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Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus*

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Aim: This randomized, double-blind study evaluated the efficacy of switching from atorvastatin (ATV) 10 mg to ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg, EZE/SIMVA 10/40 mg or doubling the dose of ATV from 10 to 20 mg in patients with type 2 diabetes (T2D).

Methods: Eligible patients had haemoglobin $A_{1C} \leq 10\%$, were aged ≥ 18 years and were on ATV 10 mg for ≥ 6 weeks before study entry. After a 4-week open-label ATV 10 mg run-in, patients were randomized to EZE/SIMVA 10/20 mg ($n = 220$), EZE/SIMVA 10/40 mg ($n = 222$) or ATV 20 g ($n = 219$) daily for 6 weeks.

Results: Greater ($p \leq 0.001$) reductions in low-density lipoprotein cholesterol (LDL-C) (the primary end-point) were achieved by switching to EZE/SIMVA 10/20 mg (26.2%) or 10/40 mg (30.1%) than by doubling the dose of ATV to 20 mg (8.5%). EZE/SIMVA 10/20 mg and 10/40 mg produced greater ($p \leq 0.001$) reductions in total cholesterol, non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B relative to ATV 20 mg. A reduction ($p \leq 0.050$) in C-reactive protein was observed with EZE/SIMVA 10/40 mg vs. ATV 20 mg. Similar reductions in triglycerides were observed across the three groups, and none of the treatments produced a significant change in HDL-C. A greater ($p \leq 0.001$) proportion of patients achieved LDL-C <2.5 mmol/l with EZE/SIMVA 10/20 mg (90.5%) and 10/40 mg (87.0%) than with ATV 20 mg (70.4%). Both EZE/SIMVA doses were generally well tolerated, with an overall safety profile similar to ATV 20 mg.

Conclusions: EZE/SIMVA 10/20 and 10/40 mg provided greater lipid-altering efficacy than doubling the dose of ATV from 10 to 20 mg and were well tolerated in patients with T2D.

Keywords: atorvastatin, ezetimibe/simvastatin, low-density lipoprotein cholesterol, type 2 diabetes mellitus
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Introduction

Type 2 diabetes (T2D) is associated with a two- to fourfold increased risk for coronary heart disease (CHD) [1]. Patients with T2D have mortality rates from coronary artery disease that are more than three times higher than in the general population [2]. Guidelines of the American Diabetes Association (ADA) [3] and the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III [4] classify T2D as a CHD risk equivalent and recommend a target low-density lipoprotein cholesterol (LDL-C) goal of <2.5 mmol/l. Recent evidence suggests that lipid lowering beyond the current ADA and NCEP ATP III goals may be desirable in patients with T2D [5,6]. An update from the NCEP indicated that an LDL-C target goal of 1.8 mmol/l was reasonable for high-risk patients, including those with both T2D and a history of cardiovascular disease (CVD) [7].

Statins are the most effective LDL-C-lowering therapeutic agents available to date. Two studies showed that treatment with simvastatin (SIMVA) 40 mg and atorvastatin (ATV) 10 and 20 mg produced significant improvements in plasma LDL-C levels and other lipid parameters among patients with T2D [8,9]. Despite the significant reductions in LDL-C produced by statins, many patients do not achieve the recommended goals, remaining at increased risk for CHD events [10–12]. While increasing the statin dose may be one therapeutic option for these patients, upward titration of statin doses may produce an increased incidence of adverse experiences (AEs) [11–13]. Moreover, doubling the statin dose has been shown to produce additional LDL-C reductions of only ~6% relative to the pre-statin baseline. Combination therapy with lipid-modifying agents with mechanisms of action that differ from, but complement, those of low-dose statins may provide significant advantages over statin monotherapy. However, successful combination therapy using statins co-administered with such agents as bile acid sequestrants, fibric acid derivatives and niacin has been hampered by an increased risk of AEs and/or poor tolerability.

