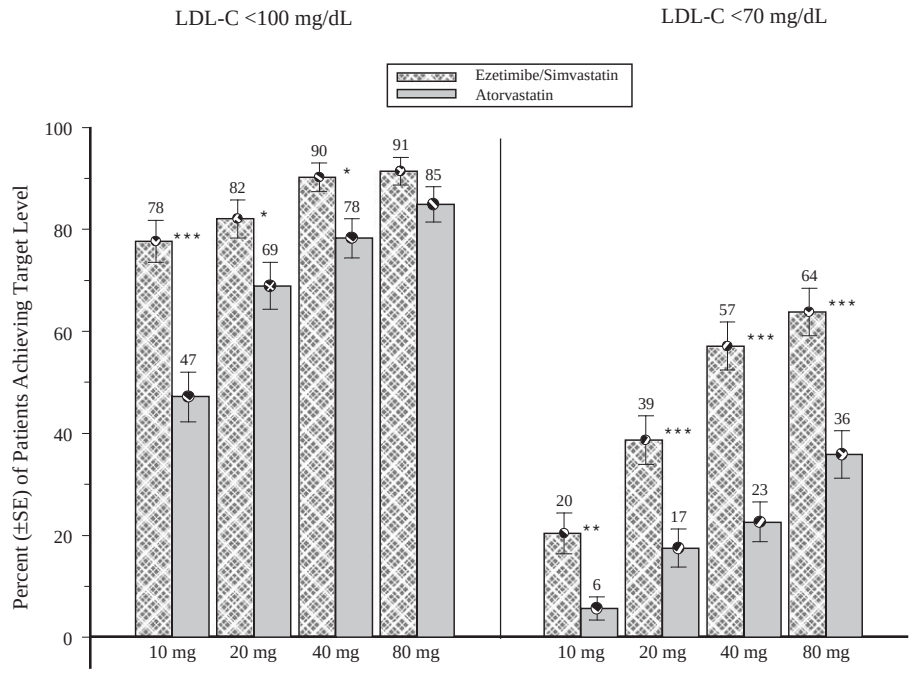
The distribution of patient demographics and NCEP ATP III risk categories was comparable across treatment groups (Table I). Nearly half of all patients (46%) had CHD or a CHD risk equivalent, whereas 37% had multiple (≥2) risk factors conferring a 10-year risk for CHD ≤20%, and 17% of patients had <2 risk factors. The mean patient age was 59 years, with 52.3% of patients being men and 86.2% being white.

Efficacy

Averaged across the dose range and at each milligram-equivalent statin dose comparison, patients treated with ezetimibe/simvastatin demonstrated significantly greater reductions in LDL-C compared with patients treated with atorvastatin monotherapy (Table II and Figure 1*A*). At the recommended starting doses, ezetimibe/simvastatin 10/20 mg resulted in a decrease in LDL-C of 50.6% compared with 36.1% for atorvastatin 10 mg (between-treatment difference −14.5%, 95% CI −17.2 to −11.9, $P < .001$) and 43.7% for atorvastatin 20 mg (between-treatment difference −6.9, 95% CI −9.5 to −4.3, $P < .001$). Ezetimibe/simvastatin 10/40 mg resulted in a 57.4% decrease in LDL-C from baseline compared with 48.3% for atorvastatin 40 mg (between-treatment difference −9.1%, 95% CI −11.7 to −6.5, $P < .001$). Ezetimibe/simvastatin 10/80 mg resulted in a 58.6% decrease in LDL-C from baseline compared with 52.9% for atorvastatin 80 mg (between-treatment difference −5.7%, 95% CI −8.4 to −3.0%, $P < .001$). The distribution of percent change from baseline in LDL-C for each group is presented as a box-and-whisker plot in Figure 2. These descriptive data are consistent with data in Figure 1*A*. Outliers in Figure 2 (showing subjects who had little or no reductions in LDL-C) may be reflective of other factors (ie, noncompliance with diet or study medication, non-fasting sampling, etc) in addition to lower responsiveness to study therapy.

