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ORIGINAL RESEARCH

Efficacy of Ezetimibe/Simvastatin 10/20 mg Versus Rosuvastatin 10 mg in High-Risk Patients With or Without Obesity

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ABSTRACT

Introduction: This post-hoc analysis compared the effects of switching to ezetimibe/simvastatin 10/20 mg (EZE/SIMVA) or rosuvastatin 10 mg (ROSUVA) in high-risk hypercholesterolemic patients with/without obesity. ***Methods:*** Patients (n=618) at high-risk for coronary heart disease with elevated low-density lipoprotein cholesterol (LDL-C) ≥2.59 and ≤4.92 mmol/L, while on a statin, entered a 6-week open-label stabilization/screening period during which they continued on the same statin. Patients were then randomized 1:1 to double-blind EZE/SIMVA 10/20 mg or ROSUVA 10 mg for 6 weeks. Patients were classified as non-obese (n=437) or obese (n=180) based on body mass index <30 or ≥30 kg/m^2, respectively. ***Results:*** EZE/SIMVA was more effective than ROSUVA at lowering LDL-C, total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein (apo) B in the overall population (P<0.001 for all). These results were consistent for obese and non-obese patients as demonstrated by the lack of significant treatment-by-subgroup interaction terms for LDL-C, TC, non-HDL-C, and apo B (P>0.050 for all). ***Conclusions:*** In this post-hoc analysis of high-risk patients with elevated LDL-C, despite prior use of statin therapy, switching to EZE/SIMVA 10/20 mg

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versus ROSUVA 10 mg provided superior reductions in LDL-C, TC, and non-HDL-C in obese and non-obese patients.

Keywords: apolipoprotein B; ezetimibe; low-density lipoprotein; non-high-density lipoprotein; obesity; simvastatin; total cholesterol; triglycerides

INTRODUCTION

Obesity has reached global epidemic proportions, and its prevalence continues to increase in many developed countries. Obesity is strongly related to the development of vascular diseases and metabolic complications.[1] Adipose tissue is metabolically active, since it contributes to the atherogenic dyslipidemia, hyperinsulinemia, and hypertension that consequently place obese individuals at increased risk of coronary heart disease (CHD).

Comprehensive medical management can reduce the risk of CHD in obese patients through lifestyle modification (eg, diet and exercise) and pharmacologic intervention aimed at improving control of blood glucose and hypertension, as well as the overall lipoprotein profile.

Treatment guidelines for managing dyslipidemia have traditionally focused on lowering low-density lipoprotein cholesterol (LDL-C) levels, which has been proven to reduce cardiovascular events and mortality.[2] However, the primary dyslipidemia observed in obese patients is often characterized by low levels of high-density lipoprotein cholesterol (HDL-C), increased levels of non-HDL-C, triglycerides (TG), apolipoprotein B-100 (apo B), and abnormal LDL composition (ie, increased levels of small, dense LDL-C particles).[3,4] The pathogenesis of the dyslipidemia seen in obese patients is likely due to the state of insulin resistance resulting from the accumulation of excess body fat.[5,6] As a result, dyslipidemia may be undertreated in patients with obesity even following intensive LDL-C-lowering with statins. To this end, the 2008 American Diabetes Association and American College of Cardiology Foundation (ADA/ACC) consensus report recommends non-HDL-C and apo B treatment targets for managing dyslipidemia in patients with elevated cardiometabolic risk, including obese patients (Table 1).[7]

In view of the need to aggressively manage atherogenic dyslipidemia, the use of combination lipid-lowering therapies may be warranted to facilitate the achievement of optimal lipid and lipoprotein levels. This post-hoc exploratory analysis of data from a previously reported multicenter, randomized, double-blind,

Table 1. Recommended lipid/lipoprotein treatment goals for patients with cardiometabolic risk according to the joint consensus statement issued by the American Diabetes Association and American College of Cardiology Foundation.[6]

	Treatment goals		
Level of risk	LDL-C	Non-HDL-C	Apo B
Very high-risk patients*	<1.81 mmol/L (<70 mg/dL)	<2.59 mmol/L (<100 mg/dL)	<0.8 g/L (<80 mg/dL)
High-risk patients†	<2.59 mmol/L (<100 mg/dL)	<3.37 mmol/L (130 mg/dL)	<0.9 g/L (<90 mg/dL)

*Includes patients with: 1) known cardiovascular disease (CVD), or 2) diabetes plus one or more additional major CVD risk factors beyond dyslipoproteinemia (ie, smoking, hypertension, family history of premature coronary heart disease).

†Includes patients with 1) no diabetes or known clinical CVD but with two or more additional major CVD risk factors, or 2) diabetes with no other major CVD risk factors.

Apo B=apolipoprotein B; LDL-C=low-density lipoprotein cholesterol; non-HDL-C=non-high-density lipoprotein cholesterol.

active-controlled, 6-week, parallel-group study[8] (NCT00479713; Merck protocol 809) compared the lipid/lipoprotein-altering effects of switching from a stable dose of statin monotherapy to the initial recommended starting doses of ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg monotherapy in high-risk hypercholesterolemic obese (body mass index [BMI] ≥30 kg/m^2) and non-obese patients.

