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The Effect of Atorvastatin Plus Ezetimibe Therapy Versus Atorvastatin Monotherapy On Clinical Outcome in Acute ST-Segment Elevation Myocardial Infaction(STEMI)

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Abstract

Introduction:*An acute ST-elevation myocardial infarction (STEMI) is an event in which transmural myocardial ischemia results in myocardial injury or necrosis. The current 2018 clinical definition of myocardial infarction (MI) requires the confirmation of the myocardial ischemic injury with abnormal cardiac biomarkers. Acute coronary syndrome is the leading cause of death in the world and this is a consequence of unstable plaque due to dyslipidemia, reviewing with elevated LDL cholesterol. Reduction in LDL-c repeated clinical outcomes in patients with the acute coronary syndrome.* ***Objectives:*** *To assess the effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on clinical outcome in acute ST-Segment Elevation Myocardial Infaction(STEMI).* ***Materials and Methods:*** *A cross-sectional study was performed at dept. of Cardiology, Parkview Medical College, Sylhet, Bangladesh from June to December 2022. A total of 50 patients were evaluated in the study, including 42 patients with acute coronary syndrome with LDL-c levels≥70mg/dL at Can Tho Central General Hospital, we divided randomly into 2 groups: group A: control LDL-c by atorvastatin 40mg and ezetimibe 10mg; group B: control LDL-c by atorvastatin 40mg monotherapy. Then we compared the effect of control LDL-c between two groups after 10 follow-up days.* ***Results:*** *50 patients with acute coronary syndrome: 60.0% male and 40.0% female, the average age was 66.03 ± 12.06 years, 82.0% LDL- c levels ≥7 mg/dL. After 10 days of treatment, the target LDL-c concentration in the group treated with atorvastatin 40mg+ ezetimibe 10mg was 48.1%, in the group treated with atorvastatin 40mg was 29.9% ($p<0.05$).* ***Conclusion:*** *: LDL-c ratio reaches the target in the treatment group by atorvastatin 40mg + ezetimibe 10mg was 48.1% in the treatment group with atorvastatin 40 mg was 29.9% ($p<0.05$). From the results of our study, we recommend the combination therapy of atorvastatin and ezetimibe control LDL-c in patients with acute coronary syndrome better than atorvastatin monotherapy, thus physicians to treat patients with the acute coronary syndrome should combine early atorvastatin with ezetimibe since hospitalization.*

Keywords: *Acute coronary syndrome; LDL-C; Atorvastatin combination with ezetimibe.*

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Introduction:

An acute ST-elevation myocardial infarction (STEMI) is an event in which transmural myocardial ischemia results in myocardial injury or necrosis[1]. The current 2018 clinical definition of myocardial infarction (MI) requires the confirmation of the myocardial ischemic injury with abnormal cardiac biomarkers[2]. It is a clinical syndrome involving myocardial ischemia, EKG changes and chest pain. Acute coronary syndrome (ACS) is defined as acute ST-segment elevation myocardial infarction (MI), non-ST segment

