Effectiveness and tolerability of ezetimibe co-administered with statins versus statin dose-doubling in high-risk patients with persistent hyperlipidemia: *The EZE(STAT)2 trial*

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Abstract

Introduction: When a standard dose of statins fails to achieve lipid control in patients at high risk for coronary artery disease (CAD), increasing the statin dosage or co-administration of additional agents is recommended. The aim of this study was to compare the safety and lipid-lowering efficacy of doubling the standard statin dose (STAT2) to that of co-administering ezetimibe 10 mg/day (EZE + *statin*) in Canadian patients at high CAD risk with persistent hyperlipidemia upon statin treatment.

Material and methods: Six-week, open-label, randomized, multicentre study. The primary outcome was the change in plasma LDL-C and secondary measures included the change in additional lipid parameters. Safety was assessed with the incidence of emergent adverse events (AEs).

Results: Eight hundred eighty-five patients (EZE + *statin*, n = 586; STAT2, n = 299) completed the study. The mean (SD) percent change in low-density lipoprotein cholesterol (LDL-C) was – 30.9% (18.2) for the EZE + *statin* group and –18.4% (19.0) for the STAT2 group (p = 0.001). Percent and absolute decreases in total cholesterol (TC), triglycerides and the TC to high-density lipoprotein cholesterol ratio (TC/HDL-C) were significantly greater for the EZE + *statin* group (p = 0.001). After 6 weeks of treatment, 70% of the patients in the EZE + *statin* group and 48% of patients in the STAT2 group (OR = 2.45, p < 0.001) achieved target LDL-C levels of < 2.5 mmol/l. Incidence of AEs was similar between groups, with the exception of a higher incidence of muscle disorders in the STAT2 group.

Conclusions: In patients at high CAD risk who are above the LDL-C target while on statin monotherapy, co-administration of ezetimibe is well tolerated and more effective in improving the lipid profile compared to doubling the existing statin dose.

Key words: ezetimibe, hypercholesterolemia, low-density lipoprotein cholesterol, statin.

Introduction

Cardiovascular disease is the major cause of death globally, accounting for 29% of all deaths, and its prevalence is expected to increase within the

next 2 decades [1]. The importance of hypercholesterolemia in increasing the risk of developing cardiovascular artery disease (CAD) has been well documented by numerous epidemiological studies [2, 3]. Currently, the gold standard for treating CAD involves modifications in lifestyle and pharmacological intervention with statins to reduce the low-density lipoprotein cholesterol (LDL-C). For a large number of patients, however, statin monotherapy is not effective in achieving target LDL-C levels [4-6]. For these patients, titration to higher statin doses or co-administration of additional complementary lipid-lowering agents is recommended by the Canadian Cardiovascular Society [7].

Ezetimibe is a cholesterol absorption inhibitor which interferes with the uptake of dietary and biliary cholesterol from the small intestine [8]. Co-administration of ezetimibe with statins results in a greater reduction of LDL-C levels and enhanced improvement of the lipid profile compared with statin monotherapy [9-14], while protecting against the risk of adverse events when using high-dose statins [15-17].

The purpose of this open-label randomized trial was to compare, in a real-life setting, the effectiveness and tolerability of ezetimibe 10 mg/day co-administered with the existing statin regimen versus doubling of the current statin dose in patients at high CAD risk who had not achieved target LDL-C levels while on statin monotherapy.

Material and methods

Patient population

Male and female adults with a diagnosis of primary hypercholesterolemia, who were at high risk for coronary artery disease (as defined by a Framingham 10-year risk for CAD ≥ 20%, or medical history of diabetes mellitus and/or atherosclerosis disease) and had LDL-C ≥ 2.5 mmol/l while on statin treatment, were eligible for the study [18]. Additional inclusion criteria included a stable medication regimen and a stable diet for at least 4 weeks prior to study screening. Patients were excluded if they were treated with any other investigational drug within 30 days prior to study recruitment, had any clinically significant concomitant disease which would render them unable to complete the study or place them at risk, were treated with any medication that might interact negatively with statins or ezetimibe or affect the patient's serum lipid levels within eight weeks, or experienced myocardial infarction or coronary intervention within 3 months. Use of cardiovascular medication was allowed provided that the dose was stable for at least 6 weeks prior to study entry and the duration of the study. Hormone replacement therapy in women was also allowed at a stable dose for at least 8 weeks prior to the screening visit and during the study.

