Efficacy and Safety of *Ezetimibe* Added to *Atorvastatin* Versus *Atorvastatin* Uptitration or Switching to *Rosuvastatin* in Patients With Primary Hypercholesterolemia

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Hypercholesterolemic patients (n = 1,547) at high atherosclerotic cardiovascular disease risk with low-density lipoprotein cholesterol (LDL-C) levels ≥100 and ≤160 mg/dl while treated with atorvastatin 10 mg/day entered a multicenter, randomized, double-blind, active-controlled, clinical trial using two 6-week study periods. Period I compared the efficacy/safety of (1) adding ezetimibe 10 mg (ezetimibe) to stable atorvastatin 10 mg, (2) doubling atorvastatin to 20 mg, or (3) switching to rosuvastatin 10 mg. Subjects in the latter 2 groups who persisted with elevated LDL-C levels (≥100 and ≤160 mg/dl) after period I, entered period II; subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin 20 mg, or uptitrated their atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated their rosuvastatin to 20 mg. Some subjects on atorvastatin 10 mg plus ezetimibe continued the same treatment into period II. At the end of period I, ezetimibe plus atorvastatin 10 mg reduced LDL-C significantly more than atorvastatin 20 mg or rosuvastatin 10 mg (22.2% vs 9.5% or 13.0%, respectively, p <0.001). At the end of period II, ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than atorvastatin 40 mg (17.4% vs 6.9%, p <0.001); switching from rosuvastatin 10 mg to ezetimibe plus atorvastatin 20 mg reduced LDL-C significantly more than uptitrating to rosuvastatin 20 mg (17.1% vs 7.5%, p <0.001). Relative to comparative treatments, ezetimibe added to atorvastatin 10 mg (period I) or atorvastatin 20 mg (period II) produced significantly greater percent attainment of LDL-C targets <100 or <70 mg/dl, and significantly greater percent reductions in total cholesterol, non−high-density lipoprotein cholesterol, most lipid and lipoprotein ratios, and apolipoprotein B (except ezetimibe plus atorvastatin 20 vs atorvastatin 40 mg). Reports of adverse experiences were generally similar among groups. In conclusion, treatment of hypercholesterolemic subjects at high cardiovascular risk with ezetimibe added to atorvastatin 10 or 20 mg produced significantly greater improvements in key lipid parameters and significantly greater attainment of LDL-C treatment targets than doubling atorvastatin or switching to (or doubling) rosuvastatin at the compared doses. **(Am J Cardiol 2013;112:1885−1895)**

Few studies have used treat-to-target designs that compare sequential "real-life" treatment options in lipid management among the most challenging patients, including those at high cardiovascular disease (CVD) risk with intensive low-density lipoprotein cholesterol (LDL-C) treatment targets. This 2-period study (each 6 weeks) examined patients at high CVD risk who did not achieve LDL-C targets while treated with a commonly prescribed statin at a commonly used dose (atorvastatin 10 mg/day). The primary objective of period I was to compare the LDL-C-lowering efficacy of ezetimibe 10 mg add-on to atorvastatin 10 mg versus doubling atorvastatin to 20 mg or switching to rosuvastatin 10 mg. The main objective of period II was to examine subjects who did not achieve an LDL-C target of <100 mg/dl after period I, compare the LDL-C-lowering efficacy of adding ezetimibe 10 mg to atorvastatin 20 mg versus doubling the atorvastatin dose from 20 mg (period I) to 40 mg, and compare switching from rosuvastatin 10 mg (period I) to ezetimibe 10 mg plus atorvastatin 20 mg versus doubling rosuvastatin to 20 mg. Finally, this study evaluated these sequential treatment options with regard to achievement of LDL-C treatment targets of <100 or <70 mg/dl, consistent with National

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This study (MK653C in High Cardiovascular Risk Patients with High Cholesterol) is registered at ClinicalTrials.gov (NCT01154036).

See page 1894 for disclosure information.

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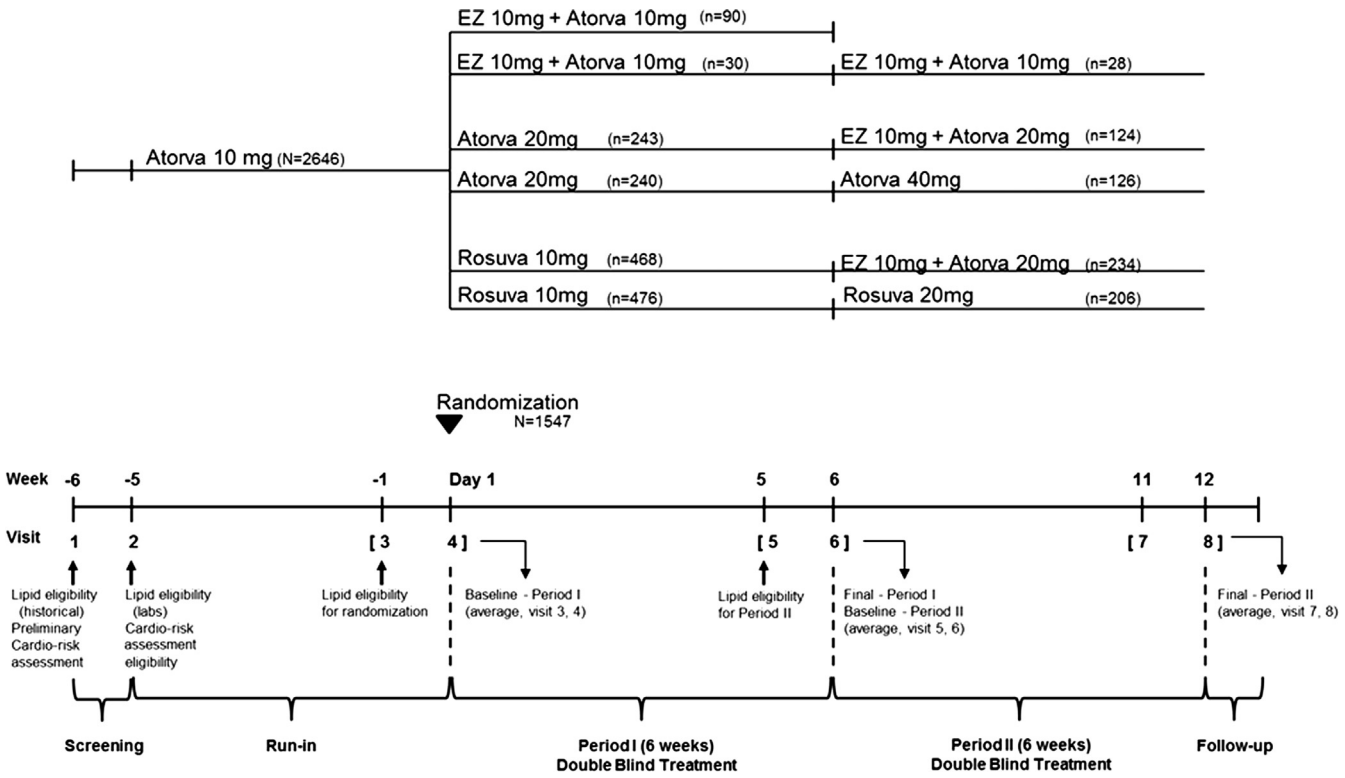

Figure 1. Study design. Atorva = atorvastatin; EZ = ezetimibe; Rosuva = rosuvastatin.

