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Switching from statin monotherapy to ezetimibe/simvastatin or rosuvastatin modifies the relationships between apolipoprotein B, LDL cholesterol, and non-HDL cholesterol in patients at high risk of coronary disease☆,☆☆

Helena Vaverkova [a,*], Michel Farnier [b], Maurizio Averna [c], Luc Missault [d], Margus Viigimaa [e], Qian Dong [f], Arvind Shah [f], Amy O. Johnson-Levonas [f], Philippe Brudi [g]

[a] 3rd Department of Internal Medicine, Medical Faculty, University Hospital Olomouc, Olomouc, Czech Republic
[b] Point Medical, Dijon, France
[c] Dipartimento di Medicina Clinica e delle Patologie Emergenti-Policlinico "Paolo Giaccone," Palermo, Italy
[d] St. Jan Hospital, Department of Cardiology, Bruges, Belgium
[e] Tallinn University of Technology, North-Estonia Regional Hospital, Tallinn, Estonia
[f] Merck, Whitehouse Station, NJ, USA
[g] Merck Medical Affairs, Whitehouse Station, NJ, USA

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ABSTRACT

Objective: To evaluate relationships between apolipoprotein B (Apo B), LDL cholesterol (LDL-C), and non-HDL-C in high-risk patients treated with lipid-lowering therapy.

Design and methods: This post-hoc analysis calculated LDL-C and non-HDL-C levels corresponding to an Apo B of 0.9 g/L following treatment with 1) statin monotherapy (baseline) and 2) ezetimibe/simvastatin 10/20 mg or rosuvastatin 10 mg (study end). The percentages of patients reaching LDL-C, non-HDL-C, and Apo B targets were calculated at study end.

Results: After switching to ezetimibe/simvastatin or rosuvastatin, the LDL-C and non-HDL-C corresponding to Apo B = 0.9 g/L were closer to the more aggressive LDL-C and non-HDL-C goals (1.81 and 2.59 mmol/L, respectively). Only slightly >50% of the patients who reached minimum recommended LDL-C or non-HDL-C at study end also had an Apo B level <0.9 g/L with both treatments.

Conclusion: The use of Apo B for monitoring the efficacy of lipid-altering therapy would likely lead to more stringent criteria for lipid lowering.

Introduction

Both national and international guidelines identify low-density lipoprotein cholesterol (LDL-C) as the primary treatment target for reducing coronary heart disease (CHD) risk in patients with hypercholesterolemia [1,16,18,29]. Cholesterol management guidelines endorse a minimum LDL-C goal of <2.59 mmol/L in high risk patients with an optional target of <1.99 or <1.81 mmol/L in persons at very high risk of CHD [1,16,18,29]. Some patients with lipoprotein abnormalities, particularly those with increased triglyceride (TG) levels, may have excess levels of other apolipoprotein (Apo) B-containing lipoproteins (e.g., very low-density lipoprotein, intermediate-density lipoprotein, lipoprotein (a), and a preponderance of cholesterol-depleted, small, dense LDL particles), which confer additional atherogenic risk beyond that represented by LDL-C alone [8]. In such patients, non-high-density lipoprotein cholesterol (non-HDL-C; i.e., the sum of cholesterol carried by chylomicrons, very low-density lipoprotein, intermediate-density lipoprotein plus LDL) may be a more accurate predictor of CHD risk compared with LDL-C, especially among patients receiving statin therapy [2,15,19].

Apo B is another parameter with proven utility in assessing CHD risk [8]. Apo B is a reliable measure of the total number of atherogenic particles in the blood stream since each atherogenic lipoprotein contains a single molecule of Apo B [26,32]. Several studies have shown that Apo B is a more accurate parameter for assessing CHD risk compared with LDL-C [15,22,25,27,34,36]. LDL-C is inadequate at assessing the total

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* Corresponding author. Fax: +42 585 852526.
E-mail address: Helena.Vaverkova@fnol.cz (H. Vaverkova).

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concentration of atherogenic particles particularly among high-risk patients who frequently have a preponderance of cholesterol-depleted, small, dense LDL particles [3,17,21,31].

To this end, the consensus statement issued by the American Diabetes Association (ADA) and the American College of Cardiology (ACC) Foundation identifies non-HDL-C and apo B as co-primary targets of therapy in high cardiometabolic risk patients [8]. Non-HDL-C goals of 3.37 and <2.59 mmol/L and apo B goals of<0.9 g/L and 0.8 g/L are recommended for high-risk and very high-risk individuals, respectively [8].

The use of Apo B in clinical practice to guide patient management is not widespread. The main reason is probably because Apo B is not currently recommended as a primary screening parameter by most international and national lipid treatment guidelines. Non-HDL-C and Apo B have been shown to correlate relatively strongly both in non-treated and statin-treated patients, although the strength of these associations varies depending on the population studied [4,6,24,28,33]. As a result, some have proposed using non-HDL-C as a surrogate measure of Apo B, thus obviating the need to introduce a new assay into the standard lipid panel [6].

Previous literature demonstrated that statins provide larger reductions in plasma LDL-C levels and result in a lowering of LDL-C to lower population percentile level than that seen for Apo B [4,6,9,10,30]. Thus, the use of LDL-C as the sole parameter in guiding the management of statin-treated patients may result in the underachievement of recommended non-HDL-C and most especially Apo B targets, thereby placing patients at unnecessary risk [7,8]. Although three recent studies evaluated the effects of statin therapy on the correlations between Apo B:LDL-C and Apo B:non-HDL-C [4,6,9], relatively little is known about the effects of other lipid-altering therapies on these correlations.

This post-hoc analysis of a previously published study [12] evaluated the relationship of Apo B with LDL-C and non-HDL-C values in a population of 618 high-risk hypercholesterolemic patients (i.e., defined by prior history of CHD; type 2 diabetes with high cardiovascular risk; or 10 year Framingham risk, >20%) who did not achieve their LDL-C goals while taking a stable dose of open-label statin monotherapy. Following 6 weeks of treatment with statin monotherapy, patients with LDL-C >2.59 mmol/L were switched to double-blind ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg for 6 weeks. Both EZE/SIMVA 10/20 mg and ROSUVA 10 mg were chosen for use in this study because they were expected to show greater LDL-C-lowering efficacy compared with the statins used at baseline. This analysis evaluated the correlations between Apo B and LDL-C or non-HDL-C following 1) 6 weeks of open-label treatment with statin monotherapy (i.e., baseline) and 2) 6 weeks of double-blind treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg (i.e., study end). Simple linear regression (SLR) analyses were also performed at baseline and study end to evaluate the LDL-C and non-HDL-C values that are equivalent to the recommended Apo B targets of <0.9 and <0.8 g/L. Additional analyses were performed in patient subgroups defined by baseline TG values (i.e., TG, < and >2.26 mmol/L) and relative potency of the pre-randomization statin monotherapy (i.e., low and high). Analyses were performed to evaluate the proportions of patients reaching LDL-C, non-HDL-C, and Apo B targets.

