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The effectiveness of ezetimibe and atorvastatin combination therapy related to low density cholesterol goal levels attainment in patients with acute coronary syndromes

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Abstract

The use of statins is essential for aggressive lipid-lowering treatment in acute coronary syndrome (ACS) patients. The purpose of the present study was to examine the impact of ezetimibe, a selective intestinal cholesterol transporter inhibitor, in ACS patients. We conducted a 16-week one-center, prospective, randomized, and open-label clinical trial, involving 323 patients who had been hospitalized for an acute coronary syndrome
within the preceding 14 days. They were received atorvastatin 20 mg during 28 days and after those 292 patients, who had low density cholesterol (LDL-C) levels ≥ 1.81 mmol/L, were randomized to ezetimibe 10 mg/day co-administered with atorvastatin therapy (EZE + Statin) or doubling their current atorvastatin dose. The primary efficacy end point was absolute reduction in LDL-C for ezetimibe plus atorvastatin versus atorvastatin-monotherapy treatment groups. At

16 weeks, the mean LDL cholesterol level during the study was 1.60 mmol per liter in the atorvastatine-ezetimibe group, as compared with 1.91 mmol per liter in the atorvastatin-monotherapy group (P<0.001). Patients receiving ezetimibe and statin were more likely to achieve target LDL-C after 16 weeks compared to patients doubling their statin dose. Ezetimibe/statin combination therapy was well tolerated among this ACS patients, without safety concerns.

KEYWORDS: Acute Coronary Syndrome; atorvastatin; ezetimibe; low-density lipoprotein cholesterol

Introduction

Aggressive lipid-lowering treatment is crucial to secondary prevention for patients with acute coronary syndrome (ACS) [1,2]. While statin therapy has been shown to be highly effective in lowering low-density lipoprotein cholesterol (LDL-C) and reducing cardiovascular disease risk [3,4,5]. many high-risk coronary heart diseases (CHD) and/or CHD risk-equivalent patients do not achieve their guideline-recommended LDL-C goals. [6,7]. Several studies have shown that while approximately two thirds of high-risk CHD patients achieve LDL-C levels of, 2.6 mmol/L, only about one third of these patients attain LDL-C ,1.81 mmol/L levels [6,8,9,10,11]. For these patients, clinical guidelines recommend more intensive LDL-C-lowering therapy, including statin uptitration to maximally tolerated doses, and/or combination therapy [4,5]. However, many patients may not be able to tolerate higher statin doses, and combination therapy may be a better alternative. In several clinical studies, the addition of ezetimibe to ongoing statin therapy has been shown to improve lowering of LDL-C as well as goal attainment more than statins alone and is generally well tolerated in various patient populations [12].

The purpose of this open-label randomized trial was to compare the effectiveness and tolerability of ezetimibe 10 mg/day coadministered 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.

Materials and methods

Study design

A 16-week one-center, prospective, randomized, and open-label clinical trial. involving 323 patients who had been hospitalized for an acute coronary syndrome (STEMI, NSTEMI, or UA) within the preceding 14 days. They were received atorvastatin 20 mg during 28 days, and after that 292 patients, who had LDL cholesterol levels of LDL-C ≥1.81 mmol/L, were randomized to ezetimibe 10 mg/day co-administered with atorvastatin therapy (EZE + Statin) or doubling their current atorvastatin dose. Statin-naive patients and patients unable to have their statin dose doubled due to maximal statin dosing already, or tolerability/safety concerns, were excluded. Additional exclusion criteria were: (i) treatment with bile acid sequestrants, niacin, or fibrates, and; (ii) active liver disease, uncontrolled endocrine illness, kidney disease, and creatine kinase (CK)>50% 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 4 clinic visits. At screening (visit 1) the fasting lipid profile, and liver function parameters were assessed. eligible patients entered a four week stabilization phase during which they continued taking their current statin dose (Fig. 1). At Visit 2, eligibility for randomization was confirmed with another fasting lipid profile. Patients who remained eligible (LDL-C≥1.81 mmol/L) were randomized (1:1 ratio), using a computer-generated random table, to receive either ezetimibe 10 mg daily coadministered with current statin dosing (EZE + Atorvastatin) or doubling of current Atorvastatin dose. Bloodwork for exploratory marker (Creactive protein (CRP)) was obtained at Visit 2 and 4. After 8 weeks (Visit 3), a brief exam, blood draw for fasting lipid profile, liver panel, and review of any adverse events occurred. For EZE + Statin patients, if LDL-C levels were LDL-C ≥ 1.81 mmol/L, the statin dose was doubled for the next 8 weeks. For atorvastatin patients with LDL-C ≥1.81 mmol/L, the statin dose was again doubled for the next 8 weeks. At week 16 (Visit4), patients underwent a brief exam, review of adverse events, liver panel, and fasting lipid profile. If the atorvastatin-monotherapy patients were already at maximum statin dose (80mg) and LDL-C ≥1.81 mmol/L, ezetimibe 10 mg/day could be added at the physician's discretion.

