Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin

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Background Despite the efficacy of statins in lowering low-density lipoprotein cholesterol (LDL-C) levels, many patients who are at high risk for heart disease with hypercholesterolemia require additional LDL-C level reduction. The cholesterol absorption inhibitor, ezetimibe, has been shown to provide significant incremental reductions in LDL-C levels when co-administered with statins. This study was performed to compare the efficacy and safety of ezetimibe (10 mg) plus response-based atorvastatin titration versus response-based atorvastatin titration alone in the attainment of LDL-C goals in subjects who are at high risk for coronary heart disease (CHD) and are not at their LDL-C goal on the starting dose of atorvastatin.

Methods This was a 14-week, multicenter, randomized, double-blind, active-controlled study conducted in 113 clinical research centers in 21 countries. Participants were adults with heterozygous familial hypercholesterolemia (HeFH), CHD, or multiple (≥2) cardiovascular risk factors, and a LDL-C level ≥130 mg/dL after a 6- to10-week dietary stabilization and atorvastatin (10 mg/day) open-label run-in period. Eligible subjects continued to receive atorvastatin (10 mg) and were randomized to receive blinded treatment with ezetimibe (10 mg/day; n = 305) or an additional 10 mg/day of atorvastatin (n = 316). The atorvastatin dose in both groups was doubled after 4 weeks, 9 weeks, or both when the LDL-C level was not at its goal (≤100 mg/dL), so that patients receiving combined therapy could reach 40 mg/day and patients receiving atorvastatin alone could reach 80 mg/day. The primary end point was the proportion of subjects achieving their LDL-C level goal at week 14. A secondary end point was the change in LDL-C level and other lipid parameters at 4 weeks after ezetimibe co-administration with 10 mg/day of atorvastatin versus 20 mg/day of atorvastatin monotherapy.

Results The proportion of subjects reaching their target LDL-C level goal of ≤100 mg/dL was significantly higher in the co-administration group than in the atorvastatin monotherapy group (22% vs 7%; $P < .01$). At 4 weeks, levels of LDL-C, triglycerides, and non-high-density lipoprotein cholesterol were reduced significantly more by combination therapy than by doubling the dose of atorvastatin (LDL-C −22.8% versus −8.6%; $P < .01$). The combination regimen had a safety and tolerability profile similar to that of atorvastatin alone.

Conclusions The addition of ezetimibe to the starting dose of 10 mg/day of atorvastatin followed by response-based atorvastatin dose titration to a maximum of 40 mg/day provides a more effective means for reducing LDL-C levels in patients at high risk for CHD than continued doubling of atorvastatin as high as 80 mg/day alone. (Am Heart J 2004;148: 447–55.)

The reduction of low-density lipoprotein cholesterol (LDL-C) levels in individuals with and without pre-existing coronary heart disease (CHD) and elevated LDL-C levels has been shown to reduce cardiovascular and total mortality rates.[1-3] These large placebo controlled outcome trials have resulted in international guidelines for dyslipidemia treatment.[4,5] However, despite the widespread availability and use during the last decade of statins, recent studies have shown that most patients do not reach established goals.[4,6-8] In

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addition, patients who are at high risk, such as those with CHD, multiple cardiovascular risk factors, or the presence of heterozygous familial hypercholesterolemia (HeFH), who are most in need of and likely to benefit from effective LDL-C reduction, are least likely to reach established goals.[6,7,9] Both Eurospire II[6,10] and the Lipid Treatment Assessment Project (L-TAP)[7] studies demonstrated that the proportion of patients achieving National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II or Joint European specified total or LDL cholesterol target levels ranged from 41% to 18% among patients with CHD in Europe and the USA, respectively. This failure to achieve goal attainment in the higher-risk population has been related to a number of factors, including insufficient pharmacologic effect at the starting dose of a statin and a subsequent lack of willingness to either perform multiple statin dose escalations or a concern for the safety at the highest doses.[9] The L-TAP study[7] authors also suggested that even titration to the maximal dose of available statins would permit the attainment of lipid goals in only a minority of patients. Thus, there is a clear need for either more effective, but safe, single agents or agents that can tolerably, safely, and effectively be combined with current statins to increase the attainment of lipid goals.