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elevation MI, and unstable angina. Intensive lipid-lowering therapy is important in patients with the acute coronary syndrome (ACS). This is an emergency disease that needs to be diagnosed and treated early with high mortality. The most common cause is dyslipidemia, mainly with elevated LDL-c. Increased LDL-c will disturb the function of endothelial blood vessels, lipid accumulation in the walls of arteries, leading to atherosclerosis, narrowing of the arteries, clogged arteries, resulting in myocardial ischemia, ACS[3,4]. Myocardial infarction in general can be classified[5] from Type 1 to Type 5 MI based on the etiology and pathogenesis. Type 1 MI is due to acute coronary atherothrombotic myocardial injury with plaque rupture. Most patients with ST-segment elevation MI (STEMI) and many with nonST-segment elevation MI (NSTEMI) comprise this category. Type 2 MI is the most common type of MI encountered in clinical settings in which is there is demand-supply mismatch resulting in myocardial ischemia. This demand supply mismatch can be due to multiple reasons including but not limited to presence of a fixed stable coronary obstruction, tachycardia, hypoxia or stress. However, the presence of fixed coronary obstruction is not necessary. However, reaching the LDL-c target is not easy, even with the maximum dose of atorvastatin. The guideline suggests that low-density lipoprotein cholesterol (LDL-c) should be the primary target, so the treatment goal of LDL-c is <70mg/dL for patients with ACS. Statins are usually the first-line therapy. High-intensity statins are preferred, and up-titration to the highest recommended and tolerable dose to reach the target is necessary. Combination therapy with statins and ezetimibe can also be considered. Ezetimibe is one kind of lipidlowering drug known as cholesterol absorption inhibitors that have a different metabolic pathway with statins repeated cardiovascular outcomes in patients with the acute coronary syndrome and does not increase the side effects of atorvastatin[6].

Materials and Methods:

A cross-sectional study was performed at dept. of Cardiology, Parkview Medical College, Sylhet, Bangladesh from June to December 2022. A total of 50 patients were evaluated in the study, including 42 patients with acute coronary syndrome with LDL-c levels≥70mg/dL at Can Tho Central General Hospital, we divided randomly into 2 groups: group A: control LDL-c by atorvastatin 40mg and ezetimibe 10mg; group B: control LDL-c by atorvastatin 40mg monotherapy. Then we compared the effect of control LDL-c between two groups after 10 follow-up days. Patients diagnosed with ACS (ST-segment elevation myocardial infarction (MI), non-ST segment elevation MI and unstable angina) following the 2014 American Heart Association Standards7. Exclusion criteria were patients who had a renal failure with serum creatinine>2mg/dL, abnormal liver enzymes, muscle diseases, active hepatitis, secondary hyperlipidemia, or who refused to participate in the study. Statistical analysis was performed by using SPSS Statistics version 20.0.0 computer software. After making the diagnosis of acute ST-elevation myocardial infarction, intravenous access should be obtained, and cardiac monitoring started. Patients that are hypoxemic or at risk for hypoxemia benefit from oxygen therapy; however, recent studies show possible deleterious effects in normoxic patients [8, 9]. Patients should undergo percutaneous coronary intervention (PCI) within 90 minutes of presentation at a PCI capable hospital or within 120 minutes if transfer to a PCI capable hospital is required [10]. If PCI is not possible within the first 120 minutes of first medical contact, fibrinolytic therapy should be initiated within 30 minutes of patient arrival at the hospital [10]. It is important to rule out conditions that can mimic an acute coronary syndrome like acute aortic dissection or acute pulmonary embolism.

Result:

Table I: Baseline clinical characteristics (n = 50)

Characteristic	Mean ± SD or n (%)
Age (year)	66.03 ± 12.06
Male sex, n (%)	30 (60.0)
BMI mean (Kg/m^2 ± SD)	22.59 ± 3.26
Hypertension	40 (80.0)
Diabetes	11 (22.0)
Lack of physical activity	29 (58.0)
Smoking	23(46.0)
Family history of cardiovascular diseases	2(4.0)

This study included 50 patients diagnosed with ACS. The average age of the patient was 66.03 ± 12.06 years; 60.0 % were male.

Table II: LDL-c levels ≥70mg/dl mg/dL (N=50)

LDL-c levels ≥70 mg/dL	Frequency (n = 50)	Proportion (%)
Yes	41	82.0
No	9	18.0
Total	50	100

Comment: 82.0% patients with ACS had LDL-c levels ≥ 70mg/dl. Target LDL-c levels after treatment in ACS patients.

