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Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – The IN-CROSS study

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SUMMARY

Aims: To evaluate the efficacy of switching from a previous statin monotherapy to ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg vs. rosuvastatin (ROSUVA) 10 mg. **Methods:** In this randomised, double-blind study, 618 patients with documented hypercholesterolaemia [low-density lipoprotein cholesterol (LDL-C) ≥ 2.59 and ≤ 4.92 mmol/l] and with high cardiovascular risk who were taking a stable daily dose of one of several statin medications for ≥ 6 weeks prior to the study randomisation visit entered a 6-week open-label stabilisation/screening period during which they continued to receive their prestudy statin dose. Following stratification by study site and statin dose/potency, patients were randomised to EZE/SIMVA 10/20 mg ($n = 314$) or ROSUVA 10 mg ($n = 304$) for 6 weeks. **Results:** EZE/SIMVA produced greater reductions in LDL-C (−27.7% vs. −16.9%; $p \leq 0.001$), total cholesterol (−17.5% vs. −10.3%; $p \leq 0.001$), non-high-density lipoprotein cholesterol (HDL-C) (−23.4% vs. −14.0%; $p \leq 0.001$) and apolipoprotein B (−17.9% vs. −9.8%; $p \leq 0.001$) compared with ROSUVA, while both treatments were equally effective at increasing HDL-C (2.1% vs. 3.0%; $p = 0.433$). More patients achieved LDL-C levels < 2.59 mmol/l (73% vs. 56%), < 2.00 mmol/l (38% vs. 19%) and < 1.81 mmol/l (25% vs. 11%) with EZE/SIMVA than ROSUVA ($p \leq 0.001$). A borderline significantly greater reduction in triglycerides ($p = 0.056$) was observed for EZE/SIMVA (−11.0%) vs. ROSUVA (−5.3%). There were no between-group differences in the incidences of adverse events or liver transaminase and creatine kinase elevations. **Conclusion:** EZE/SIMVA 10/20 mg produced greater improvements in LDL-C, total cholesterol, non-HDL-C and apoB with a similar safety profile as for ROSUVA 10 mg.

What's known

- Optimal management of plasma LDL-C levels is the primary goal of therapeutic intervention in patients at risk of coronary events.
- A substantial proportion of patients at risk of coronary events fail to achieve recommended LDL-C goals with statin monotherapy and are therefore at increased risk of future coronary events.

What's new

- The present study was designed to evaluate the efficacy of switching hypercholesterolaemic patients at high cardiovascular risk who failed to achieve adequate lowering of LDL-C with prior statin monotherapy to ezetimibe/simvastatin 10/20 mg vs. rosuvastatin 10 mg.
- Ezetimibe/simvastatin 10/20 mg produced greater improvements in LDL-C, total cholesterol, non-HDL-C and apolipoprotein B with a similar safety profile as for rosuvastatin 10 mg.

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Disclosures
Amy O. Johnson-Levonas is an employee of Merck & Co., Inc. and holds stock in the company. Rachid Massaad and Kristel Vandormael are employees of Merck, Sharp & Dohme and hold stock in the company. Philippe Brudi is an employee of Merck/Schering Plough and holds stock in Merck. Margus Viigimaa and Maurizio Averna participated in the conduct of this study. Michel Farnier, Luc Missault and Helena Vaverkova participated in the conduct of this study and are members of Speaker Boards and Consultant/Advisory Boards.

Introduction

Elevated plasma low-density lipoprotein cholesterol (LDL-C) is a pivotal risk factor in the development of atherosclerotic coronary heart disease (CHD) (1). Hence, optimal management of plasma LDL-C levels is the primary goal of therapeutic intervention in patients at risk of coronary events (2–4). The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e. statins), the most effective LDL-C-lowering therapeutic agents available to date, operate by inhibiting cholesterol biosynthesis (5). Of the various statins available for use, rosuvastatin (ROSUVA) 10–40 mg/day (Crestor®, AstraZeneca, London, UK) is the most potent and provides LDL-C reductions in the range of 52–63%, depending on the dose (6,7).

The effectiveness of statin therapy in high-risk patient populations and the importance of aggressive lowering of LDL-C to minimise cardiovascular risk have been widely documented (8–13). Cholesterol management guidelines issued by international expert panels endorse a minimal LDL-C goal of < 2.59 mmol/l (< 100 mg/dl) in high-risk patients, with an optional target of < 2.00 mmol/l (< 77 mg/dl) or < 1.81 mmol/l (< 70 mg/dl) in persons at very high risk (2–4,14). Despite the proven efficacy of statins, a substantial proportion of high risk-patients fail to achieve recommended

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LDL-C goals with statin monotherapy and therefore remain at increased risk of future coronary events (15,16).

A major factor impeding LDL-C goal attainment among patients at the highest risk is the actual magnitude of LDL-C reductions they require to attain optimal levels (15,17). Many high-risk patients require a ≥ 50% reduction in LDL-C to achieve the most stringent LDL-C goals, and only the highest doses of the most potent statins are capable of providing these reductions. The practice of upwardly titrating the statin dose or switching to more potent statin regimens are therapeutic options for these patients; however, statin-induced muscle and liver-related adverse events (AEs) are known to occur frequently at higher statin doses. The initial dose of a statin provides the largest magnitude reduction in LDL-C, whereas each doubling of the statin dose results in only a 6–8% additional reduction relative to the prestatin (i.e. untreated) baseline levels. Moreover, the response to statin therapy is variable. Several factors can affect this response, among them the variability in cholesterol synthesis and cholesterol absorption. The challenge of attaining more aggressive LDL-C goals has stimulated research into possible new combinations of lipid-lowering agents with complementary mechanisms of actions (5). Ezetimibe (EZE) is a cholesterol absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol without affecting the uptake of triglycerides (TG) or fat-soluble vitamins (18). Clinical trials have shown that the co-administration of EZE 10 mg with simvastatin (SIMVA) (10, 20, 40, or 80 mg), a combination therapy that inhibits cholesterol biosynthesis and blocks its intestinal absorption, is more effective at lowering LDL-C than any one of the agent alone (19–21). As a result, a fixed-dose combination tablet containing EZE with a range of doses of SIMVA [EZE/SIMVA 10/10, 10/20, 10/40 and 10/80 mg; (Inegy®, MSD-SP Ltd, Hoddesdon, UK)] is available worldwide for the treatment of hypercholesterolaemia. Across the dose range, EZE/SIMVA has been shown to reduce LDL-C by 45–60%, with an overall safety profile similar to the respective monotherapies (22,23).

In Europe, EZE/SIMVA 10/20 mg/day represents the most commonly prescribed starting dose of this second line LDL-C-lowering agent (23). The usual starting dose for ROSUVA is 5 or 10 mg, depending on the country and taking into account the individual patient's cholesterol level as well as their future cardiovascular risk. According to the product labels for these two agents, EZE/SIMVA 10/20 mg and ROSUVA 10 mg provide comparable LDL-C reductions of approximately 52% (6,22).