MATERIALS AND METHODS

Patients and Study Design

Patients were deemed to be of high cardiovascular risk if they met one or more of the following criteria: 1) history of CHD or established vascular atherosclerotic disease (ie, peripheral vascular disease, ischemic stroke); 2) type 2 diabetes mellitus without a history of vascular disease and/or with high cardiovascular risk with at least 2 CHD risk factors per Framingham criteria; 3) CHD risk >20% over 10 years as determined by the Framingham risk calculation.[9]

The study enrolled men and women ≥18 and <80 years of age. At screening, LDL-C levels ranged from ≥2.59 and ≤4.92 mmol/L. Following a 6-week open-label statin dose stabilization run-in phase, eligible patients with elevated LDL-C ≥2.59 and ≤4.14 mmol/L, despite the continued use of their usual statins, were stratified by study center and baseline statin dose/potency and randomized 1:1 to double-blind treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg for 6 weeks.[8] The protocol for the original study was approved by the institutional review board or ethics committee of each participating center, and all patients provided written informed consent. All lipid and safety laboratory analyses were conducted at a central laboratory. Additional details of the study design and patient population have been reported.[8,10]

Statistical Analyses

Efficacy and safety analyses were conducted in the overall analysis population, as well as within obese and non-obese patient subgroups. The overall analysis population consisted of all randomized patients with known baseline BMI values. The primary efficacy endpoint was the effects of treatment on the mean percentage change from baseline to the last post-baseline measurement in LDL-C. Other efficacy endpoints included percent change from baseline in total cholesterol (TC), TG, HDL-C, non-HDL-C, LDL-C:HDL-C ratio, TC:HDL-C ratio, apo B, and high-sensitivity C-reactive protein (hs-CRP). The percentage of patients achieving target LDL-C (<2.59 and <1.81 mmol/L), non-HDL-C (<3.37 and <2.59 mmol/L), and apo B goals (<0.9 and <0.8 g/L) at study endpoint were assessed.

This subgroup analysis was performed on the full-analysis set (FAS) population, which included all patients with known baseline BMI values who received at least one dose of study medication, had a baseline efficacy measurement, and had at least one post-randomization efficacy measurement. Missing data were imputed using the last-observation-carried-forward method.

Continuous efficacy results for percent change from baseline in normally distributed parameters (ie, LDL- C, TC, HDL-C, non-HDL-C, LDL-C:HDL-C ratio, TC:HDL-C ratio, and apo B) were analyzed using a parametric analysis of variance (ANOVA) model with terms for treatment, stratum, baseline efficacy variable (categorized based on quartiles), study center, obesity status (yes, no), and treatment-by-subgroup interaction. Least squares means and 95% CIs within each patient

subgroup (ie, obese/non-obese) using the above model (except the last two terms involving subgroup) were computed and used to quantify the differences between treatment groups.

Continuous efficacy results for percent change from baseline in non-normally distributed parameters (ie, TG and hs-CRP) were analyzed using an ANOVA model on rank-transformed data for these efficacy variables with terms for treatment, stratum, baseline efficacy variable (categorized based on quartiles), study center, obesity status, and treatment-by-subgroup interaction. Differences between treatment groups were quantified as differences in medians and 95% CIs using Hodges-Lehmann estimates within each patient subgroup.

The percentages of patients achieving lipid/lipoprotein goals at study end were analyzed using a logistic regression model with terms for treatment, stratum, baseline efficacy variable, obesity status, and treatment-by-subgroup interaction. Odds ratio estimates and 95% CIs using the above model (except the last two terms involving subgroup) were computed and used to quantify the treatment effect within each patient subgroup.

Due to the exploratory nature of this analysis, no multiplicity adjustments were employed. Between-group differences and treatment-by-subgroup interaction tests with a P value <0.050 were considered statistically significant.

The safety analysis was based on the all-patients-as-treated population of patients with known BMI values at baseline who received at least one dose of study medication. Adverse experiences (AEs) were assessed throughout the study. The investigators determined the severity of AEs and the relationship to study drug. Prespecified AEs of special interest included those that were gastrointestinal, gallbladder or hepatobiliary related, allergic reaction or rash, elevations in alanine aminotransferase and/or aspartate aminotransferase ≥3 times the upper limit of normal (ULN), and creatine kinase elevations ≥10 times ULN with or without muscle symptoms.

RESULTS

Patients

Of the 618 patients enrolled, one patient had a missing BMI value at baseline and was excluded from both the efficacy and safety analyses. Within each patient subgroup, the baseline demographic and anthropometric characteristics were generally well balanced across the EZE/SIMVA and ROSUVA treatment groups (Table 2). The only exception was finding more diabetic patients in the EZE/SIMVA group than in the ROSUVA group within the obese subgroup. The obese (n=180) and non-obese (n=437) subgroups were similar in terms of age, race, duration of hypercholesterolemia, blood pressure values, and medical history of CHD. A greater percentage of women were classified as obese, versus men. Obese patients had higher mean BMI and fasting plasma glucose values at baseline than non-obese patients. Also, more obese patients had medical histories of hypertension and diabetes than did non-obese patients. With regard to lipid/lipoprotein/biochemical parameters, obese patients had higher median baseline TG and hs-CRP levels and lower mean HDL-C levels compared with non-obese patients (Table 2). Baseline LDL-C values were generally similar between treatment groups and obesity subgroups.