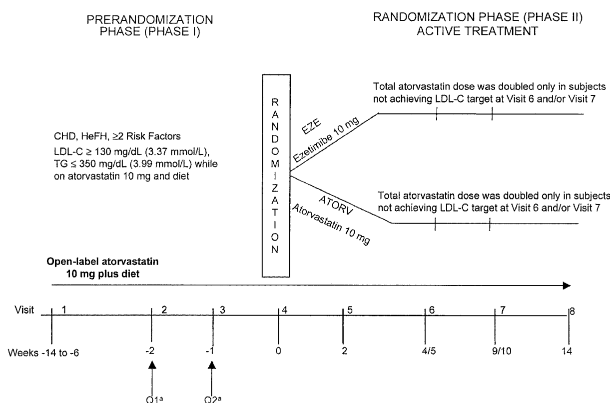
Ezetimibe is a cholesterol absorption inhibitor that potently inhibits biliary and dietary cholesterol absorption at the brush border of the intestine without affecting the absorption of fat-soluble vitamins or triglycerides.[11,12] Co-administration of ezetimibe with statins, including atorvastatin, produced significant incremental LDL-C level reductions and favorably affected total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels.[13–18]

This prospective randomized double-blind study was performed to test the hypothesis that adding ezetimibe to the 10 mg/day starting dose of atorvastatin, followed by response-based atorvastatin titration to 40 mg/day, would be more effective in lowering LDL-C levels than an initial doubling of atorvastatin and subsequent titration to 80 mg/day in patients with high cardiovascular disease risk.

Methods

Eligible patients were ≥18 years old, with primary hypercholesterolemia and documented CHD, at least 2 cardiovascular risk factors, or HeFH with a LDL-C level ≥130 mg/dL despite treatment with 10 mg/day of atorvastatin and diet (NCEP step 1 or stricter). HeFH was diagnosed by the presence of a mutation affecting at least 1 allele at the LDL receptor locus or using established clinical criteria of plasma LDL-C concentration >190 mg/dL and 1 of the following: 1) xanthoma in a first- or second-degree relative; 2) family history of myocardial infarction at an age <60 or 50 years in a first-degree relative or second-degree relative, respectively; or 3) family history of total cholesterol level >290 mg/dL in a first- or second-degree relative. Cardiovascular risk factors were based on the NCEP ATP II[19] guidelines that were in effect when the study was initiated.

Figure 1



Study design. *Q1* and *Q2*, First and second qualifying LDL-C, respectively, using the Friedewald calculation; Q1 and Q2 must be drawn at least 1 week apart.

Exclusion criteria included: serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) determinations >2-times the upper limit of normal (ULN); significant renal or endocrine disease; pregnancy or lactation; advanced congestive heart failure (New York Heart Association class III or IV); uncontrolled cardiac arrhythmias; unstable angina pectoris, myocardial infarction, or surgical or percutaneous coronary revascularization within 3 months of study entry; or ongoing treatment with lipid-lowering agents other than 10 mg/day of atorvastatin.

Study design

This was a randomized, double-blind, multicenter, double-dummy, active controlled comparator study conducted at 113 centers in 21 countries. The study was approved by the institutional review board or ethics committee at each study center, and all subjects gave written informed consent. The study protocol included 2 phases: a 6- to 14-week non-blinded phase, during which 10 mg/day of atorvastatin was initiated, other lipid-lowering medications were discontinued, and a NCEP step 1 or stricter diet was stabilized; and a 14-week phase, in which subjects with a LDL-C level ≥130 mg/dL and triglyceride level ≤350 mg/dL at the end of the open label phase were randomized to receive blinded treatment with either 10 mg/day of ezetimibe (EZE group) or an additional 10 mg/d of atorvastatin (20 mg/d-ATORV group). All subjects continued to receive 10 mg/day of open-label atorvastatin throughout the study (Figure 1).

