Research Article

Efficacy of rosuvastatin and atorvastatin in Vietnamese patients with acute coronary syndrome: A randomized trial

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ABSTRACT

High-intensity statins have been recommended to initiate in patients after acute coronary syndrome (ACS) to reduce the risk of death and recurrent cardiovascular events. There have been few studies comparing the effectiveness of high-intensity statins in Vietnam. Therefore, we conducted a randomized controlled trial to compare the effects of rosuvastatin versus atorvastatin in Vietnamese patients with ACS. A total of 96 ACS patients were randomized into 2 groups at a ratio of 1:1 to receive rosuvastatin 20 mg/day or atorvastatin 40 mg/day in addition to the standard treatment of ACS. LDL-c and hs-CRP levels were measured before and after the intervention for analysis. No significant differences were found between the two groups at baseline. LDL-c levels were significantly reduced from baseline to 4-day in both groups ($p<0.001$ in both groups), but the difference in LDL-c levels at 4-day between the groups was not statistically significant ($p=0.251$). hs-CRP did not increase significantly in the rosuvastatin group but significantly in the atorvastatin group ($p=0.209$ and $p<0.001$, respectively). hs-CRP at 4-day was not significantly different between the two groups ($p=0.250$). The proportion of LDL <1.8 mmol/L after 4 days in the rosuvastatin group was significantly higher than that of the atorvastatin group (OR=4.592; 95% CI 1.365-15.449; $p=0.014$). There was no significant difference in the LDL-c reduction ≥50% and hs-CRP ≤3 mg/L at 4-day between two groups. In conclusion, rosuvastatin is more effective than atorvastatin in achieving LDL-c targets of <1.8 mmol/L after 4 days in Vietnamese patients with ACS.

Keywords:
Acute coronary syndrome, Atorvastatin, High-sensitivity C-reactive protein (hs-CRP), Low-density lipoprotein cholesterol (LDL-c), Rosuvastatin.

1. INTRODUCTION

Ischemic heart disease, including acute coronary syndrome (ACS), is the leading cause of morbidity and mortality worldwide. It caused more than 9 million deaths globally in 2016, according to World Health Organization statistics[1,2]. The increase of low-density lipoprotein cholesterol (LDL-c) and high-sensitivity C-reactive protein (hs-CRP) in patients with ACS has been shown to be associated with the increase of mortality and recurrent adverse cardiovascular events[3-5]. Therefore, reducing LDL-c and hs-CRP have become important

targets for treatment in ACS[6-8].

Statins have been recommended as the first choice to lower LDL-c levels[6]. Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting 3-hydroxyl-3-methylglutaryl coenzyme A reductase activity. Statins are effective in reducing triglycerides, LDL-c and total cholesterol. Besides, they also slightly increase high-density lipoprotein cholesterol[9]. In addition to their beneficial effects on blood lipids, statins have been shown to reduce hs-CRP levels[10].

American and European Guidelines have recommended initiating high-intensity statins as soon as

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possible and prolonged maintaining in patients after ACS to cut down the risk of death and secondary cardiovascular events, regardless of baseline LDL-c[6,8,11-13]. The target for LDL-c is <1.8 mmol/L (70 mg/dL) or LDL-c reduction by at least 50% of the baseline value[12,13]. High-intensity statins are the statins that effectively lower LDL-c by approximately >50%, including atorvastatin at doses of 40 mg/day or 80 mg/day; and rosuvastatin at doses of 20 mg/day or 40 mg/day[14].

Different statins with different doses have different levels of LDL-c reduction. There are different levels of response among individuals even with the same dose of statin. The variation in response to statin treatment may be due to differences in genes that regulate cholesterol metabolism as well as statin absorption and metabolism in the liver[13].

In recent years, several studies have been done to compare the effects of high-intensity statins in patients after ACS around the world. Rosuvastatin seems to be more effective than atorvastatin in reducing LDL-c and hs-CRP levels[15,16]. However, very few clinical trials have been conducted in Vietnam to discuss this issue. Therefore, we conducted this study with the purpose of comparing the effects of rosuvastatin versus atorvastatin in Vietnamese patients after acute coronary syndrome.

2. MATERIALS AND METHODS

2.1. Study design and setting

We conducted an open-label, parallel-group, single-center, randomized trial to compare the effects of treatment with rosuvastatin versus atorvastatin in Vietnamese patients after acute coronary syndrome. The study was performed at Can Tho University of Medicine and Pharmacy Hospital in Vietnam from June 2017 to April 2019.