Effects of Treatment on Lipid/Lipoprotein Parameters and hs-CRP

The effects of EZE/SIMVA 10/20 mg and ROSUVA 10 mg on plasma concentrations of

Table 2. Baseline characteristics for randomized obese and non-obese patients.

	Obese *n*=180		Non-obese *n*=437	
Baseline characteristics	EZE/SIMVA 10/20 mg *n*=97	ROSUVA 10 mg *n*=83	EZE/SIMVA 10/20 mg *n*=216	ROSUVA 10 mg *n*=221
Gender				
Male	55 (56.7%)	43 (51.8%)	130 (60.2%)	142 (64.3%)
Age, yr	63.5 ± 9.1	62.0 ± 9.0	63.1 ± 10.2	63.5 ± 10.4
Race				
White	97 (100%)	82 (98.8%)	216 (100%)	220 (99.5%)
Other	0	1 (1.2%)	0	1 (0.5%)
Body mass index, kg/m^{2}*	33.6 ± 3.7	33.9 ± 3.4	25.7 ± 2.7	25.8 ± 2.7
LDL-C, mmol/L	3.2 ± 0.4	3.3 ± 0.4	3.2 ± 0.4	3.2 ± 0.4
TC, mmol/L	5.3 ± 0.5	5.4 ± 0.6	5.4 ± 0.6	5.4 ± 0.6
TG, mmol/L†	1.6 ± 0.9	1.6 ± 1.1	1.4 ± 0.8	1.3 ± 0.8
HDL-C, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.5 ± 0.4	1.5 ± 0.4
Non-HDL-C	4.0 ± 0.5	4.1 ± 0.5	3.9 ± 0.6	3.9 ± 0.6
LDL-C:HDL-C	2.5 ± 0.6	2.6 ± 0.6	2.3 ± 0.6	2.4 ± 0.7
TC-C:HDL-C	4.2 ± 0.9	4.2 ± 0.9	3.8 ± 0.9	3.9 ± 0.9
Apo B, g/L	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
hs-CRP, mg/dL†	0.2 ± 0.3	0.2 ± 0.3	0.1 ± 0.2	0.1 ± 0.2
FPG, mmol/L	6.6 ± 1.7	6.1 ± 1.3	5.6 ± 1.3	5.7 ± 1.5
Duration of hypercholesterolemia, yr	7.9 ± 5.8	8.8 ± 5.6	8.4 ± 5.6	9.4 ± 7.0
Systolic blood pressure, mm Hg	135.4 ± 11.0	134.5 ± 11.7	131.7 ± 12.6	133.2 ± 12.6
Diastolic blood pressure, mm Hg	79.9 ± 7.1	79.0 ± 8.7	77.6 ± 7.1	78.4 ± 7.5
History of hypertension	70 (72.2%)	56 (67.5%)	132 (61.1%)	133 (60.2%)
History of CHD	46 (47.4%)	40 (48.2%)	106 (49.1%)	104 (47.1%)
History of T2DM‡	51 (52.6%)	31 (37.3%)	49 (22.7%)	51 (23.1%)
Statin potency stratum				
Low potency§	61 (62.9%)	46 (55.4%)	128 (59.3%)	134 (60.6%)
High potency§	36 (37.1%)	37 (44.6%)	88 (40.7%)	87 (39.4%)

All data are shown as mean ± SD or *n* (%), unless otherwise noted.
*Excludes one randomized patient in the non-obese group with unknown body mass index at baseline.
†Data shown as median ± SD.
‡Two randomized patients had unknown diabetes status at baseline, one is obese on EZE/SIMVA and one is non-obese on ROSUVA.
§Low potency stratum: simvastatin 20 mg, pravastatin 40 mg, fluvastatin 80 mg, atorvastatin 10 mg; high potency stratum: simvastatin 40 mg, atorvastatin 20 mg, rosuvastatin 5 mg.
Apo B=apolipoprotein B; CHD=coronary heart disease; EZE/SIMVA=ezetimibe/simvastatin combination tablet; FPG=fasting plasma glucose; HDL-C=high-density lipoprotein cholesterol; hs-CRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; ROSUVA=rosuvastatin; SD=standard deviation; T2DM=type 2 diabetes mellitus; TC=total cholesterol; TG=triglyceride.

lipids, lipoproteins, and hs-CRP within the obese and non-obese subgroups are shown in Table 3. Results for the overall population are provided for comparative purposes. In the overall population, switching from statin monotherapy to EZE/SIMVA 10/20 mg compared

with ROSUVA 10 mg for 6 weeks resulted in significantly larger reductions from baseline in LDL-C (10.6%; $P<0.001$), TC (7.2%; $P<0.001$), non-HDL-C (9.4%; $P<0.001$), LDL-C:HDL-C (9.5%; $P<0.001$), TC:HDL-C (6.2%; $P<0.001$) and apo B (8.1%: $P<0.001$) at study endpoint (Table 3; Figure 1). A borderline significantly greater reduction in TG was seen, favoring EZE/SIMVA therapy (5.1%; $P=0.053$) (Table 3; Figure 1). Both EZE/SIMVA and ROSUVA produced significant increases from baseline in HDL-C; however, the between-group difference did not reach significance. Neither EZE/SIMVA nor ROSUVA produced significant within- or between-group changes from baseline in hs-CRP (Table 3).

