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Effect of Combination Therapy of Low-Dose Atorvastatin Plus Ezetimibe Versus Moderate-Intensity Atorvastatin on Hypercholesterolemia in Patients with Acute Coronary Syndrome

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Abstract: ***Background:*** Acute coronary syndrome (ACS) is the leading cause of death in the world and it is a consequence of unstable plaque due to dyslipidemia, mainly elevated LDL cholesterol (LDL-C). ***Methods:*** This randomized controlled trial was conducted on 80 diagnosed ACS patients with hypercholesterolemia at the department of Pharmacology and Therapeutics in collaboration with the Department of Cardiology, Rajshahi Medical College and Hospital, Rajshahi. The study population was divided into 2 groups. In study group, 40 patients were treated with combination therapy of tablet Atorvastatin (10 mg) plus Ezetimibe (10 mg) and in control group, 40 patients were treated with tablet Atorvastatin (20 mg) alone for 12 weeks. Serum triglyceride, total cholesterol, HDL-C and LDL-C were measured initially at baseline and at the end of the 8th and 12th weeks of drug administration. ***Results:*** The reduction of serum total cholesterol and LDL-C from baseline to the 12th week of drug administration was greater in combination therapy group than the monotherapy group which were statistically highly significant ($p < 0.001$ and $p < 0.01$, respectively). But the reduction of serum triglyceride and HDL-C from baseline to the 12th week of drug administration in the combination therapy and monotherapy groups were not statistically significant ($p > 0.05$ in both cases). The efficacy was greater in the combination therapy group than in the monotherapy group on considering the achievement rate of LDL-C less than 70 mg/dl and it was found statistically significant ($p < 0.05$). ***Conclusion:*** It might be stated that the combination therapy of Atorvastatin and Ezetimibe for reducing hypercholesterolemia is more beneficial than doubling the dose of Atorvastatin in the case of hypercholesterolemic patients with ACS.

Keywords: Hypercholesterolemia, Acute coronary syndrome, Atorvastatin and Ezetimibe.

Original Researcher Article

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Article at a glance:

Study Purpose: *The purpose of this study was to evaluate the effect of combination therapy of low-dose Atorvastatin plus Ezetimibe versus moderate-intensity Atorvastatin on hypercholesterolemia in patients with acute coronary syndrome.*

Key findings: *Combination therapy reduced LDL-C and serum total cholesterol more effectively than monotherapy.*

Newer findings: *The LDL-C reached the target levels in the Atorvastatin 10 mg + Ezetimibe 10 mg group 80.00% but only 20.00% in the Atorvastatin 20 mg group and it was statistically significant ($p < 0.05$).*

Abbreviations: *ACS=Acute coronary syndrome, BMI=Body mass index, CABG=Coronary artery bypass graft, CVD=Cardiovascular disease, HDL-C= High-density lipoprotein cholesterol and LDL-C= Low-density lipoprotein cholesterol.*

INTRODUCTION

In humans, atherosclerotic disease in the coronary and carotid arteries can have major effects. Individuals who have atherosclerotic disease are more susceptible to stroke and heart problems. The term "acute coronary syndrome" refers to a group of three coronary artery illnesses that annually impact millions of individuals.[1] These potentially fatal illnesses can also arise from abruptly slowing or stopping blood flow to the heart due to blockages. Unstable angina or a heart attack (myocardial infarction) are possible side effects for those with ACS. Chest discomfort, dyspnea, or lightheadedness are typical symptoms.[2,3] ACS is the most common cause of mortality worldwide and is a medical emergency that has to be attended to right now. As one of the main risk factors for acute coronary syndrome, dyslipidemia, which is characterized by an increase in total cholesterol, low-density lipoprotein cholesterol, triglycerides, and a reduction in high-density lipoprotein cholesterol, accounts for more than 50% of population risk.[4]

The main culprit among lipid profiles is high LDL-C. Thus, controlling cholesterol plays a crucial part in lowering the risk of cardiovascular disease in those with coronary heart disease. For hypercholesterolemia, statins are typically the first line of treatment. To achieve the desired lipid profile, high-intensity statins are suggested and uptitration to the highest recommended and tolerable dose is required to reach the target lipid profile.[5] However, barely one-third of individuals using statin therapy alone meet the goals outlined in many guidelines. Their cardiovascular risk is higher than the normal population even if they meet their goals; this is known as "residual risk." An inhibitor of cholesterol absorption, ezetimibe prevents the intestinal absorption of dietary and biliary cholesterol while leaving triglycerides and lipid-soluble vitamins unaffected. The combination of ezetimibe with atorvastatin inhibits both intestinal cholesterol absorption and cholesterol production, resulting in a 10-20% greater reduction in low-density lipoprotein cholesterol than Atorvastatin alone.[6,7]

