



The rate of patients at high risk for cardiovascular disease with an optimal low-density cholesterol level: a multicenter study from Thailand

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Abstract

Background Hypercholesterolemia is a major risk factor for cardiovascular events in patients with established atherosclerotic disease (EAD) and in those with multiple risk factors (MRFs). This study aimed to investigate the rate of optimal low-density lipoprotein (LDL) cholesterol level in a multicenter registry of patients at high risk for cardiovascular events. **Methods** A multicenter registry of EAD and MRF patients was conducted. Demographic data, medical history, cardiovascular risk factors, anthropometric data, laboratory data, and medications were recorded and analyzed. We classified patients according to target LDL levels based on recommendation by the European Society of Cardiology (ESC) 2011 into Group 1 which is EAD and diabetes or chronic kidney disease (CKD)—target LDL below 70 mg/dL, and Group 2 which is MRF without diabetes or CKD—target LDL below 100 mg/dL. The rate of optimal LDL level in patients with Group 1 and Group 2 was analyzed and stratified according to the treatment pattern of lipid-lowering medications. **Results** A total of 3100 patients were included. Of those, 51.7% were male. Average age was 65.8 ± 9.7 years. Average LDL level was 96.3 ± 32.6 mg/dL. A vast majority (92.7%) received statin and 9.3% received ezetimibe. Optimal LDL level was achieved in 20.3% of patients in Group 1 (LDL < 70 mg/dL), and in 46.6% in Group 2 (LDL < 100 mg/dL). The overall rate of optimal LDL control was 23% since 89.6% of study population belongs to Group 1. The rate of optimal LDL was not different between high and low potency statin. Factors that were associated with optimal LDL control were older age, the presence of coronary artery disease or peripheral artery disease. **Conclusions** The rates of optimal LDL level were unacceptably low in this study population. As such, a strategy to improve LDL control in high-risk population should be implemented.

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1 Introduction

Cardiovascular disease is the leading cause of death in both high income and middle income countries.^[1] Low-density lipoprotein (LDL) cholesterol control has been shown to

be a very important factor for decreasing cardiovascular events, both in patients with atherosclerotic disease and in those with risk factors for developing atherosclerotic disease.^[2] LDL cholesterol level was found to be strongly predicted cardiovascular events in a wide range of populations, including post-acute cardiovascular event patients, stable cardiovascular disease patients, and in those who do not have disease.^[3]

It has been recommended by the European Society Cardiology (ESC) in 2011 that among those at very high risk for cardiovascular event such as patients with documented cardiovascular disease, the LDL cholesterol level should be lower than 70 mg/dL, and the level should be lower than 100 mg/dL in patients in the high-risk category but have no

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cardiovascular disease or very high risk features.^[4] The updated guideline in 2016 also keep the same recommendation.^[5] However, there are some discrepancies among practice guidelines. The American College of Cardiology (ACC) 2013 guideline for treatment of blood cholesterol recommends that moderate- or high-intensity statin be prescribed based on patient risk category, as opposed to a drug decision based on LDL cholesterol target.^[6] The recent guideline for management of dyslipidemia for prevention of cardiovascular disease by American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE) in 2017 also recommended the treatment to target concept with the suggestion of target LDL cholesterol level for patients at different levels of similar to recommendation by ESC.^[7] Many studies found that despite the aforementioned LDL cholesterol-lowering recommendations, the control of LDL cholesterol levels continues to be suboptimal.^[8–11]

The primary aim of this study was to investigate the rate of optimal LDL cholesterol level in a multicenter registry of patients at high risk for cardiovascular events. The secondary objectives of this study were: (1) to determine the rate of optimal LDL cholesterol level among patients with different LDL targets; and (2) to determine independent predictors of optimal LDL cholesterol level.

2 Methods

We conducted a registry of data from patients at high risk for cardiovascular event (a cohort of patients with high risk for cardiovascular events or CORE registry) during the 2011 to 2014 study period. The cohort included twenty-five hospitals. The main registry aimed to study the management pattern of patients with established atherosclerotic disease (EAD) and those with multiple risk factors (MRFs). The description of the main registry has been previously reported.^[12] There were twelve hospitals participate in retrieving statin information, of which eight are university hospitals and four are regional or general hospitals. The study protocol was approved by the institutional review board of each participating hospital, and written informed consent was obtained from all patients prior to inclusion in this study. The study procedures were in accord with the ethical standards of the Declaration of Helsinki.