Methods

Patients and study design

Full details of the methods of the INCROSS study are reported elsewhere [12]. In this multicenter, randomized, double-blind trial, active-controlled, parallel group study, 618 patients with documented hypercholesterolemia (LDL-C, 2.59–4.92 mmol/L at the screening visit and 2.59–4.14 mmol/L at the randomization visit) and high cardiovascular risk who were taking a stable daily dose of one of several statin medications for >6 weeks prior to the study randomization visit entered a 6 week open-label stabilization/screening period during which they continued to receive their pre-study statin dose. Patients were deemed to be of high cardiovascular risk if they met one or more of the following criteria: (i) history of CHD (i.e., stable and unstable angina, revascularization procedure, myocardial infarction, documented myocardial ischemia) or with established vascular atherosclerotic disease (i.e., peripheral vascular disease, ischemic stroke); (ii) type 2 diabetes without a history of vascular disease and with high cardiovascular risk (i.e., renal impairment [proteinuria, >300 mg/24 h, or creatinine clearance standardized for body surface area, <1.002 mL/s] and/or at least 2 CHD risk factors per Framingham risk calculation); (iii) CHD risk >20% over 10 years as determined by Framingham risk calculation. Fasting TG levels had to be <3.96 mmol/L 1 week prior to the randomization visit (i.e., week 0/baseline) to allow for the calculation of LDL-C by the Friedewald equation.

Patients who did not achieve their minimum recommended LDL-C goals (i.e., <2.59 mmol/L) after taking a stable dose (>6 weeks) of open-label statin monotherapy were stratified by study site and potency of their pre-randomization statin brand/dose (low [stratum 1: atorvastatin, 10 mg; fluvastatin, 80 mg; lovastatin, 20 mg; pravastatin, 40 mg; simvastatin, 20 mg] or high [stratum 2: atorvastatin, 20 mg; rosuvastatin, 5 mg; simvastatin, 40 mg]) and subsequently randomized in equal proportions to receive double-blind EZE/SIMVA 10/20 mg ($n = 314$) or ROSUVA 10 mg ($n = 304$) for 6 weeks. Both these treatments represent starting doses of more potent lipid-lowering therapies, and according to the product labels, should yield similar LDL-C reductions.

As previously described, the primary efficacy endpoint for this study was the percentage change from baseline (i.e., week 0) to study endpoint (i.e., last post baseline measurement during the 6 week active treatment period) in LDL-C. Secondary efficacy measurements included the proportion of patients achieving LDL-C goals (<2.59 and <1.81 mmol/L) as well as the mean percentage changes from baseline in total cholesterol, TG, HDL-C, non-HDL-C, and Apo B after 6 weeks of treatment.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies, and all patients provided written informed consent.

Laboratory methods

All analyses were conducted on fasting blood samples at a certified central laboratory (MRLI, Brussels, Belgium) according to standards specified by the National Heart Lung and Blood Institute and Centers for Disease Control and Prevention [23]. Plasma concentrations of TC, TG, and HDL-C were quantified enzymatically using the Hitachi 747 analyzer (Roche Diagnostics Corporation, Indianapolis, IN). LDL-C levels were calculated using the equation of Friedewald et al. [LDL-C = TC − HDL-C − (TG/2.2)] [14]. Ultracentrifugation was used to measure LDL-C values in patients with TG >4.5 mmol/L. HDL-C was quantified enzymatically after the removal of Apo B-containing lipoproteins by heparin and manganese chloride precipitation [20,37]. Non-HDL-C levels were calculated by subtracting HDL-C from TC values. Apo B concentrations in whole plasma were measured by immunonephelometry using a Dade Behring GmbH Nephelometer (Marburg, Germany) [13]. International Federation of Clinical Chemistry (IFCC) standards were used to calibrate the Apo B measurements.

Statistical analyses

The current report describes the results of a post-hoc exploratory analysis performed to evaluate the relationship between Apo B and LDL-C or non-HDL-C following (i) 6 weeks of open-label treatment with statin monotherapy (i.e., baseline/week 0) and (ii) 6 weeks of double-

blind treatment with EZE/SIMVA or ROSUVA (i.e., study end). All analyses reported herein were performed in the full analysis set population ($n=602$) which included all randomized patients who had baseline vales, had received at least 1 dose of study medication, and had a 6 week value. In total, 593 patients (of 618 study participants) had paired baseline and week 6 values for Apo B and LDL-C or Apo B and non-HDL-C (i.e., referred to in the text as the overall cohort). Additional analyses were performed in patient subgroups defined by baseline TG values <2.26 mmol/L (i.e., normal or borderline-high TG; $n=497$) and >2.26 mmol/L (i.e., hypertriglyceridemic; $n=96$).

Changes from baseline in lipids, lipoproteins, and apolipoproteins were calculated using an analysis-of-variance (ANOVA) model with terms for treatment, stratum (according to potency of the prerandomization statin brand/dose), baseline lipid value under assessment, and study center. Within- and between-group least squares (LS) means and 95% confidence intervals (CIs) were estimated from the ANOVA model. A non-parametric ANOVA analysis was performed for TG because this parameter is not normally distributed. The differences between treatment groups were quantified using the difference in medians and 95% CIs using Hodges–Lehmann for estimates.

The overall distributions of Apo B and LDL-C or non-HDL-C were explored with scatter plots of Apo B versus LDL-C or non-HDL-C at baseline and study end. Different colors and symbols were used to differentiate the two treatment arms in these plots (i.e., red = EZE/SIMVA, 10/20 mg; blue = ROSUVA, 10 mg). The correlations between Apo B:LDL-C and Apo B:non-HDL-C were assessed using Pearson correlation coefficients. In addition, SLR analyses were performed to explore the relationships between Apo B and LDL-C or non-HDL-C at baseline and study end. The predicted values of LDL-C and non-HDL-C corresponding to an Apo B value of 0.9 g/L were calculated from the SLR. All analyses were performed with SAS statistical software (version 9.1.3) at a two-sided significance level of 0.05.