Prior research has demonstrated that in certain patients, low-dose atorvastatin alone is ineffective in controlling hypercholesterolemia. It is necessary to double or quadruple the dosage of atorvastatin in this case. Compared to combination therapy using low-dose Atorvastatin + Ezetimibe, high-dose Atorvastatin carries a greater risk of side effects. Regarding the comparison of combination therapy and moderate-intensity atorvastatin monotherapy in patients with acute coronary syndrome, as well as the effects of treatment on lipid profiles, no published research has been conducted in Bangladesh. Therefore, the purpose of this study was to evaluate the impact of low-dose atorvastatin plus ezetimibe combination therapy against moderate-intensity atorvastatin on hypercholesterolemia in patients with acute coronary syndrome (ACS).

METHODS

This randomized clinical trial on hypercholesterolemic patients with acute coronary syndrome was conducted in the Department of Pharmacology and Therapeutics at Rajshahi Medical College, Rajshahi, in collaboration with Department of Cardiology, Rajshahi Medical College Hospital, Rajshahi, for 1 year from July 2022 to June 2023. The study was conducted after obtaining ethical clearance from the Institutional Review Board (IRB) of Rajshahi Medical College and consent from the patients. A total 80 patients who met the eligibility criteria were recruited in the study. All consenting patients, in the age group of 40-70 years, who were diagnosed by the cardiologist as suffering from acute coronary syndrome with hypercholesterolemia were included in the study. Patients who were pregnant, lactating and nonconsensual as well as those who had a history of lipid-lowering agent treatment within two months prior to baseline visit were excluded from the study. After informed written consent, the patient's history like age, sex, family history, precipitating factors (diabetes, hypertension), past history of dyslipidemia and treatments, duration of current condition and associated disorders were obtained and recorded in the data-sheet. The patients were examined by the designated physicians and fasting lipid profile was done. Patients were divided into group A and group B on the basis of drug allotment by lottery. Out of the 80 patients, 40 received tablet Atorvastatin (10 mg) plus Ezetimibe (10 mg) (study group) for 12 weeks and the other 40 received tablet Atorvastatin (20 mg) (control group) for 12 weeks

orally which were prescribed by the consulting physician. Patient compliance was assessed by pill-count method on every visit. Patients were instructed to consult the physician immediately in case if any unusual side effects (nausea, abdominal pain, vomiting, diarrhea, appetite changes, headaches and vertigo) occur before the follow-up date. They were followed up at 8 weeks and 12 weeks and after the end of this time again fasting lipid profile was done. Any reported adverse drug reactions were also noted. The therapeutic efficacy was evaluated by normalization of hypercholesterolemia. Categorical variables were summarized by using numbers and percentages while continuous variables were summarized by means ± standard deviation (SD) and median. Repeated measure ANOVA statistics was used to compare the level of the serum triglyceride, total cholesterol, HDL-C and LDL-C between group-A and group-B. Efficacy of combination therapy over monotherapy based on achievement rate of LDL-C less than 70 mg/dl was estimated by Chi-square test. Level of significance was set at 0.05 and p-value < 0.05 was considered statistically significant for all tests.

RESULTS

Table 1: Comparison of baseline variables between the two groups (n=40 in each group).

Variables	Group		
	Combination therapy group (n=40)	Monotherapy group (n=40)	p-value
Mean age (Years)	53.65±7.20	50.93±6.66	0.08#
Mean monthly family income (taka)	16300.00±9265.87	15125.00±9400.46	0.58#
Mean BMI (Kg/m²)	23.39 ± 3.28	23.56 ± 3.79	0.07#
Gender			
Male	30 (75.00%)	25 (62.50%)	0.23*
Female	10 (25.00%)	15 (37.50%)	
Presence of risk factors			
DM	14 (35.00%)	14 (35.00%)	1.00*
HTN	24 (60.00%)	23 (57.50%)	0.82*
Smoking	16 (40.00%)	9 (22.50%)	0.09*
Family H/O of CAD	14 (35.00%)	22 (55.00%)	0.07*
Prior CABG	0 (0%)	6 (15.00%)	0.03*

#Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD**.
***Chi-squared Test (χ^2)** was done to analyze the data and were presented as frequency (%)**.**

The mean age, monthly family income and BMI were 53.65±7.20 years, 16300.00±9265.87 taka and 23.39 ± 3.28 kg/m², respectively in combination therapy group and 50.93±6.66 years, 15125.00±9400.46 taka and 23.56 ± 3.79 kg/m², respectively in monotherapy group and they were statistically non-significant (p=0.08, p=0.58 and p=0.07, respectively). Gender was almost identical between the two groups (p=0.23). Regarding risk factors, there were no statistically significant difference between the two groups in terms of DM, HTN, smoking and family history of CAD (p=1.00, p=0.82, p=0.09 and p=0.07, respectively). But prior CABG was significantly increased in monotherapy group (p=0.03).