The treatment effects within the subgroups were generally consistent with those in the overall population as indicated by the absence of treatment-by-subgroup interactions for all of the lipid/lipoprotein and biochemical parameters analyzed (Figure 1). EZE/SIMVA 10/20 mg was significantly more effective than ROSUVA 10 mg at lowering LDL-C, TC, non-HDL-C, and TC:HDL-C in both obese and non-obese patients (Table 3; Figure 1). Significant between-group reductions in LDL-C:HDL-C and apo B also were observed in non-obese patients favoring EZE/SIMVA therapy (Table 3; Figure 1). In obese patients, numerically larger reductions from baseline in LDL-C:HDL-C and apo B were observed with EZE/SIMVA versus ROSUVA therapy; however, the between-group differences did not reach statistical significance (Table 3; Figure 2). Treatment with EZE/SIMVA or ROSUVA produced significant reductions from baseline in TG within the subgroups (Table 3; Figure 1). Reductions from baseline in TG were numerically larger in the EZE/SIMVA group than in the ROSUVA group; however, the between-group differences did not reach statistical significance. Treatment with EZE/SIMVA or ROSUVA produced small but significant increases from baseline in HDL-C in the non-obese subgroup, whereas no significant changes from baseline were observed in obese patients (Table 3; Figure 1). No significant within- or between-treatment group changes from baseline in hs-CRP were observed in either subgroup at study endpoint (Table 3).

Lipid/Lipoprotein Goal Attainment

In the overall population, significantly higher percentages of patients achieved LDL-C levels of <2.59 and <1.81 mmol/L ($P<0.001$ for both targets; Figure 2), non-HDL-C levels of <3.37 and <2.59 mmol/L ($P<0.001$ for both targets; Figure 2), and apo B levels of <0.9 and <0.8 g/L ($P=0.004$ and $P<0.001$, respectively; Figure 2) at study endpoint in the EZE/SIMVA group than in the ROSUVA group.

Safety and Tolerability

Treatment with EZE/SIMVA and ROSUVA was generally well tolerated in obese and non-obese patients. The incidences and types of clinical AEs were generally consistent across the patient subgroups and treatment groups (Table 4). There were no clinically meaningful differences between obese and non-obese patients with respect to the incidences of hepatobiliary-related, gallbladder-related, gastrointestinal-related, or allergic reaction AEs. Presumed consecutive elevations in alanine aminotransferase and/or aspartate aminotransferase values ≥3 times ULN were observed in one patient receiving EZE/SIMVA in each of the subgroups; no such elevations were seen in patients taking ROSUVA in either subgroup. There were no reports of creatine kinase elevations >10 times ULN in any patients.

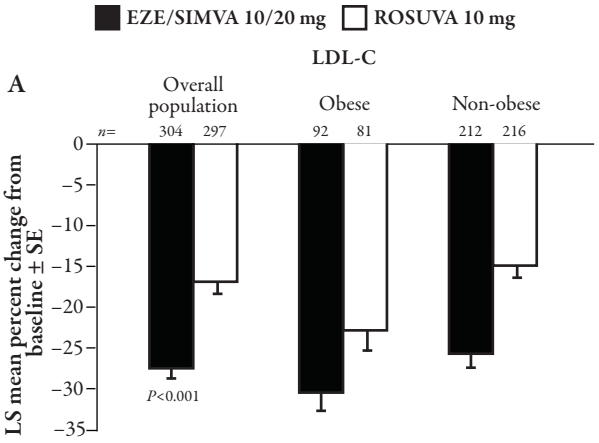
Table 3. Baseline characteristics for randomized obese and non-obese patients *(continued on next page)*.