Analyses were performed to calculate the proportion of patients achieving various LDL-C (<2.59, <1.99, and <1.81 mmol/L), non-HDL-C (<3.37 and <2.59 mmol/L), and Apo B targets (<0.9 and <0.8 g/L). In addition, of those who achieved a single specified LDL-C, non-HDL-C, or Apo B target at study end, the proportions of patients who achieved the second target were also analyzed. Raw proportions of patients achieving these targets and the corresponding 95% confidence interval (CI) based on Wilson's method were reported. Target attainment analyses were conducted in all patients who had week 6 data within each of the treatment groups and broken down by baseline TG subgroup.

Results

The complete results of the INCROSS study have been reported previously [12]. In this study of high-risk hypercholesterolemic patients who did not achieve the minimum recommended LDL-C goal (i.e., ≥2.59 mmol/L) while taking statin monotherapy, switching to EZE/SIMVA 10/20 mg compared with ROSUVA 10 mg was shown to produce significantly greater LS mean reductions from baseline in LDL-C (27.7% versus 16.9%; $p<0.001$), non-HDL-C (23.4% versus 14.0%; $p<0.001$), and Apo B (17.9% versus 9.8%; $p<0.001$) after 6 weeks of double-blind treatment [12]. The demographic and lipid characteristics for the cohort of patients included in the current post-hoc analysis are presented in Table 1. The treatment groups were generally well-balanced with respect to baseline demographic and lipid/lipoprotein characteristics (Table 1). Patients with hypertriglyceridemia (TG, >2.27 mmol/L) had a higher mean body weight and body mass index compared with non-hypertriglyceridemic patients. A greater proportion of patients in the TG >2.26 mmol/L subgroup had a history of type 2 diabetes as evidenced by their lipid/lipoprotein profile (i.e., elevated TG and Apo B levels with low HDL-C levels).

The overall distributions of Apo B versus LDL-C and non-HDL-C for patients with paired data at baseline and study end are plotted in Figs. 1 and 2, respectively. An SLR model was fitted and the results are summarized in Tables 2 and 3, respectively. The relationships between Apo B:LDL-C and Apo B:non-HDL-C were well described by linear regression lines both following treatment with a stable dose of statin monotherapy (i.e., baseline) and after switching to a more potent lipid-lowering therapy (i.e., study end). The similarities in the regression line characteristics and r^2 values (Pearson correlation coefficients) across statin potency strata (i.e., low/high) at baseline demonstrated that the relationships between Apo B and LDL-C or non-HDL-C appeared to be independent of the LDL-C-lowering potency of the statin monotherapy received during the open-label run-in phase of the study (data not shown). Therefore, data from both strata were pooled in all subsequent

Table 1
Summary of baseline characteristics and lipid values for overall analysis cohort (FAS) presented by treatment group.

	EZE/SIMVA 10/20 mg; $N=305$	ROSUVA 10 mg; $N=297$
Demographic parameters		
Mean age (SD), years		
Overall analysis cohort	63.3 (9.9)	63.1 (10.1)
TG, <2.26 mmol/L	63.9 (10.1) [$n=253$]	63.1 (10.2) [$n=250$]
TG, ≥2.26 mmol/L	60.3 (8.4) [$n=52$]	62.7 (9.2) [$n=47$]
Females, *n* (%)		
Overall analysis cohort	125 (41.0)	117 (39.4)
TG, <2.26 mmol/L	108 (42.7) [$n=253$]	94 (37.6) [$n=250$]
TG, ≥2.26 mmol/L	17 (32.7) [$n=52$]	23 (48.9) [$n=47$]
Mean body weight (SD), kg		
Overall analysis cohort	78.6 (15.7)	79.4 (14.3)
TG, <2.26 mmol/L	77.3 (15.8) [$n=253$]	78.3 (14.0) [$n=250$]
TG, ≥2.26 mmol/L	85.0 (13.8) [$n=52$]	84.9 (14.7) [$n=47$]
Mean body mass index (SD), kg/m^2		
Overall analysis cohort	28.1 (4.8)	28.0 (4.6)
TG, <2.26 mmol/L	27.7 (4.8) [$n=253$]	27.5 (4.4) [$n=250$]
TG, ≥2.26 mmol/L	29.9 (4.1) [$n=51$]	30.7 (4.7) [$n=47$]
History of diabetes, *n* (%)		
Overall analysis cohort	89 (29.2)	76 (25.6)
TG, <2.26 mmol/L	62 (24.5) [$n=253$]	60 (24.0) [$n=250$]
TG, ≥2.26 mmol/L	27 (51.9) [$n=52$]	16 (34.0) [$n=47$]
History of CHD, *n* (%)		
Overall analysis cohort	148 (48.5)	140 (47.1)
TG, <2.26 mmol/L	126 (49.8) [$n=253$]	119 (47.6) [$n=250$]
TG, ≥2.26 mmol/L	22 (42.3) [$n=52$]	21 (44.7) [$n=47$]
Baseline lipid values		
Mean LDL-C (SD), mmol/L		
Overall analysis cohort	3.2 (0.4)	3.2 (0.4)
TG, <2.26 mmol/L	3.2 (0.4) [$n=253$]	3.2 (0.4) [$n=250$]
TG, ≥2.26 mmol/L	3.3 (0.4) [$n=52$]	3.3 (0.4) [$n=47$]
Mean total cholesterol (SD), mmol/L		
Overall analysis cohort	5.4 (0.6)	5.4 (0.6)
TG, <2.26 mmol/L	5.3 (0.5) [$n=253$]	5.3 (0.6) [$n=250$]
TG, ≥2.26 mmol/L	5.8 (0.6) [$n=52$]	5.8 (0.6) [$n=47$]
Median TG (SD), mmol/L		
Overall analysis cohort	1.5 (0.8)	1.4 (0.8)
TG, <2.26 mmol/L	1.3 (0.6) [$n=253$]	1.3 (0.6) [$n=250$]
TG, ≥2.26 mmol/L	2.6 (0.7) [$n=52$]	2.8 (0.6) [$n=47$]
Mean HDL-C (SD), mmol/L		
Overall analysis cohort	1.4 (0.4)	1.4 (0.4)
TG, <2.26 mmol/L	1.5 (0.4) [$n=253$]	1.5 (0.4) [$n=250$]
TG, ≥2.26 mmol/L	1.2 (0.3) [$n=52$]	1.2 (0.3) [$n=47$]
Mean non-HDL-C (SD), mmol/L		
Overall analysis cohort	3.9 (0.6)	4.0 (0.6)
TG, <2.26 mmol/L	3.8 (0.5) [$n=253$]	3.8 (0.5) [$n=250$]
TG, ≥2.26 mmol/L	4.5 (0.5) [$n=52$]	4.6 (0.5) [$n=47$]
Mean Apo B (SD), g/L		
Overall analysis cohort	1.2 (0.2)	1.2 (0.2)
TG, <2.26 mmol/L	1.2 (0.2) [$n=251$]	1.1 (0.2) [$n=246$]
TG, ≥2.26 mmol/L	1.3 (0.2) [$n=50$]	1.4 (0.2) [$n=46$]

Apo indicates apolipoprotein; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; TG, triglyceride.
Standard deviation for median is calculated by (Q3 − Q1)/1.075.