2.2. Study population

The study population consisted of patients over 18 years of age in both genders admitted to the hospital with the diagnoses of acute coronary syndrome and with baseline LDL-c levels of 1.8 mmol/L and above. Acute coronary syndrome included ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA) according to the European Society of Cardiology criteria[6,8].

We excluded patients who were already using statins and/or other hypolipidemic drugs, and/or any other drug which strongly inhibits CYP3A4 (anti-retroviral drugs, ketoconazole, itraconazole, clarithromycin) or CYP2C9 (fluconazole), patients with any history of hypersensitivity or allergy to statins or any contraindication to the use of statins, patients with severe cardiac dysfunction (ejection fraction <30%), and any other comorbidity including severe anemia, malignancy, chronic liver disease, chronic renal failure, pregnancy or lactation. Patients who had a history of operation or injury within 2 months were also excluded from the study.

2.3. Sample size

The sample size of this study was calculated based on information from the study on the efficacy and tolerability of rosuvastatin and atorvastatin in patients with primary hypercholesterolemia[17]. In the study, the proportion of LDL-c <1.8mmol/L after treatment with high doses of rosuvastatin and atorvastatin in the high-risk group was estimated at 37% and 12%, respectively. We assumed that the probability of a type 1 error (alpha) was 0.05 (95% confidence level) and that type 2 error (beta) was 0.20 (80% power). Therefore, the minimum sample size needed for each group was 36 participants. Nevertheless, to prevent loss of follow-up, the sample size was increased by 20%. In fact, we recruited 48 patients per group.

2.4. Randomization and intervention

Patients who met the criteria of the study and signed the informed consent were randomized at a 1:1 ratio into either group A or group B based on their inpatient code. Each patient has an inpatient code provided by the nurses from the clinic on admission. Group A included the patients whose inpatient codes were even numbers. Group B included the patients whose inpatient codes were odd numbers. Group A received 20 mg rosuvastatin daily and group B received 40 mg atorvastatin daily along with standard treatment including aspirin, clopidogrel, beta-blockers, nitrates, and an angiotensin-converting enzyme inhibitor.

2.5. Data collection

Firstly, we collected data from medical records and via face to face interviews included general characteristics (age, gender, body mass index), coronary artery disease risk factors (hypertension, diabetes, dyslipidemia, lack of physical activity, overweight or obesity, smoking, early coronary artery disease family history), medical history and comorbidities (current medications, drug allergies, severe anemia, severe heart failure, malignancy, chronic renal failure, chronic liver disease, pregnancy or lactation, operation or injury within 2 months) and diagnosis. Serum low-density lipoprotein cholesterol (LDL-c) and high-sensitivity C-reactive protein (hs-CRP) were recorded for all patients

at baseline (before starting therapy). Next, eligible patients and their relatives were consulted to agree on participation in the study. They were clearly explained the objectives and process of the research. The patients who voluntarily took part in the study signed into informed consent. Then, these patients were randomized into intervention groups. Finally, serum LDL-c and hs-CRP were recorded again after four-day treatment.

Serum LDL-c levels were measured by the chemistry autoanalyzer (ARCHITECT ci4100, Abbott Diagnostics, USA) via enzymatic colorimetric methods. Serum hs-CPR levels were determined with the enzyme-linked immunosorbent assay technique by the chemistry autoanalyzer (ARCHITECT ci4100, Abbott Diagnostics, USA).

2.6. Study outcomes

Primary outcome measures included levels of hs-CRP and LDL-c after 4 days of treatment. Secondary outcomes included (1) the proportion of patients achieving the LDL-c goal of <1.8 mmol/L after 4 days; (2) the proportion of patients achieving an LDL-c reduction of at least 50%; (3) proportion of patients with hs-CRP ≤ 3 mg/L after 4 days.

2.7. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 20th (SPSS 20). The distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation if normally distributed and as median (interquartile range) if non-normally distributed. Categorical variables were recorded as frequency (percentage). Continuous variables with normal distribution were compared within groups by using independent sample t-test and between two groups by using paired sample t-test. Continuous variables without normal distribution were compared within groups by using the Mann-Whitney's U test and between two groups by using Wilcoxon signed-rank test. Categorical variables were compared using Chi-square test. Univariable and multivariable logistic regression models were used to estimate the odds ratio (OR) with 95% confidence interval (CI) of the outcomes. The variables entered on step 1 of the multivariate analysis included intervention status, age and gender. All tests were two-sided. A p-value <0.05 was considered to be statistically significant for all tests.