Statistical analysis

Analysis of the results was carried out using the software packages SPSS 23, StatSoft Statisca 10 and SigmaPlot 12.5. mean group value and standard deviation

(SD) were determined for each quantitative index. Data are presented as M ± SD. All analyses were performed in the intent-to-treat (ITT) population including all patients who were randomized. For publication quality, figure 3 was derived from SigmaPlot 12.5. The independent-samples Student's t-test was used to assess between-group differences in LDL-C target achievement. All statistical tests were two-sided with an alpha level of 0.05. Sample size calculation was based on the primary outcome measure. It was calculated via StatSoft Statisca 10 (Independent sample t-test, H0: $Pi_1 = Pi_2$). From medical literature Pi_1=1mmol/l for atorvastatin + EZE and for atorvastatin monotherapy – Pi_2=0.4mmol/l. Population Sigma is about 0.8 mmol/l. In order to detect a similar magnitude of difference for this outcome, with 5% significance and 90% power, a total of 86 patients per group were required.

Results and discussion

Study participants: 351 acute coronary syndrome patients hospitalized in Bokhua Memorial Cardiovascular Center intensive coronary care unit, were informed of the purpose of the trial and had to give their signed informed consent before being enrolled. 5 patients declined to participate without giving a reason. From 346 patients 323 met eligibility criteria. From 323 patients screened, 292 met the inclusion/exclusion criteria and were randomized. The most common reason for exclusion was a Baseline LDL-C<1.81mmol/L. Among the 292 patients enrolled, 283 (97%) patients completed the 8-week assessment and 263 (90%) completed the 16-week assessment. During the course of the study, there were 16 patients who were prematurely discontinued (3 were lost to follow-up and 13 had adverse events) and 13 patients were died. Of the 127 statin of patients who completed 16 weeks treatment, 60 were eligible for a crossover since they had not achieved LDL-C target while treated with the maximum statin dose (80mg) for 8 weeks. All of them had ezetimibe 10 mg added to their statin treatment and were, therefore, crossed over to the EZE + Statin group after 16 weeks (End of study). 17 from the 136 EZE + Statin of patients, who completed 16 weeks treatment and had not achieved LDL-C target, doubled the statin dose (80 mg).

There were no clinically significant differences in baseline demographic or lipide level characteristics across the two treatment groups (Table 1 and 2). The were some differences in baseline coexisting diseases (Table 1 and fig. 2). At the time of randomization (at 4 weeks), the mean LDL-C4 cholesterol level was 2.83 mmol/l in atorvastatin + EZE group and 2.74 mmol/l in atorvastatin group (P = 0.170). Among

patients who had blood samples obtained at 16 weeks, the mean LDL-C16 cholesterol level was 1.91 mmol/l in the atorvastatin-monotherapy group and 1.60 mmol/l in the atorvastatin-ezetimibe group (P<0.0001) (Table 2).

