Original Article

Early Achievement of LDL-C Target in Post ACS and Cardiovascular Outcomes

Phattararuethai Sabkaewyod MD[1], Krissada Meemook MD[1], Piyamitr Sritara MD[1]

[1] Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: Risk factor control may be an essential role to reduce subsequent major cardiovascular events in post-acute coronary syndrome (ACS) patients especially low-density lipoprotein cholesterol (LDL-C). Whether early LDL-C achievement in post ACS can provide additional cardiovascular benefit, the evidence is scared.

Objective: To determine the impact of early achievement of LDL-C target and cardiovascular outcome in post ACS.

Materials and Methods: A retrospective cohort study of patients with diagnosis of ACS who had been admitted at Ramathibodi Hospital Bangkok, Thailand between January 1, 2013 and December 31, 2017 were enrolled. Early LDL-C achieved was defined by LDL-C level below 70 mg/dL or at least 50% reduction from baseline within 12 weeks. Composite outcomes of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and re-revascularization major adverse cardiovascular event (MACE) had been followed for one year. Multivariable Cox proportional hazard model was used to analyze the impact of the early LDL-C achievement.

Results: Of the 352 patients studied, mean baseline LDL-C was 119±45 mg/dL. There were 117 patients (33.2%) in the early LDL-C achieved group and 235 patients (66.8%) in LDL-C non-achieved group at 12 weeks. During the 1-year follow-up, MACE occurred in 25 patients (7.2%) with three patients (2.6%) in early LDL-C achieved group and 22 patients (9.4%) in LDL-C non-achieved group. Multivariable Cox proportional hazard model showed that the early LDL-C achieved group independently associated with reduction of MACE (HR 0.286, 95% CI 0.085 to 0.960, p=0.043).

Conclusion: Among post ACS patients who are very high-risk of further cardiovascular event especially within the first year, not only LDL-C target is to be considered but the earlier LDL-C achievement is also associated with better cardiovascular prognosis. To provide the effective LDL-C control, early LDL-C achievement is necessary.

Keywords: Acute coronary syndrome, Low density lipoprotein cholesterol

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Cardiovascular disease is an important non-communicable diseases leading to morbidity and mortality, globally. Data from the Ministry of Public Health of Thailand shows that 305,943 Thai people suffered from cardiovascular diseases and 20,855 died in 2018, which means that two persons die every hour[1]. Furthermore, the mortality rate of cardiovascular diseases is still increasing[2]. Despite the improvement of acute coronary syndrome (ACS) management in the last three decades, ACS is still the main leading cause of cardiovascular burdens and mortality. Post ACS patients are recognized as a high-risk group for further cardiovascular event. Optimal medical therapies including of antiplatelet, beta-blocker, renin-angiotensin-aldosterone system (RAAS) blockage, and lipid lowering agent play an essential role in term of secondary prevention. The 2013 American Heart Association (AHA) and the American College of Cardiology (ACC) Guideline recommended using high-intensity statin therapy to achieve a percent reduction of low-density lipoprotein cholesterol (LDL-C) level and the European Society of Cardiology (ESC) 2016 recommend the target LDL-C of less than 70 mg/dL or 50% LDL reduction from baseline[3,4]. In 2017, ACC has updated the target LDL-C to be less than 70 mg/dL and to consider adding on non-statin therapies after a reduction of 50% of LDL-C from baseline to the maximal tolerated statin dose[5] to meet the target.

Previous studies have showed the benefit of starting statin early on short-term mortality[6]. The Euro Heart Survey found that patients with ACS

Correspondence to:

Meemook K.

Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Bangkok 10400, Thailand.