2.8. Ethical approval

The study was approved by the biomedical research ethics committee and the management board of the study hospital in May 2017 with the number 34.2017/HDDD-DHYDCT.

3. RESULTS

A total of 106 patients presenting with ACS were assessed for eligibility. Of these, 96 (90.6%) patients were included; 10 (9.4%) patients were excluded due to exclusion criteria. Of 96 patients included, 48 were randomized to the group received rosuvastatin 20mg daily and 48 to the group received atorvastatin 40mg daily. The follow-up took 4 days. All patients were measured serum LDL-c and hs-CRP levels before and after intervention for analysis (Figure 1).

The mean age (SD) was 63.0 (12.0) years and patients aged ≥ 60 years were more common (61.5%). 67.7% were males and median (IQR) Body Mass Index was 23.7 (21.8; 24.6) kg/m^2. Risk factors for coronary artery disease that predominated in our patients included hypertension, dyslipidemia, physical inactivity, overweight or obesity and smoking. The majority of patients had a diagnosis of non-ST elevation acute coronary syndrome (53.1%). Mean LDL-c level was 3.38 mmol/L with standard deviation of 0.92 mmol/L. Median hs-CRP level of these patients was 4.80 mg/L (interquartile range 1.55 to 10.25 mg/L). The baseline characteristics of the groups are presented in Table 1, and there were no significant differences between the two groups.

There was a significant decrease in mean serum LDL-c levels from baseline to 4 days in both groups: group A (3.32 ± 0.81 vs. 2.24 ± 0.81, p<0.001) and group B (3.45 ± 1.02 vs. 2.41 ± 0.67, p<0.001). Unlike LDL-c levels, median serum hs-CRP levels significantly increased from baseline to 4 days in group B [4.40 (1.30; 8.38) vs. 11.58 (5.12; 24.86), p<0.001]. There was also an increase in median serum hs-CRP levels from baseline to 4 days in group A but this increase was not statistically significant [5.00 (2.13; 15.55) vs. 8.65 (3.16; 20.85), p=0.209]. Mean serum LDL-c levels and median serum hs-CRP levels were not significantly different between the 2 groups at 4 days (p=0.251 and p=0.250, respectively) (Table 2).

The proportion of patients with serum LDL-c levels <1.8 mmol/L at 4 days was significantly higher in group A than group B (OR=4.592, 95% CI: 1.365 - 15.449, p=0.014). The proportions of patients with LDL-c reduction at least 50% compared with baseline levels and hs-CRP levels ≤ 3 mg/L at 4 days were higher in group A than group B (OR=3.007, 95% CI 0.942 - 9.599 and OR=1.818, 95% CI 0.596 - 5.542, respectively). Nevertheless, these were not significantly different between the 2 groups (p=0.063 and p=0.293, respectively) (Table 3).

Table 1. Baseline characteristics of the study population.

Patient characteristics	Overall (N=96), n (%)	Group A (N=48), n (%)	Group B (N=48), n (%)	P-value[a]
Ages ≥ 60	56 (61.5)	30 (62.5)	29 (60.4)	0.834
Age (years), mean ± SD	63.0 ± 12.0	63.6 ± 11.8	62.4 ± 12.2	0.617[b]
Male	65 (67.7)	31 (64.6)	34 (70.8)	0.513
BMI (kg/m²), median (IQR)	23.7 (21.8; 24.6)	23.8 (21.8; 24.6)	23.5 (21.6; 24.6)	0.778[c]
Hypertension	71 (74.0)	32 (66.7)	39 (81.3)	0.104
Diabetes	25 (26.0)	9 (18.8)	16 (33.3)	0.104
Dyslipidemia	51 (53.1)	25 (52.1)	26 (54.2)	0.838
Physical inactivity	75 (78.1)	37 (77.1)	38 (79.2)	0.805
Overweight or obesity	66 (68.8)	32 (66.7)	34 (70.8)	0.660
Smoking	53 (55.2)	24 (50.0)	29 (60.4)	0.305
Early CAD family history	35 (36.5)	18 (37.5)	17 (35.4)	0.832
STEACS	45 (46.9)	22 (45.8)	23 (47.9)	0.838
NSTEACS	51 (53.1)	26 (54.2)	25 (52.1)	0.811
LDL-c (mmol/L), mean ± SD	3.38 ± 0.92	3.32 ± 0.81	3.45 ± 1.02	0.508[b]
hs-CRP (mg/L), median (IQR)	4.80 (1.55; 10.25)	5.00 (2.13; 15.55)	4.40 (1.30; 8.38)	0.319[c]