The present study was undertaken to compare the lipid-altering efficacy, LDL-C goal attainment and safety/tolerability profile of switching from on-going statin monotherapy to either EZE/SIMVA 10/20 mg or ROSUVA 10 mg in a population of patients at high-risk of CHD (i.e. defined by prior history of CHD, type 2 diabetes with high cardiovascular risk, or 10-year Framingham risk > 20%) and not at their LDL-C goal. This study design reflects the usual approach taken in clinical practice of switching patients to more potent LDL-C-lowering regimens (either by upwardly titrating the statin dose, switching to a more potent statin monotherapy, or switching to combination therapy) after they fail to meet their LDL-C goals.

Materials and methods

Patients

This study enrolled men and women (≥ 18 and < 80 years) with documented hypercholesterolaemia [LDL-C ≥ 2.59 to ≤ 4.92 mmol/l (≥ 100 and ≤ 190 mg/dl) at screening visit and ≥ 2.59 to ≤ 4.14 mmol/l (≥ 100 and ≤ 160 mg/dl) at randomisation visit] and high cardiovascular risk who were taking a stable daily dose of one of the following statin medications for ≥ 6 weeks prior to the study randomisation visit (Visit 1): atorvastatin (10 or 20 mg); fluvastatin (80 mg); pravastatin (40 mg); ROSUVA (5 mg); or SIMVA (20 or 40 mg) (Figure 1). 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, revascularisation procedure, myocardial infarction, documented silent myocardial ischaemia), or with established vascular atherosclerotic disease (i.e. peripheral vascular disease, ischaemic 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 (standardised for body surface area) < 1.002 ml/s] and/or at least two CHD risk factors per Framingham risk calculation}; (iii) CHD risk > 20% over 10 years as determined by the Framingham risk calculation. Fasting TG levels had to be ≤ 3.96 mmol/l (≤ 350 mg/dl) at week–one before the randomisation visit (Visit 2) to allow for LDL-C calculation by the Friedewald equation (24).

Study design

Exclusion criteria included conditions or medications, other than reported statin medications, that could have affected lipid levels; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels > 1.5 × the upper limit of normal (ULN); active

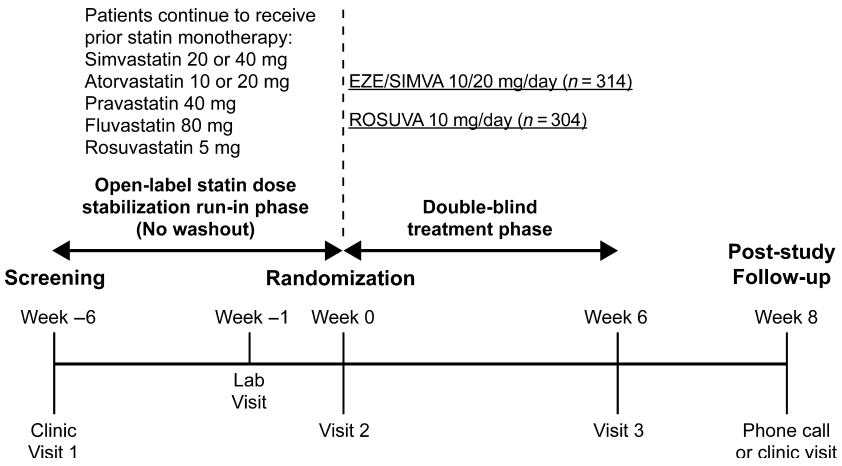

Figure 1 Study design. Patient's medical history and current brand/dose of statin reviewed at Visit 1. Eligibility of study entry based on LDL-C ≥ 2.59 mmol/l and ≤ 4.92 mmol/l. Randomisation to treatment (ezetimibe 10/20 mg or rosuvastatin 10 mg) at Visit 2 after stratification by baseline statin potency (low or high) and eligibility based on acceptable serum chemistry values for alanine aminotransferase, aspartate aminotransferase, creatine kinase, triglycerides and low-density lipoprotein cholesterol (LDL-C)

liver disease; creatine kinase (CK) levels > 3 × ULN; patients with congestive heart failure defined by New York Heart Association Class III or IV; patients with poorly controlled [haemoglobin A1c (HbA1c) ≥ 8.5%] diabetes; uncontrolled hypertension (systolic > 160 mmHg or diastolic >100 mmHg); impaired renal function (creatinine ≥ 176.8 μmol/l) or history of nephrotic range proteinuria; partial ileal bypass surgery or other significant intestinal malabsorption; positive pregnancy test for female patients of childbearing potential; and treatment with excluded concomitant medications (i.e. immunosuppressants, corticosteroids, or potent inhibitors of cytochrome P450 3A4).

This was a Phase IV, multicentre, randomised, double-blind, active-controlled, parallel group study conducted between March 2007 and March 2008 according to Good Clinical Research Practice at 85 sites in 10 countries (Belgium, Czech Republic, Estonia, France, Greece, Italy, Latvia, Lithuania, the Netherlands and Portugal). The study protocol was reviewed and approved by the appropriate ethics committees and institutional review boards, and all patients provided written informed consent before any study procedures were administered. Clinic visits occurred at week −6 (Visit 1; screening/dose stabilisation visit); week 0 (Visit 2; randomisation/baseline visit); week 6 (Visit 3; postrandomisation efficacy and safety assessment visit); and week 8 (Visit 4; poststudy follow-up safety assessment) (Figure 1). At the screening visit, qualifying patients with LDL-C values ≥ 2.59 to ≤ 4.92 mmol/l (≥ 100 and ≤ 190 mg/dl) were allowed to enrol in the screening phase of the study and continued to receive their current dose/brand of statin medication for up to 6 weeks in an open-label manner. At the randomisation visit, patients with inadequately controlled LDL-C (≥ 2.59 to ≤ 4.14 mmol/l [≥ 100 to ≤ 160 mg/dl]) despite prior treatment with statin monotherapy were stratified by study centre and potency of their statin brand/dose [low (Stratum 1: atorvastatin 10 mg, fluvastatin 80 mg, pravastatin 40 mg, SIMVA 20 mg) or high (Stratum 2: atorvastatin 20 mg, ROSUVA 5 mg, SIMVA 40 mg)] and randomised in equal proportions to receive double-blind EZE/SIMVA 10/20 mg/day or ROSUVA 10 mg/day for 6 weeks. Patients received diet and exercise counselling at every clinic visit during the open-label treatment stabilisation run-in period and the entire 6-week active treatment phase. A follow-up phone call or poststudy visit, if necessary, was scheduled 14 days after the final dose of study medication was received (week 8) for the purpose of collecting safety information. Patients with ALT or AST levels ≥ 3 × ULN and CK levels ≥ 10 × ULN were followed up with a subsequent chemistry evaluation.