When averaged across all doses, patients treated with ezetimibe/simvastatin demonstrated a significantly greater increase in HDL-C compared with patients treated with atorvastatin monotherapy. At the milligram-equivalent statin dose comparisons, treatment with ezetimibe/simvastatin 10/40 and 10/80 mg resulted in significantly

Figure 3



Attainment of LDL-C targets of <100 and <70 mg/dL in patients with CHD or CHD risk equivalent. *P < .05 versus atorvastatin, **P < .01 versus atorvastatin, ***P < .001 versus atorvastatin. Statin doses are listed on the x-axis; ezetimibe is a fixed 10-mg dose.

Table III. Summary of hs-CRP results in the modified intention-to-treat population

	Atorva 10 mg (n = 231)	EZ/Simva 10 mg (n = 226)	Atorva 20 mg (n = 228)	EZ/Simva 20 mg (n = 232)	Atorva 40 mg (n = 228)	EZ/Simva 40 mg (n = 234)	Atorva 80 mg (n = 230)	EZ/Simva 80 mg (n = 223)	All Atorva (n = 917)	EZ/All Simva (n = 915)
Baseline mean (mg/L)*	2.41	2.11	2.27	2.26	2.41	2.46	2.37	2.21	2.37	2.26
Study end mean (mg/L)*	2.00	1.66	1.76	1.78	1.72	1.73	1.63	1.61	1.77	1.70
Percent change†	−17.3	−21.1	−22.4	−21.4	−28.6	−29.5	−31.4	−26.9	−25.1	−24.8

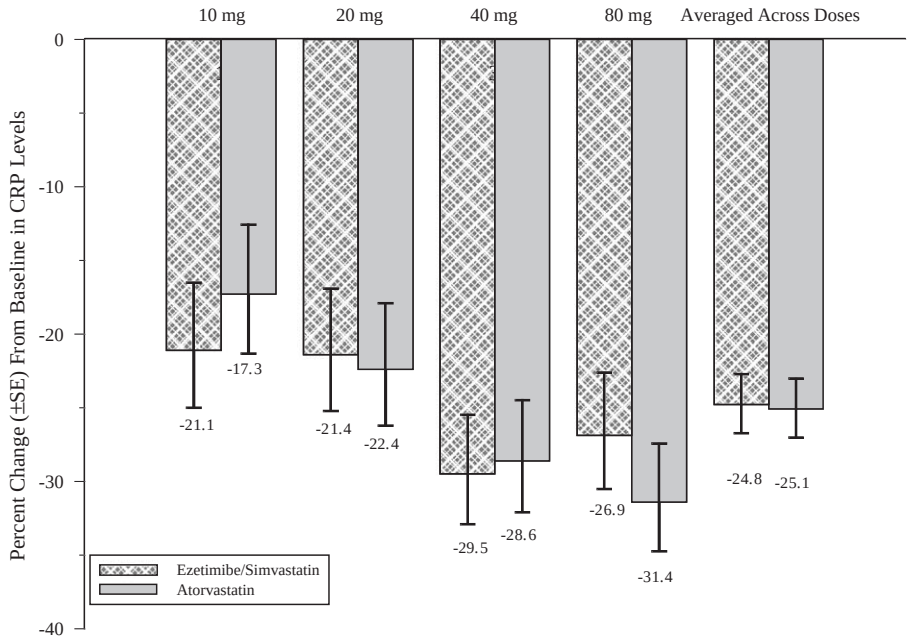
EZ, Ezetimibe 10 mg; *All Atorva*, atorvastatin (10, 20, 40, 80 mg) pooled across all doses; *EZ/All Simva*, ezetimibe/simvastatin (10/10, 10/20, 10/40, 10/80 mg) pooled across all doses.
*Means are geometric means (based on exponentiation of log-transformed values).
†Geometric mean percent changes were calculated based on back-transformation via exponentiation of the LS means obtained from the ANOVA model with terms for treatment and visit 2 LDL-C stratum (≥130 to <160 and ≥160 to <190 mg/dL). Additional terms of baseline hs-CRP level and the interaction of treatment and baseline hs-CRP level were included in the ANOVA model for the subgroup analysis.

greater increases in HDL-C compared with the respective doses of atorvastatin 40 and 80 mg (Figure 1*B*). HDL-C increases with patients treated with ezetimibe/simvastatin 10/10 and 10/20 mg were numerically higher compared with atorvastatin 10 and 20 mg monotherapy, including the dose comparison of ezetimibe/simvastatin 10/20 mg and atorvastatin 10 mg, although these differences were not statistically significant. HDL-C results are summarized in Table II. Reductions in TGs were similar for both groups (Table II and Figure 1*C*).