2.1 Study population

Study patients were divided into two groups. Patients who had EAD, including coronary artery disease, cerebrovascular disease, or peripheral arterial disease (PAD), and patients with MRFs for developing atherosclerotic dis-

ease. Patients included in the MRF group had at least three risk factors for vascular disease, including diabetes mellitus (DM) or impaired fasting plasma glucose, hypertension, defined as systolic blood pressure (SBP) of at least 140 mmHg or diastolic blood pressure (DBP) of at least 90 mmHg or being treated with medications; chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) of less than 60 mL/min; dyslipidemia, defined as total cholesterol of at least 200 mg/dL; LDL cholesterol of at least 130 mg/dL; triglycerides^[13] of at least 150 mg/dL or HDL cholesterol of less than 40 mg/dL or being treated with medications; current smoker of at least one cigarette per day; male older than 55 or female older than 65 years; and family history of premature atherosclerosis. Patients were excluded if they met one or more of the following criteria: (1) acute stroke or acute coronary syndrome within three months; (2) current participation in a clinical trial with blinded treatment; (3) short life expectancy within three years, such as advanced cancer; (4) large aortic aneurysm with indication for surgical treatment; (5) inability to commit to attending scheduled follow-up visits; and (6) refusal to participate. Only patients with available LDL cholesterol level and type of statin data were included. Principal CORE investigators were instructed to enroll only consecutive cases.

2.2 Data collection

Data were collected at baseline and at 6, 12, 24, 36, and 48 months. The following data were recorded at baseline: demographic data, medical history, and physical examination data; such as vital signs, weight, height, waist circumference (WC), laboratory data, and medications. All included laboratory data had to be ≤ 6 months old. Cardiovascular events that occurred during follow-up period were recorded at each follow-up visit. Weight was measured in indoor clothing without shoes. Height was measured with back square against the wall without shoes. WC was measured at midpoint between the iliac crest and the lowest rib.

Patient data were recorded on a case record form, and each case record form was faxed to the central data management team of the Medical Research Network (MedResNet). MedResNet is a research data management unit based in Bangkok, Thailand organized by the network of medical school university. It serves the research projects mainly funded by the government funding agency. The data management group verified the data in the case record form, and they generated an inquiry when an error was suspected. Data cleaning and analysis was performed by experienced statisticians. Study site monitoring was randomly performed to determine the level of data quality, and to improve data collection and recording methods as needed.

2.3 Anti-lipid medications and LDL cholesterol levels

Type of lipid medications and type of statin were recorded in all patients. Simvastatin, pravastatin, and fluvastatin were classified as low-potency statins, whereas atorvastatin, rosuvastatin, and pitavastatin were classified as high-potency statins.^[4]

To study the rate of reaching optimal LDL control target, we classified patients according to target LDL levels based on recommendation by the European Society of Cardiology (ESC) 2011^[4] into Group 1 which is EAD or diabetes or CKD—target LDL below 70 mg/dL, and Group 2 which is MRF excluding diabetes or CKD—target LDL below 100 mg/dL. Patients in Group 1 with LDL level above 70 mg/dL and those in Group 2 who had LDL level above 100 mg/dL was defined as suboptimal LDL control.

2.4 Statistical analysis

SPSS Statistics version 22 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous data are expressed as mean \pm SD, and categorical data are expressed as number and percentage. Continuous data were compared using Student's *t*-test for unpaired data between two groups. Categorical data were compared using chi-square test or Fisher's exact test. Associations of four cho-

lesterol management strategies (low-potency statin, high-potency statin, statin plus ezetimibe, and no drugs) and optimal LDL levels was performed by 1-way ANOVA test. Associations of four cholesterol management strategies on LDL target was performed by chi-square test. When *P*-value < 0.05 , post hoc analysis was performed by the Bonferroni method both for continuous data and category data to look for the pairs with statistically significant difference. Univariate analysis and multivariable logistic regression analysis were performed to identify independent factors associated with optimal LDL level. Variables with a *P*-value less than 0.2 in univariate analysis were included in multivariable analysis. In multivariable analysis, a *P*-value of less than 0.05 was considered to be statistically significant. Since this is a prospective study, we have very little problem with the missing data.