The primary efficacy variable was mean per cent change in LDL-C from baseline (week 0) to study end-point (last postbaseline measurement during the 6-week active treatment period). Key secondary efficacy variables were the percentages of patients achieving LDL-C < 2.59 mmol/l (< 100 mg/dl) and < 1.81 mmol/l (< 70 mg/dl) at study end-point. Predefined secondary efficacy variables included the mean per cent change at study end-point in total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C and TC/HDL-C ratios, apolipoprotein (apo) B and high-sensitivity C-reactive protein (hs-CRP).

Safety and tolerability assessments included collection of AEs, physical examination, vital signs and 12-lead electrocardiograms. Laboratory safety measurements included blood chemistry, haematology and urinalysis. Blood chemistry included ALT, AST and CK measurements. Prespecified AEs of interest included those that were gastrointestinal related, gallbladder related, associated with an allergic reaction or rash, and hepatitis related as well as incidences of clinically significant elevations in ALT and AST $\geq 3\times$ ULN and CK elevations $\geq 5\times$ ULN either with or without muscle symptoms, and drug relationship.

Statistical analysis

Efficacy analyses of biological parameters (i.e. lipids, lipoproteins and hs-CRP) were performed in the full analysis set population, which included all patients who had taken at least one dose of randomised medication and who had a baseline efficacy measurement and at least one efficacy measurement during the active treatment period. Efficacy end-points were analysed using an analysis-of-variance (ANOVA) model with terms for treatment, stratum (according to potency of the prerandomisation statin brand/dose), baseline LDL-C (categorised based on quartiles), and study centre. Within and between-treatment groups least squares (LS) means and 95% confidence intervals (CIs) were estimated from the above model. A non-parametric ANOVA analysis was performed for TG and CRP because these parameters were not normally distributed. The difference between treatment groups was quantified using the difference in medians and 95% CIs using Hodges–Lehmann estimates. A logistic regression model with terms for treatment, stratum and baseline LDL-C (continuous variable) was used to analyse the percentage of patients reaching LDL-C targets of < 2.59 mmol/l (< 100 mg/dl), < 2.00 mmol/l (< 77 mg/dl), and < 1.81 mmol/l (< 70 mg/dl). Odds ratio estimates derived from the logistic regression model and 95% CIs were used to quantify the treatment effect. For the primary efficacy variable, the consistency of the treatment effect across subgroups was performed for the following: stratum [low (Stratum 1) and high (Stratum 2) statin potency], age (< 65 vs. ≥ 65 years); gender (male, female); baseline LDL-C (categorised based on quartiles); prior statin therapy (atorvastatin, fluvastatin, pravastatin, ROSUVA, or SIMVA), hypertension (yes, no) and diabetes mellitus (yes, no). Treatment-by-subgroup interaction tests were performed for the predefined categories of age and gender, while the other remaining subgroups were informally evaluated through the inspection of point estimates and 95% CIs. For the prespecified subgroups of stratum, age and gender, the treatment-by-subgroup interaction was tested at the $\alpha = 0.100$ level using an ANOVA model, similar to the main model but included the additional terms for subgroup and the treatment-by-subgroup interaction (if the subgroup factor was stratum, it was included in the model once). No formal interaction tests were performed for the remaining subgroups to minimise Type 1 error introduced with multiple testing.

Data from the all-patients-as-treated (APaT) population, including all randomised patients who took at least one dose from the double-blind study medication container, were included in safety and tolerability assessments. Fisher's exact test was used to compare between-treatment incidences of AEs of special interest (specified above) and 95% CIs for the between-group differences using Wilson's score method were provided. For predefined AEs (i.e. patients with any clinical AE, treatment-related AEs, serious AEs, or discontinuations because of AEs), 95% CIs for treatment differences in proportions were provided (no inferential testing).

Results

Patients

A total of 1212 patients were screened for inclusion in the study, and 618 of those screened were randomised in similar numbers to receive qd treatment with EZE/SIMVA 10/20 mg ($n = 314$) or ROSUVA 10 mg ($n = 304$) (Figure 2). Of the 594 patients excluded from participation in this study during the screening phase, 41 were excluded because of lack of follow up or withdrawal of consent and 553 patients were excluded because they did not meet specified inclusion or exclusion criteria. Of those randomised, 301 patients (96%) in the EZE/SIMVA group and 295 patients (97%) in the ROSUVA group successfully completed the 6-week, double-blind, treatment period. Twenty-two (4%) randomised patients were discontinued from the study because of clinical AEs ($n = 15$), consent withdrawal ($n = 5$), lost to follow up ($n = 1$), or protocol deviation ($n = 1$). The incidences and reasons for discontinuation were similar across the two groups.

There were no clinically meaningful differences in baseline demographic, anthropometric, or disease characteristics across the two treatment groups (Table 1). The majority of study participants were Caucasian men, and approximately half were under the age of 65 years. CHD was present in approximately half of the patients, hypertension in 63% and diabetes in 30%. Baseline lipid/lipoprotein variables, secondary diagnoses and concomitant drug therapies

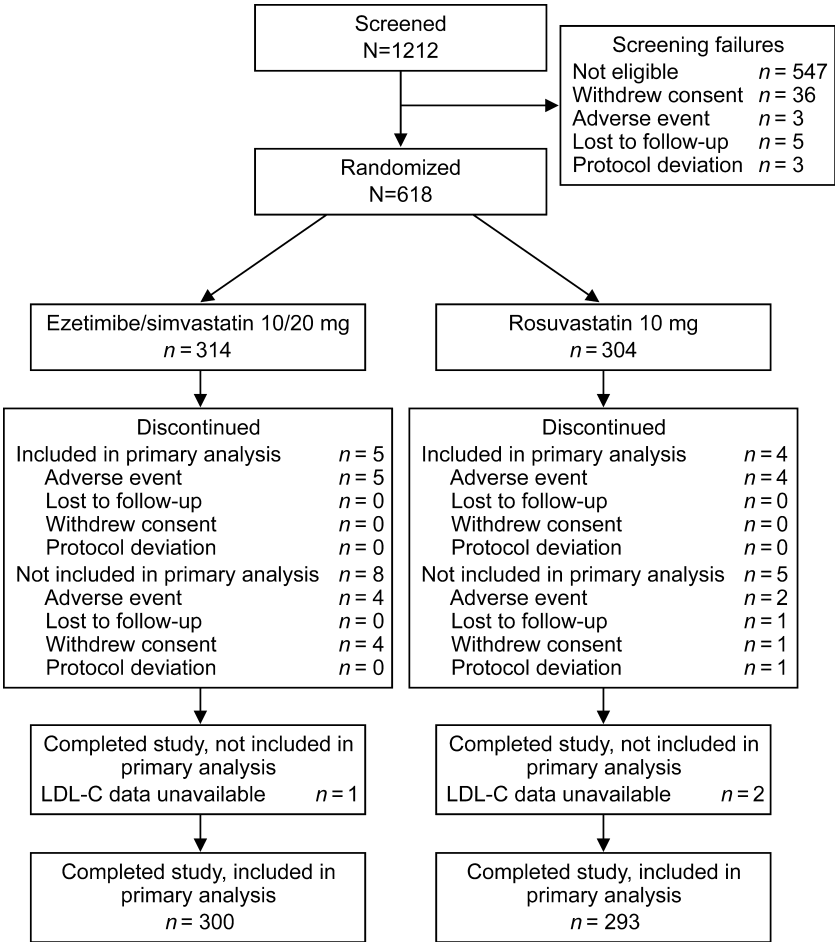

Figure 2 Flow chart of patient accounting in the study

were generally similar across the treatment groups. The only exception was a slightly longer mean duration of hypercholesterolaemia in the ROSUVA group vs. EZE/SIMVA (9 and 8 years, respectively). Most patients in this study were taking low (60%) potency statin therapies at the time of randomisation (Table 2). There were no clinically meaningful differences between the treatment groups in the frequencies and types of prerandomisation statin regimens. One patient in the EZE/SIMVA group received lovastatin 20 mg prior to randomisation, but was retrospectively issued a waiver to continue in the study.