LDL-C treatment goal attainment

The percentage of patients who achieved their NCEP ATP III LDL-C goal at the end of the study was significantly greater when averaged across dose ranges for patients treated with ezetimibe/simvastatin compared with those treated with atorvastatin (89.7% ± 1.00% vs 81.1% ± 1.29%, P < .001). Similarly, a significantly greater proportion of patients achieved their NCEP ATP III LDL-C goal with the combination of ezetimibe/simvastatin at the ezetimibe/simvastatin 10/10 mg

Figure 4



Geometric mean percent change from baseline in hs-CRP. $P > .05$ for all pairwise comparisons. Statin doses are listed on the x-axis; ezetimibe is a fixed 10-mg dose.

Table IV. Percentage of patients with predefined elevations in ALT, AST, and CK

	Pooled treatment groups		EZ/All Simva minus All Atorva	
	All Atorva (n = 939)	**EZ/All Simva (n = 933)**	**Difference (95% CI)***	***P*†**
ALT ≥3 × ULN, presumed consecutive	10 (1.1)	0 (0.0)	−1.1 (−1.9–−0.4)	.002
AST ≥3 × ULN, presumed consecutive	7 (0.7)	1 (0.1)	−0.6 (−1.4–−0.0)	.070
ALT and /or AST ≥3 × ULN, presumed consecutive	11 (1.2)	1 (0.1)	−1.1 (−2.0–−0.3)	.006
CK ≥10 × ULN	1 (0.1)‡	0 (0.0)	−0.1 (−0.6–0.3)	1.000
CK ≥10 × ULN with muscle symptoms	0 (0.0)	0 (0.0)	0.0 (−0.4–0.4)	—

Data are given as n (%) or difference (95% CI). *EZ* = Ezetimibe 10 mg; *All Atorva*, atorvastatin (10, 20, 40, and 80 mg) pooled across all doses; *EZ/All Simva*, ezetimibe/simvastatin (10/10, 10/20, 10/40, and 10/80 mg) pooled across all doses.
*CIs were calculated using a method based on Wilson's score method.
†*P* values were from Fisher exact test.
‡CK elevation occurred 2 weeks after study completion.
—Not applicable.

versus atorvastatin 10 mg (86.1% ± 2.28% vs 69.4% ± 3.01%, $P < .001$), ezetimibe/simvastatin 10/20 mg versus atorvastatin 10 mg (87.6% ± 2.16% vs 69.4% ± 3.01%, $P < .001$), ezetimibe/simvastatin 10/20 mg versus atorvastatin 20 mg (87.6% ± 2.16% vs 80.9% ± 2.59%, $P = .018$), and ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg (93.6% ± 1.59% vs 85.3% ± 2.32%, $P = .005$) dose comparisons.

Although the proportion of patients who achieved their NCEP ATP III LDL-C goal with the combination of ezetimibe/simvastatin 10/80 mg was similar to that for atorvastatin 80 mg (91.5% vs 89.1%, SE = 1.86, 2.05, $P = .416$); for those patients with CHD or CHD risk equivalent, a greater percentage of patients treated with ezetimibe/simvastatin achieved the NCEP ATP III LDL-C treatment goal of <100 mg/dL and achieved an optional target of <70 mg/dL, compared with those treated with atorvastatin at all milligram-equivalent statin dose comparisons (Figure 3) and when averaged across all doses (85.4% vs 70.0%, $P < .001$, for LDL-C goal <100 mg/dL, and 45.3% vs 20.5%, $P < .001$, for LDL-C goal <70 mg/dL).

Comparisons of approved alternative starting doses revealed that 57.1% of patients in the CHD or CHD risk equivalent category reached an optional LDL-C treat-

ment target of <70 mg/dL with the 10/40 mg starting dose of ezetimibe/simvastatin compared with 22.6% of those patients who were treated with 40 mg of atorvastatin ($P < .001$) (Figure 3). The difference in percentages of patients who attained the optional target of <70 mg/dL was higher for ezetimibe/simvastatin (64%) at the highest milligram-equivalent statin dose (10/80 mg) than for atorvastatin at the 80-mg dose (36%) ($P < .001$).