Subjects in either group who did not reach a plasma LDL-C concentration ≤100mg/dL in the 4 weeks after randomization had their total daily dose of atorvastatin doubled 1 week later (week 5), and when they still failed to reach their goal at week 9, their dose of atorvastatin was doubled again 1

week later (week 10). Thus, the maximum possible daily dose of atorvastatin in the EZE group subjects was 40 mg (10 mg open-label plus 30 mg blinded treatment). The ATORV monotherapy group had a potential maximum dose of 80 mg/day (10 mg open-label plus 70 mg blinded). Visits occurred at 2- to 5-week intervals, during which lipid and safety variables were measured.

The primary efficacy parameter was the percentage of subjects in the 2 treatment groups achieving a LDL-C level ≤100 mg/dL after 14 weeks of randomized treatment. Pre-defined secondary efficacy end points included the effects on other lipid parameters 4 weeks after randomization, permitting a direct comparison of adding ezetimibe to the 10 mg/day of atorvastatin versus doubling the atorvastatin dose.

Laboratory methods

All analyses were conducted on fasting blood samples at a College of American Patholgists accredited and Centers for Disease Control and Prevention standardized[20] central laboratory (Medical Research Laboratories International, Highland Heights, Ky, and Zaventem, Belgium, for the European and South African sites) according to standard procedures.[21-23] Total cholesterol, HDL-C, and triglyceride levels were measured at all visits, and LDL-C levels were calculated with the Friedewald equation (LDL-C = total cholesterol − (TG/5) − HDL-C) and with ultracentrifugation (beta quantification).[21] Non-HDL-C levels were calculated by subtracting the level of HDL-C from the total cholesterol level.

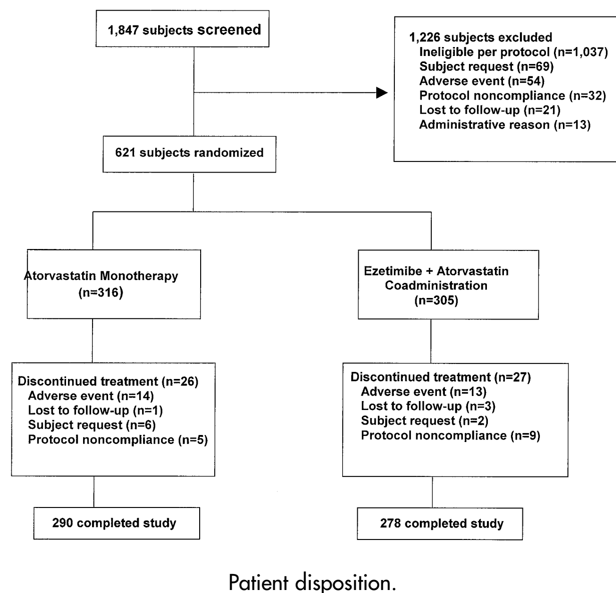
Safety and tolerability assessments

Safety and tolerability were evaluated by reviewing voluntary subject reports, investigators' observations, physical examinations, and results of specific laboratory tests (including frequent liver function tests and creatine phosphokinase [CPK] levels) at each visit. Clinically significant laboratory abnormalities included elevations in ALT or AST levels to at least 3-times the ULN on 2 consecutive occasions or a transaminase level ≥3-tomes the ULN on the final laboratory examination (considered "presumed consecutive"), and an increase in CPK levels ≥10-times the ULN.

Statistics

A sample size of 480 subjects was needed to detect a difference of at least 15% in the 2 treatment groups for the proportion of subjects achieving an LDL-C level ≤100 mg/dL after 14 weeks of randomized therapy with 90% power and a significance level of 0.05 (two-tailed). Categorical data were analyzed between treatment groups with the χ^2 analysis. Non-categorical data were analyzed with an analysis of variance (ANOVA) model that extracted the source of variation caused by treatment. Data are expressed as the least square mean plus or minus SEM; P values ≤.05 were considered to be statistically significant. Median percentage changes were calculated for triglycerides, because this parameter is known to be asymmetrically distributed.

Figure 2



Patient disposition.