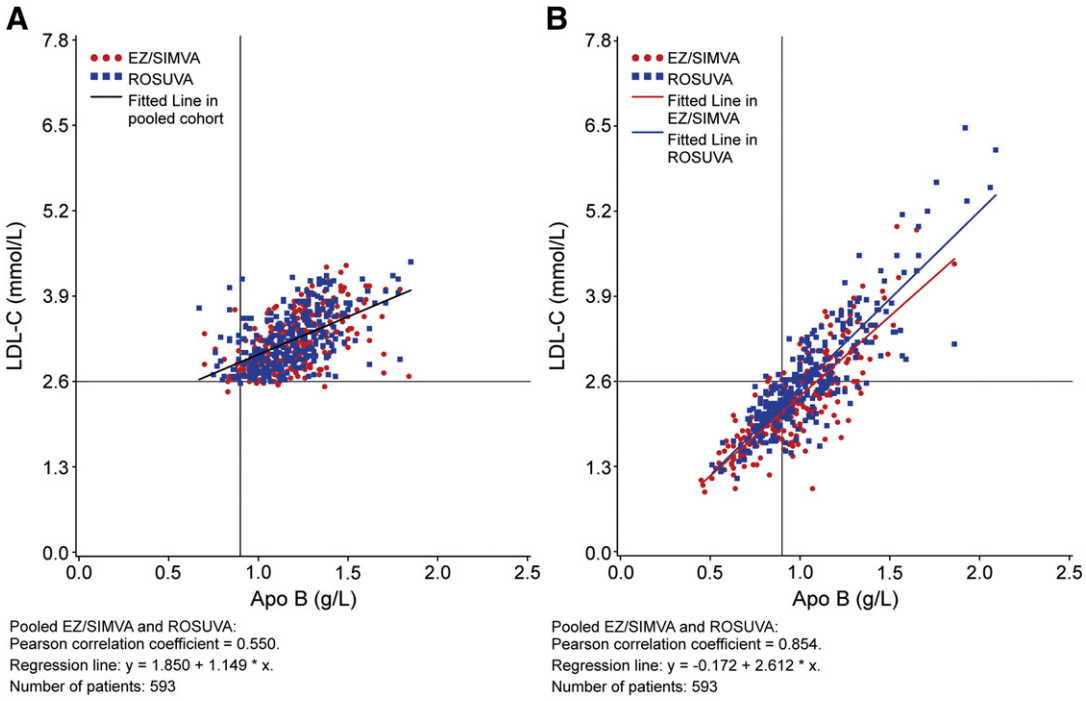

Fig. 1. Scatterplots of Apo B versus LDL-C at baseline (A) and following 6 weeks of treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg (B). The upper thresholds for the less-stringent LDL-C <2.59 mmol/L and Apo B <0.9 g/L targets are denoted by horizontal and vertical lines, respectively. Right lower quadrant in (B) shows the subjects who met LDL-C goal <2.59 mmol/L but did not reach Apo B value <0.9 g/L. EZE/SIMVA indicates ezetimibe/simvastatin; ROSUVA, rosuvastatin; LDL-C, low-density lipoprotein cholesterol; Apo, apolipoprotein.

analyses to yield a more robust data set for examining the effects of lipid-lowering therapy on the relationships between the lipoprotein and lipid parameters. A single regression line was calculated for all statin-treated patients at baseline (Figs. 1A and 2A), whereas 2 regression lines were calculated for the individual treatment arms at study end (Figs. 1B and 2B).

For the study entry criteria, patients were required to have an LDL-C value in the range of 2.59–4.14 mmol/L after receiving a stable dose of open-label statin monotherapy during the run-in period in order to be eligible for enrollment. As a result, the majority of the data points at baseline fell within the upper right quadrant of the Apo B versus LDL-C and Apo B versus non-HDL-C scatter plots (Figs. 1A and 2A,