C-reactive protein

Table III and Figure 4 present baseline and postbaseline geometric mean hs-CRP levels and percent changes from baseline after 6 weeks of treatment. Geometric mean baseline hs-CRP levels were similar across treatment groups. After 6 weeks of treatment, the mean percentage reduction from baseline in hs-CRP levels was 24.8% for ezetimibe/simvastatin averaged across all doses and 25.1% for atorvastatin averaged across all doses. Between-treatment differences were not statistically significant for any pairwise comparisons performed. A supportive nonparametric analysis was performed and was found to corroborate the log-transformed approach.

Safety

The percentages of patients with clinical and laboratory adverse experiences was comparable between the 2 treatments. A greater percentage of patients had elevations in hepatic transaminase levels (ALT and/or AST) ≥3 times the upper limit of normal in the atorvastatin treatment groups (Table IV). No patient had clinical myopathy or a CK ≥10 times the upper limit of normal while on study therapy.

Discussion

In this study, dual inhibition of cholesterol biosynthesis and absorption provided by ezetimibe/simvastatin was overall the more-effective option in reduction of LDL-C and for attainment of LDL-C treatment goals compared with atorvastatin. Averaged across the dose range, and at each milligram-equivalent statin dose comparison, patients treated with ezetimibe/simvastatin demonstrated significantly greater reductions in LDL-C compared with patients treated with atorvastatin monotherapy. A significantly greater proportion of patients achieved their NCEP ATP III LDL-C goal with the recommended initial and alternative starting dosages of ezetimibe/simvastatin (87.6% on 10/20 mg and 93.6% on 10/40 mg) compared with those on the recommended initial and alternative starting dosages of atorvastatin (69.4% on 10 mg, 80.9% on 20 mg, and 85.3% on 40 mg).

Recently, the NCEP ATP III reviewed the evidence from clinical trials of cholesterol-lowering therapy completed after publication of the NCEP ATP III guidelines.[2] Based on the results of the Heart Protection Study,[12] the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial,[13] and other clinical trials, ATP III has reinforced the treatment goal of an LDL-C <100 mg/dL in patients at high risk (CHD or CHD risk equivalent) and recognized an optional target of <70 mg/dL as a reasonable clinical strategy in those patients considered to be at very high risk. In addition, it is recognized that for patients with higher levels of LDL-C at baseline, achieving even greater reductions in LDL-C may require combinations of lipid-lowering drugs.[2]

A post hoc analysis of attainment of an optional LDL-C target of <70 mg/dL in patients with CHD or CHD risk equivalent confirmed that the more aggressive optional treatment target of <70 mg/dL in this subgroup was difficult to attain. At the recommended starting dose of 10/20 mg of ezetimibe/simvastatin and at the alternative starting dose of 10/40 mg, 39% and 57% of these patients achieved an LDL-C goal of <70 mg/dL, compared with 6%, 18%, and 23% of patients treated with the recommended initial (10 and 20 mg) and alternative (40 mg) starting doses of atorvastatin, respectively. At the maximum dose of atorvastatin 80 mg, only 36% of these patients attained the optional goal of <70 mg/dL compared with 64% with ezetimibe/simvastatin.

It has been postulated that lipid-modifying therapies, including statins and fibrates, potentially could have pleotropic and anti-inflammatory effects. Although hs-CRP is an indicator of inflammation, and thus a potentially important marker of cardiovascular risk, the clinical benefit of lowering hs-CRP with lipid-altering therapy has not been established. In this study, the overall magnitude of hs-CRP reduction with ezetimibe/simvastatin averaged across the dose range was similar to that with atorvastatin averaged across the dose range. Specifically, the reduction in hs-CRP was similar at the usual recommended starting doses for atorvastatin (10 and 20 mg) and ezetimibe/simvastatin (20 mg). At the alternative recommended starting doses (40 mg for atorvastatin and 10/40 mg for ezetimibe/simvastatin), the reduction in hs-CRP was also similar. These findings are particularly interesting in light of speculation about whether a "statin-sparing" regimen may have less of an effect on markers of inflammation because ezetimibe/simvastatin demonstrated an effect on hs-CRP similar to higher doses of atorvastatin.