Results

Demographics and baseline characteristics

Of 1847 subjects screened, 1037 (66%) did not meet protocol eligibility during the diet-10 mg/day of atorvastatin lead-in period, and an additional 189 subjects were excluded for the reasons outlined in Figure 2. Thus, 621 subjects (34%) were randomized (Figure 2), with 568 subjects (91.5%) completing the 14-week double-blind treatment period.

Randomized subject demographics, baseline characteristics, and lipid levels are summarized in Table I and demonstrate balance in the 2 treatment groups. Despite receiving 10 mg/day of atorvastatin, which is known to lower LDL-C levels by approximately 34% to 36%,[24] the patients still maintained a high LDL-C level at entry (186 mg/dL for the total cohort and 197 mg/dL for the HeFH subgroup). HeFH was present in 58% of subjects (genotype confirmed in 30%), and the remaining subjects had CHD or at least 2 cardiovascular risk factors. Ninety percent of subjects required washout from existing lipid-lowering therapies and were changed to 10 mg/day of atorvastatin.

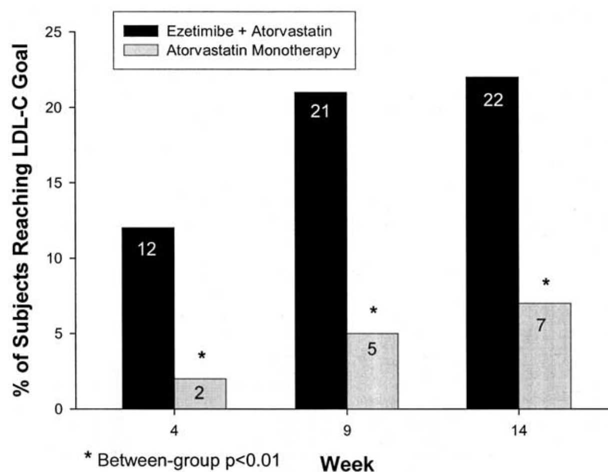
Significantly more subjects in the EZE group compared with the ATORV group achieved a direct LDL-C level ≤100 mg/dL after 14 weeks of randomized treatment (22% vs 7%, P <.01; Figure 3). In the HeFH subgroup, the target LDL-C level was achieved in approximately 4 times more subjects in the EZE group (17% vs 4% P <.01). Similarly, even in subjects without HeFH, the LDL-C goal was achieved in almost 3 times as many subjects in the EZE group as in the ATORV group (29% vs 11%, P <.01). More subjects reached the LDL-C level goal of ≤100 mg/dL at weeks 4 and 9 (Figure 3) after the co-administration of ezetimibe with atorvastatin than with continued atorvastatin titration

Table I. Baseline demographics, clinical characteristics and lipid levels at randomization (on atorvastatin 10 mg/d)

Characteristic	Ezetimibe plus atorvastatin (n = 305)	Atorvastatin monotherapy (n = 316)
Age (y)		
Mean (median)	53.0 (54)	51.6 (53)
Range	18–82	18–80
Age group, no. (%)		
≥65 y	65 (21)	50 (16)
Male, no. (%)	159 (52)	171 (54)
Race, no. (%)		
White	279 (91)	289 (91)
Non-white	26 (9)	27 (9)
Heterozygous familial hypercholesterolemia, no. (%)	181 (59)	181 (57)
Genetic diagnosis	52 (17)	58 (18)
Clinical diagnosis	129 (42)	123 (39)
Patient history documented CHD, no. (%)	90 (30)	100 (32)
Myocardial infarction	58 (19)	56 (18)
Coronary artery bypass graft	43 (14)	54 (17)
Multiple risk factors CHD (≥2 risk factors), no. (%)	120 (39)	118 (37)
History of hypertension	108 (35)	124 (39)
History of diabetes mellitus	19 (6)	23 (7)
Smoker, no. (%)	76 (25)	85 (27)
Lipid values at randomization (mg/dL; mean SE)		
Direct LDL-C*	186.2 (2.7)	187.3 (2.6)
Calculated LDL-C†	185.9 (2.7)	186.8 (2.6)
Total cholesterol	262.0 (2.7)	264.2 (2.7)
HDL-C	50.0 (0.7)	49.9 (0.7)
Non-HDL-C	212.1 (2.8)	214.3 (2.7)
Triglycerides (median, SE)	117.3 (3.9)	118.8 (4.2)
LDL-C:HDL-C ratio	3.95 (.08)	4.00 (.08)
TC:HDL-C ratio	5.52 (.09)	5.60 (.09)
Washout information, no. (%)‡		
Previous statin use	270 (89)	279 (88)
Other	93 (30)	83 (26)