Study design

This was a 6-week, prospective, randomized, open-label trial on patients recruited from the practices of 241 Canadian general practitioners. Eligible patients signed informed consent prior to study enrolment. The study was approved by two independent ethics review boards (IRB services in Aurora, Ontario, Canada; College of Physicians and Surgeons of Alberta, Canada). Patients were assessed for eligibility and underwent a review of medical history, with emphasis on cardiovascular history and risk, as well as a review of lipid-lowering medication use at the screening visit. Baseline 12-h fasting measurements of LDL-C, total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were conducted at local facilities within three days of the screening visit. The LDL-C was calculated using the standard Friedewald estimation method. However, when TG levels were > 3.99 mmol/L, LDL-C was determined by ultracentrifugation since high TG levels have been shown to interfere with the accurate determination of LDL-C by the Friedewald equation [19]. Furthermore, direct enzymatic LDL-C assays which require less time and money have been shown to overestimate LDL-C when TG values are greater than 400 mg/dl, leading to misclassification of the severity of dyslipidemia [20].

At the baseline visit, which took place within two weeks of the screening visit, patients were randomly assigned in a 1 : 1 ratio to either receive 10 mg/day ezetimibe (Ezetrol®, Merck) co-administered with their existing statin regimen (EZE + *statin* group), or double their current statin dose, for 6 weeks (STAT2 group). During randomized allocation the practitioner contacted an Interactive Voice Response System (IVRS) which issued a randomization number along with the treatment allocation. Randomization was centrally coordinated by a third-party data management center and was stratified by center. Patients allocated to the STAT2 group, who were on the highest possible dose of statin or were intolerant of higher statin doses as per the patient's or physician's assessment, were converted to the EZE + *statin* group. All patients were instructed not to change their diet or exercise habits during the study. There were no limitations on the type or dose of statin used at baseline. Ezetimibe was provided at no cost to the patient while statins were acquired via the existing insurance coverage. The final study visit took place 6 weeks after the baseline visit.

Outcome measures

The primary efficacy outcome measure was the percent change in plasma LDL-C concentration during the 6-week treatment period. Secondary efficacy measures included the changes in TC, TG,

Table I. Demographics and baseline characteristics of patients

Characteristics	Treatment group		Total (n = 936)	Value of p
	EZE + *statin* (n = 620)	STAT2 (n = 316)		
Age				
Mean (SD)	63 (11.3)	63 (11.4)	63 (11.3)	0.604
Range	26-89	28-87	26-89	
Age categories, *n* (%)				
≤ 45	40 (6.5)	18 (5.7)	58 (6.2)	0.181
46-65	334 (53.9)	151 (47.8)	485 (51.8)	
65-85	237 (38.2)	144 (45.6)	381 (40.7)	
≥ 85	9 (1.5)	3 (0.9)	12 (1.3)	
Gender, *n* (%)				
Male	392 (63.2)	191 (60.4)	583 (62.3)	0.406
Female	228 (36.8)	125 (39.6)	353 (37.7)	
Co-morbidity and risk factor profile, *n* (%)				
Smoking status				
Current smoker	130 (21.0)	68 (21.5)	198 (21.2)	0.611
Ex-smoker	206 (33.2)	95 (30.1)	301 (32.2)	
Non-smoker	284 (45.8)	153 (48.4)	437 (46.7)	
Hypertension	345 (55.6)	179 (56.6)	524 (56.0)	0.809
Diabetes mellitus	129 (20.8)	83 (26.3)	212 (22.6)	0.059
Metabolic syndrome	82 (13.2)	24 (7.6)	106 (11.3)	0.010
Diabetes mellitus and metabolic syndrome	174 (28.1)	91 (28.8)	265 (28.3)	0.464
Neither diabetes mellitus nor metabolic syndrome	235 (37.9)	118 (37.3)	353 (37.7)	0.867
Coronary artery disease	262 (42.3)	129 (40.8)	391 (41.8)	0.674
Cerebrovascular disease	73 (11.8)	35 (11.1)	108 (11.5)	0.752
Peripheral vascular disease	60 (9.7)	26 (8.2)	86 (9.2)	0.468
Chronic kidney disease	18 (2.9)	12 (3.8)	30 (3.2)	0.463
Family history of CVD	300 (48.4)	163 (51.6)	463 (49.5)	0.418
Menopausal status (n = 353)				
Pre-menopause	15 (6.6)	7 (5.6)	22 (6.2)	0.497
Peri-menopause	7 (3.1)	4 (3.2)	11 (3.1)	
Post-menopause	202 (88.6)	114 (91.2)	316 (89.5)	
Use of hormone replacement therapy	37 (16.2)	17 (13.6)	54 (15.3)	0.486

