Kardiologia Polska 2017; 75, 8: 770–778; DOI: 10.5603/KP.a2017.0074

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The short-term effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on clinical outcome in acute coronary syndrome patients by gender

Lasha Japaridze, Maia Sadunishvili

Amtel Hospital First Clinical, The Centre of Vascular and Heart Diseases, Tbilisi State Medical University, Chapidze Heart Centre, Georgia

Abstract

Background: Atorvastatin reduces low-density lipoprotein cholesterol (LDL-C) levels and the risk of cardiovascular events, but whether the addition of ezetimibe (EZE), a non-statin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further, and if there any sex differences, is not known.

Aim: To evaluate the effects of atorvastatin and EZE combination in acute coronary syndrome (ACS) patients on the incidence of composite endpoint in short-term follow-up and to assess differences according their gender.

Methods: We conducted a 16-week, single-centre, prospective, randomised, open-label clinical trial involving 323 patients who had been hospitalised for an ACS within the preceding 14 days. They received atorvastatin 20 mg for 28 days, and after that 292 patients who had LDL-C levels ≥ 1.81 mmol/L were randomised to EZE 10 mg/day co-administered with atorvastatin therapy (EZE + statin) or double their current atorvastatin dose. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalisation, coronary revascularisation (≥ 30 days after randomisation), or nonfatal stroke.

Results: The Kaplan-Meier event-free survival rate at 16 weeks was 88.1% in the EZE + statin group patients and 77.0% in the atorvastatin monotherapy group (absolute risk reduction: 11.1 percentage points; hazard ratio: 2.099; 95% confidence interval: 1.165–3.781; p = 0.014). The log rank test indicated that there was not a statistically significant difference between male and female survival rates in both treatment groups (p = 0.897).

Conclusions: The results of our study demonstrated that when added to statin therapy, EZE resulted in improved cardiovascular outcomes, and the response to atorvastatin and EZE combination was similar for both men and women.

Key words: acute coronary syndrome, atorvastatin, ezetimibe, gender, low-density lipoprotein cholesterol

Kardiol Pol 2017; 75, 8: 770–778

INTRODUCTION

The average lifetime risk for cardiovascular disease (CVD) in women is very high, approaching one in two women [1]. Accordingly, the 2011 update to the Guidelines for Cardiovascular Disease Prevention in Women asserts that nearly all women are at risk of CVD, and it stresses the importance of CVD prevention and appropriate treatment based on appropriate risk assessment [2]. Elucidation of sex-related efficacy of specific lipid-lowering treatments may help provide perspective for evidence based decision making, tailor preventive interventions based on individual risk and benefit, and increase the number of patients attaining individual treatment goals. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of ezetimibe (EZE) combined with simvastatin, as compared with that of simvastatin alone, in stable patients who had had an acute coronary syndrome (ACS) and whose low-density lipoprotein cholesterol (LDL-C) values were within guideline

Address for correspondence:
Lasha Japaridze MD, Tbilisi State Medical University, The Centre of Vascular and Heart Diseases, Chachava str.#1, 0159 Tbilisi, Georgia, tel: +995 599227746, e-mail: lashadoctor67@yahoo.com
Maia Sadunishvili, MD, Chapidze Heart Centre, Lubliana str.#4, 0159 Tbilisi, Georgia, e-mail: maiasadunishvili@yahoo.com
Received: 28.02.2016 **Accepted:** 23.03.2017 **Available as AoP:** 11.04.2017

recommendations [3–7]. The IMPROVE-IT study showed that following ACS, high-risk patients demonstrated a reduction in the primary endpoints.

Whether further lowering of LDL-C levels in ACS patients achieved with the addition of EZE to atorvastatin therapy leads to a benefit in clinical outcomes, and if there are any sex differences, is unknown. The objectives of our study were to evaluate the effects of atorvastatin and EZE combination in ACS patients on the incidence of primary composite endpoint in short-term follow-up and to assess differences according their gender. The primary composite endpoint was the composite of death from CVD, major coronary event (nonfatal myocardial infarction [MI], documented unstable angina requiring hospital admission, or coronary revascularisation occurring at least 30 days after randomisation), and nonfatal stroke, assessed from the time of randomisation until the first occurrence of one of these events.