Phone: +66-2-2011301, **Fax**: +66-2-2012426

Email: krissada.mee@mahidol.ac.th

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receiving statin therapy within 24 hours associated with reducing the 7-day mortality, especially in patient presenting with ST-elevation acute coronary syndrome (STE-ACS). Furthermore, a meta-analysis that included 20 randomized controlled trials (RCTs) demonstrated that earlier statin administration correlated significantly with lower risk of myocardial infarction (MI), major adverse cardiovascular event (MACE), and major adverse cardiac and cerebrovascular events (MACCE) at 30 days[7,8]. However, when the authors focused on the achievement rate of LDL-C reduction, many previous studies found that more than half of the patients have not achieved the LDL-C target (LDL-C below 70 mg/dL)[9-16]. Additionally, the optimal period to achieve LDL-C target has not well established.

The early reduction of LDL in post ACS patients was significantly associated with reduction of MACE at three years. However, the intensity of statin therapy in previous study was fixed to moderate intensity[17,18].

The present study aimed to assess the impact of early LDL achievement defined by LDL below 70 mg/dL or at least 50% LDL reduction according to the ESC 2016 guideline for the management of dyslipidemias and 2016 the Royal College of Physicians of Thailand Dyslipidemia Clinical Practice Guideline within 12 weeks in post ACS patients and cardiovascular outcomes at one year[19].

Materials and Methods

Study population and Outcomes

The present study was a retrospective cohort study of all consecutive patients with diagnosis of ACS admitted at Ramathibodi Hospital Bangkok, Thailand between January 1, 2013 and December 31, 2017. Using the electronic medical record (EMR) database, the patients who diagnosed as ACS according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, code of I20 (angina pectoris) and I21 (acute MI) were identified, and patient's information was retrieved. All patients who met the following criteria were included, 1) age at least 18 years, 2) diagnoses of ACS including unstable angina (UA), 3) non ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) were made between January 1, 2013 and December 31, 2017, 4) statins or non-statin therapy were prescribed in hospital or by the discharged date, 5) LDL-C measurement at admission considered as baseline LDL-C. If there was no LDL-C measurement on admission, the last documented LDL-C level was considered as baseline LDL-C and the first LDL-C level follow-up after discharge as reported LDL-C level within 12 weeks and more than 12 weeks, and 6) followed for cardiovascular events for one year after discharged. Pregnant women, patients with end-stage malignancy or chronic disease, patients who planned for coronary artery bypass grafting, patients with persistent hemodynamic instabilities or serious myocardial complication needing emergency surgery, patients with active liver disease or end-stage renal disease requiring renal replacement therapy, patients who were contraindicated to statin were excluded from the present study.

LDL-C achievement was classified into the early LDL-C achievement group defined by LDL-C below 70 mg/dL or at least 50% reduction from baselined LDL-C according to the ESC 2016 guideline for the management of dyslipidemias and 2016 The Royal College of Physicians of Thailand Dyslipidemia Clinical Practice Guideline in 12 weeks and LDL-C non-achievement in 12 weeks.

Primary end point was MACE including cardiovascular death, non-fatal MI, non-fatal stroke, and re-revascularization provided by the EMR database. MI was defined as acute MI and unstable angina requiring hospitalization. Stroke was diagnosed based on neurologic deficits and computed tomography (CT) or magnetic resonance imaging (MRI) confirmed by neurologist. Time to cardiovascular outcomes was the period between discharged date and the date of the first cardiovascular event. The detailed of study flow is provided in Figure 1.

Ethical approval

The present study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed and approved by the Office of The Committee for Research, Faculty of Medicine Ramathibodi Hospital Mahidol University (COA. MURA2019/852).

Statistical analysis

The descriptive data provided in baseline characteristics including of age, gender, physical exam data, comorbidities, laboratory results, medications, and left ventricular ejection fraction were presented as categorical variables, which reported as frequencies and percentage, and continuous variables, which reported as mean and standard deviation or median. Fisher's exact test or chi-square test and independent t-test were used to determine the statistical differences