LDL-C, Low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *CHD,* coronary heart disease; *TC,* total cholesterol.
*Measured by preparative ultracentrifugation.
†By Friedewald Formula [LDL-C = total cholesterol − (TG/5) − HDL − C].
‡Subjects may have used more than one lipid lowering agent requiring washout.

Figure 3



Percentage of patients in the total study cohort reaching LDL-C goal (≤100 mg/dL) at weeks 4, 9, and 14 (P <.01 for each comparison).

alone. These results were obtained despite a higher rate of maximal titrations in the ATORV group to 80 mg/day. At 14 weeks, 60% of subjects in the EZE group underwent titration to 40 mg compared with 85% of subjects in the ATORV group who underwent titration to 80 mg. A similar distribution was observed in the HeFH subgroup (67% vs 86%). The enhanced ability of the co-administration regimen to achieve LDL-C levels ≤100 mg/dL was independent of sex, race (white vs non-white), body mass index, and diagnosis of HeFH, hypertension, and diabetes mellitus.

The most reliable and statistically valid estimation of the effect of ezetimibe co-administration with atorvastatin versus atorvastatin monotherapy on LDL-C was at 4 weeks, when all subjects had been receiving either ezetimibe plus 10 mg/day of atorvastatin or 20 mg/day of atorvastatin (Table II, Figure 4). This prespecified analysis demonstrated that LDL-C levels were reduced significantly more by adding ezetimibe to 10 mg of atorvastatin (−22.8%; 186.2 ± 2.6 mg/dL to 144.3 ± 2.6 mg/dL) than by doubling the atorvastatin dose to 20 mg/day (−8.6%; 187.3 ± 2.6 mg/dL to 169.6 ± 2.6 mg/dL; between-group P <.01). In the HeFH population, subjects in the EZE group also had LDL-C levels reduced by a significantly greater extent (−23.6%; 197.9 ± 3.6 mg/dL to 151.6 ± 3.5 mg/dL) compared with subjects in the ATORV group (−7.4%; 196.7 ± 3.6 mg/dL to 180.4 ± 3.5 mg/dL; between-group P <.01).

Combination therapy with ezetimibe and 10 mg/day of atorvastatin also resulted in beneficial effects on other lipid parameters at week 4 (Table II, Figure 4), incrementally reducing the total cholesterol level by 11.3%, the triglyceride level by 5.4%, the non-HDL-C level by 14.2%, the LDL-C-to-HDL-C ratio by 14.6%, and the total cholesterol-to-HDL-C ratio by 11.8%. All these changes were significant when compared with doubling the dose of atorvastatin alone (P <.01). A similar lipid-lowering response was observed in subjects with HeFH who received the co-administration therapy (Table III). A small but non-significant increase in HDL-C levels with the addition of ezetimibe relative to atorvastatin monotherapy was observed in both cohorts.

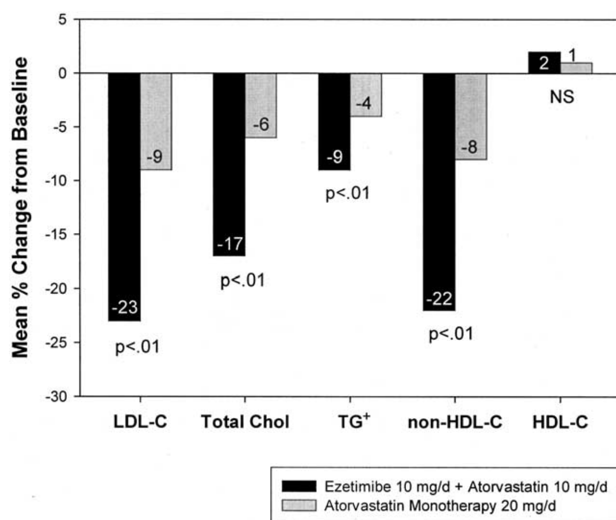
The lipid profile changes at week 14, including mean LDL-C level reductions (−33.2% vs −20.3%),