METHODS

Study design

A 16-week, single-centre, prospective, randomised, open-label clinical trial involved 323 ACS (MI, instable angina) patients who had been hospitalised within the preceding 14 days at our department. They received atorvastatin 20 mg for 28 days, and after that 292 patients who had LDL-C levels ≥ 1.81 mmol/L were randomised to EZE 10 mg/day co-administered with atorvastatin therapy (EZE + statin group) or double their current atorvastatin dose (statin group). All patients in both groups received clopidogrel, a beta-blocker, aspirin, and an angiotensin-converting enzyme inhibitor during hospitalisation and after discharge. Intravenous heparin or low molecular weight heparin was administered during hospitalisation to all patients in both treatment groups. In the EZE + statin group 52 patients underwent primary percutaneous coronary intervention (PCI) with bare metal stent, and in the statin group 56 patients underwent primary PCI with bare metal stent. Statin-naive patients (individuals who had never received statin treatment) and patients unable to have their statin dose doubled due to already receiving maximal statin dosing, or tolerability/safety concerns, were excluded. Additional exclusion criteria were: I. Treatment with bile acid sequestrants, niacin, or fibrates; and II. Active liver disease (positive test for hepatitis B surface antigen; positive hepatitis C antibody confirmed with positive RNA testing), uncontrolled endocrine illness (recent diagnosis of hypothyroidism or hyperthyroidism for which treatment was initiated within one month prior to screening visit), kidney disease (eGFR < 30 mL/min/1.73 m^2 according to MDRD Study equation), and creatine phosphokinase (CPK) > 3 × above the upper limit of normal (ULN). The study was approved by the Tbilisi Medical State University research ethics board. After providing informed consent, study participants attended four clinic visits. At screening (visit 1) the fasting lipid profile and liver function parameters were assessed. Eligible patients entered a four-week stabilisation phase during which they continued taking their current statin dose. At visit 2, eligibility for randomisation was confirmed with another fasting lipid profile. Patients who remained eligible (LDL-C ≥ 1.81 mmol/L) were randomised (1:1 ratio), using a statistical software-generated random table, to receive either EZE 10 mg daily co-administered with current statin dosing (EZE + statin group) or double their current atorvastatin dose. Bloodwork for inflammatory marker C-reactive protein (CRP) was obtained at visit 2 (randomisation) and visit 4 (the end of study). After eight weeks (visit 3), a brief exam, blood draw for fasting lipid profile, liver panel, CPK, and review of any adverse events occurred. For EZE + statin group patients, if LDL-C levels were ≥ 1.81 mmol/L, the statin dose was doubled for the next eight weeks. For statin group patients with LDL-C ≥ 1.81 mmol/L, the statin dose was also doubled for the next eight weeks (Fig. 1). At week 16 (visit 4, the end of study), patients underwent a brief exam, review of adverse events, liver panel, CPK, and fasting lipid profile. If the atorvastatin-monotherapy patients were already at maximum statin dose (80 mg) and LDL-C ≥ 1.81 mmol/L, EZE 10 mg/day were added for all of them.

Statistical analysis

Analysis of the results was carried out using the software package IBM SPSS 22, and data are presented as mean ± standard deviation. All analyses were performed in the intent-to-treat population including all patients who were randomised. Estimates of the hazard ratios and associated 95% confidence intervals (CI) for the comparison of atorvastatin–EZE with atorvastatin monotherapy were obtained with the use of Cox proportional-hazards model. The cumulative survival for males and females was estimated with Kaplan-Meier method, and differences between sexes were evaluated with the log rank test. The independent-samples Student's *t*-test was used to assess between-group and between-gender differences in LDL-C target achievement. Differences between groups for categorical variables were tested using χ^2 test. We used two-way ANOVA to test for the effects of gender and treatment group on LDL-C level at the end of the study, and to test for a linear trend between treatment group and LDL-C level at the end of study. All statistical tests were two-sided with an alpha level of 0.05. Sample size calculation was based only on the primary outcome measure for treatment groups. It was calculated using Statsoft Statistica 10 software (Survival — Log-Rank Test H0: Pi1 = Pi2). From our educated guess the survival rate for atorvastatin + EZE is approximately Pi1 = 0.70, and the survival rate for atorvastatin monotherapy — Pi2 = 0.65. In order to detect a similar magnitude of difference for this outcome, with 5% significance and 80% power, a total of 1364 patients per group were required. Due to the small sample size the results of this study must be interpreted with caution.