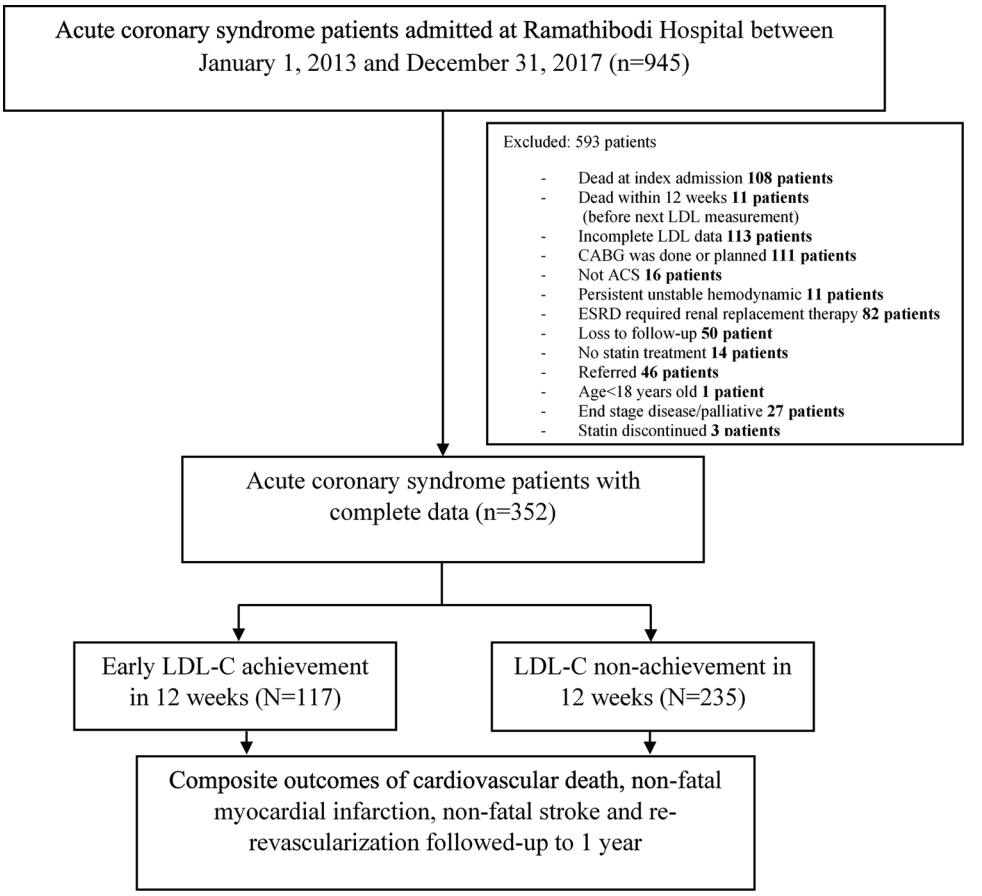

Figure 1. Study flow chart.

between groups for categorical variables and continuous variables, respectively.

The impact of the early LDL-C achievement in post ACS patients and cardiovascular outcomes was analyzed by multivariable Cox proportional hazard regression model and adjusted with traditional cardiovascular risk factors including of age, gender, hypertension, diabetes mellitus, and smoking status.

All p-values reported were two sided, and a p-value of less than 0.05 was considered significant. All analyses were performed by IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Three hundred fifty-two patients were enrolled in the present study. Mean age was 66±14 years, 61.9% were male, 64.8% had hypertension, and 40.3% had diabetes mellitus. Half of the patients were NSTEMI. The remaining were STEMI and unstable angina, diagnosed in 45.7% and 3.7%, respectively. Patients with history of revascularization were 15.6% in case of percutaneous coronary intervention and 8.5% were coronary artery bypass grafting surgery. Left ventricular ejection fraction below 50% was 40% of the patients. Coronary angiogram was performed on 91.2% of the patients. Mean baseline LDL-C was 119±45.1 mg/dL, and LDL-C at 12 weeks was 83.6±26.4 mg/dL. Aspirin, P2Y12 inhibitors, and high intensity statins were prescribed in 96%, 95%, and 75.3% as medications at discharge. Thirty-six-point-five percent of the patients were statin naïve. Other information is provided in Table 1.