3 Results

A total of 3100 patients were included. Of those, 51.7% were male, 89.6% were in Group 1, and 10.4% were in Group 2. The average age of patients was 65.8 ± 9.7 years. Flow of study population and overall picture of the main study is shown in Figure 1. Baseline characteristics of patients with optimal and suboptimal LDL cholesterol level in

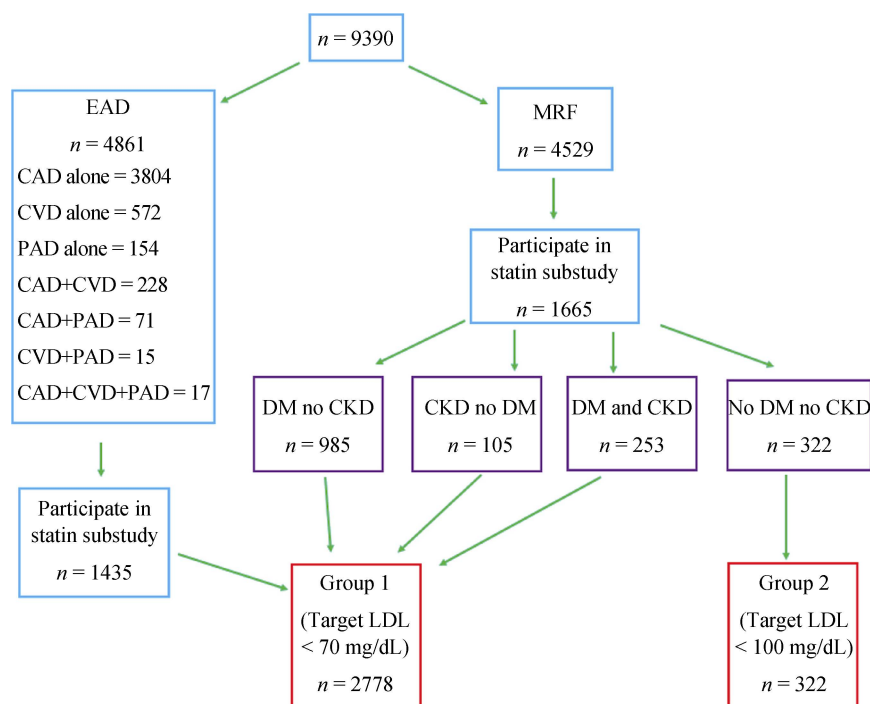


Figure 1. Flow of study population. CAD: coronary artery disease; CKD: chronic kidney disease; CVD: cerebrovascular disease; DM: diabetes mellitus; EAD: established atherosclerotic disease; LDL: low-density lipoprotein; MRF: multiple risk factors; PAD: peripheral arterial disease.

Table 1. Baseline demographic, anthropometric, behavioral, and clinical characteristics by optimal LDL level group in patients with Group 1 and Group 2.

Variables	LDL control							
	Group 1 (n = 2778)				Group 2 (n = 322)			
	All	LDL < 70 mg/dL (n = 563)	LDL ≥ 70 mg/dL (n = 2215)	P-value	All	LDL < 100 mg/dL (n = 150)	LDL ≥ 100 mg/dL (n = 172)	P-value
Age, yrs	65.3 ± 9.9	66.0 ± 9.8	65.1 ± 9.9	0.040*	69.8 ± 7.5	71.0 ± 6.8	68.8 ± 8.1	0.011*
M > 55 or F > 65 yrs	1939 (69.8%)	425 (75.5%)	1514 (68.4%)	< 0.001*	313 (97.2%)	145 (96.7%)	168 (97.7%)	0.738
Male gender	1459 (52.5%)	322 (57.2%)	1137 (51.3%)	0.013*	143 (44.4%)	69 (46.0%)	74 (43.0%)	0.592
DM	1865 (67.1%)	378 (67.1%)	1487 (67.1%)	0.997	-	-	-	-
HT	2597 (93.5%)	541 (96.1%)	2056 (92.8%)	0.005*	319 (99.1%)	149 (99.3%)	170 (98.8%)	1.000
CKD	643 (23.1%)	120 (21.3%)	523 (23.6%)	0.248	-	-	-	-
DLP	2503 (90.1%)	495 (87.9%)	2008 (90.7%)	0.053*	321 (99.7%)	150 (100.0%)	171 (99.4%)	1.000
Smoker	95 (3.4%)	14 (2.5%)	81 (3.7%)	0.172*	12 (3.7%)	4 (2.7%)	8 (4.7%)	0.348
Family history	201 (7.2%)	33 (5.9%)	168 (7.6%)	0.159*	17 (5.3%)	10 (6.7%)	7 (4.1%)	0.299
BMI	25.3 ± 4.3	24.9 ± 3.7	25.5 ± 4.4	0.001*	25.1 ± 4.4	24.5 ± 3.6	25.6 ± 4.9	0.034*
WC	88.6 ± 11.2	88.0 ± 10.9	88.7 ± 11.3	0.170*	86.6 ± 10.0	86.0 ± 9.0	87.1 ± 10.7	0.371
CAD	1195 (43.0%)	294 (52.2%)	901 (40.7%)	< 0.001*	-	-	-	-
CVD	298 (10.7%)	67 (11.9%)	231 (10.4%)	0.314	-	-	-	-
PAD	61 (2.2%)	24 (4.3%)	37 (1.7%)	< 0.001*	-	-	-	-
Statin use	2579 (92.8%)	536 (95.2%)	2043 (92.2%)	0.015*	294 (91.3%)	135 (90.0%)	159 (92.4%)	0.438
Ezetimibe	154 (5.5%)	30 (5.3%)	124 (5.6%)	0.803	12 (3.7%)	2 (1.3%)	10 (5.8%)	0.034*