Cholesterol Education Program, Adult Treatment Panel III and European Society of Cardiology/European Atherosclerosis Society guidelines.[1,2]

Methods

This clinical trial entitled A Randomized, Double-Blind, Active-Controlled, Multicenter Study of Patients with **P**rimary Hypercholesterolemia and High Cardiovascular Risk Who Are Not Adequately Controlled with **A**torvastatin 10 mg: A **C**omparison of the Efficacy and Safety of Switching to Coadministration **E**zetimibe and Atorvastatin Versus Doubling the Dose of Atorvastatin or Switching to Rosuvastatin (PACE), was conducted from September 29, 2010 to October 17, 2012 (study MK653C-162, *http://clinicaltrials.gov*, identifier NCT01154036) and included subjects evaluated from 296 research sites across 29 countries (Argentina [18], Belgium [2], Bulgaria [11], Canada [15], Chile [7], Columbia [5], Croatia [4], Czech Republic [19], Denmark [5], Estonia [4], Finland [5], France [7], Germany [9], Hungary [13], Israel [14], Italy [8], Lithuania [8], the Netherlands [4], Norway [4], Poland [14], Portugal [4], Romania [18], Slovakia [12], Slovenia [3], Spain [11], Sweden [6], Turkey [8], the United Kingdom [12], and the United States [46]). The study was conducted in accordance with principles of the ICH Good Clinical Practice and all local and/or national regulations and directives. The appropriate institutional review boards approved the protocol, and all subjects documented their agreement to participate by written informed consent.

Subjects included in the present study were men and women of nonchildbearing potential and aged $\geq$18 and $<$80 years with primary hypercholesterolemia. Subjects were required to be at high CVD risk and meet prespecified lipid entry criteria. The high CVD risk study entry criteria included subjects without CVD who had type 2 diabetes mellitus or $\geq$2 CVD risk factors and a 10-year risk for coronary heart disease $>$20% (as determined by the Framingham risk calculation) or subjects with known CVD, including patients with established coronary and other atherosclerotic vascular diseases.[2–4] The lipid study entry criteria included subjects naive to lipid-lowering therapy (never treated or no therapy for $\geq$6 weeks before the prescreen visit) with an LDL-C level in the predetermined range of 166 to 190 mg/dl or subjects on a stable dose of statin, ezetimibe, or statin plus ezetimibe having LDL-C-lowering efficacy equivalent to or less than atorvastatin 10 mg and with historic lipid values within a range that might reasonably meet randomization lipid criteria (described later).

Main exclusion criteria included alanine aminotransferase or aspartate aminotransferase levels $>2\times$ the upper limit of normal (ULN); creatine kinase $>3\times$ the ULN; a history of significant myopathy or rhabdomyolysis with any statin or ezetimibe; hypersensitivity or intolerance to ezetimibe, atorvastatin, rosuvastatin, or any component of these medications; congestive heart failure (New York Heart Association class III or IV); previous myocardial infarction, coronary artery bypass surgery, angioplasty, or acute coronary syndrome within 3 months before screening; uncontrolled cardiac arrhythmias or recent significant changes on an electrocardiogram within 6 months before screening; homozygous familial hypercholesterolemia or LDL-C apheresis; partial ileal bypass, gastric bypass, or other significant intestinal malabsorption; uncontrolled hypertension; poorly controlled type 1 or 2 diabetes

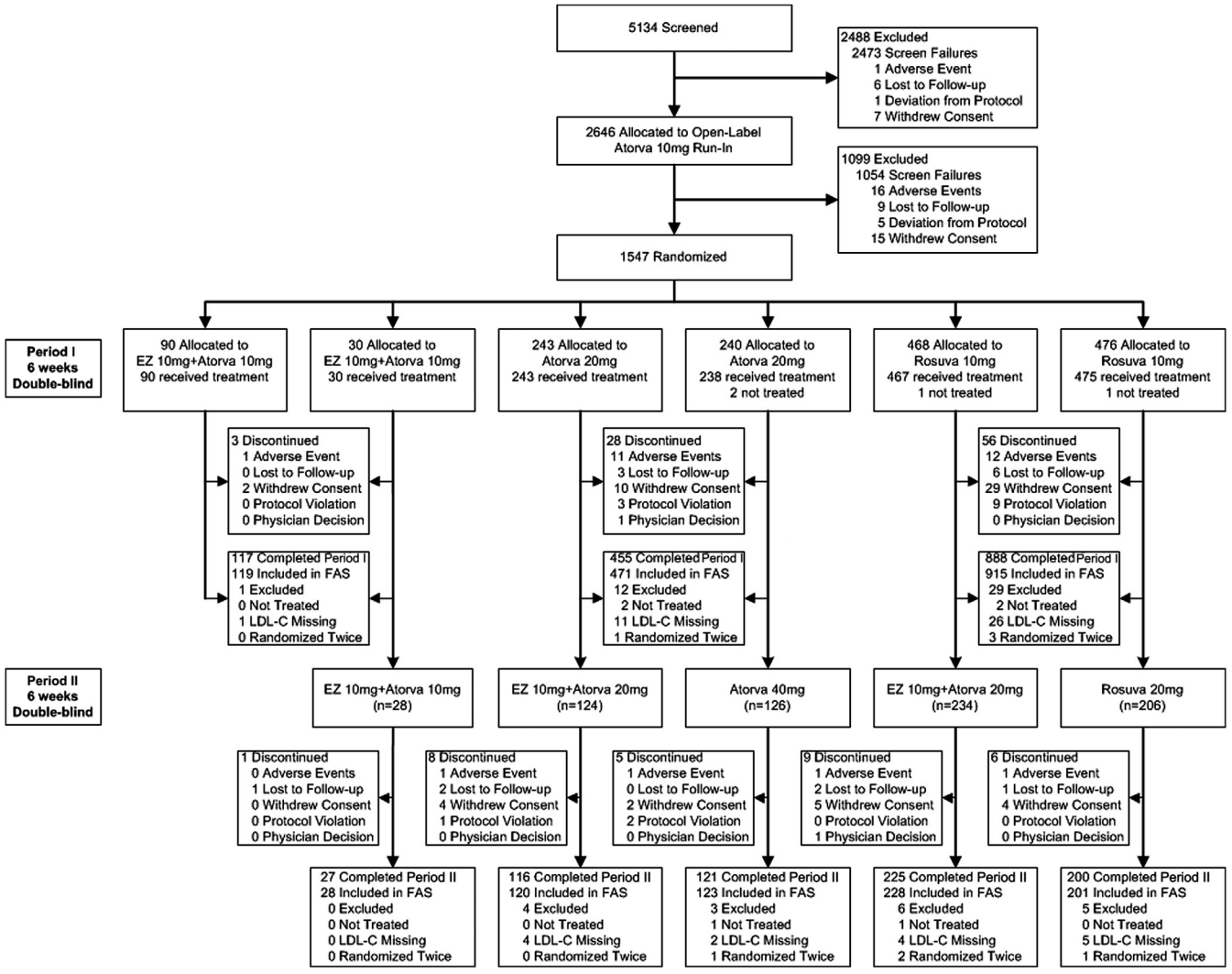

Figure 2. Participant distribution. Atorva = atorvastatin; EZ = ezetimibe; FAS = full analysis set (includes all randomized patients with baseline and at least 1 valid postbaseline evaluation); Rosuva = rosuvastatin.

mellitus (defined by HbA1c $\geq$ 8.5%); estimated glomerular filtration rate $<$30 ml/min/1.73 m^2 based on the 4-variable Modification of Diet in Renal Disease equation, nephrotic syndrome, or other clinically significant renal disease; active liver disease; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; disorders of the hematologic, digestive, or central nervous systems including cerebrovascular disease (e.g., stroke, transient ischemic attack) and degenerative disease that would limit study evaluation or participation.