Ezetimibe (EZE), the first member of a new class of cholesterol-lowering agents, blocks the intestinal uptake of dietary and biliary cholesterol, without affecting the absorption of triglycerides (TGs) or fat-soluble vitamins [14–16]. Its novel mechanism of action is complementary to that of the statins: EZE plus a statin inhibits both the intestinal absorption and the hepatic synthesis of cholesterol, significantly lowering LDL-C compared with statin monotherapy [17–21]. The combination is generally well tolerated, with an overall safety profile similar to that of statin monotherapy. EZE/SIMVA(Vytorin™, Inegy™; Merck/Schering Plough Pharmaceuticals, North Wales, PA, USA) is a drug that combines a fixed dose of EZE (10 mg) with a range of doses of SIMVA (10, 20, 40 and 80 mg).

A previous randomized, double-blind trial showed significantly greater LDL-C reductions by adding EZE 10 mg to SIMVA 20 mg than by doubling the dose of SIMVA to 40 mg in patients with T2D treated with thiazolidinediones [22]. The present study examined the lipid-altering efficacy and safety profiles of switching from ATV 10 mg/day to EZE/SIMVA 10/20 mg/day or EZE/SIMVA 10/40 mg/day vs. doubling the dose of ATV (to 20 mg/day) in patients with T2D.

Subjects and Methods

Patients

Eligible patients included men and women ≥18 years of age, diagnosed with T2D, with whole blood haemoglobin A_{1C} (HbA_{1c}) ≤10%, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels ≤1.5 times the upper limit of normal (ULN), and creatine kinase (CK) levels ≤1.5 times ULN. Patients had to be on ATV 10 mg for >6 weeks prior to study entry and complete a 4-week, open-label ATV 10 mg/day run-in baseline period. Patients of childbearing age were eligible to participate if they had negative pregnancy test results and were considered by the study investigator to be highly unlikely to conceive.

Key exclusion criteria included congestive heart failure defined by New York Heart Association class III or IV; myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months; uncontrolled hypertension (systolic >160 mm Hg or diastolic >100 mm Hg); uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; impaired renal function (creatinine ≥177 μmol/l) or nephrotic syndrome; alcohol consumption >14 drinks per week and treatment with excluded concomitant medications (i.e. immunosuppressants, corticosteroids or potent inhibitors of cytochrome P450 3A4).

Patients could be withdrawn from the study for the following pre-defined reasons: positive pregnancy test, treatment with excluded concomitant medications, consecutive elevations in ALT and AST levels ≥3 times ULN, consecutive elevations in CK levels of ≥10 times ULN with or without muscle symptoms or a significant clinical or laboratory AE.

Study Design

This randomized, double-blind, active-controlled, parallel-group study was conducted between February and September of 2005 according to the Good Clinical Research Practice at 84 sites in 21 countries (Australia, Belgium, Bulgaria, Canada, Colombia, Costa Rica, France, Germany, Greece, Italy, Republic of Korea, Lithuania, Malaysia, Norway, Panama, Portugal, Singapore, Slovenia, Spain, Taiwan and Turkey). The protocol was approved by the Institutional Review Board at each study centre, and all patients provided written informed consent. Patients discontinued from all lipid-altering treatments other than ATV 10 mg for at least 6 weeks before the study start ($\geq$8 weeks for fibrates). Eligible patients entered a 4-week baseline period while continuing to receive open-label ATV 10 mg and counselling for a low cholesterol diet. Qualifying patients were randomized (1: 1: 1) by a computer-generated allocation schedule to receive blinded EZE/SIMVA 10/20 mg, EZE/SIMVA 10/40 mg or ATV 20 mg once-daily for 6 weeks. Clinic visits were scheduled at week -4 (visit 1; screening), week 0 (visit 2; randomization) and week 6 (visit 3; lipid profile and efficacy assessment). A follow-up phone call or visit, if necessary, was scheduled 14 days after the final dose of study medication (week 8). Per cent compliance with study medication was defined as follows: (number of compliant therapy days/number of days between randomization and the last day of treatment) $\times$ 100.