Data are presented as means ± SD or n (%). *P-value < 0.05 indicates statistical significance. Group 1—EAD, diabetes, or CKD; Group 2—multiple risk factors excluding diabetes and CKD. BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; CVD: cerebrovascular disease; DLP: dyslipidemia; DM: diabetes mellitus; EAD: established atherosclerotic disease; F: female; HT: hypertension; LDL: low-density lipoprotein; M: male; PAD: peripheral arterial disease; WC: waist circumference.

patients with Group 1 and Group 2 are shown in Table 1. A vast majority (92.7%) of patients received statin. Among the patients who received statin therapy, 2294 patients (79.8%) received low-potency statin and 579 patients (20.2%) received high-potency statin. Among the 227 patients who did not receive statin therapy, 21 (9.3%) received ezetimibe. Average LDL cholesterol level was 94.9 ± 32.4 mg/dL in Group 1, and 108.3 ± 31.7 mg/dL in Group 2 ($P < 0.001$). LDL levels stratified by cholesterol management treatment group are shown in Figure 2.

Rate of achievement of LDL cholesterol level by cholesterol management treatment group in patients with Group 1 and Group 2 is shown in Table 2 and Figure 2. Optimal LDL cholesterol level was achieved in 20.3% of patients in Group 1 (LDL cholesterol < 70 mg/dL) and in 46.6% of patients in Group 2 (LDL cholesterol < 100 mg/dL). There was a statistical significant difference between rate of LDL control of Group 1 in comparison to Group 2 ($P < 0.001$). The overall rate of LDL control for the whole study population (LDL cholesterol < 70 mg/dL in Group 1 and LDL cholesterol < 100 mg/dL in group 2) was 23%. From Table 2 there were significant differences in LDL levels and achievement of LDL target of 70 mg/dL among the four

cholesterol management strategies (low-potency statin, high-potency statin, statin plus ezetimibe, and no drugs) in Group 1. From post hoc analysis the significant differences for Group 1 were between patients with no drug versus high-potency statin and no drug versus low-potency statin while there was no significant difference between low-potency statin and high-potency statin. For Group 2, there was no significant difference among four cholesterol management strategies (low-potency statin, high-potency statin, statin plus ezetimibe, and no drugs) for LDL levels and LDL target of 100 mg/dL. The number of patients with LDL < 70 mg/dL in Group 2 were too small to interpret the comparison results.

Table 3 shows bivariate analysis of factors potentially associated with optimal LDL level for Group 1 and Group 2. For Group 1, factors that have significant association with optimal LDL levels were older age, male gender, hypertension, coronary artery disease (CAD), PAD, and statin use. High-potency statin had a slightly higher odds ratio compared to low-potency statin when no drug was used as a reference. Multivariable analysis for Group 1 indicated that only three factors remained in the final model including older age, CAD, and PAD. For Group 2, variables with po-