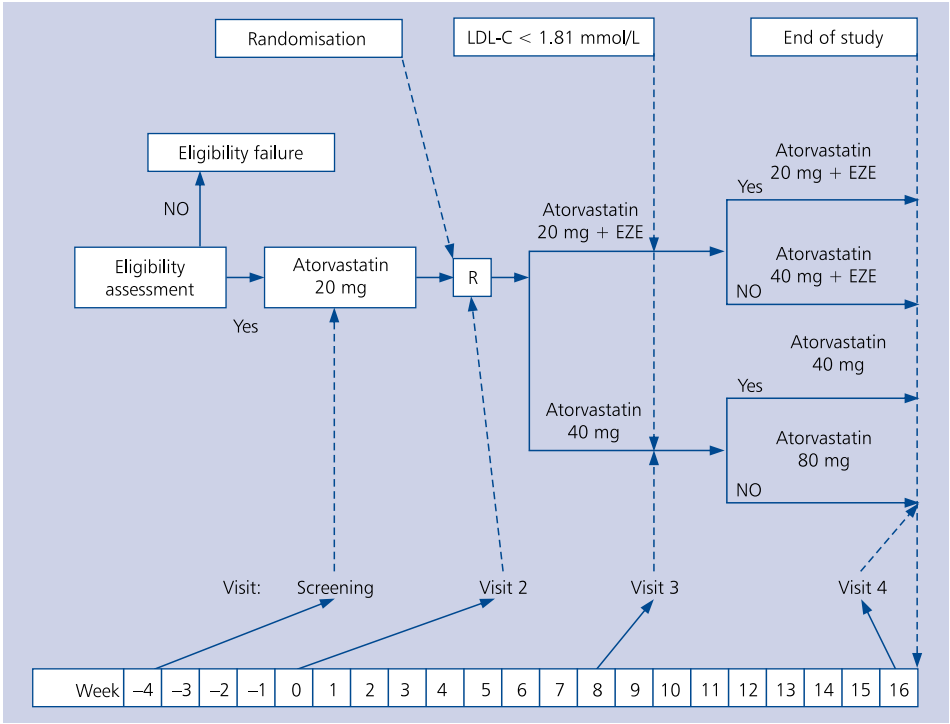

Figure 1. Study design; EZE — ezetimibe; LDL-C — low density lipoprotein cholesterol; R — randomisation

RESULTS

Study participants

Between May 2011 and December 2013, 351 ACS patients hospitalised in Amtel Hospital First Clinical intensive coronary care unit were informed of the purpose of the trial and gave their signed informed consent before being enrolled. Five patients declined to participate without giving a reason. From 346 ACS patients, 323 met the eligibility criteria for screening. From 323 patients screened, 292 met the inclusion/exclusion criteria and were randomised. The most common reason for exclusion was a baseline LDL-C < 1.81 mmol/L. Among the 292 patients enrolled, 283 (97%) patients completed the eight-week assessment, and 263 (90%) completed the 16--week assessment. During the course of the study, 16 patients were prematurely discontinued (three patient were lost to follow-up and 13 had adverse events) and 13 patients died. Of the 127 patients from the atorvastatin treatment group who completed 16 weeks of treatment, 60 patients did not achieve LDL-C target while treated with the maximum statin dose (80 mg) for eight weeks. All of them had EZE 10 mg added to their statin treatment at the end of study. Seventeen patients from the 136 EZE + statin group, who completed 16 weeks of treatment and had not achieved LDL-C target, were given double the atorvastatin dose (80 mg) (Fig. 2). There were no clinically significant differences in baseline demographic or LDL-C4 level (LDL-C level at four weeks, at randomisation) characteristics across the two treatment groups of patients (Table 1, Table 2, and row A; Table 2 and row B). There were statistically significant differences for some baseline coexisting diseases with regard to treatment groups (Table 1). There were four patients in the EZE + statin group (two patients received atorvastatin 20 mg and two — atorvastatin 40 mg) with alanine aminotransferase (ALT), aspartate aminotransferase (AST), or both ≥ 3 × ULN. There were nine patients in the statin group (five patients received atorvastatin 40 mg and four — atorvastatin 80 mg) with ALT, AST, or both ≥ 3 × ULN. All elevations in hepatic enzymes were asymptomatic, and no hepatitis, jaundice, or other clinical signs of liver dysfunction were reported. Discontinuation of study medication owing to these adverse events occurred in 6.2% of the patients in the statin group and in 2.7% of those in the EZE + statin group. The weighted mean of statin dose for the EZE + statin group patients was 38.2 mg and for the statin group was 74.3 mg. There was not a significant difference in LDL-C16 levels (LDL-C level at 16 weeks, at the end of study) between males and females in both treatment groups (Table 2 and row C, Table 2 and row D). However, the difference was statistically significant for patients' LDL-C16 levels with regard to the treatment groups (Table 2 and row E). Table 3 shows unadjusted mean LDL-C levels at the end of study in ACS patients by gender and treatment group. The F and P values were derived from a two-way ANOVA. There was no significant difference in LDL-C levels between males and females. Pairwise contrasts showed that the difference in marginal means between males and females