	Overall analysis population* *n*=617		Obese *n*=180		Non-obese* *n*=437	
	EZE/SIMVA 10/20 mg *n*=301-304†	ROSUVA 10 mg *n*=292-297†	EZE/SIMVA 10/20 mg *n*=91-92†	ROSUVA 10 mg *n*=79-81†	EZE/SIMVA 10/20 mg *n*=210-212†	ROSUVA 10 mg *n*=213-216†
LDL-C, mmol/L						
% change from baseline	−27.6 (−30.2, −25.0)	−17.0 (−19.6, −14.3)	−30.5 (−35.4, −25.7)	−22.8 (−28.1, −17.5)	−25.6 (−29.1, −22.0)	−14.7 (−18.2, −11.3)
Difference vs. ROSUVA	−10.6 (−14.0, −7.2)§	–	−7.7 (−14.5, −0.9)	–	−10.8 (−15.0, −6.7)	–
TC, mmol/L						
% change from baseline	−17.5 (−19.3, −15.7)	−10.4 (−12.2, −8.5)	−19.4 (−22.7, −16.1)	−13.5 (−17.0, −10.0)	−15.9 (−18.4, −13.4)	−9.0 (−11.4, −6.6)
Difference vs. ROSUVA	−7.2 (−9.5, −4.8)§	–	−5.9 (−10.5, −1.3)	–	−6.9 (−9.8, −3.9)	–
TG, mmol/L‡						
% change from baseline	−11.2 (−15.6, −7.0)	−5.3 (−9.9, −1.2)	−14.3 (−19.6, −6.6)	−10.4 (−17.4, −1.7)	−9.9 (−15.3, −5.4)	−3.7 (−8.6, 0.0)
Difference vs. ROSUVA	−5.1 (−9.6, −0.3)‖	–	−4.5 (−13.1, 3.4)	–	−5.1 (−10.5, 0.7)	–
HDL-C, mmol/L						
% change from baseline	2.1 (0.3, 3.9)	3.0 (1.2, 4.9)	2.2 (−1.1, 5.5)	2.5 (−1.1, 6.1)	3.0 (0.6, 5.3)	3.2 (0.9, 5.5)
Difference vs. ROSUVA	−0.9 (−3.2, 1.4)	–	−0.2 (−4.7, 4.2)	–	−1.9 (−3.0, 2.6)	–
Non-HDL-C, mmol/L						
% change from baseline	−23.4 (−25.8, −21.0)	−14.0 (−16.5, −11.6)	−24.9 (−29.2, −20.6)	−18.2 (−22.8, −13.5)	−22.3 (−25.6, −19.0)	−12.6 (−15.8, −9.4)
Difference vs. ROSUVA	−9.4 (−12.4, −6.3)§	–	−6.8 (−12.8, −0.8)	–	−9.8 (−13.7, −5.8)	–
LDL-C:HDL-C						
% change from baseline	−27.3 (−30.3, −24.3)	−17.9 (−20.9, −14.8)	−27.8 (−33.3, −22.2)	−22.8 (−28.9, −16.6)	−26.2 (−30.3, −22.1)	−15.6 (−19.6, −11.7)
Difference vs. ROSUVA	−9.5 (−13.4, −5.6)§	–	−5.0 (−12.6, 2.7)	–	−10.6 (−15.5, −5.8)	–
TC:HDL-C						
% change from baseline	−17.7 (−19.9, −15.5)	−11.5 (−13.8, −9.3)	−18.3 (−22.6, −14.1)	−14.6 (−19.1, −10.1)	−17.1 (−20.1, −14.1)	−10.4 (−13.2, −7.5)
Difference vs. ROSUVA	−6.2 (−9.0, −3.4)§	–	−3.8 (−9.4, −1.8)	–	−6.8 (−10.3, −3.2)	–
Apo B, g/L						
% change from baseline	−17.9 (−20.1, −15.7)	−9.8 (−12.0, −7.6)	−18.8 (−22.9, −14.7)	−13.5 (−17.8, −9.1)	−16.7 (−19.6, −13.8)	−8.1 (−10.9, −5.2)
Difference vs. ROSUVA	−8.1 (−10.9, −5.3)§	–	−5.3 (−10.8, 0.2)	–	−8.7 (−12.1, −5.2)	–

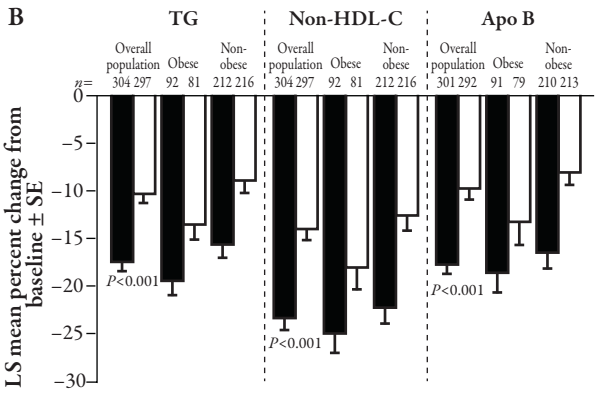
Table 3. ***(continued)*** Baseline characteristics for randomized obese and non-obese patients.

	Overall analysis population* *n*=617		Obese *n*=180		Non-obese* *n*=437	
	EZE/SIMVA 10/20 mg *n*=301-304†	ROSUVA 10 mg *n*=292-297†	EZE/SIMVA 10/20 mg *n*=91-92†	ROSUVA 10 mg *n*=79-81†	EZE/SIMVA 10/20 mg *n*=210-212†	ROSUVA 10 mg *n*=213-216†
hs-CRP, mg/dL‡						
% change from baseline	−8.3 (−16.7, 0.0)	0.0 (−7.1, 6.3)	−5.3 (−18.2, 10.0)	−8.1 (−15.4, 0.0)	−10.0 (−18.2, 0.0)	0.0 (0.0, 16.7)
Difference vs. ROSUVA	−6.7 (−16.7, 2.9)	–	3.3 (−13.6, 20.3)	–	−11.1 (−23.3, 0.0)	–

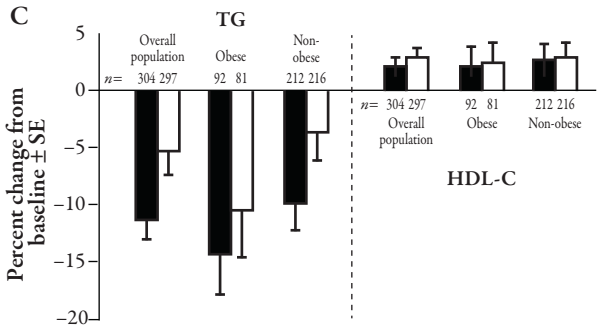
Data are expressed as least squares mean (95% CI) unless otherwise noted.
*618 patients were randomized; number of patients shown excludes data for one randomized patients with unknown body mass index at baseline.
†Ranges shown represent the range of patients numbers that contribute to calculations for each parameter.
‡Data are expressed as median (95% CI).
§P<0.001 vs. ROSUVA; ||P=0.053 vs. ROSUVA.
Apo B=apolipoprotein; EZE/SIMVA=ezetimibe/simvastatin combination tablet; HDL-C=high-density lipoprotein cholesterol; hs-CRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; LDL-C:HDL-C=ratio of LDL-C/HDL-C; ROSUVA=rosuvastatin; TC=total cholesterol; TG=triglycerides.