After study entry, lipid-altering drug−naïve subjects were administered open-label atorvastatin 10 mg/day. For subjects previously treated with lipid-altering drugs, these lipid-altering drugs were discontinued, and the subjects were switched to open-label atorvastatin 10 mg/day. After 5 weeks of open-label atorvastatin 10 mg/day, subjects were required to meet a second set of randomization entry criteria which included LDL-C levels $\geq$100 and $\leq$160 mg/dl and triglyceride levels $\leq$400 mg/dl. Subjects meeting these criteria were randomized to 1 of 6 blinded treatment sequences in a 3:1:8:8:16:16 ratio based on sample size assumptions (see later), which determined treatment in period I (first 6 weeks) and period II (second 6 weeks) of the study (Figure 1). Treatment during period I included (1) adding ezetimibe 10 mg to stable atorvastatin 10 mg therapy, (2) doubling atorvastatin to 20 mg, or (3) switching to rosuvastatin 10 mg. Subjects in the latter 2 groups who persisted with LDL-C levels $\geq$100 and $\leq$160 mg/dl at the end of period I entered period II; subjects on atorvastatin 20 mg received atorvastatin 20 mg plus ezetimibe 10 mg or atorvastatin uptitrated to 40 mg; those on rosuvastatin 10 mg were switched to atorvastatin 20 mg plus ezetimibe 10 mg or uptitrated to rosuvastatin 20 mg. Approximately 25% of those receiving atorvastatin 10 mg plus ezetimibe during period I continued into period II irrespective of LDL-C levels to maintain study blinding. Randomization was performed using a central interactive voice response system. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study; the final database

Table 1
Baseline characteristics (all randomized subjects)

Characteristic	Period I			Period II				
	E10 + A10 (n = 120)	A20 (n = 483)	R10 (n = 944)	E10 + A10 → E10 + A10 (n = 28)	A20 → E10 + A20 (n = 124)	A20 → A40 (n = 126)	R10 → E10 + A20 (n = 234)	R10 → R20 (n = 206)
Men	49 (40.8)	230 (47.6)	455 (48.2)	14 (50.0)	69 (55.6)	63 (50.0)	111 (47.4)	107 (51.9)
Women	71 (59.2)	253 (52.4)	489 (51.8)	14 (50.0)	55 (44.4)	63 (50.0)	123 (52.6)	99 (48.1)
Age (yrs)	60.4 ± 9.4	59.6 ± 10.2	59.9 ± 9.7	61.9 ± 8.7	59.6 ± 10.9	58.2 ± 10.9	59.1 ± 10.2	57.6 ± 10.1
Race								
American Indian/ Alaska Native	1 (0.8)	1 (0.2)	0	0	0	1 (0.8)	0	0
Asian	0	0	0	0	0	0	0	0
Black	4 (3.3)	11 (2.3)	28 (3.0)	2 (7.1)	3 (2.4)	3 (2.4)	9 (3.8)	8 (3.9)
Multiracial	2 (1.7)	6 (1.2)	18 (1.9)	0	1 (0.8)	0	3 (1.3)	2 (1.0)
White	113 (94.2)	465 (96.3)	897 (95.0)	26 (92.9)	120 (96.8)	122 (96.8)	222 (94.9)	196 (95.1)
Unknown	0	0	1 (0.1)	0	0	0	0	0
Ethnicity								
Hispanic or Latino	32 (26.7)	112 (23.2)	228 (24.2)	9 (32.1)	31 (25.0)	32 (25.4)	52 (22.2)	55 (26.7)
Not Hispanic or Latino	88 (73.3)	369 (76.4)	714 (75.6)	19 (67.9)	92 (74.2)	94 (74.6)	182 (77.8)	151 (73.3)
Unknown	0	2 (0.4)	2 (0.2)	0	1 (0.8)	0	0	0
Body mass index (kg/m^2)	30.3 ± 5.2	29.6 ± 5.0	29.6 ± 5.0	31.9 ± 5.1	29.1 ± 4.8	29.7 ± 4.4	29.8 ± 5.0	29.0 ± 5.0
Metabolic syndrome*	81 (67.5)	310 (64.2)	620 (65.7)	22 (78.6)	80 (64.5)	80 (63.5)	159 (67.9)	117 (56.8)
CVD†								
No	59 (49.2)	245 (50.7)	465 (49.3)	15 (53.6)	61 (49.2)	70 (55.6)	116 (49.6)	105 (51.0)
Yes	61 (50.8)	238 (49.3)	479 (50.7)	13 (46.4)	63 (50.8)	56 (44.4)	118 (50.4)	101 (49.0)
Diabetes mellitus	60 (50.0)	222 (46.0)	451 (47.8)	11 (39.3)	55 (44.4)	57 (45.2)	116 (49.6)	92 (44.7)

Data are presented as n (%) or mean ± SD.

A10/20/40 = atorvastatin 10 mg, 20 mg, or 40 mg; E10 = ezetimibe 10 mg; R10/20 = rosuvastatin 10 mg or 20 mg.

* Having ≥3 of the following 5 characteristics: waist circumference ≥102 cm for men or ≥88 cm for women; triglycerides ≥150 mg/dl; HDL-C <40 mg/dl in men or <50 mg/dl in women; ≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure, or on antihypertensive drug treatment in a subject with a history of hypertension; fasting glucose ≥100 mg/dl or on drug treatment for elevated glucose.

† CVD is defined as the National Cholesterol Education Program-Adult Treatment Panel III and American Heart Association/American College of Cardiology guideline definition of "established atherosclerotic vascular disease."

was not unblinded until medical/scientific review was performed, protocol violators were identified, and data were declared final and complete.

The primary efficacy end point variable was the percent change from treated baseline in LDL-C levels at the end of period I. Key secondary end point variables included percent change from treated baseline in LDL-C at the end of period II; percentage of subjects achieving LDL-C <100 or <70 mg/dl at the end of periods I and II; percent change from treated baseline in other lipids, lipoproteins, and high-sensitivity C-reactive protein (hs-CRP) at the end of periods I and II; assessment of safety and tolerability.

Primary and secondary efficacy end point variables were evaluated using the full analysis set population, including all randomized subjects receiving ≥1 dose of blinded study treatment with baseline and ≥1 postbaseline measurement. Because normality was rejected (at the alpha = 0.001 level) for the primary end point of percent change from baseline in LDL-C levels after period I, the analysis used a prespecified 2-step multiple imputation method[5] followed by a robust regression approach[6,7] that included terms for treatment and baseline LDL-C. The robust regression provided iteratively reweighted-least-square means[6] and associated p values to determine within- and between-treatment effects. Evaluation of the percentage of patients reaching LDL-C targets <100 or <70 mg/dl used a logistic regression model with terms for treatment and baseline LDL-C categories (3 categories based on tertiles). Odds ratio estimates and 95% confidence intervals were used to quantify treatment effects. The percent change from baseline in other lipid and lipoprotein parameters (except triglycerides and hs-CRP) was evaluated using the robust regression approach as described previously. The percent change from baseline in log-transformed data for triglycerides and hs-CRP was assessed using a constrained longitudinal data analysis method because of the non-normal distribution seen in previous studies.[8] As this study design employed the use of serial treatment assessments, a parallel gatekeeping testing approach was applied to control the overall type-I error rate at an α value of 0.05 for comparisons of percent change from baseline in LDL-C after periods I and II. For other evaluations, the false discovery rate was controlled at 5%. Analysis of prespecified subgroups provided least squares means and 95% confidence intervals by fitting an analysis of covariance repeated measure model with terms for treatment and baseline LDL-C.

