Chapter 3

Roles of statin potency and LDL-C goal attainment

Publication of short communication in this chapter is listed below.

Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, Phrommintikul A. Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency. Ther Clin Risk Manag. 2015;11:127-136.

Efficacy of statins in reducing LDL-C levels

Abundant evidence has demonstrated that reduced LDL-C is associated with decreased CVD; [1-7] the LDL-C goal is therefore the primary target of therapy.[8,9] Statins (the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are recognized as the first line drugs for lipid-lowering therapy in preventing progression of CAD.[8-10] Statins lower cholesterol by inhibiting the enzyme HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis.[8] All statins have a similar therapeutic effect but differ in their chemical structures, pharmacokinetics, and relative efficacy in lipid-lowering.[11] The degree of LDL-C lowered by each statin differs depending on dose of each statin.[11] A systematic review and meta-analysis based on 75 studies to compare lipid-lowering effects of different statins in various doses are shown in Figure 3.1.[11,12] In the general trend, the effect on lowering of LDL-C increases with the dose of the statins, although not in a linear fashion. [11,12] Figure 3.1 also shows the potency of statins used in our study with green for high potency statins and red for low potency statins.

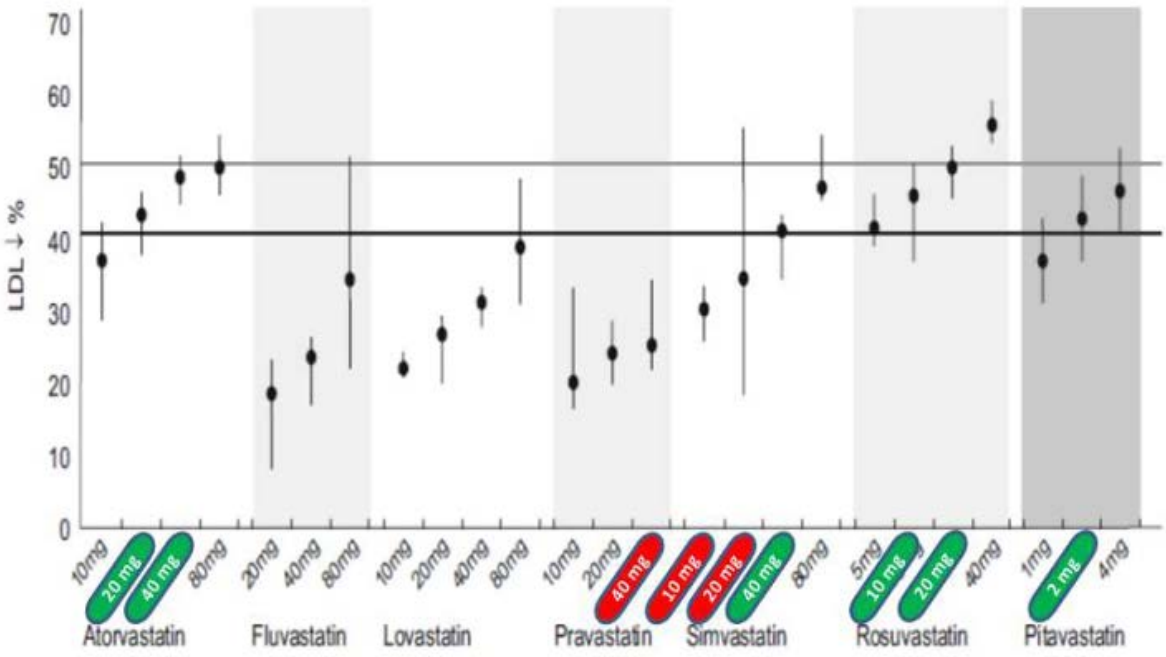

Figure 3.1 Lowering in LDL-C levels among individual statins, modified from[12]

The ACC/AHA guidelines (2013) classified the intensity of statins in 3 groups based on a statin and dose: high-, moderate-, and low-intensity statins, as shown in Table 3.1.[13]