LDL-C achievement and cardiovascular outcomes

One hundred seventeen (33.2%) patients were in the early LDL-C achieved group, defined as achieve the LDL-C target within 12 weeks and 235 patients (66.8%) were in LDL-C non-achieved group. Compared to the early LDL-C achieved group, LDL-C non-achieved group was about 1.5 folds more diabetes mellitus and prior percutaneous coronary intervention. Additionally, CABG were also more frequent in

Table 1. Baseline characteristics

	All patients (n=352); n (%)	LDL achieved in 12 weeks (n=117); n (%)	LDL non-achieved in 12 weeks (n=235); n (%)	p-value
Sex: male	218 (62)	76 (65)	142 (60)	0.418
Age (years); mean±SD	66±14	65±13	67±14	0.164
Current smoke	69 (21)	23 (20)	46 (21)	0.244
Body weight (kg); mean±SD	65±13	67±13	64±13	0.082
Height (cm)	162±9	163±9	162±8	0.127
BMI (kg/m^2); mean±SD	25±4	25±4	25±4	0.223
SBP (mmHg); mean±SD	137±27	138±28	136±27	0.550
DBP (mmHg); mean±SD	77±15	77±16	76±15	0.493
In hospital diagnosis				
STE-ACS	161 (46)	58 (50)	103 (44)	0.497
NSTE-ACS	178 (51)	54 (46)	124 (53)	
Unstable angina	13 (4)	5 (4)	8 (3)	
Length of stay (day); mean±SD	4±4	4±4	4±4	0.854
Performed coronary angiogram	321 (91)	109 (93)	212 (90)	0.428
Statin naïve	133 (38)	59 (50)	74 (32)	0.001
Comorbidities				
Prior PCI	55 (16)	12 (10)	43 (18)	0.061
Prior CABG	30 (9)	7 (6)	23 (10)	0.311
Hypertension	228 (65)	74 (63)	154 (66)	0.723
Diabetes mellitus	142 (40)	36 (31)	106 (45)	0.011
Dyslipidemia	213 (61)	68 (58)	145 (62)	0.563
CKD	56 (16)	15 (13)	41 (17)	0.283
Atrial fibrillation	36 (10)	7 (6)	29 (12)	0.091
CHF	51 (15)	13 (11)	38 (16)	0.260
Stroke	19 (5)	7 (6)	12 (5)	0.803
Peripheral arterial disease	5 (1)	1 (1)	4 (2)	1.000
Laboratory; mean±SD				
Hct (mg/dL)	39±6	40±6	38±6	0.011
Creatinine (mg/dL)	1.1±0.5	1.0±0.3	1.2±0.6	0.021
eGFR (mL/minute/1.73 m^2)	71±26	75±23	69±28	0.029
FBS (mg/dL)	134±57	126±42	138±62	0.075
HbA1C (%)	6.6±1.5	6.3±1.4	6.7±1.6	0.057
Total cholesterol (mg/dL)	187±52	199±53	181±50	0.002
HDL (mg/dL)	43±11	43±11	43±11	0.891
Triglyceride (mg/dL)	138±104	128±52	143±121	0.214
LDL (mg/dL)	119±45	135±50	111±40	<0.001
LDL within 12 weeks (mg/dL)	84±26	66±17	93±26	<0.001
Medications at discharged				
Aspirin	338 (96)	113 (97)	225 (96)	0.477
P2Y12 inhibitor				0.028
• Clopidogrel	248 (71)	81 (69)	167 (71)	
• Ticagrelor	72 (21)	28 (24)	44 (19)	
• Prasugrel	14 (4)	7 (6)	7 (3)	
Anticoagulants				0.057
• Warfarin	33 (9)	4 (3)	29 (2)	
• Dabigatran	3 (1)	1 (1)	2 (1)	
• Rivaroxaban	2 (1)	1 (1)	1 (0.4)	
Beta blocker	268 (76)	89 (76)	179 (76)	0.541
ACEI/ARB	174 (49)	58 (50)	116 (49)	0.530
Mineralocorticoid antagonist	16 (5)	5 (4)	11 (5)	0.550
Calcium channel blockers	62 (18)	15 (13)	47 (20)	0.062
Furosemide	42 (12)	10 (9)	32 (14)	0.221
Nitrate	87 (25)	20 (17)	67 (29)	0.025
Hydralazine	32 (9)	7 (6)	25 (11)	0.173
Amiodarone	11 (3)	3 (3)	8 (3)	1.000
Statin				0.406
• High intensity	265 (75)	93 (80)	172 (73)	
• Intermediate intensity	82 (23)	23 (20)	59 (25)	
• Low intensity	5 (1)	1 (1)	4 (2)	
Ezetimibe	17 (5)	2 (2)	15 (6)	0.065
Antidiabetes drugs				
• Metformin	56 (16)	18 (15)	38 (16)	1.000
• Insulin secretagogue	43 (12)	8 (7)	35 (15)	0.037
• DPP4 inhibitor	17 (5)	5 (4)	12 (5)	1.000
• Insulin	27 (8)	2 (2)	25 (11)	0.002
• Thiazolidinedione	9 (3)	2 (2)	7 (3)	0.723
• SGLT2 inhibitors	3 (1)	2 (2)	1 (0.4)	0.257
Left ventricular ejection fraction <50%	116 (40)	38 (38)	78 (41)	0.615