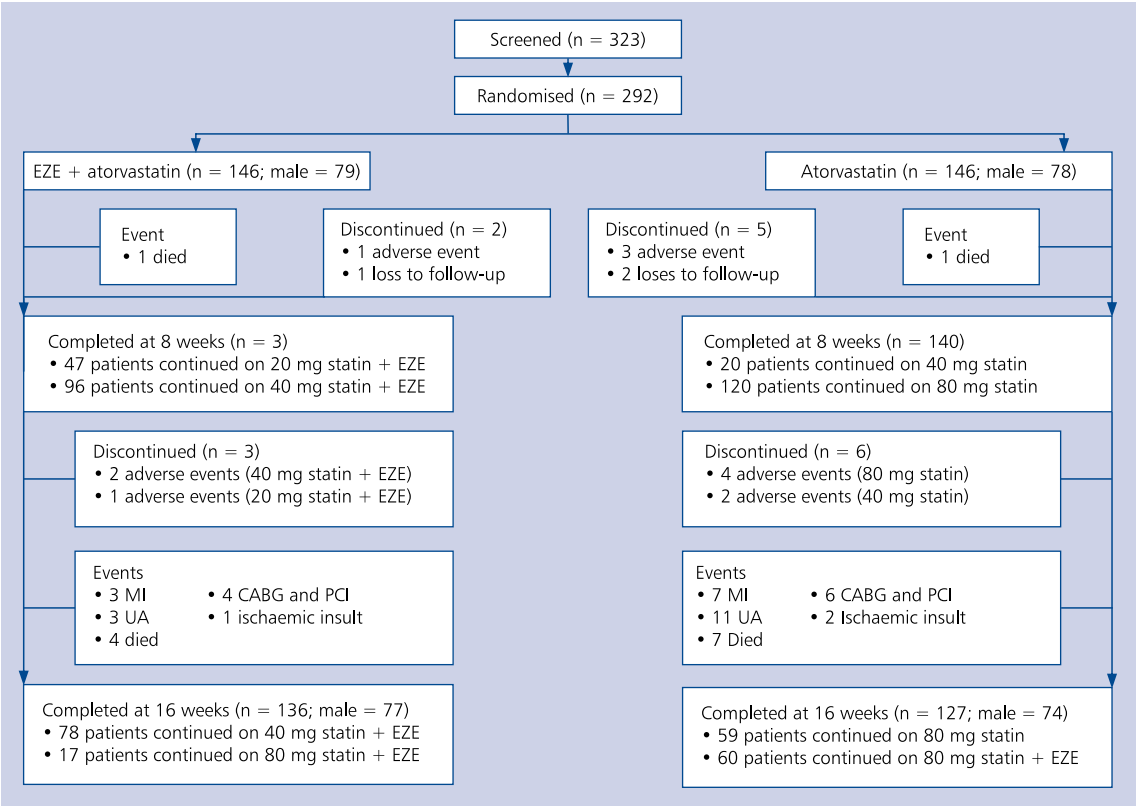

Figure 2. Enrolment, randomisation, and follow-up of study participants; EZE — ezetimibe; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; UA — unstable angina; MI — myocardial infarction

Table 1. Baseline characteristics by treatment group and by gender

Characteristic	EZE + atorvastatin (n = 146)	Atorvastatin (n = 146)	p
Women	67 (45.9%)	68 (46.9%)	NS
Age [years], mean ± SD	62.21 ± 11.36	62.62 ± 11.03	NS
Body mass index, mean ± SD	25.22 ± 3.43	24.87 ± 2.88	NS
Diabetes	7 (4.8%)	2 (1.4%)	NS
Peripheral artery disease	58 (39.7%)	67 (45.9%)	NS
Old MI	25 (17.1%)	4 (2.7%)	< 0.0001
CABG	23 (15.8%)	12 (8.2%)	< 0.0001
PCI	12 (8.2%)	22 (15.1%)	NS
Stroke or TIA	21 (14.4%)	39 (26.7%)	< 0.0001
LDL-C4 [mmol/L], mean ± SD	2.83 ± 0.55	2.74 ± 0.64	0.170
Characteristic	**Females (n = 135)**	**Males (n = 157)**	**p**
Age [years], mean ± SD	62.37 ± 10.54	62.46 ± 11.73	NS
body mass index, mean ± SD	24.74 ± 3.23	25.31 ± 3.1	NS
Diabetes	7 (5.2%)	2 (1.3%)	NS
Peripheral artery disease	55 (40.7%)	70 (44.6%)	NS
Old MI	12 (8.9%)	17 (10.8%)	NS
CABG	18 (13.3%)	17 (10.8%)	NS
PCI	13 (9.6%)	21 (13.4%)	NS
Stroke or TIA	30 (22.2%)	30 (19.1%)	NS

CABG — coronary artery bypass graft; EZE — ezetimibe; LDL-C4 — low-density lipoprotein cholesterol level at four weeks; MI — myocardial infarction; NS — not significant; PCI — percutaneous coronary intervention; SD — standard deviation; TIA — transient ischaemic attach

Table 2. Low-density lipoprotein cholesterol (LDL-C) levels at randomisation and at the end of study in patients who received atorvastatin + ezetimibe (EZE) combination therapy (statin + EZE) and atorvastatin monotherapy (statin) according their gender and treatment group

	Males Mean ± SD	Females Mean ± SD	Effect size (d)	Mean difference and 95% CI	p
A. LDL-C4	2.84 ± 0.51	2.82 ± 0.60	0.04	0.023 (–0.16, 0.20)	0.804
B. LDL-C4	2.81 ± 0.64	2.66 ± 0.64	0.23	0.14 (–0.07, 0.35)	0.178
C. LDL-C16	1.6 ± 0.35	1.6001 ± 0.44	–0.0002	–0.00003 (–0.13, 0.13)	1
D. LDL-C16	1.91 ± 0.38	1.92 ± 0.42	–0.02	–0.012 (–0.15, 0.13)	0.868
	Statin + EZE **Mean ± SD**	**Statin** **Mean ± SD**	**Effect size** **(d)**	**Mean difference** **and 95% CI**	**p**
E. LDL-C16	1.60 ± 0.39	1.91 ± 0.40	–0.78	–0.31 (–0.4, –0.22)	< 0.0001