P-value is for EZE/SIMVA 10/20 mg vs. ROSUVA 10mg.
Treatment by subgroup interaction *P*-value=0.533.



Treatment-by-subgroup interaction *P*-values for TG, non-HDL-C, and apo B were 0.931, 0.525, and 0.428, respectively.



Treatment-by-subgroup interaction *P*-values for TG, non-HDL-C were 0.752, and 0.479, respectively.

Figure 1. Least squares (LS) mean percent change from baseline in low-density lipoprotein cholesterol (LDL-C) (A), total cholesterol, non-high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (apo B) (B), and triglycerides (median) and HDL-C (C) for the overall population and within patient subgroups defined by the presence/absence of obesity. The numbers of patients shown for each parameter represent the full-analysis set population.
EZE/SIMVA=ezetimibe/simvastatin; ROSUVA=rosuvastatin; SE=standard error; TC=total cholesterol; TG=triglycerides.

Table 4. Summary of adverse experiences (AEs).

	Overall analysis population *n*=615*		Obese *n*=178		Non-obese *n*=437	
	EZE/SIMVA 10/20 mg *n*=311	ROSUVA 10 mg *n*=304	EZE/SIMVA 10/20 mg *n*=95	ROSUVA 10 mg *n*=83	EZE/SIMVA 10/20 mg *n*=216	ROSUVA 10 mg *n*=221
Number of patients (%)*						
With one or more clinical AEs	22 (7.1%)	34 (11.2%)	4 (4.2%)	13 (15.7%)	18 (8.3%)	21 (9.5%)
With treatment-related clinical AEs†	8 (2.6%)	10 (3.3%)	2 (2.1%)	4 (4.8%)	6 (2.8%)	6 (2.7%)
With serious clinical AEs	3 (1.0%)	5 (1.6%)	1 (1.1%)	0	2 (0.9%)	5 (2.3%)
With serious treatment-related clinical AEs†	1 (0.3%)	1 (0.3%)	0	0	1 (0.5%)	1 (0.5%)
Death	1 (0.3%)‡	0	0	0	1 (0.5%)‡	0
Discontinued						
Clinical AEs	9 (2.9%)	6 (2.0%)	3 (3.2%)	2 (2.4%)	6 (2.8%)	4 (1.8%)
Treatment-related clinical AEs†	7 (2.3%)	3 (1.0%)	2 (2.1%)	1 (1.2%)	5 (2.3%)	2 (0.9%)
Serious clinical AE	1 (0.3%)	1 (0.3%)	0	0	1 (0.5%)	1 (0.5%)
Serious treatment-related clinical AEs†	0	1 (0.3%)	0	0	0	1 (0.5%) 0
Hepatobiliary-related AEs	1/31 (0.3%)	0	1/95 (1.1%)	0	0	
Gallbladder-related AEs	0	0	0	0	0	0
Gastrointestinal-related AEs	9/311 (2.9%)	7/304 (2.3%)	1/95 (1.1%)	4/83 (4.8%)	8/216 (3.7%)	3/221 (1.4%)
Allergic reaction or rash AEs	2/311 (0.6%)	2/304 (0.7%)	0	1/83 (1.2%)	2/216 (0.9%)	1/221 (0.5%)
Consecutive ≤3× ULN elevations in ALT and/or AST§	2/301 (0.7%)	0	1/91 (1.1%)	0	1/210 (0.5%)	0
CK ≥10× ULN§	0	0	0	0	0	0

*Excludes one randomized patient from the EZE/SIMVA group with unknown body mass index at baseline.
†Determined by study investigator to be related to the drug.
‡One death that occurred from a traumatic brain injury and subarachnoid hemorrhage was deemed not related to study drug by the investigator.
§Includes subjects with two consecutive measurements for ALT and/or AST ≥3× ULN and a single, last measurement ≥3× ULN or a measurement ≥3× ULN followed by a measurement <3× ULN that was taken more than 2 days after the last dose of study medication.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CK=creatine kinase; EZE/SIMVA=ezetimibe/simvastatin; ROSUVA=rosuvastatin; ULN=upper limit of normal.

DISCUSSION

In this population of hypercholesterolemic obese and non-obese patients at high cardiovascular risk who failed to reach their minimum recommended LDL-C level of <4.14 mmol/L while taking statin monotherapy, switching to EZE/SIMVA 10/20 mg resulted in significantly greater improvements in LDL-C, TC, and non-HDL-C than switching to ROSUVA 10 mg. Switching to combination therapy resulted in consistent changes in LDL-C, TC, non-HDL-C, and apo B, irrespective of obesity status. The absence of significant treatment-by-subgroup interaction terms for all LDL-C and non-HDL-C values analyzed indicate that the proportions of patients attaining these levels within both subgroups were generally consistent with those seen in the overall analysis population.