Table 3.1 High-, moderate-, and low-intensity statin therapy according to the ACC/AHA 2013 guidelines[13]

Low-intensity statin therapy	**Moderate-intensity statin therapy**	**High-intensity statin therapy**
Daily dose lowers LDL-C, on average, by <30%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by approximately ≥50%
Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 2-4 mg	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

Modified from[13]

Statin therapy in study I

LDL-C goal attainment

Currently, six statins are commonly used for lipid-lowering therapy in Thailand and during our study period from 2009 to 2011. These comprise rosuvastain, atorvastatin, simvastatin, fluvastatin, pravastatin, and pitavastatin. To date, few studies in Thailand have been conducted on LDL-C reduction in patients treated with statins, and even fewer in those patients at high cardiovascular risk such as ACS patients, as shown in Table 3.5. Thus, study I was designed to investigate LDL-C goal attainment (<70 mg/dL) in ACS patients treated with statin therapy.

In study I, a retrospective study conducted among 396 ACS patients treated with statins, we found that 24% of patients achieved LDL-C goal of <70mg/dL. This is in line with other studies worldwide that found LDL-C goal attainment in less than 30% of

patients at very high cardiovascular risk;[14-20] some other studies reported higher rates (30-45%) of attaining goal.[21-27] The highest success rate in achieving this goal came from a study in Hong Kong (83.1%),[28] while the lowest reported success rate was reported in Greece (10%).[16] Nevertheless, one half of patients could not achieve their goal, suggesting that they were at higher risk of cardiac events. Compared with studies conducted in Thailand, our finding showed a higher rate of achieving LDL-C goal of <70 mg/dL than two previous cross-sectional studies with the same goal: 11.6 % was reported in a study by Silaruks et al,[14] and 16.7% in the study of CEPHEUS Thailand by Sukonthasarn et al.[15] Recently, findings from a study conducted among STEMI patients at the Siriraj Hospital, a university affiliated hospital, has just been released and showed a similar result of achieving rate of LDL-C goal <70 mg/dL: 26% in the study at Siriraj Hospital[29] compared with 24% in our study.[30] In short, a trend was observed of a higher rate of achieving LDL-C goal <70 mg/dL among patients at very high cardiovascular risk in Thailand since 2008.

Monotherapy or combination therapy with statin

In study I, statin monotherapy dominated (approximately 98.2%), and simvastatin (approximately 80%) was the most used in our study, similar to other studies.[15,24,28,31,32] A total of 38% of patients were treated with simvastatin 40 mg/day, 39% with simvastatin 20 mg/day and 3% with simvastatin 10 mg/day (Tables 3.2 and 3.3). According to the updated NCEP/ATP III and ESC/EAS guidelines, when the LDL-C goal is not achieved with statin monotherapy, combination therapy with statins is recommended;[8-10] however, combination therapy with statins was infrequently used in our study (7 patients, 1.8%) and also in other studies.[24,32 33,34] Although all physicians in study I were cardiologists, they may be possibly reluctant to titrate statin doses upwards. Two possible reasons for this are concern regarding potential adverse events, e.g., an increase in muscle toxicity, and the “rule of 6”: doubling the dose of a statin will lower LDL-C by only an additional 6%.[35,36] It is possible that inadequate statin therapy for lowering LDL-C might play a role in the failure of achieving the LDL-C target. Other possible reasons for the low rate of LDL-C goal should be explored in the future.