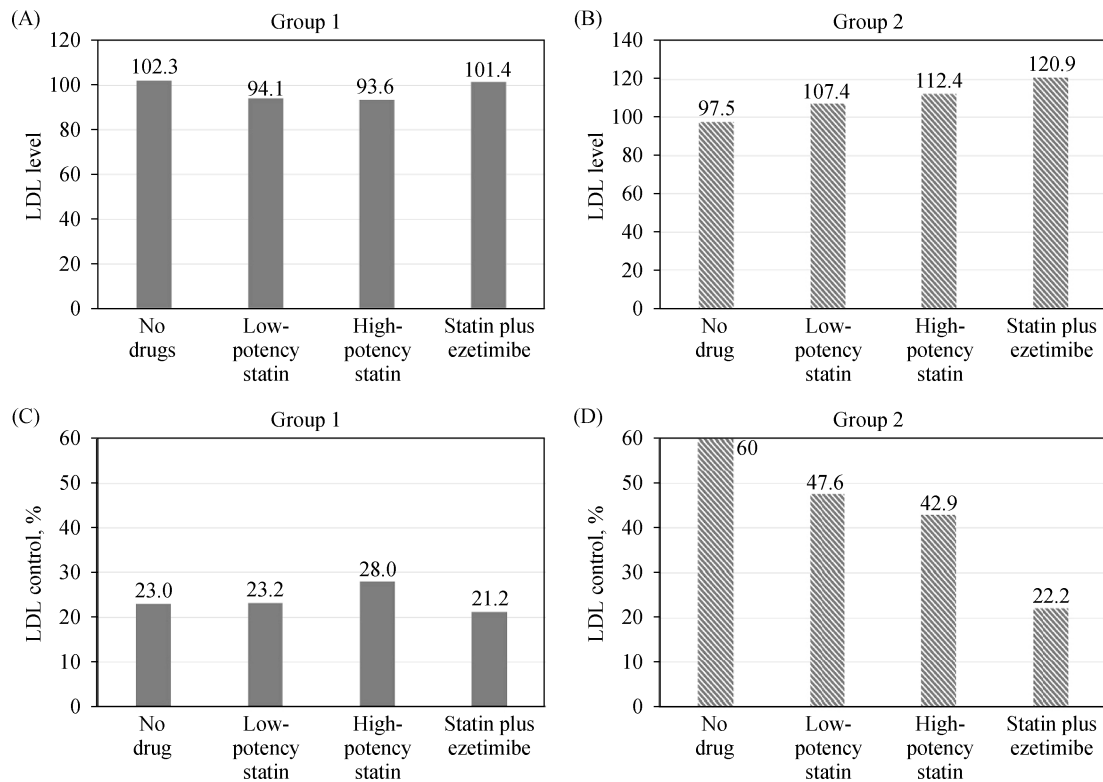


Figure 2. LDL levels (A & B) and rate of optimal LDL cholesterol level (C & D) stratified by cholesterol management treatment group in patients with established atherosclerotic disease (Group 1) and multiple risk factors (Group 2). LDL: low-density lipoprotein.

Table 2. Level of achievement of LDL cholesterol control by cholesterol management treatment group in patients with Group 1 and Group 2.

Variables	All	Cholesterol lowering medications				P-value
		No drugs	Low-potency statin	High-potency statin	Statin plus ezetimibe	
Group 1	2788	181	2001	442	136	
LDL level	94.9 ± 32.4	102.3 ± 32.0	94.1 ± 31.5	93.6 ± 33.5	101.4 ± 39.4	0.001 ^a
LDL < 100 mg/dL	1750 (63.0%)	95 (52.5%)	1278 (63.9%)	289 (65.4%)	77 (56.6%)	0.005 ^b
LDL < 70 mg/dL	563 (20.3%)	23 (12.7%)	409 (20.4%)	101 (22.9%)	26 (19.1%)	0.039 ^c
Group 2	322	25	229	56	9	
LDL level	108.3 ± 31.7	97.5 ± 37.9	107.4 ± 30.4	112.4 ± 31.8	120.9 ± 33.2	0.139
LDL < 100 mg/dL	150 (46.6%)	15 (60.0%)	109 (47.6%)	24 (42.9%)	2 (22.2%)	0.237
LDL < 70 mg/dL	22 (6.8%)	6 (24.0%)	10 (4.4%)	5 (8.9%)	1 (11.1%)	0.005 ^d

Data are presented as means ± SD or *n* (%). Group 1—EAD, diabetes, or CKD; Group 2—multiple risk factors excluding diabetes and CKD. ^aPost Hoc analysis using Bonferroni of 1-way ANOVA found significant difference (*P*-value < 0.05) between no drug vs. high-potency statin and between no drug vs. low-potency statin; ^bPost Hoc analysis using chi-square test found significant difference (*P*-value < 0.05) between no drug vs. high-potency statin and between no drug vs. low-potency statin; ^cPost Hoc analysis using chi-square test found significant difference (*P*-value < 0.05) between no drug vs. high-potency statin and between no drug vs. low-potency statin; ^dPost Hoc analysis using chi-square test found significant difference (*P*-value < 0.05) between no drug vs. low-potency statin. CKD: chronic kidney disease; EAD: established atherosclerotic disease; LDL: low-density lipoprotein.

tential associations with optimal LDL control were selected from analysis shown in Table 1 for bivariate and multivariate analysis. The result of bivariate analysis and multivariate analysis could not identify significant factors associated with optimal LDL level.