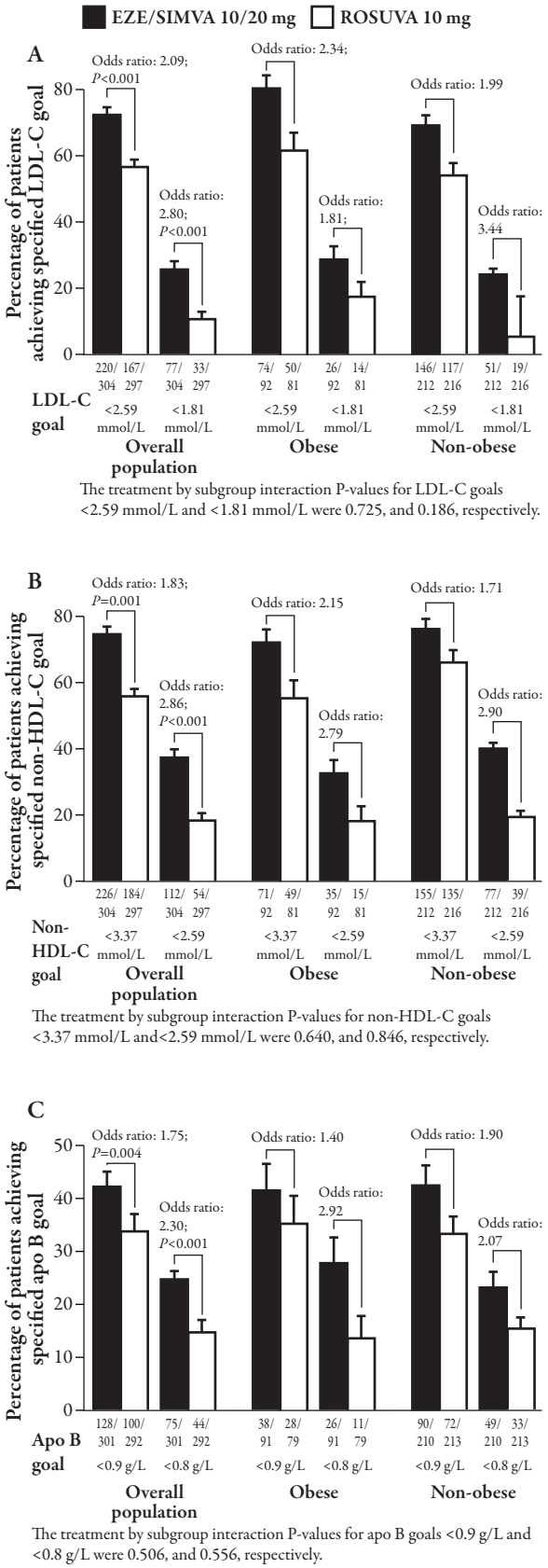


Figure 2. Proportion of patients who achieved low-density lipoprotein cholesterol (LDL-C) levels <2.59 mmol/L (100 mg/dL) and <1.81 mmol/L (70 mg/dL) (A), non-high-density lipoprotein cholesterol (HDL-C) levels <3.37 mmol/L (130 mg/dL) and <2.59 mmol/L (100 mg/dL) (B), and apolipoprotein B (apo B) levels <0.9 g/L (90 mg/dL) and <0.8 g/L (80 mg/dL) (C) at study endpoint for the overall population and within patient subgroups defined by the presence/absence of obesity. The numbers of patients shown for each parameter represent the full-analysis set population. EZE/SIMVA=ezetimibe/simvastatin; ROSUVA=rosuvastatin

In addition to elevated plasma LDL-C levels, hypertriglyceridemia and high levels of apo B have been shown to contribute to increased cardiovascular risk.[11,12] Obese patients tend to present with higher levels of small dense LDL particles in conjunction with hypertriglyceridemia and lower HDL-C levels compared with the general population.[13] Both EZE/SIMVA and ROSUVA produced significant reductions from baseline in TG and apo B in the overall population and within the subgroups. The incremental between-group reductions in TG and apo B seen in the overall population were borderline statistically significant for TG (P=0.053) and significant for apo B (P<0.001), favoring EZE/SIMVA therapy. Treatment with EZE/SIMVA appeared numerically more effective than ROSUVA at lowering both TG and apo B within each subgroup; however, except for a significantly greater improvement in apo B with EZE/SIMVA versus ROSUVA therapy in non-obese patients, the between-group differences in TG and apo B did not reach statistical significance for either subgroup. The finding of non-significant between-group differences in TG and apo B may be due to the inherent variability associated with TG values and the limited number of patients contributing to the subgroup analyses. Nevertheless, the lack of significant treatment-by-subgroup

interactions for TG and apo B suggests the treatment effects seen in both subgroups were consistent with those in the overall population, where significant treatment differences in favor of EZE/SIMVA were observed.