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; STE-ACS=ST-elevation acute coronary syndrome; NSTE-ACS=non ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; CABG=coronary artery bypass surgery; CKD=chronic kidney disease; CHF=congestive heart failure; Hct=hematocrit; eGFR=estimated glomerular filtration rate; FBS=fasting Blood Sugar; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; DPP4=dipeptidyl peptidase 4; SGLT2=Sodium-glucose cotransporter 2; SD=standard deviation

Table 2. Factors associated with early LDL-C achieved analyzed by univariate analysis

Factors	OR (95% CI)	p-value
Age	0.99 (0.97 to 1.00)	0.164
Sex: male	1.21 (0.77 to 1.93)	0.410
DM	0.54 (0.34 to 0.86)	0.010
Baseline LDL-C >100 mg/dL	1.85 (1.16 to 2.96)	0.010
Statin naïve	2.21 (1.40 to 3.49)	0.001
High intensity statin	1.42 (0.83 to 2.42)	0.198
eGFR >60 mL/minute/1.73 m^2	1.72 (1.06 to 2.80)	0.029

DM=diabetes mellitus; LDL-C=low density

LDL-C non-achieved group but insignificantly at 10.3% versus 18.3% (p-value 0.061), 6% versus 9.8%, (p-value 0.311), respectively). Baseline LDL-C was significantly higher in the early LDL-C achieved group at 134.5±50.1 versus 110.7±40.3 (p<0.001). Within 12 weeks, LDL-C was significantly lower in the early LDL-C achieved group than in the LDL-C non-achieved group at 65.6±17.1 versus 92.6±25.7 (p<0.001). High intensity statins used in both groups were not significantly different at 79.5% versus 73.2% (p=0.406). Strong P2Y12 inhibitors were also more prescribed in the early LDL-C achieved group. About half of the early LDL-C achieved group was statin naïve, which was significantly higher than in the non-achieved group at 50.4% versus 31.5% (p=0.001). Whereas baseline LDL-C of less than 100 mg/dL, statin naïve, and glomerular filtration rate greater than 60 mL/minute/1.73 m^2 were significantly associated with the early LDL-C achievement. Diabetes mellitus was inversely associated with the early LDL-C achievement, analyzed by binary logistic regression (Table 2).