For the primary and secondary efficacy end points, with a sample size of approximately 1,500 patients planned for randomization, the study was anticipated to have at least 90% power to demonstrate a difference between ezetimibe coadministered with atorvastatin and the comparative atorvastatin or rosuvastatin monotherapy, assuming a drop-out rate of ~8%, a SD of 20% (α-level of 0.045 [period I] or

Table 2
Baseline parameters (all randomized subjects)

Parameter	Period I			Period II				
	E10 + A10 (n = 120)*	A20 (n = 483)*	R10 (n = 944)*	E10 + A10 → E10 + A10 (n = 28)*	A20 → E10 + A20 (n = 124)*	A20 → A40 (n = 126)*	R10 → E10 + A20 (n = 234)*	R10 → R20 (n = 206)*
LDL-C (mg/dl)†	121 ± 18	120 ± 17	121 ± 18	107 ± 37	119 ± 16	121 ± 21	119 ± 16	120 ± 17
Total cholesterol (mg/dl)	203 ± 25	203 ± 23	205 ± 24	190 ± 46	202 ± 23	203 ± 25	204 ± 24	203 ± 23
Non-HDL-C (mg/dl)	150 ± 25	150 ± 22	152 ± 23	137 ± 42	151 ± 22	151 ± 24	151 ± 21	150 ± 21
Triglycerides (mg/dl)‡	127 ± 80	148 ± 75	147 ± 73	139 ± 105	144 ± 79	141 ± 65	150 ± 61	137 ± 73
HDL-C (mg/dl)	53 ± 13	53 ± 12	53 ± 13	53 ± 15	51 ± 12	52 ± 13	53 ± 15	54 ± 13
Apolipoprotein B (mg/dl)	102 ± 20	103 ± 19	104 ± 19	97 ± 21	102 ± 19	103 ± 18	102 ± 18	103 ± 18
Apolipoprotein AI (mg/dl)	148 ± 26	149 ± 24	148 ± 24	144 ± 29	143 ± 24	147 ± 23	147 ± 26	149 ± 25
Total/HDL-C	4.0 ± 0.9	4.0 ± 0.9	4.1 ± 0.9	3.7 ± 1.0	4.2 ± 1.0	4.1 ± 1.0	4.1 ± 1.0	4.0 ± 0.9
LDL-C/HDL-C	2.4 ± 0.7	2.4 ± 0.6	2.4 ± 0.7	2.1 ± 0.8	2.5 ± 0.7	2.5 ± 0.7	2.4 ± 0.7	2.4 ± 0.6
Non-HDL-C/HDL-C	3.0 ± 0.9	3.0 ± 0.9	3.1 ± 0.9	2.7 ± 1.0	3.2 ± 1.0	3.1 ± 1.0	3.1 ± 1.0	3.0 ± 0.9
Apolipoprotein B/ apolipoprotein AI	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Hs-CRP (mg/L)‡	1.9 ± 3.0	2.2 ± 3.0	2.2 ± 3.1	2.0 ± 4.7	2.1 ± 3.0	2.2 ± 3.0	1.9 ± 3.1	2.0 ± 2.8

Data are presented as mean ± SD.

Baseline values refer to values measured at randomization (after atorvastatin 10 mg run-in) for period I and values measured at the end of period I for period II. A10/20/40 = atorvastatin 10 mg, 20 mg, or 40 mg; E10 = ezetimibe 10 mg; R10/20 = rosuvastatin 10 mg or 20 mg.

* Number of all randomized patients evaluated (may vary slightly within each parameter).

† LDL-C was calculated using Friedewald method when triglycerides were <350 mg/dl (3.95 mmol/L) and beta quantification ultracentrifugation when triglycerides were ≥350 mg/dl.

‡ Median ± robust SD (SD calculated as interquartile range/1.075, in which the interquartile range is the third quartile minus the first quartile.

0.050 [period II], 2 sided), and an anticipated number of patients not adequately controlled on atorvastatin 20 mg/day (50%) or rosuvastatin 10 mg/day (40%) after period I. These sample size assumptions account for the differences in n values planned for the various treatment arms.

Safety was evaluated using the all-patients-as-treated population, including all randomized subjects who received ≥1 dose of study treatment. Prespecified safety end points of special interest for this study were subject to inferential testing, with p values and 95% confidence intervals determined for between-group comparisons using a stratified Miettinen and Nurminen method.[9] Confidence intervals (95%) for between-group differences were provided for adverse experience (AE) categories including ≥1 AE, serious AEs, drug-related AEs, serious drug-related AEs, and discontinuations due to an AE. Assessment of drug causality was determined by the investigator during blinded study treatment, using the criteria of definitely, probably, possibly, probably not, and definitely not related to study drug. An AE was defined as "drug related" if the investigator reported the AE as being possibly, probably, or definitely due to study drug.

Results

Of the 1,547 patients randomized, 1,460 (94%) completed period I. Afterward, 718 subjects with LDL-C levels high enough to be eligible to participate proceeded to period II. Of these, 689 (96%) completed period II (Figure 2). Study subject discontinuations were 5.6% during period I (range, 2.5%−5.9%) and 4.0% during period II (range, 2.9%−6.5%). Baseline characteristics (Table 1) and lipid and lipoprotein levels (Table 2) were generally similar across treatment regimens within each period. Patients randomized to period I had a mean age of 60 years, 53% were women, 95% were white, 50% had CVD, and 47% had diabetes mellitus (0.4% with type 1, 32.4% with type 2, and 14.6% with unknown type). The overall mean baseline LDL-C level was ~120 mg/dl. Baseline characteristics and lipid and lipoprotein levels for uncontrolled patients who continued into period II were similar to those for patients in period I. Overall, mean compliance at the >95% level of the prescribed dose was 94% during atorvastatin 10 mg run-in, 91% during period I, and 92% during period II.

For patients with LDL-C levels ≥100 and ≤160 mg/dl after atorvastatin 10 mg run-in, the addition of ezetimibe to atorvastatin 10 mg produced a significantly greater reduction in LDL-C than doubling the atorvastatin dose to 20 mg or switching to rosuvastatin 10 mg (Table 3). Furthermore, the addition of ezetimibe to atorvastatin 10 mg produced significantly greater attainment of LDL-C <100 or <70 mg/dl (Figure 3) and significantly greater reductions in total cholesterol, non−high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, and LDL-C/HDL-C, total/HDL-C, and non-HDL-C/HDL-C ratios (Table 3) than atorvastatin 20 mg or rosuvastatin 10 mg. The change from baseline in HDL-C, triglycerides, apolipoprotein AI, and hs-CRP were similar among treatments (Table 3). Treatment effects were similar for percent change from baseline in LDL-C across all prespecified subgroups of age, gender, race, and diabetic status (Figure 4).