Efficacy

The primary efficacy variable was per cent change from baseline in LDL-C at study end-point (i.e. the last post-baseline lipid measurement during the 6-week double-blind treatment period). Pre-defined secondary efficacy variables included per cent change from baseline to study end-point in total cholesterol (TC, key secondary variable), high-density lipoprotein cholesterol (HDL-C, key secondary variable), TGs, non-HDL-C, LDL-C/HDL-C and TC/HDL-C ratios and apolipoprotein B (apoB). Exploratory variables included per cent change from baseline to study end-point in C-reactive protein (CRP) and percentage of patients reaching LDL-C $<$2.5 mmol/l at study end-point. *Post hoc* analyses of the percentage of patients in each treatment group achieving LDL-C $<$1.8 mmol/l and the percentage of patients achieving LDL-C $<$2.5 and $<$1.8 mmol/l among those above these respective levels at baseline were also performed.

Safety and Tolerability

Safety and tolerability were evaluated by reviewing patient-reported AEs, investigators' observations and assessments and various laboratory tests including blood analyses. Investigators determined the severity of AEs (mild, moderate, severe or life threatening) and the potential relationship to study drug (definitely not, probably not, possibly, probably, definitely) while blinded to study medication. Key safety variables were the incidence of any clinical or laboratory AEs, treatment-related AEs, serious AEs and discontinuations because of AEs. Pre-specified safety variables included the incidence of consecutive or presumed consecutive elevations in ALT and AST $\geq$3 times ULN and single CK elevations of 5–10 times or $\geq$10 times ULN. Myopathy was prospectively defined as CK elevations $\geq$10 times ULN associated with muscle symptoms with no other plausible aetiology such as exercise or trauma.

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]. All lipid measurements were blinded after randomization. TC, HDL-C, TG and apoB were measured at all visits, and LDL-C levels were calculated using the Friedewald equation (LDL-C = TC $-$ (TG/5) $-$ HDL-C) [24]. Ultracentrifugation was used to measure LDL-C values in patients with TG $\geq$4.52 mmol/l. Non-HDL-C levels were calculated by subtracting HDL-C from TC values. ApoB was quantified using radioimmunoassay methods.

Statistical Analysis

The sample size was calculated based on a conservative assumption of 9% for the detectable difference between the EZE/SIMVA dose group (10/40 or 10/20 mg) and the ATV 20 mg dose group, and a standard deviation of 21%. With 145 patients in each treatment group, there is 95% power to detect a difference of 9% in the per cent change from baseline in LDL-C. The primary efficacy analysis was based on an all patients–treated (APT) approach, which included those patients who received at least one dose of randomized treatment, had a lipid measurement at baseline and had at least one lipid measurement following the start of treatment. The per cent changes from baseline to end-point in LDL-C and other lipid parameters were assessed by an analysis of variance (ANOVA) model with terms for treatment and study centre. Data were expressed as within-group means and pairwise between-group differences in least square mean $\pm$ standard error of the mean. Median per cent change was

calculated for TG and CRP because these parameters are asymmetrically distributed; the pairwise between-treatment group difference was computed using the Hodges-Lehmann estimate. Pre-defined subgroup analyses were performed for the per cent change from baseline in LDL-C across the following subgroups: age (<65 vs. ≥65 years), gender, race (Caucasian, Black, and others; an analysis of subgroups Caucasian and non-Caucasian was subsequently performed because of small numbers of Black patients enrolled in the study), baseline LDL-C (<3.00 vs. ≥3.00 mmol/l), body mass index (BMI; <30 vs. ≥30 kg/m^2), HbA_{1C} (<7% vs. ≥7%) and patient history of hypertension (no, yes) or hypercholesterolaemia (no, yes). An ANOVA model with terms for treatment, centre, subgroup and treatment-by-subgroup interaction was used to examine the interactions; treatment-by-subgroup effect was tested at the $\alpha = 0.100$ level. The Gail–Simon test (with $\alpha = 0.050$) applied in a pairwise fashion was used to determine the nature (qualitative vs. quantitative) of significant treatment-by-subgroup interaction terms.

A logistic regression model with terms for treatment and baseline LDL-C was used to analyse the percentage of patients reaching the LDL-C target of <2.5 mmol/l. Odds ratio estimates derived from the logistic regression model and 95% confidence intervals were used to quantify the treatment effect.