Table 2: Monitoring of serum triglyceride and total cholesterol at different time interval (4 patients in combination therapy group and 5 patients in monotherapy group dropped out).

Time of evaluation	Combination therapy group mean ± SD (mg/dl)	Monotherapy group	p-value#
Serum triglyceride			
At baseline	209.86±61.74	208.77±25.24	0.03, > 0.05
At 8 weeks	186.14±44.35	187.69±47.96	
At 12 weeks	171.72±44.16	171.71±43.47	
Serum total cholesterol			
At baseline	232.03±13.47	233.17±32.91	9.51, < 0.001
At 8 weeks	176.72±11.29	192.40±12.39	
At 12 weeks	132.92±17.58	158.43±20.99	

(#Data were analyzed with Repeated Measure ANOVA statistics and were presented as mean ± SD.)

The reduction of serum triglyceride between the two groups was found statistically non-significant ($p > 0.05$) but serum total cholesterol was significantly decreased in combination therapy group in comparison to monotherapy group ($p < 0.001$) (Table-02).

Table 3: Monitoring of serum LDL-cholesterol and HDL-cholesterol level at different time interval (4 patients in combination therapy group and 5 patients in monotherapy group dropped out).

Time of evaluation	Combination therapy group mean ± SD (mg/dl)	Monotherapy group	p-value#
Serum LDL-cholesterol			
At baseline	164.81±21.37	163.91±33.83	4.94, < 0.01
At 8 weeks	101.19±20.97	109.20±21.77	
At 12 weeks	78.89±16.50	94.80±25.24	
Serum HDL-cholesterol			
At baseline	39.22±4.19	39.80±1.76	0.21, > 0.05
At 8 weeks	41.00±2.22	41.11±2.22	
At 12 weeks	42.69±2.30	42.89±2.39	

(#Data were analyzed with Repeated Measure ANOVA statistics and were presented as mean ± SD.)

The reduction of serum LDL-cholesterol was significantly decreased in combination therapy group in comparison to monotherapy group ($p < 0.01$) but the rise of serum HDL-cholesterol between the two groups was found statistically non-significant ($p > 0.05$) (Table-03).

Table 4: Efficacy of combination therapy over monotherapy on the basis of achievement rate of LDL-C less than 70 mg/dl (Combination therapy group=36 and monotherapy group=35).

LDL-cholesterol	Group Combination therapy group Frequency (%)	Monotherapy group Frequency (%)	Total Frequency (%)
< 70 mg/dl	8 (80.00%)	2 (20.00%)	10 (14.10%)
≥ 70 mg/dl	28 (45.90%)	33 (54.10%)	61 (85.90%)
Total	36 (50.70%)	35 (49.30%)	71 (100.00%)

$\chi^2 = 3.99$, df=1, $p < 0.05$

The relationship of efficacy between combination therapy and monotherapy on the basis of achievement rate of LDL-C less than 70 mg/dl was found statistically significant ($p < 0.05$) (Table-04).

DISCUSSION AND CONCLUSION

Dyslipidemia is one of the main risk factors for coronary artery disease. Therefore, good management of dyslipidemia reduces the incidence of acute coronary artery disease. Atorvastatin, 10 mg to 80 mg, has been conventionally used in the control of hypercholesterolemia for many years. Combination therapy (low dose Atorvastatin plus Ezetimibe) is the newer addition as a therapeutic option for hypercholesterolemia due to its better efficacy, convenience, cost-effectiveness and fewer side effects. In this study, the reduction of serum triglyceride between the two groups was found to be statistically non-significant ($p > 0.05$). Similar findings were found in a study done by Watanabe *et al*.[8] where after 12 weeks of treatment, there was no significant difference in serum triglyceride level between the combination therapy and monotherapy groups. Similar findings were also found in the studies done by Nakamura *et al*.[9] and Li *et al*.[10]. But the findings were not similar to those of a study done by Ai *et al*.[11] where the overall effectiveness of combination therapy of Ezetimibe and Atorvastatin was significantly better than Atorvastatin monotherapy in lowering serum triglyceride. Contradictory findings were also found in the study done by Zhu *et al*.[12]