During the one-year follow-up, the composite outcomes of cardiovascular death, non-fatal MI, non-fatal stroke, and re-revascularization (MACE) occurred in 25 patients (7.2%). Three patients (2.6%) were in early LDL-C achieved group and 22 patients (9.4%) in LDL-C non-achieved group. Multivariable Cox proportional hazard model showed the early LDL-C achieved group independently associated with reduction of MACE (HR 0.29, 95% CI 0.09 to 0.96, p=0.043) with 6.8% of absolute risk reduction and number needed to treat was 15 (Table 3). Comparison of cumulative survival between LDL-C achieved in 12 weeks group and LDL-C non-achieved in 12 weeks group is shown in Figure 2.

Discussion

The present study was the first study showing that the patients who achieved LDL-C early, defined as LDL-C below 70 mg/dL or at least 50% reduction from baseline within 12 weeks with statin therapy in post ACS patients in Thailand had a significant reduction of the combined endpoints of cardiovascular death, non-fatal MI, non-fatal stroke, and re-revascularization at one-year follow-up. First, the authors demonstrated that the early LDL-C achievement of post ACS patients in Ramathibodi Hospital in 2013 to 2017 was 33.2% higher than in previous studies[20-22]. The present study also reported that high intensity statins, mainly 40 mg of atorvastatin were prescribed in 75% of ACS patients. This compared with previous studies where high intensity statins were prescribed in only 11.1% and 7.6%[20,21].

Data from the Dyslipidemia International Study (DYSIS) shows that 320 ACS patients from seven sites in Thailand between 2013 and 2014 reported that at 4-month followed-up, the mean atorvastatin equivalent dose was 28±16 mg/day[22]. Non-achieved group had more cardiovascular risk factors such as prior CABG and PCI, age, hypertension, and especially diabetes, which was 1.5 folds than in the early achieved group. All of them contributed to non-achieved group to have higher risk of further cardiovascular event. Therefore, not surprisingly, the

Table 3. Multivariated Cox proportional hazard analysis showed the effect of early LDL-C achieved in 12 weeks and MACE

	Incidence; n (%)		HR (95% CI)	p-value
	LDL-C achieved in 12 weeks (n=117)	LDL-C non-achieved in 12 weeks (n=235)		
MACE	3 (2.6)	22 (9.4)	0.29 (0.09 to 0.96)	0.043
Myocardial infarction (non-fatal)	2 (1.7)	12 (5.1)	0.38 (0.08 to 1.69)	0.202
Cerebrovascular events (non-fatal)	0 (0.0)	6 (2.6)		
Re-revascularization	1 (0.9)	0 (0.0)		
Cardiovascular death	0 (0.0)	4 (1.7)		

MACE=major adverse cardiovascular event; LDL-C=low density lipoprotein cholesterol; HR=hazard ratio; CI=confidence interval

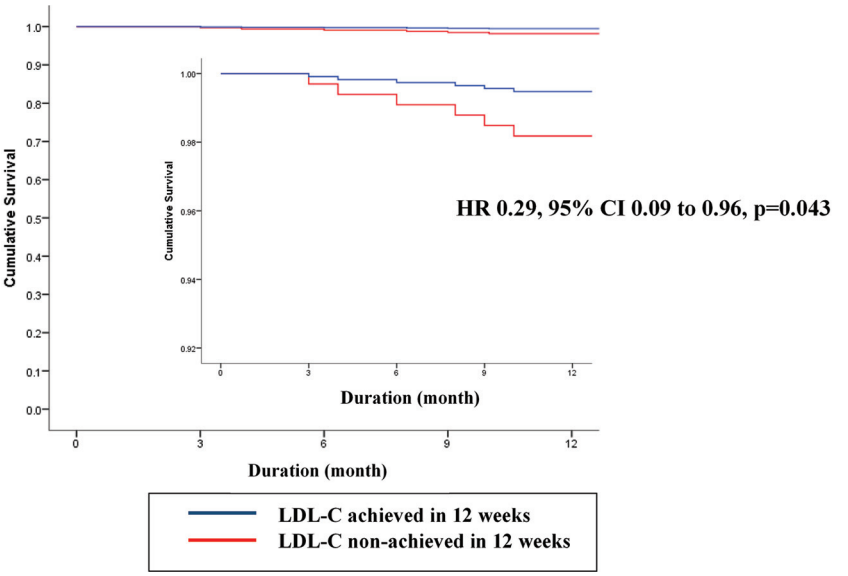

Figure 2. Comparison of cumulative survival between LDL-C achieved in 12 weeks group and LDL-C non-achieved in 12 weeks group.

authors found that the non-achieved group had prior statin therapy before the index event, and this might explain the lower baseline LDL-C than the early achieved group in which half of them were statin naïve. Furthermore, high intensity statin prescription in the early achieved group was also higher.