Table III: Baseline characteristics in the two groups before treatment (n=40)

Characteristics	Group A (n = 21)	Group B (n = 20)	P
Female, n (%)	15 (48.4)	16 (51.6)	0.282
Age, mean	64.67	67.23	0.258
BMI, Kg / m^2	22.37	22.92	0.254
MI with ST-segment elevation n (%)	6(60.0)	4 (40.0)	0.531
LDL-c levels (mmol/L)	3.65	3.30	0.103

Comment: Baseline characteristics of the two groups including sex, age, BMI, percentage of STEMI, and LDL-c levels showed no significant difference (all p-value>0,05).The proportion of patients achieving target LDL-c levels after the treatment therapies.

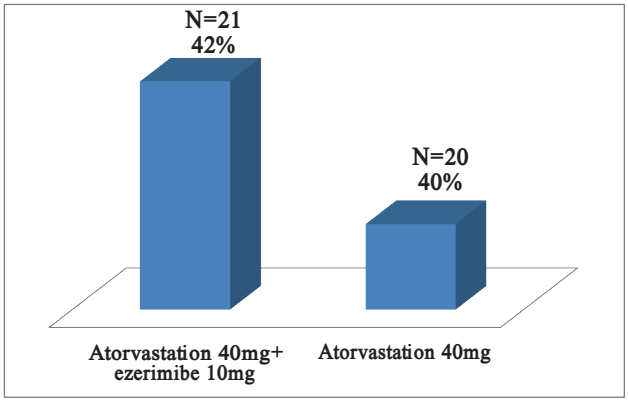

Figure 1: Rate of target LDL-c levels after 10 days of follow-up.

The LDL-c levels results achieved higher post-treatment targets in group A (42%) compared to group B (40%) with p<0.05.

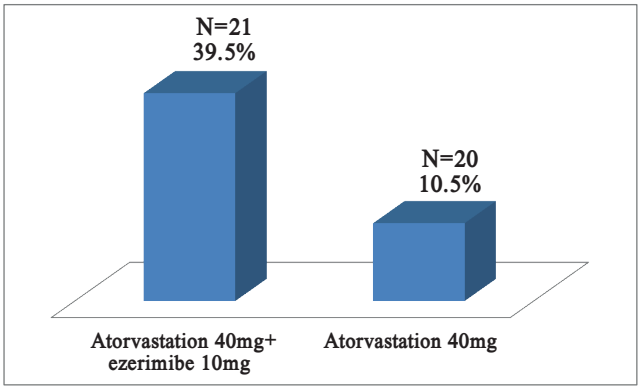

Figure 2: LDL-c levels decreased 50% after 10 days of followup.

The percentage of LDL-c concentration decreased by 50% in the combination treatment in group A (39.5%) which was higher than that in group B (10.5%), with p<0.05.

Table IV: LDL-c levels before and after treatment (N=40)

Group	LDL-c levels (mmol/L)		P
	Before treatment	After treatment	
A (n = 21)	3.65 ± 1.09	1.92 ± 0.58	<0.05
B (n = 20)	3.30 ± 1.09	2.27 ± 0.76	<0.05
Total	3.48 ± 1.10	2.09 ± 0.69	<0.05

Comment: LDL-c levels after treatment in group A (1.92 ± 0.58mmol/L) were lower than group B (2.27 ± 0.76 mmol/L) with p<0.05.

Table V: Mean LDL-c levels reduction before and after treatment (N=40)

Group	LDL-c levels (mmol/L)	
	Before treatment	After treatment
A (n = 21)	3.65±1.09	1.92±0.58
B (n = 20	3.30±1.09	2.27±0.76
p	0.103	<0.05

Comment: Decreasing LDL-c levels from baseline were significantly greater with the recommended usual dose of group A (3.65±1.09 to 1.92 ± 0.58) with p<0.05, group B (3.30 ± 1.09 to 2.27 ± 0.76) with p<0.05.