Table 3.2 Statin therapy in study I (n=396)

Statins in daily use (n, percent of LDL- C reduction)	Number	%	Intensity of statins*
High potency statins (229, ≥ 40)			
Simavastatin 40 mg	149	37.6	Moderate
Rosuvastatin 10 mg	15	3.8	Moderate
Rosuvastain 20 mg	9	2.3	High
Atorvastatin 20 mg	33	8.3	Moderate
Atorvastatin 40 mg	21	5.3	High
Pitavastatin 2 mg	2	0.5	Moderate
Low potency statins (167, < 40)			
Simvastatin 10 mg	11	2.8	Low
Simvastatin 20 mg	155	39.1	Moderate
Pravastatin 40 mg	1	0.3	Moderate

* based on 2013 ACC/AHA guidelines[13]

Table 3.3 Monotherapy or combination therapy with statin in study I (n=396)

Monotherapy/combination therapy	n (%)
Statin monotherapy	389 (98.2)
Statin combination therapy	7 (1.8)
Statin + Ezetimibe 10 mg	2
Statin + Gemfibrozil 300 mg	2
Statin + Gemfibrozil 900 mg	1
Statin + Fenofibrate cap 160 mg	1
Statin + Niacin 375 mg	1

Statin therapy with different potency

Six statins are available for use in Thailand; the reduction in LDL-C of each statin differs, leading to the question of their therapeutic equivalence in treating ACS patients in study I. Thus, in addition to investigating the LDL-C goal attainment, study I also investigated the effect of statins, in differing potencies or intensity, on achieving LDL-C goal <70 mg/dL.

In our study, classification of statin potency as either high or low depends on the cut-off point of 40% reduction in LDL-C: ≥ 40% for high potency statins and <40% for low potency statins. Thus, the high potency statins include simvastatin 40 mg, rosuvastatin 10 mg or 20 mg, atorvastatin 20 mg or 40 mg, and pitavastatin 2 mg. Low potency statins include simvastatin 10 mg or 20 mg and pravastatin 40 mg, as shown in Table 3.2. Our classification of potency of statins differs from that classified by the 2013 ACC/AHA guidelines with cut-off point of 50% reduction in LDL-C as high potency statins, i.e., rosuvastatin 20-40 mg, and atorvastatin 40-80 mg. When the intensity of statins was based on the definition of high-, moderate-, or low-intensity statins by the ACC/AHA guidelines, most patients in our study were treated with low to moderate-intensity statins. Patients in our study were infrequently treated with high-intensity statins; only 30 ACS patients (7.6%) were treated with high-intensity statins: 9 patients (2.3%) with rosuvastatin 20 mg, 21 patients (5.3%) with atorvastatin 40 mg. This suggests that ACS patients in our study were rarely treated with high-intensity statins as recommended in the guidelines of ACC/AHA 2013.[13] Similar to another Thai study conducted in Siriraj Hospital with 216 patients with STEMI, simvastatin dominated.[29]

Effect of statin potency on LDL-C goal attainment

Study I showed that treatment with a high potency statin was not associated with an increased likelihood of attaining the LDL-C goal in routine clinical practice. The effect of statin potency on reducing LDL-C remains controversial in observational studies, although a positive relationship between statin potency and LDL-C goal attainment has been well established in randomized controlled trials.[37,38] This study is in agreement with certain other studies showing that the potency of the statin used does not increase the likelihood of reaching the recommended goal.[22,24,32,39] However, the results from other studies indicate that patients treated with high potency statins are more likely to achieve LDL-C goal.[16,19,40,41] The discrepancy of results between studies might reflect differences in the definition of high or low potency of statins used in the studies, which could affect the percent of LDL-C reduction and lead to differences in successful goal attainment. Intensity of statins used in our study differed from that used in a study by Rallidis et al, [19] simvastatin 40 mg was considered as high intensity

in ours but low intensity in the study by Rallidis et al. Nevertheless, our study used a similar definition of intensity statins as the study at the Siriraj Hospital.[29]

Another reason may be due to the levels of LDL-C at baseline. LDL-C level at baseline is an important determinant of goal achievement; patients with lower baseline LDL-C levels were more likely to achieve LDL-C goal, both <100 mg/dL and <70 mg/dL, as compared with those with higher baseline LDL-C levels.[42] LDL-C at baseline of this study was not high, that is about 120 mg/dL for all included ACS patients. Thus, this study should be interpreted with caution that achieving LDL-C goal <70 mg/dL did not differ between those patients on high or low potency statin when their baseline LDL-C was approximately 120 mg/dL for included ACS patients. The results should be carefully applied in ACS patients with higher baseline LDL-C levels.

