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COMPARISON OF THE EFFECT OF ATORVASTATIN PLUS EZETIMIBE THERAPY VERSUS ATORVASTATIN MONOTHERAPY ON PATIENTS WITH ACUTE CORONARY SYNDROME AT CAN THO CENTRAL GENERAL HOSPITAL 2018-2019

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ABSTRACT

Background: *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. The combination therapy of atorvastatin and ezetimibe produces reductions in LDL-c compared to atorvastatin monotherapy.* ***Objective:*** *To compare the effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on patients with the acute coronary syndrome at Can Tho Central General Hospital.* ***Subjects and methods:*** *A cross-sectional study was performed. A total of 193 patients were evaluated in the study, including 158 patients with acute coronary syndrome with LDL-c levels ≥70 mg/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:*** *193 patients with acute coronary syndrome: 60.6% male and 39.4% female, the average age was 66.03 ± 12.06 years, 81.9 % LDL-c levels ≥70 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).* ***Conclusions:*** *the combination therapy of atorvastatin and ezetimibe controls LDL-c in patients with the acute coronary syndrome better than atorvastatin monotherapy.*

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

I. INTRODUCTION

Acute coronary syndrome (ACS) is defined as acute ST-segment elevation myocardial infarction (MI), non-ST segment 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 [1], [2].

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 lipid-lowering 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 [3]. In Vietnam, there has not been any research on the comparison of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on patients with the acute coronary syndrome and changes in LDL-c levels after treatment, thus we did this study with these objectives:

1. To identify the proportion of the increase LDL-c in patients with the acute coronary syndrome at Can Tho General Hospital from September 2018 to September 2019.
2. To compare the effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on patients with the acute coronary syndrome at Can Tho General Hospital from September 2018 to September 2019.

II. METHODS

2.1. Study population: All patients diagnosed with ACS were admitted to Can Tho Central General Hospital from September 2018 to September 2019.

Clinical enrollment criteria: Patients diagnosed with ACS (ST-segment elevation myocardial infarction (MI), non-ST segment elevation MI and unstable angina) following the 2014 American Heart Association Standards [4].

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.

Place and time to study: The study was conducted from September 2018 to September 2019 at Can Tho Central General Hospital, Can Tho City, Vietnam.

2.2. Study design:

Study design: A prospective cross-sectional study was conducted.

Sample size and sampling method: 193 patients diagnosed with ACS from September 2018 to September 2019 were numbered from 1 to 193.

Including 158 patients ACS with LDL-c levels ≥70mg/dL, we randomly divided into 2 groups A and B:

- Group A (odd numbers): control LDL-c by atorvastatin 40mg and ezetimibe 10mg.
- Group B (even numbers): control LDL-c by atorvastatin 40mg monotherapy.

2.3. Study contents*:* Baseline clinical characteristics, increase LDL-c, and compare the effect to control the LDL-c level between atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on patients with acute coronary syndrome after 10 days follow-up.

Methods of evaluating: Clinical examination, blood sample, interventional treatment by atorvastatin 40 mg plus ezetimibe 10 mg (group A) or atorvastatin 40 mg (group B), and 10 follow-up days.

2.4. Statistical Analysis*:* Statistical analysis was performed by using SPSS Statistics version 20.0.0 computer software.

III. RESULTS: This study included 193 patients diagnosed with ACS, the result as:

3.1. Baseline clinical characteristics

Table 1. Baseline clinical characteristics (n = 193).

Characteristic	Mean ± SD or n (%)
Age (year)	66.03 ± 12.06
Male sex, n (%)	117 (60.60)
BMI mean (Kg/m^2 ± SD)	22.59 ± 3.26
Hypertension	155 (80.3)
Diabetes	44 (22.8)
Lack of physical activity	114 (59.1)
Smoking	91(47.2)
Family history of cardiovascular diseases	8(4.1)

Comment: The average age of the patient was 66.03 ± 12.06 years; 60.6 % were male.

3.2. Increase LDL-c levels proportion

Table 2. LDL-c levels ≥70 mg/dL.

LDL-c levels ≥70 mg/dL	Frequency (n = 193)	Proportion (%)
Yes	158	81.90
No	35	18.10
Total	**193**	**100**

Comment: 81.90% patients with ACS had LDL-c levels ≥70mg/dL.

3.3. Target LDL-c levels after treatment in ACS patients

3.3.1. Baseline characteristics in the two groups before treatment

Table 3. Baseline characteristics in the two groups before treatment.

Characteristics	Group A (n = 81)	Group B (n = 77)	p
Female, n (%)	30 (46.20)	35 (53.80)	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 (%)	44 (55.70)	35 (44.30)	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).