Table VI: Side effects of medications (N=40)

Symptoms	Group A (n = 21)		Group B (n = 20)	
	(n)	(%)	(n)	(%)
Increase AST	0	0.00	1	5.00
Increase ALT	2	9.5	2	10.0
Increase CK	0	0.00	1	5.00
Muscle symptoms	0	0.00	0	0.00
Digestive disorder	0	0.00	0	0.00

Comment: Nobody had muscle symptoms and digestive disorder. An elevation of creatine kinase (CK) from 5 or more to less than 10 times the upper limit of normal (ULN) occurred in 1 patient (5.0%) treated in group B. Consecutive elevation of ALT to 3 or more times to the ULN was observed in group A in 2 patients (9.5%) and 2 patients (10.0%) in group B. One patient (5.0%) had a consecutive elevation of aspartate aminotransferase (AST) treated in group B.

Discussion:

For an acute thrombotic coronary event to cause ST-segment elevation on a surface ECG, there needs to be a complete and persistent occlusion of blood flow. Coronary atherosclerosis and presence of high risk thin cap fibroatheroma (TCFA) can result in sudden onset plaque rupture[11]. This results in changes in vascular endothelium resulting in cascade of platelet adhesion , activation and aggregartion[12] resulting in thrombosis formation. Coronary artery occlusion in animal models shows a "wave-front" of myocardial injury that spreads from the sub-endocardial myocardium to the sub-epicardial myocardium resulting in a transmural infarction that appears as an ST elevation on surface ECG[13]. Myocardial damage occurs as soon as the blood flow is interrupted which makes timely management a necessity. Sudden onset acute ischmemia can result in severe microvascualr dysfunction. The mean age of the patients was 66.03 ± 12.06 years. Male patients accounted for 60.0%. Other studies also showed that the mean age was similar to that of author Nguyen Hoang Tai My which recorded the mean age of patients was 63 ± 11.8 years, male patients accounted for 69.9% [14]; Duong Dinh Chinh studied 764 cases of ACS recorded a mean age of patients was 66.63 ± 12.54 years [15]; The mean age of 14,213 ACS patients was 57.6 ± 9.3 years in Toth PP. et al. study [16]; Andrikopoulos G et al. studied 800 patients with ACS in 37 hospitals in Greece showed that male patients accounted for 78% which was three times higher than female patients [17]. In our study, 82.0% of patients had LDL- e levels ≥70mg/dl. This result is similar to that of the authors Nguyen Ngoc Quang and Dam Trung Hieu who performed cross- sectional descriptive studies on 819 patients with acute MI with an increase in LDL-c, accounting for 66.83%. The rate of atherosclerotic dyslipidemia was 77.46% [14]. In Chau Ngoc