Data from all randomized patients who received at least one dose of study medication were included in safety and tolerability assessments. Fisher's exact test was used to compare the treatment groups pairwise with regard to the incidence of pre-defined AEs (patients with any AE, treatment-related AEs, serious AEs and discontinuations because of AEs) and the proportion of patients with clinically important elevations in ALT and AST (individual and consecutive elevations ≥3 times ULN) as well as CK (≥10 times ULN).

Results

Patients

Overall, 832 patients were screened for inclusion in the study and, of these, 661 patients met the inclusion criteria and were randomized to treatment (220 patients in the EZE/SIMVA 10/20 mg group, 222 patients in the EZE/SIMVA 10/40 mg group and 219 patients in the ATV 20 mg group). In total, 648 patients (98.0%) completed the study; 13 patients discontinued prior to completion of the study. Twelve patients discontinued because of clinical AEs and one patient discontinued because of protocol deviation; this patient took a double dose of ATV 20 mg for 23 consecutive days.

There were no clinically meaningful differences in baseline demographic, anthropometric or disease characteristics across treatment groups (table 1). The majority of patients were Caucasian (73.7%) and ~60% had LDL-C <2.5 mmol/l at baseline. The proportions of patients with LDL-C levels ≥ 2.5 mmol/l at baseline were 36.1%, 43.8% and 38.1% in the EZE/SIMVA 10/20 mg, EZE/SIMVA 10/40 mg and ATV 20 mg groups, respectively. The mean duration of T2D was ~10 years in the EZE/SIMVA 10/20 mg group and ~9 years in both EZE/SIMVA 10/40 mg and ATV 20 mg groups. Baseline lipid variables, secondary diagnoses and previous and concomitant drug therapies were generally similar across the treatment groups.

Efficacy Parameters

Significantly ($p \leq 0.001$) greater mean per cent reductions from baseline in LDL-C were observed with EZE/SIMVA 10/20 mg and EZE/SIMVA 10/40 mg vs. the incremental benefit of doubling the ATV dose from 10 to 20 mg (figure 1, table 2). In the APT population, a significantly greater proportion of patients achieved LDL-C <2.5 mmol/l at study end-point in the EZE/SIMVA 10/20 and 10/40 mg groups than in the ATV 20 mg group ($p \leq 0.001$ for both pairwise between-treatment group comparisons); the percentages of patients who achieved this LDL-C level were 90.5, 87.0 and 70.4% in the EZE/SIMVA 10/20, 10/40 and ATV 20 mg groups, respectively. The percentages of patients who achieved LDL-C <1.8 mmol/l were 65.4, 65.3 and 31.9% in the EZE/SIMVA 10/20, EZE/SIMVA 10/40 and ATV 20 mg groups, respectively ($p \leq 0.001$ for both pairwise between-treatment group comparisons). When restricted to only patients having LDL-C above the 2.5 mmol/l level at baseline, 77.0, 81.7 and 41.5% in the EZE/SIMVA 10/20, EZE/SIMVA 10/40 and ATV 20 mg groups, respectively, reached the LDL-C level of <2.5 mmol/l and 37.8, 45.2 and 6.1% in the EZE/SIMVA 10/20, EZE/SIMVA 10/40 and ATV 20 mg groups, respectively, reached the LDL-C level of <1.8 mmol/l; among the patients having LDL-C above the 1.8 mmol/l level at baseline, 58.8, 60.3 and 22.3% in the EZE/SIMVA 10/20, EZE/SIMVA 10/40 and ATV 20 mg groups reached the LDL-C level of <1.8 mmol/l, respectively. The LDL-C-lowering treatment effects were generally consistent across pre-specified subgroups defined by patient baseline characteristics, including age (<65 vs. ≥65 years), race (Caucasian and non-Caucasian), baseline LDL-C (<3.0 vs. ≥3.0 mmol/l), BMI (<30 vs. ≥30 kg/m^2), hypercholesterolaemia, hypertension and HbA_{1c} (<7 vs. ≥7%). A significant ($p = 0.055$) interaction between treatment and gender was detected. This