The authors also found that statin naïve and baseline LDL-C at greater than 100 mg/dL were significant determinant of early achievement of LDL-C, consistent with the post hoc sub analysis study of extended-ESTABLISH trial that enrolled 180 ACS patients with high baseline LDL-C, which was LDL-C of at least 100 mg/dL, significantly decreased LDL-C level from baseline of –41.0±28.9% versus –9.0±28.6% from low baseline LDL-C, which were LDL-C below100 mg/dL, after being treated for six months with 20 mg atorvastatin[23]. In the same way, the greater reduction of LDL-C level might be due to most of high baseline LDL-C was statin naïve, thus, both can amplify the greater and earlier LDL-C reduction leading to cardiovascular benefits. The authors also found that diabetes mellitus was inversely associated with early achievement of LDL-C in contrast with Ho et al study[24]. However, diabetic patients in the present study had prior statin usage. The change of dosage and type of statins before and after the index event were not compared in the present study.

Miura et al[18] study included ACS patients treated with moderated intensity statins from The Assessment of Lipophilic versus Hydrophilic Statin Therapy in AMI (ALPS-AMI) study and classified into early reduction group defined by target LDL-C reduction of at least 30% within four weeks and late reduction group defined as not reached within four weeks. There was significant reduction of MACE by reduction of cardiovascular death at 36 months followed-up[18]. The present study showed a significant reduction of MACE by reduction of non-fatal MI at 12 months in the patients with early LDL-C reduction defined by LDL-C below 70 mg/dL or at least 50% reduction in 12 weeks. Hence, the present study demonstrated the earlier cardiovascular benefits as short term within one year, which was the highest rate of recurrent atherosclerotic events in ACS patients.

The present study also showed that 79.5% in the early achieved LDL-C within 12 weeks received high intensity statin, which provided the greater cardiovascular benefits supporting the combination of early intensive strategy with the short duration to achieve the LDL-C reduction. Thus, the physician should manage strictly on short duration to achieve the target of LDL-C. In patients who cannot reach LDL-C target with maximally tolerated statin, ezetimibe and PCSK9 inhibitors should be promptly considered after four to six weeks[25].

Strength and limitation

The present study is the first to provide the 5-year ACS patient data with definite 1-year cardiovascular outcomes in term of early LDL-C reduction within 12 weeks with statin therapy in Asia population.

There are some limitations that should be noted. First, the study was a single site in Thailand. Second, due to retrospective cohort study, there was some residual confounding bias. Finally, the authors used the most recent lipid measurement recorded in EMR as baseline LDL-C in patients who did not have LDL-C measurement in the index events, so there was variability in time of LDL-C measurement.

Conclusion

Post ACS patients are the very high-risk of further cardiovascular events especially in the first year. Not only achieving LDL-C target should be considered, but the earlier LDL-C achievement was also associated with better cardiovascular prognosis. To provide the effective LDL-C control, optimal time to achieved the target is necessary.

What is already known on this topic?

LDL-C below 70 mg/dL or 50% reduction from baseline is recommended in post ACS to reduce further cardiovascular events. Time to LDL-C achievement may be a crucial factor to provide additional cardiovascular benefit.

What this study adds?

Early LDL-C achievement within 12 weeks could reduce subsequent cardiovascular events in the first year among post ACS patients. To provide the effective LDL-C control, early LDL-C achievement is necessary.

Conflicts of interest

The authors declare no conflict of interest.

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