A total of 16 patients (nine patients on EZE/SIMVA and seven on ROSUVA) were excluded from the primary efficacy analysis because of withdrawal of consent (n = 6), clinical AE (n = 5), lack of baseline LDL-C values (n = 3), or other reason (n = 2; protocol deviation, lost to follow-up). Mean compliance with study medication was 99% in both groups, and the mean number of days on treatment was similar between the two groups (41.8 and 41.5 days for EZE/SIMVA and ROSUVA respectively).

Efficacy

In high-risk patients with hypercholesterolaemia, despite prior use of statin monotherapy, treatment with EZE/SIMVA 10/20 mg for 6 weeks produced a −27.7% (95% CI: −30.3, −25.0; $p \leq 0.001$ vs. baseline) LS mean change from baseline in LDL-C compared with −16.9% (95% CI: −19.6, −14.3; $p \leq 0.001$ vs. baseline) for the ROSUVA 10 mg group (Table 3), resulting in a significant between-group difference of −10.7% (95% CI: −14.1, −7.3) favouring EZE/SIMVA therapy ($p \leq 0.001$) (Table 3; Figure 3).

An examination of the treatment response within each statin potency stratum showed that EZE/SIMVA 10/20 mg consistently provided greater incremental reductions in LDL-C compared with ROSUVA 10 mg (Figure 4). When the between-group LDL-C response was examined across each stratum, a significant treatment-by-stratum interaction ($p = 0.013$) was detected, indicating that there was a trend towards greater between-group LDL-C reductions in patients who were taking higher potency statin monotherapy prior to randomisation (between-group difference of

Table 1 Patient characteristics and baseline biological parameters presented by treatment group

	EZE/SIMVA 10/20 mg (*n* = 314)	ROSUVA 10 mg (*n* = 304)
Age, years	63.2 (9.8)	63.1 (10)
Range	38–82	27–80
No. (%) patients ≥ 65 years	145 (46.2)	151 (49.7)
Females, *n* (%)	129 (41.1)	119 (39.1)
Race, *n* (%)		
White	314 (100)	302 (99.3)
Black	0 (0)	2 (0.7)
Ethnicity, *n* (%):		
Hispanic/Latino	37 (11.8)	43 (14.1)
Non-Hispanic/Latino	277 (88.2)	261 (85.9)
Weight, kg	78.7 (15.8)	79.2 (14.2)
Body mass index, kg/m^2	28.1 (4.8)	28.0 (4.6)
Tobacco use		
Smoker	93 (29.6)	96 (31.6)
Ex-smoker	77 (24.5)	70 (23.0)
Non-smoker	144 (45.9)	138 (45.4)
Duration of hypercholesterolaemia, years	8.3 (5.6)	9.2 (6.6)
Patient history of disease: *n* (%)		
Hypertension	203 (64.6)	189 (62.2)
DM	95 (30.3)	78 (25.7)
CHD	152 (48.4)	144 (47.4)
PVD	28 (8.9)	26 (8.6)
Stroke	3 (1.0)	2 (0.7)
Concomitant therapies, *n* (%)		
Drugs used in diabetes	73 (23.5)	61 (20.1)
Antithrombotic agents	61 (19.4)	48 (15.8)
Antihypertensive agents*	244 (77.7)	232 (76.3)
Cardiac therapy†	50 (15.9)	41 (13.5)
Baseline lipids		
LDL-C, mmol/l	3.21 (0.42)	3.24 (0.44)
TC, mmol/l	5.38 (0.57)	5.38 (0.61)
TG, mmol/l‡	1.46 (0.80)	1.41 (0.81)
HDL-C, mmol/l	1.43 (0.37)	1.43 (0.36)
non-HDL-C, mmol/l	3.95 (0.55)	3.95 (0.56)
LDL-C/HDL-C, ratio	2.38 (0.65)	2.40 (0.65)
TC/HDL-C, ratio	3.95 (0.89)	3.95 (0.89)
apo B, g/l	1.20 (0.20)	1.18 (0.21)
hs-CRP, g/dl‡	0.16 (0.24)	0.15 (0.24)

Data are expressed as mean (SD) unless stated otherwise. *Includes agents acting on the renin–angiotensin system, beta blocking agents, calcium channel blockers and diuretics. †Includes cardiac glycosides, anti-arrhythmics class I and III, vasodilators used in cardiac diseases and other cardiac preparations. ‡Median values (standard deviation for medians calculated by [Q3–Q1]/1.075). apo, apolipoprotein; CHD, coronary heart disease; DM, diabetes mellitus; EZE/SIMVA, ezetimibe/simvastatin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; ROSUVA, rosuvastatin; SD, standard deviation; TC, total cholesterol; TG, triglycerides.

7% [95% CI: −11.3, −3.2] in Stratum 1 and 17% [95% CI: −23.1, −9.9] in Stratum 2). However, the treatment-by-stratum interaction was found to be quantitative (i.e. not qualitative) in nature and directionally consistent with overall study results favouring EZE/SIMVA therapy.