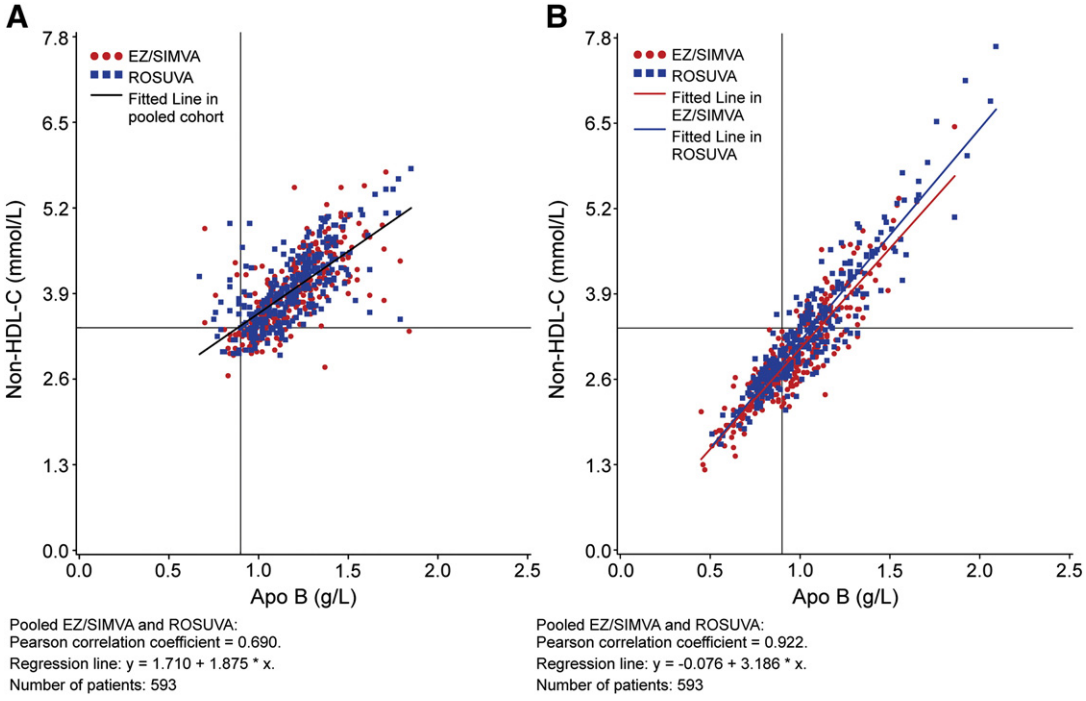

Fig. 2. Scatterplots of Apo B versus non-HDL-C at baseline (A) and following 6 weeks of treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg (B). The upper thresholds for the less-stringent non-HDL-C <3.37 mmol/L and Apo B <0.9 g/L targets are denoted by horizontal and vertical lines, respectively. Right lower quadrant in (B) shows the subjects who met non-HDL-C goal <3.37 mmol/L but did not reach Apo B target <0.9 g/L. EZ/SIMVA indicates ezetimibe/simvastatin; ROSUVA, rosuvastatin; non-HDL-C, non-high-density lipoprotein cholesterol; Apo, apolipoprotein.

Table 2
Slope, intercept, Pearson correlation coefficient, and predicted LDL-C values based on simple linear regression analyses of Apo B versus LDL-C at baseline (i.e., while on stable dose of statin monotherapy) and following 6 weeks of treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg.

	N	Slope	Intercept	Pearson correlation coefficient (r^2)	Predicted LDL-C value[a]
Baseline (i.e., while on stable dose of statin monotherapy)					
Pooled treatment groups					
Overall analysis cohort	593	1.15	1.85	0.550 (0.30)	2.9
TG, <2.26 mmol/L	497	1.27	1.73	0.566 (0.32)	2.9
TG, ≥2.26 mmol/L	96	1.26	1.55	0.589 (0.35)	2.7
Week 6 (i.e., after switching from statin monotherapy to EZE/SIMVA or ROSUVA)					
Pooled treatment groups					
Overall analysis cohort	593	2.61	−0.17	0.854 (0.73)	2.2
TG, <2.26 mmol/L	497	2.70	−0.21	0.881 (0.78)	2.2
TG, ≥2.26 mmol/L	96	2.62	−0.48	0.820 (0.67)	1.9
EZE/SIMVA, 10/20 mg					
Overall analysis cohort	301	2.43	−0.06	0.829 (0.69)	2.1
TG, <2.26 mmol/L	251	2.59	−0.15	0.873 (0.76)	2.2
TG, ≥2.26 mmol/L	50	2.25	−0.21	0.771 (0.59)	1.8
ROSUVA, 10 mg					
Overall analysis cohort	292	2.68	−0.17	0.867 (0.75)	2.2
TG, <2.26 mmol/L	246	2.73	−0.18	0.883 (0.78)	2.3
TG, ≥2.26 mmol/L	46	2.77	−0.53	0.851 (0.72)	2.0

EZE/SIMVA indicates ezetimibe/simvastatin; ROSUVA, rosuvastatin; TG, triglyceride.
[a] Predicted LDL-C value (mmol/L) assuming Apo B value of 0.9 g/L.

respectively), the boundaries of which were established by the minimum recommended targets of 0.9 g/L for Apo B and 2.59 mmol/L for LDL-C or 3.37 mmol/L for non-HDL-C. Six patients with an LDL-C value slightly below the LDL-C entry threshold of 2.59 mmol/L were enrolled in this study and received randomized treatment assignment. Following treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg, the observed reductions in LDL-C and non-HDL-C led to a shift in the distribution of the data points toward the lower left and right quadrants which encompassed the LDL-C (Fig. 1B) and non-HDL-C targets (Fig. 2B). The regression lines for the 2 treatment arms are identified by different colors and symbols in Figs. 1B and 2B. Relative to baseline, treatment with EZE/SIMVA and ROSUVA led to decreases in the scatter of the data points (implying increases in correlations) and roughly a doubling of the slopes for the Apo B versus LDL-C and non-HDL-C regression lines at study end. The regression lines for the Apo B versus LDL-C and non-HDL-C scatter plots were very similar across the 2 treatment groups with the EZE/SIMVA regression line falling slightly underneath the line for ROSUVA in both scatter plots.

Both LDL-C and non-HDL-C were positively correlated with Apo B at baseline while patients were taking a stable dose of statin monotherapy with *r* values of 0.550 and 0.690, respectively (Tables 2 and 3). Switching from statin monotherapy to the more potent EZE/SIMVA 10/20 mg or ROSUVA 10 mg substantially increased the strength of the correlations between Apo B:LDL-C and Apo B:non-HDL-C at study end compared with baseline (Tables 2 and 3). At study end, the strength of the Apo B:LDL-C (r^2 values of 0.829 and 0.867, respectively) and Apo B:non-HDL-C (r^2 values of 0.908 and 0.930, respectively) correlations were similar across the EZE/SIMVA and ROSUVA groups (Tables 2 and 3).

The fitted linear regression models were used to predict the modeled LDL-C and non-HDL-C values corresponding to Apo B value of 0.9 g/L. At baseline (i.e., week 0), an Apo B value of 0.9 g/L corresponded to LDL-C and non-HDL-C values that were close to the minimum recommended LDL-C and non-HDL-C targets for high-risk CHD patients (i.e., 2.59 and 3.37 mmol/L, respectively) (Tables 2 and 3). At baseline, a mean Apo B value of 0.9 g/L corresponded to mean LDL-C and non-HDL-C values of 2.89 mmol/L and 3.38 mmol/L for the pooled treatment groups,

Table 3
Slope, intercept, Pearson correlation coefficient, and predicted non-HDL-C values based on simple linear regression analyses of Apo B versus non-HDL-C at baseline (i.e., while on stable dose of statin monotherapy) and following 6 weeks of treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg.