Table 1 Baseline characteristics of randomized patients by treatment group

	EZE/SIMVA 10/20 mg (n = 220)	EZE/SIMVA 10/40 mg (n = 222)	ATV 20 mg (n = 219)
Age (years)			
Mean	62.1	62.4	61.7
Range	28–86	35–84	29–82
Gender, n (%)			
Male	112 (50.9)	112 (50.5)	108 (49.3)
Female	108 (49.1)	110 (49.5)	111 (50.7)
BMI [mean (s.d.), kg/m^2]	29.1 (5.2)	29.7 (5.2)	29.2 (4.9)
History of hypercholesterolaemia, n (%)			
Yes	101 (45.9)	84 (37.8)	90 (41.1)
No	119 (54.1)	138 (62.2)	129 (58.9)
History of hypertension, n (%)			
Yes	166* (75.5)	151 (68.0)	158 (72.1)
No	54 (24.5)	71 (32.0)	61 (27.9)
Duration of T2D [mean (s.d.), years]	9.7 (8.1)	8.8 (7.8)	8.9 (8.0)
HbA_{1c} [mean (s.d.), %]	7.26 (1.15)	7.06 (1.13)	7.13 (1.07)
Lipids [mean (s.d.), mmol/l]			
TC	4.45 (0.91)	4.57 (0.86)	4.55 (0.88)
LDL-C	2.35 (0.69)	2.48 (0.69)	2.42 (0.69)
TG [median (s.d.†)]	1.53 (1.01)	1.51 (0.89)	1.62 (1.09)
HDL-C	1.27 (0.33)	1.31 (0.33)	1.25 (0.33)
CRP [median (s.d.†), mg/l]	0.15 (0.24)	0.17 (0.27)	0.16 (0.30)

ATV, atorvastatin; BMI, body mass index; CRP, C-reactive protein; EZE, ezetimibe; HbA_{1c}, haemoglobin A_{1C}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; s.d., standard deviation; SIMVA, simvastatin; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides.

*Includes two patients with essential hypertension.

†s.d. for medians calculated by the following equation: $[Q_3 - Q_1]/1.075$.

interaction was further assessed in a pairwise fashion, and a significant quantitative interaction was detected for the pairwise comparison of EZE/SIMVA 10/40 mg and ATV 20 mg ($p = 0.077$), suggesting a slightly greater treatment difference in men. In the male category, the mean per cent reduction from baseline was 34.6% with EZE/SIMVA 10/40 mg vs. 8.4% with ATV 20 mg; in the female category, the reduction was 22.8% with EZE/SIMVA 10/40 mg vs. 5.4% with ATV 20 mg. However, the interaction was not qualitative in nature; thus, the reductions were directionally consistent with the total cohort results. All other treatment-by-subgroup interaction tests were non-significant.

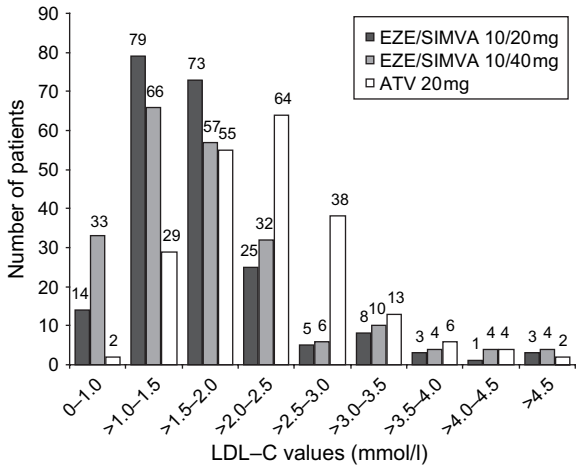

Fig. 1 Distribution of low-density lipoprotein cholesterol (LDL-C) values at end-point in each treatment group.