In addition, this study showed the low rate of ACS patients reaching LDL-C goal <70 mg/dL, that is, about one fourth of ACS patients could achieve LDL-L goal. The low rate of patients achieving their LDL-C goals might reflect physician inertia or adherence to statin therapy, which should be further investigated. Studies found a positive relationship between adherence to statin therapy and achieving the LDL-C goal.[43-45] Adherence to statins of patients tends to decline after their first prescription; a study showed approximately 40% of 2-year adherence to statin therapy in ACS patients.[46]

Other factors may have also influenced the results, such as comorbidities, variation in response to statin therapy of each patient, and variation in eating habit or food modification, or lifestyle. The length of follow-up for LDL-C levels vary from study to study that may have influenced the results. A single follow-up visit between 2 weeks and 1 year after hospitalization for ACS was used in this study, whereas the follow-up duration in a study in Thailand was 3 months,[29] and a study conducted in Europe and Canada was at least 3 months.[40] We performed further analyses to assess effect of statin potency on achieving LDL-C goal with varying lengths of follow-up, e.g., 1 month, 2 months, 3 months, and 6 months; however, the results remained the same.

Thais may need a lower intensity of statins

Major guidelines, e.g., the 2013 ACC/AHA, recommend treating ACS patients with high-intensity statins: atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day, soon after ACS is diagnosed. However, ACS patients in our study seem to use lower intensity of statins than suggested by the guidelines.

Asians patients may respond differently from patients in other parts of the world such as Europe or the US,[47] where most guidelines have been established. Most physicians in a survey in Singapore felt that high-intensity stains were not required because low doses of statins achieved sufficient LDL-C reduction and worked well among Asians. Most physicians also believed that Asians are intolerant to high doses of statins.[48] A study indicates that lower statin doses achieve lipid improvements in Asian patients comparable with those observed with higher doses among Caucasians.[47]

Typically, Asians achieve similar benefits as Westerners at lower intensity statins.[47] In Japan, none of the statins is approved at the highest doses approved in the United States. Japanese patients use statins at lower doses compared with US patients.[47] For instance, recommended dose ranges for simvastatin for Japanese is 5-20 mg/day, but 20-80 mg/day for US patients.[47] Thais may be similar to Japanese and would not need high-intensity statins as used in Caucasian populations. Likewise, Thais and Asians are possibly intolerant to high-intensity statins,[48] and do not need high-intensity statins. Thus, it would be interesting to investigate the appropriate intensity of statins for Thai patients.

National List of Essential Medicines and LDL-C goal attainment

The National List of Essential Medicines (NLEM), under Thai national policy on rational drug use, may have an impact on physicians' choices of statins for LDL-C control of ACS patients, resulting in lowered rates of achieving LDL-C goal. In Thailand, most Thai citizens are under health insurance scheme. About 96% of the Thai population are covered by one of three health insurance schemes: 1) Civil Servant Medical Benefit Scheme (CSMBS) for the government officers and their dependents; 2) Social Security Scheme (SSS) for private sector employees and 3) Universal Coverage (UC) for people

who are not eligible for either the CSMBS or SSS.[49] Thailand has adopted the NLEM to encourage rational drug use and to control drug costs in the country. Therefore, medicines listed in the NLEM are allowed for patients under the health insurance schemes, but patients have to pay for drugs not listed in the NLEM.[49,50] Statins are one of the top groups in the drug expenditure in Thailand. Not all statins are listed in the NLEM. Simvastatin is the only statin lipid-regulating drug listed in the NLEM 2008 during the study period from 2009 to 2011.[51] However, simvastatin 40 mg (the most used high potency statin) can only reduce LDL-C by about 43%[52] and cannot decrease LDL-C level to below 70 mg/dL in those patients with LDL-C levels higher than 140 mg/dL at baseline. In this case, atorvastatin or rosuvastatin should be used to lower LDL-C to the target goal, but rosuvastatin and atorvastatin are not included in the NLEM during the study period. Study I suggests that physicians may have limited choices of statin therapy for ACS patients and impacting LDL-C outcomes due to NLEM regulations. This finding is similar to a finding from Iceland that a new reimbursement system allowing 10 mg and 20 mg simvastatin to treat hyperlipidaemia increased cholesterol levels for patients with heart disease.[53]