Table II. Changes in plasma lipid/lipoprotein concentrations at week 4 after addition of ezetimibe to atorvastatin 10 mg/d or doubling the dose of atorvastatin to 20 mg/d

	Ezetimibe 10 mg + Atorvastatin 10 mg (n = 293)		Atorvastatin Monotherapy 20 mg (n = 303)			
Variable	**Absolute change (mg/dL)**	**Mean % change (SE)**	**Absolute change (mg/dL)**	**Mean % change (SE)**	**Between group % change**	***P***
Direct LDL-C	−42.6	−22.8 (0.7)	−16.1	−8.6 (0.7)	−14.2	<.01
Calculated LDL-C	−44.4	−23.8 (0.7)	−16.6	−9.0 (0.7)	−14.8	<.01
Total cholesterol	−45.8	−17.3 (0.6)	−16.2	−6.1 (0.6)	−11.3	<.01
HDL-C	0.8	2.1 (0.6)	0.4	1.3 (0.6)	0.9	N.S.
Non-HDL-C	−46.6	−22.0 (0.7)	−16.7	−7.8 (0.7)	−14.2	<.01
Triglycerides (median)	−9.0	−9.3 (1.7)	−5.0	−3.9 (1.7)	−5.4	<.01
LDL-C:HDL-C ratio	−1.0	−23.8 (0.8)	−0.4	−9.2 (0.8)	−14.6	<.01
TC:HDL-C ratio	−1.1	−18.6 (0.7)	−0.4	−6.8 (0.6)	−11.8	<.01

LDL-C, Low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *CHD,* coronary heart disease; *TC,* total cholesterol.

Figure 4



Effect of 10 mg/day of ezetimibe plus 10 mg/day of atorvastatin versus 20 mg/day of atorvastatin on the lipid profile of patients in the whole study cohort at week 4. All values are means, except triglyceride levels, which are medians. *Total-Chol,* Total cholesterol; *TG,* triglyceride.

were also more favorable in the EZE group and were consistent with the week-4 differences (Table IV). Statistical comparisons were not performed at this point because this was a response-based, not forced titration, study design.

Discontinuations and adverse events

Of the 621 randomized subjects, 91.5% completed treatment, and discontinuation rates were similar in both treatment groups (Figure 2). Fifty-three patients (9%; 27 subjects in the EZE group and 26 subjects in the ATORV group) discontinued treatment prematurely for these reasons, with a similar balance in the 2 groups: adverse event (n = 27, 4%), lost to follow-up (n = 4, <1%), non-compliance with protocol (n = 14, 2%), and subject request to discontinue (n = 8, 1%).

There were no clinically meaningful differences in the treatment groups for the incidence of adverse events or in the number of discontinuations because of adverse events (Table V). Serious adverse events occurred in 12 subjects (4%) in the co-administration group and 9 subjects (3%) in the ATORV group. One subject in the ATORV group died of a myocardial infarction, which was thought to be unrelated to the study drug. Three of the 21 serious adverse events were considered possibly or probably related to study treatment: an episode of pruritus, vasculitis, and macular papular rash (ATORV group); myalgia without a CPK increase (EZE group); and increased ALT reaching a value >3-times the ULN, initially labeled as "hepatitis," in an iron worker with concurrent hemolytic anemia of unknown etiology (EZE group). The latter subject was also receiving diclofenac, which may elevate liver function tests.