Ezetimibe/simvastatin was well tolerated in this study and did not increase the risk of clinically significant increases in muscle or liver enzymes compared with atorvastatin. These safety observations are consistent with another trial that studied the coadministration of ezetimibe plus simvastatin compared with atorvastatin, in which there were no statistically significant differences in elevations of ALT and/or AST levels ≥3 times the upper limit of normal between these 2 treatments (2.4% atorvastatin group; 2.3% ezetimibe plus simvastatin

group).[7] In addition, the overall lipid-lowering efficacy profile demonstrated in this study also confirmed the results demonstrated in other trials.[6,7]

In summary, the dual cholesterol-lowering mechanisms provided by ezetimibe/simvastatin resulted in greater overall LDL-C–lowering efficacy across dose ranges, better general LDL-C treatment goal attainment, increased HDL-C efficacy averaged across dose ranges and at higher doses and equivalent effects on hs-CRP and TG, compared with atorvastatin monotherapy.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
2. Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-39.
3. Foley KA, Massing MW, Simpson RJ, et al. Population implications of changes in lipid management in patients with coronary heart disease. Am J Cardiol 2004;93:193-5.
4. Van Heek M, France C, Compton D, et al. In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH 58235, in the rat and rhesus monkey through the identification of active metabolites of SCH 48461. J Pharmacol Exp Ther 1997;283:157-63.
5. Gagne C, Bays H, Weiss S, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1084-91.
6. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002;40:2125-34.
7. Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe coadministered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol 2004;93:1487-94.
8. Myers GL, Cooper GR, Winn CL, et al. The Centers for Disease Control—National Heart, Lung, Blood Institute Lipid Standardization Program. An approach to accurate and precise measurements Clin Lab Med 1989;9:105-35.
9. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
10. Sager PT, Melani L, Lipka L, et al. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. Am J Cardiol 2003;92:1414-8.
11. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-2.
12. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of Cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
13. Cannon CP, Braunwald E, McCabe CM, et al. Intensive versus moderate lipid lowering statins after acute coronary syndromes. N Engl J Med 2004;380:1495-504.

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Lipid-independent effects of statins on endothelial function and bioavailability of nitric oxide in hypercholesterolemic patients

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Background Experimental evidence suggests a lipid-independent effect of statins on endothelial function and nitric oxide (NO) availability in humans. We investigated whether improvement in NO availability in hypercholesterolemia can be achieved rapidly with statins before lipid-lowering therapy is complete.

Methods We studied 41 patients (52 ± 11 years) with low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL (179 ± 45 mg/dL) randomly assigned to treatment either with atorvastatin (20 mg/day) or cerivastatin (0.4 mg/day). Endothelium-dependent vasodilation of the forearm vasculature was measured by plethysmography and intra-arterial infusion of acetylcholine (ACh) after 3 days (n = 18) and 14 days (n = 39) of treatment. NO availability and oxidative stress were assessed by coinfusion of L-NMMA and vitamin C.

Results After 3 days of treatment, LDL-cholesterol decreased by 11.9% with a further decrease to 29.6% after 14 days ($P < .001$). Endothelium-dependent vasodilation improved by +46.7% after 3 days of statin therapy compared with before therapy (ACh 48 μg/min: +15.7 ± 10.6 vs +10.7 ± 10.8 mL/min per 100 mL, $P < .05$). No further improvement in endothelium-dependent vasodilation (+42.7% compared with before therapy) could be demonstrated after 14 days of treatment (ACh 48 μg/min: +17.7 ± 10.3 vs +12.4 ± 9.3 mL/min per 100 mL before therapy, $P < .001$). Coinfusion of ACh plus vitamin C was able to improve endothelium-dependent vasodilation before but not after 3 or 14 days of statin therapy either. The improvement in endothelium-dependent vasodilation after therapy was no longer observed when the NO-synthase inhibitor L-NMMA was coinfused together with ACh.

Conclusions Short-term lipid-lowering therapy with statins is able to improve endothelial function and NO availability almost completely after 3 days in hypercholesterolemic patients probably by decreasing oxidative stress. This improvement seems to be more rapid than the accompanying decline in LDL-cholesterol and not related to these lipid changes. This finding can support the concept of lipid-independent effects of statins in humans. (Am Heart J 2005;149:473.e1-473.e10 [doi:10.1016/j.ahj.2004.06.027].)