HDL-C and the TC/HDL-C ratio, as well as the proportion of patients achieving the recommended target LDL-C of < 2.5 mmol/l (2003 Canadian recommendations for the management of dyslipidemia and the prevention of cardiovascular disease [18]) or < 2.0 mmol/l (2009 Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease [7]). Sample size requirements for the study were based on the primary efficacy measure. In order to detect a difference of 15% in the percent plasma LDL-C change between the two treatment groups with 90% power and 5% significance, a sample size of 90 patients per group or 180 patients in total would be required. Similarly, for the subgroup analysis (diabetes and metabolic syndrome subgroup, diabetes subgroup, metabolic syndrome subgroup, and subgroup with neither of the two conditions) 180 patients per subgroup would be required. Based on the patients actually recruited in the current study (265 patients with diabetes and the metabolic syndrome, 212 patients with diabetes only, 106 patients with the metabolic syndrome only, and 353 patients with neither of the two

Table II. Statin therapy at baseline*

Statin	Patients, *n* (%)†	Total daily statin dose, *n* (%)							
		10 mg		20 mg		40 mg		80 mg	
		EZE + *statin*	STAT2	EZE + *statin*	STAT2	EZE + *statin*	STAT2	EZE + *statin*	STAT2
Atorvastatin	491 (52.5)	100 (16.1)	82 (25.9)	117 (18.9)	67 (21.2)	75 (12.1)	24 (7.6)	15 (2.4)	NA
Simvastatin	167 (17.8)	14 (2.3)	16 (5.1)	45 (7.3)	19 (6.0)	54 (8.7)	10 (3.2)	4 (0.6)	NA
Rosuvastatin	162 (17.3)	71 (11.5)	39 (12.3)	25 (4.0)	10 (3.2)	7 (1.1)	NA	NA	NA
Pravastatin	81 (8.7)	3 (0.5)	1 (0.3)	21 (3.4)	24 (7.6)	19 (3.1)	7 (2.2)	4 (0.6)	NA
Lovastatin	27 (2.9)	2 (0.3)	NA	7 (1.1)	6 (1.9)	8 (1.3)	3 (0.9)	1 (0.2)	NA
Fluvastatin	8 (0.9)	NA	NA	2 (0.4)	2 (0.7)	1 (0.2)	2 (0.7)	1 (0.2)	NA
Total	936 (100)	190 (30.6)	138 (43.7)	217 (35.0)	128 (40.5)	164 (26.5)	46 (14.6)	25 (4.0)	NA

**Before dose doubling, †Percentages are out of 936 patients enrolled: 620 in the EZE + statin group and 316 in the STAT2 group, §One patient reported taking atorvastatin 5 mg/day, 3 patients were taking 30 mg/day and 7 patients were taking 60 mg/day; 1 patient each reported taking simvastatin 5 mg/day, 30 mg/day, 50 mg/day, and 2 patients reported taking simvastatin 60 mg/day; 8 patients reported taking rosuvastatin 5 mg/day and 1 patient each reported taking 30 mg/day and 60 mg/day; 1 patient each reported taking a dose of 30 mg/day and 60 mg/day of pravastatin*

conditions) the statistical power of the current study was > 0.99 for the total population, the diabetes and metabolic syndrome subgroup, the diabetes subgroup and the subgroup with neither of the two conditions, while it was 0.63 for the metabolic subgroup.