No significant treatment-by-subgroup interaction was detected for the subgroup of age ($p = 0.324$), confirming the consistency of the incremental LDL-C-lowering response to EZE/SIMVA vs. ROSUVA in patients < 65 or ≥ 65 years of age (Figure 4). A significant treatment-by-subgroup interaction was observed for gender ($p = 0.017$), with men experiencing slightly larger between-group reductions in LDL-C than women did. The treatment-by-gender interaction was found to be quantitative (i.e. not

Table 2 Baseline LDL-C concentrations and number (%) of patients in each statin potency stratum receiving specific brands and doses of statin monotherapies

	EZE/SIMVA 10/20 mg (*n* = 314)		ROSUVA 10 mg (*n* = 304)	
	Baseline LDL-C (mmol/l)	No. of patients (%)	Baseline LDL-C (mmol/l)	No. of patients (%)
Low potency statin (Stratum 1)	3.25 (0.42)	189 (60.2)	3.23 (0.44)	180 (59.2)
Fluvastatin 80 mg	3.12 (0.48)	18 (9.5)	3.20 (0.45)	17 (9.4)
Lovastatin 20 mg*	–	0	2.75 (–)	1 (0.6)
Pravastatin 40 mg	3.39 (0.39)	40 (21.2)	3.20 (0.39)	30 (16.7)
Atorvastatin 10 mg	3.23 (0.40)	66 (34.9)	3.30 (0.49)	63 (35.0)
Simvastatin 20 mg	3.22 (0.44)	65 (34.4)	3.19 (0.41)	69 (38.3)
High potency statin (Stratum 2)	3.16 (0.42)	125 (39.8)	3.27 (0.43)	124 (40.8)
Atorvastatin 20 mg	3.10 (0.41)	52 (41.6)	3.21 (0.38)	51 (41.1)
Rosuvastatin 5 mg	3.22 (0.42)	44 (35.2)	3.33 (0.49)	50 (40.3)
Simvastatin 40 mg	3.16 (0.44)	29 (23.2)	3.24 (0.40)	23 (18.5)

*One patient taking lovastatin 20 mg was allowed to participate in this study.
EZE/SIMVA, ezetimibe/simvastatin; LDL-C, low-density lipoprotein cholesterol; ROSUVA, rosuvastatin.

Table 3 Least squares mean percent change from baseline and between-group differences (EZE/SIMVA – ROSUVA) in efficacy parameters at the last available postbaseline evaluation during the 6-week study period

	Least-squares mean % change (95% CI)			
Efficacy parameter	EZE/SIMVA 10/20 mg (*n* = 301–305)‡	ROSUVA 10 mg (*n* = 292–297)‡	Between-group difference (95% CI)	p-value
LDL-C	−27.7 (−30.3, −25.0)***	−16.9 (−19.6, −14.3)***	−10.7 (−14.1, −7.3)	≤ 0.001
TC	−17.5 (−19.4, −15.7)***	−10.3 (−12.2, −8.5)***	−7.2 (−9.6, −4.8)	≤ 0.001
HDL-C	2.1 (0.3, 3.9)**	3.0 (1.2, 4.9)***	−0.9 (−3.2, 1.4)	0.433
TG†	−11.0 (−15.3, −6.8)***	−5.3 (−9.9, −1.2)**	−5.1 (−9.6, −0.3)	0.056
non-HDL-C	−23.4 (−25.8, −21.0)***	−14.0 (−16.5, −11.6)***	−9.4 (−12.5, −6.3)	≤ 0.001
apo B	−17.9 (−20.1, −15.7)***	−9.8 (−12.0, −7.6)***	−8.1 (−10.9, −5.3)	≤ 0.001
LDL-C/HDL-C ratio	−27.4 (−30.4, −24.4)***	−17.8 (−20.9, −14.8)***	−9.6 (−13.5, −5.7)	≤ 0.001
TC/HDL-C ratio	−17.8 (−19.9, −15.6)***	−11.5 (−13.7, −9.3)***	−6.3 (−9.1, −3.4)	≤ 0.001
hs-CRP†	−8.3 (−16.7, 0.0)**	0.0 (−7.1, 6.3)	−6.7 (−16.7, 2.9)	0.172

**p ≤ 0.05 vs. baseline; ***p ≤ 0.001 vs. baseline.
†Expressed as median study endpoint value (95% CI of median); the difference in medians was obtained by Hodges-Lehman estimation.
‡The number of patients contributing to the efficacy analyses varied for each of the parameters shown.
apo, apolipoprotein; CI, confidence interval; EZE/SIMVA, ezetimibe/simvastatin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; ROSUVA, rosuvastatin; TC, total cholesterol; TG, triglycerides.

qualitative) in nature, indicating that EZE/SIMVA was more effective than ROSUVA at lowering LDL-C regardless of gender. Further inspection of the point estimates and 95% CIs for the between-treatment group differences in the remaining subgroups showed, in general, greater LDL-C reductions with EZE/SIMVA compared with ROSUVA.

A significantly greater proportion of patients in the EZE/SIMVA group compared with the ROSUVA group achieved LDL-C goals of < 2.59 mmol/l (72.5% vs. 56.2%, respectively), < 2.00 mmol/l (38.0% vs. 18.9%, respectively) and < 1.81 mmol/l (25.2% vs. 11.1%, respectively) at study end-point (Figure 5). The corresponding logistic regression odds ratio for

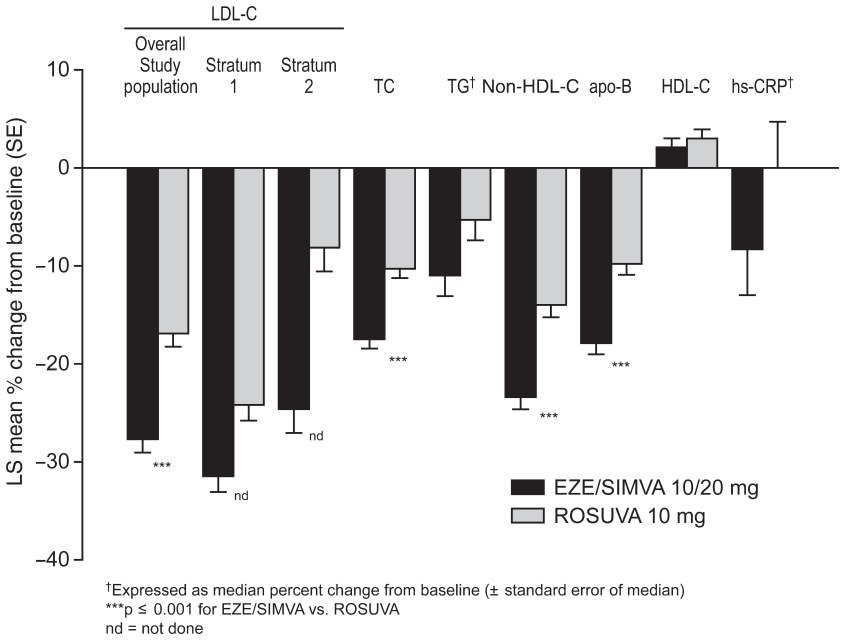

Figure 3 Mean per cent change (±standard error) from baseline in lipid parameters following 6 weeks of treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg

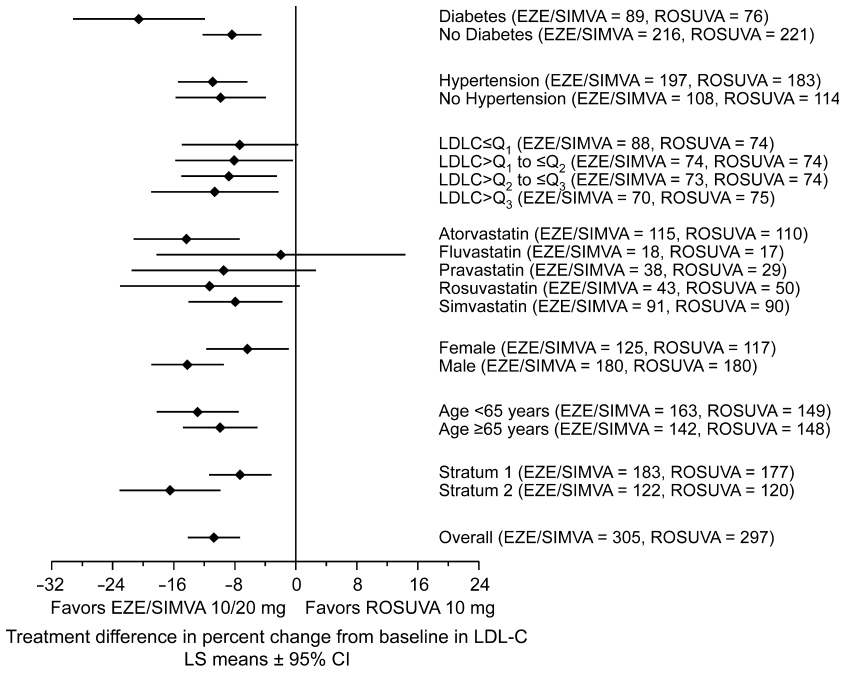

Figure 4 Between-treatment group differences (ezetimibe/simvastatin vs. rosuvastatin) in least squares mean per cent change in low-density lipoprotein cholesterol (LDL-C) at study end-point (95% CI) in the overall study population and within subgroups defined by statin potency stratum [use of low (Stratum 1) and high (Stratum 2) potency statin monotherapy prior to randomisation], statin brand used prior to randomisation, gender, age, baseline LDL-C (stratified by quartile) and prior history of diabetes or hypertension. Numbers in parentheses indicate number of patients in each treatment group in the respective subcategory

achieving these three LDL-C targets were 2.1 (95% CI: 1.5, 3.0; $p \leq 0.001$), 2.8 (95% CI: 1.9, 4.0; $p \leq 0.001$) and 2.8 (95% CI: 1.8, 4.4; $p \leq 0.001$), respectively, in favour of EZE/SIMVA.

For the secondary efficacy end-points, both EZE/SIMVA 10/20 mg and ROSUVA 10 mg produced significant improvements from baseline in TC (−17.5% and −10.3%, respectively), TG (−11.0% and

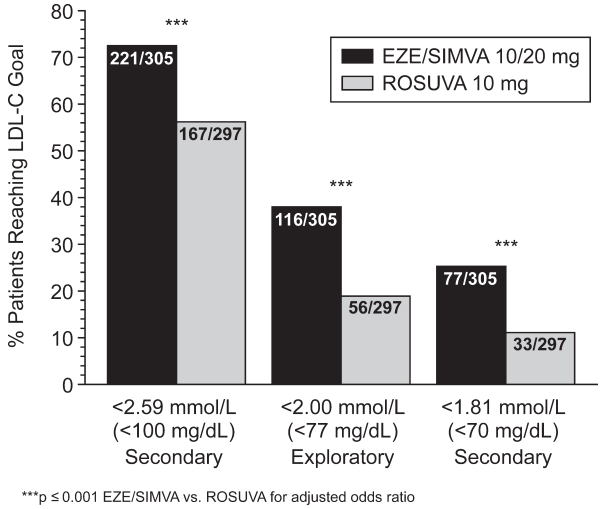

Figure 5 Secondary and exploratory analyses of the percentage of patients achieving key low-density lipoprotein cholesterol (LDL-C) goal attainment following 6 weeks of treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg. Data in each bar represent number of patients achieving specified LDL goals over total number of patients analysed in that treatment group

−5.3%, respectively), non-HDL-C (−23.4% and −14.0%, respectively), apo B (−17.9% and −9.8%, respectively), LDL-C/HDL-C (−27.4% and −17.8%, respectively), TC/HDL-C (−17.8% and −11.5%, respectively) and HDL-C (2.1% and 3.0%, respectively) (Table 3). Treatment with EZE/SIMVA was significantly more effective than ROSUVA in lowering TC (−7.2%; $p \leq 0.001$), non-HDL-C (−9.4%; $p \leq 0.001$), apo B (−8.1%; $p \leq 0.001$), LDL-C/HDL-C (−9.6%; $p \leq 0.001$) and TC/HDL-C (−6.3%; $p \leq 0.001$), whereas both treatments were equally effective at raising HDL-C (−0.9%; $p = 0.433$) (Table 3; Figure 3). The median per cent reduction from baseline in TG was greater for EZE/SIMVA 10/20 mg than for ROSUVA 10 mg; the difference was borderline significant (−5.1%; $p = 0.056$). EZE/SIMVA therapy produced small significant reductions from baseline in hs-CRP (−8.3%) with no within-group effect seen for ROSUVA; the between-group difference for this parameter was not significant (−6.7%; $p = 0.172$).

Safety and tolerability

Treatment with EZE/SIMVA 10/20 mg and ROSUVA 10 mg was generally well tolerated. Clinical AEs were reported by 22 patients (7.1%) in the EZE/SIMVA group and 34 patients (11.2%) in the ROSUVA group (Table 4). There were no meaningful differences between the two treatment groups with regard to the types or frequencies of clinical AEs, treatment-related clinical AEs, discontinuation because of clinical AEs, or serious clinical AEs. A single death occurred during this study in the EZE/SIMVA group; the patient died from a subarachnoid haemorrhage resulting from a traumatic brain injury, and the death was judged not related to study medication by the investigator.

Two patients in the EZE/SIMVA 10/20 mg group (0.7%) had presumed consecutive elevations in ALT and/or AST values $\geq 3 \times$ ULN, whereas none of the patients in the ROSUVA 10 mg group had such elevations. The between-group difference in the incidence of ALT/AST elevations $\geq 3 \times$ ULN was not significant ($p = 0.499$). There were no clinical AEs of hepatitis or jaundice reported in this study. One patient in the EZE/SIMVA group experienced a hepatobiliary-related clinical AE of cholangitis, which was deemed not related to study medication by the investigator. No patient in either group had CK elevations $\geq 5 \times$ ULN with or without muscle symptoms, and there were no reported cases of myopathy or rhabdomyolysis. Results of other laboratory tests including routine serum chemistries, and haematological parameters as well as vital signs and findings on physical examinations revealed no evidence of additional safety concerns with EZE/SIMVA therapy.