	N	Slope	Intercept	Pearson correlation coefficient (r^2)	Predicted non-HDL-C value[a]
Baseline (i.e., while on stable dose of statin monotherapy)					
Pooled treatment groups					
Overall analysis cohort	593	1.88	1.71	0.690 (0.48)	3.4
TG, <2.26 mmol/L	497	1.66	1.90	0.650 (0.42)	3.4
TG, ≥2.26 mmol/L	96	1.40	2.65	0.559 (0.31)	3.9
Week 6 (i.e., after switching from statin monotherapy to EZE/SIMVA or ROSUVA)					
Pooled treatment groups					
Overall analysis cohort	593	3.19	−0.08	0.922 (0.85)	2.8
TG, <2.26 mmol/L	497	3.19	−0.08	0.926 (0.86)	2.8
TG, ≥2.26 mmol/L	96	3.15	−0.02	0.896 (0.80)	2.8
EZE/SIMVA 10/20 mg					
Overall analysis cohort	301	3.05	0.00	0.908 (0.83)	2.7
TG, <2.26 mmol/L	251	3.10	−0.04	0.914 (0.84)	2.8
TG, ≥2.26 mmol/L	50	2.85	0.19	0.869 (0.76)	2.8
ROSUVA, 10 mg					
Overall analysis cohort	292	3.23	−0.07	0.930 (0.87)	2.8
TG, <2.26 mmol/L	246	3.21	−0.06	0.932 (0.87)	2.8
TG, ≥2.26 mmol/L	46	3.25	−0.03	0.915 (0.84)	2.9

EZE/SIMVA indicates ezetimibe/simvastatin; ROSUVA, rosuvastatin; TG, triglyceride.
[a] Predicted non-HDL-C (mmol/L) assuming Apo B value of 0.9 g/L.

respectively. After switching to EZE/SIMVA or ROSUVA (i.e., week 6/study end), the LDL-C and non-HDL-C values corresponding to an Apo B of 90 mg/dL were closer to the more aggressive LDL-C and non-HDL-C targets (i.e., 1.81 and 2.59 mmol/L, respectively) (Tables 2 and 3). At study end, a mean Apo B value of 0.9 g/L corresponded to mean predicted LDL-C and non-HDL-C values of 2.18 mmol/L and 2.79 mmol/L for the pooled treatment groups, respectively.

Analysis of TG subgroups < and >2.26 mmol/L showed similar changes in the relationships of Apo B with LDL-C and non-HDL-C with an overall strengthening of the correlations following treatment with EZE/SIVMA 10/20 mg and ROSUVA 10 mg relative to baseline in both subgroups (Tables 2 and 3). At study end, the *r* values for the Apo B:LDL-C and Apo B:non-HDL-C correlations were somewhat weaker in the subgroup of patients with baseline TG level >2.26 mmol/L versus those with TG level <2.26 mmol/L both when examined in the overall analysis cohort and broken down by treatment group. For the subgroup of patients with elevated baseline TG level >2.26 mmol/L, the baseline and study end LDL-C values corresponding to an Apo B value of 0.9 g/L were lower compared with the TG <2.26 mmol/L subgroup. The predicted LDL-C value for the TG <2.26 mmol/L subgroup was similar to that seen for the overall analysis cohort (i.e., 2.23 versus 2.18 mmol/L for the pooled treatment groups, respectively) but lower than the minimum recommended LDL-C goal of 2.59 mmol/L for high-risk CHD patients. In contrast, the predicted LDL-C value for the TG >2.26 mmol/L subgroup was substantially lower than that seen for the overall analysis cohort (i.e., 1.88 versus 2.18 mmol/L for the pooled treatment groups, respectively) and similar to the optional recommended LDL-C goal of 1.81 mmol/L for high-risk CHD patients. For the subgroup of patients with an elevated baseline TG level >2.26 mmol/L, the predicted baseline and study end non-HDL-C values corresponding to an Apo B value of 0.9 g/L were similar compared with those seen for the TG <2.26 mmol/L subgroup.

In general, numerically higher proportions of patients reached LDL-C 2.59 mmol/L, non-HDL-C <3.37 mmol/L, and Apo B <0.9 g/L targets with EZE/SIMVA 10/20 mg versus ROSUVA 10 mg irrespective of baseline TG level (Table 4). Among the patients who attained LDL-C 2.59 mmol/L or non-HDL-C <3.37 mmol/L goals while taking EZE/SIMVA 10/20 mg or ROSUVA 10 mg, only slightly more than half of them also reached the Apo B target <0.9 g/L at study end (Table 4; Figs. 1 and 2). The percentages of patients who attained these dual targets (i.e., LDL-C, 2.59 mmol/L, and Apo B, <0.9 g/L; non-HDL-C, 3.37 mmol/L, and Apo B, 0.9 g/L) did not differ across the two treatment groups. Thus, a large proportion of patients in the EZE/SIMVA and ROSUVA groups remained at increased risk of coronary events, especially among the subgroup of patients with high baseline TG ≥2.26 mmol/L. In contrast, among the patients who met the Apo B target <0.9 g/L with EZE/SIMVA 10/20 mg or ROSUVA 10 mg, the vast majority of them also achieved the minimum recommended LDL-C and non-HDL-C goals (Table 5; Figs. 1 and 2).

Discussion

Most international and national lipid treatment guidelines consider LDL-C the primary goal of hypolipidemic therapy (e.g., NCEP ATP III, European, AHA/ACC) [1,16,18,29]. In hypertriglyceridemic subjects with TG values ≥2.26 mmol/L, non-HDL-C is considered a secondary target of therapy as this parameter reflects the total amount of cholesterol transported in all atherogenic lipoprotein particles [1]. Statin therapy reduces plasma levels of LDL-C and non-HDL-C to a much greater extent compared with that seen for Apo B [4,10,32]. Although patients may achieve the minimum recommended LDL-C or non-HDL-C goals while taking statin therapy, many patients still have a high number of atherogenic particles in the circulation and thus remain at increased risk for future coronary events [7,32,35]. This is especially true for patients with insulin resistance because they commonly have a greater number of atherogenic particles than can be predicted based solely on their LDL-C levels [3,17,31]. To this end, the ADA/ACCF statement endorses the achievement of Apo B targets for patients with cardiometabolic risk (i.e., 0.9 g/L and <0.8 g/L for high and very high risk, respectively) in addition to LDL-C and non-HDL-C goals [8].