Two subjects in the EZE group and 1 subject in the ATORV group had asymptomatic increases in serum ALT, AST, or both ≥3-times the ULN. Jaundice did not develop in any subject, and no subject in the EZE group had a significant increase in bilirubin or alkaline phosphatase. Additionally, cholelithiasis and cholestasis were each reported (both in the ATORV group), but no subject required a cholecystectomy. One subject in the ATORV group had an increase in CPK ≥10-times the ULN, which was associated with muscle pain but

Table III. Changes in plasma lipid/lipoprotein concentrations at week 4 after addition of ezetimibe to atorvastatin 10 mg/d or doubling the dose of atorvastatin to 20 mg/d (HeFH group)

	Ezetimibe 10 mg + atorvastatin 10 mg (n = 177)		Atorvastatin monotherapy 20 mg (n = 172)			
Variable	**Absolute change (mg/dL)**	**Mean % change (SE)**	**Absolute change (mg/dL)**	**Mean % change (SE)**	**Between group % change**	***P***
Direct LDL-C	−46.7	−23.6 (0.9)	−15.0	−7.4 (1.0)	−16.2	<.01
Calculated LDL-C	−48.3	−24.4 (1.0)	−15.7	−8.0 (1.0)	−16.5	<.01
Total cholesterol	−49.5	−18.1 (0.7)	−15.3	−5.5 (0.7)	−12.6	<.01
HDL-C	0.7	1.9 (0.7)	0.2	0.8 (0.8)	1.2	N.S.
Non-HDL-C	−50.2	−22.7 (0.9)	−15.5	−7.0 (0.9)	−15.8	<.01
Triglycerides (median)	−8.3	−9.3 (2.1)	−4.0	−3.8 (2.3)	−5.5	<.01
LDL-C:HDL-C ratio	−1.0	−24.4 (1.0)	−0.3	−7.6 (1.1)	−16.9	<.01
TC:HDL-C ratio	−1.1	−19.2 (0.8)	−0.3	−5.9 (0.8)	−13.4	<.01

LDL-C, Low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *CHD,* coronary heart disease; *TC,* total cholesterol.

Table IV. Changes in plasma lipid/lipoprotein concentrations after 14 weeks of treatment with ezetimibe 10 mg/d + atorvastatin 10 mg/d or atorvastatin 20 mg/d followed by response-based atorvastatin titration in both treatment groups

	Mean % change from randomization (SE)	
Lipid parameter	**Ezetimibe 10 mg + atorvastatin (10–40 mg)**	**Atorvastatin monotherapy (20–80 mg)**
Direct LDL-C	−33.2 (0.9)	−20.3 (0.9)
Calculated LDL-C	−34.9 (0.9)	−21.3 (0.9)
Total cholesterol	−26.1 (0.7)	−16.0 (0.7)
HDL-C	3.7 (0.7)	1.0 (0.7)
Triglycerides (median)	−19.7 (1.6)	−11.3 (1.7)
Apo B	−25.8 (1.0)	−15.2 (0.9)

LDL-C, Low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *Apo,* apolipoprotein.

was thought to be caused by weight training. There were no episodes of rhabdomyolysis.

Discussion

This large, randomized, double-blind trial of subjects with HeFH or CHD or ≥2 cardiovascular risk factors who had elevated LDL-C levels despite treatment with 10 mg/day of atorvastatin clearly demonstrated that the strategy of adding ezetimibe to atorvastatin followed by atorvastatin titration as needed is more effective at lowering LDL-C levels than atorvastatin titration alone. Despite 85% of the subjects receiving ATORV monotherapy undergoing titration to 80 mg/day compared with only 60% of subjects in the EZE group undergoing titration to 40 mg/day, the percentage of subjects reaching the LDL-C goal was only a third of the

Table V. Adverse events

	Ezetimibe 10 mg + atorvastatin (10–40 mg) (n = 305)	Atorvastatin monotherapy (20–80 mg) (n = 316)
Adverse events	193 (63%)	184 (58%)
Most frequent adverse events*	72 (24%)	68 (22%)
Upper respiratory tract infection	9%	8%
Myalgia	8%	9%
Abdominal pain	6%	5%
Headache	7%	6%
Muscular skeletal pain	4%	6%
Arthralgia	5%	5%
Discontinued study due to adverse event	13 (4%)	14 (4%)
Liver function test elevations ≥3× ULN		
ALT and/or AST†	3 (1%)	1 (<1%)
Total bilirubin	0 (0%)	0 (0%)
Alkaline phosphatase	0 (0%)	1 (<1%)
Creatine phosphokinase ≥10× ULN	0 (0%)	1 (<1%)
Rhabdomyolysis	0 (0%)	0 (0%)