For patients who persisted with LDL-C levels ≥100 and ≤160 mg/dl after an additional 6 weeks on atorvastatin 20 mg or rosuvastatin 10 mg (which followed the atorvastatin 10 mg run-in), the addition of ezetimibe to atorvastatin 20 mg produced significantly greater reductions in LDL-C and significantly greater attainment of LDL-C <100 or <70 mg/dl than uptitration of atorvastatin to 40 mg

Table 3
Percent change from treated baseline in assessed parameters (full analysis set population)

Parameter	Period I					Period II					
	Percent Change from Baseline[†]			Treatment Difference		Percent Change from Baseline[†]				Treatment Difference	
	E10 + A10 (n = 120)[‡]	A20 (n = 480)[‡]	R10 (n = 939)[‡]	E10 + A10 vs A20	E10 + A10 vs R10	A20→		R10→		E10 + A20 vs A40	E10 + A20 vs R20
						E10 + A20 (n = 124)[‡]	A40 (n = 124)[‡]	E10 + A20 (n = 231)[‡]	R20 (n = 205)[‡]		
LDL-C	−22.2	−9.5	−13.0	−12.7***	−9.1***	−17.4	−6.9	−17.1	−7.5	−10.5***	−9.5***
Total cholesterol	−13.5	−6.4	−7.7	−7.1***	−5.8***	−10.7	−3.8	−11.8	−4.5	−6.8***	−7.4***
Non-HDL-C	−18.3	−8.1	−10.6	−10.1***	−7.6***	−15.1	−5.8	−16.2	−6.4	−9.3***	−9.8***
HDL-C	0.6	−1.1	1.1	1.7	−0.6	0.7	1.7	0.1	0.8	−1.0	−0.7
Triglycerides[§]	−6.0	−3.9	−1.1	−2.1	−4.9	−5.9	−3.1	−10.2	−3.2	−2.8	−7.1*
Apolipoprotein B	−11.3	−6.0	−6.9	−5.3**	−4.3*	−9.8	−5.4	−11.9	−4.1	−4.3	−7.7***
Apolipoprotein AI	0.2	−1.4	1.0	1.6	−0.9	1.2	0.7	0.0	1.0	0.5	−1.0
LDL-C/HDL-C	−21.7	−8.0	−13.9	−13.7***	−7.8***	−19.0	−8.7	−16.5	−8.2	−10.4***	−8.3***
Total/HDL-C	−13.5	−5.5	−8.7	−8.1***	−4.8**	−12.4	−5.5	−11.3	−4.9	−6.9***	−6.4***
Non-HDL-C/ HDL-C	−17.6	−7.0	−11.4	−10.6***	−6.2**	−16.7	−7.3	−15.1	−6.7	−9.3***	−8.4***
Apolipoprotein B/ apolipoprotein AI	−11.5	−5.3	−8.0	−6.3***	−3.5	−11.3	−5.5	−11.5	−5.4	−5.8*	−6.1**
Hs-CRP (mg/L)[§]	−10.5	−6.6	−9.0	−3.9	−1.5	−19.5	−6.4	−10.9	0.7	−13.1	−11.6

A10/20/40 = atorvastatin 10 mg, 20 mg, or 40 mg; E10 = ezetimibe 10 mg; R10/20 = rosuvastatin 10 mg or 20 mg.
*p <0.05; **p <0.01; ***p <0.001.
[†] Iteratively reweighted-least squares means (all values except triglycerides and hs-CRP), which are M-estimates based on the method by Huber[6]; 95% confidence interval and p value were obtained from fitting a robust regression model with terms for treatment and baseline, after imputing missing values (based on the method by Rubin[5]).
[‡] n = Number of all randomized patients evaluated (may vary slightly within each parameter). Includes patients who may only have either a baseline or an end point observation and those who have both.
[§] Least squares means based on analysis of log-transformed data, using a constrained longitudinal data analysis model with the log-transformed baseline and log-transformed postbaseline measurements in the response vector and with fixed effects for treatment, time, and the interaction of time by treatment.

(Table 3, Figure 3). Switching from rosuvastatin 10 mg to ezetimibe plus atorvastatin 20 mg produced significantly greater reductions in LDL-C and attainment of LDL-C <100 or <70 mg/dl than uptitration of rosuvastatin to 20 mg (Table 3, Figure 3). The addition of ezetimibe to atorvastatin 20 mg also produced significantly greater reductions in total cholesterol, non-HDL-C, and all measured lipid and lipoprotein ratios than either atorvastatin 40 mg or rosuvastatin 20 mg (Table 3). The change from treated baseline in apolipoprotein B and triglycerides with ezetimibe plus atorvastatin 20 mg was significantly greater than rosuvastatin 20 mg but similar to atorvastatin 40 mg. No significant between-treatment differences were seen for change from treated baseline in HDL-C, apolipoprotein AI, or hs-CRP. Treatment effects were similar for percent change from baseline in LDL-C across prespecified subgroup categories of age, gender, race, and diabetic status (Figure 4).

Ezetimibe plus atorvastatin (10 mg or 20 mg), atorvastatin monotherapy (10 mg, 20 mg, or 40 mg), and rosuvastatin monotherapy (10 mg or 20 mg) were generally well tolerated during this 18-week study (Table 4). Overall, at least 1 AE occurred in 12.6% of patients during period I and 11.1% of patients during period II. No patient in any treatment group experienced a serious drug-related AE. No meaningful treatment differences were observed in the percentage of patients who experienced any AE, any drug-related AE, any serious AE, or who discontinued study drug because of an AE.

Comparisons of treatment regimens during period I showed a similar incidence of ≥1 AE, drug-related AEs, and serious AEs (Table 4). For period II, the incidence of ≥1 AE, drug-related AEs, and serious AEs were similar for patients who received ezetimibe added to atorvastatin 20 mg versus atorvastatin doubling to 40 mg. Comparing patients switching from rosuvastatin 10 mg (period I) to ezetimibe plus atorvastatin 20 mg versus rosuvastatin doubling to 20 mg, the incidence of drug-related and serious AEs were similar, whereas a numerically greater incidence of ≥1 AE was seen with ezetimibe plus atorvastatin 20 mg (Table 4). This difference was associated with a greater number of musculoskeletal and connective tissue disorder events, none of which were myopathy (8 patients [3.5%] vs 1 patient [0.5%]). No specific AE was experienced by >3 patients within any treatment group, and individual AEs were not indicative of a pattern suggesting a clinically meaningful difference. Details of investigator-reported, drug-related AEs occurring during period I (43 patients total) and period II (16 patients total) are listed in Table 4.

The incidence of prespecified AEs of special interest was low, with no significant difference seen among the groups (Table 4). The most frequently reported AE of special interest during period I and II was gastrointestinal related. No patient in any treatment group experienced hepatitis-related or gall bladder–related AEs or met the Hy's law criteria for potential drug-induced liver injury.[10] No subject experienced postbaseline creatine kinase elevations ≥10×