Safety was assessed with clinical laboratory parameters and the incidence of treatment-emergent adverse events that were attributed to ezetimibe or the statin regimen according to the treating physician's judgment. All adverse events were reported according to the MedDRA dictionary of terms, version 9 [21].

Statistical analysis

The intention-to-treat (ITT) principle, including all patients who received at least one dose of ezetimibe or double statin dose, was employed to analyze the study outcomes. All analyses were conducted for the total patient population, patients with diabetes and the metabolic syndrome (as defined by the 2005 modified International Diabetes Federation criteria [22]), patients with diabetes only, patients with the metabolic syndrome only, and patients with neither of the two conditions, using the SPSS software, version 12.0. Statistical significance for between-group differences in continuous outcomes was assessed with the two-tailed Student's *t*-test for independent samples, while the non-parametric Mann-Whitney test was used for patient subgroups. Multiple linear regression and general linear models (GLM) were used to assess between-group differences with respect to the primary efficacy measure (dependent variable: % change in LDL-C), adjusting for potential confounders (independent variables: treatment group, baseline statin dose).

Results

Baseline characteristics

A total of 1,155 patients were screened between May 2005 and June 2006, among whom 936 underwent randomization. Of these patients, 459 (49.0%) were initially randomized to the EZE + *statin* group and 477 (51.0%) to the STAT2 group. A total of 161 patients (33.8%) in the STAT2 group were converted to the EZE + *statin* group: 150 (93.2%) because of patient or physician concerns about the tolerance of higher statin doses, and 11 (6.8%) because they were at the maximum statin dose. Therefore, the final treatment allocation was 620 patients (66.2%) in the EZE + *statin* group and 316 patients (33.8%) in the STAT2 group. No differences with respect to baseline characteristics between the STAT2 patients who were converted to the EZE + *statin* group and those who were maintained in the STAT2 group were observed. There were 51 patients (5.4%), 34 (5.5%) in the EZE + *statin* group and 17 (5.4%) in the STAT2 group, who were withdrawn prior to the 6-week final assessment. Reasons for withdrawal were as follows: loss to follow-up for 30 (3.2%), adverse events for 15 (1.6%), withdrawal of consent for 5 (0.5%), while one patient in the EZE + *statin* group was withdrawn due to intolerance to the statin.

As summarized in Table I, demographics and baseline clinical characteristics for the ITT population exhibited no significant differences between groups. The mean (SD) age of the study sample was 63 (11.3) years while 62.3% were male. A total of 859 patients (91.8%) were classified as being at high (≥ 20%) 10-year risk for CAD on the basis of confirmed diabetes or atherosclerotic disease and the remaining 77 (8.2%) were classified

Table III. Baseline lipid profile, absolute and percent change in lipid profile at week 6 from baseline