LDL-C4 — LDL-C serum level at the randomisation (after four weeks of stabilisation phase); LDL-C16 — LDL-C serum level at the end of study (after 16 weeks of intervention); row A and C — data for statin + ezetimibe (EZE) group; row B and D — data for statin group; CI — confidence interval; SD — standard deviation

Table 3. Mean low-density lipoprotein cholesterol (LDL-C) levels at the end of study in acute coronary syndrome patients by gender and treatment group derived from two-way ANOVA

	N	LDL-C16 [mmol/L] Mean ± SD	F (df)	Mean difference (F – M)	95% CI for difference Lower bound	 Upper bound	p	p trend
Gender			0.014 (1, 273)	0.006	–0.09	0.1	0.906	–
Males	151	1.75 ± 0.4						
Females	125	1.76 ± 0.46						
Treatment group			42.992 (1, 273)	0.048	0.22	0.40	0.000	0.000
Ezetimibe + statin	141	1.60 ± 0.39						
Statin	135	1.91 ± 0.40						

CI — confidence interval; SD — standard deviation; F — female; M — male

was 0.006 mmol/L (95% CI –0.09 to 0.1, p = 0.906). However, the difference in marginal means between treatment groups was statistically significant at 0.31 mmol/L (95% CI 0.22 to 0.40, p = 0.000). A polynomial contrast indicated that there was a significant linear trend between treatment groups and LDL-C levels at the end of the study (p < 0.001). The Kaplan-Meier event-free cumulative survival rates at 16 weeks were 88.1% in the EZE + statin group patients and 77.0% in the statin group patients (absolute risk reduction: 11.1%; hazard ratio: 2.099; 95% CI: 1.165 to 3.781; p = 0.014) (Fig. 3). The Kaplan-Meier estimates indicated that the event-free cumulative survival rate for 79 male patients given the new treatment (atorvastatin + EZE) was 86% and for the 67 female patients was 91% (p = 0.360 [log rank]). The event-free survival rate for 78 male patients given the standard treatment (atorvastatin) was 79% and for 68 female patients was 75% (p = 0.611 [log rank]). The log rank test indicated that there was not a statistically significant difference between the males' and females' event-free survival rates combining the treatment groups (p = 0.896). Collectively, these results suggest that the new treatment was as effective for males as for females (Figs. 4–6, Table 4).

DISCUSSION

In our study, the combination of atorvastatin and EZE resulted in a significantly lower risk of cardiovascular events than that with statin monotherapy, with a 11.1-percentage-point lower rate of the primary composite endpoint of cardiovascular death, major coronary events, or nonfatal stroke (hazard ratio: 2.099; Fig. 3). Patients receiving ezetimibe and statin were more likely to achieve target LDL-C after 16 weeks compared to patients doubling their statin dose (Table 2 and row E). However, the responses in atorvastatin-monotherapy and atorvastatin + EZE groups were similar for both men and women according to LDL-C levels and composite endpoints (Table 2 and row C, Table 2 and row D, Table 4 and Figs. 4–6). Analyses of changes in LDL-C by sex subgroups have been presented in several previous reports, and demonstrated that men

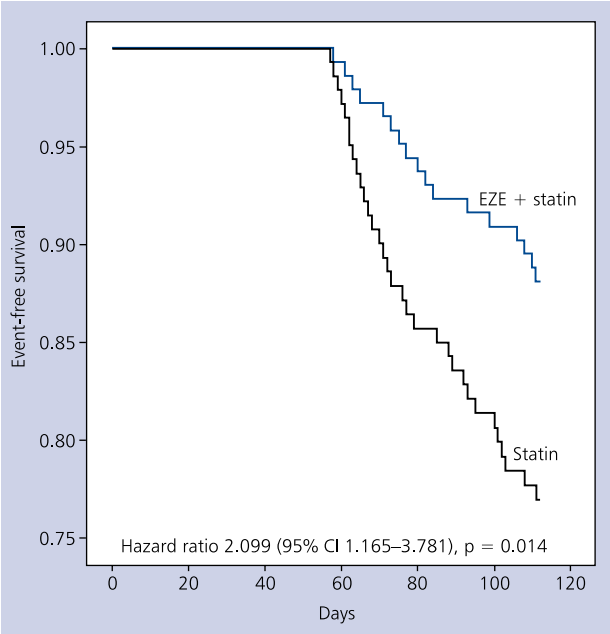

Figure 3. Kaplan-Meier survival curves by the treatment group (ezetimibe [EZE] + statin and statin). Hazard ratio was derived by Cox proportional-hazards model