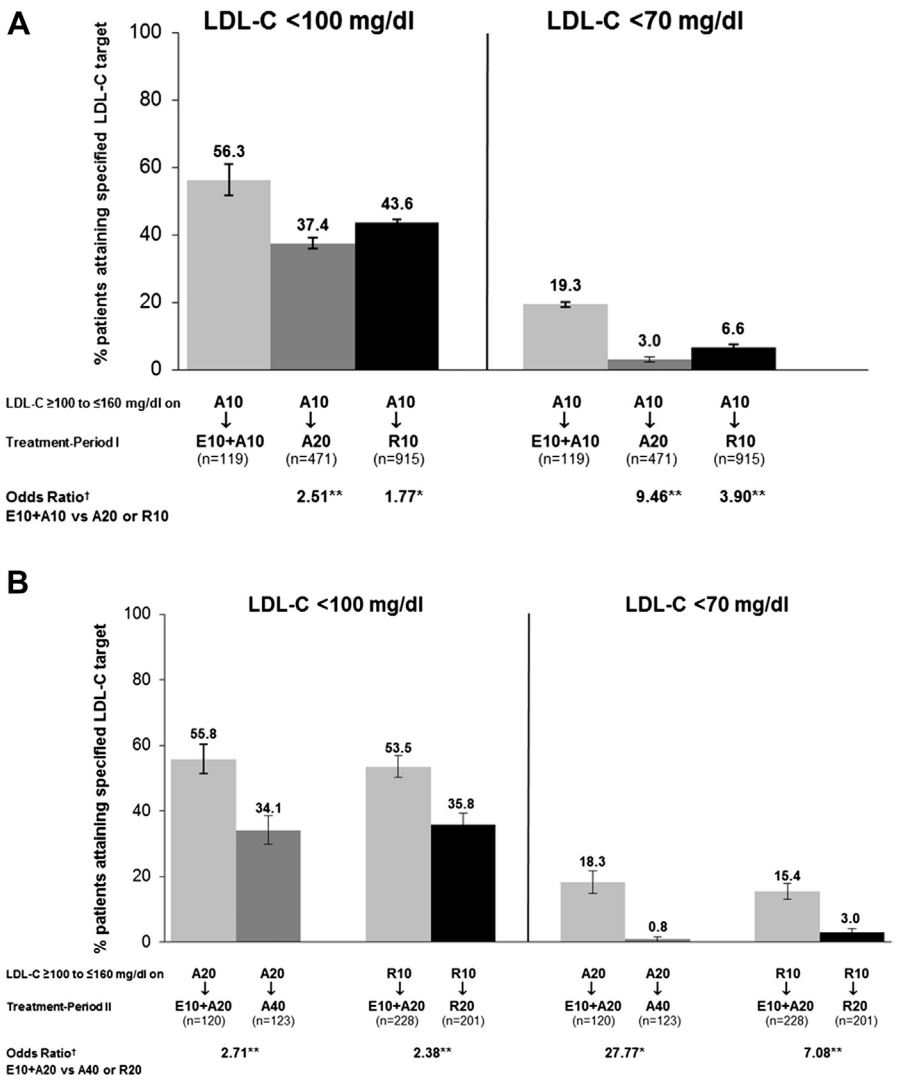

Figure 3. *(A)* Percent attainment of prespecified LDL-C target after 6 weeks—period I. †Ratio of the predictive odds of achieving LDL-C level on E10 + A10 versus either A20 or R10. *p <0.01; **p <0.001. *(B)* Percent attainment of prespecified LDL-C target after 6 weeks—period II. †Ratio of the predictive odds of achieving LDL-C level on E10 + A20 versus either A40 or R20. *p <0.01; **p <0.001. A10/20/40 = atorvastatin 10 mg, 20 mg, or 40 mg; E10 = ezetimibe 10 mg; R10/20 = rosuvastatin 10 mg or 20 mg.

the ULN with or without associated muscle symptoms during period I or II.

A total of 4 patients experienced consecutive alanine aminotransferase or aspartate aminotransferase values $\geq 3\times$ the ULN during period I or II. During period I, 2 patients receiving rosuvastatin 10 mg treatment experienced consecutive elevations in alanine aminotransferase $\geq 3\times$ the ULN (mild intensity) during the last week of treatment. One of the 2 enzyme elevations was reported as related to study drug, and both patients discontinued treatment and withdrew from the study. During period II, 2 patients experienced elevated liver enzymes. One patient in the atorvastatin 20 mg uptitrated to atorvastatin 40 mg group had an elevated alanine aminotransferase result $\geq 3\times$ the ULN, which was considered of mild intensity and not related to study drug. A second patient who switched from rosuvastatin 10 mg in period I to ezetimibe 10 mg plus atorvastatin 20 mg in period II experienced consecutive elevations of alanine aminotransferase and aspartate aminotransferase $\geq 10\times$ the ULN, which were reported by the investigator as AEs of moderate severity and not considered to be related to study medication. AEs experienced by both patients occurred at the end of period II, and both patients completed the study without interruption or discontinuation of study drug.

Discussion

This clinical trial examined various lipid treatment options in patients at high CVD risk who did not achieve LDL-C treatment targets during 2 treatment periods. One unique aspect of the study was its "real-life" study design. The study began by requiring initial therapy with atorvastatin 10 mg/day as run-in before randomization. This reflects

Table 4
Summary of safety data (all patients as treated)

Adverse Experience*	Period I							Period II							
	Number (%) of Events			Difference in % of Events				Number (%) of Events)					Difference in % of Events		
	E10 + A10 (n = 120)*	A20 (n = 480)*	R10 (n = 939)*	E10 + A10 vs A20, Mean (95% CI)†	p†	E10 + A10 vs R10, Mean (95% CI)†	p†	E10 + A10 ↓ E10 + A10 (n = 28)*	A20 ↙ E10 + A20 (n = 124)*	A20 ↘ A40 (n = 124)*	R10 ↙ E10 + A20 (n = 231)*	R10 ↘ R20 (n = 205)*	E10 + A20 vs A40, Mean (95% CI)†	p†	E10 + A20 vs R20, Mean (95% CI)†	p†
All patients																
≥1 AE	9 (7.5)	57 (11.9)	128 (13.6)	−4.4 (−9.2, 2.2)		−6.1 (−10.4, 0.3)		1 (3.6)	11 (8.9)	13 (10.5)	36 (15.6)	18 (8.8)	−1.6 (−9.4, 6.0)		6.8 (0.6, 13.0)	
Drug related‡	1 (0.8)	15 (3.1)	27 (2.9)	−2.3 (−4.5, 1.6)		−2.0 (−3.6, 1.7)		1 (3.6)	2 (1.6)	3 (2.4)	8 (3.5)	2 (1.0)	−0.8 (−5.5, 3.6)		2.5 (−0.4, 5.8)	
Serious	0	3 (0.6)	10 (1.1)	−0.6 (−0.8, 2.5)		−1.1 (−1.9, 2.0)		0	2 (1.6)	2 (1.6)	5 (2.2)	1 (0.5)	0.0 (−4.3, 4.3)		1.7 (−0.7, 4.5)	
Serious drug related‡	0	0	0	0.0 (−0.8, 3.1)		0.0 (−0.4, 3.1)		0	0	0	0	0	0.0 (−3.0, 3.0)		0.0 (−1.8, 1.6)	
Discontinuations§	1 (0.8)	9 (1.9)	11 (1.2)	−1.0 (−2.9, 2.8)		−0.3 (−1.5, 3.4)		0	1 (0.8)	1 (0.8)	1 (0.4)	1 (0.5)	0.0 (−3.7, 3.7)		−0.1 (−2.3, 2.0)	
Deaths	0	0	2 (0.2)					0	0	0	1 (0.4)	0				
Prespecified AEs‖																
Alanine aminotransferase ≥3 × ULN¶	0	0	2 (0.2)	0 (−0.8, 3.1)	>0.999	−0.2 (−0.8, 2.9)	0.613	0	0	1 (0.8)	1 (0.4)	0	−0.8 (−4.4, 2.2)	0.317	0.4 (−1.4, 2.4)	0.346
Alanine aminotransferase ≥5 × ULN	0	0	1 (0.1)	0 (−0.8, 3.1)	>0.999	−0.1 (−0.6, 3.0)	0.721	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Alanine aminotransferase ≥10 × ULN	0	0	1 (0.1)	0 (−0.8, 3.1)	>0.999	−0.1 (−0.6, 3.0)	0.721	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Aspartate aminotransferase ≥3 × ULN¶	0	0	0	0 (−0.8, 3.1)	>0.999	0.0 (−0.4, 3.1)	>0.999	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Aspartate aminotransferase ≥5 × ULN	0	0	0	0 (−0.8, 3.1)	>0.999	0.0 (−0.4, 3.1)	>0.999	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Aspartate aminotransferase ≥10 × ULN	0	0	0	0 (−0.8, 3.1)	>0.999	0.0 (−0.4, 3.1)	>0.999	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Alanine aminotransferase and/or aspartate aminotransferase ≥3 × ULN¶	0	0	2 (0.2)	0 (−0.8, 3.1)	>0.999	−0.2 (−0.8, 2.9)	0.613	0	0	1 (0.8)	1 (0.4)	0	−0.8 (−4.4, 2.2)	0.317	0.4 (−1.4, 2.4)	0.346
Alanine aminotransferase and/or aspartate aminotransferase ≥5 × ULN	0	0	1 (0.1)	0 (−0.8, 3.1)	>0.999	−0.1 (−0.6, 3.0)	0.721	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Alanine aminotransferase and/or aspartate aminotransferase ≥10 × ULN	0	0	1 (0.1)	0 (−0.8, 3.1)	>0.999	−0.1 (−0.6, 3.0)	0.721	0	0	0	1 (0.4)	0	0.0 (−3.0, 3.0)	>0.999	0.4 (−1.4, 2.4)	0.346
Gastrointestinal-related AE	2 (1.7)	12 (2.5)	19 (2.0)	−0.8 (−3.1, 3.5)	0.589	−0.4 (−2.1, 3.9)	0.792	1 (3.6)	2 (1.6)	2 (1.6)	2 (0.9)	2 (1.0)	0.0 (−4.3, 4.3)	>0.999	−0.1 (−2.7, 2.2)	0.905
Allergic reaction or rash AE	0	2 (0.4)	8 (0.9)	−0.4 (−1.5, 2.7)	0.479	−0.9 (−1.7, 2.3)	0.310	0	0	1 (0.8)	0	0	−0.8 (−4.4, 2.2)	0.317	0.0 (−1.8, 1.6)	>0.999