Additional analysis was performed to identify the proportion of patients with very high LDL cholesterol level (>190 mg/dL) that mimics familial hypercholesterolemia. In our study population, 47 patients (1.5%) had LDL cholesterol level of greater than 190 mg/dL. Seven of 47 patients

Table 3. Univariate and multivariate analysis of factors potentially associated with optimal LDL levels in Group 1 and Group 2.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Group 1				
M > 55 or F > 65, yrs	1.43 (1.15–1.76)	0.001	1.33 (1.06–1.66)	0.013
Male gender	1.27 (1.05–1.53)	0.013		
HT	1.90 (1.21–3.00)	0.006		
DLP	0.75 (0.56–1.00)	0.053		
Smoker	0.67 (0.37–1.19)	0.175		
Family history	0.76 (0.52–1.12)	0.160		
BMI > 25 kg/m ²	0.85 (0.70–1.02)	0.084		
WC > 90 M or > 80 F	1.03 (0.84–1.25)	0.790		
CAD	1.59 (1.32–1.92)	< 0.001	1.50 (1.23–1.82)	< 0.001
PAD	2.62 (1.56–4.42)	< 0.001	2.61 (1.52–4.48)	< 0.001
Low-potency statin	1.64 (1.08–2.49)	0.021		
High-potency statin	1.80 (1.14–2.85)	0.011		
Group 2				
BMI > 25 kg/m ²	0.72 (0.46–1.13)	0.152		
Ezetimibe	0.23 (0.05–1.02)	0.052		

P-value < 0.05 indicates statistical significance. Group 1—EAD, diabetes, or CKD; Group 2—multiple risk factors excluding diabetes and CKD. BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; DLP: dyslipidemia; EAD: established atherosclerotic disease; F: female; HT: hypertension; LDL: low-density lipoprotein; M: male; OR: odds ratio; PAD: peripheral arterial disease; WC: waist circumference.

(14.9%) had a family history of premature atherosclerosis. Forty-five of 47 patients (95.7%) received statin (30 received low-intensity statin and 15 received high-intensity statin), and five of 47 patients (10.6%) received ezetimibe.

4 Discussion

In this study, we set forth to investigate the rate of optimal LDL cholesterol level in a multicenter registry of patients at high risk for cardiovascular events. We found a rate of optimal LDL cholesterol level of 20.3% in patients with EAD, diabetes, or CKD, and 46.6% in patients with MRF for development of atherosclerotic disease excluding diabetes and CKD. Most (92.7%) of the patients in our study received statin therapy.

Evidence from epidemiologic and clinical trials suggested that the level of LDL cholesterol is related to the risk of cardiovascular events, and the lower the LDL level the lower the risk that an event will occur.^[2] Several studies on both secondary and primary prevention showed a similar results on a lower cardiovascular event rate in patients who had a lower LDL cholesterol level.^[14] In addition, prolonged exposure to a high LDL cholesterol level increases risk of cardiovascular event over time^[15] indicating the significance of sustained suboptimal LDL cholesterol level. However, suboptimal treatment to lower LDL cholesterol level has been reported in many clinical registries in Caucasian and

Asian populations in both primary prevention and secondary prevention settings.^[16,17] The reported rate of optimal LDL cholesterol level in real-world data from Western population or Australia among those with documented cardiovascular disease ranged from 19% to 43% when considered target LDL levels below 70 mg/dL, even when including those who had coronary intervention or who suffered ischemic stroke.^[8–11,18] In these studies, if using a target LDL cholesterol level of 100 mg/dL, the rate of optimal level ranged from 50% to 89%. The results of this study showed a trend similar to the trends described in previous reports. Among patients in Group 1, 20% had LDL level below 70 mg/dL and 63% had LDL level below 100 mg/dL. For Group 2, 60% had LDL levels below 100 mg/dL. This finding is similar to a finding reported from the MONICA study that described a greater decrease and a faster decline in LDL cholesterol levels among patients at higher risk for cardiovascular disease which is defined by a history of myocardial infarction or stroke.^[19] The results of our study showed that Group 1 which target LDL below 70 mg/dL achieved LDL control significantly less than Group 2 which target LDL below 100 mg/dL ($P < 0.001$). The main reason for a better LDL control in Group 2 should be related to a higher LDL target in Group 2 compared to Group 1. If Group 1 had a target LDL below 100 mg/dL, the rate of achievement is higher than Group 2 as indicated in Table 2.