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *ULN,* upper limit of normal.
*≥5% Incidence in either treatment group.
†Two consecutive determinations (see methods).

subjects who received co-administration. Even the 1-step addition of ezetimibe to the lowest starting dose of atorvastatin (10 mg/day) resulted in more of these high-risk subjects (12%) reaching the LDL-C goal after 4 weeks than was achieved at 14 weeks after 3 doublings of atorvastatin monotherapy (7%). Although increasing atorvastatin to 20 mg combined with ezetimibe achieved the goal in 21% of patients, a further doubling to 40 mg resulted in only 1% more of

these patients reducing their LDL-C to ≤100 mg/dL. This diminishing return of continued escalation of atorvastatin was also highlighted in the monotherapy treatment arm, in which 5% of subjects achieved the goal with 40 mg of atorvastatin, and this increased by only another 2% with the 80-mg dose. These results are remarkably consistent with those reported recently in a large trial in subjects with HeFH, in which subjects also underwent titration to 80 mg of atorvastatin.[25] The differences in goal attainment in subjects with HeFH were even more marked than those of the whole study cohort. In this large study, adverse events and hepatic and muscle laboratory parameters were closely evaluated, and co-administration with ezetimibe demonstrated a safety profile similar to atorvastatin alone.

The highest dose of atorvastatin (80 mg) has become the most commonly used statin therapy for severe hypercholesterolemia and familial hypercholesterolemia.[26] However, a recent study demonstrated that adding ezetimibe to maximal dose atorvastatin or simvastatin in homozygous familial hypercholesterolemia provided an incremental 20% ($P < .001$) LDL-C level reduction.[13] Other treatment alternatives for achieving LDL-C goals in high-risk patients who are already receiving the maximal tolerated dose of statin include the addition of bile acid sequestrants, niacin, and/or plant stanols, or even multiple combination therapy with these classes. Unfortunately, although moderately effective, these therapies are generally poorly tolerated and infrequently used successfully by physicians in routine practice.

The applicability of these results to a large segment of the population who are at high risk for an initial or additional coronary artery disease (CAD) events and currently under-treated in terms of LDL-C can been calculated from both the frequency of HeFH (1:500 of the population in the United States and other Western countries) and from National Health and Nutrtion Examination (NHANES) III data.[27] There are approximately 8,500,000 Americans with CAD and 38,000,000 with >2 CAD risk factors. Of these patients, approximately 15%, or 7,000,000, have baseline LDL-C levels >190 mg/dL. Because 10 mg of atorvastatin (or the equivalent doses for other statins) lowers LDL-C levels by approximately 34%, few if any of these patients will achieve LDL-C levels close to the ATP III goal of <100 mg/dL. It would require a reduction of ~50% for patients whose levels were just 190 mg/dL to achieve such a goal. This reduction is the mean achieved by only atorvastatin at its top dose of 80 mg or the recently approved rosuvastatin at its top dose of 40 mg. Thus, assuming that at best half these high risk patients achieve the goal, one can estimate that approximately 3 million would not do so with maximal statin therapy.

In summary, this study confirms the added efficacy of ezetimibe co-administered with atorvastatin and provides evidence that ezetimibe can facilitate LDL-C goal attainment in high-risk patients with hypercholesterolemia, even with lower doses of the statin. It also demonstrates the need for lipid-lowering therapies that are well tolerated and effective when added to low- and high-dose statins. The novel mechanism of cholesterol absorption inhibition provided by ezetimibe makes it an excellent agent to co-administer with statins, which inhibit cholesterol synthesis. Thus, through dual inhibition of 2 sources of plasma cholesterol, ezetimibe co-administered with statins such as atorvastatin will increase treatment options for patients and provide a greater ability to bring plasma cholesterol to more optimal levels than is currently possible, even with the highest doses of the most effective statins.

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