% = (number of patients within the AE category/number of treated patients) × 100; A10/20/40 = atorvastatin 10 mg, 20 mg, or 40 mg; E10 = ezetimibe 10 mg; R10/20 = rosuvastatin 10 mg or 20 mg.

* All-patients-as-treated population; all randomized patients who took at least 1 dose of study medication. For laboratory safety (alanine aminotransferase, aspartate aminotransferase, creatine kinase, and potential Hy's law condition), patients must have taken at least 1 dose of study medication and have at least 1 postbaseline measurement within 14 days of the last dose of study therapy to be included in the analysis.

† Confidence intervals and p values calculated using the Miettinen and Nurminen method.

‡ Determined by the investigator to be related to the drug; assessment of drug causality determined using following criteria: definitely, probably, or possibly related defined as "drug related"; probably not and definitely not related defined as "not related." Investigator-reported nonserious drug-related AEs were reported as follows. period I (43 patients total): 1 patient (0.8%) receiving ezetimibe plus atorvastatin 10 mg (muscle spasms); 15 patients (3.1%) receiving atorvastatin 20 mg (abdominal pain upper in 2, breath odor in 1, constipation in 1, dry mouth in 2, dyspepsia in 1, nausea in 2, edema peripheral in 1, alanine aminotransferase increase in 1, blood creatine kinase increase in 3, myalgia in 1, emotional disorder in 1, rash pruritic in 1, and urticaria in 2); and 27 patients (2.9%) receiving rosuvastatin 10 mg (abdominal pain upper in 3, constipation in 1, dyspepsia in 1, nausea in 2, asthenia in 2, rhinitis in 1, alanine aminotransferase increase in 3, aspartate aminotransferase increase in 3, blood creatine kinase increase in 4, gamma glutamyltransferase increase in 2, muscle spasms in 2, musculoskeletal chest pain in 2, myalgia in 3, dizziness in 1, headache in 4, paresthesia in 1, mood altered in 1, dermatitis allergic in 1, hyperhidrosis in 1, rash pruritic in 1, and pallor in 1). Period II (16 patients total): 1 patient (3.6%) receiving ezetimibe 10 mg plus atorvastatin 10 mg → ezetimibe 10 mg plus atorvastatin 10 mg (abdominal pain upper), 2 patients (1.6%) receiving atorvastatin 20 mg → ezetimibe 10 mg plus atorvastatin 20 mg (fatigue in 1 and alanine aminotransferase increase in 1), 3 patients (2.4%) receiving atorvastatin 20 mg → atorvastatin 40 mg (abdominal pain upper in 1, alanine aminotransferase increase in 1, aspartate aminotransferase increase in 1, dysgeusia in 1, and headache in 1), 8 patients (3.5%) receiving rosuvastatin 10 mg → ezetimibe 10 mg plus atorvastatin 20 mg (flatulence in 1, alanine aminotransferase increase in 1, aspartate aminotransferase increase in 2, blood creatine kinase increase in 1, arthralgia in 1, muscle spasms in 1, musculoskeletal pain in 1, dizziness in 1, and headache in 1), and 2 patients (1.0%) receiving rosuvastatin 10 mg → rosuvastatin 20 mg (blood creatine kinase increase in 2).

§ Study medication withdrawn.

‖ Prespecified AEs of special interest. There were no reports of creatine kinase ≥10× the ULN, potential Hy's law (alanine aminotransferase or aspartate aminotransferase elevations >3× the ULN, with serum alkaline phosphatase <2× the ULN and total bilirubin ≥2× the ULN), hepatitis-related AEs, or gall bladder−related AEs.

¶ Patients with ≥2 consecutive measurements of ≥3× the ULN, a single last measurement of ≥3× the ULN, or a measurement of ≥3× the ULN followed by a measurement of <3× the ULN taken >2 days after the last dose of study medication.