	Baseline		Value of *p**	Absolute change, mean (SD)		Value of *p**	Percent change, mean (SD)		Value of *p**
	EZE + *statin*	STAT2		EZE + *statin*	STAT2		EZE + *statin*	STAT2	
All patients, *n*	620	316		586	299		586	299	
LDL-C [mmol/l]	3.20 (0.66)	3.18 (0.62)	0.564	–1.00 (0.69)	–0.62 (0.70)	0.001	–30.85 (18.18)	–18.45 (18.99)	0.001
Total cholesterol [mmol/l]	5.26 (0.83)	5.24 (0.81)	0.658	–1.10 (0.83)	–0.66 (0.82)	0.001	–20.47 (14.09)	–11.87 (13.83)	0.001
HDL-C [mmol/l]	1.27 (0.33)	1.27 (0.34)	0.914	0.00 (0.21)	0.00 (0.19)	0.562	0.61 (17.22)	1.14 (19.32)	0.604
Triglycerides [mmol/l]	1.80 (0.88)	1.74 (0.80)	0.303	–0.23 (0.75)	–0.09 (0.62)	0.003	–8.62 (36.66)	0.82 (37.77)	0.001
Total cholesterol/HDL-C ratio	4.37 (1.17)	4.34 (1.15)	0.747	–0.91 (0.90)	–0.56 (0.90)	0.001	–19.37 (18.44)	–11.18 (16.47)	0.001
Metabolic syndrome and diabetes, *n*†	174	91		166	83		166	83	
LDL-C [mmol/l]	3.23 (0.67)	3.14 (0.51)	0.687	–1.04 (0.75)	–0.66 (0.67)	0.001	–31.68 (20.69)	–20.20 (18.64)	0.001
Total cholesterol [mmol/l]	5.33 (0.84)	5.32 (0.79)	0.850	–1.19 (0.91)	–0.73 (0.85)	0.001	–21.92 (15.52)	–13.16 (14.58)	0.001
HDL-C [mmol/l]	1.17 (0.28)	1.18 (0.29)	0.773	0.01 (0.16)	0.01 (0.18)	0.353	0.84 (13.78)	1.35 (14.80)	0.415
Triglycerides [mmol/l]	2.15 (0.96)	2.15 (0.87)	0.957	–0.35 (0.76)	–0.19 (0.70)	0.039	–12.52 (32.96)	–4.01 (36.74)	0.019
Total cholesterol/HDL-C ratio	4.76 (1.10)	4.69 (1.09)	0.647	–1.08 (0.89)	–0.69 (0.81)	0.001	–21.82 (16.39)	–13.33 (14.38)	0.001
Diabetes/no metabolic syndrome, *n*†	129	83		116	77		116	77	
LDL-C [mmol/l]	3.13 (0.53)	3.08 (0.53)	0.392	–1.10 (0.61)	–0.66 (0.74)	0.001	–35.21 (17.98)	–20.59 (21.68)	0.001
Total cholesterol [mmol/l]	5.15 (0.71)	5.08 (0.72)	0.221	–1.16 (0.77)	–0.72 (0.84)	0.001	–22.39 (14.03)	–13.44 (14.65)	0.001
HDL-C [mmol/l]	1.34 (0.32)	1.33 (0.34)	0.606	–0.01 (0.19)	–0.02 (0.17)	0.780	–0.13 (13.87)	–1.27 (13.66)	0.577
Triglycerides [mmol/l]	1.59 (0.90)	1.48 (0.56)	0.896	–0.20 (0.64)	–0.08 (0.62)	0.181	–7.20 (39.77)	1.71 (44.99)	0.150
Total cholesterol/HDL-C ratio	4.00 (0.90)	3.99 (0.83)	0.902	–0.88 (0.76)	–0.48 (0.82)	0.001	–21.11 (16.37)	–10.90 (18.48)	0.001
Metabolic syndrome/no diabetes, *n*†	82	24		79	23		79	23	
LDL-C [mmol/l]	3.36 (0.76)	3.40 (0.82)	0.985	–0.98 (0.64)	–0.77 (0.88)	0.025	–29.12 (16.25)	–19.44 (18.21)	0.006
Total cholesterol [mmol/l]	5.39 (0.94)	5.32 (0.91)	0.818	–1.07 (0.83)	–0.78 (0.87)	0.009	–19.35 (15.15)	–13.13 (12.53)	0.006
HDL-C [mmol/l]	1.15 (0.29)	1.08 (0.32)	0.152	–0.02 (0.20)	0.02 (0.20)	0.971	–0.19 (15.17)	2.15 (18.62)	0.949
Triglycerides [mmol/l]	2.11 (0.82)	1.98 (0.64)	0.723	–0.28 (1.00)	–0.16 (0.50)	0.248	–11.07 (38.40)	–2.90 (31.08)	0.154
Total cholesterol/HDL-C ratio	4.97 (1.47)	5.20 (1.43)	0.768	–0.98 (0.98)	–0.76 (1.19)	0.035	–17.08 (24.86)	–12.77 (17.26)	0.029

Table III. cont.