Discussion

Previously published studies conducted in high-risk patients (i.e. defined by a history of stable CHD, type 2 diabetes or recently hospitalised for a coronary event) have shown that switching to EZE/SIMVA (10/20 or 10/40 mg/day, depending on the study)

Table 4 Summary of adverse events

	Within-group comparison		Between-group comparison	
	EZE/SIMVA 10/20 mg (*n* = 314)	ROSUVA 10 mg (*n* = 304)	Difference in percentages (95% CI)*	p-value†
No. of patients (%)				
With one or more clinical AEs	22 (7.1)	34 (11.2)	−4.1 (−8.8, 0.4)	–
With treatment-related clinical AEs‡	8 (2.6)	10 (3.3)	−0.7 (−3.7, 2.1)	–
With serious clinical AEs	3 (1.0)	5 (1.6)	−0.7 (−2.9, 1.4)	–
With serious treatment-related clinical AEs‡	1 (0.3)	1 (0.3)	–	–
Death	1 (0.3)§	0	–	–
Discontinued				
Clinical AEs	9 (2.9)	6 (2.0)	0.9 (−1.7, 3.6)	–
Treatment-related clinical AEs‡	7 (2.2)	3 (1.0)	–	–
Serious clinical AE	1 (0.3)	1 (0.3)	–	–
Serious treatment-related clinical AEs‡	0	1 (0.3)	–	–
With one or more laboratory AEs	0	0	0.0 (−1.2, 1.2)	1.000
Individual clinical AEs of interest, *n* (%)				
Allergic reaction or rash	2 (0.6)	2 (0.7)	0 (−1.8, 1.7)	1.000
Gallbladder-related	0	0	0 (−1.2, 1.2)	1.000
Gastrointestinal-related	9 (2.9)	7 (2.3)	0.6 (−2.2, 3.4)	0.801
Hepatobiliary-related	1 (0.3)	0	0.3 (−1.0, 1.8)	1.000
Consecutive ≥ 3× ULN elevations in ALT and/or AST¶	2/302 (0.7%)	0/293	0.7 (−0.7, 2.4)	0.499
CK ≥5× ULN§	0/302	0/293	0.0 (−1.3, 1.3)	1.000

*Computed using Wilson's Score method.
†Based on Fisher's Exact test.
‡Determined by study investigator to be related to the drug.
§One death that occurred from a traumatic brain injury and subarachnoid haemorrhage 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.
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; EZE/SIMVA, ezetimibe/simvastatin; LS, least squares; ROSUVA, rosuvastatin; ULN, upper limit of normal; –, not calculated.

provides greater LDL-C reductions compared with doubling the initial dose of statin monotherapy (25–28). The present study is the first to compare the LDL-C-lowering efficacy of switching patients who are not at their LDL-C goal from a stable dose of statin monotherapy with the widely prescribed starting dose of EZE/SIMVA (10/20 mg) or the most potent statin ROSUVA at 10 mg. This study enrolled a population of hypercholesterolaemic patients at high cardiovascular risk who failed to achieve adequate lowering of LDL-C with prior statin monotherapy. The mean duration of hypercholesterolaemia in this study was 8 years, suggesting that the patients in this study had been candidates for lipid-lowering therapy for many years prior to enrolment and still had not achieved their optimal LDL-C therapeutic targets. The results of the recently published EUROASPIRE III survey indicate that a significant proportion of high-risk hypercholesterolaemic patients with CHD are not adequately treated with current statin treatment regimens (29). Thus, more aggressive lipid-lowering therapies are required to achieve recommended cholesterol goals.

The present study provided evidence that switching from statin monotherapy to EZE/SIMVA 10/20 mg was more effective in reducing LDL-C levels than was ROSUVA 10 mg. Treatment with the usual recommended starting dose of EZE/SIMVA 10/20 mg/day provided an additional 11% reduction in statin-treated baseline values of LDL-C compared with that achieved with ROSUVA 10 mg after 6 weeks of treatment.

Treatment with EZE/SIMVA 10/20 mg provided greater LDL-C-lowering efficacy in all the examined

patient subgroups [age, gender, stratum, baseline LDL-C, previous statin therapy and patient history of disease (hypertension, type 2 diabetes)]. Significantly more patients in the EZE/SIMVA group achieved their minimum recommended LDL-C goal of < 2.59 mmol/l (< 100 mg/dl) per European and US treatment guidelines (73% vs. 56%; $p \leq 0.001$) (2,3). Moreover, a greater proportion of patients treated with EZE/SIMVA reached the more aggressive, but optional, European LDL-C goal of < 2.00 mmol/l (< 77 mg/dl; 38% vs. 19%; $p \leq 0.001$) and US goal of < 1.81 mmol/l (< 70 mg/dl; 25% vs. 11%; $p \leq 0.001$) (3,14).

In addition to producing beneficial effects on LDL-C, administration of EZE/SIMVA 10/20 mg led to significantly greater reductions in TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, and apo B relative to ROSUVA 10 mg. These findings indicate that EZE/SIMVA was significantly more effective than ROSUVA at improving plasma concentrations of a wide array of apo B-containing lipids and lipoproteins. Reductions in hs-CRP and increases in HDL-C were significant for EZE/SIMVA therapy relative to baseline but did not differ from those achieved with ROSUVA therapy. For TG, a borderline significant between-group difference was seen in favour of EZE/SIMVA treatment.

EZE/SIMVA 10/20 mg and ROSUVA 10 mg were generally well tolerated in this population of high-risk patients. The overall rates of clinical AEs, treatment-related clinical AEs, discontinuations because of clinical AEs and serious clinical AEs were similar between the groups. There were no clinically meaningful differences between the groups with respect to the incidence of the prespecified AEs of interest, including allergic reaction or rash, gallbladder-related, gastrointestinal-related, or hepatobiliary-related clinical AEs. A low incidence of elevated liver transaminase levels was observed in the EZE/SIMVA group, but these elevations were asymptomatic in nature, and there were no cases of hepatitis or jaundice reported in this study. In addition, there were no instances of CK elevations $\geq 5 \times$ ULN with or without muscle symptoms in either group and there were no reports of myopathy or rhabdomyolysis. It should be noted that this study was only 6 weeks in duration, thus precluding an assessment of long-term safety profile of EZE/SIMVA.

In a previously published study of the efficacy of EZE/SIMVA and ROSUVA, hypercholesterolaemic (LDL-C $\geq$ 3.7 and $\leq$ 6.5 mmol/l) patients spanning all three CHD risk categories (CHD/CHD risk-equivalent, $\geq$ 2 CHD risk factors and 0–1 CHD risk factor) and without any lipid-lowering drug, were randomised in equal proportions to qd EZE/SIMVA (10/20 mg, 10/40 mg or 10/80 mg) or ROSUVA (10, 20, or 40 mg) for 6 weeks (30). Treatment with EZE/SIMVA was significantly more effective than ROSUVA at lowering LDL-C, with between-group reductions of 5.7%, 2.5% and 4.3% at the lowest dose, next highest dose and maximum dose comparisons respectively.

The magnitude of the between-group LDL-C reduction observed in the present study with either EZE/SIMVA 10/20 mg or ROSUVA 10 mg was approximately twofold larger than that seen in the previously published study (−11% vs. −6%, respectively) (30). This finding may be because of differences in the study designs and/or the average baseline LDL-C values observed at randomisation in these two studies. Patients in the previous study were washed off of lipid-lowering therapies during a 4-week placebo run-in phase, whereas patients in the present study had to be above their LDL-C goal while taking a stable dose of statin therapy for $\geq$ 6 weeks before randomisation. Add-on and switch study designs frequently demonstrate larger magnitude LDL-C reductions relative to those observed in factorial designed studies, even when the treatments under evaluation are identical (19,25,27,28).