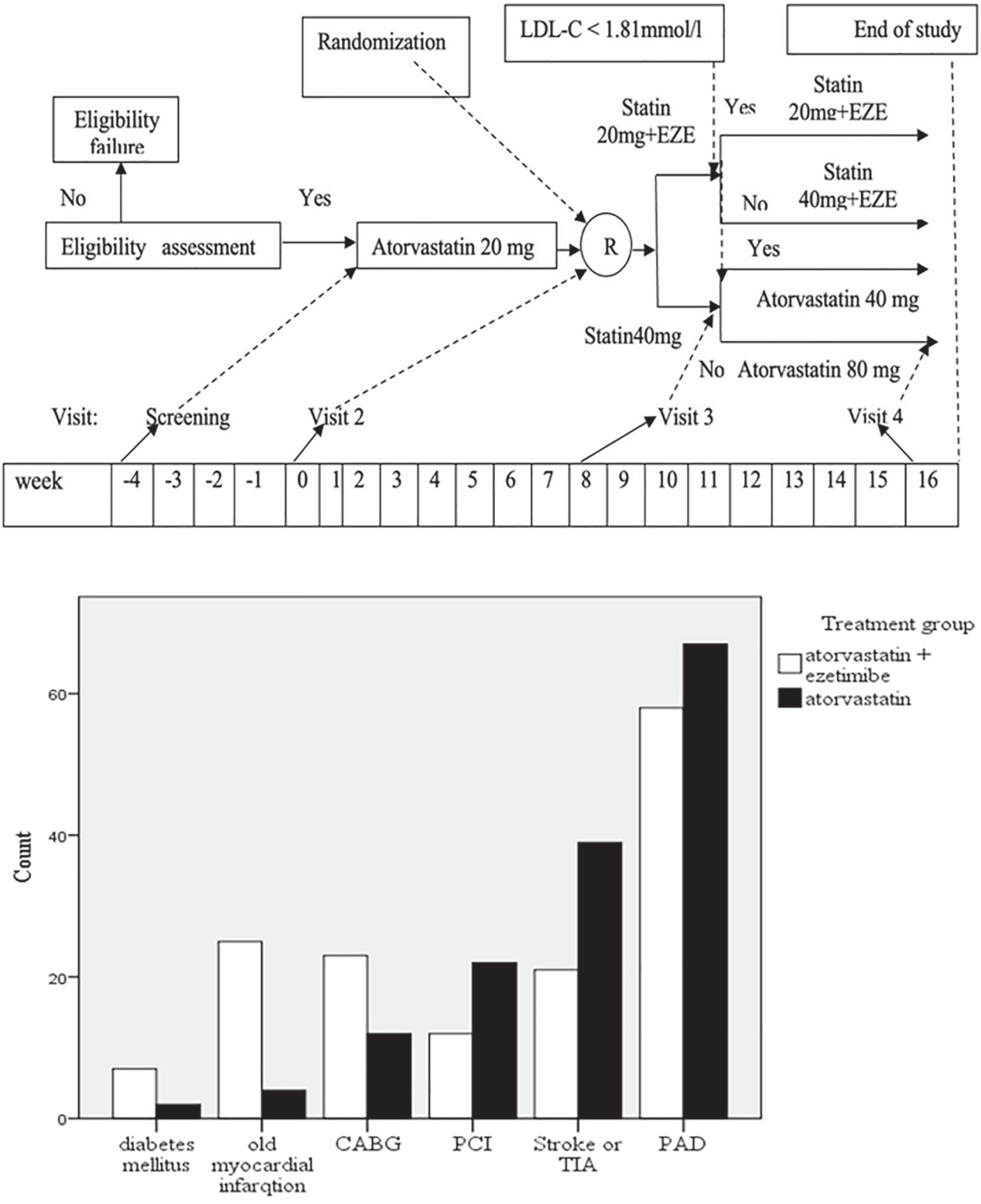

Fig. 2. History of coexisting conditions.

This difference of 0.31 mmol/l (P<0.0001) represented a 16% further lowering of LDL cholesterol level when ezetimibe was combined with atorvastatin than when atorvastatin was administered alone (fig.3). Some between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range (ULN). There were 4 patients in the atorvastatin–ezetimibe group (2 patients had received atorvastatin 20 mg and 2 patients – atorvastatin 40 mg) with ALT, AST, or both ≥3× ULN. There were 9 patients in the atorvastatin group (5 patients had received atorvastatin 40 mg and 4 patients-atorvastatin 80mg) 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 the adverse event occurred in 6.2 % of the patients in the atorvastatin-monotherapy group and in 2.7 % of those in the atorvastatin–ezetimibe group. Although LDL-C goal attainment rates have recently improved overall through an increased awareness and use of lipid-lowering therapy, many high-risk CHD patients still do not meet guideline-recommended LDL-C goals on statin monotherapy [6,8,13,14]. Guidelines recommend that more intensive therapy, such as statin titration and/or combination therapy, may be needed for patients who are not at LDL-C goal [4,5]. While statins remain the first-line therapy for LDL-C reduction based on clinical trial data, many patients may not tolerate high doses required to achieve clinical targets. Combination therapy with ezetimibe plus statins has been shown to be safe and efficacious in numerous randomized, controlled clinical studies [12,15]. In our study, ezetimibe added onto atorvastatin therapy resulted in greater percent LDL-C changes from baseline (43%) compared with statin up titration (30%), consistent with the LDL-C reductions (30 %) observed previously in clinical studies in which ezetimibe was added onto ongoing simvastatin, atorvastatin, or rosuvastatin monotherapy [12,15]. Moreover, the significant additional 13% LDL-C reduction observed in our study with ezetimibe add-on versus statin uptitration is also in line with clinical studies in which the addition of ezetimibe to statin therapy significantly reduced LDL-C by 14% more than doubling the statin dose [12]. Multiple observational and randomized clinical studies have shown that statin uptitration and/or combination therapy with higher LDL-C-lowering efficacy is more effective than therapy for moderate-potency reducing LDL-C and improving goal attainment in high-risk patients [16,17,18,19,20,21,22]. A strength of our study is the assessment of the effects of lipid-lowering therapy in a real-world clinical practice setting. However, several limitations of our study should be considered. First, we evaluated patients who had had an acute coronary syndrome, and our results are most relevant to that population. Second, 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 to further evaluate the clinical effect of the combined therapy in larger population of ACS patients with enough longer follow-up.