	Baseline		Value of *p**	Absolute change, mean (SD)		Value of *p**	Percent change, mean (SD)		Value of *p**
	EZE + *statin*	STAT2		EZE + *statin*	STAT2		EZE + *statin*	STAT2	
Neither metabolic syndrome nor diabetes, *n*†	235	118		225	116		225	116	
LDL-C [mmol/l]	3.18 (0.66)	3.22 (0.71)	0.770	–0.93 (0.70)	–0.53 (0.65)	0.001	–28.60 (16.53)	–15.57 (17.27)	0.001
Total cholesterol [mmol/l]	5.23 (0.84)	5.27 (0.85)	0.714	–1.01 (0.79)	–0.54 (0.76)	0.001	–18.80 (12.39)	–9.65 (12.80)	0.001
HDL-C [mmol/l]	1.35 (0.36)	1.34 (0.36)	0.821	0.00 (0.25)	0.01 (0.21)	0.861	1.10 (21.33)	2.38 (24.81)	0.966
Triglycerides [mmol/l]	1.54 (0.68)	1.54 (0.78)	0.571	–0.14 (0.69)	0.02 (0.57)	0.002	–5.63 (36.89)	4.42 (34.34)	0.003
Total cholesterol/HDL-C ratio	4.08 (1.08)	4.15 (1.18)	0.652	–0.77 (0.92)	–0.47 (0.94)	0.001	–17.47 (18.04)	–9.52 (16.30)	0.001

**Value of p based on Student's t-test for independent samples for between-group comparisons, †Value of p based on non-parametric Mann-Whitney test for between-group comparisons*

as high risk on the basis of the Framingham model. There were 212 patients (22.6%) with diabetes but not the metabolic syndrome, 106 (11.3%) with the metabolic syndrome but not diabetes, 265 (28.3%) with both diabetes mellitus and the metabolic syndrome and 353 (37.7%) with neither diabetes nor the metabolic syndrome. The profile of statin therapy at baseline is shown in Table II, with more than half (52.5%) of the study subjects taking atorvastatin, followed by simvastatin (17.8%), rosuvastatin (17.3%) and pravastatin (8.7%).

Lipid profile

After 6 weeks of treatment, patients in the EZE + *statin* group experienced a significantly larger reduction in LDL-C (–30.8% vs. –18.4% in EZE + *statin* and STAT2, respectively), TC (–20.5% vs. –11.9% in EZE + *statin* and STAT2, respectively), TG (–8.6% vs. –0.8% in EZE + *statin* and STAT2, respectively) and TC/HDL-C ratio (–19.4% vs. –11.2% in EZE + *statin* and STAT2, respectively) (Table III). Changes in HDL-C, however, were not significantly different between the two groups (0.6% vs. 1.1% in EZE + *statin* and STAT2, respectively). These differences were observed for both the total study sample and all patient subgroups. Similar results were observed for the subgroup of patients who converted to the EZE + *statin* group (data not shown).

Multivariate linear regression analysis was further used to adjust the between-group differences with respect to the percent change in LDL-C during the six-week treatment period for the effect of the baseline statin dose. This analysis indicated that co-administration of ezetimibe had a significant effect ($p < 0.001$) on reducing LDL-C by an additional 19.7% (SE: 1.36) over and above the statin effect (Table IVA). The results also showed that for every doubling of the baseline statin dose used, the additional decrease in LDL-C is 5.4% (SE: 0.52). Table IVB summarizes the least-squares mean estimates of the adjusted mean percent reduction in LDL-C for the two treatment groups by baseline statin dose. These results show that for the sample as a whole the adjusted mean (SD) percent decrease in LDL-C after co-administration of ezetimibe with the current statin was 30.8% (4.95) compared to a mean (SD) decrease of 9.3% (3.87) for doubling the statin dose ($p < 0.001$). The difference was consistent across all statin doses.