Low plasma HDL-C levels, a characteristic frequently associated with abdominal obesity and insulin resistance,[14,15] has been shown to be a strong and independent risk factor for future cardiovascular events and mortality.[16] HDL particles are believed to be antiatherogenic by virtue of facilitating cholesterol transport to the liver following efflux from peripheral tissues, and also by exerting antioxidant, antithrombotic, and anti-inflammatory effects.[17,18] In the current study, treatment with EZE/SIMVA or ROSUVA produced significant increases from baseline in HDL-C, both in the overall study population and non-obese patients; however, neither treatment led to significant improvements in HDL-C within the obese subgroup. The magnitude of the differences, however, was very small and the lack of significant changes from baseline seen with both individual therapies in the obese population may be due to the small number of patients contributing to the analysis. There were no significant between-treatment differences in HDL-C in the overall population or within either subgroup, indicating that EZE/SIMVA and ROSUVA produced similar effects on HDL-C, irrespective of the patient population examined.

Plasma hs-CRP is an inflammatory biomarker that has been shown to independently predict cardiovascular events and contribute to an individual's global risk classification, irrespective of plasma LDL-C levels.[19] Low grade inflammation, as measured by elevated plasma levels of hs-CRP, is a feature of central obesity.[20] Additionally, hs-CRP has been shown to have deleterious effects on vascular biology.[21] Previous studies suggest that statins lower hs-CRP levels independent of LDL-C.[22,23] Furthermore, EZE 10 mg administered in combination with statins has been shown to significantly enhance hs-CRP reductions beyond what is seen with statin monotherapy.[24] In the current analysis, treatment with EZE/SIMVA and ROSUVA did not produce significant within- or between-group changes from baseline in hs-CRP either in the overall study population or within the subgroups. It is not clear why neither EZE/SIMVA 10/20 mg nor ROSUVA 10 mg produced significant reductions in hs-CRP in the current study; however, the inherent variability in hs-CRP within the population and the limited sample size may have contributed to this finding. Most publications demonstrating significant effects of statins and ezetimibe plus statin combination therapy on hs-CRP have come from studies enrolling larger numbers of patients or analyses conducted in pooled studies or databases.[22,24]

Lowering LDL-C is the primary aim of lipid-lowering therapy patients with high risk for CVD. Irrespective of the obesity status of the patients, the reduction in LDL-C seen in the present study following treatment with EZE/SIMVA 10/20 mg significantly exceeded that seen for ROSUVA 10 mg at study end. The enhanced LDL-C-lowering efficacy of EZE/SIMVA versus ROSUVA resulted in significant increases in the percentages of obese and non-obese patients achieving recommended LDL-C levels of <2.59 and <1.81 mmol/L. Recent literature suggests that non-HDL-C and apo B are more accurate markers of CHD risk[25] and treatment targets,[26] especially in cardiometabolic risk patients, including those with obesity.[7] In the current study, treatment with EZE/SIMVA 10/20 mg produced significantly greater reductions than ROSUVA 10 mg in non-HDL-C and apo B among patients in both subgroups. Furthermore, a

significantly higher percentage of patients in both subgroups achieved specified levels of non-HDL-C (<3.37 and <2.59 mmol/L) and apo B (<0.9 and <0.8 g/L) with EZE/SIMVA versus ROSUVA.

The overall safety and tolerability profile of EZE/SIMVA was similar to that seen with ROSUVA in obese and non-obese patients. There was no evidence of a clinically meaningful difference in the incidences of AEs, including those related to muscle or liver toxicity in patients taking either EZE/SIMVA or ROSUVA.

These collective findings suggest that combination therapy with the minimum recommended starting dose of EZE/SIMVA (10/20 mg) may allow more obese and non-obese patients to achieve recommended LDL-C, non-HDL-C, and apo B levels compared with the starting dose of ROSUVA monotherapy (10 mg), without increased safety/tolerability concerns. The results of this analysis in obese and non-obese patients are consistent with previous reports showing the consistency in the lipid- and lipoprotein-lowering effects of EZE/SIMVA therapy in diabetic and metabolic syndrome patients who frequently are also obese.[10,27-30]

The finding that EZE/SIMVA therapy effectively treats dyslipidemia, irrespective of obesity status, may be of particular interest because the lipoprotein profile in obese patients is similar to that seen in patients with chronic kidney disease. The recent Study of Heart and Renal Protection (SHARP) trial demonstrated that EZE/SIMVA 10/20mg safely reduced cardiovascular events in patients with advanced chronic kidney disease.[31] The observed reduction in cardiovascular risk was consistent with what would be predicted based on the achieved LDL-C reductions. Whether the beneficial effects of combination therapy with EZE and a statin will translate to improved outcomes in patients with coronary heart disease is currently being evaluated in the ongoing IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT trial).[32,33]

The present analysis has several limitations that should be considered when interpreting the findings. First, this was an exploratory post-hoc analysis, and statistical comparisons were made without adjustment for multiplicity; thus, increasing the probability of false positive observations (eg, spurious findings of statistical significance). The small number of obese patients enrolled in this study is a further limitation, which may have contributed to false negative observations (eg, absence of statistical significance within subgroups). Finally, patients were classified as obese or non-obese on the basis of baseline BMI values because other markers (waist circumference, waist-to-hip measurements) of visceral adiposity were not recorded. As a result, it is not certain that the findings presented in this paper can be extrapolated to patients who are classified as visceral obese based on waist circumference and waist-to-hip ratio measurements.

CONCLUSION

In this post-hoc analysis of high-risk patients with elevated LDL-C, despite prior use of statin therapy, switching to EZE/SIMVA 10/20 mg versus ROSUVA 10 mg provided superior reductions in LDL-C, TC, and non-HDL-C in obese and non-obese patients.

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