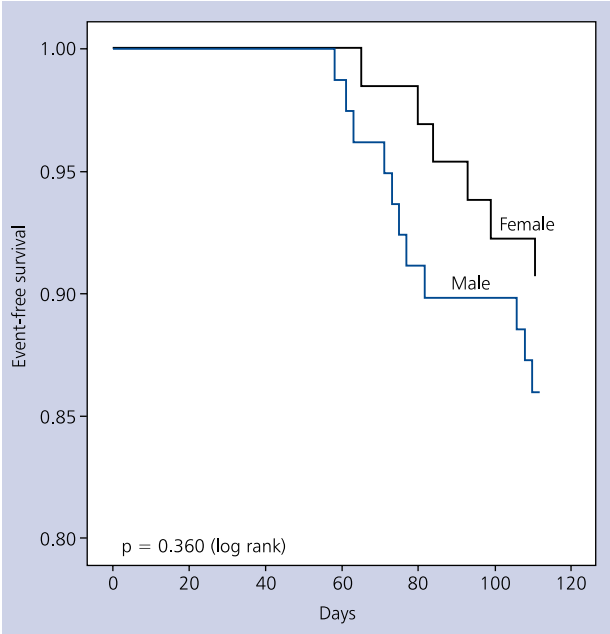

Figure 4. Kaplan-Meier survival curves for males and females in ezetimibe (EZE) + statin treatment group

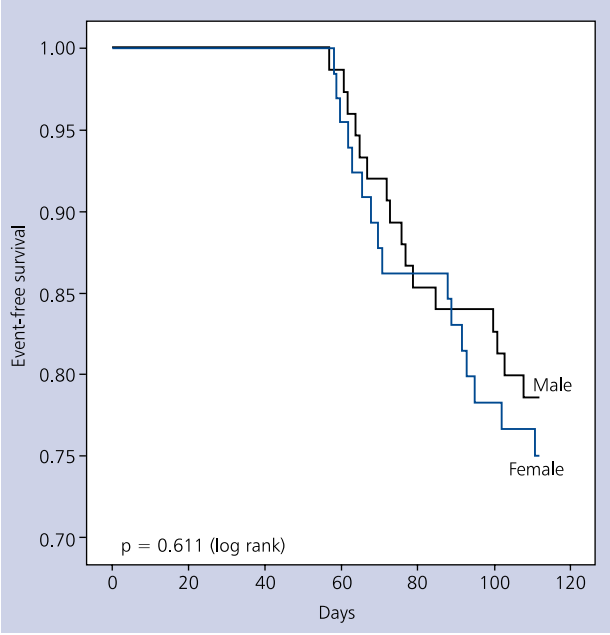

Figure 5. Kaplan-Meier survival curves for males and females in statin treatment group

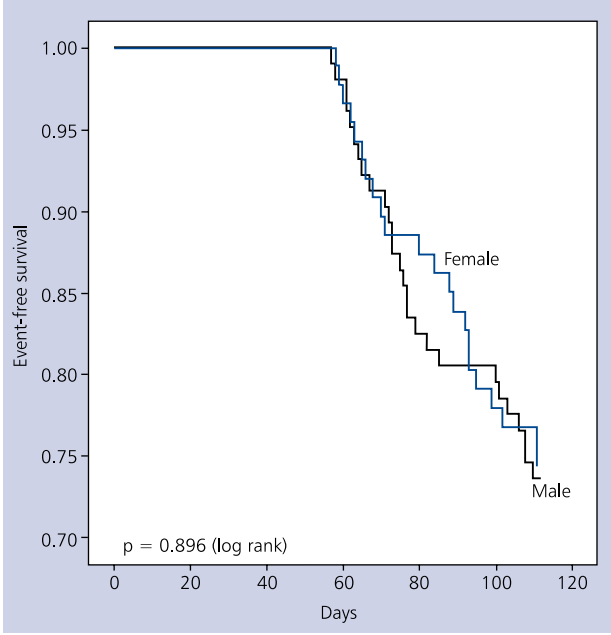

Figure 6. Kaplan-Meier survival curves for males and females combining the treatment groups

and women responded to treatment similarly to the overall population [8–12]. In those studies, the subgroups by sex were relatively small; although the analyses of change in LDL-C were pre-specified, they were not powered to show statistical differences between the sex subgroups. Lipid-lowering treatment reduces coronary events [13], but the consistency of this effect in women has been controversial until recently [14, 15]. Stronger contemporary data have provided some

Table 4. Event-free survival characteristics of study sample

Treatment group	No. of cases	No. of events	No. censored (%)	Mean event-free survival times in days (95% CI)
Statin + ezetimibe				
Gender				
Male	79	11	86.1	108 (105, 110)
Female	67	6	91	110 (108, 112)
Overall	146	17	88.4	109 (107, 110)
Statin				
Gender				
Male	78	16	79.5	105 (101, 108)
Female	68	16	76.5	104 (100, 108)
Overall	146	32	78.1	104 (105, 108)