3.3.2. The proportion of patients achieving target LDL-c levels after the treatment therapies

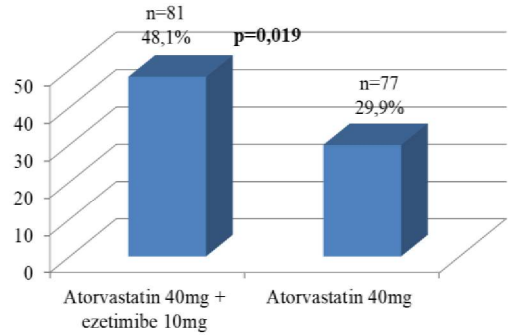

Figure 1. Rate of target LDL-c levels after 10 days of follow-up.

Comment: The LDL-c levels results achieved higher post-treatment targets in group A (48.1%) compared to group B (29.9 %) with p<0.05.

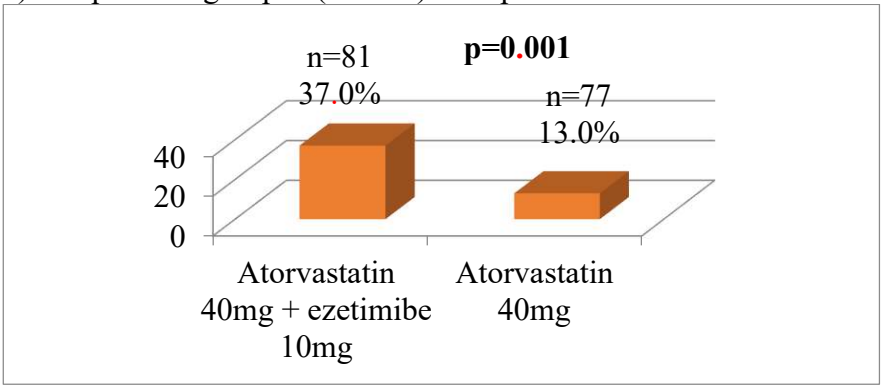

Figure 2. LDL-c levels decreased 50% after 10 days of follow-up.

Comment: The percentage of LDL-c concentration decreased by 50% in the combination treatment in group A (37.0%) which was higher than that in group B (13.0%), with p<0.05.

3.3.3. LDL-c levels before and after treatment

Table 4. LDL-c levels before and after treatment.

Group	LDL-c levels (mmol/L)	
	Before treatment	After treatment
A (n = 81)	3.65±1.09	1.92±0.58
B (n = 77)	3.30±1.09	2.27±0.76
p	**0.103**	**<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.

3.3.4. Mean LDL-c levels reduction before and after treatment

Table 5. Mean LDL-c levels reduction before and after treatment.

Group	LDL-c levels (mmol/L)		p
	Before treatment	After treatment	
A (n = 81)	3.65 ± 1.09	1.92 ± 0.58	**<0.05**
B (n = 77)	3.30 ± 1.09	2.27 ± 0.76	**<0.05**
Total	3.48 ± 1.10	2.09 ± 0.69	**<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.

3.3.5. Side effects of medications

Table 6. Side effects of medications.

Symptoms	Group A (n = 81)		Group B (n = 77)	
	(n)	(%)	(n)	(%)
Increase AST	0	0.00	2	2.60
Increase ALT	5	6.20	6	7.80
Increase CK	0	0.00	1	1.30
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 (1.3%) treated in group B. Consecutive elevation of ALT to 3 or more times to the ULN was observed in group A in 5 patients (6.2%) and 6 patients (7.8%) in group B. Two patients (2.6%) had a consecutive elevation of aspartate aminotransferase (AST) treated in group B.

IV. DISCUSSION

4.1. General characteristics of the subjects

The mean age of the patients was 66.03 ± 12.06 years. Male patients accounted for 60.6%. 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% [5]; Duong Dinh Chinh studied 764 cases of ACS recorded a mean age of patients was 66.63 ± 12.54 years [6]; The mean age of 14,213 ACS patients was 57.6 ± 9.3 years in Toth PP. et al. study [7]; 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 [8].

4.2. LDL-c levels

In our study, 81.9% of patients had LDL-c 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% [9]. 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 were 88.41% [10]. In Jiang J et al. study, 2034 Chinese patients who experienced acute coronary syndrome associated with LDL-c disorders were 61.5% [11].

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.

4.3. The proportion of patients achieving target LDL-C after treatment

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 [12].

LDL-c concentration after treatment

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 [13]. 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.

Side effects of medications

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 (1.3 %) treated in group B. Consecutive elevation of ALT to 3 or more times to the ULN were observed in group A in 5 patients (6.2%) and 6 patients (7.8%) with group B. Two patients (2.6%) 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% [15]. 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.

V. 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: The authors declare that they have no conflict of interest.

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