In the current study, the reduction of serum total cholesterol between the two groups was found to be statistically highly significant ($p < 0.001$). Similar findings were found in a study done by Watanabe *et al*.[8] where, after 12 weeks of treatment, the serum levels of total cholesterol showed a significant decrease in the combination therapy group compared to the monotherapy group. Similar findings were also found in the studies done by Ai *et al*.[11], Zhu *et al*.[12] and Nakamura *et al*.[9]. It has been demonstrated that preventing intestinal cholesterol absorption is crucial for both primary and secondary cardiovascular event prevention. In individuals with lower cholesterol absorbers, the clinical event prevention provided by statins was adequate; however, in patients with larger cholesterol absorbers, the prevention was inadequate. [13] In the present study, the reduction of serum LDL-cholesterol between the two groups was found to be statistically highly significant ($p < 0.01$). Similar findings were found in a study done by Watanabe *et al*.,[8] where, after 12 weeks of treatment, the serum levels of LDL-cholesterol showed a significant decrease in the combination therapy group compared to the monotherapy group. Similar findings were also found with the studies done by An *et al*.[5], Liu *et al*.[14], Ben-Yehuda *et al*.[15], Constance *et al*.[16], Ai *et al*.[11], Scheen[17], Zhu *et al*.[12], Conard *et al*.[18], Leiter *et al*.[19], Nakamura *et al*.[9] and Li *et al*.[10].

Previous studies reported that Ezetimibe added to statin therapy was the most effective strategy for LDL-C lowering in hyperlipidemic patients with high levels of baseline cholesterol absorption markers.[20] In this study, the rise of serum HDL-cholesterol between the two groups was found to be statistically non-significant ($p > 0.05$). Similar findings were found in a study done by Watanabe *et al*.[8] where after 12 weeks of treatment, there was no significant difference in HDL-cholesterol levels between the combination therapy and monotherapy groups. Similar findings were also found in the studies done by Nakamura *et al*.[9] and Li *et al*.[10]. But findings were not similar to those of a study done by Ai *et al*.[11] where the overall effectiveness of combination therapy of Ezetimibe and Atorvastatin was significantly better than Atorvastatin monotherapy on increasing HDL-cholesterol.

In this study, the relationship of efficacy between combination therapy and monotherapy on the basis of an achievement rate of LDL-C less than 70 mg/dl was found to be statistically significant ($p < 0.05$). Similar findings were found with the study done by An *et al*.[5] where the LDL-C level results achieved higher post-treatment targets in the combination therapy group (48.1%) compared to the monotherapy group (29.9%) with $p < 0.05$. Similar findings were also found with the studies done by Dai *et al*.[21].Many previously published reports support the efficacy of Ezetimibe added to a statin for LDL-C lowering and the achievement of NCEP ATP III recommended LDL-C targets in patients 65 years and older. In patients > 75 years, Ezetimibe add-on resulted in numerically greater changes in most lipids than doubling and quadrupling the Atorvastatin dose, although the

magnitude of differences between the treatment groups diminished after uptitration to Atorvastatin 40 mg. These results demonstrate improved LDL-C reduction with the addition of Ezetimibe even when using the lowest dose of Atorvastatin (10 mg) in patients older than 65 years, consistent with previous reports indicating that adding of Ezetimibe to the recommended starting and next higher dose of Atorvastatin is more effective than doubling the dose of Atorvastatin regardless of age.[18,19] These findings correlate with our present study. Acute coronary syndrome is now a global epidemic. There are several causes behind it. Hypercholesterolemia is a significant one among them. Based on the discussion above, we have determined that in hypercholesterolemic patients with acute coronary syndrome (ACS), combination therapy involving low-dose Atorvastatin and Ezetimibe (10 mg) reduces LDL-C better than Atorvastatin (20 mg) monotherapy.

CONCLUSION

The study concluded that the LDL-C reaches the target levels in the combination therapy group in comparison to monotherapy group. Combination therapy also reduces serum total cholesterol more effectively than monotherapy. The Atorvastatin plus Ezetimibe combination produced more favorable improvements in most lipids in comparison to double or quadruple the Atorvastatin dose. According to this finding, this combination therapy might be the right therapeutic approach for hypercholesterolemic patients with acute coronary syndrome (ACS).

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Authors' contributions:

MA, SA, SYM and MAH: Concept and design, data acquisition, interpretation, drafting and final approval. RKG, RK, NA, MHR and MMI: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Declarations

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Conflict of interest

Authors declared no conflict of interest.

Ethical approval

Ethical approval of the study was obtained from the Ethical Review Committee, Rajshahi Medical College, Rajshahi. Informed consent was taken from all participants. All the study methodology was carried out following the relevant ethical guidelines and regulations.

Consent for publication: Taken.

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