Group A: Rosuvastatin 20 mg/day. Group B: Atorvastatin 40 mg/day.
Abbreviation: SD, standard deviation; IQR, interquartile range; BMI, body mass index; CAD, coronary artery disease; STEACS, ST elevation acute coronary syndrome; NSTEACS, non-ST elevation acute coronary syndrome; LDL-c, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.
[a]Using Chi-square test if other tests were not mentioned. [b]Using independent sample t-test. [c]Using Mann-Whitney's U test.

Table 2. LDL-c and hs-CRP levels at baseline and 4-day.

	Baseline		4-day				
	Group A	Group B	Group A	Group B	P¹	P²	P³
LDL-c (mmol/L), mean ± SD	3.32 ± 0.81	3.45 ± 1.02	2.24 ± 0.81	2.41 ± 0.67	<0.001[a]	<0.001[a]	0.251[b]
hs-CRP (mg/L), median (IQR)	5.00 (2.13; 15.55)	4.40 (1.30; 8.38)	8.65 (3.16; 20.85)	11.58 (5.12; 24.86)	0.209[c]	<0.001[c]	0.250[d]

Group A: Rosuvastatin 20 mg/day. Group B: Atorvastatin 40 mg/day.
Abbreviation: SD, standard deviation; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.
[a]Using paired sample t-test. [b]Using independent sample t-test. [c]Using Wilcoxon signed-rank test. [d]Using Mann-Whitney's U test. p₁: comparison between baseline and 4-day in group A. p₂: comparison between baseline and 4-day in group B. p₃: comparison between group A and group B at 4-day.

Table 3. Comparison of the effects of rosuvastatin versus atorvastatin on achieving LDL-c and hs-CRP goals.

	Group A	Group B	Univariable analysis			Multivariable analysis*		
			OR	95% CI	p	OR	95% CI	p
LDL-c < 1.8mmol/L at 4-day, n (%)	14 (29.2)	4 (8.3)	4.529	1.367 – 15.007	0.009	4.592	1.365 – 15.449	0.014
LDL-c reduction ≥ 50%, n (%)	12 (25.0)	5 (10.4)	2.867	0.923 – 8.904	0.061	3.007	0.942 – 9.599	0.063
hs-CRP ≤ 3 mg/L at 4-day, n (%)	10 (20.8)	6 (12.5)	1.842	0.611 – 5.551	0.273	1.818	0.596 – 5.542	0.293