Significantly greater mean per cent reductions with EZE/SIMVA 10/20 and 10/40 mg compared with ATV 20 mg were observed for TC, non-HDL-C, apoB and the ratios of TC and LDL-C to HDL-C (table 2). Similar median per cent reductions from baseline in TG were observed across the three groups, and none of the treatments produced a significant change in HDL-C (table 2). The median per cent reduction from baseline in CRP was significantly greater for the EZE/SIMVA 10/40 mg group than for the ATV 20 mg group; no significant difference between EZE/SIMVA 10/20 mg and ATV 20 mg was observed (table 2).

Safety and Tolerability

Clinical AEs were reported by 143 (21.6%) of the 661 randomized patients. The incidence of clinical AEs was similar among the treatment groups (table 3), and there were no meaningful differences in the incidence of any

Table 2 Effects of treatment on lipid parameters and CRP

	EZE/SIMVA 10/20 mg				EZE/SIMVA 10/40 mg				ATV 20 mg		
	n	Baseline*	LS mean % change (s.d.)	Between treatment p value vs. ATV 20 mg	n	Baseline*	LS mean % change (s.d.)	Between treatment p value vs. ATV 20 mg	n	Baseline*	LS mean % change (s.d.)
LDL-C	210	2.34 (0.68)	−26.15 (26.89)	≤0.001	215	2.48 (0.70)	−30.13 (26.99)	≤0.001	213	2.43 (0.69)	−8.49 (26.83)
TC	219	4.45 (0.91)	−14.15 (17.49)	≤0.001	220	4.57 (0.87)	−16.83 (17.54)	≤0.001	218	4.55 (0.88)	−5.47 (17.49)
HDL-C	219	1.27 (0.33)	2.37 (13.85)	0.569	220	1.31 (0.33)	1.29 (13.89)	0.795	218	1.25 (0.33)	1.63 (13.85)
TG† (median)	219	1.53 (1.01)	−9.72 (34.39)	0.279‡	220	1.51 (0.90)	−8.40 (38.15)	0.117‡	218	1.62 (1.08)	−5.46 (34.96)
Non-HDL-C	219	3.18 (0.85)	−20.91 (24.18)	≤0.001	220	3.26 (0.83)	−23.80 (24.25)	≤0.001	218	3.30 (0.88)	−7.43 (24.17)
ApoB	218	1.02 (0.24)	−14.93 (20.08)	≤0.001	214	1.05 (0.24)	−19.54 (20.08)	≤0.001	213	1.06 (0.26)	−6.70 (20.09)
LDL-C:HDL-C	210	1.90 (0.61)	−27.46 (28.52)	≤0.001	215	1.97 (0.66)	−30.04 (28.63)	≤0.001	213	2.03 (0.71)	−9.02 (28.47)
TC:HDL-C	219	3.65 (0.97)	−15.31 (19.82)	≤0.001	220	3.64 (0.95)	−17.14 (19.87)	≤0.001	218	3.84 (1.24)	−5.90 (19.81)
CRP† (median; mg/l)	218	0.16 (0.24)	−4.52 (63.21)	0.337‡	214	0.18 (0.27)	−16.03 (57.36)	0.006‡	215	0.16 (0.30)	0.00 (74.42)

apoB, apolipoprotein B; ATV, atorvastatin; CRP, C-reactive protein; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol, s.d., standard deviation; SIMVA, simvastatin; TC, total cholesterol; TG, triglycerides. Values expressed as mean (s.d.); mmol/l unless otherwise noted.

*Corresponds to the value on ATV 10 mg at the time of randomization.

†s.d. for medians calculated by the following equation: $[Q_3 - Q_1]/1.075$.

‡Test based on non-parametric analysis using analysis of variance on the rank transformation.

individual clinical AE. Overall, 13 (5.9%) EZE/SIMVA 10/20 mg, 9 (4.1%) EZE/SIMVA 10/40 mg and 11 (5.0%) ATV 20 mg patients experienced AEs determined by the investigator to be possibly, probably or definitely treatment related; however, only three (1.4%), four (1.8%) and zero (0.0%) in the three groups, respectively, discontinued because of treatment-related AEs. Of the patients who discontinued because of drug-related AEs, one (0.5%) in the EZE/SIMVA 10/20 mg group and one (0.5%) in the EZE/SIMVA 10/40 mg group had myalgia. Two deaths (one in the EZE/SIMVA 10/40 mg group and one in the ATV 20 mg group) were reported during the study; neither death was considered to be treatment related. Laboratory AEs were reported by 28 (4.2%) of the 661 randomized patients. The incidence of laboratory AEs was similar among the treatment groups (table 3), and there were no meaningful differences in the incidence of any individual laboratory AE.