Hoa and Nguyen Vinh Trinh study at Cho Ray Hospital from February 2015 to June 2015, patients who had LDL- c ≥70 mg% at admission was 88.41% [18]. In Jiang J et al. study, 2034 Chinese patien ts who experienced acute coronary syndrome associated with LDL-c disorders were 61.5% [19]. Dyslipidemia is one of the main factors of coronary artery disease. However, this is a reversible risk factor. Therefore, good management of dyslipidemia reduces the incidence of acute coronary artery disease. There was a correlation with the results of the two groups: the percentage of patients achieving LDL-C target in the combination group was higher than the monotherapy group (48.9% and 29.9% respectively, p = 0.019). In terms of the target of 50% reduction of LDL- c concentration, the proportion in the group treated with atorvastatin 40mg in combination with ezetimibe 10mg was two times higher than in the group treated with atorvastatin 40mg 37.0% and 13.0%, respectively (p <0.05). Dai YY et al. studied in 202 patients with acute coronary syndrome with percutaneous coronary intervention and dyslipidemia were divided into 2 groups: a group treated with atorvastatin + ezetimibe and the group treated with atorvastatin alone. After one month, the reduction in LDL-C was significantly higher in the ezetimibe-statin combination group than the 40mg statin group (p <0.001). The proportion of patients achieving LDL-C targets was higher in the ezetimibe-statin combination group (69.1%, p = 0.007) and the statin group 80mg (67.9%, P = 0.047) compared with the statin group 40mg (46.9%) at 1 month after the PCI [20]. Estimated that 55% of cholesterol is absorbed in the digestive tract (heavily influenced by genetic factors). Although the mechanism of cholesterol absorption is unknown, Niemann-Pick C1 Like 1 protein (NPC1L1) has been identified in the intestinal epithelial cells to be shown to play an important role in this mechanism. Statins reduce the synthesis of cholesterol in the liver through inhibition of HMG-CoA reductase. Many studies show that a decrease in cholesterol synthesis in the liver under the effect of statins is offset by an increase in intestinal cholesterol absorption. When high doses of statins will increase intestinal NPC1L1 expression increases the statist's limited LDL-c reduction. Liu Y et al. (2017) studied in 230 ACS patients recorded LDL-c before treatment in the combination group (2.2 ± 0.6mmol/L) higher than the monotherapy group (2.3 ± 0.8mmol/L). After treatment, LDL-c concentration decreased in the combination group was 1.4± 0.5mmol/L and in the monotherapy, group was 1.5 ± 0.6mmol/L and this difference was statistically significant [21]. This result is similar to our research's result that the LDL- c concentration after treatment in the atorvastatin 40mg group combined with ezetimibe 10mg was 1.92 ± 0.58mmol/L lower than the control with group Atorvastatin 40mg was 2.27 ± 0.76mmol/L and this difference was statistically significant with p=0.008. The LDL-c concentration value decreased after treatment in the atorvastatin group 40mg combined with ezetimibe 10mg was 1.72 ± 1.05 mmol/L higher than the group treated with atorvastatin 40mg only 1.03 ± 0.90 mmol/L with p <0.05. Therefore, controlling LDL-c by combining atorvastatin 40mg and ezetimibe 10mg as soon as possible after admission is necessary for the acute coronary syndrome. Nobody had muscle symptoms and digestive disorder. A creatine kinase (CK) elevation 5 or more to less than 10 times the upper limit of normal (ULN) occurred in 1 patient (5.0 %) treated in group B. Consecutive elevation of ALT to 3 or more times to the ULN were observed in group A in 2 patients (9.5%) and 2 patients (10.0%) with group B. One patient (5.0%) had a consecutive elevation of aspartate aminotransferase (AST) treated in group B. IMPROVE-IT research results noted the side effects of the drug include: 2.5% increase in liver enzymes, adverse reactions in the gallbladder 3.1%, myalgia 0.1%, stretch 0.2% [22]. It is possible that our study had (Our study may have) a short follow-up period (10 days) so we have not fully noted the side effects of the drug which needs to follow up with longer time. Prior to performing an ECG and collecting troponins the history and physical provide the only clues that lead to a diagnosis of myocardial infarction. Initial evaluation should include a focused physical examination and a brief history. Patients should be asked about the characteristics of the pain and associated symptoms, risk factors or history of cardiovascular disease, and recent drug use [7]. Risk factors for an ST-elevation myocardial infarction include age, gender, family history of premature coronary artery disease, tobacco use, dyslipidemia, diabetes mellitus, hypertension, abdominal obesity, sedentary lifestyle, a diet low in fruits and vegetables, psychosocial stressors [23]. Cocaine use can cause an ST-elevation myocardial infarction regardless of risk factors [24] . History of known congential abnormalities can be helpful[25].

Conclusions:

LDL-c ratio reaches the target in the treatment group by atorvastatin 40mg + ezetimibe 10mg was 48.1% in the treatment group with atorvastatin 40 mg was 29.9% (p<0.05). From the results of our study, we recommend the combination therapy of atorvastatin and ezetimibe control LDL-c in patients with acute coronary syndrome better than atorvastatin monotherapy, thus physicians to treat patients with the acute coronary syndrome should combine early atorvastatin with ezetimibe since hospitalization.

Conflict of Interest: None.

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