Group A: Rosuvastatin 20 mg/day; Group B: Atorvastatin 40 mg/day.
Abbreviation: LDL-c, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; CI, confidence interval.
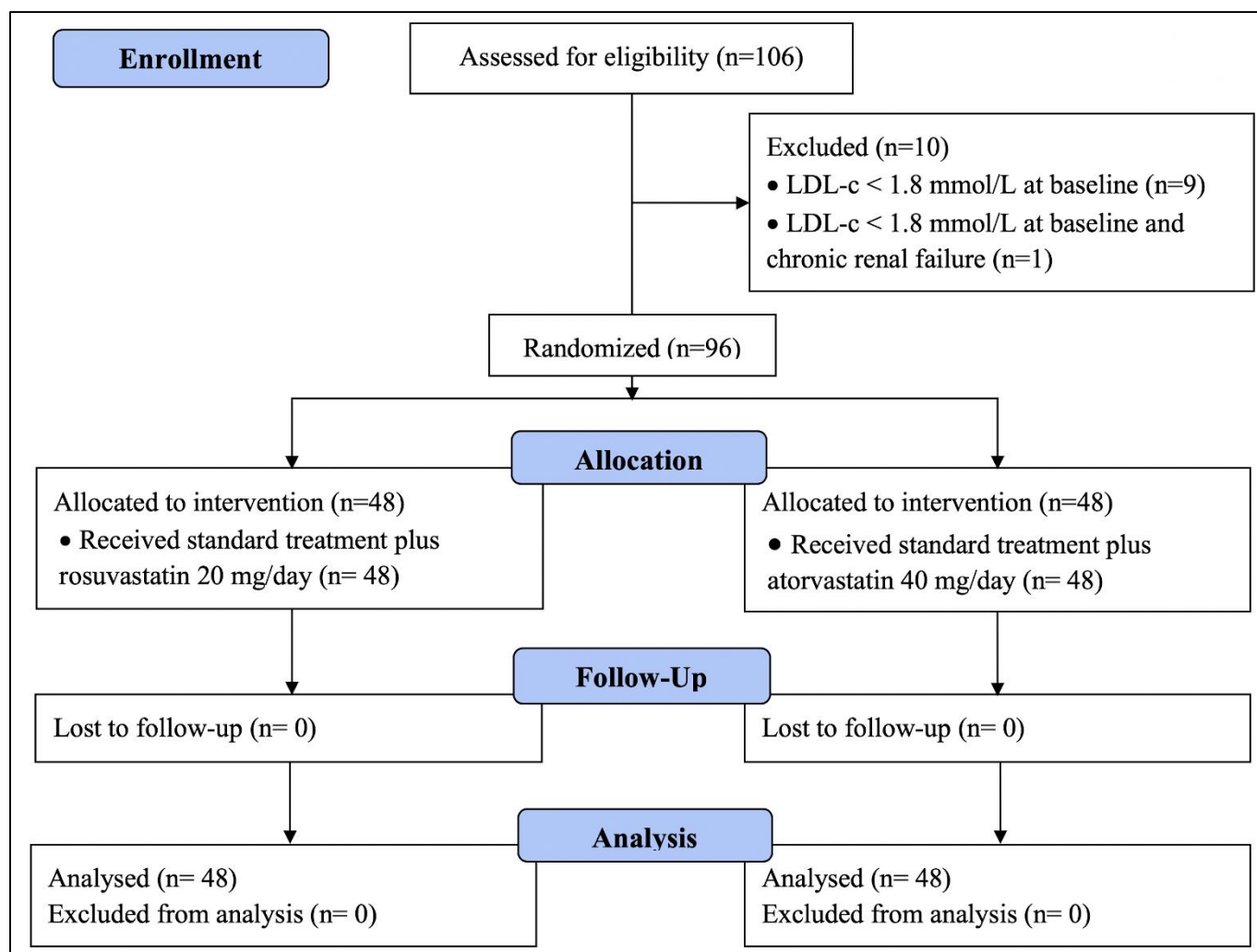*Using Enter method. Variables entered on step 1: intervention status, age, gender.

Figure 1. Flow diagram of the study population
Abbreviation: LDL-c, low-density lipoprotein cholesterol.

4. DISCUSSION

This study was a clinical trial with 2 intervention groups randomly assigned at a ratio of 1: 1 to receive rosuvastatin 20 mg/day or atorvastatin 40 mg/day. There was no statistically significant difference between the two study groups in the demographic characteristics, coronary artery disease risk factors, type of ACS, LDL-c and hs-CRP levels at baseline. The observation period of the study was only 4 days. All patients remained in the hospital for treatment, so no patients were lost to follow-up or dropped out of the study.

Several studies showed that LDL-c levels dropped within the first 24 to 48 hours, reached a maximum within 4 to 7 days after admission[18,19]. Other studies have reported that hs-CRP levels increase after admission and peak within 2-4 days[20,21]. Therefore, we used LDL-c and hs-CRP levels on day 4 to evaluate the early efficacy of high-intensity statins in reducing these biomarkers.

Our study has supported the role of statins in lowering serum LDL-c levels. After only 4 days of treatment, LDL-c levels were significantly reduced in both groups treated with rosuvastatin and atorvastatin. Previous studies with longer follow-up times have shown similar results. An open-label randomized clinical trial conducted on 100 patients with ACS showed that both rosuvastatin 20 mg and atorvastatin 40 mg were effective in lowering LDL-c levels after 4 weeks[22]. Another study with the same 4-week observation period but higher doses of statins also showed a significant reduction in LDL-c levels[23]. Our study has not demonstrated a significant difference in LDL-c levels at 4-day between the two intervention groups. A few previous studies have also reached a similar conclusion that atorvastatin and rosuvastatin reduced LDL-c levels equally[22,24]. The results from LUNAR study showed that compared to atorvastatin 80mg, rosuvastatin 40 mg was significantly more effective in reducing LDL-c, but rosuvastatin 20mg was equally effective[16]. It is deduced that despite being high-intensity statins, different doses of statins can have different therapeutic effects. In our study, the percentage of patients achieving the LDL-c goal of

< 1.8 mmol/L after 4 days of the rosuvastatin group was significantly higher than the atorvastatin group. Our study may be one of the few studies that used the proportion of patients achieving the LDL-c goal of < 1.8 mmol/L to compare the effects of rosuvastatin versus atorvastatin.