At present, atorvastatin 40 mg has been added to the updated Thailand NLEM in 2013.[54] Patients will be treated with atorvastatin when 1) they have been treated with simvastatin for a period of 6 months and remain unable to control their LDL-C or 2) patients who are unable to use simvastatin due to side effects of simvastatin.[54] Thus, further research is warranted to investigate the impact of adding atorvastatin in the NLEM on achievement of LDL-C goal.

Treating to LDL-C target or fire and forget

LDL-C has been identified as the primary target for lipid-lowering therapy based on major guidelines such as the NCEP ATP III (National Cholesterol Education Program/Adult Treatment Panel III) guidelines,[10] the ESC/EAS 2013,[8] and the National Lipid Association.[55] The LDL-C target goals for each patient are determined based on risk factors of patients and the level of risk for future CAD events. ACS patients are at very high risk of cardiovascular disease; the LDL-C goal of <70mg/dL is recommended by the ESC/EAS guidelines[8] and updated NCEP/ATP III.[9] Thus, in this thesis, all three

studies used the LDL-C of <70mg/dL as a target therapy for ACS patients, as recommended by the updated NCEP/ATP III guidelines in 2004 and the ESC/EAS guidelines in 2011.

Recently, treating to LDL-C target has been the subject of debate[56] after the release of new guidelines, the 2013 ACC/AHA cholesterol guidelines[13] and the lipid modification in the National Institute for Health and Care Excellence (NICE) clinical guideline 181.[57] These new guidelines no longer recommend LDL-C target as a treatment goal due to the lack of large randomized controlled trials showing treating to LDL-C target was associated with reduced cardiovascular events. ACS patients are recommended to use high-intensity statins right away, ignoring to lower their LDL-C to below <70 mg/dL as a target therapy but to monitor LDL-C as a means to measure adherence with statin therapy and to check whether patients had LDL-C reduction at least 50%. As mentioned earlier, very few ACS patients in our study I were treated with high-intensity statins[30] based on the intensity of statins classified by the 2013 ACC/AHA guidelines. Our findings do not seem to support these guidelines. Rather, our findings support the ESC/EAS[8] and 2014 National Lipid Association[55] recommendations that maintaining the LDL-C goal and monitoring of LDL-C levels are beneficial for physicians and patients in following the patient's progress. In study I, for example, monitoring of LDL-C was essential to identify the 75% of patients failing to achieve their LDL-C goal. Many ACS patients will be at increased risk of further cardiovascular events if they are not monitored of their LDL-C levels to achieve goal.

Treating to LDL-C target should be appropriate in the Thai situation because the use of statins is limited by the NLEM, and very few Thai patients were treated with high-intensity statins, as suggested by the 2013 ACC/AHA guidelines. Thai ACS patients should be treated at the hospital with a statin, soon after being the diagnosis of ACS, based on the NLEM. Then they should be monitored for their LDL-C goal attainment as well as adherence to statin therapy. Communication between physicians or health care professionals, (i.e., pharmacists or nurses) and patients should focus on the importance of LDL-C goal attainment associated with lowered risk of recurrent cardiovascular events. Table 3.4 summarized approaches used by the guidelines on lipid management.