Mean treatment compliance was ~98% in both EZE/SIMVA groups and ~99% in the ATV 20 mg treatment group. There were no significant differences among EZE/SIMVA 10/20, 10/40 and ATV 20 mg treatment groups with regard to allergic reaction or rash AEs, gallbladder-related AEs or gastrointestinal-related AEs (table 3). There were no significant differences in the ALT and AST findings between EZE/SIMVA (10/20 and 10/40 mg) and ATV 20 mg. Two (0.9%), one (0.5%) and one (0.5%) patients in the EZE/SIMVA 10/20 mg, EZE/

Table 3 Overall summary of adverse experiences [number (%) patients]

	EZE/SIMVA 10/20 mg (n = 220)	EZE/SIMVA 10/40 mg (n = 222)	ATV 20 mg (n = 219)
Clinical AE	51 (23.2)	50 (22.5)	42 (19.2)
Treatment-related clinical AE	13 (5.9)	9 (4.1)	11 (5.0)
Serious clinical AE	1 (0.5)	1 (0.5)	5 (2.3)
Discontinuations due to AE	3 (1.4)	7 (3.2)	2 (0.9)
Discontinuations due to treatment-related AE	3 (1.4)	4 (1.8)	0
Individual AE of interest			
Allergic reaction/rash AE	4 (1.8)	0	3 (1.4)
Gallbladder-related AE	0	1 (0.5)	1 (0.5)
Gastrointestinal-related AE	9 (4.1)	10 (4.5)	5 (2.3)
Laboratory AE	10 (4.5)	10 (4.5)	8 (3.7)
Treatment-related laboratory AE	5 (2.3)	4 (1.8)	3 (1.4)

AE, adverse experience; ATV, atorvastatin; EZE, ezetimibe; SIMVA, simvastatin.

SIMVA 10/40 mg and ATV 20 mg groups, respectively, had consecutive ≥3 times ULN increases in ALT. Two (0.9%) patients in the EZE/SIMVA 10/20 mg group and one (0.5%) patient in the ATV 20 mg group experienced consecutive elevations in AST ≥3 times ULN. No elevations in CK ≥5 ULN were observed in any of the treatment groups.

Discussion

The dyslipidaemia in patients with T2D is typically characterized by mild hypertriglyceridaemia, low HDL-C, an accumulation of cholesterol-rich remnant particles and a preponderance of LDL particles that are smaller and denser than those observed in the general population [25]. While the plasma LDL-C level in patients with and without T2D may be similar, the altered quality of the apoB-containing particles in T2D patients is believed to render them more atherogenic. Accordingly, the NCEP ATP III has identified elevations in small, dense LDL particles as a CHD risk factor [4]. An update from the NCEP advocates a target LDL-C goal of 1.8 mmol/l for high-risk patients, including those with T2D and a history of CVD [7]. Thus, aggressive LDL-C lowering in patients with T2D is an urgent healthcare priority and may produce a greater benefit in CVD risk reduction in this patient population relative to those without T2D. In 2001, CVD risk reduction was cited as a key treatment priority for patients with T2D by the International Diabetes Federation [26]. Despite these recommendations, widespread under treatment of hyperlipidaemia remains among high-risk patients [10,27].