Data from Asian population also showed a low rate of

optimal LDL level. Even in patients after acute coronary syndrome the rate of LDL below 70 mg/dL at four months was only 37% and even lower during follow-up.^[20] Previous reports from Thailand showed the rate of LDL below 100 mg/dL and 70 mg/dL of 51% and 11% among 1240 patients with documented cardiovascular disease in the majority.^[21] A physician's survey study in Thailand reported that 86% and 53% of patients with documented cardiovascular disease had LDL below 100 mg/dL and 70 mg/dL respectively.^[22]

According to the protocol set forth in our national healthcare policy, we start with simvastatin in a majority of patients with dyslipidemia. However, that protocol was recently made more flexible by allowing more use of high-potency statins. This change in policy can partly be explained by the fact that the generic version of simvastatin was available many years before the generic brand of atorvastatin. As such, simvastatin was prescribed in the majority of our patients. Data from a multinational study conducted in Asia showed simvastatin to be well-tolerated and to have good efficacy in Asian population.^[23] Despite data from clinical study that showed that high-potency statin is better than simvastatin for lowering LDL cholesterol in Asian population,^[24] simvastatin is still the most commonly prescribed drug.

Pharmacokinetic study of statins found that Asian population may have higher plasma exposure than Caucasians.^[25] Even at a very low dose, simvastatin was found to have a sustained effect in LDL cholesterol reduction in Japanese population.^[26] Data from randomized clinical trials in Japan showed that, even at a higher target LDL cholesterol level compared to Western populations, Japanese population can achieve a reduction in cardiovascular events from statin therapy.^[27] A meta-analysis of the effect of statin for reduction of atherosclerotic plaque by intravascular ultrasound revealed that Asian population required a lower dose of statin than Western population.^[28]

Although high-potency statin can reduce LDL cholesterol to a greater extent than low-potency statin,^[29] data from our study did not show significant difference in the rate of optimal LDL level between these two statin potencies. Given that the number of patients that did not receive statin in our study was small, the results of between group comparisons in our study had to be interpreted with caution. However, we were able to clearly demonstrate that LDL cholesterol levels were significantly lower in patients that receive statin therapy. A recent study in Thai diabetes patients that compared between LDL cholesterol reduction of < 50% and \geq 50% showed that target LDL cholesterol level of 70 mg/dL and 100 mg/dL can be achieved with low-in-

tensity statin (mostly simvastatin) at a rate similar to that observed when using moderate- or high-intensity statin (mostly atorvastatin).^[30]

A plausible explanation regarding why LDL cholesterol levels were not different between patients prescribed low-intensity and high-intensity statins in this study may be that high-intensity statins were given at a suboptimal dose, since the prescribing physicians did not intend to adjust the dose in an attempt to achieve the levels recommended by the guidelines. A previous study reported that physicians tend not to adjust the dose and type of statin during follow-up visit despite the LDL cholesterol level not being at the LDL target level.^[20] Another reason that no significant difference was observed between statin potencies may be due to a patient-related factor. According to our experience, Asian patients tend to complain about adverse effects of statin therapy, and they have a fear of using statins based on a belief that the drug may cause muscle pain and liver toxicity, and that statin must be used lifelong once statin therapy has commenced. Previous study reported that some patients are fearful of statin use based on a belief that statins cause cancer and/or they increase the risk of developing diabetes.^[31] In the same report, when treating physicians prescribe statin therapy, many patients proceed with an intention to skip many doses based on a fear of using statins. A retrospective study from a medical insurance system in United States reported that only 41% of statin therapy patients were in the high adherence group or were taking the drug on more than 80% of the days that their prescription covered.^[32]

Factors from our study that were associated with optimal LDL cholesterol level for Group 1 were older age, and presence of CAD, or PAD. Among patients with target LDL below 70 mg/dL, those with EAD such as CAD and PAD were more likely to achieved LDL target compared to patients without EAD such as DM or CKD. For Group 2, with the target LDL of 100 mg/dL, we could not identify factors that were associated with optimal LDL control. Possible reasons may be a relatively small number of patients for Group 2, LDL levels were already low for those who did not received cholesterol lower agents, and poor compliance to statin in patients who just had risk factors without established disease.^[33]

In the IMPROVE-IT study, ezetimibe was shown to deliver additional benefit when combined with statin in patients who cannot tolerate statins or in those unable to achieve guideline-recommended levels with statin alone.^[34] In contrast, we were not able to demonstrate that statin combined with ezetimibe is more effective for lowering LDL cholesterol level than statin alone.