Table 3.4 Guidelines of approaches related to dyslipidaemia management for patients with ACS

Guidelines	Target for dyslipidaemia management for ACS patients
Treat to target	
NCEP ATP IIII (2001[10] and updated in 2004[9])	LDL-C<100 mg/dL or <70 mg/dL (optional in updated guidelines 2004)
ESC/EAS (2011)[8]	LDL-C<70 mg/dL and/or ≥ 50% LDL-C reduction when target level cannot be reached
National Lipid Association recommendations for patient-centered management of dyslipidemia (2015)[55]	LDL-C<70 mg/dL
The International Atherosclerosis Society (2014)[1]	LDL-C<70 mg/dL
2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult (2012)[58]	LDL-C ≤ 2 mmol/L or ≥ 50% decrease in LDL-C
Fire and forget	
ACC/AHA (2013)[13]	High-intensity statins (rosuvastatin 20-40 mg/day; atorvastatin 40-80 mg/day)
NICE guidelines (2014)[57]	High-intensity statins (Atorvastatin 80 mg/day)

Thai studies on statin therapy in patients presenting with ACS

As discussed earlier, few studies have been conducted among ACS patients in Thailand with respect to LDL-C goal attainment, and the summary of each study so far is presented in Table 3.5. Study I added to current knowledge on the association between potency of statins and the goal attainment. Up to now and to the best of our knowledge, our study may be the largest retrospective study conducted among only ACS patients in Thailand to focus on LDL-C goal attainment of <70 mg/dL; thus, this may represent the LDL-C goal attainment in ACS patients treated at a university-affiliated hospital in Thailand.

In short, 24% of ACS patients (24.9% with high-intensity statins, and 23.4% with low-intensity statins) in our study could attain LDL-C of<70 mg/dL; we found no association between intensity of statins (high or low) and achieving LDL-C goal.

However, definitions of potency of statins used in our study differed from those used in the ACC/AHA guidelines and other studies; thus, comparing studies should consider this aspect. The LDL-C target of <70mg/dL was used as the primary target in our study, consistent with many guidelines (Table 3.4) such as the ESC/EAS guidelines and the National Lipid Association guidelines. Our finding supports treating ACS patients to LDL-C goal <70 mg/dL. When using the LDL-C goal <70 mg/dL as a target therapy in dyslipidaemia management, we identified a high proportion of patients who cannot achieve this goal – approximately 75% in our study. As a result, active intensive care must be encouraged to help these patients achieve their goal to prevent the risk of further cardiovascular events.

Table 3.5 Studies to assess impact of statins on LDL-C goal attainment based on NCEP ATP III guidelines in Thailand

Study	Study design	Risk group	LDL-C goal (mg/dL)	% LDL-C goal attainment
LTAP I[59] Thailand(1998)	Cross-sectional	Low risk	<160	72.7
		High risk	<130	39.2
		CHD or CHD risk equivalent	<100	11.9
		Total		40.5
LATP II[60] Thailand (2002-2003)	Cross-sectional	Low risk	<160	76.8
		High risk	<130	56.4
		CHD or CHD risk equivalent	<100	34.6
		Total		46.5
Silaruks et al[61] (2008)	Cross-sectional	Moderate risk	<130	47.0
		High risk	<100	54.2
		Very high risk	<70	11.6
		Total		51.1
CEPHEUS Thailand [15] (2009)	Cross-sectional	moderately high-risk	<130	84.7
		High	<100	60.6
		very high risk	<70	16.7
		Total		52.7
Praipaisarnkit et al[62] (2007-2009)	Retrospective cohort study (at least 1-year follow-up)	STEMI and NSTEMI (n=179)	<100	84.9
Chinwong et al[30] (2009-2011)	Retrospective cohort study (2-week to 1 year follow-up)	ACS (n=396)	<70	24.0
		High potency statins (n=229)	<70	24.9
		Low potency statins (n=167)	<70	23.4
Tungsubutra et al[29] (June1, 2008 - May 31, 2011)	Retrospective cohort study (3-month follow-up)	STEMI (n=216)	<70	26.0
			LDL-C reduction ≥50%	19.0
			< 70 or LDL-C reduction ≥50%	30.1

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