The present study examined the lipid-modifying efficacy and safety of EZE/SIMVA 10/20 and 10/40 mg vs. doubling the dose of ATV from 10 to 20 mg in patients with T2D. Both doses of EZE/SIMVA were significantly more effective at reducing LDL-C than doubling the dose of ATV. The greater LDL-C-lowering effect of EZE/SIMVA was generally consistent across all patient subgroups examined, including age, race, baseline LDL-C, BMI, hypercholesterolaemia, hypertension and HbA_{1c}. Although a significantly greater treatment difference in men was detected for the pairwise comparison of EZE/SIMVA 10/40 mg vs. ATV 20 mg, the reductions were directionally consistent with the total cohort results. Additionally, a greater proportion of patients in both EZE/SIMVA groups attained LDL-C level <2.5 and <1.8 mmol/l by the end of the study compared with patients in the ATV 20 mg group. These findings are consistent with results from a previous randomized study in patients with T2D that compared EZE co-administered with SIMVA vs. doubling the dose of SIMVA; the results indicated that greater LDL-C lowering can be achieved more effectively through the dual inhibition effect of EZE/SIMVA than by increasing the dose of statin monotherapy [22]. Similarly, a previous *post hoc* analysis of data from a randomized, double-blind placebo-controlled trial [28] showed that the addition of EZE 10 mg/day to on-going statin therapy produced significant reductions (27.3%) in LDL-C and improved other lipid parameters (HDL-C, TG and non-HDL-C) relative to placebo in the subset of patients with T2D (n = 191). The LDL-C-lowering responses observed in the present study are also in agreement with results from a recent study that showed greater reductions in LDL-C with EZE/SIMVA vs. ATV in patients with hypercholesterolaemia [29].

Although cardiovascular outcome–based data are not yet available for EZE/SIMVA, the results of numerous clinical trials with statin monotherapy have shown that lowering LDL-C is associated with a reduction in the risk of CVD events in high-risk patients, including those with T2D [5,6,30–32]. Moreover, an LDL-C threshold below which further reduction yields no additional clinical benefit has not been identified.

Greater reductions in TC, non-HDL-C, apoB, and the ratios of TC and LDL-C to HDL-C were also observed with both EZE/SIMVA doses compared with doubling the ATV dose. Non-HDL-C and apoB have been identified as predictors of CVD [33,34]. Non-HDL-C, the plasma TC concentration minus the HDL-C concentration, includes cholesterol and all atherogenic apoB-containing lipoproteins and thus may reflect CHD risk not captured by LDL-C levels alone, especially in patients with elevated TG. The NCEP ATP III has recommended non-HDL-C as a measure to assess CVD risk in patients with TG levels ≥2.3 mmol/l. Similar reductions in TG were observed with EZE/SIMVA and ATV, and ATV is known to have good TG-lowering efficacy. Although plasma HDL-C levels did not change significantly with any treatment, baseline HDL-C levels were relatively high in each treatment group (≥1.2 mmol/l), possibly owing to the ATV pre-treatment period because lower doses of ATV are known to increase HDL-C [35].

It is now recognized that an inflammatory process has an important role in the formation and progression of atherosclerosis and thrombosis. The inflammatory marker, CRP, is believed to predict CHD-related morbidity and mortality independent of traditional risk factors [36–39]. Statins reduce blood levels of CRP, and EZE has been shown to produce incremental CRP-lowering when co-administered with SIMVA [40]. In the present study, significantly greater reductions in CRP were observed with EZE/SIMVA 10/40 mg than with ATV 20 mg. There was no difference between EZE/SIMVA 10/20 mg

and ATV 20 mg in lowering CRP. It should be noted, however, that clinical benefit attributable specifically to lowering of CRP through any therapeutic intervention has not been shown.

In the present study, EZE/SIMVA was well tolerated and had a favourable safety profile in patients with T2D. The incidences of treatment-related AEs and discontinuations because of treatment-related AEs were low and not significantly different across the treatment groups. Similarly, there were no significant differences across the treatment groups for muscle or liver toxicity.

In summary, EZE/SIMVA, at both 10/20 and 10/40 mg doses, was significantly more efficacious than doubling the dose of ATV from 10 to 20 mg in lowering LDL-C and other lipid parameters in patients with T2D. EZE/SIMVA was generally well tolerated, with few side-effects. Thus, EZE/SIMVA, through dual inhibition of the synthesis and absorption of cholesterol, may be a more effective means by which to reduce LDL-C vs. statin titration alone in patients with T2D.

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Appendix 1

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