The purpose of the INCROSS study was to evaluate the lipid-lowering efficacy of switching from a lower potency statin monotherapy to the usual recommended starting dose of EZE/SIMVA 10/20 mg or ROSUVA 10 mg in a population of high-risk CHD patients who did not achieve the minimum recommended LDL-C goal (i.e., LDL-C, <2.59 mmol/L) despite taking previous statin monotherapy [12]. The primary analysis of this study showed that treatment with EZE/SIMVA 10/20 mg produced significantly larger mean incremental reductions from baseline in LDL-C of 11%, non-HDL-C of 9%, and Apo B of 8% beyond that achieved with ROSUVA 10 mg. The safety and tolerability profiles of EZE/SIMVA 10/20 mg and ROSUVA 10 mg were quite similar as described in the primary publication of the INCROSS study [12].

The current post-hoc analysis of the INCROSS study showed linear correlations between Apo B:LDL-C and Apo B:non-HDL-C both during treatment with statin monotherapy and after switching to more potent lipid-lowering therapy. The LDL-C-lowering potency of the treatment did not appear to affect the strength of these correlations as demonstrated by the similarity in the *r* values across the statin potency strata at baseline (i.e., low/high) and between the EZE/SIMVA and ROSUVA groups at study end. Nevertheless, the strengths of the Apo B:LDL-C and Apo B:non-HDL-C correlations were substantially improved after patients were switched from lower potency statin monotherapy to higher potency EZE/SIMVA 10/20 mg or ROSUVA 10 mg therapy. The absence of divergence in the between-group findings at study end suggests that the different mechanisms of actions of EZE/SIMVA and ROSUVA (i.e., EZE/SIMVA lowers cholesterol via inhibition of cholesterol biosynthesis and absorption while ROSUVA lowers cholesterol via

Table 4
Percentages of patients reaching various LDL-C, non-HDL-C, or Apo B targets who also achieved Apo B <0.9 g/L after 6 weeks of treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg.

	Percentages of patients reaching individual target				Percentages of patients at LDL-C or non-HDL-C target who also reached Apo B <0.9 g/L			
	EZE/SIMVA, 10/20 mg		ROSUVA, 10 mg		EZE/SIMVA, 10/20 mg		ROSUVA, 10 mg	
	n/*N*[a]	% (95% CI)	*n*/*N*[a]	% (95% CI)	*n*/*N*[b]	% (95% CI)	*n*/*N*[b]	% (95% CI)
LDL-C, <2.59 mmol/L								
All patients	221/305	72.5% (67.2, 77.2)	167/297	56.2% (50.5, 61.8)	126/217	58.1% (51.4, 64.4)	98/166	59.0% (51.4, 66.2)
TG, <2.26 mmol/L	178/253	70.4% (64.5, 75.6)	138/250	55.2% (49.0, 61.2)	114/176	64.8% (57.5, 71.5)	88/137	64.2% (55.9, 71.8)
TG, ≥2.26 mmol/L	43/52	82.7% (70.3, 90.6)	29/47	61.7% (47.4, 74.2)	12/41	29.3% (17.6, 44.5)	10/29	34.5% (19.9, 52.7)
Non-HDL-C, <3.37 mmol/L								
All patients	227/305	74.4% (69.3, 79.0)	184/297	62.0% (56.3, 67.3)	128/223	57.4% (50.8, 63.7)	99/183	54.1% (46.9, 61.2)
TG, <2.26 mmol/L	190/253	75.1% (69.4, 80.0)	163/250	65.2% (59.1, 70.8)	116/188	61.7% (54.6, 68.4)	90/162	55.6% (47.9, 63.0)
TG, ≥2.26 mmol/L	37/52	71.2% (57.7, 81.7)	21/47	44.7% (31.4, 58.8)	12/35	34.3% (20.8, 50.9)	9/21	42.9% (24.5, 63.5)

Apo indicates apolipoprotein; EZE/SIMVA, ezetimibe/simvastatin; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; ROSUVA, rosuvastatin; TG, triglyceride.

[a] Number of patients achieving specified lipoprotein target out of the total number of patients in the treatment group with efficacy measurement.

[b] Number of patients achieving Apo B value out of the total number of patients already having achieved specified lipoprotein goals in each treatment group.

Table 5
Percentages of patients at an Apo B target of <0.9 g/L who also reached LDL-C or non-HDL-C goals after 6 weeks of treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg.

	Percentages of patients reaching Apo B <0.9 g/L target				Percentages of patients at Apo B <0.9 g/L target who also reached LDL-C or non-HDL-C target			
	EZE/SIMVA, 10/20 mg		ROSUVA, 10 mg		EZE/SIMVA, 10/20 mg		ROSUVA, 10 mg	
	n/*N*[a]	% (95% CI)	*n*/*N*[a]	% (95% CI)	*n*/*N*[b]	% (95% CI)	*n*/*N*[b]	% (95% CI)
Apo B, <0.9 g/L					*LDL-C, <2.59 mmol/L*			
All patients	128/301	42.5% (37.1, 48.2)	100/292	34.2% (29.0, 39.9)	126/128	98.4% (94.5, 99.6)	98/100	98.0% (93.0, 99.5)
TG, <2.26 mmol/L	116/251	46.2% (40.2, 52.4)	90/246	36.6% (30.8, 42.8)	114/116	98.3% (93.9, 99.5)	88/90	97.8% (92.3, 99.4)
TG, <2.26 mmol/L	12/50	24.0% (14.3, 37.4)	10/46	21.7% (12.3, 35.6)	12/12	100% (75.8, 100)	10/10	100% (75.3, 100)
Apo B, <0.9 g/L					*Non-HDL-C, <3.37 mmol/L*			
All patients	128/301	42.5% (37.1, 48.2)	100/292	34.2% (29.0, 39.9)	128/128	100% (97.1, 100)	99/100	99.0% (94.6, 99.8)
TG, <2.26 mmol/L	116/251	46.2% (40.2, 52.4)	90/246	36.6% (30.8, 42.8)	116/116	100% (96.8, 100)	90/90	100% (95.9, 100)
TG, <2.26 mmol/L	12/50	24.0% (14.3, 37.4)	10/46	21.7% (12.3, 35.6)	12/12	100% (75.8, 100)	9/10	90.0% (59.6, 98.2)

Apo indicates apolipoprotein; EZE/SIMVA, ezetimibe/simvastatin; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; ROSUVA, rosuvastatin; TG, triglyceride.
[a] Number of patients achieving specified lipoprotein target out of the total number of patients in the treatment group with efficacy measurement.
[b] Number of patients achieving Apo B value out of the total number of patients already having achieved specified lipoprotein goals in each treatment group.

inhibition of cholesterol biosynthesis only) did not translate to differences in the correlations or linear characteristics describing the relationships between Apo B and LDL-C or Apo B and non-HDL-C to any measurable degree.