TABLE 1. Baseline characteristics

Characteristic	EZE + Atorvastatin *n = 146*	Atorvastatin *n = 146*
Women, *n* (%)	67 (49.6)	68 (50.4)
Age, years, mean ± SD	62.21 ± 11.36	62.62 ± 11.03
body mass index, mean ± SD	25.22 ± 3.43	24.87 ± 2.88
Diabetes, *n* (%)	7 (77.8)	2 (22.2)
PAD, *n* (%)	58 (46.4)	67 (53.6)
Old MI, *n* (%)	25 (86.2)	4 (13.8)
CABG, *n* (%)	23 (65.7)	12 (34.3)
PCI, *n* (%)	12 (35.3)	22 (64.7)
Stroke or TIA, *n* (%)	21 (35)	39 (65)

TABLE 2. LDL-C at randomization and 16 weeks

Parameter	Atorvastatin + Ezetimibe	Atorvastatin	P value (between group)
	n=146	n=146	
Randomization, mmol/L (mean ± SD)			
LDL-C4	2.83±0.55	2.74± 0.64	0.170
	n=136	n = 127	
16 weeks,mmol/L (mean ± SD)			
LDL-C16	1.60 ± 0.39	1.91 ± 0.40	< 0.0001

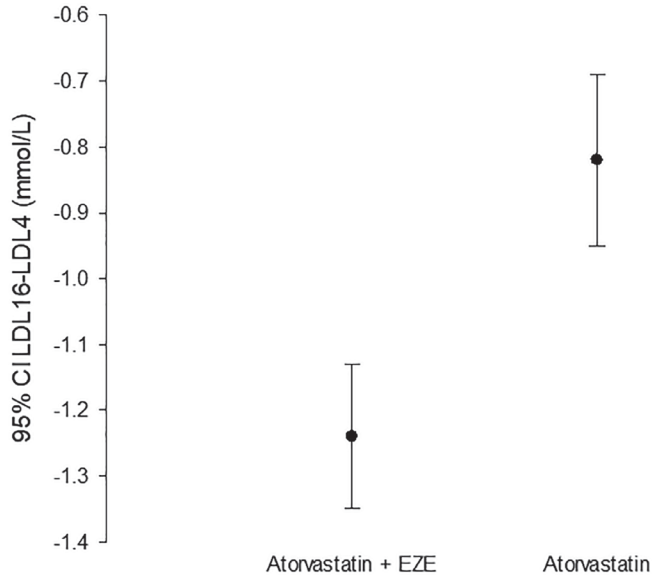

Fig. 3. Mean of LDL-C16-LDL-C4 at 16 weeks by treatment group.

TABLE 3. Absolute change in LDL-C parameters from randomization to 16 weeks

Parameter	Atorvastatin + Ezetimibe	Atorvastatin	P value (between group)
	n = 146	n =146	
mmol/L, (mean±SD), LDL-C16 – LDL-C4	– 1.24 ± 0.67	-0.82 ±0.76	< 0.0001

Conclusion

Ezetimibe coadministered with atorvastatin may enable more ACS patients to achieve recommended target LDL-C levels by offering greater LDL-C lowering with fewer dose titrations than uptitration of atorvastatin alone.

Acknowledgments

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