CI — confidence interval

evidence toward answers to that debate. A meta-analysis of primary prevention trials that included sex-specific clinical outcomes in coronary vascular disease demonstrated that cardiovascular events were reduced by about one-third in women after 12 months of statin treatment, during which subjects experienced a 51 mg/dL (1.32 mmol/L) reduction from baseline in LDL-C [16]. Similar relative risk reductions were observed in men. The Cholesterol Treatment Trialists' (CTT) Collaboration showed that further reductions in LDL-C produce definite further reductions in the incidence of cardiovascular events in the overall population, with a significant proportional risk reduction of 17% ($p < 0.001$) per 39 mg/dL (1 mmol/L) reduction in LDL-C among women in first major vascular events [17]. Taken together, these data support the utility of intensive lipid lowering for reducing the risk of cardiovascular events in both men and women. Both treatments were generally well tolerated in the overall population and in both sexes. This is consistent with previous reports, which have shown generally comparable safety and tolerability profiles with statin monotherapy and EZE + statin co-administration treatment [18].

Limitations of the study

However, in spite of these clear benefits, several limitations of our study should be considered. First, we evaluated patients who had had ACS, and our results are most relevant to that population. Second, due to the small sample size recruited, the results of this study must be interpreted with caution. Finally, this trial had a particularly small duration of follow-up, and the open-label study design may have biased the assessment or reporting of adverse events. It is worth further evaluating the clinical effect of the atorvastatin and EZE combined therapy in larger populations of ACS patients with longer follow-up.

CONCLUSIONS

In our study, the addition of EZE to atorvastatin therapy in patients who had had ACS further lowered the risk of cardiovascular events, and no offsetting adverse events were observed. Our trial reinforced the well-documented "lower is better" relationship between LDL-C levels and reduction in cardiovascular events. The small sex-related differences in this combination therapy effectiveness were not statistically and clinically meaningful, and these results underscored the ongoing need for appropriate management of lipid levels in women.

Acknowledgements

We thank the Pharmaceutical Company PSP-GMP, Pfizer Pharmaceutical Company's Georgian office, and Gedeon Richter Pharmaceutical Company's Georgian office for partial financial support. We periodically received payments as a consultant and for lectures sponsored by these pharmaceutical companies. These pharmaceutical companies had no role in the planning and execution of the study and in the analysis of results. They had no impact on the content of the paper.

Conflict of interest: *none declared*

References

1. Lloyd-Jones DM. Short-term versus long-term risk for coronary artery disease: implications for lipid guidelines. Curr Opin Lipidol. 2006; 17(6): 619–625, doi: 10.1097/MOL.0b013e3280108740, indexed in Pubmed: 17095905.
2. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. Circulation. 2011; 123(11): 1243–1262, doi: 10.1161/CIR.0b013e31820faaf8, indexed in Pubmed: 21325087.
3. 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(2): 227–239, doi: 10.1161/01.CIR.0000133317.49796.0E, indexed in Pubmed: 15249516.

4. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth 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. 2012; 33(13): 1635–1701, doi: 10.1093/eurheartj/ehs092, indexed in Pubmed: 22555213.
5. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008; 156(5): 826–832, doi: 10.1016/j.ahj.2008.07.023, indexed in Pubmed: 19061694.
6. Blazing MA, Giugliano RP, Cannon CP, et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. Am Heart J. 2014; 168(2): 205–212.e1, doi: 10.1016/j.ahj.2014.05.004, indexed in Pubmed: 25066560.
7. Califf RM, Lokhnygina Y, Cannon CP, et al. An update on the IMProved reduction of outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) design. Am Heart J. 2010; 159(5): 705–709, doi: 10.1016/j.ahj.2010.03.004, indexed in Pubmed: 20435175.
8. Conard SE, Bays HE, Leiter LA, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol. 2008; 102(11): 1489–1494, doi: 10.1016/j.amjcard.2008.09.075, indexed in Pubmed: 19026302.
9. Leiter LA, Bays H, Conard S, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol. 2008; 102(11): 1495–1501, doi: 10.1016/j.amjcard.2008.09.076, indexed in Pubmed: 19026303.
10. Pearson TA, Denke MA, McBride PE, et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc. 2005; 80(5): 587–595, doi: 10.4065/80.5.587, indexed in Pubmed: 15887425.
11. Reckless JPD, 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(4): 539–554, doi: 10.1111/j.1742-1241.2008.01697.x, indexed in Pubmed: 18266852.
12. Zieve F, Wenger NK, Ben-Yehuda O, et al. Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). Am J Cardiol. 2010; 105(5): 656–663, doi: 10.1016/j.amjcard.2009.10.029, indexed in Pubmed: 20185012.
13. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA. 1999; 282(24): 2340–2346, doi: 10.1001/jama.282.24.2340, indexed in Pubmed: 10612322.
14. Grundy SM. Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? Yes. BMJ. 2007; 334(7601): 982, doi: 10.1136/bmj.39202.399942.AD, indexed in Pubmed: 17494017.
15. Kendrick M. Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? No. BMJ. 2007; 334(7601): 983, doi: 10.1136/bmj.39202.397488.AD, indexed in Pubmed: 17494018.
16. Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation. 2010; 121(9): 1069–1077, doi: 10.1161/CIRCULATIONAHA.109.906479, indexed in Pubmed: 20176986.
17. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376(9753): 1670–1681, doi: 10.1016/S0140-6736(10)61350-5, indexed in Pubmed: 21067804.
18. Bennett S, Sager P, Lipka L, et al. Consistency in efficacy and safety of ezetimibe coadministered with statins for treatment of hypercholesterolemia in women and men. J Womens Health (Larchmt). 2004; 13(10): 1101–1107, doi: 10.1089/jwh.2004.13.1101, indexed in Pubmed: 15650343.