Another difference between the previous comparative study and the present study concerns the selection of patients. The population enrolled in this study could have been enriched with patients who do not respond as effectively to statin monotherapy (i.e. poor responders), whereas the previous study enrolled patients regardless of their response to prior statin therapy. It is conceivable that some patients could have higher baseline rates of cholesterol absorption and lower baseline rates of hepatic cholesterol biosynthesis, and *vice versa*. The former group of patients might be less responsive to statin therapy and more responsive to EZE therapy with the reverse being true for the latter group. This hypothesis might, at least in part, explain the recent observation of a strong negative correlation between the LDL-C-lowering response to statin therapy and the subsequent response to ezetimibe in patients with heterozygous familial hypercholesterolaemia (31). The results obtained in the current study support informal observations made in clinical practice that poor responders to statin therapy tend to have a more pronounced response to ezetimibe therapy. It is interesting to note that the magnitudes of the between-group LDL-C reductions observed in this study were the greatest in the group of patients who received the most potent statin monotherapy prior to randomisation (i.e. Stratum 2; between-group differences in LDL-C were 17% for Stratum 2 vs. 7% for Stratum 1) suggesting that Stratum 2 contained a

larger proportion of poor responders to statin therapy compared with Stratum 1.

Unlike the head-to-head comparator study, which examined the effects of EZE/SIMVA and ROSUVA in drug-naive patients, the current study is more reflective of routine clinical practice whereby patients are switched to more intensive LDL-C-lowering therapy after they fail to meet their LDL-C goals with prior statin monotherapy. Thus, the use of EZE/SIMVA 10/20 could limit the need for future titration steps in patients who are at the highest risk of coronary events and therefore have the most stringent LDL-C targets.

In summary, the present study showed that switching from statin monotherapy to EZE/SIMVA 10/20 mg provides greater reductions in LDL-C than with ROSUVA 10 mg, resulting in clinically significant increases in the proportion of high-risk patients achieving LDL-C goals. The incidence of AEs with EZE/SIMVA 10/20 mg was similar to that seen with ROSUVA 10 mg. Thus switching from statin monotherapy to EZE/SIMVA 10/20 mg, which inhibits the synthesis and blocks the intestinal absorption of cholesterol, could offer an efficacious and convenient strategy to enhance further LDL-C reduction and goal attainment in high-risk patients. Future studies are needed to assess the possible benefit of EZE/SIMVA on cardiovascular outcomes.

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Author contributions

Amy O. Johnson-Levonas was involved in drafting, critical review and approval of the manuscript. Rachid Massaad and Kristel Vandormael were involved in data interpretation/analysis and critical review and approval of the manuscript. Philippe Brudi was involved in all phases of the study (including study design) and critical review and approval of the manuscript. Margus Viigimaa, Maurizio Averna, Michel Farnier, Luc Missault and Helena Vaverkova participated in the conduct of this study and were involved in critical review and approval of the manuscript.

References

1 La Rosa JC. Low-density lipoprotein cholesterol reduction: the end is more important than the means. *Am J Cardiol* 2007; **100**: 240–2.

2 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.

3 Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2007; **28**: 2375–414.

4 Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227–39.

5 Jones PH. Statins as the cornerstone of drug therapy for dyslipidemia: monotherapy and combination therapy options. *Am Heart J* 2004; **148**(1 Suppl): S9–13.

6 AstraZeneca Pharmaceuticals LP. *Crestor (Rosuvastatin)*. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2008 [prescriber information].

7 Jones PH, Davidson MH, Stein EA et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; **92**: 152–60.

8 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.

9 Baigent C, Keech A, Kearney PM et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267–78.

10 Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495–504.

11 LaRosa JC, Grundy SM, Waters DD et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425–35.

12 Pedersen TR, Faergeman O, Kastelein JJ et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005; **294**: 2437–45.

13 Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* 2006; **48**: 438–45.

14 Smith SC Jr, Allen J, Blair SN et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006; **113**: 2363–72.

15 Davidson MH, Maki KC, Pearson TA et al. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol* 2005; **96**: 556–63.

16 Laforest L, Moulin P, Souchet T et al. Correlates of LDL-cholesterol goal attainment in patients under lipid lowering therapy. *Atherosclerosis* 2008; **199**: 368–77.

17 Andrews TC, Ballantyne CM, Hsia JA, Kramer JH. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *Am J Med* 2001; **111**: 185–91.

18 Knopp RH, Gitter H, Truitt T et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003; **24**: 729–41.

19 Bays HE, Ose L, Fraser N et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy

in patients with primary hypercholesterolemia. *Clin Ther* 2004; **26**: 1758–73.
20 Davidson MH, McGarry T, Bettis R et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002; **40**: 2125–34.
21 Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2004; **79**: 620–9.
22 MERCK/Schering-Plough Pharmaceuticals. *Vytorin (Ezetimibe/Simvastatin) Tablet*. North Wales, PA: MERCK/Schering-Plough Pharmaceuticals, 2008 [prescriber information].
23 MSD-SP Limited. *Inegy (Ezetimibe/Simvastatin)*. Hoddesdon, Hertfordshire, UK: MSD-SP Limited, 2008 [package leaflet].
24 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.
25 Barrios V, Amabile N, Paganelli F et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. *Int J Clin Pract* 2005; **59**: 1377–86.
26 Constance C, Westphal S, Chung N et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2007; **9**: 575–84.
27 Reckless JP, Henry P, Pomykaj T et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: the INFORCE study. *Int J Clin Pract* 2008; **62**: 539–54.
28 Roeters van Lennep HW, Liem AH, Dunselman PH et al. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. *Curr Med Res Opin* 2008; **24**: 685–94.
29 Kindermann M, Adam O, Werner N, Böhm M. Clinical Trial Updates and Hotline Sessions presented at the European Society of Cardiology Congress 2007. FINESSE, CARESS, OASIS 5, PRAGUE-8, OPTIMIST, GRACE, STEEPLE, SCAAR, STRATEGY, DANAMI-2, ExTRACT-TIMI-25, ISAR-REACT 2, ACUITY, ALOFT, 3CPO, PROSPECT, EVEREST, COACH, BENEFiT, MERLIN-TIMI 36, SEARCH-MI, ADVANCE, WENBIT, EUROASPIRE I-III, ARISE, getABI, RIO. *Clin Res Cardiol* 2007; **96**: 767–86. Epub 2007 Oct 25.
30 Catapano AL, Davidson MH, Ballantyne CM et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. *Curr Med Res Opin* 2006; **22**: 2041–53.
31 Pisciotta L, Fasano T, Bellocchio A et al. Effect of ezetimibe coadministered with statins in genotype-confirmed heterozygous FH patients. *Atherosclerosis* 2007; **194**: e116–22.

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