After 6 weeks of treatment, 70% of patients in the EZE + *statin* group and 48% of patients in the STAT2 group who completed the study achieved target LDL-C levels of less than 2.5 mmol/l (odds ratio [OR] 2.45, 95% CI 1.85-3.24, $p < 0.001$). Similarly, a significantly higher proportion of patients in the EZE + *statin* group (40%) compared with the STAT2 group (18%) achieved final serum LDL-C levels less than 2.0 mmol/l (OR 2.97, 95% CI

2.14-4.13, $p < 0.001$). Similar results were observed for all four patient subgroups analyzed (Figure 1).

Safety

The incidence and profile of adverse events between the study groups were in general similar between the two groups, with the exception of a higher incidence of myalgia and muscle spasms in patients in the STAT2 group (2.8% and 0.9% of patients, respectively) compared with the EZE + *statin* group (0.8% and 0% of patients, respectively). A total of 62 non-serious adverse events (NSAEs) were reported by 42 patients (6.8%) in the EZE + *statin* group. Of these, 16 (25.8%) NSAEs were reported by 16 (9.9%) of the 161 patients who were converted from the STAT2 to the EZE + *statin* group. There were 22 NSAEs reported by 18 patients (5.7%) in the STAT2 group. The majority (97.6%) of the treatment-emergent NSAEs were mild or moderate in severity. Two (2.4%) treatment-emergent NSAEs of severe intensity, diarrhoea and abdominal pain, were reported by one patient in the EZE + *statin* group. Two patients in the EZE + *statin* group (1 randomized and 1 converted) experienced non-specified increases in hepatic enzymes. No serious adverse events were reported in this trial.

Table IVA. Multivariate linear regression analysis results

Variable	Coefficient		Value of *p*
	Estimate	SE	
Group*	–19.66	1.36	< 0.001
Baseline statin dose†	–5.41	0.52	< 0.001

Table IVB. Least-squares mean estimates of percent change in LDL-C

Baseline statin dose [mg/day]	Treatment group, LS mean (SD)		
	EZE + *statin*	STAT2	All patients
10‡	–25.0 (0.05)	–5.4 (0.01)	–16.9 (9.69)
20£	–30.5 (0.03)	–10.8 (0.05)	–23.2 (9.52)
40	–35.9 (0.05)	–16.2 (0.11)	–31.3 (8.37)
80€	–41.4 (0.05)	NA	–41.4 (0.05)
Total	–30.8 (4.95)	–9.3 (3.87)	–23.5 (11.22)

*Multivariate linear regression dependent variable: percent change in LDL-C during 6-week treatment period; independent variables: treatment group, baseline statin dose, SE – standard error, LS mean – least-squares mean, *Group – EZE +statin = 1, STAT2 = 0, †Baseline statin dose: 10 mg/day = 1, 20 mg/day = 2, 40 mg/day = 3, 80 mg/day = 4, ‡Includes 10 patients who reported taking a statin dose of 5 mg/day, £Includes 6 patients who reported taking a statin dose of 30 mg/day, €Includes 12 patients who reported taking a statin dose of 50 mg/day or 60 mg/day*

Discussion

Although statin treatment is the predominant lipid-lowering strategy, a significant proportion of patients with hypercholesterolemia do not achieve target LDL-C levels on statin monotherapy [4-6]. Combination of ezetimibe with low-dose statin has been shown to be effective in improving the lipid profile in the context of controlled clinical trials, providing an additional 20% to 25% reduction in low density lipoprotein cholesterol (LDL-C) compared with statin monotherapy [23, 24]. In this study we compared the efficacy and safety of ezetimibe added to the existing statin regimen with that of doubling the dose of the statin, in a real-life setting; patients were recruited from physicians' practices regardless of their treating statin and they continued to receive their existing statin, either in combination with ezetimibe or at a double dose, throughout the course of the study.