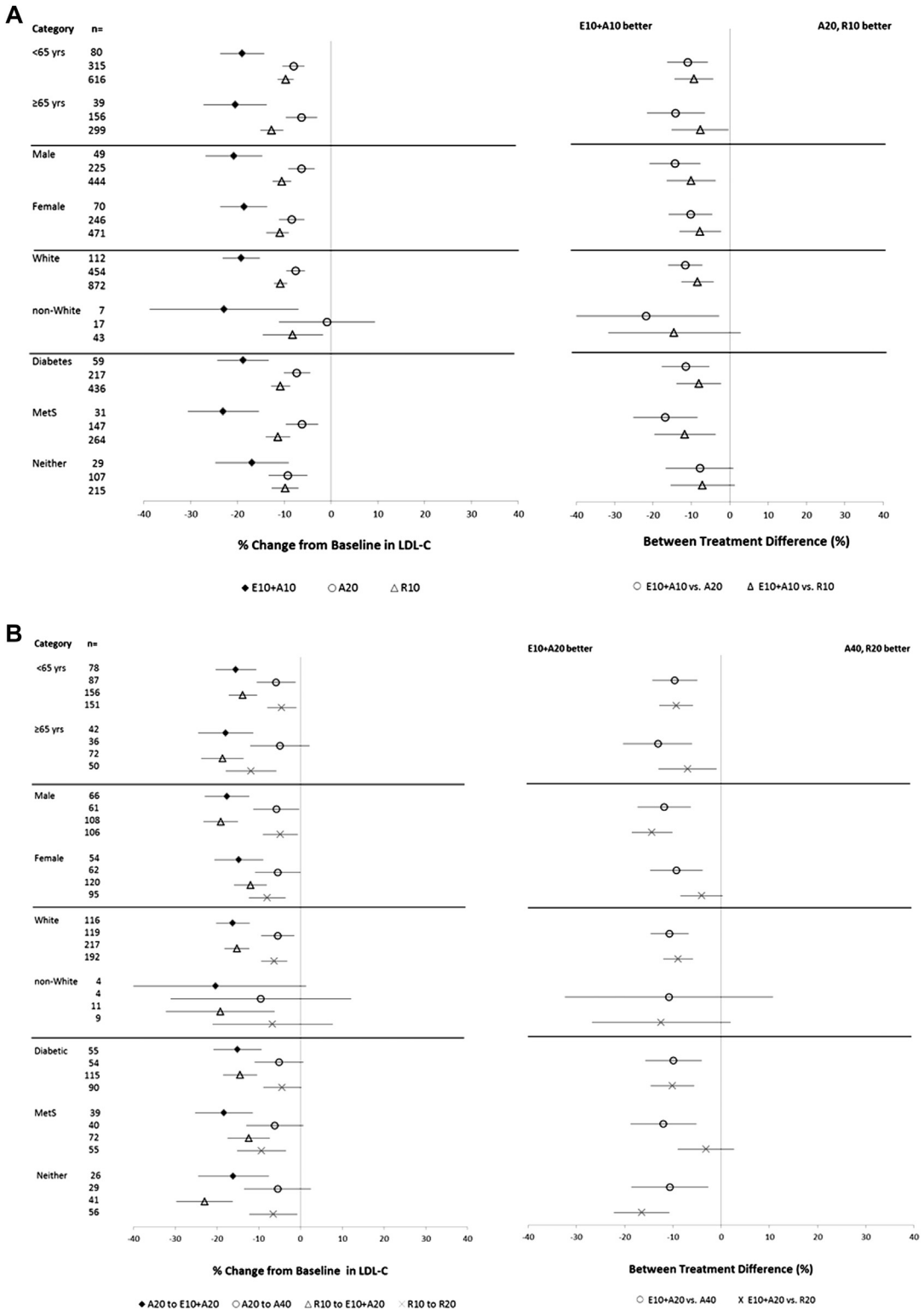

Figure 4. *(A)* Percent change from treated baseline in LDL-C for prespecified subgroups after 6 weeks—period I. Treatments were (1) ezetimibe plus atorvastatin 10 mg *(closed diamonds)*, (2) atorvastatin 20 mg *(open circles)*, or (3) rosuvastatin 10 mg *(open triangles)*. MetS = subgroup of patients with metabolic syndrome and no diabetes; Neither = no metabolic syndrome or diabetes; n = number of subjects in each subgroup for ezetimibe plus atorvastatin 10 mg, atorvastatin 20 mg, and rosuvastatin 10 mg, respectively. Between-treatment differences within each subgroup are ezetimibe plus atorvastatin 10 mg minus atorvastatin 20 mg *(open circles)* and ezetimibe plus atorvastatin 10 mg minus rosuvastatin 10 mg *(open triangles)*. *(B)* Percent change from treated baseline in LDL-C for prespecified subgroups after 6 weeks—period II. Treatments during periods I and II were (1) atorvastatin 20 mg → atorvastatin 20 mg plus ezetimibe *(closed diamonds)*, (2) atorvastatin 20 mg → atorvastatin 40 mg *(open circles)*, (3) rosuvastatin 10 mg → atorvastatin 20 mg plus ezetimibe *(open triangles)*, or (4) rosuvastatin 10 mg → rosuvastatin 20 mg *(×)*. n = number of subjects in subgroup for each treatment regimen (1, 2, 3, 4, as aforementioned). Treatment differences within a subgroup are ezetimibe plus atorvastatin 20 mg minus atorvastatin 40 mg *(open circles)* and ezetimibe plus atorvastatin 20 mg minus rosuvastatin 20 mg (×).

the common clinical practice of prescribing a statin (which is often a generic statin) as the initial pharmacologic therapy to treat hypercholesterolemia in patients at high CVD risk. After the 5 week run-in on atorvastatin 10 mg/day, study subjects who were not at LDL-C treatment target were then randomized to a number of therapeutic approaches, with each being illustrative examples of cholesterol-lowering options often considered for the purpose of achieving LDL-C treatment targets. The study went yet further in evaluating treatment options among those who still did not achieve LDL-C treatment targets, despite initial treatment with atorvastatin 10 mg/day and subsequent adjustment in lipid-altering drug therapy. The findings of this study can be summarized as follows:

1) Among hypercholesterolemic patients at high CVD risk treated with atorvastatin 10 mg/day having LDL-C levels that continued to exceed LDL-C treatment targets (i.e., $\geq$100 and $\leq$160 mg/dl), ezetimibe 10 mg plus atorvastatin 10 mg reduced LDL-C significantly more than doubling atorvastatin from 10 to 20 mg and significantly more than switching atorvastatin 10 mg to rosuvastatin 10 mg.
2) Among hypercholesterolemic patients at high CVD risk who had their atorvastatin 10 mg/day doubled to 20 mg/day and who continued to have LDL-C levels that exceeded treatment targets, ezetimibe 10 mg plus atorvastatin 20 mg reduced LDL-C significantly more than doubling atorvastatin 20 to 40 mg.
3) Among hypercholesterolemic patients at high CVD risk who had switched from atorvastatin 10 mg/day to rosuvastatin 10 mg/day and who continued to have LDL-C levels that exceeded treatment targets, switching to ezetimibe 10 mg plus atorvastatin 20 mg reduced LDL-C significantly more than doubling rosuvastatin from 10 to 20 mg.

Concomitant with greater LDL-C lowering, relative to comparative treatments, ezetimibe added to atorvastatin 10 mg (period I) or atorvastatin 20 mg (period II) produced significantly greater percent attainment of LDL-C targets of $<$100 or $<$70 mg/dl[1,2] and produced significantly greater percent reductions in total cholesterol, non-HDL-C, apolipoprotein B (except ezetimibe plus atorvastatin 20 mg vs atorvastatin 40 mg) and lipid and lipoprotein ratios. These results are consistent with the comparative effects of adding ezetimibe to ongoing statins versus statin titration seen in other studies of moderately high- to high-risk subjects with inadequately controlled LDL-C during statin therapy.[11–13]

Previous studies suggest that doubling of the statin dose typically results in an incremental reduction of 5% to 7% from untreated baseline.[14] This is consistent with the findings of the present study, wherein doubling atorvastatin or rosuvastatin reduced LDL-C by an additional 6.9% to 9.5%. Switching to a different statin represents a second option for management of hypercholesterolemia.[14,15] In the present study, switching from atorvastatin 10 mg to rosuvastatin 10 mg resulted in greater LDL-C lowering. Adding ezetimibe to ongoing statin therapy represents yet another therapeutic alternative.[16] In the present study, addition of ezetimibe to ongoing atorvastatin 10 mg during period I reduced LDL-C by 22%, and adding ezetimibe to atorvastatin 20 mg during period II reduced LDL-C by 17%. Few clinical trials have evaluated the sequential modification of lipid-altering therapy on LDL-C lowering and attainment of treatment targets.[17] Results from the present trial suggest that statin doubling and ezetimibe add-on treatment strategies produce incremental LDL-C-lowering for patients with persistent LDL-C levels $\geq$100 mg/dl after 6 weeks of atorvastatin 10 mg (period I) or after atorvastatin 10 mg followed by an additional 6 weeks on atorvastatin 20 mg or rosuvastatin 10 mg (period II).

Study treatment approaches were generally similar with regard to safety and tolerability and generally consistent with previous clinical studies of similar duration. Study limitations include the short duration of the study and a study population that was mostly white, thus limiting the generalizability of study results for long-term therapy or more diverse populations. Additionally, although this trial evaluated the effect of study medications on lipids and other parameters, this study was neither designed to evaluate nor did it evaluate the effect of ezetimibe on CVD outcomes.

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