Previous studies also demonstrated linear relationships and strong correlations between Apo B:LDL-C and Apo B:non-HDL-C in untreated as well as statin-treated patients [4,6,9]. In these prior studies, the strength of the Apo B:LDL-C and Apo B:non-HDL-C correlations were more robust in statin-treated patients compared with untreated patients. The results of the current analysis build upon these previous findings, demonstrating that combination therapy with EZE/SIMVA alters the relationships between Apo B and LDL-C as well as non-HDL-C in a manner similar to that seen with ROSUVA monotherapy. Marked changes in the slopes of the linear regression lines were observed at study end, indicating that Apo B particles became less lipid rich after patients were switched from less intensive statin monotherapy to more potent treatment with EZE/SIMVA and ROSUVA. These results can be explained by Cromwell et al. [11] who demonstrated that LDL particles, as assessed by nuclear magnetic resonance methodology, are more cholesterol depleted when LDL-C concentrations are lower independent of LDL particle size. These findings explain why patients with low LDL-C levels often have disproportionately higher numbers of LDL particles and thus plasma Apo B levels.

Of note, the *r* values observed in the current analysis among statin-treated patients at baseline were similar to those previously reported in untreated patients [6]. The reason underlying this observation may in part be due to variation in LDL-C entry criteria between the studies. The range of LDL-C values in the INCROSS study was more restricted (2.59–4.14 mmol/L) compared with that seen in the MERCURY II study (3.37–6.48 mmol/L) [5,12].

Compared with LDL-C, non-HDL-C correlated better with Apo B both at baseline while patients were taking statin monotherapy and at study end following 6 weeks of treatment with EZE/SIMVA 10/20 mg and ROSUVA 10 mg. These findings confirm those of previous studies showing that non-HDL-C levels are better correlated with Apo B compared with LDL-C in statin-treated patients and extend this observation to include EZE/SIMVA combination therapy [4,6,9].

At baseline, the mean predicted LDL-C and non-HDL-C levels corresponding to an Apo B value of 0.9 g/L (i.e., 2.87 mmol/L and 3.38 mmol/L, respectively) were similar to the minimum recommended LDL-C (i.e., <2.59 mmol/L) and non-HDL-C (i.e., <3.37 mmol/L) targets for high risk patients according to the NCEP ATP III guidelines [1]. After switching from less potent statin monotherapy to more potent EZE/SIMVA 10/20 mg or ROSUVA 10 mg therapy, the predicted LDL-C and HDL-C values corresponding to an Apo B value of 0.9 g/L (i.e., 2.17 mmol/L and 2.79 mmol/L, respectively) for the overall pooled population were closer to the more stringent LDL-C (i.e., <1.81 mmol/L) and non-HDL-C (i.e., <2.59 mmol/L) targets for high risk patients [18]. Of note, the predicted LDL-C and non-HDL-C values were similar between EZE/SIMVA and ROSUVA groups at study end, indicating that these treatments had similar effects on the characteristics of the modeled linear relationships between Apo B:LDL-C and Apo B:non-HDL-C. Taken together, these data suggest that more aggressive LDL-C and non-HDL-C targets must be achieved in order to normalize the concentration of Apo B-containing atherogenic lipoproteins in this population of high-risk CHD patients who failed to attain their minimum recommended LDL-C goal with prior statin monotherapy.

When the linear regression analyses were examined by baseline TG, the predicted LDL-C values corresponding to an Apo B value of 0.9 g/L were consistently lower (by 0.2–0.4 mmol/L) in hypertriglyceridemic compared with normotriglyceridemic patients. Furthermore, this finding was observed irrespective of treatment (i.e., statin monotherapy at baseline as well as EZE/SIMVA and ROSUVA at study end). In contrast, the predicted non-HDL-C levels for subjects with high and low TG levels were nearly identical across the EZE/SIMVA and ROSUVA groups at study end. This observation is not surprising given that, unlike non-HDL-C, LDL-C is known to underestimate the number of atherogenic lipoprotein particles in the circulation due to the preponderance of small, dense, cholesterol depleted LDL particles in hypertriglyceridemic patients [3,17,21,31]. As a result, larger reductions from baseline in LDL-C are required to reach optimal Apo B levels in patients with high TG levels.

The target attainment analyses demonstrated excellent congruence between the LDL-C and non-HDL-C goal attainment rates among patients who had achieved Apo B value <0.9 g/L at study end (i.e., 90% of patients with Apo B <0.9 g/L also had LDL-C <2.59 mmol/L or non-HDL-C <3.37 mmol/L in both the EZE/SIMVA and ROSUVA groups). The proportions of patients who achieved these dual Apo B/LDL-C and Apo B/non-HDL-C targets did not differ across the EZE/SIMVA and ROSUVA groups and among patients with low and high TG values at baseline. In contrast, only slightly more than half of the patients who reached an LDL-C level <2.59 mmol/L or non-HDL-C level <3.37 mmol/L at study end also had an Apo B level <0.9 g/L following treatment with EZE/SIMVA or ROSUVA.

Conclusion

Taken together, the correlation and linear regression analyses suggest that much lower LDL-C and non-HDL-C levels are required to obtain a desirable number of atherogenic particles (i.e., attainment of Apo B target levels) following aggressive lipid lowering treatment with EZE/SIMVA and ROSUVA. Goal attainment analysis shows that

substantial number of patients reaching the recommended LDL-C and non-HDL-C goals for high risk patients were not at the minimum Apo B target of 0.9 g/L. This finding was especially true for the subgroup of patients with high baseline triglyceride levels. In contrast, treating patients to the Apo B target of <0.9 g/L ensured concurrent achievement of LDL-C and non-HDL-C goals in both normotriglyceridemic and hypertriglyceridemic patients.

Apo B measurements can be performed by most high volume analyzers which are available in most laboratories and have been standardized (with use of international reference material) by the World Health Organization [10]. This parameter does not need to be measured in the fasting state and is not influenced by hypertriglyceridemia up to 10 mmol/L.

The results of the current analysis suggest that Apo B is a good marker for monitoring the efficacy of lipid lowering therapy. The use of Apo B to monitor treatment efficacy would likely lead to more stringent criteria for LDL-C lowering. In those instances where Apo B cannot be measured, non-HDL-C may be used as a surrogate marker. Nevertheless, a non-HDL-C goal <2.59 mmol/L should be used to ensure achievement of the minimum recommended Apo B level (i.e., 0.9 g/L) and normalize the atherogenic particle number.

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