The role of statins in reducing hs-CRP was not found in this study. After 4 days of treatment, hs-CRP levels increased in both groups. However, the increase in hs-CRP from baseline to 4-day treatment was not significant in the rosuvastatin group but significant in the atorvastatin group. This has shown that rosuvastatin may have been more effective than atorvastatin in limiting the increase in hs-CRP. Nevertheless, this difference was not really clear. This may be because our research period is too short. In other studies, the effect of decreasing hs-CRP of the statins was evident after 4 weeks, 6 weeks, and 12 weeks of treatment[15,25].

There were differences in follow-up time in the studies. The follow-up time in our study was 4 days. Meanwhile, other studies had a longer follow-up period[15,16,24]. The duration of treatment may have affected the efficiency of statins. A previous study was performed to evaluate the efficacy and safety of rosuvastatin 40 mg[25]. In the study, the hs-CRP level was not significantly reduced at 6 weeks from the baseline. However, a significant reduction in hs-CRP levels was observed after 12 weeks. Dosages of statins were also different among studies. Our study used a dose of rosuvastatin 20 mg daily and atorvastatin 40 mg daily. In other studies, the dose of statins (rosuvastatin/atorvastatin) used was 40/80 or 40/20 mg daily[15,23,24]. Different doses of statins may have produced different results. A study was conducted to compare the effects of different doses of rosuvastatin[26]. The study had three groups including the non-statin group, the rosuvastatin 10 mg/day group, and the rosuvastatin 20 mg/day group. The hs-CRP level of patients in 3 groups did not differ significantly after 1 week. Nevertheless, after 6 weeks and 12 weeks, the hs-CRP level in the rosuvastatin 20 mg group was significantly lower than the other groups.

There were several limitations to our study. This study was only conducted on patients in a hospital and thus, the results may not represent all Vietnamese residents from other areas. The sample size of the study was small and the monitoring time was short, so the difference in efficacy of the statins could not be clearly seen. Further studies should be conducted with larger sample sizes, longer follow-up and multiple centers to demonstrate a significant superiority of rosuvastatin over atorvastatin in achieving LDL-c and hs-CRP treatment goals as well as preventions recurrent cardiovascular events in patients after ACS in Vietnam. The short follow-up may not be the best for assessing patients' outcomes. Because the hospital stay of the inpatient was not long enough to monitor the patient's long-term outcomes and there were some financial and timeframe limitations of the study, the comparison of the efficacy of rosuvastatin versus atorvastatin in this study was based only on early changes in LDL-c and hs-CRP levels. The evaluation of the long-term effect of statins on patient outcomes should be considered in future studies. The changes in LDL-c and hs-CRP levels may be affected by confounding factors including age, gender, type of ACS, interventions, patient adherence, etc. Further studies should consider confounding factors and perform subgroup analysis to assess their effects on study results. For clinical practice, rosuvastatin should be used more than atorvastatin in patients after ACS to achieve LDL-c goal of < 1.8 mmol/L.

5. CONCLUSIONS

Rosuvastatin 20 mg daily and atorvastatin 40 mg daily were both significantly effective in reducing LDL-c after 4 days in patients with ACS, but not with hs-CRP. Differences between the groups were not statistically significant. Rosuvastatin is more effective than atorvastatin in achieving LDC-c goals of 1.8 mmol/L after 4 days, but not in reducing LDL-c levels by at least 50% and reaching hs-CRP levels of ≤ 3 mg/dL. This study supported clinicians to choose rosuvastatin rather than atorvastatin to attain LDL-c levels of <1.8 mmol/L in Vietnamese patients with ACS. Further studies with longer follow-up and larger sample sizes should be conducted to assess the long-term effects of the high-intensity statins on reducing LDL-c, hs-CRP levels as well as prevention recurrent cardiovascular events in Vietnamese patients post-ACS.

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