The results of the EZE(STAT)[2] study indicate that co-administration of ezetimibe 10 mg/day with any statin regimen is more effective in reducing serum

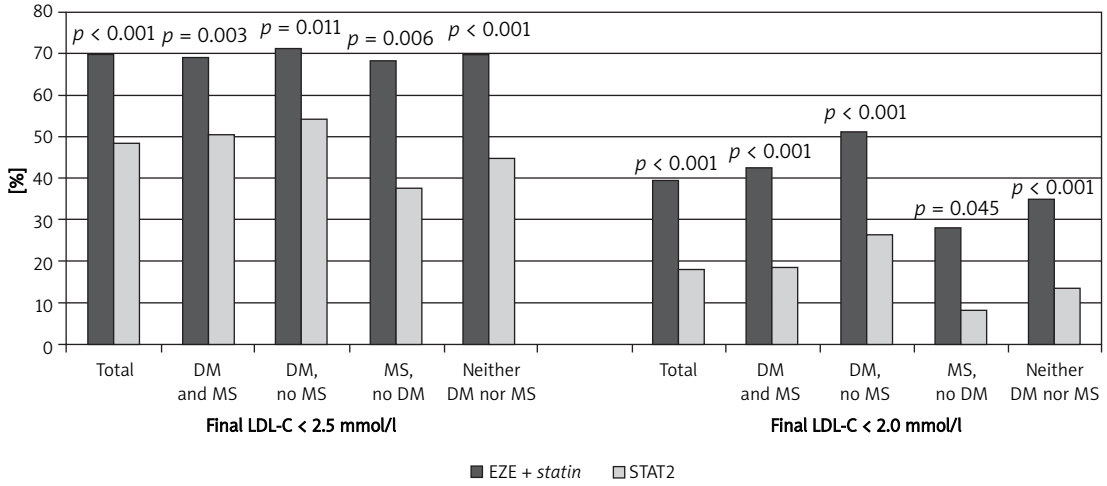

Figure 1. Final LDL-C targets by treatment group
DM – diabetes mellitus, MS – metabolic syndrome

LDL-C compared to doubling of the statin dose (change in LDL-C levels: 30.9% vs. 18.5% in the EZE + *statin* and STAT2 group, respectively, or 30.8% vs. 9.3%, respectively, when adjusting for the statin dose; % of patients achieving LDL-C < 2.5 mmol/l: 70% vs. 48%, respectively). Moreover, significantly more patients in the EZE + *statin* group achieved the LDL-C targets of < 2.5 and < 2.0 mmol/l currently recommended by the European Society of Cardiology (ESC) and the US treatment guidelines, or the Canadian Cardiovascular Society, respectively [7, 25, 26]. In addition, co-administration of ezetimibe with statins produced a more profound beneficial effect on the patient's overall lipid profile (TC, TG, TC/HDL-C ratio) compared with doubling the statin dose. The above-mentioned differences were observed across patient subgroups with diabetes and/or the metabolic syndrome that are at increased risk for cardiovascular disease. Our results are in agreement with recent studies showing a similar lipid-lowering beneficial effect of co-administering ezetimibe with atorvastatin [9, 10, 14] and simvastatin [11-13].

Ezetimibe co-administered with statin was generally well tolerated, with a similar safety profile and incidence of adverse events to the statin treatment, again in agreement with recent studies [9-14]. The only exception was a higher incidence of myalgia and muscle spasms observed in the STAT2 group, an effect that has been previously associated with high doses of statins [16, 17].

Reduction of serum LDL-C levels is the primary factor in preventing coronary heart disease [27]. In addition to their cholesterol-reducing function, statins exert additional pleiotropic effects such as improving endothelial dysfunction, thrombosis and vascular inflammation [28]. Our study was not designed to define the effect of ezetimibe on these parameters. However, recent studies indicate that ezetimibe may also have similar pleiotropic effects [29-32] and additional trials are ongoing which will further examine the impact of ezetimibe on these effects [33-35].

In conclusion, our study demonstrates that, in patients at high risk for coronary artery disease who have not achieved the LDL-C target with statin monotherapy, co-administration of ezetimibe is a well-tolerated and more effective strategy in improving the lipid profile compared with doubling the existing statin dose.

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