Cite this article as: Japaridze L, Sadunishvili M. The short-term effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on clinical outcome in acute coronary syndrome patients by gender. Kardiol Pol. 2017; 75(8): 770–778, doi: 10.5603/KP.a2017.0074.

Krótkoterminowy wpływ terapii atorwastatyną i ezetimibem w porównaniu z monoterapią atorwastatyną na stan kliniczny chorych z ostrym zespołem wieńcowym w zależności od płci

Lasha Japaridze, Maia Sadunishvili

Amtel Hospital First Clinical, The Centre of Vascular and Heart Diseases, Tbilisi State Medical University, Chapidze Heart Centre, Gruzja

Streszczenie

Wstęp: Atorwastatyna zmniejsza stężenie frakcji cholesterolu lipoprotein o małej gęstości (LDL) oraz ryzyko zdarzeń sercowo-naczyniowych. Jednak nie wiadomo, czy dołączenie ezetimibu (EZE), leku nienależącego do statyn, który ogranicza jelitową absorpcję cholesterolu, może spowodować dodatkową redukcję częstości zdarzeń sercowo-naczyniowych i czy istnieją różnice zależne od płci.

Cel: Badanie przeprowadzono w celu oceny wpływu stosowania terapii skojarzonej atorwastatyną i EZE u chorych z ostrym zespołem wieńcowym (ACS) na występowanie złożonego punktu końcowego w obserwacji krótkoterminowej oraz analizy różnic zależnych od płci.

Metody: Do tego trwającego 16 tygodni, jednoośrodkowego, prospektywnego badania z randomizacją, przeprowadzonego metodą otwartej próby, włączono 323 chorych hospitalizowanych z powodu ACS, który wystąpił w ciągu ostatnich 14 dni. Pacjentom podawano atorwastatynę w dawce 20 mg przez 28 dni, a następnie 292 chorych, u których stężenie cholesterolu frakcji LDL wynosiło ≥ 1,81 mmol/l, przydzielono losowo do grupy otrzymującej EZE w dawce 10 mg/d. w skojarzeniu z atorwastatyną (EZE + statyna) lub do leczenia samą atorwastatyną w dawce 2-krotnie większej niż dotychczas stosowana. Główny punkt końcowy obejmował: zgon sercowo-naczyniowy, zawał serca niezakończony zgonem, niestabilną dławicę piersiową wymagającą hospitalizacji, rewaskularyzację wieńcową (≥ 30 dni po randomizacji) i udar serca niezakończony zgonem.

Wyniki: Określony na podstawie analizy przeżycia Kaplana-Meiera odsetek chorych, u których w ciągu 16 tygodni nie wystąpiły zdarzenia zaliczane do punktu końcowego, wynosił 88,1% w grupie terapii skojarzonej EZE + statyna i 77,0% w grupie stosującej monoterapię atorwastatyną (bezwzględne zmniejszenie ryzyka wyniosło 11,1 punktu procentowego; hazard względny: 2,099; 95% przedział ufności: 1,165–3,781; p = 0,014). W teście logarytmicznym rang stwierdzono brak statystycznie istotnych różnic pomiędzy kobietami i mężczyznami między odsetkiem przeżycia bez wystąpienia zdarzeń w obu grupach terapeutycznych (p = 0,897).

Wnioski: Wyniki badania dowodzą, że dołączenie EZE do terapii statyną pozwala uzyskać poprawę w zakresie ryzyka sercowo-naczyniowego, a odpowiedź na leczenie skojarzone EZE + statyna była podobna w przypadku obu płci.

Słowa kluczowe: ostry zespół wieńcowy, atorwastatyna, ezetimib, płeć, frakcja cholesterolu lipoprotein o małej gęstości

Kardiol Pol 2017; 75, 8: 770–778

Adres do korespondencji:
Lasha Japaridze MD, Tbilisi State Medical University, The Centre of Vascular and Heart Diseases, Chachava str.#1, 0159 Tbilisi, Georgia, tel: +995 599227746, e-mail: lashadoctor67@yahoo.com
Maia Sadunishvili, MD, Chapidze Heart Centre, Lubliana str.#4, 0159 Tbilisi, Georgia, e-mail: maiasadunishvili@yahoo.com
Praca wpłynęła: 28.02.2016 r. **Zaakceptowana do druku:** 23.03.2017 r. **Data publikacji AoP:** 11.04.2017 r.