Possible reasons for no differences in LDL target achie-

vement between high-potency and low-potency statin may be explained by three factors. Firstly, this is a registry data. The treatment that the patients received is based on the clinical judgement. It is possible that the patients who were not on statin might be the ones that the LDL levels were already low. As you can see in Table 2 that for Group 1, patients with no drugs had a lower rate of LDL achievement compared to low or high-potency statin. But for Group 2, patients with no drugs tend to have a higher rate of LDL achievement compared to statin which is due to the fact that the LDL levels was already low in Group 2, therefore, they may not need statin. This may also be true for the selection of moderate or high intensity statin. Clinicians tend to use high intensity statin in patients with very high LDL levels and moderate intensity statin in those with the LDL levels were not very high. Therefore, the achievement of target LDL levels may not truly reflect the effect of high-intensity or moderate-intensity statin that has been shown in clinical trial setting. Secondly, according to the reimbursement system policy by the government to save the cost of treatment during the time of study, clinicians were allowed to start with only simvastatin which is a low-potency statin. If the targets were not achieved, clinicians were recommended to increase the dose of simvastatin. If the LDL is not achieved, then, clinicians were allowed to use high-intensity statin. The system changed after the availability of generic brand of atorvastatin. As you can see in the results of our data that even patients at high risk for cardiovascular events such as those with EAD or DM or CKD, only 18.8% of them received high-intensity statin. Last but not least, as mentioned earlier Asian population tend to respond to low-potency statin better than Western population.^[26,28]

About future considerations, the patients that have not achieved a guideline-based LDL target level need to be identified, and their statin therapy regimens need to be adjusted to achieve maximum effect at a tolerable dose and at the appropriate intensity in initial step. Many studies have tried to prove the benefit of using many drugs combined and formulated into one pill (*i.e.*, a polypill that contains an anti-hypertensive, a statin, and aspirin) to treat patients at risk of cardiovascular event. A 2009 reported the effectiveness of polypill for controlling risk factors for a cardiovascular event.^[35] By improving adherence and access to these important medications, use of polypill is projected to reduce the risk of premature death due to atherosclerosis by 25% by 2025.^[36] Heart outcomes prevention evaluation-3 is another study that proved the benefit of using statin in a wide range of population at risk of atherosclerosis.^[37]

Since lower LDL cholesterol level was found to be significantly associated with better patient outcomes in many

clinical trials, new drug classes have been developed.^[38] Pre-protein convertase subtilisin kexin (PCSK)-9 inhibitor is a new class of drug that has been proven to be very effective for lowering LDL cholesterol. Results from phase 2 and phase 3 study revealed that PCSK-9 drugs are more potent than statin relative to LDL cholesterol reduction. Recent studies reported that in addition to reducing LDL cholesterol, PCSK-9 drugs also reduce cardiovascular events in high-risk group patients.^[39,40] In addition, the adverse effect of this new class of medication appears to be minimal. However, contrary to the stated benefits, PCSK-9 drugs have to be administered by subcutaneous injection. This new drug is indicated in high-risk patients who cannot achieve target LDL cholesterol levels, and as primary prevention in patients with familial hypercholesterolemia. In this study, 1.5% of patients had an LDL cholesterol level of greater than 190 mg/dL that mimics familial hypercholesterolemia.

4.1 Limitations

This study has some mentionable limitations. Firstly, we did not record the dose of statin, so we were unable to classify patients into high-intensity or low-intensity statin groups. Secondly, we did have data on statin compliance, which could have a significant impact on the results of this study. Thirdly, we did not have the necessary follow-up data available to compare the impact of different types of statin, or to evaluate the significance of LDL cholesterol level on cardiovascular outcome. Fourthly, the reference of optimal LDL-cholesterol level in our study was based on ESC guideline 2011 for management of dyslipidemia.^[4] Recent guidelines tend to be more aggressive in term of LDL-cholesterol lowering.^[7,41] Last but not least, the results of this study may not be generalizable to the whole population of the country, but our data were from twelve hospitals distributed in different regions all over Thailand.

4.2 Conclusion

The rates of optimal LDL level were unacceptably low in this study population. As such, a strategy to improve LDL control in high-risk population should be implemented.

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